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A Multimodal Strategic Approach to Integrative Oncology

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ABSTRACT

The term "integrative oncology" can mean particular things to different audiences. For the purposes of this article, I intend it to mean the simultaneous use of multiple anti-cancer strategies that can have a synergistic effect against the tumor, its microenvironment, and its propensity to metastasize. Thereby, having a maximum impact against the cancer with a minimum of side effects for the patient to endure. As noted in the references, this paper briefly describes the five prevailing evidence-based systematic approaches in use today. Each of these approaches has varying degrees of effectiveness which, in my experience, when clinically integrated, produces exponentially better efficacy, hence shifting progression-free survival into the possibility of increased overall survival and a durable remission. This paper is an attempt to offer some perspective of how to apply these disparate methodologies so that they may be more effectively integrated, resulting in consistently better clinical responses.

Keywords: Integrative oncology; oncology; multimodal strategic; cancer.

1. INTRODUCTION

Cancer, as a disease of our time, has been described as a "wound that does not heal" [1] because it has a multitude of biochemical dysfunctions at its core. However, in order for these genetically and phenotypically abnormal cells to survive and thrive, the watchdog of the

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body, the immune system, must itself be suffering from a number of serious areas of structural and functional damage. From a perspective of ten thousand feet, there are two basic characteristics of cancer: genetic instability and the propensity to metastasize. From those two basic observational characteristics, the hallmarks of cancer were derived by Drs. Hanahan and Weinberg in 2000 as follows:

Self-sufficiency in growth signals. Insensitivity to antigrowth signals. Evading apoptosis, Limitless replicative potential, Sustained angiogenesis, Tissue invasion and metastasis.

And then the following were added in 2011:

Deregulating cellular energetics, Avoiding immune destruction, Genome instability and mutation, Tumor-promoting inflammation [2,3].

Based upon the characteristics of the cancer, there are five common office-based/out-patient strategies that we can employ. Each of these strategies is made up of a number of tactics based upon the unique expressed characteristics of the target cancer and the physiological individuality of the patient. Those five strategies are first, to balance and normalize the metabolism of the patient while inhibiting the physiology of the cancer. Second, to identify and seek to repair areas of damage within the structure and function of the immune system. Third, to identify actionable genetic and protein mutations that are driving the cancer and address them. Forth, to employ agents that can inhibit, suppress, or destroy the root of the problem, the cancer stem cells. And fifth, to directly attack the cancer with cytotoxic (chemotherapeutic) agents and radiation therapy. Utilizing agents that can decisively accomplish one of these strategies or that can engage and strike two or more of these objectives with less toxicity can lead to greater quality and quantity of life for our patients.

2. METABOLIC APPROACH

2.1 Biochemical Support of the Patient Milieu

Metabolic targeting is the first anti-cancer strategy because it lays the foundation for the improved response for all of the other strategies that follow. In 1498, Albrecht Durer created the famous woodcut entitled “The Four Horsemen, from the Apocalypse” which, in a sense, foreshadowed the epidemic of severe and chronic diseases that we now face. From a metabolic, thousand-foot perspective, there are four major processes that are common pathways for the initiation and promotion of cancer. Each of which should be assessed for every patient: Glycation; which can be easily measured with blood sugar, hemoglobin A1C, and GlycoMark; **I**nflammation; for which there are a myriad of markers including ESR, CRP, plasma viscosity, adiponectin, monocyte chemoattractant protein 1 (MCP-1), CD40 ligand and lipoprotein-associated phospholipase A(2) (Lp-PLA(2)), and ferritin to name but a few; Methylation; which can be watched with homocysteine levels; and finally, we come to Oxidation; which is largely reflected in levels of lipid peroxides and oxidized LDL. Current research demonstrates that cancer is largely a metabolic disease involving disturbances in energy production (deregulating cellular energetics) through a shift from respiration to fermentation, but this is not the only aberrant energy pathway that cancer cells can utilize. The genomic instability observed in tumor cells, leading to the other recognized hallmarks of cancer listed above, is now considered downstream epiphenomena of the initial disturbance of cellular energy metabolism which is often caused by a toxin [4]. The disturbances in tumor cell energy metabolism can be linked to demonstrated abnormalities in the structure and function of and within the mitochondria [5-7]. Extrapolating upon this research we come to several conclusions for therapeutic intervention.

Glycation starts with diet. Diet has been recognized and is now accepted by mainstream medicine as a viable strategy for minimizing the risk of getting cancer [8-10]. Furthermore, “a higher frequency of organic food consumption was associated with a reduced risk of cancer” [11]. A proper diet can address issues of nutritional deficiency and some toxin exposure while supplying necessary anti-oxidants and helping to manage glycation (while hopefully being delicious). When we apply a dietary strategy to someone with cancer, while recognizing the dysregulated metabolic mitochondrial foundation of the tumors, we come to a low carbohydrate/ketogenic diet. Because cancer is biochemically dependant upon sugar to maintain its fermentation metabolism, depriving it as much as possible, of sugar will further destabilize the cancer cells making it easier to trigger apoptosis, with the addition of other therapeutic agents [12,13]. One of those therapeutic agents is Metformin. In addition to

lowering blood sugar levels and thus minimizing the fuel source for cancer cells, Metformin interferes directly with cell proliferation and supports apoptosis in a non-insulin-mediated manner. Accumulated research and clinical evidence suggest that Metformin exerts its positive effect on the clinical course of neoplastic diseases, primarily through the stimulation of 5' AMP-activated protein kinase (AMPK) in association with the upstream liver kinase B1 (LKB1) [14,15]. AMPK is a key cellular energy sensor, activation of which by Metformin leads to suppression of energy-consuming processes such as gluconeogenesis [16,17]. In carcinoma cells, the stimulation of AMPK, mediated by Metformin, resulted in the inhibition of the mTOR/ribosomal S6 kinase pathway and thus inhibition of the pathological cell cycle progression, cell growth, and angiogenesis [18,19]. This is a particularly important effect when there is a mutation of phosphatase and tensin homolog (PTEN) which would normally downregulate this pathway [20].

Inflammation is another metabolic pathway that drives cancer, therefore, anti-inflammatory strategies are of critical importance against cancer [21]. Inflammation results from or is triggered by virtually every disease known to man and has cellular pathways, plasma cascades, and acute and chronic markers. Some of the markers associated with cancer include CRP, IL-6, IL-8, and TNF-alpha. Inflammation can stimulate cancer stem cells as well as more mature tumor cells, triggering disease progression. Inflammation is a defense mechanism that serves to protect us from acute inflammatory illnesses (infections) and injuries that historically, from an evolutionary point of view, were the main causes of death. Inflammatory proteins activate the Th2 pathway which generates more inflammation. In doing so, in an apparent effort to focus and conserve resources, when the Th2 pathway becomes chronically stimulated by infection, vaccinations, nutritional deficiency, sugar, alcohol, trauma, stress, or toxins, it suppresses the Th1 pathway which is a critical pathway of the immune system, needed to protect us from, and fight cancer. Cimetidine can help to restore the Th1/Th2 balance and overcome pro-inflammatory Th2 dominance [22]. Activation of the Th1 pathway and its downstream effector cells results in the production of Reactive Oxygen Species (ROS). Which are inflammatory molecules that act locally to kill cancer cells, so we don't want to negate all inflammatory responses [23].

An important enzyme for the inflammatory response is cyclooxygenase (COX), which is critical for the conversion of arachidonic acid to prostaglandins and other Eicosanoids. It exists as two isoforms: COX-1 and COX-2; COX-1 is constitutively expressed whereas COX-2 is a highly inducible gene that is activated by cytokines, growth factors, phorbol esters, oncogens, and chemical carcinogens. COX-2 plays a key role in carcinogenesis as has been demonstrated in numerous cancer cell types. Multiple pathways have been proposed to explain how increased COX-2 expression might contribute to carcinogenesis including elevated BCL-2 protein levels and inhibition of apoptosis, increased angiogenesis, and enhanced metastatic activity. Suppressing COX-2 activity, or at least not stimulating it, which many chemotherapeutic agents do, is an important part of any anticancer strategy. Many agents have been identified that suppress COX-2 activity, which can be assayed in vitro and is reflected clinically in decreased levels of CRP, interleukin-6 (IL-6), P-selectin, matrix metalloproteinase-9 (MMP-9), tumor necrosis factor (TNF-α), and other inflammatory markers. Some of the anti-inflammatory agents that are helpful against cancer include Celecoxib, fish oil, (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), white willow tree, curcumin, green tea, pycnogenol, Boswellia, resveratrol, cats claw, and capsaicin to name just a few of the most common medicaments[24-49].

Methylation seems to still be incompletely understood when it comes to cancer. On the one hand, people with the fairly common methylenetetrahydrofolate reductase (MTHFR) mutation are at a higher risk of getting certain (and maybe all) cancers [50]. This makes sense because that gene affects some of the liver detox pathways and when it isn't working well it can lead to known increased risks for cardiovascular heart disease, leukemia, breast cancer, colon cancer, and many other illnesses [51]. The mutation can be tested for and some of its effects monitored with homocysteine blood levels. Many of the negative effects can be bypassed with methylated B vitamins. On the other hand, gene expression can be significantly modulated by alterations in DNA methylation patterns. Methylation within the promoter regions of tumor suppressor genes causes their silencing, and methylation within the gene itself can induce mutational events. These mechanisms may play a fundamental role in precipitating the development of a large and diverse number of

human cancers[52]. It is important to monitor homocysteine and B vitamin levels while treating people with cancer, because overshooting your mark may make some cancers worse [53]. When a woman is pregnant we give prenatal vitamins which are largely B vitamins to stimulate the cell growth of the fetus, and when you're fighting cancer you don't want to do that. However, it is important to note that, B vitamin deficiencies will inhibit many immune functions that are desperately needed for the fight [54]. Nothing about fighting cancer is easy, getting biochemical moieties to and maintaining them within the normal range is a safe bet, from a metabolic perspective.

Oxidation, like the rest of metabolic activity, is also a bit of a double-edged sword when it comes to cancer. Oxidative stress is caused by many things including; obesity, high fat diet, sugar, the chemicals in processed foods, radiation, smoking, alcohol, Covid-19, environmental pollution and chemicals, etc., etc., etc..(i.e. life) [55]. Damage from oxidative stress occurs when the cells and tissues are unable to keep up with harm done by the free radicals that are generated from the above, and other causes. A free radical is an atom, molecule, or ion that has an unpaired valence electron that can bind to, and damage, DNA and messenger molecules but is normally kept in check by the body's store of anti-oxidants. This damage is carcinogenic. Anti-oxidants can mitigate oxidative stress and are found in vegetables such as broccoli, spinach, carrots, cabbage, and vitamins C, E, D, A, etc., etc., etc... Uncontrolled oxidative stress can activate a variety of transcription factors including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein *1* (AP-1), tumor protein 53 (p53), Hypoxia-inducible factor-1a (HIF-1α), Peroxisome proliferator- activated receptor gamma (PPAR-γ), β-catenin/Wnt, and nuclear factor erythroid 2–related factor 2 (Nrf2). Activation of these transcription factors can lead to the expression of over 500 different genes, including those for growth factors, inflammatory cytokines, chemokines, and cell cycle regulatory molecules. Activation of these molecules by oxidative stress stimulates inflammatory pathways leading to the transformation of a normal cell to a tumor cell, increases tumor cell survival, proliferation, chemoresistance, radioresistance, invasion, angiogenesis and supports cancer stem cell survival [56]. On the other side of the sword, the production of oxidative reactive oxygen species (ROS) is required for the function of another major effector of the innate immune system, Natural Killer (NK) cells—hydroxyl radical production is responsible for NK cells-mediated cytolysis, by promoting the secretion of cytotoxic factors from NK cells granules [57-62]. ROS can promote carcinogenesis by inducing genetic mutations, activating oncogenes, and raising oxidative stress, which can stimulate cell proliferation, survival, and reduce apoptosis. Over the past few decades, natural compounds have attracted attention as potential cancer therapies because of their ability to maintain cellular redox homeostasis with minimal toxicity. Research and clinical studies show that bioactive dietary polyphenols exert antitumor effects by inducing ROS-mediated cytotoxicity in cancer cells. These bioactive compounds also regulate cell proliferation, survival, and apoptotic and antiapoptotic signaling pathways [63]. Amongst many other examples, this is demonstrated in the ability of Aronia melanocarpa to increase the expression and activity of p53 and p73 that leads to the down-regulation of the expression of cyclin B1, which contributes to the cell cycle arrest of cancer cells [64-66].

Some commonly used anti-cancer agents include:

Glycation
Metformin [67,68]
Berberine [69,70]
Azadirachta indica (neem) [71,72]
Inflammation
Celebrex [73]
Curcumin [74,75]
Grape Seed Extract [76,77]
Cimetidine [78]
Viscum [79]
Methylation
Decitabine [80]
EGCG [81]
Oxidation
DMSO [82]
Raloxifene [83]
Vitamin C and MANY other vitamins and minerals [84]

2.2 Biochemical Targets of the Tumor: The Micro-environment

A closer look at the cancer itself demonstrates that by corrupting and recruiting non-malignant cells in the area, the tumor has created its own biochemical tumor microenvironment (TME)

suitable for its self-protection and propagation [85]. Many different cell types, besides the cancer, can be found in the TME including; adipocytes, fibroblasts, dendritic cells, lymphocytic endothelial cells, myeloid-derived suppressor cells, pericytes, tumor-associated macrophages, tumor-associated neutrophils, and vascular endothelial cells, to name but a few [86]. Other cells to be found in TME include T-cells, NK cells, NKT cells, and some B-cells that are there to fight the good fight. Dendritic cells and macrophages found just outside of the TME are also engaged in the battle against the cancer, but if consumed by the tumor, seem to become corrupted and aid in its survival [87]. The dynamic interactions of the cancer cells with the stromal cells (cellular part) and extracellular matrix (ECM) components (non-cellular structures) are essential for stimulating the multiple cell lines of the cancer, as well as its clonal evolution and propensity to develop multidrug resistance, resulting in cancer cell progression and metastasis [88]. The ECM holds cells, tissues, and organs together and maintains the three-dimensional structure of the body. For a cancer cell to metastasize from the primary tumor to other organs, it must locally degrade the ECM components that are the physical barriers to cell motility. Cancer cells build, shape, and recruit support for their TME through the release of many different types of molecules including; matrix remodeling enzymes, mediators of inflammation (which can stimulate the activity of the matrix metalloproteinases), cytokines, cell-free DNA (cfDNA, which we can now test for [89] chemokines, growth factors, exosomes, and can facilitate horizontal gene transfer [90]. The reciprocal and self-supporting cell-cell/ECM interaction forces the expression of new phenotypes of non-cancer cells that promotes the development and invasion of the cancer at large [91].

Trying to bring order back to such a maelstrom is the focus of a great deal of research at this time as it is an important piece of a durable remission. Targeting the TME has proven to be no easy feat and has been based upon trying to undermine the major components of it. Starting with the milieu itself, it has long been noted that the TME is more acidic than normal tissue in the local area, while the intracellular Ph is often more alkaline [92]. However, just trying to inject the TME with sodium bicarbonate does not seem to be a reliably effective treatment because the active biological processes that created the abnormal gradient, to begin with, will rebound and increase its level of activity to re-establish its supportive environment. Combining sodium bicarb with cytotoxic agents seems to offer a better strategy [93,94]. Changing the electro-chemical gradient of the TME, and thus the Ph, with an electrical current has also shown to be effective in some cases [95-97].

Another strategy that targets the TME is to inhibit the matrix metalloproteinases(MMPs) that degrade the extracellular matrix (ECM) components that then allows for local metastasis. Research has identified many substances that can inhibit these MMP's. Resveratrol, a polyphenol present in various plants, food products, red wine, and grapes, has been demonstrated to suppress MMP-2 and MMP-9 [98]. Additionally, resveratrol can inhibit the expression of Vascular endothelial growth factor (VEGF) and act as an anti-inflammatory agent [99]. Agents derived from marine sources have also been found to inhibit MMP's including various plant and animal sources of saccharoids, flavonoids, polyphones, and fatty acids but thus far, few have been shown to be reliably clinically effective [100]. One agent that did make it into clinical trials was AE-941/Neovastat. According to the National Cancer Institute, "shark cartilage extract, AE-941 competitively inhibits the binding of pro-angiogenic vascular endothelial growth factor (VEGF) to its cell receptor, thereby inhibiting endothelial cell proliferation". This agent also inhibits matrix metalloproteinases (MMPs), but at this time, there are no clinical studies involving its use [101]. Chlorella, a protein extract from algae has also been shown to have MMP's inhibitory properties [102]. Tissue inhibitors of metalloproteinases (TIMP's) naturally impede the activity of the MMP's and its the imbalance between the activation and inhibition of them that is largely responsible for the progression of a tumor's growth [103]. Other polyphenols that can inhibit the MMP's are quercetin, epigallocatechin gallate, and curcumin. They act as dynamic antioxidants, and are able to interact with cell-signaling pathways, modulating gene expression in three different ways: i) influencing the activity of transcription factors, ii) epigenetically, modulating microRNAs, and iii) having an anti-inflammatory effect, all of these actions serve to down-regulate MMP activity [104]. Combining polyphenols with amino acids that are used in the production of the ECM along with vitamin C which, too, is critical for ECM support, has been shown to be an effective strategy for slowing the progression of tumors. Their combined anti-cancer effects include

inhibition of: metastasis, tumor cell growth, matrix metalloproteinase secretion and activity, local invasion, angiogenesis, as well as induction of apoptosis of the cancer cells [105-108]. This combination has been effective both in vitro and in vivo against many different cancers and cancer cell lines including ovarian, melanoma, squamous cell, and others in a dose-dependant curve [109]. A chief problem for the use of polyphenolic compounds against cancer is their low bioavailability [110]. Different types of formulations have been designed to address this issue, nanonization being one of the most notable approaches among them. Variations of nanoformulations are designed to be effectively transported through the relevant biological barriers to the targeted organs, tissues, and cells. Research on natural polyphenols as bioactive agents include: resveratrol, curcumin, quercetin, epigallocatechin-3-gallate, chrysin, baicalein, luteolin, honokiol, silibinin, and coumarin derivatives, which have shown efficacy in a dose-dependent manner and may result in better treatments of cancer [111].

The tumor microenvironment, created by the cancer, further supports its dysfunctional growth and ability to metastasize through epigenetic changes. Epigenetic changes are heritable but, unlike genetic nucleotide modification, are reversible and therefore targetable as part of an oncolytic therapy. A variety of epigenetic mechanisms have been identified that can induce and/or support a cancer, such as: silencing of tumor suppressor genes, activation of oncogenes by altered cytosine phosphorus guanine (CpG) island methylation patterns, histone modifications, and dysregulation of DNA binding proteins. A quick search in https://www.ncbi.nlm.nih.gov/pmc for “epigenetic toxins and human cancers” will yield thousands of articles about substances both natural and synthetic that can create such changes [112]. Not only are the epigenetic changes potential targets for treatment, but their inducers are as well [113,114]. The TME creates and supports epigenetic biochemical reactions that dynamically regulate DNA expression. Nucleotide methylation and histone modification induce the dysregulation of genes related to proliferation, apoptosis, and metastasis [115]. DNA methylation is strongly associated with the repression of transcription of tumor suppressor genes through adding a methyl group by DNA methyltransferases (DNMTs) [116]. Other reactions by histone deacetylases (HDACs) contribute to transcriptional repression by removing the acetyl group at lysine residues leading to tumorigenesis, as a result of the research, both biochemical pathways have become the focus of intense research to develop DNMT and HDAC inhibitors [117]. Histone acetyltransferases (HAT), erasers (histone demethylases (HDM) and histone methylases (HMT) have also become epigenetic targets of research [118]. Some drugs are currently available and used for their epigenetic effects such as Decitabine, which can prevent DNA re-methylation and re-activate silenced suppressor genes [119]. Azacitidine is considered a global DNMT inhibitor and upon treatment of breast cancer cells, DNA re-methylation was inhibited for 23 out of 26 tested hypermethylated genes, allowing 5 tumor suppressor genes to be re-expressed [120]. The problem with these and the many other drugs, thus far developed for their epigenetic effects, are the unintended consequences (side effects) on normal, healthy cells elsewhere in the body. Reducing and pulsing the doses given has helped somewhat to reduce the side effects while maintaining efficacy [121].

The tactics for targeting the TME have a certain amount of overlap with those that seek the destruction of the cancer stem cells because they are the major architects of their immediate environment. However, the chief goal of an anti-metabolic cancer therapy is to disrupt the energy production pathways that support the cancer cells. For example, ENOX2 is a gene located on the long arm of the X chromosome and encodes for the Ecto-NOX protein. It is a member of the NOX family of NADPH oxidases which are important for energy production and the growth of the cell. Tumor-associated NADH oxidase (tNOX), has been identified as a target for low-dose cell killing (apoptosis) of cancer cells by green tea catechins and Capsicum vanilloid combinations [122-125]. This protein is uniquely associated with all forms of cancer and is absent from normal cells and tissues. Another anti-cancer metabolic strategy is to use the combination of two nutraceuticals: lipoic acid and calcium hydroxycitrate, which target two cancer energy enzymes ATP citrate lyase and pyruvate dehydrogenase kinase. Experimentally, this treatment was as efficient as chemotherapy in the mouse cancer models that were tested [126,127]. Clinically, in combination with low-dose naltrexone, this anti-metabolic tactic has also been effective even against advanced chemo-resistant carcinomas [128, 129].

2.3 Genetic Molecular Targeting

Targeting the abnormal genetics of cancer is the second anti-cancer strategy. Before we even begin to specifically target aberrant genetics, there are therapies that can be instituted for generally stabilizing genes which buys time for more definitive testing that allows for precise targeting of the cancer genome. Each of these agents has a multitude of beneficial effects, but chief among them is their ability to stabilize aberrant genetics, creating the time and opportunity for an integrative anticancer strategy. During the course of oncogenesis and tumor progression, cancer cells constitutively upregulate signaling pathways relevant to cell proliferation as a result of any number of genetic mutations. It is that genetic instability that leads to cancer cells acting as cancer in the first place, and it is those unstable mutations that account for the multiple cell lines that compose every tumor. Many agents have been identified that can aid in cell differentiation and reversion back to a phenotypically normal cell type [130]. Some of them are considered as follows.

First on our list of genetic stabilizers is dimethyl sulfoxide. Dimethyl sulfoxide (DMSO) is an organosulfur compound with polar, aprotic, and amphiphilic properties. It serves as a solvent for many polar and nonpolar molecules and continues to be one of the most used solvents (vehicle) in medical applications and scientific research. It also displays a diversity of antitumor activities[131]. Previous studies have demonstrated that DMSO can modulate AP-1 activity and lead to cell cycle arrest at the G1 phase [132]. The fibrinolytic system, more appropriately referred to as the plasminogen activator (PA) system, controls not only the intravascular fibrin deposition (with its effects on cardio-vascular disease) but also participates in a wide variety of other physiologic and pathologic processes. In cancer, the components of this system are involved in tumor growth, invasion, and metastasis through their effect on angiogenesis and cell migration, by way of its effects on the extracellular matrix of the tumor microenvironment. Plasminogen activator components are found in most tumors and their expression signifies not only their function but also carries a prognostic value. Their expression is in turn modulated by cytokines and growth factors, many of which are up-regulated in cancer and found throughout the TME. DMSO can inhibit the activity of PA's which helps to stabilize the TME and reduce the risk of metastasis [133]. Furthermore, DMSO can cause the maturation/differentiation, of at least some cancers, into a benign, more normal cell type [134,135].

Vitamin D is next on our list of genetic stabilizers. In addition to enhancing DNA repair, vitamin D also induces growth arrest and apoptosis of tumor cells and their nonneoplastic progenitors. Cell-based studies show that the active metabolite 1,25 dihydroxyvitamin D is the biologically active form that works through the vitamin D receptor to regulate gene transcription. Vitamin D (D_3) is produced from 7-dehydrocholesterol when skin is directly exposed to UVB light which, in more northern locations, is largely filtered out by the atmosphere. Vitamin D is readily sourced from various foods including fish, eggs, caviar (for the gourmets among us), some mushrooms, beef liver, and cheese. Regardless of whether vitamin D comes from the skin or the diet, vitamin D_3 is transported through the blood by the vitamin D Binding Protein (DBP). Once delivered to the liver, vitamin D is hydroxylated on its side chain to form 25 hydroxyvitamin D (25OH D). This is a stable metabolite whose serum levels are commonly used to assess vitamin D status. As needed and if available, D_3 circulates to the kidneys which is the primary site where the active form of vitamin D, $1,25(OH)_2$ D, is produced through the genomic actions of $1\alpha,25(OH)_2$ via the vitamin D receptor (VDR), and its analogs inhibit cell cycle progression and tumor cell growth. Mechanisms of action range from preventing cell proliferation (through cell cycle arrest) in cancer cells to inducing apoptosis, or suppressing cell adhesion molecules and growth factors that promote cellular homing and metastasis. It also affords important antioxidant protection and serves as an immunomodulatory for both the innate and adaptive arms of the immune system [136-140].

Next comes indole-3-carbinol and its metabolite 3,3′-diindolylmethane (DIM). They target multiple aspects of cancer cell cycle regulation and survival including Akt-NFκB signaling, caspase activation, and cyclin-dependent kinase activities. Furthermore, they stabilize estrogen metabolism, normalize estrogen receptor signaling, reduce endoplasmic reticulum stress, and limit BRCA gene expression. DNA hypermethylation is a common feature of cancer genetics. When methylation detox pathways start to fail, certain regions of the genome will accumulate too many methyl groups, such as at CpG promoter regions (segments of the DNA involved in DNA and RNA

transcription); this can lead to increased mutagenesis and eventual cancer development. Much research has demonstrated how DIM reduced methylation at 5 CpG promoter regions. For example, in split population studies, mice given Transgenic Adenocarcinoma of the Mouse Prostate (TRAMP) prostate cancer cells were also given DIM. The mice given the DIM showed a much lower incidence of cancer and metastasis than controls, as well as much higher expression of antioxidant/anticarcinogen protective enzymes NQO1 and NFR2 in prostate tissues [141-146].

Curcumin, a component of turmeric (*Curcuma longa*), is a low molecular weight molecule that has antiproliferative activity and inhibits tumor initiation and propagation through a variety of pathways. It accomplishes this through several epigenetic effects that result in genetic modulation that then changes the expression of several key proteins, some of which are the cysteine-aspartic acid proteases (caspases). Caspases are a family of enzymes that play an essential role in apoptosis, necrosis, and inflammation. Research demonstrates that curcumin activates caspases-3 and -8 but not caspase-9, indicating that the apoptosis induced in cancer cells occurs via a membrane-mediated mechanism. Membrane-bound enzymes play other important roles in the perpetuation of cancer cells such as the ECTO-NOX 2 system.

p53 (TP53) is a tumor suppressor gene and is responsible for protecting cells from tumorigenic alterations. Mutational inactivation of p53 is frequently observed in many cancers. Curcumin selectively increases p53 expression during the G2 phase of the cell cycle of carcinoma cells and releases cytochromes from the mitochondria, which is an essential requirement for then inducing p53-dependent apoptosis in the cancer cell.

Another protein affected by curcumin is Akt (protein kinase B), a serine/threonine kinase. It is a critical enzyme in signal transduction pathways involved in cell proliferation, apoptosis, and angiogenesis. Curcumin inhibited the phosphorylation of Akt in a dose-dependent manner leading to another pathway of apoptosis.

Curcumin also induces the upregulation of carcinogen-detoxifying enzymes, such as glutathione *S*-transferases, which have antioxidation effects and suppresses cyclooxygenase that in turn lead to the reduction of the level of inflammation and the stimulation of cancer stem cells. Real-time animal model studies have demonstrated that curcumin also decreased the expression of DNA damage response genes, including serine/threonine kinase (ATM), ataxia telangiectasia and Rad3-related protein (ATR), breast cancer 1 (BRCA1), 14-3-3σ, DNA-dependent protein kinase (DNA-PK), and O6-methylguanine-DNA methyltransferase (MGMT); thus, the reduction of a DNA damage response is but a part of the reason for curcumin-induced growth inhibition of cancer cells [147-149].

Sulforaphane (SFN) is an isothiocyanate found in cruciferous vegetables such as broccoli, brussel sprouts, cauliflower, and cabbage. Experimentally, in cell cultures and animal models, SFN was shown to be a highly effective chemoprotective against carcinogen-induced, and genetic animal cancer models, as well as in xenograft transplant models of cancer. The early research focused on the detoxification ability of SFN to induce phase 2 enzyme pathways. Later studies showed that SFN could cause cancer cells to enter G2/M phase arrest and result in apoptotic cell death, with the latter being evidenced by caspase-mediated cleavage of poly(ADP-ribose) polymerase and increased release of histone-associated DNA fragments from the tumor downstream. Furthermore, it leads to the transcriptional activation of genes including tumor suppressor genes. The effect on cancer genetics is profound and therapeutically beneficial [150-153].

Fish oil rounds out our list of top genetic stabilizing supplements. One of many changes that occur to the cancer cell's biochemistry and genetics is in the production, metabolism, and expression of microRNAs (miRNAs). First discovered in the early 1990s, their importance as a distinct class of biological regulators was not appreciated for another decade. MicroRNAs (miRNAs) are short molecules, just 21–25 nucleotides long, but can have powerful effects on gene expression. More than 2000 miRNAs have been identified including many specific miRNAs that have been found to be associated with cancer and the risk of metastasis. The identification of circulating miRNA specific to metastatic cancer presents a unique opportunity for early disease identification and for monitoring disease burden as a circulating biomarker. For example, abnormal activation of some miRNAs found in the blood, let-151a, miR-21, miR-155, miR-,145 miR-18a, and miR-16, as well as tissue-specific miRNAs, miR-182, miR-145, miR-

21, miR-155/154, miR-203, miR-213, and miR-7, are often found in patients affected by breast cancer. Furthermore, there is a growing body of evidence on the value of miRNAs associated with the development of drug resistance, suggesting their values, once targeted, as a potential approach to overcoming chemoresistance. miRNAs that are absorbed into our bloodstream from genetically modified organism (GMO) foods are currently being studied for their oncogenic potential, as they are normally foreign to human biology. Fish oil can modulate the expression of the miRNAs which can significantly reduce the risk of metastasis while having many other anticancer effects [154-159].

The science of genetics studies the genes that make up our chromosomes, which lead to inherited characteristics; think Gregor Mendle and his peas. Genomics is the study of large groups of genes or even the entire genome, looking for mutations, fusions, deletions, loss of heterozygosity, etc. variations and alterations that lead to the expression of cancer. Aberrations of the genome lead to the transcription of the faulty gene into a messenger RNA (mRNA) molecule, that leaves the cell nucleus and enters the cytoplasm, where it directs the synthesis of the protein for which it encodes. Abnormal genes lead to abnormal proteins. The study of proteins is called proteomics; it's primarily the functional proteins, which includes enzyme activities, as well as protein/protein interactions (such as immune receptor sites) and post-translational modifications of the proteins that are of the most interest because they are the most antigenic and hence the most targetable/treatable. The sciences of genomics and proteomics have opened the door to what is being referred to as "precision medicine" [160]. Precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person". This personalized approach allows clinicians to predict more accurately which treatment is more likely to work for which person [161]. This is in contrast to a one-size-fits-all approach, in which cancer treatment strategies are developed for the average person based upon group clinical trials (cohorts), with little consideration for the differences between individuals.

Precision medicine works by profiling live or preserved cells for biomarkers that indicate an abnormal process, gene or protein is present that is carcinogenic and/or cancer-promoting [162]. Cancer inhibiting genes that have been abnormally silenced are also tested for. Cutting edge technologies that can detect these clinically useful aberrations include: Next-Generation Sequencing (which allows for whole-exome DNA sequencing and whole transcriptome RNA sequencing), DNA Sequencing (sequence analysis reliably detects DNA mutations, copy number variations, and gene fusions across the entire exome), RNA Sequencing (is done to detect clinically relevant aberrations, in particular, gene-fusion events and splice variants), Immunohistochemistry biomarkers, in situ hybridization (to detect amplification and fusion events), and methylation analysis. When evaluated as a group, disease-specific lab test panels are developed which can then zero in on the aberrations for any individual patient to improve the therapeutic response [163-165].

Based upon the biomarkers found, clinically beneficial therapies may be employed including the use of; hormone therapies, signal transduction inhibitors, gene expression modulators, apoptosis inducers, angiogenesis inhibitors, immunotherapies, and toxin delivery molecules [166,167]. Some of the commonly used small molecules include the "nibs" (tyrosine-kinase and serine/threonine kinase inhibitors) and the "mabs" (monoclonal antibodies). Monoclonal antibodies have been developed to attack growth receptors of the cancer cells, growth factors for new blood vessels that feed the tumor, and targets on cells of the immune system to dis-inhibit their activity [168]. Natural substances too can be used to target specific aberrations; a few, of many, examples [169,170]:

p53, p73	Aronia melanocarpa [171,172]
VEGF	Omega-3 Fatty Acids [173]
JAK/STAT-3	Astaxanthin [174,175]
PI3K/AKT	Viscum alb [176]
KDR	Artemisinin [177]
MMP2, MMP9	Curcumin [178]
HER2-neu	Quercetin [179]
EGFR	Silymarin [180]
VE-cadherin	Camellia sinensis [181]
HIF-1α	Ginseng [182]
NF-κB	Liquorice [183]
BCL2	Scutellaria baicalensis[184]
KRAS	Coffee [185]
Mcl-1	Piperlongumine [186]

2.4 Immunotherapy

Immuno-therapy is the third anti-cancer strategy. Edward Jenner was a pioneering English physician and scientist who improved the procedure of smallpox inoculation to create the smallpox vaccine in 1796 [187,188]. In the scientific fashion, he purposely exposed people that he had vaccinated against smallpox to prove that the cowpox pus that he used did indeed confer protective resistance. Although others before him had used cowpox to provide protection from smallpox, he was the first to then demonstrate that it did in fact work and that the effect was reproducible in subsequent patients [189-191]. Although not understanding the intricacies of the immune system, because he applied the scientific method, as it existed in his time, he is referred to as the "Father of Immunology" [192].

Since Jenner's time, imuno-therapy has evolved into an office-based strategy for which they write very thick books and, in the broadest terms possible, it is a treatment that uses the immune system, in some way, to identify, attack, and destroy the cancer. Using the immune system against cancer can be accomplished through active or passive pathways. As a quick overview, there are over one hundred and eighty-seven cell types identified within the immune system. It includes the lymphatic system along with the bone marrow, spleen, thymus, and, of course, lymph nodes. Cells known as CD4 T cells are the "apparent brains" of the immune system and they coordinate the central immune response to any serious health threat. Activated B cells become plasma cells and, in most instances, generate an antibody response against bacterial and viral invasion. Lymphokine activated killer cells and cytotoxic T cells respond to viruses and cancer. Suppressor T cells are used to downregulate the actions of the immune system after the threat has been eliminated through negative feedback. Macrophages are voracious amoeboid-like lymphocytes that eat foreign substances and send a message back to the rest of the immune system indicating what further immune response is necessary. Macrophages and their cousins, the dendritic cells, are involved in all aspects of the immune response by initially sending out the alarm that something is amiss. Natural Killer cells are preprogrammed at their birth to destroy virally infected cells, cancer cells, some bacteria, and parasites on contact without the need for further direction from the CD4 cells. Some mushroom extracts and the bioengineered nutraceutical AiE10^{TM} can increase the concentration and activity of natural killer cells.

The immune response cascade operates according to three directives. The first is to recognize that which is foreign and sound the alarm soon enough to thwart the invader. Molecules and cell surfaces that are identified as foreign are referred to as antigens and have the ability to elicit an immunogenic response. The second directive is to respond to the alarm with enough of a counterattack to effectively neutralize the invader quickly. The third directive is to remember what happened so that if the same situation were to arise again, an effective response could be generated faster. The length and efficacy of the immune response depends upon the "intactness" of the underlying biochemistry. The immune response cascade is the ultimate biological information processing and transfer vehicle designed to define, defend, and integrate oneself relative to the environment that surrounds us. When there is a miscommunication, disease ensues due to corruption, misdirection, or a lack of that informational flow.

Active immune therapies include, among other agents, IL-2, IFN-g, and IFN-a cytokines to stimulate the TH1 cells, pathways, and natural killer cells. Monoclonal antibodies, checkpoint inhibitors, that disinhibit an immune response are also an active immunotherapy that seems to be most effective when some support has been given to the immune system first. Other active therapies include creating primed dendritic cells (for example, Sipuleucel-T (Provenge)) and natural killer cells and then infusing them into the patient to "patch" holes and reconstitute an effective anticancer response.

Passive immunotherapies include the use of infused antibodies to bind to cancer cells. Then, when natural killer cells encounter antibody-coated cells, the latter's Fc regions interact with their Fc receptors, releasing perforin and granzyme B to kill the tumor cell. Adoptive T cell therapy is another passive immunotherapy. Several ways of producing and obtaining tumor-targeted T cells have been developed. T cell Infiltrating Lymphocytes (TILs), specific to the tumor antigens, can be removed from a tumor sample with a core biopsy and then purified with a cell separator or filtered from the blood. Subsequent activation with cytokines and cell culturing is performed *ex vivo*, and then the results were reinfused into the patient. Activation

can take place through gene therapy or by exposing the T cells to tumor antigens in the presence of cytokines. TILs can also be stimulated in vivo with hypofractionated SBRT to induce an abscopal effect, which when achieved can have miraculous results. According to the National Cancer Institute, the abscopal effect "describes the shrinking or disappearance of tumors in parts of the body that were not the direct target of local therapy" [193]. It was first described in 1953, by a researcher named R. H. Mole who demonstrated that radiation could shrink a tumor on one side of a mouse and lead to the regression of an untreated tumor on the other side of the animal[194]. He coined the term "abscopal effect" from the Latin *ab* (position away from) and *scopus* (mark or target). Since the phenomena was first observed using radiation, it was assumed that that was the key to the response. A lot of research has been done on varying different parameters of the radiation in order to reliably reproduce the effect [195]. Tumor-infiltrating lymphocytes are seen as an important part of the "recipe" as they can signal and initiate a counter-tumor cascade and bode well prognostically [196]. Further research has demonstrated that cryotherapy, too, can trigger an abscopal response [197]. In my experience, it seems that any locally applied treatment that causes the sudden death of a large number of cancer cells, thus quickly releasing antigens, without suppressing normal systemic physiology (i.e. the immune system), can trigger a cascade of events that can lead to the death of tumors far removed from the point of the therapy. This includes; radio frequency ablation (RFA), hyperthermia, hi frequency ultrasound (HiFu), cryotherapy, and of course fractional dose radiation therapy [198-204].

Combining these "mildly" oncolytic therapies with checkpoint inhibitors has yielded better results [205,206]. The checkpoint inhibitors are helpful only to the point that the immune system is still basically structurally intact and functionally effective. When the principles of immune reconstitution are followed, the therapeutic response can be much more beneficial [207].

A "new", state-of-the-art, passive immunotherapy is the use of chimeric antigen receptors (CARs, also known as chimeric immunoreceptors, chimeric T cell receptors, or artificial T cell receptors) which are bioengineered cell receptors that combine a new specificity with an immune cell to target cancer cells. Essentially, what is done is that specific monoclonal antibody fractions are grafted onto T cell receptors. The receptors are referred to as chimeric because they are a fusion of proteins and receptors from different immune sources. CAR-T cell therapy refers to an infusion of such specifically transformed cells for targeted cancer therapy. CAR-T cells destroy the cancer cells through several mechanisms such as having a direct cytotoxic effect and/or stimulating other cells of the immune system through the release of various cytokines and growth factors. Due to the CAR-T cells very narrow specificity, less prominent tumor cell lines can be missed allowing for a future recurrence [208-218].

Overall, immunotherapy is designed to correct, stimulate, direct, or reconstitute an effective anticancer response. Immune reconstitution is the evolving clinical science of restoring immune competence by correcting biochemical imbalances, augmenting cytokines, restoring cascade pathways, and/or implanting specific stem cells to bridge areas of damage. All severe or chronic diseases are known to have one or more significant defects in the immune system adversely affecting the immunological imperatives of recognition, response, and memory which, in the case of cancer, leads to anergy and tolerance. Testing for and breaking anergy is the first step in immune reconstitution [219]. Correcting anergy is of critical importance because it directly correlates to the stage of cancer: over 90% of patients with Stage 4 disease are found to be anergic [220]. The immune system cannot fight something that it doesn't know is there, and that's exactly what arises with anergy. Anergy manifests when there is a failure of signal transmission at ANY point in the immune response cascade. Before we can break anergy, and wake up the immune system, we must make sure that we are dealing with true anergy as opposed to another pathology.

Of historical interest, some years ago the Mérieux Company manufactured a skin test called the "Multitest Mérieux" or "CMI Multitest" system (Istituto Merieux Italia, Rome, Italy). It is used as a general test for the level of the cellular immune response. It is an intradermal test of skin reactivity (similar to allergy tests) in which a control (glycerol) is used with seven common antigens of bacterial or fungal origin (tetanus toxoid, tuberculin, diphtheria, streptococcus, candida, trichophyton, and proteus). In this test, reactions are categorized according to the number of antigens provoking a response, and the summed magnitude of the skin response to

all seven antigens. Based on the chart and information supplied with the simple skin test, basic anergy can be quickly assessed and quantified [221]. Unfortunately, this test cannot tell us where in the recognition/response chain of events the problem lies. However, specialized blood tests are now generally able to do that. Once this state of unresponsiveness has been confirmed, the next step in breaking anergy is with an immunotherapy protocol specific to the area(s) of immune response dysfunction as briefly described above.

2.5 Cancer Stem Cells

As a short overview, cancer stem cells (CSCs) are cancer cells (found within tumors or hematological cancers) that possess characteristics associated with normal stem cells, specifically the ability to give rise to all of the heterogeneous cancer cell lines found in a particular tumor. Targeting them is the fourth anti-cancer strategy. Until recently, attacking them would have been included in the general biochemical targeting strategy but recent research has shown them to be a separate and viable strategy. CSCs mediate tumor initiation, progression, and metastasis, and inhibiting them is an emerging new area of research to prevent, stop, and reverse tumor growth. They play key roles in tumor metastasis, drug resistance, and cancer relapse. Oncologic research has established that subpopulations of cells, identified by monoclonal antibodies to specific cell surface markers, behaved like developmental stem cells in their capacity to regrow the human tumors, for multiple generations, in experimental immune-deficient animal hosts. In all of the cancers studied so far, there is good evidence that CSCs are relatively resistant to radiation therapy and chemotherapy because of their slow rate of growth, indicating that novel CSC-targeted therapies are needed. Several pathways are promising targets against CSCs including inducing their apoptosis, inhibiting stem cell self-renewal to either stop their division or to promote their differentiation, or targeting the CSC milieu in the TME that supports them. The anti-CSC agents are categorized under two broad headings: small- and macromolecules with different subclasses such as kinase inhibitors and polypeptides. One of the first and safest agents to be recognized as a CSC inhibitor is Metformin [222-235].

Tumor initiation can either be driven by transformed differentiated cells or transformed tissue-resident stem cells forming the new cancer stem cells [236,237]. As tissue stem cells already possess unlimited growth potential, it is believed that the transformation into a CSC requires only a very small number of genomic changes [238]. Multiple biomarkers that characterize CSCs have been identified and correlated to diagnosis, therapy, and prognosis [239]. They have been shown to display a high degree of plasticity, which changes their phenotypic and functional appearance making it harder to track them and predict their activity. Such shifts in their expression can be induced by chemo- and radiation therapy as well as by senescent tumor cells. Therapeutic regimens such as chemo- or radiation therapy shift the composition of tumor cell subpopulations changes by first killing some of the tumor cells, those with the highest proliferative capacity, causing a decrease in tumor size, while CSCs which multiply at a much slower rate survive. Instead of dying, some of the tumor cells will become senescent which causes further alterations in the tumor microenvironment that better support the CSCs [240].

The transformation to a cancer stem cell can take place during tissue regeneration or can be initiated and/or accelerated as a response to infections, toxins, radiation, or metabolic epigenetic influences that cause mutations [241]. During the process of transformation, oncogenes are overexpressed and tumor suppressor genes are inactivated, hence promoting the creation of, and uncontrolled growth of the CSCs. As a consequence of the transformative process, the affected cells “de-differentiate” and acquire stem cell self-renewal characteristics forming the nucleus of the cancer [242,243]. The mutations of the CSC progeny have a higher rate of replication which leads to the formation of a tumor [244].

Anti-CSC research has yielded some very promising therapeutic approaches. Nutraceuticals derived from herb and vegetable extracts show anti-CSC activity at various levels of clinical utility. Cruciferous vegetables belong to the *Cruciferae* family such as arugula, bok choy, broccoli, broccoli rabe, brussel sprouts, cabbage, and others, contain anti-cancer isothiocyanates including sulforaphane, that are enzymatically hydrolyzed from glucosinolates [245]. Normal dietary “doses” of isothiocyanate sulforaphane have been shown to have anti-CSC activity by altering phosphorylation of several kinases and their substrates including Glycogen synthase

kinase 3 (GSK3), Jun N-terminal Kinase (JNK), and Protein Kinase C (PKC) [246]. Soy isoflavones like genistein have been shown to have a potent anti-CSC effect by inhibiting the phosphorylation of Protein kinase B (AKT) and Forkhead Box O 3a (FOXO3a) [247]. Polyphenolic catechins including epigallocatechin-3-gallate (EGCG) found in green tea extracts have demonstrated anti-CSC activity, against a variety of cancers, through its ability to inhibit NF-κB activity, Mitogen-Activated Protein Kinase (MAPK) pathway, activator protein-1 (AP1) activity, and EGFR-mediated downstream signaling pathways [248,249]. Other anti-CSC nutraceuticals are derived from quercetin, curcumin, resveratrol, and ginger [250]. More potent anti-CSC pharmaceuticals are also derived from plant sources. Taxol is derived from the bark of the Pacific yew tree (*Taxus brevifolia*) and was discovered, through a random screening of approximately 15,000 species of plants, to have powerful anti-CSC activity against many different cancers [251]. Vinca alkaloids are a group of drugs that were originally extracted from the Madagascar periwinkle plant, *Catharanthus roseus G. Don*, and have anti-CSC activity as well as cytotoxic effects. There are three major vinca alkaloids in clinical use: Vinblastine (VBL), vinorelbine (VRL), and vincristine (VCR) [252].

Several pharmaceuticals have been "re-purposed" as anti-cancer agents when their anti-CSC "side-effect" was noticed. Studies have demonstrated that Metformins' anti-cancer, anti-CSC effects go far beyond its ability to lower blood sugar in that Metformin impairs cellular metabolism and suppresses oncogenic signaling pathways, including tyrosine kinase receptors, PI3K/Akt, and mTOR pathways [253]. Furthermore, it suppressed the self-renewal ability of cancer stem cells and induced G0/G1 phase arrest by blocking the activity of cyclin-dependent kinases. In studies on osteosarcoma cancer cells Metformin-induced apoptosis through a mitochondria-dependent pathway, leading to the collapse of the mitochondrial transmembrane potential and the production of oxidatively destructive reactive oxygen species [254]. This destruction of the already compromised mitochondria further decreased ATP synthesis and triggered autophagy cancer cell death [255]. Thus, Metformin is an excellent addition to a metabolic strategy in that its activity is synergistic with the goals of further degrading the already damaged mitochondria in CSCs and cancer cells [256]. When combined with a beta-blocker and aspirin the anti-CSC and anti-metastasis effects are even more pronounced [257,258].

Doxycycline too has been "re-purposed" for the fight against cancer. One of the FDA recognized side effects of doxycycline is the inhibition of mitochondrial biogenesis. Currently, in the https://www.anticancerfund.org/en/redo-db database, there is a listing of 356 "non-cancer drugs" which have shown some evidence of anticancer activity. Amongst them, doxycycline is high on the list of beneficial activity [259]. Sorting them out into a generally useful algorithm is a research project for WATSON, but for now, we have some important clues.

Doxycycline is a known inhibitor of the small mitochondrial ribosome (28S) and, as a consequence, is an inhibitor of mitochondrial protein translation necessary for biogenesis [260]. In vitro and in vivo evidence demonstrates the inhibitory effects of Doxycycline on cancer growth through mitochondrial destruction and the consequence of CSC suppression [261]. Azithromycin inhibits the large mitochondrial ribosome (39S) and enhanced the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) activity, which selectively targets tumor cells without damaging healthy cells as an off-target "side-effect" [262]. Together, these two antibiotics have a synergistic, anti-metabolic effect on CSCs that is greater than either one alone. We can add to the targeted anti-metabolic CSC effect with vitamin C that, in high dose IV's (greater than 15 grams), acts as a pro-oxidant, which can produce free radicals further stressing the already dysfunctional mitochondria and hastening their destruction [263]. This combination of antibiotics and vitamin C has shown efficacy both in vitro and in vivo [264]. Further compromising the CSCs mitochondria leading to their destruction, seems to be an important process for stopping cancer. A shift from respiration to fermentation (glucose pathway) is not the only energy production shift that cancer cells, and in particular that CSCs can use, but it does seem to be an important and common one. To an extent, CSCs are metabolically flexible so multiple pathways may need to be blocked, often simultaneously, to minimize the risk of selective metabolic escape. In addition to inhibiting the major glucose pathway, as described above, fatty acids and glutamine can also be used by many CSCs to support their deranged metabolism. Lipophilic statins can inhibit the use of fatty acids as an

energy source for many types of cancer [265]. Hydroxychloroquine blocks cancer cells' ability to scavenge nutrients, including glutamine, through macropinocytosis, thereby closing yet another pathway for energy generation by the mutated cells [266]. Research on new anti-CSC strategies focuses on their signaling pathways and cellular communication system including; Hedgehog, Wnt/beta-catenin, Notch, Toll-like receptor 4 (TLR-4), Toll-like receptor 9 (TLR-9), Integrins, EGFR, IL-1, IL-6, Peroxisome proliferator-activated receptor (PPAR), and others.

CSCs and tumor cells, like all eukaryotic cells, produce structures called exosomes in their endosomal compartment [267]. They are approximately 100 nm in diameter and are surrounded by a lipid bilayer membrane. Exosomes have been recognized as potent vehicles of intercellular communication due to their capacity to transfer proteins, lipids, and nucleic acids; thereby influencing various physiological and pathological functions of both recipient and parent cells [268]. The involvement of exosomes in the phenotype transformation from non-CSC to CSC has been recently evidenced by research on the X chromosome long non-coding RNA, which is overexpressed in malignant tumor tissues and activates Toll-like receptor (TLR) 7 and NF-κB inflammatory signaling [269].

Exosomes have been reported to interact with the cells of the immune system, modulating and downregulating its response thus allowing for tumor progression [270]. Tumor-derived exosomes (TEXs) induce apoptosis of the activated CD8+ (cluster of differentiation 8) T cells (which have an anti-cancer surveillance function), suppress natural killer (NK) cell activity, promote the induction of regulatory T cells (Tregs) and myeloid-derived suppressor cells, and interfere with monocyte differentiation into anti-cancer dendritic cells [271]. While TEXs form the immunosuppressive microenvironment, Treg-derived exosomes inhibit the induction of cytotoxic T lymphocytes, further allowing for the growth and spread of the tumor [272]. As a result of the research on tumor cell exosomes, they have become a promising target for the treatment of cancer but as of yet this therapy is not available [273-276].

2.6 Cytotoxic Cancer Therapy

Cytotoxic cancer treatments are traditionally covered by the term chemotherapy and have come to imply the use of agents that act, separately from the body at large, as intracellular poisons to inhibit mitosis or directly induce some sort of cell death and is the fifth anti-cancer strategy. Substances that accomplish this as a secondary effect through blocking extracellular signals or which act through a specific genetic, enzymatic, or hormonal pathway are excluded from this therapeutic strategy as they are referred to as targeted therapies and elsewhere described. Chemotherapeutic agents are characteristically purified to the point of being a chemical, and may be of natural origin or synthetically created. The deliberate use of natural, herbal source agents began in the early 1920s, including Viscum alkaloids and lectins, and they are still used today, whereas the first synthetic agent, nitrogen mustard, was “discovered accidentally” during World War II when it was observed that it could shrink lymphoma tumors in mice. A few years later, it was discovered that alkaloids extracted from the Vinca rosea plant were useful in treating Hodgkin’s disease, and so a multibillion dollar industry was birthed creating and extracting new substances helpful in the “war on cancer”. Unfortunately, many of these substances have similar effects on healthy cells, thus creating a multitude of side effects and limiting their usefulness. Newer protocols that use lower doses of these agents, such as metronomic or insulin potentiated chemotherapy, are showing good results with far fewer side effects. Metronomic, low dose chemotherapy has been in development for two decades and seems to act through several mechanisms including inhibiting the growth of new blood vessels, the restoration of an anticancer immune response, and the induction of tumor dormancy. Whereas Insulin Potentiated Therapy (IPT), another low dose strategy, takes physiologic advantage of the excessive number of insulin receptors found on the cell surface of cancer cells. Giving insulin just prior to the infusion of low dose chemotherapeutic agents, usually in a combination designed to intervene at several sites of the cell cycle, causes much fewer side effects and can hold the cancer at bay, while buying time to reconstitute an effective immune response or integrate another anti-cancer therapeutic strategy. IPT has been in development and clinical use since the 1930s and has been used to help treat other chronic diseases as well [277-290].

Cytotoxic chemotherapy is usually administered as per a protocol derived by treating a group of

people (cohorts) with a similar diagnosis. These clinical trials are done to determine the general dose and combination of agents that are most effective and least toxic according to the structure of the trial for that disease diagnosis. This approach is designed to attack different genetic targets and the aspects of DNA transcription of rapidly dividing cells [291-293]. A more contemporary way for using cytotoxic agents is to target them so that the agents affect biochemical factors or cellular pathways that are unique to the malignant cells or characteristic of tumors based upon genetic studies.

Cytotoxic chemotherapy can be very good at killing rapidly dividing cells, such as those found in a growing tumor, but are not good at killing the slow-growing cancer stem cells that are at the root of the problem. This leads to the observed high risk for recurrence and to eventual multi-drug resistance [294]. There is a great deal of research currently engaged in addressing this problem and certain drug combinations have been found that can lessen this issue by making the cytotoxic response more effective [295]. At this point, we know that P-glycoprotein (also known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1)) plays a crucial role in determining the neutralizing response against chemotherapy. P-glycoprotein (p-gp) acts as an ATP-dependent pump that pumps out small molecules from cells, including chemotherapeutic agents, before they can exert their cytotoxic effects. Research demonstrates that p-glycoprotein expression levels correlate inversely with drug efficacy, which suggests the rationale for developing p-glycoprotein inhibitors for treatment against cancer [296]. While new agents are being developed and going through drug trials, some currently available pharmaceuticals are helpful against multi-drug resistance. Verapamil is an L-type calcium channel blocker with antiarrhythmic, antianginal, and antihypertensive activity, but is also a p-gp inhibitor. Unfortunately, the dose required to achieve this effect can cause significant hypotension thus limiting its usefulness [297]. Other agents that may be helpful are to be found within the class of drugs known as proton pump inhibitors (PPIs) [298].

Proton pump inhibitors (PPIs) given before the chemotherapy have been shown to inhibit mRNA levels of vacuolar-type ATPase (V-ATPases), multidrug resistance mutation 1 (MDR1), multidrug resistance protein 1 (MRP1), phosphatidylinositol 3-kinases (PI3K), Akt, mTOR, and HIF-1α. PPIs inhibited V-ATPases and down-regulated the expressions of P-gp and MRP1 in a dose-dependent manner both in vitro and in vivo [299].

There are also low concentration natural agents that are cytotoxic to cancer cells that may be used with low doses of cytotoxic chemotherapy to reduce side effects and improve the quality of life. In use for a 100 years, research has shown that Viscum album (mistletoe) extracts (VAE) have a significant positive impact on the quality of life and the reduction of the side effects from conventional therapies (chemotherapy, radiation) in experimental trials as well as in routine daily application [300,301]. Furthermore, pooled data from multiple clinical studies demonstrate that adjuvant treatment of cancer patients with the VAE is associated with better overall survival [302]. In some cases not only is VAE effective as an additional cytotoxic, anti-cancer agent, but it may succeed when more conventional chemotherapy and immunotherapy have failed [303-310].

Another important benefit of VAE is its ability to overcome some scenarios of chemoresistance. Axl protein is a receptor for tyrosine kinases. Some reports showed that targeting anexelekto (Axl) enhanced EGFR TKI response in selected EGFR wild type (WT) NSCLC patients. Studies have found that when targeting Axl in EGFR WT NSCLC cells, the cells showed a more sensitive response to erlotinib than those that overexpressed Axl thereby overcoming chemoresistance [311,312].

Chemoresistance is a big problem with chemotherapy as the agents seem to have an almost evolutionary effect on tumors, selecting for the most sensitive cancer cells and leaving the rest, including the CSCs untouched, or more mutated, therein setting the stage for a recurrence. Radiation therapy has similar drawbacks. Doxycycline is helpful with both treatment modalities to reduce chemoresistance, largely through interrupting oxidative phosphorylation by inhibiting moieties of the electron transport chain [313,314]. This brings us back to the necessity for targeting CSCs to help overcome chemoresistance [315-319].

Another cytotoxic strategy that generates much less chemoresistance because it also targets CSCs is the use of vitamin C (VC) and vitamin K(3) (VK(3). administered intravenously in a VC:VK(3) ratio of 100:1 exhibit synergistic antitumor activity and preferentially kills tumor

cells without harming normal cells [320]. This natural vitamin combination accomplishes this through a process of autoschizis, a novel type of necrosis characterized by exaggerated membrane damage and progressive loss of organelle-free cytoplasm through a series of self-excisions [321]. This combination also attacks the DNA of cancer cells since a deficiency of alkaline and acid DNase is a hallmark in all living cancer cells and they are reactivated in the early stages of cancer cell death by vitamin C (acid DNase) and vitamin K(3) (alkaline DNase) leading to DNA fragmentation [322]. Vitamin C by itself can regulate the proliferation and differentiation of cancer stem cells, the amount and stability of collagen, extracellular matrix remodeling, anti-cancer immunity, and hypoxia in the tumor microenvironment, hence epigenetically suppressing the CSCs and downregulating chemoresistance [323-326]. When combined with doxycycline, the effect is even more pronounced [327,328].

2.7 Supportive Tactics

There are other therapeutic tactics that may be synergistic, but they are not considered strategies unto themselves because their anti-cancer effects are less reliable. This includes energy-based therapies such as homeopathy and acupuncture, and psychodynamic tactics like psychoneuroimmunology, visualization, prayer, and meditation practices. Other tactics employ the use of oncolytic viruses, oxidative therapies (ozone), Traditional Chinese Medicine, Naturopathy, Ayurvedic herbal medicines, and detoxification protocols, to name but a few. There is no doubt that some of them can be extraordinarily beneficial to the patient by reducing physical symptoms, psychological stress and by engendering a feeling of more self-control against a disease that threatens total chaos. Indeed hundreds of books and articles have been scribed as to their use and intermittent efficacy by notable physicians and practitioners; to this day the well-documented phenomena of the spontaneous remission of cancer remains a medical mystery. Early in my career, the immunotherapeutic strategy that I employed against cancer was still considered something just short of quackery, and the clinical responses to it were often attributed to this phenomenon.

3. DISCUSSION

An evidence-based medical practice is established through the application and integration of the best clinical research available at the time, balanced with the clinicians' expertise and the patients' life values and beliefs [329]. Evidence-based medicine may be considered as an interdisciplinary approach itself, which uses techniques from science, engineering, biostatistics, and epidemiology, such as meta-analysis, decision analysis, risk-benefit analysis, verified case reports, and randomized controlled trials to deliver "the right care at the right time to the right patient" [330]. Every time that a physician treats a patient for anything, it is essentially a clinical trial with an "n" of 1. Thus the practice of evidence-based medicine tacitly dictates that physicians should make "conscientious, explicit, and judicious use of their understanding of the best medical information available" for the validation of the proposed treatment and its application in patient care in partnership with the patient and their expectations [331].

Cancer is a serious and often life-threatening disease that deserves careful consideration of the benefits and long-term risks of each of these five strategic approaches, evolving beyond cohort-based trials into an integrated, personalized approach for the treatment of each patient. Champions for the exclusive use of any one of these strategies abound, but it is my belief and experience that the best answer for cancer, for any one patient, will be found in their integration into an individualized cohesive clinical protocol.

Research is needed to codify the algorithm necessary for applying the best integrative therapeutic strategy given the dynamics of the cancer and the patient's biochemistry, genetics, and immunology at any given point in their treatment.

4. CONCLUSION

Cancer, as a disease of our time, has been described as a "wound that does not heal" and is characterized as having numerous biochemical dysfunctions at its core, which lead to a multitude of genetic aberrations and pathologic phenotypic expression. However, in order for these genetically and phenotypically abnormal cells to survive and thrive, the watchdog of the body, the immune system, must itself be suffering from a number of serious areas of structural and functional damage. There are many tactics that can support the therapeutic strategies briefly described above, and they should be applied in an integrative manner as they are nonexclusive

with each other and can be mutually supportive [332]. However, more aggressive cytotoxic strategies, i.e., full-dose chemotherapy and radiation, can render many of these strategies null and void but may be considered for possible later use. When treating cancer, the physician and patient should make the decisions together, since the stakes can be no higher, using the best information available at the time, and then never look back. When treating cancer there is but one direction to go and that is forward, striving for ever-increasing improvements in the quality and quantity of life with the hope of achieving a durable remission [333-336].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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