International Journal of Clinical and Molecular Oncology
2024 Volume 3, Issue 1
DOI: 10.59657/2993-0197.brs.24.011

BioRes Scientia
Value your Research

Review Article

Open Access

Reflections on Integrative Oncology: An Independent Clinician's Long-Term Perspective

Dwight L McKee MD, CNS, ABIHM

Diplomate, American Board of Medical Oncology, Integrative Oncology Consulting, Soquel, CA; Life Plus International, Batesville, Arkansas; St Neots, UK; Mederi Academy, Ashland Oregon.

Abstract

I became interested in the problem of cancer while still in medical school, when I also became interested in nutrition, lifestyle, exercise, and what was at that time termed 'Holistic Medicine'. After an internship in 1975, I joined Integral Health Services in Putnam CT, which was one of the first integrative medical clinics on the east coast, and I also became a founding member of the American Holistic Medical Association, the first organization of its kind in the US. In my practice at Integral Health Services (which was made up of chiropractors, nutritionists, massage therapists, psychotherapists, and medical doctors—2 of each category) I studied 'alternative cancer therapies', and implemented many of them with cancer patients in my practice with cancer patients who either wanted an alternative to conventional cancer therapy, or an addition to conventional cancer therapy.

Keywords: reflections; integrative; oncology; independent clinician; long-term perspective

Introduction

I became interested in the problem of cancer while still in medical school, when I also became interested in nutrition, lifestyle, exercise, and what was at that time termed 'Holistic Medicine'. After an internship in 1975, I joined Integral Health Services in Putnam CT, which was one of the first integrative medical clinics on the east coast, and I also became a founding member of the American Holistic Medical Association, the first organization of its kind in the US. In my practice at Integral Health Services (which was made up of chiropractors, nutritionists, massage therapists, psychotherapists, and medical doctors—2 of each category) I studied 'alternative cancer therapies', and implemented many of them with cancer patients in my practice with cancer patients who either wanted an alternative to conventional cancer therapy, or an addition to conventional cancer therapy. I found that I could significantly help about 20% of patients with advanced cancers. After 12 years of such practice, I decided to formally train in oncology, which involved a second internship (in Internal Medicine), followed by 2 years of Internal Medicine Residency—done at Valley Medical Center in San Jose, and Stanford, which was then followed by a 3-year fellowship in Medical Oncology and Hematology at Scripps Clinic , which I completed in 1995, and became board certified in Internal Medicine, Medical Oncology, and Hematology (and later in nutrition, and integrative/holistic medicine). During and after my heme/onc fellowship, I worked for 3 years as a guest scientist doing tumor immunology research at the Scripps Research Institute in LaJolla. I then practiced what had become known as Integrative Oncology for 6 years, in an office and hospital setting. After that I developed a consulting practice for practitioners working with integrative cancer medicine, writing detailed consultations for their patients, which they would then implement with each patient that I had consulted for. I continued this consulting practice for 15 years. In this review I will cover what I see as the major contributing factors to the dramatic increase in cancer incidence over the past century, review the areas where I think the most progress in treatment and prevention can be made, some of which includes clinical trials for therapies that have been used primarily in late-stage cancer patients, which, in my view, need to be studied in patients with potentially life-threatening cancer diagnoses, as soon after diagnosis as possible.

Contributing factors to the current global pandemic of cancer

Although cardiovascular disease and stroke (also uncommon 100 years ago) are the leading cause of morbidity and mortality in the US, cancer is second, with over 1.8 million new cases per year, and over .6 million deaths annually. Cancer treatment costs are

escalating faster than those for cardiovascular disease, and newer treatments such as immunotherapy which can be lifesaving, are often beyond the reach of low- and middle-income patients., even with insurance.; [1,2]. Although cancer death rates are slowly declining due to better screening and treatments, the incidence of cancer continues to climb, and little progress has been made in the cure rate of metastatic disease which is responsible for 90% of cancer deaths, over the past 20 years, with a few exceptions involving surgical treatment of oligometastatic colorectal carcinoma. [3] Causes of cancer are often framed as 'stochastic', meaning the 'bad luck' to have a mistake in cell division. On the other hand, we do not have to look too far to find reasons for such mistakes (mutations) occurring during DNA replication in cellular division. Environmental factors such as the innumerable toxins associated with industrial revolution and concurrent urbanization, tobacco smoking, fundamental changes in the food supply ranging from the industrial isolation of agriculture to the dramatic rise in production and consumption of processed foods which involve the introduction of over 3000 chemicals to the foods that a significant majority of the population has been consuming for several generations now, as well as a dramatic reduction of the micronutrients available in most conventional diets in developed countries, together with increased wealth, associated with better medical services and extended lifespan, has been considered responsible for the dramatic increase in the incidence of cancer since world war II 4. But it's not only that people are living longer—those who survived the infectious diseases of the day in the early 1900s (when half the population died from tuberculosis), often lived well into their 80s and 90s, and cancer was still uncommon, even in the aged population. There is no question that the environment is vastly more toxic than a century ago, due to multiple industrial revolutions, and many of the toxins that were thoughtlessly discharged into the environment as the most expedient method of disposal are known carcinogens. Over a similar period of time our food supply has been industrialized, both in terms of fundamental plant and animal food agricultural production, as well as in food 'processing', resulting in a food supply that has dramatically lowered micronutrient content, (as well as over 3,000 chemicals that are routinely added as preservatives, colorings, flavor and texture enhancers,)~ each one of which is tested individually for carcinogenicity, but never in combination—and recent research has suggested that combinations of chemicals added to the food supply acting in concert may have carcinogenic effects, by the action of multiple chemicals promoting each of the established 10hallmarks of cancer within the human organism. [5, 6] Unfortunately, improved efficiency in growing, harvesting, and storing fruits and vegetables has also had impact on their nutritional content. The introduction of 'NPK' fertilizer (nitrogen, phosphorus, potassium), allowed plants to grow, but the abandonment of composting soil has led to widespread loss of trace-minerals as well as dramatic alteration of the soil's microbiome, which is intimately involved in the health of plants grown in it, just as our own intestinal microbiome is intimately involved in the health of virtually all systems of the human body. [7] The USDA published data between1950 and 1999, indicating that the content of calcium and carotene in broccoli has decreased nearly 50% over that 37-year period. The amount of carotenoids in collard greens has fallen about 42%, potassium has dropped nearly 60%, and magnesium is only16% of its 1963 level. Vitamin C in peppers has dropped from 128 mg to 89 mg. Beta-carotene in apples has dropped from 90 to 53 mg. Calcium in pineapple has dropped from17 mg (per 100 grams raw fruit) to 7 mg. Cauliflower has lost nearly half of its vitamins B1, B2, and C over the past 37 years. Many important nutrients not recorded in the past (some of these are still not measured), such as selenium, chromium, zinc, folic acid, indole-3-carbinol, and flavonoids, have no known status. Some of these declines may be due to changes in soil quality, others may be due to plant hybridization (and later GMO technologies) designed to increase sweetness, size, appearance, growth speed, and shelf life—nutrient value has not been one of the priorities in this process. [8] Research by Bruce Ames Ph.D. (inventor of the "Ames test", the most widely used method to assess mutagenicity and carcinogenicity of any discrete molecule or groups of molecules)was done at the University of California, Berkeley, and has documented that the toxicity of known carcinogens is dramatically amplified in animal models by subclinical deficiencies in many micronutrients; indeed, Ames' work has shown that human micronutrient deficiencies alone "mimic radiation in damaging DNA by causing single- and double-strand breaks, oxidative lesions, or both". [9] Ames' research in animal models and human cell culture identified

that deficiencies of at least 7 micronutrients: iron, magnesium, zinc, pyridoxine, ascorbate, reduced folate, and biotin result in increased DNA damage—even modest levels of deficiency of one or more can result in increased DNA damage and increased cancer rates. Dr. Ames' "triage therapy" provides a causal link between chronic modest micronutrient deficiency and many of the degenerative diseases that accompany aging including cancer, cognitive decline, cardiovascular disease and stroke, and immune dysfunction. In the category of "micronutrients" he includes over 40 essential vitamins, minerals, fibers, polyphenols, fatty acids, and amino acids. The triage theory states that throughout evolution there has been variation in the availability of vitamins and minerals in the diet and that enzymes dependent on these micronutrients (as coenzymes), if they were essential to short-term survival, developed strong binding constants so that they would preferentially utilize essential micronutrients in short supply, whereas enzymes and proteins needed for long-term survival would receive less of a limiting micronutrient thus becoming less functional, but without causing acute short-term viability consequences. Just as micronutrient content of foods available in the environment prior to the development of civilization and agriculture were intermittently deficient, even with modern diets we still see micronutrient intakes below recommended levels both in poor countries (where there is a lack of food) but also in developed countries in all segments of society, in which consumption of calorie rich, micronutrient poor unbalanced diets are common. Over half of the US population has inadequate intakes of magnesium, virtually all vitamin K, dark skinned people living in northern latitudes are extremely deficient in vitamin D and much of the population is low in various micronutrients including selenium, potassium, calcium, vitamin K, vitamin C, vitamin E, and omega-3 fatty acids. [10] There has been very little public health concern regarding these marginals to moderate levels of micronutrient deficiencies in the population, because no overt pathologies have been associated with them. However, Dr. Ames' triage therapy provides a causal link between modest micronutrient deficiencies and the "diseases of aging", one of these of course being cancer, the incidence of which increases steadily with age [11]. In his most recent paper, Dr. Ames presents experimental evidence that proteins and enzymes which preferentially receive critical micronutrients in short supply (which he refers to as "survival proteins"), and those which have access to micronutrient coenzymes only when there is an abundant supply as "longevity proteins" With animal model data from a longtime collaborator, Dr. Joyce McCann, the essentiality of vitamin/mineral/micronutrient dependent proteins were categorized according to the viability of Murine "knock out" mutants. If a given micronutrient dependent protein is a 'survival protein', and the gene for it is removed, such a mouse is nonviable. Conversely, if a given micronutrient dependent protein is a "longevity protein" the mouse is viable despite that protein's gene being knocked out, however such mice have increased diseases of aging [12]. This makes a strong case for even more careful research into dietary change to organically grown foods, and routine supplementation of vitamins, minerals, and accessory factors such as alpha lipoic acid, N-acetyl carnitine and ubiquinol, as a cancer prevention strategy (as well as other degenerative conditions associated with aging). In a 2018 update of his Triage hypothesis, published in PNAS, Ames outlines 18 'longevity nutrients', which reduce the incidence of many of the diseases of aging including cancer: these include PQQ (pyrroloquinoline quinone), ergothioniene, queuine, and 7 carotenoids-- lutein, zeaxanthin, lycopene, α- and β-carotene, β-cryptoxanthin, and astaxanthin. Choline, taurine, magnesium, DHA/EPA, and vit D/vit K, and selenium, complete the list. [13] There have been a significant number of studies of nutrients and botanicals in both the prevention and treatment of cancer, however the vast majority of these have been limited to just a few nutrients or single botanicals, using the model developed for clinical evaluation with drug research. However, nutrients and botanicals are not drugs and they act and interact in very complex ways that are not yet well understood. What is needed are well-designed clinical trials of complex mixtures, both of the approximately 40 essential nutrient factors identified by Bruce Ames' research, and also with complex mixtures of botanicals with proven anticancer activity in preclinical models, as suggested by Block at al. in a comprehensive paper published in 2015. [14] Role of stress in cancer outcomes and utility of nonselective beta-blockers. In the past 10 years it's also become quite clear, both through clinical observation, clinical trials, and preclinical research models, the role that chronic stress plays in both the development and progression of cancer. [15] The covid pandemic has dramatically amplified

chronic stress for many people, both in terms of fear of infection personally and also for loved ones, loss of social connection, loss of physical contact ('social distancing') loss of jobs and income, and uncertainty about many things. In addition, the covid pandemic has had a major impact on cancer care, both in terms of diagnosis and delivery of therapies 16. It is likely that we have not yet seen the impact of this collective increase in stress in cancer occurrence and treatment responses. [17] Over a decade ago it was noticed that cancer patients who were taking non-selective beta-blockers for other reasons (hypertension, cardiac arrythmia, or post myocardial infarction management) had better outcomes, overall survival, or relapse free survival in several tumor types. For instance, a 2015 paper found that amongst patients with epithelial ovarian cancer, that use of a non-selective beta-blocker was associated with an overall survival average of 90 months, vs survival averages in the low 40 months for those on no beta-blocker therapy, or on beta-1 selective beta blocker therapy. It was suggested that these findings 'may have implications for new therapeutic approaches [18]. A large meta-analysis of 13 retrospective reviews of beta-blocker uses in just over 100,000 patients with early breast cancer published in Feb of 2021 published a "highlights "summary. Their conclusions included: in preclinical models of breast cancer beta-blockers inhibit proliferation invasiveness and angiogenesis; beta-blocker use is associated with improved prognosis in patients with breast cancer (from retrospective studies); beta-blocker use was associated with relapse free survival improvement in patients with early stage breast cancer (meta-analysis); in patients with triple negative breast cancer there was a more pronounced effect on prognosis associated with beta-blocker use. The final conclusion of this meta-analysis was that beta-blockers appear to be a low cost and safe option to be repositioned for the treatment of early-stage breast cancer [19].

A preclinical research paper published in Dec of 2020 revealed some of the mechanisms related to stress/adrenergic signaling and cancer progression. Editorial commentary summarized this as "stressed neutrophils are a tumors alarm clock" 20. In this study, mice in which tumors had been induced and then resected, were immobilized (which is very stressful for mice), and this resulted in tumor cell reactivation. If the mice were treated with non-selective beta blockers to inhibit stress hormone signaling, tumor cell reactivation was prevented. In a human clinical correlation, the authors noted that serum concentrations of stress-associated proteins correlated with earlier tumor recurrence after resection of lung cancers in a cohort of patients. They concluded that "pharmacologically inhibiting stress hormone signaling with β-blockers may help to prevent tumor recurrence" [20].

It's now well accepted that chronic inflammation increases the risk for emergence of many different types of cancer, that cancers develop mechanisms in the tumor microenvironment to further promote chronic inflammation, and that chronic inflammation promotes tumor growth and metastasis21. Research has also shown that chronic stress leads to elevated levels of cortisol, which ultimately results in decreased tissue sensitivity to cortisol, resulting in decreased ability for cortisol to regulate inflammation—so that chronic inflammation becomes a response to chronic stress [22].

There are few events in life more stressful than the diagnosis of cancer, especially if it's a high-risk type, such as pancreatic cancer, or diagnosed at an advanced stage. The research findings support the use of propranolol, the first and most non-selective of all the beta-blockers, in patients who didn't have any contraindications (such as asthma) to beta-blocker therapy. Simultaneously, patients should (if not previously doing so) begin to engage in regular physical exercise 23 and also introduce regular practice of stress management techniques, such as Progressive Muscle Relaxation (derived from hatha yoga), meditation, and/or visualization practices (seeing their tumor shrinking, seeing themselves well, active and happy, etc). [24,25] People in cancer treatment (and post cancer treatment) should study and try a full range of stress management techniques, and choose what they felt the most drawn to, or whatever worked best for them. These choices included various form of biofeedback, including HeartMath (based on feedback of heart rate variability) [26] neurofeedback (using eeg) [27] or even very simple galvanic skin response biofeedback. However, it takes time for people under chronic stress to develop skill with stress management/mitigation techniques, so immediate beta-blocker therapy can be extremely useful. Patients must first traverse the 'white water' rapids of initial cancer treatment. Later, when they are feeling confident, have embraced a lifestyle that includes a high quality whole foods diet, supplementation of micronutrients and specific botanical mixtures, regular enjoyable physical activity,

and regular stress management practices—in short, have embraced an integrative oncology system, they then can work on healing their relationships, letting go of grudges and resentment (often with professional psychological coaching with therapists who are experienced with the psychological terrain of cancer patients). It's also important to redevelop robust social support systems with people who support their choices and lifestyle. When all of these primary objectives have been accomplished, it seems reasonable to discontinue pharmacologic therapy with beta blockers, but only if this can be done without creating an anxiety about it in the patient.

Repurposing Drugs for Cancer

Repurposed pharmaceuticals used in cancer are often referred to as 'off label', meaning they have never been studied in large clinical trials for cancer to show benefit, and therefore don't have an FDA 'indication' for treatment of cancer, though they can be legally prescribed by any licensed physician for treatment of any disease, as long as there is no evidence of harm. The just discussed non-selective beta-blockers are in this category. Not having an FDA indication for cancer means that insurance will not pay for such medications, though most such medications are affordable for most cancer patients as an 'out of pocket' expense. However, without an FDA indication for cancer treatment, most oncologists hesitate to prescribe repurposed 'off label' pharmaceuticals, without clinical evidence from large randomized trials, which document clinical benefit (and are very expensive to carry out).

There are currently a number of well-designed Randomized Controlled Trials on propranolol (repurposed from cardiovascular indications and discussed previously) and metformin (repurposed from diabetes) currently in progress. Propranolol is being studied in Hematopoietic cell transplantation for hematological malignancies as well, [28] and also in the perioperative setting (along with cox-2 inhibitors), for colorectal cancer. [29] Metformin is being studied in the ASAMET trial: a randomized, phase II, double-blind, placebo-controlled, multicenter, 2 × 2 factorial biomarker study of tertiary prevention with low-dose aspirin and metformin in stage I-III colorectal cancer patients [30] as well as in endometrial cancer, where its activity in reducing a proliferative marker is being studied. [31] Of note, in the repurposed pharmaceuticals for cancer arena, Ivermectin, arguably one of the most controversial of the repurposed pharmaceuticals for Covid-19, holds major promise for cancer, and particularly for its synergy with checkpoint inhibitor immunotherapy for cancer. It also synergizes with many chemotherapy drugs and targeted agents, and reverses MDR (multiple drug resistance, often acquired by tumor cells that survive chemotherapy. Clinical trials regarding ivermectin in cancer however, are in their infancy, and recommended dose ranges are not yet available; however, ivermectin has a broad 'therapeutic index'. In pre-clinical mouse models, 5 mg/kg given by oral gavage, was highly active in turning immunologically 'cold' tumors into 'hot' ones (meaning many more anti-tumor lymphocytes in the tumor microenvironment) which in human/mouse equivalents would be 400 mcg/kg, well within the dose range in which ivermectin has been used in other condition in humans. [32-37] Stress and the "Military Model" of cancer treatment.One of the mostly unseen/unrecognized factors that contributes to the 'stress milieu' of cancer diagnosis and treatment, is the military model which is so deeply embedded in how we talk about, approach, and organize cancer treatment—the 'War on Cancer', originally declared and funded during the Nixon administration in the 1970s, has been going on now for 5 decades, with small increases in cure rates for the common cancers, and continuing increase in global cancer incidence. Indeed this 'military model of medicine' is an issue with our collective approach to virtually all chronic illnesses—we 'battle' them, whether it's a virus, an autoimmune problem, or cancer. What we need to do is study and understand the diseases that affect us, rather than waging war on them. As we 'go to war' with cancer, the model is to 'bomb' or poison the enemy, and hope that the 'civilian population' survives. The entire experience is very fear driven, and if patients hesitate about accepting the conventional treatments, oncologists are trained to use fear to motivate them to comply 'for their own good.' All of this leads to the previously described overdominance of the sympathetic nervous system, even though its well established that digestive and immune function, two of the most critical body functions for healing, require high parasympathetic tone—and theses two branches of the autonomic nervous system interact with one and other in a 'yin/yang' type of relationship—when the activity of one rise, the activity of the other necessarily decreases. Healing happens in a state of relaxation when we are 'parasympathetic'. There is a lot of evidence that high 'sympathetic tone' (stress, fight/flight/freeze) drives the malignant

process in multiple ways. [38] Military language, e.g. 'targets', can be avoided in the clinical setting (although sometimes difficult to avoid, such as when using the anti-cancer drug class known as 'targeted agents'), 'arsenal' etc. The physician/practitioner can simply talk about medicines, 'tool boxes', remedies, re-education of the immune system, and restoration of harmony and balance. However, it's so much a part of our medical milieu, in both conventional and natural medicine, that it's easy for 'attack/battle' language to slip in.

Study of Exceptional Responders from clinical trials

The familiar Kaplan-Meier, survival curve, in which the Y-axis is the percentage of patients in the trial remaining alive, and the X axis is time, contains what is referred to as a "tail". The 'tail' of the survival curve is a long flat line at the right-hand end of the curve displaying the 1% to 10% of patients in the trial who become long-term survivors. Such 'exceptional responders' occur in virtually every clinical trial going back many decades. After decades of disinterest in the mystery of these patients, there are now 2 studies of these patients ongoing, and it's quite likely that there will be more to come. One is The Exceptional Responders study at the NCI and the other is the NEER project at Harvard. These studies include deep sequencing of the genomics of tumors of exceptional responders, and hope to use their health information to improve treatment [39-41]. There is also the possibility that 'exceptional survivorship', may be as much or more related to changes in lifestyle, emotional states, diet, etc, as it is to genomics of tumors of exceptional responders. Only careful analysis from many perspectives of these patients who live many years beyond those of others in their clinical trial, will be able to develop testable hypotheses regarding why this small number of patients in virtually every clinical trial, even of patients with metastatic disease, live far beyond the other patients in their clinical trial.

End of life experiences and the use of hallucinogens/entheogens

When cancer reaches the point that both conventional oncologists as well as integrative cancer care physicians and other integrative therapists feel that recovery is unlikely, patients are faced with one of our greatest collective fears—the fear of what we call death, which is fundamentally fear of the unknown. Those with a spiritual perspective see it as a 'transition' to a new phase of life, but the fact is that none of us, not even those who have had 'near death experiences', know for sure what lies beyond the time that our physical body ceases to function. Research over the past 2 decades at major universities, such as Johns Hopkins and UCLA, predominantly with end stage cancer patients, using psilocybin and other 'hallucinogens' (another name for this class of agents is 'entheogens', translated literally as putting in touch with the 'divinity within') in a therapeutic setting, has documented truly transformational effects. Often only a single therapy session has been needed to reverse depression and anxiety, and for people to dramatically reduce their fear of dying—and these therapeutic effects, from a single therapy session, have recently been shown to persist nearly 5 years later. [42] Going back in history a bit, to the early 1960s and 70s, there were several open label trials in academic medical centers using serotoninergic psychedelic agents (primarily LSD) in combination given in a psychotherapeutic setting to study its effects on existential and psychological distress in terminal cancer patients, which involved several hundred patients. These studies showed decreases in anxiety, depression, fear of dying, and pain, and an overall improved quality of life. [43, 44] Such research ended in the early 1970s with the passage of the Controlled Substance Act of 1970, which placed all of the serotoninergic psychedelic compounds into Schedule 1 of the US DEA's classification of regulated psychoactive substances (along with cannabis, which still remains in Schedule 1 at the federal level, although legalized for medical use in 36 states, and legalized for recreational use in 19).

When research with 'psychedelics' began again in the late 1990s, psilocybin became the most utilized substance. Although the precise mechanisms of its activity in enhancing the effectiveness of psychotherapy and having major beneficial impact on the psychological distress of late-stage cancer patients are not fully understood, it appears that this class of agents can contribute to making the brain more flexible and receptive to new thought patterns and ideas. Research indicates that the psychedelics/entheogens significantly suppress the activity of a specific network of the brain known as the 'default mode network'. This network appears to contribute to our sense of coherent narrative identity (sense of 'self'). In patients suffering from cancer related anxiety and depression, this network becomes hyperactive and is associated with worry, rigid

thinking, and rumination. Normally the default mode network is activated when we engage in self-reflection and mind wandering, but its overactivity contributes to significant dysphoria, fixation, and worry. Psilocybin and the other compounds in this class, both plants derived, and synthetic, acutely shift and suppress activity in this network, which helps people to view a more broadened perspective on their life situation, which can be enhanced by concomitant psychotherapy. [45- 46] In 2016 Roland Griffiths and his team at Johns Hopkins published a controlled study of psilocybin in 51 patients with life threatening cancers. Depression and anxiety are common in such patients, and were present in all 51 patients. A randomized, double-blind cross-over trial design was used, between very low (placebo like—1-3 mg/70 kg), and therapeutic dosing (22 or 30 mg/70 kg), with 5 weeks between the very low dose and the therapeutic dose experiences. Patients, staff and community observers recorded and reported changes in behaviors, attitudes, and mood throughout the study, which included 6 month follow up evaluations. The therapeutic dose sessions produced large decreases in both clinician- and patient-rated assessment of anxiety and depressed mood, concomitant with increases in optimism, life meaning, and quality of life, as well as significant reduction in anxieties regarding death. At 6 month follow up, all these changes were sustained, with 80% of patients continuing to show clinically significant decreases in anxiety and depressed mood along with greatly increased overall well-being and life satisfactions. Community observer (friends and family) reports corresponded well with patient and staff assessments [47]. Also in 2016, Stephen Ross, associate professor of psychiatry at NYU Grossman School of medicine led a double-blind placebo (niacin 250 mg) cross-over design-controlled study with 29 cancer patients suffering from cancer related depression and anxiety. The treatment arm consisted of moderate dose psilocybin (.3 mg/kg), in a therapeutic setting with experienced therapists assisting. Results of the study found that psilocybin in a therapeutic setting produced substantial, immediate, and sustained improvements in anxiety and depression. This was associated with decreases in cancer related hopelessness and demoralization, greater spiritual wellbeing, and increased quality of life. When the study participants were interviewed 6.5 months after their initial single psilocybin therapy session 60 to 80% of the study participants were found to have sustained clinically significant reductions in depression or anxiety. They also showed sustained benefits in quality of life, sustained benefits in existential distress, as well as improved attitudes toward death. It was concluded that the psilocybin induced mystical experience mediated the therapeutic effect of psilocybin on anxiety and depression. [48] Years after the original study, of 16 surviving patients, 15 agreed to undergo follow up at 3.2 and 4.5 years after the original single psilocybin assisted therapy session, which they published in February 2020. Essentially, they found that all of the reductions in anxiety, depression, hopelessness, demoralization, and fear of death that were found to be sustained at 6.5 months were still sustained in a similar percentage of the study participants at 3.2 years and 4.5-year follow-ups. Participants overwhelmingly attributed positive life changes to the single psilocybin assisted therapy session. The vast majority of the participants rated the experience among the most personally meaningful and spiritually significant experiences of their lives. This form of therapy has the potential to produce a paradigm shift in the existential and psychological care of patients with cancer. [49] It is of particular interest that 16 of 29 patients were still alive 4.5 years after the original study, 15 of whom agreed to long term follow up. In the original study group, 62% of the group of 29 had stage III or IV cancers, meaning that 18 had advanced stage and 11 had earlier stage cancers, though all were suffering from anxiety and depression, so presumably the 11 earlier stage patients were not doing well at the time of their recruitment into the study. Two thirds of the group had received prior anxiolytic and/or anti-depressant therapy with little help, and none were on psychotropic medications at the time of their participation in the psilocybin study. Large randomized placebo controlled clinical trials could be funded to study the effect of a single guided therapeutic psilocybin session, using the model pioneered in 'end of life' cancer patients, but recruiting patients with life threatening cancers being treated with curative intent, early in the course, or prior to beginning treatment. Many endpoints such as treatment response, percentage of complete responses, minimal residual disease assessment, as well as progression free and overall survival, could be studied and published. Classically in the oncology field, when dramatic therapeutic effects are seen with a therapy in late-stage cancer patients, clinical trials typically study the same intervention earlier and earlier in the course of therapy, some of which

ultimately become 'first line' therapies. It is currently unknown whether the dramatic psychological effects seen with such therapy in late-stage cancer patients has an impact on survival, though there are hints that it may, and the fact that it is well established that cancer patients with chronic depression and anxiety have worse outcomes than similar patients who are free of these psychological states, [50] suggest that this is an area deserving of intensive study, which could result in major improvements in cancer outcomes. If psilocybin becomes available as a pharmaceutical (again—since it was in fact marketed as a prescription drug by Sandoz—now Novartis—for several years in the early 1960s), and if clinical trials show that a psilocybin therapy session soon after the diagnosis of a potentially life threatening cancer improves outcomes, 'entheogen therapists' could easily be trained in the psycho-oncology divisions of cancer centers, using the techniques pioneered in the above and similar clinical trials, most of which have been considered as part of 'end of life' care. Removing fear in a large percentage of cancer patients who are fearful, soon after the initial diagnosis of cancer would at the very least improve quality of life, and at the very most, significantly improve the cancer cure rate. Cannabis has also become big business in the US, with legalization of cannabis for medical use (requiring a doctor's recommendation) in 36 states, and legalized for recreational use by adults over 21 years of age, in another 19 states, (20 counting Washington DC). 51 Although there is evidence for anticancer activity of multiple cannabinoids, both separately and in combination in preclinical models, 52 human clinical trials are lacking at this point although there are many anecdotes of impressive remissions even of advanced cancers after use of high dose cannabinoids (typically 1 gram of extract containing 60-80% cannabinoids, with varying ratios of THC to CBD, taken twice daily). Clinical use of THC containing cannabis and its extracts in cancer care are currently limited to management of pain, nausea, anxiety, and other symptoms associated with cancer or its treatment. CBD, a major but non-psychoactive cannabinoid has been legalized in all 50 states of the US by the 2018 farm bill, requiring all plant and plant extracts to contain no more than .3% THC to be legal for interstate commerce (there is no allowed interstate commerce with cannabis containing higher amounts of THC than this), and is widely used for anxiety, pain, and sleep, both by cancer patients and non-cancer patients. Given the wide public utilization of CBD, it's important to point out that with doses of CBD exceeding 40 mg per day, there can be significant inhibition of the hepatic CYP450 enzymes designated as 3A4, 2C19, 2D6, and 2C9, so it's important that in any patient taking doses of CBD of 40 mg or more per day be assessed for concurrent medications and their respective hepatic metabolizing enzymes, as its likely that CBD in this dose range may increase levels of medications that depend on these particular CYP450 hepatic enzymes for part or all of their metabolism. For medications without a narrow therapeutic index (the ratio between efficacy and toxicity), this is not an issue. For medications with a narrow therapeutic index (such as chemotherapy and targeted agents), dose reduction of those agents metabolized by the CYP 450 enzyme subsets (noted above) that are inhibited by CBD in doses above 40 mg/day, should be considered if CBD is co-administered (or CBD should be discontinued), and if available, serum anti-cancer drug medication levels monitored. [53] Herb-Nutrient-Drug interactions and genetic variation in drug-metabolizing enzymes.

The issue raised by higher dose CBD's inhibition of specific subsets of CYP450 hepatic enzymes (3A4 alone plays a major role in the metabolism of about 50% of pharmaceuticals, and 2D6 metabolizes the majority of psychoactive pharmaceuticals) raises another issue of concern in medical oncology. Chemotherapy and targeted agents are notorious for the narrowness of their therapeutic index (meaning that the difference between an effective dose and a toxic dose can be quite small). Clinicians can routinely order serum digitalis levels, drug levels of virtually every anti-seizure medication, and many other routinely used medications, but this is not the case for most drugs used in the treatment of cancer. Chemotherapy, and later the so called 'targeted agent' therapies (which specifically target genomic/proteomic 'drivers' that are upregulated in a particular tumor) were developed before the field of pharmacogenomics became well developed. Many oncologists tell their patients not to take any nutritional supplements because they might interact with the metabolism of chemotherapy and/or targeted agent therapies (all of which are metabolized in the liver)—the new immunotherapies are largely monoclonal antibodies which are not metabolized in the liver and are therefore not subject to such interactions. It's true that nutritional supplements and botanicals can interact with chemotherapy and

other medications– 54–but many foods beyond grapefruit (which many people are aware of as a potent 3A4 inhibitor which can lead to increased levels of drugs metabolized by 3A4, just as the herb St John's wort does the opposite–inducing higher levels of 3A4, leading to reduced levels of drugs that are substantially metabolized by 3A4–many other much less well known dietary components can have significant interaction with the metabolism of a wide range of pharmaceuticals, including cancer drugs. However, all of these dietary and nutritional/botanical supplement interactions pale in comparison to the pharmacogenomic variations, which are largely inherited, but can also be influenced by epigenetic effects, which influence which genes are expressed, and to what degree. Many people are born with small mutations (referred to as SNPs, for Single Nucleotide Polymorphisms), which result in a single amino acid difference in key areas of certain enzymes, which change the affinity and activity of that enzyme in the metabolism of certain drugs. If we could order levels of all the medications used in cancer therapy – timed to obtain so called 'peak' and 'trough' levels, it would be a simple matter to adjust the medication dose to an established therapeutic range, so that patients would not receive insufficient nor toxic levels of medication. Some of these important enzymes' genetic variations are known for certain cancer medication metabolism, and tests for the activity of the enzyme (rather than the drug level) as in the case of uridine diphosphate glucuronosyltransferase isoform 1A1 (UGT1A1), the genetically determined activity level of which dictates the efficacy and toxicity of irinotecan, widely used in colon cancer therapy, but this is often not done in clinical practice unless a patient has a severe toxic reaction to the first dose of medication. Underdosing often goes unnoticed, and may contribute to lack of response to treatment. It would be quite useful to lessen toxicity and increase efficacy of cancer therapy if regulations were installed requiring the clinical availability of tests to measure cancer medication 'peak' and 'trough' blood levels routinely.

Reducing toxicity of conventional cancer therapies

Aside from the as yet unavailable practice of measuring cancer medicine drug levels in patients' blood, there are several ways to make chemotherapy less toxic and more effective. One way is to fast for 72 hours during chemotherapy (day before, day of, and day after, on water, herbal teas, and/or broths); this causes normal cells to dramatically reduce their metabolism, whereas cancer cells are unable to modulate their metabolic rate, and so are more vulnerable to chemotherapy, whereas the normal cells are relatively protected. [55] Another way to reduce chemotherapy toxicity is so-called 'metronomic' chemotherapy–giving low weekly doses for a considerable period of time rather than the maximal tolerated dose every 2-4 weeks–this has antiangiogenic effects (breaks down tumor's ability to maintain its blood supply which is required for it to grow and spread. Metronomic chemotherapy can often control and even reduce cancer, even when the cancer cells themselves are not very sensitive to the chemotherapy agents used, due primarily to the anti-angiogenic effects of metronomic chemotherapy. [56 ,57] Another way to better target chemotherapy, immunotherapy, and targeted agents, is by chemotherapy sensitivity/resistance testing of each patients live tumor cells, in specialized laboratories experienced in this. Such chemosensitivity analysis requires a minimum of 1 gram of tumor tissue removed by surgical biopsy, by a surgeon experienced in tumor biopsies for this type of testing–for example, use of electro-cautery to stop bleeding, which will thermally damage tumor cells, needs to be avoided, and minimal trauma should be caused to the tumor sample in its removal, which is not the case for routine surgical biopsies for routine pathology examination of tissue for diagnosis. Tumor samples are optimally transferred to sterile culture media for transport by overnight shipping to the labs which then create cultures of tumor cells, each grown with different anti-cancer or mixtures of anti-cancer agents, and viability of tumor cells assessed after 96 hours. This approach to chemotherapy selection (it can also be applied to targeted agents, and to some of the new immunotherapies, by including lymphocytes isolated from the patient's blood in the tissue culture with tumor cells and checkpoint inhibitor antibodies), appears to have great clinical value to patients to oncologists who use it. Funding of large randomized clinical trials of this approach, designed and carried out by pioneers in the field, would be money well spent. [58-61] In the past 10 years, changes in cancer drug reimbursement practices have eliminated most private practice independent oncologists, and moved most of them into the employ of hospitals and large companies that employ them, and which also largely dictate which cancer drugs can be used for which cancers, which has made it more difficult for many

oncologists to use this extremely useful approach to customizing cancer drug therapies.

Targeting cancer via the Tumor Microenvironment (TME)

One of the hallmarks of integrative cancer therapies, in addition to choosing the least toxic, most effective strategies to maximally reduce tumor load (the single focus of conventional oncology), is to focus on the 'terrain' in which that tumor exists, both in terms of what is referred to as the Tumor Microenvironment (TME), and also the terrain of the patient in general. Many natural products influence the tumor microenvironment in ways that favor the immune response and impede tumor growth, as well as enhancing the overall metabolic terrain of the patient.

TME and the anti-tumor immune response

The immune system is composed of two types of immunity. Innate immunity is nonspecific and fast acting, working within minutes to days of an injury or insult. By contrast, adaptive immunity is specific and occurs over time. T and B cells play critical roles here because they develop memory. Upon second exposure to a pathogen, these cells can eliminate a threat much more efficiently because they learned to recognize and respond to it during a previous, first encounter. The goal of immunotherapy for cancer, in terms of checkpoint inhibition, is to educate and then liberate the natural underlying cancer immune responses in the adaptive immune system. The seven steps of the cancer immunity cycle include: 1) release of cancer cell antigens, (2) cancer antigen presentation, (3) priming and activation, (4) trafficking of T cells to tumors, (5) infiltration of T cells into tumors, (6) recognition of cancer cells by T cells, and (7) killing of cancer cells. 62

Numerous factors can help drive or suppress anticancer immunity at each step of the cancer-immunity cycle. These include suppressive factors in the tumor microenvironment (TME), including the cell-associated factor programmed death-ligand 1 (PD-L1) and its interaction with one of its receptors, programmed death-1 (PD-1). Other immunosuppressive factors include soluble mediators that impair cancer antigen-presentation capabilities, thereby indirectly causing suboptimal T-cell priming and activation (steps 2 and 3), or inhibit expression of adhesion molecules on endothelial cells to impede T-cell infiltration (step 5). In the case of PD-L1, expression by tumor cells and tumor-infiltrating immune cells impairs cytolytic T-cell activity (step 7). In addition to PD-1, PD-L1 also binds to B7.1 expressed on activated antigen-presenting cells (APCs), which inhibit T-cell responses. [62] The tumor microenvironment can prevent the expansion of tumor antigen-specific helper and cytotoxic T cells and instead promote the production of proinflammatory cytokines and other factors, leading to the accumulation of suppressive cell populations that inhibit instead of promote immunity. [63] Local production of IL-1 & 6 by tumor-associated macrophages promotes angiogenesis, tumor growth, & metastasis. Tumor microenvironments regulate distinct signal cascades that are critical for determining macrophage polarization and facilitating the expression of key molecules that control interactions with cancer stem cells. During an immune response to cancer, a tumor produces antigens that are delivered to antigen-presenting cells, such as dendritic cells and macrophages, which can then activate tumor-specific T cells. This crosstalk between dendritic and T cells typically occurs within the lymph nodes. Activated T cells traffic to the site of the originating tumor, recognize that tumor-specific antigen on the surface of cancer cells, produce cytokines that help to drive further T-cell expansion, and, ultimately, lyse or kill cancer cells in the tumor microenvironment. This normal immune process can be circumvented when PD-L1, expressed by cancer cells in the tumor microenvironment, binds PD-1 on T cells, rendering them inert. Essentially, the immune system is rendered nonfunctional regarding this cancer. Immunotherapy (via checkpoint inhibition) works by turning it back on, by 'taking the foot off the brake. T cells receive and respond to both activating and inhibitory signals. Activating signals stimulate the immune system and accelerate its ability, for example, to fend off viruses or bacteria, whereas inhibitory signals "brake" the immune system and can dampen or inhibit T-cell responses. In general, without these inhibitory mechanisms, rampant autoimmune disease would emerge. Checkpoint inhibitors such as those against CTLA-4 and PD-1 or PDL-1, however, are an advantageous example of circumventing these inhibitory signaling mechanisms. Aside from providing information regarding potential efficacy of immunotherapy by measuring these factors, and neutralizing them with check point inhibitor monoclonal antibodies as a form of immunotherapy, there are also prognostic implication of tumor infiltrating lymphocyte subsets in breast cancer. Prognostic value of tumor infiltrating lymphocyte

subsets in breast cancer depends on hormone receptor status. Interaction between immune-regulatory proteins and tumor infiltrating lymphocytes (TILs) within the TME is complex, and their associations may have significant clinical implications. In survival analyses, increased CD4+ TIL infiltration was associated with better prognosis of the patients. In subgroup analyses, high CD4+ TIL infiltration was revealed as an independent good prognostic factor in hormone receptor-negative subgroup while high FOXP3+/CD8+ T cell ratio was found to be an independent adverse prognostic factor in hormone receptor-positive subgroup, especially in luminal A subtype. [64] FOXP3 is a marker of regulatory T-cells (Tregs) which promote immune tolerance and suppress anti-cancer immune responses, analogous to checkpoint proteins in cancer patients, immunosuppression through Tregs is a crucial component of tumor immune evasion and contributes to disease progression. Tumor-infiltrating Tregs in particular suppress local effector T cell responses and are associated with poor prognosis in tumors such as human pancreatic cancer or hepatocellular carcinoma. The chemokine CCL22 is known to recruit Tregs into the tumor tissue and many types of human tumors are known to express high levels of CCL22. Suppression of CCL22 by IL-1 receptor blockade inhibits Tregs migration. [65, 66] The tumor metabolic stress shapes an immunosuppressive tumor microenvironment. An overview of metabolic stress in the TME that mediates immune suppression includes the fact that cancer cells exhibit a substantial demand of nutrients, including glucose, amino acids, and fatty acids, and this contributes to a lack of hydroxyl radicals and maintains high production of H+ ions (as lactic acid fermentation from glucose for energy by tumor cells). These metabolic stresses promote tumor cell growth, increase the expression of immune checkpoint proteins and immunosuppressive cytokine secretion, enhance the inhibitory function of regulatory T cells, and inhibit the anti-tumor effect of tumor-infiltrating cytotoxic T cells, thereby leading to an immunosuppressive TME [66,67].

Natural Products that support cancer therapy by modifying the TME

Resveratrol modulates the natural killer group 2D (NKG2D) and its ligands by increasing expression in transformed target cells and in NK cells. Enhanced expression of NKG2D receptor and cytotoxins in NK cells together with upregulation of NKG2D ligands on target cell surfaces leads to enhanced killing efficacy. NK cells use two different mechanisms to kill the targets: 1) using cytotoxic granule exocytosis and 2) by induction of death receptor-mediated apoptosis. Increased IFN-γ production by resveratrol enhances TRAIL expression, which can facilitate apoptosis induction. Inhibitory signaling is often too weak to prevent NK cell killing due to downregulated expression of MHC I proteins in malignantly transformed or virus-infected cells. [68] Botanical Extract Compound PHY906 is an herb formula used in traditional Chinese medicine for over 1800 years for treating a variety of gastrointestinal distress such as diarrhea, cramps, nausea, vomiting etc. Yale Medical Center conducted PHY906 research as an adjunct to chemotherapy in a Phase I/II double-blind, randomized study. Patients had advanced colorectal cancer. Herbal extract ingredients: Chinese Skullcap (Sctuellaria baicalensis), Peonia (Paeonia lactiflora), Chinese Licorice (Glycyrrhiza uralensis), Ziziphis (Fructus ziziphi). 69 PHY906 has been shown To enhance the chemotherapeutic efficacy while decrease chemotherapy-related toxicities and side effects of a variety of anticancer agents in various cancers. The PHY906 clinical program consists of five trials in three different types of cancers in both the United States and Taiwan. To date, approximately 150 subjects have received PHY906 in combination with chemotherapy in these five clinical studies. 70 PHY906 enhanced the anti-tumor activity of Sorafenib by changing the tumor microenvironment. PHY906 potentiated the anti-hepatoma activity of Sorafenib by multiple mechanisms targeting the inflammatory state of the microenvironment of tumor tissue via two major ingredients, primarily Scutellaria baicalensis and secondly Paeonia lactiflora. PHY906 enhanced infiltration of macrophages (M-1 type) into tumors. [71] A cocktail of Turmeric/curcumin, green tea/epicatechin gallate (EGCG) and resveratrol, increased levels of tumor-infiltrating NK cells and CD8+ cytolytic T cells in C57BL/6 mice bearing HPV+ mouse lung cancer (TC-1 cells). The combination formula repolarized M2-like TAMs (Arg-1highIL-10highIL-12low) to M1-like TAMs (iNOShighIL-10lowIL-12high) in the tumors [66, 72].

Role of Stress and Sympathetic Nervous System in the TME

High vascularization and locally secreted factors make the bone marrow (BM) microenvironment particularly hospitable for tumor cells making bones a preferred metastatic site for disseminated cancer cells

of different origins. Stress, and subsequent sympathetic nervous system signaling has been shown to significantly drive this metastatic process. Stress and catecholamine neurotransmitters released in response to activation of the sympathetic nervous system modulate various BM cells and may thereby influence cancer progression. Epinephrine (EPI) and norepinephrine (NOR)are released in the BM microenvironment from sympathetic nervous system (SNS) fibers entering the bone with blood vessels. EPI and NOR influence interaction of tumor cells with chemokine-expressing BM niche cells, e.g., CXCL12 abundant reticular (CAR) cells, osteo- blasts and osteoclasts. In response to adrenergic signaling niche cells release (1) CXCL16 chemokine that interacts with CXCR6 expressed on the surface of several tumor cells types, (2) CXCL12 that chemoattracts CXCR4 expressing cancer cells and (3) RANKL protein that binds RANK-expressing malignant cells. In addition, adrenergic signaling in osteoblasts and also directly in tumor cells themselves can promote release of angiogenic factors thus promoting bone marrow colonization by tumor cells through increased blood vessel density. [73] In addition to the products of sympathetic nervous system signaling, some energy-rich metabolites (e.g., L-lactate, ketones and fatty acids) derived from the tumor stroma can be transferred to the adjacent cancer cells and used for energy production via mitochondrial oxidative phosphorylation. Similarly, Pierre et al. reported that lactate generated by hypoxic tumor cells is a prominent substrate that fuels the oxidative metabolism of oxygenated tumor cells. These observations imply that glycolytic and oxidative tumor cells mutually regulate their access to energy metabolites. Tumor stroma metabolites such as lactate and ketones may thus promote tumor growth by acting as high-energy metabolites. Metformin, an anti-diabetic agent, inhibits both lipolysis in adipocytes and oxidative phosphorylation, preventing cancer cells from using the energy-rich metabolites derived from the tumor stroma [66, 74].

Acidity of the tumor microenvironment

The glycolytic nature of malignant tumors contributes to high levels of extracellular acidity in the tumor microenvironment. Tumor acidity tends to correlate with cancer aggressiveness; in part, this reflects the ability of hypoxia inducing factor 1 (HIF-1) to promote invasiveness and angiogenesis. Oral administration of pH buffers can reduce the development of spontaneous and experimental metastases in mice. [75] Microenvironmental acidity plays an important role in the response of malignant tumors to a wide variety of drugs and contributes to chemotherapeutic failure in cancer treatment. Lactate released as a waste product of glycolytic energy production in the hypoxic tumor microenvironment has been demonstrated to constitute a prominent substrate that fuels the oxidative metabolism of tumor cells in oxygenated regions, and has been shown to be involved in lactate uptake by cancer cells that preferentially utilize lactate for oxidative metabolism. [76, 77] Hydrogen ions flow along concentration gradients into adjacent normal tissue causing normal cell death, extracellular matrix degradation, and also stimulates angiogenesis. [66, 76] Lactate is metabolized by human lung tumors in vivo. Lactate use by tumor cells correlates with high FDG-PET signal and occurs in diverse onco-genotypes. Mono-carboxy transporter 1 (MCT1) enables lactate consumption by some lung cancer xenografts. Lactate's contribution to the TCA (Krebs) cycle in vivo can exceed that of glucose. 78 There are multiple therapeutic strategies which target acidity within the TME. Oral administration of potassium and/or sodium bicarbonate can raise the extracellular pH of tumors, an effect associated with inhibition of metastasis and improved responsiveness to certain cytotoxic agents; clinical application of this strategy appears feasible. Bicarbonate has the highest buffering capacity of any substance and is a specific for Lactic acidosis. Research with mice showed that oral intake of bicarbonate increased the pH of the TME, significantly reducing the spread of metastatic breast cancer. [79] Tumor pH buffering reduced optimal conditions for enzymes involved in tumor invasion such as cathepsins and matrix metalloproteins. In MDA-MB-231 tumor-bearing mice treated with bicarbonate showed significantly lower numbers of circulating tumor cells (CTCs) than untreated mice ($P < 0.01$). Doses of ½ to 1 tsp of sodium and/or potassium bicarbonate, once to twice daily, with a goal of maintaining a urine pH of 7 has been suggested. [80] In a mouse model of endogenously arising aggressive B-cell lymphoma, systemic alkalization resulted in concomitant IFN-γ upregulation in NK cells that were sufficient to significantly delay tumor growth without any other immunotherapy. This effect was strictly dependent on NK cells. [81] Acidic pH within the tumor microenvironment has significant immunosuppressive effects, which include suppressed

T-cell responses, and an abrogation of IFNγ and TNFα secretion. Mice given oral sodium bicarbonate didn't show a direct impact on reducing the size of melanoma tumors, but there was an increase in T cells within the tumor. Treatment with bicarbonate and CTLA-4 or PD-1 inhibitors reduced melanoma and pancreatic tumor growth in these mouse models when compared to checkpoint inhibitor treatment alone. The human equivalent daily dose would be about 4-5 grams (a heaping teaspoon; [66, 82, 83] Working with the terrain of someone with cancer is an art as well as a science, as many things affect it—detoxification techniques, diet, nutrient and botanical supplementation, acid-alkaline balance (particularly alkalinizing the TME), exercise, mental and emotional states, autonomic balance—so that the task is truly a holistic one, akin to sculpting, yet guided by science and laboratory testing for specific endpoints. This approach is often referred to as 'metabolic therapy'. There is significant evidence that cancer is not only related to gene mutations, but also to metabolic disturbances, often involving the mitochondria [84].

Intra-tumoral Immunotherapy

Also related to the tumor microenvironment is current research known as 'intratumoral immunotherapy', which holds great promise, and is also an area where investment of funding in large clinical trials is likely to pay a significant dividend in less toxic cancer therapies and improved outcomes. Intratumoral immunotherapy refers to injecting checkpoint inhibitor antibodies and other immune modulators directly into tumors. This field has largely been pioneered by interventional radiologists, who are now sometimes being referred to as 'interventional oncologists'. The direct injection of immune stimulating agents into the tumor microenvironment can prime the local tumor-specific immunity to generate a systemic, durable clinical response. Intratumoral immunotherapy is an increasingly active area of investigation with an ever-increasing number of agents, such as immune receptor agonists, non-oncolytic and oncolytic viral therapies, tumor necrosis inducing agents, and ex vivo expanded immune cells, which often have been modified in the laboratory to increase tumor antigen targeting, being tested in both preclinical models and in clinical settings. More than 20 neoadjuvant clinical trials exploring multiple intratumoral immune stimulatory agents alone, and in complex combinations are currently ongoing. This approach can be used with large primary tumors that are inoperable to potentially make them operable (and simultaneously generate long lasting anti-tumor immune memory), can be used in both the neoadjuvant and adjuvant settings, as wellas for treatment of metastatic disease with curative intent, alone, and in combination with other forms of cancer therapy. Many practical considerations, including optimal local delivery of immune stimulatory agents, appropriate timing and frequency of dosing all play an important role in the safety and efficacy of this approach. [85 – 87]

Maintaining remission via oral copper chelation therapy

When treated cancer patients have achieved the condition abbreviated as "NED" (No Evidence of Disease), meaning that scans show no tumor and if tumor markers (such as CEA, CA19-9, CA-125, etc) were previously elevated and are now within the normal range, there is an innovative treatment that may dramatically prolong remission. It consists of a carefully titrated treatment known as 'oral copper chelation' using a compound called ammonium tetra-thio-molybdate (TM). In the early 2000s, based on a prior phase 1 clinical trial of TM from the University of Michigan, 88 I observed in clinical practice that if the marker for this therapy, known as ceruloplasmin (the major copper binding protein of the body, which the liver synthesizes in direct proportion to total body copper), were kept in its therapeutic range (8-15 mg/dl) for 3 years in NED cancer patients and then stopped, that most patients, even those who had been stage IV NED (with essentially 100% risk of relapse) stayed in continuous remission, in the majority of cases. There have been many clinical trials of TM in patients with active tumors, and it generally slowed progression, but not much else. [89,90] The first clinician-scientist to try TM in a clinical trial with NED patients (with breast cancer) was Dr. Linda Vadaht, then at Cornell Weil School of Medicine, now at Sloan-Kettering Cancer Center. She saw 50% long term survival in stage IV NED triple negative (TN) breast cancer patients, which is far superior to any other therapy in stage IV NED TN breast cancer. [91] Dr Vadaht's clinical trial is still open and recruiting all stages of NED breast cancer patients. [92] George Brewer MD, the father of the concept of using TM for cancer wrote a review paper in 2014, in which some of my clinical results were described. In this review he specifically discussed that TM is only effective in NED patients, and related this back to his original mouse models, in which it was curative in

animal models with micro metastatic disease only. 93 Reduction of systemic copper levels appears to influence cancer by inhibiting angiogenesis and metastasis via suppression of the NFkB signaling pathway. [94] though there are likely many other mechanisms involved. [95] One working theory about why oral copper chelation with TM appears to have remarkable efficacy in NED cancer patients, but much less dramatic effects in patients with tumors that can be seen by imaging and/or evidenced by elevated tumor markers, is that many of the known angiogenic factors, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF), tumor necrosis factor-α (TNF-α), interleukin 1 and 8, SPARC (an extracellular matrix binding protein), and angiogenin, are all copper dependent. 96 Existing tumors that we can see on imaging studies are already angiogenesis competent (which is required to grow larger than 2 cubic mm, which is smaller than our imaging studies are currently able to show) 97. Despite copper deprivation, angiogenesis competent tumors appear to be able to recruit and generate angiogenesis growth factors that are not copper dependent, so, when confronted by copper deprivation, after an initial slowing of growth, and even regression, most of these tumors eventually progress, which would require non-copper dependent (or low copper tolerant) angiogenesis growth factors. On the other hand, it may be that tumors smaller than 2 cubic mm (non-angiogenesis competent) may be unable to initiate angiogenesis (the so-called 'angiogenesis switch') in the micro metastatic tumor colony with angiogenesis growth factors that are not copper dependent—in other words that 'flipping the angiogenesis switch' may require normal levels of copper in the body. Further research will be necessary to investigate this hypothesis.

Model for Implementing Comprehensive Integrative Cancer Care

It is conceptually useful to divide comprehensive integrative cancer care into 6 'phases', a treatment strategy that includes 1) Building health and vitality with diet, exercise, adaptogens (botanicals that increase resilience to stress) and other botanicals, nutritional supplements, acupuncture, energy medicine, and mind-body medicine, 2) maximal reduction of the tumor cell load in the body, favoring methods that have the least negative impact on the immune system 3) rebuilding and optimizing the immune function, 4) nonspecific immune stimulation, 5) immune education for specific and durable anti-tumor activities, and 6) angiogenesis blockade, which inhibits the growth of new blood vessels, essential to the growth and spread of tumors, especially to micro metastatic deposits smaller than 2 cubic mm, which are not yet 'angiogenesis competent'. All six phase are designed to reduce pain, optimize recovery and produce long-term immunity to cancerous tumors [98].

Conclusion

All in all, we appear to be standing on the threshold of changing cancer from a life threatening, and all too often life shortening disease, into a chronic manageable one, in which markers of disease activity give us feedback as to when we are not taking adequate care of ourselves, which holds the potential to actually result in more robust health after cancer than before. At the same time, we continue to essentially ignore conditions, such as global contamination of the environment with industrial and consumer product waste, lack of essential micronutrients in the diet, sedentary and stressful lifestyles, all of which are likely stoking the somewhat invisible 'pandemic' of cancer. It will take generations to course correct. It is useful to remain hopeful, and to stimulate awareness of these issues in both the general population, the scientific community and within regulatory agencies of government.

References

1. Anne B. Martin, Micah Hartman, David Lassman, et al. (2020). National Health Care Spending In 2019: Steady Growth For The Fourth Consecutive Year; Health Affairs, 40(1).
2. Elie Dolgin; Bringing down the cost of cancer treatment; Cancer's cost conundrum. Nature 555, outlook; S26-S29 (2018).
3. (2021). Doctors, researchers re-thinking metastatic cancer treatments; 02, newsletter, Cancer Treatment Centers of America.
4. You W, Henneberg M. (2017). Cancer incidence increasing globally: The role of relaxed natural selection. Evol Appl. 11(2):140-152.
5. Hanahan D, Weinberg RA. (2011). Hallmarks of cancer: the next generation. Cell. 144(5):646-674.
6. Goodson, William H., Lowe, et al. (2020). Testing the low dose mixtures hypothesis from the Halifax project, Reviews on Environmental Health, 35(4):333-357.

7. Abdul Rahman, Nur Sabrina, Natasha et al. (2021). "Effects of Abiotic Stress on Soil Microbiome.; International journal of molecular sciences, 22(16):9036.
8. Donald R. Davis, Melvin D. Epp, Hugh D. Riordan. (2004). Changes in USDA Food Composition Data for 43 Garden Crops, 1950 to 1999; *Journal of the American College of Nutrition*, 23(6):669-682
9. Ames Bruce. (2001). DNA damage from micronutrient deficiencies is likely to be a major cause of cancer. Mutation research. 475(1-2):7-20.
10. Ames Bruce N. (2018). "Prolonging healthy aging: Longevity vitamins and proteins." Proceedings of the National Academy of Sciences of the United States of America, 115(43):10836-10844.
11. Ames Bruce N. (2010). Prevention of mutation, cancer, and other age-associated diseases by optimizing micronutrient intake.; Journal of nucleic acids, 725071.
12. Ames BN. (2022). Musings in the twilight of my career. Free Radic Biol Med. 178:219-225.
13. Bruce N. Ames. (2018). Prolonging healthy aging: Longevity vitamins and proteins; 10836–10844 | PNAS, 115(43).
14. Block KI, Gyllenhaal C, Lowe L, et al. (2015). Designing a broad-spectrum integrative approach for cancer prevention and treatment.; Semin Cancer Biol. 35(S):S276-S304.
15. Dai, Shirui et al. (2020). Chronic Stress Promotes Cancer Development.; Frontiers in oncology, 10:1492.
16. Richards, M., Anderson, M., Carter, P. et al. (2020). The impact of the COVID-19 pandemic on cancer care. Nat Cancer 1:565–567.
17. Momenimovahed Zohre, Salehiniya Hamid, Hadavandsiri Fatemeh, et al. (2021). Psychological Distress Among Cancer Patients During COVID-19 Pandemic in the World: A Systematic Review ; Frontiers in Psychology, 12.
18. Watkins, Jack & Thaker, Premal & Nick, et.al. (2015). Clinical Impact of Selective and Nonselective Beta-Blockers on Survival in Patients with Ovarian Cancer.; Cancer.
19. R. Caparica, M. Bruzzone, E. Agostinetto. (2021). Beta-blockers in early-stage breast cancer: a systematic review and meta-analysis, Esmoopen Cancer Horizon; 6(2).
20. Perego M, Tyurin VA, Tyurina YY, et al. (2020). Reactivation of dormant tumor cells by modified lipids derived from stress-activated neutrophils.; Sci Transl Med. 12(572):eabb5817.
21. Greten, Florian R, and Sergei I Grivennikov. (2019). Inflammation and Cancer: Triggers, Mechanisms, and Consequences.; Immunity vol. 51(1):27-41.
22. Sheldon Cohen, Denise Janicki-Deverts, William J. Doyle, et.al. (2012). Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk; PNAS. 109(16).
23. Bente K Pedersen. (2020). Regular Exercise Helps Patients Combat Cancer; The Scientist.
24. Mehta, Ria et al. (2019). Evidence for the Role of Mindfulness in Cancer: Benefits and Techniques.; Cureus, 11(5):e4629.
25. Lee, Mi Hye et al. (2013). The effect of guided imagery on stress and fatigue in patients with thyroid cancer undergoing radioactive iodine therapy; Evidence-based complementary and alternative medicine, 130324.
26. Kloter, Evelyne et al. (2018). Heart Rate Variability as a Prognostic Factor for Cancer Survival - A Systematic Review.; Frontiers in physiology. 9:623.
27. Hetkamp, Madeleine et al. (2019). Systematic Review of the Effect of Neuro feedback in Cancer Patients.; Integrative cancer therapies, 18:1534735419832361.
28. Knight JM, Rizzo JD, Hari P, et al. (2020). Propranolol inhibits molecular risk markers in HCT recipients: a phase 2 randomized controlled biomarker trial; *Blood Adv*.4(3):467-476.
29. Haldar R, Ricon-Becker I, Radin A, et al. (2020). Perioperative COX2 and β-adrenergic blockade improves biomarkers of tumor metastasis, immunity, and inflammation in colorectal cancer: A randomized controlled trial; Cancer. 126(17):3991-4001.
30. Petrera M, Paleari L, Clavarezza M, et al. (2018). The ASAMET trial: a randomized, phase II, double-blind, placebo-controlled, multicenter, 2 × 2 factorial biomarker study of tertiary prevention with low-dose aspirin and metformin in stage I-III colorectal cancer patients; *BMC Cancer*.18(1):1210.
31. Petchsila K, Prueksaritanond N, Insin P, etal. (2020). Effect of Metformin For Decreasing Proliferative Marker in Women with Endometrial Cancer: A Randomized Double-blind Placebo-Controlled Trial; Asian Pac J Cancer Prev. 21(3):733-741.

32. Draganov, D., Han, Z., Rana, A. et al. (2021). Ivermectin converts cold tumors hot,and synergizes with immune checkpoint blockade for treatment of breast cancer; npj Breast Cancer 7(22).
33. Lee, Peter P. (2021). Use of the Anti-Parasitic Drug Ivermectin to Treat Breast Cancer, *Oncology Times*: 43(9):10.
34. Paul Zhang. (2021). Anti-Parasite drug Ivermectin shows promise against cancer; *Omega Precision Oncology*.
35. M Tang, X Hu, YiWang, et al. (2021). Ivermectin, a potential anticancer drug derived from an anti parasitic drug,; *Pharmacological Research*, 163:105207.
36. Letisia Marquez. (2021). Drug Combo Shows Promise Against Triple Negative Breast Cancer; city of hope, breakthroughs.
37. Ominguez-Gomez, G., Chavez-Blanco, A., Medina-Franco, et.al. (2018). Ivermectin as an inhibitor of cancer stem-like cells.; *Molecular Medicine Reports.* 17(2):3397-3403.
38. Cole, Steven W et al. (2015). Sympathetic nervous system regulation of the tumour micro-environment.; Nature reviews. Cancer vol. 15(9):563-572.
39. Bilusic M, Girardi D, Zhou Y, et al. (2021). Molecular Profiling of Exceptional Responders to Cancer Therapy.; Oncologist. 26(3):186-195.
40. Jocelyn Kaiser (2020). Exceptional cancer patients yield clues to better drug treatments Science, News, Health.
41. Carey Goldberg. (2018). Harvard Project Seeks 'Exceptional Responder' Cancer Patients to Figure Out What Went Right; WBUR.
42. Agin- Liebes GI, Malone T, Yalch MM, et al. (2020). Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer.; *J Psycho pharmacol*. 34(2):155-166.
43. Grof S, Goodman L. E, Richards W. A, et al. (1973). LSD-Assisted Psychotherapy in Patients with Terminal Cancer.; *Int Pharmacopsychiatry*. 8:129-144.
44. Pahnke WN, Kurland AA, Goodman LE, et al. (1969). LSD-assisted psychotherapy with terminal cancer patients.; *Curr Psychiatr Ther*. 9:144-152.
45. Andreescu C, Wu M, Butters MA, et al. (2011). The default mode network in late-life anxious depression.; *Am J Geriatr Psychiatry*. 19(11):980-983.
46. João Castelhano, Gisela Lima, Marta Teixeira. (2021). The Effects of Tryptamine Psychedelics in the Brain: A meta-Analysis of Functional and Review of Molecular Imaging Studies; *Front. Pharmacol.*
47. Griffiths, Roland R et al. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial.; *Journal of psychopharmacology*, vol. 30(12):1181-1197.
48. Ross S, Bossis A, Guss J, et al. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial.; *J Psychopharmacol*. 30(12):1165-1180.
49. Agin-Liebes GI, Malone T, Yalch MM, et al. (2020). Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer.; *J Psychopharmacol*. 34(2):155-166.
50. Wang X, Wang N, Zhong L, et al. (2020). Prognostic value of depression and anxiety on breast cancer recurrence and mortality: a systematic review and meta-analysis of 282,203 patients.; *Mol Psychiatry*. 25(12):3186-3197.
51. Claire Hansen, Horus Alas, and Elliott Davis Jr. (2022). Where Is Marijuana Legal? A Guide to Marijuana Legalization; US News and World Reports.
52. Tomko AM, Whynot EG, Ellis LD, Dupré DJ. (2020). Anti-Cancer Potential of Cannabinoids, Terpenes, and Flavonoids Present in Cannabis. *Cancers*. 12(7):1985.
53. Brown JD, Winterstein AG. (2019). Potential Adverse Drug Events and Drug-Drug Interactions with Medical and Consumer Cannabidiol (CBD) Use.; *Journal of Clinical Medicine*. 8(7).
54. Mitchell Bebel Stargrove, Jonathan Treasure, Dwight L. McKee (2008). Herb, Nutrient, and Drug Interactions: *Clinical Implications and Therapeutic Strategies Revised Edition*.
55. Dorff, T.B., Groshen, S., Garcia, A. et al. (2016). Safety and feasibility of fasting in combination with platinum-based chemotherapy; BMC Cancer 16:360.
56. Liu Y, Gu F, Liang J, et al. (2017). The efficacy and toxicity profile of metronomic chemotherapy for metastatic breast cancer: A meta-analysis; *PLOS ONE* 12(3):e0173693.

57. F Mpekris, James W. Baish, T Stylianopoulos, Rakesh K. Jain (2017). Role of vascular normalization in benefit from metronomic chemotherapy. *Proceedings of the National Academy of Sciences*8.
58. Nagourney RA, Blitzer JB, Shuman RL, et al. (2012). Functional profiling to select chemotherapy in untreated, advanced or metastatic non-small cell lung cancer.; *Anticancer Res*. 32(10):4453-4460.
59. Usón Junior PLS, Wagner J, Corpa MVN, et al. (2019). Metastatic carcinoma of unknown primary with complete metabolic response following sorafenib-based chemotherapy.; SAGE Open Med Case Rep.
60. Nagourney RA. (2006). Ex vivo programmed cell death and the prediction of response to chemotherapy.; *Curr Treat Options Oncol*. 7(2):103-110.
61. Kubota T, Weisenthal L. (2006). Chemotherapy sensitivity and resistance testing: to be "standard" or to be individualized, that is the question.; *Gastric Cancer*. 9(2):82-87.
62. Daniel S. Chen, Ira Mellman. (2013). Oncology Meets Immunology: The Cancer-Immunity Cycle; Immunity, 39(1):1-10.
63. Finn OJ.; Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. *Ann Oncol.* 23(S8):viii6-viii9.
64. Chung YR, Kim HJ, Jang MH, et al. (2017). Prognostic value of tumor infiltrating lymphocyte subsets in breast cancer depends on hormone receptor status. *Breast Cancer Res Treat*. 161(3):409-420.
65. Gabriela M Wiedemann, M M L Knott, Viola K Vetter. (2016). Cancer cell-derived IL-1α induces CCL22 and the recruitment of regulatory T cells; *OncoImmunology*. 5:9.
66. Dwight L. McKee1, Mamoona S. Lodhi, Najia Mansoor. (2020). Review Article: The Influence of Tumor Microenvironment on Tumor Progression and Anticancer Therapies; *Journal of Cancer Research Updates*. 9:75-81
67. Jiang, Zhou et al. (2020). Cancer Cell Metabolism Bolsters Immunotherapy Resistance by Promoting an Immunosuppressive Tumor Microenvironment. *Frontiers in oncology*.
68. Leischner C, Burkard M, Pfeiffer MM, et al. (2016). Nutritional immunology: function of natural killer cells and their modulation by resveratrol for cancer prevention and treatment.; *Nutr J*. 15(1):47.
69. W Lam, S Bussom, F Guan, et al. (2010). The Four-Herb Chinese Medicine PHY906 Reduces Chemotherapy-Induced Gastrointestinal Toxicity; *Science Translational Medicine*, 2(45) 45ra59.
70. Liu SH, Cheng YC. (2012). Old formula, new Rx: the journey of PHY906 as cancer adjuvant therapy. *J Ethnopharmacol*. 140(3):614-623.
71. Lam, W., Jiang, Z., Guan, F. et al. (2015). PHY906(KD018), an adjuvant based on a 1800-year-old Chinese medicine, enhanced the anti-tumor activity of Sorafenib by changing the tumor microenvironment.; *Sci Rep* 5, 9384.
72. Mukherjee S, Hussaini R, White R, et al. (2018). TriCurin, a synergistic formulation of curcumin, resveratrol, and epicatechin gallate, repolarizes tumor-associated macrophages and triggers an immune response to cause suppression of HPV+ tumors.; *Cancer Immunol Immunother.* 67(5):761-774.
73. Hanns, Pauline et al. (2019). Stress and catecholamines modulate the bone marrow microenvironment to promote tumorigenesis.; *Cell stress* vol. 3(7):221-235.
74. Zhang, Yi, and Jin-Ming Yang. (2013). Altered energy metabolism in cancer: a unique opportunity for therapeutic intervention.; Cancer biology & therapy vol. 14(2):81-89.
75. McCarty MF, Whitaker J. (2010). Manipulating tumor acidification as a cancer treatment strategy. *Altern Med Rev*. 15(3):264-272.
76. Fais S, Venturi G, Gatenby B. (2014). Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy; *Cancer Metastasis Rev*. 33(4):1095-1108.
77. Gregg L. Semenza. (2008). Tumor metabolism: cancer cells give and take lactate; *J Clin Invest*. 118(12):3835-3837.
78. Brandon Faubert, Kevin Y. Li, Ling Cai, et al. (2017). Lactate Metabolism in Human Lung Tumors; Cell. 171(2): P358-371.E9.
79. Ribeiro MD, Silva AS, Bailey KM, et al. (2012). Buffer Therapy for Cancer.; *J Nutr Food Sci*. 2:6.
80. Robey IF, Nesbit LA. (2013). Investigating mechanisms of alkalinization for reducing primary breast tumor invasion.; *Biomed Res Int*. 485196.
81. Pötzl J, Roser D, Bankel L, et al. (2017). Reversal of tumor acidosis by systemic buffering reactivates

NK cells to express IFN-γ and induces NK cell-dependent lymphoma control without other immunotherapies.; *Int J Cancer*. 140(9):2125-2133.
82. John Schieszer; Neutralizing Intratumoral pH May Improve Responses to Immunotherapy; 2016. *Cancer Network.*
83. Pilon-Thomas S, Kodumudi KN, El-Kenawi AE, et al. (2016). Neutralization of Tumor Acidity Improves Antitumor Responses to Immunotherapy; *Cancer Res*.76(6):1381-1390.
84. Dwight L. McKee, R Rountree. (2015). Alternative Theories of Cancer Causation—Are DNA Mutations Primary? A Clinical Conversation with Dwight L. McKee, MD, and Robert Rountree. *Alternative and Complementary Therapies*, 21(4).
85. A. Marabelle, L. Tselikas, T. de Baere, et al. (2017). Intratumoral immunotherapy: using the tumor as the remedy; *Annals of Oncology*, 28(S12):xii33-xii43.
86. S Champiat, L Tselikas, S Farhane; et. al. (2021). Intratumoral Immunotherapy: From Trial Design to Clinical Practice; *Clin Cancer Res* 27(3):665-679.
87. Wan X Hong, S Haebe, Andrew S. Lee, et.al. (2020). Intratumoral Immunotherapy for Early-stage Solid Tumors; *Clin Cancer Res* 26(13):3091-3099.
88. George J. Brewer, Robert D. Dick, Damanjit K. Grover, .et. al. (2000). Treatment of Metastatic Cancer with Tetrathiomolybdate, an Anticopper, Antiangiogenic Agent: Phase I Study1 *Clin Cancer Res* 6 (1): 1–10.
89. Bruce G. Redman; Peg Esper; Quintin Pan et.al. (2003). Phase II Trial of Tetrathiomolybdate in Patients with Advanced Kidney Cancer1; *Clin Cancer Res* 9(5):1666-1672.
90. Henry NL, Dunn R, Merjaver S, et al. (2006). Phase II trial of copper depletion with tetrathiomolybdate as an antiangiogenesis strategy in patients with hormone-refractory prostate cancer.; *Oncology*. 71(3-4):168-175.
91. N Chan, A Willis, N Kornhauser, et.al. (2017). Influencing the Tumor Microenvironment: A Phase II Study of Copper Depletion Using Tetrathiomolybdate in Patients with Breast Cancer at High Risk for Recurrence and in Preclinical Models of Lung Metastases; *Clin Cancer Res*; 23(3).
92. (2005). U.S. National Library of Medicine; ClinicalTrials.gov; A Phase II Study of Tetrathiomolybdate (TM) in Patients with Breast Cancer at Moderate to High Risk of Recurrence.
93. Brewer GJ. (2014). The promise of copper lowering therapy with tetrathiomolybdate in the cure of cancer and in the treatment of inflammatory disease. *J Trace Elem Med Biol*. 28(4):372-378.
94. Pan Q, Bao LW, Merajver SD. (2003). Tetrathiomolybdate inhibits angiogenesis and metastasis through suppression of the NFkappaB signaling cascade.; *Mol Cancer Res*.1(10):701-706.
95. Baldari, Silvia et al. (2020). Current Biomedical Use of Copper Chelation Therapy.; *International journal of molecular sciences* vol. 21(3):1069.
96. Cori Vanchieri (2000). Cutting Copper Curbs Angiogenesis, Studies Show; JNCI: Journal of the National Cancer Institute, Volume 92(15)1202-1203.
97. H Femke, Arjan W Griffioen. (2007). Tumour vascularization: sprouting angiogenesis and beyond.; Cancer metastasis reviews vol. 26(3-4):489-502.
98. Dwight McKee (2013). Integrative Cancer Medicine: An Oncologist Takes a Practical Look at Facts, Fiction and the Future; Cancer Strategies Journal, *Advances in Integrative Cancer Medicine and Research.* 1(1).

Cite this article: Dwight L McKee. (2024). Reflections on Integrative Oncology: An Independent Clinician's Long-Term Perspective. *International Journal of Clinical and Molecular Oncology*. BioRes Scientia Publishers. 3(1):1-18. DOI: 10.59657/2993-0197.brs.24.011

Article History: **Received:** February 12, 2024 | **Accepted:** February 26, 2024 | **Published:** March 06, 2024