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CANCER CARE

THE ROLE OF REPURPOSED DRUGS AND METABOLIC INTERVENTIONS IN TREATING CANCER

2ND EDITION

October 1, 2024

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Disclaimer

This monograph is a review of the published peer-reviewed literature evaluating treatment options for repurposed drugs and lifestyle/dietary changes that can be used as part of a holistic treatment plan for patients with cancer. This monograph is not intended as a stand-alone guide to treating cancer. Nothing in this document should be taken as a basis to initiate treatment without guidance from a medical professional or avoid any treatment prescribed by your treating physician. This information is offered as a basis to assist mutual decision-making between the patient and his/her providers. Cancer care should always be supervised by a healthcare provider. Patients with cancer should ALWAYS consult with their regular oncologist/integrative oncologist as well as an integrative provider, in addition to their primary care provider.

The treatment interventions outlined in this monograph should be used primarily as adjunctive therapy in addition to the treatment provided by an oncologist. The goal is to reduce the toxicity of standard chemotherapy/radiotherapy (and lower the dose of chemotherapy when possible) to prevent severe immunosuppression, organ toxicities, and death from standard chemotherapy and to improve the Quality of Life (QoL). However, the patient may decide to forego conventional chemotherapy and radiotherapy and follow a “holistic” treatment approach based on repurposed drugs and lifestyle interventions; under the principles of true informed consent, patient autonomy and personal decision making the patient has the right to make this choice. It is best that the treatment plan be discussed with the patient’s family and the patient’s primary health care provider(s) who should supervise the patient’s treatment.

Standard chemotherapy targets the rapidly dividing population of cancer cells; these agents commonly adversely affect the tumor microenvironment and may promote the proliferation of cancer stem cells, increasing the potential for metastases. Almost all the interventions listed in this document limit the negative effects on the tumor microenvironment. In addition, many of the agents described herein also target cancer stem cells. This data suggests that these interventions should be used simultaneously with conventional chemotherapy to achieve the best outcomes for our patients.

Note that this document mentions some potential interactions, such as between antioxidants and chemotherapeutic agents, that must be considered.

Target Audience

This information should be of particular interest to patients with cancer, to help guide them through the complicated issue of using repurposed drugs and lifestyle changes for cancer treatment. However, as noted above, it should not be used by patients to self-treat and should be supervised by a qualified healthcare provider. Primary care providers and integrative providers of patients with cancer will find essential information within this document. Furthermore, this document will be of interest to people who would like to reduce their risk of getting cancer. Patients with existing cancers should attempt to discuss the topics of dietary

caloric restriction and adjuvant (concurrent) repurposed drugs with their regular oncologist; however, for obvious reasons (vested interests) many oncologists may be unwilling to discuss these topics. In such circumstances patients should engage with an integrative oncologist or integrative primary care provider.

Caution to Patients

This document is based on the highest level of scientific evidence. Patients should review this information, independently validate the reliability of the data, and discuss the treatment options with their family/healthcare advocates. Patients should formulate a treatment plan with their healthcare provider that is compatible with their values and goals. Patients should, however, vigorously avoid unproven and unscientific interventions that only benefit unscrupulous practitioners (see Alternative Medicine; Chapter 1)).

A repurposed drug is one that is used "off-label," a common basis for prescribing but which means that it has not been reviewed and approved by the U.S. Food and Drug Administration for that indication. Some recommendations may be subject to controversy and differences of opinion among medical authorities. While we believe this monograph offers an accurate view of the current state of science as it is based on solid evidence and pathophysiological principles, public health agencies and regulatory bodies may take contrary positions.

This document represents the author's effort to provide educational material and is not a peer-reviewed publication. The author is not responsible or liable for the use or misuse of the information provided. No guarantees of benefit or the absence of harm can be offered, and reliance on any information provided is solely at your own risk.

Acknowledgments

I would like to thank Dr. Pierre Kory, Dr. 'Justus Hope', Dr. Mobeen Syed, Dr Kathleen Ruddy and Dr. Nathan Goodyear for their valuable contributions to this piece of work. Additionally, I would like to acknowledge the authors of several books on metabolic oncology that were very useful in guiding my thinking. These include Thomas Seyfried ("Cancer as a Metabolic Disease"), Otto Warburg ("The Metabolism of Tumors"), Jane McLelland ("How to Starve Cancer"), Travis Christofferson ("Tripping over the Truth"), Jeffrey Dach ("Cracking the Cancer Toolkit") and Nasha Winter and Jess Higgins Kelley ("The Metabolic Approach to Cancer: Integrating deep nutrition, the ketogenic diet, and nontoxic bio-individualized therapies)". I am also grateful for groups like Anticancer Fund and the Repurposing Drugs in Oncology (ReDO) group, who provided a framework for this work.

FOREWORD

by Dr. Justus Hope

As a physician and board-certified specialist, I have spent over 30 years caring for patients, mainly those suffering from intractable pain. In January 2020, when my friend contracted glioblastoma, I began researching to figure out how to help him. What I found annoyed me: My friend could do far better if his doctors would add repurposed drug cocktails to his chemotherapy, radiation, and surgery.

A Harvard professor first stumbled upon repurposed drugs for cancer in the 1990s when he used them to cure his own glioblastoma. That man is still alive today.

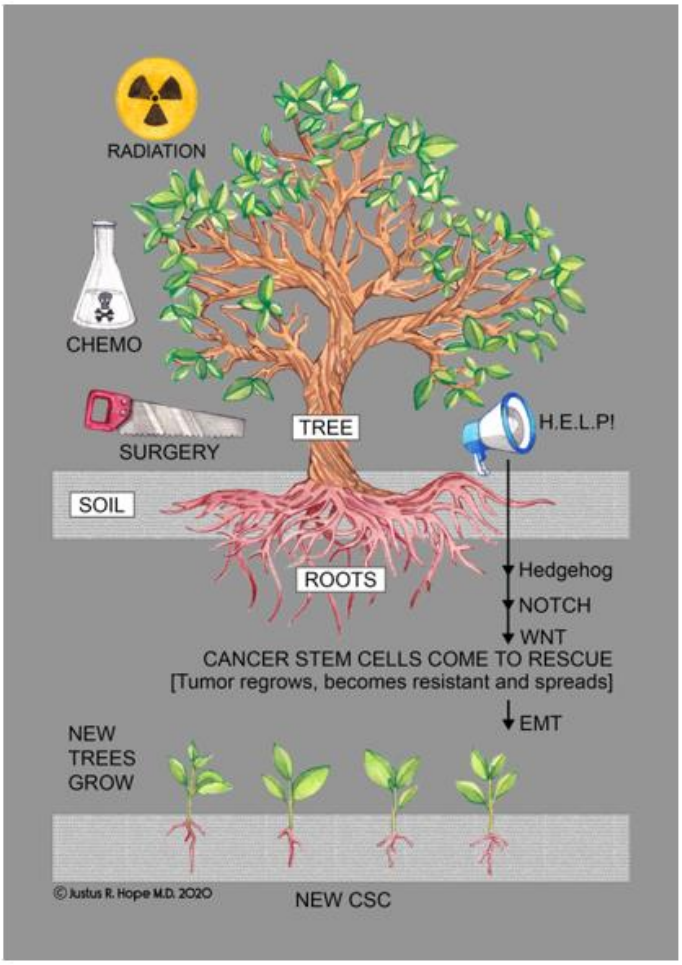


Figure 1: Cancer stem cells are the root of cancer (Source: Dr. Justus Hope)

The most significant problem I see repeatedly is that cancer recurs with resistant metastases. At that point, even with repurposed drugs, it is often a losing battle. This tragedy occurs because the standard treatments of surgery, radiation, and chemotherapy stimulate the growth of cancer stem cells (see Figure 1). Proactively adding repurposed drugs as early as possible can help prevent cancer stem cells from regrowing the tumor into a more resistant and sometimes indestructible form. If we could get all patients and their oncologists to read this document and add a repurposed drug cocktail, along with lifestyle changes, at the onset of a cancer diagnosis (and do this in concert with their treatment plan — whether it be surgery, chemotherapy, and radiation treatment) we would likely see a lot more of these patients not only survive but live better, longer lives.

Justus Hope is a pen name. The author practices medicine under his given name. He has written several books, including *Surviving Cancer, COVID-19, and Disease: The Repurposed Drug Revolution*.

FOREWORD for 2nd EDITION OF CANCER CARE

by Dr. Justus Hope

Dr. Paul Marik, the most published Critical Care Specialist in the United States, has tackled Cancer. Dr. Marik reviewed thousands of studies, and in the process, uncovered fundamental truths and busted persistent myths in publishing *Cancer Care 1st Edition*. This 2nd edition expands these and adds propranolol, a relatively unknown anticancer agent. Moreover, ivermectin is moved up to Tier One based on emerging evidence.

There are numerous practical suggestions, and all are based on PubMed studies so no one can dispute the scientific and evidence basis. Marik gives us some guidance on which three repurposed drugs to take before cancer surgery or biopsy to decrease the risk of spreading the cancer through surgical manipulation. Cutting a tumor has long been known to pose a risk of spreading cancer, yet patients have not been warned of this. Marik notes that studies have shown that these risks can be reduced with the pre-operative use of celecoxib, propranolol, or cimetidine. Better yet, combining all three may have a synergistic effect.

However, my review of the 2nd edition of Dr. Marik's *Cancer* provided much more, and I am honored to share it here. First, let me start with the root cause of cancer. Dr. Marik notes the Somatic Mutation Theory, the one we are all taught in medical school, is not supported by the growing data. Cancer, as we have been told for decades, is not caused by a series of mutations that result eventually in out-of-control cell division.

Instead, the data provides much more support for the Mitochondrial Dysfunction Model as espoused by Dr. Thomas Seyfried. When cancer cells' mitochondria are transplanted into normal cells, the normal cells become cancerous. However, when cancer cells' nuclei are transplanted into normal cells, the cancer does not transfer. The causative agent is carried in the mitochondria, not in the nucleus. The central issue in cancer is defective mitochondria, not DNA mutations.

Why has this myth that cancer arises from DNA mutations persisted?

Because the Somatic Mutation Theory is the narrative, and the narrative produces expensive and profitable treatments. The results remain lacking. The narrative probably won't change any time soon, however, Dr. Marik notes that addressing cancer treatment according to the Mitochondrial Dysfunction Model produces different therapies and much better outcomes. These treatments, which can be done in addition to the standard of care for most patients, can result in longer survival times - in some cases complete remission. Perhaps more importantly, Marik's recommendations may result in avoiding cancer altogether, a prospect that could demolish the cancer industry's profits.

But I digress.

Let us get to some of the other myths that Marik busts.
"Sunlight is bad for you as it increases your risk of cancer and sunscreen is healthy for you as it decreases your cancer risk."

Wrong. It is quite the opposite. In the 2nd Edition, Dr. Marik convincingly shows, via multiple studies, how sunlight reduces melanoma risk and improves survival and how sunscreen does the opposite.

When my friend and colleague developed Glioblastoma, a serious brain cancer with an average survival of 12.7 months, I dove into the medical literature and found repurposed drugs. After publishing a book in 2020 – *Surviving Cancer COVID-19 and Disease: The Repurposed Drug Revolution* – on my findings including the vast evidence base on Repurposed Drugs for Cancer, my friend added four of these - Atorvastatin, Mebendazole, Metformin, and Doxycycline - to his treatment plan through the US Care Oncology Clinic, and he survived some 46 months - almost 4 times longer than expected.

For this his family was grateful. However, we had all hoped for more. And when he ultimately passed, it was the radiation damage that played the largest role, not the cancer. Dr. Thomas Seyfried has noticed the same issue in his interviews on Glioblastoma. Seyfried explains the brain should never be irradiated.

I only wish we had this information in 2020. We needed Dr. Seyfried's and Dr. Marik's cancer knowledge then. My friend could have done better and lived longer.

Which brings me to propranolol. Dr. Marik ranks this second in evidence support only to Vitamin D3. Why? The book covers all the technical and detailed anti-cancer pathways of propranolol. However, the gist of it is this:
Propranolol is a beta blocker that shields the effect of catecholamines on the body. Catecholamines like norepinephrine and epinephrine are released when we encounter stress, and stress increases the likelihood of developing cancer. Therefore, by blocking the catecholamines, propranolol reduces the risk of developing cancer.
However, the key property of this beta blocker is that it reduces metastatic spread.

This brings me to one of Dr. Marik's favorite parts of his upcoming book. Three repurposed drugs can offer preventative effects against metastatic spread in those undergoing cancer surgery. These include celecoxib, cimetidine, and propranolol. Dr. Marik writes the combination may be synergistic.

Dr. Paul Marik has taken the science of Repurposed Drugs in Cancer to a world-class level. *Cancer Care 1st Edition* is worthy of a PhD thesis with more than 1200 PubMed citations. Marik has earned another PhD with more than 1300 references in this new edition. The most

published Critical Care Specialist in the United States has become the most credible scientific voice for repurposed drugs in preventing and treating Cancer.

And on a personal note, talking with Dr. Marik has been a pleasant adventure. Speaking with him is like talking to your best friend albeit with a South African accent and an AI-like knowledge of the subject. He has the most remarkable combination of intellect, compassion, and humility of anyone I know.

The 1st and 2nd editions of Dr. Marik's *Cancer Care* will change how the world approaches cancer.

Justus R. Hope, MD
Redding, California
May 2024

PREFACE

By Dr. Paul Marik

"It is more important to know what kind of person has a disease than to know what kind of disease a person has."
Hippocrates (460-370 BC)

"When we have the power to help, we have the duty of doing so."
Mirko Beljanski (1923-1998)

Years ago, when I had more hair and COVID-19 wasn't even a twinkle in anyone's eye, I became known for developing a treatment for one of the most common causes of death in hospitals — medical sepsis, which takes the lives of around 1,000 people each day in this country alone. My 'cocktail' consisted of three safe, inexpensive, easily accessible drugs that could be repurposed for sepsis. Time after time when I gave patients vitamin C, hydrocortisone, and thiamine, their condition turned around within hours. (1)

Repurposing drugs is nothing new. Around 30 percent of all prescriptions in the United States are written for off-label uses. (2) Bringing new drugs to market can take decades and cost billions of dollars while existing licensed drugs can be repositioned to offer safe, affordable, and effective treatments in a short period of time.

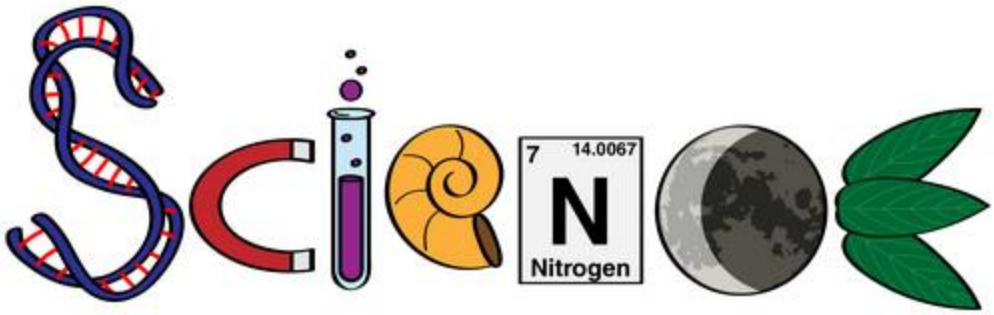
We have had great success in using repurposed drugs, as well as vitamins, supplements, and lifestyle changes, to treat COVID, long COVID, and COVID vaccine complications over the past few years. (3) While researching and developing protocols for the above conditions, I began reading huge volumes of information and saw an interesting pattern emerging that led me to investigate the potential role repurposed drugs could play in the treatment of cancer, along with some amazing non-pharmaceutical interventions like intermittent fasting. In doing so, I learned that much of what I once understood about what causes cancer and how it should be treated was wrong or at least misguided.

In putting this document together, I have invested thousands of hours, read more than 1800 peer-reviewed papers, and consulted with dozens of doctors and experts. I want to be clear that I am not suggesting I have found a cure for cancer, nor am I the first to propose using repurposed drugs for cancer. (4-7) What I hope to provide is a well-researched clearinghouse of information that picks up where traditional cancer therapies leave off. I aim to inspire providers caring for cancer patients to broaden their horizons and think creatively about readily available interventions, with science to back up their efficacy, that could improve their patients' outcomes.

While I no longer see patients directly, I will forever be bound by my Hippocratic Oath to 'first do no harm'. I offer this compendium of information as my latest contribution toward that end.

PREFACE to 2nd Edition.

The basic concepts and treatment approach outlined in the 1St Edition of this monograph have not changed. However, many of the concepts are refined and expanded. A number of additional repurposed drugs have been added to the list. Most importantly, the stratification of the list of preferred repurposed drugs has changed based on newly acquired clinical information. This is a dynamic process, and it is likely that this list will change in future updates.



We Need to follow the true science.

Glossary of common abbreviations

AKT: protein kinase B (PKB or *Akt*)
ALA: alpha-linolenic acid
AMPK: adenosine monophosphate-activated kinase
ARG-1: arginase 1
BRACA1: breast cancer gene 1
BAX/BAK: members of the Bcl-2 family of apoptotic proteins
CCR6: chemokine receptor 6
CSC: cancer stem cells
CI: confidence interval
CGM: continuous glucose monitor
COX: cyclooxygenase
DC: dendritic cell
FOXO1: Forkhead Box O1
EGFR: epidermal growth factor
EGCG: epigallocatechin gallate
ERKs: extracellular-signal-regulated kinases
FGF: fibroblast growth factor
GI: glycemic index
GTCs: green tea catechins
GDH: glutamate dehydrogenase
HDL: high density lipoprotein
HIF: hypoxia inducible factor
HR: hazard ratio
HK2- hexokinase-2
HSP: heat shock protein
Hh: Hedgehog pathway
HER2: human epidermal growth factor receptor 2
IGF-1: Insulin-like growth factor 1
IκBα: inhibitor of nuclear factor kappa B
INF: interferon
in vitro: performed in a test tube or culture dish
in vivo: performed in a living organism
GH: growth hormone
IL: interleukin
JAK2: Janus kinase 2
JNK: c-Jun N-terminal kinase
MAPK: mitogen-activated protein kinase
MAMs: metastasis-associated macrophages
MDSC: Myeloid-derived suppressor cells
MMPs: matrix metalloproteinases
mTOR: mammalian target of rapamycin
NAD: nicotinamide adenine dinucleotide

NF-KB: nuclear factor Kappa beta
NOS: nitric oxide synthase
NK cells: natural killer cells
NSAID: non-steroidal anti-inflammatory drug
Nrf2: nuclear factor E2–related factor 2
OR: odds ratio
PDE5 inhibitor: phosphodiesterase 5 inhibitors
PD-1/PD-1L: Programmed cell death protein 1/ligand
PI3K: phosphoinositide 3-kinase signaling pathway
PGE2: prostaglandin E2
RCT: randomized controlled trial
REM: rapid eye movement
ROS: reactive oxygen species
ReDO: Repurposing Drugs in Oncology
RFS: recurrence-free survival
RR: relative risk
STAT3: signal transducer and activator of transcription 3
TAM: Tumor-associated macrophages
TGF: transforming growth factor
TG: triglyceride
TME: tumor microenvironment
TCR: T cell receptor
TLR: Toll like-receptor
TCGA: The Cancer Genome Atlas Program
TNF: tumor necrosis factor
TRAIL: tumor necrosis factor-related apoptosis-inducing ligand
Tregs: T-regulatory cells
USPSTF: U.S. Preventive Services Taskforce
UV: ultraviolet
VDAC: voltage-dependent anion channel
VCAM1*:* vascular cell adhesion molecule *1*
VEGF: vascular endothelial growth factor
WNT: WNT signaling pathway

CHAPTER 1: INTRODUCTION

We strongly endorse an Integrative approach to the management of patients with cancer. There is much confusion amongst patients (and many health care providers) as to the characteristics of integrative oncology. Furthermore, complementary and alternative medicine (CAM) strategies while outside of the conventional medicine paradigm are quite distinct and should be considered separately. The use of CAM is frequently seen in the oncology setting, with nearly half of cancer patients reporting CAM use following diagnosis and as many as 91% during active chemotherapy and radiation treatment. (8, 9) It is, therefore, imperative that the distinction between complementary and alternative medicine be reviewed with the patient and that oncologists have open non-judgmental discussions with their patients and families and appreciate the potential risks and benefits of CAM to facilitate open and inclusive discussion. This has the potential to allow for the safe integration of complementary (and not alternative) strategies into conventional care and for increased knowledge-sharing between patients and providers. (10)

Integrative oncology and other models of Patient Care.

- **Integrative Oncology**. Provision of care by a "true integrative oncologist" is the preferred model of care for the patient with cancer. An integrative oncologist is dual qualified/certified in orthodox medicine (oncology) as well as in integrative medicine (complementary medicine). In many countries — including Israel, Germany, Switzerland, India, and other countries in Asia — by default most oncologists are dually trained and function as integrative oncologists. This is distinct from the United States, Australia, and some European countries, where most oncologists follow the traditional orthodox approach.

  The integrative oncologist has a diverse array of tools (therapeutic options) in his/her toolbox and formulates an individualized and unique treatment plan for each patient. The integrative physician and patient co-design an integrative treatment plan, recruiting the "best of both worlds." This may entail the use of chemotherapeutic agents/radiotherapy together with complementary medicine or complementary medicine alone. Patients participate in their treatment plans in a shared decision-making model. There is open patient-physician communication that is non-judgmental and in keeping with the patient's cultural beliefs.

  Integrative oncology involves a multidisciplinary team with caregivers committed to an integrative care model. The major focus of care is the patient's quality of life with an emphasis on a) relief of symptoms, anxiety, and pain, b) quality of sleep, c) nutrition, d) nutraceutical/herbs and repurposed drugs, and e) lifestyle changes. Integrative oncology complements conventional medicine while keeping within the *boundaries of scientific rigor.* Integrative medicine strives to be based on *rigorous research, conducted in accordance with scientific methodologies*. Integrative oncology focuses on pragmatic research; pragmatic trials test interventions in the full spectrum of everyday clinical settings, in order to

maximize applicability and generalizability. Such pragmatic trials allow for a multimodal integrative approach, are individualized, and with patient-centered outcomes. Patients in countries where care is being managed by “orthodox” oncologists should consult with integrative primary care physicians.

- **Complementary medicine.** Complementary medicine involves techniques not considered within the scope of traditional orthodox medicine, but which have a scientific underpinning and are often practiced by non-orthodox practitioners. Examples of complementary approaches include herbal medicine, tai chi, yoga, acupuncture, massage therapy, spinal manipulation, art therapy, music therapy, mindfulness-based stress reduction, and many others. Complementary medicine complements traditional orthodox medicine and when applied by a traditional physician it is known as integrative care.

- **Alternative medicine.** Alternative medicine is used in place of (as an alternative to) conventional medicine. Alternative medicine is ***NOT science-based***. Alternative medicine is any practice that aims to achieve the healing effects of medicine despite lacking biological plausibility, testability, repeatability, or evidence of effectiveness. Unlike orthodox and integrative medicine, which employs the scientific method to test plausible therapies by way of responsible and ethical clinical trials, producing repeatable evidence of either effect or of no effect, *alternative therapies reside outside of medical science* and do not originate from using the scientific method, but instead rely on testimonials, anecdotes, religion, tradition, superstition, belief in supernatural "energies" and pseudoscience. Some alternative practices are based on theories that contradict the established science of how the human body works.

The Societal Impact of Cancer

Cancer is a global threat that seriously affects human life, with a prevalence of more than 10 million deaths every year. Nearly 2 million Americans were diagnosed with cancer in 2023, with approximately 609,820 deaths (see Table 1). (11)

Cancer is the second most common cause of death in the United States, exceeded only by heart disease. At least 42% of newly diagnosed cancers in this country are potentially avoidable, including 19% of cancers caused by smoking and at least 18% caused by a combination of excess body weight, alcohol consumption, poor nutrition, and physical inactivity. (11)

Types of Cancer (MALES)	# of cases	% of cases	Types of Cancer (FEMALES)	# of cases	% of cases
Lung & bronchus	61,170	21	Lung & bronchus	59,910	21
Prostate	34,700	11	Breast	43,170	15
Colon & rectum	28,470	9	Colon & rectum	24,080	8
Pancreas	26,620	8	Pancreas	23,930	8
Liver	19,000	6	Ovary	13,270	5
Leukemia	13,900	4	Uterus	13,030	5
ALL SITES	**322,080**		**ALL SITES**	**287,740**	

Table 1: Leading sites of cancer deaths - 2023 estimates (Source: American Cancer Society)

In addition, due to the 'chemicalization' of our society, humans are exposed to numerous carcinogens daily. (12) While these environmental carcinogens have likely contributed to the increasing risk of cancer, the impact is difficult to quantify.

The doctor who goes by the pen name 'Justus Hope' and who wrote a book on cancer and repurposed drugs, said almost everyone who gets cancer shares at least one common risk factor. These include cigarette smoking (40%), insulin resistance (40%), viruses (10%), and hereditary cancers such as familial adenomatous polyposis, BRACA mutations, etc. (10%). (13)

Curiously, it is not being overweight or obese that is most related to cancer; it is the presence of insulin resistance. (13) Furthermore, patients who have insulin resistance and an elevated

TG/HDL ratio (a measure of cholesterol levels) are at an increased risk of not only heart disease and Alzheimer's disease but also cancer. (13, 14)

Current cancer treatments are highly complex and based on multiple modalities (see Figure 2), many of which are extremely expensive, have limited benefit (in terms of quality of life and five-year survival rate), many are highly toxic. The National Cancer Institute estimated that in 2020 cancer-related medical costs in the U.S. were $208.9 billion, which is likely a gross underestimate due to the increasing costs of individual medications. (11)

In 2000, only two oncology drugs garnered more than $1 billion in sales. Just 10 years later, the top 10 oncology drugs each exceeded $1 billion in revenue. By 2010, there were three oncology drug sales representatives for every 10 oncologists in the United States. Cancer, you see, is big business. Patients and their families frequently face extreme financial burdens and distress as a result of cancer treatment — this is known as “financial toxicity.” (15)

Despite the vast spending on treating common cancers like lung, breast, colorectal, prostate, and pancreas, age-adjusted death rates have remained remarkably stable or have even increased since 1930. (11) Compared to the improvements in preventing and treating heart disease, cancer mortality has remained relatively unchanged over the past 30 years. (16)

Based on data collected between 1992 and 1997 for the 22 most common malignancies, Morgan et al estimated the overall contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults was estimated to be 2.3% in Australia and 2.1 % in the U.S. (17) More recent data from the U.S. indicate that the 5-year cancer survival rate has only increased from 63% to 68% over the last 25 years (1995 to 2018). Ladanie et al. showed that over the past 15 years, the improvement in overall survival by new cancer therapies is a meager 2.4 months.(18) The study by Del Paggio et al reports an improvement of 3.4 months over the last 30 years. (19) This data suggests that despite the billions of dollars spent on cancer therapy, the “traditional” approach has largely failed; alternative, less expensive, less toxic, and more effective therapies are urgently required.

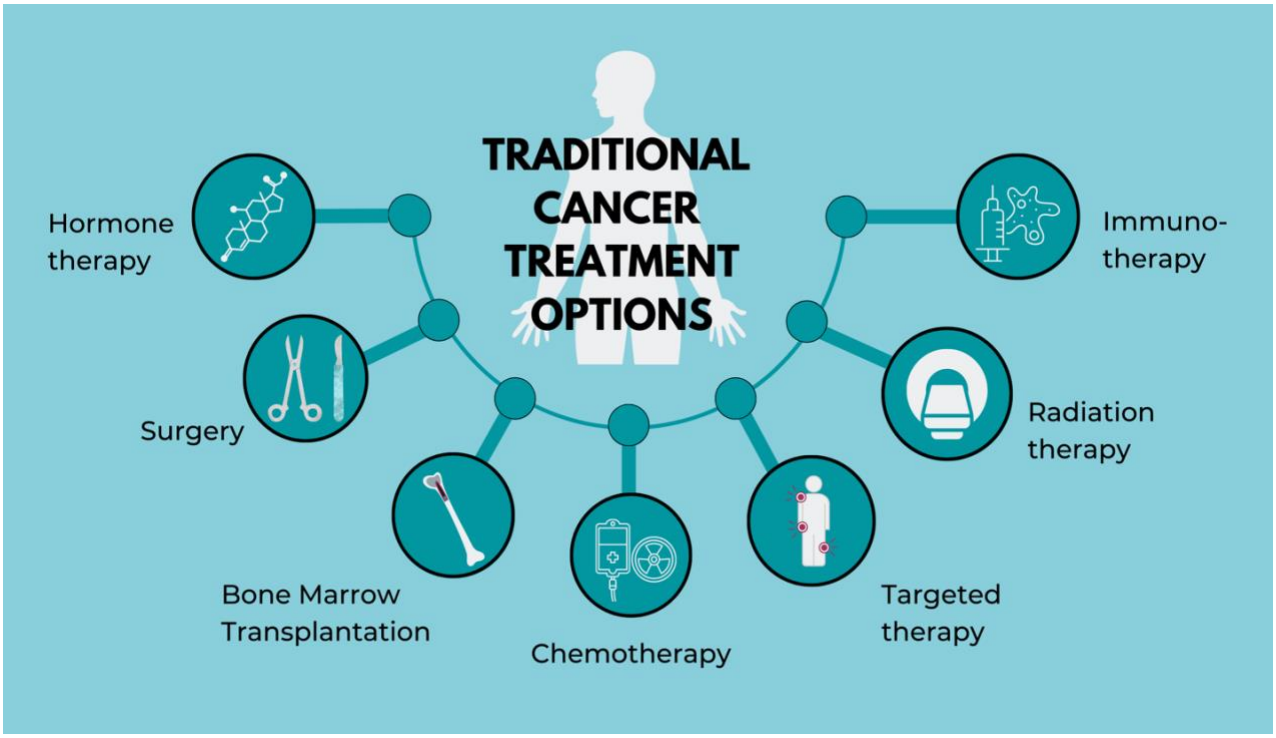


Figure 2: "Modern" cancer treatments are expensive and have limited benefit (Source: FLCCC)

CHAPTER 2: WHAT IS CANCER: UNDERSTANDING ITS PATHOGENETIC CAUSES

A basic tenet in medicine is that to treat a disease, one needs to understand the disease. Cancers are, simply, a disease of uncontrolled cell growth and division, wherein the various natural processes for containing them have partially or completely failed.

The conventional theory is that cancer is caused by genetic mutations and/or genomic instability, which drives a population of cells with the following six "classic" biological properties: (20)

1. Sustaining proliferative signaling
2. Evading growth suppressors
3. Resisting cell death (apoptosis)
4. Enabling replicative immortality
5. Inducing angiogenesis
6. Activating invasion and metastasis

Hanahan and Weinberg, who elucidated these "hallmarks of cancer," excluded the most important and universal finding in all cancer cells, (21) namely the metabolic reprogramming of cancer cells, with aerobic glycolysis — the so-called "Warburg effect" that we will explore below. (22, 23)

Conventional thinking suggests cancer arises from a single cell due to specific mutations in that cell, which are then characteristic of the patient's "cancer genome." The loss of genomic "caretakers" or "guardians," involved in sensing and repairing DNA damage, has been proposed to explain the increased mutability of tumor cells. The loss of these caretaker systems allows genomic instability, thus enabling pre-malignant cells to reach the six essential hallmarks of cancer.

The Cancer Genome Atlas Program (TCGA), modeled after the human genome project, was an attempt to determine the characteristic mutations of common cancers. (24) The TCGA assessed mutational signatures using 84,729,690 somatic mutations from 4,645 whole-genome and 19,184 exome sequences that encompassed most types of cancer. (25, 26) The finding of this massive project raises serious doubts concerning the mutation theory of cancer.

The TCGA identified 49 single-base-substitution, 11 double-base-substitution, 4 clustered-base-substitution, and 17 small insertion-and-deletion signatures. However, no specific mutation was characteristic of any particular cancer (except CML and the Philadelphia chromosome). In many tumors no mutation was found, and there was marked heterogeneity of mutations between tumors of the same cell type (intertumoral heterogeneity) and within the same tumor (intratumoral heterogeneity). (7) In pediatric tumors such as medulloblastoma, the number of driver genes was low (zero to two). In common adult tumors, such as pancreatic, colorectal,

breast, and brain cancers, the number of mutated driver genes was frequently between three to six, but several tumors had only one or two driver mutations. The notion that cancer is caused solely by mutations to key genes is becoming harder to maintain. (7) The inconsistencies are too numerous and pronounced.

An Alternate Theory: Cancer is a Metabolic Disease

Travis Christofferson, in his book titled "Tripping over the Truth", articulated the following:

"*No researcher can point to any single mutation or combination of mutations and say with confidence that it is alone the cause of cancer. Nor can researchers point to a series of cellular systems rendered dysfunctional by mutations and make the same claims with confidence*." (7)

In a 2009 op-ed for The New York Times, James Watson, a Nobel Prize winner known as the "father of DNA," suggested that "*we may have to turn our main research focus away from decoding the genetic instructions behind cancer and toward understanding the chemical reactions within cancer cells*." (27)

Although very specific processes underlie malignant transformation, many non-specific influences can initiate diseases — including radiation, chemicals, viruses and inflammation. Indeed, it appears that prolonged exposure to almost any provocative agent in the environment can potentially cause cancer. (28) That a very specific process could be initiated in very unspecific ways was considered "the oncogenic paradox" by Szent-Gyorgyi. (28) This paradox remains largely unresolved. (29)

Still, the concept of genetic mutations and genetic instability underpins most conventional cancer treatments. Big Pharma and the medical establishment have propagated this concept to promote the use of very expensive and toxic chemotherapeutic drugs; as mentioned above, cancer is profitable for the pharmaceutical industry. Curing cancer is not the goal.

There is considerable evidence that the genetic mutation theory may not be entirely correct. Dr. Thomas Seyfried provides a compelling argument that cancer is primarily a metabolic rather than a genetic disease. (29, 30) His underlying hypothesis is that cancer is a mitochondrial disorder with impaired oxidative phosphorylation and energy production; the genomic abnormalities are likely secondary to disordered energy production and cellular metabolism. Dr. Seyfried has clearly demonstrated that disordered mitochondrial function and energy production are common to all cancers. (29, 30) The view of cancer as primarily a metabolic disease will dramatically impact the approach to cancer management and prevention. However, it is clear that a very complex and bi-directional relationship exists between genetic instability and mitochondrial dysfunction.

The idea that cancer is a metabolic disease was first noted in 1927 by Otto Warburg who was awarded the Nobel Prize in Physiology or Medicine in 1931 for his discoveries. (22, 23) Dr. Warburg, reported that cancer cells are dependent on aerobic glycolysis (breakdown of glucose

to lactate) with impaired oxidative phosphorylation (pyruvate does not enter the Krebs cycle in the mitochondria). (22, 23) In simple terms, this means cancer feeds on glucose.

In contrast to normal differentiated cells, which rely primarily on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes, most cancer cells instead rely on aerobic glycolysis, a phenomenon termed “the Warburg effect.” (31) Dr. Warburg proposed that irreversible damage to respiration was the prime cause of cancer. Aerobic glycolysis in cancer cells involves elevated glucose uptake with lactic acid production in the presence of oxygen. (29)

Following his extensive research on tumor metabolism, Dr. Warburg stated: “Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in the normal body cell by fermentation of sugar.” (22, 23)

This metabolic phenotype is the basis for tumor imaging using labeled glucose analogs and has become an important diagnostic tool for cancer detection and management. Genes for glycolysis are overexpressed in the majority of cancers examined. (29) Numerous studies show that tumor mitochondria are structurally and functionally abnormal and incapable of generating normal levels of energy. (32-37) In addition, there is compelling evidence that mitochondrial dysfunction, operating largely through the RTG response (mitochondrial stress signaling), underlies the mutator phenotype of tumor cells. (38-42) Impaired mitochondrial function can induce abnormalities in tumor suppressor genes and oncogenes.

It is well documented that tumorigenicity can be suppressed when cytoplasm from enucleated normal cells is fused with tumor cells to form cybrids, suggesting that normal mitochondria can suppress the tumorigenic phenotype. (43, 44) Singh and co-workers provided additional evidence for the role of mitochondria in the suppression of tumorigenicity by showing that exogenous transfer of wild-type mitochondria to cells with depleted mitochondria (rho0 cells) could reverse the altered expression of the APE1 multifunctional protein and the tumorigenic phenotype. (45) It is also well documented that nuclei from cancer cells can be reprogrammed to form normal tissues when transplanted into normal cytoplasm, despite the continued presence of the tumor-associated genomic defects in the cells of the derived tissues. (46, 47)

Viruses have long been recognized as the cause of some cancers. It is interesting that several cancer-associated viruses localize to, or accumulate in, the mitochondria. Viral alteration of mitochondrial function could potentially disrupt energy metabolism, thus altering expression of tumor suppressor genes and oncogenes over time. Viruses that can affect mitochondrial function include the Epstein-Barr virus (EBV), Kaposi’s sarcoma-associated herpes virus (KSHV), human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human T-cell leukemia virus type 1 (HTLV-1) as well as SARS-CoV-2. (48-50)

A cell’s first line of defense against becoming cancerous is apoptosis. The apoptotic pathway is kept in check by anti-apoptotic factors; these two systems function in balance, and when one or

the other becomes dominant, the cell either apoptoses, or it resists apoptotic signals. *The metabolic approach to cancer treatment promotes apoptotic pathways.*

In addition to the ultrastructural abnormalities in mitochondria and mitochondrial-associated membranes, no cancer cell has been found with a normal content or composition of cardiolipin, the cristae-enriched phospholipid that contributes to oxidative phosphorylation (OxPhos). Cardiolipin is recognized as essential for the proper function of the electron transport chain (ETC) super complex structures, which are linked directly to cristae ultrastructure. (51) Apart from these documented abnormalities in mitochondria structure and function, genetic abnormalities that alter mitochondrial function have also been recognized in many cancers. The p53 mutation, which is found in many cancers, can disrupt mitochondrial OxPhos. The retinoblastoma tumor suppressor protein, Rb, has been linked to abnormalities in mitochondrial mass and OxPhos function. (51) It appears that few, if any, cancer types are free of mitochondrial abnormalities, whether structural or functional, making OxPhos inefficiency the signature metabolic hallmark of cancer. As tumor cells require a significant ATP/ADP ratio for invasion, an alternative system for ATP synthesis must be in place to compensate for OxPhos inefficiency. A reliance on cytoplasmic (glycolysis) and mitochondrial substrate level phosphorylation (SLP) can provide both the necessary ATP and the metabolic building blocks needed for tumor cell proliferation and invasion in either aerobic or anaerobic growth environments. (51)

Cells using oxygen consumption for ATP synthesis will die quickly under hypoxia or when treated with cyanide. As many cancer cells can survive when treated with cyanide or in hypoxia, ATP synthesis in these cells must come from sources other than OxPhos. (51) The genomic instability and random somatic mutations seen in most cancers arise largely as downstream epiphenomenon of ROS production and OxPhos dysfunction.

Since the 1950s, it has been recognized that tumors require large amounts of glutamine for growth and survival (hence the inclusion of glutamine in most culture media). The high-affinity glutamine transporter Slc1a5 (ASCT2) is upregulated in multiple types of cancer including glioblastoma multiforme (GBM) and has been implicated in mediating net glutamine uptake. (52) Several decades later, it was recognized that glutamine is a major energy source in tumor cells including GBM. (29, 30, 51-54) The interconversion of glutamine and glutamate is bidirectional in normal cells, with glutamine synthetase catalyzing glutamine formation. In tumors, however, overexpression of glutaminases and suppression of glutamine synthetase favor the forward reaction toward glutamate. Glutaminase activity correlates well with tumor growth rates in vivo. Glutamine not only provides nitrogen for synthesis of nucleotides and NEAAs but also provides a-ketoglutarate to serve as a precursor for ATP synthesis through substrate-level phosphorylation in the citric acid cycle.

Abnormalities in the cancer cell mitochondrial network would reduce OxPhos efficiency, thus forcing the cell to rely more heavily on SLP for ATP synthesis. The succinate-CoA ligase (SUCL) is a mitochondrial matrix enzyme that catalyzes the conversion of succinyl-CoA and ADP to CoA-SH, succinate, and ATP. Notably, when the SUCL proceeds toward ATP formation it is termed

‘‘mitochondrial substrate-level phosphorylation” (mSLP), a process that can yield high-energy phosphates in the absence of oxygen. Energy generation through mSLP is critically important in several metabolic pathways and could compensate for inefficient energy production through Ox-Phos in cancer cells. The glutaminolysis pathway would support production of high-energy phosphates through the sequential metabolism of glutamine → glutamate → α-ketoglutarate → succinyl CoA → succinate. (29, 30, 51-54) Glutamine has long been considered an essential metabolite for tumor cell growth. (55) Glutaminase is an enzyme that catalyzes the production of glutamate from the amino acid glutamine, which then feeds into the TCA cycle.

Chen et al. showed that glutamine utilization is a common feature of cells with partial defects in OxPhos, irrespective of the specific OxPhos complex affected. (56) OxPhos inefficiency could account in large part for the glutamine addiction of cancers. Glutamine-supported mSLP can compensate for OxPhos deficiency in either hypoxic or normoxic growth environments.

It is well recognized that most, if not all, tumor cells are dependent on glucose and glutamine for growth. Although amino acids other than glutamine can also provide energy through mSLP, glutamine is the only amino acid not requiring expenditure of energy for the metabolic interconversions necessary to produce succinyl-CoA. (51)

Mitochondrial substrate level phosphorylation (mSLP) in the glutamine-driven glutaminolysis pathway, substantiated by the succinate-CoA ligase reaction in the TCA cycle, can partially compensate for reduced ATP synthesis through both Ox- Phos and glycolysis. A protracted insufficiency of OxPhos coupled with elevated glycolysis and an auxiliary, fully operational mSLP, would cause a cell to enter its default state of unbridled proliferation with consequent dedifferentiation and apoptotic resistance, i.e., cancer. (51) The simultaneous restriction of glucose and glutamine offers a therapeutic strategy for managing cancer.

Insulin and cancer

Insulin, insulin-growth factor-1 (IGF-1), phosphoinositide 3-kinase (PI3K) and mTOR are nutrient sensors and cellular growth factor associated with initiation and propagation of cancer.(57) Established risk factors for cancers include obesity, sedentary lifestyle and type 2 diabetes mellitus which are characterized by hyperinsulinemia and insulin resistance. (58) Higher circulating insulin and C-peptide (a marker of insulin resistance and long-term insulin secretion) have also been associated with an increased risk of cancer. The association between hyperinsulinemia and cancer suggests that a diet inducing an elevated insulin response may contribute to tumor growth. A recent study showed that higher dietary glycemic load was associated with an increased risk of recurrence and death in stage III colon cancer patients. (59) Yuan et al determined the association of post-diagnosis dietary insulin scores with survival among 2006 patients from two large prospective cohorts who were diagnosed with colorectal cancer.(58) The insulin score was developed to quantify postprandial insulin response for various food items. In the study by Yuan et al the adjusted Hazard Ratios (HRs) for colorectal cancer specific mortality comparing the highest to the lowest quintiles of the dietary insulin load was 1.82 (95% CI: 1.20–2.75, p=0.006).

Carcinogens
Carcinogens and other environmental factors are strongly associated with the development of cancer. These factors are likely due to chronic cellular injury and mitochondrial damage. See Table 3.

COVID-19, Spike Protein and "Turbo Cancers"

Published case reports and social media reports have reported that exposure to the spike protein, particularly following mRNA vaccination for COVID-19, is associated with "turbo cancers" (hyperprogressive disease). (60-69) These include new cancers that are highly malignant, often in young patients and rare cell types/locations, as well as tumor recurrences in patients after remission. It has also been proposed that long COVID-19 can predispose recovered patients to develop cancer and accelerate cancer progression. (70) The U.S. Department of Defense Medical Epidemiology Database (DMED) reported a 664% increase in malignant neoplasms following the deployment of COVID-19 mRNA vaccination in the military (until this data was erroneously removed). This information is now supported by an analysis of the VAERS database which has demonstrated a strong "safety signal" for many cancers but particularly for breast, colon, liver lung and kidney cancer. (71) Death trends for cancers in the USA (ICD codes C00-D48) for individuals aged 15-44 demonstrated a rise which started in 2020 (1.7%) and accelerated substantially in 2021 (5.6%) and 2022 (7.9%). (72) A similar trend has been reported in the UK.(73) It is likely that this trend has continued into 2023 and 2024. It should be noted that cancer is largely a disease of the aged and the increase in cancers deaths in this young cohort of patients is alarming. A recent Japanese study demonstrated a significant increase in age-adjusted mortality rates from cancer as a whole, as well as some specific types of cancer, namely leukemia, as well as ovarian, prostate, oropharyngeal, pancreatic, and breast cancers.(74) In this study some excess cancer mortalities were observed in 2021 after mass vaccination with the first and second vaccine doses, and significant excess mortalities were observed for all cancers after mass vaccination with the third dose in 2022. The increasing risk of cancer with the increasing number of "shots" may be related to increasing immuno-suppression likely caused by immunological imprinting (antigenic sin).(75, 76) In addition, the systemic toxicity of spike protein (spikopathy) increases with the number of vaccines.(77)

It has been suggested that SARS-CoV-2 converts normal cells into cancer cells by modulating central metabolic pathways or hampering genomic integrity mechanisms, consequently inhibiting the apoptotic machinery and/or enhancing cell proliferation. (70, 78) It is likely that decreased CD8+ cells with impaired immune surveillance plays a major role in turbo cancers. This may explain the explosion of turbo cancers after repeated "boosters" rather than the primary vaccine series. Angues and Bustos have suggested a multi-hit hypothesis to explain the increased risk of cancer associated with COVID mRNA vaccination.(79) The specific pathogenic mechanisms by which SARS-CoV-2 and/or the spike protein leads to increased tumorigenesis have not been well studied, however, several possible mechanisms exist. The spike protein damages mitochondria and alters mitochondrial function; this may play a central role in cancer cell development and propagation. (80-83) SARS-CoV-2 results in dysregulated innate and adaptive immunity. Depletion of CD8+ and natural killer cells reduces immune surveillance and

alters the tumor microenvironment to promote tumor proliferation and metastases. (84) The retinoblastoma protein (pRB) is a tumor suppressor protein that prevents excessive cell growth by inhibiting cell cycle until a cell is ready to divide. The non-structural protein 15 (Nsp15) of coronaviruses induces the nuclear export and ubiquitination of pRB leading to its degradation via proteasomes. (85) A second potential oncogenic mechanism has been hypothesized for SARS-CoV-2 consisting of the degradation of the tumor suppressor protein p53 mediated by NSP 2 and Nsp3. (86) The open reading frame 8 (ORF8) protein of SARS-CoV-2 interacts with p62, the main autophagic cargo receptor, thereby inhibiting autophagy. (87) Jiang et al reported that spike protein localizes in the nucleus and inhibits DNA damage repair by impeding key DNA repair protein BRCA1 and 53BP1 recruitment to the damage site. (88) Spike protein impairs type I IFN signaling increasing the risk of cancer as type I IFN signaling suppresses proliferation of cancer cells by arresting the cell cycle, in part through upregulation of p53 and various cyclin-dependent kinase inhibitors. (89, 90) Metabolic reprogramming is a distinctive feature of SARS-CoV-2, and this may play a role in tumorigenesis. Metabolic reprogramming includes amino acid and lipid metabolism, carbohydrate, and energy metabolism, and immune-related pathways. (70) More recently Simian Virus 40 (SV40) DNA plasmids have been isolated in the vials of the COVID-19 vaccines (social media reports). SV40 is a known oncogenic virus. (91) IgG4 Antibodies are induced by repeated COVID-19 vaccination.(92, 93) IgG4 plays an essential role in cancer immune evasion. (94-96) IgG4 induces tolerogenic M2-like macrophages and correlates with disease progression in colon cancer. (97) In addition, Zang et al have demonstrated that the combination of glutathione and IgG4 promotes tumor growth through the effect of the Fc-Fc reaction between IgG4 and other tissue-bound IgG subtypes resulting in local immunosuppression. (98)

In a patient with cancer, it may be difficult to establish a causal role with SARS-CoV-2/spike protein. However, the tumor can be stained for spike protein, establishing this causal association. As these “turbo” cancers are frequently highly malignant, an aggressive treatment is suggested including the guidance offered in this monograph.

Table 3. Exposure to 'carcinogens" and environmental factors and impact on cancer.

Factor	Trend	Impact on cancer in isolation	Exposure level
Smoking	Global decrease of 28% for men and 38% for women between 1990 and 2019 (100)	RR=46 for small cell lung cancer (SCLC) for male current smokers compared to men who have never smoked. RR=22 for SCLC for female current smokers compared to women who have never smoked (101)	11.5% of US adults smoke (2021) (102)
Pesticide exposure-occupational	Increase in pesticide use 7% between 1996 and 2011 (103)	Non-Hodgkins Lymphoma associated with glyphosate exposure: RR=1.3 (104) RR=2.02 (105)	2.4 million farmworkers in USA (2013) (106) 0.6% of USA farming acreage is organic
Glyphosate use	Glyphosate tonnage grew by 17% on average annually between 1990 and 2014 (107)	Organic food consumption associated with a decreased risk (RR=0.79) of non-Hodgkin Lymphoma (108)	On average 1.0kg per hectare of farmland applied in USA (107) 59% of corn and soy samples test positive for glyphosate and glufosinate residues
Beauty products	Global annual growth rate of 4.5% over the last 20 years Decrease of 13% in North America from 1998 to 2007	Breast cancer hazard ratio 1.15 for frequent white female users of beauty products relative to infrequent users (109)	85% of adolescent girls use body products on a daily basis (110)
Fire retardants in furniture	Production of chlorinated organophosphate flame retardants increases from 14,000 tons per year (mid-1980's) to 38,000 tons per year (2012) (111)	Flame retardants decabromodiphenyl ether and tris(2-chloroethyl) phosphate associated with greater risk (RR=2.3) of papillary thyroid cancer (112)	Ubiquitous in furniture owing to flame-retardant requirements of furniture (113, 114)
Radon exposure	Should be stable, Radon's source primarily geological (115)	Every 100 Bq/m^3 increase in Radon concentrated estimated to increase relative risk for lung cancer by 8-16% (116)	Second biggest cause of non-occupational lung cancer behind smoking (116)

Azo dyes	Azo dyes banned in EU (117)	Unknown	Azo dyes comprise majority of industrial dyes (118)
Antibiotics	Drop in recent years in USA. 5% decrease in number of prescriptions between 2011 and 2016. 25% drop between 2016 and 2020 Global increase from 9.8 defined daily doses (DDD) per 1000 per day in 2000 to 14.3 DDD per 1000 per day in 2018 (119)	RR=1.37 between lowest and highest exposure group for cancer (120)	In USA, 613 antibiotic prescriptions per 1000 persons in 2020
EMF exposure	Increasing (121)	Increased RR=2.0 for childhood leukemia for exposures of ≥0.4 μT compared to <0.1 μT (122)	Ubiquitous
Sedentary lifestyle	Increase in 39% in rates of meeting physical activity guidelines between 1998 and 2013. (123)	Combined healthy lifestyle reduced risk of cancer (RR=0.29 compared to those reporting no physical exercise or positive health behaviors) (124)	2/3 of adults do not meet physical activity guidelines (150 min per week of moderate to vigorous physical activity) (123)
Sleep deprivation	Relatively stable sleep duration in adults (125, 126) but decreases in sleep quality (127)	Increased risk of colorectal cancer (RR=1.08) and lung cancer (RR=1.11) in poor sleep category (128)	More than 1/3 of US adults sleep fewer than 7 hours per night (2014) (129)
Stress	Work stress has been on the rise in Europe (130)	Association between work stress and risk of colorectal (RR=1.36), lung (RR=1.24) and esophageal (RR=2.12) cancers (131)	71% of employees typically feel tense or stressed out during the workday (2019)

Caesarean birth	Increase in rate of caesarean section from 30% in 2003 to 37% in 2010 (132, 133)	Increased rate of childhood kidney cancer (RR=1.25) (134)	Approximately one-third of North American births in 2010 (135)
Family size	Decrease from 3.33 in 1960 to 2.50 in 2022	Hodgkin's Lymphoma risk lower for increased number of older siblings: RR=0.72 for three or more older siblings compared to none (136) RR=0.41 for five or more older siblings compared to none (137) acute monocytic leukemia RR=0.35 for three or more older siblings compared to none (137) acute lymphoblastic leukemia RR=0.69 for three or more older siblings compared to none (137)	Average family size of 2.50 in 2022
Mother's age at first birth	Increasing (138)	RR~1/3 for women giving birth before age 18 compared to those giving birth after 35 (139, 140)	Average age in USA is 27.1 years (2020)
Febrile illness	No trend in presentation rates to emergency department (141)	Lower rates on non-breast cancers for adults experiencing childhood febrile illness (142)	2.8 million children <2 years with fever present to emergency departments annually in USA (141)
Hormonal birth control	In the UK, hormonal birth control prescription proportion dropped 45% between 2000 and 2018. (143) Between 1995 and 2010, approximately 82% of sexually experienced women use the pill, staying relatively constant (144)	RR=1.20 for breast cancer for users compared to non-users (145)	one in four US women aged 15-44 using oral contraceptives (2013) (146)

Breastfeeding (mother)	Increase in proportion of mothers breastfeeding from 75% in 2010 to 81.1% in 2016	Decrease in 2% breast cancer risk for every 5 months breastfeeding. (147) Decreased risk of premenopausal breast cancer (RR=0.88) (148) RR=0.76 for invasive epithelial ovarian cancer (149)	81.1% of mothers breastfeed at birth (2016)
Breastfeeding (child)	See above box	No association (148)	83.2% of infants are ever breastfed (Born 2019)

Cancer Signal Pathways

Signaling pathways are a core system in which cells regulate various physiological processes and respond to external stimuli. Normally, cells have a complete set of regulatory mechanisms for initiating and/or inhibiting signal reception, cascade transmission, and ultimately gene expression, but in cancer cells, the signaling pathway is usually overactivated, and the balance is broken. Almost all the nutraceutical and repurposed drugs listed in this document have anticarcinogenic effects by promoting and/or inhibiting signal transmission through the targeted regulation of multiple links in important signal pathways. The most relevant pathways include the following:

Hexokinase-2 (HK2) pathway. In 1977, Pete Pedersen isolated the metabolic defect responsible for the Warburg effect: the hijacking of normal hexokinase by hexokinase II (HK2), followed by its massive overproduction. (7, 150) Hexokinase is the first step in glycolysis in the cytoplasm. Cancer cells have switched to an embryonic form of hexokinase (HK2), which then translocates from the cytoplasm to the outer mitochondrial membrane, where it is attached to the voltage-dependent anion channel (VDAC). (151-153) The VDAC is a pore-like opening in the outer membrane involved in shuttling nutrients and signaling molecules in and out of the mitochondria. HK2 is the major bound hexokinase isoform expressed in cancer cells that exhibit the Warburg effect. By stationing itself on the outer mitochondrial membrane, HK2 helps immortalize cancer cells, escapes product inhibition, and gains preferential access to newly synthesized ATP for phosphorylating glucose. (154) The attachment of HK2 to the VDAC on the outer mitochondrial membrane creates a state of apoptosis resistance and shunts ATP out of the mitochondria to the cytoplasm to support glycolysis. When bound to HK2, the VDAC gate is “locked”, preventing the release of cytochrome c, thereby preventing apoptosis, and effectively immortalizing the cell. Several drugs target HK2, separating the enzyme from the outer mitochondrial membrane; these include 3-bromopyruvate, curcumin, resveratrol, and its derivatives pterostilbene and quercetin.

The p53 pathway (the tumor suppressor pathway). (155) The p53 pathway is activated by sensor kinases which monitor the cell’s DNA for damage or errors. Upon detection of damage, they phosphorylate the nuclear localization factor of the p53 tumor suppressor protein, allowing it to translocate to the cell nucleus and begin expressing p21, p16, p15, and p19; this activates the cell cycle arrest pathway, initiating DNA repair, and preventing cell division. If the repair is deemed to have failed, BAX, BAK, and/or PUMA are expressed, among others, initiating the mitochondrial caspase cascade, which initiates apoptosis.

The TGF-β pathway. The TGF-β pathway plays a crucial role in regulating cell growth, differentiation, and apoptosis. (156) Upon binding to its cell surface receptors, TGF-β activates SMAD transcription factors, leading to the repression of anti-apoptotic genes and the activation of pro-apoptotic genes. This pathway acts as a tumor suppressor by promoting apoptosis in abnormal cells and inhibiting the growth of precancerous cells. Defects in this pathway can lead to uncontrolled cell growth and the development of cancer.

The Wnt signaling pathway. The Wnt/beta-catenin pathway is a family of proteins that is implicated in many vital cellular functions such as stem cell regeneration and organogenesis. The Wnt signaling pathway plays a crucial role in the regulation of cell proliferation and differentiation. (157) In normal conditions, Wnt signaling maintains the balance between cell proliferation and apoptosis to ensure healthy tissue growth. However, when the pathway is activated excessively or inappropriately, it can lead to the development of cancer. Wnt activation has been observed in breast, lung, and hematopoietic malignancies and contributes to tumor recurrence.(158) The Wnt pathway cross talks with the Notch and Sonic Hedgehog pathways, which has implications for therapeutic interventions in cancers.

The Notch signaling pathway. The Notch signaling pathway is a signaling mechanism that plays a role in cell differentiation, proliferation, and apoptosis. (159) Disruptions in the Notch pathway, such as mutations in Notch receptors or ligands, can lead to the dysregulation of cell proliferation and differentiation, contributing to the development of cancer. Notch signaling plays a crucial role in the development of colon cancer; targeting the Notch pathway may sensitize colon cancers to various adjuvant agents.(160)

The PI3K/AKT signaling pathway. The phosphoinositide 3-kinase (PI3K) signaling pathway is linked to both growth control and glucose metabolism. The activation of the PI3K/AKT signaling pathway occurs when growth factor receptors on the cell surface bind to their ligands, triggering the activation of PI3K. (161) Once activated, AKT phosphorylates and inhibits the activity of pro-apoptotic proteins, such as BAD and FOXO. AKT also activates mTORC1, which regulates cellular metabolism and promotes cell survival by stimulating the expression of anti-apoptotic genes Bcl-2 and Bcl-xL.

The Hedgehog Pathway. Hedgehog (Hh) is one of the few signaling pathways that is frequently used during development for intercellular communication. (162) Hh is important for the organogenesis of almost all organs in mammals, as well as in regeneration and homeostasis. Further, Hh signaling is disrupted in diverse types of cancer. Mebendazole decreases the activity of the Hedgehog pathway, which is common in gliomas, melanomas, lung cancers, ovarian cancers, and colorectal cancer. (163)

The insulin growth factor-1 (IGF-1) pathway. Insulin-like growth factor 1 (IGF-1) is produced primarily by the liver as an endocrine hormone, as well as in target tissues in a paracrine/autocrine manner. IGF-1 signaling is mainly mediated by binding to its specific receptor, the insulin-like growth factor 1 receptor (IGF-1R) leading to the activation of the AKT signaling pathway resulting in cell growth, proliferation, and inhibition of programmed cell death. An elevated level of circulating IGF-1 is an established risk factor for many cancer types, whereas a decrease in IGF-1 levels is associated with lower cancer incidence.

Cancer Immunity

Inflammation is an essential pillar of immune defense. However, chronic inflammation is considered a hallmark of cancer initiation and progression. Chronic inflammation demonstrates a potential to induce complex changes at the molecular, cellular, and organ level and thereby alter the tumor microenvironment (TME). Cancer cells frequently secrete several growth factors that stimulate myelopoiesis and recruit myeloid cells to TME (see Figure 3). (164, 165) Therefore, the TMEs of various cancers are characterized by the high infiltration of monocytes, macrophages, granulocytes, and dendritic cells. Most myeloid cells within TMEs are present in an immature form; however, cancer-derived growth factors modify these myeloid cells into cells that support carcinogenesis by enhancing proliferation, migration, and metastasis and enabling cancer cell survival and immune evasion. Therefore, in addition to abnormalities in apoptosis, patients with cancer have derangements in immunity with the immune system failing to recognize the cancer cell as foreign. The cells in Figure 3 play a major role in altering the TME and promoting carcinogenesis.

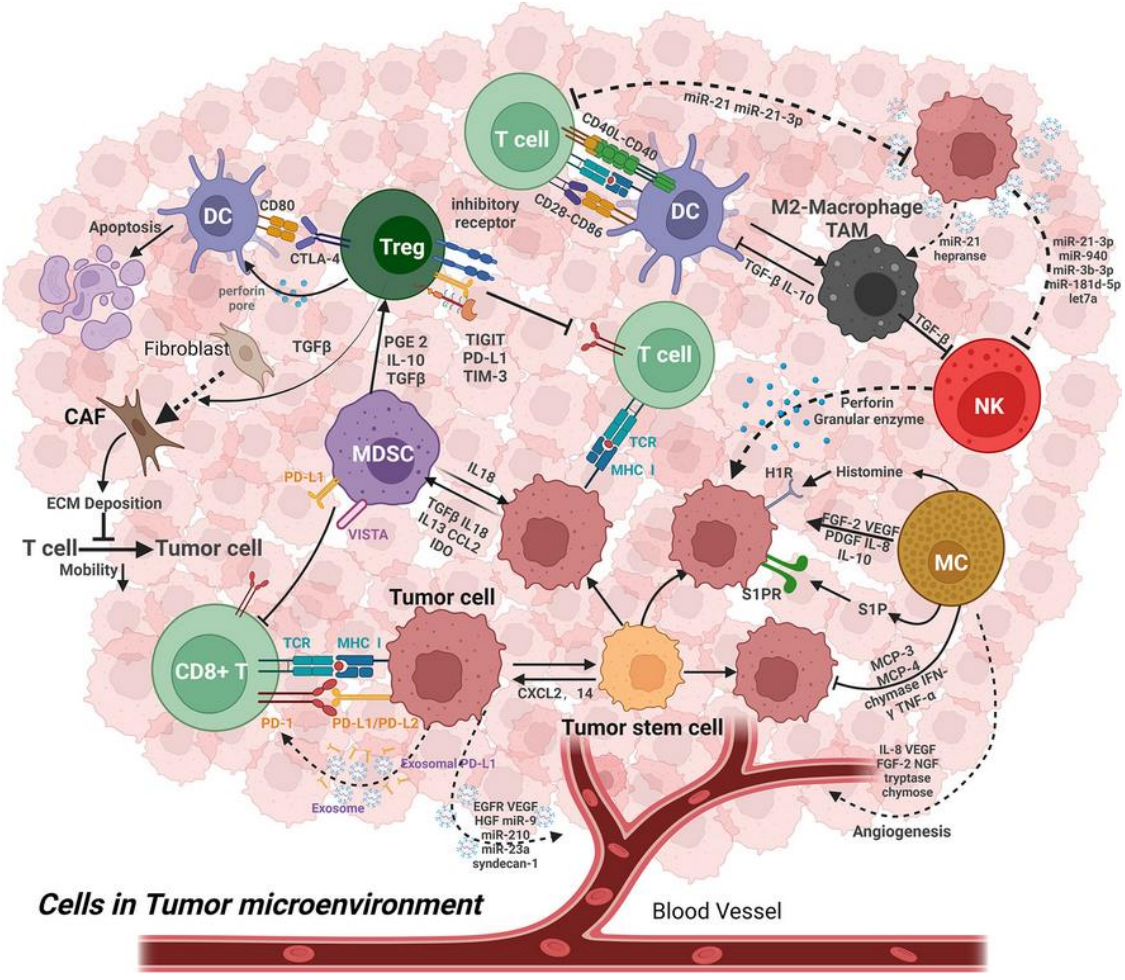


Figure 3. The cellular and structural components in the tumor microenvironment (source: Wang et al. Reproduced under Creative Commons Attribution International license) (165)

Myeloid-derived suppressor cells (MDSC). The establishment of primary tumor cells in distant organs, termed metastasis, is the principal cause of cancer mortality. Despite "curative" resection of the primary tumor, many patients have disseminated tumor cells at the time of diagnosis. Tumor cells can be found in the bone marrow of cancer patients at the time of their primary tumor resection. (166) These patients may then develop overt metastases months, years, or even decades later. This latency period, during which cancer cells do not grow and remain in a quiescent or equilibrium state, is known as "cancer dormancy." The timeline of metastatic dormancy is regulated by interactions between the tumor, its microenvironment, angiogenesis, and tumor antigen-specific T-cell responses. One such mediator of dormancy is myeloid-derived suppressor cells (MDSCs), whose number in infiltrating tumors has been associated with cancer stage, grade, patient survival, and metastasis in a broad range of tumor pathologies (see Figure 4). (167, 168)

Extensive studies have revealed a role for MDSCs in tumor escape from adaptive and innate immune responses, facilitating tumor progression and metastasis. (167, 169-173) Host immunity via tumor-specific cytotoxic T-lymphocytes can control disseminated tumor cell

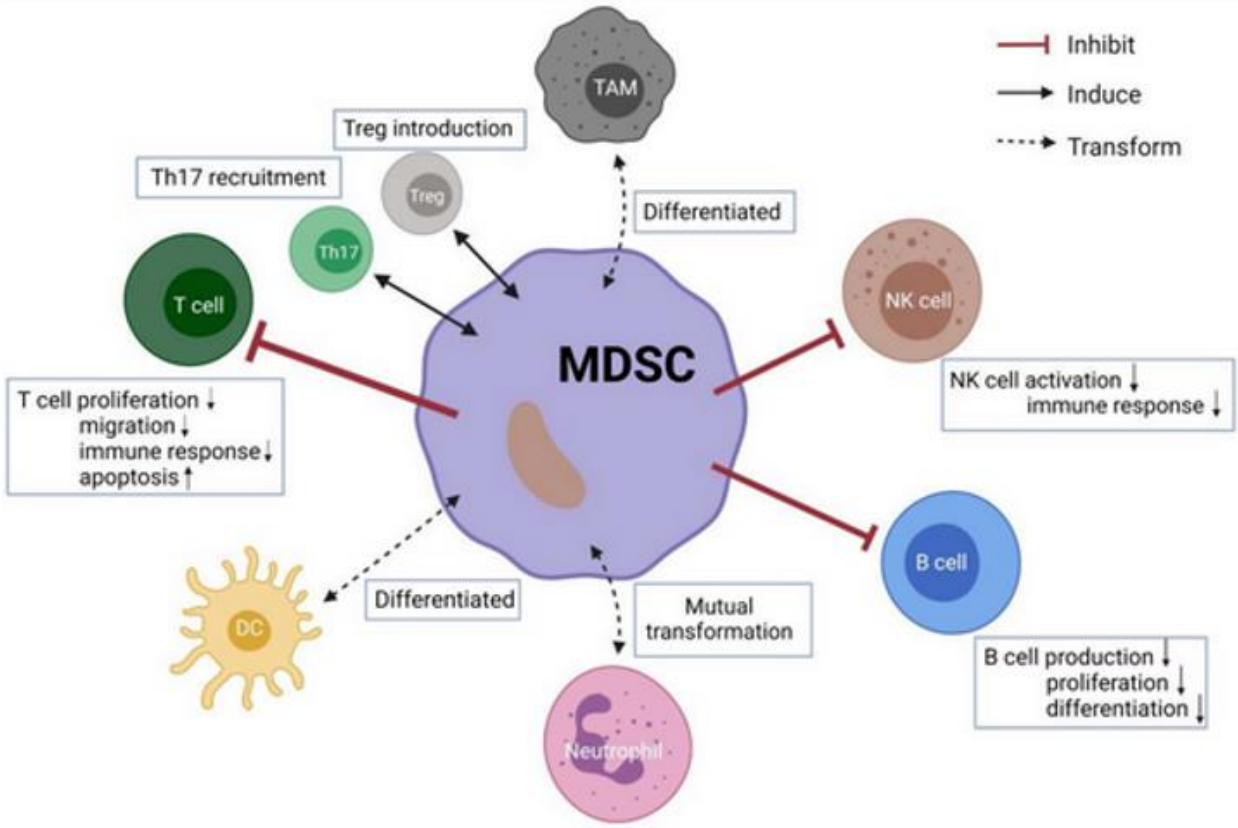


Figure 4. Crosstalk between MDSCs and other immune cells. Up arrows mean increased, and down arrows mean decreased. (Source Ma et al. Reproduced under Creative Commons Attribution International License) (168)

growth resulting in a dormant lesion that can be held in stasis for years or decades until released from dormancy in association with an increase in MDSCs reversing host T-cell responses. MDSCs contribute to immune evasion by inducing T-cell dysfunction through the production of reactive oxygen species, arginase-1 (ARG1), and nitric oxide synthase (NOS). ARG1 hydrolyzes extracellular L-arginine into urea and ornithine. L-arginine is required for T-cell proliferation, cytokine production, and expression of the T-cell receptor. (174)

MDSCs can not only inhibit clonal expansion of activated effector T cells, but also induce tumor-specific Treg lymphocytes to further establish and maintain T-cell tolerance in the tumor-bearing host. (172, 175, 176) In addition, by downregulating interferon, overexpressing inflammatory cytokines, and creating leaky vasculature by overexpressing matrix metalloproteinase 9 and other remodeling factors which compromise the integrity of the extracellular matrix and the basal membrane, MDSCs promote cancer cell invasion. (171)

T-regulatory cells (Tregs). Tregs universally labeled by CD4+CD25+Foxp3+CD127low/− are differentiated from traditional T lymphocytes. (177-180) To maintain immune homeostasis, Treg cells inhibit abnormal or excessive immune reactions to self- and non-self-antigens. By stifling the anti-tumor immune response of effector T cells, natural killer cells, and dendritic cells, Treg cells contribute to the growth and spread of tumors in the TME. (178, 180, 181) An unfavorable prognosis is associated with high Treg cell infiltration in the TME in patients with diverse cancer types. (181-187) Treg cells cause immune suppression by the production of immunosuppressive cytokines, the consumption of interleukin-2 and IL 2 receptors, modulation of CD80 and CD86 expression by dendritic cells, and direct killing of effector T cells. (181) Tregs also contribute significantly to angiogenesis via the vascular endothelial growth factor (VEGF)/VEGFR pathway.

Natural Killer Cells (NK cells). NK cells are the most relevant cancer-fighting cells of the innate immune system. NK cells play a vital role in recognizing and responding to abnormal cells, including cancerous and infected cells, in the immune system. T-cells possess T-cell receptors (TCRs) that allow them to bind MHC-I-peptide complexes on the cell surface, which determines whether an immune response will be initiated. Failures occur in the expression of the transporter associated with antigen processing (TAP) complex, and β2-microglobulin; these cause a loss of MHC-I self-antigen transport and surface presentation capacity, which causes the failure of the NK cell to destroy the cancerous cell.

Tumor-associated macrophages (TAMs) . Macrophages recruited from circulating monocytes to tumors and influenced by the presence of cancer to promote tumor malignancy and progression are often referred to as tumor-associated macrophages (TAMs) (see Figure 5).(188-190) Macrophages are divided into the M1 and M2 subgroups based on morphological, phenotypic, and functional variability. M2 macrophages have been shown to have protumor characteristics and to promote tumor development and metastasis, whereas M1 macrophages play a critical role in antitumor immunity and largely mediate proinflammatory activities in the tumor microenvironment (TME). (190-192) In metastatic tumors, macrophages have different

phenotypes and functions from primary tumors and are often called metastasis-associated macrophages (MAMs).
TAMs mostly arise from bone-marrow-derived monocytes with the chemokine CCL2 produced by tumor cells being the major recruitment factor. Bone-marrow-derived monocytes include both classical monocytes and monocytic MDSCs (M-MDSCs), (193) and are crucial for the negative regulation of immune responses. (194, 195)

The immune system is skewed toward a tumor-promoting response because of the release of IL-10 by MDSCs, which inhibits the secretion of IL-12 by macrophages. Macrophages also cause MDSCs to produce more IL-10, which raises levels of IL-6 and TNF- in macrophages. (194) MDSC IL-6 was reported to be elevated by tumor cells, and vice versa. (194) The ratio of tumor cells to MDSC and macrophages controls inflammation within solid tumors, and interactions between these cells have the potential to drastically change the inflammatory environment within the tumor microenvironment. (191, 194) A high infiltration of macrophages in human solid tumors is associated with poor clinical outcomes. (190-192, 194-203) Similarly, the expression of macrophage growth factors or their chemoattractants, such as CSF1 and CCL2, in tumors or in the circulation is often associated with poor prognosis. (188)

TAMs are the crucial and dominant immune cells in the TME and significantly contribute to tumor progression by promoting angiogenesis, mediating tumor immunosuppression by inhibiting T cell function, they secrete chemokines which contribute to the recruitment of T regulatory cells in the tumor microenvironment and promote tumor cell intravasation via VEGF expression (see Figure 5). TAMs are activated by mediators secreted from tumor-infiltrating lymphocytes such as Th2, Treg cells, IL-10, TGF-β. (204) By reducing antitumor immunity, Foxp3+ regulatory T (Treg) cells and TAMs both aid in the growth of tumors. Researchers identified TAMs and Tregs as responsible for direct tumor immune evasion. (205) TAMs and Tregs combine to form a cellular network that is partially redundant and contributes to the robustness of tumor immunosuppression as well as resistance to immunotherapy. (191, 205)

TAMs play a major role in tumor metastases. (206) Cancer-associated fibroblast are produced because of the mesenchymal transition of endothelial cells during the growth of tumors, and they secrete Heat shock protein-90 alpha (*Hsp90α)*, which promotes M2 polarization and maintains an immunosuppressive milieu. (207) By secreting different mediators that alter the tumor promoting TME, TAMs can accelerate the growth of tumors. Proangiogenic growth factors, such as VEGF, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor- (TGF-), NF-kB-mediated factors that prevent apoptosis, and proangiogenic growth factors (198) that promote cancer cell migration and metastasis. (191) TAMs can also increase the tumor stemness, which upregulates the release of immunosuppressive cytokines such as IL-1ra. (191, 208) By releasing growth factors like the epidermal growth factor receptor (EGFR), which encourages the proliferation of cancer cells, TAMs may directly drive the proliferation of cancer cells. (209) In hepatocellular carcinoma, active Wnt/-catenin signaling induced by a greater number of invading macrophages can promote the proliferation of tumor progenitor cells, and targeted macrophage reduction can diminish Wnt and slow tumor growth. (210)

By controlling the PI3k/Akt pathways in cancer cells, TAMs may block proapoptotic cytokines such tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). (211) By introducing miRNAs into cancer cells, such as colorectal cancer and pancreatic ductal adenocarcinoma cells, exosomes produced by M2 macrophages spread malignancy. (212) Metastatic cells use the Cysteine-cysteine motif chemokine ligand 20 (CCL20), also known as macrophage inflammatory protein-3α, MIP*3α*) - Chemokine receptor 6 (CCR6) axis/pathway to attract monocytes and differentiate them into metastasis-associated macrophages (MAMs) that support tumor cell survival and metastasis by suppressing T cells. (191, 197) Additionally, TAMs release several enzymes, such as matrix metalloproteinases (MMPs) and cyclooxygenase type-2 (COX-2), which all work to promote angiogenesis by destroying the matrix and enabling endothelial cells to invade. (213) Despite TAMs having pro-tumorigenic characteristics, they can ingest tumor cells, and cause tumor apoptosis by releasing NO, ROS, and IL-12, which encourage anti-tumor responses and limit tumor growth in specific situations. (214) This suggests that immunosuppressive and immunostimulatory TAM can coexist in the same tumor. (191, 194, 215)

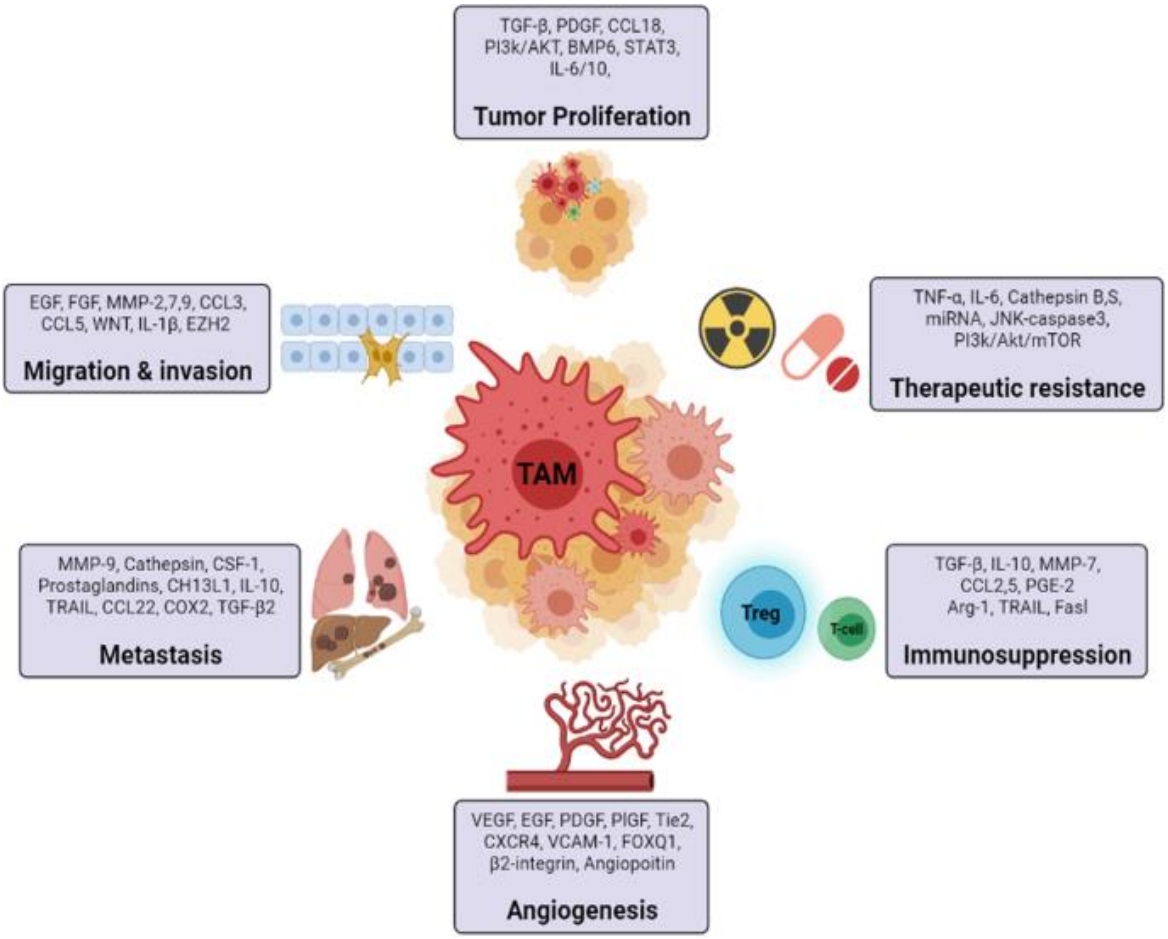


Figure 5. The role of tumor associated macrophages in cancer. (Source: Reproduced from Kumari et al under Creative Commons Attribution 4.0 International License). (190)

Platelets and Cancer

Platelets have been implicated in enabling successful metastasis and worsening the prognosis of patients with cancer by guarding tumor cells from immune elimination and promoting arrest and extravasation of tumor cells. (216-218) Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Platelet-derived TGFβ and direct platelet-tumor cell contacts synergistically activate the TGFβ/Smad and NF-κB pathways in cancer cells, resulting in their transition to an invasive mesenchymal-like phenotype and enhanced metastasis in vivo. (216) In a symbiotic manner, tumor-derived bioactive molecules have been shown to prompt an increase in platelet activation and production. (219, 220)

Angiogenesis and Metastasis

Angiogenesis involves neovascularization or the formation of new capillaries from existing blood vessels and is associated with the processes of tissue inflammation, wound healing, and tumorigenesis. Angiogenesis is required for most tumors to grow beyond an approximate size of 0.2-2.0 mm. In addition to its role in up-regulating glycolysis in response to hypoxia, HIF-1α is the main transcription factor for VEGF, which stimulates angiogenesis.

Metastasis is the general term used to describe the spread of cancer cells from the primary tumor to surrounding tissues and to distant organs and is a primary cause of cancer morbidity and mortality. To complete the metastatic cascade, cancer cells must detach from the primary tumor, intravasate into the circulatory and lymphatic systems, evade immune attack, extravasate at distant capillary beds, and invade and proliferate in distant organs. The macrophage hypothesis of metastasis suggests that metastatic cells arise following fusions of macrophages or bone marrow-derived hematopoietic cells with committed tumor cells. (206)

Cancer Stem Cells (CSC)

Cancer stem cells (CSC) were first identified in the 1990s, in acute myeloid leukemia (AML).(221) Further studies observed CSC in a wide range of malignancies including glioblastoma, breast, endometrial, pancreatic, prostate, lung and colon cancers, and a range of other tumor types. (221-223) Overall CSC are characterized as having distinct key properties including self-renewal, the ability to differentiate, active anti-apoptotic pathways, the expression of CD44, aldehyde dehydrogenase, CD133 and other markers also expressed by normal tissue specific somatic stem cells. (221, 224)

Despite arising initially from a single cell, almost all tumors become very heterogeneous, expressing different markers, and containing proliferative and more differentiated cells. Tumor heterogeneity may be responsible for tumor progression, metastasis, resistance to therapy, and relapse. (225) Fast-growing cancer cells make up the bulk of a tumor with a smaller population of cancer stem cells (CSC). CSCs are a cell population similar to stem cells with characteristics of

self-renewal and differentiation potential in tumor tissue. (226) Although CSCs are similar to stem cells in terms of function, because of the lack of a negative feedback regulation mechanism for stem cell self-renewal, their powerful proliferation and multidirectional differentiation abilities are unrestricted, which allows CSCs to maintain certain activities during chemotherapy and radiotherapy. When the external environment is suitable, CSCs will rapidly proliferate to reactivate the formation and growth of tumors. (224)

CSCs are defined by their functional properties and can self-renew and propagate the tumor over an extended period and recapitulate the different cell lineages found in the primary tumors. CSCs reside in particular tumor microenvironment niches that play an important role in regulating their proliferation, renewal, differentiation, and stemness. (225) Inflammation and hypoxia promote the acquisition of a CSC phenotype and its maintenance. (225) Chemotherapy induces changes in the tumor microenvironment that support CSC survival and tumor relapse.

The CSC colony is slow-growing and resembles normal cells in many respects. Chemotherapy and radiation all attempt to kill the fast-dividing cancer cells; however, they also kill fast-dividing normal cells, including the hair, lining of the gastrointestinal tract, and bone marrow.(13) However, like normal cells, chemotherapy spares CSC. Furthermore, both chemotherapy and radiation treatment have a stimulating effect on the CSC population, causing them to grow resistant new tumor cells and replace the bulk of what was removed (See Figure 1). (13, 225, 227) Dr. Hope considers this like the effect of “pruning a tree thereby stimulating new growth” (see Foreword). The tumors of patients with breast cancer brain metastasis were reported to be highly cancer stem-like cell-enriched, suggesting that brain metastases probably arise by the seeding of cancer cells with stem features. (228) In bladder cancer, the resistance of tumor cells to chemotherapy was caused by slow-cycling CSCs that were stimulated to proliferate in between cycles of chemotherapy. (229) The proliferative response of CSCs was promoted by prostaglandin E2 (PGE2) release by cancer cells that were killed by the chemotherapy. Targeting PGE2 by monoclonal blocking antibody or by the administration of cyclooxygenase-2 inhibitor attenuated chemoresistance and suggested that targeting this pathway in between cycles of chemotherapy may enhance the therapeutic response in bladder cancer.

The successful elimination of a cancer requires an anticancer therapy that will affect both differentiated cancer cells and CSC. At present, conventional therapy that includes radio-, chemo-, and immunotherapy kills rapidly proliferating and differentiated cells. These treatments may cause the tumor to shrink but will not prevent it from recurring. Thus, a combination of treatments that target both rapidly-proliferating cancer cells and the quiescent or slow-proliferating CSC is required. (154)

Adding repurposed drugs to attack CSC should be a priority and should be done at the time of initiation of chemotherapy and radiation therapy. (13) Common repurposed drugs that can attack CSC include green tea extract, melatonin, vitamin D3, metformin, curcumin, statins (atorvastatin), berberine, mebendazole, doxycycline, ivermectin, resveratrol, aspirin, diclofenac phosphodiesterase 5-inhibitors, and omega-3 fatty acids. (13, 230-233)

How Chemotherapy Activates Cancer Aggressivity

Another problem with chemotherapy is that the drugs make cancer more aggressive by activating massive inflammation in the body. Chemotherapy activates the inflammatory master controller, NF-KB, which produces the inflammatory cytokine IL-6. (234) This massive, chemotherapy-induced increase in inflammation has the following consequences: (154)

- Stimulates more rapid cancer growth (proliferation).
- Increases resistance to apoptosis (programmed cell death).
- Promotes more invasive and metastatic behavior of the cancer.
- Stimulates angiogenesis.
- Creates a chemo-resistant cancer cell population.

These findings suggest that patients should receive anti-inflammatory therapies concomitant with chemotherapeutic agents. In addition, almost all the repurposed anticancer drugs listed in this monograph potentiate the effects of standard chemotherapy agents, allowing a dose reduction of these agents.

CHAPTER 3: PREVENTING CANCER

As previously mentioned, at least 42% of newly diagnosed cancers in the United States could potentially be avoided. (11, 235) The most important interventions to reduce the risk of cancer include: quitting smoking, limiting (or stopping) alcohol consumption, improving nutrition, adopting time-restricted eating, treating metabolic syndrome/insulin resistance, engaging in moderate physical exercise, and supplementation with vitamin D3. (11) Smoked and processed meats should be avoided as they are related to several cancers, most notably gastric cancer. (236, 237) In addition, the topical application, consumption, and inhalation of carcinogenic substances should be limited as much as possible. (12) The World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) published ten Cancer Prevention Recommendations, updated in 2018, that encourage a healthy lifestyle pattern, including eating a healthy diet, maintaining a healthy body weight, and undertaking adequate physical activity.(238) Greater adherence to these recommendations was associated with a reduced risk of all cancers combined and of breast, colorectal, kidney, oesophageal, ovarian, liver, and gallbladder cancers. (235)

The DO-HEALTH trial was a three-year, multicenter, 2 × 2 × 2 factorial design double-blind, randomized controlled trial (RCT) to test the individual and combined benefit of supplemental vitamin D3 (2000 IU/day), and/or 1 g per day of marine Omega-3s, and/or a simple home strength exercise program. These were compared to placebo and control exercise. (239, 240) While each intervention individually reduced the risk of cancer, the combination was synergistically highly effective in reducing the risk of cancer (the adjusted hazard ratio of adjusted HR was 0.39). Although reported as a negative study, the Vitamin D and Omega-3 Trial (VITAL) funded by the NIH further corroborated the protective effect of vitamin D on cancer mortality, reporting lower rates of death caused by cancer among participants randomized to vitamin D3 vs placebo (HR, 0.72 [95% CI, 0.52-1.00]). (241) In addition, many other nutraceuticals appear to be highly effective in preventing cancer. Published peer-reviewed studies strongly support the use of green tea catechins in reducing the risk of numerous cancers. (242, 243) In addition, melatonin has numerous health benefits including increasing health span and decreasing the risk of neurodegenerative diseases; it is likely that this natural product may be highly effective in preventing cancer.

Metformin suppresses tumor initiation, growth, and spread and is recognized as an effective anticancer drug even for non-diabetics. Diabetics taking metformin had a lower all-cause mortality than normal non-diabetics not taking it. (244) Metformin has been demonstrated to reduce the risk of prostate cancer in men with type 2 diabetes. (245) Meta-analyses have examined the role of metformin in the primary prevention of cancer, where it was found to significantly reduce overall cancer incidence. (246, 247) Metformin should be considered as an add on in those patients at high risk of developing cancer. i.e., strong family history, previous cancer, increased genetic risk, etc.

Based on this data we suggest the following interventions for all individuals to reduce their risk of cancer:

- Quit smoking and high air pollution.
- Reduce or limit the use of alcohol.
- Lose weight: adopt a healthy diet, manage insulin resistance, and follow a time-restricted eating plan.
- Avoid processed food and processed vegetable oils. (248)
- Avoid sugary beverages and pure fruit juices. (249, 250)
- Limit consumption of red meat to no more than 3 portions/week. (238)
- Take Vitamin D3: 5000 u/day and adjusted according to vitamin D3 level (see Table 3). Target a Vit D level of 50-70 ng/mL.
- Take omega 3 fatty acids: 2-4 g/day.
- Take green tea catechins: 500-1000 mg/day. (242, 251) Green tea extract should be taken during/after a meal, rather than on an empty stomach. (252) See precautions in the section labeled 'Green Tea'.
- Take melatonin: 0.75–5 mg (extended/slow release) at night. (230, 253)
- Metformin 250-2000 mg/day: Metformin should be considered in anyone at high risk of cancer, whether their risk extends from diabetes, prediabetes, insulin resistance, chronic viral infection, smoking, or genetics. It requires a doctor's evaluation, approval, and prescription.(13)
- Do regular aerobic exercise and resistance training 30 minutes/day (walking, home strength training, etc.).
- Reduce stress (meditation, yoga, mindfulness exercises, etc.). (254-256)
- Get at least 8 hours of high-quality sleep (ensure adequate sleep hygiene). (256-259)
- Avoid known carcinogens. (12)

Familial adenomatous polyposis (FAP) is a hereditary condition that causes colon cancer at a young age. Many patients choose to have a total colectomy before the age of 20 rather than risk fatal cancer development. In a mouse model of FAP, the combination of mebendazole and sulindac (an NSAID) reduced the number of polyps by 90%. (260) (160) In an experimental adenomatous polyposis coli model, ashwagandha was associated with a 59% reduction of tumor and polyp initiation and progression. (261)

These preclinical findings support the consideration of clinical trials for patients with FAP as well as other high-risk cancer patients. The use of phosphodiesterase-5 inhibitors (e.g., sildenafil) is associated with a lower risk of colorectal cancer in men with benign colorectal neoplasms. (262)

Female patients with the BRACA 1 and 2 mutations are at an approximately 70% lifetime risk of developing breast cancer and a 20-40% risk of developing ovarian cancer. (263) However, it should be noted that the risk of these patients developing a malignancy has doubled over the last four decades, suggesting that environmental and lifestyle factors may increase the risk of

cancers in this population. The management of these patients is complex and needs to be individualized. Oral selenium is a good candidate for chemoprevention in women who carry a mutation in the BRCA1 gene.(264) The guidance as provided in the monograph should be considered even in those patients that elect to undergo prophylactic surgery. The non-selective beta-blocker propranolol has been demonstrated to reduce the risk of breast cancer, as well as metastases and mortality in those with breast cancer (see section on propranolol).(265, 266) Women at high risk of developing breast cancer should consider taking propranolol.

CHAPTER 4: THE METABOLIC APPROACH TO TREATING CANCER

Although mitochondrial replacement therapy could, in principle, restore a more normal energy metabolism and differentiated state to tumor cells, it is unlikely that this therapeutic approach would be available in the foreseeable future. (29, 30) However, if cancer is primarily a disease of energy metabolism, then rational approaches to cancer management can be found in therapies that specifically target energy metabolism.

The goal of metabolic adjunctive treatments is to "starve the cancer cell" by modulating energy pathways that are important to the survival of cancer cells and thereby reduce cancer growth and cancer metastases (the cause of death in over 90% of cancer patients). An approach to cancer treatment is emerging with research showing impressive results from the use of metabolically targeted drug cocktails alongside conventional chemotherapy. The metabolic protocol is designed to work primarily by restricting the overall ability of cancer cells to take up and use (i.e., 'metabolize') energy. By starving cancer cells of energy substrates, metabolic interventions may reduce the capacity of cancer cells to defend themselves against chemotherapy and radiation. The metabolic protocol may also act on the many dysregulated signaling pathways within cancer cells helping to enable apoptosis, or "programmed cell death," allowing chemotherapy and radiation to kill cancer cells more effectively.

The most important and central approach to the metabolic treatment of cancers is dietary calorie (glucose) restriction. This is supplemented with pharmacologic and nutraceutical compounds that target specific cancer pathways and interventions that restore "normal" anticancer immunity and prevent metastases.

It is important to emphasize that there is no single "magic bullet" and that multiple interventions act synergistically and simultaneously to promote cancer cell death. The combination of dietary interventions together with multiple repurposed drugs/nutraceuticals that act synergistically is strongly recommended. This approach is similar to that of the Care Oncology Clinic, which used the patented *Metabolic Oncology COC Protocol™* consisting of a combination of conventional pharmaceuticals (metformin, atorvastatin, mebendazole, doxycycline, and an NSAID) that theoretically work together to restrict the overall ability of cancer cells to take up and use energy. (267) However, similar to the work of Jane McLelland, (4) we suggest a more extensive and targeted list of pharmacologic and nutraceutical compounds combined with glucose restriction and a ketogenic diet. (Please note that the Care Oncology Clinic has now been dissolved in the United States and our mention of it herein is in no way an endorsement or recommendation.)

The metabolic approach to cancer should be considered as adjunctive to more "traditional" approaches to cancer treatment. The metabolic treatments will likely act synergistically with the more traditional approaches, thereby increasing tumor response rate, limiting the toxicities of standard chemotherapy, limiting the risk of metastasis, and leading to an improvement in

overall quality of life. This combined approach will allow for reduced dosages of standard chemotherapeutic agents, drastically reducing their toxicity (see metronomic dosing, Chapter 12).

Dietary Caloric Restriction, The Ketogenic Diet, and "Real" Food

Numerous studies show that dietary energy restriction is a general metabolic therapy that naturally lowers circulating glucose levels and significantly reduces the growth and progression of numerous tumor types, including cancers of the breast, brain, colon, pancreas, lung, and prostate. (268-274) An impressive body of evidence indicates that dietary energy restriction can retard the growth rate of many tumors regardless of the specific genetic defects expressed within the tumor. (268-274) Hyperglycemia with high insulin levels is associated with tumor recurrence. (59, 275) Sugar sweetened beverages are associated with an increased risk of cancer. (276-278) Both experimental and clinical data suggest that fructose, particularly fructose-corn syrup, is more carcinogenic than glucose. (250, 279, 280)

As demonstrated by Dr. Otto Warburg, almost all cancer cells are dependent on glucose as a metabolic fuel via aerobic glycolysis, (22, 23) with hyperglycemia being a potent promotor of tumor cell proliferation and associated with poor survival. (281) Although the mechanisms responsible for the caloric-restriction-mediated reduction in tumorigenesis have not been unequivocally identified, they may involve caloric-restriction-induced epigenetic changes as well as changes in growth signals and in the sirtuin pathway. (282)

Insulin resistance plays a major role in the initiation and propagation of cancer. (283) Reversing insulin resistance is therefore a major goal in patients with cancer. Dietary energy restriction specifically targets the IGF-1/PI3K/Akt/HIF-1α signaling pathway, which underlies several cancer hallmarks including cell proliferation, evasion of apoptosis, and angiogenesis. IGF-1 production is stimulated by growth hormone (GH) and can be inhibited by calorie restriction, suggesting it could play a central role in the protective effect of calorie restriction. In this regard, humans with mutations in the GH receptor (known as Laron syndrome) have low serum IGF-1 levels, and have a remarkably low risk of developing cancer. (282) Glucose reduction not only reduces insulin but also reduces circulating levels of IGF-1, which is necessary for driving tumor cell metabolism and growth. In diabetics, those on insulin or insulin secretagogues were demonstrated to be more likely to develop solid cancers than those on metformin. (284)

Dietary energy restriction targets inflammation and the signaling pathways involved with driving tumor angiogenesis. Indeed, calorie restriction is considered a simple and effective therapy for targeting tumor angiogenesis and inflammation. Calorie restriction results in the downregulation of multiple genes and metabolic pathways regulating glycolysis. Besides lowering circulating glucose levels, dietary energy restriction elevates circulating levels of fatty acids and ketone bodies (β-hydroxybutyrate and acetoacetate). Fats, and especially ketones, can replace glucose as a primary metabolic fuel under calorie restriction. This is a conserved physiological adaptation that evolved to spare protein during periods of starvation. Many tumors, however, have abnormalities in the genes and enzymes needed to metabolize ketone

bodies for energy. Elevation in ketone bodies is well known to be able to suppress blood glucose levels and glycolysis, which are major drivers of tumor growth. A transition from carbohydrates to ketones for energy is a simple way to target energy metabolism in glycolysis-dependent tumor cells while enhancing the metabolic efficiency of normal cells. Metabolism of ketone bodies and fatty acids for energy requires inner mitochondrial membrane integrity and efficient respiration, which tumor cells largely lack. Under fasting conditions, ketone bodies are produced in the liver from fatty acids as the main source of brain energy. Ketone bodies bypass the glycolytic pathway in the cytoplasm and are metabolized directly to acetyl CoA in the mitochondria.

The ketogenic diet is a high-fat, low-carbohydrate diet with adequate protein and calories originally developed in the 1920s as a treatment for intractable epilepsy.(285) The traditional ketogenic diet is a 4:1 formulation of fat content to carbohydrate plus protein. (285) A classic 4:1 ketogenic diet delivers 90% of its calories from fat, 8% from protein and only 2% from carbohydrate. Ketogenic diets of the 1920s and 1930s were extremely bland and restrictive diets and, therefore, prone to noncompliance. In recent years, alternative keto-genic protocols have emerged, making adherence to the diet much easier.(286) Alternatives to the traditional keto-genic diet includes a medium-chain triglyceride (MCT)-based ketogenic diet and the Atkins diet. Compared to long-chain triglycerides, MCTs are more rapidly absorbed into the bloodstream and oxidized for energy because of their ability to passively diffuse through membranes. Another characteristic of MCTs is their unique ability to promote ketone body synthesis in the liver. Thus, adding MCTs to a ketogenic diet would allow significantly more carbohydrates to be included. (286)

A ketogenic diet has tumor growth-limiting effects, protects healthy cells from damage by chemotherapy or radiation, accelerates chemotherapeutic toxicity toward cancer cells, and lowers inflammation. (286) Altered availability of glucose and induction of ketosis influence all the classically defined hallmarks of cancer.(287) Weber et al demonstrated that ketogenic diets slow melanoma growth in vivo regardless of tumor genetics and metabolic plasticity. (288) Moreover, ketogenic diets simultaneously affected multiple metabolic pathways to create an unfavorable environment for melanoma cell proliferation. In glioma cancer models a ketogenic diet has been shown to reduce angiogenesis, inflammation, peri-tumoral edema, migration and invasion. (289) Similarly, a ketogenic diet altered the hypoxic response and affects expression of proteins associated with angiogenesis, invasive potential and vascular permeability in a mouse glioma model. (290) The ketogenic diet may work in part as an immune adjuvant, boosting tumor-reactive immune responses in the microenvironment by alleviating immune suppression.(291) A meta-analysis on the use of ketogenic diet in animal models demonstrated significantly prolonged survival time and reduced tumor weight and tumor volume. (292) The ketogenic diet was effective across a broad range of cancers. The ketogenic diet is an effective adjuvant to radiation therapy for the treatment of malignant glioma.(293)

Ketone bodies have been shown to inhibit histone deacetylases and may decrease tumor growth. In addition, the ketone body β -hydroxybutyrate acts as an endogenous histone deacetylase inhibitor, resulting in downstream signaling that protects against oxidative stress.

(294-297) Calorie restriction, which lowers blood glucose and elevates blood beta-hydroxybutyrate, reduces nuclear expression of phosphorylated NF-kB (p65), cytosolic expression of phosphorylated IkB, total IkB, and DNA promoter binding activity of activated NF-kB. (298) NF-kB is a major driver of inflammation in the tumor microenvironment.
The randomized controlled trial by Chi et al describes how adhering to a caloric-restricted diet for 6 months can have therapeutic benefits in slowing the growth of prostate cancer. (299) The men in the control group were instructed to avoid any dietary changes, whereas the men in the calorie-restricted group were coached by a dietician to restrict dietary carbohydrates to <20 grams/day. The authors found that elevated levels of serum ketone bodies (3- hydroxy-2-methylbutyric acid) at both 3 and 6 months were associated with significantly longer prostate cancer antigen doubling time ($p < 0.0001$), which is a marker of prostate cancer growth rate. Similarly, in a post hoc exploratory analysis of the CAPS2 randomized study the PSA doubling time was significantly longer in the low carbohydrate diet versus control diet (28 vs. 13 months, $P = 0.021$) arms.(300) These findings support the concept that elevations in ketone bodies are associated with reduced tumor growth. In a randomized trial in women with endometrial or ovarian a ketogenic diet was associated with a significant improvement in physical function scores with less fatigue.(301) In this study the ketogenic diet resulted in the selective loss of fat mass, retention of lean mass with lower fasting serum insulin levels. (302) In a RCT Khodabakshi et al determined the feasibility, safety, and beneficial effects of an MCT-based Ketogenic diet in patients with locally advanced or metastatic breast cancer and planned chemotherapy. (303) Compared to the control group, fasting blood glucose, BMI, body weight, and fat% were significantly decreased in intervention group ($P < 0.001$). Overall survival in neoadjuvant patients was higher in the ketogenic group compared to the control ($P = 0.04$).

A ketogenic diet following completed courses of chemotherapy and radiotherapy was further reported to be associated with long-term survival in a patient with metastatic non-small cell lung cancer. (304) “Long-term” survival has been reported in patients with glioblastoma on a ketogenic diet. (304, 305) Furthermore, evidence shows that therapeutic ketosis can act synergistically with conventional chemotherapeutic drugs, irradiation, and surgery to enhance cancer management, thus improving both progression-free and overall survival. (305) In addition, it is highly likely that therapeutic ketosis acts synergistically with the repurposed anticancer drugs reviewed in this document. Therapeutic ketosis requires a blood glucose < 90 mg/dl and a blood ketone > 2 mmol/l, aiming for a glucose-ketone index (GKI) < 2. (306) See the GKI calculator in the section on caloric restriction. There are no known drugs that can simultaneously target as many tumor-associated signaling pathways as can calorie restriction. Hence, energy restriction can be a cost-effective adjuvant therapy to traditional chemo- or radiation therapies, which are more toxic, costly, and generally less focused in their therapeutic action than dietary energy restriction. It should be noted that the medium-chain fatty acids that are present during the consumption of a ketogenic diet directly inhibit glutamate receptors. (307) Shukla et al observed reduced glycolytic flux in tumor cells upon treatment with ketone bodies. Ketone bodies also diminished glutamine uptake, overall ATP content, and survival in multiple pancreatic cancer cell lines, while inducing apoptosis. (308)
According to Dr. Seyfried: “Most human metastatic cancers have multiple characteristics of macrophages. We found that neoplastic cells with macrophage characteristics are heavily

dependent on glutamine for growth. We have not yet found any tumor cell that can survive for very long under prolonged restriction of glucose and glutamine. Furthermore, we have not yet found any fatty acid or ketone body that can replace either glucose or glutamine as a growth metabolite. It, therefore, becomes essential to simultaneously restrict both glucose and glutamine while placing the person in nutritional ketosis for successful cancer management."

Although dietary energy restriction and anti-glycolytic cancer drugs will have therapeutic efficacy against many tumors that depend largely on glycolysis and glucose for growth, these therapeutic approaches could be less effective against those tumor cells that depend more heavily on glutamine than on glucose for energy. Glutamine is a major energy metabolite for many tumor cells and especially for cells of hematopoietic or myeloid lineage. Green tea polyphenol (EGCG) targets glutamine metabolism by inhibiting glutamate dehydrogenase activity under low glucose conditions (see section below). (242, 309-313) In addition, mebendazole, curcumin and resveratrol inhibit glutaminolysis. (13, 314) Glioblastoma, breast cancer, pancreatic cancer, lung cancer, prostate cancer, and lymphoma may depend on glutamine as a source of energy. (13)

Real Food: The Banting Diet

Patients are strongly recommended to eat "real food" and not processed food. If it looks like food, it is likely food. If it comes in a box or carton, has a food label, and/or a long list of chemicals and additives with long and complex names it is not food. A high proportion of the population (60-80%) eating a Western diet are addicted to processed food. (315) Processed food addiction is a recognized "substance use disorder" (SUD) and should be treated as such.(315) Animal experiments demonstrate that sugar and fructose are more addictive than cocaine and heroin and that carbohydrate addicts demonstrated many of the behaviors of those with an SUD. (315) Results from the NutriNet-Santé prospective cohort study demonstrated that a 10% increase in the proportion of ultra-processed foods in the diet was associated with a significant increase of greater than 10% in risks of overall and breast cancer.(248) The EPIC Cohort study investigated the association between dietary intake according to amount of food processing and risk of cancer at 25 anatomical sites using data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. (316) In this study, in a multivariate model, substitution of 10% of processed foods with an equal amount of minimally processed foods was associated with reduced risk of overall cancer (hazard ratio 0·96, 95% CI 0·95-0·97), head and neck cancers (0·80, 0·75-0·85), oesophageal squamous cell carcinoma (0·57, 0·51-0·64), colon cancer (0·88, 0·85-0·92), rectal cancer (0·90, 0·85-0·94), hepatocellular carcinoma (0·77, 0·68-0·87), and postmenopausal breast cancer (0·93, 0·90-0·97).

A low carbohydrate-high fat (LCHF) dietary pattern is especially important for patients with cancer. As already discussed, a low carbohydrate ketogenic diet is essential to control blood glucose levels. Furthermore, a real food diet high in both soluble and insoluble fiber and fermented foods is critical to normalize the microbiome. Alterations in the microbiome play an important role in both tumorigenesis and tumor propagation. Altered gut microbiota is

associated with resistance to chemotherapeutic drugs while restoration of a normal microbiome improves the response to the anticancer drugs. (317-320) Antibiotics cause severe dysbiosis which is associated with an increased risk of cancer and reduced response to chemotherapy. (321, 322)

The Banting Diet comes close to meeting the criteria of the ideal real-food diet. (323-325) William Banting (1796-1878), a Victorian undertaker, is regarded as the father of the low-carbohydrate diet. In 1863, Banting wrote a booklet called *Letter on Corpulence, Address to the Public,* which contained the particular plan for the diet he followed. (323, 325) It was written as an open letter in the form of a personal testimonial. Banting described all of his unsuccessful fasts, diets, spa visits, and exercise regimens all of which had been advised by various medical experts. He then described the dietary change that finally had worked for him, following the advice of another medical expert. "My kind and valued medical adviser is not a doctor for obesity, but stands on the pinnacle of fame in the treatment of another malady, which, as he well knows, is frequently induced by [corpulence]." His own diet consisted of meat, greens, fruits, and dry wine. The emphasis was on avoiding sugar, saccharine matter, starch, beer, and milk. Banting's pamphlet was popular for years to come and would be used as a model for modern diets.

The Banting diet consists mainly of animal protein (including poultry, eggs, and fish), saturated animal fats (including lard, duck fat, and butter), coconut oil, olive oil, and macadamia oil, some cheeses and dairy products, some nuts and seeds, fresh vegetables grown mainly above the ground and a few berries. (324) The Banting diet excludes all processed package foods and fast foods. It also excludes all foods with sugar, fructose, and maltose as well as grain products (wheat, barley, oats, rye) and soy products. (324) Soy products are genetically modified, toxic non-foods. (324) Replace all seed oils (canola, sunflower, safflower, cottonseed, soy) with healthy saturated fats, extra virgin olive oil and virgin coconut oil are freely encouraged. High-fat dairy products are suggested but not skimmed or fat-free dairy products.

Management of Cancer Cachexia

A high percentage of patients with cancer are nutritionally impaired and at risk for malnutrition.(326) Cancer-associated cachexia is a disorder characterized by loss of body weight with specific losses of skeletal muscle and adipose tissue. (327, 328) It is characterized by a negative protein and energy balance. Cancer cachexia is driven by a variable combination of reduced food intake and metabolic changes, including elevated energy expenditure, excess catabolism, and inflammation. (327) Cancer cachexia is defined as weight loss greater than 5%, or BMI <20 and any degree of weight loss >2%; or skeletal muscle index consistent with sarcopenia (males <7·26 kg/m²; females <5·45 kg/m²). (329) Cancer cachexia is associated with reduced physical function, reduced tolerance to anticancer therapy, and reduced survival. (327, 328) Cancer cachexia is common in patients with advanced cancer.

The therapeutic strategy is to address coexisting treatable factors. The treatment of cancer cachexia should be chosen in a way that can be continued according to the patient's condition and lifestyle. Patients with advanced cancer who can complete an exercise program show improvements in physical function and quality of life (see exercise [intervention 2] in section on lifestyle interventions for the treatment of cancer). In RCTs in patients with advanced cancer, nutritional therapy alone has not demonstrated consistent efficacy on weight, quality of life, and survival. (330, 331) Nevertheless, we suggest three nutrient-dense meals a day (following the Banting Diet). Intermittent fasting/time-restricted feeding should be avoided (except during chemotherapy); however, patients should avoid snacking between meals and should avoid eating within 3-4 hours before going to sleep (to promote autophagy while sleeping).

Shukla et al demonstrated that ketone body-induced intracellular metabolomic reprogramming in pancreatic cancer cells leads to a significantly diminished cachexia in cell line models. The cachectic phenotype is in part due to metabolic alterations in tumor cells, which can be reverted by a ketogenic diet, causing reduced tumor growth and inhibition of muscle and body weight loss. (308) In addition, we suggest a complete nutritional "shake" containing superfoods such as plant protein, super green, omega-3 fatty acids, vitamins, adaptogenic herbs, probiotics, fiber, mushrooms, and berries (e.g., Ka'Chava ™ https://www.kachava.com/ and 310 Shakes™ https://310nutrition.com/). These "superfood shakes" are preferred over regular protein shakes. Tube feeding should be avoided as this may negatively impact quality of life. Pharmacological therapies for cachexia have limited efficacy and are difficult to improve the severely reduced muscle mass in patients with cachexia. (328) Anamorelin, a ghrelin receptor agonist, is currently the only drug available for the indication of cancer cachexia in a limited number of countries. (332) However, it has been reported that anamorelin elevates IGF-1 which promotes tumor growth. (333)

Intermittent Fasting, Autophagy, and Cancer

Fasting has a profound effect on promoting immune system homeostasis, improving mitochondrial health, and increasing stem cell production. (334-338) Fasting stimulates the clearing of damaged mitochondria (mitophagy), misfolded and foreign proteins, and damaged cells (autophagy). Intermittent fasting/time-restricted eating is the single most effective method to activate autophagy. However, the role of intermittent fasting and autophagy in cancer is complex (see below).

The 2016 Nobel Prize in Physiology or Medicine was awarded to Yoshinori Ohsumi for his initial elucidation of the morphological and molecular mechanisms of autophagy in the 1990s. (339, 340) Macroautophagy (herein referred to as autophagy) is a conserved lysosomal degradation pathway for the intracellular recycling of macromolecules and clearance of damaged organelles and misfolded proteins to ensure cellular homeostasis. (341) Dysfunctional autophagy contributes to many diseases, including cancer. However, theoretically autophagy can suppress or promote tumors depending on their developmental stage and type. Modulating autophagy for cancer treatment is a therapeutic approach currently under intense investigation.

During autophagy, cytoplasmic constituents (damaged proteins, misfolded proteins, foreign proteins) are engulfed within double-membrane vesicles called autophagosomes, which subsequently fuse with lysosomes to form autolysosomes, where the cargo is degraded or recycled (see Figure 6). Autophagy occurs at basal levels under physiological conditions and can be upregulated in response to stressful stimuli such as hypoxia, nutritional deprivation, DNA damage, and cytotoxic agents. (341) The molecular machinery that mediates the autophagic process is evolutionarily conserved in higher eukaryotes and regulated by specific genes (ATG genes), which were initially characterized in yeast. The process of macroautophagy can also lead to cell death or "autophagic cell death," as a result of the accumulation of autophagosomes and autolysosomes in the cytoplasm. The effects of fasting, autophagy and cancer are still under study, but many researchers propose that intermittent fasting could help with the treatment and eradication of tumors and cancer cells.(342)

Intermittent fasting/time-restricted eating is the most effective therapy for the treatment of insulin resistance, metabolic syndrome, and type II diabetes. Intermittent fasting has additional benefits in prolonging health span, alleviating the symptoms/curing many chronic diseases, as well as preventing cardiovascular disease, Alzheimer's disease and cancer. (343, 344) To gain the maximum benefits of intermittent fasting, it is thought that feeding times should be scheduled to align with circadian rhythms and activities so that timely nutrient metabolism favors healthy physiology.

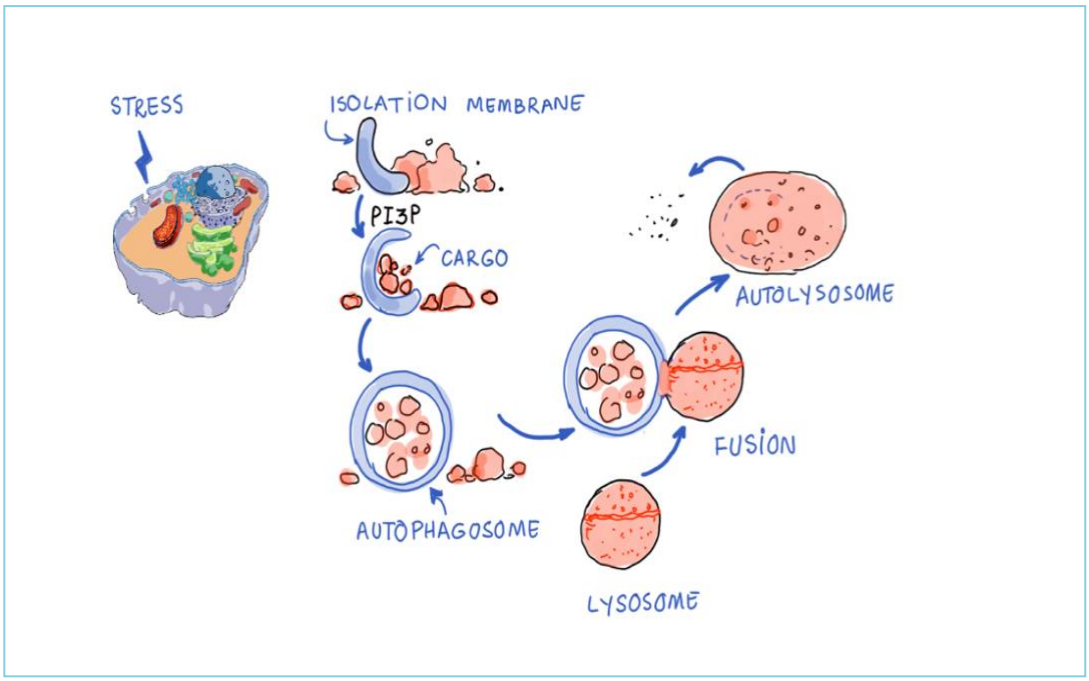


Figure 6. Autophagy pathway (Source: Dr. Mobeen Syed)

The metabolic effects of intermittent fasting are numerous and include increasing insulin sensitivity, decreasing blood glucose levels, decreasing insulin levels, decreasing insulin-like growth factor, activating the sirtuin pathway, and activating autophagy. Intermittent fasting is the most effective means of activating autophagy and accounts for many of its beneficial effects. These effects likely explain the benefits of intermittent fasting in patients with cancer.

There has been some concern that while autophagy may play an important role in preventing the development of cancer, it may paradoxically promote cancer cell proliferation. Once a tumor is established, the main function of autophagy is to provide a means to cope with cellular stressors, including hypoxia, nutritional and growth factor deprivation, and damaging stimuli, thus allowing tumor adaptation, proliferation, survival, and dissemination. Autophagy, by degrading macromolecules and defective organelles, supplies metabolites and upregulates mitochondrial function, supporting tumor cell viability. While autophagy may theoretically promote cancer cell proliferation multiple studies have demonstrated that autophagy leads to cancer cell death. (345) Almost all the repurposed drugs listed in this monograph have been demonstrated to enhance tumor cell death by activating the autophagy pathway.

Limited rodent studies and human studies have evaluated the independent effects of intermittent fasting/time restricted eating in modulating cancer progression. In a study of a high-fat driven, postmenopausal breast cancer mouse model, intermittent fasting markedly inhibited tumor initiation, progression, and metastasis compared with mice fed *ad libitum* in the absence of calorie restriction or weight loss. (346) This beneficial effect of intermittent feeding was probably mediated, at least in part, by reduced insulin signaling because systemic insulin infusion through implanted pumps reversed the intermittent fasting-mediated cancer-protective actions. (346) Additional animal models have demonstrated the benefit of intermittent fasting on cancer progression. (347-349)

Recent in vitro and in vivo models have shown that intermittent fasting improved the chemotherapeutic response to multiple chemotherapeutic agents in models of glioma, neuroblastoma, melanoma, fibrosarcoma and breast cancer, colon cancer, pancreatic cancer, hepatocellular cancer, and lung cancer. (341) Fasting seems to improve the response to chemotherapy by several mechanisms including:

- Enhances DNA repair in normal cells but not in malignant cells
- Improves autophagy mechanisms as a protection against damage to organelles
- Promotes apoptosis by both increasing tumor cell susceptibility to apoptotic stimuli, and averting apoptosis-mediated damage to normal cells
- Decreases regulatory T cells and enhances stimulation of CD8 cells

Interestingly, fasting in combination with cytotoxic agents elicited differential responses in normal and cancer cells, a phenomenon known as differential stress resistance (DSR). For DSR, normal cells prioritize maintenance pathways and inactivate growth factor signaling when nutrients are absent. In contrast, cancer cells, due to oncogene activation, do not inhibit stress resistance pathways, thus becoming vulnerable to cytotoxic treatment. In a colon cancer

model, intermittent fasting inhibited tumor growth without causing permanent weight loss and decreased M2 polarization of tumor-associated macrophages in mice. (350) When intermittent fasting cycles were combined with chemotherapy, tumor growth was slowed and overall survival was prolonged in breast cancer, melanoma, and neuroblastoma animal models. (351)

The role of intermittent fasting and the enhancement of autophagy in patients with cancer is complex. While animal models demonstrate a benefit of intermittent fasting in several tumor models, clinical data in humans is limited. While time-restricted feeding (intermittent fasting) may theoretically promote cancer cell proliferation, this concept has not been observed in patients with cancer. Furthermore, more prolonged fasting of 24-96 hours has been well tolerated in patients with cancer and appears to improve quality of life and disease symptoms.(12) This data suggests that the approach to intermittent fasting should be individualized in patients with cancer according to each patient's response.

Data from small trials in humans suggest that many types of intermittent fasting regimens positively affect risk factors for poor breast cancer outcomes, such as glucoregulation, inflammation, obesity, and sleep. Experimental animal models and human data support the hypothesis that a prolonged nightly fasting interval (time restricted eating) could reduce cancer risk and improve cancer outcomes. Marinac et al investigated whether the duration of nightly fasting predicted recurrence and mortality among women with early-stage breast cancer. (352) Data were collected from 2413 women with breast cancer but without diabetes mellitus who were aged 27 to 70 years at diagnosis and participated in the prospective Women's Healthy Eating and Living study. Nightly fasting duration was estimated from 24-hour dietary recalls collected at baseline, year 1, and year 4. The mean fasting duration was 12.5 ± 1.7 hours per night. In repeated-measures Cox proportional hazards regression models, fasting less than 13 hours per night was associated with an increase in the risk of breast cancer recurrence compared with fasting 13 or more hours per night (HR 1.36; 95% CI, 1.05-1.76).

Insulin Potentiation Therapy for Cancer?

In vitro studies suggest that insulin may potentiate the effects of chemotherapeutic drugs.(353) However, there are no clinical studies to support this concept. Furthermore, such treatment may be hazardous (causing severe hypoglycemia) and is counterintuitive, as it may likely promote tumor cell proliferation. Insulin is responsible for cellular glucose uptake and mitogenic signaling cascades in cancer cells and can promote cell proliferation, survival, invasiveness, angiogenesis, immunomodulation, and chemoresistance (as reviewed in this document). (354) Tumor cells express significantly more insulin receptors on their cell surface as compared to normal effects. (12) Insulin will promote further glycolysis and provide metabolic fuel for the cancer cell!

Some medical practitioners claim that the combined use of insulin and glucose (insulin potentiation therapy) can improve the outcomes of patients with cancer and facilitate cancer therapy de-escalation? (154, 355) Supporters of insulin potentiation therapy (IPT) and IPT with low-dose chemotherapy (IPTLD) for patients with cancer claim that insulin increases cancer

cells' permeability to chemotherapeutics relative to surrounding healthy tissues, because of the high expression of insulin receptors on these cells. (354) Other supporters suggest anticancer drugs enter cells through the same mechanism as that of glucose, conflating glucose transport with multidrug uptake transport.

There are only two published clinical trials assessing insulin potentiation therapy. Damyanov et al enrolled 16 patients with castration-resistant prostate cancer to receive insulin (0.4 U/kg) and docetaxel or a non-standard drug combination. (354) Those patients who received insulin and chemotherapy had a worse outcome (median survival of 11 months compared with 18.9 months). The second prospective study examined methotrexate response and toxicity in 30 patients with metastatic breast cancer. (356) Stable disease was reported to be more frequent in the group receiving methotrexate plus insulin compared with those receiving methotrexate alone; however, patient-centered outcomes were not provided.

Practitioners of IPT are convinced by the efficacy of this technique despite the lack of convincing scientific evidence. The role of this treatment modality therefore remains uncertain.

CHAPTER 5: METABOLIC AND LIFESTYLE INTERVENTIONS FOR CANCER TREATMENT

1. Glucose Management and the Ketogenic Diet

A carbohydrate-restricted diet (less than 25 g of carbs per day) that is high in saturated fat and Omega-3 fatty acids (ketogenic diet) is suggested. Avoid all processed food. (248) Contrary to current dogma, saturated fatty acids are "healthy," but avoid processed omega-6 vegetable oils (see below). (357, 358) Avoid foods that are high on the glycemic index and follow the "hacks" to flatten the blood glucose curve (see below). (359)

A continuous glucose monitor (CGM) is essential to track changes in blood glucose levels. Patients must keep accurate records to identify (and avoid) any food that might spike blood glucose. Target a baseline blood glucose of 60-80 mg/dl (3.3 – 4.4 mmol/l) and a postprandial (after a meal) glucose of less than 120 mg/dl (6.6 mmol/l). The ideal is a flat blood glucose curve; the blood glucose should not increase by more than 20 mg/dl after a meal. In addition, a blood ketone meter (blood level of beta-hydroxybutyrate) is recommended to confirm that the patient has entered ketosis (normal level < 0.5 mmol/l). Ideally, the blood ketone level should be over 2 mmol/l. The optimal therapeutic range is between 3 and 5 mmol/l. It is important to track changes in blood glucose and ketones with both fasting and exercise. Therapeutic ketosis requires a blood glucose < 90 mg/dl and a blood ketone > 2 mmol/l, aiming for a GKI of < 2. (306)

The GKI can be calculated at: https://keto-mojo.com/glucose-ketone-index-gki/ and https://perfectketo.com/glucose-ketone-index-calculator/

The Glycemic Index

The glycemic index (GI) is a value assigned to foods based on how quickly those foods cause increases in blood glucose levels and how high they spike. The glycemic index ranks food on a scale from 0 to 100. Pure glucose is arbitrarily given a value of 100, which represents the relative rise in the blood glucose level after two hours (see Figure 7). The GI of a specific food depends primarily on the quantity and type of carbohydrate it contains (see Table 4). Foods that are low on the GI scale tend to release glucose slowly and steadily. Foods that are high on the glycemic index release glucose rapidly. It should be noted that the glycemic index varies among individuals. (360, 361) A continuous glucose monitor allows for the individual assessment of the glucose excursion (GI) of various foods.

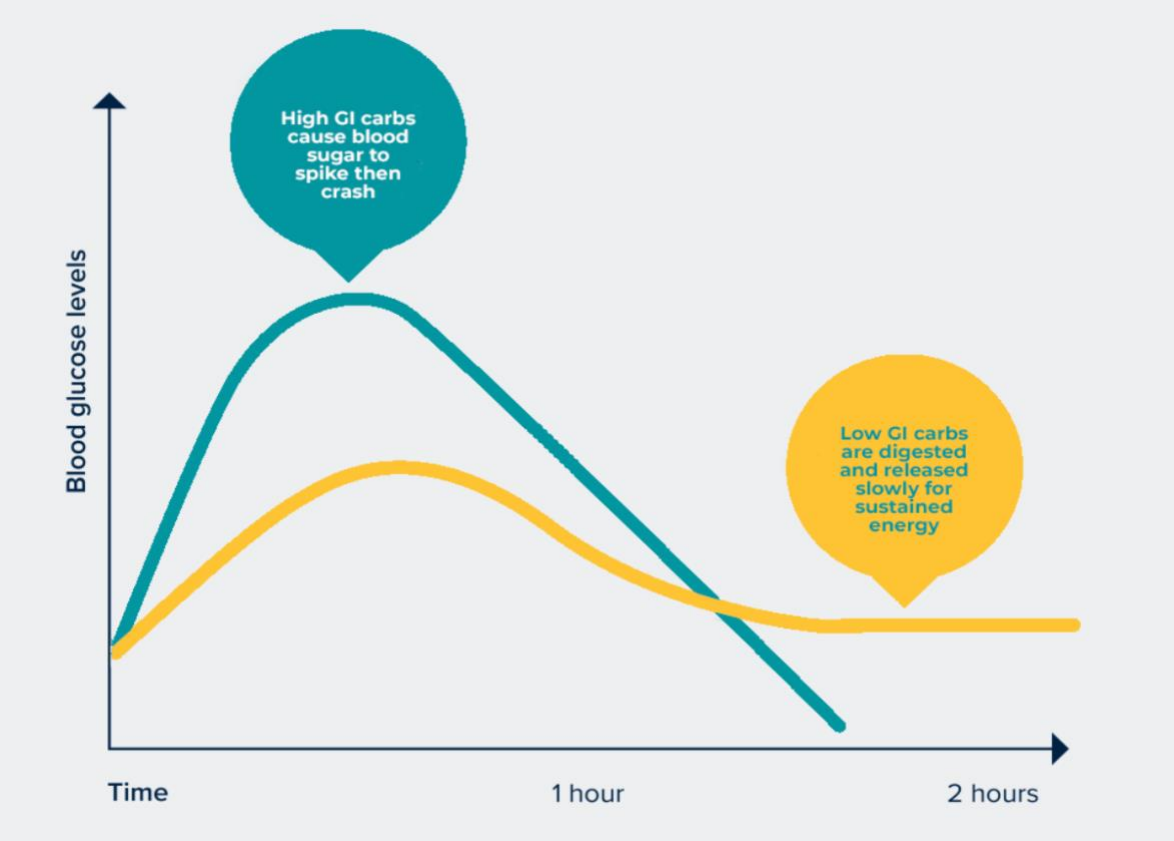


Figure 7: The blood glucose profile of high and low glycemic index foods (Source: adapted from Glycemic Index Foundation)

What To Eat and What Not to Eat

The most important intervention to reduce obesity, metabolic syndrome, type II diabetes, cancer, cardiac disease, neurodegenerative diseases, autoimmune diseases etc., is to eat real food and not processed food. (248, 315, 362) Telling the difference is quite simple. If it looks like food, it is real. If it comes in a box or has a food label, it's likely processed. The more ingredients listed on a product's label and the more chemicals you see with strange and unpronounceable names, the more processing the product has undergone. Recent evidence suggests that processed foods in themselves can cause insulin resistance. (363)

Healthy foods include:

- All vegetables, especially avocados, and cruciferous and leafy vegetables.
- Nuts especially almonds, brazil nuts, cashews, and pistachios.
- Unsweetened Peanut butter (but avoid the white bread and grape jelly!) and Chia seeds
- Fish (wild caught fresh fish especially Alaskan/Pacific salmon and sardines)
- Chicken breast (free range, no hormones, no antibiotics)
- Eggs (they've been giving a bad rap!); free range "organic" eggs are suggested

- Meat (grass-fed, no hormones, avoid processed meats)
- Blueberries (limit volume if insulin resistant)
- Coffee, with heavy cream or coconut oil; choose Stevia (without erythritol) over sugar or artificial sweeteners.

Table 4: Glycemic index of selected foods (Source: FLCCC)

Food Item	Glycemic Index
White rice	87
Watermelon	76
White bread	75
Orange juice	53
Banana	51
Pineapple	66
Papaya	60
Grape	46
Orange	42
Strawberry	40
Apple	34
Grapefruit	25
Fresh berries	25
Most vegetables	<20
Peanuts	7

Flattening the Glucose Curve

Apart from carbohydrate restriction/ketogenic diet and time-restricted eating, several simple interventions (or hacks) prevent the high glucose spikes that fuel cancer. The book “Glucose Revolution” by Jessie Inchauspe is highly recommended and provides more details on interventions to flatten the blood glucose curve, such as. (359)

Eat Foods in the Right Order

Veggies (greens/fiber) should be eaten first, protein and fat second, and starch (sugars) last; this slows gastric emptying, as well as the breakdown and absorption of glucose. Eat fruit last; always preceded by fiber. Don’t begin a meal with bread (starch).

- Begin all meals with a salad or green vegetables. Use olive oil and vinegar as salad dressing.
- Avoid starchy foods with no fiber.

- Avoid fruit juices and smoothies, which cause a large glucose spike.
- Skip breakfast. Breakfast is the worst time to eat sugar and starches; this results in a large glucose spike. Cereal for breakfast causes a rapid spike in glucose.
- Avoid snacking throughout the day.
- Drink a tablespoon of vinegar stirred into a tall glass of water before eating starch or something sweet. Apple cider vinegar is recommended. The acetic acid in vinegar decreases the enzymatic breakdown of starch, increases glycogen synthesis (and glucose uptake), and increases fatty acid oxidation. (364-367) Vinegar may be beneficial even if consumed up to 20 minutes after a starchy food. Apple cider vinegar is usually unpasteurized and should be avoided in pregnancy.
- If vinegar is not readily available, consume a few fiber tablets (esp. glucomannan tablets) before eating a starchy/sweet treat.
- Go for a 20-minute walk within an hour of eating/having starchy food. During exercise, muscles take up glucose for energy while increasing mitochondrial oxidative capacity. (368-370) Going to the gym or doing resistance exercise is an alternative. Climbing a few stairs is an option at work. If sedentary, do sitting calf raises (the soleal pump). The soleal pump is strongly recommended; it has been demonstrated to reduce postprandial glucose by about 50%, reduce hyperinsulinemia, and improved lipid metabolism. (371) When engaging in fasted exercise (before eating), the liver releases glucose into the bloodstream to fuel the mitochondria in the muscles causing a glucose spike. This is mediated by an increased release of cortisol, epinephrine, and norepinephrine (with decreased glucagon); i.e., release of harmful stress hormones. If exercising before eating, we suggest instead of a regular protein shake, consider a shake with 'superfoods,' e.g., Ka'Chava ™ or 310 Shakes.™ Shakes should include ingredients like plant protein, a super green, omega-3 fatty acids, vitamins, adaptogenic herbs, probiotics, fiber, super mushrooms, and berries.

Establishing/Restoring a "Normal" Microbiome

The microbiome has a remarkable effect on blood sugar levels and insulin sensitivity. (372-378) Establishing a normal microbiome is important for regulating blood glucose levels and improving insulin sensitivity. Furthermore, alterations in the microbiome play an important role in both tumorigenesis and tumor propagation. Follow these suggestions to help establish a "normal microbiome":

- Eat a diverse range of foods.
- Eat lots of vegetables, legumes, and beans.
- Eat fermented foods like yogurt (unsweetened), kefir, apple cider vinegar, kombucha, pickles, sauerkraut, tempeh, and kimchi.
- Eat foods rich in polyphenols (dark fruits). Include resveratrol supplements.
- Eat prebiotic fiber. Glucomannan is a dietary fiber (soluble and insoluble) made from the root of the konjac plant.
- Eat chia seeds, high in insoluble and soluble fiber.

- Eat less sugar and sweeteners.
- Reduce stress.
- Avoid taking antibiotics unnecessarily.
- Stop snacking.
- Exercise regularly.
- Spend time outdoors in the natural world to get exposure to millions of microbes, many of which can benefit microbiome diversity.
- Get enough sleep.

The consumption of fermented foods may be particularly important in restoring/maintaining a normal microbiome. Large cohort studies as well as limited interventional studies have linked the consumption of fermented foods with weight maintenance and decreased diabetes, cancer, and cardiovascular disease risks. (379)

The Saturated Fat-Cholesterol Hoax

The Cholesterol-Saturated fatty acid hoax (357, 380, 381) began to proliferate in the 1960s. Dr. Ancel Keys popularized the notion that saturated fats and high cholesterol were the primary causes of atherosclerotic heart disease — the so-called Diet-Heart Hypothesis. (382, 383) This concept has been vigorously studied, including in many RCTs, and has been convincingly proven to be false. (357, 384, 385) Indeed, replacing saturated fats with a diet high in vegetable oils (linoleic acid) was associated with higher rates of death, cardiovascular and coronary heart disease as well as a significantly increased risk of cancer. (386)

Healthy and Unhealthy Oils

Avoid seed oils high in linoleic acid. Linoleic acid is an Omega-6 fatty acid that our bodies require in small amounts. Unfortunately, many people eat up to 10 times the desired amount of linoleic acid, because of excess consumption of foods made with seed oils. Too much linoleic acid is associated with inflammation, obesity, heart disease, and other unfavorable conditions. Therefore, avoid the following oils:

- Soybean oil
- Corn oil
- Cottonseed oil
- Sunflower oil
- Sesame oil
- Grapeseed oil
- Safflower oil
- Rice bran oil
- Margarine

Instead, opt for healthy oils and fats such as the ones listed below. Use only high-quality products and check production and expiration dates.

- Olive oil (oleic acid, omega-9 monounsaturated fatty acids); never heat olive oil to the point where it produces smoke.
- Avocado oil (oleic acid, omega-9 monounsaturated fatty acids)
- Coconut oil (medium chain fatty acid)
- Flaxseed oil (alpha-linolenic acid, ALA omega-3)
- Walnut and pecan oils; should be refrigerated to avoid spoilage
- Butter (saturated fat)

2. Exercise (Aerobic and Resistance Training)

Lifestyle modification — with an emphasis on exercise, a healthy diet, and stress reduction — plays a major role in reducing the risk of death from cancer and improving quality of life. (387, 388) As already discussed, obesity and metabolic syndrome increase the risk of death in patients with cancer. In a study involving early-stage breast cancer, patients with metabolic syndrome were at a significantly increased risk of distant metastasis (HR 2.45, 95% CI 1.24–4.82) compared with those without the syndrome. (389)

Regular exercise combining both aerobic activity and resistance training is recommended in patients undergoing treatment for cancer. Aerobic exercises such as walking, high-intensity interval training (HIIT), cycling and swimming, improve overall cardiovascular fitness with improved indicators of quality of life, including better cognition and mood with less fatigue and reduced anxiety and depression. (390-395) Resistance training preserves lean body mass (muscle mass), which reduces insulin resistance and improves glucose control and may be an important factor in increasing overall survival as sarcopenia is a major negative prognostic factor in patients with cancer. (396)

The Combined Aerobic and Resistance Exercise (CARE) Trial compared different types and doses of exercise performed during breast cancer chemotherapy. (397) In this study a combined dose of 50-60 minutes of aerobic and resistance exercise performed three times weekly was significantly associated with better patient-reported outcomes and health-related compared to performing aerobic exercise alone. Meta-analyses that focused on specific types of cancer reported benefits in breast cancer treated with adjuvant chemotherapy and/or radiotherapy, colorectal cancer treated with chemotherapy, lung cancer treated with chemotherapy, prostate cancer treated with radiation therapy, and hematologic malignancies. (390) A meta-analysis of 22 prospective cohort studies found that breast cancer mortality was significantly reduced among women who reported participating in recreational physical activity after their breast cancer diagnosis (HR 0.59, 95% CI 0.45–0.78). (398)

Patients should be encouraged to engage in at least 30 minutes of moderate-intensity physical activity at least five days of the week, or 75 minutes of more vigorous exercise, along with two to three weekly strength training sessions, including exercises for major muscle groups. (387, 395) However, more hours of exercise (but not more vigorous activity) may have increased benefits. Two analyses showed a substantial inverse dose-response effect between hours per week engaged in physical activity and breast cancer mortality. (399, 400) Walking, particularly in the sunshine, has enormous physical, emotional, and psychological benefits. (401, 402)

3. Stress Reduction and Sleep

A substantial body of research has investigated the associations between stress-related psychosocial factors and cancer outcomes. (403) This data demonstrates that psychosocial stress is associated with a higher incidence of cancer and poorer survival in patients with diagnosed cancer. (403) It is critically important that patients engage in activities that reduce stress (meditation, yoga, mindfulness exercises, etc.) and get at least 8 hours of high-quality sleep (ensure adequate sleep hygiene). (254-259, 404) See section on propranolol and the use of propranolol to mitigate against catecholamine induced cancer proliferation and metastases.

Adaptogens are herbs that help in combating stress. These herbs normalize physiological processes and help the body adapt to stress. In Ayurvedic medicine (traditional medicine native to India), *Ashwagandha* has proven to be a safe and effective adaptogen. Randomized controlled trials (RCTs) have shown a significant benefit in terms of stress reduction, improved cognition and mood, and quality of sleep. (405-407) In a double-blind, placebo-controlled RCT, participants who had chronic stress were randomized to ashwagandha extract (300 mg twice daily) or placebo for 60 days. (408) At the end of 60 days, participants in the active treatment group had a 44% ($p< 0.001$) reduction in stress scores and a 28% ($p< 0.001$) reduction in cortisol levels. In a similar study, Ashwagandha resulted in a marked improvement in the quality of sleep in patients with insomnia. (409) A meta-analysis of 12 RCTs demonstrated that Ashwagandha supplementation significantly reduced anxiety ($p = .005$) and stress levels ($p = .005$) compared to placebo. (410) In this study, the non-linear dose-response analysis indicated a favorable effect of Ashwagandha supplementation on anxiety up to 12,000 mg daily and on stress up to 300-600 mg daily.

As Ashwagandha is an immune system activator (inhibits NF-κB), it should not be used concomitantly with immunosuppressive drugs such as tacrolimus and cyclosporine. Furthermore, the safety of Ashwagandha has not been established during pregnancy and in breastfeeding women.

Healthy sleep is essential for neural development, learning, memory, cardiovascular, and metabolic regulation. Sufficient sleep is needed to provide recovery after preceding waking activities and to ensure optimal functioning during subsequent wakefulness. (411) As recommended by the National Sleep Foundation, in a healthy individual, the recommended sleep duration for younger adults is seven to nine hours, and for older adults it is seven to eight hours. (412) Other than adequate duration, healthy sleep is good quality sleep. A study of

23,620 Europeans found that those who slept for less than 6 hours per day were 41% more likely to experience strokes and 44-78% more likely to experience heart attacks.(413)

The National Sleep Foundation endorses the following sleep quality indicators: 1) sleep latency of 15 minutes and less, 2) a maximum of one awakening of more than five minutes per night, 3) wake time after sleep onset of 20 minutes and less, and 4) sleep efficiency of 85% or more.(414) Insomnia is defined by the complaints of difficulty initiating sleep, difficulty maintaining sleep, or early morning awakenings and is associated with one or more daytime symptoms such as fatigue, cognitive impairment, or mood disturbance (depression). (415) A systematic review demonstrated that short sleep duration, defined as less than 6 hours of sleep per 24 hours, is associated with a significant mortality increase. (416)

Numerous studies have found an association between sleep deprivation and cancer. An English study of 10,036 people over 50 found that poor sleep resulted in a 33-62% increased risk of cancer.(417) A study of 23,620 Europeans found that those who slept for less than 6 hours per day were 43-46% more likely to develop cancer. (413) When healthy young men slept for four hours, compared to nights where they slept eight hours, there was a 72% decrease in their circulating NK cells.(418) This finding is particularly important in the context of cancer immune surveillance. Furthermore, data shows that sleeping pills (which disrupt normal sleep) are associated with a large increase in one's risk of cancer. (419, 420)

Most sleeping pills are sedatives, not sleep aids. What this means is the person taking them is longer conscious, but since this is done through sedating the brain, its ability to initiate restorative sleep functions is greatly impaired. As a result, people who take sleeping pills effectively have greatly reduced sleep, and in turn, are tired throughout the day (because they did not have a restorative night of sleep) and are at high risk of developing a wide range of health issues associated with poor sleep. For example, one study found people who used sleeping pills were twice as likely to die as those who did not (and three times more likely if they were daily users).(421) Another study that compared 10,529 sleeping pill users to 23,676 controls, found that over the course of 2.5 years, the sleeping pill users were 3.6-5.4 times more likely to die. (420)

A meta-analysis of five RCTs demonstrated that Ashwagandha supplementation significantly improved sleep, particularly in a subgroup of adults diagnosed with insomnia; the treatment dosage was > 600 mg daily and the treatment duration was > 8 weeks. (415) Ashwagandha showed improvement in sleep compared to the placebo for the Sleep Quality Scale, sleep onset latency, total sleep time, wake time after sleep onset, and sleep efficiency. In addition, extensive studies have demonstrated that ashwagandha has potent in vivo and in vitro anti-cancer effects has been demonstrated to improve the quality of life in patients with breast cancer undergoing chemotherapy. (422) For this reason we strongly recommend supplementation with ashwagandha as adjuvant therapy in patients with cancer.

4. Comprehensive Lifestyle Changes

We recommend comprehensive lifestyle changes for both the prevention and treatment of cancer. A landmark prospective, randomized study evaluated the short- and long-term effects of a comprehensive lifestyle intervention on women with stage II or stage II breast cancer who had undergone surgery. (423-427) The intervention included techniques to reduce stress, improve “quality of life,” and promote healthy behaviors including guidance on diet, exercise, relaxation techniques, social support and healthy living. Patients in the intervention group attended regular sessions with follow-up appointments to ensure compliance with the lifestyle program. Eleven years later, women who participated in the intervention had a 45% lower risk of cancer recurrence than those in the control group and were 56% less likely to have died from breast cancer compared to women in the control group. Intervention patients were also 49% less likely than women in the control group to die from any cause. The study also demonstrated that women who took part in the intervention had significantly improved psychological, behavioral, and health outcomes, as well as improved immune function compared with patients in the control group.

5. Health Benefits of Sunshine

Sunlight has great therapeutic powers. Our forefathers roamed the earth and were exposed to sunlight on a daily basis, likely with profoundly important health benefits. (428) During the 1918 influenza pandemic, “open-air treatment of influenzae” appeared to be the most effective treatment for seriously ill patients. (429) A recent large prospective study demonstrated that avoiding sun exposure is a risk factor for all-cause mortality. (430) In this study, the mortality rate amongst avoiders of sun exposure was approximately twofold higher compared with the highest sun exposure group. A large epidemiological study found women with higher solar UVB exposure had only half the incidence of breast cancer as those with lower solar exposure and that men with higher residential solar exposure had only half the incidence of fatal prostate cancer.(431) The cancers for which solar UVB is significantly associated with reduced incidence are bladder, brain (males), breast, corpus uteri, esophageal, gastric, non-Hodgkin’s lymphoma, pancreatic, and renal cancer. (432) Sunlight is critical for mental health; this is most well appreciated with depression but in reality, the effects are far more broad reaching.

Apart from UV radiation stimulating vitamin D synthesis, near-infrared (NIR) radiation has a profound effect on human physiology. (433) Approximately 40% of the sun’s radiation in the NIR spectrum (700- 1500 nm). NIR activates mitochondria to produce melatonin (locally). In addition, NIR enhances mitochondrial electron transport and the generation of ATP. We suggest that patients expose themselves to about 30 minutes of midday sunshine whenever possible (at least 3 times a week). A brisk midday walk has a doubly beneficial effect, the exposure to sunlight and the health benefits of walking. (401, 402)

6. Sunshine and Skin Cancer

Skin cancer is the most common cancer in the United States.(434) Current estimates are that one in five Americans will develop skin cancer in their lifetime. By far the most common type of skin cancer is basal cell carcinoma (BCC) (comprising 80% of all skin cancers). (435, 436) The three primary risk factors for BCC are excessive sun exposure, fair skin (which makes one more susceptible to excessive sunlight penetrating the skin), and a family history of skin cancer. Because BCC almost never metastasizes it is generally a very benign cancer. Cutaneous Squamous Cell Carcinoma (SCC) is the second most common type of skin cancer, SCC is also caused by sunlight. (435) Unlike BCC, SCC can be dangerous, as it does metastasize. In turn, if it is removed prior to metastasizing, it has a 99% survival rate, but if removed after metastasis, this drops to 56%. Because the face is the most sun exposed area and the commonest site of BCC and SCC, we suggest wearing a hat when exposed to sunshine and avoiding sunscreens (see below). Melanoma comprises 1% of all skin cancer diagnoses, however, melanoma is responsible for most of the deaths from skin cancer. (437-439) Survival is greatly improved by early detection. The five-year survival rate for melanoma depends upon how far it has spread at the time of its diagnosis (ranging from 99% to 35% and averaging 94%). Skin cancers are by far the most diagnosed cancers in the United States, so to prevent them, the public is constantly told to avoid the sun. However, while the relatively benign skin cancers are caused by sun exposure (BCC and SCC), melanoma responsible for most skin cancer deaths are due to a lack of sunlight.(440, 441) This is unfortunate because sunlight is arguably the most important nutrient for the human body, as avoiding it doubles one's rate of dying and significantly increases their risk of cancer.

Paradoxically, while sun exposure (UVb) increases the risk of non-melanoma skin cancer, sun exposure reduces the risk of melanoma and the overall risk of dying from cancer. (440, 442) In 1937, Peller and Stephenson reported that soldiers of the U.S. Navy, intensively exposed to open air, sun rays, and salt water, had eight-fold higher frequency of skin cancer and lip cancer, but the death rate among these cases of cancer was three-fold lower than expected. In addition, they reported a 44% lower incidence of other cancer-related deaths. (443) In patients with melanoma sun exposure is strongly negatively associated with death from melanoma. (444) An Italian study reported that sunbathing holidays after a diagnosis of melanoma were related to reduced rates of relapses (HR=0.3, 95% CI=0.1-0.9). (445) In the MISS study (Melanoma in Southern Sweden), there was a dose dependent increase in the risk of death with lower sun exposure, with a 40% higher risk of cancer-related death in the group with low sun exposure [sHR=1.4, 95% CI=1.04-1.6] as compared to those with greatest sun exposure. (442) It should be noted that Sunscreen users in Sweden have been reported to be at an 80% increased risk of skin cancer. (OR=1.8, 95%CI=1.1-2.9). (446) In addition, research suggests that using sunscreen either has no effect on the rates of malignant melanoma or increases the risk. A plausible explanation of this increased risk might be that the application of a sunscreen inhibits the redness of the skin but allows prolonged UV exposure.

It is critically important to understand that while melanoma is widely considered to be linked to sunlight exposure this conjecture is false:

- Most importantly, 87% of all SCC cases occur in regions of the body that have significant sunlight exposure, such as the face, while 82.5% of BCC occurs in those regions. Conversely, only 22% of melanomas occur in sun exposed regions. This indicates that SCC and BCC are linked to sun exposure, but melanoma is not.(440)
- Outdoor workers get three to ten 10 times the annual UV dose that indoor workers get, yet they have lower incidences of cutaneous malignant melanoma and an odds ratio (risk) that is half that of their indoor colleagues.(447)
- A study of 528 patients with melanoma found those who had solar elastosis (a common change in the skin that follows excessive sun exposure) were 60% less likely to die from melanoma. (444)
- A 1997 meta-analysis of the available literature found workers with significant occupational sunlight exposure were 14% less likely to get melanoma.(441)
- In many areas of the world there has been a significant increase in the incidence of melanoma, which argues against sunlight being the primary issue as sun exposure has not significantly changed in the last few decades.(447, 448) As discussed elsewhere in this document this increase is likely due to insulin resistance, omega-6 vegetable oils, processed food and topical carcinogens

CHAPTER 6: REPURPOSED DRUGS r

Remarkably, unlike conventional chemotherapeutic drugs that mostly act via a single cellular biological pathway, almost all the repurposed drugs/nutraceuticals used as adjunctive treatments for cancer have multiple modes of action. These mechanisms can generally be divided into two major groups, namely:

i. those that act directly on cancer cell pathways promoting cell death (apoptosis); and
ii. those that alter the tumor microenvironment (TME) restoring immune function and T cell cytotoxicity, limiting angiogenesis and metastatic spread, and inhibiting cancer stem cells.

Those nutraceuticals and repurposed drugs that have been demonstrated to reduce the risk of developing cancer are likely to be highly effective in treating cancer. Furthermore, it is likely that the metabolic pathways involved in cancer prevention play a major role in limiting cancer growth and spread. Consequently, an evaluation of a repurposed drug's efficacy in preventing cancer is important in considering the role of that drug in the treatment of cancer.

Most published studies demonstrating the benefit of nutraceuticals and repurposed drugs are in vitro mechanistic experiments and studies performed in animal models. Prospective clinical studies are generally small, focusing on mechanisms of action or surrogate markers of efficacy. Indeed, most of the published clinical data consists of epidemiological studies, retrospective observational studies, small case series, and case reports with few prospective clinical studies. This is not unexpected due to the "war on repurposed drugs" that is being waged by Big Pharma and its supporters; there is little funding to support well-designed clinical studies using cheap, potentially effective, and lifesaving drugs.

A 2014 ProPublica investigation found that "Big Pharma's focus on blockbuster cancer drugs squeezes out research into potential treatments that are more affordable." (449) A researcher at Harvard Medical School who has tried for many years to find funding for a study on the effects of aspirin on breast cancer told the reporter: "For some reason, a drug that could be patented would get a randomized trial, but aspirin, which has amazing properties, goes unexplored because it's 99 cents at CVS." (449)

Large, pharma-funded, randomized, double-blind controlled trials (RCTs) — considered by the medical establishment and those in the ivory towers to be the gold standard — have numerous limitations, however, and frequently don't reflect real-world clinical practice. Furthermore, there is now strong scientific data and a growing consensus that well-conducted observational studies produce results statistically similar to those of traditional RCTs. (450) It is, therefore, possible, and indeed desirable to design prospective observational studies to study the clinical efficacy of the metabolic approach to cancer and specifically the combined use of multiple repurposed drugs. As the metabolic approach to cancer necessitates a combination of interventions, including caloric reduction and a ketogenic diet, and multiple off-label anticancer

drugs, it would be nearly impossible to design a double-blind randomized study; indeed, such an approach may be considered unethical.

The METRICS study (NCT02201381) is an example of an off-label drug protocol for the treatment of patients with glioblastoma. (267) METRICS is a novel, participant-funded, open-label, non-randomized, single-arm real-world study designed to gather high-quality evidence on the safety, tolerability, and effectiveness of the combination of four off-label metabolically targeted medicines (metformin, atorvastatin, mebendazole, and doxycycline) as an adjunctive cancer treatment for glioblastoma and other tumors. (267) The retrospective arm of the METRICS study has produced very encouraging results, with a significant increase in disease-free survival of patients compared to a control group.

The Repurposing Drugs in Oncology (ReDO) project has cataloged 371 approved drugs with anticancer effects. (5) See Appendix 2 for an abbreviated list of repurposed drugs, and nutraceuticals. In addition, over three thousand plant species have anti-cancer activity.(451) It would be impossible to review all the drugs in ReDo's database in this monograph; rather, we have focused on and evaluated the drugs that appear to have the greatest clinical utility. These repurposed drugs are listed in priority according to the strength of the supporting clinical and mechanistic evidence (see Appendix 1 which outlines the stratification methodology).

Patients with cancer should consider taking at least the first 6-10 listed interventions; this can be modified according to the tumor type and the patient's individual clinical response and preferences. Furthermore, it is important to recognize that many of these interventions act additively/synergistically with one another and with conventional chemotherapy. For example, PDE5-inhibitors have apoptotic effects when combined with the green tea polyphenol EGCG in multiple myeloma, gastric, pancreatic and prostate cell lines, while EGCG and the PD5-inhibitor alone had little impact on tumor viability.(452-454) This suggests that the use of a single repurposed drug/nutraceutical is likely to be ineffective. Furthermore, with regards to conventional chemotherapy, metronomic dosing is preferred (see below).

Patients should monitor the response to treatment with a PET scan (glucose uptake scan) every three months and then at least every six months once in remission/cancer stable. Patients should follow their tumor markers concomitantly. Circulating tumor DNA (in blood specimens) is an emerging technology that may prove useful for monitoring tumor progression. (455, 456) Patients and their healthcare providers should dynamically follow their tumor markers and adjust their treatment protocol accordingly. Patients who demonstrate a good clinical response should not stop their treatment protocol abruptly, as this may result in a relapse, (4) but rather reduce the number of interventions dynamically.

Antioxidant supplements (vitamins A, C, and E; coenzyme Q10, and N-acetyl cysteine (NAC) should be avoided in patients with cancer. In an experimental model, Wang et al demonstrated that vitamin C, vitamin E and NAC increased tumor angiogenesis by BACH1 mechanism (redox-sensitive transcription factor BTB and CNC homology 1). (457) These antioxidants should specifically be avoided in patients undergoing chemotherapy and radiotherapy, as these

interventions act largely by increasing oxidant injury, which is minimized by antioxidant supplements. (458, 459) Paradoxically, while oral vitamin C is a potent antioxidant, (460) high-dose intravenous vitamin C generates reactive oxygen species that potentiates the effects of chemotherapy and radiation therapy (see section on intravenous vitamin C).

Summary of Repurposed Drugs to Control Cancer

Listed in order of priority, stratified based on the totality of evidence (see Appendix 1) and reviewed in detail below. The summary of the anticancer pathways of the repurposed drugs are listed in Table 5. A list of the ReDo drugs is provided in Appendix 2. (5) Those drugs which have strong clinical AND safety data are given a strong recommendation. Those drugs which have a lower level of clinical and safety data are given a weak recommendation. Those drugs for which there is insufficient clinical and safety data to be confident in recommending the drug are considered a TiER THREE drug. Those drugs which are ineffective and/or have safety concerns are considered a TIER FOUR drug.

Tier One Repurposed Drugs: Strong Recommendation

1. Vitamin D3: 20,000 to 50,000 IU daily – NOTE: dosage should be adjusted according to blood vitamin D levels, aiming for a 25-OH level of at least 55-90 ng/dl
2. Propranolol 40 – 180 mg daily
3. Melatonin: Start at 1-5 mg and increase to 20-40 mg at night
4. Metformin: 1,000 mg twice daily
5. Curcumin (nanocurcumin): 600 mg daily or as per manufacturer's suggested dosing
6. Ivermectin 12-18 mg daily (? 1mg/kg/day)
7. Mebendazole: 100-200 mg daily
8. Green tea catechins: 500-1,000 mg daily
9. Omega 3 fatty acids: 2-4 g daily
10. Berberine: 1,000-1,500 mg daily or 500-600 mg two or three times daily. (Depending on blood glucose levels, metformin and berberine can be used together or alternating months)
11. Atorvastatin: 40 mg twice daily. (Simvastatin 20 mg twice daily is an alternative.)
12. Sildenafil: 20 mg daily. (Tadalafil 5 mg daily is an alternative)
13. Disulfiram: 80 mg three times daily or 500 mg once daily
14. Ashwagandha 600- 1200 mg daily
15. Itraconazole 100 -600 mg daily
16. Mistletoe: (given subcutaneously by an integrative oncologist)
17. Cimetidine: 200-400 mg twice daily (predominantly for perioperative prophylaxis)

Tier Two Repurposed drugs: Weak Recommendation

18. Valproic acid 15-20 mg/kg/day
19. Low dose naltrexone: 1-4.5 mg daily
20. Doxycycline: 100 mg daily (for cycles of 2 weeks)
21. Spironolactone 50-100 mg daily
22. Resveratrol: 1,000 mg daily (bioavailable enhanced formulation)/Pterostilbene
23. Wheatgrass 3- 6 g daily
24. Captopril 25 mg two or three times daily
25. Clarithromycin 500 mg twice daily

Tier Three Repurposed Drugs: Insufficient Data

26. Cyclooxygenase inhibitors: aspirin 325 mg daily or Diclofenac 75-100 mg daily
27. Nigella sativa: 400-500 mg encapsulated oil twice daily
28. Ganoderma lucidum (Reishi) and other medicinal mushrooms
29. Dipyridamole: 100 mg twice daily
30. High-dose intravenous vitamin C (50-75 g IV as per protocol)
31. Dichloroacetate 500 mg two or three times daily
32. Nitroglycerin
33. Sulforaphane
34. Artemisinin
35. Cannabinoids
36. Fenofibrate
37. Niclosamide
38. Pao Pereira
39. Dandelion extract
40. Annona muricata (Soursop or Graviola)

Tier Four Repurposed Drugs: Not Recommended

41. B-complex vitamins
42. Colchicine
43. Essiac and Flor-Essence
44. Shark cartilage
45. Laetrile (amygdalin)

Pre-operative Repurposed drugs to reduce metastases

The phenomenon of post-surgical distant recurrence is common in a number of cancers, including breast, non-small cell lung cancer, osteosarcoma and others. Across a broad range of solid tumors, the pattern of early distant recurrence following surgical resection is remarkably consistent and yet there has been little sustained effort to address the issue. Tumor excision facilitates both pro-metastatic and anti-metastatic processes, which, within each domain, are often synergistic and self-propagating.(461) Minor perioperative dominance of either pro-metastatic or anti-metastatic processes can trigger a "snowball-like effect", leading to either accelerated progression of minimal residual disease (MRD), or to its dormancy/elimination, establishing the "surgical metastatic roulette". Thus, the immediate perioperative period should become a significant anti-metastatic therapeutic arena, exploiting feasible approaches including manipulations/modifications of inflammatory-stress responses, surgical procedures, and hormonal status. (461)The use of this intervention strategy more widely in surgical models of care has the potential to provide highly cost-effective improvements in control and cure.

Beta-adrenergic signalling is implicated in the post-surgical metastatic process and numerous in vivo studies have reported that peri-operative propranolol is associated with a reduced rate of metastases. (462) In a phase II randomized trial Hiller et al evaluated the use of preoperative β-Blockade with propranolol on metastatic tumor biomarkers in women undergoing surgery for breast cancer. (463) In this triple-blind placebo-controlled clinical trial, 60 patients were randomly assigned to receive an escalating dose of oral propranolol (n = 30; 80-160 mg daily) or placebo (n = 30) for 7 days prior to surgery. In this study, propranolol downregulated primary tumor expression of mesenchymal genes and altered intratumoral neutrophil, natural killer cell, and dendritic cell recruitment with elevated tumor infiltration of CD68(+) macrophages (M1 macrophage polarization) and CD8(+) T cells. In addition, the release of pro-inflammatory mediators increase the risk of metastases.(461) The combination of propranolol with a COX-2/PGE2 inhibitor, such as ketorolac or etodolac, has the potential to show synergism in a peri-operative setting. (464, 465) Cimetidine has been studied in the post-operative period predominantly in patients undergoing colorectal surgery. (466) In a Cochrane meta-analysis of five studies (n=421) adjuvant cimetidine was associated with an improvement in overall survival (HR 0.53; 95% CI 0.32 to 0.87). (467)

Forget and colleagues reported on a retrospective analysis of breast cancer patients treated with conservative surgery, with and without intraoperative NSAIDs (DCF or ketorolac). (468) Patients treated pre-incisionally with ketorolac (20 mg -30 mg) or DCF (75 mg) showed improved disease-free survival (HR = 0.57, 95% CI: 0.37–0.89, *P* = 0.01) and an improved overall survival (HR = 0.35, CI: 0.17–0.70, *P* = 0.03), compared to patients not treated with NSAIDs. (469) The findings of this study were, however, not replicated in a prospective RCT (see section on NSAIDS). (470) Perioperative cimetidine reverses histamine-induced suppression of lymphocyte proliferation and increases the number of tumor-infiltrating lymphocytes (see section on cimetidine). (471, 472) It should be noted that cimetidine increases the plasma levels of propranolol, hence propranolol should be dosed carefully. (473)

NCT02596867 is a Phase II open-label 'window of opportunity' trial in newly diagnosed breast cancer.(265) Propranolol at a dose of 1.5 mg/kg BID, is administered for three weeks prior to surgical resection. The primary outcome is a reduction in the proliferative index (Ki-67), secondary outcomes relate to safety, toxicity and adherence. NCT00888797 is a Phase III randomized, placebo-controlled trial of peri-operative propranolol and etodolac (a COX-2 inhibitor) in colorectal cancer patients undergoing resection (COMPIT trial).(265) Patients in the treatment arm receive etodolac 800 mg BID for the entire intervention period, propranolol 20 mg BID for 5 pre-operative days, 80 mg BID on the day of surgery, 40 mg BID for the first postoperative week, 20 mg PO BID for the second postoperative week. The primary clinical endpoint of this study is the rate of local and distant recurrence rate at five years. Provisional results of this study demonstrated that adverse event rates were equivalent between the two groups while Intent-to-treat analyses of 5-year follow-up showed that 2/16 (12.5%) vs 9/18 (50%) patients exhibited recurrence in treatment vs placebo groups, respectively (p=0.033).(474)

Perioperative propranolol together with a COX-2 inhibitor and possibly low dose cimetidine (200 mg BID) given for 7-10 days prior to surgical resection of a tumor (including a biopsy) may reduce the risk of metastatic disease. A dose of propranolol of 40-80 mg BID to keep the resting pulse > 60-70 bpm is suggested. Careful dosage adjustment of propranolol is required in patients receiving cimetidine. The anesthesiologist should be aware the patient is taking a beta-blocker. The addition of vitamin D (20 000 IU/day) may have additional benefits. Postoperatively patients should continue a tapering dose of propranolol for 2 weeks (together with the COX-2 inhibitor) followed by a maintenance program of dietary management and repurposed drugs as based on the recommendations presented in this monograph. The clinician may elect to include propranolol, vitamin D and a COX-2 inhibitor in the maintenance regimen.

Table 5. Summary of the anti-cancer pathways of the repurposed drugs and nutraceuticals

	↑ Apoptosis	↑ autophagy	↓ cell proliferation	Cell cycle arrest	↑ Immune	↓ TME	Antiinflamm.	↓ Stem Cells	↓angiogenesis	↓ glucose	↓ glutamine
Vitamin D	+	+	+	+	+	+	+	+	+	-	-
Propranolol	+	+	+	+	+	+	+	+	+	+	-
Melatonin	+	+	+	+	+	+	+	+	+	+	-
Green Tea	+	+	+	-	+	+	+	+	+	+	+
Metformin	+	+	+	+	+	+	+	+	+	+	-
Curcumin	+	+	+	+	+	+	+	+	+	+	+
Ivermectin	+	+	+	+	+	+	+	+	+	+	-
Mebendazole	+	+	+	+	+	+	+	+	+	+	+
Omega-3 FA	+	+	+	+	+	+	+	+	+	+	-
Berberine	+	+	+	+	+	+	+	+	+	+	+
Atorvastatin	+	+	+	+	+	+	+	+	+	-	-
Disulfiram	+	+	+	+	+	+	+	+	+	+	-
Cimetidine	+	+	+	+	+	+	+	+	+	-	+
Mistletoe	+	+	+	+	+	+	+	+	+	+	-
Sildenafil	+	+	+	+	+	+	+	+	+	+	-
Itraconazole	+	+	+	+	+	+	+	+	+	+	-
LDN	+	+	+	+	+	+	+	+	+	-	-
Doxycycline	+	+	+	+	+	+	+	+	+	+	-
Spironolactone	+	+	+	+	+	+	+	+	+	-	-
wheatgrass	+	+	+	+	+	+	+	+	+	+	-
Resveratrol	+	+	+	+	+	+	+	+	+	+	+
COX inhibitor	+	+	+	+	+	+	+	+	+	+	-
Nigella sativa	+	+	+	+	+	+	+	+	+	+	+
Reishi	+	+	+	+	+	+	+	+	+	+	-

CHAPTER 7: TIER ONE REPURPOSED DRUGS – STRONG RECOMMENDATION

1. Vitamin D

Vitamin D is synthesized in human skin after the photoisomerization of 7-dehydrocholesterol to pre-vitamin D3 under the influence of UV B radiation (wavelength, 280-315 nm). (553) The major factors influencing this process are either environmental (latitude, season, time of day, ozone and clouds, reflectivity of the surface) or personal (skin type, age, clothing, use of sunscreen, genetics). (554) From the skin, parental vitamin D3 (*cholecalciferol*) finds its way into the general circulation, and it is then metabolized in the liver to 25-hydroxyvitamin D3 [25(OH)D3] (*calcifediol*). 25(OH)D3 is an immediate precursor metabolite to the active form of vitamin D3, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] (*calcitriol*), that is the product of the mitochondrial CYP27B1-hydroxylase confined primarily but not entirely to the proximal tubular epithelial cell of the kidney. (554, 555)

As vitamin D has a much shorter half-life than 25(OH)D3 (1-2 days versus 2-3 weeks), 25(OH)D3 is considered the best indicator of vitamin D status; hence 25(OH)D3 is the most widely used test indicating vitamin D status. (554, 555) A vitamin D level > 30 ng/mL is widely considered "normal" while a level between 20-30 ng/mL is considered vitamin D insufficient and a level <20 ng/mL is considered vitamin D deficient. (554-556) However, more recent data suggests that a level > 50 ng/mL is desirable, and ideally targeting a level of 55- 90 ng/mL is preferable.(553, 557-559)

It may take many months or even years to achieve optimal levels in patients with low vitamin D levels (< 20 ng/mL) taking the standard recommended dose of 5,000 IU/day. It is therefore important that the optimal regimen for vitamin D supplementation be followed to achieve adequate circulating levels (see Table 6). (558, 559) Since the highest dose of commercially available vitamin D3 is 50,000 IU capsules, and due to its affordability and better gastrointestinal absorption, we recommend using 50,000 IU D3 capsules for community setups.(553, 558, 559) Together, a number of these capsules can be taken as a bolus dose [i.e., single upfront doses such as 100,000 to 400,000 IU]. However, the liver has a limited 25-hydroxylase capacity to convert vitamin D to 25(OH)D: thus, taking 50,000 IU capsules over a few days provides better bioavailability. (553, 558, 559)

Vitamin D2 is manufactured through the ultraviolet irradiation of ergosterol from yeast, while vitamin D3 is synthesized trough the ultraviolet irradiation of 7-dehydrocholesterol from lanolin; both are used in over-the-counter vitamin D supplements. (554) Vitamin D2 has 30% of the biological activity of vitamin D3. It is best to include both vitamin K2 (menaquinone [MK7] 100 mcg/day, or 800 mcg/week) and magnesium (250-500 mg/day) when doses of vitamin D > 8 000 IU/day are taken. (560, 561) It should be noted that vitamin K2 itself has anticancer properties and an inverse relationship exists between vitamin K2 (and not K1) intake and cancer mortality. (562-565)

Table 6. Guidance on Upfront Loading Dose Regimens to Replenish Vitamin D Stores in the Body

When serum vitamin D levels are available, the doses provided in this table can be used for the longer-term maintenance of serum 25(OH)D concentration above 50 ng/mL (125 nmol/L). The table provides the initial bolus dose, weekly dose, frequency, and duration of administration of oral vitamin D in non-emergency situations, in a non-obese, 70 kg adult.

Serum Vitamin D (ng/mL) **	Vitamin D Dose: Using 50,000 IU Capsules: Initial and Weekly $		Duration (Number of Weeks)	Total Amount Needed to Correct Vit. D, Deficiency (IU, in Millions) #
	Initial Bolus Dose (IU)	Follow-Up: $$ The Number of 50,000 IU Caps/Week		
<10	300,000	×3	8 to 10	1.5 to 1.8
11–15	200,000	×2	8 to 10	1.0 to 1.2
16–20	200,000	×2	6 to 8	0.8 to 1.0
21–30	100,000	× 2	4 to 6	0.5 to 0.7
31–40	100,000	×2	2 to 4	0.3 to 0.5
41–50	100,000	×1	2 to 4	0.2 to 0.3

(Source Nutrients – Special Issue: "Vitamin D – Calciferol and COVID" (558) Reproduced with permission from the author.

More than half of human tissues express the gene for the vitamin D receptor, with vitamin D having pleiotropic functions in pathways of energy metabolism, immunity, and cellular growth and differentiation that clearly extend the control of calcium homeostasis. (566) The biologically active form of vitamin D, 1,25(OH)D3, regulates over 1200 genes within the human genome. (553) The most important extra-skeletal function of vitamin D is its role in the modulation of the immune system. Vitamin D receptors are present on immune cells, with this vitamin playing a critical role in both innate and adaptive host immunity. (567, 568)

Vitamin D has anticancer effects both directly *via* controlling the differentiation, proliferation, and apoptosis of neoplastic cells as well as indirectly through regulating immune cells that affect the microenvironment of malignant tumors. Evidence from observational and randomized controlled studies indicates that low vitamin D status is associated with higher mortality from life-threatening conditions such as cancer and cardiovascular disease. (569, 570) In a real-world analysis of 445,601 participants, aged 40–73 years, from the UK Biobank cohort, both vitamin D deficiency and insufficiency were strongly associated with all-cause mortality.(571) A Cochrane analysis demonstrated that supplementation with vitamin D3 (cholecalciferol) decreased all-cause mortality (RR 0.94, 95% CI 0.91 to 0.98, p = 0.002); however, supplementation with vitamin D2, calcifediol, and calcitriol did not affect mortality. (572)

Vitamin D deficiency has been demonstrated to increase the risk of breast cancer while supplemental vitamin D intake had an inverse relationship with this outcome. (573) Both prospective and retrospective epidemiologic studies indicate that levels of 25-hydroxyvitamin D below 20 ng/mL are associated with a 30 to 50% increased risk of incident colon, prostate, and breast cancer, along with higher mortality from these cancers. (554) People living at higher latitudes are at increased risk for vitamin D deficiency and are reported to have an increased risk of Hodgkin's lymphoma as well as colon, pancreatic, prostate, ovarian, breast, and other cancers and are more likely to die from these cancers, as compared with people living at lower latitudes. (345, 554) Vitamin D supplementation likely plays an important role in the prevention of cancer, as highlighted in the prospective study by Bischoff-Ferrari et al (see section on Primary Cancer Prevention). (239, 240) Furthermore, in a meta-analysis of 50 trials with a total of 74,655 participants, Zhang et al reported that Vitamin D supplementation significantly reduced the risk of cancer death (0.85,0.74 to 0.97, 0%). (574) In subgroup analyses, all-cause mortality was significantly lower in trials with vitamin D3 supplementation than in trials with vitamin D2 supplementation. An analysis of 25(OH)D-cancer incidence rates suggests that achieving a vitamin D level of 80 ng/mL vs. 10 ng/mL would reduce cancer incidence rates by 70 ± 10%. (345)

The VITamin D and OmegA-3 TriaL (VITAL) was a nationwide, randomized, placebo-controlled, 2X2 factorial trial of vitamin D3 (cholecalciferol, 2000 IU/day) and marine omega-3 fatty acids (1 g/day) for the prevention of cancer and cardiovascular disease. (575) The primary endpoints of this study were total invasive cancer and major cardiovascular events. While the hazard ratios for cancer deaths comparing vitamin D to placebo were HR 0.83 (0.67–1.02) none of the primary or secondary endpoints reached statistical significance. It should be recognized that in this study both the dose of vitamin D and omega 3 fatty acids were absurdly low; and it is likely that this study was designed to fail. Nevertheless, the results of the VITAL study differ significantly from the DO-HEALTH trial which used similarly low doses of vitamin D and omega-3 fatty acids. (239, 240) In this study the HR for the prevention of cancer with vitamin D3 and omega 3 fatty acids compared to placebo was 0.53 (0.28-1.0).

Anticancer pathways and mechanisms

Experimental evidence indicates that vitamin D has diverse antineoplastic activity (see Figure 8). Binding of vitamin D to its target, the vitamin D receptor, leads to transcriptional activation and repression of target genes and results in induction of differentiation and apoptosis, inhibition of CSCs, and decreased proliferation, angiogenesis, and metastatic potential. (576) Vitamin D induces apoptosis of cancer cells, (577) counteracts aberrant WNT-β catenin signaling, (578) and has broad anti-inflammatory effects via downregulation of nuclear factor-Kβ and inhibition of cyclooxygenase expression. (579) In colon, prostate, and breast carcinoma cells, 1,25-(OH)2D3 upregulates several pro-apoptotic proteins (BAX, BAK, BAG, BAD, G0S2) and suppresses survival and anti-apoptotic proteins (thymidylate synthase, survivin, BCL-2, BCL-XL). (580) In this way, it favors the release of cytochrome C from mitochondria and the activation of caspases 3 and 9 that lead to apoptosis. 1,25-(OH)2D3 and metformin have additive/synergistic antiproliferative and proapoptotic effects in colon carcinoma and other types of cells. (581)

In many cancer cell types, 1,25-(OH)2 D3 directly arrests the cell cycle in the G0/G1 phase by downregulating cyclin-dependent kinases and repressing genes that encode cyclins D1 and C. (582) 1,25-(OH)2D3 decreases the expression of EGFR and interferes with the insulin-like growth factor (IGF)-I/II pathway. (345) Vitamin D has activity against human breast cancer cell lines by targeting the Ras/MEK/ERK pathway. (580) In addition, 1,25-(OH)2D3 diminishes the proliferation of breast cancer cells by inhibiting estrogen synthesis and signaling through estrogen receptor (ER)α. (583) In colon carcinoma cells, 1,25-(OH)2 D3 upregulates an array of intercellular adhesion molecules that are constituents of adherens junctions and tight junctions, including E-cadherin, occludin, claudin-2 and -12, and ZO-1 and -2. (584) The Wnt/β-catenin pathway plays an important role in cancer. Antagonism of the Wnt/β-catenin pathway by 1,25-(OH)2 D3 was reported in colon carcinoma cells by a double mechanism: (a) liganded VDR binds nuclear β-catenin, which hampers the formation of transcriptionally active β-catenin/TCF complexes, and (b) induction E-cadherin expression that attracts newly synthesized β-catenin protein to the plasma membrane adherens junctions. In that way, it decreases β-catenin nuclear accumulation. (585)

1,25-(OH)2 D3 is an important modulator of the immune system, as reflected by the expression of vitamin D receptors by almost all types of immune cells. 1,25-(OH)2D 3 is an enhancer of innate immune reactions against tumor cells by activating macrophages, NK cells, and neutrophils. (345) An important mechanism of 1,25-(OH)2D3 is the inhibition of the NF-KB pathway. In turn, this causes the downregulation of multiple cytokines and their effects. 1,25(OH)2 D3 reduces the protumorigenic effect of PG E2 in prostate cancer cells by inhibiting COX-2 and so decreasing the levels of PG E2 and two PG receptors (EP2 and FP). (586)

Autophagy is a process of elimination of cytoplasmic waste materials and dysfunctional organelles that serves as a cytoprotective mechanism but that, when excessive, leads to cell death. (345) In cancer, VDR ligands trigger autophagic death by inducing crucial genes in several cancer cell types. Thus, 1,25-(OH)2 D3 de-represses the key autophagic MAP1LC3B (LC3B) gene and activates 50-AMP-activated protein kinase (AMPK). In Kaposi's sarcoma cells and myeloid leukemia cells, vitamin D compounds inhibit PI3K/AKT/mTOR signaling and activate Beclin-1-dependent autophagy. 1,25-(OH)2D3 has a pro-differentiation effect on several types of carcinoma cells by direct upregulation of epithelial genes and/or the repression of key epithelial mesenchymal transcription factors (EMT-TFs). (587)

In diverse types of carcinoma cells (colon, prostate, and breast), the antiangiogenic action of 1,25-(OH)2 D3 relies to a great extent on its ability to inhibit two major angiogenesis promoters: it suppresses the expression and activity of HIF-1α, a key transcription factor in hypoxia-induced angiogenesis, and of VEGF. (345) 1,25-(OH)2D3 also has inhibitory effects on tumor-derived endothelial cells. It reduces their proliferation and sprouting in vitro and diminishes the blood vessel density in cancer models. (588)

Clinical studies

Data suggest that the majority of patients with cancer are vitamin D deficient (level < 20 ng/mL).(570, 576, 589, 590) Several prospective observational studies have shown that higher levels of plasma 25-hydroxyvitamin D were associated with improved survival among patients with colorectal cancer. (589, 591-593) Similarly, elevated 25-OH D levels were associated with better overall survival in patients with breast and gastric cancer and lymphoma. (594) In a population-based study of patients with cancer of the breast, colon, lung, and lymphoma a 25-OHD level below 18 ng/mL at diagnosis experienced shorter survival. (595) In a meta-analysis of 19 studies Robsahm et al reported an inverse relationship between 25-hydroxyvitamin D and cancer survival. (596)

Chen performed a meta-analysis of observational cohort studies and randomized trials which assessed the role of post-diagnosis vitamin D supplement intake on survival among cancer patients. (597) The meta-analysis included 11 publications consisting of 5 RCTs and 6 observational cohort studies. The summary relative risk (SRR) for overall survival of vitamin D supplement use vs. non-use, pooling cohort studies and randomized trials, was 0.87 (95% CI, 0.78–0.98; p = 0.02). Vaughan-Shaw et al performed a meta-analysis of 7 studies evaluating the use of supplemental vitamin D in patients with colorectal cancer. (598) The study reported a 30% reduction in adverse outcomes and a beneficial effect on progression-free survival (HR = 0.65; 95% CI: 0.36–0.94). In a meta-analysis by Kuznia et al, subgroup analysis revealed that vitamin D3 administered daily, in contrast to bolus supplementation, reduced cancer mortality by 12 %. (599) It should be recognized that a daily dose of between 800 IU and 4000 IU was administered in the studies included in this meta-analysis and that vitamin D levels were not monitored. A more dramatic reduction in mortality would likely be realized if patients were dosed more appropriately.

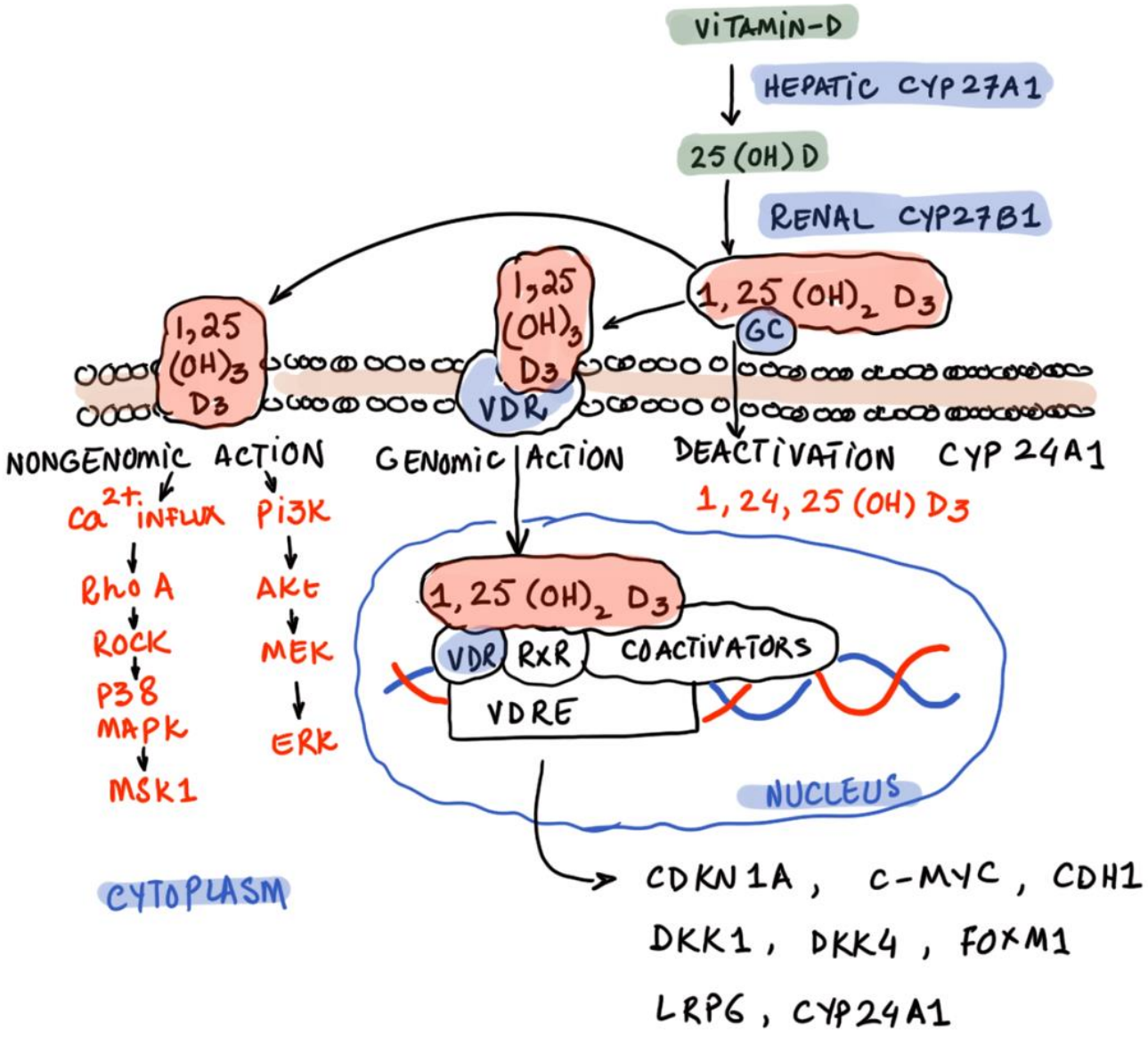


Figure 8. Overview of metabolic pathways of Vitamin D. {Source: Dr. Mobeen Syed}

Footnote for Figure 9: CYP27A1: Cytochrome P450 family 27 subfamily A member 1, CYP27B1: Cytochrome P450 family 27 subfamily B member 1, 25(OH)D: 25-hydroxyvitamin D, 1,25(OH)2 D3: 1,25-dihydroxyvitamin D3, GC: Vitamin D-binding protein (Gc protein), VDR: Vitamin D receptor, RXR: Retinoid X receptor, VDRE: Vitamin D response element, CDKN1A: Cyclin-dependent kinase inhibitor 1A, C-MYC: Cellular Myelocytomatosis oncogene, CDH1: Cadherin-1, DKK1: Dickkopf-1, DKK4: Dickkopf-4, FOXM1: Forkhead box protein M1, LRP6: Low-density lipoprotein receptor-related protein 6, PI3K: Phosphatidylinositol 3-kinase, Akt: Protein kinase B, MEK: Mitogen-activated protein kinase, ERK: Extracellular signal-regulated kinase, Rho A: Ras homolog gene family member A, ROCK: Rho-associated protein kinase, P38: p38 mitogen-activated protein kinase, MAPK: Mitogen-activated protein kinase, MSK1: Mitogen- and stress-activated protein kinase 1

SUNSHINE was a double-blind, multicenter, randomized clinical trial designed to evaluate the efficacy of “high dose” vitamin D3 compared with standard-dose vitamin D3 given in combination with standard chemotherapy in patients with metastatic colorectal cancer. (576) The high-dose group received a loading dose of 8,000 IU per day of vitamin D3 (two 4,000 IU capsules) for cycle 1 followed by 4,000 IU/d for subsequent cycles. The standard dose group received 400 IU/d of vitamin D3 during all cycles. In this underpowered (n=139) RCT, multivariable HR for progression-free survival or death was 0.64 (95% CI, 0-0.90; p = .02) in favor of the high dose group. Comparison of progression-free survival between the high-dose and standard-dose vitamin D3 groups using a log-rank test stratified by ECOG performance status was statistically significant (p = .03). At baseline, median plasma 25-hydroxyvitamin D levels were deficient in both the high-dose vitamin D3 group (16.1 ng/mL [IQR, 10.1 to 23.0 ng/mL]) and in the standard-dose vitamin D3 group (18.7 ng/mL [IQR, 13.5 to 22.7 ng/mL]). Only 9% of the total study population had sufficient levels (≥30 ng/mL) of 25-hydroxyvitamin D at baseline. At treatment discontinuation, patients in the high-dose vitamin D3 group had a median 25-hydroxyvitamin D level of 34.8 ng/mL (IQR, 24.9-44.7 ng/mL), whereas those in the standard-dose vitamin D3 group were still deficient in vitamin D and had a median 25-hydroxyvitamin D level of 18.7 ng/mL(IQR, 13.9-23.0ng/mL) (difference, 16.2 ng/mL [95% CI, 9.9-22.4 ng/mL]; *P* < .001). It is important to note that based on these levels the “high dose” group was profoundly underdosed. As indicated above, vitamin D dosing should be based on a serum level aiming for a level of > 50 ng/mL (target 55-90 ng/mL). Based on the data from this study we would suggest a daily dose of vitamin D3 of 20,000 to 50,000 IU/day until a vitamin D level is obtained. It is possible that patients with cancer may require an even higher level, approximating 150 ug/dL.

Wang et al demonstrated that postoperative vitamin D supplementation in esophageal cancer patients undergoing esophagectomy was associated with improved quality of life and with improved disease-free survival. (600) Similarly, vitamin D use post-diagnosis was found to be associated with a reduction in breast cancer-specific mortality. (601) Two recent clinical trials in prostate cancer patients suggest that vitamin D supplementation may prevent prostate cancer progression. (602, 603) Vitamin D has additive or synergistic effects when combined with conventional chemotherapy. (581) Zeichner et al demonstrated that the use of vitamin D during neoadjuvant chemotherapy in HER2-positive nonmetastatic breast cancer was associated with improved disease-free survival (HR, 0.36; 95% CI, 0.15-0.88; p=0.026). (604)

Types of cancers that Vitamin D may be beneficial for

Vitamin D supplementation is likely beneficial in most cancers, but particularly in patients with breast, colorectal, gastric, esophagus, lung, and prostate cancer as well as those with lymphomas and melanoma.

Dosing and cautions

As almost all patients with cancer are severely vitamin D deficient, a high loading dose of vitamin D is suggested followed by dose titration according to vitamin D blood levels, aiming for a level of > 50 ng/mL (target 55-90 ng/mL). However current data suggest that levels up to 150 ng/mL are necessary for certain types of cancer to stop growth and metastasis. Vitamin D

intoxication is observed when serum levels of 25-hydroxyvitamin D are greater than 150 ng/mL (374 nmol per liter). (554) Hypercalcemia will usually not occur until levels exceed over 250 ng/mL. We, therefore, suggest a daily dose of 20,000 to 50,000 IU until a vitamin D level is obtained. With the suggested doses, serum 25(OH)D concentrations rise above 100 ng/mL within a week or two, but unless a suitable higher maintenance dose is used (~ 10,000 IU/day), the level will start to drop to baseline after three weeks or so, and the benefit of vitamin D will be lost. If measuring vitamin D levels is not feasible/possible, we would suggest a loading dose of 100,000 IU followed by 10,000 IU/day. Doses of 10,000 IU of vitamin D3 per day for up to 5 months were reported to be safe and without toxicity. (554, 557) It should be noted that dosages of vitamin D up to 80,000 IU/day have been reported to be safe. (605, 606) We recommended vitamin D3 over D2 as vitamin D2 is approximately 30% as effective as vitamin D3 in maintaining serum 25-hydroxyvitamin D levels. (554) Furthermore, vitamin D3 should be dosed daily rather than large intermittent bolus dosing. It is best to include both vitamin K2 (menaquinone [MK4/MK7] 100 mcg/day, or 800 mcg/week) and magnesium (250-500 mg/day) when doses of vitamin D > 8 000 IU/day are taken. (560, 561) Patients taking coumadin need to be closely monitored and the need to consult with their PCP before taking vitamin K2. Further, we suggest measuring PTH (parathyroid) levels and calcium levels and titrating the dose of Vitamin D according to the PTH levels as follows (Coimbra Protocol): (607, 608) i) if the PTH level is below the lower end of the reference range, reduce the dose of vitamin D ii) if the PTH level is at (or close too) the lower end of the reference range, maintain dose, iii) if PTH is within the reference range but not near to the low end of the reference range increase the dose of vitamin D.

2. Propranolol

This chapter is based in part on the chapter on propranolol from the book by Jeffrey Dach, MD entitled "*Cracking Cancer Toolkit"*.(154) Chronic stress activates the sympathetic nervous system, which secretes catecholamines which feed cancer growth.(609, 610) Accumulating data indicate that the psychological stress caused by chronic stressors is a major risk factor for cancer occurrence, growth and metastasis.(609, 610) "*Experimental analyses with* in vivo *animal models have now shown that behavioral stress can accelerate the progression of breast, prostate, and ovarian carcinomas, neuroblastomas, malignant melanomas, pancreatic carcinoma and some hemopoietic cancers such as leukemia. In many of these experimental models, the biological effects of stress could be efficiently blocked by beta-adrenergic antagonists and mimicked by pharmacologic beta agonists*."(611) In a mouse ovarian cancer model chronic stress promoted cancer progression.(612) Similarly chronic stress enhanced metastatic spread in a mouse model of Lewis lung cancer. (613) Partecke et al demonstrated that chronic stress increases experimental pancreatic cancer growth, reduces survival and could be antagonized by beta-adrenergic receptor blockade.(614)

Anticancer pathways and mechanisms

Propranolol is a commonly used non-selective, beta-adrenergic receptor antagonist used in the treatment of hypertension, angina, anxiety, cardiac arrhythmia, hyperthyroidism, essential tremor and as a prophylaxis against migraine, variceal bleeding and myocardial infarction. First developed in the 1960s, the drug is now available globally in generic form and is on the WHO List of Essential Medicines.(615)

Propranolol is a well-known and widely used beta-blocker with a range of actions that are of interest in an oncological context. Propranolol displays effects on cellular proliferation and invasion, on the immune system, on the angiogenic cascade, and on tumor cell sensitivity to existing treatments. Both pre-clinical and clinical evidence of these effects exist, in multiple cancer types. (615)

Propranolol blocks activation of the sympathetic nervous system. In a murine model of acute lymphoblastic leukemia (ALL) Lamkin et al found that chronic stress enhanced tumor growth and dissemination and that the effect could be inhibited by propranolol.(616) In a mouse model, Sloan et al reported that stress induced beta-adrenergic signaling increased macrophage infiltration into the tumor (M2 polarization), induced pro-metastatic gene expression and induced a 30-fold increase in distant metastatic lesions. (617) In this study, pharmacologic activation of β-adrenergic signaling induced similar effects, and treatment of stressed animals with the β-antagonist propranolol reversed the stress-induced macrophage infiltration and inhibited tumor spread to distant tissues.

Beta-adrenergic receptors are overexpressed in many cancers, playing a key role in invasion and metastatic behavior.(618) In addition, beta-adrenergic signaling plays a role in the tumor micro-environment, inducing immunosuppression, and enhancing tumor evasion by impairing host anti-tumor immunity. (619) Infiltration by nerve fibers is a feature of the tumor microenvironment that is associated with aggressiveness and involves nerve growth factor (NGF) production by cancer cells.(620) Catecholamines expressed in the tumor microenvironment greatly potentiate the pro-inflammatory milieu. Adrenergic signalling impairs anti-tumor CD8+ T cell responses which is reversed by propranolol.(619) Propranolol down-regulates hexokinase 2 and inhibits glucose metabolism.(621, 622) In a late stage breast cancer patient treated with neoadjuvant propranolol, propranolol decreased the expression of the pro-proliferative and pro-survival markers, while increasing pro-apoptotic p53 expression.(622) In addition, propranolol has pro-apoptotic activity in cancer cells lines independent of p53 status.(623)

Neuroblastoma is a pediatric tumor of the sympathetic nervous system, which is often associated with elevated catecholamines. Wolter et al demonstrated that propranolol inhibited growth of a panel of 15 neuroblastoma cell lines and treatment induced apoptosis and decreased proliferation. Activity was dependent on inhibition of the β2, not β1, adrenergic receptor, and treatment resulted in activation of p53 and p73 signaling in vitro.(623)

Furthermore, β-blockers increase the response to chemotherapy via direct antitumor and anti-angiogenic mechanisms in neuroblastoma. (624)

The most important function of propranolol acting via multiple mechanisms is to reduce metastatic spread. (625) Propranolol has been shown to inhibit the expression of the tissue modelling factor matrix metalloproteinase-2 (MMP-2), MMP-9 and the pro-angiogenic VEGF.(626-628) The anti-angiogenic effect of propranolol, via down-regulation of VEGF has also been shown in a range of cancer cell lines including nasopharyngeal carcinoma, melanoma, pancreatic cancer, leukemia, head and neck squamous cell carcinoma and infantile hemangiomas. (615) Guo et al observed that norepinephrine promoted the invasiveness of a pancreatic cell line in a concentration dependent manner and that norepinephrine increased the expression of MMP-2, MMP-9, and VEGF.(628) In this model these effects were inhibited by propranolol. Xia et al demonstrated that catecholamines contribute to the neovascularization of lung cancer via tumor-associated macrophages.(629) Park *et al* showed that hypoxia-inducible factor 1α (HIF-1α) expression is upregulated by norepinephrine and abrogated by propranolol. (630, 631)

Propranolol reduces migratory activity of breast cancer cells. In a breast cancer model the combination of metformin and propranolol reduced cancer progression, metastases, and reduced migratory and invasive behavior of cancer cells.(632) In this study the metabolic pathway of the cancer cell was skewed away from mitochondrial oxidative phosphorylation and towards glycolysis. In an experimental model, Brohee et al demonstrated that propranolol sensitizes prostate cancer cells to glucose metabolism inhibition and prevents cancer progression.(633)

In a number of cancer cell lines propranolol exerts synergistic anti-tumor activity when combined with conventional chemotherapy. (615, 624) Pasquier et al demonstrated that propranolol potentiates the anti-angiogenic effects and anti-tumor efficacy of chemotherapy agents.(634)

Clinical studies

Chang et al reviewed the use of propranolol in a database of 24,238 patients over a 12-year follow-up period. (635) These authors reported that propranolol treatment significantly lowered the risk of cancers of the head and neck (HRL 0.58), esophagus (HR:0.35), stomach (HR: 0.54) colon (HR 0.68) and prostate (HR:0.52).

In an observational study of 800 women who underwent removal of a triple-negative breast cancer, the hazard ratio for women on beta-blockers was 0.32 for metastases and 0.42 for death from breast cancer, compared to controls not on beta-blockers.(636) Melhem-Bertrandt reported relapse-free survival in a cohort of women using beta-blockers (HR=0.32). (637)
In a meta-analysis of 4 studies the risk of death from breast cancer was reduced by half with the use of beta-blockers (HR 0.5; 95% CI 0.32-0.8). (638) In a meta-analysis of 13 studies evaluating the use of beta-blockers in early stage breast cancer, the use of beta-blockers was

associated with a significant improvement in the recurrence free survival (RFS) in the overall population (HR 0.73; 95% CI, 0.56-0.96; P = 0.025) and in patients with triple-negative disease (HR 0.53; 95% CI, 0.35-0.81; P = 0.003).(639)

Data from a National Cancer Registry demonstrated that the cumulative probability of breast cancer-specific mortality was significantly lower for propranolol users compared with matched nonusers (hazard ratio, 0.19; 95% CI, 0.06 to 0.60). (265) It is important to note that in this study the protective effect of beta-blockers was restricted to propranolol and not the selective beta-blocker atenolol. A long term epidemiological study of breast cancer patients demonstrated that those patients receiving propranolol had a 57% reduction in distant metastases and a 71% reduced risk of dying from breast cancer compared to control patients.(266) In a 10 year follow up study of patients with breast cancer, patients treated with beta-blockers showed a significant reduction in metastasis development (p=0.026), tumor recurrence (p=0.001), and a longer disease free interval (p=0.01).(266)

In patients with ovarian cancer users of non-selective beta blockers had more than double the overall survival time when compared to non-users (90 months vs. 38.2 months, p<0,001).(640) In a retrospective evaluation of 1971 patients with multiple myeloma, the intake of beta-blockers was associated with a reduced risk of disease-specific death (0.53, 95% CI 0.42-0.67 in comparison to non-BB).(641) Multivariable analysis showed the same pattern for overall survival. In a non-randomized prospective study in patients with melanoma, the use of propranolol (80 mg daily) at the time of diagnosis was significantly inversely associated with recurrence of melanoma (80% risk reduction; hazard ratio, 0.18; 95% CI, 0.04-0.89; P = .03).(642)

Types of cancers propranolol may be beneficial for

It is likely that propranolol is effective against a broad range of cancers but may have particular activity against the following tumors: neuroblastoma, breast, melanoma, angiosarcoma, lung, multiple myeloma, cervical, hepatocellular carcinoma, ovarian, prostate, pancreatic cancer and brain sarcoma.(154, 615) In light of the positive clinical experience of propranolol in the treatment of infantile hemangioma, most recently confirmed in a large multi-center RCT, (643) and evidence of beta-adrenergic receptor expression in a range of vascular tumors including angiosarcomas propranolol is indicated in the management of these tumors.(644)

Dosing and cautions

The anti-hypertensive dose of propranolol is in the range 160 – 240 mg/day, starting at 80 mg and increasing as required to a maintenance dose that is generally 160 mg – 240 mg.(615) In patients with cancer we suggest a starting dose of 40 mg twice a day increased to 80 mg twice daily as tolerated. Propranolol should be avoided in patients with severe asthma, uncontrolled heart failure, and those with symptomatic bradycardia. Sudden termination of treatment is not advised.

3. Melatonin

Melatonin, N-acetyl-5-methoxytryptamine, is a small lipophilic molecule that is secreted by the pineal gland and its synthesis shows a circadian pattern. Melatonin is mainly produced by the pineal gland in response to darkness. (645) At night, melatonin levels increase, then start to decrease in the early morning and throughout the day. Elevated levels of melatonin at night stimulate target organs to enter into suitable homeostatic metabolic rhythms, which help protect the body from developing different diseases. (253)

Exposing the body to light at night may result in disruption of melatonin production and the circadian rhythm. Peak melatonin levels in the blood vary between individuals and depend on age, with levels decreasing rapidly after age 40. (646)

Melatonin has specific receptors to regulate many physiological functions namely MT1 and MT2; both are members of the seven transmembrane G-protein coupled receptor family. (647) Melatonin receptors are found throughout the body, which explains its multiple biological functions. (645) In addition, mitochondria of all cells produce melatonin in an autocrine fashion under the influence of near-infrared irradiation. (648, 649) Melatonin has numerous biological properties acting both directly and indirectly as a potent antioxidant. (645) Melatonin plays a critical role in normal mitochondrial function, being a strong inducer of oxidative phosphorylation.

Anticancer pathways and mechanisms

Low melatonin levels have been implicated in the etiology of cancer. Several studies have shown reduced levels of melatonin in patients with certain types of cancers, compared with normal, healthy people of the same age. (646) Disruption of nocturnal melatonin secretion in night shift workers has been associated with a modestly increased risk for breast and other cancer types. A meta-analysis of 26 observational studies found significantly increased breast cancer incidence among female airline cabin crew. (650) The International Agency for Research on Cancer reclassified “shiftwork that involves circadian disruption“ from a possible to a probable human carcinogen, in recognition of this relationship. (651)

In experimental models, melatonin has demonstrated a broad spectrum of anticancer activity with multiple underlying mechanisms being proposed (see Figure 9). (230, 253) Melatonin exerts cytotoxic, anti-mitotic, and pro-apoptotic actions in breast cancer cells. The antiproliferative activity of melatonin has been demonstrated in both ER-positive and ER-negative human breast cancer cell lines. In most of these reports, melatonin acted via the MT1 membrane receptor. In addition, melatonin activates cancer cell apoptosis; this may be mediated by PUMA up-regulation. Melatonin increases the expression of pro-apoptotic mediators such as BAX/BAK, Apaf-1, caspases, and p53. (652) Melatonin has been demonstrated to inhibit the proliferation of CSCs and to reduce the expression of Ki67 and matrix metalloproteinase 9. (653) Melatonin can cause cancer cells to switch from anaerobic glycolysis to conventional oxidative phosphorylation via the Krebs cycle. This slows down the proliferative activity of cancer cells, reduces their metastatic potential, and directs the cells to

undergo apoptosis. Melatonin stimulates the synthesis of acetyl-CoA from pyruvate by inhibiting the mitochondrial enzyme pyruvate dehydrogenase kinase. (654) A study demonstrated that melatonin altered Ewing sarcoma metabolic profile by inhibiting the Warburg effect. (655) In prostate cancer cells, melatonin was able to reduce glucose metabolism via the downregulation of glycolysis and the pentose phosphate pathway. (656) The antiestrogenic action of melatonin could also enhance the ability of this hormone to limit the proliferation of hormone-sensitive breast cancer. (230) It is likely that melatonin acts synergistically with other repurposed medications. Proietti et al demonstrated that melatonin and vitamin D3 synergistically down-regulated Akt and MDM2 (a regulator of p53) leading to inhibition of breast cancer cells.(232)

Anti-angiogenesis is one of the major mechanisms by which melatonin exerts its anticancer effects. Melatonin inhibits hypoxia-induced factor 1-α thereby preventing VEGF expression. Melatonin also inhibits endothelial cell migration, endothelial cell invasion, and endothelial cell tube formation. It also prevents cancer cell migration via alteration of PI3K and MAPK signaling pathways in both receptor-dependent and independent manner. (653) Melatonin has been demonstrated to stimulate T cell and NK production and reduce regulatory T cells (Tregs). (657, 658)

Melatonin may benefit cancer patients who are also receiving chemotherapy, radiotherapy, supportive therapy, or palliative therapy by improving survival and ameliorating the side effects of chemotherapy.

Clinical studies

In addition to case studies, (659-661) the clinical benefit of melatonin in patients with cancer is supported by the highest level of evidence, namely meta-analyses of RCTs. (662, 663) Seely et al systematically reviewed the effects of melatonin in conjunction with chemotherapy, radiotherapy, supportive care, and palliative care on 1-year survival, complete response, partial response, stable disease, and chemotherapy-associated toxicities. (663) This analysis included 21 randomized studies all of which studied solid tumors. The pooled relative risk (RR) for 1-year mortality was 0.63 (95% CI = 0.53-0.74; $P < 0.001$). Improved effects were found for complete response, partial response, and stable disease. In trials combining melatonin with chemotherapy, adjuvant melatonin decreased 1-year mortality (RR = 0.60; 95% CI = 0.54-0.67). In a meta-analysis of RCT's, Wang reported that melatonin as an adjuvant therapy for cancer led to substantial improvements in tumor remission, 1-year survival, and alleviation of radiochemotherapy-related side effects. (664)

Types of cancers that melatonin may be beneficial for

Melatonin may be active in several cancers including cancers of the breast, ovary, pancreas, liver, kidney, mouth, stomach, colon/rectum, brain, lung, prostate, head and neck, and various leukemias and sarcomas. (230, 253)

Dosing and cautions

The optimal dosing regimen for melatonin is not clear. Most studies have used a dose of 20-40 mg at night. (662, 663) In patients with advanced disease and/or highly malignant disease the night-time dose can be increased to 60 mg with an additional 20 mg dose at midday. (662, 663) A higher dosage has been suggested in patients with severe disease; namely 20-30 mg at 10 am and 4 pm with 60 mg at nighttime (personal communication Dr Russel Reiter). Considering the impressive safety profile of melatonin (see below) a therapeutic trial of the higher dose should be explored. A proportion of patients are intolerant of higher doses of melatonin due to REM sleep induced nightmares (slow metabolizers with reduced first pass effect). Consequently, providers should advise patients to begin with 1 -5 mg at night; a slow-release/extended-release preparation at nighttime may minimize REM sleep-induced nightmares (best taken an hour before retiring). The dose should be increased up to 20-30 mg, as tolerated. Melatonin is probably the safest medical compound available, with a LD50 of infinity (it is impossible to kill an animal with industrial doses of melatonin). The only side effects reported are early morning drowsiness and "bad dreams" (when the dose is increased too rapidly). (645)

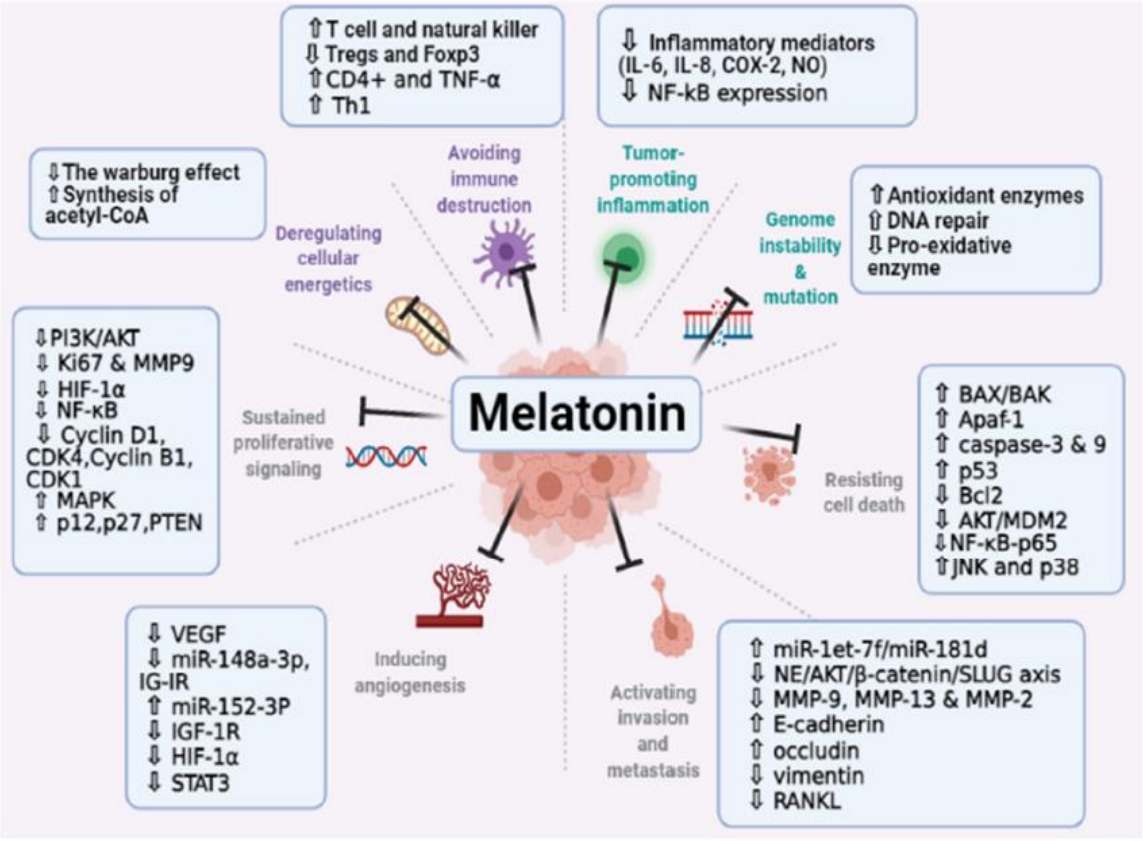


Figure 9. Multiple anticancer pathways affected by melatonin (Source: Reproduced from Talib et al under Creative Commons 4.0 license). (253)

4. Metformin

Numerous trials have shown that metformin, routinely used to treat diabetes, also inhibits the development of cancer cells, and reduces cancer cell proliferation.

Anticancer pathways and mechanisms

Metformin has been shown to have anticancer activity both in vivo and in vitro. (665) It has been proposed that the anticancer properties of metformin result from both direct effects on cancer cells, particularly through inhibition of the AMPK/mTOR pathway, (666) and indirect effects on the host, by its blood glucose-lowering properties and anti-inflammatory effects. Metformin inhibits complex I of the electron transport chain in mitochondria, putting cancer cells under bioenergetic stress and forcing them to rely on glycolysis for ATP synthesis. (667) Metformin's inhibition of GPD2 activity alters the cytosolic redox balance, which prevents redox-dependent substrates from entering the gluconeogenic pathway. (668) Metformin suppresses protein synthesis and cell development by activating ATM (ataxia telangiectasia mutated), LKB1 (liver kinase B1), and adenosine monophosphate-activated kinase (AMPK). This reduces mTOR action. (669) By turning on AMPK, metformin can activate p53, which ultimately stops the cell cycle. (669) Peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1), a distinct molecular pathway, is upregulated due to AMPK activation following metformin exposure. Low levels of PGC-1 have been linked to poorer outcomes, and it is a transcriptional coactivator involved in mitochondrial biogenesis. Metformin boosts PGC-1 and suppresses gluconeogenesis activation. (668) Metformin interacts with the S1RT1 pathway: The sirtuin 1 (SIRT1) route, which is activated by the NAD (+)-dependent protein sirtuin 1 (SIRT1) with deacetylase activity, is another significant mechanism that connects metabolism with cell proliferation. (668) Unlike most standard chemotherapy, metformin suppresses CSCs, the root of cancer. (670)

Metformin regulates the EGFR and IGFR pathways, which are involved in cell growth, proliferation, and the coordination of several metabolic processes. A similar circuit performs profound functions in apoptosis and cell proliferation and is a critical axis for metabolism and cell growth. Additional research has revealed that a poor prognosis, metastasis, and disease progression are linked to elevated IGF-1 and IGF-2 expression and IGFBP-3 abnormalities. Evidence suggests that metformin treatment may prevent some of these alterations and exert an antitumor effect. Both the EGFR and IGFR pathways can boost metabolic cell modifications in a coordinated manner, acting as neoplasm promoters and forming a feedback system. (668)

Clinical studies

Meta-analyses have examined the role of metformin in the primary prevention of cancer, where it was found to significantly reduce overall cancer incidence. (246, 247) Lega et al performed a meta-analysis of 21 observational studies, evaluating the outcomes of diabetic patients with cancer who were receiving metformin. (671) In this study, metformin was associated with a reduction in all-cause mortality [HR, 0.73; 95% confidence intervals (CI), 0.64-0.83] and cancer-specific mortality (HR, 0.74; 95% CI, 0.62-0.88); patients with colorectal cancer demonstrated the greatest benefit. In a similar analysis performed by Yin et al, metformin

improved overall survival in patients with lung, breast, and prostate cancer. (672) In diabetic patients with colorectal cancer Mei et al demonstrated that metformin reduced the risk of all causes of death by 44% and the specific risk of colorectal cancer death by 34%. (673) Coyle et al performed a meta-analysis of 27 observational studies that investigated the use of metformin as an adjunctive treatment for cancer. (674) The findings of this study suggested that metformin was associated with significant benefit in the early treatment of patients with colorectal and prostate cancer, particularly in those receiving radical radiotherapy.

Types of cancers that metformin may be beneficial for

Various malignancies can be prevented with the use of metformin. In general, metformin can: i) lower cancer incidence, ii) lower cancer mortality, iii) improve cancer cell response to radiotherapy and chemotherapy, iv) optimize tumor migration and lower malignancy, v) lower relapse risk, and vi) lessen the harmful effects of androgen derivatives. (668, 669) Collective findings show that metformin has a broad spectrum of anticancer activity against breast, pancreatic, gastric, colorectal, endometrial, pancreatic prostate, non-small cell lung cancer, and bladder cancers. (668, 673-679) However, the greatest benefit may be in patients with colorectal and prostate cancer, (673, 679), particularly when used as an adjunctive therapy.

Dosing and cautions

A dose of metformin of 1,000 mg twice daily is suggested. Metformin is a remarkably safe drug with very few side effects. The most common adverse effects include abdominal or stomach discomfort, cough, hoarseness, decreased appetite, and diarrhea. Prolonged use is associated with vitamin B12 deficiency; supplementation with a B complex vitamin is therefore suggested. Metformin may cause very low blood glucose when combined with berberine; hence the blood glucose should be very closely monitored in patients taking this combination; if low glucose does occur, we would suggest alternating metformin and berberine (monthly).

5. Curcumin

Curcumin, popularly called "curry powder" or turmeric, is a polyphenol extracted from Curcuma longa. Curcumin has antioxidant, anti-inflammatory, antimicrobial, antiviral, and anticancer properties. (680)

Anticancer pathways and mechanisms

Curcumin has been shown to interfere with multiple cell signaling pathways in cancer cells (see Figure 10), including: (681-698)

i. Cell cycle (cyclin D1 and cyclin E)
ii. Apoptosis (activation of caspases and down-regulation of antiapoptotic gene products), proliferation (HER-2, EGFR, and AP-1)
iii. Survival (PI3K/AKT pathway)
iv. Invasion (MMP-9 and adhesion molecules)

v. Angiogenesis (VEGF)
vi. Metastasis (CXCR-4)
vii. Inflammation (NF-kappa B, TNF, IL-6, IL-1, COX-2, and 5-LOX)

Aberrant activation of NF-κB is characteristic of cancer, with NF-κB playing a major role in cancer angiogenesis, proliferation, metastasis, inflammation, and through the induction of cell survival pathways and inhibition of apoptosis. Phosphorylated NF-KB binds DNA and starts the transcription of oncogenes that block apoptosis and initiates cellular proliferation and angiogenesis. (680) Curcumin suppresses NF-KB activity by inhibiting the phosphorylation by I kappa B kinase and impeding nuclear translocation of the NF-KB p65 subunit. STAT3, is a common target for several signaling pathways regulating oncogenes, as well as modulating the transduction of pro-inflammatory cytokines and growth factors. (680) STAT3 contributes to the growth and survival of the cancer cell, increasing the expression of anti-apoptotic proteins such as Bcl-2 and Bcl-xL, thereby blocking apoptosis. Several factors, such as IL-6, as well as EGFR and PDGF, are reported to be STAT3 activators. (699) STAT3 is reported to be a molecular target of curcumin in several tumors, both directly and indirectly by inhibition of IL-6. (700) The accumulation and activation of immune suppressive cells like Treg, Th17, and MDSCs, the differentiation of macrophages toward the M2 phenotype, and the absence of functional DCs are all caused by STAT3 activation. Curcumin significantly decreases STAT3 phosphorylation. (689) Curcumin inhibits breast cancer cell lines through inhibiting HER2-tyrosine kinase. (701) Curcumin inhibits the phosphorylation of Akt, mTOR, and their downstream proteins, resulting in cell cycle arrest in various breast cancer cell lines. (702)

Curcumin downregulates hexokinase-2 and dissociates HK-2 from the mitochondria inducing apoptosis. (703) Curcumin is also able to interfere with the cell signaling pathway of EGFR, a family of receptor tyrosine kinases, that is reported to be associated with the proliferation, adhesion, migration, and differentiation of cancer cells. (704, 705) Curcumin inhibited the growth and proliferation of breast cancer cells by reducing EGFR signaling and decreasing EGFR and Akt levels. (704) Curcumin has been demonstrated to induce apoptosis of triple-negative breast cancer cells by inhibition of EGFR expression. (705) In pancreatic cancer cells, curcumin potentiates the anticancer activity of gemcitabine via inhibition of NF-κB and proliferation, angiogenesis and expression of Cdc20, which is associated with enhanced cell proliferation and invasion. (706)

Curcumin has an impact on the tumor microenvironment by inhibiting angiogenesis even under the hypoxic status within the tumor microenvironment. (686) Furthermore, curcumin has activity against CSCs in addition to promoting apoptosis. (686, 690, 697, 707) Curcumin induces apoptosis in tumor cells, (681) through ROS-mediated endoplasmic reticulum (ER) stress and mitochondrion-dependent pathways. (686) In addition, curcumin acts through the Wnt/-catenin pathway. (688, 698)

Clinical studies
Despite the broad anticancer activities of curcumin in experimental models, its clinical use has been limited by its poor bioavailability. Its oral bioavailability is low due to its poor absorption,

extensive phase I and II biotransformation, and rapid elimination through the gall bladder. (708) Due to its low solubility in water and poor absorption, it is traditionally taken with full-fat milk and black pepper, which enhance its absorption. To improve the bioavailability, various curcumin analogs and novel drug delivery systems (e.g., phospholipids, nanoparticles, and liposomes) are under investigation.

While a few case series describing the use of curcumin in cancer have been published, (682, 695, 709-713) the clinical efficacy of curcumin has been evaluated in a limited number of studies. In a pilot randomized clinical trial in patients with multiple myeloma, the addition of curcumin (4 g twice daily for 28 days) to treatment with melphalan and prednisone increased the rates of remission ([75% vs. 33.3%, p=0.009]. (684) In this study NF-KB, VEGF, and TNF levels were significantly lower in the curcumin group with TNF levels being strongly correlated with remission [OR=1.35; 95% CI=1.03-1.76, p=0.03]. In a phase IIa, open-labeled trial patients with metastatic colorectal cancer were randomized to fluorouracil/oxaliplatin chemotherapy (FOLFOX) compared with FOLFOX + 2 g oral curcumin/d (CUFOX). (714) In the intention-to-treat population, the HR for overall survival was 0.34 (95% CI: 0.14, 0.82; P = 0.02) (median of 200 and 502 days for FOLFOX and CUFOX, respectively). In a prospective, single-arm phase II study, Pastorelli et al evaluated the use of a phytosome complex of curcumin (2 g/day) as adjunctive therapy with gemcitabine in patients with advanced pancreatic cancer. (715) The median overall survival of patients treated with gemcitabine as a single agent is 5.7 months. (716) These investigators reported a 27.3% response rate with 34.1% of cases having stable disease, with a total disease control rate of 61.4%. The median progression-free survival and overall survival were 8.4 and 10.2 months, respectively. Saghatelyan et al randomized 150 women with advanced metastatic breast cancer to receive either paclitaxel plus placebo or paclitaxel plus curcumin once per week for 12 weeks with 3 months of follow-up. (717) In this study, the curcumin was given intravenously. The intention-to-treat analysis revealed that the objective response rate of curcumin was significantly higher than that of the placebo (51% vs. 33%, p<0.01) at 4 weeks of follow-up. The difference between the groups was even greater when only patients who had completed the treatment (61% vs. 38%, odds ratio =2.64, p<0.01) were included.

In dose escalation studies, up to 10 g of curcumin taken daily has been shown to be well tolerated. Patients with breast cancer taking 6 g/day of curcumin for 7 weeks, and patients with prostate cancer who took 3 g/day of curcumin for 9 weeks exhibited no adverse effects. [301,353,389]

***Types of cancers that curcumin (turmeric) may be beneficial** for*
Curcumin (turmeric) may be beneficial for the following types of cancer: colorectal, lung, pancreatic, breast, prostate, chronic myeloid leukemia, liver, gastric, brain tumors, ovarian, skin, head and neck, lymphoma, esophageal and myeloma. (680, 698)

Drug formulations and cautions
The use of curcumin has been limited by its poor solubility, absorption, and bioavailability. The manipulation and encapsulation of curcumin into a nanocarrier formulation can overcome

these major drawbacks and potentially may lead to a far superior therapeutic efficacy. In a murine Hodgkin's Lymphoma model, formulating curcumin in solid lipid nanoparticles exhibited greater anticancer activity compared to curcumin alone. (718) Nano-curcumin preparations or formulations designed to enhance absorption are therefore recommended. (719-722)

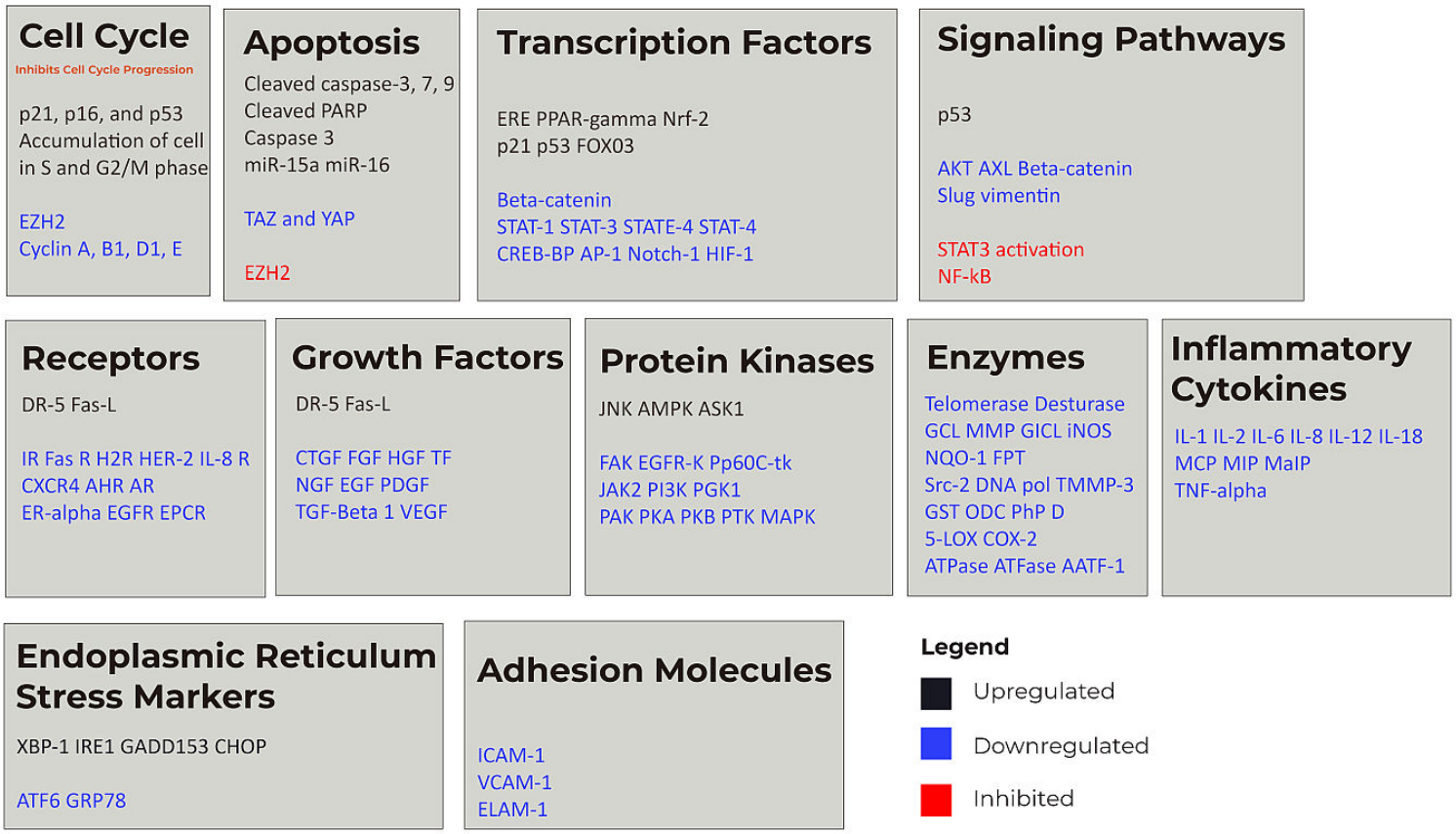


Figure 10. Curcumin - a multifaceted anticancer agent [Source: Dr. Mobeen Syed]
Footnote for Figure 10. See Appendix 3.

In the U.S., a large share (55%) of the turmeric dietary supplement market is comprised of products formulated to enhance curcumin bioavailability, including proprietary products where curcuminoid extracts are often combined with some type of lipophilic carrier to increase absorption, or products combining curcumin with piperine to decrease metabolism. (723) However, as the quality of these products may vary, we would recommend the use of USP-grade supplements. Furthermore, nanoformulation-based combination therapy has emerged as a potent approach for drug delivery systems. (724) A nanodrug co-delivery system incorporating chemotherapeutic agents has demonstrated greater cancer cell sensitivity. (725, 726)

Curcumin has been characterized as "generally safe" by the US Food and Drug Administration (FDA). (727) No toxicity is seen for doses of up to 8–10 g/day. (695, 696, 698, 712, 728, 729)

However, diarrhea can be a frequent side effect, especially if the daily dose exceeds 4 g. (695) Hepatic injury (hepatitis) is a rare complication and therefore liver function tests should be monitored during long-term use. (730)

Curcumin does not appear to have any overt negative effects, but it has been noted that this compound can inhibit several cytochromes P450 subtypes, including CYP2C9 and CYP3A4. (698, 731) Consequently, curcumin has been reported to interact with several different drugs, including antidepressants, antibiotics, and anticoagulants like coumadin and clopidogrel. (698, 732) Curcumin has anticoagulant effects and may prolong bleeding in people using anticoagulants. (698, 733)

6. Ivermectin

Ivermectin is a macrolide antiparasitic drug that is widely used for the treatment of many parasitic diseases, such as river blindness, elephantiasis, and scabies. Satoshi Ōmura and William C. Campbell won the 2015 Nobel Prize in Physiology or Medicine for the discovery of the efficacy of ivermectin against parasitic diseases. Ivermectin was approved by the FDA for use in humans in 1978. Recently, scientists have discovered that ivermectin has strong anticancer effects. Ivermectin has been reported to inhibit the proliferation of several tumor cells by regulating multiple signaling pathways. (734-736)

Anticancer pathways and mechanisms

In 1996, Didier et al. found that ivermectin may effectively reverse tumor multidrug resistance, this is the first reported antitumorigenic activity of ivermectin.(737) Since then, many studies revealed that ivermectin exerted antitumor effects through multiple targets including chloride channel, PAK1 protein, Akt/mTOR signaling, P2X4/P2X7 receptors, WNTTCF pathway, SIN3 domain, NS3 DDX23 helicase and Nanog/Sox2/Oct4 genes. (738)

Experimental data demonstrated that ivermectin inhibited the proliferation of multiple breast cancer cell lines. (739) The mechanism involved the inhibition by ivermectin of the Akt/mTOR pathway to induce autophagy. Ivermectin has been demonstrated to inhibit the proliferation of canine breast tumor cell lines by blocking the cell cycle related to the inhibition of the Wnt pathway. (740) In a study that screened Wnt pathway inhibitors, ivermectin inhibited the proliferation of multiple cancers, including the colorectal cancer cell, and promoted apoptosis by blocking the Wnt pathway. (741) Other cancers that show an active Wnt pathway and are inhibited by ivermectin include carcinomas of the lung, stomach, cervix, endometrium, and lung, as well as melanomas and gliomas. (741)

Triple-negative breast cancer (TNBC) refers to cancer that is negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) and is the most aggressive subtype of breast cancer with the worst prognosis. (742) In addition, there is also no clinically applicable therapeutic drug currently available. A drug screening study of TNBC showed that ivermectin resulted in impairment of clonogenic self-renewal in vitro and

inhibition of tumor growth and metastasis in vivo by blocking the SIN3-interaction domain.(743) Ivermectin exerts an antitumor effect through the autophagy pathway. Using the autophagy inhibitors chloroquine and wortmannin or knocking down Bclin1 and Atg5 by siRNA to inhibit autophagy, the anticancer activity of ivermectin reduced significantly. (739)

Ivermectin induces cancer cell apoptosis mainly through the mitochondrial pathway. (734) Chen et al demonstrated that ivermectin inhibited the viability and induced apoptosis of esophageal squamous cancer cells through a mitochondrial-dependent pathway. (744) Heat shock protein-27 (HSP27) is highly expressed in and supports oncogene expression of many cancers. Ivermectin inhibits MAPKAP2-mediated HSP27 phosphorylation and depolymerization, thereby blocking HSP27-regulated survival signaling and client-oncoprotein interactions. (745) Chen et al demonstrated that ivermectin inhibited the viability and induced apoptosis of esophageal squamous carcinoma cells through a mitochondrial-dependent manner. In addition, Sharmeen et al demonstrated that ivermectin induced chloride-dependent membrane hyperpolarization and cell death in leukemia cells. (746) Li et al demonstrated that Ivermectin induces nonprotective autophagy by downregulating PAK1 and apoptosis in lung adenocarcinoma cells. (738) Hu et al demonstrated that ivermectin augmented the efficacy of chemotherapy in an osteosarcoma cell line. (747)

Ivermectin has anticancer activity by influencing the tumor microenvironment. Ivermectin decreases MDSC and Tregs and targets CSCs. (233, 748) Furthermore, ivermectin acts to suppress the action of TAMs, which otherwise produce aberrant cytokine signals that act to suppress tumor apoptosis via a number of pathways, particularly TGF-β, and also upregulates the expression of the p53 tumor suppressor gene.

Although a number of antiparasitic drugs including ivermectin, mebendazole and niclosamide have proven anti-cancer effects it is important to recognize that cancer is NOT a parasitic disease as has been suggested in the “popular press” and by misguided clinicians. There is no evidence that cancer is caused by or related to any parasitic disease. These drugs act via specific biochemical pathways specific to the cancer cell which are distinct from their anti-parasitic mechanisms of action.

Clinical studies

While many in vitro studies have demonstrated the effectiveness of ivermectin against multiple cancers, the reported clinical effectiveness is limited to small case series. (749, 750) However, it appears that ivermectin is widely prescribed across the world for cancer. Further, we are aware of multiple “anecdotal” reports of solid tumors that have shown a dramatic response to repurposed drug regimens that included ivermectin.

Types of cancers ivermectin may be beneficial for

Ivermectin has shown in vitro activity against the following cancer breast (including TNBC), stomach, cervix, esophageal, endometrium, liver, prostate, kidney and ovarian cancer as well as cholangiocarcinoma, melanomas, leukemia, lymphoma and gliomas. (734)

Dosing and cautions
The optimal dosing strategy with ivermectin is unclear. De Castro et al reported the use of 1mg/kg/day for up to 6 months in three pediatric patients with refractory AML without untoward side effects. (749) Ishiguro et al reported the use of ivermectin 12 mg twice weekly.(750) Anecdotal evidence suggest that a daily dose of 12-18 mg may be effective (prescribed indefinitely). As ivermectin has a remarkable safety record long term treatment at this dose appears safe. As mentioned previously, ivermectin may be synergistic with mebendazole. As ivermectin does not cross the blood-brain barrier, it is likely ineffective for brain tumors. Furthermore, caution is advised in patients with disruption of the blood-brain barrier.

7. Mebendazole/ Fenbendazole/Albendazole

Anticancer pathways and mechanisms
A compound originally developed as a treatment for parasitic worms, mebendazole (MBZ) works by fatally disrupting the cellular microtubule formation in abnormal cancer cells that occurs as the cell is attempting to divide. Like the other benzimidazoles, BMZ binds to the tubulin colchicine-binding domain and appears to act by both p53-dependent and independent mechanisms. (751) MBZ inhibits many factors involved in tumor progressions such as tubulin polymerization, angiogenesis, pro-survival pathways, matrix metalloproteinases, and multi-drug resistance protein transporters. (752) MBZ inhibits CSCs; this mechanism of action is critical in preventing metastasis. (231, 752) In addition, in a juvenile glioblastoma mouse model MBZ reduced tumor cell growth and invasion when evaluated under *in-vitro* and *in-vivo* conditions through inhibition of both the glutaminolysis and the glycolysis pathways. (314) In this study the effect of ketosis and MBZ were synergistic in inhibiting tumor growth.

MBZ decreases the activity of the Hedgehog pathway, which is common in gliomas, melanomas, lung cancers, ovarian cancers, and colorectal cancer. (163) MBZ inactivates Bcl-2 and activates caspases to promote apoptosis in cancer cells and the release of cytochrome c which has also been shown to trigger apoptosis in malignant cells. Benzimidazole modulates the typically overactivated MAPK pathway, switching it to activate the apoptotic pathway, rather than the anti-apoptotic pathway; it also destabilizes microtubules, structural proteins required to maintain a cell's integrity during the process of mitosis, among other functions; it *also* interferes with cancer cells' glycolysis-dependent metabolism, upon which *most* cancers are heavily preferentially dependent, as well as functioning as an inhibitor of mitochondrial oxidative phosphorylation, or OXPHOS, which reduces the residual energy available via the ordinary metabolic ATP production pathway.

MBZ can cross the blood-brain barrier and has been demonstrated to slow the growth of gliomas by targeting signaling pathways involved in cell proliferation, apoptosis, invasion, and migration, as well as by making glioma cells more susceptible to conventional chemotherapy and radiotherapy. (753)

MBZ can also sensitize cancer cells to conventional therapy, such as chemotherapeutics and radiation, enhancing their combined antitumor potential, confirming that MBZ may be useful as an adjuvant therapeutic combined with traditional chemotherapy. (753) When combined with low-dose chemotherapy there is also evidence these drugs help to destroy the tumor-associated macrophage cells that may help maintain a favorable environment for the cancer to flourish.

Clinical studies

The use of benzimidazoles in cancer is limited to a few case reports (754, 755) and a small case series. (756) Mebendazole is a component of the multidrug cocktail used in the METRICS study.(267) The use of benzimidazoles, and in particular fenbendazole, has achieved much attention as a repurposed drug for cancer due to the reported experience of Joe Tippens. (154) In 2016, Tippens was diagnosed with non-small-cell lung cancer with extensive metastatic disease. At the advice of a veterinarian friend, he took Fenbendazole together with nanocurcumin, and three months after starting these drugs his PET scan was completely clear. He remains alive and disease-free up until the present; however, some questions surround his apparent cure.

Types of cancers that mebendazole may be beneficial for

A wide variety of cancers, including non-small cell lung cancer, adrenocortical, colorectal, chemo-resistant melanoma, glioblastoma multiforme, colon, leukemia, osteosarcoma/soft tissue sarcoma, acute myeloid sarcoma, breast (ER+ invasive ductal), kidney, and ovarian carcinoma, have been shown to be responsive to benzimidazoles, including MBZ. (260, 751-753, 757-766)

Dosing and cautions

We suggest mebendazole 100-200 mg/day. The cost of mebendazole in the U.S. skyrocketed once this drug was discovered to have activity against cancer ($555 for a single 100 mg tablet?). However, mebendazole is available from international (India) and local compounding pharmacies for between 25c to $2 for a 100 mg tablet. Ivermectin can be considered an alternative if mebendazole is unavailable. However, it is likely that both drugs combined may have additive or synergistic anticancer activity.

8. Green Tea

Anticancer pathways and mechanisms

Green tea is a significant source of a type of flavonoid called catechin, which includes epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC). The most abundant individual catechin in fresh tea leaves is EGCG, which is more than 40% of the total content of catechins. (242) Green tea catechins (GTCs) have been proven to be effective in inhibiting cancer growth in several experimental models. (767-769) In addition, GTCs may have synergistic anticancer activity when combined with other

phytochemicals, particularly resveratrol. (770, 771) GTCs, particularly EGCG, may have a role in both the prevention and treatment of cancers, (772) specifically those dependent on the glutamate pathway as a source of energy. Mitochondrial glutamate dehydrogenase (GDH) catalyzes the oxidative deamination of L-glutamate. Activation of GDH is tightly correlated with increased glutaminolysis. Furthermore, glutamate serves as a mitochondrial intracellular messenger when glucose is being oxidized and the GDH participates in this process by synthesizing glutamate. (773) Li and colleagues demonstrated in vitro that EGCG allosterically inhibits GDH in nanomolar concentrations. (311, 312)

GTCs have an important anticarcinogenic role by promoting and/or inhibiting signal transmission through the targeted regulation of multiple links in the signal pathways that are activated or inhibited in cancer cells. (242) EGCG regulates signaling pathways by interacting with membrane receptors. EGCG significantly inhibited the expression of VEGF and reduced VEGF receptors. Inactivation of the VEGF signaling pathway suppresses angiogenesis, a common strategy for inhibiting carcinogenesis. EGCG activates PKA, which dephosphorylates related proteins such as the tumor suppressor Merlin and inhibits the proliferation of cancer cells. (774) EGCG inhibits STAT3 phosphorylation by blocking JAK2 phosphorylation. STAT3 suppresses anti-tumor immune responses and promotes the proliferation and migration of cancer cells. EGCG inhibits the MAPK signaling by competing for the phosphorylation sites of downstream proteins. EGCG inhibits the Wnt pathway by phosphorylating β-catenin and promoting its degradation. EGCG inhibits transcription factors involved in activating the Sonic hedgehog pathway. EGCG inhibited the activities of MMP2 and MMP9 and promoted the expression of tissue inhibitor of MMPs (TIMp1/2) to suppress the invasion and metastasis of tumor cells. (774) Green tea extract has been demonstrated to suppress CSCs. (775, 776)

GTCs have anticancer effects via additional pathways. (242) GTCs exert potent and selective in vitro and in vivo pro-apoptotic activity in cancer cells via several pathways. (767, 768, 777) GTC inhibits A549 cells by regulating its cell cycle arrest, increasing the expressions of p21 and p27, and inhibiting the expressions of p-AKT and cyclin E1 in a dose-dependent manner in the cancer cells. (778) EGCG inhibited the proliferation of human lung cancer cells by targeting the EGFR signaling pathway.

GTCs have been demonstrated to alter the tumor microenvironment (TME) thereby attenuating immunosuppression and the risk of metastases. (771) Flavonoids including GTCs (and resveratrol) are potent modulators of pro-inflammatory gene expression being, therefore, of great interest as agents selectively suppressing molecular targets within pro-inflammatory TME. GTCs have been demonstrated to increase the ratio of active cytotoxic T lymphocytes to Tregs in tumors, indicating a switch of “cold” tumors to “hot” with significantly improved anti-tumor immune therapeutics. (779) GTCs have anticancer effects by enhancing anticancer immunity via PD-1 axis and TLR4 pathways. (780, 781) In addition, GTCs repolarize tumor-associated macrophages (M2 to M1 macrophages), triggering an immune response and limiting metastases. (782) GTCs have been demonstrated to attenuate MDSC-mediated immunosuppression and increased the proportions of CD4+ and CD8+ T cells. (783)

Studies have shown that 20% of cancer-related deaths were directly due to TLR-induced cancer cachexia, in which cancer cells released heat shock proteins that acted as TLR-4 agonists in macrophages, skeletal muscle, and fat cells, causing downstream signal transduction. EGCG effectively downregulates the TLR-4 signal pathway. (781)

GTCs inhibit the accumulation of MDSCs, leading to restoration of the IFN-γ, enhancing the activity of CD8+ T-cells, and improvement of the ratio of CD4(+) to CD8(+) T-cells, which is beneficial to the improvement of the immune system's attack on tumor cells. (242) In addition, a phytochemical mixture including GTCs exerted anti-tumor activity by repolarization of M2-polarized macrophages and induced the production of IL-12, which recruit cytotoxic T lymphocytes and NKs within the tumor microenvironment. (782)

In addition to all these beneficial effects, GTCs potentiate the effects of conventional chemotherapeutic agents. Due to their effects on the important signaling pathways in vivo, catechins are often used as sensitizing agents in combination with chemotherapeutic drugs. The combination of anticancer drugs with catechins, whether before or after drug administration, reduced the toxicity of these drugs and enhanced the clinical efficacy by accelerating apoptosis of cancer cells. (242) Importantly, the combination of a number of chemotherapeutic drugs with GTCs will improve the chemotherapeutic sensitivity of cells to the drug, allowing a reduction in the dose of the chemotherapeutic drug. (242)

Clinical studies

Numerous experimental models have explored the mechanistic anticancer effects of GTCs; this data is supported by epidemiologic data, a case series of patients with B cell malignancies,(784) several case reports,(785, 786) and a RCT. A meta-analysis including 18 prospective cohorts and 25 case-control studies showed a significant inverse association between intake of tea catechins and risk of various cancers, with a relative risk (RR) being 0.935 (95% CI = 0.891-0.981). (242) Similarly an umbrella review and meta-analysis by Kim et al, which included 64 observational studies (case-control or cohort) demonstrated that GTC significantly reduced the risk of gastrointestinal cancer (oral, gastric, colorectal, biliary tract, and liver), breast cancer, and gynecological cancer (endometrial and ovarian cancer) as well as leukemia, lung cancer, and thyroid cancer. (251) In a phase I dose finding study in patients with Chronic Lymphocytic Leukemia EGCG was well tolerated and a decline in the absolute lymphocyte count and/or lymphadenopathy was observed in the majority of patients. (787) Lemanne et al reported on a patient who demonstrated a complete and durable remission of chronic lymphocytic leukemia (CLL) following high dose EGCG. (786) In a randomized, double-blind, placebo-controlled study, treatment with 600 mg/day of green tea catechins reduced the risk of prostate cancer from 30% to 3% in men with high-grade prostate intraepithelial neoplasia. (313)

Types of cancers that green tea may be beneficial for

Green tea catechins may be effective against a range of tumors including cancers of the prostate, breast, uterus, ovary, colorectal, lung, liver and gallbladder as well as glioblastoma and melanoma. (242) GTCs appear to be particularly beneficial for prostate cancer as well as breast cancer. (309, 313, 767-770, 783, 788)

Dosing and cautions
Green tea catechins should be taken in a dose of 500-1000 mg/day. Green tea extract should be taken during/after a meal rather than on an empty stomach. (252) Green tea extract has rarely been associated with liver toxicity. (789) The safety of green tea extract was evaluated by the US Pharmacopeia (USP) Dietary Supplement Information Expert Committee (DSIEC). (252) The DSIEC concluded that "*when dietary supplement products containing green tea extracts are used and formulated appropriately the Committee is unaware of significant safety issues that would prohibit monograph development.*" (252) Based on this data we suggest that green tea extracts be taken in the dosages recommended by the manufacturer. Regular liver function tests are suggested in patients taking green tea extract and green tea extract should be avoided/used cautiously in those with underlying liver disease.

9. Omega-3 Fatty Acids

The term omega-3 polyunsaturated fatty acids (omega-3 FAs) refers to a group of polyunsaturated fatty acids (PUFA) that contain a double carbon bond at the third carbon atom (n-3 position) from the methyl end of the carbon chain. Alpha-linolenic acid (ALA, 18-carbon PUFA obtained from plant sources), eicosapentaenoic acid (EPA, 20-carbon PUFA form fish) and docosahexaenoic acid (DHA, 22-carbon PUFA obtained from marine source) are the most common omega-3 FAs. (790)

Over the past decades, extensive studies have addressed the therapeutic effects of omega-3 FAs against different human diseases such as cardiovascular and neurodegenerative diseases and cancer. (790) These studies have demonstrated the clinical utility and safety of these natural occurring substances. Furthermore, more recently, omega-3 FAs have been demonstrated to improve the outcome against certain types of cancer, improve the efficacy and tolerability of chemotherapy and improve quality of life indicators. (790) In addition, omega 3 FA improve cancer cachexia.

Anticancer pathways and mechanisms
The four main antineoplastic activities omega-3 FA that have been proposed are (i) modulation of cyclooxygenase (COX) activity; (ii) alteration of membrane dynamics and cell surface receptor function, (iii) increased cellular oxidative stress, and iv) the production of novel anti-inflammatory lipid mediators including resolvins, protectins and maresins. (791, 792)

Omega-3 FAs compete with linoleic acids (LA) as a key nutrient in cancer. The ratio of the two classes of FAs is important since omega-3 and omega-6 share the same biochemical pathways and can compete to generate imbalances. The precursor of the omega-6 FA, LA, is associated with pro-inflammatory response. Cancer progression seems to be influenced by the ratio omega-3/omega-6 FA in the diet, rather than by their singular intake. (790) While LA promotes the survival of tumor cells preventing their death, omega-3 FAs promote the self-destruction of the tumor cells, thus limiting the expansion of cancer. Omega-3 FAs, especially EPA and DHA,

affect cancer cell replication, cell cycle, and cell death. In this context, in vitro and in vivo studies have shown that omega-3 FAs sensitize tumor cells to anticancer drugs. Omega-3 FAs also modulate several pathways including modulating gene expression involved in multiple signaling pathways including NF-κB, Notch, Hedgehog, Wnt, and mitogen-activated protein kinases (MAPKs). (793) Omega-3 FAs suppress the formation of arachidonic acid derived prostanoids (prostaglandin E2), which are responsible for inflammatory response, cell growth, apoptosis, angiogenesis, and metastasis. (794) EPA and DHA induce apoptosis in breast cancer cell lines by activation of Bcl2 expression and pro-caspase 8, together with reduction of EGFR activation. (794) Omega-3 FAs can block the activity of self-renewing colon cancer stem cells (CSC). (795, 796)

Clinical studies

In a prospective RCT, the intake of omega-3 FAs and vitamin D was associated with a dramatic reduction in the risk of developing cancer. (240) In the VITAL cohort study conducted in postmenopausal women, the current use of fish oil was associated with reduced risk of breast cancer (HR 0.68, 95% CI: 0.50-0.92). (797) A meta-analysis of 16 prospective cohort studies examining marine omega-3 FAs intake suggests a reduction in breast cancer risk when individuals with highest intakes are compared with those with lowest intakes of marine PUFA. (798) Two large observational studies have demonstrated significant inverse relationships between omega-3 FAs intake and the risk of colorectal neoplasia. (799, 800)

A recent meta-analysis of six prospective case–control studies and five cohort studies evaluated the omega-3:omega-6 intake ratio and/or omega-3:omega-6 ratio in serum phospholipids in relation to the risk of developing breast cancer. (801) The authors concluded that each 1/10 increment in the dietary n-3:n-6 ratio was associated with a 6% reduction in breast cancer risk, and each 1/10 increment in the serum n-3:n-6 phospholipid ratio was associated with a 27% reduction in breast cancer risk.

Patients with familial adenomatous polyposis who had previously undergone colectomy and ileorectal anastomosis were randomized to 2g EPA/day or placebo. In this RCT there was a 22.4% reduction in polyp number in the EPA group (p=0.01). (802) A phase II study evaluated addition of 1.8 g DHA daily to an anthracycline based chemotherapy regimen for metastatic breast cancer. The DHA group had a significantly longer time to disease progression and overall survival (median 34 months vs 18 months). (803) In a small RCT, supplementation with fish oil increased first line chemotherapy efficacy in patients with advanced non-small cell lung cancer.(804)

Higher intakes of EPA and DHA from dietary sources were reported to be associated with a 25% reduction in breast cancer recurrence and improved overall mortality in a large cohort of over 3,000 women with early-stage breast cancer followed for a median of 7 years. (805) Cohort studies assessing the risk of prostate cancer mortality and fish omega-3 FAs intake suggest an association between higher intake of fish and decreased risk of prostate cancer–related death.(806) In a small RCT, patients with leukemia or lymphoma concurrently receiving

chemotherapy were randomized to receive 2g /day of fish oil or placebo for 9 weeks. (807) Overall long-term survival was greater in the fish oil group ($p < 0.05$). In a meta-analysis that included 12 RCT and 1184 patients with cancer cachexia, the use of omega-3 FAs was associated with a significant improvement in quality of life and duration of survival (median survival ratio, 1.10; 95% CI, 1.02-1.19; P = .014). (808)

Types of cancers that omega-3 fatty acids may be beneficial for

Omega-3 FAs may be beneficial for breast cancer, colorectal cancer, leukemia, gastric cancer, pancreatic cancer, esophageal cancer, prostate cancer, lung cancer, and head and neck cancer.(790)

Dosing and cautions

We suggest a dose of 2-4 g omega-3 FAs daily. Omega-3 fatty acids may increase the risk of bleeding and should be used cautiously in patients on anticoagulants.

10. Berberine

Depending on the patient's blood glucose levels, providers can consider using metformin and berberine together or alternating (switching back and forth for one month at a time).

Anticancer pathways and mechanisms

Berberine's anticancer mechanisms include reducing the growth of cancer cells, preventing metastasis, inducing apoptosis, activating autophagy, controlling the microbiota in the gut, and enhancing the effects of other cancer treatments by focusing on antibacterial action, which includes controlling the microbiota in the gut and preventing intratumoral microbes. (809-813)

Berberine may prevent the growth of cancer cells through the upregulation of miR-214-3p, the downregulation of SCT protein levels, the regulation of catenin, the inhibition of telomerase activity, and the deactivation of MAPK signaling pathways. (814-816) By increasing p21, p27, and p38 and lowering CDK1, CDK4, cyclin A, and cyclin D1, berberine may inhibit the growth of cancer cells. (809, 817) Through the AMPK-p53, PI3K/AKT/mTOR, miR19a/TF/MAPK signaling pathways, and modulation of the CASC2/ AUF1/B-cell/Bcl-2 axis, berberine promotes cancer cells apoptosis. (811, 818-820) Berberine downregulates many TME-related genes, including PDGFRB, COL1A2, and BMP7, and upregulates E-cadherin, thereby inhibiting metastatic spread. (821-823)

Berberine has anticancer effects by influencing the gut microbiota. For example, berberine increases the Firmicutes/Bacteroidetes ratio and the relative abundance of Clostridiales, Lactobacillaceae, Bacteroides, and Akkermansia muciniphila. (812, 813)

Berberine increases radiation sensitivity and enhances the effects of anticancer medications such as cisplatin, 5-fluorouracil, doxorubicin, niraparib, and icotinib. (824-827)

Clinical studies
While there is limited clinical data on the benefits of berberine, a randomized, double-blind study demonstrated that berberine in a dose of 300 mg twice daily significantly reduced the risk of recurrent colorectal adenomas following polypectomy. (828)

Types of cancers that berberine may be beneficial for
Berberine shows anticancer effects on various cancers, such as breast, lung, gastric, liver, colorectal, ovarian, cervical, and prostate. (809-811, 814-820, 822-827, 829)

Dosing and cautions
A total daily dose of 1000-1500 mg (take 500 mg two or three times daily or 600 mg twice daily) is suggested. As insulin release is glucose-dependent hypoglycemia has not been reported with this herb; however, blood glucose should be monitored and the additive/synergistic effect of metformin on the blood glucose profile should be determined. Berberine should not be taken in patients taking cyclosporine as this combination will increase cyclosporine levels (absolute contraindication). Berberine may alter the metabolism of the following drugs, which should be used with caution (monitor effects): anticoagulants, dextromethorphan, tacrolimus (Prograf), phenobarbitone, losartan (inhibits effect) and sedative drugs (see https://www.webmd.com/vitamins/ai/ingredientmono-1126/berberine). If you are scheduled for surgery, please notify your anesthesia team if you are taking berberine. Patients may need to stop taking berberine one week prior to surgery.

11. Atorvastatin or Simvastatin.

The lipophilic statins appear to be highly effective in the management of several cancers.

Anticancer pathways and mechanisms
Statins may affect tumor cells directly in four main ways: i) growth suppression, ii) apoptosis induction, iii) anti-invasive and anti-metastatic effects, and iv) anti-angiogenic effects. A primary effect is that statins block activity of the cholesterol-producing enzyme HMG CoA, which means less cholesterol is available to produce new cell walls in rapidly proliferating tumors. Rapidly multiplying cancer cells require more cholesterol to allow the creation of cell membranes. (830, 831) A reduction in the availability of cholesterol may limit the cellular proliferation required for cancer growth and metastasis. In addition, statins alter the expression of genes regulating the balance between life-promoting and death-promoting proteins in cancer and may have a number of benefits in killing cancer cells. Studies have shown statins also reactivate caspases and upregulate the production of PPARγ, another protein that programs cell death. Statins also reduce the number of cell surface GLUT-1 glucose receptors, thus reducing cancer cell activity by limiting the amount of energy available. Additionally, statins' direct inhibition of HMGCR

depletes the body's stores of isoprenoids, which play a crucial role in controlling the growth and spread of cancer cells. (832)

Clinical studies

Lipophilic statins have been demonstrated to reduce the incidence and all-cause mortality from a number of cancers. A 10-year retrospective cohort study by Farwell et al compared statin usage in a veteran population taking antihypertensive medications and found that, on average, statin users had a 31% lower risk of prostate cancer incidence. (833) NSAIDs have been found to significantly reduce prostate cancer risk and may act synergistically with statins to prevent prostate cancer. (834)

Nielsen et al assessed mortality among patients from the entire Danish population who had received a diagnosis of cancer between 1995 and 2007. (835) In this study multivariable-adjusted hazard ratios for statin users, as compared with patients who had never used statins, was 0.85 (95% CI, 0.82 to 0.87) for death from cancer. The reduced cancer-related mortality rates among statin users as compared with patients who had never used statins was observed for 13 cancer types. Zhong et al demonstrated that patients who used statins after a diagnosis of cancer had an HR of 0.81 (95% CI: 0.72–0.91) for all-cause mortality compared to non-users; the benefit was most marked for colorectal, prostate, and breast cancer. (836)

In a population-based retrospective cohort study that looked at the usage of statins after a prostate cancer diagnosis, (837) the post-diagnostic use of statins was associated with a decreased risk of prostate cancer mortality (HR, 0.76; 95% CI, 0.66 to 0.88) and all-cause mortality (HR, 0.86; 95% CI, 0.78 to 0.95); longer and higher dosages led to a lower incidence in mortality, as well as distant site metastasis.

In a meta-analysis of 10 studies, statin use was associated with improved recurrence-free survival (RFS; HR 0.64; 95% CI 0.53–0.79) in women with breast cancer. (838) Furthermore, this survival benefit appeared to be confined to use of lipophilic statins. Similarly, Ahern et al performed a population study of women with stages I–III breast cancer; they reported a 10% reduction in breast cancer recurrence among women who were prescribed a lipophilic statin (most commonly simvastatin). (839) Similarly, in colorectal and hepatocellular cancer, statin usage reduces cancer-specific mortality, in particular when used either prior to diagnosis or prior to recurrence. (840-842) In lung cancer, retrospective studies have shown that statins reduce cancer-specific mortality. (843) It should be noted that in the LUNGSTAR study, the addition of pravastatin to first-line chemotherapy in small cell lung cancer (SCLC) failed to improve patient outcomes.(844) While this was an adequately powered RCT the use of pravastatin, a non-lipophilic statin was unfortunate, and supports the notion that only the lipophilic statins are beneficial in patients with cancer.

Types of cancers that statins may be beneficial for

Breast, prostate, colorectal, hepatocellular, lung, testicular, pancreatic, gastric, ovarian, leukemia, brain, and kidney. (676, 832, 835, 845)

12. **Phosphodiesterase 5 Inhibitors: Sildenafil, Tadalafil, and Vardenafil**

Selective phosphodiesterase 5 inhibitors, including sildenafil, tadalafil, and vardenafil, are widely used in the treatment of erectile dysfunction and pulmonary arterial hypertension. These drugs may also be effective cancer treatments.

Anticancer pathways and mechanisms

Sildenafil treatment affects HSP90 expression, a chaperone protein that promotes degradation of PKD2, a serine threonine kinase with an important role in cancer cell proliferation and viability. (846) Sildenafil and tadalafil were shown to inhibit the development and progression of aflatoxin B1 induced hepatocellular carcinoma. (847) PDE5 inhibitors can reduce the incidence of intestinal cancer by altering epithelial homeostasis via cGMP. In a rodent model, sildenafil-treated mice showed less polyp formation with greater differentiation, less proliferation, and less inflammation. (848)

Booth et al demonstrated that PDE5 inhibitors interacted in a greater than additive fashion with numerous cytotoxic agents to cause cell death. (849) The most potent PDE5 inhibitor was sildenafil. In this study, treatment with PDE5 inhibitors and chemotherapy drugs promoted autophagy with knock out of Beclin1 reducing the drug combination lethality by about 50%. Furthermore, these authors demonstrated that celecoxib (an NSAID) and PDE5 inhibitors interacted in a greater than additive fashion to kill multiple tumor cell types including human glioma cells. (850) The effects of celecoxib were COX2 independent. The drug combination inactivated mTOR and increased the levels of autophagy and activated the JNK pathway. The combined use of platinum-based chemotherapeutic agents and PDE inhibitors have a higher antiproliferative effect on lung cancer cells than platinum monotherapy. (851) Sildenafil combined with curcumin increases the efficacy of 5-Fluorouracil in controlling colorectal tumors. (852)

Sildenafil could inhibit colonic tumorigenesis via blocking the recruitment of MDSCs. (853) Treatment with sildenafil reduced MDSC numbers infiltrating primary tumors and metastatic lesions and increased CD8+ T cells. (854) PDE5 inhibitors reduce Tregs and CSCs and impair MDSC function. (854, 855) Klutzny et al demonstrated that PDE5 inhibition eliminates CSCs via induction of PKA signaling. (856)

Clinical studies

In a study of 192,661 patients, the use of PDE5 inhibitors was shown to be associated with a decreased risk of developing colon cancer. (857) The use of PDE5 inhibitors is associated with a lower risk of colorectal cancer in men with benign colorectal neoplasms. (262) Two recent clinical trials, conducted among patients with head and neck squamous cell carcinoma, reported that tadalafil can enhance systematic immune responsiveness as well as tumor-

specific immunity by reducing MDSCs, regulatory T cells, and improving T-cell function. (858, 859) Huang et al demonstrated that in patients with colorectal cancer, the post-diagnostic use of PDE5 inhibitors was associated with a decreased risk of cancer-specific mortality (adjusted HR = 0.82, 95% CI 0.67-0.99) as well as a decreased risk of metastasis (adjusted HR = 0.85, 95% CI 0.74-0.98). (860) In a retrospective cohort analysis of 3100 patients with prostate cancer treated with radical prostatectomy between 2003 and 2015, patients were divided into those receiving a PDE-5 inhibitor or non-recipients (controls). In this study, multivariate analysis documented that PDE-5 inhibitor administration was associated with a lower risk of biochemical recurrence and death. (861)

Types of cancers that phosphodiesterase 5 inhibitors may be beneficial for
Phosphodiesterase 5 inhibitors have been shown to be beneficial for prostate, breast, hepatocellular, colorectal, lung and head and neck cancers as well as glioblastoma, and leukemias. (854)

Dosing and cautions
Sildenafil 20 mg daily or tadalafil 5mg daily. PDE5 inhibitors are contraindicated in patients receiving nitrates or with a previous history of non-arteritic anterior ischemic optic neuropathy. Despite its wide therapeutic window, sildenafil may show serious cardiovascular side effects in patients.

13. Disulfiram

As an inhibitor of aldehyde dehydrogenase (ALDH), disulfiram (DSF) inhibits all the currently identified cytosolic and mitochondrial ALDH isoforms, resulting in the specific accumulation of acetaldehyde, which causes unpleasant effects when alcohol is consumed, and thus it functions as an anti-alcoholism drug. Recently, DSF has been repurposed because of its potent effect as a cancer treatment in preclinical studies.

Disulfiram's anti-tumor effect has been reported in many preclinical studies and recently on seven types of cancer in humans: non-small cell lung cancer, liver cancer, breast cancer, prostate cancer, pancreatic cancer, glioblastoma and melanoma and has a successful breakthrough in the treatment of non-small cell lung cancer and glioblastoma.(862)

Anticancer pathways and mechanisms
DSF inhibits NF-kB signaling, proteasome activity, and aldehyde dehydrogenase (ALDH) activity. It induces endoplasmic reticulum (ER) stress and autophagy and has been used as an adjuvant therapy with irradiation or chemotherapy drugs. DSF not only kills the normal cancer cells but also targets CSCs. (863) Disulfiram binds to nuclear protein localization protein 4 (NPL4), induce its immobilization and dysfunction, ultimately leading to cell death.

The cytotoxicity of DSF depends on copper (Cu). (864) DSF penetrates cancer cells and chelates Cu intracellularly. Compared with normal tissues, many cancers exhibit higher levels of

intracellular Cu (2‑3 fold). (865) Copper plays a crucial role in redox reactions and triggers the generation of reactive oxygen species (ROS). DSF/Cu is a strong inducer of ROS production and an effective proteasome inhibitor, resulting in the inhibition of NF-κB. NF-κB is an ROS-induced transcription factor with strong anti-apoptotic activity, which in turn reduces the pro-apoptotic effect of ROS. (864, 866) DSF/Cu simultaneously activate the ROS-JNK pro-apoptotic pathway and downregulate anti-apoptotic pathways such as NF-kB signaling. (867) The activation of executioner caspases, such as an increased ratio of Bax and Bcl2 proteins, indicated that the intrinsic apoptotic pathway may be involved in DSF/Cu-induced apoptosis. (868) As a bivalent metal ion chelator, DSF has been considered to form a complex with Cu (DSF/Cu), which is more readily taken up by cells and exerts cytotoxic effects on a variety of cancer cells while sparing normal cells. When chelated with copper, DSF down-regulates the expression of several genes involved in DNA repair pathways.

Recently, an increasing number of clinical trials have verified the hypothesis that the binding of disulfiram or its metabolites to copper produces antitumor effects. In a study of head and neck squamous cell carcinoma, a DSF/Cu injection markedly inhibited tumor growth at a concentration of 50 mg/kg, while DSF alone showed limited efficacy compared to DSF in combination with copper. (869) DSF ultimately exerted inhibitory effects on head and neck carcinoma cell lines mainly by inducing autophagic cell death and inhibited tumor progression in xenograft model.

DSF shows cytotoxicity towards several model cancer cell lines in vitro, including breast, lung, pancreatic, prostate, liver, and ovarian cancer, as well as acute myeloid leukemia, glioblastoma and melanoma, effectively inducing apoptosis in cancer cells. For example, DSF inhibits the growth of temozolomide-resistant glioblastoma cells, (IC90 = 100 nM), but does not affect normal human astrocytes. These classically temozolomide-resistant cells were sensitive to 500 nM DSF, a sufficient concentration to suppress tumor cell growth over 72 h, and the self-renewal ability of these cells was also completely inhibited. (870, 871) Tumor-associated macrophages (TAM) affect tumor progression and resistance to chemotherapeutic agents. FROUNT is highly expressed in macrophages, and its myeloid-specific deletion impairs tumor growth. Further, DSF acts as a potent inhibitor of FROUNT and decreases macrophage tumor-promoting activity. (872)

In preclinical studies, when administered in combination with other conventional therapies, DSF exerts a synergetic therapeutic effect on cancer. According to in vivo studies, the activities of chemotherapeutic drugs such as cisplatin, temozolomide cyclophosphamide, 5-fluorouracil, sunitinib and auranofin are all potentiated by DSF. (862)

Clinical studies

In a double blind trial, 64 women with breast cancer were treated with sodium ditiocarb (diethyldithiocarbamate) or a placebo. (873) After 6 years, a significantly higher overall survival rate was observed in the ditiocarb group than in the placebo group (81 vs 55%, respectively). The disease-free survival rates were 76% and 55% in the ditiocarb and placebo groups,

respectively. Ditiocarb is the main DSF metabolite in the human body that contributes to its mechanism of action.

In a phase IIb clinical trial the addition of DSF to a combination regimen of cisplatin and vinorelbine was well tolerated and appeared to prolong survival in patients with newly diagnosed non-small cell lung cancer. (874) The addition of DSF plus copper to temozolomide appears to prolong the disease-free survival in patients with glioblastoma. (875-877)

Types of cancers disulphiram may be beneficial for

DSF may be beneficial in the following cancers: breast, lung, pancreatic, prostate, liver, and ovarian cancer, as well as acute myeloid leukemia, glioblastoma, and melanoma. DSF and copper may have a particular role in patients with glioblastoma. (862, 864)

Dosing and cautions

DSF is inexpensive, and its tolerability and safety have been demonstrated over years of clinical experience with many patients. DSF is generally administered at a dose of 80 mg three times a day or 250 mg once daily, which appears to be the maximal tolerable dose. (875, 877) Copper at a dose of 2 mg three times a day should be added. (876)

14. Ashwagandha

Anticancer pathways and mechanisms

Ashwagandha (*Withania somnifera*, WS) has been used in the Mediterranean region and Ayurvedic medicine for millennia as a functional food and a medicinal plant with anticancer activity. (878) The plant is an erect, grayish, evergreen shrub with long tuberous roots, short stems, ovate and petiolate leaves, and greenish axillary and bisexual flowers The leaves, roots, stems, and flowers bear medicinal values with 29 common metabolites derived from the leaves and root extracts. (878) Its active substances that play a crucial role in pharmacological action are withanolides and alkaloids. (879)

Preclinical studies have demonstrated the ability of this plant to regulate mitochondrial function and apoptosis and reduce inflammation by inhibiting inflammatory markers such as cytokines (including IL-6 and TNF-a), nitric oxide, and reactive oxygen species. Ashwagandha plays a major role in the induction of cancer cell apoptosis, it inhibits cell proliferation and inhibits cell migration. (879-881) In glioblastoma cells ashwagandha triggers cell cycle arrest and apoptosis. (882) In a human head and neck cell line ashwagandha showed dose-dependent growth-inhibitory activity attributed to caspase-dependent apoptosis. (883) Loss of mitochondrial membrane potential, release of cytochrome c, and activation of caspase 9 suggested that ashwagandha leads to activation of mitochondria-mediated apoptosis.

Widodo et al demonstrated the cancer killing activity of ashwagandha mediated by p53, apoptosis and insulin/IGF signaling pathways linked to the ROS signaling and that the selective killing of cancer cells was mediated by induction of oxidative stress. (884) The anti-cancer

effects of ashwagandha on the proliferation and migration of colorectal cell lines has been shown to be due to reduced transcriptional activity of STAT3. (885) In addition, Notch 1 and Notch/AKT/mTOR signaling is inhibited by ashwagandha in a colon cell line. (160) In an experimental adenomatous polyposis coli model ashwagandha was associated with a 59% reduction of tumor and polyp initiation and progression. (261)

Ashwagandha has potent anti-inflammatory activity that likely has a major effect on the tumor microenvironment inhibiting angiogenesis and metastasis. In a study using the HaCaT human keratinocyte cell line, an aqueous solution from Ashwagandha root was found to inhibit the NF-KB and MAPK (mitogen-activated protein kinase) pathways by decreasing the expression of proinflammatory cytokines, including interleukin (IL)-8, IL-6, tumor necrosis factor (TNF-α), IL-1β, and IL-12, and increasing the expression of anti-inflammatory cytokines. (886)
In an vivo and in vitro model, Jawarneh et al. demonstrated that a combination of Ashwagandha extract and intermittent fasting has potential as an effective breast cancer treatment that may be used in conjunction with cisplatin. (881) The combination was found to decrease cancer cell proliferation through apoptosis induction, while also reducing cisplatin-induced toxicity in the liver and kidney.

Clinical studies
In the setting of cancer, Ashwagandha has been studied almost exclusively in experimental models, with limited clinical data regarding its clinical efficacy. Biswell et al performed an open-label prospective non-randomized comparative trial on 100 patients with breast cancer to receive either a combination of chemotherapy with Ashwagandha or chemotherapy alone.(422) *Withania somnifera* root extract was administered to patients in the study group at a dose of 2 g every 8 hours, throughout the course of chemotherapy. Patients in the treatment group had significantly less fatigue and higher quality of life scores. The 24-month overall survival for all stages in study and control group patients were 72% versus 56%, respectively; however, the result was not significant.

As discussed under the section of stress reduction and sleep, *Ashwagandha* has proven to be a safe and effective adaptogen. RCTs have shown a significant benefit in terms of stress reduction, improved cognition and mood, and quality of sleep. (405-407) A meta-analysis of 12 RCTs demonstrated that ashwagandha supplementation significantly reduced anxiety (p = .005) and stress levels (p = .005) compared to placebo. (410) While ashwagandha has not been proven to improve the outcome of patients with cancer, because of its effects on stress reduction, sleep, and quality of life we have included this herb as a recommend therapy in patients with cancer.

Types of cancers that ashwagandha may be beneficial for
Ashwagandha may be effective against cancers such as breast, colon, lung, prostate, glioblastoma multiforme, melanoma and blood cancers. (878, 879) Ashwagandha can be used to treat cancer alone or in combination with other chemotherapeutic agents.

15. Itraconazole

Itraconazole is a common anti-fungal agent that was developed in the 1980s, which decreases ergosterol synthesis by inhibiting lanosterol 14α-demethylase, resulting in the destruction of the fungal membrane. (887) The anti-fungal effect of itraconazole is unlikely to be associated with its anticancer activity; which appears to be mediated by reversing chemoresistance mediated by P-glycoprotein, modulating the signal transduction pathways of Hedgehog, mechanistic target of rapamycin (mTOR) and Wnt/β-catenin in cancer cells, inhibiting angiogenesis and lymphangiogenesis, and possibly interfering with cancer-stromal cell interactions. (887)

Anticancer pathways and mechanisms

Itraconazole's anticancer mechanisms likely entail blocking the resistant protein P-glycoprotein, interfering with the tumor microenvironment, and mediating other signaling pathways linked to tumor formation. (887-889) Itraconazole prevents the growth and spread of tumor cells by blocking the abnormally active Hedgehog and Wnt/-catenin signaling pathways. (887, 888, 890-892) Itraconazole also inhibits angiogenesis, reduces the proliferation of endothelial cells, and triggers cell cycle arrest and autophagocytosis. (888, 889, 892-897) Itraconazole slows down the progression of cancer by preventing the phosphorylation of proteins in the PI3K/AKT/mTOR/S6K signaling pathway, which in turn prevents the growth and proliferation of cancer cells. (888, 892, 898) Furthermore, by inhibiting the PDGF/PI3K/Akt/mTOR pathway, itraconazole dramatically reduced angiogenesis. (888, 899)

Itraconazole binds to the sterol-sensing domain of NPC1, a lysosomal protein closely associated with cholesterol trafficking, resulting in a thorough inhibition of cell proliferation and angiogenesis. Itraconazole also directly targets the mitochondrial protein voltage-dependent anion channel 1 (VDAC1) to regulate AMP-activated protein kinase pathway and mTOR activity. (887, 888, 898, 900)

The receptor tyrosine kinase known as human epidermal growth factor receptor 2 (HER2) is a member of the HER family. (901) The HER signaling pathways involved in cell survival, proliferation, adhesion, migration, differentiation, and death are phosphoinositide-3-kinase (PI3K)/Akt signaling, protein kinase C (PKC), and mitogen-activated protein kinase (MAPK) pathway activation. (901) Itraconazole inhibits the growth of cancer cells by blocking the HER2/Akt signaling pathway. In esophageal cancer cells, it reduces the phosphorylation of downstream ribosomal protein S6, transcriptional expression of the upstream receptor tyrosine kinase HER2, and phosphorylation of upstream PI3K. (901)

Itraconazole activates the ROS pathway, which in turn activates downstream caspase and PAPR proteins, causing apoptosis. (892) This is accomplished by controlling the ratio of pro- and anti-apoptotic proteins. (892) Itraconazole also stimulates the pathway of the death receptor. It

enhances the activation of the promoter caspase-8, which in turn promotes the activation of caspase-3, ultimately resulting in apoptosis, by up-regulating the production of FAS protein. (892)

Tumor growth is dependent on angiogenesis, which is driven by the secretion of growth factors from the tumor itself. Itraconazole prevents vascular endothelial growth factor/basic fibroblast growth factor-dependent angiogenesis in vivo and inhibits endothelial cell cycle progression at the G1 phase in vitro. (895, 898) Itraconazole dramatically reduces the ability of vascular endothelial growth factor (VEGF) to bind to VEGF receptor 2 (VEGFR2), preventing the activation of both VEGFR2 and phospholipase C1, a direct downstream substrate of VEGFR2. (895, 898)

Clinical studies

Itraconazole preclinical or clinical data suggested potential anticancer efficacy in single-agent or combination therapy. (888-891, 893, 894, 896, 897, 899, 902-908) Itraconazole with conventional chemotherapy (pemetrexed) significantly increased both progression-free and overall survival for lung cancer patients, according to a phase II clinical study, indicating that the drug's antiangiogenic qualities are responsible for the positive results. (888)

Retrospective studies supported the survival advantage of itraconazole treatment in refractory malignancies including ovarian clear cell, triple-negative breast, pancreatic and biliary tract cancer, as compared with the previous reports. (907-910)

In pancreatic cancer, itraconazole treatment combined with chemotherapy was conducted in progressive disease during chemotherapy. (907) A total of 38 patients received docetaxel (35 mg/m2), gemcitabine (1,000 mg/m2) and carboplatin (4 mg/min/mL) in combination with itraconazole (400 mg), following which a median OS of 11.4 months was observed. One complete response and 13 partial responses were observed, for a response rate of 37%.

In a randomized phase II clinical trial of metastatic castration-resistant prostate cancer, 46 chemotherapy-naïve patients were enrolled, of whom 29 received high-dose (600 mg/day) and 17 received low-dose (200 mg/day) itraconazole treatment. (893) Prostate-specific antigen progression free survival (PFS) rates at 24 weeks were 48.0 and 11.8% with median PFS of 11.9 and 35.9 weeks in the high-and low-dose arm, respectively.

Itraconazole exhibits concentration-dependent early anti-vascular, anti-metabolic, and anticancer effects in patients with non-small cell lung cancer (NSCLC), according to a cohort study. (902)

Types of cancers that Itraconazole may be beneficial for

Itraconazole may be helpful as an adjuvant drug in the treatment of prostate cancer, pancreatic cancer, lung cancer, hemangioma, breast cancer, acute myeloid leukemia, basal cell carcinoma, medulloblastoma, biliary tract cancer, hepatocellular carcinoma, esophageal cancer and gastric cancer. (887, 888, 890-892, 894, 897, 901, 904, 905, 907)

Dosing and cautions
Itraconazole in a dose of 100 mg /day is recommended. The dose may be escalated to 400 mg/day however with this dosage liver function tests must be closely monitored due to hepatotoxicity. Itraconazole is a conventional antifungal drug that has received FDA approval and has an excellent safety record. (888) However, several studies have suggested that itraconazole has some contraindications, particularly when it comes to interactions with other cancer medications including rituximab, cimetidine and statins. (911, 912)

16. Mistletoe

The European white-berry mistletoe (Viscum album L.), an evergreen plant that grows as a semi parasite on trees, has a long tradition in the treatment of cancer patients, particularly in continental Europe. A large percentage of patients with cancer use adjunctive mistletoe extracts to reduce disease- and treatment-related symptoms and to improve quality of life. (913) Mistletoe extracts are aqueous, total plant extracts from European mistletoe, manufactured and marketed as injectable drugs with indications in oncology. Mistletoe extracts are administered subcutaneously, normally two to three times per week. They may also be administered intravenously by integrative oncologists.

Anticancer pathways and mechanisms
Mistletoe extracts mediate numerous antitumor, antiapoptotic, anti-proliferative and immunomodulatory effects in models of cancer. Mistletoe contains biologically active molecules including lectins, flavonoids, viscotoxins, oligo- and polysaccharides, alkaloids, membrane lipids and other substances. (914) Although the exact pharmacological mode of action of mistletoe is not completely elucidated, there is a growing number of biological studies with a clear focus on lectins. Lectins mediate many immunological activities including increasing the natural killer cytotoxicity and the number of activated lymphocytes; they increase the antioxidant system and mistletoe stimulated the production of granulocyte-macrophage colony-stimulating factor (GMCSF), Interleukin 5 and Interferon gamma. (915, 916) Cytotoxic effects of the mistletoe extract are reported to be a result of protein synthesis interference, cell-cycle inhibition, and induced apoptosis. (917, 918) Ben-Arye et al demonstrated that mistletoe exhibited significant anti-cancer activity in cisplatin- sensitive and resistant ovarian cells and increased chemosensitivity in both cancer cell lines. (919) It has also been suggested that mistletoe has antiangiogenic properties.

Clinical studies
Over 50 prospective studies, including over 30 RCTs, have evaluated the role of mistletoe in patients with cancer. A Cochrane review published in 2008 which included 21 studies demonstrated a benefit in terms of QoL, performance index, symptom scales and reduction of adverse effects of chemotherapy. (920) In 2010 Kienle and Kiene reported the results of a systematic review assessing the effect of mistle extract on the QoL in patients with cancer. (921) This study included 26 RCTs' and 10 non-RCTS. Half of the studies investigated mistletoe

concomitant with chemotherapy, radiotherapy, or surgery. Almost all the studies included in this review reported that mistletoe improved QoL. In an update meta-analysis published in 2020 Loef and Walach reported that the pooled standardized mean difference for global QoL after treatment with mistletoe extracts vs. control was SMD = 0.61 (95% CI 0.41–0.81, p < 0,00001). (914) The authors performed an additional meta-analysis evaluating the effect of mistletoe on survival in patients with cancer. (922) For RCTs, the pooled effect estimate of mistletoe on survival was HR = 0.81 (95% CI 0.69-0.95, *P* = .01). A meta-analysis that included 12 RCTs demonstrated that mistletoe reduced cancer related fatigue (SMD −0.48; 95% CI −0.82 to −0.14; *p* = 0.006). (923) A phase I trial of intravenous mistletoe extract in patients with advanced cancer demonstrated a disease control rate (percentage of complete/partial response and stable disease) of 23.8% with improved indicators of QoL. (924) In summary, mistletoe is used by integrative oncologists to improve the QoL, increase the tolerability of chemotherapy, and exert a possible benefit on tumor control and survival.

Types of cancers mistletoe may be beneficial for

Mistletoe improves the QoL in patients with most cancers. Mistletoe has been used in breast cancer, bladder cancer, gynecological cancers (cervical, corpus uteri and ovarian), colorectal cancer, gastric cancer and pancreatic cancer, glioma, head and neck cancer, lung cancer, melanoma, and osteosarcoma.

Dosing and cautions

The limitation of mistletoe is that it is administered parenterally (subcutaneously or intravenously) and is therefore administered under the supervision of an integrative oncologist used as a component in a personalized treatment protocol. (925)

17. Cimetidine

Anticancer pathways and mechanisms

Cimetidine, commonly used to treat ulcers and gastroesophageal reflux disease, has been demonstrated to have four different anti-tumor effects: Anti-proliferative, immunomodulatory, anti-cell adhesion, and anti-angiogenic effects on cancer cells. (466)

Anti-proliferative: Histamine, the principal mast cell mediator, and its receptors (HR1-HR4) were increased in several malignancies and associated with cancer survival, metastasis, and recruitment of suppressive cells to the TME. Mast cells and their mediators have previously been linked with tumor progression and metastasis. (926)

L-histidine decarboxylase (HDC), an enzyme that produces histamine, is expressed by a variety of tumor types both in vitro and in vivo. Tumors are also capable of secreting large amounts of histamine in a paracrine and/or autocrine manner. Histamine has a wide range of actions, including inflammatory and immunological effects. Four histamine receptors, of which H2 and H4 are involved in cancer cell proliferation, invasion, and angiogenesis, mediate these physiological effects. By blocking H2 receptors, cimetidine reduces cancer cell

proliferation.(466, 927-929) In addition, cimetidine upregulates Caspase 3 level to induce apoptosis of cancer cells and has synergistic activity when combined with vitamin C. (927)

Immunomodulation: Cimetidine has been demonstrated to kill MDSCs, decrease Tregs, and increase NK cell. Histamine has been linked to an immunosuppressive tumor microenvironment in cancer, which includes increased CD4+CD25+ regulatory T cell (Treg) activity, decreased dendritic cell (DC) antigen-presenting activity, decreased NK cell activity, and increased MDSC activity. (466, 930, 931). MDSCs express H_1–H_3 receptors, and there is in vitro and in vivo evidence that blockade of H_1 (using the H_1RA cetirizine) or H_2 (using cimetidine), can reverse the immunosuppressive action of these cells. (466, 931) Cimetidine causes an increase in NK activity compared to non-cimetidine-treated controls in patients undergoing cardiopulmonary bypass surgery. (466, 932)

Additionally, it has been demonstrated that in patients with colorectal and gastric cancer, perioperative cimetidine reverses the histamine-induced suppression of lymphocyte proliferation and increases the number of tumor-infiltrating lymphocytes (TIL). (471, 472) Increased tumor-infiltrating lymphocytes were linked to improved prognosis in these studies and are also thought to be significant in several other cancer types, such as breast, ovarian, brain, and head and neck cancers. (466)

The heterodimeric cytokine interleukin-12, which is mostly produced by monocytes and macrophages, is a crucial inducer of cell-mediated immunity because it promotes the growth, proliferation, and activity of Th1 cells. (466) IL-12 overproduction may have a role in the etiology of autoimmune disease. Histamine binding to the H2 receptor, which is connected to the suppression of IL-12 and enhancement of IL-10 production, is associated with a shift in the Th1/Th2 balance toward Th2-dominance of the immune response. Studies showed that cimetidine prevented this effect in human peripheral blood mononuclear cells. (466, 933-935)

Anti-cell adhesion: It has been demonstrated that cimetidine inhibits cancer cells' ability to adhere to endothelial cells without affecting their H2RA activity. (466)

Anti-angiogenesis: Angiogenesis accelerates the development and progression of tumors. (927) Evidence from mouse and rat bladder cancer models suggested that the anti-angiogenic impact of cimetidine may be connected to a decreased expression of platelet-derived endothelial growth factor (PDECGF) and VEGF via the H2R/cAMP/PKA pathway. (466, 471, 927, 936, 937) TNF-α plays a variety of roles within the TME and promotes tumor growth through several methods. Cimetidine has anti-angiogenic effects by downregulating TNF-α. (927)

Clinical studies

There is limited data on the clinical benefits of cimetidine in patients with cancer. Most of the studies have been performed in the post-operative period in patients undergoing colorectal surgery. (466) In a Cochrane meta-analysis of five studies (n=421) that prescribed cimetidine as

an adjunct to curative surgical resection of colorectal cancers, a statistically significant improvement in overall survival (HR 0.53; 95% CI 0.32 to 0.87) was demonstrated. (467) In two small series of patients with melanoma, the combination of cimetidine and interferon was associated with a clinical response ranging from complete regression to partial regression and prolonged disease stabilization. (938, 939) A report from Denmark assessed overall survival of gastric cancer patients treated with oral cimetidine 400 mg twice daily for 2 years. In this double-blinded study, 181 patients were randomized to cimetidine or placebo immediately after surgery. Median survival in the cimetidine group was 450 days and 316 days in the placebo group (p = 0.02). (940) Relative survival rates (cimetidine/placebo) were 45%/28% at 1 year.

Types of cancers cimetidine may be beneficial for

While cimetidine appears to be beneficial in patients with colorectal cancer (466, 471, 935, 941-943), melanoma (466, 944), and gastric cancer (466, 471, 472, 928, 942), this drug may have some benefit in patients with pancreatic cancer (466, 945), ovarian carcinoma (466, 946), prostate cancer (466), Kaposi's Sarcoma (466), salivary gland tumors (466, 947), renal cell carcinoma (466, 944, 948, 949), breast cancer (466, 927, 950), glioblastoma (466, 951) and bladder cancer (466, 937). Cimetidine's major role may be as part of a pre-operative protocol to reduce metastases.

Dosing and cautions

Most studies used a standard dose of 400 mg twice daily. Cimetidine has few side effects, with the most frequent being gynecomastia. However, Cimetidine has a number of potentially serious drug-drug interactions by interfering with the CYP450 metabolizing enzymes; drug-drug interactions should therefore be evaluated before prescribing cimetidine. Cimetidine should not be combined with itraconazole and metformin. In addition, cimetidine should be used with caution in patients with renal and hepatic impairment.

CHAPTER 8: TIER TWO REPURPOSED DRUGS – WEAK RECOMMENDATION

18. Valproic Acid

Valproic Acid (VPA) is a broad-spectrum antiseizure medication that is used alone and in combination for the treatment of generalized and focal seizures. Valproate is considered the most effective antiseizure medication for idiopathic generalized epilepsy with generalized tonic-clonic seizure.(952) Valproic acid (VPA) is also commonly used as a mood stabilizer and migraine prophylactic. It was first synthesized from *Valeriana officinalis* by Burton in 1882.(953) VPA is a short-chain chain branched fatty acid administered orally or intravenously.(954) VPA has been reported to exert its epigenetic modulation effect via the inhibition of histone deacetylase (HDAC) and has been found to be helpful in the treatment of various malignancies.(954)

Epigenetics is defined as alterations occurring in the phenotype without any changes in the DNA sequence. DNA methylation on cytosine residues and acetylation on lysine residues are two major epigenetic mechanisms controlling chromatin modifications. (955) Histone proteins consist of an octamer comprising of four core subunits which forms a winding framework for DNA. Histone tails protruding from the core tetramer undergo acetylation on their lysine residues as a post translational modification. This acetylation confers a negative charge to the histone tail and prevents strong electrostatic interactions with DNA thus allowing open chromatin conformation and smooth gene transcription. The acetylation levels of the lysine residues are controlled by a balance between two enzymes -Histone Acetyl Transferases (HAT's) and Histone Deacetylases (HDAC's). (955) HDAC enzymes are upregulated in malignant transformed cells leading to hypo-acetylation of the core Histones. Consequent chromatin de-condensation prohibits the transcription machinery from coming in contact with the gene to be transcribed. (955) Augmented HDAC over-expression is associated with inactivation of vital tumor suppressor genes and subsequent abnormal cellular metabolism. HDACs can regulate proteins involved in tumor progression; thus, the presence or overexpression of some HDACs is associated with poor survival in patients with cancer.(954) The Cancer Genome Atlas (TCGA) project demonstrated frequent mutations in critical epigenetic regulators, strengthening the link between genetic and epigenetic events in cancer.

HDAC inhibitors bind the zinc catalytic site of the HDAC enzyme, thus inhibiting its activity and restoring acetylation levels of histone amino acid residues. (955) Histone Deacetylases are 18 mammalian enzymes that are classified into four different classes.(955) Class I consists of HDAC's 1, 2, 3 and 8, that are located in the nucleus and present in all tissues. Valproic acid (VPA) is a class I histone deacetylase inhibitor. (956) Due to its low cost, favorable side effect profile and its ease in crossing the blood brain barrier, VPA is an attractive drug candidate for a variety of cancers.

Anticancer pathways and mechanisms
VPA has anti-tumor activity by modulating multiple pathways including the induction of cell cycle arrest *via* the upregulation of cyclin-dependent protein kinase inhibitors; induction of Apo2 ligand or tumor necrosis factor-related apoptosis- inducing ligand-induced apoptosis, inhibition of Janus kinase/signal transducer and activator of transcription, phosphoinositide 3-kinase/Akt, and nuclear factor kappa B signaling pathways; and strengthening of tumor immunosurveillance.(954)

VPA decreases cellular proliferation of prostate cancer cells in vitro and also affects gene expression suggestive of an anti-angiogenic effect. (957) Xia et al demonstrated that VPA induces autophagy by suppressing the Akt/mTOR pathway in human prostate cancer cells. (958) VPA inhibited the growth of triple negative breast cancer (TNBC) cells and triggered apoptotic cell death through G0/G1 arrest.(959) Li et al demonstrated that VPA suppresses breast cancer cell growth through triggering pyruvate kinase M2 isoform mediated Warburg effect.(960) Shan et al demonstrated that VPA inhibited the proliferation of ovarian cancer cells in a dose and time dependent fashion.(961) Furthermore, VPA increased the anticancer effect of a chemotherapeutic agent. In addition, in an ovarian cancer model these authors demonstrated that endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) were decreased. Zhao et al demonstrated that VPA inhibits the angiogenic potential of cervical cancer cells via HIF-1α/VEGF signals. (962) Machado et al demonstrated that VPA inhibits human hepatocellular cancer cells growth in vitro and in vivo.(963) Greenblatt et al demonstrated that VPA activates Notch1 signaling and induces apoptosis in medullary thyroid cancer cells.(964)

Sami et al demonstrated that VPA inhibits the growth of cervical cancer both in vitro and in vivo. (965) Furthermore, these authors demonstrated that VPA had a direct anti-angiogenic effect. In a glioma cell line VPA inhibited the Epithelial-mesenchymal transition (EMT) process by altering the expression level of Smad4 thereby potentially inhibiting glioma invasion and metastasis.(966)

Both metformin (MET) and VPA appear promising as anti-cancer agents, but at doses required for anti-cancer effects they both exhibit limitations related to toxicity. However, MET and VPA act *via* different molecular biological pathways even though they both induce cell-cycle arrest, and have anti-proliferative and anti-apoptotic effects. (967) Tran et al reported that MET and VPA in combination synergistically reduced the proliferation of prostate cancer cell lines in vitro with minimal adverse effects in normal prostatic epithelial cells.(968) In a xenograft model these authors demonstrated that the combination of MET and VPA had a greater anti-tumoral effect than either drug alone. (967) Furthermore, VPA induced increase in H3 acetylation has also been shown to prevent the emergence of resistance to MTOR inhibitors in a renal cancer cell line. (969)

Clinical studies
As VPA has modest activity as monotherapy in patients with cancer, the majority of evidence for a possible role of VPA as an anticancer drug is based on its effects observed in combination

with other drugs.(955) This includes combination therapies with other epigenetic modifiers, combinations with cytotoxic chemotherapy agents, combinations with immune-modulators and combinations with other repurposed drugs (MET). In patients with NSCLC, it has been demonstrated that the epigenetic changes induced by HDAC inhibitors restored sensitivity to previously used chemotherapeutic agents. (970)

In a phase II study in patients with metastatic breast cancer, VPA in combination with 5-FU, epirubicin and cyclophosphamide produced objective responses in 64% of patients. (971) Synergy between VPA and doxorubicin was also observed in a phase II study of patients with unresectable and platinum-refractory mesothelioma. (972) In combination with a topoisomerase I inhibitor, VPA use led to disease stabilization in 47% of patients treated in a phase I/II study for metastatic melanoma. (973) In a randomized phase III, placebo-controlled study in patients with advanced cervical cancer, hydralazine and VPA added to cisplatin resulted in a significant increase in progression-free survival (PFS).(974)

A meta-analysis of 5 observational studies demonstrated that the addition of VPA prolonged the survival of patients with glioblastoma (HR, 0.56; 95% CI, 0.44–0.71).(975) Similarly, Wang et al demonstrated that patients with glioma who received VPA had a more favorable prognosis and a lower recurrence rate.(976)

Drott et al reported that VPA in combination with rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (R-CHOP) showed a positive outcome and tolerable safety level in patients with diffuse large B-cell lymphoma (DLBCL) in a phase 1 clinical trial. (977) VPA is clinically useful in low-risk myelodysplastic syndrome (MDS). (978, 979) In patients with high-risk MDS and AML, VPA may be combined with chemotherapy or demethylating drugs.(978, 980-982)

Dosage and cautions

The bioavailability of VPA is >80% after oral administration, and its peak blood concentration is observed within 2 hr.(954) Several pathways are employed in VPA metabolism in the human body, including glucuronidation, β-oxidation, and cytochrome P450 (CYP)-mediated oxidation pathways. VPA is metabolized extensively by the liver via glucuronic acid conjugation and beta and omega oxidation to produce multiple metabolites, some of which are biologically active. The half-life of VPA varies significantly from 9 to 18 hr.

As an antiseizure drug, an appropriate VPA dose for common use is initially 15 mg/kg, with slow titration to the therapeutic dose. The dose may be increased at one-week intervals by 5 to 10 mg/kg per day as needed. A serum level should be checked one to two weeks after the initial dose but can be checked three to four days after initiation or dose adjustment. Dosages of 25-30 mg/kg/day may be required for some patients.(954) Valproic acid is best administered as divided dosage (BID/TID) and taken with meals. For long term use in patients with cancer a dose of 20 -30 mg/kg/day is suggested, which can be titrated to achieve serum concentrations in the range of the recommended values for the treatment of epilepsy, namely 50–100 mcg/mL (346 to 875 micromol/L). (972, 974) For short term use (days) when combined with cyclic

chemotherapy an initiation dose of 35 mg/kg/day is suggested with a titrated increase in subsequent cycles with the maximum dose not exceeding 50 mg/kg/day. (971, 977, 980, 983) The most common adverse effects of VPA include nausea, vomiting, hair loss, easy bruising, and tremor. VPA can cause thrombocytopenia and other coagulation disturbances and has also been associated with subclinical hypothyroidism with mild to moderate elevations in thyrotropin (TSH) levels. A number of case reports and case series have described a syndrome of reversible parkinsonism and cognitive decline associated with VPA use. (984)

Valproic acid has a **Black Box** warning for hepatotoxicity. Serious and fatal cases of hepatic failure have occurred, usually during the first 6 months of therapy.(985, 986) Acute VPA ingestion may result in dose-related and reversible hepatotoxicity, which manifests as minor elevations in aminotransferases. (987-989) Chronic dosing of VPA is also associated with mild aminotransferase elevations in up to 44 percent of patients.(988) Discontinuation of the drug usually results in complete resolution of these liver function abnormalities. The rates of both non-fatal and fatal hepatic failure appear to be higher when VPA is administered with another medication (most often antiepileptics or benzodiazepines) as opposed to monotherapy.(989) Monitoring of LFTs is therefore suggested especially during the 1st 6 months of therapy. The majority of patients with acute VPA intoxication experience mild to moderate lethargy and recover uneventfully.(987) Central nervous system (CNS) dysfunction is the most common manifestation of toxicity, ranging in severity from mild drowsiness to coma or fatal cerebral edema.(989) Life threatening pancreatitis has also been reported. (990)

VPA interacts with numerous medications, mostly notably neuropsychiatric medications, and therefore drug interactions should be checked in all patients. Using VPA together with melatonin may increase side effects such as dizziness, drowsiness, confusion, and difficulty concentrating. Apart from melatonin, there are no drug interactions with VPA and the strongly recommend drugs. The concomitant use of Lamictal (lamotrigine) is contraindicated. The risk or severity of methemoglobinemia can be increased when VPA is combined with acetaminophen. The risk or severity of CNS depression can be increased when VPA is combined with Acetazolamide. Using valproic acid together with diphenhydramine may increase side effects such as dizziness, drowsiness, confusion, and difficulty concentrating.

In summary, pre-clinical studies have demonstrated that VPA inhibits a variety of cancer cells via multiple pathways. This data is supported by clinical studies in which VPA is combined with chemotherapeutic agents. Due to the requirements for drug monitoring and the numerous drug interactions, VPA should be considered in those patients receiving repurposed drugs (esp. metformin) who have responded poorly to the primary regimen.

19. Low Dose Naltrexone

Naltrexone is an opiate receptor antagonist preventing opiate stimulation; it has been used for decades as a treatment for addiction to opiates as it prevented the euphoria induced by recreational use of morphine and heroin. It was noted that in certain patients being treated with naltrexone for an opioid addiction many reported significant secondary benefit when being weaned off naltrexone. This group of patients had chronic inflammatory and autoimmune conditions and reported improvements while using the lower dosages of naltrexone. There have also been recent anecdotal reports of cancer resolution following the use of low doses of naltrexone (LDN). (991) Of note, a number of these anecdotal reports of response to LDN have been reported when both administered as single agents or more usually in combination with another agent.

Anticancer pathways and mechanisms

In vivo studies performed in the 1980s, highlighted the importance of dose in determining the overall effect of naltrexone as mice that were treated with clinically conventional doses of 10mg/kg induced a continuous occupancy of the opioid receptors, which was associated with increased tumor growth. (992) However, if doses were reduced to 1 or 0.1 mg/ kg, the receptor blockade was incomplete. Binding sites were thus available to exogenous opiates and endogenous endorphins, resulting in activation of their anti-tumor actions. In addition to dose, the schedule of naltrexone administration was also crucial, with intermittent administration of LDN achieving the greatest anti-tumor response.

LDN can influence cancer progression via three mechanisms; namely, (a) antagonism of receptors to which LDN binds, which include toll-like receptors 7-9 that lead to IL-6 suppression b) modulation of immune function in patients; and c) direct inhibition of signaling pathways involved in cancer cell control, including the priming of pro-apoptotic pathways. (991)

LDN has potent anti-inflammatory qualities, it appears to modulate and modify different elements of the immune system. In vitro investigations using models of individual components of immunity have described naltrexone altering the intracellular signaling in and subsequent cytokine output of immune cells. (991) In patients administered LDN, the systemic levels of cytokines that drive both humeral and cell mediated inflammation, such as G-CSF, IL-4, IL-6, IL-10, IFN-α and TNF-β, were significantly reduced after eight weeks. (993) Naltrexone can disrupt immune responses by inhibiting cytokine production by peripheral blood mononuclear cells by antagonizing TLRs. (994) More specifically, Liu et al screened a panel of available inflammation receptors and confirmed that naltrexone could completely block TLR-9 on immune cells, with some activity in TLR-7 and TLR-8. (991) Additionally, LDN is also thought to improve adaptive immune responses by enhancing the maturation of professional antigen presenting cells, as studies have shown increased expression of maturation markers on dendritic cells (DCs) following culture with LDN. (995)

Naltrexone in low doses can reduce tumor growth by interfering with cell signaling. The μ-opioid receptor (MOR) is up-regulated in several types of cancer including non-small cell lung

cancer. MOR is an important regulator of cancer progression. In an in vitro model MOR overexpression increased Akt and mTOR activation, cell proliferation, tumor growth and metastases. (996) Liu et al demonstrated that the anticancer action of LDN is associated in part with changes to pERK and Pl3-K signaling. (997) Tripold et al demonstrated that opioid-exposed breast cancer cells showed enhanced migration and strong STAT3 activation, which was efficiently blocked by an opiate receptor antagonist. (998) Furthermore, opioid treatment resulted in down-regulation of E-Cadherin and increased expression of epithelial-mesenchymal transition markers.

LDN is alters the balance of pro and antiapoptotic proteins that regulate cell killing. Specifically, in vitro and in vivo models show how the pro-apoptotic proteins BAX and BAD can be enhanced by a short-term exposure to LDN. (991, 999) LDN acts as an Opioid Growth Factor receptor (OGFr) antagonist and the OGF-OGFr axis is an inhibitory biological pathway present in human cancer cells and tissues, being a target for the treatment with LDN. (1000) In an in vitro model, Ma et al demonstrated that LDN reduces tumor size by increasing levels of M1-like macrophages and activating the Bax/Bcl-2/caspase-3/PARP signaling pathway to induce apoptosis. (999)

Clinical studies

The benefit of LDN in patients with cancer is limited to several case reports and a small case series. Case reports have described the benefit of LDN in patients with lung adenocarcinoma, adenoid cystic tongue carcinoma (in combination with vitamin D3), renal cell cancer (together with Alpha Lipoic Acid (ALA)), B cell lymphoma (with ALA) and pancreatic cancer (with ALA).(1001-1006) Lissoni et al. report four partial responses and one stable disease in nine patients with renal cell cancer treated with IL-2 and LDN. (1007) Significantly, however, these patients had disease progression when using IL-2 alone.

Types of cancers LDN may be beneficial for

LDN shows promising results for people with primary cancer of the bladder, breast, liver, lung, lymph nodes, colon, and rectum. (1000)

Dosing and cautions

A dose of between 2 mg and 4.5 mg daily is suggested. Begin with 2 mg/day and increase to 4.5 mg/day. The dose should not be increased beyond 4.5mg as this paradoxically reduces the anti-inflammatory effects of LDN. Furthermore, the use of traditional doses of opiates for pain control in patients with cancer may activate oncogenic pathways. (998)

20. Doxycycline

Anticancer pathways and mechanisms

Doxycycline and minocycline were introduced into medicine as more potent, active, and stable semisynthetic tetracycline antibiotics. In general, the incidence of adverse effects caused by minocycline and doxycycline is very low. In addition, they show many non-antibiotic properties, including anti-inflammatory, antioxidant, neuroprotective, immunomodulatory, and anticancer effects. (1008, 1009) Recently published studies and analyses considered the repurposing of minocycline and doxycycline as anti-melanoma agents. (1010, 1011)

Mechanisms of the anticancer activity of doxycycline and minocycline involve reduction of STAT3 phosphorylation, prevention of NF-KB activation, repression of tumor necrosis factor (TNF) - α expression and inhibition of matrix metalloproteinases. (1009, 1012) Minocycline and doxycycline have been demonstrated to exert anti-melanoma effects. (1010, 1011) These drugs inhibited cell proliferation, decreased cell viability, and induced apoptosis. Rok et al demonstrated similar findings in amelanotic melanoma cells. (1008) In this study, the treatment caused changes in the cell cycle profile and decreased the intracellular level of reduced thiols and mitochondrial membrane potential. In addition, exposure of melanoma cells to minocycline and doxycycline triggered the release of cytochrome c and activated initiator and effector caspases. In this study, doxycycline was a more potent drug than minocycline in mediating these anticancer effects.

Doxycycline blocks the activity of metalloproteinases, which would otherwise be involved in the breakdown of the extracellular matrix that allows individual cancer cells to break free and seed new metastatic cancer growth around the body. Considering the potent inhibitory effects of tetracyclines against metalloproteinases, their anticancer potential has been studied in a variety of cancers, including melanoma, lung, breast, and prostate cancers. (1013) When combined with celecoxib, minocycline inhibited the osseous metastasis of breast cancer in nude (hairless) mice, by increasing tumor cell death and decreasing tumor expression of MMP-9 and VEGF. (1014) Minocycline has been shown to inhibit in vitro invasion and experimental pulmonary metastasis in mouse renal adenocarcinoma. In addition, these drugs have been demonstrated to inhibit angiogenesis in vitro by a non-metalloproteinase-dependent mechanism. (1015)

Weiler et al demonstrated that minocycline inhibited the TNF-α-induced fusion of cancer cells with breast epithelial cells; (1012) this may have an important role in limited metastatic cancer spread. Minocycline has been demonstrated to act synergistically with cisplatin in the treatment of hepatocellular carcinoma. (1016) Anti-proliferative and anti-metastatic properties of minocycline have also been demonstrated in various other types of cancer, including renal adenocarcinoma, (1017) breast cancer, (1014) and malignant gliomas. (1018)

Clinical studies

Despite the numerous experimental models, there are no published reports that have investigated the clinical benefits of these drugs in patients with cancer.

Types of cancers doxycycline may be beneficial for
Despite the absence of clinical data, doxycycline may have clinical efficacy in the following cancers: melanoma, renal adenocarcinoma, breast cancer, prostate, and malignant gliomas.

Dosing and cautions
The standard dose of doxycycline is 100 to 150 mg daily. The duration of therapy in patients with cancer has not been studied; therefore, a course lasting no longer than 2 weeks is suggested. Serious adverse effects are uncommon, with the most common adverse effects being headache and nausea. Because of the effects of antibiotics on the microbiome a prolonged course of doxycycline should be avoided.

21. Spironolactone

Anticancer pathways and mechanisms
Spironolactone's primary mechanism of action in the therapy of cancer seems to be the regulation of DNA damage response. Spironolactone affects the hallmarks of immune protection, invasion, and metastasis activation, and cell death resistance. (1019) Through the prevention of DNA damage repair, spironolactone also affects the genomic instability that is a contributing factor in the development of cancer. (1019) Cancer cells can be made more susceptible to platinum-base substances by spironolactone. (888)

The worst kind of DNA damage is called a double-strand break (DSB). DSBs are repaired using homology-directed repair (HDR) or non-homologous end-joining (NHEJ) pathways. (1020) Many malignancies have mutant or aberrantly expressed HDR pathways, and spironolactone decreases HDR activity, which limits the ability of cancer cells to survive. Additionally, spironolactone reduces the development of Rad51 foci and makes cancer cells more susceptible to substances that damage DNA, such as PARP inhibitors and cross-linking agents. (1020)

Spironolactone has recently been discovered to be a DNA nucleotide excision repair (NER) inhibitor. (1021) The multi-subunit complex known as transcription factor II-H (TFIIH), which is crucial for both the start of transcription and NER, contains the enzyme xeroderma pigmentosum group B (XPB). Spironolactone can prevent cancer cells from repairing DNA damage by inducing the proteolytic degradation of the TFIIH complex's (XPB) protein. (888, 1021-1024)

Given the crucial roles that XPB and TFIIH play in the DNA repair process, mutagenesis could result from the loss of XPB caused by spironolactone. (1024) However, the negative effects of spironolactone's ability to reduce the incidence of cancer may be partially offset by its capacity to increase the death of CSCs and facilitate immune identification. (1022, 1024)

Additionally, spironolactone can interfere with cisplatin-induced DNA crosslinks in lung cancer by inhibiting SIRT2-mediated transcription-coupled nucleotide excision repair. (888)

In patients with colon cancer, tumor metastasis and absence of NKG2D ligand (NKG2DL) expression are linked to a poor prognosis. (1025) By activating the ATM-Chk2-mediated checkpoint pathway, spironolactone can increase the expression of NKG2DL in a variety of colon cancer cell lines, enhancing the removal of tumors by NK cells. (1025) It can also up-regulate the expression of metastasis-suppressor genes TIMP2 and TIMP3, thereby reducing tumor cell invasiveness. (1025)

Hepcidin is a regulating hormone produced by the liver that modifies iron fluxes to match body iron needs. Since cancer cells have abnormally high requirements for iron, starving them with iron-sequestering medications prevents the growth of tumors. (1026) Hepcidin expression is primarily and most effectively stimulated by bone morphogenetic proteins (BMPs). (1026) A component of cancer cells' metastatic invasion strategy seems to involve the overexpression of hepcidin by some BMPs. (1026) When BMP signaling is blocked, the ability of cancer cells to spread through lymphatic and blood arteries is reduced. (1026)Spironolactone inhibits the expression of hepcidin, hence preventing metastasis. (1027)

Spironolactone reduces oxidative stress, cellular death, and inflammation. When spironolactone is given to PCOS mice, inflammation biomarkers such NF-kB, TNF-, and IL-6 in adipose tissues drastically decrease. (1028)

Spironolactone chemosensitizers cancer cells and CSCs to anticancer drugs like gemcitabine and osimertinib while suppressing the expression of survivin, an anti-apoptotic protein, at a dose that was safe for non-cancer cells. (1029)

Clinical studies

Given that spironolactone is a progesterone derivative, and it has a secondary affinity for both androgen receptor and progesterone receptor, it was thought that spironolactone might have some clinical value in the treatment of prostate cancer. (1019) Spironolactone dramatically decreased the incidence of prostate cancer in clinical investigations. (1030-1032) At first, spironolactone was said to further lower testosterone levels in men with prostate cancer who had undergone orchidectomy in the 1970s, indicating that the medication would be helpful as an adjuvant in these individuals. (1019) More recently, a French case report describing the normalization of prostate-specific antigen in a patient with prior prostate cancer following spironolactone therapy was published. (1019)

Researchers discovered that spironolactone exposure significantly decreased the occurrences of prostate cancer among 18,562 males with newly diagnosed heart failure (95% confidence interval 0.31-0.98, P =.043). (1030) Additionally, Spironolactone is proven to be connected with a low rate of prostate cancer in a meta-analysis by Bommareddy et al.(1032) Spironolactone was linked to a significantly decreased incidence of prostate cancer in a score-matched cohort analysis of 74,272 participants in the UK (hazard ratio 0.69; 95% confidence interval 0.60-0.80, P 0.001). (1031)

Spironolactone can pass the blood-brain barrier because it is a lipophilic medication. (1022, 1033) Data shown that spironolactone has a cytotoxic effect on U87-MG glioblastoma cancer cells through a mechanism reliant on the activation of apoptosis. (1022)

Types of cancer Spironolactone may be beneficial in treating.
In addition to treating prostate cancer, spironolactone may also be helpful for treating lung cancer, (888), colon cancer, (1025) invasive bladder cancer, (1034) glioblastoma, (1022) and breast cancer. (1035)

Dosing and cautions
While the optimal dose of spironolactone for the treatment of cancer is unknown, a dose of 50-100 mg/day is suggested. Potassium levels should be monitored particularly when using a higher dose and the concomitant use of other drugs that interfere with potassium elimination. There was concern that spironolactone use might raise the incidence of bladder, breast, and ovarian cancer. To date, however, the results of meta-analyses indicated that spironolactone use was not significantly linked to an increased risk of cancer and was instead linked to a lower risk of prostate cancer. (1032)

22. Resveratrol

Resveratrol (3,40,5-trihydroxy-trans-stilbene) is a non-flavonoid polyphenol that occurs naturally in many species of plants, including peanuts, grapes, and berries. (550) Pterostilbene is a naturally occurring analog of resveratrol.

A significant amount of research, including preclinical, clinical, and epidemiological studies, has indicated that dietary consumption of polyphenols, found at high levels in vegetables and fruits, may prevent the evolution of an array of diseases, including cancer. (550) Resveratrol and other flavonoids (quercetin, turmeric) have numerous anticancer activities.

Anticancer pathways and mechanisms
Resveratrol has also been reported to possess a significant anticancer property in various preclinical animal models. (550) Resveratrol affects a variety of cancer stages, from initiation and promotion to progression, by affecting the diverse signal-transduction pathways that control cell growth and division, inflammation, apoptosis, metastasis, and angiogenesis. It has been shown that resveratrol has in vitro cytotoxic effects against a large range of human tumor cells, including myeloid and lymphoid cancer cells, and breast, skin, cervix, ovary, stomach, prostate, colon, liver, pancreas, and thyroid carcinoma cells. (550, 1036-1038)

Studies conducted in vitro have discovered that resveratrol exerts an anti-proliferative activity by inducing apoptosis. Resveratrol modifies the balance of cyclins as well as cyclin-dependent kinases (CDKs), resulting in cell cycle inhibition at G0/G1 phase. (1039) Resveratrol causes activation of the p53-dependent pathway. (1040) The inhibition of anti-apoptotic proteins of

the Bcl-2 family, and activation of pro-apoptotic proteins such as Bad, Bak or Bax, by resveratrol has also been shown to be a mechanism for caspase activation and cytochrome c release. (1041) It has also been shown that resveratrol induces apoptosis via inhibiting the PI3K/Akt/mTOR pathway, modulating the mitogen-activated protein kinase pathway (MAPK) and inhibiting NF-KB activation. (550) Resveratrol also causes inhibition of signal transducers and activators of transcription 3 (STAT3), which adds to its pro-apoptotic and anti-proliferative potential. (1042) In addition, resveratrol may inhibit CSCs. (1043)

Flavonoids, as antioxidants, inhibit regulatory enzymes and transcription factors important for controlling inflammatory mediators. Moreover, they modulate cellular oxidative stress by interacting with DNA and enhancing genomic stability. (771) Resveratrol also augments the activity and expression of antioxidant and phase-II detoxifying enzymes through the activation of nuclear factor E2–related factor 2 (Nrf2).

Preclinical research has demonstrated the effectiveness of flavonoids against inflammation-associated cancer progression. (771) Due to the association between inflammation and angiogenesis in tumor cells, experimental models demonstrate that flavonoids decrease angiogenesis and tumor metastasis. Resveratrol has been suggested to inhibit metastatic spread by inhibiting the expression of MMP (mainly MMP-9) and angiogenesis markers such as VEGF, EGFR, or FGF-2. (550, 1044). Luteolin showed a potent capacity to target HIF-1α/VEGF signaling and angiogenesis. (551)

It has been reported that resveratrol can reverse multidrug resistance in cancer cells, and, when used in combination with clinically used drugs, it can sensitize cancer cells to standard chemotherapeutic agents. (550) In addition, it is likely that resveratrol has synergic activity against cancers when combined with GTCs.

Pterostilbene appears to be the most promising of the resveratrol analogs and significantly inhibited tumor growth, progression, local invasion and spontaneous metastasis in a mouse model of prostate cancer.(1045) Studies have confirmed that pterostilbene exerts anti-proliferative and pro-apoptotic effects in various cancer cell types including lung, gastric, prostate, colon, breast cancers and Chronic myeloid leukemia and Chronic lymphocytic leukemia.(1046-1048)

Clinical studies

Although resveratrol has shown excellent anticancer properties, most of the studies were performed in cell culture and pre-clinical models. Furthermore, resveratrol's poor bioavailability is a significant issue regarding extrapolating its effects on humans. (550) Pterostilbene may be the preferred formulation.

Types of cancers that resveratrol may be beneficial for

Resveratrol likely has anticancer effects in patients with breast, prostate, colorectal, hepatocellular, pancreatic, lung, and ovarian cancer. (550)

Dosing and cautions
Various approaches have been created to enhance the bioavailability of resveratrol, including consuming it with various foods, using it in combination with an additional phytochemical — piperine — and using a prodrug approach, micronized powders, or nanotechnological formulations. (550) A resveratrol dose of 500 mg twice daily is suggested. A bio-enhanced formulation containing trans-resveratrol from Japanese Knotweed Root appears to have improved bioavailability.

23. Wheatgrass

A wide range of health benefits have been attributed to wheatgrass, the young grass of the common wheat plant Triticum aestivum. Its components include chlorophyll, flavonoids, and vitamins C and E. Wheatgrass is also known as “green blood” because of its high chlorophyll content, i.e., 70% of its chemical composition. (1049) Moreover, it has structural similarity with hemoglobin. Wheatgrass also contains the antioxidant enzymes superoxide dismutase and cytochrome oxidase that have the potential to convert reactive oxygen species to hydrogen peroxide and oxygen molecule. Forms of wheatgrass include fresh juice, frozen juice, tablets, and powders, with compositions varying according to their production processes, as well as to the growing conditions of the wheatgrass. Laboratory in vitro studies, mostly using the fermented wheat germ extract, have demonstrated anti-cancer potential and have identified apoptosis as a possible mechanism. (1050) There is limited clinical data on the role of wheatgrass in patients with cancer.

In a study with colon cancer patients, after six-month supplementation of wheat germ extract to anticancer treatments, lower recurrences of metastatic disease and mortality were reported in the intervention group. (1051) This open-label cohort trial compared anticancer treatments plus wheatgrass vs anticancer treatments alone. Sixty-six patients received wheatgrass supplement for more than 6 months and 104 patients served as controls. End-point analysis revealed that progression-related events were significantly less frequent in the wheatgrass group; new recurrences: 3.0 vs 17.3%, P= 0.01; new metastases: 7.6 vs 23.1%, P=0.01; deaths: 12.1 vs 31.7%, P=0.01). Survival analysis showed significant improvements in the wheatgrass group regarding progression-free (P=0.0184) and overall survivals (P=0.0278). In a controlled prospective trial of 100 patients with stage II–III colorectal cancer Avisar et al examined the effect of daily wheatgrass juice intake in addition to chemotherapy on immune parameters including IL-6, IL-8, IL-10, and IL-12 and white cell count (WBC). (1052) In this study the anti-inflammatory cytokine IL-10 concentrations were significantly higher and the decline in WBC counts between was significantly lower in the wheatgrass group. The higher levels of IL-10 and the attenuating of WBC decline during chemotherapy may constitute preliminary evidence of the beneficial effects of wheatgrass on immune parameters, when given as a supplement to standard care. In a study of patients with breast cancer receiving adjuvant chemotherapy wheatgrass was associated with a reduction in neutropenic fever events and in neutropenic infections. (1053)

24. Captopril

The angiotensin converting enzyme (ACE) inhibitors are used widely as antihypertensive agents, and it has been suggested that they have anti-cancer. (1054) Angiotensin II, the product of ACE, has oncogenic and pro-proliferative qualities, which suggests that ACE inhibitors may have anti-cancer activity. (1055) Captopril is unique among ACE inhibitors as it appears to reduce the risk of prostate cancer and possibly other cancers. (1056) Liu *et al.* demonstrated that lisinopril extends the median survival time of patients with non-metastatic pancreatic ductal adenocarcinoma from 19.3 to 36.3 months. (1057)

The efficacy of ACE inhibitors in reducing angiogenesis and tumor growth has been largely attributed to the overexpression of angiotensin II type I receptor (AGTR1). In fact, it has been widely studied that the overexpression of AGTR1 has been found in liver, breast, renal, pancreatic, bladder, prostate, ovarian, cervical, laryngeal, head and neck, and skin squamous cell cancer. (1055) In cancer, angiotensin II up-regulates *AGTR1*, which in turn activates the extracellular signal-related kinase/protein kinase B pathways, resulting in increased VEGF production. As a result, inhibition of AGTR1 through ACE inhibitors is theorized to reduce not only VEGF but also angiogenesis and tumor growth. (1055) Captopril has been demonstrated to be an inhibitor of angiogenesis and block neovascularization and may therefore play a role in decreasing metastases. (741)

In a mouse model injected with highly tumorigenic LNM35 human lung cells as xenografts captopril resulted in a significant reduction of tumor growth (58%, $P < 0.01$) and lymph node metastasis (50%, $P = 0.088$). (1054) In this study captopril inhibited the viability of LNM35 cells by inducing apoptosis. The Wnt/β-catenin pathway plays an important role in tumorigenesis. Wnt signaling modulates multiple genes of the renin-angiotensin system (RAS), and Wnt inhibition can improve cancer outcomes via diverse mechanisms. Captopril induces significant down-regulation of Wnt target genes, c-myc and cyclin D1. (1058) In addition, captopril's known anti-cancer effects include inhibition of matrix metalloproteinase-2 (MMP-2), an endopeptidase that selectively breaks down the extracellular matrix to promote cell migration. (1059) in a rat intracranial gliosarcoma model captopril decreased gliosarcoma cell migration, mediated by reduction in MMP-2 protein expression. (1059) The effect of captopril on MMP-2 may be potentiated by the addition of disulfiram as well as other repurposed drugs. (1060) In a rat cirrhosis model captopril prevented fibrotic liver disease and progression toward hepatocellular carcinoma. (1061) In this model captopril suppressed the expression of pathways mediating fibrogenesis, inflammation, and carcinogenesis, including epidermal growth factor receptor (EGFR) signaling. While a number of in vivo and in vitro studies support the anticancer activity of captopril and other ACE inhibitors there are limited clinical studies to support the use of these drugs. (1056, 1057)

25. Clarithromycin

Clarithromycin (CAM) is a macrolide antibiotic with a high bioavailability which has been available as a generic drug worldwide since 2005. Preclinical and clinical data demonstrate a potential role for CAM to treat various tumors in combination with conventional treatment. The mechanisms of action underlying the anti-tumor activity of CAM include prolonged reduction of pro-inflammatory cytokines and anti-angiogenesis.(1062)

Anticancer pathways and mechanisms

Treatment with CAM alone was able to significantly delay the growth of Lewis lung carcinoma and reduce the number of tumor nodules in mice. (1063) In a melanoma model, CAM reduced the size of melanoma tumors by increasing apoptosis of tumor cells and suppressing metastases.(1064) CAM induced apoptosis in a murine B cell lymphoma cell line. (1065) In addition to a direct effect on tumor cells, there is evidence that CAM can inhibit tumor-induced angiogenesis in mice. (1066) CAM treatment reduces tumor growth and increases the overall survival in colorectal cancer mouse xenograft models.(1067)

CAM administered after vindesine, or cisplatin significantly enhanced the effect of chemotherapy by increasing natural killer cell activity and CD8+ T cell cytotoxicity. (1063) In a melanoma tumor model, CAM potentiated the inhibition caused by cyclophosphamide, cisplatin, doxorubicin, or vindesine, possibly via an anti-angiogenic effect. (1068) Zhou et al demonstrated that CAM synergizes with cisplatin to inhibit ovarian cancer growth in vitro and in vivo. (1069)

Clinical studies

Numerous clinical trials have been reported with CAM in combination with other drugs in patients with multiple myeloma (MM) and Waldenström's macroglobulinemia (WM). (1062) In contrast to the low efficacy as a monotherapy, the combination of CAM with steroids, with or without concomitant thalidomide or its analogues, resulted in high response rates. (1062) Coleman *et al* reported that the combination of CAM with dexamethasone and low-dose thalidomide in patients with MM or WM resulted in a 93% response rate. (1070) According to Niesvizky *et al* the addition of CAM allows a lower dose of dexamethasone while maintaining a high response rate.(1071) Carella *et al* reported that CAM could improve clinical outcome of CML patients in combination with a tyrosine kinase inhibitor, either dasatinib or nilotinib. (1072) CAM is considered the drug of choice for the treatment of *Helicobacter pylori* associated Mucosa-associated lymphoid tissue lymphoma (MALT lymphoma). (1073, 1074)

In addition to MM and lymphomas, there is evidence of anticancer activity of CAM in solid tumors. In a randomized trial in 49 patients with advanced lung cancer, Mikasa *et al* found that the 25 patients treated with maintenance CAM (200 mg b.i.d.), had a significantly longer survival (median of 395 days) than patients who did not receive CAM (median of 256 days).(1075)

In summary, the anti-tumor activity of CAM has been demonstrated in tumor cell lines and mouse models. Clinical trials have confirmed the potential of CAM in NSCLC and lymphoma, even as a single treatment. In combination with other treatments CAM has proven effective in

early-stage multiple myeloma, and Waldenström macroglobulinemia.(1062) Additional clinical studies are required, particularly in solid tumors, to determine the role of CAM in treating patients with cancer.

Dosage and cautions

CAM is usually administered, in tablet or oral suspension form, at a dose of 250 mg twice daily.(1062) A dose of 500 mg twice daily is recommended for severe infections. The most frequent and common adverse reactions are abdominal pain, diarrhoea, nausea, vomiting, and dysgeusia. Other common adverse reactions described are insomnia and rash. Because of the risk of prolonging the heart's QT interval, CAM should not be given to patients with history of QT prolongation, cardiac arrhythmias, patients with hypokalemia, or to patients treated with drugs that may result in QT prolongation and cardiac arrhythmias. CAM inhibits cytochrome P450 3A4 (CYP3A4) which is involved in the hepatic metabolism of many drugs. Co-administration of CAM with statins known to be metabolized by CYP3A4 (lovastatin and simvastatin) is contraindicated.

CHAPTER 9: TIER THREE REPURPOSED DRUGS - INSUFICIENT DATA

26. Cyclooxygenase inhibitors – Aspirin (ASA) and NSAIDs (Diclofenac)

There are more than 20 different nonsteroidal anti-inflammatory drugs (NSAIDs), from six major classes determined by their chemical structures; they differ in their dose, drug interactions, and side effects. The primary effect of NSAIDs is to inhibit cyclooxygenase (COX), thereby impairing the transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. COX inhibition is central to the mechanism of action of both aspirin and the non-salicylate NSAIDs.

Two related isoforms of the COX enzyme have been described, namely COX-1 and COX-2. COX-1 is expressed in most tissues but variably and is described as a "housekeeping" enzyme, regulating normal cellular processes. COX-2 is a highly regulated enzyme that is constitutively expressed in the brain, kidney, and bone. Its expression is increased during states of inflammation. The extent of enzyme inhibition varies among the different NSAIDs. The degree to which a particular NSAID inhibits an isoform of cyclooxygenase affects both its activity and toxicity.

NSAIDs have additional modes of action beyond that of COX inhibition, including Inhibition of neutrophil activation, Inhibition of the expression of inducible nitric oxide synthase (iNOS), Inhibition of the activation of nuclear factor (NF)-kappa β, and inhibition of Erk kinase activation. While there has long been an interest in the use of aspirin (ASA) and NSAIDs in chemoprevention, there is now emerging evidence that such drugs may have activity in a treatment setting.

Aspirin

Aspirin, also known as acetylsalicylic acid (ASA), is an NSAID that exhibits a broad range of pharmacologic activities, including analgesic, antipyretic, and antiplatelet properties. Low doses (typically 75 to 81 mg/day) irreversibly acetylate cyclooxygenase (COX)-1. This effect inhibits platelet generation of thromboxane A2, resulting in an antithrombotic effect. Intermediate doses (650 mg to 4 g/day) inhibit COX-1 and COX-2, blocking prostaglandin production, and have anti-inflammatory, analgesic, and antipyretic effects. High doses (between 4 and 8 g/day) are effective as anti-inflammatory agents in rheumatic disorders; however, the usefulness of aspirin at these high doses is limited by toxicity, including tinnitus, hearing loss, and gastric intolerance. ASA 325 mg daily appears to be at least as effective as 75 mg daily in terms of cardiovascular and cerebrovascular protection. Furthermore, there does not appear to be a difference in safety across the low dose range of 75-325 mg. (1076) Leukocytes, endothelial cells, mucosal cells, and vascular smooth muscle cells express COX-2. Selective targeting of COX-2 suppresses the prostaglandins, particularly prostacyclin, at sites of vascular inflammation. In cancer, the possible mechanisms by which aspirin may provide benefit range from a direct

inhibitory effect on cancer cells themselves to antiplatelet effects, including reducing platelet–tumor cell interactions or reducing platelet secretion of proangiogenic and growth factors, cytokines, and chemokines. (1077) Malignant tumors within the proinflammatory and antiapoptotic tumor microenvironment have been shown to aberrantly express COX-1 and COX-2. (1078, 1079) Therefore, aspirin may exert an antitumor effect by way of a COX-related inhibition of inflammation and apoptosis. (1080) The extent of this effect would likely vary by tumor subtype; for instance, the relative expression of COX-1 and COX-2 in ovarian cancer was shown to vary by the histological grade and subtype of the cancer. (1079) In addition, COX-independent mechanisms have been suggested, including the suppression of signaling by IκB kinase β and extracellular signal regulated kinase, leading to reduced inflammation and proliferation. (1081, 1082)

Clinical studies

The Cancer Prevention Study II, published in 1991, showed a 40% reduction in colon cancer mortality associated with the regular use of aspirin in a cohort of 662,424 patients. (1083) Subsequently, two trials published in the *New England Journal of Medicine* in 2003 demonstrated clear benefits of low-dose aspirin (81 -325 mg/day) in secondary prevention of colorectal cancer. (1084, 1085) The issue becomes more complex as these trials were followed by negative studies, (1086, 1087) and in 2007 the U.S. Preventive Services Taskforce (UPSTF) recommended against the routine use of aspirin for any cancer prevention. (1088)

Shortly after the UPSTF recommendation, large meta-analyses of prospective trials of aspirin for cardiovascular disease were published, which found a clear benefit of aspirin in reducing both cancer incidence and mortality. (217, 1089) In 2016, the UPSTF reversed its position, stating that adults between the ages of 50 and 69 years would in fact derive cancer benefits from the preventive use of low-dose aspirin, defined as ≤325 mg per day. (1090) However, the benefit in patients without a history of cancer was small and outweighed by the risk of major bleeding. (1091)

This was followed by the ARRIVE trial, which was published in 2018. The ARRIVE trial enrolled nearly 13,000 patients with a mean age of 64 years. Patients in ARRIVE were randomly assigned to 100 mg of enteric-coated aspirin or placebo and followed up for an average of 5 years. Differences in cancer incidence were not significant but favored placebo. (548) Published one month later, the ASPREE trial was larger than ARRIVE and enrolled an older population, presumably at higher risk for cancer; 19,114 patients were randomly assigned to 100 mg of enteric-coated aspirin vs placebo. (1092, 1093) Surprisingly, aspirin was associated with an increase in all-cause mortality (HR, 1.14; 95% CI, 1.01-1.29), which was driven largely by an increase in deaths resulting from cancer (HR, 1.31; 95% CI, 1.10-1.56).

In the most recent USPSTF guideline, the use of aspirin was not associated with reductions in cardiovascular disease mortality or all-cause mortality. (1094) While the studies for colorectal cancer were highly heterogenous, for events occurring within the RCT periods only, low-dose aspirin had no statistically significant association with colorectal cancer incidence at 5 to 10

years of follow-up. In summary, the role of aspirin for the prevention of colorectal cancer is uncertain.

Clinical evidence supporting the role of aspirin in cancer prevention is greatest in those at high risk of colorectal cancer, as was demonstrated in the CAPP2 trial for patients with Lynch syndrome. (549) However, there is suggestive evidence in several other cancer types as well. Hepatocellular carcinoma rates were lower among patients with chronic viral hepatitis with low-dose aspirin use. (1095) The use of aspirin may be associated with a lower risk of pancreatic cancer. (1096, 1097) Until additional studies are available, the use of aspirin for cancer prevention is limited to specific high-risk patients.

The role of ASA in the treatment of cancer is equally as contradictory as for the prevention of cancer. Observational studies tend to demonstrate a survival advantage with the use of ASA; however, this benefit has not been replicated in prospective studies. In an observational study that included 70 studies with 18 different cancers, Elwood reported aspirin to be associated with a 20% reduction in cancer deaths (HR of 0.79; 95% confidence intervals: 0.73- 0.84). (1098) Wang et al evaluated 13 published cohort studies with 65,768 patients in order to estimate the overall risk of cancer-specific mortality associated with post-diagnosis low-dose aspirin use.(1099) The authors reported a significant decreased cancer-specific mortality with an odds ratio (OR) of 0.84 (95% CI 0.75-0.93). However, these findings have not been replicated in prospective clinical trials. (1100, 1101) The ABC trial was a randomized, phase III, double-blind placebo-controlled trial of aspirin as adjuvant therapy for high-risk, HER2-2 negative breast cancer. In this study, 3,021 patients were randomized to 300 mg aspirin or placebo daily for 5 years. (1101) The HR for invasive disease-free survival comparing aspirin to placebo was 1.27, which exceeded the prespecified HR of futility.

A011502 was a RCT conducted in the United States and Canada with 3020 participants who had high-risk nonmetastatic breast cancer. (1102) Participants were randomized to receive 300 mg of aspirin (n = 1510) or placebo once daily (n = 1510) for 5 years. The study was closed after the first interim analysis due to futility. All invasive disease–free survival events, including death, invasive progression, and new primary events, were numerically higher in the aspirin group, although the differences were not statistically significant. There was no difference in overall survival (hazard ratio, 1.19; 95% CI, 0.82-1.72).

NSAIDS (Diclofenac)

Diclofenac (DCF) is a well-known and widely used non-steroidal anti-inflammatory drug (NSAID), with a range of actions of interest in an oncological context. (1103) There is considerable variation in COX-1/COX-2 selectivity between different NSAIDs, and some evidence that DCF binds to COX-2 via a different mechanism than other commonly used drugs.(1104) DCF was developed by Ciba-Geigy and is now available globally as a generic medication. Common trade names include Voltaren, Voltarol, Cataflam, Cambia, Zipsor, and Zorvolex. In some countries, low-dose formulations of oral DCF (typically 25 mg tablets) are

available over the counter. In the U.S., DCF requires a prescription and is available as 25, 50, 75, and 100 mg delayed-release tablets.

DCF, which is a potent inhibitor of COX-2 and prostaglandin E2 synthesis, displays a range of effects on the immune system, the angiogenic cascade, chemo- and radio-sensitivity, and tumor metabolism. PGE2 are found in a range of different cancer types and are associated with the chronic inflammation that is found in a pro-tumor microenvironment. (1105)

Anticancer pathways and mechanisms

There are multiple mechanisms of action postulated to explain the diverse anticancer effects of DCF. These include anti-angiogenic, immunomodulation, pro-apoptotic, effect on platelet function, effects on Myc and glucose metabolism, and increasing treatment sensitivity. In addition, NSAIDs are associated with phosphodiesterase (PDE) 5 inhibition and activation of cGMP signaling which are closely associated with its ability to induce apoptosis of tumor cells. (1106)

Experimental models demonstrate DCF decrease in tumor angiogenesis, which was associated with a reduction of PGE2 synthesis. (1107) One mechanistic explanation is that PGE2 upregulates the production of VEGF. (1108) In experimental models, DCF decreased the expression of both VGEF and monocyte chemoattractant protein (MCP-1). (1109) PGE2 has been shown to induce the differentiation of bone marrow stem cells into MDSCs in a number of animal models of cancer. Decreases in PGE2 break the positive feedback loop of PGE2-MDSC expansion. (1110) It has been shown in autochthonous tumor models that blockade of PGE2 synthesis results in the downregulation of ARG1 expression and ROS production by MDSCs, followed by improved antitumor T-cell function and cancer chemoprevention. (1111, 1112)

Fujita and colleagues showed that in a mouse model of glioma, COX-2 blockade inhibited PGE2 production and delayed tumor progression. (1113) This was associated with reduced accumulation of MDSCs and an increased presence of cytotoxic T lymphocytes. Reduction of tumor-induced PGE2 using both selective and non-selective COX inhibitors has been shown to reduce T-reg populations and activity. (1114) DCF was able to reduce the intra-tumoral accumulation and activation of T-regs in a murine glioblastoma model. (1115) In addition to modulation of angiogenesis and immune suppression, there is some evidence for a pro-apoptotic mechanism of action for DCF in cancer. (1103, 1116) There is also some evidence that DCF has an impact on tumor metabolism that is independent of its action as a COX-inhibitor. Gottfried and colleagues showed that DCF downregulated Myc gene expression and glucose metabolism in a number of leukemia, prostate cancer, and melanoma cell lines in vitro and in an in vivo melanoma model. (1117)

Dysregulation of Wnt β-catenin/Tcf signaling pathway contributes to tumor progression. Sareddy et al demonstrated that diclofenac and celecoxib are potential therapeutic agents against glioblastoma cells by suppressing the activation of Wntβ-catenin/Tcf signaling. (1118) It is likely that DCF act synergistically with convention chemotherapeutic agents as well as with other adjunctive therapies. Indeed, Gerhofer demonstrated synergistic anti-migratory and anti-

proliferative effects of the combined treatment with metformin and diclofenac on brain tumor initiating cells. (1119)

Clinical studies
In contrast to the wide range of in vitro and in vivo results, there is a relative paucity of clinical data with respect to the use of DCF as an anticancer agent. Forget and colleagues reported on a retrospective analysis of breast cancer patients treated with conservative surgery, with and without intraoperative NSAIDs (DCF or ketorolac). (468) Patients treated pre-incisionally with ketorolac (20 mg -30 mg) or DCF (75 mg) showed improved disease-free survival (HR = 0.57, 95% CI: 0.37–0.89, *P* = 0.01) and an improved overall survival (HR = 0.35, CI: 0.17–0.70, *P* = 0.03), compared to patients not treated with NSAIDs. (469) The findings of this study were, however, not replicated in a prospective RCT. (470)

Types of cancers diclofenac may be beneficial for
While there is limited data, diclofenac may be effective against the following tumors; (1103) desmoid tumors, inflammatory myofibroblastic tumors, neuroblastoma, osteosarcoma, head and neck cancers, esophageal cancer, breast cancer, ovarian cancer and non-small cell lung cancer.

Dosing and cautions
A dose of 75 to 100 mg/day diclofenac is suggested. As a potent COX2 inhibitor, DCF can increase the risk of peptic ulcer disease. For this reason, we suggest that DCF be combined with cimetidine, which is used to treat/prevent peptic ulcers; this drug combination likely has synergistic anticancer properties. NSAIDs cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. Diclofenac is contraindicated in the setting of coronary artery bypass graft surgery. DCF should be used cautiously in patients with known coronary artery disease; however, interventions that manage metabolic syndrome (and optimize the TG/DHL ratio) may mitigate this risk.

27. Nigella sativa

Anticancer pathways and mechanisms
The primary bioactive substance in Nigella sativa, thymoquinone (TQ), has anti-inflammatory and chemotherapeutic properties and can limit cell proliferation, increase cancer cell death, prevent cell invasion and metastasis, and inhibit angiogenesis. TQ disrupts the phosphorylation and subsequent activation of a few upstream tyrosine kinases (such as MAPK, Akt, mTOR, and PIP3) implicated in signaling pathways for tumor cell growth. (1120-1122)

TQ's anticancer effects predominantly involve the nuclear factor (NF)-κB, phosphoinositide 3 kinases (PI3K)/Akt, Notch, transforming growth factor (TGF)-β, c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK) signaling pathways as well as the regulation of the cell cycle, matrix metallopeptidase (MMP)-9 expression, and pyruvate kinase isozyme type M2 (PKM2) activity. (1120, 1121, 1123-1127) Additionally, TQ exhibits chemopreventive

properties by upregulating cytoprotective enzymes (such as glutathione S-transferase, superoxide dismutase, and oxidoreductase), downregulating carcinogen metabolizing enzymes (such as CYP 1A2, CYP 3A4), and attenuating the production of pro-inflammatory mediators (e.g., cytokines, chemokines, and prostaglandins). (1121, 1123, 1128)

Clinical studies
Unfortunately, there are no published clinical studies that have investigated the effects of Nigella sativa in patients with cancer.

Types of cancers that Nigella sativa may be beneficial for
In vitro and in vivo experimental findings suggest that Nigella sativa may have anticancer action against a variety of malignancies, including ovarian, (1121, 1129, 1130) myeloblastic leukemia and other blood cancers, (1131) cervical, (1122, 1132, 1133) colon, (1122, 1128, 1134-1136) hepatic, (1128, 1137-1140) prostate, (1120, 1141) breast, (1120, 1134, 1136) renal, (1122, 1142) pancreatic, (1120, 1127, 1143) and lung carcinomas. (1120, 1134, 1144, 1145)

Dosing and cautions
Patients can be directed to take seeds (80 mg/kg once daily) or encapsulated oil (400 to 500 mg twice daily). The safety of Nigella sativa in pregnancy has not been established and it should probably be avoided.

28. Ganoderma Lucidum (Reishi) and other Medicinal Mushrooms

More than 50 different types of mushrooms — such as Ganoderma lucidum (Reishi), G. tsugae, Sparassis crispa, Pleurotus tuberregium, P. rhinoceros, Trametes robiniophila Murill, Coriolus versicolor, Lentinus edodes, Grifola frondosa, Flammulina velutipes and others —have produced potential immunoceuticals with anticancer and immunomodulatory effects in vitro, in vivo, and in human malignancies. (1146)

The most research has been done on G. lucidum (Reishi). Beta-glucan polysaccharides and triterpenes are the bioactive compounds in Reishi mushroom. (1147)

Anticancer pathways and mechanisms
Antroquinonol, cordycepin, hispolon, lectin, krestin, polysaccharide, sulfated polysaccharide, lentinan, and Maitake D Fraction are the main anticancer compounds found in mushrooms. (1146) The therapeutic effects of these compounds include suppression of cancer cell growth, induction of autophagy and phagocytosis, improved immune system response, and induction of apoptotic cell death through upregulation of pro-apoptotic factors and downregulation of anti-apoptotic genes. (1148) The expression of caspase-3, -8, and -9, AKT, p27, p53, BAX, BCL2, NF-kB pathway, and mTOR (1149) were significantly implicated in these activities. (1148, 1150)

Bioactive substances derived from mushrooms stimulate and/or regulate the immune system by influencing the maturation, differentiation, and proliferation of immune cells, hence

preventing the spread and growth of cancer cells. (1147) The strongest anticancer and immunomodulatory chemicals found in mushrooms are polysaccharides. (1147) By attaching to pathogen recognition receptors, chemicals produced from mushrooms stimulate immune cells to cause either cell-mediated or direct cytotoxicity in cancer cells. (1147, 1151, 1152) In addition, mushroom-derived compounds induce innate and adaptive immunity by enhancing immune surveillance against cancer by affecting monocytes, macrophages, NK cells, and B cells (1147, 1150-1155) which leads to cancer cell apoptosis, cell cycle arrest, and prevention of angiogenesis and metastasis. (1146) Consumption of mushroom compounds also boosts the secretion of antitumor cytokines by Directed Cytotoxic T Lymphocytes (CTLs) and activation of immune organs, thereby eliminating cancer cells and strengthening the weakened immune system. (1147, 1153)

By controlling a single molecule of a particular signaling pathway or by having many targets in the same or different signaling route(s), such as the PI3K/Akt, Wnt/-catenin, and MAPK pathways, mushroom compounds exhibit anticancer potential. Studies have demonstrated the effectiveness of components derived from mushrooms as standalone and adjunctive treatment agents in reversing multidrug resistance (MDR) by focusing on interactions between PD-1/PD-L1 and CTLA-4/CD80. (1147) Furthermore, the prebiotic benefits of medicinal mushrooms may help restore the gut microbiome. (1147)

A new, inflammatory type of programmed cell death called pyroptosis is defined by the executive protein gasdermin creating pores in the plasma membrane, which causes the cells to lyse and expel their contents. (1153, 1156) By activating caspase 3 and further cleaving the gasdermin E (GSDME) protein to create pores on the cell membrane, Ganoderma lucidum extract (GLE) causes pyroptosis, which releases many inflammatory factors into breast cancer cells. (1153) GLE blocks multi-steps of tumor metastasis including adhesion, migration, invasion, colonization, and angiogenesis. (1153)

Clinical studies

In a trial of patients with colorectal adenomas, a water-soluble Reishi extract (1.5 g/d, administered for 12 months) significantly reduced the number and overall size of adenomas in the intervention group as compared to the control group. (1157) G. lucidum (Reishi) at a dose of 5.4 g/day was demonstrated to have immuno-modulating properties in patients with advanced colorectal cancer. (1158) Patients with advanced-stage cancer who consumed a Reishi polysaccharide preparation showed increased natural killer cell activity. (1159) In a review of the literature, Huber et al reported that medicinal mushrooms improve the quality of life during and after conventional cancer therapy. (1160)

Types of cancers that Reishi and other medicinal mushrooms may be beneficial for

It is noteworthy that mushroom extracts have the strongest anticancer effects against breast cancer. (1146, 1147, 1161) Mushrooms may also have activity against colorectal carcinoma, (1146, 1147, 1149, 1160, 1161) cervical, ovarian and endometrial cancers, (1146, 1160, 1161) lung cancer, (1146, 1160) astrocytoma, (1161) bladder cancer, (1146, 1161) esophageal cancer, (1161) fibrosarcoma, (1161) gastric cancer, (1146, 1161) glioblastoma, (1161) hepatocellular

carcinoma, (1146, 1147, 1161) kidney cancer, (1161) laryngeal cancer, (1161) leukemia, (1146, 1161) melanoma, (1147, 1161) neuroblastoma, (1161) oral cancer, (1161) pancreatic cancer, (1161) prostate cancer, (1146, 1161) sarcoma, (1161) and skin epidermoid cancer. (1161)

Dosing and cautions
It is suggested that 6 to 12 g of Reishi extract be taken daily. (1162) Reishi has antiplatelet properties; hence it may increase the risk of bleeding, especially when taken in conjunction with anticoagulants.

29. Dipyridamole

Anticancer pathways and mechanisms
Dipyridamole is a vasodilator and antithrombotic drug. Its major effects involve the blocking of nucleoside uptake and phosphodiesterase inhibition, leading to increased levels of intracellular cAMP. Dipyridamole is a non-selective phosphodiesterase 5 inhibitor. (854) Several studies have shown that, in vitro, dipyridamole can significantly increase the cytotoxic and antitumor activities of a variety of chemotherapeutic agents. (1163) Furthermore, there is evidence for a contribution of platelets in metastasis formation with platelets interacting with tumor cells to form aggregates. The interaction of cancer cells with platelets leads to platelet activation and the pro-metastatic activities of platelets. (1164) Consequently, agents that interfere with platelet aggregation could prevent tumor metastases. (1165)

In a murine triple negative breast cancer model dipyridamole significantly reduced primary tumor growth and metastasis formation. (1163) In this study dipyridamole effects were mediated by Wnt, ERK1/2-MAPK and NF-kB pathways. Moreover, dipyridamole significantly decreased the infiltration of tumor-associated macrophages (TAM) and myeloid-derived suppressor cells (MDSC) in the primary tumors. Molecular chaperone HSP90 has been considered a promising target for anticancer drug development. Dipyridamole inhibits the growth and proliferation of human cancer cells by downregulating cell cycle regulators and upregulating apoptotic cell signaling, which are mediated by the binding of dipyridamole to HSP90 and phosphodiesterase. (1166)

Clinical studies
Dipyridamole has been used in combination with cytotoxic drugs in a number of small clinical trials. (1167-1170) The benefit or lack thereof of dipyridamole in these studies is difficult to ascertain.

30. High-Dose Intravenous Vitamin C

The use of high-dose vitamin C for the treatment of cancer dates back to the 1970s, largely due to the work of Nobel laureate Linus Pauling. (1171) In the early 1970s, Cameron and Pauling published a thesis claiming that ascorbic acid is able to potentiate the intrinsic production of serum physiological hyaluronidase inhibitor, thereby protecting against the spreading of cancer cells. (1172) In 1976, these authors published the results of an observational case-control study in which 100 terminal cancer patients were given supplemental ascorbate (10 g IV for 10 days then 10 g orally) as a part of their routine management and were compared to 1,000 matched controls. (1173) The study showed that the mean survival time was more than four times longer for the ascorbate-treated subjects. In response to the data obtained by Cameron and Pauling, Creagan et al conducted in 1979 a randomized, controlled double-blind trial to evaluate the effect of vitamin C (10 g daily by oral route) on the severity of symptoms and survival rate in 123 patients with advanced and preterminal cancer. (1174) The study proved a lack of vitamin C effect, with no difference in survival time between ascorbate and control groups. Similarly, Moertel et al. in a double-blind placebo-controlled study with 100 advanced colorectal cancer patients failed to demonstrate a benefit of vitamin C (10 g orally). (1175)

The studies by Creagen et al and Moertel et al essentially ended the use of vitamin C for cancer at that time. It should, however, be appreciated that these studies used oral vitamin C and therefore did not replicate the work of Cameron and Pauling. It has subsequently been established that vitamin C is absorbed by the gut through vitamin C transporters that are saturated at a dose of about 500 mg.

In 2004 Padayatty et al demonstrated that 1.25 g vitamin C given orally produced a peak concentration of 180 umol/l where the same dose given IV resulted in a peak plasma concentration of about 1,000 umol/l. (1176) In this study, 50 g of vitamin C given intravenously produced a peak serum concentration of 12 mmol/l. It has subsequently been demonstrated that millimolar concentrations of vitamin C are toxic to cancer cells and that such concentrations can only be achieved through intravenous administration. (1177-1180)

Vitamin C has potent antioxidant effects when given orally, however, the millimolar concentration achieved with intravenous vitamin C has pro-oxidant effects, which are largely responsible for the cytotoxic effects on cancer cells. (460) While liposomal vitamin C is widely touted to produce serum levels similar to intravenous use, this contention is false, with liposomal formulations producing serum levels almost identical to that of regular vitamin C given orally. (1181-1184)

Animal and in vitro studies have indicated that free radicals such as reactive oxygen species can cause cellular damage and lead to cancer by altering cellular regulatory pathways. Vitamin C is an antioxidant that can prevent ROS-induced cellular damage. However, the efficacy of vitamin C supplements for prevention of cancer is controversial. Lee et al performed a meta-analysis of RCTs to investigate the efficacy of vitamin C supplements for prevention of cancer. (1185) Seven trials which enrolled 62,619 participants were included in this analysis. The

demonstrated no association between vitamin C supplementation and cancer (relative risk, 1.00; 95% confidence intervals, 0.95–1.05). Similarly, subgroup meta-analysis by dose of vitamin C administered singly or in combination with other supplements demonstrated no reduction in the risk of cancer.

Anticancer pathways and mechanisms

Benade et al were the first to propose that the main cytotoxic mechanism of ascorbate was connected with intracellular generation of hydrogen peroxide (H_2O_2) produced upon oxidation of vitamin C. (1186) This occurs because cancer cells selectively take up more ascorbate compared to normal cells through the facilitated transport with participation of glucose transporters (GLUTs) due to an increased metabolic need for glucose. Catalase decomposes H_2O_2 to oxygen and water. Catalase activity in cancer cells is 10- to 100-fold lower than in normal cells, making them over-sensitive to ascorbate. (1186)

Yun et al reported that cultured human colorectal cancer cells with KRAS or BRAF mutations were selectively killed when exposed to high concentrations of vitamin C, and that effect resulted from an increased dehydroascorbate (DHA) uptake via the GLUT1 glucose transporter.(1187) Inside the cell, DHA is reduced by GSH, NADH, and NADPH-dependent enzymes leading to the depletion of glutathione, thioredoxin, and NADPH, thus increasing the intracellular oxidative stress. ROS accumulation inside cells inactivates glyceraldehyde 3-phosphate dehydrogenase (GAPDH), which leads to a decreased formation of glycolytic adenosine 5’-triphosphate (ATP) and pyruvate, causing an energetic crisis that triggers cell death. (1187) In experimental rodents after parenteral administration of vitamin C, not only the increased production of H2O2 was observed, but also the altered expression of genes involved in protein synthesis, cell cycle progression and angiogenesis, and reduced levels of HIF-1 and VEGF. (1171)

Clinical studies

While case reports of complete cancer remission or reduction in metastatic lesions have been reported, (1188-1190) case series that have administered high-dose intravenous vitamin C as a single anticancer treatment have not demonstrated beneficial results. (1171, 1191, 1192)

In vitro and animal studies have demonstrated that concomitant administration of vitamin C with many chemotherapeutic agents and radiotherapy works synergistically, resulting in a decreased tumor size and increased survival. (1193) These findings have not been reproduced in the small clinical trials conducted to date. (1171, 1194, 1195) In a phase III RCT, high-dose vitamin C plus chemotherapy failed to show superior progression-free survival compared with chemotherapy in patients with metastatic colorectal cancer as first-line treatment. (1196) In summary, high-dose intravenous vitamin C represents a promising and inexpensive anticancer therapeutic option that currently has limited supportive clinical data but should be further explored in clinical trials.

Dosing and cautions
High-dose IV vitamin C is considered to have a relatively good safety profile providing that appropriate precautions are taken, although it also can cause serious side effects in some patients. (1171) Vitamin C in gram doses is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, due to a risk of developing intravascular hemolysis.

31. Dichloroacetate (DCA)

The Warburg effect is mediated in part by cancer cells inactivating a key enzyme complex called the pyruvate dehydrogenase complex (PDC), which acts as the control point for the entry of pyruvate into the mitochondria. Pyruvate is derived from glucose (glycolysis) and is the main fuel for mitochondrial oxidative phosphorylation. The mitochondrial PDC irreversibly decarboxylates pyruvate to acetyl coenzyme A, thereby linking glycolysis to the tricarboxylic acid cycle and a defining step in cellular bioenergetics. (1197) Cancer cells turn off PDC by upregulating pyruvate dehydrogenase kinase (PDK). Inhibition of PDC in the cancer cell is the key step in metabolic reprogramming.

The glycolysis inhibitor dichloroacetate (DCA) inhibits PDK. The inhibition of PDK by DCA results in diminished glycolysis in the cancer cell, forcing the cancer cell to use oxidative phosphorylation in the mitochondria as the main source of ATP. (1197, 1198) DCA has other anticancer effects, including the induction of protective autophagy, reduction of hypoxia-inducible factor (HIF-1) and angiogenesis, and eradication of CSCs. (1197) Metformin, curcumin, fenbendazole, ivermectin, and doxycycline act synergistically to increase the efficacy of DCA. (750, 1199) Both thiamine and alpha lipoic acid are cofactors for PDC and are routinely recommended with DCA.

Clinical studies
A phase II study of dichloroacetate in combination with chemoradiotherapy for unresected, locally advanced head and neck squamous cell carcinoma reported an end-of-treatment complete response rate that was significantly higher in the DCA group compared to placebo (71.4% vs 37.5%, p=0.03); however, survival outcomes were not significantly different between groups. (1200) Case reports have demonstrated “long-term stabilization” of patients with metastatic melanoma, colon cancer, and non-Hodgkin’s lymphoma treated with DCA. (1201-1203)

Types of cancers dichloroacetate may be beneficial for
Dichloroacetate may show benefit in non-Hodgkin’s lymphoma, colorectal cancer, endometrial cancer, breast cancer, glioblastoma, lung cancer, pancreatic cancer, gastric cancer, hepatocellular cancer, and multiple myeloma.

Dosing and cautions
An oral dose of 1,000 mg daily or 500 mg three times daily has been recommended. Neurotoxicity is a well-known reversible adverse effect of DCA, with peripheral neuropathy the most common symptom. Severe encephalopathy has also been described, (1204) suggesting that patients being treated with DCA be closely monitored.

DCA is available as a dietary supplement, though its use as a compounded medication has been discontinued by the FDA based upon a review in which it determined that there was insufficient evidence for its use in cancer. The FDA expressed the view that the evidence of benefit and concerns about potential toxicity if not properly dosed, did not outweigh the evidence favoring the use of approved chemotherapies or other agents for cancer.

32. Nitroglycerin

Nitroglycerin (NTG) has been in clinical use for more than a century. It has a long history of use as a coronary vasodilator, most commonly used for prophylaxis and treatment of angina pectoris, but also used as a treatment for hypertension and congestive heart failure. The main mechanism of action of NTG is via the production of nitric oxide (NO), which improves cardiac oxygenation via multiple mechanisms including improved blood flow (vasodilation), decreased platelet aggregation, increased erythrocyte O2 release and decreased mitochondrial utilization of oxygen.(1205) NTG's vasoactive properties has the potential to increase the delivery of anti-cancer drugs to tumor tissues.(1206) In addition, NTG can reduce HIF-1α and VGEF levels in hypoxic tumor tissues, and this may have anti-angiogenic and pro-apoptotic effects.(1205, 1207, 1208) Furthermore, NTG may enhance anti-tumor immunity. (1205)

Anticancer pathways and mechanisms
In the setting of cancer, NO is known to have dichotomous effects, both pro- and anti-tumor, depending on concentration, microenvironment and cell type. In particular, low concentrations of NO (<100 nM) are associated with increases in angiogenesis, proliferation and resistance to apoptosis, whereas high NO concentrations (>500 nM) are associated with increased cytotoxicity and apoptosis.(1209-1211)

Hypoxia is a known driver of increased tumor invasiveness an effect abolished by the use of NTG.(1212) Similarly, in vivo investigations in a melanoma model showed that NTG reversed the increase in metastatic nodules induced by hypoxic conditions. (1213) Escape from immunosurveillance may also be a consequence of tumor hypoxia. In prostate cancer cell lines and a murine xenograft model, Siemens et al demonstrated that impaired NO signalling associated with hypoxia contributed to immune escape and that this effect could be reversed with NTG. (1214) In mouse models of cancer, Seki and colleagues demonstrated that the topical application of NTG ointment increased accumulation of anticancer drugs within the tumors.(1215) In a murine lung cancer model the combination of the anti-folate chemotherapeutic drug pemetrexed and NTG demonstrated enhanced reduction in tumor growth.(1216)

Clinical studies
A number of clinical trials have demonstrated that adding nitroglycerin to cisplatin-based chemotherapy improves the overall survival (OS) of patients with non-small cell lung cancer (NSCLC) probably due to better drug delivery. (1207, 1217, 1218) Yasuda et al randomized 120 patients with stage IIIB/IV NSCLC to vinorelbine 25 mg/m2 on days 1 and 8 and cisplatin 80 mg/m2 on day 1, with transdermally applied nitroglycerin (25 mg/patient daily for 5 days) or placebo every 3 weeks for a maximum of four cycles in a double-blind and controlled trial. (1217) In this study the response rate was 72% in the NTG arm compared to 42% in the placebo arm ($p < 0.001$). However, a number of trials in patients with NSCLC were negative (1205, 1219) including a large phase III clinical trial. (1220)

In prostate cancer a prospective, open-label trial of 29 men with an increasing prostate-specific antigen (PSA) level after surgery or radiotherapy investigated the use of transdermal NTG.(1208) Patients were enrolled on a 24-month trial to compare PSA doubling time (PSADT) before and after treatment initiation, as well as comparison with a matched control group. Of the 29 patients in the trial, 17 completed the full 24-months of treatment, and only 3 of 29 had documented disease progression (10%) by the end of the trial. The results showed that the treatment group had a calculated PSADT of 31.8 months, compared to the pre-treatment rate of 13.3 months or that of the matched control group at 12.8 months.
In summary, while NTG increases the effects of various cancer treatments in preclinical studies, clinical trials have shown variable with conflicting results. (1220) NTG may therefore be considered as an add-on in patients not responding to first line therapy.

Dosage and cautions
NTG is available in sublingual tablet and spray form for oral use, as a transdermal patch, as an ointment and as an intravenous infusion. For the prevention or treatment of angina attacks sublingual tablets are used at a dose of 0.3–1.0 mg, the dose repeated as required. Transdermal patches are used for longer term prophylaxis of angina, with typical dosages being 5 mg/day–15 mg/day. (1205) NTG has low systemic toxicity. Common side effects include headache, dizziness, postural hypotension and tachycardia. NTG is contraindicated for those with known hypersensitivity to nitrates, severe anaemia, increased intracranial pressure or some hypotensive conditions and the concurrent treatment with PDE-5 inhibitors. (1205)

33. Sulforaphane

Anticancer pathways and mechanisms
Epidemiologic studies suggest that cruciferous vegetable intake may lower overall cancer risk, including colon and prostate cancer. Sulforaphane (SFN) is an isothiocyanate found in cruciferous vegetables and is especially high in broccoli and broccoli sprouts.
The three major anti-cancer properties of sulforaphane include anti-angiogenesis, anti-metastatic and activation of protective autophagy. (1221) Sulforaphane inhibits HIF-1, NF-KB and proto-oncogene myc, resulting in the downregulation of key angiogenic and metastatic

regulators, VEGF and matrix metallopeptidase 9 (MMP-9) and thus the reduction of angiogenic and metastatic potential. (1221) In vitro experiments with sulforaphane indicate a pronounced role for cell cycle arrest in its anticancer properties. (1222) Sulforaphane and its metabolites act as histone deacetylase (HDAC) inhibitors.(1222) In a breast cancer mouse model sulforaphane was shown to be highly potent for the elimination of CSCs. (1223, 1224) Sulforaphane was demonstrated to inhibit pancreatic CSCs by inhibition of the sonic Hedgehog pathway. (1225) In preclinical in vitro and in vivo studies sulforaphane has shown activity against various CSCs, including, triple negative breast cancer stem cells, lung, gastric and chronic leukemia stem cells.(1226-1228) Sulforaphane has synergistic anti-cancer activity with quercetin and EGCG.(1229, 1230)

Clinical studies

While the anticancer activity of sulforaphane has been established in many experimental models, clinical studies evaluating efficacy are limited. Cipolla performed a double-blind RCT in 78 males with rising PSA after radical prostatectomy for prostate cancer.(1231) Treatment consisted of 60 mg sulforaphane for 6 months over which time the sulforaphane group had a mean increase in PSA of 0.01 ng/mL compared to a 0.62 ng/mL increase for placebo. PSA doubling time in the sulforaphane group was 28.9 months compared to 15.5 months for the placebo group. Sulforaphane prolonged PSA doubling time, thus delaying "biochemical recurrence". These findings were not replicated in men with metastatic prostate cancer.(1232)

Dosing

The pharmacology and optimal dosing of sulforaphane are complex. Sulforaphane itself is unstable. The supplement should contain the two precursors, *glucoraphanin* and *myrosinase*, which react when the supplement is consumed. Broccoli "extracts" are produced in a way that completely destroys the activity of the myrosinase enzyme. As such, these extracts are incapable of producing sulforaphane when consumed in a supplement or food. (1233, 1234) We recommend a 100% whole broccoli sprout powder, which maximally retains both glucoraphanin and myrosinase while at the same time, deactivating the inhibitors.

34. Artemisinin

Anticancer pathways and mechanisms

Artesunate (ART) is a derivative of artemisinin, the active principle of the Chinese herb Artemisia annua L. Artesunate is approved for the treatment of multidrug-resistant malaria and has an excellent safety profile. It has been shown that Artesunate, apart from its anti-malarial activity, has cytotoxic effects on a number of human cancer cell lines, including leukemia, colon cancer and melanoma. Artemisinin and its derivatives have been reported effective against 55 cancer cell lines with inhibitory effects against pancreatic cancer, osteosarcoma, lung cancer, colon cancer, melanoma, breast cancer, ovarian cancer, prostate cancer, central nervous system cancer, lymphoma, leukemia and renal cancer cells. In addition, artesunate potentiates the effects of common chemotherapy drugs. (1235) A number of compounds such as

resveratrol, pterostilbene, curcumin and high dose IV vitamin C have synergistic activity with artemisinin. (1236-1238)

The molecular mechanism by which artemisinin compounds serve as effective anti-cancer agents can be found in a feature of its molecular structure, the endoperoxide bridge, which reacts with the iron molecule producing a Fenton reaction, in which reactive oxygen species are generated. (154) These endogenously formed reactive species attack proteins, RNA and DNA, inducing oxidative DNA lesions such as 8-oxo-guanine and DNA double-strand breaks (DSBs). The rapid metabolic rate and rapid proliferation of cancer cells requires a large amount of iron.(1239) Cancer cells express high levels of transferrin receptors needed for internalization.(1235)The more aggressive the tumor, the greater the number of transferrin receptors.(1240) The higher iron content of cancer cells as compared to normal cells results in selective killing of cancer cells.

Artemisinin enters the cancer cell lysosome, which already contains iron as a degradation product from ferritin. The endoperoxide oxygen bridge in artemisinin with iron causing a "Fenton Reaction" producing hydroxyl radicals.(1241) Artemisinin enters cancers cells along with iron loaded ferritin. Both enter the lysosome, which then triggers ROS in mitochondria and caspase-3 programmed cell death. Artemisinin arrests the cell cycle and induce not only iron-dependent cell death (ferroptosis) but also other modes of cell death such as apoptosis. (1242) The cell death mode of ferroptosis is completely different from cell necrosis, autophagy, and apoptosis in terms of cell morphology, genetics, and biology. Artesunate is also an inducer of autophagy. Artesunate exerts antiproliferative effects by activating the ROS-triggered AMPK-mTOR axis.

Clinical studies

Artesunate administered at a dose of 200 mg per day orally was reported in a case series of 12 patients with glioblastoma.(1242) In this case series 4 patients showed a median survival of 46 months. A number of small phase I/II studies and case reports have been reported in patients with metastatic breast cancer as well as other solid tumors.(1243-1246) In a small single center, randomized, double-blind, placebo-controlled trial patients planned for curative resection of biopsy confirmed single primary site colorectal cancer were randomized (n = 23) to receive preoperatively either 14 daily doses of oral artesunate (200 mg) or placebo.(1247) The primary outcome measure was the proportion of tumor cells undergoing apoptosis. Apoptosis of greater than 7% was seen in 67% and 55% of patients in artesunate and placebo groups. During a median follow up of 42 months 1 patient in the artesunate and 6 patients in the placebo group developed recurrent CRC.

Dosing and Drug Availability

Generally, a dose of 200 mg orally daily is suggested. Anecdotal cases of hepatotoxicity, bone marrow suppression and cerebellar dysfunction have been reported; patients should be monitored for these side effects. The use of oral artemisinin-based monotherapies is considered to be a major factor contributing to the development of malarial resistance to artemisinin derivatives. The WHO has therefore urged the regulatory authorities to halt the

production and marketing of oral monotherapy. Oral medication may therefore be scarce. Although IV artesunate 60 mg vials are widely used as first line malaria treatment in third world areas, inside the us this drug is neither DFA approved nor commercially available.(154)

35. Cannabinoids

Cannabis has been used as a healing herb since ancient times and is currently approved in many countries for recreational and medicinal use. There has been extraordinary public interest in the use of cannabis and cannabinoids for the treatment of cancer and cancer-related side effects. The prevalence of cannabis use in patients with a variety of malignant diagnoses ranges from 18% to 40% in surveys conducted in the U.S., Canada, and Israel. (1248) Despite the public enthusiasm for the efficacy of cannabinoids in treating cancer, the evidence supporting the use of cannabinoids is contradictory and controversial. (1249)

The *Cannabis sativa* plant contains over 400 different chemical compounds. Over 100 of these are 21-carbon terpenophenolic cannabinoids. Delta-9-tetrahydrocannabinol (THC), the main psychoactive component, is found in the highest concentration in the resin exuded from the flowers of the female plant. Dronabinol and nabilone are delta-9-THC medications that have been licensed and approved for the treatment of chemotherapy-induced nausea and vomiting since 1986.

Two cannabinoid receptors have been identified in the human body — CB1 and CB2. These are 7-transmembrane domain G-protein coupled receptors. (1248) The CB1 receptor is one of the most densely populated receptors in the human brain. The CB2 receptor was initially detected in macrophages and the marginal zone of the spleen, with a high concentration in B lymphocytes and NK cells. The receptors have been identified in all animal species. Animals have these receptors not because they were meant to use cannabis, but because, like endogenous opioids, endogenous cannabinoids also exist. It has been suggested that the reason for the existence of the system of endocannabinoids and cannabinoid receptors is to facilitate the modulation of pain.

Orally ingested cannabis has low (6–20%) and variable bioavailability. (1249) When inhaled, cannabinoids are rapidly absorbed into the bloodstream (with a peak concentration of about 2 to 10 minutes, declining rapidly for 30 minutes) and minimally generate the psychoactive 11-OH metabolite. Smoking remains the most common and fastest route of administration and is especially helpful for the treatment of acute symptoms. There are many medications based on natural or synthetic cannabinoids or cannabinoid analogs. (1249) Dronabinol (Marinol®, Mariette GA) is a 9-tetrahydrocannabinol (THC), used as an appetite stimulant, antiemetic, and analgesic. Nabilone (Cesamet®, Aliso Viejo CA) is a synthetic THC analog in oral form that is 10 times more potent than natural THC, approved in 2006 for chemotherapy-induced nausea and vomiting, and which has been used off-label for pain. Nabiximols is a mixture in an oro-mucosal spray form of THC and cannabidiol (CBD).

Cannabis maintains its U.S. federal status as a Schedule I substance with high potential for abuse and limited medical indications. Cannabinoids have demonstrated efficacy in the treatment of chemotherapy-induced nausea and vomiting in adults and in appetite stimulation in adults. (10) Delta-8-THC was reported to be an effective anti-emetic in children receiving chemotherapy. (1250) A Cochrane Review published in 2015 that included 23 RCTs concluded that cannabis-based medicines may be useful in treating refractory chemotherapy-induced nausea and vomiting. (1251) Most of the anti-emetic research that was conducted compared medical cannabis treatment to placebo or various neuroleptic drugs. However, these studies did not compare cannabinoids with the anti-emetogenic new medicines, as the potential role of smoked marijuana in treating chemotherapy-induced nausea and vomiting. Thus, cannabis should be prescribed as an anti-emetic drug only when conventional anti-emetogenic treatment has failed. (1249) Indeed, the American Society of Clinical Oncology convened an Expert Panel that concluded that "evidence remains insufficient for a recommendation regarding medical marijuana for the prevention of nausea and vomiting in patients with cancer receiving chemotherapy or radiation therapy." (1252)

A randomized, placebo-controlled trial that included 177 patients with cancer pain who experienced inadequate analgesia despite chronic opioid dosing showed statistically significant pain reduction with THC/CBD compared with placebo, while the THC group showed a non-significant improvement. (546) Twice as many patients taking THC/CBD showed a reduction of more than 30% from baseline pain numerical rating scale (NRS) score when compared with placebo. The long-term use of the THC/CBD spray is generally well-tolerated, with no evidence of a loss of effect for the relief of cancer-related pain with long-term use. (545) In a randomized, double-blind, placebo-controlled, graded-dose study, patients with advanced cancer and opioid-refractory pain nabiximols at a low dose (1–4 sprays/day) proved effective for pain control. (1253) However, in two double-blind, randomized, placebo-controlled phase 3 studies, nabiximols (Sativex®) did not demonstrate superiority to placebo in reducing self-reported pain numerical rating scale (NRS) scores in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy. (1254)

There is evidence from in vitro studies and animal models that cannabis and cannabinoids may have anti-tumoral activity that has not yet been convincingly translated into benefit in humans. (1248) Cannabinoids have direct tumor-killing effects by complexing with the CB1 receptor. This interaction leads to autophagy and increased apoptosis. In addition, cannabinoids have been demonstrated to inhibit vascular endothelial growth factor, thereby impairing angiogenesis, and decreasing tumor viability. In vitro studies also reveal that cannabinoids inhibit matrix mettaloproteinase-2, which allows cancer cells to become invasive and metastasize. Hence, pre-clinical evidence suggests that cannabinoids may inhibit tumor growth and proliferation by way of several mechanisms.

Nearly 40% of patients with cancer using cannabis believe it will treat their cancer, with numerous anecdotal reports shared online through social media platforms. Case reports have been published in peer-reviewed journals, but often lack key clinical information to validate anticancer claims. Guggisberg et al reviewed case reports published in peer-reviewed journals

and appraised them as weak, moderate, or strong based on the quality of evidence provided supporting an anticancer effect. (1255) A total of 77 unique case reports described patients with various cancers (breast, central nervous system, gynecological, leukemia, lung, prostate, and pancreatic) using cannabis. These authors' appraisal showed 14% of the case reports were considered strong, 5% moderate, and the remaining 81% were weak. They concluded that the review of clinical data suggests most published, peer-reviewed case reports provide insufficient data to support the claim for cannabis as an anticancer agent. However, Likar et al described a case series of 9 patients with glioblastoma who received CBD in a daily dose of 400 mg concomitantly to the standard therapeutic procedure of maximal resection followed by radio-chemotherapy. (1256) By the end of follow-up, all but one patient was alive with a mean survival time of 22.3 months as compared to the median expected survival of 14 to 16 months.

Guzman et al performed a pilot phase I trial in which nine patients with recurrent glioblastoma multiforme were administered THC intratumorally. (1257) Median survival of the cohort from the beginning of cannabinoid administration was 24 weeks. D9-Tetrahydrocannabinol inhibited tumor-cell proliferation in vitro and decreased tumor cell immunostaining when administered to two patients. In a phase 1b RCT, Twelves et al studied nabiximols oro-mucosal cannabinoid spray plus dose-intense temozolomide in patients with first recurrence of GBM. (1258) Survival at 1 year was 83% for nabiximols and 44% for placebo-treated patients (p = 0.042).

In summary, while the clinical data is contradictory, cannabinoids may prolong survival in patients with cancer, particularly those with GBM. Therefore, with the current state of evidence, the widespread use of cannabis cannot be recommended. (1249) However, the use of the THC/CBD spray may be helpful in patients with advanced cancer and opioid-refractory pain. Cannabinoids may also be useful in patients with refractory chemotherapy-induced nausea and vomiting.

36. Fenofibrate

Since its clinical introduction as a third-generation fibrate in 1975, fenofibrate has been widely used in the treatment of hypercholesterolemia and hyperlipidemia. The lipid-lowering effect of fenofibrate is believed to be mediated through its stimulation of peroxisome proliferator-activated receptor α (PPARα). More recently, PPARα-specific agonists were reported to have anticancer effects in human cancer including acute myeloid leukemia, chronic lymphocytic leukemia, and solid tumors, including those of the liver, ovary, breast, skin, and lungs. (1259) Fenofibrate may exert anticancer effects *via* a variety of pathways involved in apoptosis, cell-cycle arrest, invasion, and migration. Fenofibrate exerted antitumor effects in several human cancer cell lines, such as breast, liver, glioma, prostate, pancreas, and lung cancer cell lines. Fenofibrate was found to inhibit the proliferation of breast cancer MDA-MB-231 cell lines by inducing apoptosis and cell-cycle arrest. Fenofibrate increased the expression of Bad, but decreased that of Bcl-xL and Survivin, and activated caspase-3. (1260) Fenofibrate also induced cell-cycle arrest at the G0/G1 phase by upregulation of p21, p27/Kip1, and downregulation of

cyclin D1 and Cdk4. Activation of NF-κB pathway played an important role in the induction of apoptosis by fenofibrate.

Fenofibrate has been established to decrease the viability of human Hepatocellular carcinoma HepG2 cells partly by necrotic cell death. (1261) Fenofibrate can also lead to cell-cycle arrest in liver cancer cells. Fenofibrate significantly inhibited cell proliferation and induced apoptosis in human glioblastoma cell lines. (1262) Furthermore, the drug obviously reduced glioma stem cells (GSC) invasion probably through decreasing the expression of CD133. Fenofibrate can also inhibit cell growth through its impact on Fork-head box (Fox) family. (1263) FOX is a family of transcription factors that plays important roles in the regulation of the expression of genes involved in cell growth, proliferation, differentiation, and longevity. Low concentrations of fenofibrate induced cell-cycle arrest and apoptosis in the androgen-dependent prostate cancer cell line. (1264)

Despite the experimental data supporting the anticancer effects of fenofibrate there is no clinical data to support the use of this agent.

37. Niclosamide

Anticancer pathways and mechanisms

Niclosamide is an antiparasitic drug that was FDA approved for the treatment of tapeworm in 1982. Niclosamide has a broader clinical application including cancer, bacterial and viral infection and metabolic diseases such as type II diabetes and nonalcoholic steatohepatitis (NASH), endometriosis, rheumatoid arthritis and systemic sclerosis.(1265)

Niclosamide is a remarkable repurposed anti-cancer drug, achieving therapeutic levels at doses commonly used for treating parasites with no toxicity. The major anti-cancer mechanisms are mitochondrial uncoupling, which serves as an oxidative phosphorylation inhibitor which triggers protective autophagy, (1266, 1267) and inhibition of the Wnt/β catenin pathway. (1268, 1269) Niclosamide targets multiple additional signaling pathways including NF-KB, Notch, ROS, mTORC1 and Stat3. (1270-1272) Niclosamide was reported to target ovarian CSCs in vitro and in vivo.(1273)

In cancer cells, antegrade trafficking or movement of lysosomes to the cell periphery near the cell membrane is associated with aggressive behavior and tumor cell invasion. The opposite, called perinuclear clustering is associated with a more benign state, with inhibition of tumor invasion.(1274) In a prostate cancer cell line Circu et al demonstrated that niclosamide caused antegrade lysosome trafficking inhibition (i.e. perinuclear clustering).(1275) This effect is related to loss of lysosomal acidity.

Clinical studies

Inspired by the promising results from the pre-clinical studies, several clinical trials are ongoing to assess the therapeutic effect of niclosamide in cancer patients. There are, however, currently

no published case reports or clinical series which have reported the use of niclosamide in patients with cancer.

38. Pao Pereira

Pao extract is the extract of the bark of a tree that grows in the Amazon rain forest, *Geissospermum vellosii* Allemao (familiarly known as Pao Pereira), which has been used as a medicine by South American Indian tribes. In the 1990s, Mirko Beljanski reported that Pao extract had anticancer effects against melanoma and glioblastoma cells in vitro. (1276, 1277) Francois Mitterrand, the former President of France, was apparently treated somewhat successfully with Pao extract for metastatic prostate cancer. (6)

Pao extract has subsequently been evaluated against several cancer cell lines. Chang et al demonstrated that Pao extract suppressed castration-resistant prostate cancer (CRPC) cell growth in a dose- and time-dependent manner, through induction of apoptosis and cell cycle arrest. (1278) Furthermore, Pao extract induced the upregulation of pro-apoptotic Bax, reduction of anti-apoptotic Bcl-2, Bcl-xL, and XIAP expression, which were associated with the cleavage of PARP protein. Moreover, Pao extract treatment blocked CRPC cell migration and invasion. Chen et al investigated two plant extracts from the medicinal plants Pao Pereira (Pao) and *Rauwolfia vomitoria* (Rau) each for their activities against ovarian CSCs. (1279) Both Pao and Rau inhibited overall proliferation of human ovarian cancer cell lines and had limited cytotoxicity to normal epithelial cells. Furthermore, both Pao and Rau treatment significantly reduced the ovarian cancer stem cell population. Nuclear β-catenin levels were decreased, suggesting suppression of Wnt/β-catenin signaling pathway. Similarly, Dong et al demonstrated that an extract of Pao inhibited proliferation of human pancreatic cancer cell lines and had limited cytotoxicity to normal epithelial cells. (1280)

Bemis et al demonstrated that Pao Pereira extract significantly suppressed cell growth of a human prostate cancer cell line (LnCaP) in a dose-dependent fashion and induced apoptosis. (1281) Furthermore, immunodeficient mice heterotopically xenografted with LNCaP cells were gavaged daily with Pao Pereira extract or vehicle control over 6 weeks. Tumor growth was suppressed by up to 80% compared with tumors in vehicle-treated mice

Yu et al demonstrated that Pao Pereira selectively inhibited ovarian cancer cell growth. (1282) Pao induced apoptosis in a dose- and time-dependent manner. Pao greatly enhanced carboplatin cytotoxicity. Furthermore, when Pao was combined with carboplatin, tumor inhibition reached 97% and ascites were completely eradicated. Similarly, these authors demonstrated activity against a pancreatic cell line with synergy when combined with gemcitabine. (1283)

Despite the in vitro and animal model data, there is no human data to support the safety and efficacy of Pao Pereira in patients.

39. Dandelion Extract

Dandelion (Taraxacum genus), named “Pugongying” in China, is a perennial plant belonging to the Asteraceae family. In Asia, the Taraxacum genus is widely cultivated and also found wild in most parts of China, North Korea, Mongolia, and Russia. (1284) It grows in temperate regions globally, including on lawns, on roadsides, on disturbed banks and shores of waterways, and in other areas with moist soils.

As an edible medicinal herb and vegetable, dandelion has long been utilized for centuries in traditional medicine, folk remedies, and substitution therapies in many countries to treat diverse diseases. Dandelion extract has anti-inflammatory, antibacterial, immune enhancing, anti-oxidative, anti-depressant, and anti-cancer properties. Dandelion extract contains multiple bioactive compounds including sesquiterpenoids, phenolic compounds, essential oils, saccharides, flavonoids, sphingolipids, triterpenoids, sterols and coumarins. (1284)

Li et al demonstrated that dandelion seed extract significantly inhibited the growth, proliferation, migration, invasion, and angiogenesis and induced the apoptosis in human esophageal squamous carcinoma (ESCC) cells. (1285) In this study dandelion seed extract reduced survival rate and suppressed proliferation of ESCC cells by inhibiting the PI3K/Akt pathway and by down-regulation of MMP2, MMP9 and VEGF. In addition, dandelion seed extract induced apoptosis of human ESCC cells via regulating the expression of survivin, the ratio of Bcl-2 and Bax, and the levels of caspase3 and caspase9 proteins. Ovadje et al demonstrated that dandelion root extract affects colorectal cancer proliferation and survival through the activation of multiple death signaling pathways. (1286) In this study dandelion extract induced programmed cell death selectively in > 95% of colon cancer cells, irrespective of their p53 status, by 48 hours of treatment. The anti-cancer efficacy of this extract was confirmed in in-vivo studies, as the oral administration of DRE retarded the growth of human colon xenograft models by more than 90%. The induction of apoptosis was dependent on caspase-8 activation. Zhu et al demonstrated that that dandelion root extract specifically and effectively suppresses proliferation and migration in human gastric cells without inducing toxicity in noncancerous cells. (1287)

Deng et al demonstrated that dandelion may serve as a promising therapeutic strategy for breast cancer by modulating the tumor immune microenvironment. (1288) These authors demonstrated that dandelion extract inhibited the malignant property of triple negative breast cancer cells (TNBC) induced by tumor associated macrophages. In this study dandelion extract exerted inhibition on STAT3 and PD-L1 in TNBC cells under tumor associated macrophage microenvironment. Furthermore, in M2 macrophages, dandelion extract promoted the expression of M1-like marker TNF-α, IL-8, and iNOS, but reduced M2-like marker IL-10, CD206, Arginase-1, and TGF-β, indicative of macrophage repolarization. Similarly, Wang et al demonstrated the antitumor effects of dandelion extract against TNBC cells in vitro and demonstrated that dandelion extract could interfere with glycerophospholipids and unsaturated fatty acids metabolism via downregulating the CHKA (Choline kinase alpha) expression and inhibiting PI3K/AKT/SREBP/FADS2 axis. (1289) Lin et al demonstrated that

dandelion exerted cytotoxic effects against breast cancer cell lines (including TNBC) by induction of apoptosis, the reduction of cell proliferation and the disruption of the mitochondrial membrane potential. (1290)

Despite the in vivo and in vitro data demonstrating the anti-cancer activity of dandelion extract there are no clinical studies to support the use of this botanical.

40. Annona muricata (Soursop or Graviola)

Annona muricata is a member of the family Annonaceae and is familiar for its medicinal properties. All of this plant's aerial parts are utilized as natural medicines. (1291) *A. muricata* has been identified to have promising compounds that could potentially be utilized for the treatment of cancer. The Annonaceae family includes about 130 genera and 2300 species, including *A. muricata* also known as soursop, graviola, guanabana, pawpaw, and sirsak. *A. muricata* is native to the warmest tropical areas of South and North America, but now it has spread across the world's tropical and subtropical countries, including India, Malaysia, Nigeria, Australia, and Africa.(1291) *A. muricata* is an evergreen, terrestrial tree which grows to a height of 5 to 8 m with a broad, glossy, dark green, open, and round canopy. Individual yellow flowers on woody stalks are larger on this tree. The edible fruits of the tree are large, oval, or heart-shaped, green in color with more than 4 kg weight, with a diameter of 15 to 20 cm.

Anticancer pathways and mechanisms

There have been reports of widespread use of *A. muricata* by people with cancer in numerous places throughout the globe.(1291) In a Jamaican study on the opinions of cancer patients regarding using medicinal plants for self-medication, 60% of participants disclosed using *A. muricata* for the treatment of various malignancies, especially breast and prostate cancer.(1292) Similarly, 80.9% of patients with breast, prostate, or colorectal cancer have been reported to use A. muricata in specialty oncology clinics in Trinidad.(1293)

The most prevalent phytochemical components identified and isolated from this plant are alkaloids, phenols, and acetogenins. *A. muricata* extract has been demonstrated to downregulate anti-apoptotic and several genes involved in the pro-cancer metabolic pathways and decreasing the expression of proteins involved in cell invasion and metastasis while upregulating proapoptotic genes and genes involved in the destruction of cancer cells.(1)

The alkaloids and phenolic compounds from *A. muricata* root have been demonstrated to have anti-cancer effects in numerous human cell lines. (1291, 1294) Acetogenins (AGEs) are a type of bioactive substance found in the *A. muricata* plant and some of the acetogenins are Annomuricin A, B, and C, Muricatocin C, cis-Goniothalamicin, Muricatacin, Arianacin, Annonacin-10-one, cis-Annonacin, and Javoricin. (1295) More than 500 Acetogenins (ACG's) have been recorded from various parts of the plant, and these acetogenins specifically target cancer cells without harming normal cells. (1294, 1296) Isolated acetogenins exert cytotoxicity against numerous cell lines.(1291) The active ACGs have been shown to successfully induce death in cancer cells resistant even to chemotherapeutic drugs. (1294) ACG's mechanism for

inducing the apoptotic process involves blocking ATP production by inhibiting the NADH: ubiquinone oxidoreductase (Complex I) in the electron transport system in the mitochondria of cancer cells. Apoptosis can be induced by acetogenins by decreasing the expression of Bcl-2 and Bcl-xL, thereby allowing the expression of Bax and Bad pro-apoptotic proteins to increase and by enhancing the expression of caspase 3/7 and caspase 9. (1296, 1297) Antiproliferative effects of *A. muricata* has been demonstrated in pancreatic cancer and subcutaneous xenografts; these actions involved induction of cell cycle arrest accompanied by apoptosis.(1298) *A. muricata* inhibited the motility and invasion of pancreatic cancer by downregulating mucin MUC4.(1298, 1299) In addition, *A. muricata* has been shown to cause cancer cell death by modifying glucose metabolism and inducing metabolic failure by downregulation of HIF-1 α , GLUT1, GLUT4, HK2.(1298) *A. muricata* has a role as a modulator of the Epithelial-Mesenchymal Transitions (EMTs).(1291)

Clinical studies

Despite the fact that extracts of *A. muricata* have been widely used to treat cancer and in-vitro data demonstrates the anti-cancer properties of these extracts, there is very limited safety and efficacy data to support this use of this extract.(1291) Acetogenins (AGE) are environmental neurotoxins responsible for neurodegenerative tauopathy, as suggested by a study in the Caribbean island of Guadeloupe, which found a correlation between AGE consumption and the prevalence of the neurodegenerative disease. (1300, 1301) *A. muricata*'s primary acetogenin, annonacin, has been shown to kill striatal neurons in vitro and promote the redistribution of tau protein from the axon to the cell body. (1302) Studies on the neurotoxicity of annonacin suggest that prolonged exposure to this molecule is required. However, clinical studies demonstrating the safety of this extract are lacking; this is particularly important considering the association of AGE consumption and neurodegenerative disease.

Two clinical studies evaluated *A. muricata* in patients who had undergone resection for colorectal cancer. Thirty outpatients with colorectal cancer who had undergone primary tumor resection were enrolled in a randomized double-blind placebo-controlled pre‑post-trial. They were divided into two groups: those who ingested *A. muricata* leaf extract (n=14) and those who ingested a placebo (n=14) daily for 8 weeks. (1303) Twenty-eight subjects completed the trial. *Ex vivo* studies showed higher cytotoxicity in the supplemented group compared with the placebo group. Surono et al randomized 20 patients who had undergone colorectal resection to *A. muricata* leaf extract or placebo and followed serum cytokine levels for 8 weeks.(1304) There was no significant difference of inflammatory cytokines level (TNF-α, IFN-γ), and antiinflammatory cytokine IL-10 between group or within groups.

Graviola has been shown to have therapeutic effects against a variety of human malignancies and disease agents in in vitro culture and preclinical animal model systems, where it has been shown to have minimal to no effect on normal cell viability while targeting the disease.(1291) However, more research is needed to determine the safety, tolerability and efficacy of *A. muricata* leaf extract in range of patients with various malignancies before this extract can be recommended.

CHAPTER 10: TIER FOUR REPURPOSED DRUGS – RECOMMEND AGAINST

41. B Complex Vitamins and Antioxidants

B complex vitamins containing folate (folic acid) and vitamin B12 should be avoided in patients with cancer as they increase the risk of tumor progression and metastases. Indeed, these vitamins act as growth factor for the tumor. This observation is supported by the fact that anti-metabolites which block folate metabolism are effective anti-cancer chemotherapeutic agents.

Folic acid (Vitamin B9) is a water-soluble B vitamin found in leafy greens, legumes and cereals. In the US folate supplementation of flour is mandated. Even in well-nourished Western societies, routine supplementation of pregnant women with folate significantly reduces the risk of neural tube defects. Observational studies in the 1980 s suggested that a low-folate diet increased the risk of heart disease and colorectal cancer. (57) The enthusiasm for B vitamin supplementation led to studies to determine if it could reduce these diseases. Unfortunately, these studies proved harmful.

In observational studies, lower homocysteine levels are associated with lower rates of coronary heart disease and stroke. Folic acid and vitamins B6 and B12 lower homocysteine levels. In 2006 the HOPE2 study assessed whether supplementation with these vitamins reduced the risk of major cardiovascular events in patients with vascular disease. (1305) The HOPE2 found that supplementation with folate, vitamin B6 and B12 failed to reduce heart disease. However, the study demonstrated a worrisome 36% increased risk of colon cancer (not statistically significant) and a 21% increased risk of prostate cancer. The Aspirin/Folate prevention of large bowel polyps clinical trial found that six years of folate supplementation increased the risk of advanced cancer by 67%. (1306)

In the Cooperative Group Clinical Trial (SWOG S0221) patients with breast cancer randomly assigned to an intergroup metronomic trial of cyclophosphamide, doxorubicin, and paclitaxel were queried on their use of supplements at registration and during treatment. (458) In this study the use of any antioxidant supplement (vitamins A, C, and E; carotenoids; coenzyme Q10) both before and during treatment was associated with an increased hazard of recurrence (HR 1.41; 95% CI, 0.98 to 2.04; P = .06) Furthermore, vitamin B12 use both before and during chemotherapy was significantly associated with poorer disease-free survival (HR, 1.83; 95% CI, 1.15 to 2.92; P , .01) and overall survival (HR, 2.04; 95% CI, 1.22 to 3.40; P,.01).

Two large trials, the Norwegian Vitamin (NORVIT) trial and the Western Norway B intervention trial (WENBIT) confirmed that high dose B vitamin supplements did not reduce heart disease. (1307, 1308) It should be noted that folate supplementation of grains and other produce is not performed in Norway. Ebbing et al performed a combined analysis and extended follow-up of participants from these two studies focusing on the risk of cancer. (1309) After a mean follow-up of 77 months, participants who received folic acid plus vitamin B12 vs placebo had an

increased risk of cancer (HR, 1.21; 95% CI 1.03-1.41; *P*=.02). and an increased death from cancer (HR, 1.38; 95% CI, 1.07-1.79; *P*=.01). Vitamin B6 treatment was not associated with any significant effects.

It should be noted that in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) vitamin E was associated with a significant increased risk of prostate cancer (HR 1.17, 99% CI 1.004-1.36, p=.008). (1310)

Antioxidant supplements (vitamins A, C, and E; coenzyme Q10, and N-acetyl cysteine) should be avoided in patients with cancer. In an experimental model, Wang et al demonstrated that vitamin C, vitamin E and n-acetylcysteine (NAC) increased tumor angiogenesis by BACH1 mechanism (redox-sensitive transcription factor BTB and CNC homology 1). (457)
In addition, Zang et al have demonstrated that the combination of glutathione and IgG4 promotes tumor growth by promoting local immunosuppression. (98)

42. Colchicine

Colchicine, the main alkaloid of the poisonous plant meadow saffron (Colchicum autumnale L.), is a classical drug used for the treatment of gout and familial Mediterranean fever. (1311-1313)

Colchicine exerts antiproliferative effects through the inhibition of microtubule formation by blocking the cell cycle at the G2/M phase and triggering apoptosis. (1313) Due to its toxicity colchicine is rarely used to treat cancer. However, numerous analogues of colchicine have been synthesized in the hope of developing novel, useful drugs with more favorable pharmacological profiles. (1311, 1312, 1314) Several colchicine semisynthetics are less toxic than colchicine and research is being carried out on effective, less toxic colchicine semisynthetic formulations with potential drug-delivery strategies directly targeting multiple solid cancers.

Anticancer pathways and mechanisms
Colchicine, a well-known anti-mitotic drug, keeps mitotic cells from progressing into the metaphase. (1311) Colchicine forms the tubulin-colchicine (TC) complex by attaching to the ends of microtubules. This prevents the production and polymerization of microtubules by interfering with the dynamics of the tubulin lattice. (1311, 1315-1317) Colchicine interferes with numerous cellular activities, including cell migration, cell division, ion channel regulation and cell shape which are dependent on microtubule function. (1311, 1318) Colchicine has anti-inflammatory characteristics, which are mostly brought on by the disruption of leukocytes and microtubule downstream cellular functions. (1311) Colchicine inhibits angiogenesis and suppresses cell invasion, cell migration, and adhesion via MMP9 and FAK/SRC reduced expression. (1311, 1319, 1320) Colchicine promoted caspase-3-mediated apoptosis through the suppression of the PI3K/Akt/mTOR signaling pathway in NCI-N87 cells. (1311, 1321-1324) The pro-apoptotic protein p21 has also been activated in cells by derivatives of colchicine. (1311, 1325)

Clinical studies
The majority of clinical investigations are in vitro or vivo, and data indicated that colchicine may be a viable adjunctive treatment for hypopharyngeal, gastric, breast, and other cancers, prostate, colon, liver, leukemia, and pancreatic cancers. (1311, 1326-1329) Kuo et al reported that colchicine use was linked to a lower incidence of incident all-cause malignancies, especially in prostate and colorectal cancers, among male Taiwanese patients with gout, according to findings from a 12-year cohort research. (1330)

Safety of colchicine
Colchicine has a narrow therapeutic index, with no clear-cut distinction between nontoxic, toxic, and lethal doses, causing substantial safety concerns with this drug. (1313, 1331) Furthermore, drug accumulation and high dosages can be associated with severe, often fatal, consequences. (1332) Although colchicine poisoning is sometimes intentional, unintentional toxicity is common and often associated with a poor outcome. (1332)

Gastrointestinal effects, including nausea, vomiting, and diarrhea, are the most common side effects associated with colchicine therapy. (1313) However, colchicine can cause myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia, which can be life-threatening or fatal. In addition, colchicine is associated with neuromuscular and hepatic toxicity and rhabdomyolysis. Due to its narrow therapeutic index and toxicity, colchicine is not recommended for routine use in patients with cancer.

43. Essiac and Flor-Essence

Essiac and Flor-Essence are herbal tea mixtures that have been used as anticancer treatments. They have been used to treat other health conditions, including diabetes, AIDS, and gastrointestinal diseases. There is however no clinical data to support the use of Essiac for any indication.

Constituents of Essiac: Burdock (*Arctium lappa*), rhubarb (*Rheum palmatum*), sheep sorrel (*Rumex acetosella*), and slippery elm (*Ulmus rubra*).
Constituents of Flor-Essence: Essiac, red clover (*Trifolium pratense*), blessed thistle (*Carduus benedictus*), kelp (*Laminaria digitata*), and watercress (*Nasturtium officinale*).(1333, 1334)

Essiac, a botanical formulation of four herbs, was popularized as a cancer treatment in the 1920s by Rene Caisse, a Canadian nurse (Essiac is Caisse spelled backwards). (1333) It is believed that she obtained the formula from a patient who claimed to have learned about it from an Ojibwa healer, and who said that the mixture had cured her breast cancer. Caisse began to use the formula in the form of tea and as an injection to treat cancer patients. However, concerns about the use of Essiac led to an investigation by the Cancer Commission of Ontario in 1938, which failed to find evidence of Essiac' s effectiveness. However, Caisse continued to offer it to patients and modified the original product to further promote its use by adding four more herbs.(1333) The new formula, Flor-Essence, was thought to be more potent

than Essiac, had improved taste, and could be taken orally by patients, thereby eliminating the need for injection. Essiac and its variant Flor-essence are manufactured by various companies and marketed worldwide in the form of powders, capsules, teas, and liquid extracts. More than 40 Essiac formulations are available in the United Kingdom, Australia, and North America.(1335) Essiac and Flor-Essence is widely available in the USA with sales exceeding $8 million in 2000.(1334)

Essiac and Flor-Essence, are sold as nutritional supplements and used by patients to treat chronic conditions, particularly cancer. Evidence of anticancer activity for the herbal teas is limited to anecdotal reports recorded for some 40 years in Canada. Individual case reports suggest that the tea improves quality of life, alleviates pain, and in some cases, impacts cancer progression among cancer patients. Although Essiac is currently unavailable for sale in Canada, the Canadian government allows Essiac to be sold to patients on compassionate grounds. A survey conducted in 2000 found almost 15% of Canadian women with breast cancer to be using some form of Essiac. (1336)

Essiac exhibits significant immunomodulatory effects, specifically through stimulation of granulocyte phagocytosis, increases in CD8+ cell activation, and moderately inhibiting inflammatory pathways. (1337) In vitro studies show that Essiac has antioxidant (1338), and cytotoxic properties (1337, 1339); however, it also stimulated growth of human breast cancer cells. (1340) Studies of its antiproliferative effects on prostate cancer cells also yielded conflicting results. (1341, 1342) A retrospective study of breast cancer patients found that Essiac did not improve quality of life or mood. (1343) Essiac inhibits several CYP450 enzymes, most notably CYP1A2 and CYP2C19. (1337)

During the 1970s and 80s, several researchers in Canada and in the United States, including those at the National Cancer Institute, studied Essiac.(1344, 1345) All failed to find any evidence of effectiveness. In the mid-1970s, researchers at the Memorial Sloan Kettering Cancer Center (MSKCC) were unable to detect anticancer activity of Essiac in 17 separate experiments that utilized a variety of animal leukemia and tumor models.(1345) In 1983, the National Cancer Institute tested a liquid sample of Essiac after the Canadian Department of National Health and Welfare (Health Protection Branch) requested that it be tested in animals.(1345) These studies revealed no anticancer activity in the mouse P388 lymphocytic leukemia tumor system and found lethal toxicity at the highest concentrations of Essiac administered to test animals. The 2004 *in vivo* study of Flor Essence in a rat model looked at mammary tumor development following administration of the herbal compound. Sprague-Dawley rats (N = 112) were assigned to one of three groups.(1345) The control group (n = 35) received water only. The second group (n = 40) received 3% Flor Essence in their drinking water in an attempt to provide a dose equivalent to that recommended in the popular literature. The third group (n =37) received 6% Flor Essence in their drinking water to investigate the dose-response relationship. Mammary tumors were induced by a 40 mg/kg of body weight dose of 7,12-dimethylbenz(a)anthracene. At 19 weeks, palpable mammary tumor incidence was higher (65% and 59.4%) in both Flor Essence groups, compared with controls (51%).(1345, 1346) The

findings of this study are in keeping with the study by Kulp et al demonstrating the Essiac stimulated the in vitro growth of human breast cancer cells. (1340)

In the early 1980s, the Canadian Department of National Health and Welfare conducted a retrospective review of data voluntarily submitted by physicians for 86 cancer patients who had obtained Essiac under Canada's Emergency Drug Release Program between 1978 and 1982. (1345) The Bureau found 47 patients who did not benefit from Essiac; 1 had subjective improvement, 5 required fewer analgesics, 4 had an objective response, and four were in stable condition. Among the remaining 25 patients, 17 had died, and the reports for 8 were considered unevaluable.

Despite unsubstantiated claims, Essiac remains a popular anticancer therapy today. There is a lack of both human safety and efficacy data for Essiac and Essiac formulations. Consumers should be aware that there are many varieties of Essiac formulas and only one trademarked Essiac, the formula of which is unknown. Adverse effects and interactions may occur from any of the constituents. Well-designed trials testing Essiac and assessing clinical outcomes are necessary to draw stronger conclusions. (1335)

44. Shark Cartilage

Since the publication of W Lane's '*Sharks Don't Get Cancer'* in 1992, shark cartilage was touted as the new "cancer cure" of the 1990s. In 1995, the annual world market for shark cartilage products exceeded US $30 million, and dozens of products, usually as food supplements, are on the market. (1347)

The promotion of crude shark cartilage extracts as a cure for cancer has contributed to at least two significant negative outcomes: a dramatic decline in shark populations and a diversion of patients from effective cancer treatments. (1348)

An alleged lack of cancer in sharks constitutes a key justification for its use. (1348) The proponents of this therapy assume that since the largest part of sharks' bulk is cartilage, something in shark cartilage must account for the rarity of cancer in this animal. Therefore, the argument goes, if patients simply ingest an arbitrary quantity of this cartilage (which presumably has been ground up and made into pills), cancer will regress. The explanation is simple and superficially appealing and offers hope that a nontoxic substance can eliminate cancer. Unfortunately, the claims for the benefits of shark cartilage are completely unsubstantiated by any objective data from controlled clinical trials.

The proposed mechanisms of antitumor action of shark cartilage includes direct or indirect inhibition of angiogenesis. Two glycoproteins, sphyrnastatin 1 and 2, have been isolated from cartilage of the hammerhead shark and reported to have strong antiangiogenic activity and to inhibit tumor neovascularization. (1349)

Miller et al performed a phase I/II clinical trial evaluating the safety and efficacy of shark cartilage in the treatment of advanced cancer. (1350) Sixty patients were treated with shark cartilage at a dose of 1 g/kg daily orally in three divided doses. Five patients were taken off the study because of gastrointestinal toxicity or intolerance to shark cartilage. Progressive disease at 12 weeks occurred in 27 patients. No complete (CRs) or partial responses (PRs) were noted. Median time to tumor progression in the entire study population was 7+/-9.7 weeks. It was concluded that in patients with advanced-stage cancer, shark cartilage had no salutary effect on quality of life. The 16.7% rate of stable disease was similar to results in patients with advanced cancer treated with supportive care alone.

The North Central Cancer Treatment Group trial studied patients with breast or colorectal carcinoma receiving the standard care and who were randomized to receive a shark cartilage product or an identical-appearing and smelling placebo 3 to 4 times each day. (1351) Data on a total of 83 evaluable patients were analyzed. There was no difference in overall survival between patients receiving standard care plus a shark cartilage product versus standard care plus placebo. Likewise, there was no suggestion of improvement in quality of life for patients receiving shark cartilage, compared with those receiving placebo.

45. Laetrile (Amygdalin)

The use of Laetrile for the treatment of cancer is highly controversial, with claims of an organized coverup to suppress in-vitro efficacy data as well as conspiracy theories. In summary, while laetrile does have some in-vitro anti-cancer activity, reliable reproducible animal model data is lacking with no credible anti-cancer efficacy in patients. Furthermore, the potential of significant toxicity exists.

Amygdalin is a natural cyanogenic glycoside occurring in the seeds of some edible plants, such as bitter almonds and peaches. Bitter almonds have been used since ancient times to treat fevers, headache (via their purging activity) and as a diuretic. (1352) Amygdalin is composed of two molecules of glucose, plus one molecule each of benzaldehyde and hydrogen cyanide. The anticancer activity of amygdalin is thought to be related to the cytotoxic effects of enzymatically released HCN and non-hydrolyzed cyanogenic glycosides.

In 1952, Ernst Theodore Krebs, Jr. synthesized a less harmful amygdalin derivative of amygdalin with one subunit of glucose, which he called Laetrile. The mixture of amygdalin and its modified form was described by Krebs as “vitamin B17”, although in the literal sense neither amygdalin nor Laetrile are vitamins. (1352) In 1977, the U.S. FDA issued a statement indicating that there was no evidence of the safety and efficacy of Laetrile. It is forbidden to sell amygdalin and Laetrile in the U.S. and Europe.

Laetrile, which is derived from amygdalin, has been used as an alternative natural medicine in the treatment of cancer for over 30 years. The use of Laetrile/amygdalin in the treatment of cancer is controversial; on the one hand, this compound has in vitro anticancer activity; however, it can be toxic via enzymatic degradation and production of hydrogen cyanide. (1352) Furthermore, despite studies demonstrating anti-cancer activity on cancer cell lines, the clinical evidence for the anticancer activity of amygdalin has not been established. Moreover, high dose exposures to amygdalin can produce cyanide toxicity. (1352)

In vitro cell culture studies show several amygdalin activities that would be beneficial in cancer treatment.(1353, 1354) For example, amygdalin has the capacity to control apoptotic proteins and signaling molecules, which may be an explanation for a decrease in tumor proliferation. Amygdalin treatment increased expression of Bax, decreased expression of Bcl-2 and induced caspase-3 activation in human DU145 and LNCaP prostate cancer cells, (1355) induced apoptosis of HeLa cervical cancer cells mediated by endogenous mitochondrial pathway, (1356) and reduced adhesion and migration of UMUC-3 and RT112 bladder cancer cells through activation of focal adhesion kinase (FAK) and modulation of β1 integrin. (1357)

Laetrile was studied in a mouse model By Dr Konematsu Suguira at Sloan Kettering Cancer institute during the 1970's. This research was never published in a peer reviewed paper but was promoted in the media by Ralf Moss a science writer originally employed by Sloan Kettering. In a series of 6 experiments with CD8F1 mice with spontaneous mammary adenocarcinomas Sugiura noted by macrovisual observation with some histology an overall average of 21% of mice with lung metastases when treated with 1,000--2,000 mg/kg/day of amygdalin compared with 90% of the control mice. (1358) The significance attributed to these early observations is challenged by the negative findings of 3 independent investigators, by 2 out of 3 negative cooperative experiments in which Sugiura participated, and particularly by the blind experiment in which he and others under blind readings found no anticancer activity. (1358) Control animals often lived longer than those treated with various doses and schedules of amygdalin.(1359) However, the accuracy of these negative findings has been questioned and a "coverup" has been suggested. In a documentary entitled "*Second Opinion: Laetrile at Sloan-Kettering*" Mr. Moss claims that "laetrile stopped the spread of cancer, yet they lied to us about it" http://www.secondopinionfilm.com/. The true findings of Dr Suguira's research are unclear as his data was never published nor has his work been reproduced by other investigators. However, the lack of proven clinical efficacy of laetrile (as outlined below) raises serious questions as to the validity of his findings.

In 1978 the National Cancer Institute (NCI) published a special report on Laetrile based on a national retrospective analysis. (1360) Cases thought to have shown objective benefit from Laetrile were solicited by mail request to 385,000 physicians and 70,000 other health professionals in the US. Although it is estimated that at least 70,000 Americans used Laetrile, only 93 cases were submitted for evaluation. Twenty-six of these Laetrile cases had to be eliminated because of insufficient documentation. an equal number of conventionally treated cases selected from the institute's files were added to the records to be analyzed. A panel of 12 oncologists, who had no knowledge of the actual treatments given, was then asked to evaluate

the results of 160 courses of treatment (68 Laetrile, 68 chemotherapy, 24 "no treatment") in the abstracted records from 93 patients. The panel judged six Laetrile courses to have produced a response (two complete and four partial). These results allow no definite conclusions supporting the anti-cancer activity of Laetrile.

In 1982, a clinical trial of 178 patients with cancer who were treated with Laetrile was published in the *New England Journal of Medicine*. (1361) No substantive benefit was observed in terms of cure, improvement, or stabilization of cancer, improvement of symptoms related to cancer, or extension of life span. The hazards of amygdalin therapy were evidenced in several patients by symptoms of cyanide toxicity. The paper concluded with this statement: “Amygdalin (Laetrile) is a toxic drug that is not effective as a cancer treatment.” Fatal and nonfatal toxicities from orally ingested cyanogenic glycosides have been reported worldwide.(1359) A systematic review published in 2007 included 36 studies, none of which “proved the effectiveness of laetrile.” (1356) A Cochrane systematic review published in 2015 failed to identify any studies that met their inclusion criteria. (1362) The authors of this review concluded that “the claims that laetrile or amygdalin have beneficial effects for cancer patients are not currently supported by sound clinical data.” Based on the “best available” data the use of laetrile cannot be recommended.

CHAPTER 11: POTENTIAL ADJUNCTIVE THERAPIES

Therapeutic Hyperthermia

Beginning with the early observations by Dr. William Cooley in the 1890s that infections in cancer patients are associated with tumor regression and that injection of cocktails of attenuated bacterial cultures induces a fever and a significant anti-tumor effect, there has been a revival of interest in therapeutic hyperthermia (TH) for cancer therapy. (1363) TH can be defined as a therapy able to raise the temperature in the tumor mass between 41 and 45°C by external physical means.(1364, 1365) TH was first used in combination with radiotherapy by Warren in 1935. (1366) In this series all 32 patients appeared to respond to this treatment modality. Subsequently TH has been combined with radiotherapy and/or chemotherapy with remarkable success in treating advanced and recurrent cancers. Phase II/III clinical trials have demonstrated that hyperthermia combination therapy is beneficial for local tumor control and survival in patients with high-risk tumors including cervical cancer, recurrent breast cancer, head and neck cancer, melanoma, sarcomas, liver, glioblastoma and pancreatic cancer. (1365, 1367-1370) Various in vitro and in vivo studies conducted during 1970s to 2000s have conclusively shown that radiation induced damage is enhanced by hyperthermia at 41–43°C.(1371) A review by Horsman has clearly demonstrated that hyperthermia is a potent enhancer of radiotherapy.(1372) The clinical data show that the synergism between hyperthermia and radiotherapy can be observed applying HT before or after RT for a period of 4-8 hours. Chemotherapy may be used synchronously, and its activity is additive. Preclinical studies have demonstrated the synergetic effects by combining hyperthermia with immune check point inhibitors. (1373) Despite this data a recent systematic review concluded that the "*clinical evidence for the benefit of alternative hyperthermia in cancer patients is lacking. Neither for whole-body hyperthermia nor for electro hyperthermia there is any evidence with respect to improvement of survival or quality of life in cancer patients*."(1374) However a systematic review and meta-analysis showed that concurrent chemoradiotherapy with HT significantly improved overall survival in locally advanced cervical cancer patients without increasing acute and chronic toxicity. (1375) Furthermore, it would appear that HT alone has limited benefit in patients with cancer. There is a paucity of data regarding the effect of sauna bathing/steam baths on patients with cancer.(1376) A prospective cohort study demonstrated that sauna bathing does not increase or decrease the risk of cancer in men. (1377) However, a RCT demonstrated the positive and cost-effectiveness effect of spa therapy on the resumption of occupational and non-occupational activities in women in breast cancer remission. (1378)

Current hyperthermia strategies generally include local, regional, and whole-body hyperthermia, which can be implemented by many heating methods, such as microwave, radiofrequency, laser, and ultrasound. (1365) A relatively new entrant in the field of hyperthermia is nanotechnology which capitalizes on locally injected or systemically administered nanoparticles that are activated by extrinsic energy sources to generate heat.

(1365, 1379, 1380) In this method, the nanoparticles which are usually administered in a suspension are small heat-absorbers that are selectively heated up by outside magnetic field, which acts exclusively only on these nanoparticles.

The biological response of the tumor to heat depends on both the intrinsic characteristics of the tumor cell itself and on the surrounding environment. Indeed, modifications of the tumor microenvironment may increase or decrease the response to heat. Between the range of 40 and 43^{o}C, the majority of cancer cells tend to die, while the majority of healthy cells tend to survive. (1365) When cancer cells are subjected to high temperatures (40-43^{o}C) they suffer irreversible damage, in a time and dose dependent way.

The biochemical processes affected by heat are several, as outlined by Pietrangeli and Mondovi and summarized below:(1381)

- DNA, RNA synthesis, DNA repair mechanism and cell respiration are inhibited.
- Tumor cell membranes in the presence of heat become more permeable and fluid. This may partially explain the increased uptake of drugs.
- DNA polymerases- β key enzymes in multistep repair system and are strongly inhibited.
- Mitochondria suffer structural alterations in their cristae
- Enhanced production of heat shock proteins (HSP) affects thermo-tolerance and tumor immunogenicity.
- Heat increases the influx of reactive oxygen radicals mediating cytotoxicity.
- Hyperthermia is a potent inducer of cancer cell apoptosis. (1382) Hyperthermia in combination with drugs promotes synergistic cancer cell apoptosis.

In addition, the tumor microenvironment alters the sensitivity to hyperthermia, while HT alters the microenvironment itself. HT modulates many aspects of innate and adaptive immunity, such as Natural Killers or heat shock proteins. (1383) HT and radiation therapy decrease the recruitment of the regulatory T cells, compared to hyperthermia alone, and macrophages seems to be affected by this association, with decreased expression of M2 macrophages. Another important anti-tumor effect of HT is the capacity to inhibit angiogenesis. TH- induced cellular damage is cell-cycle-independent, in contrast to radiation therapy and many chemotherapy regimens that are more cytotoxic when cells are in specific phases of the cell cycle.(1379)

Intraperitoneal chemotherapy during surgery that can be delivered under hyperthermic conditions is termed hyperthermic intraperitoneal chemotherapy (HIPEC). (1384) Hyperthermia increases the penetration of chemotherapy at the peritoneal surface and increases the sensitivity of the cancer to chemotherapy. The addition of HIPEC to interval cytoreductive surgery for the treatment of ovarian cancer has been demonstrated to improve event free survival. (1384)

Hyperthermia modulates the immune status of tumor microenvironment by providing danger signals with HSPs as well as subsequent activation of immune systems. The immunomodulatory effects not only make hyperthermia a treatment capable of defending against cancer but also make hyperthermia a reliable treatment that creates a type I-like tumor microenvironment (overexpression of PD-L1 and enrichment of tumor infiltrating lymphocytes) in complementary for the enhancement of the immune checkpoint inhibitors.(1373) The effect of hyperthermia on the immune enhancing properties of repurposed drugs (as reviewed in this monograph) have not been studied; while hyperthermia is a low risk intervention due to the lack of data this combination cannot be strongly endorsed at this time. A single case report described the successful treatment of a patient with widely metastatic breast cancer who was treated with the combination of metabolically supported chemotherapy (insulin potentiated therapy), ketosis and hyperthermia. (1385) Sauna bathing has been shown to reduce all-cause mortality.(1386) As sauna bathing is a low risk intervention that may positively improve the immune function of the tumor micro-environment it may be reasonable for cancer patients to consider this intervention.

Tumor Treating Fields

Tumor treating fields (TTF) are a non-invasive antimitotic therapy that delivers alternating electric fields via the Optune® system. (1387) TTF are 100 – 400 kHz alternating current (AC) electric fields transmitted transdermally to tumors using two orthogonal sets of transducer arrays. Transducer arrays are activated sequentially each second, effecting a direction change of the incident field on the target. (1388) TTF mechanism of action involves polarizable intra-cellular structures and mitotic disruption. TTF induces mitotic spindle assembly checkpoint arrest leading to a cell-cycle arrest, followed by mitotic slippage, and subsequent cell death or senescence. (1388) In addition, TTF promotes autophagy by inducing AMPK, miR29b and other drivers of autophagy. TTF has immunological effects including activation of the STING pathway, increased expression of MHC ll, CD80, and CD40 on dendritic cells and M1 macrophage polarization. (1388) TTF has been shown to suppress the migration and invasion of LN-18 glioma cells in experimental models. TTF do not have a systemic half-life like oral or intravenous therapies and exert their therapeutic effect while the electric fields are being applied only on actively dividing cancer cells but not on healthy cells. Thus, compliance with treatment is critical to maximize effectiveness. (1387)

TTF has been studied most extensively in patients with glioblastoma multiforme (GBM). TTF is currently undergoing evaluation as an adjunctive treatment in patients with NSCLC, pancreatic and ovarian cancer. (1388) In patients with GBM, TTF is delivered to the region of the tumor via transducer arrays placed on the patient's scalp. The Phase III EF-14 RCT (n=695) in newly diagnosed GBM patients demonstrated significantly improved progression-free survival (HR, 0.63; 95%CI, 0.52-0.76; $P < .001$) and overall survival (HR, 0.63; 95%CI, 0.53-0.76; $P < .001$) when TTF were used together with maintenance temozolomide (TMZ) compared with TMZ alone. (1389, 1390) The National Comprehensive Cancer Network (NCCN) recommends TTF in

combination with TMZ for the treatment of patients with both newly diagnosed and recurrent glioblastoma. Based on this information patients with GBM should consider TTF, when feasible, as an adjunctive treatment option. (1391)

Photodynamic Therapy

Photodynamic therapy (PDT) is a treatment approach that causes tissue destruction by visible light in the presence of a photosensitizer and oxygen. (1392) When sensitizer molecules are exposed to light energy, electrons at low-energy singlet states jump to high-energy singlet states, and some spontaneously convert to excited triplet states. The excited triplet state interacts with oxygen-producing reactive oxygen species. Reactive oxygen species cause cell death locally through a complex interplay of apoptosis, necrosis, and autophagy-associated cell death. (1393)

Light has been known to provide a therapeutic potential for several thousands of years. Over 3,000 years ago, since the ancient Indian and Chinese civilizations, it has been used for the treatment of various diseases mainly in combination with reactive chemicals, for example, to treat conditions like vitiligo, psoriasis, and skin cancer. Sunshine has enormous therapeutic effects both due to ultraviolet-B (UVB) and the synthesis of vitamin D in the skin and near infrared (NIR) radiation (about 40% of solar radiation), which has enormous health benefits including mitochondrial melatonin synthesis. (1394, 1395) Due to our modern lifestyle, modern man has a profound deficiency of NIR exposure. (1395)

Of all the wavelengths of sunlight, NIR-A radiation has the deepest penetration into tissues, up to 23 cm. During the 1918 influenza pandemic, “open-air treatment of influenzae” (sunshine) appears to have been the most effective treatment for seriously ill patients. (429) A more recent prospective study demonstrated that avoiding sun exposure is a risk factor for all-cause mortality. (430) In this study, the mortality rate amongst avoiders of sun exposure was approximately twofold higher compared with the highest sun exposure group.

Dermatologists commonly use PDT with a topical photosensitizing agent for the treatment of actinic keratoses and early nonmelanoma skin cancers, but the potential applications for PDT are far broader, including solid tumors. (1392) When PDT is utilized to treat malignant and premalignant tumors, a patient is administered a sensitizer agent that preferentially accumulates in neoplastic lesions and is activated by light to produce cell death. (1393)

PDT for cutaneous indications commonly utilizes a topical photosensitizer, such as 5-aminolevulinic acid or methyl aminolevulinate, which are precursors of protoporphyrin IX. (1392) Treatment of visceral tumors requires an intravenous or oral photosensitizer, and the most commonly used photosensitizing agent for this indication is porfimer sodium. Porfimer sodium absorbs light at 630 nm (red light). PDT has been performed with various light sources including lasers, incandescent light, laser-emitting diodes, transcutaneous fiberoptic devices, and daylight. (1396)

While the efficacy of PDT in killing cancer cells has been demonstrated in experimental models, (1397) clinical studies demonstrating the benefit of this modality in patients with non-cutaneous malignancies is limited. (1396, 1398-1400) The role of PDT and photobiomodulation in patients with non-cutaneous cancer requires further evaluation. However, to improve mitochondrial function we suggest that all patients expose themselves to about 30 minutes of midday sunshine whenever possible (at least 3 times a week); this is best achieved with a brisk midday walk.

Hyperbaric Oxygen Therapy

Hypoxia is a critical hallmark of solid tumors and involves enhanced cell survival, angiogenesis, glycolytic metabolism, and metastasis. Hyperbaric oxygen treatment (HBOT) has for centuries been used to improve or cure disorders involving hypoxia and ischemia, by enhancing the amount of dissolved oxygen in the plasma and thereby increasing O2 delivery to the tissue. (1401)

HBOT leads to hyperoxia and elevated levels of reactive oxygen species (ROS), which overwhelm the cancer cells' antioxidant defense and lead to cell death. (1402, 1403) The molecular mechanisms behind hyperoxia-induced cell death involve a complex signaling system including protein kinases and receptors such as RAGE, CXCR2, TLR3, and TLR4. (1404) Furthermore, contrary to what would be expected, HBOT has been shown to induce an antiangiogenic effect in tumor models. (1402, 1405)

While HBOT appears to have limited effects on cancer growth, it may potentiate the effects of other treatment modalities. Hoff et al demonstrated that a ketogenic diet combined with HBO had significant anticancer effects in a natural model of systemic metastatic cancer. (1406) Hypoxia has been described as an important factor for chemotherapeutic resistance. (1401) Studies on HBOT as a chemotherapeutic adjuvant have shown augmented effects both in vitro and in vivo. (1401) However, it is important to emphasize Mayer et al. list five chemotherapeutic agents (doxorubicin, bleomycin, disulfiram, cisplatin, and mafenide acetate) which are strongly contraindicated in combination with HBOT due to potential potentiation of toxicity. Radiotherapy in combination with HBOT has been used clinically in two different applications: (a) as a therapeutic agent for treating late radiation injury and (b) as a radiosensitizer, aiming to increase the effect of radiotherapy. (1401) Yen demonstrated both in vitro and in vivo that HBO therapy shows promise as an adjuvant treatment for GBM by reducing cancer stem cell formation and enhancing sensitivity to chemotherapy and radiotherapy.(1407) An updated Cochrane systematic review concluded that "there is some evidence that HBOT improves local tumor control and mortality in tumors of the head and neck; however, the outcomes seem to be related to the use of unusual fractionation schemes, and thereby conclude that the benefits of HBOT should be interpreted with caution." (1408) While HBOT may have promise as an anticancer intervention, especially when combined with other treatment modalities, the clinical data to support this intervention is limited at this time.

CHAPTER 12: CHEMOTHERAPY: A BASIC PRIMER

Metronomic Dosing

Metronomic therapy is a new type of chemotherapy in which anti-cancer drugs are administered in a lower dose than the maximum tolerated dose repetitively over a long period to treat cancers with fewer side effects. (1409) Metronomic therapy is shown to affect both tumor microenvironment and tumor cells to achieve its therapeutic effects. Metronomic therapy is also cost-effective as a lower dose is used compared to conventional chemotherapy. Metronomic dosing will avoid side effects by administering low doses continuously, and efficacy should be seen as prolonged progression free survival and overall survival, rather than in rapid tumor responses. (1410) Metronomic chemotherapy has been most commonly used in patients with metastatic breast cancer, non-small cell lung cancer, and glioblastoma. (1410) A meta-analysis of 22 clinical trials reported promising results in patients with advanced breast cancer. (1411)

The Basics of Chemotherapy

Despite the introduction of a significant number of new cancer therapeutics that target specific molecular pathways within malignant cells, the use of DNA damaging cytotoxic chemotherapy currently remains the mainstay in the management of most malignancies. (1412) Chemotherapy drugs typically kill cancer cells by interrupting DNA synthesis in all cells but will most significantly inhibit cells that are multiplying the fastest. Most chemotherapy drugs act by altering the structure/function of DNA thereby preventing cell division. (1413-1415) The mitotic spindle inhibitors modify the function/formation of spindle microtubules leading to mitotic arrest and cell death. Chemotherapy drugs cause cell death by apoptosis, either by directly interfering with DNA, or by targeting the key proteins required for cell division. (1416)

Unfortunately, they can also be ‘cytotoxic’ to normal dividing cells, particularly those with a high turnover, such as the bone marrow and mucous membranes. Chemotherapy agents in general act by killing rapidly dividing cells. Therefore, these agents act on the rapidly proliferating population of cancer cells. As the tumor increases in size the degree of cellular heterogeneity increases. The greater the degree of heterogeneity the less likely will be the response to chemotherapy. Chemotherapy is often poorly effective with metastatic disease because of the large tumor burden, the cell population is highly heterogenous, with a population of CSCs that divide very slowly. Further as already discussed, rather than killing CSCs, chemotherapy may potentiate the growth and dissemination of CSCs. Excluding germ cell tumors and lymphomas, most patients with solid tumors diagnosed with metastatic disease are not curable and treatment is with palliative intent (see Table 7). (1415)

Since their introduction in the 1940s there are now over 50 licensed drugs for the management of malignant disease. (1415) Chemotherapy drugs can be divided into two classes depending on their origin. They can be either plant derived or of synthetic origin. (1413, 1414) Depending on

their mechanism of action, they can be divided into alkylating agents, antimetabolites, topoisomerase inhibitors, mitotic spindle inhibitors and others (see Figure 11). (1413, 1414, 1416) Most chemotherapy regimens in clinical practice consist of several agents from different classes used in combination. (1415, 1416) Disadvantages of many cytotoxic agents include bone marrow suppression, gastrointestinal tract lesions, hair loss, nausea, and the development of clinical resistance. These side effects occur because cytotoxic agents act on both tumor cells and healthy cells. (1414)

The duration of the cell cycle is similar in tumors and healthy tissues, but tumors present a higher proportion of cells undergoing mitosis. Metastases commonly have a growth rate almost twice that of the primary tumor. At any one time less than 10% of cancer cells from solid tumors are actively dividing. (1417) Chemotherapeutic agents that work at certain points in the cell cycle are called cell cycle specific agents and need the cancer cells to be actively dividing to be maximally effective. Cell cycle specific chemotherapeutic drugs include Taxol, etoposide, vincristine and bleomycin as well as the antimetabolite drugs methotrexate and 5-fluorouracil. Some of the more common chemotherapeutic drugs that are not cell cycle specific include cyclophosphamide, cisplatin, and doxorubicin.

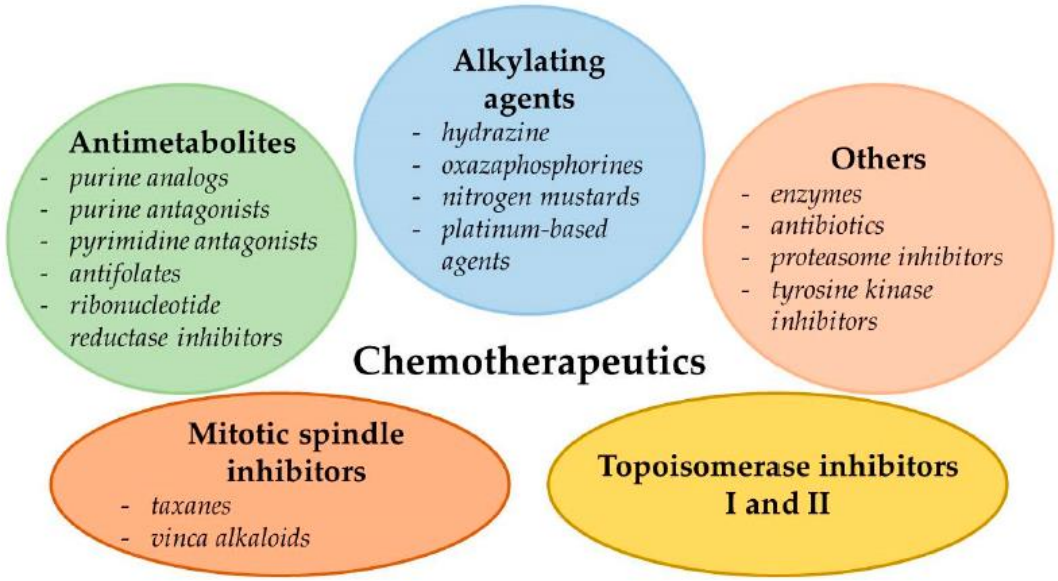
Individualized decisions regarding chemotherapy should be based on the expected response of the tumor (curability), the stage and extent of the disease (tumor bulk), the presence of metastases and the patients' comorbidities counterbalanced by the toxicity of the chemotherapy. The curability of various cancers in response to chemotherapy is listed in Table 4. (11, 221) Patients with metastatic solid tumors generally have incurable disease. The sites of metastases of common tumors are listed in Table 8. Patients with local disease may be cured with surgery (see Table 9). (11) The standard full chemotherapy protocol is suggested in patients with "chemotherapy curable tumors" and treatment should be initiated as soon as possible. The curability of "chemotherapy curable malignancies" may be related to the natural apoptotic sensitivity of the CSCs of these tumors. (221, 1418, 1419) Repurposed drugs and metabolic therapy should be strongly considered in all cancer types (curability) and adapted to the patients' individual preferences (see Figure 12). The contrasting effect of conventional chemotherapy and repurposed anti-cancer drugs are illustrated in Table 10.

Traditional chemotherapy often fails for solid tumors for the following reasons:

- Solid tumors are composed of heterogeneous population of cells many of which are slowly growing.
- Most of the tumor cells are in the rest phase of the cell cycle.
- Chemotherapy does not correct the cancer microenvironment (which promotes cancer cell proliferation) and likely makes it worse.
- Chemotherapy enhances rather than kills CSCs.
- Cancer cells become resistant to the chemotherapeutic agent. (1413)

Cancer Curable	Improves Survival	Palliation Only (metastatic)
Choriocarcinoma	Breast cancer	Colorectal, gallbladder
Acute lymphatic leukemia	Ovarian Cancer	Pancreatic, stomach
Chronic lymphatic leukemia	ALL in adults	Esophageal, liver
Acute promyelocytic leukemia	AML	Prostate, bladder, kidney
Testicular cancer	Thyroid Cancer	Endometrial and cervical
Ovarian germ cell tumor	Small cell lung cancer	NSCLC (lung cancer)
Hodgkin's lymphoma	Multiple myeloma	Brain, adrenal, melanoma
High Grade non-Hodgkin's lymphoma	Osteosarcoma	Adenocarcinoma primary unknown
Rare childhood malignancies	Wilms tumor	H&N cancer

Table 7. Tumor stratification according to response to chemotherapy.



Cancer	Major Site of Metastases
Bladder	Regional lymph nodes, bone, lung, liver
Breast	Bone, brain, liver, lung
Colorectal	Regional lymph nodes, liver, lung, peritoneal cavity
Kidney	Adrenal gland, bone, brain, liver, lung
Leukemia	Lymph nodes, spleen, major blood vessels, central nervous system
Liver	Lung, portal vein, portal lymph nodes
Lung	Adrenal gland, bone, brain, liver, other lung
Melanoma	Other areas of skin, subcutaneous tissue, bone, brain, liver, lung
Head and Neck	Lymph noes neck, salivary glands, lung
Ovary	Peritoneal cavity, omentum, fallopian tube
Pancreas	Liver, peritoneal cavity, lung, bone, stomach, intestine
Prostate	Bone, lung, liver, adrenal gland
Stomach	Liver, lung, peritoneal cavity
Thyroid	Regional lymph node, lung, bone, spine
Uterus and cervix	Vagina, peritoneal cavity, pelvic lymph nodes

Table 8. Some common cancers and sites of metastases. (1420)

Cancer	5-year Survival (%)
Breast	99
Prostate	99
Thyroid	99
Melanoma of skin	99
Endometrial cancer	95
Kidney cancer	93
Ovarian cancer	92
Uterine Cervix	93
Colorectal	91

Table 9. Surgically "Curable" cancers: Five-year survival for local disease with surgical removal.(11) Local disease- An invasive malignant cancer confined entirely to the organ of origin.

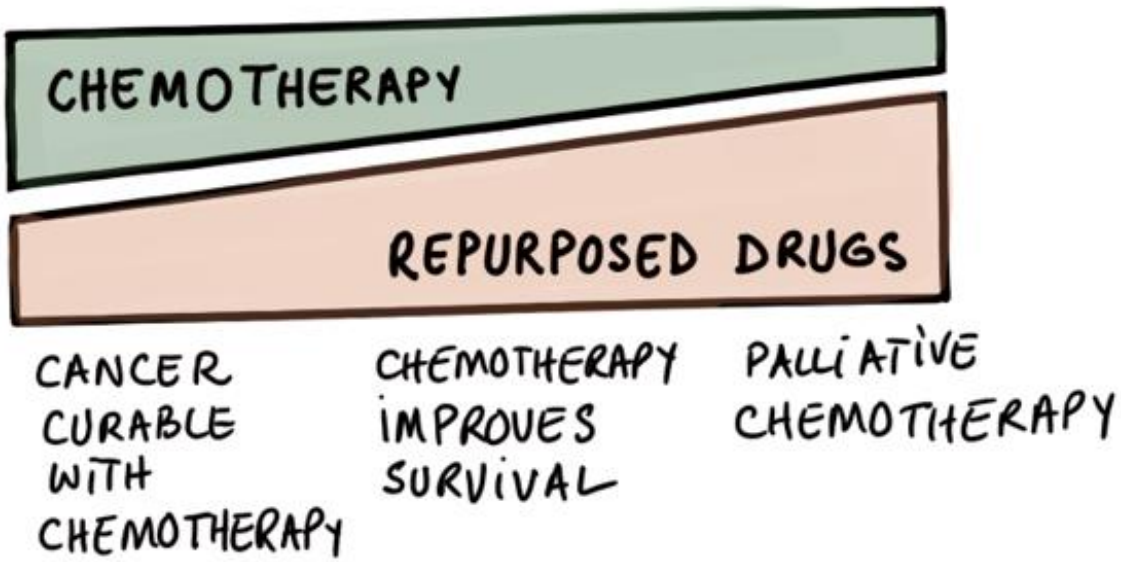


Figure 12. Role of chemotherapy and repurposed drugs according to "chemotherapy curability" [Source: Dr. Mobeen Syed].

The kinetics of tumor growth are crucial in determining the prognosis and are also factors in determining response to chemotherapy. The doubling time is the time that it takes for tumor cells to double. The faster the doubling time, the more likely the cancer will respond to chemotherapy but also the quicker (if no therapy is given) the cancer will kill the person. It is generally believed that once a tumor has reached the size of clinical detectability (1 cm size) has already undergone approximately 30 doublings to reach 10^9 cells (See figure 13). Only 10 further doubling cycles are required to produce a tumor burden of approximately 1 kg (2.2 pounds), which is usually lethal. The average doubling time for breast tumors has been reported to be 180 days while that for small cell lung cancer (SCLC) averages 86 days. (1421-1424)

	Chemotherapy	Repurposed Drugs
Tumor Cell population	Actively dividing cells only (~ 10% of cells)	All malignant cells
Tumor selectivity	++	+++
Tumor Stem Cells	Enhances	Suppresses/kills
Effect on adaptive immunity	Suppressive	Enhances
Effect on Tumor Microenvironment	Negative effect	Improves/enhances
Myelotoxic	Yes	No
Severe systemic side effects	Yes	No
Tumor cell resistance develops	Yes	No
Cost	+++++	+

Table 10. Contrasting effects of conventional chemotherapy versus metabolic treatment and repurposed drugs for cancer treatment.

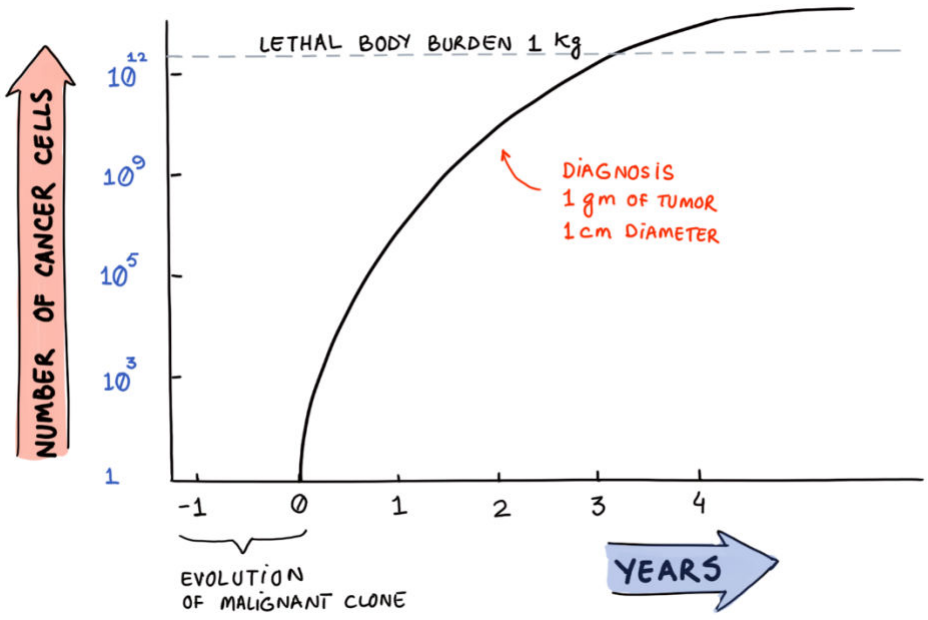


Figure 13. Tumor burden and tumor growth kinetics [Source: Dr. Mobeen Syed].

Integrative Approaches to the Treatment of Chemotherapy-Related Adverse Events

Oral Mucositis/Xerostomia/Altered taste

Oral mucositis is an inflammatory mucosal destruction characterized by erythema and/or ulceration of oral mucosa as a result of chemotherapy (30-76%) and/or radiation therapy (over 50%) for the treatment of cancer all over the body. (1425) The most common features of oral mucositis include oedema, erythema, ulcerations, bleeding, and pain, problems in swallowing, eating, drinking, talking and taste changes appearing in different levels of severity. In severe cases (grade 3, 4) it can impair patients' quality of life.

In recent years, various natural agents in plants have been studied in mucositis, which can improve oral mucositis symptoms via different interventions, e.g., their antioxidant and anti-inflammatory properties. (1425) These natural treatments include: (1425, 1426)

- Honey application (1427, 1428)
- Topical application of aloe vera (1429-1431)
- Topical chamomile (1432, 1433)
- Turmeric mouthwash (1434, 1435)
- Sage tea (1436, 1437)
- Indigo wood root (1426)
- Milk thistle (1438)

- Sage tea-thyme-peppermint solution (1439)
- Propolis, aloe vera, calendula, and chamomile solution (1440)
- Carob, Sage, Tahini mix

Chemo induced nausea and vomiting

- Ginger root extract, tea, etc. (1441-1446)
- Chamomile (1445, 1446)
- Cannabinoids (1251, 1447, 1448)
- Lemon extract/juice

Chemo/cancer fatigue

- Ginseng (1449-1452)
- Ashwagandha (878, 879, 1453)
- Mistletoe (914, 920, 923)
- Nigella sativa
- Wheatgrass

Chemo/cancer anxiety/stress

- Ashwagandha (405, 410, 1454)
- Chamomile
- Mistletoe (914, 920, 1455, 1456)
- Lavender (1457)
- Peppermint

APPENDICES

APPENDIX 1. Hierarchy of evidence for the stratification of repurposed drugs/nutraceuticals

It is critically important that the highest level of scientific evidence be used to justify a clinical intervention. If an observation is scientifically valid, it is reproducible, over and over again. Traditionally a meta-analysis of RCT's is considered the highest level of evidence. However, RCTs have many limitations including the fact that they don't reflect real world medicine and they can generally only test a single intervention (e.g., drug A vs placebo). Furthermore, RCT's are very expensive to perform and hence most are funded by Big Pharma who have inherent conflicts of interest. Nevertheless, emerging data suggests that the results of well conducted prospective longitudinal studies produce results quantitatively similar to those of RCTs. (450) For this monograph we therefore consider prospective observational studies and meta-analyses of these studies to be equivalent to RCTs in the hierarchy of evidence.

While in vitro and in vivo experimental studies are essential starting points to prove that a repurposed drug or nutraceutical has anti-cancer, it is essential that this data be supplemented by clinical data which demonstrates the SAFETY and EFFECTIVENESS of the compound in humans with the disease of interest. Furthermore, in vitro and in vivo studies are critical in evaluating the synergy between different interventions and the effects of these interventions on the tumor micro-environment. However, this data is insufficient to extrapolate the effects to patients. The failure of Laetrile to improve the outcome of patients with cancer despite encouraging experimental data, is an example of this issue. Furthermore, while case studies can provide useful information (especially safety data), in general they have too many confounding variables that can provide alternative explanations for the observed results. For these reasons well reported case series, retrospective observational studies, prospective longitudinal studies, epidemiological studies or RCTs are the preferred level of evidence to support any particular intervention.

Hierarchy of Evidence

1. Meta analysis of observational and/or RCTs.
2. Prospective RCTs and/or observational studies.
3. Epidemiological data demonstrating that the agent reduces the risk of cancer and/or improves survival in those with cancer.
4. Case series (≥ 3 cases).
5. Individual case reports (at least 2).
6. In vivo model demonstrating favorable effect on tumor microenvironment.
7. In vivo/in vitro model demonstrating synergistic/additive cancer cell killing in presence of cancer chemotherapeutic agent(s).
8. In vivo model demonstrating killing of tumor cells and/or CSCs.
9. In vitro model (cell culture) demonstrating killing of cancer cells.

APPENDIX 2. Other potential agents with limited evidence of anti-cancer activity

These listed drugs/nutraceuticals/botanicals* have in vitro and/or in vivo, and in some cases limited human data demonstrating anti-cancer activity. This list is adapted from the ReDO database. (5)

In order for a "medication" to be recommended for clinical use it requires *in vitro* data demonstrating that the compound kills cancer cells (apoptosis) and that this killing is enhanced in the presence of chemotherapeutic drugs, that the agent kills/inhibits CSCs, that the compound kills cancer cells in animal models (in vivo) and that in these models the agent favorably alters the tumor microenvironment. Furthermore, to be recommended in humans there needs to be *sufficient scientific evidence* that the agent is both "safe and effective". This *does not* require the "gold standard" RCT, but *sufficient and reproducible* data from case reports, case series, and observational studies. This is an evolving process and when sufficient evidence accumulates the medication can then be included in the list of recommended agents.

It should be noted that while "anecdotes" are important in the totality of evidence, anecdotes do not represent objective scientific evidence and are not listed in Chapter 7 and 8. If a practitioner claims to have *"cured hundreds of patients*" with a particular intervention, it should be relatively simple to publish this data in a peer-reviewed medical journal.

Acetaminophen
Allopurinol
Alpha-Lipoic Acid
Allium Sativum (Garlic)
Aminophylline
Amiodarone
Annona muricata (soursop, graviola or guanabana)
Aprotinin
Atovaquone
Atrial Natriuretic Peptide
Azithromycin
Bosentan
Bromocriptine
Caffeine
Carvedilol
Chloroquine
Clarithromycin
Clopidogrel
Cyproheptadine
Dapagliflozin
Deferoxamine
Digoxin
Enalapril

Enoxaparin
Esomeprazole
Famotidine
Fenofibrate
Finasteride
Gallic Acid (tea other plants)
Ganciclovir
Hydroxychloroquine
Imipramine
Irbesartan
Ketoconazole
Levofloxacin
Licorice root
Loratadine
Losartan
Meclizine
Metoclopramide
Miconazole
Nicardipine
Nifedipine
Nitroglycerine
Omeprazole
Pentoxifylline
Phenytoin
Propranolol
Propolis (*honeybee extract)*
Pyridoxine (Vitamin B6)
Spironolactone
Sulfasalazine
Valproic Acid

* Nutraceuticals/Botanicals indicated by *italics.*

APPENDIX 3. Footnote for Figure 10

Cell Cycle. p21: Protein 21, p16: Protein 16, p53: Protein 53, EZH2: Enhancer of Zeste Homolog 2, Cyclin A: Cyclin A, Cyclin B1: Cyclin B1, Cyclin D1: Cyclin D1, Cyclin E: Cyclin. **Apoptosis.** Cleaved caspase-3, 7, 9: Cleaved caspase-3, 7, 9, Cleaved PARP: Cleaved Poly (ADP-ribose) polymerase, Caspase 3: Caspase-3, miR-15a: microRNA-15a, miR-16: microRNA-16, TAZ: Transcriptional coactivator with PDZ-binding motif, YAP: Yes-associated protein, EZH2: Enhancer of Zeste Homolog 2. **Transcription Factors.** ERE: Estrogen Response Element, PPAR-gamma: Peroxisome Proliferator-Activated Receptor Gamma, Nrf-2: Nuclear factor erythroid 2-related factor 2, p21: Protein 21, p53: Protein 53, FOX03: Forkhead box O3, Beta-catenin: Beta-catenin, STAT-1: Signal Transducer and Activator of Transcription 1, STAT-3: Signal Transducer and Activator of Transcription 3, STATE-4: Signal Transducer and Activator of Transcription 4, STAT-4: Signal Transducer and Activator of Transcription 4, CREB-BP: cAMP Response Element-Binding Protein Binding Protein, AP-1: Activator Protein 1, Notch-1: Notch receptor 1, HIF-1: Hypoxia-Inducible Factor 1. **Signaling Pathways.** AKT: Protein Kinase B (also known as Akt), AXL: AXL Receptor Tyrosine Kinase, Beta-catenin: Beta-catenin, Slug: Snail Family Transcriptional Repressor 2, Vimentin: Vimentin (an intermediate filament protein), STAT3: Signal Transducer and Activator of Transcription 3, NF-kB: Nuclear Factor-kappa B, **Receptors.** DR-5: Death Receptor 5, Fas-L: Fas Ligand, IR: Insulin Receptor, Fas: Fas Receptor, R: Receptor, H2R: Histamine H2 Receptor, HER-2: Human Epidermal Growth Factor Receptor 2, IL-8: Interleukin-8, CXCR4: C-X-C chemokine receptor type 4, AHR: Aryl Hydrocarbon Receptor, AR: Androgen Receptor, ER-alpha: Estrogen Receptor-alpha, EGFR: Epidermal Growth Factor Receptor, EPCR: Endothelial Protein C Receptor. **Growth Factors.** DR-5: Death Receptor 5, Fas-L: Fas Ligand, CTGF: Connective Tissue Growth Factor, FGF: Fibroblast Growth Factor, HGF: Hepatocyte Growth Factor, TF: Transcription Factor, NGF: Nerve Growth Factor, EGF: Epidermal Growth Factor, PDGF: Platelet-Derived Growth Factor, TGF-Beta 1: Transforming Growth Factor-Beta 1, VEGF: Vascular Endothelial Growth Factor. **Protein Kinases.** JNK: c-Jun N-terminal Kinase, AMPK: AMP-activated Protein Kinase, ASK1: Apoptosis Signal-regulating Kinase 1, FAK: Focal Adhesion Kinase, EGFR-K: Epidermal Growth Factor Receptor-Kinase, Pp60C-tk: Protein Tyrosine Kinase p60c-src, JAK2: Janus Kinase 2, PI3K: Phosphoinositide 3-Kinase, PGK1: Phosphoglycerate Kinase 1, PAK: p21-Activated Kinase, PKA: Protein Kinase A, PKB: Protein Kinase B (Akt), PTK: Protein Tyrosine Kinase, MAPK: Mitogen-Activated Protein Kinase. **Enzymes.** Telomerase: Telomerase, Desaturase: Desaturase, GCL: Glutamate-Cysteine Ligase, MMP: Matrix Metalloproteinase, GICL: Glutathione Induced Cancer-like Protein, iNOS: Inducible Nitric Oxide Synthase, NQO-1: NAD(P)H Quinone Dehydrogenase 1, FPT: Farnesyl Protein Transferase, Src-2: Steroid Receptor Coactivator 2, DNA pol: DNA Polymerase, TMMP-3: Tissue Matrix Metalloproteinase-3, GST: Glutathione S-transferase, ODC: Ornithine Decarboxylase, PhP: Phosphohexose Isomerase, D: D-aminopeptidase, 5-LOX: 5-Lipoxygenase, COX-2: Cyclooxygenase-2, ATPase: Adenosine Triphosphatase, ATFase: Adenosine Triphosphatase (ATPase) Activator, AATF-1: Apoptosis Antagonizing Transcription Factor 1. **Inflammatory Cytokines.** IL-1: Interleukin-1, IL-2: Interleukin-2, IL-6: Interleukin-6, IL-8: Interleukin-8, IL-12: Interleukin-12, IL-18: Interleukin-18, MCP: Monocyte Chemoattractant Protein, MIP: Macrophage Inflammatory Protein, MaIP: Macrophage-activating Inflammatory Protein, TNF-alpha: Tumor Necrosis Factor-alpha. **Endoplasmic Reticulum Stress Markers.** XBP-1: X-Box

Binding Protein 1, IRE1: Inositol-Requiring Enzyme 1, GADD153: Growth Arrest and DNA Damage-Inducible Protein 153, CHOP: C/EBP Homologous Protein, ATF6: Activating, Transcription Factor 6, GRP78: Glucose-Regulated Protein 78. **Adhesion Molecules.** ICAM-1: Intercellular Adhesion Molecule-1, VCAM-1: Vascular Cell Adhesion Molecule-1, ELAM-1: Endothelial Leukocyte Adhesion Molecule-1.

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