MHR

A. G. PAYNE [2005] MED HYPOTHESES RES 2: 553-565.

PREVENTING METASTASIS AND ACHIEVING ONCOLYSIS IN SOLID TUMORS BY INHIBITING SPECIFIC METALLOPROTEINASES AND MANIPULATING KEY METABOLIC PATHWAYS

ANTHONY G. PAYNE*

STEENBLOCK RESEARCH INSTITUTE, 1064 CALLE NEGOCIO, SAN CLEMENTE, CA 92673, USA.

REVIEW ◊ HYPOTHESIS

ABSTRACT. APPROXIMATELY 50% of solid tumors bear mutations to the p53 gene and typically contain hypoxic microclusters. By artfully manipulating key metabolic anaerobic biochemical pathways, it should be possible to increase lactate and block its excretion, resulting in lethal reductions in intracellular pH. Compounds are advanced for accomplishing this as well as helping eradicate non-hypoxic regions of tumors, based on predecessor methods which results in long term remissions in persons with a host of solid tumor malignancies. A number of measures are also introduced for inducing oncostasis and preventing metastasis. Any remaining tumor mass can be treated using whatever standard chemotherapeutic, radiotherapeutic, surgical or immunologic interventions or combinations thereof are deemed most likely to result in oncolysis.

*ADDRESS ALL CORRESPONDENCE TO: DR. ANTHONY G. PAYNE, STEENBLOCK RESEARCH INSTITUTE, 1064 CALLE NEGOCIO #B, SAN CLEMENTE, CA 92673 USA.
PHONE: 949-248-7034; FAX: 949-388-3441. E-MAIL: DrAGPayne@yahoo.com

• MEDICAL HYPOTHESES AND RESEARCH • THE JOURNAL FOR INNOVATIVE IDEAS IN BIOMEDICAL RESEARCH •

1. INTRODUCTION

The hypothesis outlined in this paper is based on an approach to achieving lysis in solid tumors pioneered by Dr. Clarence Cone, Jr. (NASA, retired). Dr. Cone's novel therapy, which is reflected in patents granted various versions of same [U.S. patents, No. 4,724,230 (1988), 4,724,234 (1988), and 4,935,450 (1990)], essentially involves manipulating various metabolic and biochemical pathways such that tumors should produce prodigious quantities of lactic acid.

The principle shortcoming of the Cone therapy lies in the fact that it is hypoxic clusters within certain solid tumors—and not the entire tumor—which synthesizes and exports lactic acid (Something which came to light after Dr. Cone's original patent application was filed). The Cone therapy is thus very appropriate and quite effective in helping eradicate hypoxic intratumor cell communities. It does not, however, address the lysis of the non-hypoxic regions of solid tumors per se.

This paper contains the framework for an approach to achieving oncolysis that is a marriage of Cone's basic hypoxic tumor cell lysing technique with others geared to deal a lethal blow to both hypoxic and non-hypoxic tumor cells, as well as preventing metastasis. It also incorporates compounds and therapeutic techniques which complement Cone's approach (Most of which were not available and/or widely used when Dr. Cone filed for his patents).

2. A METABOLIC ONCOLOGY APPROACH TO ACHIEVING LYSIS IN SOLID TUMORS

Fifty percent (50%) or more of solid tumors are characterized by specific genetic and extragenetic (intracellular) features that create a therapeutic "window of opportunity" for effecting oncolysis via the manipulation of various metabolic pathways. A brief review of certain aspects of tumor cell biology is needed to demonstrate this:

One of the key players in the genesis of solid tumors is the p53. In normal cells the p53 gene complex is not active. However, when cells incur damage by way of exposure to ionizing radiation, toxic agents, etc., the p53 genes switch on and begin synthesizing a protein which typically arrests cell growth (thus allowing time for DNA repair) or activates apoptosis. When mutations occur in either the maternal or paternal copy of the p53 gene in a tumor cell—but not both—the cell will produce the p53 protein and, in the increasingly hypoxic environment that accompanies tumor growth, undergoes apoptosis. In essence, the oxygen deficit encourages tumor cell lysis. Unfortunately, tumors circumvent this effect by neovascularization activities which provide needed oxygen and nutrients. These vessels are usually very leaky such that blood plasma readily infiltrates intracellular spaces. This process generates intratumor pressures that impede blood flow and thereby reestablishes an oxygen deficit.

This picture is complicated by the tendency of tumors to give rise to cells which possess mutations to both maternal and paternal copies of the p53 gene. These cells do not produce the p53 protein and thus multiply unchecked. They are typically the most aggressive and drug-resistant cells in a tumor, and tend to thrive in the most hypoxic regions of solid tumors. (NOTE: Those cells able to produce p53 protein die off in the hypoxic intratumor microenvironment. Those lacking functional p53 genes proliferate and thus give rise to clusters of like cells within the tumor).

Given this profile, it follows that the most effective therapeutic approach would be to encourage tumor microenvironment hypoxia via interference with angiogenesis (neovascularization). This will facilitate the lysis of tumor cells that synthesis viable p53 protein.

But what about those tumor cells that do not produce p53 protein? Would not encouraging intratumor hypoxia select for especially aggressive tumor cells? It will indeed. Actually, it adds nothing new to the clinical picture as this selection process is well under way early on in tumorigenesis. As we cannot presently circumvent this process, the principle objective becomes one of

introducing therapeutic agents and metabolic challenges that have a selective and lethal effect on hypoxic cells.

As the suppression of the neovascularization or angiogenesis mechanism can be effected in a rather straightforward manner via the introduction of antiangiogenic drugs or natural compounds, e.g. thalidomide, etc., the focus will primarily be on the metabolic processes unique to tumor cells in the grip of profound hypoxia (and how we can effectively exploit same). Measures to encourage oncostasis and thus retard or halt metastasis will also be included.

3. THE HYPOXIC CELLS' DEPENDENCE ON ANAEROBIC PROCESSES

Tumor cells that lack sufficient oxygen to engage aerobic metabolic pathways typically begin to rely on anaerobic ones to supply needed substrate. These cells convert most of their pyruvate to lactate (and not acetyl Coenzyme A [AcCoA]), which is then excreted [1-3]. This cellular aberration has several consequences: Only a small percentage (5-6%) of the chemical energy in glucose molecules can be liberated and utilized (Glucose is totally oxidized in normal cells) [4]. As a result, the rate at which tumor cells can generate ATP from glucose via the respiratory chain and citric acid cycle is limited. To prevent cell lysis due to energy deprivation, malignant cells begin to rely on the mitochondrial β-oxidation of fatty acids to AcCoA (which can then enter the citric acid cycle) and on the enzymatic transformation of amino acids into metabolically useful compounds [5].

The reliance of hypoxic tumor cells on this "alternative" metabolic pathway can be exploited along these lines:

- The oxidative catabolism of free fatty acids and amino acids (via the respiratory chain and citric acid cycle) might be inhibited in hypoxic cancer cells via the judicious use of agents which inhibit their availability, i.e., partially inhibit hepatic fatty acid synthesis and keep plasma amino acid levels within the normal range, thus decreasing ATP production;
- The ATP that is produced could be rapidly depleted by the use of compounds that stimulate ATPase activity.

Their net effect should be rather straightforward:

Hypoxic tumor cells will compensate for this compromised metabolic state of affairs by increasing the rate of intracellular glycolysis. This, too, can be exploited by the introduction of substances that interfere with the shuttling of lactate out of the tumor cell. This will cause a drop in the intracellular pH level that will undermine vital cancer cell metabolic processes [6]. Tumor cell lysis is anticipated. What is needed then are therapeutic agents and dietary measures that will:

- Limit the hepatic synthesis of free fatty acids plus inhibit lipolysis elsewhere in the cancer patient's body.
- Keep plasma amino acid levels within the range required to sustain general health (normal cells will rapidly utilize the amino acids liberated by the catabolism of foods. Excess amino acids—typically the end result of metabolic processes stimulated by the stress-induced release of adrenal hormones—will be available for use by cancer cells).
- Interfere with the transport of lactate out of the hypoxic tumor cells.
- Provide sufficient nourishment and caloric intake to meet the metabolic requirements of normal cells without supplying excess fats or protein that will be used to meet the metabolic needs of tumor cells.

The following are compounds that will help achieve the objectives delineated above for the p53 protein-producing tumor cells, as well as those which do not synthesis the protein.

3.1. LIMONENE

The 10-carbon compound limonene has been shown to inhibit the synthesis of ubiquinone (coenzyme Q10) in tumor cell mitochondria, thereby reducing the amount of chemical energy produced

to meet metabolic needs [7]. It also blocks protein prenylation, a process crucial to the synthesis of proteins involved in regulating cell growth and cycling. Lavender (Lavendula) oil is rich in limonene.

3.2. L-HYDROXYCITRATE

This compound inhibits ATP citrate lyase, i.e., the cytoplasmic enzyme that cleaves citrate to produce AcCoA and oxalo-acetate [8]. Numerous animal studies have shown that L-hydroxycitrate depresses in vivo lipogenesis in a dose-dependent manner in the liver, adipose tissues, and small intestine [9]. This therapeutic activity is of immense clinical value, as tumors release or bring about the release of lipolytic agents which free up fatty acids for the synthesis of new tumor cells [10].

It should be noted that L-hydroxycitrate, in both animal and human trials, has demonstrated a mild anorexiant effect which might limit its use in patients with tumor-induced anorexia and cachexia. Conversely, many recent studies indicate that L-hydroxycitrate may not exert any appreciable weight-reducing effects. In fact, in one study L-hydroxycitrate failed to induce significant weight loss in normal subjects [11]. Even if L-Hydroxycitrate attenuates appetite, this effect should be offset by the administration of exogenous thyroid hormone (thyroid is an integral part of the oncolytic regimen proposed herein).

Interestingly, the cachexia commonly associated with malignancy should in many ways be addressed by the approach proposed in this paper. In animal studies, insulin has been found to drop during certain stages of tumor formation. The use of exogenous insulin is thus advocated (see below). This insures glucose availability to normal cells, as well as increasing cell membrane permeability, which may potentiate the cytotoxicity of various agents used in this experimental program. Glucose, of course, is often converted to fat before being utilized, something L-hydroxycitrate will help circumvent by virtue of its ability to at least partially inhibit the conversion of glucose and other sugars derived from dietary carbohydrates to lipids. The remaining glucose will be available to provide energy for normal cells, as well as substrate the hypoxic tumor cells will turn into lactate (the lactate, in turn, will be at least partially blocked from being shuttled out of the tumor cells by quercetin chalcone [see below]); while most hepatic glucose processing "plugs into" the Cori Cycle, i.e., glucose from the liver is transported to the muscles where it is converted into pyruvate and back to glucose (then to lactate—which circulates back to the liver and is converted into pyruvate, then glucose—which leaves the liver and travels back to active muscles, etc.) The approach suggested in this paper should appreciably interfere with lactate transport out of not only hypoxic tumor cells, but active muscle tissue as well, thus "throwing a monkey wrench" into the Cori Cycle.

3.3. MELATONIN

The pineal-synthesized hormone melatonin is a fatty acid transport inhibitor [12]. Depriving tumor cells of metabolically useful fatty acids is an important player in compromising tumor cell viability.

3.4. CONCENTRATED GARLIC OR INSULIN

Concentrated garlic extract or preferably exogenously supplied insulin (Isophane—slow release) will elevate the level of circulating (free) insulin in cancer patients [13]. This is desirable, as insulin has a pronounced anti-lipolytic effect [14]. It also is increases cell permeability thus making it easier for chemotherapeutic drugs to have a lethal effect on tumor cells. The physicians who pioneered Insulin Potentiation Therapy (Donato Perez Garcia , M.D. , his son Donato Perez Garcia y Bellon, M.D., and grandson Donato Perez Garcia, M.D.) have reported that the doses of conventional cytotoxic and other antitumor drugs employed to lyse cancer cells is reduced by manyfold. Refer to:

http://www.iptq.com/

3.5. THYROID

Exogenous thyroid hormone should contribute to the achieve of desired (oncolytic) objectives by:

(i) increasing hepatic removal and degradation of cortisol, which brings about plasma reductions of same; and (ii) stimulating ATPase activity (so as to "waste" ATP).

The lipolytic activity of thyroid hormone should be offset by the anti-lipolytic effects of insulin and prostaglandin E_1.

It should be noted that the diet approach below (see Dietary Guidelines) closely mirrors the paleo-diet (Stone Age Diet), which has been found to boost thyroid levels in one published study (University Of Illinois At Urbana-Champaign is the original source):

http://www.sciencedaily.com/releases/2001/04/010404080611.htm

3.6. QUERCETIN CHALCONE

This bioflavinoid interferes with intracellular mechanisms that transport lactate out of cancer cells dependent on anaerobic metabolic processes (Its interaction with the calcium regulatory protein calmodulin appears to have an added antitumor effect [15]). When lactate shuttling is compromised intracellular pH falls resulting in apoptosis.

The apoptosis-inducing effect of an acidic pH has support from a study showing that alkalinization of lovastatin-treated tumor cells abolished the cytotoxicity of the drug [16]. Lovastatin's cyctotoxicity is linked primarily to its ability to create an acidic intracellular pH. The acidic pH induces the activation of a pH-dependent endonuclease which causes DNA fragmentation. It has been demonstrated that this particular enzyme can be rapidly inactivated by the stimulation of the Na/H antiporter, an acid exporter, with phorbol ester. This strongly implicates an acidic pH and pH-dependent endonuclease in effecting cell lysis.

Accordingly, it seems likely that quercetin-induced lactic acidosis in (glycolytic) tumor cells may bring about pH-endonuclease activity that leads to tumor cell die off.

NOTE: Quercetin has been shown to have cytotoxic effects via such mechanisms as: (a) Arrest of cell progression at the G_1/S interphase (two studies indicate blockage at the G_2/M interphase); (b) suppression of glycolysis and ATP production; (c) interference with ion pump systems; (d) interference with various signal transduction pathways (Protein kinase C, casein kinase II, etc.); and (e) inhibits DNA polymerase B and I [17]. (Quercitin is also an effective 5-lipoxygenase inhibitor. Published studies indicate that arachidonic acid stimulates the growth of several types of cancer viz-a-viz being metabolized through the 5-lipoxygenase pathway into 5-HETE series of eicosataenoids [18]).

Quercetin is poorly absorbed in the human gut, while the water-soluble quercetin analogue quercetin chalcone is better absorbed. For this reason, quercetin chalcone is recommended.

3.7. ESSENTIAL FATTY ACIDS

In patients whose dietary omega 3 intake is low (more below under Fats), supplementation with a source of essential fatty acids is proposed. This supplementation, in the context of this cancer treatment approach, should: (a) Help provide modest levels of those fatty acids required to maintain general health and; (b) serve as a substrate for the synthesis of various prostaglandins—PGE_1 being of immense value because it inhibits lipolysis [19]. The emphasis here would be on a high omega-3 to omega-6 fatty acids intake. The rationale? Archidonate lipoxygenase (LOX) and their metabolites appear to play an integral role in mediating growth factors which support tumor cell proliferation and growth. The LOX pathway may also be a vital component in the regulation of tumor cell survival and apoptosis [20].

4. INHIBITING ANGIOGENESIS AND MATRIX METALLOPROTEINASES ASSOCIATED WITH METASTASIS

Matrix metalloproteinases (MMPs) are zinc proteinases that degrade macromolecules which make up the extracellular matrix. These enzymes appear to play a role in tumor invasion and metastasis through degrading many extracellular

matrix proteins. MMP-2 and MMP-9 are capable of degrading type-IV collagen, which is a major component of basement membrane and are considered preeminent biomarkers of tumor invasion and metastasis [21-22].

A number of natural and pharmaceutical compounds have been found to inhibit metalloproteinases—especially MMP-9. Among them: a combination of lysine, proline, arginine, green tea extract, and ascorbic acid; grape seed extract; N-acetyl-cysteine; and tumeric extract [23-31].

Proenzyme therapy has also been found to exert a powerful antimetastatic effect on tumors in vitro and in vivo [32].

In addition, there at least a few drugs available that exert antiangiogenic properties such as thalidomide and pegaptanib sodium (Macugen). Many others are undergoing testing in clinical trials or are otherwise being eavluated. Among these are: Interleukin-12, pentosan polysulfate, platelet factor 4, TNP, angiostatin and endostatin, lucentis, tryptophanyl-tRNA synthetase (TrpRS), evizon (squalamine lactate), retaane 15 mg (anecortave acetate with depot suspension), combretastatin A4 Prodrug (CA4P), VEGF-TRAP, AdPEDF, AG-013958, avastin (bevacizumab), and JSM6427. Also, tetrathiomolybdate (TM), a pharmaceutical employed to lower serum and tissue copper levels in persons suffering from Wilson's disease, has shown promise in retarding angiogenesis in Phase I clinical trials involving patients with metastatic cancer [33].

Also, garlic raises endogenous nitric oxide levels, which has an antiangiogenic effect. Published research indicates that garlic boosts the activity of NO synthase, but not owed to its high content of arginine or to the phytochemical allicin [34,35].

5. CALMATIVES AND AUTO-SUGGESTION, COGNITIVE THERAPY, BIOFEEDBACK OR OTHER STRESS-ATTENUATING MEASURES

Cancer patients typically present with substantially elevated serum free fatty acid and amino acid levels. This is due, in part, to cancer treatment (and response) related fears and anxiety. These powerful emotions trigger adrenal hormone release—the physiological effects of which include activation of adipocyte lipase resulting in mobilization of free fatty acids and partial inhibition of protein synthesis, i.e., the plasma amino acids which are normally (readily) utilized by nonmalignant cells for protein synthesis are only partially used resulting in an increase in the availability of amino acids to meet tumor cell metabolic needs.

It is vitally important in the context of this approach to provide the cancer patient with anxiolytic phytomedicines or pharmaceuticals plus supportive psychological therapy (or biofeedback) to minimize fear and anxiety-related stress (or provide a referral to a qualified psychologist, psychiatrist, or other health care professional who can design a comprehensive stress management program). Stress can also be attenuated by sexual release in patients interested in and capable of engaging in same. There is also possible therapeutic merit in the use of certain botanic agents, such as extracts of Gotu Kola (Centella asiatica), Kava Kava Root (Piper methysticum), Valerian Root (Valeriana officinalis) or Passion Flower (Passiflora incarnata). These botanicals have demonstrated tranquilizing properties in animal and human trials).

One of the more potent natural anxiolytic/calmative formulas appears to be the Traditional Chinese drug called the Zizyphus Combination (Suan-Tsao-Jen-Tang). In a comparative double-blind study, the Zizyphus Combination (250 mg, t.i.d. per os) was fully comparable to that of diazepam (2 mg, t.i.d., per os). There was one crucial difference between the two: When taken at bedtime, the Zizyphus Combination did not leave patients drowsy or otherwise impaired upon rising [36].

6. DIETARY MEASURES

6.1. PROTEIN

Thirty-five percent of caloric intake should be in the form of protein (emphasis on non-plant protein sources. This should be sufficient to maintain

nitrogen balance). Protein with a high "biologic value", i.e., a mix of all the essential amino acids plus a high proportion of omega 3 fatty acids would be the logical choice. Ideally, a 4:1 ratio of omega 3 to omega 6 fatty acids intake is advised.

6.2. CARBOHYDRATES

Approximately 35% of caloric intake would need to come from complex carbohydrates. However, beans, bread, potatoes, and all grains should be eaten rarely, if at all. These foods were introduced only recently (neolithic period) and the emerging consensus among many experts in evolutionary nutrition is that our bodies do not benefit (in the long run) from reliance of such foods. Grains and cereals contain phytates that bind various minerals and also generate opioid compounds (exorphins) that appear to exacerbate inflammatory processes, especially in the CNS.

Raw and steamed vegetables and fruits should comprise the bulk of carbohydrate intake.

6.3. FATS

Dietary and supplemental forms of fat should provide 20–30% of (daily) calories. Example: A 70 kg. man will require approximately 2,000 calories/day–400 calories (44 grams, 20% level) of which should come from fats (primarily omega-3 rich fatty acid sources/supplement).

The diet should include plenty of potassium-rich foods. High magnesium foods and drinking water would be eschewed. The rationale is simple: Increases in potassium ion concentration stimulate the secretion of insulin (desirable in terms of treatment objectives), while high levels of magnesium appear to be inhibitory [37].

7. LOW-DOSE GAMMA-RADIATION USED IN TANDEM WITH LIPOXYGENASE INHIBITORS

Low dose radiotherapy (in tumors types with a demonstrated susceptibility to same) coupled with the use of lipoxygenase inhibiting pharmaceuticals or natural substances are a logical adjunct to the approach outlined in this paper. This combination is suggested by in vitro research carried out at the Institute of Biophysics in Czechoslovakia (Academy of Sciences of the Czech Republic). Researchers at the Institute found that when human carcinoma HS578T and monoblastoid U937 cell lines were treated with the lipoxygenase inhibitors norhydroguaiaretic (NDGA) and escultein—then exposed to low dose gamma radiation (1GY)—[^{3}H]thymidine incorporation and cell proliferation was suppressed (NOTE: Quercitin compromises lipoxygenase activities both in vitro and in vivo. The cyclooxygenase inhibitor piroxicam had no effect [38]).

When German scientists treated mice with Lewis cell lung cancer with various combinations of i.p. administered collagenase, cyclooxygenase, and lipoxygenase inhibitors plus radiation, they found that the most effective modulation of tumor growth (2.8–3.3 fold increase in tumor growth delay) was seen in animals treated with a combination of moncycline (a collagenase inhibitor)/suldinac (a cyclooxygenase inhibitor) plus radiation and phenidone (a lipoxygenase inhibitor)/suldinac plus radiation [39,40].

8. NDGA (NORDIHYDROGUARIARETIC ACID): A GENERAL LIPOXYGENASE INHIBITOR AND ATP DEPLETING AGENT

NDGA, a chemical compound present in the botanical larrea tridentata (chaparral)—once widely used in various folk treatments for cancer—has shown efficacy in inducing tumor cell lysis in numerous in vitro studies. In one laboratory experiment, NDGA and a 12-LOX selective inhibitor brought about rapid and dose-dependent apoptosis of serum cultured W256 cells (as well as other tumor cell lines including leukemia) [41]. In another study, NDGA inhibited an ATP sensitive osmolyte channel in hepatoma cell line $HepG_2$ by virtue of its ability to deplete ATP [42]. These properties make NDGA a compound worth further investigation, especially in terms of its efficacy when used in tandem with the oncolytic and anti-

metastatic treatment approaches found herein.

Larrea tridentatais is not suitable because of its demonstrated hepatotoxicity, i.e., during 1992–1994 eighteen cases of hepatoxicity were reported to the F.D.A. involving chaparral ingestion (thirteen cases did show clear evidence of liver toxicity including cholestatic hepatitis (4 persons) with progression to cirrhosis. Two of the thirteen patients developed fulminant liver failure which required liver transplantation [43]). However, there is a patented nontoxic extract of Larrea tridentata which is available on the market (U.S. Patent, No. 6,039,955, March 21, 2000). This compound would be entirely appropriate for use as part of the proposed treatment scheme.

The use of lipoxygenase inhibitors and low dose radiation is a relatively new area of medical research and to-date has primarily involved cell cultures. However, the rationale for employing both (where appropriate) is scientifically credible and consonant with extant knowledge of tumor cell biology. As radiotherapy is used quite effectively in the management and even eradication of some solid tumors, the use of a lipoxygenase inhibitor in tandem with this is certainly suggested.

9. HYPERTHERMIA: A USEFUL THERAPEUTIC ADJUNCT

Hyperthermia lowers tissue pH and thus should adroitly complement the treatment approach outlined in this paper (especially in cases involving relatively superficial solid tumors). Interestingly, quercetin is a hyperthermic sensitizer by virtue of its ability to block lactic acid transport and heat protein synthesis. Normally tumors develop thermoresistance via the production of heat shock protein. Quercetin helps circumvent this process and thus leave the tumor susceptible to hyperthermia therapy [In cervical carcinoma cells, quercetin did not exert cytotoxic effects at normal body temperatures, but did potentiate hyperthermia-induced toxicity at 41 degrees Centigrade (105.8 degrees Fahrenheit) [44]. If local or regional heating of a tumor is not feasible owed to disseminated malignancy, whole body hyperthermia can be induced. One method which has demonstrated efficacy in a randomized double blind trial at Memorial Sloan Kettering is Mixed Bacterial Vaccine (Coley's) [45]. Another is to employ a whole body hyperthermia unit such as is being utilized at the Center for Hyperthermia Cancer Treatment at Memorial Hermann Hospital, through the University of Texas Medical School at Houston:

http://www.uth.tmc.edu/thermaltherapy/Clinic.html.

10. TWO NOVEL THEORETICAL METHODS OF INDUCING INTRATUMOR HYPERTHERMIA

The following are two admittedly very theoretical approaches to inducing intratumor hyperthermia sufficient to affect tumor cell lysis.

10.1. FERRITIN-MEDIATED ELECTROMAGNETIC HYPERTHERMIA

In a paper published in the journal Medical Hypotheses [46], the authors suggest that an alternating magnetic field no greater than ~100 kHz (kilohertz) should induce heating of intracellular ferritin sufficient to lyse tumor cells without adversely effecting normal tissues and cells. The iron core in ferritin is strongly paramagnetic and thus can be utilized to produce heat via the Brown and Neel effects, respectively. Since ferritin is often found at higher levels in neoplastic cells than normal ones, this makes achieving hyperthermia by way of an externally applied high frequency magnetic field very probable.

Japanese, German, and other researchers have published many papers indicating that intracellular hyperthermia sufficient to achieve cell lysis is possible employing magnetite cationic liposomes and other 'magnetic fluids.' [47,48]. The ferritin mediated approach, while different from the aforementioned, retains many features in common and should be explored in the laboratory and in well controlled clinical trials.

This method of inducing intracellular hyperthermia is explored in a paper by the author titled

"Exploiting intracellular iron and iron-rich compounds to affect tumor cell lysis" [49].

One permutation to this approach that might prove of utility: Introduce magnetotactic bacterial vectors in vivo which have been genetically engineered or artificially selected to seek out and bind to specific tumor cell antigens. If achievable, the magnetotactic bacteria might provide sufficient iron once inside tumor cells to make achieving eletromagnetic heating more certain.

NOTE: Interestingly, there is published animal studies indicating that hyperthermia used in tandem with glucose administration enhances the tumor lysing impact of the former [50,51]. As the treatment approach outlined in this paper is geared, in part, to boost intratumor glucose levels (thus raising the rate of lactate synthesis), the use of it in combination with hyperthermia is logically compelling.

It should be noted that researchers at Jefferson Medical College found that i.v. and i.v. plus oral glucose effectively lowered tumor extracellular pH in 17 non-diabetic cancer patients at Henan Tumor Hospital. These scientists were looking into boosting tumor acidification as a potential thermoradiosensitizer [52].

10.2. IRON AND COBALT PHTHALOCYANINES MIGHT BE EXPLOITED TO ACHIEVE SUFFICIENT INTRACELLULAR HYPERTHERMIA TO LYSE TUMOR CELLS

The phthalocyanines are being employed in photodynamic oncolytic therapy (research) with varying degrees of success. Since these compounds are selectively retained by tumors, resist photochemical and chemical breakdown, are essentially non-toxic, and can be synthesized readily with a neutron-activated nuclide (boron compounds) and as conjugates with epidermal growth factor (thus making tumor cell targeting more contain), they are very attractive to cancer researchers [53].

Setting aside the photodynamic use aspect, there is the electromagnetic heating potential of the iron and cobalt-bearing phthalocyanines (PCs) to consider. As mentioned above, iron is very paramagnetic. Cobalt, while less responsive to a magnetic field than iron, might still be of merit in instances where use of iron might boost tumor growth in micrometasteses which are strongly suspected to exist but not confirmable using extant detection technology.

As a cautionary note, copper plays a role in angiogenesis and thus may be contraindicated save as a heroic measure, especially in patients on tetrathiomolybdate (TM).

11. CLINICAL EFFICACY – CONE METABOLIC METHOD

In his patent application, Dr. Clarence D. Cone, Jr., reported that partial to complete oncolysis was achieved in patients with a variety of cancers. Here is a sampling:

Female, age 52, tongue
Male, age 57, throat
Male, age 70, stomach
Female, age 47, cecum
Female, age 54, colon
Male, age 45, breast
Female, age 57, ovary
Female, age 60, uterus
Male, age 65, kidney
Male, age 59, prostate
Male, age 49, pancreas
Male, age 49, lymphoma
Male, age 47, melanoma
Female, age 48, basal cell (skin)
Male, age 66, leukemia
Male, age 50, bone sarcoma

11.1. SELECT CASE HISTORIES:

Male, age 57. Diagnosed with epidermoid carcinoma of the larynx, metastasized to the left neck. Confirmed by multiple biopsied specimens, CT scans and xerograms. No standard cancer treatments undertaken. By day 13 on the regimen the

tumor was reduced by 88%. After the resting interval and at the start of Phase II, the tumor grew back to 4 cms. By day 13 the tumor was non-palpable.

Male, age 59. Diagnosed with (moderately differentiated) Metastatic adenocarcinoma of the prostate. Confirmed by multiple biopsied specimens, cytoscopy and bone scans. Treated prior to undergoing the Cone regimen with laetrile, vitamin A, oral enzymes, hormone therapy, and surgery (TURP). By Day 22 of Phase I the patient was asymptomatic. At the start of Phase II the prostate was enlarged and very hard. By day fifteen the patient was in excellent condition and asymptomatic. Prostate size was reduced to normal.

11.2. TWO SELECT CASES OF PATIENTS WHO UNDERWENT TREATMENT USING MEASURES SUGGESTED IN THIS PAPER

Male, age 59. Diagnosed with squamous cell carcinoma (4 cm tumor – lower lobe – left lung). Metastases to the lymph nodes and mediastinum. Diagnosis confirmed by CT scan, biopsied specimens, and endoscopic examination of the tumor. Classified as inoperable and terminal, the patient elected to forego conventional treatment and undergo treatment using many of the major elements contained in this paper.

By the 26th day on the prescribed regimen, lymph nodes were no longer palpable and tumor in left lung was 95% obliterated. Patient achieved full remission and is now 11+ years post-diagnosis.

Female, age 38. Diagnosed with oral cancer (squamous cell) with metastases to the larynx and both lungs. Diagnosis confirmed by multiple biopsied specimens. Patient declined surgery, chemo- therapy and radiotherapy, as these offered little but hope of cure. After receiving material on the basic approach outlined in an earlier version of this paper, the patient chose to undergo same (Her oncologist agreed to supervise her treatment and monitor her progress or lack thereof). By the 43rd on the program, tumors at all cites were reduced an average of 78%. By day 91, no evidence of cancer could be detected by biopsy or CT scan. Patient has been in remission for 14+ years to date.

12. REVIEW

It is hypothesized that in solid tumors with hypoxic microclusters that rely on anaerobic metabolic pathways to thrive, the lactate generated by this reliance can be blocked from being excreted from the tumor cells thus lowering intracellular pH and inducing lysis. The remaining non-hypoxic tumor cells as well as surviving hypoxic aggregates would be exposed to compounds, drugs and dietary intervention aimed at depleting ATP and otherwise compromising vital metabolic activities, concomitant with measure aimed as suppressing angiogenesis and encouraging oncostasis.

The following is advanced to bring this about:

- Limonene or limonene-rich Lavendula oil
- L-hydroxycitrate
- Melatonin
- Insulin IM or concentrated garlic
- Thyroid hormone
- Quercitin chalcone

Metalloproteinase-9 (MMP-9) synthesis, which is crucial to tumor metastasis, would be retarded by use of:

A combination of L-lysine, L-proline, L-arginine, standardized green tea extract, ascorbic acid, grape seed extract, N-acetyl cysteine and tumeric extract.

High dose pancreatic enzymes may also be used, as they have been found to inhibit MMP-9.

Angiogenesis would be discouraged by use of drugs such as thalidomide or pegaptanib sodium (Macugen).

Stress-related elevations of free fatty acids and amino acids levels would be curtails by judicious use of calmatives, tranquilizers, Cognitive Therapy, suggestion and such.

The diet would be a fairly high protein one along the lines of the paleolithic diet or paleodiet.

This diet provides the right ratio of omega-3 to omega-6 fatty acids, potassium to sodium, plus abundant protein and complex carbohydrates for maintaining general health and encouraging sustained thyroid levels (a desired objective).

For patients undergoing radiotherapy, a lipoxygenase inhibitor such as non-toxic NDGA would be used. Various studies indicate that low dose radiation and lipoxygenase inhibitors are oncolytic.

Patients with tumors that can be readily treated using hyperthermia would receive thus, as hyperthermia lowers tissue pH (a desired objective).

13. CONCLUDING REMARKS

The oncolytic approach outlined in this paper is geared to produce oncostasis and oncolysis in solid tumors bearing hypoxic microclusters. Its design is based on the manipulation and adroit exploitation of biochemical processes and mechanisms in tumor cells. Its potential efficacy is suggested by case histories in which aggressive, advanced malignancies were treated using predecessor versions of this program and resulted in long-standing remissions.

It is anticipated that the core program and the permutations thereof such use in tandem with conventional chemotherapy and/or radiotherapy with LOX inhibitors and/or localized or whole body hyperthermia will produce significant tumor shrinkage and increases in survival. This is testable, of course. Patients with specific type and grade malignancies can be placed on the core program plus standard chemo- and/or radiotherapy and their survival and quality of life can be compared to matched patients who receive only the best standard therapeutic intervention available.

REFERENCES

[1] RACKER E AND SPECTOR M [1981] Warburg effect revisited: Merger of biochemistry and molecular biology. Science 213: 303-307.

[2] SPENCER TL AND LEHNINGER AL [1976] L-lactate transport in Ehrlich ascites-tumour cells. Biochem J 154: 405-414.

[3] BELT JA, THOMAS JA, BUCHSBAUM RN AND RACKER E [1979] Inhibition of lactate transport and glycolysis in Ehrlich ascites tumor cells by bioflavonoids. Biochem 18: 3506-3511.

[4] WHITE A, HANDLER P AND SMITH L [1973] Principles of Biochemistry, 5th edition, p. 441.

[5] MEDES G, THOMAS A AND WEINHOUSE S [1953] Metabol ism of neoplastic tissue. IV. A study of lipid synthesis in neoplastic tissue slices in vitro. Cancer Res 13: 27-29.

[6] SPENCER TL AND LEHNINGER AL [1976] L-lactate transport in Ehrlich ascites-tumour cells. Biochem J 154: 405-414.

[7] CROWELL PL [1999] Prevention and therapy of cancer bydietary monoterpenes. J Nutr 129: 775S-778S.

[8] WATSON JA, FANG M AND LOWENSTEIN JM [1969] Tricarballylate and hydroxycitrate: substrate and inhibitor of ATP: Citrate oxaloacetate lyase. Biol Biochem 135: 209-217.

[9] LOWENSTEIN JM [1971] Effect of (-)-hydroxycitrate on fatty acid synthesis by rat liver in vivo. J Biol Chem 246: 629-632.

[10] MCDEVITT TM, TODOROV PT, BECK SA, KHAN SH AND TISDALE MJ [1995] Purification and characterization of a lipid-mobilizing factor associated with cachexia-inducing tumors in mice and humans. Cancer Res 55: 1458-1463.

[11] MATTES RD AND BORMANN L [2000] Effects of (-)-hydroxycitric acid on appetitive variables. Physiol Behav 71: 87-94.

[12] SAUER LA, DAUCHY RT AND BLASK DE [1996] A novel mechanism for the regulation of tumor growth in vivo. Proc Amer Assoc Cancer Res 37: 224.

[13] BEVER BO AND ZAHAND GR [1979] Plants and Oral Hypoglycemic Action. Qtrly J Crude Drug Res 17: 139-196.

[14] HARPER HA [1973] Review of Physiological Chemistry, 14th edition, Lange Medical Publications, pp. 489.

[15] NISHINO H, NAITOH E, IWASHIMA A AND UMEZAWA K [1984] Quercetin interacts with calmodulin, a calcium regulatory protein. Experimentia 40: 184-185.

[16] PEREZ-SALA D, CALLADO-ESCOBAR D AND MOLLINEDO F [1995] Intracellular akalinization suppresses lovastatin-induced apoptosis in HL-60 cells through activation of a pH-dependent endonuclease. J Biol Chem 270: 6235-6242.

[17] OHO K AND NAKANE H [1990] Mechanisms of inhibition of various cellular DNA and RNA polymerases by several flavinoids. J Biochem 108: 609-661.

[18] GHOSH J AND MEYERS CE [1997] Arachiponic acid stimulates prostate cancer cell growth: Critical role of 5-lipoxygenase. Biochem Biophys Res Commun H235: 418-423.

[19] HARPER HA [1973] Review of Physiological Chemistry, pg.288.

[20] — [1994] Angiogenesis and its inhibitors. Cancer Watch 3: 169.

[21] PATEL BP, SHAH PM, RAWAL UM, DESAI AA, SHAH SV, RAWAL RM AND PATEL PS [2005] Activation of MMP-2nd MMP-9 in patients. J Surg Oncol 90: 81-88.

[22] LIOTTA LA, STEEG PS AND STETLER-STEVENSON WG [1991] Cancer metastasis and angiogenesis:an imbalance of positive and negative regulation. Cell 64: 327-336.

[23] ROOMI MW, IVANOV V, KALINOVSKY T, NIEDZWIECKI A AND RATH M [2005] In vitro and in vivo antitumorigenic activity of a mixture of lysine, proline, ascorbic acid, and green tea extract on human breast cancer lines MDA-MB-231 and MCF-7. Med Oncol 22: 129-138.

[24] ROOMI MW, IVANOV V, KALINOVSKY T, NIEDZWIECKI A AND RATH M [2005] Antitumor effect of a combination of lysine, proline, arginine, ascorbic acid, and green tea extract on pancreatic cancer cell line MIA PaCa-2. Int J Gastrointest Cancer 35: 97-102.

[25] ROOMI MW, IVANOV V, KALINOVSKY T, NIEDZWIECKI A AND RATH M [2005] In vivo antitumor effect of ascorbic acid, lysine, proline and green tea extract on human prostate cancer PC-3 xenografts in nude mice: evaluation of tumor growth and immunohistochemistry. In Vivo 19: 179-183.

[26] ROOMI MW, IVANOV V, KALINOVSKY T, NIEDZWIECKI A AND RATH M [2005] In vivo antitumor effect of ascorbic acid, lysine, proline and green tea extract on human colon cancer cell HCT 116 xenografts in nude mice: evaluation of tumor growth and immunohistochemistry. Oncol Rep 13: 421-425.

[27] ROOMI MW, ROOMI NW, IVANOV V, KALINOVSKY T, NIEDZWIECKI A AND RATH M [2005] Modulation of N-methyl-N-nitrosourea induced mammary tumors in Sprague-Dawley rats by combination of lysine, proline, arginine, ascorbic acid and green tea extract. Breast Cancer Res 7: R291-295.

[28] GARBISA S, SARTOR L, BIGGIN S, SALVATO B, BENELLI R AND ALBINI A [2001] Tumor gelatinases and invasion inhibited by the green tea flavanol epigallocatechin-3-gallate. Cancer 91: 822-832.

[29] TAKADA M, NAKAMURA Y, KOIZUMI T, TOYAMA H, KAMIGAKI T, SUZUKI Y, TAKEYAMA Y AND KURODA Y [2002] Suppression of human pancreatic carcinoma cell growth and invasion by epigallocatechin-3-gallate. Pancreas 25: 45-48.

[30] VAYALIL PK, MITTAL A AND KATIYAR SK [2004] Proanthocyanidins from grape seeds inhibit - expression of matrix metalloproteinases in human prostate carcinoma cells, which is associated with the inhibition of activation of MAPK and NF kappa B. Carcinogenesis 25: 987-995.

[31] KAWAKAMI S, KAGEYAMA Y, FUJII Y, KIHARA K AND OSHIMA H [2001] Inhibitory effect of N-acetylcysteine on invasion and MMP-9 production of T24 human bladder cancer cells. Anticancer Res 21: 213-219.

[32] NOVAK JF AND TRNKA F [2005] Proenzyme therapy of cancer. Anticancer Res 25: 1157-1177.

[33] BREWER GJ, DICK RD, GROVER DK, LECLAIRE V, TSENG M, WICHA M, PIENTA K, REDMAN BG, JAHAN T, SONDAK VK, STRAWDERMAN M, LECARPENTIER G AND MERAJVER SD [2000] Treatment of metastatic cancer with tetrathiomolybdate, an anticopper, antiangiogenic agent: Phase I study. Clin Cancer Res 1: 1-10.

[34] PIPILI-SYNETOS E, SKKOULA E, HARALABOPOULOS G, ANDRIOPOULOU P, PERSISTERIS P AND MARAGOUDAKIS ME [1994] Evidence that nitric Oxide is an endogenous antiangiogenic mediator. Br J Pharmacol 111: 894-902.

[35] DAS I, HIRANI J AND SOORANNA S [1996] Arginine is not responsible for the activation of nitric oxide synthase by garlic. J Ethnophamacol 53: 5-9.

[36] CHEN HC, HSIEH MT AND SHIBUYA TK [1986] Suan-Tsao-Jen-Tang v. diazepam: A controlled double blind study in anxiety. Int J Clin Pharmacol Ther Toxicol 24: 49-50.

[37] ISHIZUKA J, BOLD RJ, TOWNSEND CM JR AND THOMPSON JC [1994] In vitro relationship between magnesium and insulin secretion. Magnes Res 7: 17-22.

[38] KANDASWAMI C, PERKINS E, SOLONIVK DS, DRZEWIECKI G AND MIDDLETON E JR [1993] Ascorbic acid-enhanced antiproliferative effect of flavinoids on squamous cell carcinoma in vitro. Anticancer Drugs 4: 91-96.

[39] HOFMANOVA J, MUSILOVA E AND KOZUBIK A [1996] Suppression of human cancer cell proliferation by lipoxygenase inhibitors and gamma-radiation in vitro. Gen Physio Biophys 15: 317-331.

[40] TEICHER BA, KORBUTT TT, MENON K, HOLDEN SA AND ARA G [1994] Cyclooxygenase and lipoxygenase inhibitors as modulators of cancer therapies. Cancer Chemother Pharmacol 33: 512-522.

[41] TANG DG AND HONN KV [1997] J Cell Physiol 172: 155-170.

[42 BALLATORI N AND WANG W [1997] Nordihydroguaiaretic acid depletes ATP and inhibits a swelling-activated, ATP-sensitive taurine channel. Amer J Physiol 272: C1429- C1436.

[43] SHEIK NM, PHILEN RM AND LOVE LA [1997] Chaparral-associated hepatotoxicity. Arch Interl Med 157: 913-919.

[44] PONTIGI P, ROTELLA GB, SABUTO A AND CURTO FC [1996] Hyperthermia in cancer and AIDS: An updated survey. J Environ Toxicol Oncol 15: 89-97.

[45] JOHNSTON B [1962] Clinical effects of Coley's toxin. 1. Controlled study. 2. A seven year study. Cancer Chem Reports 21: 19-68.

[46] BABINCOVA M, LESZCZYNSKA D, SOURIVONG P AND BABINEC P [2000] Selective treatment of neoplastic cells using ferritin-mediated electromagnetic hyperthermia. Med Hypotheses 54: 177-179.

[47] MITSUMORI M, HIRAOKA M, SHIBATA T, OKUNO Y, NAGATA Y, NISHIMURA Y, ABE M, HASEGAWA M, NAGAE H AND EBISAWA Y [1996] Targeted hyperthermia using derxtran magnetite complex: A new treatment modality for liver tumors. Hepatogastroenterology 43: 1431-1437.

[48] YANASE M, SHINKAI M, HONDA H, WAKABAYASHI T, YOSHIDA J AND KOBAYASHI T [1988] Intracellular hyperthermia for cancer using magnetite cationic liposomes: ex vivo study. Jpn J Cancer Res 7: 630-632.

[49] PAYNE AG [2003] Exploiting intracellular iron and iron-rich compounds to effect tumor cell lysis. Med Hypotheses 61: 206-209.

[50] AKAGI K, AOKI Y, NASU R, NAGATA K, ITAGAKI Y AND SAWADA S [1999] Enhancement of antitumor effects of hyperthermia with glucose administration in murine mammary carcinoma. Oncol Res 6: 593-596.

[51] LEEPER DB, ENGIN K, THISTLETHWAITE AJ, HITCHON HD, DOVER JD, LI DJ AND TUPCHONG L [1994] Human tumor extracellular pH as a function of blood glucose concentration. Int J Radiat Oncol Biol Phys 28: 935-943.

[52] LEPPER DB, ENGIN K, WANG JH, CATER JR AND LI DJ[1998] Effect of i.v. versus combinaed i.v. plus oral glucose on human tumour extracellular pH for potential sensitization to thermoradiotherapy. Int J Hyperthermia 14: 257-269.

[53] LUTSENKO SV, FELDMAN NB, FINAKOVA GV, POSYPANOVA GA, SEVERIN SE, SKYRABIN KG, KIRPICHNIKOV MP, LUKYANETS EA AND VOROZHTSOV GN [1999] Targeting phthalocyanines to tumor cells using epidermal growth factor conjugates. Tumour Biol 20: 218-224.

RECEIVED ON 7-13-2005.

ACCEPTED ON 9-15-2005.