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DESCRIPTION

CROSS-REFERENCE TO RELATED APPLICATIONS AND CLAIM OF PRIORITY

[0001] This application is a continuation-in-part of United States patent application Serial No. 11/706,868 filed on February 14,2007, and also claims to the benefit of United Stated provisional patent application Serial No. 61/148,385 filed on January 29, 2009.

BACKGROUND

[0002] Each year, hundreds of thousands of men, women, and children in the United States are afflicted with some form of cancer. Worldwide, millions die of cancers including those of the bone, bladder, blood (leukemias), brain, breast, colon, cervix, esophagus, intestine, kidney, liver, lung, mouth, nose, nerves, ovaries, pancreas, prostate, skin, stomach, testis, throat, thyroid, uterus, and vagina.

[0003] Over the years, a number of methods have been used to treat cancer including radiation and chemotherapy. The primary goal of these treatments is to kill all the cancer cells. However, many healthy cells are invariably destroyed in a race to kill the cancer cells before the treatment(s) kill the patient. Even today, the more measured and quantitative uses of radiation and chemotherapy can cause illness and even death in some patients. At the same time, in some types of cancer, the malignant cells remain difficult to treat.

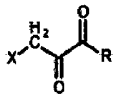
[0004] Consequently, ongoing research and developmental efforts continue in the medicinal arts involving the treatment of various cancers.

[0005] WO 2007/097989 A2 provides compositions and methods for the treatment of cancer. An inhibitor cocktail buffer includes at least one sugar, a non-potassium containing buffer, and an inhibitor including halopyruvates and derivatives thereof. However, inhibitor cocktail neither comprises a glycolysis inhibitor including 2-deoxyglucose nor a biological buffer including a citrate buffer.

SUMMARY

[0006] It has been recognized by the present inventor that it would be advantageous to develop an anti-cancer composition that is effective over an array of cancers, that is safe for use in humans, and that avoids or at least minimizes adverse drug experiences associated with traditional cancer treatments.

[0007] Briefly, and in general terms, the invention is directed to an anti-cancer composition for use in treating cancer in a human subject comprising: a) a cellular energy inhibitor having the structure according to formula I



(I)

wherein X is selected from the group consisting of: a nitro, an imidazole, a halide, sulfonate, a carboxylate, an alkoxide, and amine oxide; and R is selected from the group consisting of: OR', N(R")2, C(O)R"', C1-C6 alkyl, C6-C12 aryl, C1-C6 heteroalkyl, a C6-C 12 heteroaryl, H, and an alkali metal; where R' represents H, alkali metal, C1-C6 alkyl, C6-C12 aryl or C(O)R"', R" represents H, C1-C6 alkyl, or C6-C12 aryl, and R"' represents H, C1-C20 alkyl or C6-C12 aryl,

b) at least one sugar alcohol, which stabilizes the cellular energy inhibitor by substantially preventing the inhibitor from hydrolyzing, preferably in a concentration from about 0.1 mM to about 250 mM, more preferably about 0.5 mM to about 25 mM;

c) a glycolysis inhibitor including 2-deoxyglucose; and

d) a biological buffer including a citrate buffer that is present in an amount sufficient to at least partially deacidify the cellular energy inhibitor and neutralize metabolic by-products of the cellular energy inhibitor.

[0008] The toxicity of a cellular energy inhibitor of formula (I) is minimized by combining the cellular energy inhibitor with a biological buffer that is present in an amount sufficient to at least partially deacidify the cellular energy inhibitor and neutralize metabolic by-products of the cellular energy inhibitor due to its chemical reaction and/or cellular metabolism.

[0009] In yet another embodiment, any of the anti-cancer compositions as described herein is administered to the subject at a time when the subject's blood insulin/glucagon ratio is in the range of about 1 to about 10.

[0010] A method for assessing killing efficacy of any of the anti-cancer compositions described herein in a subject can comprise measuring a lactic acid level in the subject prior to administration of the anti-cancer composition; administering the anti-cancer composition to the subject; measuring the lactic acid level in the subject after administration of the anti-cancer composition; and determining the killing efficacy by measuring and/or correlating the difference between the lactic acid levels as a function of treatment time.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Additional features and advantages of the invention will be apparent from the detailed description which follows, taken in conjunction with the accompanying drawings, which together illustrate, by way of example, features of the invention; and, wherein:

FIG. 1 is a schematic of a cancer cell energy production;

FIG. 2 is a series of photographs of cancer cells treated with 3-bromopyruvate;

FIG. 3 is a plot of cell viability for hepatocellular carcinoma vs. µM of various anti-cancer agents; and

FIGs. 4(a) and 4(b) show a series of photographs of lungs having metastatic tumors without treatment and with treatment using 3-bromopyruvate, respectively.

[0012] Reference will now be made to the exemplary embodiments illustrated, and specific language will be used herein to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended.

DETAILED DESCRIPTION OF EXAMPLE EMBODIMENT(S)

[0013] Before the present invention is disclosed and described, it is to be understood that this disclosure is not limited to the particular process steps and materials disclosed herein because such process steps and materials may vary somewhat. It is also to be understood that the terminology used herein is used for the purpose of describing particular embodiments only. The terms are not intended to be limiting because the scope of the present disclosure is intended to be limited only by the appended claims and equivalents thereof.

[0014] It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

[0015] The composition of the present invention may include a pharmaceutically acceptable carrier, and other ingredients as dictated by the particular needs of the specific dosage formulation. Such ingredients are well known to those skilled in the art. See for example, Gennaro, A. Remington: The Science and Practice of Pharmacy 19th ed. (1995), which is incorporated by reference in its entirety.

[0016] As used herein, "administration," and "administering" refer to the manner in which a drug is presented to a subject. Administration can be accomplished by various art-known routes such as oral, alimentary, parenteral, transdermal, inhalation, implantation, etc. Thus, an oral administration can be achieved by drinking, swallowing, chewing, sucking of an oral dosage form comprising the drug. Parenteral administration can be achieved by injecting a drug composition intravenously, intra-arterially, intramuscularly, intrathecally, or subcutaneously, etc. Transdermal administration can be accomplished by applying, pasting, rolling, attaching, pouring, pressing, rubbing, etc., of a transdermal preparation onto a skin surface. These and additional methods of administration are well-known in the art.

[0017] As used herein, "non-oral administration" represents any method of administration in which a drug composition is not

provided in a solid or liquid oral dosage form, wherein such solid or liquid oral dosage form is traditionally intended to substantially release and or deliver the drug in the gastrointestinal tract beyond the mouth and/or buccal cavity. Such solid dosage forms include conventional tablets, capsules, caplets, etc., which do not substantially release the drug in the mouth or in the oral cavity.

[0018] It is appreciated that many oral liquid dosage forms such as solutions, suspensions, emulsions, etc., and some oral solid dosage forms may release some of the drug in the mouth or in the oral cavity during the swallowing of these formulations. However, due to their very short transit time through the mouth and the oral cavities, the release of drug from these formulations in the mouth or the oral cavity is considered de minimus or insubstantial, unless otherwise indicated. Thus, buccal patches, adhesive films, sublingual tablets, and lozenges that are designed to release the drug in the mouth are non-oral compositions for the present purposes.

[0019] In addition, it is understood that the term "non-oral" includes parenteral, transdermal, inhalation, implant, and vaginal or rectal formulations and administrations. Further, implant formulations are to be included in the term "non-oral," regardless of the physical location of implantation. Particularly, implantation formulations are known which are specifically designed for implantation and retention in the gastrointestinal tract. Such implants are also considered to be non-oral delivery formulations, and therefore are encompassed by the term "non-oral."

[0020] As used herein, "subject" refers to a mammal that may benefit from the administration of a drug composition or method of this invention. Examples of subjects include humans, and other animals such as horses, pigs, cattle, sheep, goats, dogs (felines), cats (canines), rabbits, rodents, primates, and aquatic mammals. In one embodiment, subject can refer to a human.

[0021] As used herein, "effective amount" or "therapeutically effective amount," or similar terms, refers to a non-toxic but sufficient amount of a drug, to achieve therapeutic results in treating a condition for which the drug is known to be effective or has been found to be effective as disclosed herein. Various biological factors may affect the ability of a delivered substance to perform its intended task or the amount of drug needed to provide a therapeutic result. Therefore, an "effective amount" or "therapeutically effective amount" may be dependent on such biological factors. The determination of an effective amount or therapeutically effective amount is well-within the ordinary skill in the art of pharmaceutical and medical sciences based on known techniques in the art as well as the present disclosure. See for example, Curtis L. Meinert & Susan Tonascia, Clinical Trials: Design, Conduct, and Analysis, Monographs in Epidemiology and Biostatistics, vol. 8 (1986).

[0022] As used herein, "drug," "active agent," "bioactive agent," "pharmaceutically active agent," "therapeutically active agent" and "pharmaceutical," may be used interchangeably to refer to an agent or substance that has measurable specified or selected physiologic activity when administered to a subject in a significant or effective amount. These terms of art are well-known in the pharmaceutical and medicinal arts.

[0023] As used herein, "cellular energy inhibitor" refers to a compound that inhibits glycolysis and mitochondria function of a cancer cell.

[0024] As used herein, "glycolysis inhibitor" refers to a compound that inhibits, reduces, or stops, glycolysis in a cancer cell.

[0025] As used herein, "mitochondria inhibitor" refers to a compound that inhibits, reduces, or stops mitochondria function in a cancer cell.

[0026] As used herein, the terms "dosage form", "formulation" and "composition" are used interchangeably and refer to a mixture of two or more compounds, elements, or molecules. In some aspects the terms "dosage form", "formulation" and "composition" may be used to refer to a mixture of one or more active agents with a carrier or other excipients.

[0027] As used herein, "carrier" or "pharmaceutically acceptable carrier" refers to a substance with which a drug may be combined to achieve a specific dosage formulation for delivery to a subject. In the some aspects of the present invention, the carriers used may or may not enhance drug delivery. As a general principle, carriers do not react with the drug in a manner which substantially degrades or otherwise adversely affects the drug, except that carriers may react with a drug to prevent it from exerting a therapeutic effect until the drug is released from the carrier. Further, the carrier, or at least a portion thereof must be suitable for administration into a subject along with the drug.

[0028] As used herein, the terms "release", "release rate" 'dissolution" "dissolution rate", are used interchangeably to refer to the discharge or liberation of a substance, including without limitation a drug, from the dosage form into a surrounding environment such as an aqueous medium either *in vitro or in vivo*.

[0029] As used herein, "controlled release," "sustained release," "modified release," "delayed release", "extended release" and "non-immediate release" are used interchangeably and refer to release of active agent or agents from a dosage form into the target environment or medium over a period of time that is at least 5% slower than the equivalent dosage containing immediate release (IR) formulations. In one embodiment, the "controlled release," "sustained release," "modified release" delayed release" "extended release" or non-immediate release" systems or compositions can provide for a release of the active agent or agents from the dosage form into the target environment or medium over a period of time that is at least 10 wt% slower than the equivalent dosage form containing immediate release (IR) formulations.

[0030] As used herein, "release modifying agent", "release modulating agent", and "release modifiers" are used interchangeably and refer to pharmaceutically acceptable agents or devices that are capable to alter, increase or decrease, or otherwise customize, the release rates of at least one of the contents of the compositions or dosage forms thereof, when exposed to an aqueous use environment.

[0031] As used herein, "admixed" means that at least two components of the composition can be partially or fully mixed, dispersed, suspended, dissolved, or emulsified in one another. In some cases, at least a portion of the drug may be admixed in at least one carrier substance.

[0032] As used herein, "adverse drug experience" refers to any adverse event associated with the use of a drug in a subject, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action. The adverse drug experience may lead to a substantial disruption of a person's ability to conduct normal life functions. In some instances, the adverse drug experience may be serious or life threatening.

[0033] While some of the adverse drug experiences may be expected, in some instances, such experiences may be unexpected. "Unexpected," refers to an adverse drug experience that has not been previously catalogued by a responsible governmental agency (such as the Food and Drug Administration of the United States) and or not provided in the current labeling for the drug product.

[0034] The unexpected adverse experiences may include events that may be symptomatically and pathophysiologically related to a known event, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the known event is elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the known event is cerebral vascular accidents. For a more comprehensive definition and description of adverse drug experience, see 21 C.F.R. § 314.80.

[0035] As used herein, "substantially" or "substantial" refers to the complete or nearly complete extent or degree of an action, characteristic, property, state, structure, item, or result. For example, an object that is "substantially" enclosed would mean that the object is either completely enclosed or nearly completely enclosed. The exact allowable degree of deviation from absolute completeness may in some cases depend on the specific context. However, generally speaking, the nearness of completion will be so as to have the same overall result as if absolute and total completion were obtained. The use of "substantially" is equally applicable when used in a negative connotation to refer to the complete or near complete lack of action, characteristic, property, state, structure, item, or result. For example, a composition that is "substantially free of" particles would either completely lack particles, or so nearly completely lack particles that the effect would be the same as if it completely lacked particles. In other words, a composition that is "substantially free of" an ingredient or element may still contain such an item as long as there is no measurable effect thereof. Unless otherwise, indicated "substantially" preventing hydrolysis or hydrolyzing refers to the ability of sugar alcohol(s) to stabilize the cellular energy inhibitor for at least one hour while such that at least 50% of the cellular energy inhibitor does not hydrolyze.

[0036] As used herein, a plurality of items, structural elements, compositional elements, and/or materials may be presented in a common list for convenience. However, these lists should be construed as though each member of the list is individually identified as a separate and unique member. Thus, no individual member of such list should be construed as a de facto equivalent of any other member of the same list solely based on their presentation in a common group without indications to the contrary.

[0037] As used herein, a plurality of items, structural elements, compositional elements, and/or materials may be presented in a common list for convenience. However, these lists should be construed as though each member of the list is individually identified as a separate and unique member. Thus, no individual member of such list should be construed as a de facto equivalent of any

other member of the same list solely based on their presentation in a common group without indications to the contrary.

[0038] Concentrations, amounts, levels and other numerical data may be expressed or presented herein in a range format.

[0039] It has been recognized by the present inventor that an alternative to tradition anti-cancer compositions and treatments can be achieved by targeting the energy production of a cancer cell. Without intending to be bound by any particular theory, the present inventor has found that certain cellular energy inhibitors can be used to treat cancers. Generally, there are two energy (ATP) production factories inside the cell, i.e., glycolysis and oxidative phosphorylation by mitochondria. In normal cells, about 5 % of the total cellular energy (ATP) production is derived from glycolysis and about 95 % from the mitochondria. In cancer cells, the energy production by glycolysis can be significantly increased (up to 60 %). This dramatic increase in glycolysis in cancer cells results in a significant increase in lactic acid production.

[0040] Most cancers (> 90 %) exhibit this common metabolic phenotype. This is called the "Warburg Effect", i.e., significant increase in glycolysis in cancer cells even in the presence of oxygen. The most frequent cancer detection method used clinically, i.e., Positron Emission Tomography (PET) is based on this metabolic phenotype, i.e., the "Warburg effect". Cancer cells that exhibit the "Warburg effect" pump out the produced lactic acid *via* a transporter (i.e., monocarboxylate transport isoforms). The number of these transporters (considered as doors or gates) in cancer cells is much greater than in normal cells.

[0041] The presently disclosed cellular energy inhibitors, shown as 3-bromopyruvate (3BP) (a lactic acid analog) in FIG. 1, are small chemicals and can mimic the lactic acid chemical structure; depicted as a small diamond in FIG. 1. Therefore, cellular energy inhibitors disguised as lactic acid can "trick" the cancer cells and enter like a Trojan horse (FIG. 1). The inhibitors have little effect on normal cells as these contain very few lactic acid transporters. Because of the present cellular energy inhibitors' highly reactive nature, it can destroy the two energy production factories (FIG. 1; one diamond above the hexokinase (HK), shown as 3BP is destroying one energy production factory, i.e., glycolysis, and another red diamond inside the mitochondrion means that 3BP is destroying also this energy production factory). As a result, the cellular energy (ATP) can be depleted very rapidly by cellular energy inhibitors; 3BP in FIG. 1, attack the two factories at the same time causing the cancer cells to rapidly explode (cell membrane rupturing). An example of this can be seen in FIG. 2, which shows liver cancer cells treated with 3BP. Here, the healthy cancer cells are round and iridescent (left picture). However, when they are treated with 3BP, the cell membranes rupture (middle picture) and then die (see cell debris in the far right picture).

[0042] In accordance with this, the present disclosure allows for safe administration and use of the present anti-cancer compositions for use in treating cancer in a human subject, as defined above.

[0043] The present inventor has recognized the need to provide safe and efficacious compositions that allow for treatment of cancers. As previously discussed, the present cellular energy inhibitors can be stabilized by the use of at least one sugar alcohol such that the sugar alcohol substantially prevents hydrolysis of the cellular energy inhibitor. In this way, the sugar alcohol can stabilize the cellular energy inhibitor for at least 1 hour such that at least 50% of the inhibitor does not hydrolyze, or the at least one sugar alcohol can stabilize the cellular energy inhibitor for at least 1 hour and prevent at least 95% of the inhibitor from hydrolyzing, or the at least one sugar alcohol can stabilize the cellular energy inhibitor for at least 2 hours such that at least 95% of the inhibitor does not hydrolyze.

[0044] The anti-cancer compositions disclosed herein generally include a compound as described by formula (I). In one embodiment, R of formula (I) can be OH and X of formula (I) can be selected from the group consisting of: a nitro, an imidazole, a halide, a sulfonate, a carboxylate, an alkoxide, and an amine oxide. Additionally, X can be a halide selected from the group consisting of: fluoride, bromide, chloride, and iodide. In one embodiment, X can be a sulfonate selected from the group consisting of: triflate, mesylate and tosylate. In another embodiment, X can be amine oxide. In still another embodiment, the amine oxide can be dimethylamine oxide.

[0045] In one embodiment, the cellular energy inhibitor can be a 3-halopyruvate and can be selected from the group consisting of: 3-fluoropyruvate, 3-chloropyruvate, 3-bromopyruvate, 3-iodopyruvate, and combinations thereof. The anti-cancer composition can comprise the cellular energy inhibitor in a concentration from about 0.1 mM to about 25.0 mM. In one embodiment, the anti-cancer composition can comprise the cellular energy inhibitor in a concentration from about 1.0 mM to about 10.0 mM.

[0046] While the anti-cancer composition generally comprises at least one sugar alcohol, in one embodiment, the anti-cancer composition can comprise other sugars alcohols, such as a second sugar alcohol. In another embodiment, the anti-cancer composition can comprise a third sugar alcohol. At least one of the sugars alcohols can be a five-carbon sugar alcohol. In one embodiment, at least two of the sugars alcohols can be five-carbon sugars alcohols. The five-carbon sugars alcohol can be

independently selected from the group consisting of mannitol, erytritol, isomalt, lactitol, maltitol, sorbitol, xyolitol, dulcitol, ribitol, inositol, sorbitol, and combinations thereof. In one embodiment, at least one of the sugars alcohols can be glycerol. In another embodiment, the sugars alcohols can be glycerol, inositol, and sorbitol. The anti-cancer composition can comprise glycerol in a range from about 0.1 wt% to about 3 wt%, inositol in a range from about 1 wt% to about 5 wt%, and sorbitol in a range from about 30 wt% to about 50 wt%. Additionally, each of the sugars alcohols may be added in a volume up to a maximum solubility of the sugar in the formulation or composition.

[0047] In one embodiment, the anti-cancer composition can comprise the at least one sugar alcohol in a concentration from about 0.1 mM to about 250 mM. In another embodiment, the anti-cancer composition can comprise the at least one sugar alcohol in a concentration from about 0.5 mM to about 25 mM.

[0048] The anti-cancer composition comprises the glycolysis inhibitor 2-deoxglucose. The anti-cancer composition can comprise the glycolysis inhibitor in a concentration from about 0.1 mM to about 25.0 mM. In one embodiment, the anti-cancer composition can comprise the glycolysis inhibitor in a concentration from about 1 mM to about 5 mM.

[0049] The anti-cancer composition includes a biological buffer that is present in an amount sufficient to at least partially deacidify the cellular energy inhibitor and neutralize metabolic by-products of the cellular energy inhibitor. The biological buffer includes a citrate buffer that can be sodium citrate, and may further include a phosphate buffer, and/or an acetate buffer.

[0050] As discussed herein, the cellular energy inhibitor is delivered to a cancer cell and is taken up by the cell. After metabolism of the cellular energy inhibitor, the cellular energy inhibitor can cause by-products. In one embodiment, the by-product can be a hydrogen halide. Additionally, the hydrogen halide can be hydrogen bromide or hydrogen iodide. In one embodiment, the hydrogen halide can be hydrogen bromide.

[0051] The anti-cancer composition can comprise the biological buffer in a concentration of from about 0.1 mM to about 200 mM. In one embodiment, the anti-cancer composition can comprise the biological buffer in a concentration of from about 1 mM to about 20 mM. Additionally, the biological buffer can maintain a physiological pH of 4.0 to 8.5. In one embodiment, the biological buffer can maintain a physiological pH of 5.5 to 8.0. In another embodiment, the biological buffer can maintain a physiological pH of 6.8 to 7.8. In still another embodiment, the biological buffer can maintain a physiological pH of 7.3 to 7.6.

[0052] In addition to the above components, the anti-cancer compositions described herein can further comprise a halo monocarboxylate compound that is separate from the cellular energy inhibitor. In the cases where the halo monocarboxylate compound can function to inhibit glycolysis and mitochondria function, the halo monocarboxylate can be considered a second cellular energy inhibitor. In one embodiment, the halo monocarboxylate compound can be a halo two-carbon monocarboxylate compound. The halo two-carbon monocarboxylate compound can be selected from the group consisting of 2-fluoroacetate, 2-chloroacetate, 2-bromoacetate, 2-iodoacetate, and mixtures thereof. In one embodiment, the halo two-carbon monocarboxylate compound can be 2-bromoacetate. The anti-cancer composition can comprise the halo two-carbon monocarboxylate compound in a concentration from about 0.01 mM to about 5.0 mM. In one embodiment, the anti-cancer composition can comprise the halo two-carbon monocarboxylate compound in a concentration from about 0.1 mM to about 0.5 mM.

[0053] Additionally, the halo monocarboxylate compound can be a halo three-carbon monocarboxylate compound. In one embodiment, the halo three-carbon monocarboxylate compound can be selected from the group consisting of 3-fluorolactate, 3-chlorolactate, 3-bromolactate, 3-iodolactate, and mixtures thereof. The anti-cancer composition can comprise the halo three-carbon monocarboxylate compound in a concentration from about 0.5 mM to about 250 mM. In one embodiment, the anti-cancer composition can comprise the halo three-carbon monocarboxylate compound in a concentration from about 10 mM to about 50 mM.

[0054] The anti-cancer compositions described herein can further comprise an antifungal agent and/or antibacterial agent. In one embodiment, the anti-cancer composition can individually comprise the antifungal agent and/or antibacterial agent in a concentration from about 0.01 mM to about 5.0 mM. In another embodiment, the anti-cancer composition can individually comprise the antifungal agent and/or antibacterial agent in a concentration from about 0.05 mM to about 0.5 mM.

[0055] The anti-cancer compositions described herein can further comprise a mitochondrial inhibitor in addition to the cellular energy inhibitor. The mitochondrial inhibitor can be selected from the group consisting of: oligomycin, efrapeptin, aurovertin, and mixtures thereof. In one embodiment, the anti-cancer composition can comprise the mitochondrial inhibitor in a concentration from about 0.001 mM to about 5.0 mM. In another embodiment, the anti-cancer composition can comprise the mitochondrial inhibitor in a concentration from about 0.01 mM to about 0.5 mM.

[0056] In addition to the above concentrations, the anti-cancer compositions can have various ratios of the components described herein. In one embodiment, the cellular energy inhibitor and biological buffer can be present in a ratio ranging from 1:1 to 1:5 by mM. In another embodiment, the cellular energy inhibitor and glycolysis inhibitor can be present in a ratio ranging from 5:1 to 1:1 by mM. In still another embodiment, the cellular energy inhibitor and the at least one sugar alcohol are present in a ratio ranging from 1:1 to 1:5 by mM. In yet another embodiment, the cellular energy inhibitor and the halo two-carbon monocarboxylate compound can be present in a ratio ranging from 20:1 to 4:1 by mM. In still yet another embodiment, the cellular energy inhibitor to mitochondrial inhibitor can be present in a ratio ranging from 20:1 to 40:1 by mM.

[0057] As described above, the present anti-cancer compositions can comprise antifungal agents, antibiotics, glycolysis inhibitors, inhibitors of mitochondria, sugars, and biological buffers. Examples of such agents include, but are not limited to, amphotericin B, Efrapeptin, doxorubicin, 2-deoxyglucose (2DOG), analogs of 2DOG, dicholoracetic acid (or salt form of dichloroacetate), oligomycin, analogs of oligomycin, glycerol, inositol, sorbitol, glycol, erythritol, threitol, arabitol, xylitol, ribitol, mannitol, dulcitol, iditol, isomalt, maltitol, lactitol, polyglycitol, sodium phosphate, sodium citrate, sodium acetate, sodium carbonate, sodium bicarbonate, sodium pyruvate, sodium lactate, oxaloacetate, isocitrate, aconitate, succinate, fumarate, malate, diluted saline solutions with varying concentrations of NaCl, and water. In addition to the sodium ion that accompanies these biological buffers, calcium and potassium cations can also accompany the biological buffers. The active agents of the anti-cancer composition can include the cellular energy inhibitor, the glycolysis inhibitor, the mitochondria inhibitor, the halo monocarboxylate compound, the antifungal agent, and the antibiotic agent.

[0058] In addition to the active agent(s), the composition can also include a pharmaceutically acceptable carrier. The carrier can be a single composition, or a mixture of compositions. Additionally, the carrier can take the form of an encapsulation coat, an absorbing agent, a coating substance, a controlled release device, a release modifying agent, surfactants, or a combination thereof. In some aspects, the carrier can comprise about 1 wt% to about 99 wt% of the total composition. In one embodiment, the carrier can comprise about 5 wt% to about 95 wt% of the total formulation. In another embodiment, the carrier can comprise about 20 wt% to about 80 wt%. In yet a further embodiment, the carrier can comprise about 30 wt% to about 60 wt%. In one embodiment, the carrier can be admixed with the active agent(s). In another embodiment, the carrier can adsorb, entrap, or encapsulate at least a portion of the active agent(s).

[0059] Non-limiting examples of compounds that can be used as at least a part of the carrier include without limitation: cetyl alcohol and its esters; stearic acid and its glycerol esters, polyoxyethylene alkyl ethers; polyethylene glycol; polyglycolyzed glycerides; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; proteins; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols with at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; tocopherol derivatives, sugar esters; sugar ethers; sucroglycerides; waxes, shellac, pharmaceutically acceptable salts thereof, and mixtures thereof.

[0060] Non-limiting examples of release modifying agents include without limitation: polyethylene glycols having a weight average molecular weight of about 1000 and more, carbomer, methyl methacrylate copolymers, methacrylate copolyers, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, ethyl cellulose, methyl cellulose and their derivatives; ion-exchange resin; mono-, di-, tri- esters of fatty acids with glycerol; tocopherol and its esters; sucrose esters with fatty acids; polyvinyl pyrollidone; xanthan gums; cetyl alcohol; waxes; fats and oils, proteins, alginate, polyvinyl polymers, gelatins, organic acids, and their derivatives and combinations thereof.

[0061] In one embodiment, the carrier can include at least one of celluloses; carbomers; methacrylates; dextrins; gums; inorganic carbonates or salts of calcium or magnesium or both; fatty acid esters; gelatin; lactoses; maltoses; mono-, di- or triglycerides; oils; polyethylene glycols; polyethylene oxide co-polymers; proteins; resins; shellac; silicates; starches; sugar stearates; partially or fully hydrogenated vegetable oils; waxes; and combinations thereof.

[0062] In yet another embodiment, the carrier can include at least one of celluloses; carbomers; methacrylates; inorganic carbonates or salts of calcium; inorganic carbonates or salts of magnesium; fatty acids; fatty acid esters; gelatin; lactoses; polyethylene glycol; polyethylene oxide co-polymers; silicates; partially or fully hydrogenated vegetable oils, and combinations thereof.

[0063] In yet a further embodiment, the carrier can include at least one of microcrystalline cellulose; hydroxypropyl methylcellulose; ethyl cellulose; silicon dioxide; magnesium aluminosilicate; lactose; xanthan gum; stearic acid; glyceryl distearate; hydrogenated vegetable oil; and combinations thereof.

[0064] The formulation, including any dosage form, can include other components or additives. Such additional components and additives are optional. In one aspect, the additive can be a solid at room temperature and have a melting point or range that is greater than about 40°C. Non-limiting examples of additives that can be included in the systems of the present invention include without limitation: fillers such as lactoses, starches, sugars, celluloses, calcium salts, silicon oxides, metallosilicates and the like; disintegrants such as starch glycolate, lauryl sulfate, pregaltinized starch, croscarmellose, crospovidone and the like; binders such as pyrrolidones, methacrylates, vinyl acetates, gums, acacia; tragacanth; kaolins; carrageenan alginates, gelatins and the like; cosolvents such as alcohols, polyethylene glycols having average molecular weight of less than 1000, propylene glycols and the like; surface tension modifiers such as hydrophilic or amphiphlic surfactants; taste-masking agents; sweeteners; microencapsulating agents; process aids such as lubricants, glidants, talc, stearates, lecithin and the like; polymeric coating agents; plasticizers; buffers; organic acids; antioxidants; flavors; colors; alkalizers; humectants; sorbitols; mannitols; osmotic salts; proteins; resins; moisture repelling agents; hygroscopic agents; desiccants; and combinations thereof.

[0065] The formulations of the present invention can be formulated into a variety of oral dosage forms including, but not limited to two piece hard gelatin capsules, soft gelatin capsules, beads, beadlets, granules, spherules, pellets, microcapsules, microspheres, nanospheres, nanocapsules, tablets, or combinations thereof. Other forms known to those of ordinary skill in the art may also be used. In one aspect, the oral dosage form may be a capsule or tablet. In another embodiment the oral dosage form may include a multicomponent dosage form such as beads in a capsule, a capsule or capsules within a capsule, a tablet or tablets in a capsule, or a multilayer tablet. It is noteworthy that, when the formulation includes multiple dosage forms, such dosage forms need not be the same. Further, such dosage forms may not be physically present together.

[0066] The dosage form, e.g. tablet, may be coated or enrobed with a hydrophilic or a hydrophobic coat material known in the art. In one embodiment, the coat can be a film coat, sugar coat, enteric coat, semipermeable coat, sustained release coat, delayed release coat, osmotic coat and the like. In a further embodiment, the coating material can be a cellulose, gelatin, methacrylate, polyvinyl acetate, povidone, polyethylene glycol, polyetyhylne oxide, poloxamers, carbomers, shellac, phthalate and the like and their derivatives and combinations thereof. In another embodiment, the coat is a dry powder coat. In one embodiment, the tablet can be a matrix tablet. It is noteworthy that, when present, the coat can be considered as part, or all, of the carrier component of the formulation.

[0067] The compositions described herein are for use in treating cancer in a human subject. The treatment comprises administering to a subject the anti-cancer compositions as described herein in a therapeutically effective amount. The anti-cancer composition can be administered to the subject when the subject's blood insulin/glucagon ratio is in the range of about 1 to about 10. Additionally, the anti-cancer composition can be administered to the subject after fasting for at least 4 hours. In one embodiment, the anti-cancer composition can be administered to the subject after fasting for 6 hours, and in another embodiment, after fasting for 8 hours. Additionally, the anti-cancer composition can be administered to the subject after fasting for 2 hours. It is noted that such times are not intended to be limiting, and that in one embodiment, the amount of time fasting can be such that the subject's blood insulin/glucagon ratio is in the range of about 2 to about 5.

[0068] In addition, the method of administration can be selected from the group consisting of: inter-arterially, intravenously, inter-peritoneally, inhalation, intra-tumorally, orally, topically, and subcutaneously. The anti-cancer compositions can also be delivered by use of a feeding tube. Intra-tumorally delivery methods can include technologies involving a bronchoscope, an endoscope, and /or a colonoscopy, suppository to any openings, eye drops, nose drops, and ear drops. Additionally, if intra-tumorally injection is going to be performed directly to/in the tumor, ultrasound imaging (or other imaging methods) can be used to aid this injection. Further, intravenous delivery can be combined with a hemodialysis apparatus (i.e. kidney dialysis equipment) to destroy the metastatic circulating cancer cells outside of the blood vessels. In addition, both intravenous and inter-peritoneal can be assisted by utilization of a port system. Furthermore, the present anti-cancer composition can be immediate release, controlled release, or time controlled release. For time controlled release, the present compositions can delivered by implanting wafers, diamond chips, and other implantable devices near or on the tumor site.

[0069] Generally, when the anti-cancer composition is administered intra-arterially or intravenously, the administration can be for a duration from about 30 minutes to about 8 hours. In one embodiment, the anti-cancer composition can be intra-arterially or intravenously administered for a duration from about 3 hours to about 5 hours. Additionally, the administration of the anti-cancer composition can be part of a dosing regimen. In one embodiment, the administration can include a regimen lasting from about 1 week to 24 weeks. In another embodiment, the regimen can last from about 4 weeks to 8 weeks.

[0070] Generally, the present anti-cancer composition is administered in a therapeutically effective amount as defined herein. In one embodiment, the therapeutically effective amount can include a dosage of, or equivalent to, about 1 mM to about 10 mM of the anti-cancer composition in a volume of 25 ml to 1000 ml.

[0071] The anti-cancer compositions described herein can be used to treat any cancer having increased glycolysis; the metabolic phenotype referred to as the "Warburg Effect", as described above. In another embodiment, the anti-cancer compositions can be used to treat any cancer that can be detected by Positron Emission Tomography (PET), which detects this metabolic phenotype. Human cancer cell lines that the present anti-cancer composition has shown to be effective against include liver, cervical, ovarian, lung, breast, colon, neuroblastoma, medulloblastoma, prostate, skin, pancreatic, childhood fibrolamellar hepatocellular carcinoma (FHCC), hepatocellular carcinoma (HCC), non small cell lung cancer. As such, the present cancers that can be treated with the present anti-cancer compositions can be selected from the group consisting of liver, cervical, ovarian, lung, breast, colon, neuroblastoma, medulloblastoma, prostate, skin, pancreatic, childhood fibrolamellar hepatocellular carcinoma (FHCC), hepatocellular carcinoma (HCC), non small cell lung cancer. The present anti-cancer compositions have been used to treat human cancer patients having childhood fibrolamellar hepatocellular carcinoma (FHCC), hepatocellular carcinoma (HCC), non small cell lung cancer, colon cancer, breast cancer, and pancreatic cancer. As such, cancers that can be treated with the present anti-cancer compositions can be selected from the group consisting of childhood fibrolamellar hepatocellular carcinoma (FHCC), hepatocellular carcinoma (HCC), non small cell lung cancer, colon cancer, breast cancer, pancreatic cancer, and combinations thereof.

[0072] In one embodiment, the anti-cancer composition can be used to treat liver cancer. In another embodiment, the anti-cancer composition can be used to treat cervical cancer. In still another embodiment, the anti-cancer composition can be used to treat ovarian cancer. In still another embodiment, the anti-cancer composition can be used to treat lung cancer. In still another embodiment, the anti-cancer composition can be used to treat breast cancer. In still another embodiment, the anti-cancer composition can be used to treat colon cancer. In still another embodiment, the anti-cancer composition can be used to treat neuroblastoma. In still another embodiment, the anti-cancer composition can be used to treat medulloblastoma. In still another embodiment, the anti-cancer composition can be used to treat prostate cancer. In still another embodiment, the anti-cancer composition can be used to treat skin cancer. In still another embodiment, the anti-cancer composition can be used to treat breast cancer. In still another embodiment, the anti-cancer composition can be used to treat pancreatic cancer. In still another embodiment, the anti-cancer composition can be used to treat childhood fibrolamellar hepatocellular carcinoma (FHCC). In still another embodiment, the anti-cancer composition can be used to treat hepatocellular carcinoma (HCC). In still another embodiment, the anti-cancer composition can be used to treat small cell and non small cell lung cancer. In still other embodiments the anti-cancer composition can be used to treat vaginal, anal, testicular, nasal, throat, mouth, esophageal, and brain cancers.

[0073] Additionally, in order to minimize an adverse drug experience associated with administration of an anti-cancer composition to a subject the anti-cancer composition can be administered to the subject at a time when the subject's blood insulin/glucagon ratio is in a range of about 1 to about 10, measured in picomolar (pM). The anti-cancer composition can be any anti-cancer composition described herein. In one embodiment, the insulin/glucagon ratio can be in a range of about 2 to about 5. Without intending to be bound by any particular theory, by administering the present anti-cancer compositions at a time where the subject's blood sugar is low, or the blood insulin/glucagon ratio is low, the normal cells can be protected against any incidental uptake of the anti-cancer active agents. Specifically, such administration can protect the hexokinase 2 (HK-2) enzyme that is present in normal tissues in small amounts. Under low blood sugar conditions, the HK-2 enzyme tends to enter the nucleus of normal cells rather than the cytosolic compartment. The nuclear location of HK-2 provides additional protection against chemo-agents such as 3-bromopyrauvate, 2-bromoacetate, and 2-iodoacetate. As discussed herein, the administration can include a therapeutically effective amount of the anti-cancer composition. In one embodiment, the adverse drug experience can be cachexia. In another embodiment, the adverse drug experience can be pain.

[0074] Further, a method for assessing killing efficacy of an anti-cancer composition in a subject can comprise measuring a lactic acid level in the subject prior to administration of the anti-cancer composition; administering the anti-cancer composition to the subject; measuring the lactic acid level in the subject after administration of the anti-cancer composition; and determining the killing efficacy by measuring and/or correlating the difference between the lactic acid levels as a function of treatment time. The anti-cancer composition can be any of those described herein.

[0075] The lactic acid levels can be measured from a biological fluid from the subject. The biological fluid can be selected from the group consisting of: blood and blood fractions, tears, sweat, urine, ascitic fluid, saliva, and combinations thereof. Additionally, the measuring can be colormetric using lactic acid binding enzymes. The measuring can be by dip-stick or strip methods, or the measuring can be by magnetic resonance imaging.

[0076] In certain embodiments, the above-described anti-cancer compositions can comprise one or more of the cellular energy inhibitors, glycolysis inhibitors, mitochondria inhibitors, halo monocarboxylate compounds, as further defined in claim 1, and a second chemotherapeutic agent.

[0077] The term chemotherapeutic agent includes, without limitation, platinum-based agents, such as carboplatin and cisplatin; nitrogen mustard alkylating agents; nitrosourea alkylating agents, such as carmustine (BCNU) and other alkylating agents; antimetabolites, such as methotrexate; purine analog antimetabolites; pyrimidine analog antimetabolites, such as fluorouracil (5-FU) and gemcitabine; hormonal antineoplastics, such as goserelin, leuprolide, and tamoxifen; natural antineoplastics, such as taxanes (e.g., docetaxel and paclitaxel), aldesleukin, interleukin-2, etoposide (VP-16), interferon alfa, and tretinoin (ATRA); antibiotic natural antineoplastics, such as bleomycin, dactinomycin, daunorubicin, doxorubicin, and mitomycin; and vinca alkaloid natural antineoplastics, such as vinblastine and vincristine.

[0078] Further, the following additional drugs may also be used in combination with the antineoplastic agent, even if not considered antineoplastic agents themselves: dactinomycin; daunorubicin HCl; docetaxel; doxorubicin HCl; epoetin alfa; etoposide (VP-16); ganciclovir sodium; gentamicin sulfate; interferon alfa; leuprolide acetate; meperidine HCl; methadone HCl; ranitidine HCl; vinblastin sulfate; and zidovudine (AZT). For example, fluorouracil has recently been formulated in conjunction with epinephrine and bovine collagen to form a particularly effective combination.

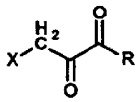
[0079] Still further, the following listing of amino acids, peptides, polypeptides, proteins, polysaccharides, and other large molecules may also be used: interleukins 1 through 18, including mutants and analogues; interferons or cytokines, such as interferons α, β, and γ; hormones, such as luteinizing hormone releasing hormone (LHRH) and analogues and, gonadotropin releasing hormone (GnRH); growth factors, such as transforming growth factor-β (TGF-), fibroblast growth factor (FGF), nerve growth factor (NGF), growth hormone releasing factor (GHRF), epidermal growth factor (EGF), fibroblast growth factor homologous factor (FGFHF), hepatocyte growth factor (HGF), and insulin growth factor (IGF); tumor necrosis factor-α & β (TNF-α & β); invasion inhibiting factor-2 (IIF-2); bone morphogenetic proteins 1-7 (BMP 1-7); somatostatin; Lhymosin-α-1; γ-globulin; superoxide dismutase (SOD); complement factors; anti-angiogenesis factors; and antigenic materials.

[0080] Preferred chemotherapeutic agents for use with the compositions and methods of treatment described herein include, but are not limited to altretamine, asparaginase, BCG, bleomycin sulfate, busulfan, carboplatin, carmusine, chlorambucil, cisplatin, claladribine, 2-chlorodeoxyadenosine, cyclophosphamide, cytarabine, dacarbazine imidazole carboxamide, dactinomycin, daunorubicin--dunomycin, dexamethosone, doxurubicin, etoposide, floxuridine, fluorouracil, fluoxymesterone, flutamide, fludarabine, goserelin, hydroxyurea, idarubicin HCL, ifosfamide, interferon alfa, interferon alfa 2a, interferon alfa 2b, interferon alfa n3, irinotecan, leucovorin calcium, leuprolide, levamisole, lomustine, megestrol, melphalan, L-sarcosylin, melphalan hydrochloride, MESNA, mechlorethamine, methotrexate, mitomycin, mitoxantrone, mercaptopurine, paclitaxel, plicamycin, prednisone, procarbazine, streptozocin, tamoxifen, 6-thioguanine, thiotepa, vinblastine, vincristine and vinorelbine tartrate.

[0081] All of the above drugs and additives may be added individually, in combination, as long as there is no negative interaction between or among the various drugs.

[0082] Additionally, the present invention provides kits for the treatment of cancer. The present kits provide the necessary ingredients with instructions such that one of ordinary skill in the art can combine the ingredients into an appropriate dosage form for delivery to a subject. At a minimum, a kit would include a cellular energy inhibitor ingredient, at least one sugar ingredient, a glycolysis inhibitor ingredient, a biological buffer ingredient, a container, and a set of instructions. Typically, the ingredients can be admixed such that the dosage form can be administered to a subject for the treatment of cancer. As described herein, such dosage can be part of a regimen for the treatment of various cancers.

[0083] In one embodiment, a kit for treatment of cancer in a human subject comprises a) a cellular energy inhibitor ingredient having the structure according to formula I



(I)

wherein X is selected from the group consisting of: a nitro, an imidazole, a halide, sulfonate, a carboxylate, an alkoxide, and amine oxide; and R is selected from the group consisting of: OR', $N(R")_2$, C(O)R"', C1-C6 alkyl, C6-C12 aryl, C1-C6 heteroalkyl, a C6-C12 heteroaryl, H, and an alkali metal; where R' represents H, alkali metal, C1-C6 alkyl, C6-C12 aryl or C(O)R"', R" represents H, C1-C6 alkyl, or C6-C12 aryl, and R'" represents H, C1-C20 alkyl or C6-C12 aryl;

b) at least one sugar alcohol ingredient, which stabilizes the cellular energy inhibitor ingredient by substantially preventing the cellular energy inhibitor ingredient from hydrolyzing;

c) a glycolysis inhibitor ingredient including 2-deoxyglucose;

d) a biological buffer ingredient including a citrate buffer that is present in an amount sufficient to at least partially deacidify the cellular energy inhibitor ingredient and neutralize metabolic byproducts of the cellular energy inhibitor ingredient;

e) a container for containing the ingredients which are preferably contained in individual containers inside the container; and

f) a set of instructions for the preparation of a dosage form using the ingredients and for administration of the dosage form to a subject.

[0084] In one embodiment, the ingredients can be further contained in individual containers inside the container.

[0085] In one embodiment, the kit can further contain a syringe filter for sterilization of at least one ingredient and sterile gloves.

[0086] In one embodiment, the kit can contain the cellular energy inhibitor in powdered form in an amount that provides a concentration of about 2.5 mM to about 5.0 mM when added to the solution.

[0087] In addition to the above, the ingredients of the kit can be modified as described herein.

[0088] The following examples serve as a reference.

EXAMPLE

Example 1 - *Rat Hepatocellular Carcinoma Study* (for reference)

[0089] Hepatocellular carcinoma cells were treated with various anti-cancer agents including 3-bromoacetate. FIG. 3 shows a graph of cancer cell viability as a function of μM amounts of the anti-cancer agents over a 23 hour period. As shown in FIG. 3, 3-bromopyruvate provided little cell viability (approx. 5%) with as little as 20 μM used. In fact, 3-bromopyruvate provided 10 times more efficiency as compared to the closest anti-cancer agent, methotrexate, measured in terms of cell viability 5% vs 55%.

Example 2 - *Lung Cancer treated with 3-Bromopyruvate* (for reference)

[0090] Table 1 provides results of cell proliferation for human lung cancer cells treated with various known anti-cancer agents compared to 3-bromopyruvate.

Table 1

Anticancer Agent at 50 μM, for 24 hrs	Inhibition of Cell Proliferation, %
None (control)	0
3-Bromopyruvate	92.5
Carboplatin	4.5
Cyclophosphamide	0
Doxorubicin	39.6
5-Fluorouracil	17.8
Methotrexate	28
Paclitaxel	0

[0091] As can be seen from Table 1, for lung cancer cells, 3-bromopyruvate was more than twice as effective as the closest comparative known anti-cancer agent. As such, the present anti-cancer compositions can provide at least a 90% inhibition of cancer cell proliferation.

Example 3 - Metastatic Lung Cancer Study (for reference)

[0092] FIG. 4(a) shows pictures of dissected lungs of a rabbits having metastatic tumors without the present treatment, while FIG. 4(b) shows lungs of a rabbits demonstrating no metastatic lung cancer after treatment using 3-bromoacetate via IP port delivery. As can be seen from FIGs. 4(a) and 4(b), the present anti-cancer composition was able to prevent metastatic lung tumors.

REFERENCES CITED IN THE DESCRIPTION

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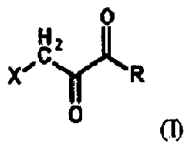
Patentkrav

1. Anticancersammensætning til anvendelse i behandling af cancer i et menneske omfattende:

a) en cellulær energiinhibitor, der har strukturen ifølge formel I



(I)

hvor X er valgt fra gruppen bestående af: en nitrogruppe, en imidazol, et halogenid, sulfonat, et carboxylat, et alkoholat, og aminoxid; og R er valgt fra gruppen bestående af: OR', N(R")2, C(O)R'", C_1-C_6-alkyl, C_6-C_{12}-aryl, C_1-C_6-heteroalkyl, en C_6-C_{12}-heteroaryl, H og et alkalimetal; hvor R' betegner H, alkalimetal, C_1-C_6-alkyl, C_6-C_{12}-aryl eller C(O)R'", R" betegner H, C_1-C_6-alkyl eller C_6-C_{12}-aryl, og R'" betegner H, C_1-C_{20}-alkyl eller C_6-C_{12} aryl;

b) mindst en sukkeralkohol, som stabiliserer den cellulære energiinhibitor ved i det væsentlige at forhindre inhibitoren fra hydrolyse, fortrinsvis i en koncentration fra ca. 0,1 mM til ca. 250 mM, mere foretrukket ca. 0,5 mM til ca. 25 mM;

c) en glycolyse-inhibitor omfattende 2-deoxyglucose; og

d) en biologisk buffer omfattende en citratpuffer, der er til stede i en tilstrækkelig mængde til mindst delvist afsuring af den cellulære energiinhibitor og neutralisere metaboliske biprodukter af den cellulære energiinhibitor.

2. Anticancersammensætning til anvendelse ifølge krav 1, hvor R i formel (I) er OH og X i formel (I) er valgt fra gruppen bestående af: et halogenid, dvs. fluorid, chlorid, bromid og iodid, et sulfonat, et carboxylat, et alkoholat, og et aminoxid.

3. Anticancersammensætning til anvendelse ifølge krav 1, hvor den cellulære energiinhibitor er et 3-halopyruvate valgt fra gruppen bestående af: 3-fluorpyruvat, 3- chlorpyruvat, 3-brompyruvat, 3-iodpyruvat, og kombinationer deraf, og er fortrinsvis 3-brompyruvat fortrinsvis i en koncentration fra ca. 0,1 mM til ca. 25,0 mM, fortrinsvis fra ca. 1,0 mM til ca. 10,0 mM.

4. Anticancersammensætning til anvendelse ifølge krav 1, hvor sammensætningen omfatter en eller to yderligere sukkeralkoholer.

5. Anticancersammensætning til anvendelse ifølge krav 4, hvor sammensætningen omfatter to yderligere sukkeralkohol og mindst et af

sukkeralkoholerne er en fem-carbon-sukkeralkohol eller glycerol.

6. Anticancer sammensætning til anvendelse ifølge krav 4, hvor sammensætningen omfatter to yderligere sukkeralkoholer og mindst to af sukkeralkoholerne er fem-carbon-sukkeralkoholer, der uafhængigt er valgt fra gruppen bestående af mannitol, erythritol, isomalt, lactitol, maltitol, sorbitol, xylitol, dulcitol, ribitol, inositol, og kombinationer deraf.

7. Anticancersammensætning til anvendelse ifølge krav 4, hvor sammensætningen omfatter yderligere to sukkeralkoholer og sukkeralkoholerne er glycerol, inositol, og sorbitol, fortrinsvis glycerol i et område fra ca. 0,1 vægt-% til ca. 3 vægt-%, inositol i et område fra omkring 1 vægt-% til ca. 5 vægt-% og sorbitol i et område fra ca. 30 vægt-% til ca. 50 vægt-% af sammensætningen.

8. Anticancer sammensætning til anvendelse ifølge krav 1, hvor glycolyse-inhibitoren 2-deoxglucose er til stede i en koncentration fra ca. 0,1 mM til ca. 25,0 mM, fortrinsvis i en koncentration fra ca. 1 mM til ca. 5 mM.

9. Anticancer sammensætning til anvendelse ifølge krav 1, hvor den biologiske puffer yderligere omfatter en biologisk puffer valgt fra gruppen bestående af en phosphatbuffer og en acetatpuffer.

10. Anticancer sammensætning til anvendelse ifølge krav 1 eller 9, hvor den biologiske puffer er til stede i en koncentration fra ca. 0,1 mM til ca. 200 mM, mere fortrinsvis fra ca. 1 mM til ca. 20 mM, hvor der fortrinsvis opretholdes et fysiologisk pH på 4,0 til 8,5, mere fortrinsvis et fysiologisk pH på 5,5 til 8,0.

11. Anticancer sammensætning til anvendelse ifølge krav 1, yderligere omfattende en halogenmonocarboxylatforbindelse, fortrinsvis en halogen to-carbon monocarboxylatforbindelse, fortrinsvis valgt fra gruppen bestående af 2-fluoracetat, 2-chloracetat, 2-bromacetat, 2-iodacetat og blandinger deraf, og er mere fortrinsvis 2-bromacetat, eller en halogen tre-carbon-monocarboxylat-forbindelse, der fortrinsvis er valgt fra gruppen bestående af 3-fluorlactat, 3-chlorlactat, 3-bromlactat, 3-iodolactat, og blandinger deraf, fortrinsvis i en koncentration fra ca. 0,5 mM til ca. 250 mM, mere foretrukket fra ca. 10 mM til ca. 50 mM.

12. Anticancer sammensætning til anvendelse ifølge krav 1, hvor den cellulære energiinhibitor og den biologiske buffer er til stede i et forhold i området fra 1:1 til 1:5 målt som mM, den cellulære energiinhibitor og glycolyse-inhibitoren er til stede i et forhold i området fra 5:1 til 1:1 målt som mM, eller den cellulære energiinhibitor og den mindst ene sukkeralkohol er tilstede i et forhold i området fra 1:1 til 1:5 som mM.

13. Anticancersammensætning til anvendelse ifølge krav 1, hvor anticancersammensætningen skal administreres til det humane individ, når individets insulin/glucagon-forhold i blodet er i området fra ca. 1 til ca. 10 og skal administreres intraarterielt, intravenøst, intraperitonalt, ved inhalation, intratumoralt, oralt, topisk og/eller subkutant, fortrinsvis i en dosis på ca. 1 mM

til ca. 10 mM af anticancersammensætningen i et volumen på 25 ml til 1000 ml.

14. Anticancer sammensætning til anvendelse ifølge krav 1, hvor canceren er udvalgt fra gruppen bestående af: barndomsfibrolamellært hepatocellulært carcinom (FHCC), hepatocellulært carcinom (HCC), ikke-småcellet lungecancer, coloncancer, pancreascancer, levercancer, og kombinationer deraf.

15. Kit til behandling af cancer hos en menneskelig patient, omfattende:

a) en cellulær energiinhibitoringrediens, der har strukturen ifølge formel I ifølge krav 1, hvor X og R er som defineret i krav 1 med hensyn til formel I

b) mindst en sukkeralkoholingrediens, som stabiliserer den cellulære energiinhibitoringrediens ved i det væsentlige at forhindre den cellulære energiinhibitoringrediens fra hydrolyse;

c) en glycolyse-inhibitoringrediens herunder 2-deoxyglucose;

d) en biologisk bufferingrediens omfattende en citratpuffer, der er til stede i en tilstrækkelig mængde til mindst delvist afsuring af den cellulære energiinhibitoringrediens og neutralisere metaboliske biprodukter af den cellulære energiinhibitoringrediens;

e) en beholder til at indeholde de ingredienser, som fortrinsvis er indeholdt i individuelle beholdere inde i beholderen og

f) et sæt instruktioner til fremstilling af en doseringsform under anvendelse af ingredienserne og til administration af doseringsformen til en patient.

DRAWINGS

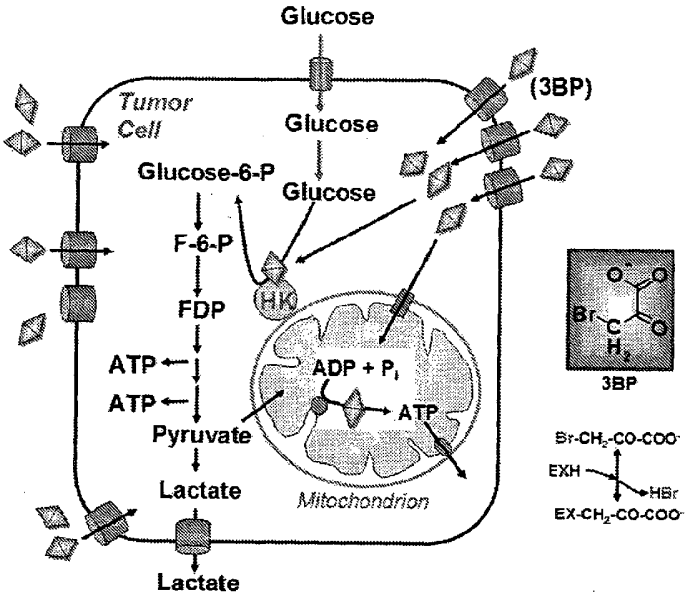


FIG. 1

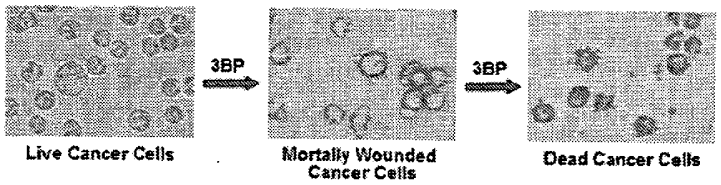


FIG. 2

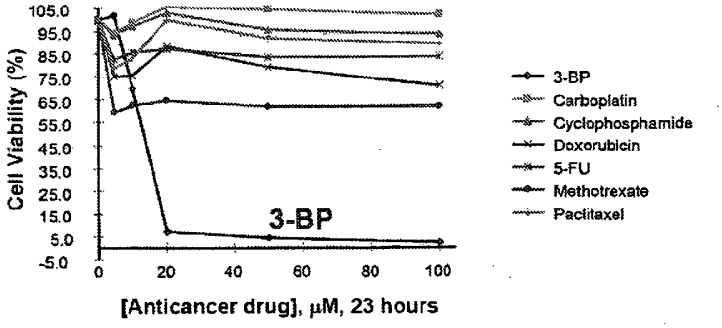


FIG. 3

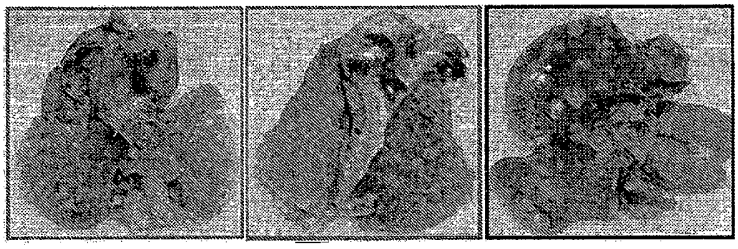


FIG. 4(a)

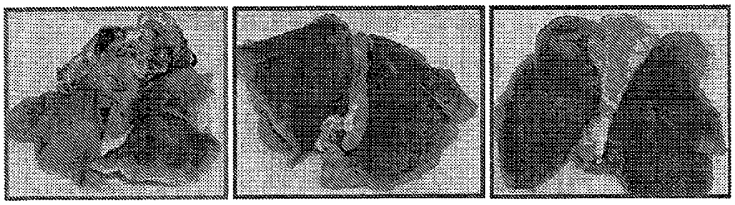


FIG. 4(b)