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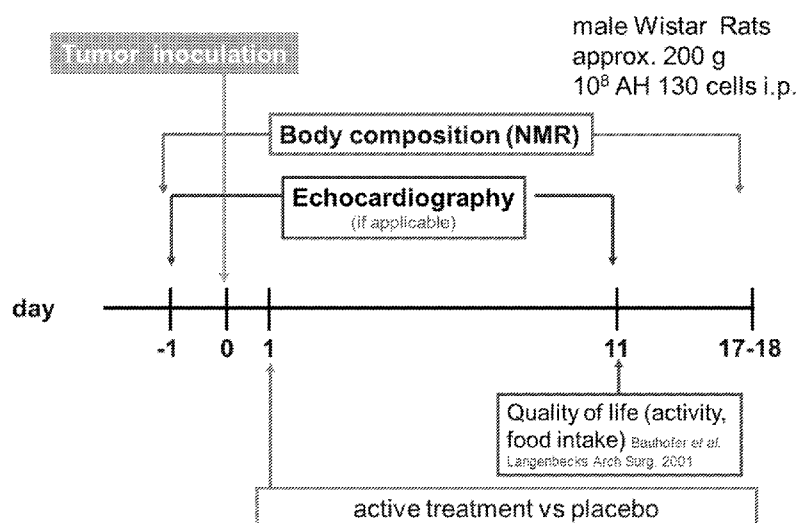
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(54) Title: CANRENOATE COMPOSITIONS FOR TREATING CANCER

Figure 1



(57) Abstract: The present invention relates to canrenoate compositions and uses thereof, including uses of the canrenoate compositions for treating cancer. The canrenoate compositions can also be used for treating cachexia, preventing body weight loss in subjects, preventing loss of lean body mass, preventing loss of adipose tissue in subjects, improving quality of life in subjects, and prolonging survival in cancer patients.

CANRENOATE COMPOSITIONS FOR TREATING CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of U.S. Provisional Patent Application Serial No. 61/786,238, filed March 14, 2013, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present invention relates to canrenoate compositions and uses thereof, including uses of the canrenoate compositions for treating cancer.

BACKGROUND

[0003] Cancer is the second most common cause of death in the United States, exceeded only by heart disease. In the United States, cancer accounts for 1 of every 4 deaths. With population growth and aging of the population, the number of new cancer patients is expected to double to 2.6 million people by 2050.

[0004] Liver cancer is the sixth most common cancer worldwide and the third most common cause of cancer-related death. The most common form of liver cancer is hepatocellular carcinoma (HCC). HCC is often diagnosed late in the course of clinical manifestation. As a result, only 10-15% of patients are candidates for curative surgery. For the majority of HCC patients, systemic chemotherapies or supportive therapies are the mainstay treatment options. Nevertheless, most chemotherapeutic agents show limited effectiveness and have not been able to improve patient survival. *See, e.g.* Ma YT, Palmer DH. Impact of restricting access to high-cost medications for hepatocellular carcinoma. [Review] Expert Review of Pharmacoeconomics & Outcomes Research. 12(4):465-73, 2012 Aug.

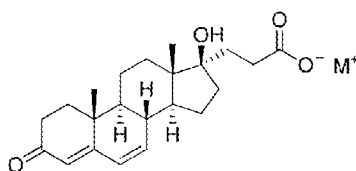
[0005] Potassium canrenoate is an aldosterone antagonist, which is a diuretic drug that antagonizes the action of aldosterone at mineralcorticoid receptors. Aldosterone antagonists are often used with other drugs for the management of chronic heart failure. Potassium canrenoate is not approved in the United States, but is used clinically in Europe and other countries as a diuretic.

[0006] The disclosure of all publications, patents, patent applications, and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

BRIEF SUMMARY OF THE INVENTION

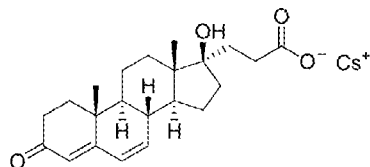
[0007] The present invention relates to canrenoate compositions and uses thereof, including uses of the canrenoate compositions for treating cancer.

[0008] The present disclosure provides, in some embodiments, a compound of the formula:



wherein M^+ is an ion of an alkali metal (Group 1) selected from the group consisting of Li^+ (lithium), Na^+ (sodium), Rb^+ (rubidium), and Cs^+ (cesium).

[0009] The present disclosure provides, in some embodiments, a compound of the formula:



(cesium canrenoate).

[0010] The present disclosure provides, in some embodiments, a pharmaceutical composition comprising cesium canrenoate.

[0011] The present disclosure provides, in some embodiments, a method of treating cancer in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate.

[0012] The present disclosure provides, in some embodiments, a method of prolonging survival of an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate.

[0013] The present disclosure provides, in some embodiments, a method of preventing body weight loss of an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate.

[0014] The present disclosure provides, in some embodiments, a method of improving quality of life in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate.

[0015] The present disclosure provides, in some embodiments, a method of preventing and/or treating loss of lean body mass in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate.

[0016] The present disclosure provides, in some embodiments, a method of preventing and/or treating muscle wasting in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate.

[0017] In some embodiments, the canrenoate is a pharmaceutically acceptable salt of canrenoate. In some embodiments, the canrenoate is selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the canrenoate is cesium canrenoate. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia. In some embodiments, the cancer is selected from the group consisting of liver cancer, lung cancer, ovarian cancer, pancreatic cancer, melanoma, and brain cancer. In some embodiments, the cancer is selected from the group consisting of gastric cancer, pancreatic cancer, lung, esophageal, colorectal, head and neck cancer, and hematological malignancies. In some embodiments, the cancer is liver cancer. In some embodiments, the cancer is an early stage cancer. In some embodiments, the cancer is a late stage cancer. In some embodiments, the composition is administered orally. In some embodiments, the amount of canrenoate in the composition is about 10 to about 200 mg daily. In some embodiments, the composition is administered daily or twice daily.

[0018] The present disclosure provides, in some embodiments, a kit comprising a pharmaceutical composition comprising a canrenoate and instruction for using the pharmaceutical composition for treating cancer.

[0019] Additional embodiments, features, and advantages of the invention will be apparent from the following detailed description and through practice of the invention.

[0020] For the sake of brevity, the disclosures of the publications cited in this specification, including patents, are herein incorporated by reference, in their entirety.

BRIEF DESCRIPTION OF THE FIGURES

[0021] Figure 1 is a diagram of the design study involving the Yoshida Hepatoma Model for cancer cachexia.

[0022] Figure 2 is a graph showing the percent survival of rat populations that were administered various dosages of cesium canrenoate (Cs-can). Comparison to placebo (plac) was also provided. The sample size in the population is indicated by "n." "HR" refers to hazard ratio. "CI" refers to confidence interval. "95% CI" is 95% confidence interval. "p" refers to p-value.

[0023] Figure 3 is a graph showing the percent survival of rat populations that were administered with various dosages of cesium canrenoate (Cs-can). The sample size in the population is indicated by "n." "HR" refers to hazard ratio. "CI" refers to confidence interval. "95% CI" is 95% confidence interval. "p" refers to p-value.

[0024] Figure 4 is a graph showing the change in body weight (in grams ("g")) of rat populations that were administered with cesium canrenoate. Comparison to placebo (P) was also provided. The asterisk (*) indicates $p < 0.05$. The two asterisks (**) indicate $p < 0.01$ vs placebo.

[0025] Figure 5 is a graph showing the change in lean body mass (in grams ("g")) of rat populations that were administered with various dosages of cesium canrenoate. Comparison to placebo (P) was also provided.

[0026] Figure 6 is a graph showing the change in fat mass (in grams ("g")) of rat populations that were administered with cesium canrenoate. Comparison to placebo (P) was also provided. The two asterisks (**) indicate $p < 0.01$ versus placebo. The three asterisks (***) indicate $p < 0.001$ vs placebo.

[0027] Figure 7A is a graph showing the weight of white adipose tissue (WAT) (in grams ("g")) of rat populations that were administered with various dosages of the cesium canrenoate at the endpoint of the study. Figure 7B is a graph showing the weight of brown adipose tissue (BAT) (in grams ("g")) of rat populations that were administered with various dosages of the cesium canrenoate at the endpoint of the study. Comparison to placebo (P) and sham (S) was also provided. The three asterisks (***) indicate $p < 0.001$ vs placebo.

[0028] Figure 8A is a graph showing the change in tumor volume (in mL) of rat populations that were administered with dosages of the cesium canrenoate. Comparison to placebo (P) was also provided. Figure 8B is a graph showing the change in total cells in a

tumor of rat populations that were administered with various dosages of cesium canrenoate. Comparison to placebo (P) was also provided. The asterisk (*) indicates $p < 0.05$ vs placebo.

[0029] Figure 9 is a graph showing effect of cesium canrenoate or doxorubicin on tumor growth, as assessed by BrdU incorporation and XTT assay with various tumor cells, namely, Kelly (neuroblastoma), Hela-93 (cervix carcinoma), and B16V (melanoma).

DETAILED DESCRIPTION OF THE INVENTION

[0030] The present invention provides use of canrenoate compositions for achieving beneficial results in individuals having cancer, such as treating cancer, prolonging survival, preventing body weight loss, improving quality of life, and/or treating muscle wasting. Also provided are pharmaceutical compositions comprising canrenoates (such as cesium canrenoate).

[0031] The present invention is based on the surprising finding that canrenoate, specifically cesium canrenoate, significantly improved survival in animals having cancer in an experiment in which an animal was inoculated with hepatocellular carcinoma cells in a well-established animal model of hepatoma. Other advantageous effects of the compositions were observed on preventing body weight loss, preserving lean body mass, and preserving fat mass in the animals. Moreover, these effects were observed in animals not developing cachexia or before the animals develop cachexia, suggesting that at least some of the effect of cesium canrenoate that we observed may be independent and/or in addition to its effect on treating cancer cachexia.

[0032] Thus, the present invention in one aspect provides methods of treating cancer, prolonging survival, preventing body weight loss, preventing and/or treating muscle wasting, or improving quality of life in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate.

[0033] In another aspect, there are provided pharmaceutical compositions comprising cesium canrenoate.

[0034] Also provided are kits, unit dosages, medicines, and articles of manufacture that are useful for methods described herein.

Definitions

[0035] The following terms have the following meanings unless otherwise indicated. Any undefined terms have their art recognized meanings.

[0036] As used herein, “treatment” or “treating” is an approach for obtaining beneficial or desired results including clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, one or more of the following: alleviating one or more symptoms resulting from the disease, delay or slowing the progression of the disease, ameliorating the disease state, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival. Also encompassed by “treatment” is a reduction of pathological consequence of cancer. The methods of the invention contemplate any one or more of these aspects of treatment.

[0037] The term “individual” refers to a mammal and includes, but is not limited to, human, bovine, horse, feline, canine, rodent, or primate. In some embodiments, the individual is a human.

[0038] As used herein, an “at risk” individual is an individual who is at risk of developing cancer. An individual “at risk” may or may not have detectable disease, and may or may not have displayed detectable disease prior to the treatment methods described herein. “At risk” denotes that an individual has one or more so-called risk factors, which are measurable parameters that correlate with development of cancer. An individual having one or more of these risk factors has a higher probability of developing cancer than an individual without these risk factor(s).

[0039] “Adjuvant setting” refers to a clinical setting in which an individual has had a history of cancer, and generally (but not necessarily) been responsive to therapy, which includes, but is not limited to, surgery (*e.g.*, surgery resection), radiotherapy, and chemotherapy. However, because of their history of cancer, these individuals are considered at risk of development of the disease. Treatment or administration in the “adjuvant setting” refers to a subsequent mode of treatment. The degree of risk (*e.g.*, when an individual in the adjuvant setting is considered as “high risk” or “low risk”) depends upon several factors, most usually the extent of disease when first treated.

[0040] “Neoadjuvant setting” refers to a clinical setting in which the method is carried out before the primary/definitive therapy.

[0041] As used herein, “delaying” the development of a disease means to defer, hinder, slow, retard, stabilize, and/or postpone development of the disease. This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease. A method that

“delays” development of a disease is a method that reduces probability of disease development in a given time frame and/or reduces the extent of the disease in a given time frame, when compared to not using the method. Such comparisons are typically based on clinical studies, using a statistically significant number of subjects.

[0042] As used herein, by “combination therapy” is meant that a first agent be administered in conjunction with another agent. “In conjunction with” refers to administration of one treatment modality in addition to another treatment modality, such as administration of a nanoparticle composition described herein in addition to administration of the other agent to the same individual. As such, “in conjunction with” refers to administration of one treatment modality before, during, or after delivery of the other treatment modality to the individual. Such combinations are considered to be part of a single treatment regimen or regime.

[0043] The term “effective amount” used herein refers to an amount of a compound or composition sufficient to treat a specified disorder, condition or disease such as ameliorate, palliate, lessen, and/or delay one or more of its symptoms.

[0044] The term “simultaneous administration,” as used herein, means that a first therapy and second therapy in a combination therapy are administered with a time separation of no more than about 15 minutes, such as no more than about any of 10, 5, or 1 minutes. When the first and second therapies are administered simultaneously, the first and second therapies may be contained in the same composition (*e.g.*, a composition comprising both a first and second therapy) or in separate compositions (*e.g.*, a first therapy in one composition and a second therapy is contained in another composition).

[0045] As used herein, the term “sequential administration” means that the first therapy and second therapy in a combination therapy are administered with a time separation of more than about 15 minutes, such as more than about any of 20, 30, 40, 50, 60, or more minutes. Either the first therapy or the second therapy may be administered first. The first and second therapies are contained in separate compositions, which may be contained in the same or different packages or kits.

[0046] As used herein, the term “concurrent administration” means that the administration of the first therapy and that of a second therapy in a combination therapy overlap with each other.

[0047] As used herein, by “pharmaceutically acceptable” or “pharmacologically compatible” is meant a material that is not biologically or otherwise undesirable, *e.g.*, the

material may be incorporated into a pharmaceutical composition administered to an individual without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. Pharmaceutically acceptable carriers or excipients have preferably met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[0048] "Progression free survival" (PFS) indicates the length of time during and after treatment that the cancer does not grow. Progression-free survival includes the amount of time individuals have experienced a complete response or a partial response, as well as the amount of time individuals have experienced stable disease. In some embodiments, an individual has a capacity to accept more courses of chemotherapy during progression free survival.

[0049] The term "pharmaceutically acceptable salt" means a salt which is acceptable for administration to a subject, such as a mammal (salts with counterions having acceptable mammalian safety for a given dosage regime). Such salts can be derived from pharmaceutically acceptable inorganic or organic bases and from pharmaceutically acceptable inorganic or organic acids. "Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound, which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, lithium, sodium, potassium, rubidium, cesium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, formate, tartrate, besylate, mesylate, acetate, maleate, oxalate, and the like.

[0050] The term "salt thereof" means a compound formed when a proton of an acid is replaced by a cation, such as a metal cation or an organic cation and the like. Where applicable, the salt is a pharmaceutically acceptable salt, although this is not required for salts of intermediate compounds that are not intended for administration to the subject. By way of example, salts of the present compounds include those wherein the compound is protonated by an inorganic or organic acid to form a cation, with the conjugate base of the inorganic or organic acid as the anionic component of the salt.

[0051] "Solvate" refers to a complex formed by combination of solvent molecules with molecules or ions of the solute. The solvent can be an organic compound, an inorganic compound, or a mixture of both. Some examples of solvents include, but are not limited to,

methanol, *N,N*-dimethylformamide, tetrahydrofuran, dimethylsulfoxide, and water. When the solvent is water, the solvate formed is a hydrate.

[0052] It will be appreciated that the term “or a salt or solvate thereof” is intended to include all permutations of salts and solvates, such as a solvate of a pharmaceutically acceptable salt of a subject compound.

[0053] As used herein, “in conjunction with” refers to administration of one treatment modality in addition to another treatment modality. As such, “in conjunction with” refers to administration of one treatment modality before, during or after administration of the other treatment modality to the individual.

[0054] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly indicates otherwise.

[0055] Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X.”

[0056] It is understood that aspects and variations of the invention described herein include “consisting” and/or “consisting essentially of” aspects and variations.

Methods of the present invention

[0057] The present application in one aspect provides methods of treating cancer. In some embodiments, there is provided a method of treating cancer in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising a canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of treating cancer in an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia.

[0058] In some embodiments, there is provided a method of prolonging survival of an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of prolonging survival of an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia. In some embodiments, the method prolongs the survival of the individual by at least any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, or 24 months.

[0059] In some embodiments, there is provided a method of prolonging progression-free survival in an individual with cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of prolonging progression-free survival in an individual with cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia.

[0060] In some embodiments, there is provided a method of alleviating one or more symptoms associated with cancer in an individual, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some

embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of alleviating one or more symptoms associated with cancer in an individual, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia.

[0061] In some embodiments, there is provided a method of preventing body weight loss of an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of preventing body weight loss of an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia. In some embodiments, the body weight loss of the individual is no more than about 10% (for example no more than about any of 10%, 9%, 8%, 7%, 6%, or 5%) of the total body weight. In some embodiments, the body weight loss is evaluated over a time period of about 1 month to 2 years (for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 months).

[0062] In some embodiments, there is provided a method of treating muscle wasting in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate,

lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of treating muscle wasting in an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia. In some embodiments, the muscle wasting of the individual is no more than about 10% (for example no more than about any of 10%, 9%, 8%, 7%, 6%, or 5%) of the total body weight. In some embodiments, the muscle wasting is evaluated over a time period of about 1 month to 2 years (for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 months). In some embodiments, the method leads to a reduction of muscle wasting, i.e., a slow-down of muscle loss in the individual. In some embodiments, the method leads to a reversal of muscle wasting, i.e., an increase in muscle weight in the individual.

[0063] In some embodiments, there is provided a method of preventing loss of lean body mass in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, there is provided a method of treating loss of lean body mass in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of preventing loss of lean body mass in an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia. In some embodiments, the loss of lean body mass of the individual is no more than about 10% (for example no more than about any of 10%, 9%, 8%, 7%, 6%, or 5%) of the total lean body mass. In some embodiments, the loss of lean body mass is evaluated over a time period of about 1 month to 2 years (for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 months).

[0064] In some embodiments, there is provided a method of preventing (or delaying) development of cancer cachexia in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of preventing (or delaying) development of cancer cachexia in an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia.

[0065] In some embodiments, the individual has one or more symptoms of cancer cachexia, and the methods described herein can be used to improve one or more symptoms of cancer cachexia in an individual having cancer, the methods comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of improving one or more symptoms of cancer cachexia in an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia. Symptoms of cachexia include but not limited to, loss of weight, muscle atrophy, fatigue, weakness, and loss of appetite.

[0066] In some embodiments, there is provided a method of improving quality of life of an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition

comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of improving quality of life of an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia. Improvement of quality of life can be assessed, for example, by food intake, locomotive activity, and improvement in fatigue or dyspnea or global patient assessment scores, in short physical performance battery scores, in standard clinical assessment of functional performance, muscle strength, gait speed, leg strength and hand grip strength, 6-minute corridor walk test, stair climbing power, ability to tolerate courses of chemotherapy and other tests or instruments or questionnaires assessing patient quality of life.

[0067] In some embodiments, there is provided a method of increasing food intake of an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of improving food intake in an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia.

[0068] In some embodiments, there is provided a method of increasing locomotive activity of an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of

cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of improving locomotive activity of an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia.

[0069] In some embodiments, there is provided a method of improving fatigue or dyspnea in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of improving fatigue or dyspnea in an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia.

[0070] In some embodiments, there is provided a method of preventing loss of body fat in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of preventing loss of body fat in an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate composition in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom

of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia. In some embodiments, the loss of body fat of the individual is no more than about 10% (for example no more than about any of 10%, 9%, 8%, 7%, 6%, or 5%) of the total body fat. In some embodiments, the loss of body fat is evaluated over a time period of about 1 month to 2 years (for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 months).

[0071] Adipose tissue appears as two types: white adipose tissue and brown adipose tissue. White adipose tissue cells contain a single large fat droplet, which forces the nucleus to be squeezed into a thin rim at the periphery. They have receptors for insulin, growth hormones, norepinephrine and glucocorticoids. White adipose tissue is used as a store of energy. White adipose tissue also acts as a thermal insulator, helping to maintain body temperature. Brown adipose tissue cells contain numerous smaller droplets and a higher number of (iron containing) mitochondria, which gives a brown color to the cell. Brown fat also contains more capillaries than white fat, since it has a greater need for oxygen than most tissues. The methods provided herein are useful for preventing loss of both white adipose tissue and brown adipose tissue in an individual having cancer.

[0072] In some embodiments, there is provided a method of providing cardioprotective effects in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate). In some embodiments, there is provided a method of preventing wasting of a heart muscle in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate). In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of providing cardioprotective effects in an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate composition in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, there is provided a method of preventing wasting of a heart muscle in an individual having cancer, comprising administering (such as orally administering) to the

individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate composition in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia. Cardioprotective effects include one or more of the following: preventing and treating atrial fibrillation and ventricular fibrillation, improving arrhythmias, improving diastolic function of a heart, and preventing and treating fibrosis of a heart. The methods described herein are therefore useful for any one or more of these cardioprotective effects.

[0073] In some embodiments, there is provided a method of preventing sudden death and/or cardiovascular death in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate). In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of preventing sudden death and/or cardiovascular death in an individual having cancer, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate composition in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia.

[0074] The methods described herein may be useful for any one or more of the following: 1) preventing loss of skeletal muscle associated with cancer; 2) treating fatigue associated with cancer; 3) treating muscle weakness associated with cancer; 4) strengthening skeletal muscle in an individual having cancer; 5) treatment of muscle wasting associated with cancer; 6) treating dyspnea associated with muscle changes in cancer; and 7) improving fatigue resistance of muscle in cancer. Skeletal muscle includes, but is not limited to, gastrocnemius muscle, tibialis muscle, soleus muscle, and extensor digitorum longus (EDL) muscle, quadriceps, hamstrings, postural muscles, hand muscles, triceps, biceps, masseter and

other jaw muscles, and intercostal and other respiratory muscles. The present application encompasses any of these methods.

[0075] In some embodiments, the individual has been diagnosed with or is suspected of having cancer. In some embodiments, the individual exhibits one or more symptoms associated with cancer. In some embodiments, the individual has a low tumor burden. In some embodiments, the individual is a human. In some embodiments, the individual is at least about any of 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, or 85 years old. In some embodiments, the individual is no more than about any of 35, 30, 20, 15, 10, 5, or 1 year old. In some embodiments, the individual is a male. In some embodiments, the individual is a female. In some embodiments, the individual has a single lesion at presentation. In some embodiments, the individual has multiple lesions at presentation. In some embodiments, the individual has been previously treated for cancer. In some embodiments, the individual has not previously been treated for cancer.

[0076] The cancer described herein can be of any stage. In general, cancers can be evaluated according to Overall Stage Grouping, outlined as follows:

Stage 0	Carcinoma <i>in situ</i>
Stage I	Cancers are localized to one part of the body
Stage II	Cancers are locally advanced
Stage III	Cancers are also locally advanced. Whether a cancer is designated as Stage II or Stage III can depend on the specific type of cancer; for example, in Hodgkin's Disease, Stage II indicates affected lymph nodes on only one side of the diaphragm, whereas Stage III indicates affected lymph nodes above and below the diaphragm. The specific criteria for Stages II and III therefore differ according to diagnosis.
Stage IV	Cancers have often metastasized, or spread to other organs or throughout the body

[0077] In some embodiments, the cancer is surgically treatable. In some embodiments, the cancer is not surgically treatable.

[0078] In some embodiments, the cancer is an early stage cancer, such as Stage 0, Stage I, or Stage II. In some embodiments, the cancer is a late stage cancer, such as Stage III or Stage IV. In some embodiments, the cancer is Stage IIIA. In some embodiments, the cancer is Stage IIIB or Stage IV. In some embodiments, the cancer is Stage IV.

[0079] In some embodiments, the cancer is early stage cancer, non-metastatic cancer, primary cancer, advanced cancer, locally advanced cancer, metastatic cancer, cancer in remission, or recurrent cancer. In some embodiments, the cancer is localized resectable,

localized unresectable, or unresectable. In some embodiments, the cancer is a progressive cancer. In some embodiments, the cancer is substantially refractory to hormone therapy. In some embodiments, the cancer is HER2 positive. In some embodiments, the cancer is HER2 negative. In some embodiments, the cancer is estrogen receptor and/or progesterone receptor positive. In some embodiments, the cancer is estrogen receptor and/or progesterone receptor negative.

[0080] The methods provided herein can be practiced in an adjuvant setting. Alternatively, the methods can be practiced in a neoadjuvant setting, i.e., the method may be carried out before the primary/definitive therapy. In some embodiments, the method is a first line therapy. In some embodiments, the method is a second line therapy.

[0081] The methods described herein can be useful for treating and providing beneficial effects to individuals having a cancer. In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is adenocarcinoma. In some embodiments, the cancer is sarcoma.

[0082] In some embodiments, the cancer is any one of the following: biliary cancer (e.g., cholangiocarcinoma), bladder cancer, breast cancer (e.g., adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast), brain cancer (e.g., glioblastoma, meningioma; glioma, e.g., astrocytoma, oligodendroglioma; medulloblastoma), cervical cancer (e.g., cervical adenocarcinoma), colorectal cancer (e.g., colon cancer, rectal cancer, colorectal adenocarcinoma), esophageal cancer, gastric cancer (e.g., stomach adenocarcinoma), gastrointestinal stromal tumor (GIST), head and neck cancer (e.g., head and neck squamous cell carcinoma, oral cancer (e.g., oral squamous cell carcinoma (OSCC)), kidney cancer (e.g., nephroblastoma a.k.a. Wilms' tumor, renal cell carcinoma), liver cancer (e.g., hepatocellular cancer (HCC), malignant hepatoma), lung cancer (e.g., bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung), leukemia (e.g., acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL)), lymphoma (e.g., Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL)), multiple myeloma (MM), myelodysplastic syndrome (MDS), myeloproliferative disorder (MPD) (e.g., polycythemia Vera (PV), essential thrombocythemia (ET), agnogenic myeloid metaplasia (AMM) a.k.a. primary myelofibrosis (PMF), chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL),

hypereosinophilic syndrome (HES)), neuroblastoma, neurofibroma (e.g., neurofibromatosis (NF) type 1 or type 2, schwannomatosis), neuroendocrine cancer (e.g., gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor), osteosarcoma, ovarian cancer (e.g., cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), pancreatic cancer (e.g., pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN)), prostate cancer (e.g., prostate adenocarcinoma), skin cancer (e.g., squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)) and soft tissue sarcoma (e.g., malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, rhabdomyosarcoma, myxosarcoma).

[0083] In some embodiments, the cancer is selected from the group consisting of bladder cancer, breast cancer, medulloblastoma, colorectal cancer, head and neck cancer, lung cancer (e.g., small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC)), leukemia (e.g., acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL)), lymphoma (e.g., Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL)), multiple myeloma (MM), chronic myeloproliferative disorder (primary myelofibrosis, polycythemia vera, essential thrombocytemia), osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, basal cell carcinoma (BCC) and chondrosarcoma.

[0084] In some embodiments, the cancer is a cancer that is difficult to treat. Examples of cancers that are difficult to treat include, but are not limited to, brain cancer (such as glioblastoma), liver cancer, lung cancer, ovarian cancer, pancreatic cancer, and skin cancer (such as melanoma).

[0085] In some embodiments, the cancer is a cancer that is or is known to be associated with cachexia. Examples of cancers that are associated with cachexia include, but are not limited to, gastric cancer, pancreatic cancer, lung, esophageal, colorectal, head and neck cancer, and hematological malignancies.

[0086] In some embodiments, the cancer is liver cancer, such as hepatocarcinoma ("HCC"), hepatoblastoma, cholangiocarcinoma, angiosarcoma, hemangiosarcoma, or lymphoma of the liver. In some embodiments, the liver cancer (such as HCC) is early stage, non-metastatic, primary, advanced, locally advanced, metastatic, liver cancer (such as HCC) in remission, or recurrent liver cancer (such as recurrent HCC). In some embodiments, the liver cancer (such as HCC) is localized resectable (i.e., tumors that are confined to a portion

of the liver that allows for complete surgical removal), localized unresectable (i.e., the localized tumors may be unresectable because crucial blood vessel structures are involved or because the liver is impaired), or unresectable (i.e., the tumors involve all lobes of the liver and/or has spread to involve other organs (e.g., lung, lymph nodes, bone). In some embodiments, the liver cancer (such as HCC) is, according to TNM classifications, a stage I tumor (single tumor without vascular invasion), a stage II tumor (single tumor with vascular invasion, or multiple tumors, none greater than 5 cm), a stage III tumor (multiple tumors, any greater than 5 cm, or tumors involving major branch of portal or hepatic veins), a stage IV tumor (tumors with direct invasion of adjacent organs other than the gallbladder, or perforation of visceral peritoneum), N1 tumor (regional lymph node metastasis), or M1 tumor (distant metastasis). In some embodiments, the liver cancer (such as HCC) is, according to AJCC (American Joint Commission on Cancer) staging criteria, stage T1, T2, T3, or T4 HCC. In some embodiments, the liver cancer is any one of liver cell carcinomas, fibrolamellar variants of HCC, and mixed hepatocellular cholangiocarcinomas.

[0087] In some embodiments, the individual is of Asian ancestry. In some embodiments, the individual is HBsAg positive. In some embodiments, the individual is HBsAg negative. In some embodiments, the individual has underlying liver cirrhosis. In some embodiments, the individual does not have the underlying liver cirrhosis. In some of embodiments, the individual is genetically or otherwise predisposed (e.g., having a risk factor) to developing liver cancer (such as HCC). These risk factors include, but are not limited to, age, sex, race, diet, history of previous disease, presence of precursor disease (e.g., hepatitis B or hepatitis C viral infection, liver cirrhosis), genetic (e.g., hereditary) considerations, and environmental exposure. In some embodiments, the individuals at risk for liver cancer (such as HCC) include, e.g., those having relatives who have experienced liver cancer (such as HCC), and those whose risk is determined by analysis of genetic or biochemical markers.

[0088] Thus, for example, in some embodiments, there is provided a method of treating liver cancer (such as HCC) in an individual having liver cancer (such as HCC), comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate.

In some embodiments, there is provided a method of treating liver cancer (such as HCC) in an individual having liver cancer (such as HCC), comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia.

[0089] In some embodiments, there is provided a method of prolonging survival of an individual having liver cancer (such as HCC), comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of prolonging survival of an individual having liver cancer (such as HCC), comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia. In some embodiments, the method prolongs the survival of the individual by at least any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, or 24 months.

[0090] In some embodiments, there is provided a method of preventing body weight loss of an individual having liver cancer (such as HCC), comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, there is provided a method of preventing (or delaying) development of cancer cachexia in an individual having liver cancer (such as HCC), comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, there is provided a method of preventing loss of lean body mass in an individual having liver cancer (such as HCC), comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, there is provided a method of preventing loss of body fat in an individual having liver cancer (such as HCC), comprising administering to the individual an effective amount of a composition

comprising canrenoate. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia.

[0091] In some embodiments, there is provided a method of alleviating one or more symptoms associated with liver cancer (such as HCC) in an individual, comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of alleviating one or more symptoms associated with liver cancer (such as HCC) in an individual, comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia.

[0092] In some embodiments, there is provided a method of prolonging progression-free survival in an individual with liver cancer (such as HCC), comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of prolonging progression-free survival in an individual with liver cancer (such as HCC), comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the individual has one or more symptoms of cancer cachexia.

[0093] In some embodiments, there is provided a method of treating muscle wasting in an individual having liver cancer (such as HCC), comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of treating muscle wasting in an individual having liver cancer (such as HCC), comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia. In some embodiments, the method leads to a reduction of muscle wasting, i.e., a slow-down of muscle loss. In some embodiments, the method leads to a reversal of muscle wasting, i.e., an increase in muscle weight.

[0094] In some embodiments, there is provided a method of improving quality of life in an individual having liver cancer (such as HCC), comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of improving quality of life in an individual having liver cancer (such as HCC), comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia.

[0095] In some embodiments, there is provided a method of increasing food intake of an individual having liver cancer (such as HCC), comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of

cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of increasing food intake of an individual having liver cancer (such as HCC), comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia.

[0096] In some embodiments, there is provided a method of increasing locomotive activity of an individual having liver cancer (such as HCC), comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of increasing locomotive activity of an individual having liver cancer (such as HCC), comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia.

[0097] In some embodiments, there is provided a method of improving fatigue and dyspnea in an individual having liver cancer (such as HCC), comprising administering to the individual an effective amount of a composition comprising canrenoate. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate. In some embodiments, there is provided a method of improving fatigue and dyspnea in an individual having liver cancer (such as HCC), comprising administering (such as orally administering) to the individual an effective amount of a composition comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition is about 10 mg to

about 200 mg (such as about 20 to about 50 mg, for example) per day. In some embodiments, the individual has no symptom of cancer cachexia.

[0098] In some embodiments, the individual being treated is no more than about 18 years old. For example, in some embodiments, there is provided a method of treating a cancer in an individual having pediatric cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate, wherein the individual is no more than about 18 years old. In some embodiments, there is provided a method of promoting growth in an individual having a cancer, wherein the individual is no more than about 18 years old. In some embodiments, there is provided a method of preventing loss of growth in an individual having cancer, wherein the individual is no more than about 18 years old. In some embodiments, there is provided a method of treating muscle wasting in an individual having cancer, wherein the individual is no more than about 18 years old. In some embodiments, there is provided a method of prolonging survival of an individual having cancer, wherein the individual is no more than about 18 years old. In some embodiments, there is provided a method of improving quality of life in an individual having cancer, wherein the individual is no more than about 18 years old. In some embodiments, the individual is no more than about any of 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 year old. In some embodiments, the individual is about 9 to about 15 years old. In some embodiments, the individual is about 5 to about 9 years old. In some embodiments, the individual is about 1 to about 5 years old. In some embodiments, the individual is no more than about 1 year old, such as about 6 months old to about 1 year old, less than about 6 months old, or less than about 3 months old. In some embodiments, the composition comprises a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition comprises a canrenoate selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and rubidium canrenoate. In some embodiments, the composition comprises cesium canrenoate.

[0099] In some embodiments, the individual no more than about 18 years old for the methods described herein has a solid tumor. In some embodiments, the solid tumor is sarcoma. In some embodiments, the solid tumor is carcinoma (such as adenocarcinoma). In some embodiments, the solid tumor is a neuroendocrine tumor. In some embodiments, the solid tumor is a cancer of the connective tissue. In some embodiments, the solid tumor is a cancer arising from mesenchymal cells (e.g., skeletal muscle progenitor cells). In some embodiments, the solid tumor is a soft tissue tumor (such as soft tissue sarcoma). In some

embodiments, the solid tumor is selected from the group consisting of neuroblastoma, rhabdomyosarcoma, osteosarcoma, retinoblastoma, CNS tumor, Wilm's tumor, and Ewing's sarcoma. In some embodiments, the solid tumor is an abdominal tumor, a soft tissue tumor, a bone tumor, or an eye tumor. In some embodiments, the solid tumor is a brain tumor. In some embodiments, the solid tumor is melanoma. In some embodiments, the solid tumor is a soft tissue sarcoma, such as rhabdomyosarcoma. In some embodiments, the solid tumor is neuroblastoma. In some embodiments, the solid tumor is osteosarcoma. In some embodiments, the solid tumor is retinoblastoma. In some embodiments, the solid tumor is a heritable retinoblastoma.

[0100] In some embodiments, the individual no more than about 18 years old for the methods described herein has a central nervous system (CNS) tumor, such as an astrocytoma, a brain stem glioma, an ependymoma, a germ cell tumor, or a medulloblastoma. Childhood central nervous system tumors do not typically spread outside the brain and spinal cord. In some embodiments, the CNS tumor is a recurrent CNS tumor.

[0101] In some embodiments, the individual no more than 18 years old for the methods described herein has Wilms' tumor (also known as nephroblastoma). In some embodiments, the individual has Stage I Wilms' tumor. In some embodiments, the individual has Stage II Wilms' tumor. In some embodiments, the individual has Stage III Wilms' tumor. In some embodiments, the individual has Stage IV Wilms' tumor. In some embodiments, the individual has Stage V Wilms' tumor. In some embodiments, the individual has recurrent Wilms' tumor.

[0102] In some embodiments, the individual no more than 18 years old for the methods described herein has soft tissue sarcoma. In some embodiments, the individual has Stage I soft tissue sarcoma. In some embodiments, the individual has Stage II soft tissue sarcoma. In some embodiments, the individual has Stage III soft tissue sarcoma. In some embodiments, the individual has Stage IV soft tissue sarcoma. In some embodiments, the individual has recurrent soft tissue sarcoma.

[0103] In some embodiments, the individual no more than about 18 years old for the methods described herein has Ewing's sarcoma. In some embodiments, the individual has localized Ewing's sarcoma. In some embodiments, the individual has metastatic Ewing's sarcoma. In some embodiments, the individual has Stage 1 Ewing's sarcoma. In some embodiments, the individual has Stage 2 Ewing's sarcoma. In some embodiments, the

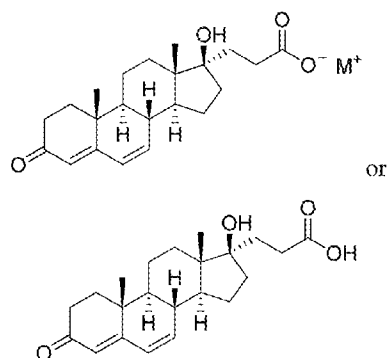
individual has Stage 3 Ewing's sarcoma. In some embodiments, the individual has Stage 4 Ewing's sarcoma. In some embodiments, the individual has recurrent Ewing's sarcoma.

[0104] In some embodiments, the individual no more than about 18 years old for the methods described herein has hepatoblastoma.

[0105] In some embodiments, the individual no more than about 18 years old for the methods described herein has a haematological disease, such as leukemia (for example acute leukemia).

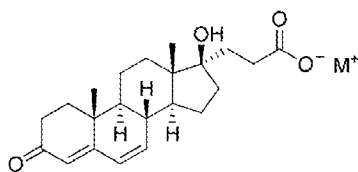
Canrenoate compositions

[0106] The methods described herein comprise administration of compositions comprising a pharmaceutically acceptable salt of canrenoate or canrenoic acid:



wherein M^+ is an ion of an alkali metal (Group 1), such as Li^+ (lithium), Na^+ (sodium), K^+ (potassium), Rb^+ (rubidium), and Cs^+ (cesium). As used herein, "canrenoate" or "a canrenoate composition" comprises a pharmaceutically acceptable salt of canrenoate and/or canrenoic acid. In some embodiments, for the use in methods, a pharmaceutically acceptable salt of canrenoate is provided. In some embodiments, for the use in methods, cesium canrenoate is provided. The present disclosure also provides such compositions which are useful for the methods disclosed herein.

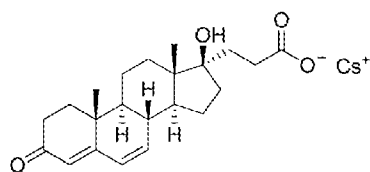
[0107] The present disclosure, in one aspect, provides a compound of the formula:



wherein M^+ is an ion of an alkali metal (Group 1) selected from the group consisting of Li^+

(lithium), Na^+ (sodium), Rb^+ (rubidium), and Cs^+ (cesium). In some embodiments, M^+ is Li^+ (lithium). In some embodiments, M^+ is Na^+ (sodium). In some embodiments, M^+ is Rb^+ (rubidium). In some embodiments, M^+ is Cs^+ (cesium).

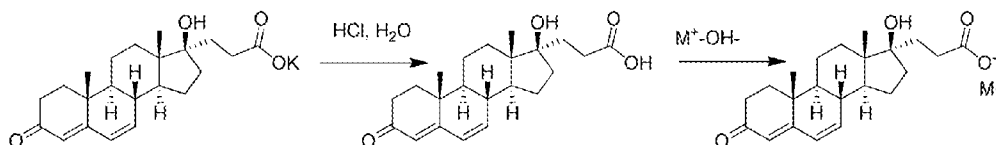
[0108] The present disclosure, in one aspect, provides a compound of the formula:



(cesium canrenoate).

[0109] The systemic (IUPAC) name for cesium canrenoate is cesium 3-[(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-hydroxy-10,13-dimethyl-3-oxo-2,8,9,11,12,14,15,16-octahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]propanoate. Cesium canrenoate has the chemical formula: $\text{C}_{22}\text{H}_{29}\text{O}_4\text{Cs}$. The molecular weight is 490.37.

[0110] The pharmaceutical salts of canrenoate can be obtained commercially or through synthesis with procedures known in the art.

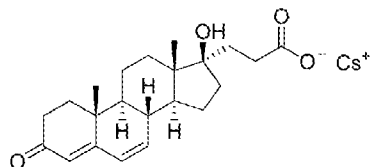


[0111] In some embodiments, pharmaceutical salts of canrenoate can be synthesized from canrenic acid. Referring to the scheme above, potassium canrenoate can be obtained commercially. Canrenic acid can be synthesized from potassium canrenoate, such as with adjustment of the pH of the reaction solution. Reaction of canrenic acid with an electrolyte having an alkali metal (Group I) would yield a pharmaceutical salt of canrenoate. In some embodiments, the electrolyte contains Li^+ (lithium), Na^+ (sodium), Rb^+ (rubidium), or Cs^+ (cesium). In some embodiments, cesium hydroxide (CsOH) can be used to prepare cesium canrenoate.

[0112] The present disclosure provides, in some embodiments, a compound having the characteristics of a compound prepared by reaction of canrenic acid and a cesium electrolyte (such as cesium hydroxide). By having the characteristics of a compound prepared by certain processes, the resulting compound has properties that are the same or similar to a compound prepared by the process. In some embodiments, the properties that

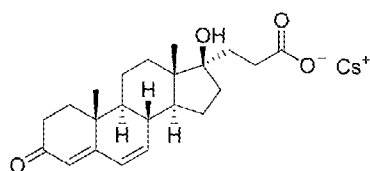
can be measured and compared are molecular weight, ^1H -NMR spectrum, IR spectrum, and melting point.

[0113] The present disclosure provides a compound of the formula:



(cesium canrenoate).

[0114] The present disclosure provides a composition comprising a compound of the formula:



(cesium canrenoate).

[0115] In some embodiments, the composition is a pharmaceutical composition. In some embodiments, the composition further comprises other salt forms of canrenoate, such as lithium canrenoate, sodium canrenoate, potassium canrenoate, or rubidium canrenoate. In some embodiments, the composition further comprises potassium canrenoate. In compositions comprising mixtures of salt forms of canrenoate, in some embodiments, the composition comprises at least 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% w/w of cesium canrenoate, where the percentage w/w is calculated by using the weight of cesium canrenoate and the total weight of canrenoate with the other salt form. In some embodiments, the composition comprises both cesium canrenoate and potassium canrenoate, wherein the weight ratio of the cesium canrenoate and the potassium canrenoate in the composition is more than about any of 2:1, 5:1, 10:1, 20:1, 30:1, 40:1, 50:1, 60:1, 70:1, 80:1, 90:1, or 100:1.

[0116] The compositions described herein, in some embodiments, are present in pharmaceutical compositions. The pharmaceutical compositions may further comprise one or more pharmaceutically acceptable carrier (or excipients). A pharmaceutically-acceptable excipient is a substance that is non-toxic and otherwise biologically suitable for administration to a subject. Such excipients facilitate administration of the compounds described herein and are compatible with the active ingredient. Examples of

pharmaceutically-acceptable excipients include stabilizers, lubricants, surfactants, diluents, anti-oxidants, binders, coloring agents, bulking agents, emulsifiers, or taste-modifying agents. In some embodiments, the pharmaceutical composition is sterile.

[0117] Also provided herein are unit dosage forms comprising a pharmaceutical composition described herein. These unit dosage forms can be stored in a suitable packaging in single or multiple unit dosages and may also be further sterilized and sealed. Unit dosage forms can be provided, for example, in the form of tablets, capsules, vials, and any other forms described herein.

[0118] In some embodiments, there is provided a composition (such as a pharmaceutical composition, for example a unit dosage) comprising canrenoate (such as cesium canrenoate), wherein the amount of canrenoate in the composition (such as pharmaceutical composition) is included in any of the following ranges: about 5 to about 10 mg, about 10 to about 20 mg, about 20 to about 30 mg, about 30 to about 40 mg, about 40 to about 50 mg, about 50 to about 60 mg, about 60 to about 70 mg, about 70 to about 80 mg, about 80 to about 90 mg, about 90 to about 100 mg, about 100 to about 110 mg, about 110 to about 120 mg, about 120 to about 130 mg, about 130 to about 140 mg, about 140 to about 150 mg, about 150 to about 160 mg. In some embodiments, the amount of canrenoate in the composition is about 20 to about 160 mg, including for example about 50 to about 150 mg, 80 to about 150 mg, about 90 to about 140 mg, about 100 to about 120 mg. In some embodiments, the composition is suitable for oral administration. In some embodiments, the composition is a pharmaceutically acceptable salt of canrenoate. In some embodiments, the composition is cesium canrenoate.

[0119] In some embodiments, the composition is provided in a slow release form.

[0120] Also provided are articles of manufacture comprising the compositions, formulations, and unit dosages described herein in suitable packaging for use in the methods of treatment, methods of administration, and dosage regimens described herein. Suitable packaging for compositions described herein are known in the art, and include, for example, vial (such as sealed vials), vessels (such as sealed vessels), ampules, bottles, jars, flexible packaging (e.g., sealed Mylar or plastic bags), and the like. These articles of manufacture may further be sterilized and/or sealed.

Dosages and Administration Route

[0121] The dosage of the compositions described herein administered to an individual (such as a human) may vary with the particular composition, the method of administration, and the particular stage of cancer. The amount should be sufficient to produce a desirable response, such as a therapeutic or prophylactic response against cancer. In some embodiments, the amount of the composition is a therapeutically effective amount. In some embodiments, that amount of the composition is a prophylactically effective amount. In some embodiments, the amount of total canrenoate in the composition is below the level that induces a toxicological effect (*i.e.*, an effect above a clinically acceptable level of toxicity) or is at a level where a potential side effect can be controlled or tolerated when the composition is administered to the individual.

[0122] In some embodiments, the amount of canrenoate (such as cesium canrenoate) in the composition is included in any of the following ranges: about 0.5 to about 5 mg, about 5 to about 10 mg, about 10 to about 15 mg, about 15 to about 20 mg, about 20 to about 25 mg, about 20 to about 50 mg, about 25 to about 50 mg, about 50 to about 75 mg, about 50 to about 100 mg, about 75 to about 100 mg, about 100 to about 125 mg, about 125 to about 150 mg, about 150 to about 175 mg, about 175 to about 200 mg. In some embodiments, the amount of canrenoate in the composition is included in any of the following ranges: about 5 to about 10 mg, about 10 to about 20 mg, about 20 to about 30 mg, about 30 to about 40 mg, about 40 to about 50 mg, about 50 to about 60 mg, about 60 to about 70 mg, about 70 to about 80 mg, about 80 to about 90 mg, about 90 to about 100 mg, about 100 to about 110 mg, about 110 to about 120 mg, about 120 to about 130 mg, about 130 to about 140 mg, about 140 to about 150 mg, about 150 to about 160 mg. In some embodiments, the amount of canrenoate (such as cesium canrenoate) in the composition is about 20 to about 160 mg, including for example about 50 to about 150 mg, 80 to about 150 mg, about 90 to about 140 mg, about 100 to about 120 mg.

[0123] In some embodiments, the amount of canrenoate (such as cesium canrenoate) in the composition includes at least about any of 0.1 mg/kg, 0.5 mg/kg, 1 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg. In some embodiments, the amount of canrenoate (such as cesium canrenoate) in the composition includes less than about any of 35 mg/kg, 30 mg/kg, 25 mg/kg, 20 mg/kg, 15 mg/kg, 10 mg/kg, 5 mg/kg, 2.5 mg/kg, 2 mg/kg, 1 mg/kg, 0.5 mg/kg, or 0.1 mg/kg.

[0124] Exemplary dosing frequencies include, but are not limited to, weekly without break; weekly, three out of four weeks; once every three weeks; once every two weeks; weekly, two out of three weeks. In some embodiments, the composition is administered about once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 6 weeks, or once every 8 weeks. In some embodiments, the composition is administered at least about any of 1x, 2x, 3x, 4x, 5x, 6x, or 7x (*i.e.*, daily) a week. In some embodiments, the intervals between each administration are less than about any of 6 months, 3 months, 1 month, 20 days, 15, days, 12 days, 10 days, 9 days, 8 days, 7 days, 6 days, 5 days, 4 days, 3 days, 2 days, or 1 day. In some embodiments, the intervals between each administration are more than about any of 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 8 months, or 12 months. In some embodiments, there is no break in the dosing schedule. In some embodiments, the interval between each administration is no more than about a week. In some embodiments, the composition is administered daily. In some embodiments, the composition is administered twice daily. In some embodiments, the composition is administered at least once (such as at least any of 2x, 3x, or 4x) daily.

[0125] The administration of the composition can be extended over an extended period of time, such as from about a month up to about seven years or life-long. In some embodiments, the composition is administered over a period of at least about any of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 30, 36, 48, 60, 72, or 84 months or life-long. In some embodiments, the composition is administered over a period of at least one month, wherein the interval between each administration is no more than about a week.

[0126] The compositions described herein can be administered to an individual (such as human) via various routes, including, for example, intravenous, intra-arterial, intraperitoneal, intraportal, intrapulmonary, oral, inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, intraocular, intrathecal, transmucosal, and transdermal. In some embodiments, sustained continuous release formulation of the composition may be used.

[0127] Once improvement of the patient's disease has occurred, the dose may be adjusted for preventative or maintenance treatment. For example, the dosage or the frequency of administration, or both, may be reduced as a function of the symptoms, to a level at which the desired therapeutic or prophylactic effect is maintained. Of course, if symptoms have been alleviated to an appropriate level, treatment may cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms. Patients may also require chronic treatment on a long-term basis.

Pharmaceutical Formulations and Administration

[0128] The pharmaceutical compositions described herein may be formulated as solutions, emulsions, suspensions, dispersions, or inclusion complexes such as cyclodextrins in suitable pharmaceutical solvents or carriers, or as pills, tablets, lozenges, suppositories, sachets, dragees, granules, powders, powders for reconstitution, or capsules along with solid carriers according to conventional methods known in the art for preparation of various dosage forms. Pharmaceutical compositions of the embodiments may be administered by a suitable route of delivery, such as oral, parenteral, rectal, nasal, topical, or ocular routes, or by inhalation. Preferably, the compositions are formulated for intravenous or oral administration.

[0129] For oral administration, the compositions may be provided in a solid form, such as a tablet or capsule, or as a solution, emulsion, or suspension. Oral tablets may include the active ingredient(s) mixed with compatible pharmaceutically acceptable excipients such as diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are exemplary disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid, or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating. The oral formulations may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0130] Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, active ingredient(s) may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the active ingredient with

water, an oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and diglycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

[0131] A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g., povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (eg sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethylcellulose in varying proportions to provide desired release profile.

[0132] Liquids for oral administration may be in the form of suspensions, solutions, emulsions, or syrups, or may be lyophilized or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

[0133] For parenteral use, including intravenous, intramuscular, intraperitoneal, intranasal, or subcutaneous routes, the compositions may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Such forms may be presented in unit-dose form such as ampoules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Formulations suitable for parenteral including intravenous administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include

suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0134] Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose or an appropriate fraction thereof, of an active ingredient.

Drug Combinations

[0135] The methods of the embodiments comprise administering an effective amount of at least one compound of the embodiments; optionally the compound may be administered in combination with one or more additional therapeutic agents, particularly therapeutic agents known to be useful for treating a cancer afflicting the subject.

[0136] The additional active ingredients may be administered in a separate pharmaceutical composition from a compound of the embodiments or may be included with a compound of the embodiments in a single pharmaceutical composition. The additional active ingredients may be administered simultaneously with, prior to, or after administration of a compound of the embodiments.

[0137] In certain embodiments, the additional therapeutic agent is selected from the group consisting of progestins, corticosteroids, metoclopramide, cannabinoids, thalidomide, melatonin, clenbuterol, anabolic steroids, omega 3 fatty acids, NSAIDs, beta-blocking agents, 5HT-modulating agents, SARMS, ghrelin, growth hormone, IGF-1, myostatin antibody, activin receptor antagonist, and agents which inhibit the renin-angiotensin systems (such as renin inhibitor, ACE inhibitors, and angiotensin receptor antagonists).

Kits

[0138] The present application also provides kits, medicines, compositions, and unit dosage forms for use in any of the methods described herein.

[0139] Kits provided herein include one or more containers comprising any one of the compositions described herein and/or other agent(s), and in some embodiments, further comprise instructions for use in accordance with any of the methods described herein. The kit may further comprise a description of selection of individual suitable for treatment.

Instructions supplied in the kits of the invention are typically written instructions on a label or package insert (e.g., a paper sheet included in the kit), but machine-readable instructions (e.g., instructions carried on a magnetic or optical storage disk) are also acceptable.

[0140] For example, in some embodiments, the kit comprises a) a composition comprising canrenoate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier and b) instructions for administering the composition for treatment of cancer (such as liver cancer).

[0141] The kits of the invention are in suitable packaging. Suitable packaging include, but is not limited to, vials, bottles, jars, flexible packaging (e.g., sealed Mylar or plastic bags), and the like. Kits may optionally provide additional components such as buffers and interpretative information. The present application thus also provides articles of manufacture, which include vials (such as sealed vials), bottles, jars, flexible packaging, and the like.

[0142] The instructions relating to the use of the compositions generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages (e.g., multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of canrenoate as disclosed herein to provide effective treatment of an individual for an extended period, such as any of a week, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the pharmaceutical compositions and instructions for use and packaged in quantities sufficient for storage and use in pharmacies, for example, hospital pharmacies and compounding pharmacies.

[0143] Also provided are medicines, compositions, and unit dosage forms useful for the methods described herein. For example, the present disclosure provides, in some embodiments, a composition comprising canrenoate for treating cancer in an individual having cancer. The present disclosure provides, in some embodiments, a composition comprising canrenoate for prolonging survival of an individual having cancer. The present disclosure provides, in some embodiments, a composition comprising canrenoate for preventing body weight loss of an individual having cancer.

[0144] For example, the present disclosure provides, in some embodiments, a composition comprising canrenoate for the manufacture of a medicament for treating cancer in an individual having cancer. The present disclosure provides, in some embodiments, a

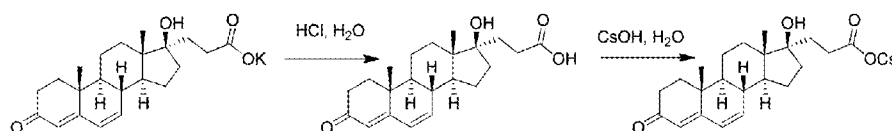
composition comprising canrenoate for the manufacture of a medicament for prolonging survival of an individual having cancer. The present disclosure provides, in some embodiments, a composition comprising canrenoate for the manufacture of a medicament for preventing body weight loss of an individual having cancer.

[0145] Those skilled in the art will recognize that several embodiments are possible within the scope and spirit of this invention. The invention will now be described in greater detail by reference to the following non-limiting examples. The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

Examples

Example 1. Synthesis of Cesium Canrenoate

[0146] The synthesis of cesium canrenoate is shown in Scheme 1.



Scheme 1

[0147] Potassium canrenoate (5.23 g, 13.2 mmol) was dissolved in water (200 mL) and the pH adjusted to pH 4 with HCl (0.125 M). The resultant precipitate was collected by filtration, washed with water (100 mL), then IMS (25 mL) and DCM (50 mL) and dried at 40 °C for 30 minutes to give the free acid (4.55 g, 96% recovery). CsOH.H₂O (2.02 g, 12.1 mmol) was added to the solid as a solution in water (200 mL). The solution was filtered through Celite and freeze-dried to give cesium canrenoate (5.84 g, 90%) as an off white solid.

[0148] ¹H NMR (DMSO-d₆) 6.09 (s, 2H), 5.55 (s, 1H), 2.00 (m, 5H), 1.50 (m, 12H), 1.02 (s, 3H), 0.81 (s, 3H).

[0149] LCMS: Rt 8.24 min, [M+H]⁺ 359.4, 99%.

Example 2. Study Protocol with Yoshida Hepatoma Model

[0150] Ascites hepatoma Yoshida AH-130 cells (10⁸ cells) were inoculated into about 200 gram male Wistar rats by i.p. injection. Alternatively animals received saline injection only (sham). The day after inoculation animals were randomized into various groups and then received twice daily treatment with either placebo or various test compositions by oral

gavage over a period of up to 17 days. The primary endpoints of the study included assessment of body weight, body composition (with and without tumor), and survival. Body composition was monitored by NMR. Echocardiography was used in instances to monitor condition of the heart. Organ weight was assessed at the end of the study (or after death) as a secondary endpoint. In addition, locomotor activity and food intake were also assessed.

Figure 1 provides a diagram showing the design study.

Example 3. Effect of Cesium Canrenoate on Survival

[0151] To study the effect of the test compounds on survival, survival was monitored over time. Figure 2 shows the percent survival of rats that were administered with cesium canrenoate (Cs-can) at dosages of 0.2, 1, 2.5, or 10 mg/kg/day. One control group received a placebo (plac). Figure 3 further shows the percent survival of rats that were administered with cesium canrenoate at dosages of 0.2, 1, 10, or 20 mg/kg/day. As shown in both Figures 2 and 3, 1 mg/kg/day of cesium canrenoate had the best effect on survival among all dosages tested. Furthermore, as shown in Figures 2 and 3, cesium canrenoate was significantly superior to placebo.

Example 4. Effect of Cesium Canrenoate on Body Weight

[0152] To study the effect of the test compounds on body weight, body weight was monitored over time. The sham body weight was 71.6 ± 1.8 g.

[0153] Figure 4 shows the change of body weight (in grams) in rats administered with cesium canrenoate (Cs-can) at dosage of 0.2, 1, 10, or 20 mg/kg/day. As shown in Figure 4, rats receiving 0.2, 1 or 10 mg/kg/day of cesium canrenoate had less body weight loss than those in the placebo group.

Example 5. Effects of Cesium Canrenoate on Preserving Lean Body Mass

[0154] To study the effect of the test compounds on lean body mass, lean mass was determined at the end of the study. The sham lean body mass was 48.6 ± 1.5 grams.

[0155] Figure 5 shows the change in lean body mass (in grams) of rats that were administered with cesium canrenoate at dosages of 0.2, 1, 10, or 20 mg/kg/day. As shown in Figure 5, rats receiving cesium canrenoate at doses of 0.2, 1, or 10 mg/kg/day had less change in lean body mass than those receiving the placebo.

Example 6. Effects of Cesium Canrenoate on Preserving Fat Mass

[0156] To study the effect of the test compounds on fat mass, the fat mass were determined at the end of the study. The sham fat mass was 13.2 ± 1.1 grams.

[0157] Figure 6 shows the change in fat mass (in grams) of rats administered with cesium canrenoate at dosages of 0.2, 1, 10, or 20 mg/kg/day. As shown in Figure 6, rats receiving cesium canrenoate at 0.2, 1, 10, or 20 mg/kg/day or higher had less fat mass loss than those in the placebo group.

[0158] Figure 7A shows the weight of white adipose tissue (WAT) (in grams) of rats administered with cesium canrenoate at dosages of 0.2, 1, 10, or 20 mg/kg/day. As shown in Figure 8A, cesium canrenoate at dosages of 0.2, 1, or 10 mg/kg/day had better effects in reducing fat wasting than the placebo group.

[0159] Figure 7B shows the weight of brown adipose tissue (BAT) (in grams) of rats administered with cesium canrenoate at dosages of 0.2, 1, 10, or 20 mg/kg/day. As shown in Figure 8B, cesium canrenoate at dosages of 0.2, 1, 10, or 20 mg/kg/day and the placebo had effects in reducing fat wasting with respect to brown adipose tissue. Cesium canrenoate at dosages of 0.2, 1, 10, or 20 mg/kg/day protect BAT mass and thus treated rats retained better control of thermogenesis.

Example 7. Effect of Cesium Canrenoate on Tumor Growth

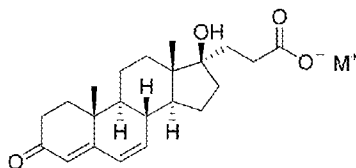
[0160] To study the effect of the test compounds on tumor growth, tumor growth was assessed at the end of the study.

[0161] Figure 8A shows the tumor volume (in ml) of rats administered with cesium canrenoate at dosages of 0.2, 1, 10, or 20 mg/kg/day. Figure 8B shows the total number of cells in a tumor of rats administered with cesium canrenoate at dosages of 0.2, 1, 10, or 20 mg/kg/day. As shown in Figures 8A and 8B, rats receiving cesium canrenoate did not have any significant effects on tumor growth compared to those in the placebo group.

[0162] The effect of the test compounds on tumor growth was also evaluated in an *in vitro* experiment with various tumor cells, namely, Kelly (neuroblastoma), Hela-93 (cervix carcinoma), and B16V (melanoma). Cell growth was assessed by BrdU incorporation (left of Figure 9) and XTT assay (right of Figure 9). Doxorubicin was used as a positive control. As shown in Figure 9, cesium canrenoate did not show any inhibitor effects on tumor cell proliferation.

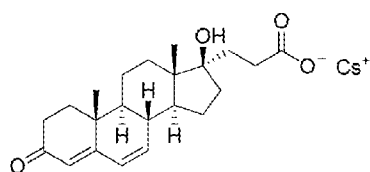
CLAIMS

1. A compound of the formula:



wherein M^+ is an ion of an alkali metal (Group 1) selected from the group consisting of Li^+ (lithium), Na^+ (sodium), Rb^+ (rubidium), and Cs^+ (cesium).

2. A compound of the formula:



(cesium canrenoate).

3. A pharmaceutical composition comprising the compound of claim 1 or 2.
4. A method of treating cancer in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate.
5. A method of prolonging survival of an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate.
6. A method of preventing body weight loss of an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate.
7. A method of improving quality of life in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate.
8. A method of preventing and treating muscle wasting in an individual having cancer, comprising administering to the individual an effective amount of a composition comprising canrenoate.
9. The method of any one of claims 4-8, wherein the canrenoate is a pharmaceutically acceptable salt of canrenoate.
10. The method of any one of claims 4-8, wherein the canrenoate is selected from the group consisting of cesium canrenoate, lithium canrenoate, sodium canrenoate, and

rubidium canrenoate.

11. The method of any one of claims 4-8, wherein the canrenoate is cesium canrenoate.
12. The method of any one of claims 4-11, wherein the individual has no symptom of cancer cachexia.
13. The method of any one of claims 4-11, wherein the individual has one or more symptoms of cancer cachexia.
14. The method of any one of claims 4-13, wherein the cancer is selected from the group consisting of liver cancer, lung cancer, ovarian cancer, pancreatic cancer, melanoma, and brain cancer.
15. The method of any one of claims 4-13, wherein the cancer is selected from the group consisting of gastric cancer, pancreatic cancer, lung, esophageal, colorectal, head and neck cancer, and hematological malignancy.
16. The method of claim 14, wherein the cancer is liver cancer.
17. The method of any one of claims 4-16, wherein the cancer is an early stage cancer.
18. The method of any one of claims 4-16, wherein the cancer is a late stage cancer.
19. The method of any one of claims 4-18, wherein the composition is administered orally.
20. The method of any one of claims 4-19, wherein the amount of canrenoate in the composition is about 10 to about 200 mg daily.
21. The method of any one of claims 4-20, wherein the composition is administered daily or twice daily.
22. A kit comprising the pharmaceutical composition of claim 3 and instruction for using the pharmaceutical composition for treating cancer.

Figure 1

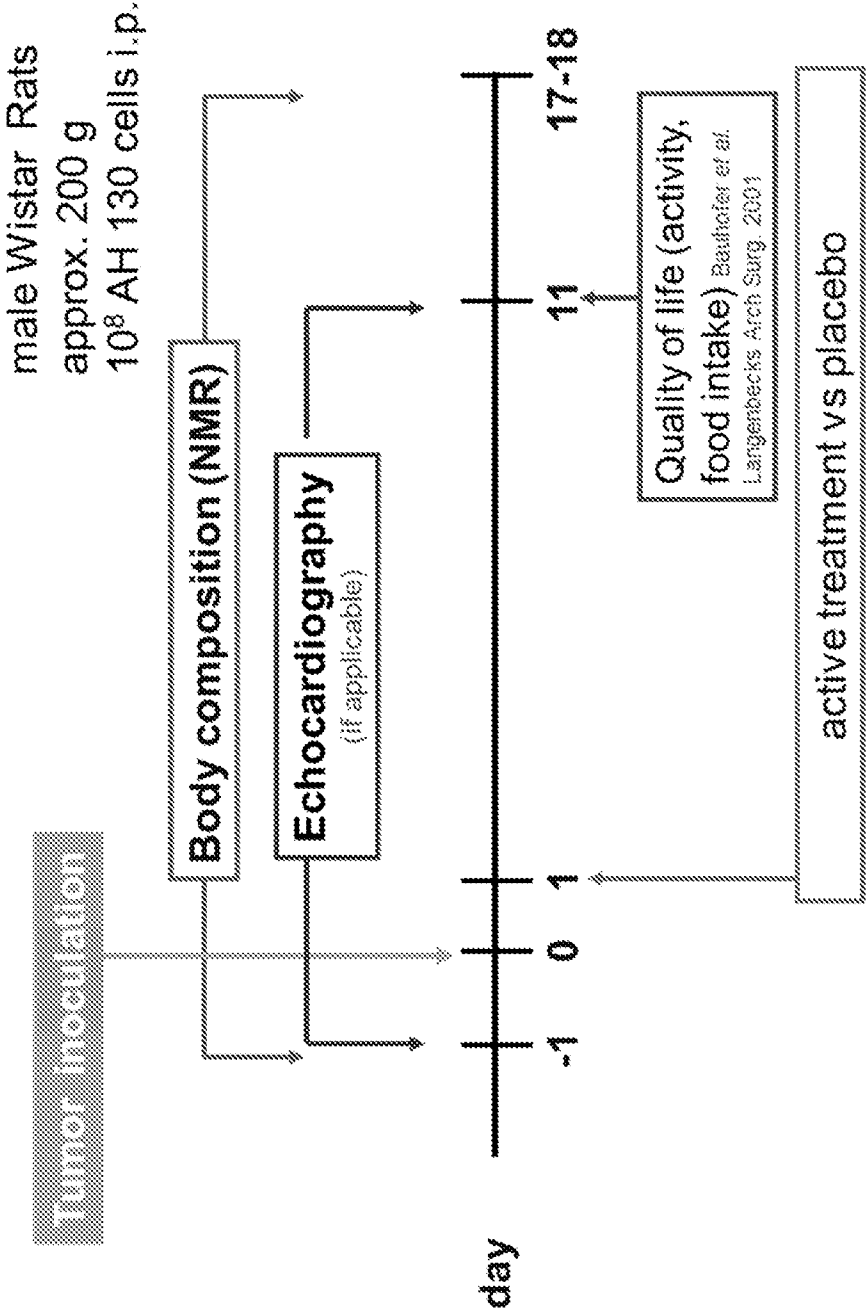


Figure 2

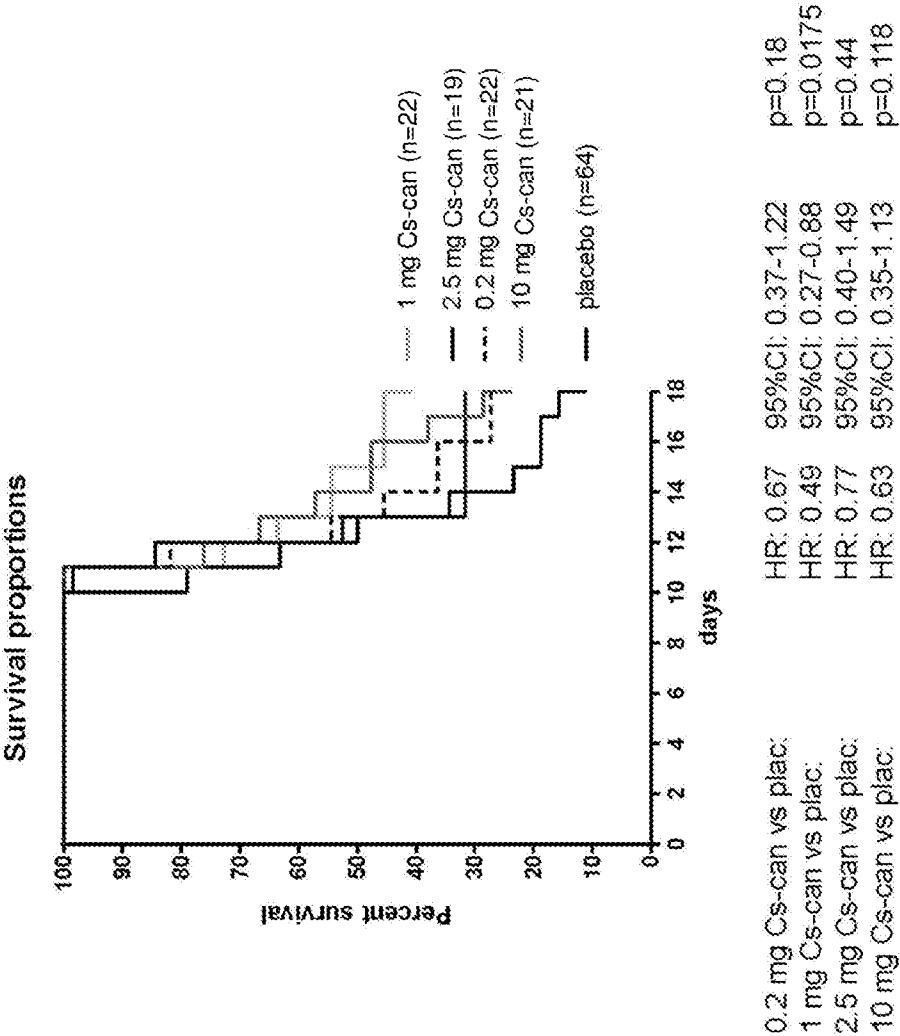


Figure 3

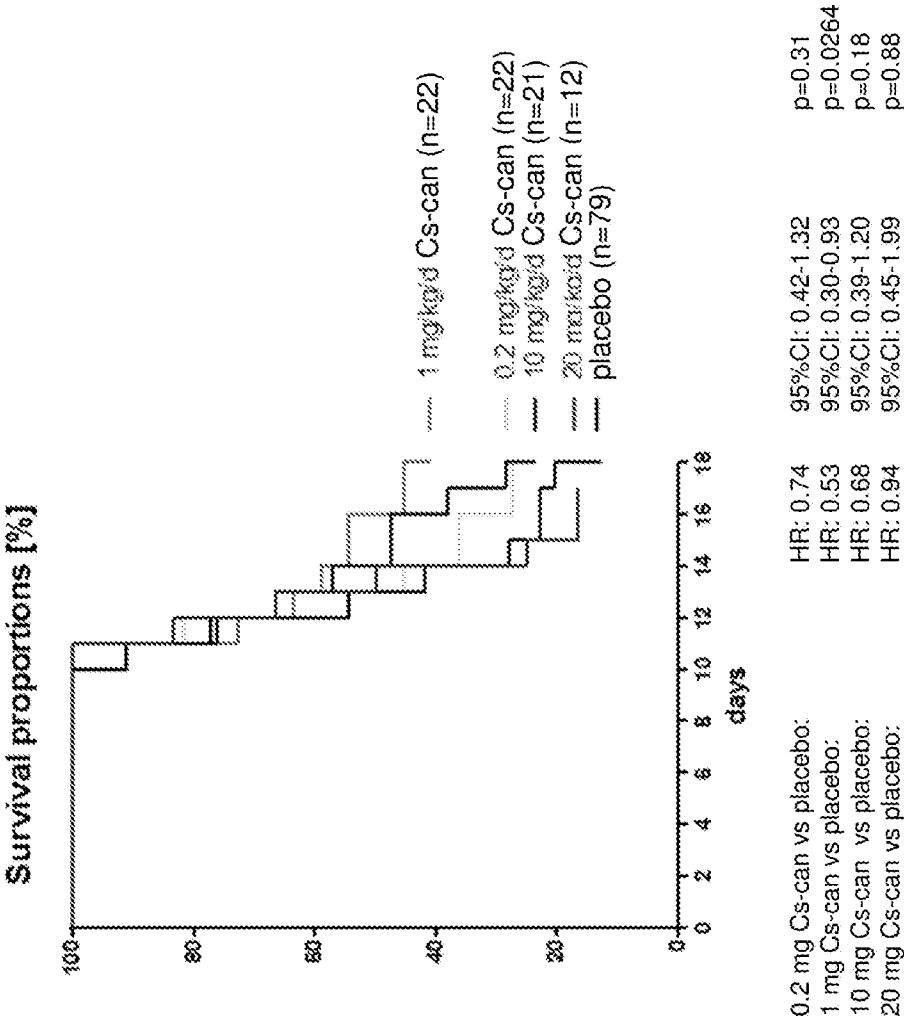


Figure 4

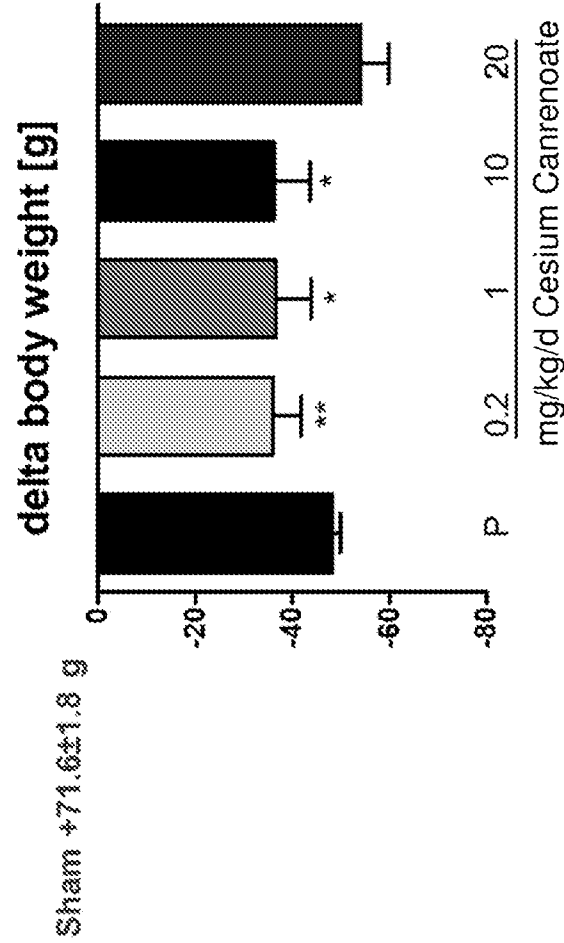


Figure 5

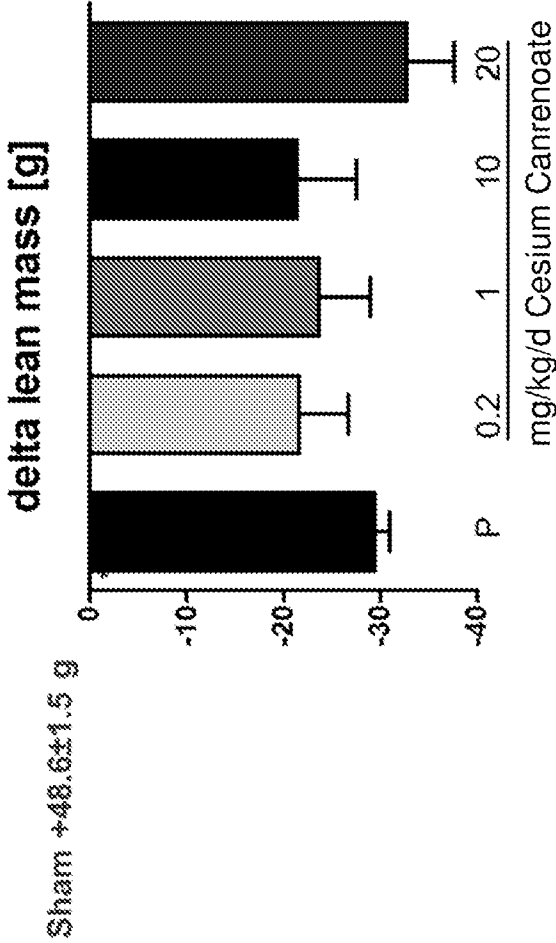


Figure 6

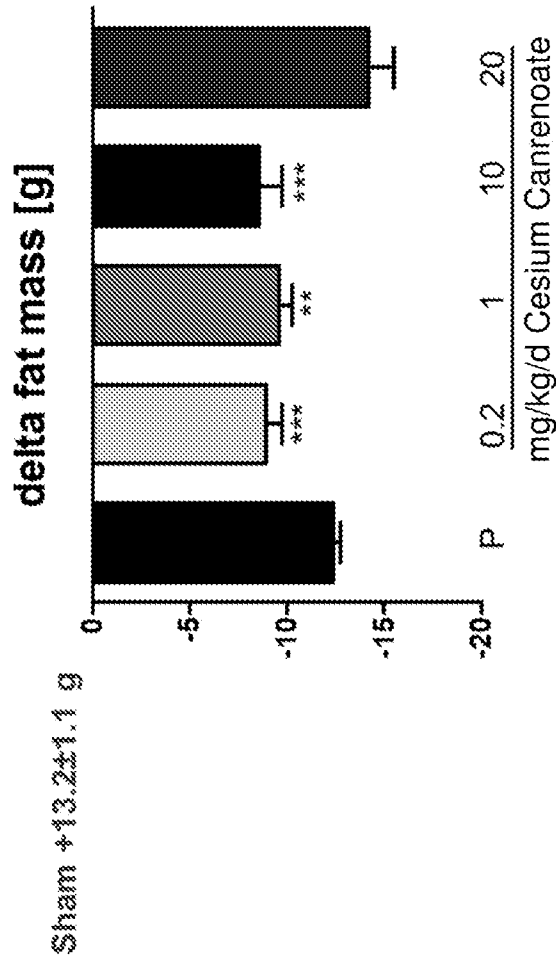


Figure 7

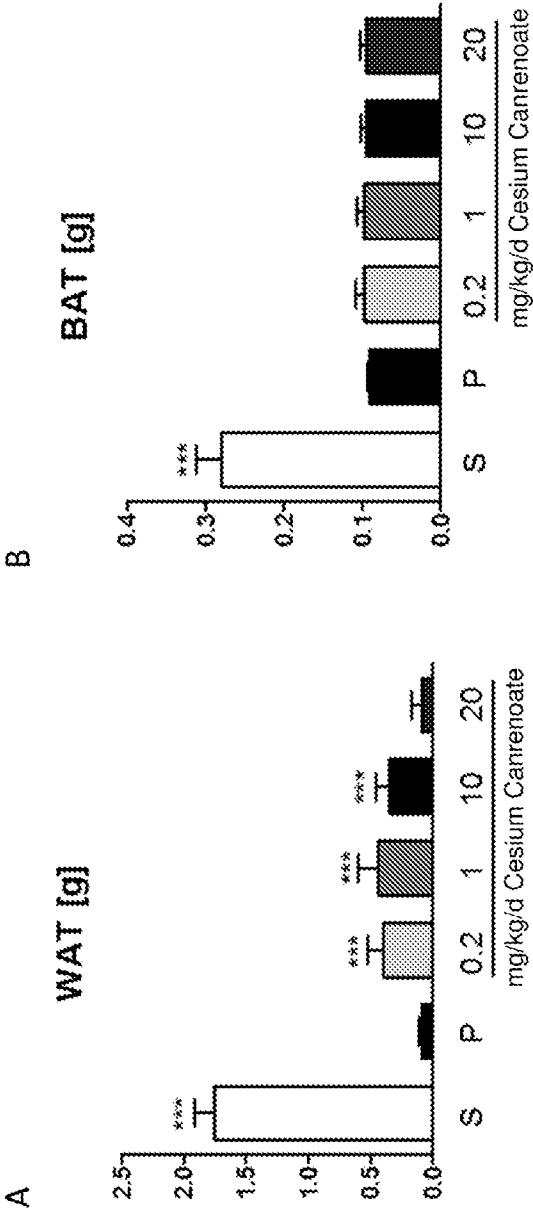


Figure 8

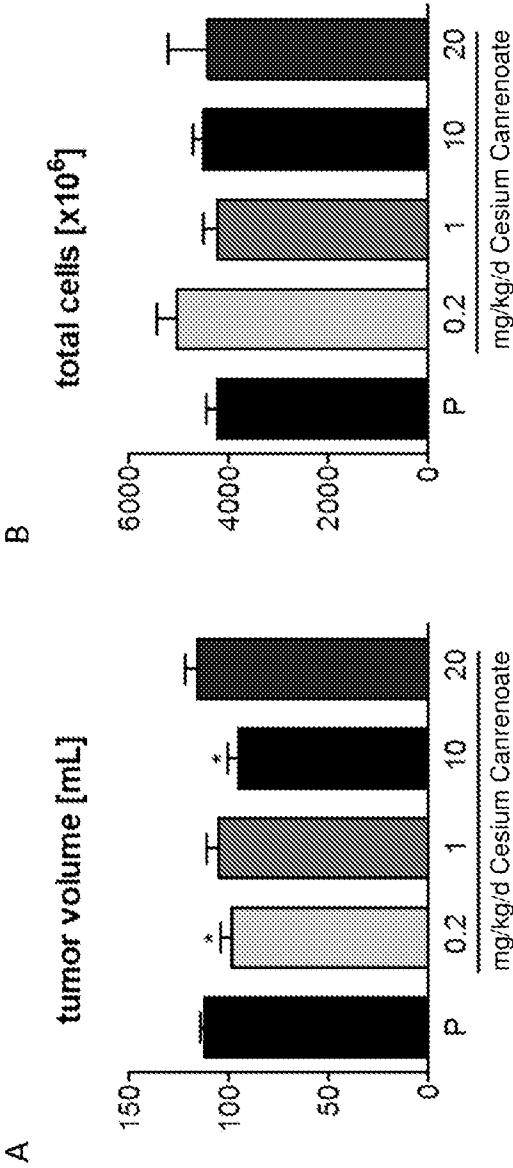
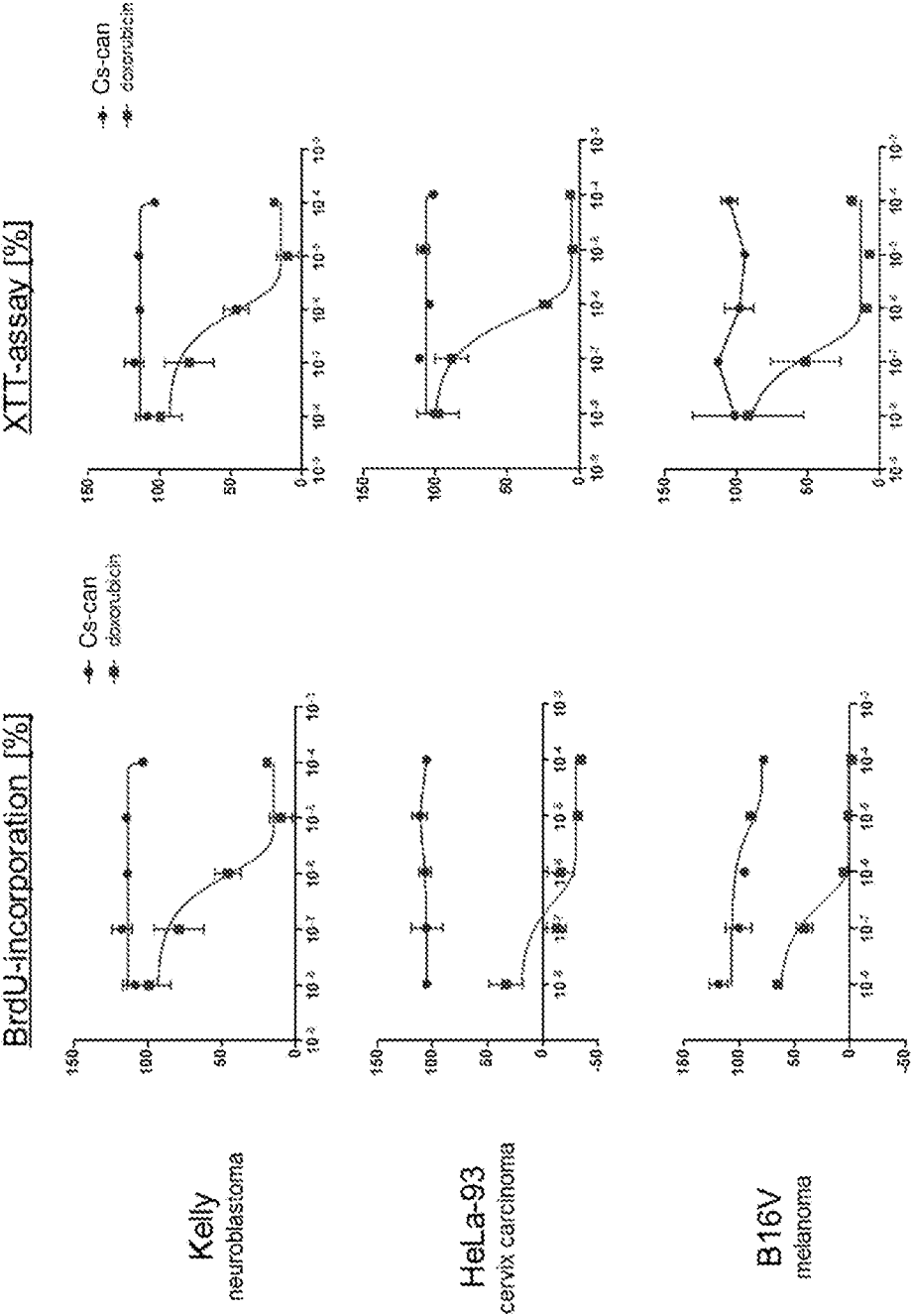


Figure 9



INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2014/000262

A. CLASSIFICATION OF SUBJECT MATTER

C07J 9/00 (2006.01) C07F 1/00 (2006.01) C07F 1/02 (2006.01) C07F 1/04 (2006.01) A61K 31/575 (2006.01)
A61P 35/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: Registry and CAlus – structure search based on canrenoate compound depicted in claim 1 and keyword search (based on cancer, tumour, oncological, angiogenesis and metathesis and like terms).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent but published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 20 June 2014	Date of mailing of the international search report 20 June 2014
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaaustralia.gov.au	Authorised officer Tina Bryant AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 2 6283 7992

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/AU2014/000262
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0256238 A1 (TANOUE et al.) 07 October 2010 Paragraphs [0022]-[0023], [0027].	1, 3
X	Coraboeuf, E. et al., "Effect of a spirinolactone derivative, sodium canrenoate, on mechanical and electrical activities of isolated rat myocardium", Journal of Pharmacology and Experimental Therapeutics, 1974, Vol. 191, No. 1, pages 128-138. Page 128 Abstract, page 129 right column lines 31-32, page 130 Figures 1 and 2, page 131 Figure 4.	1, 3
X	EP 2243494 A1 (ONTOCHEM GMBH) 27 October 2010 Page 2 Paragraph [0001], page 5 Paragraph [0021], page 6 Paragraphs [0022]-[0023], page 8 lines 1-15, page 14 Paragraph [0035], page 14 Paragraph [0038], pages 14-15 Paragraph [0040], page 15 Paragraph [0041], page 15 Paragraph [0042], Example 1, Claims 1, 4 and 13.	1-22
X	WO 2011/047383 A1 (ONCOMED PHARMACEUTICALS, INC.) 21 April 2011 Page 3 Paragraph [0012], page 4 Paragraph [0016], page 8 Paragraph [0036], pages 12-13 Paragraph [0054], page 15 Paragraph [0064], page 15 Paragraph [0066], pages 17-18 Paragraph [0073], page 20 Paragraph [0082], page 20 Paragraph [0083], pages 21-22 Paragraph [0087], page 23 Paragraph [0091], Claims 1, 4, 13 and 41.	4-9, 12-21
X	Hofslis, E. et al., "Reversal of multidrug resistance by lipophilic drugs", Cancer Research, 1990, Vol. 50, No. 13, pages 3997-4002. Page 3997 Abstract, pages 3997-3998 Materials and Methods, page 3998 left column lines 26-37, page 3998 Table 1, page 3998 left column line 53 – page 3998 right column line 8, page 3999 Figure 1, page 4002 left column lines 6-10.	4-9, 12-21
X	Klauber, N. et al., "New Activity of Spironolactone: Inhibition of Angiogenesis In Vitro and In Vivo", Circulation, 1996, Vol. 94, No. 10, pages 2566-2571. Page 2566 Abstract, Methods: Rabbit Corneal Micropocket Assay and Results: Rabbit Corneal Micropocket Assay, Figure 4.	4-9, 12-21
A	Armanini, D. et al., "In-vivo metabolites of spironolactone and potassium canrenoate: determination of potential anti-androgenic activity by a mouse kidney cytosol receptor assay", Clinical Endocrinology, 1985, Vol. 23, No. 4, pages 341-347. Page 341 Abstract	4-9, 12-21
L	Martelli, A. et al., "Genotoxicity testing of potassium canrenoate in cultured rat and human cells", Mutagenesis, 1999, Vol. 14, No. 5, pages 463-472. Citation in support of Article 6 objection	
L	Cook, C.S. et al., "Difference in metabolic profile of potassium canrenoate and spironolactone in the rat: Mutagenic metabolites unique to potassium canrenoate", Archives of Toxicology, 1988, Vol. 61, pages 201-212. Citation in support of Article 6 objection	
L	Brambilla, G. et al., "Genotoxicity and carcinogenicity studies of antihypertensive agents", Mutation Research, 2006, Vol. 612, No. 2 pages 115-149. Citation in support of Article 6 objection	
Form PCT/ISA/210 (fifth sheet) (July 2009)		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2014/000262

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Supplemental Box**Continuation of: Box III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

- Claims 1-3 and 22 (in full) and 4-21 (in part) are directed towards lithium, sodium, rubidium and cesium salts of canrenoate and pharmaceutical compositions and kits thereof, and use of alkali metal salts of canrenoate to treat cancer and other associated conditions. The feature of an alkali metal salt of canrenoate is specific to this group of claims.
- Claims 4-21 (in part) are directed towards methods of treating cancer or other associated conditions in an individual having cancer through administering a composition that contains canrenoate. The feature of treating cancer or other associated conditions with a composition comprising a form of canrenoate (other than an alkali metal salt of canrenoate) is specific to this group of claims.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed inventions and which provides a technical relationship among them is the canrenoate. However this feature does not make a contribution over the prior art because it is disclosed in many documents, including D1-D5.

D1 and D2 disclose sodium canrenoate (D1: Paragraph [0027]; D2: Page 128 Abstract, page 129 right column lines 31-32). D3 discloses Canrenoate (Page 8 lines 1-15). D4 and D5 disclose potassium canrenoate (D4: Pages 12-13 Paragraph [0054], Claim 13, Claim 41, D5: Pages 3997-3998 *Materials and Methods*, page 3998 left column lines 26-37, page 3998 Table 1).

Therefore in the light of these documents this common feature (canrenoate) cannot be a special technical feature. Therefore there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a posteriori*.

INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/AU2014/000262	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 2010/0256238 A1	07 October 2010	WO 2009028650 A1	05 Mar 2009
		JP 4526598 B2	18 Aug 2010
EP 2243494 A1	27 October 2010	WO 2010121814 A1	28 Oct 2010
WO 2011/047383 A1	21 April 2011	EP 2488204 A1	22 Aug 2012
		JP 2013508303 A	07 Mar 2013
		US 2012263721 A1	18 Oct 2012
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2009)			