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(71) Applicant: **BERG LLC** [US/US]; 1845 Elm Hill Pike, Nashville, TN 37210 (US).

(72) Inventors: **NARAIN, Niven, Rajin**; 73 Fresh Pond Parkway, Cambridge, MA 02138 (US). **SARANGARAJAN, Rangaprasad**; 454 Central Street, Boylston, MA 01505 (US).

(74) Agents: **HANLEY, Elizabeth, A.** et al.; McCarter & English, LLP, 265 Franklin Street, Boston, MA 02110 (US).

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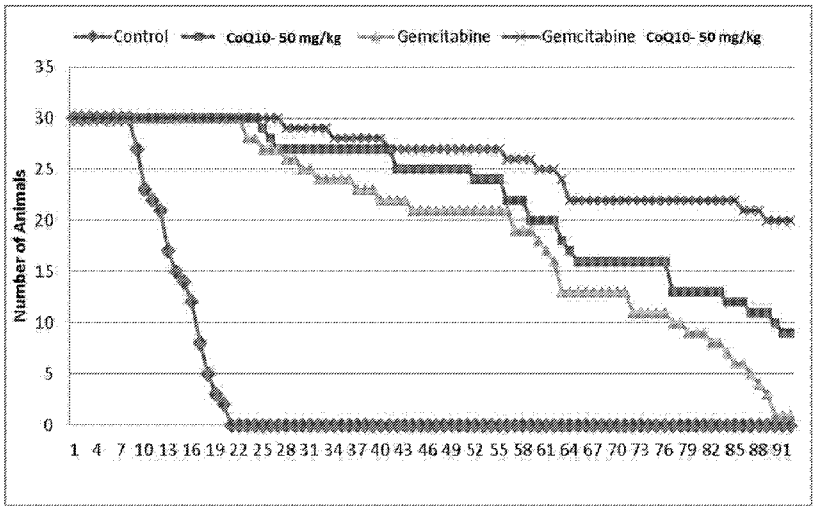
(54) Title: TREATMENT OF CANCER USING COENZYME Q10 COMBINATION THERAPIES

Figure 1



(57) Abstract: Presented herein are methods for the treatment of oncological disorders by the co¬ administration of CoQ10 formulations and chemo therapeutic agents and/or surgery. The CoQ10 formulations may be at least one of intravenous, topical, or by inhalation. The chemo therapeutic agents may be at least one of antimetabolites or anthracyc lines. Co-administration of the CoQ10 formulations may be prior to, concurrent or substantially concurrent with, intermittent with or subsequent to the administration of the chemotherapy.

TREATMENT OF CANCER USING COENZYME Q10 COMBINATION THERAPIES

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 61/809,840 filed on April 8, 2013, the contents of which are incorporated herein in their entirety.

FIELD OF THE INVENTION

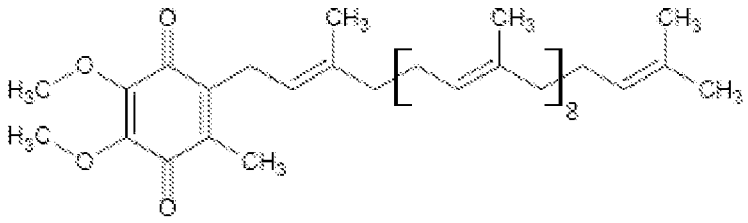
The invention generally relates to methods for the treatment of oncological disorders comprising administration of coenzyme Q10 (CoQ10) and a chemotherapeutic agent.

BACKGROUND

Cancer is presently one of the leading causes of death in developed nations. A diagnosis of cancer traditionally involves serious health complications. Cancer can cause disfigurement, chronic or acute pain, lesions, organ failure, or even death. Commonly diagnosed cancers include pancreatic cancer, breast cancer, lung cancer, melanoma, lymphoma, carcinoma, sarcoma non-Hodgkin's lymphoma, leukemia, endometrial cancer, colon and rectal cancer, prostate cancer, and bladder cancer. Traditionally, many cancers (e.g., breast cancer, leukemia, lung cancer, or the like) are treated with surgery, chemotherapy, radiation, or combinations thereof. Chemotherapeutic agents used in the treatment of cancer are known to produce several serious and unpleasant side effects in patients. For example, some chemotherapeutic agents cause neuropathy, nephrotoxicity (e.g., hyperlipidemia, proteinuria, hypoproteinemia, combinations thereof, or the like), stomatitis, mucositisemesis, alopecia, anorexia, esophagitis amenorrhoea, decreased immunity, anaemia, high tone hearing loss, cardiotoxicity, fatigue, neuropathy, or combinations thereof. Improved methods for the treatment of oncological diseases, including cancer, and composition capable of delivering bioactive agents to aid in the treatment of diseases and other conditions remain desirable.

Coenzyme Q10, also referred to herein as CoQ10, ubiquinone, or ubidecarenone, is a popular nutritional supplement and can be found in capsule form in nutritional stores, health

food stores, pharmacies, and the like, as a vitamin-like supplement to help protect the immune system through the antioxidant properties of ubiquinol, the reduced form of CoQ10. CoQ10 is found throughout most tissues of the human body and the tissues of other mammals and is concentrated in the mitochondria. CoQ10 is very lipophilic and, for the most part, insoluble in water. The insolubility is related to the 50-carbon atom isoprenoid side chain, of hydrocarbon nature as shown in the following structure of CoQ10.



SUMMARY OF THE INVENTION

The present invention provides methods for treating oncological disorders in a subject by administering CoQ10 and at least one chemotherapeutic agent to the subject, such that the oncological disorder is treated.

In some embodiments, the method comprises (a) administering coenzyme Q10 (CoQ10) to the subject; (b) discontinuing administration of CoQ10; and (c)

administering at least one chemotherapeutic agent to the subject after administration with CoQ10 has been discontinued, such that the oncological disorder is treated. In other embodiments, the method comprises (a) administering coenzyme Q10 (CoQ10) to the subject; (b) administering at least one chemotherapeutic agent to the subject after administration of the CoQ10 is initiated; and (c) continuing treatment with CoQ10 after administration of the at least one chemotherapeutic agent is initiated, such that the oncological disorder is treated.

In certain embodiments, the CoQ10 is administered prior to administration of a first dose of the at least one chemotherapeutic agent. In a preferred embodiment, the CoQ10 is administered for at least 24 hours prior to administration of a dose of the at least one chemotherapeutic agent. In another preferred embodiment, the CoQ10 is administered for at least 48 hours prior to administration of a dose of the at least one chemotherapeutic agent. In a further preferred embodiment, the CoQ10 is administered for at least 1 week prior to

administration of a dose of the at least one chemotherapeutic agent. In another preferred embodiment, the CoQ10 is administered for at least 2 weeks prior to administration of a dose of the at least one chemotherapeutic agent. In another preferred embodiment, the CoQ10 is administered for at least 3 weeks prior to administration of a dose of the at least one chemotherapeutic agent. In anothered preferred embodiment, the CoQ10 is administered for at least 4 weeks prior to administration of a dose of the at least one chemotherapeutic agent. In anothered preferred embodiment, the CoQ10 is administered for at least 5 weeks prior to administration of a dose of the at least one chemotherapeutic agent. In anothered preferred embodiment, the CoQ10 is administered for at least 6 weeks prior to administration of a dose of the at least one chemotherapeutic agent. In anothered preferred embodiment, the CoQ10 is administered for at least 7 weeks prior to administration of a dose of the at least one chemotherapeutic agent. In anothered preferred embodiment, the CoQ10 is administered for at least 8 weeks prior to administration of a dose of the at least one chemotherapeutic agent.

In other preferred embodiments, the CoQ10 is administered for about 24 hours prior to administration of a dose of the at least one chemotherapeutic agent. In another preferred embodiment, the CoQ10 is administered for about 48 hours prior to administration of a dose of the at least one chemotherapeutic agent. In a further preferred embodiment, the CoQ10 is administered for about 1 week prior to administration of a dose of the at least one chemotherapeutic agent. In another preferred embodiment, the CoQ10 is administered for about 2 weeks prior to administration of a dose of the at least one chemotherapeutic agent. In another preferred embodiment, the CoQ10 is administered for about 3 weeks prior to administration of a dose of the at least one chemotherapeutic agent. In anothered preferred embodiment, the CoQ10 is administered for about 4 weeks prior to administration of a dose of the at least one chemotherapeutic agent. In anothered preferred embodiment, the CoQ10 is administered for about 5 weeks prior to administration of a dose of the at least one chemotherapeutic agent. In anothered preferred embodiment, the CoQ10 is administered for about 6 weeks prior to administration of a dose of the at least one chemotherapeutic agent. In anothered preferred embodiment, the CoQ10 is administered for about 7 weeks prior to administration of a dose of the at least one chemotherapeutic agent. In anothered preferred embodiment, the CoQ10 is administered for about 8 weeks prior to administration of a dose of the at least one chemotherapeutic agent.

In certain embodiments, administration of the at least one chemotherapeutic agent is initiated at least 24 hours after administration of CoQ10 is initiated, one or more weeks after administration of CoQ10 is initiated, two or more weeks after administration of CoQ10 is initiated, three or more weeks after administration of CoQ10 is initiated, four or more weeks after administration of CoQ10 is initiated, five or more weeks after administration of CoQ10 is initiated, six or more weeks after administration of CoQ10 is initiated, seven or more weeks after administration of CoQ10 is initiated, or eight or more weeks after administration of CoQ10 is initiated.

In a preferred embodiment of the aforementioned methods, a response of the oncological disorder to treatment is improved relative to a treatment with the at least one chemotherapeutic agent alone, i.e., in the absence of administration of CoQ10 to the subject. In a further preferred embodiment, the response is improved by at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 100% relative to treatment with the at least one chemotherapeutic agent alone.

In certain embodiments, the response comprises any one or more of reduction in tumor burden, reduction in tumor size, inhibition of tumor growth, slowing of tumor growth, an improvement in RECIST criteria, achieving stable oncological disorder in a subject with a progressive oncological disorder prior to treatment, increased time to progression of the oncological disorder, and increased time of survival.

In a preferred embodiment of the aforementioned methods, the CoQ10 is administered topically. In another preferred embodiment, the CoQ10 is administered by inhalation. In another preferred embodiment, the CoQ10 is administered by injection or infusion. In another preferred embodiment, the CoQ10 is administered by intravenous administration. In a further preferred embodiment, the CoQ10 is administered by continuous intravenous

infusion. In a still further preferred embodiment, the dose of CoQ10 is administered by continuous infusion over 24 hours.

In certain embodiments, the CoQ10 is administered at a dose of about 5 mg/kg, about 10 mg/kg, about 12.5 mg/kg, about 20 mg/kg, about 25 mg/kg, t about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 58 mg/kg, about 58.6 mg/kg, about 60 mg/kg, about 75 mg/kg, about 78 mg/kg, about 100 mg/kg, about 104 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 300 mg/kg, or about 400 mg/kg.

The invention also provides a method of improving a chemotherapeutic treatment regimen for an oncological disorder in a subject, comprising pre-treating a subject having an oncological disorder with Coenzyme Q10 (CoQ10) for a sufficient time prior to initiation of a chemotherapeutic treatment regimen, wherein the chemotherapeutic treatment regimen comprises administration of one or more chemotherapeutic agents, such that a response of the oncological disorder is improved relative to treatment with the chemotherapeutic treatment regimen alone. In certain embodiments of the aforementioned method, the chemotherapeutic treatment regimen does not include administration of CoQ10. In some embodiments of the aforementioned methods, pre-treatment with CoQ10 is ceased prior to initiation of the chemotherapeutic treatment regimen.

In a preferred embodiment of the aforementioned methods, the subject is pre-treated with CoQ10 for at least 24 hours, at least 48 hours, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, or at least 8 weeks prior to initiation of the chemotherapeutic treatment regimen. In another preferred embodiment, the subject is pre-treated with CoQ10 for about 24 hours, about 48 hours, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, or about 8 weeks prior to initiation of the chemotherapeutic treatment regimen.

In another preferred embodiment of the aforementioned methods, the chemotherapeutic treatment regimen is initiated at least 24 hours after pre-treatment with CoQ10 is initiated, one or more weeks after pre-treatment with CoQ10 is initiated, two or more weeks after pre-treatment with CoQ10 is initiated, three or more weeks after pre-treatment with CoQ10 is initiated, four or more weeks after pre-treatment with CoQ10 is

initiated, five or more weeks after pre-treatment with CoQ10 is initiated, six or more weeks after pre-treatment with CoQ10 is initiated, seven or more weeks after pre-treatment with CoQ10 is initiated, or eight or more weeks after pre-treatment with CoQ10 is initiated.

In certain embodiments of the aforementioned methods, the response is improved by at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 100% relative to treatment with the chemotherapeutic treatment regimen alone.

In certain embodiments of the aforementioned methodsm the response comprises any one or more of reduction in tumor burden, reduction in tumor size, inhibition of tumor growth, slowing of tumor growth, an improvement in RECIST criteria, achieving stable oncological disorder in a subject with a progressive oncological disorder prior to treatment, increased time to progression of the oncological disorder, and increased time of survival.

In some embodiments, CoQ10 is administered topically. In other embodiments, CoQ10 is administered by inhalation. In other embodiments, the CoQ10 is administered by injection or infusion. In another embodiment, the CoQ10 is administered by intravenous administration.

In a further embodiment, the CoQ10 is administered by continuous intravenous infusion. In a still further embodiment, the dose of CoQ10 is administered by continuous intravenous infusion over 24 hours.

In certain embodiments, the CoQ10 is administered at a dose of about 5 mg/kg, about 10 mg/kg, about 12.5 mg/kg, about 20 mg/kg, about 25 mg/kg, t about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 58 mg/kg,

about 58.6 mg/kg, about 60 mg/kg, about 75 mg/kg, about 78 mg/kg, about 100 mg/kg, about 104 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 300 mg/kg, or about 400 mg/kg.

The invention also provides a method of treating an oncological disorder in a subject comprising: (a) administering CoQ10 to the subject; and (b) administering at least one chemotherapeutic agent to the subject at a dosage that is lower than standard dosages of the chemotherapeutic agent used to treat the oncological disorder,such that the oncological disorder is treated. In certain embodiments administration of CoQ10 is discontinued before administering the at least one chemotherapeutic agent to the subject. In other embodiments, administration of CoQ10 is continued after administration of the at least one chemotherapeutic agent to the subject.

In certain embodiments of the aforementioned methods, the CoQ10 is administered for at least 24 hours, at least 48 hours, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, or at least 8 weeks prior to administration of the at least one chemotherapeutic agent. In other embodiments of the aforementioned methods, the CoQ10 is administered for about 24 hours, about 48 hours, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, or about 8 weeks prior to administration of the at least one chemotherapeutic agent.

In other embodiments of the aforementioned methods, the at least one chemotherapeutic agent is administered at least 24 hours after administration of CoQ10 is initiated, one or more weeks after administration of with CoQ10 is initiated, two or more weeks after administration of CoQ10 is initiated, three or more weeks after administration of CoQ10 is initiated, four or more weeks after administration of CoQ10 is initiated, five or more weeks after administration of CoQ10 is initiated, six or more weeks after administration of CoQ10 is initiated, seven or more weeks after administration of CoQ10 is initiated, or eight or more weeks after administration of CoQ10 is initiated.

In certain embodiments of the aforementioned methods, the CoQ10 is administered topically. In other embodiments, the CoQ10 is administered by inhalation. In other embodiments, the CoQ10 is administered by injection or infusion. In other embodiments, the

CoQ10 is administered by intravenous administration. In other embodiments, the CoQ10 is administered by continuous intravenous infusion. In other embodiments the CoQ10 is administered by continuous infusion over 24 hours.

In certain embodiments of the aforementioned methods, the CoQ10 is administered at a dose of about 5 mg/kg, about 10 mg/kg, about 12.5 mg/kg, about 20 mg/kg, about 25 mg/kg, t about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 58 mg/kg, about 58.6 mg/kg, about 60 mg/kg, about 75 mg/kg, about 78 mg/kg, about 100 mg/kg, about 104 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 300 mg/kg, or about 400 mg/kg.

In certain embodiments of the aforementioned methods the at least one chemotherapeutic agent comprises a chemotherapeutic agent selected from the group consisting of a topoisomerase I inhibitor, a topoisomerase II inhibitor, a mitotic inhibitor, an alkylating agent, a platinum compound, and an antimetabolite. In some embodiments, the at least one chemotherapeutic agent comprises a Topoisomerase II inhibitor. In a preferred embodiment, the Topoisomerase II inhibitor comprises at least one of doxorubicin, epirubicin, idarubicin, mitoxantrone, losoxantrone, etoposide and teniposide. In other embodiments, the at least one chemotherapeutic agent comprises a Topoisomerase I inhibitor.

In a preferred embodiment, the Topoisomerase I inhibitor comprises at least one of irinotecan, topotecan, 9- nitrocamptothecin, camptothecin, and camptothecin derivatives. In other embodiments, the at least one chemotherapeutic agent comprises an antimetabolite. In a preferred embodiment the antimetabolite comprises at least one of 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate. In other embodiments, the at least one chemotherapeutic agent comprises an alkylating agent.

In a preferred embodiment the alkylating agent comprises at least one of a nitrogen mustard, an ethyleneimine compound, an alkylsulphonate, a nitrosourea, dacarbazine, cyclophosphamide, ifosfamide and melphalan. In other embodiments, the at least one chemotherapeutic agent comprises a platinum compound. In a preferred embodiment, the platinum compound comprises at least one of cisplatin, oxaliplatin and carboplatin. In other embodiments, the at least one chemotherapeutic agent comprises a mitotic inhibitor. In a

preferred embodiment, the mitotic inhibitor comprises at least one of paclitaxel, docetaxel, vinblastine, vincristine, vinorelbine and a podophyllotoxin derivative.

In certain embodiments of the aforementioned methods, the at least one chemotherapeutic agent comprises a chemotherapeutic agent selected from the group consisting of amifostine (ethyol), cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carrnustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), doxorubicin lipo (doxil), gemcitabine (gemzar), daunorubicin, daunorubicin lipo (daunoxome), procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5- fluorouracil (5-FU), vinblastine, vincristine, bleomycin, paclitaxel (taxol), docetaxel (taxotere), aldesleukin, asparaginase, busulfan, carboplatin, cladribine, camptothecin, CPT-I 1 , lO-hydroxy-7-ethyl-camptothecin (SN38), dacarbazine, S-I capecitabine, ftorafur, 5'deoxyflurouridine, UFT, eniluracil, deoxycytidine, 5-azacytosine, 5- azadeoxycytosine, allopurinol, 2-chloro adenosine, trimetrexate, aminopterin, methylene-10-deazaaminopterin (MDAM), oxaplatin, picoplatin, tetraplatin, satraplatin, platinum-DACH, ormaplatin, CI-973, JM-216, and analogs thereof, epirubicin, etoposide phosphate, 9- aminocamptothecin, 10, 11-methylenedioxycamptothecin, karenitecin, 9-nitrocamptothecin, TAS 103, vindesine, L-phenylalanine mustard, ifosphamidemefosphamide, perfosfamide, trophosphamide carmustine, semustine, epothilones A-E, tomudex, 6-mercaptopurine, 6-thioguanine, amsacrine, etoposide phosphate, karenitecin, acyclovir, valacyclovir, ganciclovir, amantadine, rimantadine, lamivudine, zidovudine, bevacizumab, trastuzumab, rituximab, 5-Fluorouracil, Capecitabine, Pentostatin, Trimetrexate, Cladribine, floxuridine, fludarabine, hydroxyurea, ifosfamide, idarubicin, mesna, irinotecan, mitoxantrone, topotecan, leuprolide, megestrol, melphalan, mercaptopurine, plicamycin, mitotane, pegaspargase, pentostatin, pipobroman, plicamycin, streptozocin, tamoxifen, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, chlorambucil, cisplatin, doxorubicin, paclitaxel (taxol), bleomycin, mTor, epidermal growth factor receptor (EGFR), and fibroblast growth factors (FGF) and combinations thereof.

In preferred embodiments of the aforementioned methods, the at least one chemotherapeutic agent comprises at least one of gemcitabine, 5-fluorouracil, cisplatin, capecitabine, methotrexate, edatrexate, docetaxel, cyclophosphamide, doxorubicin, and irinotecan.

In certain embodiments of the aforementioned methods, the oncological disorder is selected from the group consisting of a carcinoma, sarcoma, lymphoma, melanoma, and leukemia. In a preferred embodiment, the oncological disorder is selected from the group consisting of pancreatic cancer, breast cancer, liver cancer, skin cancer, lung cancer, colon cancer, prostate cancer, thyroid cancer, bladder cancer, rectal cancer, endometrial cancer, kidney cancer, bone cancer, brain cancer, cervical cancer, stomach cancer, mouth and oral cancers, neuroblastoma, testicular cancer, uterine cancer, and vulvar cancer. In a further preferred embodiment, the skin cancer is selected from the group consisting of melanoma, squamous cell carcinoma, basal cell carcinoma, and cutaneous T-cell lymphoma (CTCL). In another prefereed embodiment, the oncological disorder is triple negative breast cancer.

In certain embodiments of the aforementioned methods, the oncological disorder is a refractory disorder. In certain embodiments of the aforementioned methods, the oncological disorder has failed to respond to at least one, two, three, four, five, six, seven, eight or more previous treatments. In certain embodiments of the aforementioned methods, the oncological disorder is end stage cancer. In certain embodiments of the aforementioned methods, the methods further comprise selecting a subject having a refractory oncological disorder for treatment. In certain embodiments of the aforementioned methods, the methods further comprise selecting a subject having an oncological disorder that has failed to respond to at least one, two, three, four, five, six, seven, eight or more previous treatments for treatment. In certain embodiments of the aforementioned methods, the methods further comprise selecting a subject having end stage cancer for treatment.

In preferred embodiments of the aforementioned methods, the subject is human.

In certain embodiments of the aforementioned methods, the chemotherapeutic agent comprises at least one of gemcitabine, cisplatin, docetaxel, cyclophosphamide, doxorubicin, irinotecan, and 5-fluorouracil.

In a preferred embodiment of the aforementioned methods, the method comprises administering between about 100 mg/kg of gemcitabine and about 10 mg/kg of gemcitabine once per week for 3 weeks with one week rest.

In another preferred embodiment of the aforementioned methods, the method comprises administering 5 mg/kg docetaxel, 1 mg/kg doxorubicin, and 35 mg/kg cyclophosphamide to the subject every three weeks for six cycles.

In certain embodiments of the aforementioned methods, the chemotherapeutic agent is SN38 and the oncological disorder is prostate cancer, the chemotherapeutic agent is SN38 and the oncological disorder is liver cancer, the chemotherapeutic agent is doxorubicin and the oncological disorder is breast cancer, the chemotherapeutic agent is doxorubicin and the oncological disorder is pancreatic cancer, the chemotherapeutic agent is doxorubicin and the oncological disorder is liver cancer, the chemotherapeutic agent is 5-fluorouracil and the oncological disorder is breast cancer, the chemotherapeutic agent is 5-fluorouracil and the oncological disorder is triple-negative breast cancer, the chemotherapeutic agent is 5-fluorouracil and the oncological disorder is liver cancer, the chemotherapeutic agent is cisplatin and the oncological disorder is lung cancer, the chemotherapeutic agent is 4-HCP and the oncological disorder is breast cancer, the chemotherapeutic agent is 4-HCP and the oncological disorder is triple-negative breast cancer, the chemotherapeutic agent is 4-HCP and the oncological disorder is breast cancer, the chemotherapeutic agent is 4-HCP and the oncological disorder is ovarian cancer, the chemotherapeutic agent is tamoxifen and the oncological disorder is breast cancer, the chemotherapeutic agent is gemcitabine and the oncological disorder is lung cancer, the chemotherapeutic agent is flutamide and the oncological disorder is prostate cancer, or the chemotherapeutic agent is goserelin and the oncological disorder is prostate cancer.

In some embodiments, wherein the CoQ10 is provided in an intravenous CoQ10 formulation, the intravenous CoQ10 formulation comprises (1) an aqueous solution, (2) CoQ10 dispersed into a nano-dispersion of particles; and (3) at least one of a dispersion stabilizing agent and an opsonization reducer, wherein the nano-dispersion of the CoQ10 is dispersed into nano-particles having a mean particle size of less than 200-nm.

In some embodiments, the dispersion stabilizing agent is selected from the group consisting of pegylated castor oil, Cremophor EL, Cremophor RH 40, Pegylated vitamin E, Vitamin E TPGS, and Dimyristoylphosphatidyl choline (DMPC). In some embodiments, the dispersion stabilizing agent is preferably DMPC.

In some embodiments, the opsonization reducer is selected from the group consisting of poloxamers and poloxamines. In some preferred embodiments, the opsonization reducer is poloxamer 188. In some preferred embodiments, the opsonization reducer is poloxamer 188 and the dispersion stabilizing agent is DMPC.

In some embodiments, the CoQ10 formulation has a weight-per-volume of the CoQ10, DMPC and poloxamer 188 of 4%, 3% and 1.5%, respectively.

In some embodiments, the CoQ10 is provided in a topical CoQ10 formulation wherein the topical CoQ10 formulation is a 3% CoQ10 cream comprising: (1) a phase A having C12-15 alkyl benzoate at about 4.0% w/w of the composition, cetyl alcohol at about 2.00% w/w of the composition, stearyl alcohol at about 1.5% w/w, glyceryl stearate and PEG-100 at about 4.5% w/w; (2) a phase B having glycerin at about 2.00% w/w, propylene glycol at about 1.5% w/w, ethoxydiglycol at about 5.0% w/w, phenoxyethanol at about 0.475% w/w, a carbomer dispersion at about 40% w/w, purified water at about 16.7% w/w; (3) a phase C having triethanolamine at about 1.3% w/w, lactic acid at about 0.5% w/w, sodium lactate solution at about 2.0% w/w, water at about 2.5% w/w; (4) a phase D having titanium dioxide at about 1.0% w/w; and (5) a phase E having CoQ10 21% concentrate at about 15.0% w/w.

In certain embodiments, the CoQ10 is provided in a formulation for inhalation wherein the formulation comprises a pharmaceutical composition comprising a dispersion of liposomal particles suitable for continuous aerosolization, the composition comprising: a dispersion of liposomal particles having an average diameter between about 30 and 500 nm, each liposomal particle comprising a hydrophobic bioactive agent, a phospholipid, and an aqueous dispersion vehicle, wherein the ratio of hydrophobic bioactive agent:phospholipid is between about 5:1 and about 1:5, the hydrophobic bioactive agent is between about 0.1 and 30% w/w of the composition, the phospholipid is between about 0.1 and 30% w/w of the composition, and the liposomal particles are dispersed within the aqueous dispersion vehicle, and wherein, upon administration to a subject, the composition is characterized by continuous aerosolization sufficient to provide a therapeutic dose of the hydrophobic bioactive agent to the subject. In certain embodiments, the aqueous dispersion vehicle comprises water or an aqueous salt solution. In certain embodiments, the dispersion of liposomal particles is in the form of a continuous respirable aerosol comprising a plurality of aqueous droplets containing

a dispersion of liposomal particles and having a mass median aerodynamic diameter (MMAD) between about 1 and 5 μm. In certain embodiments, the composition is characterized by an average percent transmission (APT) between about 50 and 100% over at least 15 minutes of continuous aerosolization. In certain embodiments, the plurality of droplets has a MMAD between about 1 and 5 μm over at least 15 minutes of continuous aerosolization.

Chemotherapeutic agents include, but are not limited to, cyclophosphamide, taxanes (e.g., paclitaxel or docetaxel), busulfan, cisplatin, methotrexate, daunorubicin, doxorubicin, melphalan, cladribine, vincristine, vinblastine, chlorambucil, tamoxifen, taxol, etoposide (VP-16), adriamycin, 5-fluorouracil (5FU), camptothecin, actinomycin-D, mitomycin C, cisplatin (CDDP), combretastatin(s), and irinotecan; and derivatives and prodrugs thereof. Chemotherapeutic agents include anti-angiogenic agents. Anti-angiogenic agents include, but are not limited to, angiostatin, endostatin, 16 kDa prolactin fragment, Laminin peptides, Fibronectin peptides, tissue metalloproteinase inhibitors (TIMP 1, 2, 3, 4), Plasminogen activator inhibitors (PAI-1, -2), Tumor necrosis factor alpha, TGF-β1, Interferons (IFN-α, -.β, γ), ELR- CXC Chemokines: IL-12; SDF-1; MIG; Platelet factor 4 (PF-4); IP-10, Thrombospondin (TSP), SPARC, 2-Methoxyoestradiol Proliferin-related protein, Suramin, Thalidomide, Cortisone, Fumagillin (AGM-1470; TNP-470), tamoxifen, Korean mistletoe extract (Viscum album coloratum), retinoids, CM101, dexamethasone, and leukemia inhibitory factor (LIF). Additional chemotherapeutic agents are provided herein.

In some embodiments, the antimetabolite includes at least one of a purine or pyrimidine analogues. In some embodiments, the antimetabolite includes at least one of gemcitabine, 5-fluorouracil, capecitabine, methotrexate and edatrexate. In some preferred embodiments, the antimetabolite is gemcitabine.

In some embodiments, the anthracycline antibiotic is a Topoisomerase II inhibitor. In some embodiments, the Topoisomerase II inhibitor includes at least one of doxorubicin, epirubicin, idarubicin, mitoxantrone, losoxantrone, etoposide and teniposide. In some preferred embodiments, the topoisomerase II inhibitor is doxorubicin.

In some embodiments, the chemotherapeutic agent is a Topoisomerase I inhibitor. In some embodiments, the Topoisomerase I inhibitor includes at least one of irinotecan, topotecan, 9- nitrocamptothecin, camptothecin, and camptothecin derivatives.

Routes and methods of administration of chemotherapeutic agents are known in the art.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered at least about 50 mg/kg/dose of intravenous CoQ10 formulation once daily for 3 weeks with one week rest, co-administered with a chemotherapeutic agent for one cycle.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered at least about 50 mg/kg/dose of intravenous CoQ10 formulation twice daily for 3 weeks with one week rest, and co-administered with a chemotherapeutic agent for one cycle.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered at least about 50 mg/kg/dose of intravenous CoQ10 formulation three times daily for 3 weeks with one week rest, and co-administered with a chemotherapeutic agent for one cycle.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered at least about 75 mg/kg/dose of intravenous CoQ10 formulation once daily for 3 weeks with one week rest, co-administered with a chemotherapeutic agent for one cycle.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered at least about 75 mg/kg/dose of intravenous CoQ10 formulation twice daily for 3 weeks with one week rest, and co-administered with a chemotherapeutic agent for one cycle.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered at least about 75 mg/kg/dose of intravenous CoQ10 formulation

three times daily for 3 weeks with one week rest, and co-administered with a chemotherapeutic agent for one cycle.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered at least about 50 mg/kg/dose of intravenous CoQ10 formulation once daily for 3 weeks with one week rest, and subsequently administered with a chemotherapeutic agent for one cycle.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered at least about 50 mg/kg/dose of intravenous CoQ10 formulation twice daily for 3 weeks with one week rest, and subsequently administered with a chemotherapeutic agent for one cycle.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered at least about 50 mg/kg/dose of intravenous CoQ10 formulation three times daily for 3 weeks with one week rest, and subsequently administered with a chemotherapeutic agent for one cycle.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered at least about 75 mg/kg/dose of intravenous CoQ10 formulation once daily for 3 weeks with one week rest, and subsequently administered with a chemotherapeutic agent for one cycle.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered at least about 75 mg/kg/dose of intravenous CoQ10 formulation twice daily for 3 weeks with one week rest, and subsequently administered with a chemotherapeutic agent for one cycle.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered at least about 75 mg/kg/dose of intravenous CoQ10 formulation three times daily for 3 weeks with one week rest, and subsequently administered with a chemotherapeutic agent for one cycle.

In certain embodiments, the CoQ10 is administered every day without a week of rest at three week intervals. In certain embodiments, the CoQ10 is administered every day until limiting toxicities are observed.

In some embodiments, the method comprises a regimen wherein the subject is intravenously administered CoQ10 by continuous infusion prior to administration of a chemotherapeutic agent. In some embodiments, the continuous infusion is for 24 hours prior to administration of the chemotherapeutic agent.

In certain embodiments, administration of the chemotherapeutic agent is initiated within 24 hours of completion of administration of a dose of CoQ10. In certain embodiments, administration of the chemotherapeutic agent is initiated within 18 hours of completion of administration of a dose of CoQ10. In certain embodiments, administration of the chemotherapeutic agent is initiated within 12 hours of completion of administration of a dose of CoQ10. In certain embodiments, administration of the chemotherapeutic agent is initiated within 6 hours of completion of administration of a dose of CoQ10. In certain embodiments, administration of the chemotherapeutic agent is initiated within 4 hours of completion of administration of a dose of CoQ10. In certain embodiments, administration of the chemotherapeutic agent is initiated within 3 hours of completion of administration of a dose of CoQ10. In certain embodiments, administration of the chemotherapeutic agent is initiated within 2 hours of completion of administration of a dose of CoQ10. In certain embodiments, administration of the chemotherapeutic agent is initiated within 1 hour of completion of administration of a dose of CoQ10.

In certain embodiments, after pre-treatment with CoQ10, treatment with CoQ10 is continued during treatment with the chemotherapeutic agent.

In some embodiments wherein the CoQ10 is administered prior to the chemotherapeutic agent, two or more cycles of CoQ10 (e.g., 2, 3, 4, 5, 6, 7, 8, etc.) are administered prior to administration of two or more (e.g., 2, 3, 4, 5, 6, 7, 8, etc.) cycles of a chemotherapeutic agent.

In certain embodiments, CoQ10 is administered for a sufficient time and amount prior to administration of the chemotherapeutic agent to achieve a steady state of CoQ10.

In certain embodiments, a loading dose of CoQ10 is administered prior to initiation of treatment with a chemotherapeutic agent.

In some embodiments wherein the CoQ10 is administered prior to the chemotherapeutic agent, one cycle of CoQ10 is administered prior to administration of one cycle of a chemotherapeutic agent. In certain embodiments, CoQ10 is administered prior to each dose of chemotherapeutic agent in each treatment cycle. In certain embodiments, multiple cycles of CoQ10 are administered alternating with cycles of a chemotherapeutic agent. In certain embodiments, CoQ10 is administered prior to each dose of chemotherapeutic agent in each treatment cycle. In certain embodiments, CoQ10 is administered prior to and concurrently with each dose of chemotherapeutic agent. In certain embodiments, CoQ10 is administered prior to and concurrently with each cycle of administration of chemotherapeutic agent.

In some embodiments wherein the CoQ10 is administered prior to the chemotherapeutic agent, one cycle of CoQ10 is administered prior to administration of two or more (e.g., 2, 3, 4, 5, 6, 7, 8, etc.) cycles of a chemotherapeutic agent.

It is understood that chemotherapeutic agents are frequently administered in cocktails. As used herein, a chemotherapeutic agent should be understood as one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, etc.) chemotherapeutic agents. Moreover, it is understood that when multiple cycles of chemotherapeutic agents are administered, that the specific dosing regimens and/or chemotherapeutic agents used in each of the cycles need not be the same. However, in certain embodiments, the chemotherapeutic agents and their dosing regimens are the same for all cycles.

In certain embodiments, the CoQ10 is administered by the same route of administration as the chemotherapeutic agent. In certain embodiments, the CoQ10 is administered by a different route of administration as the chemotherapeutic agent.

In some embodiments, the subject is treated for oncological disorders including at least one of pancreatic cancer, breast cancer, skin cancer, liver cancer, carcinoma, sarcoma, lymphoma, melanoma or leukemia. In certain embodiments, the subject is treated for an

oncological disorder comprising a solid tumor. In certain embodiments, the subject is treated for an oncological disorder comprising a non-solid tumor.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the effect of once daily dosing with intravenous CoQ10, alone or in combination with gemcitabine (days), on survival time in a xenogeneic mouse model of pancreatic cancer using human pancreatic tumor MIAPaCa-2 cells. In the graph, Day 1 indicates the day that treatment was initiated.

Fig. 2 is a photograph showing the effect of once daily dosing with intravenous CoQ10, alone or in combination with gemcitabine, on tumor size at the time of death in a xenogeneic mouse model of pancreatic cancer using human pancreatic tumor MIAPaCa-2 cells. Tumors in Group 1 were harvested at 20 days after initiation of treatment. Tumors in Group 2 were harvested at 50-60 days after initiation of treatment. Tumors in Group 3 were harvested at 40-50 days after initiation of treatment. Tumors in Group 4 were harvested at 50-60 days after initiation of treatment.

Fig. 3 is a graph showing the effect of once daily dosing with intravenous CoQ10, alone or in combination with gemcitabine, on tumor size at the time of death in a xenogeneic mouse model of pancreatic cancer using human pancreatic tumor MIAPaCa-2 cells. Tumors in Group 1 were harvested at 20 days after initiation of treatment. Tumors in Group 2 were harvested at 50-60 days after initiation of treatment. Tumors in Group 3 were harvested at 40-50 days after initiation of treatment. Tumors in Group 4 were harvested at 50-60 days after initiation of treatment.

Fig. 4 is a graph showing the effect of twice daily dosing with intravenous CoQ10, alone or in combination with gemcitabine, on survival time (days) in a xenogeneic mouse model of pancreatic cancer using human pancreatic tumor MIAPaCa-2 cells. In the graph, Day 1 indicates the day that treatment was initiated.

Fig. 5A is a graph showing the effect on viability of MIAPaCa-2 pancreatic cancer cells *in vitro* of 6 hour treatment with gemcitabine, CoQ10, an intravenous formulation of CoQ10, or the intravenous formulation of CoQ10 in combination with gemcitabine.

Fig. 5B is a graph showing the effect on viability of SK-Br3 breast cancer cells *in vitro* of 6 hour treatment with gemcitabine, CoQ10, an intravenous formulation of CoQ10, or the intravenous formulation of CoQ10 in combination with gemcitabine.

Fig. 6A is a graph showing the effect on viability of MIAPaCa-2 pancreatic cancer cells *in vitro* of 6 hour treatment with doxorubicin, CoQ10, an intravenous formulation of CoQ10, or the intravenous formulation of CoQ10 in combination with doxorubicin.

Fig. 6B is a graph showing the effect on viability of SK-Br3 breast cancer cells *in vitro* of 6 hour treatment with doxorubicin, CoQ10, an intravenous formulation of CoQ10, or the intravenous formulation of CoQ10 in combination with doxorubicin.

Fig. 7 is a graph showing the effect of once daily dosing with intravenous CoQ10 with doxorubicin, or doxorubicin alone on survival time in a xenogeneic mouse model of pancreatic cancer using human pancreatic tumor MIAPaCa-2 pancreatic cancer cells.

Fig. 8 is a graph showing the effect of three times daily intraperitoneal dosing at the indicated doses with intravenous formulation of CoQ10, alone or in combination with gemcitabine, on survival time in a xenogeneic mouse model of pancreatic cancer using human pancreatic tumor MIAPaCa-2 cells. In the graph, Day 1 indicates the day that treatment was initiated.

Fig. 9A is a graph showing the effect on viability of Hep3B liver cancer cells *in vitro* of treatment with the chemotherapeutic agent irinotecan (SN38) alone or in combination with CoQ10 (100 μM). Viability was assessed by live cell counting. Values are normalized to the number of cells treated with neither CoQ10 nor the chemotherapeutic agent.

Fig. 9B is a graph showing the effect on viability in Hep3B liver cancer cells *in vitro* of treatment with the chemotherapeutic agent cisplatin alone or in combination with CoQ10 (100 μM). Viability was assessed by live cell counting. Values are normalized to the number of cells treated with neither CoQ10 nor the chemotherapeutic agent.

Fig. 9C is a graph showing the effect on viability in Hep3B liver cancer cells *in vitro* of treatment with the chemotherapeutic agent 5-fluorouracil alone or in combination with

CoQ10 (100 μM). Viability was assessed by live cell counting. Values are normalized to the number of cells treated with neither CoQ10 nor the chemotherapeutic agent.

Fig. 10 is a graph showing the effect on viability in Hep3B liver cancer cells *in vitro* of treatment with the chemotherapeutic agent doxorubicin alone or in combination with CoQ10 (100 μM). Viability is assessed by live cell counting. Values are normalized to the number of cells treated with neither CoQ10 nor the chemotherapeutic agent.

Figs. 11A-11B show images of Mia-PaCa2 pancreatic cancer cells treated with gemcitabine alone or in combination with CoQ10 (100 μM). (A) Coenzyme Q10 was added 6 hours prior to addition of chemotherapy or (B) at the same time as chemotherapy.

Figs. 12A-12B are graphs of the results from a growth inhibition/promotion of cell death assay in which MIAPaCa2 pancreatic cancer cells were treated with gemcitabine, alone or in combination with CoQ10 (100 μM). (A) Coenzyme Q10 was added 6 hours prior to addition of chemotherapy, or (B) at the same time as chemotherapy. Growth inhibition/promotion of cell death was assessed by live cell counting. Values are normalized to the number of cells treated with neither CoQ10 nor the chemotherapeutic agent.

Fig. 13 is a graph showing results from proliferation assay in which MIAPaCa2 pancreatic cancer cells were treated with gemcitabine alone or in combination with CoQ10 prior to assessment of proliferation via flow cytometric analysis using the cell tracer dye CFSE which stains live cells. Values are normalized to the number of cells treated with neither CoQ10 nor the chemotherapeutic agent.

Fig. 14 is a graph showing results from assays in which MIAPaCa2 pancratic cancer cells were treated with gemcitabine, alone or in combination with CoQ10, prior to assessment of apoptosis of remaining adherent cells via flow cytometric analysis using propidium iodide which stains dead cells.Values are normalized to the number of cells treated with neither CoQ10 nor the chemotherapeutic agent.

Fig. 15 is a graph showing the effect of three times intraperitoneal daily dosing with an intravenous formulation of CoQ10 (75 mg/kg/dose) in combination with gemcitabine (150 mg/kg/dose, 1 x per 3 weeks), on survival time in a xenogeneic mouse model of pancreatic

cancer using human pancreatic tumor MIAPaCa-2 pancreatic cancer cells. Administration of CoQ10 was initiated 0, 1, 2, or 3 weeks prior to the initation of treatment with gemcitabine. In the graph, Day 1 indicates the day that treatment was initiated.

Fig. 16 shows the effect of CoQ10 treatment on the viability of various tumor cell lines *in vitro*. Cells were treated with 100 μM CoQ10 for 48-72 hours.

Fig. 17 shows the effect of CoQ10 treatment on basal oxygen consumption rate (OCR), extracellular acidification rate (ECAR) and reactive oxygen species (ROS) in breast cancer cells (MDA-MB231 and SKBR-3) and non-tumorigenic control cells (MCF12A) *in vitro*. Cells were treated with 100 μM CoQ10 for 24 hours.

Fig. 18 shows the effect of CoQ10 treatment on caspase 3 activity in breast cancer cells (MDA-MB231 and SKBR-3).

Fig. 19 shows the effect of co-treatment vs. pre-treatment in A549, PC3 and SKOV3 cancer cells with combinations of CoQ10 and various chemotherapeutic agents.

Fig. 20 shows MDA-MB231 and SkBr-3 breast cancer cells and MCF12A control cells subjected to either cotreatment with CoQ10 (100 μM) and chemotherapeutic agents (5-fluorouracil, 5-FU; doxorubicin, Doxo; SN38, irinotecan active metabolite) or pretreatment with CoQ10 (6 h) followed by co-incubation with chemotherapeutic agents. The number of viable cells was assessed after 48 hours. p values indicate interaction by 2-way ANOVA. * $p < 0.05$ compared to chemotherapeutic agent alone.

Fig. 21 shows a survival curve for mice bearing triple-negative breast cancer (TNBC) xenografts and treated with the TAC regimen (5 mg/kg docetaxel, 1 mg/mg doxorubicin, and 35 mg/kg cyclophosphamide) with and without 75 mg/kg body weight CoQ10 (BPM 31510). TAC was given every three weeks for six cycles.

Fig. 22 shows SkBr-3 breast cancer cells cotreated with 100 μM CoQ10 (BPM 31510) and 100 ng/ml doxorubicin. Caspase 3 activity was monitored over time using a cleavable fluorescent substrate.

Fig. 23 shows MDA-MB231and SkBr-3 breast cancer cells and MCF12A non-tumorigenic control cells treated with increasing doses of CoQ10 (BPM 31510). The number of viable cells was assessed after 48 h. EC_{50} values were calculated using non-linear regression analysis.

Fig. 24 shows MDA-MB231and SkBr-3 breast cancer cells and MCF12A non-tumorigenic control cells treated with 100 μM CoQ10 (BPM 31510) for 48 hours. Propidium iodide (PI) and CFSE Cell Tracer were used to measure cell death and proliferation, respectively, in cells treated with CoQ10.

Fig. 25 shows MDA-MB231 and SkBr-3 breast cancer cells and MCF12A non-tumorigenic control cells treated with 100 μM CoQ10 (BPM 31510) for 24 hours. Mitochondrial function was assessed using sequential injection of mitochondrial toxins (oligomycin, CCCP, and rotenone) in a Seahorse XF96 analyzer. DCF fluorescence was also measured as an indicator of reactive oxygen species production in cells treated in the same manner. * $p < 0.05$ compared to control, N.S. denotes no statistical significance.

Fig. 26 shows pretreatment of human pancreatic cancer cells (PcCa2) with 100 μM CoQ10 (BPM31510) followed by treatment with gemcitabine (0.1,1 and 5 μM), or cotreatment of these cells with CoQ10 and gemcitabine. Both pretreatment and cotreatment significantly decreased the number of viable cells (*$p < 0.05$) compared to gemcitabine alone.

Fig. 27 shows three treatment regimens for evaluating the effect of CoQ10 (BPM 31510) alone or in combination with gemcitabine on animal survival in a xenograft mouse model of human pancreatic cancer.

Fig. 28 shows the effect of regimen 2 (described in Fig. 27) treatment with CoQ10 (API 31510) and gemcitabine on animal survival in a xenograft mouse model of human pancreatic cancer. Gemcitabine alone versus gemcitabine + CoQ10 (50 mg/kg) p=7.3 E-8

Fig. 29 shows the effect of regimen 3 (described in Fig. 27) treatment with CoQ10 (API 31510) and gemcitabine on animal survival in a xenograft mouse model of human pancreatic cancer. Gemcitabine alone versus gemcitabine + CoQ10 (50 mg/kg) p=7.3 E-8

Fig. 30 shows the effect of various concentrations of CoQ10 (BPM 31510) on animal survival in a xenograft mouse model of human pancreatic cancer over time (days). Continuous infusion of CoQ10 at 200 mg/kg significantly improved survival in comparison to 50mg/kg CoQ10 ($p < 0.00001$). For example, mice treated with 200 mg/kg CoQ10 had the highest survival rate (survival probability) at 300 days, mice treated with 50 mg/kg CoQ10 had the lowest survival rate (survival probability) at 300 days, and mice treated with 100 mg/kg CoQ10 had a survival rate (survival probability) at 300 days that was between the other two treatment groups.

Fig. 31 shows the effect of CoQ10 and gemcitabine on animal survival over time (days) in a mouse xenograft model of human pancreatic cancer. Pretreatment with CoQ10 (200 mg/kg) sixty days prior to start of treatment with gemcitabine + CoQ10 improved survival in comparison to treatment with gemcitabine + CoQ10 from the start of the treatment regimen in a mouse xenograft model of human pancreatic cancer. For example, at 200 days, mice treated with CoQ10 60 days prior to start of gemcitabine and continuing with CoQ10 had the highest survival rate (survival probability), mice treated with gemcitabine and CoQ10 from the start had the next highest survival rate, mice treated with CoQ10 from the start had the next highest survival rate, and control mice had the lowest survival rate.

DETAILED DESCRIPTION

I. Definitions

In accordance with the present disclosure and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

"Treatment" is an intervention performed with the intention of preventing the development or altering the pathology, symptoms, or signs of a disorder. Accordingly, "treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented. As used herein, "treatment" refers to a symptom or sign

which approaches a normalized value (for example a value obtained in a healthy patient or individual), *e.g.*, is less than 50% different from a normalized value, in embodiments less than about 25% different from a normalized value, in other embodiments is less than 10% different from a normalized value, and in yet other embodiments the presence of a symptom is not significantly different from a normalized value as determined using routine statistical tests. As used herein, treatment can include reduction of tumor burden, inhibition of tumor growth, including inducing stable disease in a subject with progressive disease prior to treatment, increasing time to progression, or increasing survival time. Increases can be determined relative to an appropriate control or expected outcomes. As used herein, treatment can include increasing survival of a subject, with or without a decrease in tumor burden, as compared to appropriate controls. Treatment need not be curative.

As used herein, a "cycle" is understood as the regimen used for administration of CoQ10 or a chemotherapeutic agent. Typically, chemotherapeutic agents are not administered as single treatment, or treatment at continuing regular intervals (e.g., daily, weekly). A cycle includes the time of chemotherapy treatment and then a break before the next treatment, to permit recovery. For example a cycle lasts 4 weeks, may have treatment on the 1st, 2nd and 3rd days and then nothing from the 4th to the 28th day. Then the cycle starts again. Or, as another example, a 3 week cycle may have treatment on the 1st and 8th days, but nothing on days 2 to 7 and days 9 to 21. In certain embodiments, a cycle can include treatment with a combination of chemotherapeutic agents, on the same or different schedules, followed by a non-treatment window to permit recovery.

In certain embodiments, one cycle of CoQ10 is administered prior to administration of at least one cycle of at least one chemotherapeutic agent. In other embodiments, two or more cycles of CoQ10 are administered prior to administration of at least one cycle of at least one chemotherapeutic agent. In further embodiments, three or more cycles of CoQ10 are administered prior to administration of at least one cycle of a chemotherapeutic agent. In yet further embodiments, four or more cycles of CoQ10 are administered prior to administration of at least one cycle of a chemotherapeutic agent.

As used herein, "continuous infusion" is understood as administration of a therapeutic agent continuously for a period of at least 24 hours. Continuous infusion is typically accomplished by the use of a pump, optionally an implantable pump. A continuous infusion

may be administered within the context of a treatment cycle. For example, a dose of a therapeutic agent can be administered by continuous infusion over a 24 hour period once per week each week. Treatment with continuous infusion does not require infusion of the therapeutic agent to the subject for the entire treatment period.

It is understood that continuous infusion can include short interruptions of administration, for example, to change the reservoir of coenzyme Q10 being administered. Continuous administration is typically facilitated by the use of a pump. Continuous infusion is carried out without including any significant interruptions of dosing by design. As used herein, interruptions to assess vital signs and/or perform laboratory assessments to ensure the safety of the patients and that no unacceptable adverse event have occurred are not considered to be significant interruptions. Interruptions resulting from equipment failure, e.g., pump failure, are not interruptions by design.

The terms "oncological disorder", "cancer" or "tumor" are well known in the art and refer to the presence, *e.g.,* in a subject, of cells possessing characteristics typical of cancer-causing cells, such as uncontrolled proliferation, immortality, metastatic potential, rapid growth and proliferation rate, decreased cell death/apoptosis, and certain characteristic morphological features.

As used herein, "oncological disorder", "cancer" or "tumor" refers to all types of cancer or neoplasm or malignant tumors found in humans, including, but not limited to: leukemias, lymphomas, melanomas, carcinomas and sarcomas. As used herein, the terms or language "oncological disorder", "cancer," "neoplasm," and "tumor," are used interchangeably and in either the singular or plural form, refer to cells that have undergone a malignant transformation that makes them pathological to the host organism. Primary cancer cells (that is, cells obtained from near the site of malignant transformation) can be readily distinguished from non-cancerous cells by well-established techniques, particularly histological examination. The definition of a cancer cell, as used herein, includes not only a primary cancer cell, but also cancer stem cells, as well as cancer progenitor cells or any cell derived from a cancer cell ancestor. This includes metastasized cancer cells, and in vitro cultures and cell lines derived from cancer cells.

A "solid tumor" is a tumor that is detectable on the basis of tumor mass; e.g., by procedures such as CAT scan, MR imaging, X-ray, ultrasound or palpation, and/or which is

detectable because of the expression of one or more cancer-specific antigens in a sample obtainable from a patient. The tumor does not need to have measurable dimensions.

When referring to a type of cancer that normally manifests as a solid tumor, a "clinically detectable" tumor is one that is detectable on the basis of tumor mass; e.g., by procedures such as CAT scan, MR imaging, X-ray, ultrasound or palpation, and/or which is detectable because of the expression of one or more cancer-specific antigens in a sample obtainable from a patient.

As used herein, a "detectable tumor" is a tumor that can be confirmed to be present in a subject, for example, using imaging methods (e.g., x-ray, CT scan, magnetic resonance imaging either with or without contrast agents, ultrasound), palpation or other physical examination methods, and/or direct observation by surgical methods or biopsy, typically coupled with histological analysis, in the case of a solid tumors; or by analysis of blood samples, e.g., completely blood count or histological analysis in the case of non-solid tumors, e.g., leukemias. In certain embodiments, a tumor can be detected based on the presence or certain markers. It is understood that diagnosis and detection of a tumor may involve multiple tests and diagnostic methods.

The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Examples of sarcomas which can be treated with a colloidal dispersion of CoQ10 in an IV formulation include, for example, a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, and telangiectaltic sarcoma.

The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas which can be treated with the colloidal dispersions of CoQ10 in IV formulation include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, and superficial spreading melanoma.

The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Carcinomas which can be treated with the colloidal dispersions of CoQ10 in IV formulation, as described herein, include, for example, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniform carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypemephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, merkel cell carcinoma, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell

carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, and carcinoma villosum.

Specific criteria for the staging of cancer are dependent on the specific cancer type based on tumor size, histological characteristics, tumor markers, and other criteria known by those of skill in the art. Generally, cancer stages can be described as follows:

Stage 0 Carcinoma in situ

Stage I, Stage II, and Stage III Higher numbers indicate more extensive disease: Larger tumor size and/or spread of the cancer beyond the organ in which it first developed to nearby lymph nodes and/or tissues or organs adjacent to the location of the primary tumor

Stage IV The cancer has spread to distant tissues or organs

As used herein, the terms "treat," "treating" or "treatment" refer, preferably, to an action to obtain a beneficial or desired clinical result including, but not limited to, alleviation or amelioration of one or more signs or symptoms of a disease or condition (e.g., regression, partial or complete), diminishing the extent of disease, stability (*i.e.*, not worsening, achieving stable disease) state of disease, amelioration or palliation of the disease state, diminishing rate of or time to progression, and remission (whether partial or total). "Treatment" of a cancer can also mean prolonging survival as compared to expected survival in the absence of treatment. Treatment need not be curative. In certain embodiments, treatment includes one or more of a decrease in pain or an increase in the quality of life (QOL) as judged by a qualified individual, e.g., a treating physician, e.g., using accepted assessment tools of pain and QOL. In certain embodiments, treatment does not include one or more of a decrease in pain or an increase in the quality of life (QOL) as judged by a qualified individual, e.g., a treating physician, e.g., using accepted assessment tools of pain and QOL.

RECIST criteria are clinically accepted assessment criteria used to provide a standard approach to solid tumor measurement and provide definitions for objective assessment of change in tumor size for use in clinical trials. Such criteria can also be used to monitor

response of an individual undergoing treatement for a solid tumor. The RECIST 1.1 criteria are discussed in detail in Eisenhauer et al., New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur. J. Cancer.* 45:228-247, 2009, which is incorporated herein by reference. Response criteria for target lesions include:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesion, taking as a reference the baseline sum diameters.

Progressive Diseases (PD): At least a 20% increase in the sum of diameters of target lesions, taking as a reference the smallest sum on the study (this includes the baseline sum if that is the smallest on the study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameters while on study.

RECIST 1.1 criteria also consider non-target lesions which are defined as lesions that may be measureable, but need not be measured, and should only be assessed qualitatively at the desired time points. Response criteria for non-target lesions include:

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/ Non-PD: Persistence of one or more non-target lesion(s) and/ or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): *Unequivocal progression* (emphasis in original) of existing non-target lesions. The appearance of one or more new lesions is also considered progression. To achieve "unequivocal progression" on the basis of non-target disease, there must be an overall level of substantial worsening of non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target

lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR in target disease will therefore be extremely rare.

Clinically acceptable criteria for response to treatment in acute leukemias are as follows:

Complete remission (CR): The patient must be free of all symptoms related to leukemia and have an absolute neutrophil count of $\geq 1.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and normal bone marrow with < 5% blasts and no Auer rods.

Complete remission with incomplete blood count recovery (Cri): As per CE, but with residual thrombocytopenia (platelet count $< 100 \times 10^9$/L) or residual neutropenia (absolute neutrophil count $< 1.0 \times 10^9$/L).

Partial remission (PR): A $\geq$ 50% decrease in bone marrow blasts to 5 to 25% abnormal cells in the marrow; or CR with $\leq$ 5% blasts if Auer rods are present.

Treatment failure: Treatment has failed to achieve CR, Cri, or PR. Recurrence.

Relapse after confirmed CR: Reappearnce of leukemic blasts in peripheral bood or $\geq$ 5% blasts in the bone marrow not attributable to any other cause (e.g., bone marrow regeneration after consolidated therapy) or appearance of new dysplastic changes.

"Chemotherapeutic agent" refers to a drug used for the treatment of cancer. Chemotherapeutic agents include, but are not limited to, small molecules, hormones and hormone analogs, and biologics (e.g., antibodies, peptide drugs, nucleic acid drugs). In certain embodiments, chemotherapy does not include hormones and hormone analogs.

A "chemotherapeutic regimen" is a clinically accepted dosing protocol for the treatment of cancer that includes administration of one or more chemotherapeutic agents to a subject in specific amounts on a specific schedule. In certain embodiments, the chemotherapeutic agent can be an agent in clinical trials.

As used herein, "co-administration" or "combination therapy" is understood as administration of two or more active agents using separate formulations or a single pharmaceutical formulation, or consecutive administration in any order such that, there is a

time period while both (or all) active agents simultaneously exert their biological activities. It is contemplated herein that one active agent (e.g., CoQ10) can improve the activity of a second agent, for example, can sensitize target cells, e.g., cancer cells, to the activities of the second agent. Co-administration does not require that the agents are administered at the same time, at the same frequency, or by the same route of administration. As used herein, "co-administration" or "combination therapy" includes administration of a CoQ10 compound with one or more additional anti-cancer agents, e.g., chemotherapeutic agents, or administration of two or more CoQ10 compounds. Examples of anticancer agents, including chemotherapeutic agents, are provided herein.

In a preferred embodiment, the additional anti-cancer agents, e.g., chemotherapeutic agents or chemotherapeutic regimen, administered in combination with CoQ10 in the methods of treatment provided herein do not include, i.e., exclude, CoQ10.

Chemotherapeutic regimens can include administration of a drug on a predetermined "cycle" including intervals of dosing and not dosing with one or more agents for the treatment of cancer. For example, an agent can be administered one or more times per week for three consecutive weeks followed by a week of no agent administered to provide a four week cycle. The cycle can be repeated so that the subject would be subjected to three treatment weeks, one no treatment week, three treatment weeks, one no treatment week, etc., for the desired number of cycles. In certain embodiments, treatment of efficacy and laboratory values (e.g., liver enzymes, blood count, kidney function) are assessed at the end of each cycle or every other cycle.

A "subject who has failed a chemotherapeutic regimen" is a subject with cancer that does not respond, or ceases to respond to treatment with a chemotherapeutic regimen per RECIST 1.1 criteria (see, Eisenhauer et al., 2009 and as discussed above), i.e., does not achieve at least stable disease (i.e., stable disease, partial response, or complete response) in the target lesion; or does not achieve at least non-CR/non-PD (i.e., non-CR/non-PD or complete response) of non-target lesions, either during or after completion of the chemotherapeutic regimen, either alone or in conjunction with surgery and/or radiation therapy which, when possible, are often clinically indicated in conjunction with chemotherapy. A failed chemotherapeutic regime results in, e.g., tumor growth, increased tumor burden, and/ or tumor metastasis. In some embodiments, failed chemotherapeutic regimen as used herein includes a treatment regimen that was terminated due to a dose

limiting toxicity, e.g., a grade III or a grade IV toxicity that cannot be resolved to allow continuation or resumption of treatment with the chemotherapeutic agent or regimen that caused the toxicity. In some embodiments, a "failed chemotherapeutic regimen includes a treatment regimen that does not result in at least stable disease for all target and non-target lesions for an extended period, e.g., at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 12 months, at least 18 months, or any time period less than a clinically defined cure. In some embodiments, a failed chemotherapeutic regimen includes a treatment regimen that results in progressive disease of at least one target lesion during treatment with the chemotherapeutic agent, or results in progressive disease less than 2 weeks, less than 1 month, less than two months, less than 3 months, less than 4 months, less than 5 months, less than 6 months, less than 12 months, or less than 18 months after the conclusion of the treatment regimen, or less than any time period less than a clinically defined cure.

A failed chemotherapeutic regimen does not include a treatment regimen wherein the subject treated for a cancer achieves a clinically defined cure, e.g., 5 years of complete response after the end of the treatment regimen, and wherein the subject is subsequently diagnosed with a distinct cancer, e.g., more than 5 years, more than 6 years, more than 7 years, more than 8 years, more than 9 years, more than 10 years, more than 11 years, more than 12 years, more than 13 years, more than 14 years, or more than 15 years after the end of the treatment regimen. For example, a subject who suffered from a pediatric cancer may develop cancer later in life after being cured of the pediatric cancer. In such a subject, the chemotherapeutic regimen to treat the pediatric cancer is considered to have been successful.

A "refractory cancer" is a malignancy for which surgery is ineffective, which is either initially unresponsive to chemo- or radiation therapy, or which becomes unresponsive to chemo- or radiation therapy over time.

A "therapeutically effective amount" is that amount sufficient to treat a disease in a subject. A therapeutically effective amount can be administered in one or more administrations.

The terms "administer", "administering" or "administration" include any method of delivery of a pharmaceutical composition or agent into a subject's system or to a particular region in or on a subject. In certain embodiments, the agent is delivered orally. In certain

embodiments, the agent is administered parenterally. In certain embodiments, the agent is delivered by injection or infusion. In certain embodiments, the agent is delivered topically including transmucosally. In certain embodiments, the agent is delivered by inhalation. In certain embodiments of the invention, an agent is administered by parenteral delivery, including, intravenous, intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections. In one embodiment, the compositions provided herein may be administered by injecting directly to a tumor. In some embodiments, the formulations of the invention may be administered by intravenous injection or intravenous infusion. In certain embodiments, the formulation of the invention can be administered by continuous infusion. In certain embodiments, administration is not oral. In certain embodiments, administration is systemic. In certain embodiments, administration is local. In some embodiments, one or more routes of administration may be combined, such as, for example, intravenous and intratumoral, or intravenous and peroral, or intravenous and oral, intravenous and topical, or intravenous and transdermal or transmucosal. Administering an agent can be performed by a number of people working in concert. Administering an agent includes, for example, prescribing an agent to be administered to a subject and/or providing instructions, directly or through another, to take a specific agent, either by self-delivery, e.g., as by oral delivery, subcutaneous delivery, intravenous delivery through a central line, etc.; or for delivery by a trained professional, e.g., intravenous delivery, intramuscular delivery, intratumoral delivery, etc.

"Adverse events" or "AEs" are characterized by grade depending on the severity. Some AE (e.g., nausea, low blood counts, pain, reduced blood clotting) can be treated so that the specific chemotherapeutic regimen can be continued or resumed. Some adverse events (e.g., loss of cardiac, liver, or kidney function; nausea) may not be treatable, requiring termination of treatment with the drug. Determination of AE grade and appropriate interventions can be determined by those of skill in the art. Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (Publish Date: May 28, 2009) provide a grading scale for adverse events as follows:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily life (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to adverse event.

As used herein, the term "survival" refers to the continuation of life of a subject which has been treated for a disease or condition, *e.g.,* cancer. The time of survival can be defined from an arbitrary point such as time of entry into a clinical trial, time from completion or failure or an earlier treatment regimen, time from diagnosis, etc.

As used herein, "opsonization" refers to the process by which a lipophilic bioactive agent as described herein is marked for ingestion and destruction by a phagocyte. Opsonization involves the binding of an opsonin to bioactive agent. After opsonin binds to the membrane, phagocytes are attracted to the active agent. An opsonin is any molecule that acts as a binding enhancer for the process of phagocytosis.

As used herein, the term "opsonization reducer" refers to any agent that works in conjunction with the active agent to reduce the ability of opsonins to act as a binding enhancer for the process of phagocytosis.

As used herein, a "dispersion" refers to a system in which particles of colloidal size of any nature (e.g., solid, liquid or gas) are dispersed in a continuous phase of a different composition or state. In intravenous drug delivery the continuous phase is substantially water and the dispersed particles can be solid (a suspension) or an immiscible liquid (emulsion).

A "subject" to be treated by the method of the invention can mean either a human or non-human animal, preferably a mammal, more preferably a human. In certain embodiments, a subject has a detectable tumor prior to initiation of treatments using the methods of the invention. In certain embodiments, the subject has a detectable tumor at the time of initiation of the treatments using the methods of the invention.

As used herein, the term “safe and therapeutic effective amount” refers to the quantity of a component which is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this disclosure.

“Therapeutically effective amount” means the amount of a compound that, when administered to a patient for treating a disease, is sufficient to effect such treatment for the disease. When administered for preventing a disease, the amount is sufficient to avoid or delay onset of the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of the patient to be treated. A therapeutically effective amount need not be curative. A therapeutically effective amount need not prevent a disease or condition from ever occurring. Instead a therapeutically effective amount is an amount that will at least delay or reduce the onset, severity, or progression of a disease or condition. Disease progression can be monitored, for example, by one or more of tumor burden, time to progression, survival time, or other clinical measurements used in the art.

The term "therapeutic effect" refers to a local or systemic effect in animals, particularly mammals, and more particularly humans caused by a pharmacologically active substance. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and conditions in an animal or human. The phrase "therapeutically-effective amount" means that amount of such a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. In certain embodiments, a therapeutically-effective amount of a compound will depend on its therapeutic index, solubility, and the like.

“Preventing” or “prevention” refers to a reduction in risk of acquiring a disease or disorder (i.e., causing at least one of the clinical signs or symptoms of the disease not to develop in a patient that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease). Prevention does not require that the disease or condition never occur, or recur, in the subject.

The terms “disorders” and “diseases” are used inclusively and refer to any deviation from the normal structure or function of any part, organ or system of the body (or any combination thereof). A specific disease is manifested by characteristic symptoms and signs, including biological, chemical and physical changes, and is often associated with a variety of other factors including, but not limited to, demographic, environmental, employment, genetic and medically historical factors. Certain characteristic signs, symptoms, and related factors can be quantitated through a variety of methods to yield important diagnostic information.

In all occurrences in this application where there are a series of recited numerical values, it is to be understood that any of the recited numerical values may be the upper limit or lower limit of a numerical range. It is to be further understood that the invention encompasses all such numerical ranges, i.e., a range having a combination of an upper numerical limit and a lower numerical limit, wherein the numerical value for each of the upper limit and the lower limit can be any numerical value recited herein. Ranges provided herein are understood to include all values within the range. For example, 1-10 is understood to include all of the values 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, and fractional values as appropriate. Ranges expressed as “up to” a certain value, e.g., up to 5, is understood as all values, including the upper limit of the range, e.g., 0, 1, 2, 3, 4, and 5, and fractional values as appropriate. Up to or within a week is understood to include, 0.5, 1, 2, 3, 4, 5, 6, or 7 days. Similarly, ranges delimited by “at least” are understood to include the lower value provided and all higher numbers.

All percent formulations are w/w unless otherwise indicated.

As used herein, “about” is understood to include within three standard deviations of the mean or within standard ranges of tolerance in the specific art. In certain embodiments, about is understood a variation of no more than 0.5.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to".

The term "or" is used inclusively herein to mean, and is used interchangeably with, the term "and/or," unless context clearly indicates otherwise.

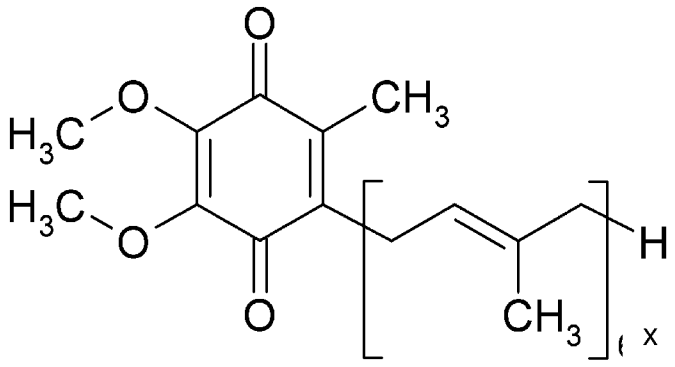
The term "such as" is used herein to mean, and is used interchangeably, with the phrase "such as but not limited to".

The term “standard dosage” as used herein refers to a dosage of a therapeutic agent that is commonly used for treatment of a disorder. For example, the recommended dosage of a therapeutic agent described in a product insert by a manufacturer of the therapeutic agent would be considered a standard dosage. Examples of standard dosages of chemotherapeutic agents are provided in Table 3.

For example, as shown in Table 3, the standard dose of gemcitabine for intravenous use for treatment of ovarian cancer is 1000 mg/m2 over 30 minutes on Days 1 and 8 of each 21-day cycle; the standard dose of gemcitabine for intravenous use for treatment of breast cancer is 1250 mg/m2 over 30 minutes on Days 1 and 8 of each 21-day cycle; the standard dose of gemcitabine for intravenous use for treatment of Non-Small Cell Lung Cancer is 1000 mg/m2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m2 over 30 minutes on Days 1 and 8 of each 21-day cycle; and the standard dose of gemcitabine for intravenous use for treatment of pancreatic Cancer: 1000 mg/m2 over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle.

II. Coenzyme Q10 Compounds

It will be understood that all of the methods provided in the instant invention may involve administration of, in place of Coenzyme Q10, any other Coenzyme Q10 compound, or a combination thereof. Coenzyme Q10 compounds are intended to include a class of CoQ10 compounds. Coenzyme Q10 compounds effective for the methods described herein include CoQ10, a metabolite of CoQ10, a biosynthetic precursor of CoQ10, an analog of CoQ10, a derivative of CoQ10, and CoQ10 related compounds. An analog of CoQ10 includes analogs having no or at least one isoprenyl repeats. CoQ10 has the following structure:



wherein x is 10. In the instant invention, CoQ10 compounds can include derivatives of CoQ10 in which x is any number of isoprenyl units from 4-10, or any number of isoprenyl units from 6-10, or any number of isoprenyl units from 8-10, or 9-10 isoprenyl units. CoQ10 includes the fully oxidized version, also known as ubiquinone, the partially oxidized version, also known as semiquinone or ubisemiquinone, or the fully reduced version, also known as ubiquinol; or any mixtures or combinations thereof. In certain embodiments, the CoQ10 compound for treatment of cancer is ubiquinone. In certain embodiments, the CoQ10 compound for treatment of cancer is ubiquinol.

In certain embodiments of the present invention, the therapeutic agent is Coenzyme Q10 (CoQ10). Coenzyme Q10, also referred to herein as CoQ10, is also known as ubiquinone, or ubidecarenone. CoQ10 is art-recognized and further described in International Publication No. WO 2005/069916 (Appln. No. PCT/US2005/001581), WO 2008/116135 (Appln. No. PCT/US08/57786), WO2010/132507 (Appln. No. PCT/US2010/034453), WO 2011/112900 (Appln. No. PCT/US2011/028042), and WO2012/174559 (Appln. No. PCT/US2012/043001) the entire contents of each of which are expressly incorporated by reference herein. CoQ10 is one of a series of polyprenyl 2,3-dimethoxy-5-methylbenzoquinone (ubiquinone) present in the mitochondrial electron transport systems of eukaryotic cells. Human cells produce CoQ10 exclusively and it is found in cell and mitochondrial membranes of all human cells, with the highest levels in organs with high energy requirements, such as the liver and the heart. The body pool of CoQ10 has been estimated to be about 2 grams, of which more than 50% is endogenous. Approximately 0.5 grams of CoQ10 is required from the diet or biosynthesis each day. CoQ10 is produced in ton quantities from the worldwide supplement market and can be obtained from Kaneka, with plants in Pasadena, Texas and Takasagoshi, Japan.

Coenzyme Q10 related compounds include, but are not limited to, benzoquinones, isoprenoids, farnesols, farnesyl acetate, farnesyl pyrophosphate, 1-phenylalanine, d-phenylalanine, dl-phenylalanine, 1-tyrosine, d- tyrosine, dl-tyrosine, 4-hydroxy-phenylpyruvate, 4-hydroxy-phenyllactate, 4-hydroxy- cinnamate, dipeptides and tripeptides of tyrosine or phenylalanine, 3,4-dihydroxymandelate, 3- methoxy-4-hydroxyphenylglycol, 3-methoxy-4-hydroxymandelate, vanillic acid, phenylacetate, pyridoxine, S-adenosyl methionine, panthenol, mevalonic acid, isopentyl pyrophosphate, phenylbutyrate, 4-hydroxy-benzoate,decaprenyl pyrophosphate, beta-hydroxybutyrate, 3- hydroxy-3-methyl-glutarate, acetylcarnitine, acetoacetylcarnitine, acetylglycine, acetoacetylglycine, carnitine, acetic acid, pyruvic acid, 3-hydroxy-3-methylglutarylcarnitine, all isomeric forms of serine, alanine, cysteine, glycine, threonine, hydroxyproline, lysine, isoleucine, and leucine, even carbon number C4 to C8 fatty acids (butyric, caproic, caprylic, capric, lauric, myristic, palmitic, and stearic acids) salts of carnitine and glycine, e.g., palmitoylcarnitine and palmitoylglycine, and 4-hydroxy-benzoate polyprenyltransferase, any salts of these compounds, as well as any combinations thereof, and the like. In certain embodiments, such agents can be used for the treatment of a cancer according to the methods provided herein..

Metabolites and biosynthetic precursors of CoQ10 include, but are not limited to, those compounds that are formed between the chemical/biological conversion of tyrosine and acetyl-CoA to ubiquinol. Intermediates of the coenzyme biosynthesis pathway include tyrosine, acetyl-CoA, 3-hexaprenyl-4-hydroxybenzoate, 3-hexaprenyl-4,5-dihydroxybenzoate, 3-hexaprenyl-4-hydroxy-5-methoxybenzoate, 2-hexaprenyl-6-methoxy-1,4-benzoquinone, 2-hexaprenyl-3-methyl-6-methoxy-1,4-benzoquinone, 2-hexaprenyl-3-methyl-5-hydroxy-6-methoxy-1,4-benzoquinone, 3-Octaprenyl-4-hydroxybenzoate, 2-octaprenylphenol, 2-octaprenyl-6-metholxyphenol, 2-octaprenyl-3-methyl-6-methoxy-1,4-benzoquinone, 2-octaprenyl-3-methyl-5-hydroxy-6-methoxy-1,4-benzoquinone, 2-decaprenyl-3-methyl-5-hydroxy-6-methoxy-1,4-benzoquinone, 2-decaprenyl-3-methyl-6-methoxy-1,4-benzoquinone, 2-decaprenyl-6-methoxy-1,4-benzoquinone, 2-decaprenyl-6-methoxyphenol, 3-decaprenyl-4-hydroxy-5-methoxybenzoate, 3-decaprenyl-4,5-dihydroxybenzoate, 3-decaprenyl-4-hydroxybenzoate, 4-hydroxy phenylpyruvate, 4-hydroxyphenyllactate, 4-hydroxy-benzoate, 4-hydroxycinnamate, and hexaprenydiphosphate. In certain embodiments, such agents can be used for the treatment of a cancer according to the methods provided herein.

III. Compositions

The present disclosure provides compositions containing a CoQ10 compound, e.g., Coenzyme Q10, for the treatment and prevention of cancer. The compositions of the present disclosure can be administered to a patient either by themselves, or in pharmaceutical compositions where it is mixed with suitable carriers or excipient(s). In treating a patient exhibiting an oncological disorder, a therapeutically effective amount of the CoQ10 compound is administered.

Suitable routes of administration of the present compositions of the invention may include parenteral delivery, including, intravenous, intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections, just to name a few. In one embodiment, the compositions provided herein may be administered by injecting directly to a tumor. In some embodiments, the formulations of the invention may be administered by intravenous injection or intravenous infusion. In some embodiments, the formulation is administered by continuous infusion. In one embodiment, the compositions of the invention are administered by intravenous injection. In one embodiment, the compositions of the invention are administered by intravenous infusion. Where the route of administration is, for example intravenous infusion, embodiments are provided herein where the IV infusion comprises the active agent, *e.g.*, CoQ10, at approximately a 40 mg/mL concentration. Where the composition is administered by IV infusion, it can be diluted in a pharmaceutically acceptable aqueous solution such as phosphate buffered saline or normal saline. In some embodiments, one or more routes of administration may be combined, such as, for example, intravenous and intratumoral, or intravenous and peroral, or intravenous and oral, or intravenous and topical, transdermal, or transmucosal.

The compositions described herein may be administered to a subject in any suitable formulation. These include, for example, liquid, semi-solid, and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, creams, lotions, liniments, ointments, or pastes, drops for administration to the eye, ear or nose, liposomes, and suppositories. The preferred form depends on the intended mode of administration and therapeutic application.

In certain embodiments, a CoQ10 compound, e.g., CoQ10,, may be prepared with a carrier that will protect against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, *e.g.*, Sustained and Controlled Release Drug Delivery Systems, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

For example, a CoQ10 compound e.g., CoQ10, can be formulated for parenteral delivery, *e.g.*, for subcutaneous, intravenous, intramuscular, or intratumoral injection. The compositions may be administered in a single bolus, multiple injections, or by continuous infusion (for example, intravenously or by peritoneal dialysis). For parenteral administration, the compositions may be formulated in a sterilized pyrogen-free form.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed, for the practice of the present invention, into dosages suitable for systemic administration is within the scope of the present disclosure. With proper choice of carrier and suitable manufacturing practice, the compositions of the present disclosure, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices may be desirable. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds may be within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve

its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers including excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for intravenous administration may be in the form of solutions of colloidal dispersion.

Pharmaceutical compositions for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

IV. Formulations

The active agent, e.g., a CoQ10 compound, e.g., CoQ10, can be delivered in any pharmaceutically acceptable carrier for the desired route of administration. As used herein, formulations including CoQ10 compounds are formulated for any route of administration unless otherwise clearly indicated. In preferred embodiments, the formulations are for administration by injection, infusion, or topical administration. In certain embodiments, the CoQ10 compounds are not delivered orally.

Preferred therapeutic formulations for use in the methods of the invention comprise the active agent (e.g., a CoQ10 compound, e.g., CoQ10) in a microparticle formation, e.g., for intravenous administration. Such intravenous formulations are provided, for example, in WO2011/112900 (Appln. No. PCT/US2011/028042), the entire contents of which are expressly incorporated herein by reference, and an exemplary intravenous formulation as described in WO2011/112900 (Appln. No. PCT/US2011/028042) is used in the examples set forth below. Through high pressure homogenization, active agent (e.g., a CoQ10 compound, e.g., CoQ10) particles are reduced to produce particles that are small enough to pass through

a 200-nm sterilizing filter. Particles that are small enough to pass through a 200-nm sterilizing filter can be injected intravenously. These particles are much smaller than blood cells and therefore will not embolize capillaries. Red blood cells for example are 6-micron x 2-micron disks. The particles are dispersed to and are encased or surrounded by a stabilizing agent. While not wishing to be bound by any theory, it is believed that the stabilizing agents are attracted to the hydrophobic therapeutic agent such that the dispersed particles of the hydrophobic therapeutic agent are surrounded by the stabilizing agent forming a suspension or an emulsion. The dispersed particles in the suspension or emulsion comprises a stabilizing agent surface and a core consisting of the hydrophobic therapeutic agent, e.g., a CoQ10 compound, e.g., CoQ10, in a solid particulate form (suspension) or in an immiscible liquid form (emulsion). The dispersed particles can be entrenched in the lipophilic regions of a liposome.

Dispersed colloidal systems permit a high drug load in the formulation without the use of co-solvents. Additionally, high and relatively reproducible plasma levels are achieved without the dependence on endogenous low-density lipoprotein carriers. More importantly, the formulations allow sustained high drug levels in solid tumors due to the passive accumulation of the colloidal particles of the hydrophobic therapeutic agent.

A preferred intravenous formulation substantially comprises a continuous phase of water and dispersed solids (suspension) or dispersed immiscible liquid (emulsion). Dispersed colloidal systems, in which the particles are composed largely of the active agent (drug) itself, can often deliver more drug per unit volume than continuous solubilizing systems, if the system can be made adequately stable.

As the formulation medium, the aqueous solution may include Hank's solution, Ringer's solution, phosphate buffered saline (PBS), physiological saline buffer or other suitable salts or combinations to achieve the appropriate pH and osmolarity for parenterally delivered formulations. Aqueous solutions can be used to dilute the formulations for administration to the desired concentration. For example, aqueous solutions can be used to dilute a formulation for intravenous administration from a concentration of about 4% w/v to a lower concentration to facilitate administration of lower doses of CoQ10. The aqueous solution may contain substances which increase the viscosity of the solution, such as sodium carboxymethyl cellulose, sorbitol, or dextran.

The active agent (e.g., a CoQ10 compound, e.g., CoQ10) is dispersed in the aqueous solution such that a colloidal dispersion is formed wherein the nano-dispersion particles of the hydrophobic therapeutic agent are covered or encased or encircled by the dispersion stabilizing agents to form nano-dispersions of the active agent (e.g., a CoQ10 compound, e.g., CoQ10) particles. The nano-dispersed active agent (e.g., a CoQ10 compound, e.g., CoQ10) particles have a core formed of the hydrophobic therapeutic agent that is surrounded by the stabilizing agent. Similarly, in certain aspects, the stabilizing agent is a phospholipid having both a hydrophilic and lipophilic portion. The phospholipids form liposomes or other nanoparticles upon homogenization. In certain aspects these liposomes are bi-layered unilamellar liposomes while in other embodiments the liposomes are bi-layered multi-lamellar liposomes. The dispersed active agent (e.g., a CoQ10 compound, e.g., CoQ10) particles are dispersed in the lipophilic portion of the bi-layered structure of the liposome formed from the phospholipids. In certain other aspects the core of the liposome, like the core of the nano-dispersion of active agent (e.g., a CoQ10 compound, e.g., CoQ10) particles, is formed of the hydrophobic therapeutic agent and the outer layer is formed of the bi-layered structure of the phospholipid. In certain embodiments the colloidal dispersions are treated by a lyophilization process whereby the nanoparticle dispersion is converted to a dry powder.

In some embodiments, the formulation for injection or infusion used is a 4% sterile aqueous colloidal dispersion containing CoQ10 in a nanosuspension as prepared in WO2011/112900. In certain embodiments, the formulation includes an aqueous solution; a hydrophobic active agent, e.g., CoQ10, a CoQ10 precursor or metabolite or a CoQ10 related compound, dispersed to form a colloidal nano-dispersion of particles; and at least one of a dispersion stabilizing agent and an opsonization reducer; wherein the colloidal nano-dispersion of the active agent is dispersed into nano-dispersion particles having a mean size of less than 200-nm.

In certain embodiments, the dispersion stabilizing agent includes, but is not limited to, pegylated castor oil, Cremphor® EL, Cremophor® RH 40, Pegylated vitamin E, Vitamin E TPGS, and Dimyristoylphosphatidyl choline (DMPC).

In certain embodiments, the opsonization reducer is a poloxamer or a poloxamines.

In certain embodiments, the colloidal nano-dispersion is a suspension or an emulsion. Optionally, a colloidal nano-dispersion is in a crystalline form or a super-cooled melt form.

In certain embodiments, the formulation for injection or infusion includes a lyoprotectant such as a nutritive sugar including, but not limited to, lactose, mannose, maltose, galactose, fructose, sorbose, raffinose, neuraminic acid, glucosamine, galactosamine, N-methylglucosamine, mannitol, sorbitol, arginine, glycine and sucrose, or any combination thereof.

In certain embodiments, the formulation for injection or infusion includes an aqueous solution; a hydrophobic active agent dispersed to form a colloidal nano-dispersion of particles; and at least one of a dispersion stabilizing agent and an opsonization reducer. The colloidal nano-dispersion of the active agent is dispersed into nano-dispersion particles having sizes of less than 200-nm. In some embodiments the dispersion stabilizing agent is selected from natural or semisynthetic phospholipids. For example, suitable stabilizing agents include polyethoxylated (a/k/a pegylated) castor oil (Cremophor® EL), polyethoxylated hydrogenated castor oil (Cremophor® RH 40), Tocopherol polyethylene glycol succinate (Pegylated vitamin E, Vitamin E TPGS), Sorbitan fatty acid esters (Spans®), Bile acids and bile-acid salts or Dimyristoylphosphatidyl choline (DMPC). In some embodiments the stabilizing agent is DMPC.

In certain embodiments the formulation is suitable for parenteral administration, including intravenous, intraperitoneal, orthotopical, intracranial, intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intranasal, or intraocular injections. In certain embodiments, the formulation contains CoQ10, dimyristoyl-phophatidylcholine, and poloxamer 188 in a ratio of 4:3:1.5 respectively that is designed to stabilize the nanosuspension of the particles. In some embodiments, the formulation includes a phosphate buffer saline solution which contains sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, sodium chloride and water for injection. In certain embodiments, the 4% sterile aqueous colloidal dispersion containing CoQ10 in a nanosuspension is diluted in the phosphate buffered saline solution provided, e.g., 1:1, 1:2, 1:3, 1:4. 1:5, 1:6, 1:7, 1:8. 1:9, 1:10, 1:11, 1:12, 1:13, 1:14. 1:15, 1:16, 1:17, 1:18. 1:19, 1:20, or other appropriate ratio bracketed by any two of the values.

In some embodiments, the formulation is a topical formulation. Topical formulations of CoQ10 compounds are provided, for example in WO2010/132507 (PCT Appln. No. PCT/US2010/034453), WO2008116135 (PCT Appln. No. PCT/US2008/116135), and

WO2005/069916 (PCT Appln. PC/US2005/001581), the entire contents of each of which are expressly incorporated herein by reference.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin, such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear, or nose. Drops according to the present disclosure may include sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and in some embodiments including a surface active agent. The resulting solution may then be clarified and sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present disclosure include those suitable for application to the skin or eye. An eye lotion may include a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes useful in the methods of the invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may include hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogels. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surface active such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

In some embodiments, the remaining component of a topical delivery vehicle may be water or a water phase, in embodiments purified, e.g. deionized, water, glycerine, propylene glycol, ethoxydiglycol, phenoxyethanol, and cross linked acrylic acid polymers. Such delivery vehicle compositions may contain water or a water phase in an amount of from about 50 to about 95 percent, based on the total weight of the composition. The specific amount of water present is not critical, however, being adjustable to obtain the desired viscosity (usually about 50 cps to about 10,000 cps) and/or concentration of the other components. The topical delivery vehicle may have a viscosity of at least about 30 centipoises.

Topical formulations can also include an oil phase including, for example, oil phase which, in turn, may include emollients, fatty alcohols, emulsifiers, combinations thereof, and the like. For example, an oil phase could include emollients such as C12-15 alkyl benzoates (commercially available as FINSOLV^{TM} TN from Finetex Inc. (Edison, N.J.)), capric-caprylic triglycerides (commercially available from Huls as MIGLYOL^{TM} 812), and the like. Other suitable emollients which may be utilized include vegetable derived oils (corn oil, safflower oil, olive oil, macadamian nut oil, etc.); various synthetic esters, including caprates, linoleates, dilinoleates, isostearates, fumarates, sebacates, lactates, citrates, stearates, palmitates, and the like; synthetic medium chain triglycerides, silicone oils or polymers; fatty alcohols such as cetyl alcohol, stearyl alcohol, cetearyl alcohol, lauryl alcohol, combinations thereof, and the like; and emulsifiers including glyceryl stearate, PEG-100 stearate, Glyceryl Stearate, Glyceryl Stearate SE, neutralized or partially neutralized fatty acids, including stearic, palmitic, oleic, and the like; vegetable oil extracts containing fatty acids, Ceteareth®-20, Ceteth®-20, PEG-150 Stearate, PEG-8 Laurate, PEG-8 Oleate, PEG-8 Stearate, PEG-20 Stearate, PEG-40 Stearate, PEG-150 Distearate, PEG-8 Distearate, combinations thereof, and the like; or other non-polar cosmetic or pharmaceutically acceptable materials used for skin emolliency within the purview of those skilled in the art, combinations thereof, and the like.

Topical formulations can also include a liposomal concentrate including, for example, a phospholipid such as lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, and combinations thereof, at least one lipophilic bioactive agent,

and at least one solubilizer. The liposomal concentrate may be in combination with at least one pharmaceutically acceptable carrier possessing at least one permeation enhancer in an amount from about 0.5% by weight to about 20% by weight of the composition. The phospholipid may present in the composition in an amount from about 2% to about 20% by weight of the composition and the bioactive agent may be present in an amount from about 0.5% to about 20% by weight of the composition.

Transdermal skin penetration enhancers can also be used to facilitate delivery of CoQ10. Illustrative are sulfoxides such as ethoxydiglycol, 1,3-butylene glycol, isopentyl diol, 1,2-pentane diol, propylene glycol, 2-methyl propan-2-ol, propan-2-ol, ethyl-2-hydroxypropanoate, hexan-2,5-diol, di(2-hydroxypropyl)ether, pentan-2,4-diol, acetone, polyoxyethylene(2)methyl ether, 2-hydroxypropionic acid, 2-hydroxyoctanoic acid, propan-1-ol, 1,4 dioxane, tetrahydrofuran, butan-1,4-diol, propylene glycol dipelargonate, polyoxypropylene 15 stearyl ether, octyl alcohol, polyoxyethylene ester of oleyl alcohol, oleyl alcohol, lauryl alcohol, dioctyl adipate, dicapryl adipate, diisopropyl adipate, diisopropyl sebacate, dibutyl sebacate, diethyl sebacate, dimethyl sebacate, dioctyl sebacate, dibuyl suberate, dioctyl azelate, dibenzyl sebacate, dibutyl phthalate, dibutyl azelate, ethyl myristate, dimethyl azelate, butyl myristate, dibutyl succinate, didecyl phthalate, decyl oleate, ethyl caproate, ethyl salicylate, isopropyl palmitate, ethyl laurate, 2-ethyl-hexyl pelargonate, isopropyl isostearate, butyl laurate, benzyl benzoate, butyl benzoate, hexyl laurate, ethyl caprate, ethyl caprylate, butyl stearate, benzyl salicylate, 2-hyroxyoctanoic acid, dimethyl sulphoxide, methyl sufonyl methane, n,n-dimethyl acetamide, n,n-dimethyl formamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, phosphine oxides, sugar esters, tetrahydrofurfural alcohol, urea, diethyl-m-toluamide, 1-dodecylazacycloheptan-2-one, and combinations thereof.

Solubilizers, particularly for topical administration can include, but are not limited to, polyoxyalkylene dextrans, fatty acid esters of saccharose, fatty alcohol ethers of oligoglucosides, fatty acid esters of glycerol, fatty acid esters of polyoxyethylenes, polyethoxylated fatty acid esters of sorbitan, fatty acid esters of poly(ethylene oxide), fatty alcohol ethers of poly(ethylene oxide), alkylphenol ethers of poly(ethylene oxide), polyoxyethylene-polyoxypropylene block copolymers, ethoxylated oils, and combinations thereof.

Topical formulations can include emollients, including, but not limited to, C12-15 alkyl benzoates, capric-caprylic triglycerides, vegetable derived oils, caprates, linoleates, dilinoleates, isostearates, fumarates, sebacates, lactates, citrates, stearates, palmitates, synthetic medium chain triglycerides, silicone oils, polymers and combinations thereof; the fatty alcohol is selected from the group consisting of cetyl alcohol, stearyl alcohol, cetearyl alcohol, lauryl alcohol and combinations thereof; and the emulsifier is selected from the group consisting of glyceryl stearate, polyethylene glycol 100 stearate, neutralized fatty acids, partially neutralized fatty acids, polyethylene glycol 150 stearate, polyethylene glycol 8 laurate, polyethylene glycol oleate, polyethylene glycol 8 stearate, polyethylene glycol 20 stearate, polyethylene glycol 40 stearate, polyethylene glycol 150 distearate, polyethylene glycol 8 distearate, and combinations thereof.

Topical formulations can include a neutralization phase comprising one or more of water, amines, sodium lactate, and lactic acid.

The water phase can further optionally include one or more of water phase comprises the permeation enhancer optionally in combination with a viscosity modifier selected from the group consisting of cross linked acrylic acid polymers, pullulan, mannan, scleroglucans, polyvinylpyrrolidone, polyvinyl alcohol, guar gum, hydroxypropyl guar gum, xanthan gum, acacia gum, arabia gum, tragacanth, galactan, carob gum, karaya gum, locust bean gum, carrageenin, pectin, amylopectin, agar, quince seed, rice starch, corn starch, potato starch, wheat starch, algae extract, dextran, succinoglucan, carboxymethyl starch, methylhydroxypropyl starch, sodium alginate, alginic acid propylene glycol esters, sodium polyacrylate, polyethylacrylate, polyacrylamide, polyethyleneimine, bentonite, aluminum magnesium silicate, laponite, hectonite, and anhydrous silicic acid.

Topical formulations can also include a pigment such as titanium dioxide.

In an embodiment, a topical formulation for use in the methods of the invention includes an oil phase comprising C12-15 alkyl benzoates or capric/caprylic triglyceride, cetyl alcohol, stearyl alcohol, glyceryl stearate, and polyethylene glycol 100 stearate, in an amount of from about 5% to about 20% by weight of the composition; a water phase comprising glycerin, propylene glycol, ethoxydiglycol, phenoxyethanol, water, and a crosslinked acrylic acid polymer, in an amount of from about 60 to about 80% by weight of the composition; a neutralization phase comprising water, triethanolamine, sodium lactate, and lactic acid, in an

amount of from about 0.1% to about 15% by weight of the composition; a pigment comprising titanium dioxide in an amount of from about 0.2% to about 2% by weight of the composition; and a liposomal concentrate comprising a polyethoxylated fatty acid ester of sorbitan, coenzyme Q10, a phosphatidylcholine lecithin, phenoxyethanol, propylene glycol, and water, in an amount of from about 0.1% to about 30% by weight of the composition, wherein the propylene glycol and ethoxydiglycol are present in a combined amount of from 3% by weight to about 15% by weight of the composition and the coenzyme Q10 is present in an amount of from about 0.75% by weight to about 10% by weight of the composition. Other formulations for use in the methods of the invention are provided, for example, in WO2008/116135 (PCT Application No. PCT/US08/57786), and in WO2010/132507 (PCT/US2010/034453), the entire contents of each of which are expressly incorporated herein by reference.

In one embodiment, a topical formulation for use in the methods of the invention is a 3% CoQ10 cream as described in US 2011/0027247, the entire contents of which are incorporated by reference herein. In one embodiment, the 3% CoQ10 comprises:

(1) a phase A having C12-15 alkyl benzoate or capric/caprylic triglyceride at about 4.0% w/w of the composition, cetyl alcohol at about 2.00% w/w of the composition, stearyl alcohol at about 1.5% w/w, glyceryl stearate and PEG-100 at about 4.5% w/w;

(2) a phase B having glycerin at about 2.00% w/w, propylene glycol at about 1.5% w/w, ethoxydiglycol at about 5.0% w/w, phenoxyethanol at about 0.475% w/w, a carbomer dispersion at about 40% w/w, purified water at about 16.7% w/w;

(3) a phase C having triethanolamine at about 1.3% w/w, lactic acid at about 0.5% w/w, sodium lactate solution at about 2.0% w/w, water at about 2.5% w/w;

(4) a phase D having titanium dioxide at about 1.0% w/w; and

(5) a phase E having CoQ10 21% concentrate at about 15.0% w/w.

A CoQ10 21% concentrate composition (phase E in above 3% cream) can be prepared by combining phases A and B as described below. Phase A includes Ubidecarenone USP (CoQ10) at 21 %w/w and polysorbate 80 NF at 25 %w/w. Phase B includes propylene glycol USP at 10.00 %w/w, phenoxyethanol NF at 0.50 %w/w, lecithin NF (PHOSPHOLIPON

85G) at 8.00 %w/w and purified water USP at 35.50 %w/w. All weight percentages are relative to the weight of the entire CoQ10 21% concentrate composition. The percentages and further details are listed in the following table.

Table 1

Phase	Trade Name	INCI Name	Percent
A	RITABATE 80	POLYSORBATE 80	25.000
A	UBIDECARENONE	UBIQUINONE	21.000
B	PURIFIED WATER	WATER	35.500
B	PROPYLENE GLYCOL	PROPYLENE GLYCOL	10.000
B	PHENOXYETHANOL	PHENOXYETHANOL	0.500
B	PHOSPHOLIPON 85G	LECITHIN	8.000
Totals			100.000

The phenoxyethanol and propylene glycol are placed in a suitable container and mixed until clear. The required amount of water is added to a second container (Mix Tank 1). Mix Tank 1 is heated to between 45 and 55 ºC while being mixed. The phenoxyethanol/propylene glycol solution is added to the water and mixed until it was clear and uniform. When the contents of the water phase in Mix Tank 1 are within the range of 45 to 55 ºC, Phospholipon G is added with low to moderate mixing. While avoiding any foaming, the contents of Mix Tank 1 is mixed until the Phospholipon 85G was uniformly dispersed. The polysorbate 89 is added to a suitable container (Mix Tank 2) and heated to between 50 and 60 ºC. The Ubidecarenone is then added to Mix Tank 2. While maintaining the temperature at between 50 and 60 ºC Mix Tank 2 is mixed until all the Ubidecarenone is dissolved. After all the Ubidecarenone has been dissolved, the water phase is slowly transferred to Mix Tank 2. When all materials have been combined, the contents are homogenized until dispersion is smooth and uniform. While being careful not to overheat, the temperature is maintained at between 50 and 60 ºC. The homogenization is then stopped and the contents of Mix Tank 2 are transferred to a suitable container for storage.

In some embodiments, a formulation for any route of administration for use in the invention may include from about 0.001% to about 20% (w/w) of CoQ10, more preferably between about 0.01% and about 15% and even more preferably between about 0.1% to about 10% (w/w) of CoQ10. In certain embodiments, a formulation for any route of administration for use in the invention may include from about 1% to about 10% (w/w) of CoQ10. In

certain embodiments, a formulation for any route of administration for use in the invention may include from about 2% to about 8% (w/w) of CoQ10. In certain embodiments, a formulation for any route of administration for use in the invention may include from about 2% to about 7% (w/w) of CoQ10. In certain embodiments, a formulation for any route of administration for use in the invention may include from about 3% to about 6% (w/w) of CoQ10. In certain embodiments, a formulation for any route of administration for use in the invention may include from about 3% to about 5% (w/w) of CoQ10. In certain embodiments, a formulation for any route of administration for use in the invention may include from about 3.5% to about 4.5% (w/w) of CoQ10. In certain embodiments, a formulation for any route of administration for use in the invention may include from about 3.5% to about 5% (w/w) of CoQ10. In one embodiment a formulation includes about 4% (w/w) of CoQ10. In one embodiment a formulation includes about 8% (w/w) of CoQ10. In various embodiments, the formulation includes about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% (w/w) of CoQ10, or any range bracketed by any two values recited. In certain embodiments, the formulations can be prepared as a percent weight to volume rather than a percent weight to weight. Depending on the formulation, the concentration of CoQ10 may be the same, or about the same in the w/w and the w/v percent formulations. CoQ10 can be obtained from Kaneka Q10 as Kaneka Q10 (USP UBIDECARENONE) in powdered form (Pasadena, Texas, USA). CoQ10 used in the methods exemplified herein have the following characteristics: residual solvents meet USP 467 requirement; water content is less than 0.0%, less than 0.05% or less than 0.2%; residue on ignition is 0.0%, less than 0.05%, or less than 0.2% less than; heavy metal content is less than 0.002%, or less than 0.001%; purity of between 98-100% or 99.9%, or 99.5%.

In certain embodiments, the concentration of CoQ10 in the formulation is 1 mg/mL to 150 mg/mL. In one embodiment, the concentration of CoQ10 in the formulation is 5 mg/mL to 125 mg/mL. In one embodiment, the concentration of CoQ10 in the formulation is 10 mg/mL to 100 mg/mL. In one embodiment, the concentration of CoQ10 in the formulation is 20 mg/mL to 90 mg/mL. In one embodiment, the concentration of CoQ10 is 30 mg/mL to 80 mg/mL. In one embodiment, the concentration of CoQ10 is 30 mg/mL to 70 mg/mL. In one embodiment, the concentration of CoQ10 is 30 mg/mL to 60 mg/mL. In one embodiment, the concentration of CoQ10 is 30 mg/mL to 50 mg/mL. In one embodiment, the concentration of CoQ10 is 35 mg/mL to 45 mg/mL. It should be understood that

additional ranges having any one of the foregoing values as the upper or lower limits are also intended to be part of this invention, *e.g.*, 10 mg/mL to 50 mg/mL, or 20 mg/mL to 60 mg/mL.

In certain embodiments, the concentration of CoQ10 in the formulation is about 10, 15, 20, 25, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 55, 60, 65, 70, 75, 80, 85, 90 or 95 mg/mL. In one embodiment, the concentration of CoQ10 in the formulation is about 50 mg/mL. In one embodiment, the concentration of CoQ10 in the formulation is about 60 mg/mL. In one embodiment, the concentration of CoQ10 in the formulation is about 30 mg/mL. In a preferred embodiment, the concentration of CoQ10 in the formulation is about 40 mg/mL. It should be understood that ranges having any one of these values as the upper or lower limits are also intended to be part of this invention, *e.g.* between 37 mg/mL and 47 mg/mL, or between 31 mg/mL and 49 mg/mL.

It is understood that formulations can similarly be prepared containing CoQ10 precursors, metabolites, and related compounds.

IV. Combination Therapies

Provided herein are methods of treating oncological disorders in a subject by co-administering CoQ10 and at least one chemotherapeutic agent to a subject in need thereof. As used herein, the term "co-administering" refers to administration of CoQ10 prior to, concurrently or substantially concurrently with, subsequently to, or intermittently with the administration of the chemotherapeutic agent. In certain embodiments, CoQ10 is administered prior to and concurrently with the chemotherapeutic agent. In certain embodiments, CoQ10 is administered prior to but not concurrently with the chemotherapeutic agent, i.e., CoQ10 admistration is discontinued prior to initiation of treatment with or administration of a chemotherapeutic agent. In one embodiment, an intravenous (IV) CoQ10 formulation can be used in combination therapy with at least one other chemotherapeutic agent according to the methods of the invention. In one embodiment, a topical CoQ10 formulation can be used in combination therapy with at least one other chemotherapeutic agent according to the methods of the invention. In one embodiment, an inhalable CoQ10 formulation can be used in combination therapy with at least one other chemotherapeutic agent according to the methods of the invention. CoQ10 and/or pharmaceutical formulations thereof and the other chemotherapeutic agent can act additively

or, more preferably, synergistically. In one embodiment, CoQ10 and/or a formulation thereof is administered concurrently with the administration of another chemotherapeutic agent. In another embodiment, CoQ10 and/or pharmaceutical formulation thereof is administered prior to or subsequent to administration of another chemotherapeutic agent. In one embodiment, the CoQ10 and additional chemotherapeutic agent act synergistically. In some embodiments the synergistic results are in the treatment of the oncological disorder. In other embodiments the synergistic results are in modulation of the toxicity associated with the chemotherapeutic agent. In one embodiment, the CoQ10 and the additional therapeutic agent act additively. In one embodiment, the CoQ10 sensitizes the oncological disorder, cancer or cancer cells to treatment with another chemotherapeutic agent. In one embodiment, pre-treatment with CoQ10 prior to treatment with the chemotherapeutic agent sensitizes the oncological disorder, cancer or cancer cells to treatment with another chemotherapeutic agent. In one embodiment, pre-treatment with CoQ10 and discontinuation of said treatment prior to treatment with the chemotherapeutic agent sensitizes the oncological disorder, cancer or cancer cells to treatment with another chemotherapeutic agent.

In some embodiments, the CoQ10 is in the form of an intravenous CoQ10 formulation, an inhalation CoQ10 formulation, or a topical CoQ10 formulation. Intravenous CoQ10 formulations are disclosed in WO2011/112900, filed on March 11, 2011. The disclosure of WO2011/112900 is incorporated herein in its entirety. Topical CoQ10 formulations are disclosed in US Patent Application Publication No. US2011/0027247, filed on May 11, 2010. The disclosure of US2011/0027247 is incorporated herein in its entirety. Inhalation CoQ10 formulations are disclosed in US Patent Publication Nos. 20120321698, filed on June 18, 2012 and 20110142914 filed December 5, 2008. The CoQ10 and the chemotherapeutic agent need not be delivered by the same route of administration. In certain embodiments, the CoQ10 is not administered orally.

In some embodiments, methods are provided for the treatment of oncological disorders by co-administering intravenous CoQ10 formulations with a chemotherapeutic agent. In certain embodiments, the chemotherapeutic agents are gemcitabine, doxorubicin, cisplatin, 5-fluorouracil, and irinotecan. In some embodiments, the chemotherapeutic agents are antimetabolites or an anthracycline. Chemotherapeutic agents generally belong to various classes including, for example: 1. Topoisomerase II inhibitors (cytotoxic antibiotics), such as the anthracyclines/anthracenediones, *e.g.*, doxorubicin, epirubicin, idarubicin and

nemorubicin, the anthraquinones, e.g., mitoxantrone and losoxantrone, and the podophillotoxines, e.g., etoposide and teniposide; 2. Agents that affect microtubule formation (mitotic inhibitors), such as plant alkaloids (e.g., a compound belonging to a family of alkaline, nitrogen-containing molecules derived from plants that are biologically active and cytotoxic), e.g., taxanes, e.g., paclitaxel and docetaxel, and the vinka alkaloids, e.g., vinblastine, vincristine, and vinorelbine, and derivatives of podophyllotoxin; 3. Alkylating agents, such as nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, dacarbazine, cyclophosphamide, ifosfamide and melphalan; 4. Antimetabolites (nucleoside inhibitors), for example, folates, e.g., folic acid, fiuropyrimidines, purine or pyrimidine analogues such as 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; 5. Topoisomerase I inhibitors, such as topotecan, irinotecan, and 9- nitrocamptothecin, and camptothecin derivatives; and 6. Platinum compounds/complexes, such as cisplatin, oxaliplatin, and carboplatin.

Exemplary chemotherapeutic agents for use in the methods of the invention include, but are not limited to, amifostine (ethyol), cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carrnustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), doxorubicin lipo (doxil), gemcitabine (gemzar), daunorubicin, daunorubicin lipo (daunoxome), procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5- fluorouracil (5-FU), vinblastine, vincristine, bleomycin, paclitaxel (taxol), docetaxel (taxotere), aldesleukin, asparaginase, busulfan, carboplatin, cladribine, camptothecin, CPT-I 1 , lO-hydroxy-7-ethyl-camptothecin (SN38), dacarbazine, S-I capecitabine, ftorafur, 5'deoxyflurouridine, UFT, eniluracil, deoxycytidine, 5-azacytosine, 5- azadeoxycytosine, allopurinol, 2-chloro adenosine, trimetrexate, aminopterin, methylene-10-deazaaminopterin (MDAM), oxaplatin, picoplatin, tetraplatin, satraplatin, platinum-DACH, ormaplatin, CI-973, JM-216, and analogs thereof, epirubicin, etoposide phosphate, 9- aminocamptothecin, 10, 11-methylenedioxycamptothecin, karenitecin, 9-nitrocamptothecin, TAS 103, vindesine, L-phenylalanine mustard, ifosphamidemefosphamide, perfosfamide, trophosphamide carmustine, semustine, epothilones A-E, tomudex, 6-mercaptopurine, 6-thioguanine, amsacrine, etoposide phosphate, karenitecin, acyclovir, valacyclovir, ganciclovir, amantadine, rimantadine, lamivudine, zidovudine, bevacizumab, trastuzumab, rituximab, 5-Fluorouracil, Capecitabine, Pentostatin, Trimetrexate, Cladribine, floxuridine, fludarabine, hydroxyurea, ifosfamide, idarubicin, mesna, irinotecan, mitoxantrone, topotecan, leuprolide, megestrol, melphalan,

mercaptopurine, plicamycin, mitotane, pegaspargase, pentostatin, pipobroman, plicamycin, streptozocin, tamoxifen, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, chlorambucil, cisplatin, doxorubicin, paclitaxel (taxol), bleomycin, mTor, epidermal growth factor receptor (EGFR), and fibroblast growth factors (FGF) and combinations thereof which are readily apparent to one of skill in the art based on the appropriate standard of care for a particular tumor or cancer.

In certain embodiments, an additional chemotherapeutic agent for use in the combination therapies of the invention is a biologic agent. Biologic agents (also called biologics) are the products of a biological system, e.g., an organism, cell, or recombinant system. Examples of such biologic agents include nucleic acid molecules (e.g., antisense nucleic acid molecules), interferons, interleukins, colony-stimulating factors, antibodies, e.g., monoclonal antibodies, anti-angiogenesis agents, and cytokines. Exemplary biologic agents are discussed in more detail below and generally belong to various classes including, for example: 1. Hormones, hormonal analogues, and hormonal complexes, e.g., estrogens and estrogen analogs, progesterone, progesterone analogs and progestins, androgens, adrenocorticosteroids, antiestrogens, antiandrogens, antitestosterones, adrenal steroid inhibitors, and anti-leuteinizing hormones; and 2. Enzymes, proteins, peptides, polyclonal and/or monoclonal antibodies, such as interleukins, interferons, colony stimulating factor, etc.

In one embodiment, the biologic is an interfereon. Interferons (IFN) are a type biologic agent that naturally occurs in the body. Interferons are also produced in the laboratory and given to cancer patients in biological therapy. They have been shown to improve the way a cancer patient's immune system acts against cancer cells.

Interferons may work directly on cancer cells to slow their growth, or they may cause cancer cells to change into cells with more normal behavior. Some interferons may also stimulate natural killer cells (NK) cells, T cells, and macrophages which are types of white blood cells in the bloodstream that help to fight cancer cells.

In one embodiment, the biologic is an interleukin. Interleukins (IL) stimulate the growth and activity of many immune cells. They are proteins (cytokines and chemokines) that occur naturally in the body, but can also be made in the laboratory. Some interleukins stimulate the growth and activity of immune cells, such as lymphocytes, which work to destroy cancer cells.

In another embodiment, the biologic is a colony-stimulating factor. Colony-stimulating factors (CSFs) are proteins given to patients to encourage stem cells within the bone marrow to produce more blood cells. The body constantly needs new white blood cells, red blood cells, and platelets, especially when cancer is present. CSFs are given, along with chemotherapy, to help boost the immune system. When cancer patients receive chemotherapy, the bone marrow's ability to produce new blood cells is suppressed, making patients more prone to developing infections. Parts of the immune system cannot function without blood cells, thus colony-stimulating factors encourage the bone marrow stem cells to produce white blood cells, platelets, and red blood cells. With proper cell production, other cancer treatments can continue enabling patients to safely receive higher doses of chemotherapy.

In another embodiment, the biologic is an antibody. Antibodies, e.g., monoclonal antibodies, are agents, produced in the laboratory, that bind to cancer cells.

Monoclonal antibody agents do not destroy healthy cells. Monoclonal antibodies achieve their therapeutic effect through various mechanisms. They can have direct effects in producing apoptosis or programmed cell death. They can block growth factor receptors, effectively arresting proliferation of tumor cells. In cells that express monoclonal antibodies, they can bring about anti-idiotype antibody formation.

Examples of antibodies which may be used in the combination treatment of the invention include anti-CD20 antibodies, such as, but not limited to, cetuximab, Tositumomab, rituximab, and Ibritumomab. Anti-HER2 antibodies may also be used in combination with coenzyme Q10 for the treatment of cancer. In one embodiment, the anti-HER2 antibody is Trastuzumab (Herceptin). Other examples of antibodies which may be used in combination with coenzyme Q10 for the treatment of cancer include anti-CD52 antibodies (e.g., Alemtuzumab), anti-CD-22 antibodies (e.g., Epratuzumab), and anti-CD33 antibodies (e.g., Gemtuzumab ozogamicin). Anti-VEGF antibodies may also be used in combination with coenzyme Q10 for the treatment of cancer. In one embodiment, the anti-VEGF antibody is bevacizumab. In other embodiments, the biologic agent is an antibody which is an anti-EGFR antibody e.g., cetuximab. Another example is the anti-glycoprotein 17-1A antibody edrecolomab. Numerous other anti-tumor antibodies are known in the art and would be understood by the skilled artisan to be encompassed by the present invention.

In another embodiment, the biologic is a cytokine. Cytokine therapy uses proteins (cytokines) to help a subject's immune system recognize and destroy those cells that are cancerous. Cytokines are produced naturally in the body by the immune system, but can also be produced in the laboratory. This therapy is used with advanced melanoma and with adjuvant therapy (therapy given after or in addition to the primary cancer treatment). Cytokine therapy reaches all parts of the body to kill cancer cells and prevent tumors from growing.

In another embodiment, the biologic is a fusion protein. For example, recombinant human Apo2L/TRAIL (GENETECH) may be used in a combination therapy. Apo2/TRAIL is the first dual pro-apoptotic receptor agonist designed to activate both pro-apoptotic receptors DR4 and DR5, which are involved in the regulation of apoptosis (programmed cell death).

In one embodiment, the biologic is a therapeutic nucleic acid molecule. Nucleic acid therapeutics are well known in the art. Nucleic acid therapeutics include both single stranded and double stranded (i.e., nucleic acid therapeutics having a complementary region of at least 15 nucleotides in length) nucleic acids that are complementary to a target sequence in a cell. Therapeutic nucleic acids can be directed against essentially any target nucleic acid sequence in a cell. In certain embodiments, the nucleic acid therapeutic is targeted against a nucleic acid sequence encoding a stimulator of angiogenesis, e.g., VEGF, FGF, or of tumor growth, e.g., EGFR.

Antisense nucleic acid therapeutic agents are single stranded nucleic acid therapeutics, typically about 16 to 30 nucleotides in length, and are complementary to a target nucleic acid sequence in the target cell, either in culture or in an organism.

In another aspect, the agent is a single-stranded antisense RNA molecule. An antisense RNA molecule is complementary to a sequence within the target mRNA. Antisense RNA can inhibit translation in a stoichiometric manner by base pairing to the mRNA and physically obstructing the translation machinery, see Dias, N. et al., (2002) Mol Cancer Ther 1:347-355. The antisense RNA molecule may have about 15-30 nucleotides that are complementary to the target mRNA. Patents directed to antisense nucleic acids, chemical modifications, and therapeutic uses are provided, for example, in U.S. Patent No. 5,898,031 related to chemically modified RNA-containing therapeutic compounds, and U.S. Patent No.

6,107,094 related methods of using these compounds as therapeutic agent. U.S. Patent No. 7,432,250 related to methods of treating patients by administering single-stranded chemically modified RNA-like compounds; and U.S. Patent No. 7,432,249 related to pharmaceutical compositions containing single-stranded chemically modified RNA-like compounds. U.S. Patent No. 7,629,321 is related to methods of cleaving target mRNA using a single-stranded oligonucleotide having a plurality RNA nucleosides and at least one chemical modification. The entire contents of each of the patents listed in this paragraph are incorporated herein by reference.

Nucleic acid therapeutic agents for use in the methods of the invention also include double stranded nucleic acid therapeutics. An "RNAi agent," "double stranded RNAi agent," double-stranded RNA (dsRNA) molecule, also referred to as "dsRNA agent," "dsRNA", "siRNA", "iRNA agent," as used interchangeably herein, refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary, as defined below, nucleic acid strands. As used herein, an RNAi agent can also include dsiRNA (see, e.g., US Patent publication 20070104688, incorporated herein by reference). In general, the majority of nucleotides of each strand are ribonucleotides, but as described herein, each or both strands can also include one or more non-ribonucleotides, e.g., a deoxyribonucleotide and/or a modified nucleotide. In addition, as used in this specification, an "RNAi agent" may include ribonucleotides with chemical modifications; an RNAi agent may include substantial modifications at multiple nucleotides. Such modifications may include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a siRNA type molecule, are encompassed by "RNAi agent" for the purposes of this specification and claims. The RNAi agents that are used in the methods of the invention include agents with chemical modifications as disclosed, for example, in U.S. Provisional Application No. 61/561,710, filed on November 18, 2011, International Application No. PCT/US2011/051597, filed on September 15, 2010, and PCT Publication WO 2009/073809, the entire contents of each of which are incorporated herein by reference.

Additional exemplary biologic agents for use in the methods of the invention include, but are not limited to, gefitinib (Iressa), anastrazole, diethylstilbesterol, estradiol, premarin, raloxifene, progesterone, norethynodrel, esthisterone, dimesthisterone, megestrol acetate, medroxyprogesterone acetate, hydroxyprogesterone caproate, norethisterone, methyltestosterone, testosterone, dexamthasone, prednisone, Cortisol, solumedrol, tamoxifen,

fulvestrant, toremifene, aminoglutethimide, testolactone, droloxifene, anastrozole, bicalutamide, flutamide, nilutamide, goserelin, flutamide, leuprolide, triptorelin, aminoglutethimide, mitotane, goserelin, cetuximab, erlotinib, imatinib, Tositumomab, Alemtuzumab, Trastuzumab, Gemtuzumab, Rituximab, Ibritumomab tiuxetan, Bevacizumab, Denileukin diftitox, Daclizumab, interferon alpha, interferon beta, anti-4-lBB, anti-4-lBBL, anti-CD40, anti-CD 154, anti- OX40, anti-OX40L, anti-CD28, anti-CD80, anti-CD86, anti-CD70, anti-CD27, anti- HVEM, anti-LIGHT, anti-GITR, anti-GITRL, anti-CTLA-4, soluble OX40L, soluble 4-IBBL, soluble CD154, soluble GITRL, soluble LIGHT, soluble CD70, soluble CD80, soluble CD86, soluble CTLA4-Ig, GVAX®, and combinations thereof which are readily apparent to one of skill in the art based on the appropriate standard of care for a particular tumor or cancer. The soluble forms of agents may be made as, for example fusion proteins, by operatively linking the agent with, for example, Ig-Fc region.

It should be noted that more than one additional anticancer chemotherapeutic agents, *e.g.*, 2, 3, 4, 5, or more, may be administered in combination with the coenzyme Q10 and coenzyme Q10 formulations provided herein. For example, in one embodiment, two additional chemotherapeutic agents may be administered in combination with coenzyme Q10. In one embodiment, three additional chemotherapeutic agents may be administered in combination with coenzyme Q10. In one embodiment, four additional chemotherapeutic agents may be administered in combination with coenzyme Q10. In one embodiment, five additional chemotherapeutic agents may be administered in combination with coenzyme Q10. Appropriate doses and routes of administration of the chemotherapeutic agents provided herein are known in the art.

In certain embodiments, the methods of the invention comprise treatment of cancer by continuous infusion of coenzyme Q10 provided and combination therapies with additional anticancer agents or interventions (e.g., radiation, surgery, bone marrow transplant). In certain embodiments, "combination therapy" includes a treatment with coenzyme Q10 to decrease tumor burden and/or improve clinical response. Administration of coenzyme Q10 with palliative treatments or treatments to mitigate drug side effects (e.g., to decrease nausea, pain, anxiety, or inflammation, to normalize clotting) is not considered to be a combination treatment of the cancer.

In certain embodiments, treatment with coenzyme Q10 by continuous infusion is combined with the standard of care for treatment of the particular cancer to be treated, for

example by administering a standard dosage of one or more chemotherapeutic agents. The standard of care for a particular cancer type can be determined by one of skill in the art based on, for example, the type and severity of the cancer, the age, weight, gender, and/or medical history of the subject, and the success or failure of prior treatments.

In certain embodiments, treatment of subjects with leukemia, particularly ALL or AML, administration (e.g., intravenous, e.g., continuous infusion) of coenzyme Q10 is combined with one, or preferably both, of the following treatments.

1. Fludarabine, preferably at a dose of 15mg/m^2 administered intravenously over 15-30 minutes $\pm$ 15 minutes, every 12 hours for 5 days (or for 4 days in patients over 65 years of age or with ECOG Performance Status of 3).

2. Cytarabine, preferably administered at 0.5 g/m^2 in 250 ml of normal saline administered intravenously over 2 hours $\pm$ 20 minutes every 12 hours $\pm$ 2 hours for 5 days (or for 4 days in patients over 65 years of age or with ECOG Performance Status of 3).

In certain embodiments, 1, 2, 3, 4, or 5 cycles of the combination therapy are administered to the subject. The subject is assessed for response criteria at the end of each cycle. The subject is also monitored throughout each cycle for adverse events (e.g., clotting, anemia, liver and kidney function, etc.) to ensure that the treatment regimen is being sufficiently tolerated.

In certain embodiments, treatment of subjects with solid tumors by continuous infusion of coenzyme Q10 is combined with one or more of the following treatments.

1. Gemcitabine, preferably by intravenous administration at a weekly dose starting at 600 mg/m^2, with the dose being adjusted based on the tolerance of the subject to the drug.

2. 5-Fluorouracil (5-FU), preferably by intravenous administration at a weekly starting dose of 350 mg/m^2, with the dose being adjusted based on the tolerance of the subject to the drug, in combination with leucovorin at 100 mg/m^2.

3. Docetaxel, preferably by intravenous administration once weekly at a starting dose of 20 mg/m^2, with the dose being adjusted based on the tolerance of the subject to the drug.

In certain embodiments, 1, 2, 3, 4, or 5 cycles of the combination therapy are administered to the subject. The subject is assessed for response criteria at the end of each cycle. The subject is also monitored throughout each cycle for adverse events (e.g., clotting, anemia, liver and kidney function, etc.) to ensure that the treatment regimen is being sufficiently tolerated.

In other embodiments, the chemotherapeutic agent is administered at a dosage that is lower than the standard dosages of the chemotherapeutic agent used to treat the oncological disorder under the standard of care for treatment for a particular oncological disorder. Standard dosages of chemotherapeutic agents are known to a person skilled in the art and may be obtained, for example, from the product insert provided by the manufacturer of the chemotherapeutic agent. Examples of standard dosages of chemotherapeutic agents are provided in Table 3. In certain embodiments, the dosage administered of the chemotherapeutic agent is 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% lower than the standard dosage of the chemotherapeutic agent for a particular oncological disorder. In certain embodiments, the dosage administered of the chemotherapeutic agent is 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10% or 5% of the standard dosage of the chemotherapeutic agent for a particular oncological disorder. In one embodiment, where a combination of non-CoQ10 chemotherapeutic agents are administered, at least one of the chemotherapeutic agents is administered at a dose that is lower than the standard dosage of the chemotherapeutic agent for a particular oncological disorder. In one embodiment, where a combination of chemotherapeutic agents (e.g., non-CoQ10) are administered, at least two of the chemotherapeutic agents are administered at a dose that is lower than the standard dosage of the chemotherapeutic agents for a particular oncological disorder. In one embodiment, where a combination of chemotherapeutic agents (e.g., non-CoQ10) are administered, at least three of the chemotherapeutic agents are administered at a dose that is lower than the standard dosage of the chemotherapeutic agents for a particular oncological disorder. In one embodiment, where a combination of chemotherapeutic agents (e.g., non-CoQ10) are administered, all of the chemotherapeutic agents are administered at a dose that is lower than the standard dosage of the chemotherapeutic agents for a particular oncological disorder.

In certain embodiments, coenzyme Q10 is administered in an amount that would be therapeutically effective if delivered alone, i.e., coenzyme Q10 is administered and/or acts as

a therapeutic anti-cancer agent, and not predominantly as an agent to ameliorate side effects of other chemotherapy or other cancer treatments.

V. Treatment of Oncological Disorders

The combination therapies of the present invention may be utilized for the treatment of oncological disorders. Accordingly, the present invention provides methods of treating or preventing an oncological disorder in a subject, comprising administering the formulations of the invention to the subject in an amount sufficient to treat or prevent the oncological disorder, thereby treating or preventing the oncological disorder. The formulations of the invention may also be utilized for inhibiting tumor cell growth. Accordingly, the invention further provides methods of inhibiting tumor cell growth in a subject, comprising intravenously administering the formulations of the invention to the subject, such that tumor cell growth is inhibited. In certain embodiments, treating cancer comprises extending survival or extending time to tumor progression as compared to control, e.g., a population control. In certain embodiments, the subject is a human subject. In preferred embodiments, the subject is identified as having a tumor prior to administration of the first dose of CoQ10. In certain embodiments, the subject has a tumor at the time of the first administration of CoQ10.

Such combination therapies include, for example, CoQ10 formulations that are co-administered with the chemotherapeutic agents described or incorporated herein. In certain embodiments, the method of treating an oncological disorder in a subject comprises: (a) administering coenzyme Q10 (CoQ10) to the subject; (b) discontinuing treatment with CoQ10; and (c) administering at least one chemotherapeutic agent to the subject after administration of CoQ10 has been discontinued, wherein the oncological disorder is treated.

In other embodiments, the method of treating an oncological disorder in a subject comprises: (a) administering coenzyme Q10 (CoQ10) to the subject; (b) administering at least one chemotherapeutic agent to the subject after administration of the CoQ10 is initiated; and (c) continuing treatment with CoQ10 after administration of the at least one chemotherapeutic agent is initiated, wherein the oncological disorder is treated.

In other embodiments, the method of treating an oncological disorder in a subject comprises: pre-treating a subject having an oncological disorder with Coenzyme Q10 (CoQ10) for a sufficient time prior to initiation of a chemotherapeutic treatment regimen, wherein the chemotherapeutic treatment regimen comprises administration of one or more chemotherapeutic agents, such that a response of the oncological disorder is improved relative to treatment with the chemotherapeutic treatment regimen alone.

In yet other embodiments, the method of treating an oncological disorder in a subject comprises: (a) administering coenzyme Q10 (CoQ10) to the subject; and (b) administering at least one chemotherapeutic agent to the subject at a dosage that is lower than standard dosages of the chemotherapeutic agent used to treat the oncological disorder, such that the oncological disorder is treated.

In the foregoing various embodiments, administration of the at least one chemotherapeutic agent may be initiated at least 24 hours after administration of CoQ10 is initiated, one or more weeks after administration of CoQ10 is initiated, two or more weeks after administration of CoQ10 is initiated, three or more weeks after administration of CoQ10 is initiated, four or more weeks after administration of CoQ10 is initiated, five or more weeks after administration of CoQ10 is initiated, six or more weeks after administration of CoQ10 is initiated, seven or more weeks after administration of CoQ10 is initiated, or eight or more weeks after administration of CoQ10 is initiated.

In a preferred embodiment, administration of the at least one chemotherapeutic agent is initiated at least 24 hours after administration of CoQ10 is initiated. In another preferred embodiment, administration of the at least one chemotherapeutic agent is initiated from 24 hours to 4 weeks after administration of CoQ10 is initiated. In a further preferred embodiment, administration of the at least one chemotherapeutic agent is initiated from 2 to 4 weeks after administration of CoQ10 is initiated. In yet a further preferred embodiment, administration of the at least one chemotherapeutic agent is initiated 2 weeks after administration of CoQ10 is initiated. In yet a further preferred embodiment, administration of the at least one chemotherapeutic agent is initiated 1 week after administration of CoQ10 is initiated. In yet a further preferred embodiment, administration of the at least one chemotherapeutic agent is initiated 3 weeks after administration of CoQ10 is initiated. In yet a further preferred embodiment, administration of the at least one chemotherapeutic agent is initiated 4 weeks after administration of CoQ10 is initiated. In yet a further preferred

embodiment, administration of the at least one chemotherapeutic agent is initiated 5 weeks after administration of CoQ10 is initiated. In yet a further preferred embodiment, administration of the at least one chemotherapeutic agent is initiated 6 weeks after administration of CoQ10 is initiated. In yet a further preferred embodiment, administration of the at least one chemotherapeutic agent is initiated 7 weeks after administration of CoQ10 is initiated. In yet a further preferred embodiment, administration of the at least one chemotherapeutic agent is initiated 8 weeks after administration of CoQ10 is initiated.

The CoQ10 formulations may be inhalation formulations, intravenous formulations or topical formulations. In certain embodiments, the CoQ10 formulation is not an oral formulation. For example, the intravenous formulations may include CoQ10 or its metabolites, in a pharmaceutically acceptable carrier. In some embodiments, such a formulation may include from about 0.001% to about 20% (w/w) of CoQ10, more preferably between about 0.01% and about 15% and even more preferably between about 0.1% to about 10% (w/w) of CoQ10, more preferably about 3% to about 5% (w/w) of CoQ10. In one embodiment a formulation includes about 4% (w/w) of CoQ10. In one embodiment a formulation includes about 8% (w/w) of CoQ10. In various embodiments, the formulation includes about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% (w/w) of CoQ10. As also noted herein, compositions of the present disclosure may be in a liquid form, capable of introduction into a subject by any means or route of administration within the purview of those skilled in the art. For example, compositions may be administered by routes of administration including, but not limited to, intravenous, intratumoral, intraperitoneal, combinations thereof, and the like.

In some embodiments, a chemotherapy regimen is co-administered with a CoQ10 formulation to treat the oncological disorder. The CoQ10 formulation may be administered prior to, concurrently or substantially concurrently with, prior to and concurrently with, intermittently with or subsequently to the administration of the chemotherapy regimen. In certain embodiments, a loading dose of CoQ10 is administered prior to administration of the chemotherapeutic agent. In certain embodiments, CoQ10 is administered to achieve a steady state level of CoQ10 prior to administration of the chemotherapeutic agent. Where the combination therapy includes intravenous CoQ10 formulations, the subject is intravenously administered the CoQ10 such that oncological disorders are treated or prevented. In one embodiment, the subject is intravenously administered the CoQ10 such that response to the

chemotherapeutic agent is improved, e.g., relative to treatment with the chemotherapeutic agent alone.

The subject is administered a dose of CoQ10 in the range of about 0.5 mg/kg to about 10,000 mg/kg, about 5 mg/kg to about 5,000 mg/kg, about 10 mg/kg to about 3,000 mg/kg. In one embodiment, Coenzyme Q10 is administered in the range of about 10 mg/kg to about 1,400 mg/kg. In one embodiment, Coenzyme Q10 is administered in the range of about 10 mg/kg to about 650 mg/kg. In one embodiment, Coenzyme Q10 is administered in the range of about 10 mg/kg to about 200 mg/kg. In various embodiments, Coenzyme Q10 is administered at a dose of about 2mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 58 mg/kg, 58.6 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 78 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, 100 mg/kg, 104 mg/kg, 110 mg/kg, 120 mg/kg, 130 mg/kg, 140 mg/kg, 150 mg/kg, 160 mg/kg, 170 mg/kg, 180 mg/kg, 190 mg/kg or 200 mg/kg. It should be understood that ranges having any one of these values as the upper or lower limits are also intended to be part of this invention, *e.g.*, about 50 mg/kg to about 200 mg/kg, or about 650 mg/kg to about 1400 mg/kg. In one embodiment the administered dose is at least about 1 mg/kg, at least about 5 mg/kg, at least about 10 mg/kg, at least about 12.5 mg/kg, at least about 20 mg/kg, at least about 25 mg/kg, at least about 30 mg/kg, at least about 35 mg/kg, at least about 40 mg/kg, at least about 45 mg/kg, at least about 50 mg/kg, at least about 55 mg/kg, at least about 58 mg/kg, at least about 58.6 mg/kg, at least about 60 mg/kg, at least about 75 mg/kg, at least about 78 mg/kg, at least about 100 mg/kg, at least about 104 mg/kg, at least about 125 mg/kg, at least about 150 mg/kg, at least about 175 mg/kg, at least about 200 mg/kg, at least about 300 mg/kg, or at least about 400 mg/kg.

In certain embodiments, the CoQ10 is administered in at least one dose per day. In certain embodiments, the CoQ10 is administered in at least two doses per day. In certain embodiments, the CoQ10 is administered in at least three dose per day. In certain embodiments, the CoQ10 is administered in one dose per day. In certain embodiments, the CoQ10 is administered in two doses per day. In certain embodiments, the CoQ10 is administered in three doses per day. In certain embodiments, the CoQ10 is administered by continuous infusion.

For example, in some embodiments, the aforementioned methods comprise a regimen of intravenously administering CoQ10, e.g., at least about 50 mg/kg of CoQ10, once daily for 3 weeks, optionally with one week rest, and subsequently administering a chemotherapeutic agent. In other embodiments, the method comprises a regimen of intravenously administering CoQ10, e.g., at least about 75 mg/kg of CoQ10, once daily for 3 weeks, optionally with one week rest, and subsequently administering a chemotherapeutic agent.

Dosing ranges for inhaled formulations of CoQ10 can be similar to those provided for administration by injection. It is understood that nebulizers or other devices for delivery by inhalation are known in the art and can be used in conjunction with the methods of the invention.

Dosages of topical CoQ10 typically depend on the size of the area to be treated. For example, topically administered CoQ10 can be used for the treatment of skin cancer. CoQ10 is applied topically, typically once or twice per day, to the site of the cancerous lesion in an amount sufficient to cover the lesion, e.g., as applying acne medicine to a pimple. If the subject has many lesions for treatment, the CoQ10 is applied to many sites, increasing the total dose administered to the subject. If the subject has a single lesion, the CoQ10 is applied to the single site.

In one embodiment, the chemotherapy agent of the combination therapy is gemcitabine. Where the combination therapy includes administration of the CoQ10 formulation and gemcitabine, the subject is administered the CoQ10 formulation and gemcitabine (e.g., both intravenously) such that oncological disorders are treated or prevented. The subject is administered a dose of gemcitabine in the range of about 10 mg/m^2 to about 10,000 mg/m^2, about 10 mg/m^2 to about 5,000 mg/m^2, about 10 mg/m^2 to about 3,000 mg/m^2. In one embodiment, gemcitabine is administered in the range of about 10 mg/m^2 to about 1,500 mg/m^2. In one embodiment, gemcitabine is administered in the range of about 10 mg/m^2 to about 1000 mg/m^2. In one embodiment, gemcitabine is administered in the range of about 10 mg/m^2 to about 750 mg/m^2. In one embodiment, gemcitabine is administered in the range of about 10 mg/m^2 to about 500 mg/m^2. In one embodiment, gemcitabine is administered in the range of about 10 mg/m^2 to about 400 mg/m^2. In one embodiment, gemcitabine is administered in the range of about 10 mg/m^2 to about 300 mg/m^2. In one embodiment, gemcitabine is administered in the range of about 10 mg/m^2 to

about 200 mg/m^2. In one embodiment, gemcitabine is administered in the range of about 10 mg/m^2 to about 100 mg/m^2. In one embodiment, gemcitabine is administered in the range of about 10 mg/m^2 to about 70 mg/m^2. In various embodiments, gemcitabine is administered at a dose of about 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 100 mg/m^2, 200 mg/m^2, 300 mg/m^2, 400 mg/m^2, 500 mg/m^2, 600 mg/m^2, 700 mg/m^2, 800 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1500 mg/m^2, 2000 mg/m^2, 3000 mg/m^2. It should be understood that ranges having any one of these values as the upper or lower limits are also intended to be part of this invention. In one embodiment the administered dose of gemcitabine is at least about 10 mg/m^2, at least about 30 mg/m^2, at least about 50 mg/m^2, at least about 65 mg/m^2, at least about 100 mg/m^2, at least about 150 mg/m^2, at least about 200 mg/m^2, at least about 300 mg/m^2, at least about 400 mg/m^2, at least about 500 mg/m^2, at least about 600 mg/m^2, at least about 700 mg/m^2, at least about 750 mg/m^2, at least about 800 mg/m^2, at least about 900 mg/m^2, at least about 1000 mg/m^2, or at least about 1500 mg/m^2. In some embodiments, a regimen comprises co-administering intravenous CoQ10 formulation and a chemotherapeutic agent such as gemcitabine.

In a first exemplary regimen (Once Daily Regimen), a dose of at least about 50 mg/kg/dose or at least about 75 mg/kg/dose of the intravenous CoQ10 formulation is administered once daily for 3 consecutive weeks followed with one week of rest, while the 150 mg/kg/dose of the gemcitabine is administered once per week for 3 consecutive weeks followed with one week rest. Figure 1, shows the results of a combination therapy regimen co-administering intravenous CoQ10 formulation and intravenous gemcitabine according to the first regimen.

In a second exemplary regimen (Twice Daily Regimen), a dose of at least about 50 mg/kg/dose or at least about 75 mg/kg of the intravenous CoQ10 formulation is administered twice daily for 3 consecutive weeks followed with one week rest, while 150 mg/kg/dose of the gemcitabine is administered once per week for 3 weeks with one week rest. Figure 4, shows the results of a combination therapy regimen co-administering intravenous CoQ10 formulation and intravenous gemcitabine according to the second regimen.

In a third exemplary regimen (Three Times Daily Regimen), a dose of at least about 50 mg/kg/dose or at least about 75 mg/kg/dose of the intravenous CoQ10 formulation is administered three times daily for 3 consecutive weeks followed with one week of rest, while

the 150 mg/kg/dose of the gemcitabine is administered once per week for 3 weeks with one week rest. Figure 8, shows the results a the combination therapy regimen co-administering intravenous CoQ10 formulation and intravenous gemcitabine according to the third regimen.

In a fourth exemplary regimen (pretreatment regimen), a dose of at least about 75 mg/kg/dose of the intravenous CoQ10 formulation is administered three times daily for at least24 hours, 1 day, 2, days, 3 days, 4, days, 5 days, 6, days, 1 week, 2 weeks, 3 weeks, or more. In certain embodiments, the pretreatment regimen is used prior to administration of the first dose of chemotherapy. In certain embodiments, the pretreatment regimen is used prior to administration of each dose of chemotherapy. In certain embodiments, the pretreatment regimen is used prior to administration of each cycle of chemotherapy.

In modified regimens 1 to 4, the CoQ10 is administered at the daily indicated dose by continuous infusion rather than in 1, 2, or 3 separate doses daily.

For example, in certain embodiments, the aforementioned methods comprise a regimen of intravenously administering at least about 50 mg/kg of intravenous CoQ10 formulation once daily for 3 weeks with one week rest, and administering between about 100 mg/kg of gemcitabine and about 10 mg/kg of gemcitabine once per week for 3 weeks with one week rest.
In other embodiments, the methods comprise a regimen of intravenously administering at least about 50 mg/kg of intravenous CoQ10 formulation twice daily for 3 weeks with one week rest, and administering between about 100 mg/kg of gemcitabine and about 10 mg/kg of gemcitabine once per week for 3 weeks with one week rest. In other embodiments, the method comprises a regimen of intravenously administering at least about 50 mg/kg of intravenous CoQ10 formulation three times daily for 3 weeks with one week rest, and administering between about 100 mg/kg of gemcitabine and about 10 mg/kg of gemcitabine once per week for 3 weeks with one week rest. In further embodiments, the methods comprise a regimen of intravenously administering at least about 75 mg/kg of intravenous CoQ10 formulation once daily for 3 weeks with one week rest, and administering between about 100 mg/kg of gemcitabine and about 10 mg/kg of gemcitabine once per week for 3 weeks with one week rest. In further embodiments, the methods comprise a regimen of intravenously administering at least about 75 mg/kg of intravenous CoQ10 formulation twice daily for 3 weeks with one week rest, and administering between about 100 mg/kg of

gemcitabine and about 10 mg/kg of gemcitabine once per week for 3 weeks with one week rest. In yet other embodiments, the methods comprise a regimen of intravenously administering at least about 75 mg/kg of intravenous CoQ10 formulation three times daily for 3 weeks with one week rest, and administering between about 100 mg/kg of gemcitabine and about 10 mg/kg of gemcitabine once per week for 3 weeks with one week rest.

In certain embodiments the aforementioned methods comprise administering 5 mg/kg docetaxel, 1 mg/kg doxorubicin, and 35 mg/kg cyclophosphamide to the subject every three weeks for six cycles.

In some embodiments, a combination therapy regimen comprises co-administering intravenous CoQ10 formulation and a chemotherapeutic agent, such as gemcitabine, to a patient in need thereof. In one embodiment, the gemcitabine of the combination therapy is administered by intravenous infusion at a dose of about 1000 mg/m^2 once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment as a first cycle of treatment. In certain embodiments, in the absence of dose limiting toxicities, the CoQ10 is administered daily at the desired dose and frequency. In one embodiment the first cycle of administration is followed by subsequent cycles consisting of infusions once weekly for 3 consecutive weeks out of every 4 weeks. In one embodiment, dosage of gemcitabine is adjusted based upon the degree of hematologic toxicity experienced by the patient. In one embodiment, when the absolute granulocyte count of the patient is greater than or equal to 1000 x 10^6 /L, and the platelet count of the patient is greater than or equal to 100,000 x 10^6 /L, a full dose of 1000 mg/m^2 once weekly may be administered to the patient. In one embodiment, when the absolute granulocyte count of the patient is between about 500-999 x 10^6 /L, or the platelet count of the patient is between about 50,000-99,000 x 10^6 /L, a 75% of full dose, e.g. 750 mg/m^2 once weekly may be administered to the patient. In one embodiment, when the absolute granulocyte count of the patient is less than 500 x 10^6 /L, or the platelet count of the patient is less than 50,000 x 10^6 /L, gemcitabine administration should be hold until the absolute granulocyte count of the patient is greater than or equal to 500 x 10^6 /L, or the platelet count of the patient is greater than or equal to 50,000 x 10^6 /L.

Guidance for appropriate dosing regimens for chemotherapeutic agents approved for use in various cancer types are known in the art. The CoQ10 treatment regimens provided herein can be combined with other known treatment regimens based on the exemplary teachings provided herein.

In some embodiments, a regimen comprises co-administering intravenous CoQ10 formulation and a chemotherapeutic agent such as gemcitabine. In the first regimen (Once Daily Regimen), a dose of at least about 58 mg/kg, at least about 58.6 mg/kg, at least about 78 mg/kg, or at least about 104 mg/kg of the intravenous CoQ10 formulation is administered once daily for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), optionally followed by subsequent cycles consisting of infusion once daily for 3 consecutive weeks out of every 4 weeks; while the at least about 1000 mg/m^2, or at least about 750 mg/m^2 of the gemcitabine is administered once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), optionally followed by subsequent cycles consisting of infusion once daily for 3 consecutive weeks out of every 4 weeks. In the second regimen (Twice Daily Regimen), a dose of at least about 58 mg/kg, at least about 58.6 mg/kg, at least about 78 mg/kg, or at least about 104 mg/kg of the intravenous CoQ10 formulation is administered twice daily for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), optionally followed by subsequent cycles consisting infusion once daily for 3 consecutive weeks out of every 4 weeks; while the at least about 1000 mg/m^2, or at least about 750 mg/m^2 of the gemcitabine is administered once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), optionally followed by subsequent cycles consisting of infusion once daily for 3 consecutive weeks out of every 4 weeks. In the third regimen (Three Times Daily Regimen), a dose of at least about 58 mg/kg, at least about 58.6 mg/kg, at least about 78 mg/kg, or at least about 104 mg/kg of the intravenous CoQ10 formulation is administered three times daily for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), optionally followed by subsequent cycles consisting infusion once daily for 3 consecutive weeks out of every 4 weeks; while the at least about 1000 mg/m^2, or at least about 750 mg/m^2 of the gemcitabine is administered once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), optionally followed by subsequent cycles consisting of infusion once daily for 3 consecutive weeks out of every 4 weeks. In certain embodiments, the CoQ10 is administered by continuous infusion with total daily doses based on those provided in regimens 1-3 above. In certain embodiments, in the absence of dose limiting toxicities, the CoQ10 is administered daily at the desired dose and frequency.

In one embodiment, the dosage of gemcitabine is adjusted based upon the degree of hematologic toxicity experienced by the patient. In one embodiment, when the absolute granulocyte count of the patient is greater than or equal to 1000 x 10^6 /L, and the platelet

count of the patient is greater than or equal to 100,000 x 10^6 /L, a full dose of 1000 mg/m^2 once weekly may be administered to the patient. In one embodiment, when the absolute granulocyte count of the patient is between about 500-999 x 10^6 /L, or the platelet count of the patient is between about 50,000-99,000 x 10^6 /L, a 75% of full dose, e.g. 750 mg/m^2 once weekly may be administered to the patient. In one embodiment, when the absolute granulocyte count of the patient is less than 500 x 10^6 /L, or the platelet count of the patient is less than 50,000 x 10^6 /L, gemcitabine administration should be hold until the absolute granulocyte count of the patient is greater than or equal to 500 x 10^6 /L, or the platelet count of the patient is greater than or equal to 50,000 x 10^6 /L.

In one embodiment of the combination treatment methods provided herein, the CoQ10 formulation is administered one time per week. In one embodiment, the CoQ10 formulation is administered 2 times per week. In one embodiment, the CoQ10 formulation is administered 3 times per week. In another embodiment, the CoQ10 formulation is administered 5 times per week. In one embodiment, the CoQ10 formulation is administered once per day. In one embodiment, the CoQ10 formulation is administered twice per day. In one embodiment, the CoQ10 formulation is administered three times per day. In some embodiments, where the IV formulation is administered by infusion, the dosage is administered by infusion over about 1 hour, 2 hours, 3 hours, 4 hours or longer. In one embodiment, the IV CoQ10 formulation is administered by infusion over about 4 hours. In certain embodiments, the IV CoQ10 formulation is administered by infusion over about 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24hours.

In another embodiment, the CoQ10 is administered in the form of a intravenous CoQ10 formulation at a dosage of between about 10 mg/kg and about 10,000 mg/kg of CoQ10, about 20 mg/kg to about 5000 mg/kg, about 50 mg/kg to about 3000 mg/kg, about 100 mg/kg to about 2000 mg/kg, about 200 mg/kg to about 1000 mg/kg, or about 300 mg/kg to about 500 mg/kg, wherein the CoQ10 formulation comprises between about 1% and 10% of Coenzyme Q10. In one embodiment, the CoQ10 formulation comprises about 3% to about 5% of Coenzyme Q10. In one embodiment, the CoQ10 formulation comprises about 4% of Coenzyme Q10. In one embodiment, the CoQ10 IV formulation comprises about 8% of Coenzyme Q10. In other embodiments, the CoQ10 IV formulation comprises about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%

or 10% of Coenzyme Q10. It should be understood that ranges having any one of these values as the upper or lower limits are also intended to be part of this invention.

In certain embodiments, administration of CoQ10 is initiated at least 8 hours, at least 12 hours, at least 18 hours, at least 24 hours, at least 36 hours, at least 48 hours, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 1 week ,at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, or at least 8 weeks prior to administration of the first dose of a chemotherapeutic agent or chemotherapeutic regimen. In one embodiment, the administration of Co10 is discontinued before initiation of treatment with the chemotherapeutic agent or chemotherapeutic regimen, i.e., and treatment with the chemotherapeutic agent excludes treatment with CoQ10. In one embodiment, the administration of Co10 is continued or resumed after initiation of treatment with the chemotherapeutic agent or chemotherapeutic regimen such that the CoQ10 and chemotherapeutic agent are concurrently administered, e.g., for at least one cycle.

Where utilized in the combination therapy to treat cancer, the intravenous CoQ10 formulations may be in a pharmaceutically acceptable carrier that may be administered in a therapeutically effective amount to an area of oncogenesis as either a mono-therapy, in combination with at least one other chemotherapeutic agent for a given indication, in combination with radiotherapy, following surgical intervention to radically remove a tumor, in combination with other alternative and/or complementary acceptable treatments for cancer, and the like. In certain embodiments, the present disclosure also provides a method for reactivating a mutated/inactivated p53 protein by administering to an area of oncogenesis in a patient a composition of the present disclosure.

In general, the combination therapy including any of the CoQ10 formulations and the chemotherapeutic agents described herein may be used to prophylactically or therapeutically treat any neoplasm. In a particular embodiment, the combination therapy is used to treat solid tumors. In various embodiments of the invention, the combination therapy is used for treatment or prevention of cancer of the brain, central nervous system, head and neck, prostate, breast, testicular, pancreas, liver, colon, bladder, urethra, gall bladder, kidney, lung, non-small cell lung, melanoma, mesothelioma, uterus, cervix, ovary, sarcoma, bone, stomach, skin, and medulloblastoma. In a preferred embodiment, the combination therapy is used to treat triple -negative breast cancer (TNBC). In one embodiment, the combination therapy

including CoQ10 described herein may be used to treat a chloroleukemia, *e.g.*, a primary chloroleukemia or a secondary or metastatic chloroleukemia, *e.g.*, that presents, migrates or metastasizes to a particular organ such as, e.g., the lung, the liver or the central nervous system.

However, treatment using combination therapies of the invention is not limited to the foregoing types of cancers. Examples of cancers amenable to treatment with the combination therapies include, but are not limited to, for example, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, breast cancer, ovarian cancer, lung cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, small-cell lung tumors, primary brain tumors, stomach cancer, colon cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, skin cancer, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, cervical cancer, endometrial cancer, adrenal cortical cancer, and prostate cancer. In one embodiment, a CoQ10 IV formulation described herein may be used in combination with a chemotherapeutic agent to treat or prevent various types of skin cancer (e.g., Squamous cell Carcinoma or Basal Cell Carcinoma), pancreatic cancer, breast cancer, prostate cancer, liver cancer, or bone cancer. In one embodiment, the combination therapy including CoQ10 is used for treatment of a skin oncological disorder including, but not limited to, squamous cell carcinomas (including SCCIS (in situ) and more aggressive squamous cell carcinomas), basal cell carcinomas (including superficial, nodular and infiltrating basal cell carcinomas), melanomas, and actinic keratosis. In one embodiment, the oncological disorder or cancer which can be treated with the combination therapy including CoQ10 is not melanoma. In one embodiment, the oncological disorder is merkel cell carcinoma (MCC). In one embodiment, the oncological disorder or cancer which can be treated with the combination therapy including CoQ10 is not skin cancer.

In certain embodiments, the effect that combination therapy including CoQ10 may have on cancer cells may depend, in part, on the various states of metabolic and oxidative flux exhibited by the cancer cells. CoQ10 may be utilized to interrupt and/or interfere with the conversion of an oncogenic cell's dependency of glycolysis and increased lactate utility. As it relates to a cancer state, this interference with the glycolytic and oxidative flux of the tumor microenvironment may influence apoptosis and angiogenesis in a manner which

reduces the development of a cancer cell. In some embodiments, the interaction of CoQ10 with glycolytic and oxidative flux factors may enhance the ability of CoQ10 to exert its restorative apoptotic effect in cancer while establishing viable drug targets for drug discovery and development.

In one embodiment, administration of CoQ10 and the chemotherapeutic agent as described or incorporated herein, reduces tumor size, weight or volume, increases time to progression, inhibits tumor growth and/or prolongs the survival time of a subject having an oncological disorder. In a preferred embodiment, CoQ10 is administered by injection, e.g., by intravenous administration, of an intravenous CoQ10 formulation as described or incorporated herein. In certain embodiments, administration of CoQ10 and the chemotherapeutic agent reduces tumor size, weight or volume, increases time to progression, inhibits tumor growth and/or prolongs the survival time of the subject by at least 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 300%, 400% or 500% relative to a corresponding control subject that is administered CoQ10 alone or the chemotherapeutic agent alone. In other embodiments, administration of CoQ10 and the chemotherapeutic agent stabilizes the oncological disorder in a subject with a progressive oncological disorder prior to treatment.

This invention also relates to a method of treating tumors in a human or other animal by intravenously administering to such human or animal an effective, non-toxic amount of CoQ10. One skilled in the art would be able, by routine experimentation, to determine what an effective, non-toxic amount of CoQ10 would be for the purpose of treating malignancies. For example, a therapeutically active amount of CoQ10 may vary according to factors such as the disease stage (e.g., stage I versus stage IV), age, sex, medical complications (e.g., immunosuppressed conditions or diseases) and weight of the subject, and the ability of the CoQ10 to elicit a desired response in the subject. The dosage regimen may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or administered by continuous infusion or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

The invention also provides, in another aspect, methods for treating or preventing aggressive oncological disorders in humans. These methods include intravenously administering CoQ10 to the human at a therapeutically effective dose while co-administering

a chemotherapeutic agent, so that treatment or prevention of the aggressive oncological disorder occurs. In one embodiment, these methods include intravenously administering CoQ10 to the subject at a selected lower dosage than a dosage regimen used or selected for less aggressive or non-aggressive oncological disorder, so that treatment or prevention of the aggressive oncological disorder occurs. In certain embodiments the aggressive oncological disorder includes pancreatic carcinoma, hepatocellular carcinoma, Ewing's sarcoma, metastatic breast cancer, metastatic melanoma, brain cancer (astrocytoma, glioblastoma), neuroendocrine cancer, colon cancer, liver cancer, lung cancer, osteosarcoma, androgen-independent prostate cancer, ovarian cancer, skin cancer, and non-Hodgkin's Lymphoma.

In another aspect, the invention provides methods for topical administration of CoQ10, especially in the treatment of skin cancer, in combination with administration of chemotherapeutic agents by any route of administration. Such methods include pre-treatment with CoQ10 prior to first administration of the chemotherapeutic agent.

In a related aspect, the invention provides a method for treating or preventing a non-aggressive oncological disorder in a human. These methods include intravenously co-administering CoQ10 and a chemotherapeutic agent to the subject at a therapeutically effective dose, so that treatment or prevention of the non-aggressive oncological disorder occurs. In one embodiment, these methods include administering CoQ10 to the subject at a selected higher dosage over a dosage regimen used or selected for aggressive oncological disorders so that treatment or prevention of the non-aggressive oncological disorder occurs. In certain embodiments, the non-aggressive oncological disorder includes non-metastatic breast cancer, androgen-dependent prostate cancer, small cell lung cancer and acute lymphocytic leukemia.

In some embodiments of the invention, the treatment or prevention of the oncological disorder occurs via an interaction of CoQ10 with a protein or other cellular component selected from the group consisting of HNF4-alpha, Bcl-xl, Bcl-xS, BNIP-2, Bcl-2, Birc6, Bcl-2-L11 (Bim), XIAP, BRAF, Bax, c-Jun, Bmf, PUMA, cMyc, transaldolase 1, CoQ1, CoQ3, CoQ6, prenyltransferase, 4-hydrobenzoate, neutrophil cytosolic factor 2, nitric oxide synthase 2A, superoxide dismutase 2, VDAC, Bax channel, ANT, Cytochrome c, complex 1, complex II, complex III, complex IV, Foxo 3a, DJ-1, IDH-1, Cpt1C and Cam Kinase II. In

some embodiments the oncological disorder is selected from the group consisting of leukemia, a lymphoma, a melanoma, a carcinoma, and a sarcoma.

In some embodiments the chemotherapeutic agent, for example gemcitabine, works by damaging RNA or DNA that tells cancerous cells how to copy itself in mitosis. If the cells are unable to divide, then they will die. In some instances, the chemotherapeutic agent induces apoptosis. Gemcitabine incorporates itself into the cancerous cells and prevents them from dividing. As with fluorouracil and other pyrimidines, the triphosphate analogue of gemcitabine replaces one of the building blocks of nucleic acids (i.e., cytidine) during DNA replication. This halts tumor growth, as only one additional nucleoside can be attached to the faulty nucleoside, which results in apoptosis. Gemcitabine also targets the enzyme ribonucleotide reductse (RNR). The diphosphate analogue binds to RNR active site and inactivates the enzyme irreversibly. Once RNA is inhibited, the cell cannot produce deoxyribonucleotides required for DNA replication and repair and the cell apoptosis occurs. In some embodiments, the gemcitabine is administered by the GemCarbo regimen, wherein gemcitabine is administered in combination with carboplatin over a 21 day cycle.

International Patent Application Publication No. WO/2009/126764, filed April 9, 2009, discloses the treatment of cancer with CoQ10 and International Patent Application Publication No. WO2011/11290, filed March 11, 2011, discloses intravenous formulations of CoQ10. US Patent Application Publication No.: US2011/0027247 filed May, 11, 2010, discloses methods of treating oncological disorders using topically administered CoQ10. International Patent Application Nos. WO2009073843, filed June 11, 2009, and WO2012174559, filed June 18, 2012 disclose formulations of CoQ10 for administration by inhalation. These applications are each hereby incorporated by reference in their entirety.In certain embodiments of the invention, the methods further include a treatment regimen which includes any one of or a combination of surgery, radiation, hormone therapy, antibody therapy, therapy with growth factors, cytokines, and chemotherapy.

Reference will now be made in detail to preferred embodiments of the invention. While the invention will be described in conjunction with the preferred embodiments, it will be understood that it is not intended to limit the invention to those preferred embodiments. To the contrary, it is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the invention as defined by the appended claims.

EXAMPLES

The following examples provide non-limiting exemplary methods and results from the treatment of oncological disorders with the combination therapy of CoQ10 and a chemotherapeutic agent.

METHODS

Example 1 - Regimen 1 -- Once Daily IV CoQ10 and Once Weekly Gemcitabine Combination

Pancreatic Carcinoma is one of the deadliest types of cancers and certainly one that is most clinically difficult to manage given that most diagnoses occur in late-stage disease. Gemcitabine is among the few FDA approved drugs used alone and in combination with other antineoplastic agents for pancreatic cancer. An intravenous 4% formulation of CoQ10 was used alone or in combination with gemcitabine in in vitro cell based assays and in a xenogeneic mouse human pancreatic cancer model to demonstrate the increased efficacy of the combination of CoQ10 with gemcitabine in the treatment of pancreatic cancer. The specific formulation used is provided in International Patent Publication WO2011/112900 filed on March 11, 2011 which is incorporated herein by reference in its entirety.

Xenogeneic Mouse Human Pancreatic Cancer Model

Equal numbers of MIAPaCa-2 human pancreatic tumor cells were suspended in MATRIGEL® and injected into NOD scid gamma (NSG) mice. The NSG mouse model is devoid of innate and adaptive immune systems and provides a biological environment suitable for the growth of human tumors *in vivo*. The MIAPaCa-2 is a well established human derived pancreatic carcinoma cell line that can be used to establish pancreatic tumors in immunosuppressed animals. MIAPaca-2 tumors were allowed to develop for, on average, at least 3 weeks in mice prior to initiation of treatment. Animals with palpable tumors were randomized into treatment groups. Results shown in graphs indicate the number of days of survival from the first day of treatment in the study.

MIAPaca-2 cells (1 x 10^7 cells per animal) were injected into NSG mice using the method provided above. Mice having palpable tumors were randomized into 4 groups of 30 mice each as follows:

i. Group 1 - No treatment.

ii. Group 2 - Intravenous dose of 4% Coenzyme Q10, 50 mg/kg/day.

iii. Group 3 - Intravenous single weekly dose of gemcitabine at 150 mg/kg/week for 3 weeks with one week rest. This cycle was repeated at four week intervals.

iv. Group 4 - Combination of intravenous dose of 4 % Coenzyme Q10, 50 mg/kg/day and intravenous single weekly dose of gemcitabine at 150 mg/kg for 3 weeks with one week rest. This cycle was repeated at four week intervals.

Mice were observed for viability and secondary symptoms, and tumor growth was monitored by palpation. At mortality, tumors were harvested from the mice, and were measured, weighed, and analyzed for the presence of tumor vasculature.

Survival curves are shown in Figure 1. As shown, the untreated group exhibited steep death rates, whereas in CoQ10, gemcitabine alone and the combination of CoQ10 resulted in prolongation of life as compared to untreated control. CoQ10 alone had significantly greater impact on survival than gemcitabine alone. Animals treated with a combination of gemcitabine and CoQ10 exhibited prolonged survival and long-term remission that was statistically significant compared to other groups.

Tumors harvested from animals at mortality are shown in Figure 2. Tumors were harvested from animals in Group 1 (control) at day 20 after the initiation of treatment. Tumors were harvested from animals in Group 2 (Coenzyme Q10 alone) at days 50-60 after the initiation of treatment. Tumors were harvested from animals in Group 3 (gemcitabine alone) at days 40-50 after the initiation of treatment. Tumors were harvested from animals in Group 4 (gemcitabine + Coenzyme Q10) at days 50-60 after the initiation of treatment. The tumor sizes shown in Figure 2 are representative of the tumor size overall observed in each group at the indicated time period.

Although tumors were harvested from animals in the control group (Group 1) 20-40 days prior to the date that the tumors were harvested from the treatment groups (Groups 2-4), it is evident from Figure 2 that the tumors in the control group, on average, were significantly larger than those in any of the treatment groups at the time of death. These results show that both Coenzyme Q10 and gemcitabine inhibited the growth of pancreatic tumors in the xenogeneic mouse human tumor model.

Additionally, tumors were weighed to quantitatively determine size. These results are shown in Figure 3. On average, tumors from the mice treated with Coenzyme Q10 alone (Group 2) were significantly smaller than tumors from mice in the control group (Group 2 vs. Group 1, $p < 0.001$) or tumors from mice in the gemcitabine treated group (Group 2 vs. Group 3, $p < 0.001$). Tumors from mice treated with a combination of Coenzyme Q10 and gemcitabine (Group 4) were found, on average, to be significantly smaller than tumors from mice treated with Coenzyme Q10 alone (Group 2 vs. Group 4, $p = 0.01$) or gemcitabine alone (Group 3 vs Group 4, $p < 0.0001$).

Similarly, palpable tumors were noted to be decreased in the treatment groups as compared to the tumors in the control group. Further, histological analysis of the tumors revealed decreased tumor vasculature in the tumors from the mice treated with Coenzyme Q10 as compared, at least, to tumors from untreated control mice (data not shown). No quantitative analysis of tumor vasculature was performed.

These data demonstrate that intravenously administering Coenzyme Q10 to mice bearing pancreatic tumors inhibits pancreatic tumor growth, as compared to control untreated mice and as compared to mice treated with gemcitabine alone, an agent approved for the treatment of pancreatic tumors in humans. Moreover, the combination of intravenously administered Coenzyme Q10 and gemcitabine was more effective at inhibiting the growth of pancreatic tumors in mice than treatment with either agent alone.

Intravenously administered Coenzyme Q10 was also observed to result in a decrease in the amount of vasculature in pancreatic tumors as compared to, at least, tumors from untreated control mice, further demonstrating the effectiveness of Coenzyme Q10 in the treatment of cancer.

These data further demonstrate that intravenously administering Coenzyme Q10 to mice bearing pancreatic tumors increases survival time of the mice, as compared to control

untreated animals and as compared to animals treated with gemcitabine alone, an agent approved for the treatment of pancreatic tumors in humans. Moreover, the combination of Coenzyme Q10 and gemcitabine was more effective at increasing survival time in mice bearing pancreatic tumors than treatment with either agent alone.

Example 2 - Regimen 2 -- Twice Daily IV CoQ10 and Once Weekly Gemcitabine Combination for Treating Pancreatic Cancer

MIAPaca-2 cells (1 x 10^7 cells per animal) were injected into NSG mice using the method provided above. Mice having palpable tumors were randomized into 4 groups of 30 mice each as follows:

In the second regimen, a dose of

i. Control, no treatment.

ii. 50 mg/kg of intravenous 4% CoQ10 intravenous formulation administered intraperitoneally twice daily for 3 weeks with one week of rest.

iii. 150 mg/kg of gemcitabine once per week for 3 weeks with one week of rest.

iv. 50 mg/kg of intravenous 4% CoQ10 intravenous formulation administered intraperitoneally twice daily for 3 weeks with one week of rest and a dose of 150 mg/kg of gemcitabine once per week for 3 weeks with one week of rest.

In this example, the intravenous formulation of CoQ10 was administered intraperitoneally to prevent vascular damage that would result from the frequency of administration.

Mice were monitored for survival. The results, as shown in Figure 4, demonstrate an increase in survival of mice treated with CoQ10, either alone or in combination with gemcitabine as compared to untreated mice or mice treated with gemcitabine alone. These data demonstrate that CoQ10, either alone or in combination with gemcitabine, is more effective in treating pancreatic cancer than gemcitabine alone.

Example 3 - In Vitro Combination Therapy (CoQ10 + Gemcitabine) of Pancreatic and Breast Cancer

In Vitro Cell Viability Assay

Cell lines (e.g., MIAPaCa-2, Hep3B, and/or SK-Br3) cell lines were maintained in culture using standard culture conditions for each cell line. Cells were treated with CoQ10 or the indicated chemotherapeutic agents at the indicated concentrations for the indicated times. After the predetermined incubation time, the cells were stained to distinguish between viable and non-viable cells using routine methods. Cells were counted by microscopy or flow cytometry. The number of cells after treatment were normalized to the number of cells in the untreated sample.

Specifically, to assess the efficacy of CoQ10 in combination with gemcitabine *in vitro*, MIAPaCa-2 pancreatic carcinoma cells were maintained in culture and exposed to increasing concentrations of gemcitabine in combination with CoQ10, the 4% CoQ10 intravenous formulation, or the excipient of the CoQ10 intravenous formulation. Figure 5A shows the effect of 6 hour treatment with CoQ10 or the 4% CoQ10 intravenous formulation, either alone or in combination with gemcitabine on MIAPaCa-2 pancreatic cancer cells. Figure 5B shows the effect of 6 hour treatment with CoQ10 or the 4% CoQ10 intravenous formulation alone, or in combination with gemcitabine, on SK-Br3 breast cancer cells. The results demonstrate increased cell death in both pancreatic and breast cancer cells following exposure to the 4% CoQ10 intravenous formulation in combination with gemcitabine, at 6 hours. The combination treatment with gemcitabine and the 4% CoQ10 intravenous formulation results in an increase in cell death as compared to gemcitabine treatment alone.

Example 4 - In Vitro Combination Therapy (CoQ10 + Doxorubicin) of Pancreatic and Breast Cancer

To assess the efficacy of CoQ10 in combination with doxorubicin *in vitro*, MIAPaCa-2 pancreatic carcinoma cells were maintained in culture and exposed to increasing concentrations of gemcitabine in combination with CoQ10, the 4% CoQ10 intravenous formulation, or the excipient of the CoQ10 intravenous formulation. Figure 6A shows the effect of 6 hour treatment with CoQ10 or the intravenous formulation of CoQ10, either alone

or in combination with doxorubicin on MIAPaCa-2 pancreatic cancer cells. Figure 6B shows the effect of 6 hour treatment with CoQ10 or the 4% CoQ10 intravenous formulation alone, or in combination with doxorubicin, on SK-Br3 breast cancer cells. The results demonstrate that both pancreatic and breast cancer cells induce increased cell death following exposure to 4% CoQ10 intravenous formulation of CoQ10 in combination with doxorubicin, at 6 hours. The combination treatment with doxorubicin and the 4% CoQ10 intravenous formulation results in an increase in cell death as compared to doxorubicin treatment alone.

To confirm the results observed in vitro, the MIAPaca-2 xenogeneic mouse model described above was used to assess the activity of doxorubicin, either alone or in combination with a CoQ10 intravenous formulation to increase survival of the mice. As shown in Figure 7, the CoQ10 intravenous formulation in combination with doxorubicin extended viability as compared to treatment with doxorubicin alone.

CoQ10 alone or CoQ10 in combination with doxorubicin was found to be more effective than gemcitabine or doxorubicin in effectuating responses associated with favorable therapeutic endpoints in the treatment of pancreatic cancer, most notably an increase in survival. Intravenous CoQ10 also has potential utility in the treatment of breast cancers. CoQ10 formulations, either alone or in combination with gemcitabine, extended viability to 42 days in a xenogeneic mouse model of pancreatic cancer up to 42 days. Administration of CoQ10 in combination with doxorubicin decreased mortality rates observed in of the xenogeneic mouse model of pancreatic cancer as compared to treatment with doxorubicin alone.

Example 5 - Regimen 3 – Three Times Daily IV CoQ10 and Once Weekly Gemcitabine Combination

Equal numbers of MIAPaca2 human pancreatic tumor cells (1×10^7) were suspended in MATRIGEL® and injected into mice. Tumors were allowed to develop for, on average, at least 3 weeks prior to initiation of treatment.

Mice having palpable tumors were randomized into 5 groups of 30 mice each as follows:

i. Group 1 - No treatment.

ii. Group 2 - Intraperitoneal dose of 4% CoQ10 intravenous formulation, 50 mg/kg/dose, 3 times daily (150 mg/kg/day).

iii. Group 3 – Intraperitoneal dose of 4% Coenzyme Q10 intravenous formulation, 75 mg/kg/dose, 3 times daily (225 mg/kg/day).

iv. Group 4 - Combination of intraperitoneal dose of 4% Coenzyme Q10 intravenous formulation, 50 mg/kg/dose, 3 times daily (150 mg/kg/day), and intravenous single weekly dose of gemcitabine 150 mg/kg for 3 weeks with one week rest. This cycle was repeated at four week intervals.

v. Group 5 - Combination of intraperitoneal dose of 4% Coenzyme Q10 intravenous formulation, 75 mg/kg/dose, 3 times daily (225 mg/kg/day), and intravenous single weekly dose of gemcitabine 150 mg/kg for 3 weeks with one week rest. This cycle was repeated at four week intervals.

The high frequency of administration of Coenzyme Q10 prevented intravenous administration of the Coenzyme Q10 due to vascular damage caused by high frequency intravenous injections. Animals were observed for viability and tumor growth was monitored by palpation.

The survival results collected through day 417 are shown in Figure 8. All of the mice in the control, untreated group (Group 1) died by day 23 after initiation of administration of therapeutic agents to the mice in Groups 2-5. In contrast, at least 50% of the animals in each of the treatment groups (Groups 2-5) were viable at day 130 after the initiation of treatment. Animals treated with Coenzyme Q10 alone at both treatment doses displayed significantly increased survival as compared to control animals. Further, animals treated with a combination of Coenzyme Q10 and gemcitabine displayed increased survival as compared to mice treated with the same dose of Coenzyme Q10 alone over the course of the treatment.

Example 6 – Relative sensitivities of oncogenic and normal cells to Coenzyme Q10

The effects of Coenzyme Q10 treatment on a variety of oncogenic and normal cell lines were examined and compared. The sensitivity of cells to Coenzyme Q10 was assessed by monitoring induction of apoptosis. CoQ10 treatment of cells was carried out as described

in detail below in the Materials and Methods. Induction of apoptosis was assessed in the treated cells by monitoring indicators of early apoptosis (*e.g.*, Bcl-2 expression, caspase activation and by using annexin V assays) as described below. From these studies, the minimal CoQ10 dosage, *e.g.*, concentration of CoQ10 and time of treatment, required to induce apoptosis in the panel of cell lines was determined.

The data demonstrated that efficacy of Coenzyme Q10 treatment was greater in cell types that exhibited increased oncogenicity and/or greater metastatic potential, *i.e.*, cell types that were derived from more aggressive cancers or tumors. The results of these studies are summarized below in the table. The data demonstrates that CoQ10 is more effective in both a time and concentration dependent manner on cells in a more aggressive cancer state. Moreover, a surprising divergent effect was observed on normal cells as compared to oncogenic cells. Specifically, Coenzyme Q10 was unexpectedly found to exhibit a slightly supportive role in a normal tissue environment, wherein increased proliferation and migration was observed in normal cells, including keratinocytes and dermal fibroblasts.

The effect of Coenzyme Q10 on gene regulatory and protein mechanisms in cancer is different in a normal cell. Key cellular machinery and components, such as cytoskeletal architecture, membrance fluidity, transport mechanisms, immunomodulation, angiogenesis, cell cycle control, genomic stability, oxidative control, glycolytic flux, metabolic control and integrity of extracellular matrix proteins, are dysregulated and thus the genetic and molecular fingerprint of the cell is altered. The disease environment favors governance of cellular control processes. The data provided herein suggests that CoQ10 exerts a greater level of efficacy (*e.g.*, in cancer cells vs. normal cells, and in cells of a more aggressive cancer state as compared to cellsl of a less aggressive or non-aggressive cancer state) by normalizing some of the key aforementioned processes in a manner that allows for restored apoptotic potential.

Minimal CoQ10 concentration and treatment time required for induction of early apoptosis in various cell types.

Tissue Origin (Cell type)	**Indication of Early apoptosis (Bcl-2, annexin V, or caspase activation)**	**Concentration (µM)**	**Time (hr)**	**Level of aggressiveness:** **1 = normal tissue** **2 = malignant** **3 = metastatic**
SKIN:				
Keratinocytes (*Heka, Hekn*)	None	N/A	N/A	1
Fibroblasts (*nFib*)	None	N/A	N/A	1
Melanocytes (*Hema, LP*)	None	N/A	N/A	1
Melanoma (*Skmel 28*)	Strong	20	24	2
Melanoma (Skmel 2)	Very Strong	25	24	3
SCC, Squamous cell carcinoma	Very Strong	25	24	3
BREAST:				
MCF-7	Strong	50	48	2
SkBr-3	Very Strong	50	24	3
BT-20	Strong	100	48	2
ZR-75	Slight	200	72	2
MDA MB 468	Strong	100	48	2
Mammary fiboblasts: 184A1 and 184B5) (Lawrence Berkeley)	None	N/A		1
PROSTATE:				
PC3	Very Strong	25	24	3
LIVER:				
HepG2	Very Strong	50	24	3
Hep3B	Very Strong	50	24	3
BONE:				
Osteosarcoma (143b)	Very Strong	50	48	2
Ewing's sarcoma (NCI)	Extremely strong	5	1	3
PANCREAS:				3
PaCa2	Very Strong	25	24	

Tissue Origin (Cell type)	Indication of Early apoptosis (Bcl-2, annexin V, or caspase activation)	Concentration (μM)	Time (hr)	Level of aggressiveness: 1 = normal tissue 2 = malignant 3 = metastatic
Heart:				
Aortic smooth muscle (HASMC)	None	N/A	N/A	1

Materials and Methods

Cell Preparation and Treatment

Cells prepared in dishes or flasks

Cells were cultured in T-75 flasks with relevant medium supplemented with 10% Fetal Bovine Serum (FBS), 1% PSA (penicillin, streptomycin, amphotericin B) (Invitrogen and Cellgro) in a 37° C incubator with 5% CO_2 levels until 70-80% confluence was reached. To harvest cells for treatment, flasks were primed with 1 mL Trypsin, aspirated, trypsinized with an additional 3mL, and incubated at 37° C for 3-5 minutes. Cells were then neutralized with an equal volμme of media and the subsequent solution was centrifuged at 10,000 rpm for 8 minutes. The supernatant was aspirated and the cells were resuspended with 8.5 ml of media. A mixture of 500ul of the resuspension and 9.5 ml of isopropanol was read twice by a coulter counter and the appropriate number of cells to be seeded into each dish was determined. Control and concentration ranging from 0-200μM groups were examined in triplicate. From a 500 μM CoQ-10 stock solution, serial dilutions were performed to achieve desired experimental concentration in appropriate dishes. Dishes were incubated in a 37° C incubator with 5% CO_2 levels for 0 – 72 hours depending on cell type and experimental protocol.

Protein Isolation and Quantification

Cells prepared in dishes

Following cell treatment incubation period was complete, protein isolation was performed. Dishes of all treatment groups were washed twice with 2ml, and once with 1ml of ice cold 1x Phosphate Buffered Saline (PBS). The PBS was aspirated from the dishes after the initial 2 washes only. Cells were gently scraped and collected into microcentrifuge tubes using the final volume from the third wash and centrifuged at 10,000 rpm for 10 minutes.

After centrifugation, the supernatant was aspirated and the pellet was lysed with 50 uL of lysis buffer (1uL of protease and phosphotase inhibitor for every 100 uL of lysis buffer). Samples were then frozen overnight at -20° C.

Cells prepared in flasks

After the cell treatment incubation period was complete, protein isolation was performed. Flasks of all treatment groups were washed twice with 5mL, and once with 3mL of ice cold 1x PBS. The PBS was aspirated from the flasks after the first 2 washes only. Cells were gently scraped and collected into 15mL centrifuge tubes using the final volume from the third wash and centrifuged for at 10,000 rpm for 10 minutes. After centrifugation, the supernatant was aspirated and the pellet was lysed with an appropriate amount of lysis buffer (1uL of protease and phosphotase inhibitor for every 100 uL of lysis buffer). Lysis buffer volµme was dependent on pellet size. Samples were transferred in microcentrifuge tubes and frozen overnight at -20° C.

Protein Quantification

Samples were thawed at -4° C and sonicated to ensure homogenization the day following protein isolation. Protein quantification was performed using the micro BCA protein assay kit (Pierce). To prepare samples for Immuno-blotting, a 1:19 solution of betamercaptoethanol (Sigma) to sample buffer (Bio-Rad) was prepared. Samples were diluted 1:1 with the betamercaptoethanol-sample buffer solution, boiled at 95° C for 5 minutes, and frozen overnight at -20° C.

Immuno-blotting

Bcl-2, caspase, 9, cyotochrome c

The volume of sample to load per well was determined using the raw mean concentration of protein obtained from the BCA protein assay. Approximately 30-60 µg of protein were loaded for each treatment time point. Proteins were run in triplicate on 12% Tris-HCl ready gels (Bio-Rad®) or hand cast gels in 1x running buffer at 85 and 100 volts. Proteins were then transferred onto nitrocellulose paper for an hour at 100 volts, and blocked for another hour in a 5% milk solution. Membranes were placed in primary antibody (1uL Ab:1000 uL TBST) (Cell Signaling) overnight at -4° C. The following day, membranes were washed three times for ten minutes each with Tris-Buffered Saline Tween®-20 (TBST), and secondary antibody (anti-rabbit; 1uL Ab: 1000 uL TBST) was applied for an hour at -4° C.

Membranes were washed again three times for ten minutes with TBST and chemoluminescence using Pico or Femto substrate was completed (Pierce®). Membranes were then developed at time intervals that produced the best visual results. After developing, membranes were kept in TBST at -4° C until Actin levels could be measured.

Actin

Membranes were placed in primary Actin antibody (1uL Ab:5000 uL TBST) (cell signaling) for 1 hour at -4° C, washed three times for ten minutes each with TBST, and secondary antibody (anti-mouse; 1uL Ab: 1000 uL TBST) was applied for an hour at -4° C. Membranes were washed again three times for ten minutes each with TBST and chemoluminescence using Pico substrate was completed (Pierce). Membranes were then developed at time intervals that produced the best visual results.

Annexin V assay

Cells were washed twice in PBS and resuspended in Binding Buffer (0.1 M HEPES, pH 7.4; 1.4 M NaCl; 25 mM $CaCl_2$). Samples of 100 µl were added to a culture tube with 5 µl of annexin-PE dye or 7-ADD. The cells were mixed and incubated without light at room temperature for 15 minutes. After which, 400 µl of 1X Binding Buffer was added to each sample and they were subjected to analysis by flow cytometry.

Example 7 – Treatment with CoQ10 Sensitizes Tumors to Chemotherapeutic Agents in vivo

Using the methods in Example 6, cells are tested to determine if the relative timing of treatment of cells with CoQ10 and chemotherapeutic agents has an effect on cell killing, e.g., by promotion of apoptosis, induction of tumor lysis, inhibition of cell proliferation.

Briefly, cells are cultured as in Example 6. Cells are treated with CoQ10 and chemotherapeutic agents, either alone or in combination, or with appropriate vehicle controls. For the cells treated with both CoQ10 and chemotherapeutic agents, the cells are contacted with the CoQ10 and chemotherapeutic agents in various sequences. Various concentrations of CoQ10 and chemotherapeutic agents are used. Various treatment times are also used. Exemplary conditions are provided in the table below.

	Treatment #1		Treatment #2	
	CoQ10	Chemotherapy	CoQ10	Chemotherapy
1	+	+	+	+
2	+	--	+	--
3	--	+	--	+
4	+	--	+	+
5	+	—	—	+

Appropriate vehicle controls for each CoQ10 and the chemotherapeutic agent are used.

After treatment with CoQ10 and chemotherapy as indicated, cells are harvested and assayed for viability and apoptosis using the methods provided above. Pretreatment with CoQ10 prior to treatment with chemotherapy is demonstrated to be more effective in cell killing than co-treatment with CoQ10 and chemotherapy or treatment with CoQ10 after chemotherapy. Specifically, pretreatment with CoQ10, followed by concurrent treatment with CoQ10 and chemotherapy, is effective in cell killing. Pretreatment with CoQ10, and discontinuation of CoQ10, followed by treatment with chemotherapy is also effective in cell killing. Without being bound by theory, it is suggested that CoQ10 "reeducates" the glycolysis addicted cancers to utilize mitochondrial respiratory chain as energy source by altering expression of key regulatory enzymes in the pentose phosphate shunt, glycolysis and oxidative phosphorylation. The metabolic switch effectuated by CoQ10 in cancer cells is associated with induction of a novel integrated signaling cross-talk involving TP53, Bcl-2/Bax and VEGF that results in the recapitulation of apoptotic pathways. The data suggest CoQ10 directly influences mitochondrial-centric pathways in sensitizing the cancer cells to the cyotoxic effects of chemotherapy agents while conferring protection to normal cells.

Example 8 – Treatment with CoQ10 Sensitizes Tumors to Chemotherapeutic Agents in vivo

In an *in vivo* tumor xenograft model, mice are implanted with tumors. For example, MIAPaCa-2 pancreatic cancer cells suspended in MATRIGEL are injected into NSG mice. Alternatively, other tumor cell lines, e.g., triple negative breast cancer, hepatic cancer, prostate cancer, melanoma, sarcoma, carcinoma cell lines, are used in the xenograft mouse model. Chemically induced tumors and other animal models of cancer can also be used. In all animals, the presence of tumors is confirmed prior to initiation of treatement.

Various sequential regimens and combinations of CoQ10 and chemotherapeutic agents are tested for the ability to reduce tumor burden and/or reduce tumor metastasis. For example, the exemplary regimens provided in the table in Example 7 are used. Each Treatment #1 and Treatment #2 as shown in the table in Example 7 can be one or more cycles of treatment with the agent. For example, in some animals, 2 or more cycles of CoQ10 are administered in Treatment 1 prior to one or more cycles of the chemotherapeutic agent in Treatment 2. In some animals, one cycle of CoQ10 is administered in Treatment 1 prior to administration of multiple cycles of chemotherapy in Treatment 2.

Tumor volumes are monitored using routine methods, e.g., calipers, imaging analysis. At the end of the study, tumors are excised and analyzed for using routine methods, e.g., for size (e.g., weight and volume), histological characteristics, grade, and vascularization. Treatment with one or more cycles of CoQ10 prior to treatment with a chemotherapeutic agents is demonstrated to be more effective than co-administration of CoQ10 with a chemotherapeutic agent or a chemotherapeutic agent alone.

Example 9 – Treatment with CoQ10 Enhances the Efficacy of Chemotherapeutic Agents in the Treatment of Liver Cancer Cells In Vitro

Hep3B liver cancer cells were cultured under standard conditions. Cells were treated with the chemotherapeutic agents irinotecan (SN38), cisplatin, 5-fluorouracil, or doxorubicin at the indicated concentrations either alone or in combination with CoQ10 (100 μM) for a predetermined time period.

Growth inhibition/promotion of cell death was assessed by live cell counting. Results are shown in Figures 9A-9C and 10. CoQ10 was demonstrated to increase the efficacy of all of the chemotherapeutic agents, increasing cell death and decreasing the number of live cells. These data suggest that the combination of these therapeutic agents is more effective in the treatment of liver cancer than the chemotherapeutic agent alone.

Example 10 -- Mitochondrial priming of apoptotic machinery in pancreatic cancer by C0Q10 to enhance efficacy of chemotherapy

Without being bound by mechanism, it is proposed that CoQ10 effectuates a metabolic switch from glycolysis towards enhanced mitochondrial oxidative phosphorylation resulting in the recapitulation of apoptosis in cancer. The effects of CoQ10 were investigated to determine if pretreatment with CoQ10 results in mitochondrial priming, thereby augmenting the cytotoxic effect of standard of care chemotherapeutic agents. MIAPaCa-2 human pancreatic cancer cells were either (a) pretreated with CoQ10 prior to treatment with gemcitabine or (b) co-treated with CoQ10 and gemcitabine. The effects of the treatments on cell viability were monitored and the results are shown in Figures 10-14.

CoQ10 treatment resulted in decreased proliferation of the MIAPaca-2 cells as compared to treatment with gemcitabine alone. Treatment of MIAPaca-2 cells with CoQ10 augmented the cytotoxic potential of gemcitabine in both the pre-treatment and the co-treatment regimen.

Example 11 -- Mitochondrial priming of apoptotic machinery in pancreatic cancer by CoQ10 to enhance efficacy of chemotherapy

Equal numbers of MIAPaCa-2 human pancreatic tumor cells (1×10^7) were suspended in MATRIGEL® and injected into mice. Tumors were allowed to develop for, on average, at least 3 weeks prior to initiation of treatment.

Mice having palpable tumors were randomized into 5 groups of 30 mice each as follows:

i. Group 1 - No treatment.

ii. Group 2 - Intraperitoneal dose of 4% Coenzyme Q10 intravenous formulation, 75 mg/kg/dose, 3 times daily (225 mg/kg/day) and intravenous single weekly dose of gemcitabine 150 mg/kg for 3 weeks with one week rest initiated on the same day.

iii. Group 3 – Intraperitoneal dose of 4% Coenzyme Q10 intravenous formulation, 75 mg/kg/dose, 3 times daily (225 mg/kg/day) and intravenous single weekly dose of

gemcitabine 150 mg/kg for 3 weeks with one week rest initiated one week after the initiation of CoQ10 treatment.

iv. Group 4 – Intraperitoneal dose of 4% Coenzyme Q10 intravenous formulation, 75 mg/kg/dose, 3 times daily (225 mg/kg/day) and intravenous single weekly dose of gemcitabine 150 mg/kg for 3 weeks with one week rest initiated two weeks after the initiation of CoQ10 treatment.

v. Group 5 – Intraperitoneal dose of 4% Coenzyme Q10 intravenous formulation, 75 mg/kg/dose, 3 times daily (225 mg/kg/day) and intravenous single weekly dose of gemcitabine 150 mg/kg for 3 weeks with one week rest initiated three weeks after the initiation of CoQ10 treatment.

The high frequency of administration of Coenzyme Q10 prevented intravenous administration of the Coenzyme Q10 due to vascular damage caused by high frequency intravenous injections. Animals were observed for survival and tumor growth by palpation.

Early time points suggest that pretreatment with intravenous CoQ10 followed by gemcitabine results in improved survival in the pancreatic cancer model compared to the co-treatment regimen (Figure 15A). Without being bound by mechanism, the data suggest that CoQ10 may be a viable mitochondrial priming agent to sensitize cancer cells to the cytotoxic effects of gemcitabine in pancreatic cancer. The data demonstrates that addition of CoQ10 increases the cytotoxic effect of gemcitabine in pancreatic cancer and increases the survival in a statistically significant manner as compared to untreated control at the latest time point (see below). In addition, treatment with CoQ10 followed by gemcitabine treatment is associated with improved survival (see, e.g., CoQ10 75mg/kg, co-initiated with chemotherapy vs. CoQ10 75mg/kg x 3 weeks then chemotherapy).

Condition 1	Condition 2	p-value
Control	CoQ10 75mg/kg, co-initiated with chemo	<0.00001
Control	CoQ10 75mg/kg x 1 week then chemo	<0.00001
Control	CoQ10 75mg/kg x 2 weeks then chemo	<0.00001
Control	CoQ10 75mg/kg x 3 weeks then chemo	<0.00001

Condition 1	Condition 2	p-value
CoQ10 75mg/kg, co-initiated with chemo	CoQ10 75mg/kg x 1 week then chemo	0.26503
CoQ10 75mg/kg, co-initiated with chemo	CoQ10 75mg/kg x 2 weeks then chemo	0.45960
CoQ10 75mg/kg, co-initiated with chemo	CoQ10 75mg/kg x 3 weeks then chemo	0.02724*
CoQ10 75mg/kg x 1 week then chemo	CoQ10 75mg/kg x 2 weeks then chemo	0.82980
CoQ10 75mg/kg x 1 week then chemo	CoQ10 75mg/kg x 3 weeks then chemo	0.20885
CoQ10 75mg/kg x 2 weeks then chemo	CoQ10 75mg/kg x 3 weeks then chemo	0.15515

Example 12 – In vitro CoQ10 monotherapy of various cancer cell types

To assess the efficacy of CoQ10 *in vitro*, various cancer cells (MIAPaCa-2 pancreatic carcinoma cells, SKOV-3 ovarian cancer cells, PC-3 prostate cancer cells, HT-29 colon cancer cells, MCF7 breast cancer cells, MDA-MB231 breast cancer cells, SKBR-3 breast cancer cells, A549 lung cancer cells, Hep3B liver cancer cells) were maintained in culture and exposed to 100 μM CoQ10 for 48-72 hours. Figure 16 shows the effect of CoQ10 treatment on the various cancer cells. The results demonstrate increased cell death in cancer cells following exposure to CoQ10.

Example 13 – Effect of CoQ10 on cell metabolism and caspase 3 activity

Basal oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured in MDA-MB213 and SKBR-3 breast cancer cells treated with 100 μM CoQ10 for 24 hours. Figure 17 shows the effect of CoQ10 treatment on OCR and ECAR in the breast cancer cells. The higher ratio of OCR to ECAR in breast cancer cells treated with CoQ10 indicates that CoQ10 increases oxidative phosphorylation (OXPHOS) and reduces glycolysis in breast cancer cells. Reactive oxygen species (ROS) production was also measured in MDA-MB213 and SKBR-3 breast cancer cells and non-tumorigenic control cells (MCF12A) treated with 100 μM CoQ10 for 24 hours. Mitochondria represent a significant source of ROS which are known to participate in activation of cell death pathways. Figure 17 shows that CoQ10 treatment increased ROS production in both breast cancer cells and control cells.

Caspase 3 activity was compared in MDA-MB213 and SKBR-3 breast cancer cells treated with 100 μM CoQ10 for 72-96 hours and control MDA-MB213 and SKBR-3 breast cancer cells that were untreated. Caspase 3 is an executioner caspase required for both intrinsic (mitochondrial) and extrinsic apoptosis pathways. Figure 18 shows that CoQ10 treatment increased caspase 3 activity in MDA-MB213 and SKBR-3 breast cancer cells.

Example 14 – In vitro assay of CoQ10 pre-treatment and co-treatment in various cancer cells

A549 lung cancer cells, PC3 prostate cancer cells, and SKOV3 ovarian cancer cells were pre-treated or co-treated with CoQ10 and the chemotherapeutic agents cisplatin, docetaxel, and cyclophosphamide, respectively. For pre-treatment, cells were treated for 6 hours with CoQ10 and then the designated chemotherapeutic agent was added to the medium. Thus CoQ10 treatment continued during treatment with the chemotherapeutic agent for the pre-treatment groups. The length of time of treatment with the chemotherapeutic agent varied by cell type. A549 cells were treated with cisplatin for 48 hours, PC3 cells were treated with docetaxel for 48 hours, and SKOV3 cells were treated with cyclophosphamide for 72 hours. Co-treated and pre-treated cells were treated with the chemotherapeutic agent for the same length of time. Figure 19 shows the effect of cotreatment or pretreatment with CoQ10 and the chemotherapeutic agent.

Example 15 – Evaluation of a triple-negative breast cancer (TNBC) animal model in response to CoQ10 alone or in combination with standard-of-care chemotherapy

Mice bearing triple-negative breast cancer (TNBC) xenografts were treated with the TAC regimen (5 mg/kg docetaxel, 1 mg/mg doxorubicin, and 35 mg/kg cyclophosphamide) with and without CoQ10. TAC was given every three weeks for six cycles. The mice were also treated with CoQ10 alone. CoQ10 alone or in combination with the TAC regimen significantly improved survival. See Fig. 21.

Example 16 – In vitro studies of breast cancer cells treated with CoQ10 and chemotherapeutic agents.

Human breast cancer cells of varying receptor status (SKBR3, MDA-MB231) were subjected to either (a) pretreatment with CoQ10 (6 h) followed by co-incubation with chemotherapeutic agents (5-fluorouracil, 5-FU; doxorubicin, Doxo; SN38, irinotecan active metabolite) for 48 h, or (b) co-treatment with CoQ10 and chemotherapeutic agents. Cancer cell responses were compared to non-tumorigenic mammary cells (MCF12A). The number of viable cells was assessed after 48 hours. Propidium iodide (PI) and CFSE Cell Tracer were used to measure cell death and proliferation, respectively, in the treated cells. Both CoQ10 alone or pretreatment and cotreatment strategies with CoQ10 plus standard of care resulted in significant decreases in viable breast cancer cells when compared to chemotherapeutic agents; however, minimal effects were observed in the non-tumorigenic MCF12A cells. See Figures 20, 23 and 24.

In addition CoQ10 in combination with chemotherapeutic agents amplified caspase 3 activation and apoptotic cell death, indicating CoQ10 enhances apoptotic signaling. See Figure 22. Taken together, these data demonstrate that CoQ10 is a novel agent that reengages the cellular metabolic and apoptotic machinery of cancer cells independent of the genetic make-up underlying malignancy. Furthermore, CoQ10 enhances the cytotoxicity of standard-of-care chemotherapeutic agents in breast cancer cells through regulation of mitochondrial metabolism and oxidative stress. These findings confirm that CoQ10 is a novel agent with multiple utilities (as a single agent or in combination) in breast cancer including TNBCs that otherwise have poor prognosis and limited therapeutic options.

To determine the effect of mitochondrial bioenergetics and reactive oxygen species production, MDA-MB231 and SkBr-3 breast cancer cells and MCF12A control cells were treated with 100 μM CoQ10 (BPM 31510) for 24 hours. Mitochondrial function was assessed using sequential injection of mitochondrial toxins (oligomycin, CCCP, and rotenone) in a Seahorse XF96 analyzer. DCF fluorescence was also measured as an indicator of reactive oxygen species production in cells treated in the same manner. Cellular bioenergetics profiling revealed that CoQ10 shifted cellular metabolism from glycolysis to mitochondrial metabolism, and this metabolic shift was associated with significant increases in reactive oxygen species (ROS). See Figure 25.

Example 17 – Effect of pretreatment, dose and route of administration of CoQ10 alone or in combination with gemcitabine in a xenograft mouse model of human pancreatic cancer

The three treatment regimens shown in Fig. 27 (Regimen 1, Regimen 2, and Regimen 3) were evaluated in a xenograft mouse model of human pancreatic cancer to determine the effect of CoQ10 alone or in combination with gemcitabine on animal survival. The effect of treatment with Regimen 1 is described in Example 1 above. CoQ10 administered in three different intravenous doses (50mg/kg or 75mg/kg body weight daily, Regimen 3) was associated with a dose dependent increase in survival and had an additive effect to gemcitabine. See Fig. 29. Continuous infusion of CoQ10 significantly improved survival rates compared to three doses (50mg/kg or 75mg/kg) of CoQ10, with best outcomes at 200mg/kg. See Fig. 30. Pretreatment for sixty days with CoQ10 alone followed by combination with gemcitabine was also associated with improved survival outcomes with either gemcitabine or CoQ10 alone. See Fig. 31. The data suggest that dose and route of administration of CoQ10 alone or in combination with standard of care chemotherapy agents influences and improves survival in an animal model of pancreatic cancer.

Example 18 – Effect CoQ10 pretreatment followed by gemcitabine treatment on survival of human pancreatic cancer cells in vitro

Human pancreatic cancer cells (PcCa2) were pretreated with 100 μM CoQ10 followed by treatment with gemcitabine (0.1,1 and 5 μM), or cotreated with CoQ10 and gemcitabine. Both pretreatment and cotreatment significantly decreased the number of viable cells ($*p < 0.05$) compared to gemcitabine alone. See Fig. 26.

Example 19 – In vitro assays of CoQ10 in combination with various chemotherapies in a range of cancer cells

Various cancer cells are treated with a combination of CoQ10 and different cancer therapeutic agents to determine the effect of the combined therapies on cell survival and cell metabolism. The cancer cells and corresponding controls cells are shown in the table below.

Breast	SKBR-3
	MDA-231
	BT549
	MCF-7
	MCF12A (control)
Pancreatic	PaCa2
	PL-45
	Panc1
Lung	A549
Colon	CaCo2
	HT29
Liver	Hep3B
	THLE-2 (control)
Cervical	Scc25
Prostate	PC-3
	LnCap
	PNT2 (control)
Ovarian	SKOV-3

The following cancer therapeutic agents are tested:

Drug	Mode of Action	Target
Herceptin	Antibody that binds HER2	Most Breast cancers/HER2 +
Irinotecan	Inhibits topoisomerase I	All dividing cells
Cisplatin	Inter and Crosslinks DNA	All dividing cells
5 fluoracil	Inhibits thymidin formation	All dividing cells
Docetaxel	Prevents depolimerization of microtubules	All dividing cells
4-Hydroxy-cyclophosphamide	Alkylating agent	All dividing cells
Gemcitabine	Nucleoside with fluorine	All dividing cells
Doxorubicine	TopoisoII inhibitor and induces oxidative stress. Inhibits mit complex 1	All dividing cells
Paclitaxel	Microtubule stabilizer	All dividing cells
Flutamide	Androgen (DHT) receptor blocker	Androgen receptor containing cells
Estramustine	Alkylating agent derivative of estrogen	Estrogen induced cells
Etoposide	Topoisomerase II inhibitor	All dividing cells
Oxaliplatin	Bidentate platinum plate that crosslinks DNA	All dividing cells
Goserelin	GnRH and LHRH agonist	
Tamoxifen	Estrogen Receptor antagonist	ER containing cells

The following assays are used to measure cell survival and metabolism:

Assay	Method	Instrument
Cell Counts	Trypan blue	Nexcelon Cellometer
Proliferation	Propidium Iodide in Fixed cells	Flow Cytometer
Cell death	Propidium iodide	Flow Cytometer
Apoptosis (Caspase 3)	Caspase 3 dye	Fluorescent microscopy
ROS	CM-DCFDA dye	Flow Cytometer
Oxygen consumption	Mitochondria stress	Seahorse Xtracellular analyzer
Extracellular acidification	Glycolysis pathway	Seahorse Xtracellular analyzer

Cells are cultured in the following growth media:

	Medium	Source	Serum	Antibiotics
PaCa2	DMEM no sodium pyruvate	Lonza	5% FBS; 2.5% HS	1x Pen/Strep/AmphoB
PC-3	DMEM no sodium pyruvate	Lonza	5% FBS	1x Pen/Strep/AmphoB
MDA231	RPMI 1640	Lonza	5% FBS	Gentamycin (GA-1000)
SKBR-3	McCoy's 5A	Lonza	5% FBS	1x Pen/Strep/AmphoB
Hep3B	EMEM	Lonza	5% FBS	1x Pen/Strep/AmphoB
A549	KF-12	Invitrogen	5% FBS	1x Pen/Strep/AmphoB
HT-29	McCoy's 5A	Lonza	5% FBS	1x Pen/Strep/AmphoB
SKOV-3	McCoy's 5A	Lonza	5% FBS	1x Pen/Strep/AmphoB
MCF-7	MEM + NEEA	Invitrogen	5% FBS	1x Pen/Strep/AmphoB
HUMEC	HUMEC media	Invitrogen	-	1x Pen/Strep/AmphoB
PNT2	RPMI 1640	Lonza	10% FBS	1x Pen/Strep/AmphoB
Panc1	DMEM	Lonza	5%FBS	1x Pen/Strep/AmphoB
MCF-12A	HAM/F-12	Lonza	5% Horse Serum	1x Pen/Strep/AmphoB
BT-549	RPMI 1640	Lonza	10%FBS	1x Pen/Strep/AmphoB

Supplements

	Supplement		
Hep3B	1x Glutamax		
MCF-7	1x Glutamax		
MCF-12A	20ng/ml hEGF	10ug/ml insulin	500ng/ml hydrocortisone
BT-549	0.5ug/ml insulin		

Method for plating cells

For cell counts, proliferation, and measurement of reactive oxygen species (ROS), the amount of cells and method for plating and treating are the same. Cells are seeded at the same time that the treatment is added. Cells are seeded in a 24-well plate as follows:

Sample	Cell/well	Sample	Cell/well	Sample	Cell/well
SKBR-3	60k	PC3	60k	HT-29	100k
MDA231	60k	PaCa2	50K	BT549	30K
MCF-7	50K	Panc-1	50K	Hep3B	60K
MCF12A	60k	A-549	100k	SKOV-3	60k

For caspase 3 assays to measure apoptosis, cells are plated in glass 12-well plates in which cells are in the ratio of 110k/well and allowed to attached from 5h to 18h, then treatment is added. To measure oxygen consumption and extracellular acidification the cells are plated in the Seahorse XF-96 plate. Examples of cell numbers for various cell lines are shown in the table below:

Sample	Cell/well
SKBR-3	10k
MDA231	10k
MCF12A	30k

Sources, solvents and stock concentrations for the chemotherapeutic agents are shown in the table below:

Stock preparation	Cat #	Solvent	vial	Stock []
SN38	Sigma H0165-10mg	255ul DMSO	10mg	100mM
Cisplatin***	Enzo ALX-400-040-M050	33ml of 0.9% Saline	50mg	5mM
Doxo	Sigma D-1515	1ml DMSO	10mg	10mg/ml
5FU	Amresco 0597-5G	1ml DMSO	weigh 13mg	100mM
Herceptin	Thermo Fisher	20ml provided H2O	400mg	20mg/ml
Cyclophosphamide	Santa Cruz sc-219703	500ul H2O + thiosulfate	25mg	4.4mM
Gemcitabine	Sigma G6423-10mg	3.3ml H2O	10mg	10mM
Paclitaxel	Sigma T7402-1mg	118ul DMSO	1mg	10mM
Docetaxel	Sigma 01885-5mg-F	618ul DMSO	5mg	10mM

Stock preparation	Cat #	Solvent	vial	Stock []
Tamoxifen	Sigma H7904	1290ul EtOH	5mg	10mM
Avastin	Myoderm Medical supply			
Estramustine	Sigma#SLBD7083V	1ml DMSO	5.6mg	100mM
Etoposide	Sigma lot# BCBH0586V	425ul DMSO	25mg	100mM
Oxaliplatin	Sigma lot# SLBD0630V	1.25ml DMSO	5mg	100mM

For each chemotherapy, concentration ranges for testing may be derived from concentration ranges known in the art. Dose response curves are generated for each chemotherapeutic agent as shown in the table below:

Drugs	Dose response curve concentrations				
SN38	0.1nM	1nM	10nM	100nM	1000nM
Cisplatin	1uM	6uM	12uM	25uM	50uM
Doxo	1ng/ml	10ng/ml	100ng/ml	1ug/ml	10ug/ml
5FU	0.1uM	1uM	10uM	100uM	1000uM
	1uM	5uM	10uM	25uM	50uM
Herceptin	10ug/ml	25ug/ml	50ug/ml	100ug/ml	250ug/ml
	1ug/ml	5ug/ml	10ug/ml	25ug/ml	50ug/ml
Cyclophosphamide	0.05uM	0.25uM	1uM	4uM	12.5uM
Gemcitabine	0.1uM	1uM	10uM	100uM	1000uM
Paclitaxel	5nM	10nM	25nM	50nM	100nM
Docetaxel	0.1nM	1nM	10nM	100nM	1000nM
Tamoxifen	0.3uM	0.62uM	1.25uM	2.5uM	5uM
Flutamide	0.01uM	0.1uM	1uM	10uM	100uM
Estramustine	0.01uM	0.1uM	1uM	10uM	100uM
Etoposide	0.01uM	0.1uM	1uM	10uM	100uM
Oxaliplatin	0.1uM	1uM	10uM	100uM	1000uM

For the cotreatment experiments, the following doses are chosen for each cell line:

	Combo Concentrations									
Drugs	SKBR-3	Hep3B	MDA231	Paca2	A549	PC-3	THL E-2	SKOV-3	HT-29	MCF-7
SN38	1, 10, 100 nM	10, 100 nM	1, 10, 25 nM			25, 100, 250 nM	1, 10 nM		0.5, 1, 10 nM	1, 5, 10 nM
Cisplatin	1, 5, 10 μM	1, 5, 10 μM			0.1, 1, 10 μM			0.5, 2.5, 5 μM		1.5, 3, 6 μM
Doxorubicine	10, 50, 100 ng/ml	10, 25, 50 ng/ml	0.1, 1, 10 ng/ml	10, 50, 100 μg/ml						2, 4, 8 ng/ml
5-fluoro-uracil	0.1, 1, 10 μM	0.1, 1, 10 μM	0.1, 1, 10 μM						0.1, 1, 10 nM	
Herceptin	10, 25, 50 μg/ml									
Cyclo-phosphamide	0.5, 1, 2 μM		1, 2, 4 μM, 0.5, 1, 2 μM					0.25, 4, 8 μM		0.5, 1, 2 μM
Gemcitabine				0.1, 1, 5 μM	0.01, 0.1, 1 μM	25, 100, 200 nM				
Paclitaxel			10, 50, 100 nM, 10, 25, 50 nM		5, 10, 25 nM	25, 100, 200 nM				
Docetaxel	0.01, 0.1, 1 nM				0.1, 1, 10 nM	1, 10, 100 μM				
Tamoxifen										2, 4, 6 μM
Flutamide						0.01, 0.1, 1 μM				
Estramustine						1, 10 100 μM				
Etoposide						0.01, 0.1, 1 μM				
Oxaliplatin				1, 10, 50 μM				10, 50, 100 μM		

Treatment time is optimized according to the endpoint assay, e.g: for metabolic assays shorter incubation times are used; for cell counts, longer incubation times are used. The incubations that involve proliferation and cell counts are chosen based on the cell doubling

time, i.e. how fast the cells grow. The table below provides incubation times for various cell types and assays.

	Cell Counts, ROS, Cell Proliferation (Propidium Iodide)	OCR, ECAR	Caspase 3
SKBR-3	48h	24h	96h
MDA-231	48h	24h	96h
BT549	48h	24h	96h
MCF-7	72h	24h	96h
MCF12A	48h	24h	96h
PaCa2	72h	24h	96h
PL-45	48h	24h	96h
Panc1	48h	24h	96h
A549	48h	24h	96h
CaCo2	48h	24h	96h
HT29	48h	24h	96h
Hep3B	48h	24h	96h
THLE-2	48h	24h	96h
Scc25	48h	24h	96h
PC-3	48h	24h	96h
LnCap	48h	24h	96h
PNT2	48h	24h	96h
SKOV-3	72h	24h	96h

Example 20 – Effect of pretreatment with CoQ10 followed by treatment with chemotherapeutic agents on various tumors in vivo

A concentrated aqueous nanodispersion of CoQ10 in a 4:3:1.5 ratio of CoQ10 (4%w/v): DMPC (3% w/v): Poloxamer 188 (1.5% w/v) in water is used; the nanodispersion concentrate contains 40 mg/mL of CoQ10 at 30-50 nm particle size. A single vehicle control group receives a sterile solution of 3% w/v DMPC and 1.5% w/v Poloxamer 188 dosed at the highest tolerated dose (1000mg API equivalent) A single negative control group receives buffered sterile physiological saline. The CoQ10 nanodispersion is prepared within 2 weeks of the start of the study and stored at 4-25 C throughout the study. Test samples are assayed for CoQ10 activity and for particle size distribution at the beginning and end of the study.

The excipients used in the nanodispersion, DMPC and Poloxamer 188, are used for the formulation of an aqueous nanodispersion of CoQ10. The concentrated nanodispersion is diluted at point of use with sterile buffered physiologic saline (PBS). The vehicle contains PBS as the diluents and PBS is used undiluted as the saline control. Immunocompromised mice from Jackson Laboratories and Harlan Laboratories are used. Immunocompromised mice lack the innate and adaptative immune systems. This provides a biological environment suitable for the growth of human tumors *in vivo*. These animals are particularly suitable for the grafting of different human cancers.

4-week old mice arrive at the facilities and 48 hours later experiments are performed. Mice are housed in litters of 5 per cage under a single identifier number. Animals are weighed on arrival and throughout the entire experiment to have another parameter in response to the different formulae. The diet employed is the formulation Lab Diet ® 5001 Rodent Diet, manufactured by PMI Nutrition International, LLC. This manufacturer is an ISO 9001:2000-certified facility. The diet is purchased every 6 months, and lot numbers can be traced to each room and will be recorded by the technician. The food administered to the NSG mice must be autoclaved before being placed in animal cages. Water is fed *ad libitum* to all mice. Water is obtained from the Florida Water Department and is dispensed in clean bottles to each cage by the animal technicians. Water is checked daily for the presence of debris and replaced with clean water. Water administered to the NSG mice must be sterile prior to administration to animals. Animals are sacrificed by CO_2 inhalation by 20 days of age. To ensure death, cervical dislocation is performed for each animal and diaphragms are punctured.

Sterile CoQ10 formula and the suitable sterile control is administered intravenously. CoQ10 doses are administered based on ongoing results. Prior experiments exhibited no signs of toxicity when CoQ10 was administered three times per week at up to 50mg/kg and the MTD in rats has been established at 250mg/kg given three times per week for 4 weeks. The effect of CoQ10 is compared with other chemotherapy regimens specific for each cancer line. Another arm of the study evaluates synergistic effects between CoQ10 and other chemotherapeutic agents.

The following cancer cells are evaluated:

		Cell Designation
Breast	Triple negative	MDA-MB-231
Lung	Small cell	H522
	Non-small cell	A549
Ovarian		SK-OV-3
Liver		HepG2
Prostate		LnCap
Acute Leukemia		Kg1, K562
Colon		HT29, CaCo
Glioblastoma		LN229

All cells are cultured in a 5% CO_2 incubator with 100% humidity at 37°C. The base medium varies according to each cell, To make the complete growth medium, the following components are added to the base medium: fetal bovine serum to a final concentration of 10%. Prior to the injection of cells into the animals, they are grown to 50% confluency, and thereafter attached or centrifuged as per cell protocol. The following organs are harvested: kidney, pancreas, lungs, heart and liver. Organs are weighed and recorded. A pathological report of routine stain Wright's or Hematoxylin/Eosin stains is performed._CoQ10 formulations and chemotherapeutic agents are administered intraperitoneally or intravenously.

The presence of lack of lactation, lethargy and decrease in body weight are observed. Such signs of moribundity are the basis of early scarification and an autopsy is performed in the animal (i.e, organ weights, pathology slides).

Under sterile conditions, animals are injected as outlined above. Litters are randomized according to the cage card number identifier and the weight of each animal is recorded. Mice are then returned to their cages. Thereafter, mice are injected intraperitoneally daily until they are sacrificed due to tumor burden or their survival.

The following chemotherapy regimens are tested on various cancer cells as indicated:

Breast Cancer (non-metastatic)

Combination Chemotherapy

Doxorubicin/Cyclophosphamide
Cyclophosphamide/Doxorubicin/5-fluororacil

Lung Cancer (small cell)

Combination Chemotherapy

Cyclophosphamide/Doxorubicin/Vincristine
Cyclophosphamide/Doxorubicin/Etoposide

Lung Cancer (non-small cell)

Combination Chemotherapy

Cisplatin/Paclitaxel
Docetaxel/Cisplatin
Gemcitabine/Cisplatin

Ovarian Cancer

Combination Chemotherapy

Cisplatin/Cyclophosphamide
Cisplatin/Paclitaxel

Hepatocellular Cancer

Single agents

Doxorubicin
Cisplatin
Capecitabine

Prostate Cancer

Combination Chemotherapy

Paclitaxel/Estramustine
Docetaxel/Estramusine

Acute Leukemia

Combination Chemotherapy

Cytarabine/Daunorubicin
Cytarabine/Idarubicin
Cytarabine/Doxorubicin

Colon Cancer

Single agent

Capecitabine

Glioblastoma

Single agent

Bevacitumab
Valganciclovir

Example 21 – In vitro assays of various cancer cell lines treated with CoQ10 and chemotherapeutic agents

Various cancer cell lines were cotreated or pretreated with CoQ10 and various chemotherapeutic agents as described in Example 14 above. Cell/chemotherapeutic agent combinations that significantly reduced viable cell numbers are shown in Table 2 below.

Table 2. Summary of *in vitro* studies with various cancer cell lines treated with CoQ10 and various chemotherapeutic agents. Co: cotreatment; Pre: pretreatment.

	PC3	SkBr-3	MB231	MCF-7	MiaPaCa2	BT549	Hep3B	A549	SKOV3
	Prostate	Breast	TNBC	Breast	Pancreatic	Breast	Liver	Lung	Ovarian
SN38		Co					Co and Pre		
Doxo		Pre		Pre	Pre	Pre	Co		
5-FU		Co	Co				Co		
Cisplatin								Pre	
4-HCP		Co	Co	Co					Co
Paclitaxel								Co	
Tamoxifen				Pre					
Gemcitabine								Pre	

	PC3	SkBr-3	MB231	MCF-7	MiaPaCa2	BT549	Hep3B	A549	SKOV3
	Prostate	Breast	TNBC	Breast	Pancreatic	Breast	Liver	Lung	Ovarian
Flutamide	Pre								
Goserelin	Pre								

Table 3. Standard dosages of chemotherapeutic agents. Standard dosages were obtained from the manufacturer's product insert for the chemotherapeutic agent.

Chemotherapeutic Agent	Recommended Dosages
Doxorubicin	Administer DOXIL at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion related reactions occur, increase rate of infusion to complete administration over 1 hour. Do not administer as bolus injection or undiluted solution. **Ovarian cancer**: 50 mg/m^2 IV every 4 weeks for 4 courses minimum **AIDS-related Kaposi's Sarcoma**: 20 mg/m^2 IV every 3 weeks **Multiple Myeloma**: 30 mg/m^2 IV on day 4 following bortezomib which is administered at 1.3 mg/m^2 bolus on days 1, 4, 8 and 11, every 3 weeks
Cyclophosphamide	**Treatment of Malignant Diseases – Adults and Children:** When used as the only oncolytic drug therapy, the initial course of CYTOXAN for patients with no hematologic deficiency usually consists of 40 to 50 mg/kg given intravenously in divided doses over a period of 2 to 5 days. Other intravenous regimens include 10 to 15 mg/kg given every 7 to 10 days or 3 to 5 mg/kg twice weekly. Oral CYTOXAN dosing is usually in the range of 1 to 5 mg/kg/day for both initial and maintenance dosing. When CYTOXAN is included in combined cytotoxic regimens, it may be necessary to reduce the dose of CYTOXAN as well as that of the other drugs. **Treatment of Nonmalignant Diseases – Biopsy Proven "Minimal Change" Nephrotic Syndrome In Children:** An oral dose of 2.5 to 3 mg/kg daily for a period of 60 to 90 days is recommended. In males, the incidence of oligospermia and azoospermia increases if the duration of CYTOXAN treatment exceeds 60 days. Treatment beyond 90 days increases the probability of sterility. Adrenocorticosteroid therapy may be tapered and discontinued during the course of CYTOXAN therapy.
5-fluorouracil	Fluorouracil Injection should be administered only intravenously. **Dosage**: 12 mg/kg are given intravenously once daily for 4 successive days. The daily dose should not exceed 800 mg. If no toxicity is observed, 6 mg/kg are given on the 6th, 8th, 10th and 12th days unless toxicity occurs.

Chemotherapeutic Agent	Recommended Dosages
	No therapy is given on the 5th, 7th, 9th or 11th days. Therapy is to be discontinued at the end of the 12th day, even if no toxicity has become apparent. Poor risk patients or those who are not in an adequate nutritional state should receive 6 mg/kg/day for 3 days. If no toxicity is observed, 3 mg/kg may be given on the 5th , 7th and 9th days unless toxicity occurs. No therapy is given on the 4th , 6th or 8th days. The daily dose should not exceed 400 mg. **Maintenance Therapy**: In instances where toxicity has not been a problem, it is recommended that therapy be continued using either of the following schedules: 1. Repeat dosage of first course every 30 days after the last day of the previous course of treatment. 2. When toxic signs resulting from the initial course of therapy have subsided, administer a maintenance dosage of 10 to 15 mg/kg/week as a single dose. Do not exceed 1 gm per week.
Vincristine	The drug is administered intravenously at weekly intervals. The usual dose of vincristine sulfate for **pediatric patients** is 2 mg/m^2. For pediatric patients weighing 10 kg or less, the starting dose should be 0.05 mg/kg, administered once a week. The usual dose of vincristine sulfate for **adults** is 1.4 mg/m^2. A 50% reduction in the dose of vincristine sulfate is recommended for patients having a direct serum bilirubin value above 3 mg/100 mL.
Etoposide	In **testicular cancer, t**he usual dose of Etoposide Injection in combination with other approved chemotherapeutic agents ranges from 50 to 100 mg/m^2/day, on days 1 through 5 to 100 mg/m^2/day, on days 1, 3, and 5. In **small cell lung cancer**, the Etoposide Injection dose in combination with other approved chemotherapeutic drugs ranges from 35 mg/m^2/day for 4 days to 50 mg/m^2/day for 5 days. Chemotherapy courses are repeated at 3 to 4 week intervals after adequate recovery from any toxicity.
Cisplatin	Cisplatin is administered by slow intravenous infusion. **Metastatic Testicular Tumors:** The usual cisplatin (cisplatin injection) dose for the treatment of testicular cancer in combination with other approved chemotherapeutic agents is 20 mg/m^2 IV daily for 5 days per cycle. **Metastatic Ovarian Tumors:** The usual cisplatin (cisplatin injection) dose for the treatment of metastatic ovarian tumors in combination with cyclophosphamide is 75 to 100 mg/m^2 IV per cycle once every 4 weeks (DAY 1).

Chemotherapeutic Agent	Recommended Dosages
	The dose of cyclophosphamide when used in combination with cisplatin (cisplatin injection)is 600 mg/m^2 IV once every 4 weeks (DAY 1). In combination therapy, cisplatin (cisplatin injection) and cyclophosphamide are administered sequentially. As a single agent, cisplatin (cisplatin injection) should be administered at a dose of 100 mg/m^2 IV per cycle once every 4 weeks. **Advanced Bladder Cancer:** cisplatin (cisplatin injection) should be administered as a single agent at a dose of 50 to 70 mg/m^2 IV per cycle once every 3 to 4 weeks depending on the extent of prior exposure to radiation therapy and/or prior chemotherapy. For heavily pretreated patients an initial dose of 50 mg/m^2 per cycle repeated every 4 weeks is recommended.
Paclitaxel	All patients should be premedicated prior to Paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before Paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to Paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before Paclitaxel. **Ovarian Carcinoma**: 1) For previously untreated patients with carcinoma of the ovary, one of the following recommended regimens may be given every 3 weeks. Paclitaxel administered intravenously over 3 hours at a dose of 175 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2; or Paclitaxel administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2. 2) In patients previously treated with chemotherapy for carcinoma of the ovary, Paclitaxel has been used at several doses and schedules; however, the optimal regimen is not yet clear. The recommended regimen is Paclitaxel 135 mg/m^2 or 175 mg/m^2 administered intravenously over 3 hours every 3 weeks. **Breast Carcinoma**: 1) For the adjuvant treatment of node-positive breast cancer, the recommended regimen is Paclitaxel, at a dose of 175 mg/m^2 intravenously over 3 hours every 3 weeks for 4 courses administered sequentially to doxorubicin-containing combination chemotherapy. 2) After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, Paclitaxel at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks has been shown to be effective. **Non-small cell lung carcinoma**: The recommended regimen, given every 3 weeks, is Paclitaxel administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin, 75 mg/m^2.

<table>
<tr><th>Chemotherapeutic Agent</th><th>Recommended Dosages</th></tr>
<tr><td></td><td>
AIDS-related Kaposi's sarcoma:
Paclitaxeladministered at a dose of 135 mg/m^2 given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m^2 given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45–50 mg/m^2/week).

Advanced HIV disease:
1) Reduce the dose of dexamethasone as 1 of the 3 premedication drugs to 10 mg PO (instead of 20 mg PO);

2) Initiate or repeat treatment with Paclitaxel only if the neutrophil count is at least 1000 cells/mm^3;

3) Reduce the dose of subsequent courses of Paclitaxel by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer); and

4) Initiate concomitant hematopoietic growth factor (G-CSF) as clinically indicated.

Hepatic Impairment:
Recommendations for dosage adjustment for the first course of therapy are shown in the table below for both 3- and 24-hour infusions. Further dose reduction in subsequent courses should be based on individual tolerance.

RECOMMENDATIONS FOR DOSING IN PATIENTS WITH HEPATIC IMPAIRMENT BASED ON CLINICAL TRIAL DATA[a]
<table>
<tr><th colspan="3">Degree of Hepatic Impairment</th><th rowspan="2">Recommended TAXOL Dose[c]</th></tr>
<tr><th>Transaminase Levels</th><th></th><th>Bilirubin Levels[b]</th></tr>
<tr><td colspan="4">24-hour infusion</td></tr>
<tr><td><2 × ULN</td><td>and</td><td>≤1.5 mg/dL</td><td>135 mg/m^2</td></tr>
<tr><td>2 to <10 × ULN</td><td>and</td><td>≤1.5 mg/dL</td><td>100 mg/m^2</td></tr>
<tr><td><10 × ULN</td><td>and</td><td>1.6–7.5 mg/dL</td><td>50 mg/m^2</td></tr>
<tr><td>≥10 × ULN</td><td>or</td><td>>7.5 mg/dL</td><td>Not recommended</td></tr>
<tr><td colspan="4">3-hour infusion</td></tr>
<tr><td><10 × ULN</td><td>and</td><td>≤1.25 × ULN</td><td>175 mg/m^2</td></tr>
<tr><td><10 × ULN</td><td>and</td><td>1.26–2.0 × ULN</td><td>135 mg/m^2</td></tr>
<tr><td><10 × ULN</td><td>and</td><td>2.01–5.0 × ULN</td><td>90 mg/m^2</td></tr>
<tr><td>≥10 × ULN</td><td>or</td><td>>5.0 × ULN</td><td>Not recommended</td></tr>
</table>
[a] These recommendations are based on dosages for patients without hepatic impairment of 135 mg/m^2 over 24 hours or 175 mg/m^2 over 3 hours; data are not available to make dose adjustment recommendations for other regimens (eg, for AIDS-related Kaposi's sarcoma).
[b] Differences in criteria for bilirubin levels between the 3- and 24-hour infusion are due to differences in clinical trial design.
[c] Dosage recommendations are for the first course of therapy; further dose reduction in subsequent courses should be based on individual tolerance.
</td></tr>
<tr><td>Docetaxel</td><td>
Administer in a facility equipped to manage possible complications (e.g., anaphylaxis). Administer intravenously (IV) over 1 hr every 3 weeks. PVC equipment is not recommended. Use only a 21 gauge needle to withdraw TAXOTERE from the vial.

BC locally advanced or metastatic: 60 mg/m^2 to 100 mg/m^2 single agent

BC adjuvant: 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles
</td></tr>
</table>

Chemotherapeutic Agent	Recommended Dosages
	NSCLC: after platinum therapy failure: 75 mg/m^2 single agent **NSCLC**: chemotherapy-naive: 75 mg/m^2 followed by cisplatin 75 mg/m^2 **HRPC**: 75 mg/m^2 with 5 mg prednisone twice a day continuously **GC**: 75 mg/m^2 followed by cisplatin 75 mg/m^2 (both on day 1 only) followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1–5), starting at end of cisplatin infusion **SCCHN**: 75 mg/m^2 followed by cisplatin 75 mg/m^2 IV (day 1), followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1–5), starting at end of cisplatin infusion; for 4 cycles **SCCHN**: 75 mg/m^2 followed by cisplatin 100 mg/m^2 IV (day 1), followed by fluorouracil 1000 mg/m^2 per day as a 24-hr IV (days 1–4); for 3 cycles For all patients: premedicate with oral corticosteroids, and adjust dose as needed
Gemcitabine	Gemzar is for intravenous use only. **Ovarian Cancer**: 1000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. **Breast Cancer**: 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. **Non-Small Cell Lung Cancer**: 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. **Pancreatic Cancer**: 1000 mg/m^2 over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle.
Capecitabine	Take XELODA with water within 30 min after a meal. **Monotherapy**: 1250 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycles. Adjuvant treatment **is recommended for a total of 6 months (8 cycles)** **In combination with docetaxel, the recommended dose of XELODA is 1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period, combined with docetaxel at 75 mg/m^2 as a 1-hour IV infusion every 3 weeks.** XELODA dosage may need to be individualized to optimize patient management. Reduce the dose of XELODA by 25% in patients with moderate renal

Chemotherapeutic Agent	Recommended Dosages
	impairment.
Estramustine	The recommended daily dose is 14 mg per kg of body weight (ie, one 140 mg capsule for each 10 kg or 22 lb of body weight), given in 3 or 4 divided doses. Most patients in studies in the United States have been treated at a dosage range of 10 to 16 mg per kg per day. Patients should be instructed to take EMCYT Capsules at least 1 hour before or 2 hours after meals. EMCYT should be swallowed with water. Milk, milk products, and calcium-rich foods or drugs (such as calcium-containing antacids) must not be taken simultaneously with EMCYT. Patients should be treated for 30 to 90 days before the physician determines the possible benefits of continued therapy. Therapy should be continued as long as the favorable response lasts. Some patients have been maintained on therapy for more than 3 years at doses ranging from 10 to 16 mg per kg of body weight per day.
Cytarabine	Cytarabine is not active orally. The schedule and method of administration varies with the program of therapy to be used. Cytarabine may be given by intravenous infusion or injection, subcutaneously, or intrathecally. In the induction therapy of **acute non-lymphocytic leukemia**, the usual cytarabine dose in combination with other anticancer drugs is 100 mg/m^2/day by continuous IV infusion (days 1 to 7) or 100 mg/m^2 IV every 12 hours (days 1 to 7). Intrathecal Use In **Meningeal Leukemia**: Cytarabine has been used intrathecally in acute leukemia in doses ranging from 5 to 75 mg/m2 of body surface area. The frequency of administration varied from once a day for 4 days to once every 4 days.
Daunorubicin	**Adult Acute Nonlymphocytic Leukemia**: In Combination: For patients under age 60, daunorubicin hydrochloride 45 mg/m^2/day IV on days 1, 2, and 3 of the first course and on days 1, 2 of subsequent courses AND cytosine arabinoside 100 mg/m^2/day IV infusion daily for 7 days for the first course and for 5 days for subsequent courses. For patients 60 years of age and above, daunorubicin hydrochloride 30 mg/m^2/day IV on days 1, 2, and 3 of the first course and on days 1, 2 of subsequent courses AND cytosine arabinoside 100 mg/m^2/day IV infusion daily for 7 days for the first course and for 5 days for subsequent courses. **Pediatric Acute Lymphocytic Leukemia:** In Combination: Daunorubicin hydrochloride 25 mg/m^2 IV on day 1 every week, vincristine 1.5 mg/m^2 IV on day 1 every week, prednisone 40 mg/m^2 PO daily. In children less than 2 years of age or below 0.5 m^2 body surface area, it has been recommended that the daunorubicin hydrochloride dosage calculation should be based on weight (1 mg/kg) instead of body surface area.

Chemotherapeutic Agent	Recommended Dosages
	Adult Acute Lymphocytic Leukemia: In Combination: Daunorubicin hydrochloride 45 mg/m^2/day IV on days 1, 2, and 3 AND vincristine 2 mg IV on days 1, 8, and 15; prednisone 40 mg/m^2/day PO on days 1 through 22, then tapered between days 22 to 29; L-asparaginase 500 IU/kg/day x 10 days IV on days 22 through 32.
Idarubicin	For induction therapy in adult patients with **AML** the following dose schedule is recommended: Idarubicin hydrochloride injection 12 mg/m^2 daily for 3 days by slow (10 to 15 min) intravenous injection in combination with cytarabine. The cytarabine may be given as 100 mg/m^2 daily by continuous infusion for 7 days or as cytarabine 25 mg/m^2 intravenous bolus followed by cytarabine 200 mg/m^2 daily for 5 days continuous infusion. In patients with unequivocal evidence of leukemia after the first induction course, a second course may be administered. Administration of the second course should be delayed in patients who experience severe mucositis, until recovery from this toxicity has occurred, and a dose reduction of 25% is recommended. In patients with hepatic and/or renal impairment, a dose reduction of idarubicin hydrochloride injection should be considered. Idarubicin hydrochloride injection should not be administered if the bilirubin level exceeds 5 mg%.
Bevacitumab	Do not administer as an IV push or bolus. Do not initiate Avastin for 28 days following major surgery and until surgical wound is fully healed. **Metastatic colorectal cancer** • 5 mg/kg IV every 2 weeks with bolus-IFL • 10 mg/kg IV every 2 weeks with FOLFOX4 • 5 mg/kg IV every 2 weeks or 7.5 mg/kg IV every 3 weeks with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy after progression on a first-line Avastin containing regimen **Non−squamous non−small cell lung cancer** • 15 mg/kg IV every 3 weeks with carboplatin/paclitaxel **Glioblastoma** • 10 mg/kg IV every 2 weeks **Metastatic renal cell carcinoma** (mRCC) • 10 mg/kg IV every 2 weeks with interferon alfa

Chemotherapeutic Agent	Recommended Dosages
Valganciclovir	**Adult Patients With Normal Renal Function** **Treatment of CMV Retinitis** Induction: The recommended dose is 900 mg (two 450 mg tablets) twice a day for 21 days. Maintenance: Following induction treatment, or in adult patients with inactive CMV retinitis, the recommended dose is 900 mg (two 450 mg tablets) once a day. **Prevention of CMV Disease** For adult patients who have received a heart or kidney-pancreas transplant, the recommended dose is 900 mg (two 450 mg tablets) once a day starting within 10 days of transplantation until 100 days posttransplantation. For adult patients who have received a kidney transplant, the recommended dose is 900 mg (two 450 mg tablets) once a day starting within 10 days of transplantation until 200 days post-transplantation. **Pediatric Patients** **Prevention of CMV Disease** For pediatric patients 4 months to 16 years of age who have received a kidney or heart transplant, the recommended once daily dose of Valcyte starting within 10 days of transplantation until 100 days post-transplantation is based on body surface area (BSA) and creatinine clearance (CrCl) derived from a modified Schwartz formula, and is calculated using the equation below: Pediatric Dose (mg) = 7 x BSA x CrCl (calculated using a modified Schwartz formula). If the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73m², then a maximum value of 150 mL/min/1.73m² should be used in the equation. Mosteller BSA (m²) = √Height (cm) xWeight (kg)/ 3600 Schwartz Creatinine Clearance mL/min/1.73m²) = k x Height (cm)/ Serum Creatinine (mg/ dL) where k = 0.45 for patients aged 4 months to < 1 year, 0.45 for patients aged 1 to < 2 years (note k value is 0.45 instead of the typical value of 0.55), 0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and 0.7 for boys aged 13 to 16 years. All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. Valcyte for oral solution is the preferred formulation since it provides the ability to administer a dose calculated according to the formula above; however, Valcyte tablets may be used if the calculated doses are within 10% of available tablet strength (450 mg). For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken

Chemotherapeutic Agent	Recommended Dosages
Methotrexate	**Neoplastic Diseases:** Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate injection may be given by the intramuscular, intravenous or intra-arterial route. **Choriocarcinoma and similar trophoblastic diseases**: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five-day course . Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful. **Leukemia**: Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other anti-leukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 33 mg/m2 in combination with 60 mg/m^2 of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows : Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m^2. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen. **Lymphomas**: In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases . Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0 .625 to 2.5 mg/kg daily. **Mycosis fungoides (cutaneous T Cell lymphoma)**: Therapy with methotrexate as a single agent appears to produce clinical responses in up to 50% of patients treated. Dosage in early stages is usually 5 to 50 mg once weekly. Dose reduction or cessation is guided by patient response and hematologic monitoring. Methotrexate has also been administered twice weekly in doses ranging from 15 to 37.5 mg in patients who have responded poorly to weekly therapy. Combination chemotherapy regimens that include

Chemotherapeutic Agent	Recommended Dosages
	intravenous methotrexate administered at higher doses with leucovorin rescue have been utilized in advanced stages of the disease . **Osteosarcoma** : An effective adjuvant chemotherapy regimen requires the administration of several cytotoxic chemotherapeutic agents . In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in the table below: The starting dose for high-dose methotrexate treatment is 12 grams/ m^2. If this dose is not sufficient to produce a peak serum methotrexate concentration of 1,000 micromolar at the end of the methotrexate infusion, the dose may be escalated to 15 grams/m^2 in subsequent treatments. If the patient is vomiting or is unable to tolerate oral medication, leucovorin is given IV or IM at the same dose and schedule . **Adult Rheumatoid Arthritis**: Recommended Starting Dosage Schedules 1. Single oral doses of 7.5 mg once weekly. 2. Divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses given as a course once weekly . **Polyarticular Course Juvenile Rheumatoid Arthritis**: The recommended starting dose is 10 mg/m^2 given once weekly. **Psoriasis**: Recommended Starting Dose Schedule : 1. Weekly single oral, IM or IV dosage schedule: 10 to 25 mg per week until adequate response is achieved 2. Divided oral dose schedule 2.5 mg at 12 hour intervals for three doses
Epirubicin	Administer intravenously in repeated 3-to 4-week cycles, either total dose on Day 1 of each cycle or divided equally and given on Days 1 and 8 of each cycle The recommended starting dose of epirubicin hydrochloride injection is 100 to 120 mg/m^2. The following regimens are recommended: CEF-120: Cyclophosphamide 75 mg/m^2 PO D1 to 14, Epirubicin hydrochloride injection 60 mg/m^2 IV D1 and 8, 5-Fluorouracil 500 mg/m^2 IV D1 and 8, Repeated every 28 days for 6 cycles FEC-100: 5-Fluorouracil 500 mg/m^2, Epirubicin hydrochloride injection 100 mg/m^2, Cyclophosphamide 500 mg/m^2 All drugs administered intravenously on Day 1 and repeated every 21 days for 6 cycles. Dosage reductions are possible when given in certain combinations. Dosage adjustments after the first treatment cycle should be made based on hematologic and nonhematologic toxicities. Reduce dose in patients with hepatic impairment.

Chemotherapeutic Agent	Recommended Dosages
	Consider lower doses in patients with severe renal impairment.
Mitoxantrone	**Multiple Sclerosis:** the recommended dosage of NOVANTRONE is 12 mg/m^2 given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months. **Hormone-Refractory Prostate Cancer:** the recommended dosage of NOVANTRONE is 12 to 14 mg/m^2 given as a short intravenous infusion every 21 days **Combination Initial Therapy for ANLL in Adults:** for induction, the recommended dosage is 12 mg/m^2 of NOVANTRONE daily on Days 1-3 given as an intravenous infusion, and 100 mg/m^2 of cytarabine for 7 days given as a continuous 24-hour infusion on Days 1-7.
Teniposide	In one study, childhood ALL patients failing induction therapy with a cytarabine-containing regimen were treated with the combination of VUMON 165 mg/m^2 and cytarabine 300 mg/m^2 intravenously, twice weekly for 8 to 9 doses. In another study, patients with childhood ALL refractory to vincristine/prednisone-containing regimens were treated with the combination of VUMON 250 mg/m^2 and vincristine 1.5 mg/m^2 intravenously, weekly for 4 to 8 weeks and prednisone 40 mg/m^2 orally for 28 days.
Irinotecan	Colorectal cancer combination regimen 1: CAMPTOSAR 125 mg/m^2 intravenous infusion over 90 minutes on days 1, 8,15, 22 with LV 20 mg/m^2 intravenous bolus infusion on days 1, 8, 15, 22 followed by 5-FU intravenous bolus infusion on days 1, 8, 15, 22 every 6 weeks. Colorectal cancer combination regimen 2: CAMPTOSAR 180 mg/m^2 intravenous infusion over 90 minutes on days 1, 15, 29 with LV 200 mg/m^2 intravenous infusion over 2 hours on days 1, 2, 15, 16, 29, 20 followed by 5-FU 400 mg/m^2 intravenous bolus infusion on days 1, 2, 15, 16, 29, 30 and 5-FU 600 mg/m^2 intravenous infusion over 22 hours on days 1, 2, 15, 16, 29, 30. Colorectal cancer single agent regimen 1: CAMPTOSAR 125 mg/m^2 intravenous infusion over 90 minutes on days 1, 8, 15, 22 then 2-week rest. Colorectal cancer single agent regimen 2: CAMPTOSAR 350 mg/m^2 intravenous infusion over 90 minutes on day 1 every 3 weeks.
Topotecan	The recommended dose of HYCAMTIN capsules is 2.3 mg/m^2/day once daily for 5 consecutive days repeated every 21 days. The recommended dose of HYCAMTIN is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21-day course. In the absence of tumor progression, a minimum of 4 courses is recommended because tumor response may be delayed.

Chemotherapeutic Agent	Recommended Dosages
	Renal Functional Impairment: dosage adjustment to 0.75 mg/m^2 is recommended for patients with moderate renal impairment (20 to 39 mL/min).
Busulfan	**Busulfan is administered orally**. The usual adult dose range for *remission induction* is 4 to 8 mg, total dose, daily. Dosing on a weight basis is the same for both pediatric patients and adults, approximately 60 mcg/kg of body weight or 1.8 mg/m^2 of body surface, daily. **BUSULFEX® (busulfan) Injection** is administered as a component of the BuCy conditioning regimen prior to bone marrow or peripheral blood progenitor cell replacement, the recommended doses are as follows: The usual adult dose is 0.8 mg/kg of ideal body weight or actual body weight, whichever is lower, administered every six hours for four days (a total of 16 doses). For obese, or severely obese patients, BUSULFEX should be administered based on adjusted ideal body weight. Ideal body weight (IBW) should be calculated as follows (height in cm, and weight in kg): IBW (kg; men)= 50 + 0.91 x (height in cm -152); IBW (kg; women)= 45 + 0.91 x (height in cm - 152). Adjusted ideal body weight (AIBW) should be calculated as follows: AIBW= IBW + 0.25 x (actual weight -IBW). Cyclophosphamide is given on each of two days as a one-hour infusion at a dose of 60 mg/kg beginning on BMT day –3, no sooner than six hours following the 16th dose of BUSULFEX.
Melphalan	**Melphalan for injection**: The usual IV dose is 16 mg/m^2. The drug is administered as a single infusion over 15 to 20 minutes. ALKERAN is administered at 2-week intervals for four doses, then, after adequate recovery from toxicity, at 4-week intervals. The dose is adjusted, as required, on the basis of blood counts done at approximately weekly intervals. After 2 to 3 weeks of treatment, the drug should be discontinued for up to 4 weeks, during which time the blood count should be followed carefully. **Melphalan tablet**: **Multiple Myeloma**: The usual oral dose is 6 mg (3 tablets) daily. **Epithelial Ovarian Cancer:** One commonly employed regimen for the treatment of ovarian carcinoma has been to administer ALKERAN at a dose of 0.2 mg/kg daily for 5 days as a single course. Courses are repeated every 4 to 5 weeks depending upon hematologic tolerance.
Cladribine	**Hairy Cell Leukemia:** the recommended dose and schedule of LEUSTATIN Injection is as a single course given by continuous infusion for 7 consecutive days at a dose of 0.09 mg/kg/day. **Chronic Lymphocytic Leukemia**: the recommended treatment consists of a continuous infusion of LEUSTATIN injection for 2 hours on days 1 to 5 of a 28 day cycle at a dose of 0.12mg/kg/day (4.8 mg/m^2/day). It is recommended that LEUSTATIN injection be administered in responding patients up to a

Chemotherapeutic Agent	Recommended Dosages
	maximum of 6 monthly cycles and that non-responding patients receive no more than 2 cycles of treatment.
Vinblastine	This preparation is for intravenous use only. **Adult patients:** A simplified and conservative incremental approach to dosage at weekly intervals for adults may be outlined as follows: First dose.....3.7 mg/m^2 bsa Second dose.....5.5 mg/m^2 bsa Third dose.....7.4 mg/m^2 bsa Fourth dose.....9.25 mg/m^2 bsa Fifth dose.....11.1 mg/m^2 bsa The above-mentioned increases may be used until a maximum dose not exceeding 18.5 mg/m^2 bsa for adults is reached. **Pediatric Patients** As a single agent for Letterer-Siwe disease (histiocytosis X), the initial dose of vinblastine sulfate was reported as 6.5 mg/m^2. When vinblastine sulfate was used in combination with other chemotherapeutic agents for the treatment of Hodgkin's disease, the initial dose was reported as 6 mg/m^2. For testicular germ cell carcinomas, the initial dose of vinblastine sulfate was reported as 3 mg/m^2 in a combination regimen. **Patients with Renal or Hepatic Impairment** A reduction of 50% in the dose of vinblastine sulfate is recommended for patients having a direct serum bilirubin value above 3 mg/100 mL. Since metabolism and excretion are primarily hepatic, no modification is recommended for patients with impaired renal function.
Chorambucil	The usual oral dosage is 0.1 to 0.2 mg/kg body weight daily for 3 to 6 weeks as required. This usually amounts to 4 to 10 mg per day for the average patient. The entire daily dose may be given at one time. Patients with **Hodgkin's disease** usually require 0.2 mg/kg daily, whereas patients with other **lymphomas or chronic lymphocytic leukemia** usually require only 0.1 mg/kg daily. When **lymphocytic infiltration of the bone marrow** is present, or when the bone marrow is hypoplastic, the daily dose should not exceed 0.1 mg/kg (about 6 mg for the average patient). Alternate schedules for the treatment of **chronic lymphocytic leukemia** employing intermittent, biweekly, or once-monthly pulse doses of chlorambucil have been reported. Intermittent schedules of chlorambucil begin with an initial single dose of 0.4 mg/kg. Doses are generally increased by 0.1 mg/kg until control of lymphocytosis or toxicity is observed. Subsequent doses are modified to produce mild hematologic toxicity. If maintenance dosage is used, it should not exceed 0.1 mg/kg daily and may well be as low as 0.03 mg/kg daily. A typical maintenance dose is 2 mg to 4 mg daily, or less, depending on the status of the blood counts.

Chemotherapeutic Agent	Recommended Dosages
Tamoxifen	For patients with **breast cancer**, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening). **Ductal Carcinoma in Situ** (DCIS): The recommended dose is 20 mg daily for 5 years. Reduction in Breast Cancer Incidence in High Risk Women: The recommended dose is 20 mg daily for 5 years.
Actinomycin-D	Not for oral administration The dose intensity per 2-week cycle for adults or children should not exceed 15 mcg/kg/day or 400-600 mcg/m^2/day intravenously for five days. **Wilms' Tumor, Childhood Rhabdomyosarcoma and Ewing's Sarcoma:** Regimens of 15 mcg/kg intravenously daily for five days administered in various combinations and schedules with other chemotherapeutic agents have been utilized in the treatment of Wilms' tumor, rhabdomyosarcoma and Ewing's sarcoma. **Metastatic Nonseminomatous Testicular Cancer:** 1000 mcg/m^2 intravenously on Day 1 as part of a combination regimen with cyclophosphamide, bleomycin, vinblastine, and cisplatin. **Gestational Trophoblastic Neoplasia**: 12 mcg/kg intravenously daily for five days as a single agent. 500 mcg intravenously on Days 1 and 2 as part of a combination regimen with etoposide, methotrexate, folinic acid, vincristine, cyclophosphamide and isplatin. **Regional Perfusion in Locally Recurrent and Locoregional Solid Malignancies:** In general, the following doses are suggested: 50 mcg (0.05 mg) per kilogram of body weight for lower extremity or pelvis. 35 mcg (0.035 mg) per kilogram of body weight for upper extremity. It may be advisable to use lower doses in obese patients, or when previous chemotherapy or radiation therapy has been employed
Mitomycin C	Mitomycin should be given intravenously only. The following dosage schedule may be used at 6 to 8 week intervals: 20 mg/m^2 intravenously as a single dose via a functioning intravenous catheter. When mitomycin is used in combination with other myelosuppressive agents, the doses should be adjusted accordingly. If the disease continues to progress after two courses of mitomycin, the drug should be stopped since chances of response are minimal.
Verapamil	**Verapamil hydrochloride extended-release tablets:** Initiate therapy with 180 mg of verapamil hydrochloride extended-release tablets given in the morning. Lower initial doses of 120 mg a day may be

Chemotherapeutic Agent	Recommended Dosages
	warranted in patients who may have an increased response to verapamil (e.g., the elderly or small people). If adequate response is not obtained with 180 mg of verapamil hydrochloride extended-release tablets, the dose may be titrated upward in the following manner: 1.240 mg each morning, 2.180 mg each morning plus 180 mg each evening; or 240 mg each morning plus 120 mg each evening, 3.240 mg every 12 hours. **Verapamil hydrochloride – injection:** The recommended intravenous doses of verapamil are as follows: **ADULT**: Initial dose: 5 to 10 mg (0.075 to 0.15 mg/kg body weight) given as an intravenous bolus over at least 2 minutes. Repeat dose: 10 mg (0.15 mg/kg body weight) 30 minutes after the first dose if the initial response is not adequate. An optimal interval for subsequent I.V. doses has not been determined, and should be individualized for each patient. Older Patients: The dose should be administered over at least 3 minutes to minimize the risk of untoward drug effects. **PEDIATRIC**: Initial dose: 0-1 yr: 0.1 to 0.2 mg/kg body weight (usual single dose range 0.75 to 2 mg) should be administered as an intravenous bolus over at least 2 minutes under continuous ECG monitoring. 1-15 yrs: 0.1 to 0.3 mg/kg body weight (usual single dose range 2 to 5 mg) should be administered as an intravenous bolus over at least 2 minutes. Do not exceed 5 mg. Repeat dose: 0-1 yr: 0.1 to 0.2 mg/kg body weight (usual single dose range 0.75 to 2 mg) 30 minutes after the first dose if the initial response is not adequate (under continuous ECG monitoring). 1-15 yrs: 0.1 to 0.3 mg/kg body weight (usual single dose range 2 to 5 mg) 30 minutes after the first dose if the initial response is not adequate. Do not exceed 10 mg as a single dose.
Podophyllotoxin	Apply twice daily morning and evening (every 12 hours), for 3 consecutive days, then withhold use for 4 consecutive days. This one week cycle of treatment may be repeated up to four times until there is no visible wart tissue.

CLAIMS

1. A method of treating an oncological disorder in a subject comprising:
   (a) administering coenzyme Q10 (CoQ10) to the subject;
   (b) discontinuing administration of CoQ10; and
   (c) administering at least one chemotherapeutic agent to the subject after administration with CoQ10 has been discontinued,

such that the oncological disorder is treated.

2. A method of treating an oncological disorder in a subject comprising:
   (a) administering coenzyme Q10 (CoQ10) to the subject;
   (b) administering at least one chemotherapeutic agent to the subject after administration of the CoQ10 is initiated; and
   (c) continuing treatment with CoQ10 after administration of the at least one chemotherapeutic agent is initiated,

such that the oncological disorder is treated.

3. The method of claim 1 or 2, wherein the CoQ10 is administered for at least 24 hours prior to administration of a dose of the at least one chemotherapeutic agent.

4. The method of claim 1 or 2, wherein the CoQ10 is administered for at least 48 hours prior to administration of a dose of the at least one chemotherapeutic agent.

5. The method of claim 1 or 2, wherein the CoQ10 is administered for at least 1 week prior to administration of a dose of the at least one chemotherapeutic agent.

6. The method of claim 1 or 2, wherein the CoQ10 is administered for at least 2 weeks prior to administration of a dose of the at least one chemotherapeutic agent.

7. The method of claim 1 or 2, wherein the CoQ10 is administered for at least 3 weeks prior to administration of a dose of the at least one chemotherapeutic agent.

8. The method of claim 1, wherein the CoQ10 is administered for at least 4 weeks prior to administration of a dose of the at least one chemotherapeutic agent.

9. The method of claim 1 or 2, wherein administration of the at least one chemotherapeutic agent is initiated at least 24 hours after administration of CoQ10 is initiated, one or more weeks after administration of CoQ10 is initiated, two or more weeks after administration of CoQ10 is initiated, three or more weeks after administration of CoQ10 is initiated, four or more weeks after administration of CoQ10 is initiated, five or more weeks after administration of CoQ10 is initiated, six or more weeks after administration of CoQ10 is initiated, seven or more weeks after administration of CoQ10 is initiated, or eight or more weeks after administration of CoQ10 is initiated.

10. The method of claim 1 or 2, wherein a response of the oncological disorder to treatment is improved relative to a treatment with the at least one chemotherapeutic agent alone [SPEC: i.e., in the absence of administration of CoQ10 to the subject].

11. The method of claim 10, wherein the response is improved by at least 5%, at least 10%, at least 15%, at least 20%, at least 30%, at least 40% or at least 50% relative to treatment with the at least one chemotherapeutic agent alone.

12. The method of claim 10 or 11, wherein the response comprises any one or more of reduction in tumor burden, reduction in tumor size, inhibition of tumor growth, achieving stable oncological disorder in a subject with a progressive oncological disorder prior to treatment, increased time to progression of the oncological disorder, and increased time of survival.

13. The method of claim 1 or 2, wherein the CoQ10 is administered topically.

14. The method of claim 1 or 2, wherein the CoQ10 is administered by inhalation.

15. The method of claim 1 or 2, wherein the CoQ10 is administered by injection or infusion.

16. The method of claim 1 or 2, wherein the CoQ10 is administered by intravenous administration.

17. The method of claim 1 or 2, wherein the CoQ10 is administered by continuous intravenous infusion.

18. The method of claim 17, wherein the dose is administered by continuous infusion over 24 hours.

19. The method of any one of claims 15-18, wherein the CoQ10 is administered at a dose of about 5 mg/kg, about 10 mg/kg, about 12.5 mg/kg, about 20 mg/kg, about 25 mg/kg, t about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 58 mg/kg, about 58.6 mg/kg, about 60 mg/kg, about 75 mg/kg, about 78 mg/kg, about 100 mg/kg, about 104 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 300 mg/kg, or about 400 mg/kg.

20. A method of improving a chemotherapeutic treatment regimen for an oncological disorder in a subject, comprising pre-treating a subject having an oncological disorder with Coenzyme Q10 (CoQ10) for a sufficient time prior to initiation of a chemotherapeutic treatment regimen, wherein the chemotherapeutic treatment regimen comprises administration of one or more chemotherapeutic agents, such that a response of the oncological disorder is improved relative to treatment with the chemotherapeutic treatment regimen alone.

21. The method of claim 20, wherein the subject is pre-treated with CoQ10 for at least 24 hours, at least 48 hours, at least 1 week, at least 2 weeks, at least 3 weeks or at least 4 weeks prior to initiation of the chemotherapeutic treatment regimen.

22. The method of claim 20, wherein the chemotherapeutic treatment regimen is initiated at least 24 hours after pre-treatment with CoQ10 is initiated, one or more weeks after pre-treatment with CoQ10 is initiated, two or more weeks after pre-treatment with CoQ10 is initiated, three or more weeks after pre-treatment with CoQ10 is initiated, four or more weeks after pre-treatment with CoQ10 is initiated, five or more weeks after pre-treatment with CoQ10 is initiated, six or more weeks after pre-treatment with CoQ10 is initiated, seven or more weeks after pre-treatment with CoQ10 is initiated, or eight or more weeks after pre-treatment with CoQ10 is initiated.

23. The method of claim 10, wherein the response is improved by at least 5%, at least 10%, at least 15%, at least 20%, at least 30%, at least 40% or at least 50% relative to treatment with the chemotherapeutic treatment regimen alone.

24. The method of any one of claims 20-23, wherein the response comprises any one or more of reduction in tumor burden, reduction in tumor size, inhibition of tumor growth, achieving stable oncological disorder in a subject with a progressive oncological disorder prior to treatment, increased time to progression of the oncological disorder, and increased time of survival.

25. The method of claim 20, wherein the CoQ10 is administered topically.

26. The method of claim 20, wherein the CoQ10 is administered by inhalation.

27. The method of claim 20, wherein the CoQ10 is administered by injection or infusion.

28. The method of claim 20, wherein the CoQ10 is administered by intravenous administration.

29. The method of claim 20, wherein the CoQ10 is administered by continuous intravenous infusion.

30. The method of claim 20, wherein the CoQ10 is administered by continuous infusion over 24 hours.

31. The method of any one of claims 27-30, wherein the CoQ10 is administered at a dose of about 5 mg/kg, about 10 mg/kg, about 12.5 mg/kg, about 20 mg/kg, about 25 mg/kg, t about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 58 mg/kg, about 58.6 mg/kg, about 60 mg/kg, about 75 mg/kg, about 78 mg/kg, about 100 mg/kg, about 104 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 300 mg/kg, or about 400 mg/kg.

32. A method of treating an oncological disorder in a subject comprising:

(a) administering coenzyme Q10 (CoQ10) to the subject; and

(b) administering at least one chemotherapeutic agent to the subject at a dosage that is lower than standard dosages of the chemotherapeutic agent used to treat the oncological disorder,

such that the oncological disorder is treated.

33. The method of claim 32, wherein administration of CoQ10 is discontinued before administering the at least one chemotherapeutic agent to the subject.

34. The method of claim 32, wherein administration of CoQ10 is continued after administration of the at least one chemotherapeutic agent to the subject.

35. The method of claim 32, wherein the CoQ10 is administered for at least 24 hours, at least 48 hours, at least 1 week, at least 2 weeks, at least 3 weeks or at least 4 weeks prior to administration of the at least one chemotherapeutic agent.

36. The method of claim 32, wherein the at least one chemotherapeutic agent is administered at least 24 hours after administration of CoQ10 is initiated, one or more weeks after administration of with CoQ10 is initiated, two or more weeks after administration of CoQ10 is initiated, three or more weeks after administration of CoQ10 is initiated, four or more weeks after administration of CoQ10 is initiated, five or more weeks after administration of CoQ10 is initiated, six or more weeks after administration of CoQ10 is initiated, seven or more weeks after administration of CoQ10 is initiated, or eight or more weeks after administration of CoQ10 is initiated.

37. The method of claim 32, wherein the CoQ10 is administered topically.

38. The method of claim 32, wherein the CoQ10 is administered by inhalation.

39. The method of claim 32, wherein the CoQ10 is administered by injection or infusion.

40. The method of claim 32, wherein the CoQ10 is administered by intravenous administration.

41. The method of claim 32, wherein the CoQ10 is administered by continuous intravenous infusion.

42. The method of claim 32, wherein the CoQ10 is administered by continuous infusion over 24 hours.

43. The method of any one of claims 39-42, wherein the CoQ10 is administered at a dose of about 5 mg/kg, about 10 mg/kg, about 12.5 mg/kg, about 20 mg/kg, about 25 mg/kg, t about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 58 mg/kg, about 58.6 mg/kg, about 60 mg/kg, about 75 mg/kg, about 78 mg/kg, about 100 mg/kg, about 104 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 300 mg/kg, or about 400 mg/kg.

44. The method of any one of the preceding claims, wherein the at least one chemotherapeutic agent comprises a chemotherapeutic agent selected from the group consisting of a topoisomerase I inhibitor, a topoisomerase II inhibitor, a mitotic inhibitor, an alkylating agent, a platinum compound, and an antimetabolite.

45. The method of claim 44, wherein the at least one chemotherapeutic agent comprises a Topoisomerase II inhibitor.

46. The method of claim 45, wherein the Topoisomerase II inhibitor comprises at least one of doxorubicin, epirubicin, idarubicin, mitoxantrone, losoxantrone, etoposide and teniposide.

47. The method of claim 44, wherein the at least one chemotherapeutic agent comprises a Topoisomerase I inhibitor.

48. The method of claim 47, wherein the Topoisomerase I inhibitor comprises at least one of irinotecan, topotecan, 9- nitrocamptothecin, camptothecin, and camptothecin derivatives.

49. The method of claim 44, wherein the at least one chemotherapeutic agent comprises an antimetabolite.

50. The method of claim 49, wherein the antimetabolite comprises at least one of 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate.

51. The method of claim 44, wherein the at least one chemotherapeutic agent comprises an alkylating agent.

52. the method of claim 51, wherein the alkylating agent comprises at least one of a nitrogen mustard, an ethyleneimine compound, an alkylsulphonate, a nitrosourea, dacarbazine, cyclophosphamide, ifosfamide and melphalan.

53. The method of claim 44, wherein the at least one chemotherapeutic agent comprises a platinum compound.

54. The method of claim 53, wherein the platinum compound comprises at least one of cisplatin, oxaliplatin and carboplatin.

55. The method of claim 44, wherein the at least one chemotherapeutic agent comprises a mitotic inhibitor.

56. The method of claim 55, wherein the mitotic inhibitor comprises at least one of paclitaxel, docetaxel, vinblastine, vincristine, vinorelbine and a podophyllotoxin derivative.

57. The method of any one of the preceding claims, wherein the at least one chemotherapeutic agent comprises a chemotherapeutic agent selected from the group consisting of amifostine (ethyol), cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carrnustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), doxorubicin lipo (doxil), gemcitabine (gemzar), daunorubicin, daunorubicin lipo (daunoxome), procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5- fluorouracil (5-FU), vinblastine, vincristine, bleomycin, paclitaxel (taxol), docetaxel (taxotere), aldesleukin, asparaginase, busulfan, carboplatin, cladribine, camptothecin, CPT-I l , lO-hydroxy-7-ethyl-camptothecin (SN38), dacarbazine, S-I capecitabine, ftorafur, 5'deoxyflurouridine, UFT, eniluracil, deoxycytidine, 5-azacytosine, 5- azadeoxycytosine, allopurinol, 2-chloro adenosine, trimetrexate, aminopterin, methylene-10-deazaaminopterin (MDAM), oxaplatin, picoplatin, tetraplatin,

satraplatin, platinum-DACH, ormaplatin, CI-973, JM-216, and analogs thereof, epirubicin, etoposide phosphate, 9- aminocamptothecin, 10, 11-methylenedioxycamptothecin, karenitecin, 9-nitrocamptothecin, TAS 103, vindesine, L-phenylalanine mustard, ifosphamidemefosphamide, perfosfamide, trophosphamide carmustine, semustine, epothilones A-E, tomudex, 6-mercaptopurine, 6-thioguanine, amsacrine, etoposide phosphate, karenitecin, acyclovir, valacyclovir, ganciclovir, amantadine, rimantadine, lamivudine, zidovudine, bevacizumab, trastuzumab, rituximab, 5-Fluorouracil, Capecitabine, Pentostatin, Trimetrexate, Cladribine, floxuridine, fludarabine, hydroxyurea, ifosfamide, idarubicin, mesna, irinotecan, mitoxantrone, topotecan, leuprolide, megestrol, melphalan, mercaptopurine, plicamycin, mitotane, pegaspargase, pentostatin, pipobroman, plicamycin, streptozocin, tamoxifen, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, chlorambucil, cisplatin, doxorubicin, paclitaxel (taxol), bleomycin, mTor, epidermal growth factor receptor (EGFR), and fibroblast growth factors (FGF) and combinations thereof .

58. The method of any one of the preceding claims, wherein the at least one chemotherapeutic agent comprises at least one of gemcitabine, 5-fluorouracil, cisplatin, capecitabine, methotrexate, edatrexate, docetaxel, cyclophosphamide, doxorubicin, and irinotecan.

59. The method of any one of the preceding claims, wherein the oncological disorder is selected from the group consisting of a carcinoma, sarcoma, lymphoma, melanoma, and leukemia.

60. The method of any one of the preceding claims, wherein the oncological disorder is selected from the group consisting of pancreatic cancer, breast cancer, liver cancer, skin cancer, lung cancer, colon cancer, prostate cancer, thyroid cancer, bladder cancer, rectal cancer, endometrial cancer, kidney cancer, bone cancer, brain cancer, cervical cancer, stomach cancer, mouth and oral cancers, neuroblastoma, testicular cancer, uterine cancer, and vulvar cancer.

61. The method of claim 60, wherein the skin cancer is selected from the group consisting of melanoma, squamous cell carcinoma, basal cell carcinoma, and cutaneous T-cell lymphoma (CTCL).

62. The method of any one of the preceding claims, wherein the oncological disorder is triple negative breast cancer.

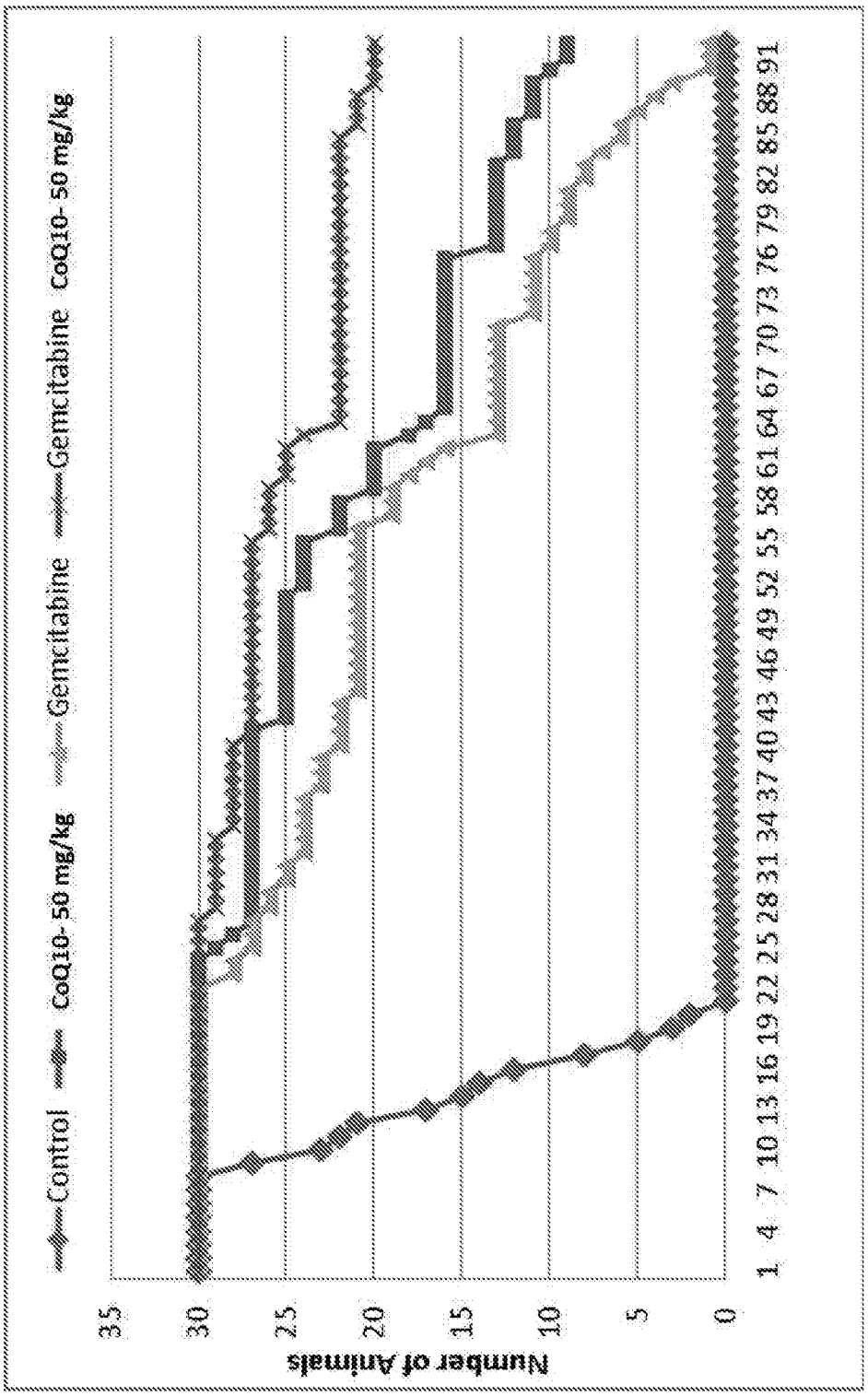
63. The method of any one of the preceding claims, wherein the subject is human.

64. The method of any one of the preceding claims, wherein the at least one chemotherapeutic agent comprises at least one of gemcitabine, cisplatin, docetaxel, cyclophosphamide, doxorubicin, irinotecan, and 5-fluorouracil.

65. The method of claim 64, wherein the method comprises administering between about 100 mg/kg of gemcitabine and about 10 mg/kg of gemcitabine once per week for 3 weeks with one week rest.

66. The method of claim 64, wherein the method comprises administering 5 mg/kg docetaxel, 1 mg/kg doxorubicin, and 35 mg/kg cyclophosphamide to the subject every three weeks for six cycles.

Figure 1


Control
CoQ10- 50 mg/kg
Gemcitabine
Gemcitabine CoQ10- 50 mg/kg
Number of Animals
0
5
10
15
20
25
30
35
1 4 7 10 13 16 19 22 25 28 31 34 37 40 43 46 49 52 55 58 61 64 67 70 73 76 79 82 85 88 91

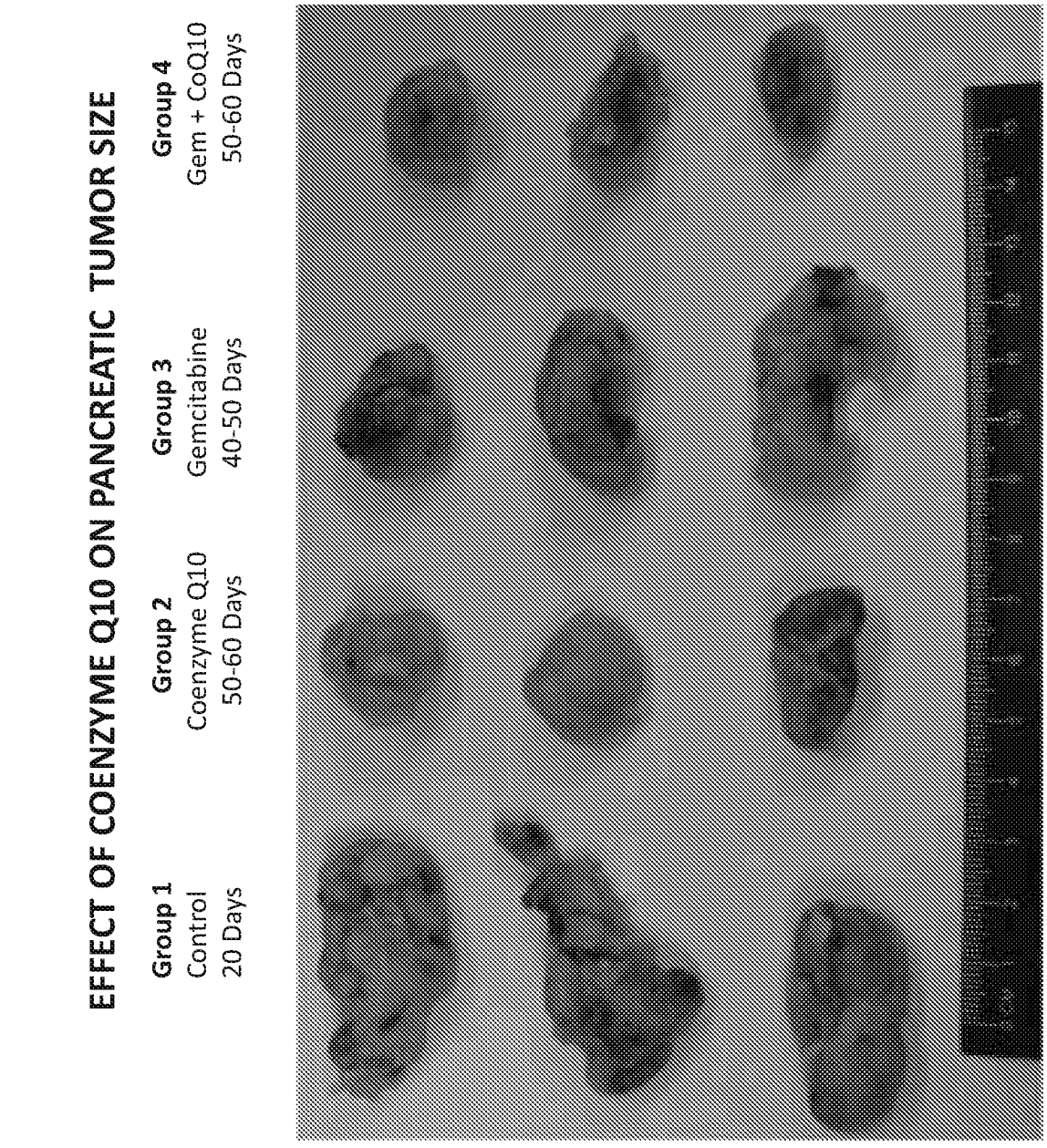

EFFECT OF COENZYME Q10 ON PANCREATIC TUMOR SIZE
Group 1
Control
20 Days
Group 2
Coenzyme Q10
50-60 Days
Group 3
Gemcitabine
40-50 Days
Group 4
Gem + CoQ10
50-60 Days

Figure 2

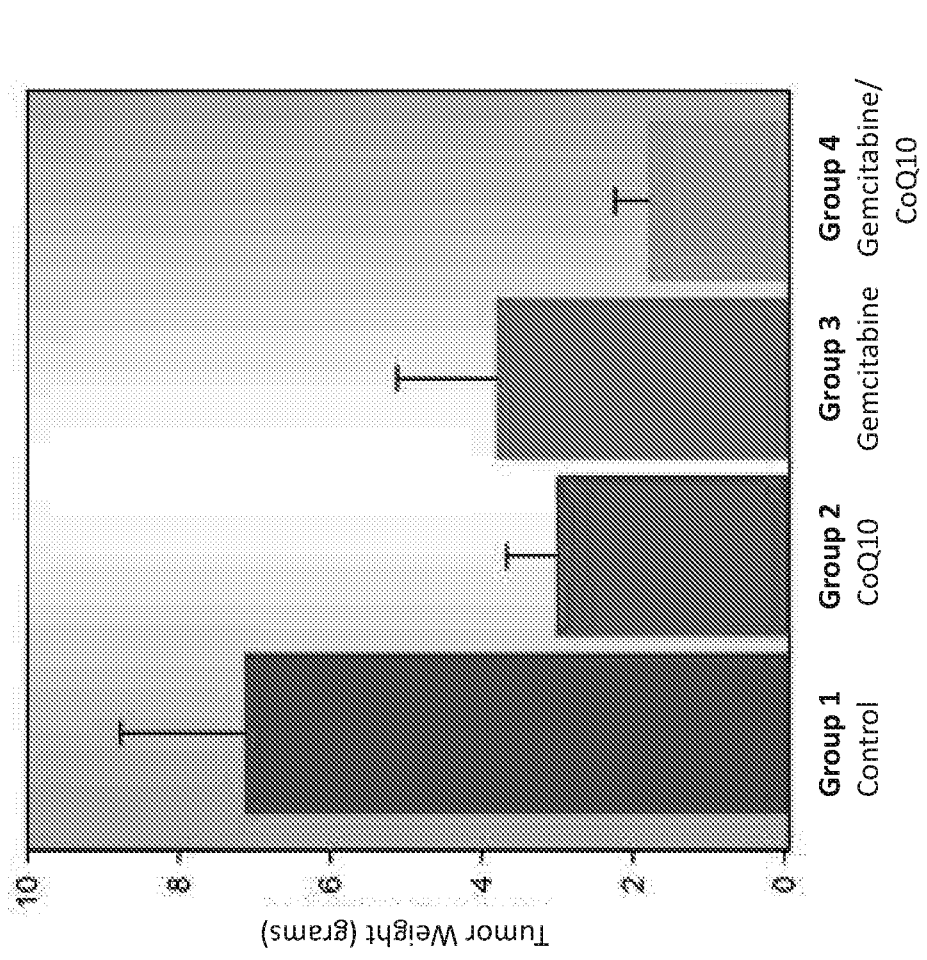

EFFECT OF COENZYME Q10 ON PANCREATIC TUMOR SIZE
Tumor Weight (grams)
0
2
4
6
8
10
Group 1 Control
Group 2 CoQ10
Group 3 Gemcitabine
Group 4 Gemcitabine/ CoQ10

Figure 3

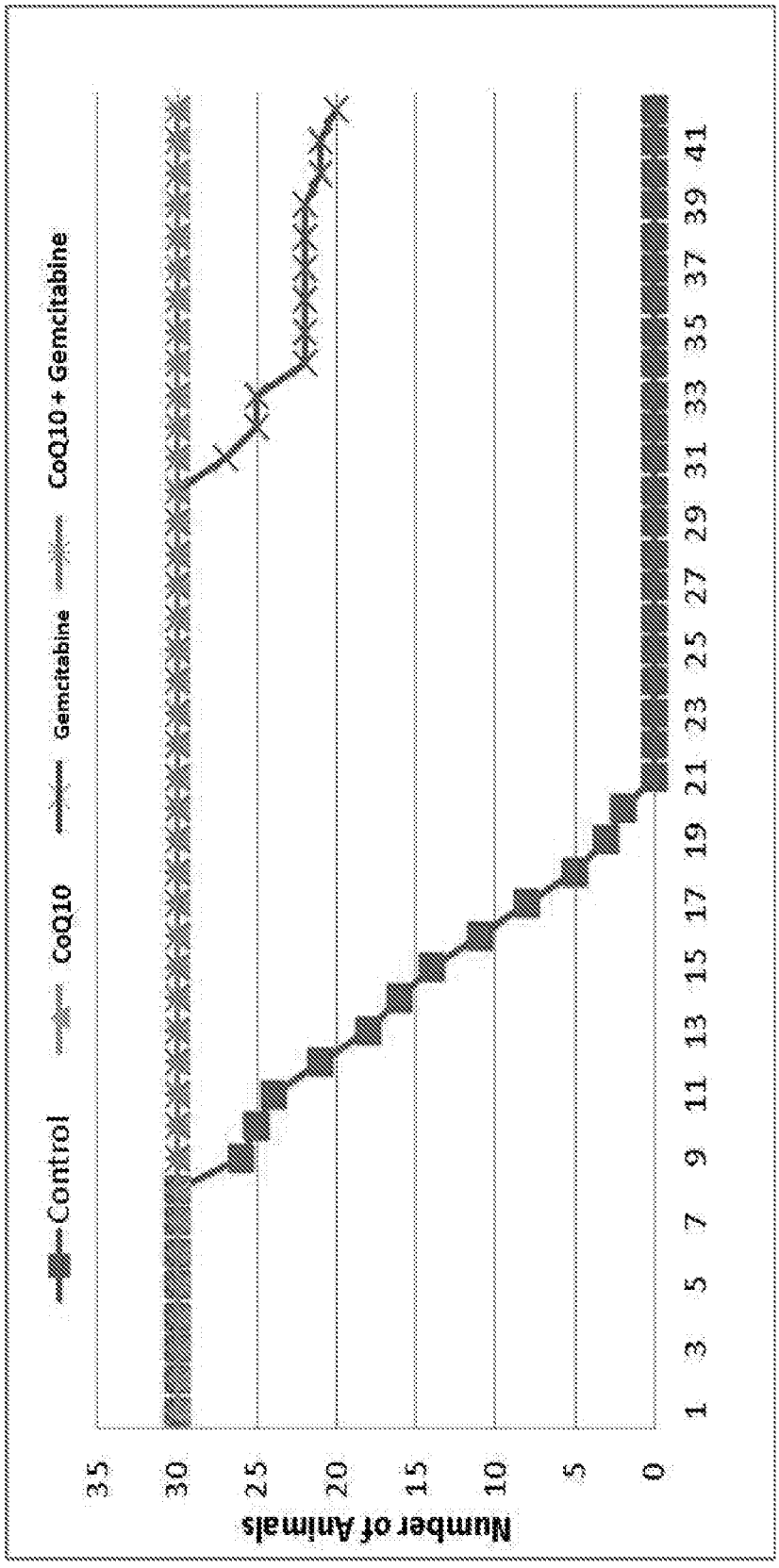

Control
CoQ10
Gemcitabine
CoQ10 + Gemcitabine
Number of Animals
0
5
10
15
20
25
30
35
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41

Figure 4

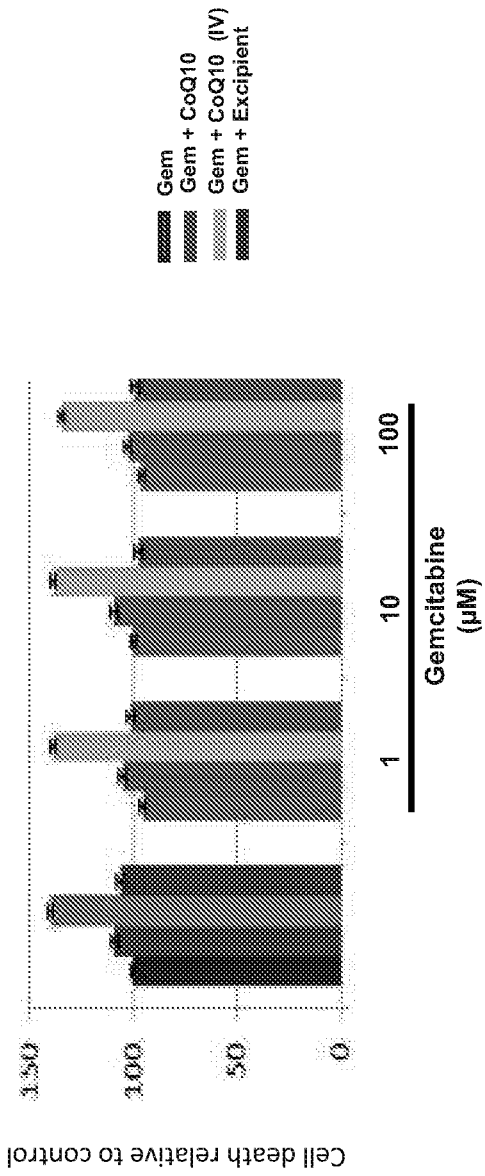


Figure 5A

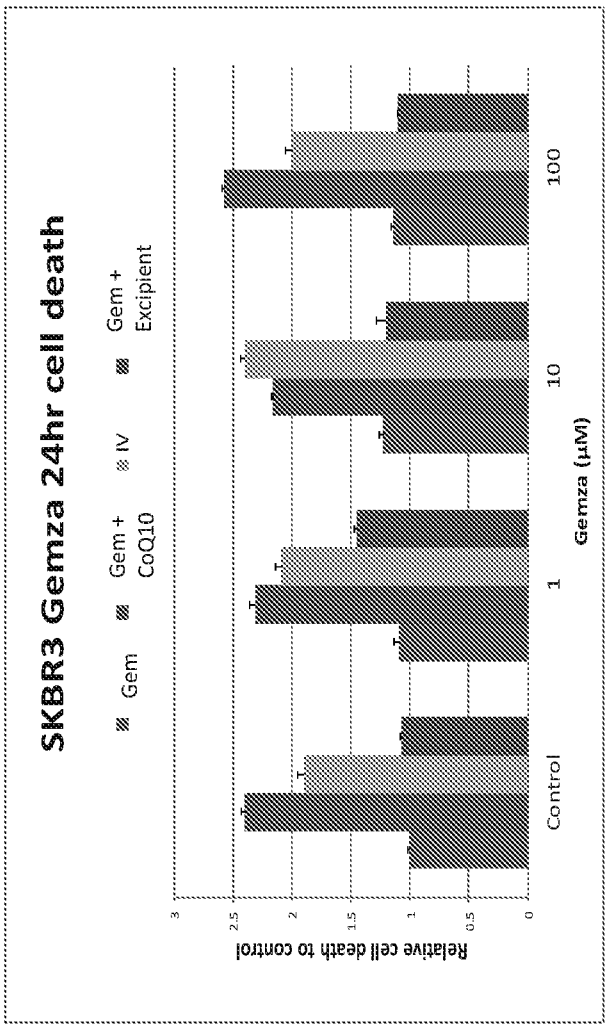


Figure 5B

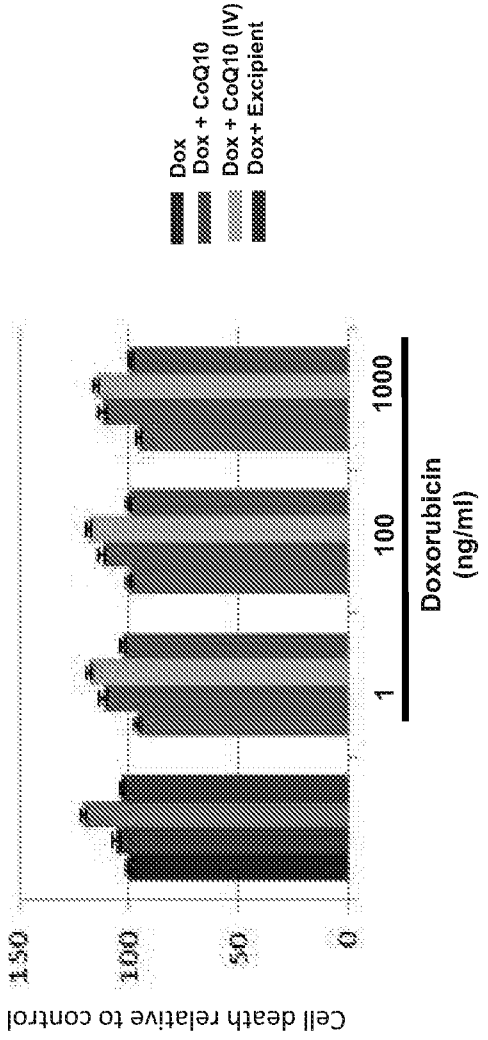


Figure 6A

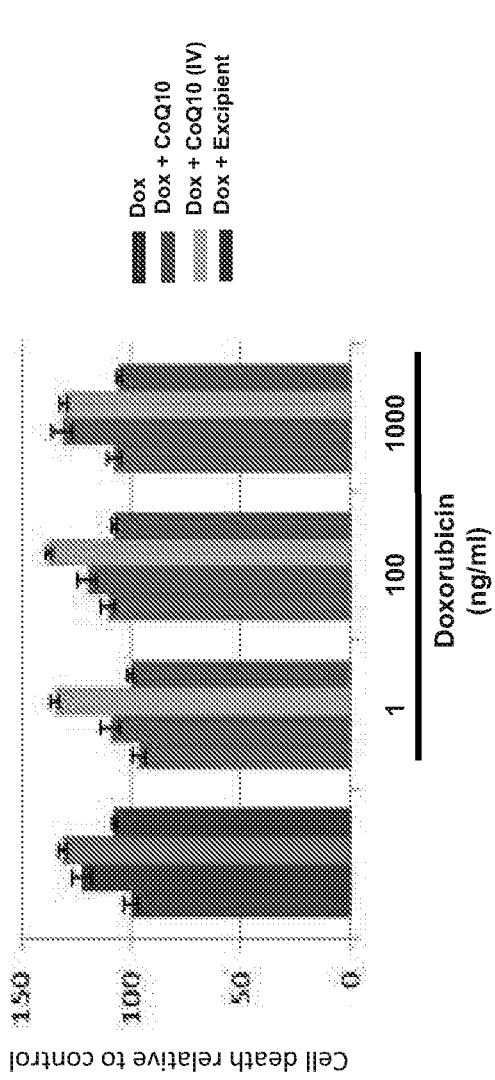


Figure 6B

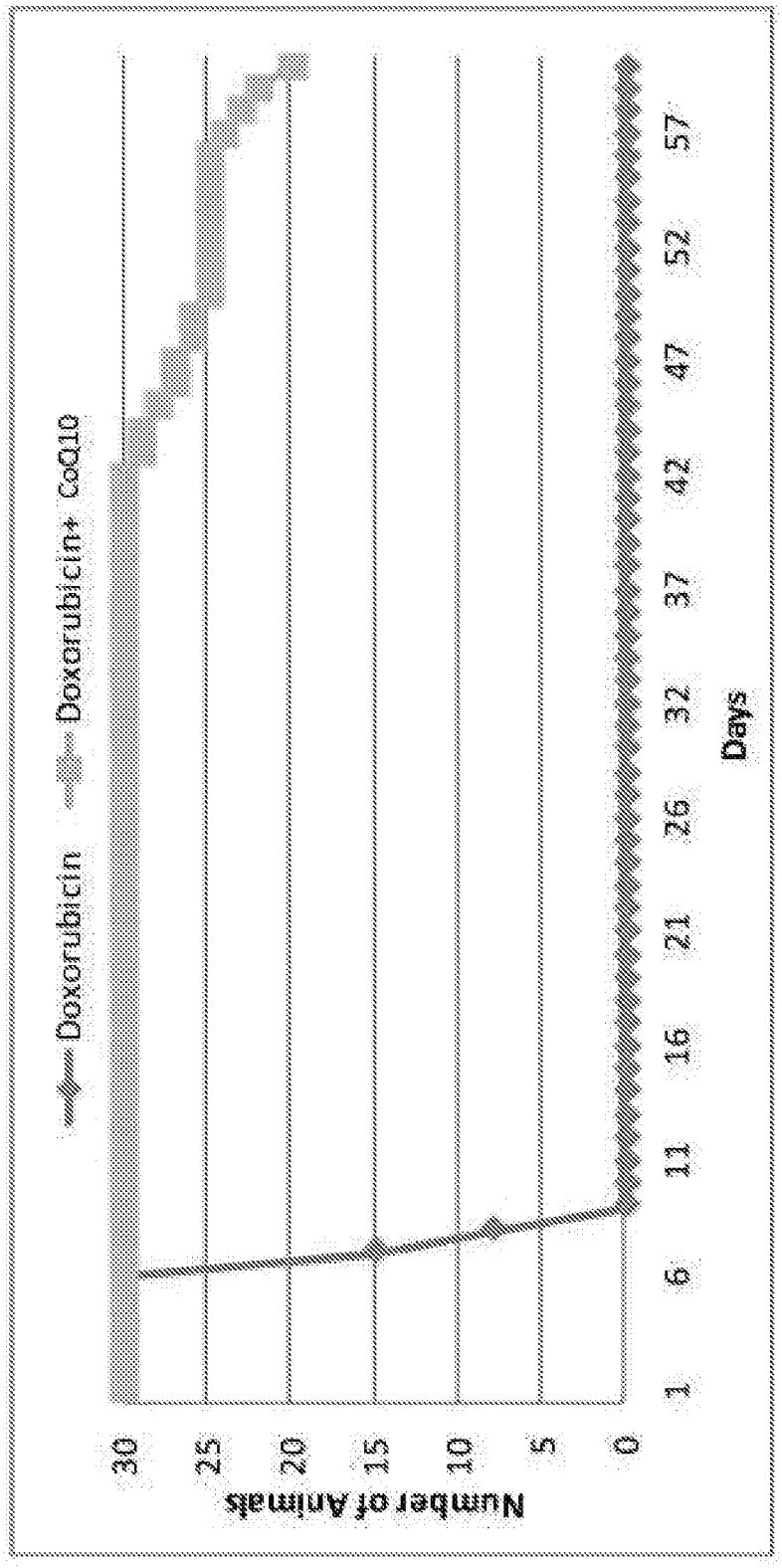

Doxorubicin
Doxorubicin+ CoQ10
Number of Animals
0
5
10
15
20
25
30
1
6
11
16
21
26
32
37
42
47
52
57
Days

Figure 7

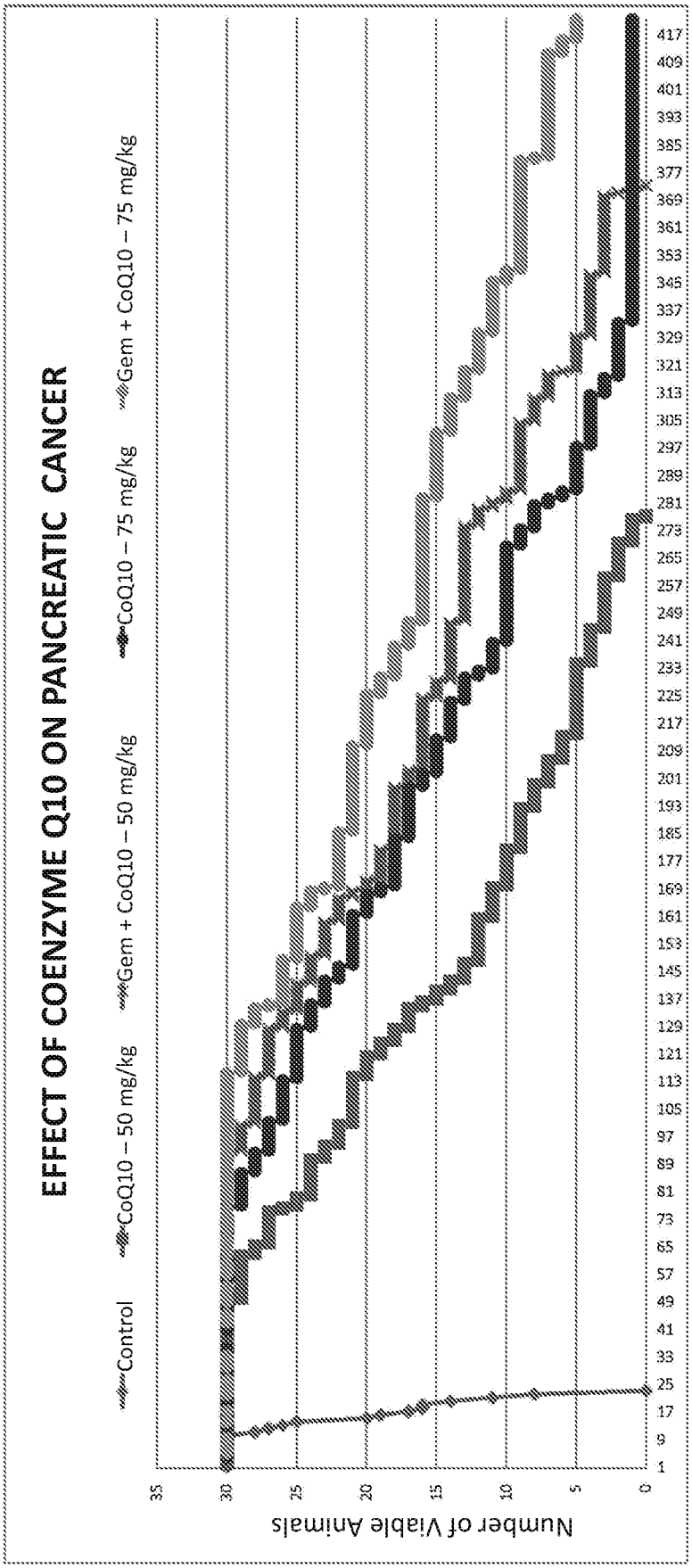

EFFECT OF COENZYME Q10 ON PANCREATIC CANCER
Control
CoQ10 – 50 mg/kg
Gem + CoQ10 – 50 mg/kg
CoQ10 – 75 mg/kg
Gem + CoQ10 – 75 mg/kg
Number of Viable Animals
Number of Days of Treatment

Figure 8

Figure 9B

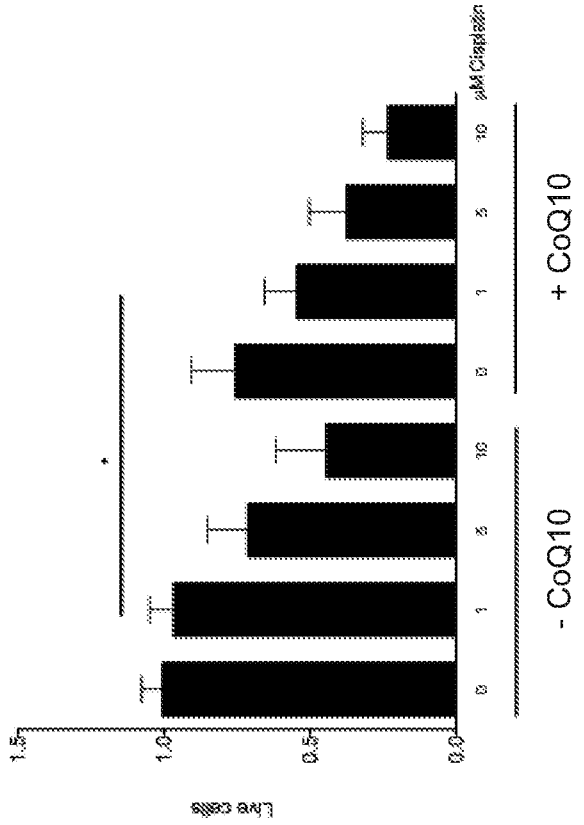
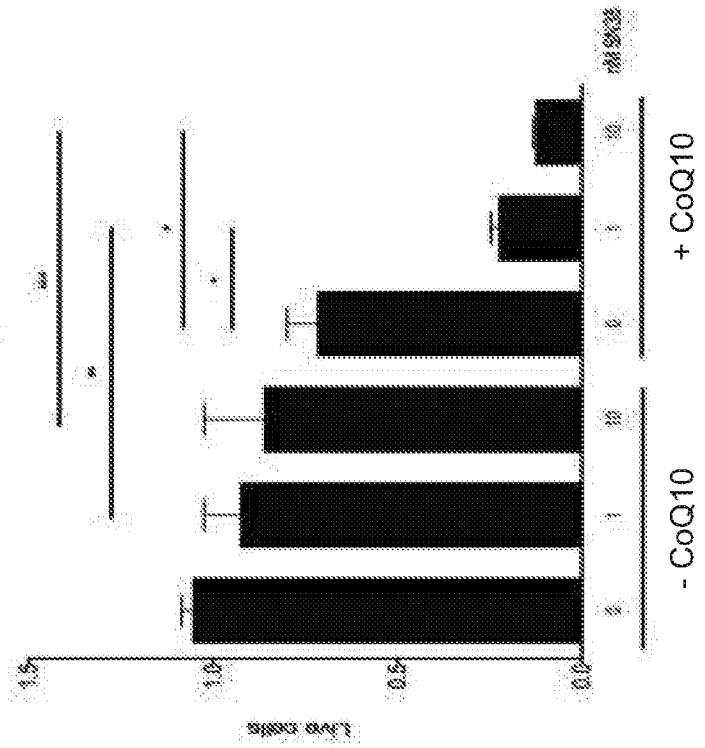


Figure 9A



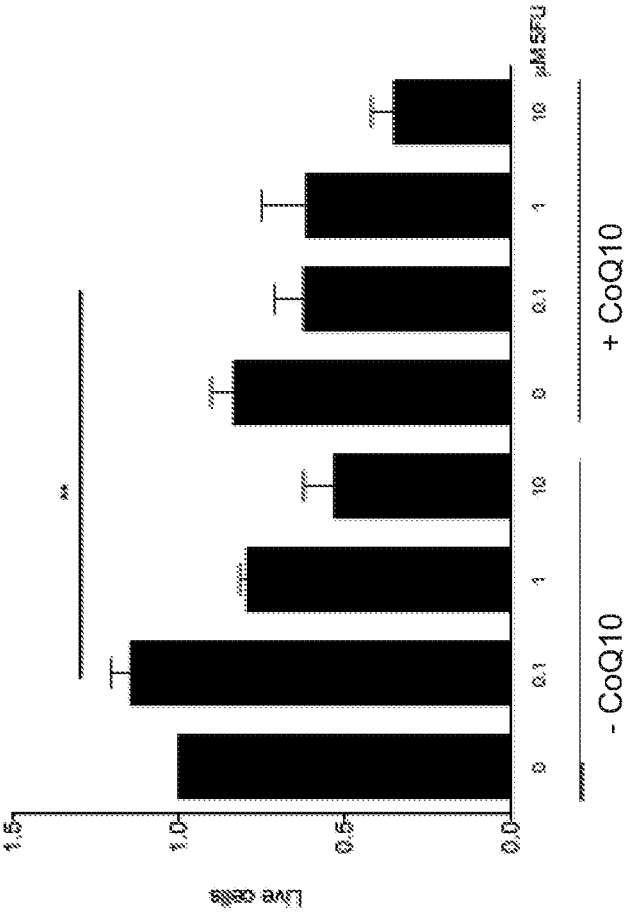


Figure 9C

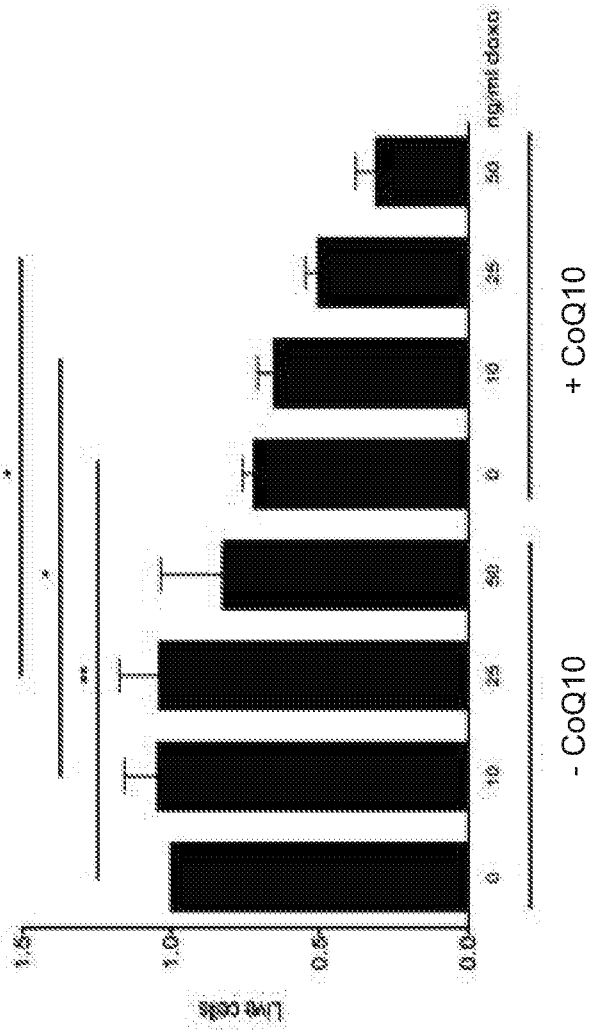
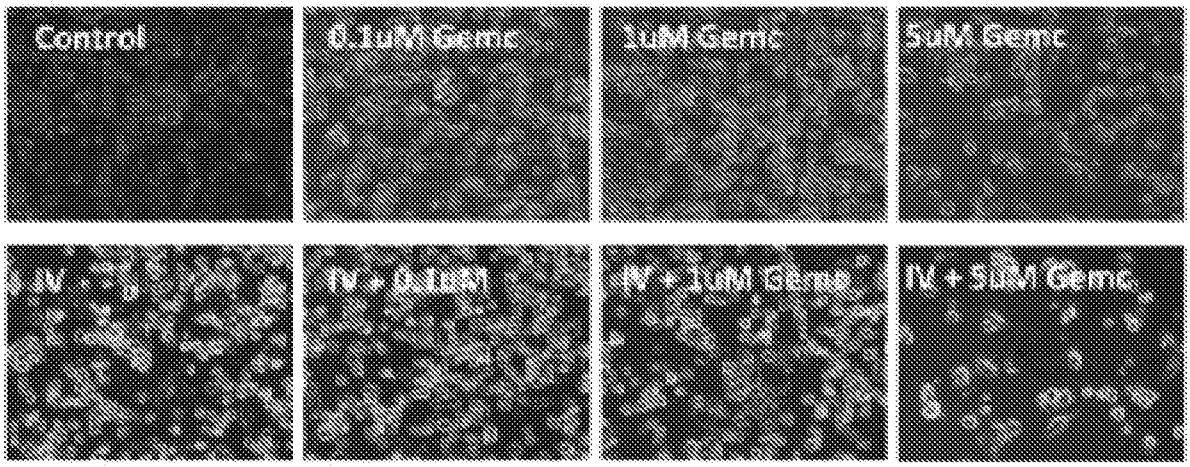


Figure 10

A


Control
0.1uM Gemc
1uM Gemc
5uM Gemc
IV
IV + 0.1uM
IV + 1uM Gemc
IV + 5uM Gemc

B

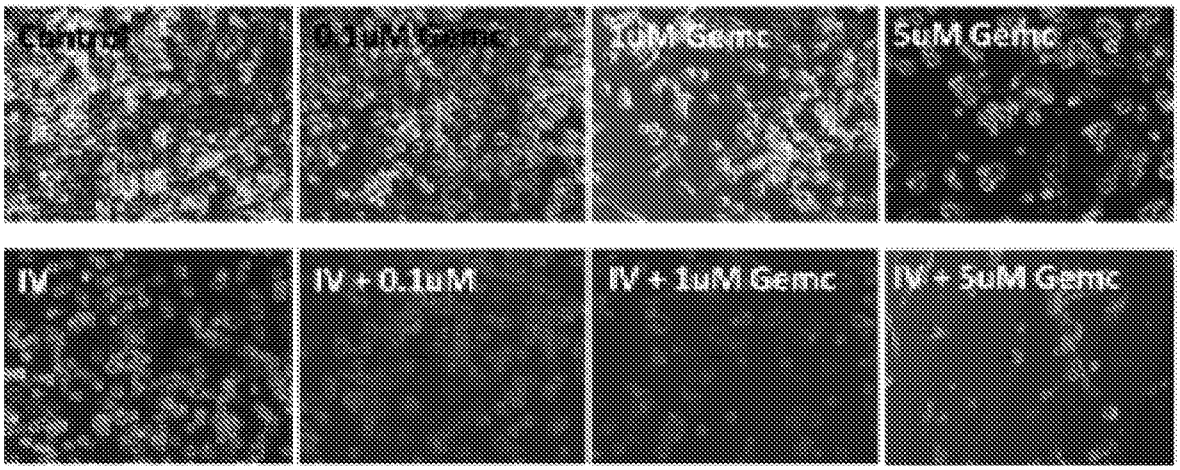

Control
0.1uM Gemc
1uM Gemc
5uM Gemc
IV
IV + 0.1uM
IV + 1uM Gemc
IV + 5uM Gemc

Figure 11

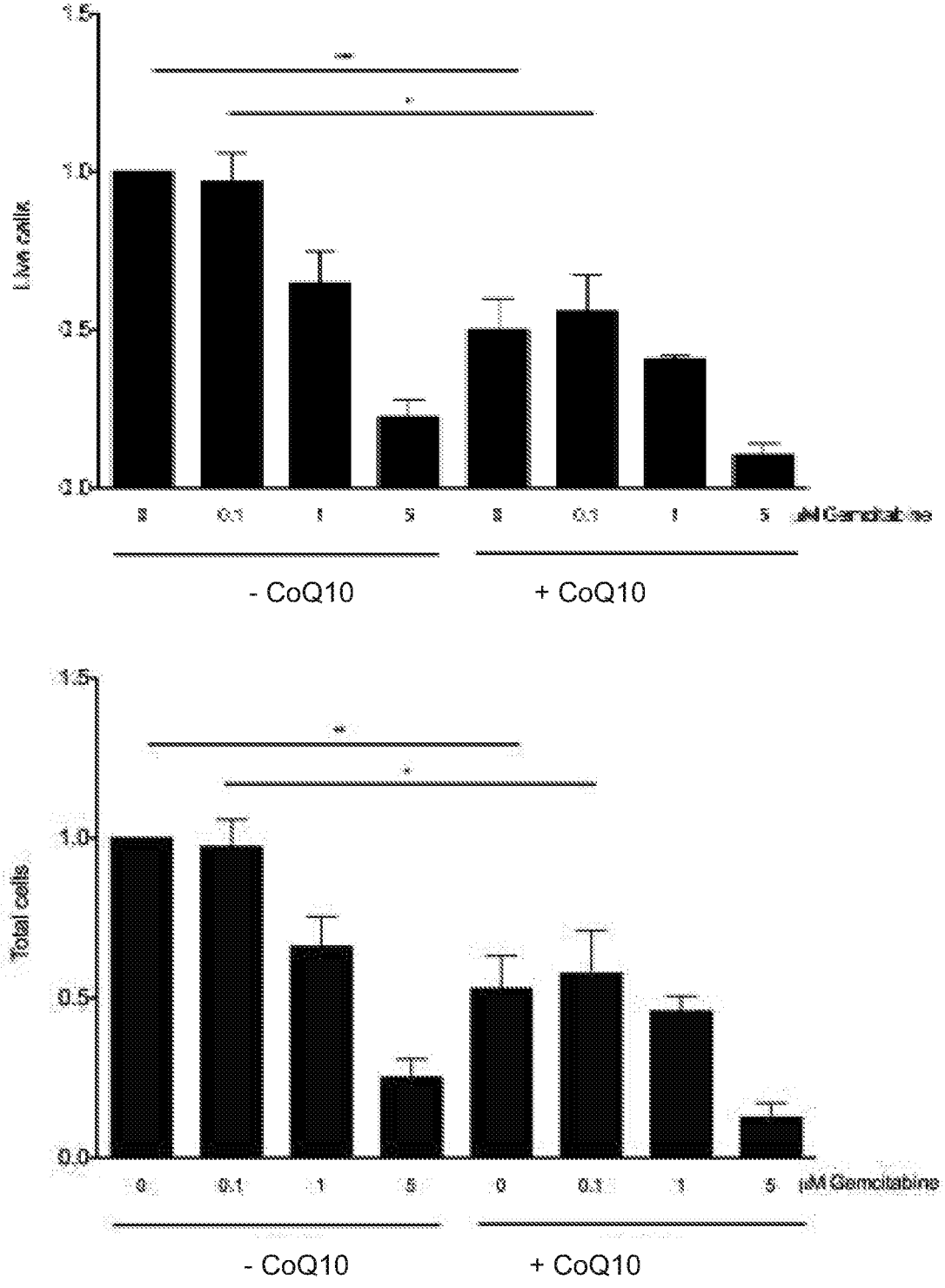

Live cells
1.5
1.0
0.5
0.0
0
0.1
1
5
0
0.1
1
5
- CoQ10
+ CoQ10
Total cells
1.5
1.0
0.5
0.0
0
0.1
1
5
0
0.1
1
5
- CoQ10
+ CoQ10

Figure 12A

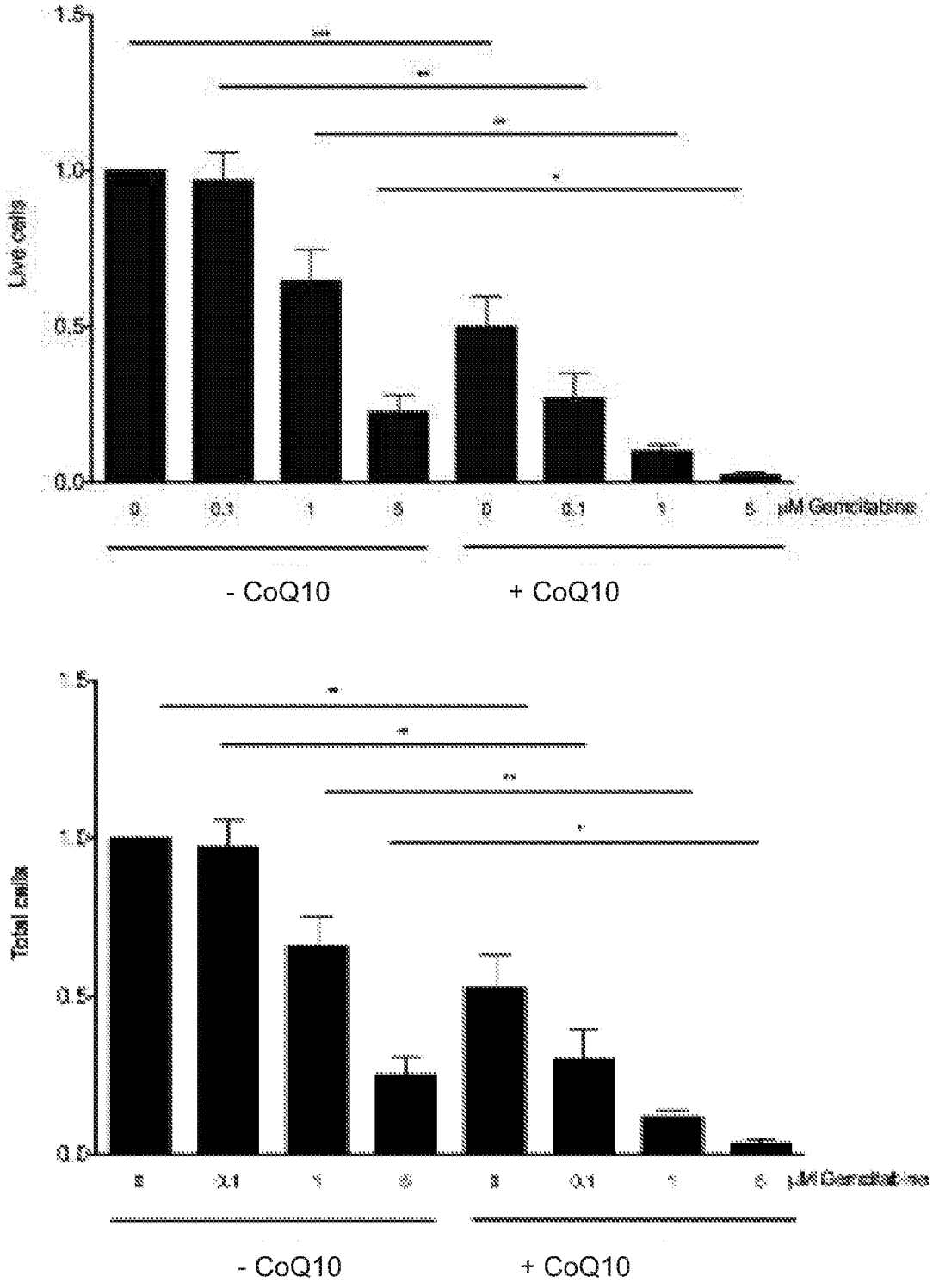

Live cells
1.5
1.0
0.5
0.0
0
0.1
1
5
0
0.1
1
5
μM Gemcitabine
- CoQ10
+ CoQ10
Total cells
μM Gemcitabine
- CoQ10
+ CoQ10

Figure 12B

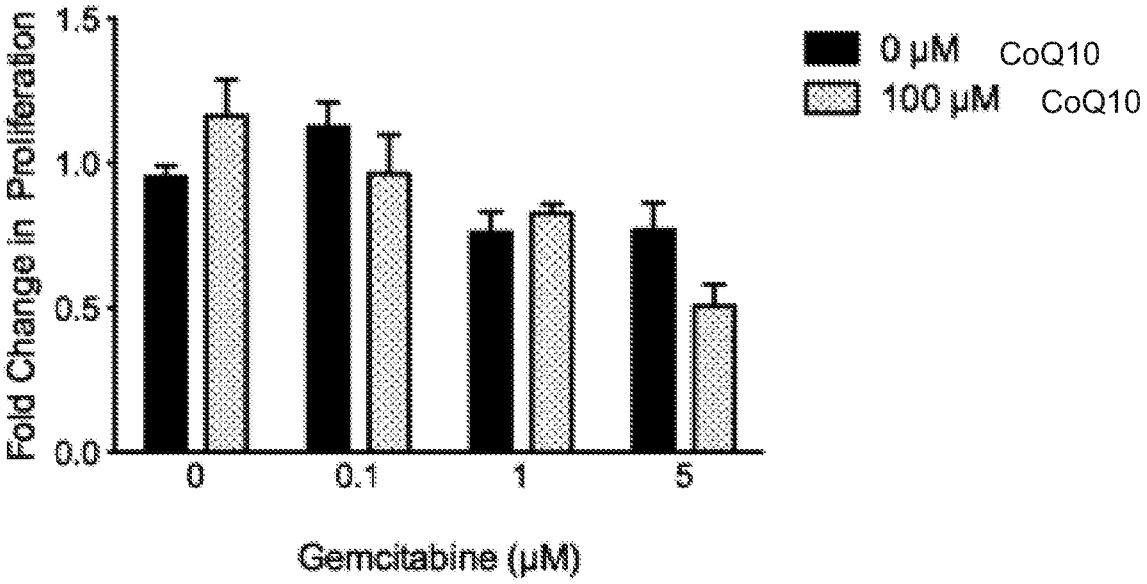


Figure 13

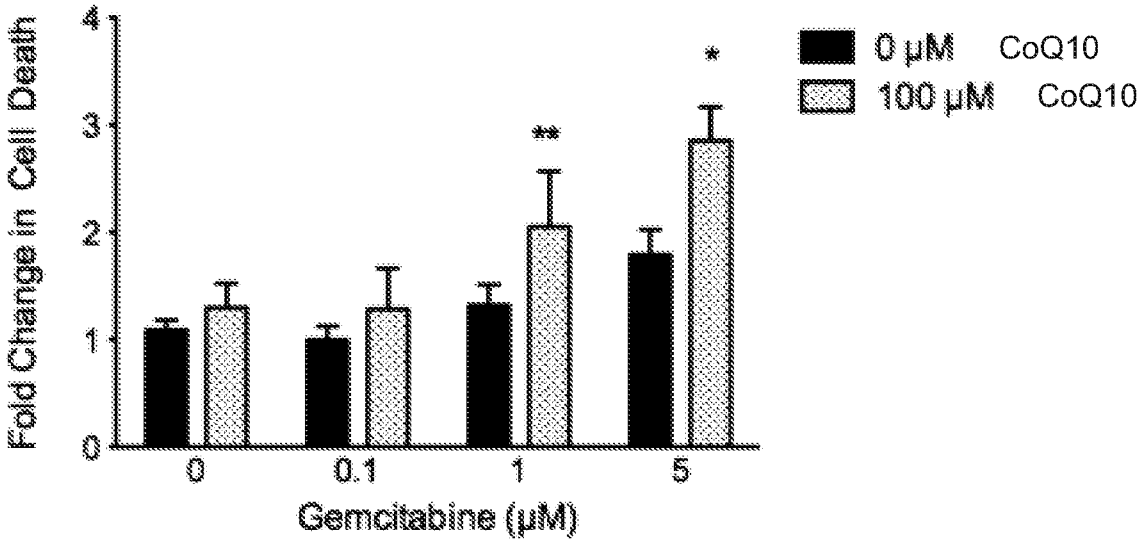


Figure 14

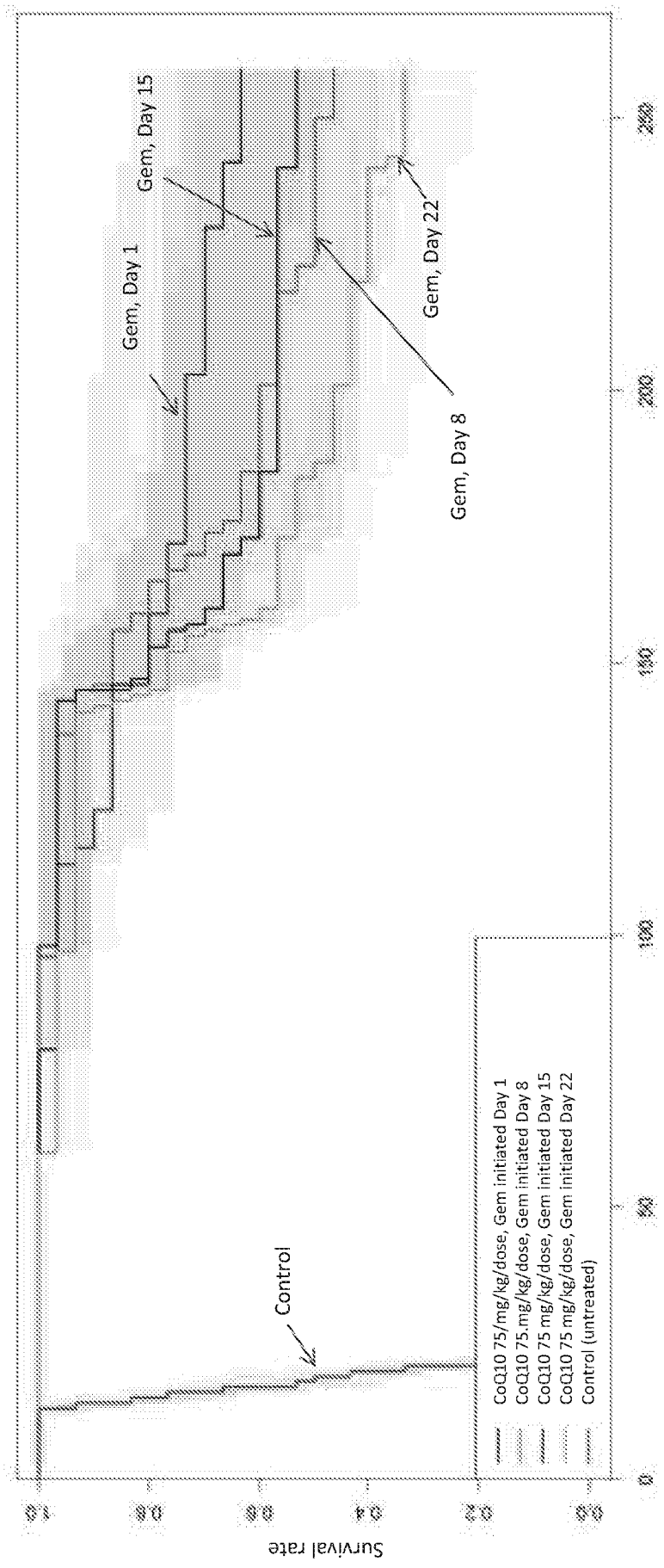

Survival rate
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
200
Days
Gem, Day 1
Gem, Day 15
Gem, Day 22
Gem, Day 8
Control
CoQ10 75/mg/kg/dose, Gem initiated Day 1
CoQ10 75.mg/kg/dose, Gem initiated Day 8
CoQ10 75 mg/kg/dose, Gem initiated Day 15
CoQ10 75 mg/kg/dose, Gem initiated Day 22
Control (untreated)

Figure 15

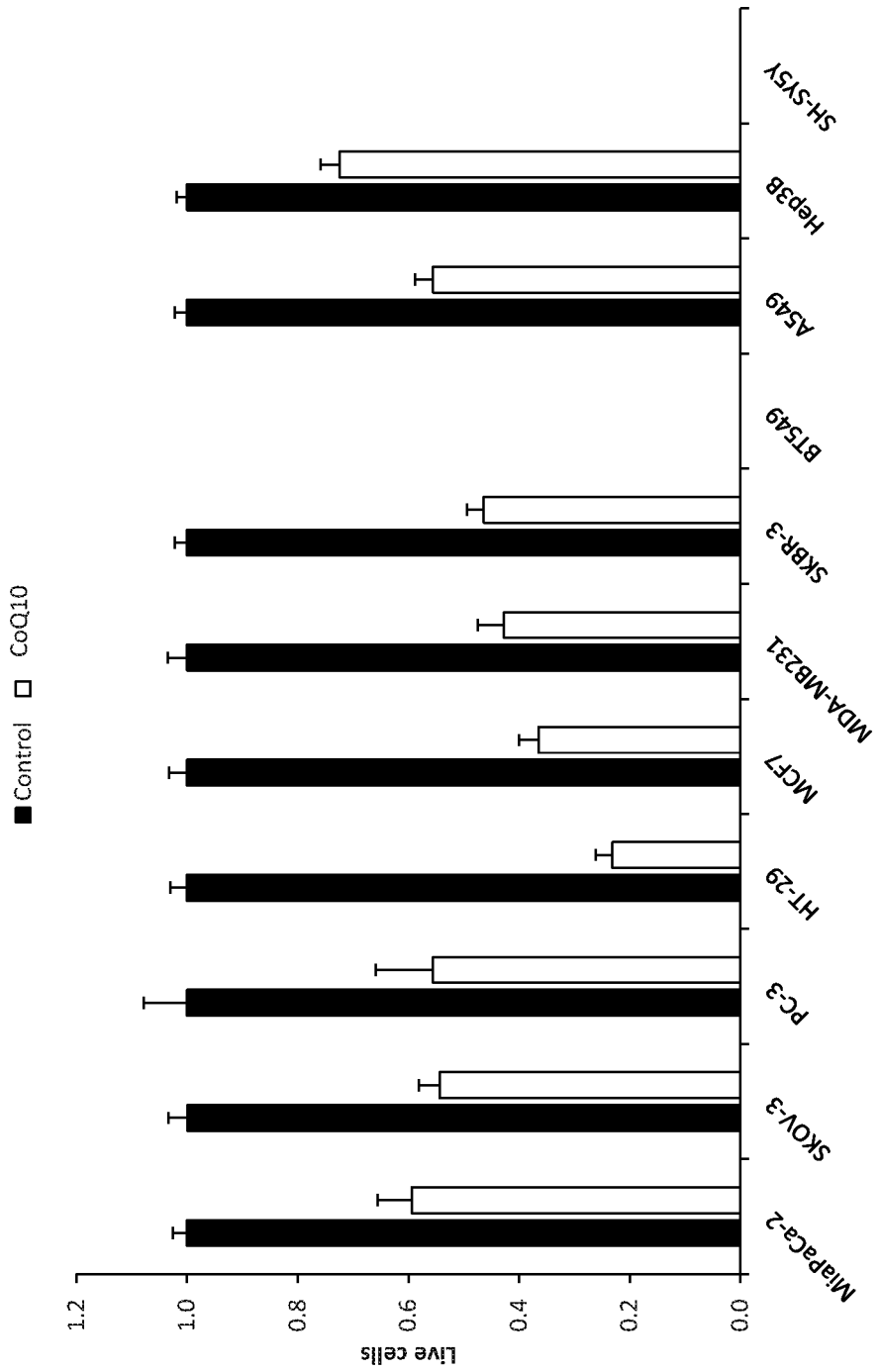

Control
CoQ10
Live cells
0.0
0.2
0.4
0.6
0.8
1.0
1.2
MiaPaCa-2
SKOV-3
PC-3
HT-29
MCF7
MDA-MB231
SKBR-3
BT549
A549
Hep3B
SH-SY5Y

Figure 16

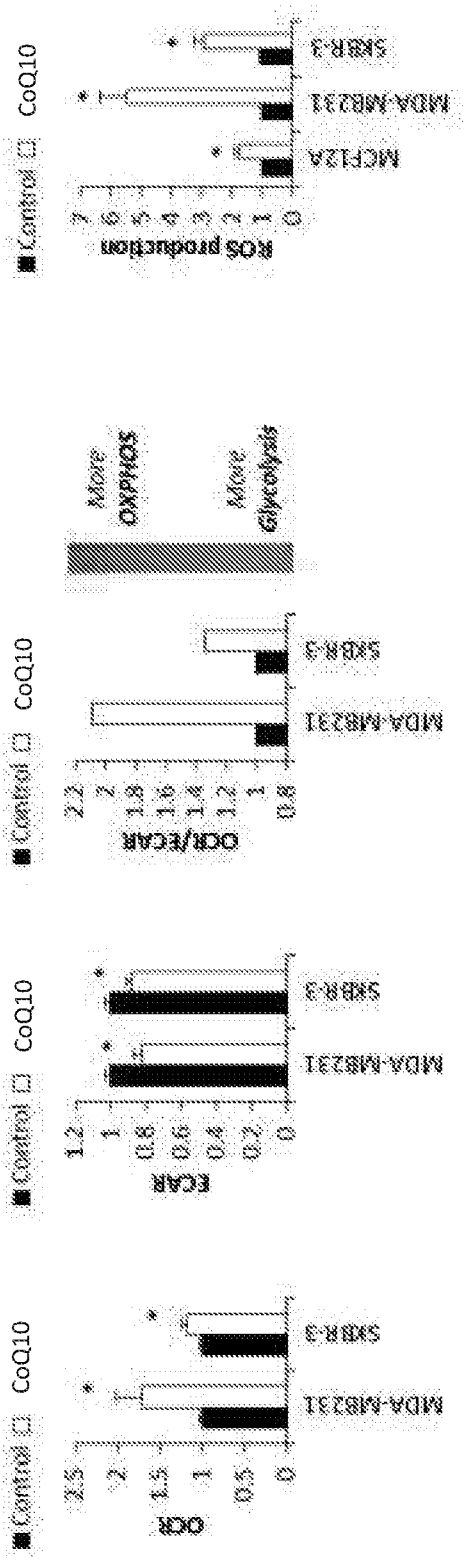

Control
CoQ10
OCR
2.5
2
1.5
1
0.5
0
MDA-MB231
SKBR-3
ECAR
1.2
1
0.8
0.6
0.4
0.2
0
OCR/ECAR
2.2
2
1.8
1.6
1.4
1.2
1
0.8
More OXPHOS
More Glycolysis
ROS production
7
6
5
4
3
2
1
0
MCF12A

Figure 17

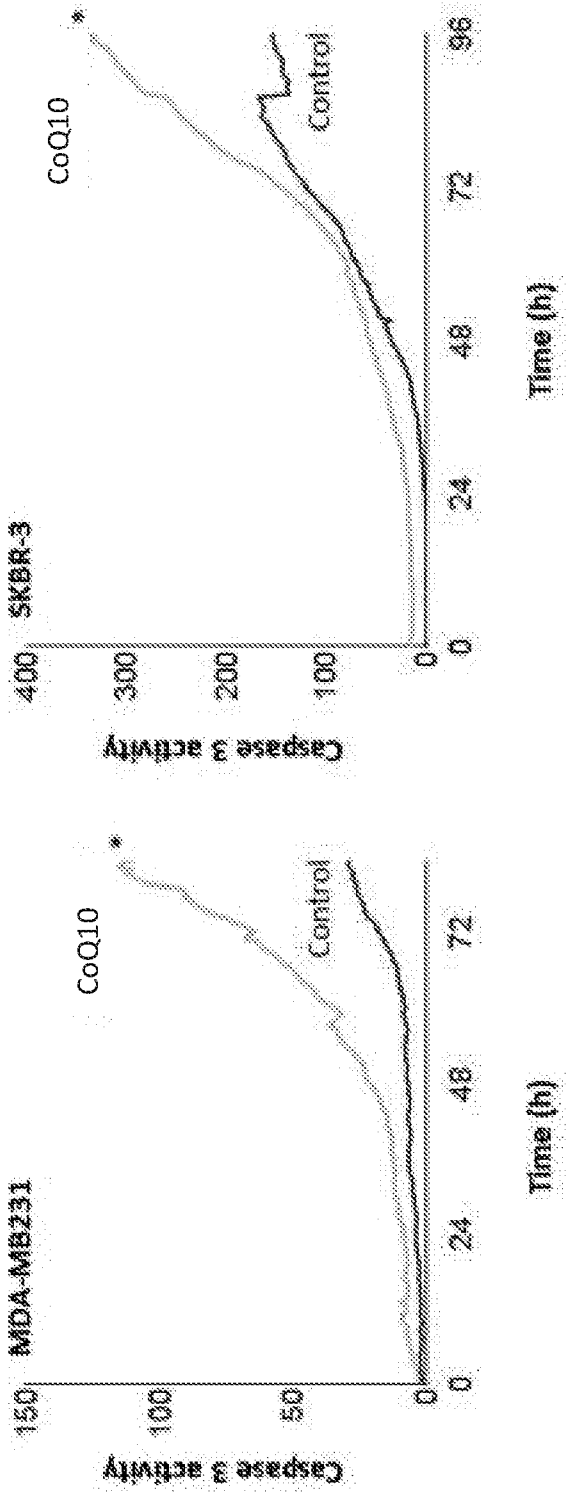

SKBR-3
Caspase 3 activity
400
300
200
100
0
0
24
48
72
96
Time (h)
CoQ10
Control
*
MDA-MB231
Caspase 3 activity
150
100
50
0
0
24
48
72
Time (h)
CoQ10
Control
*

Figure 18

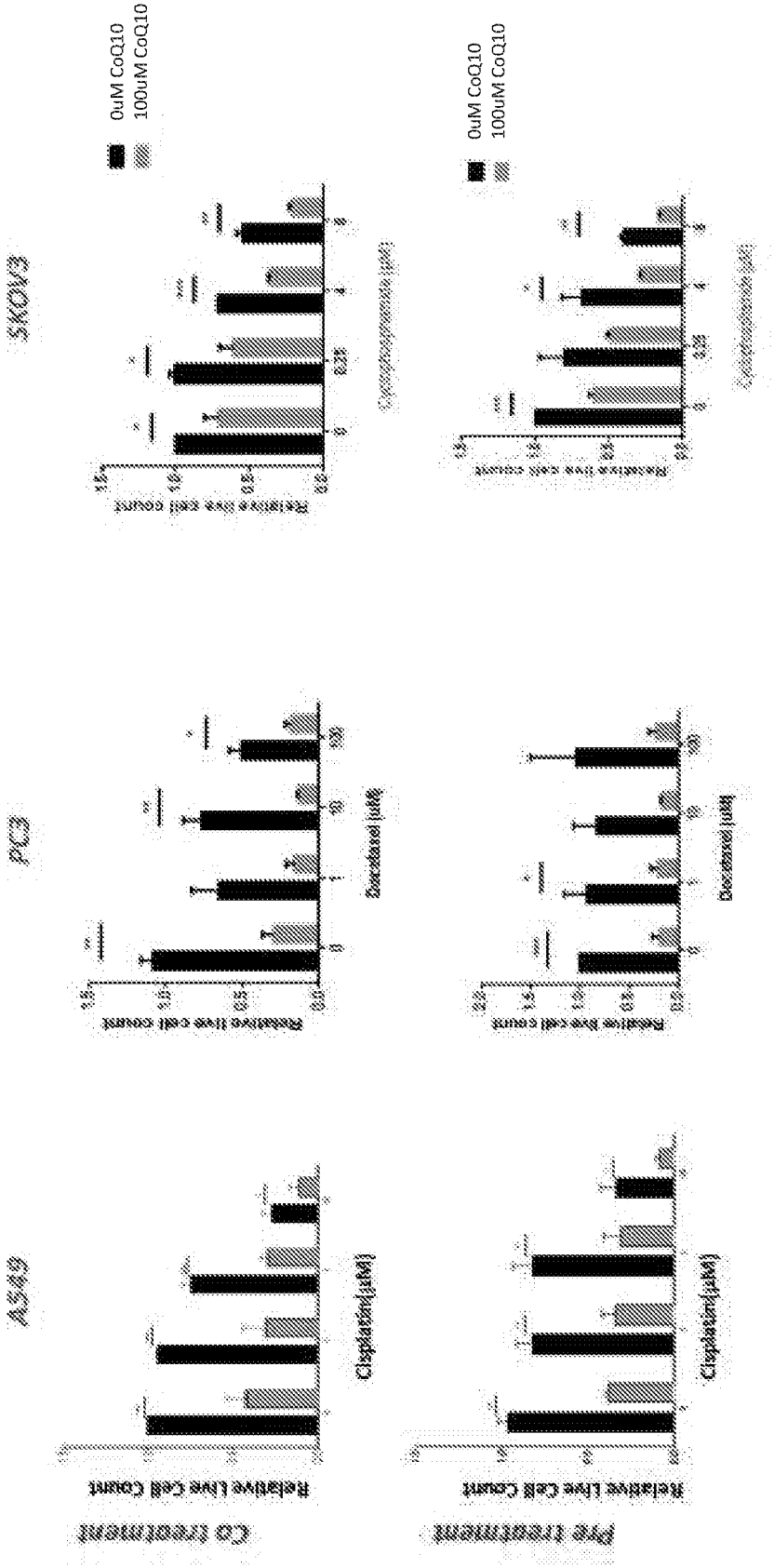

A549
PC3
SKOV3
Co treatment
Pre treatment
0uM CoQ10
100uM CoQ10
Relative live cell count
Cisplatin(μM)
Docetaxel (μM)

Figure 19

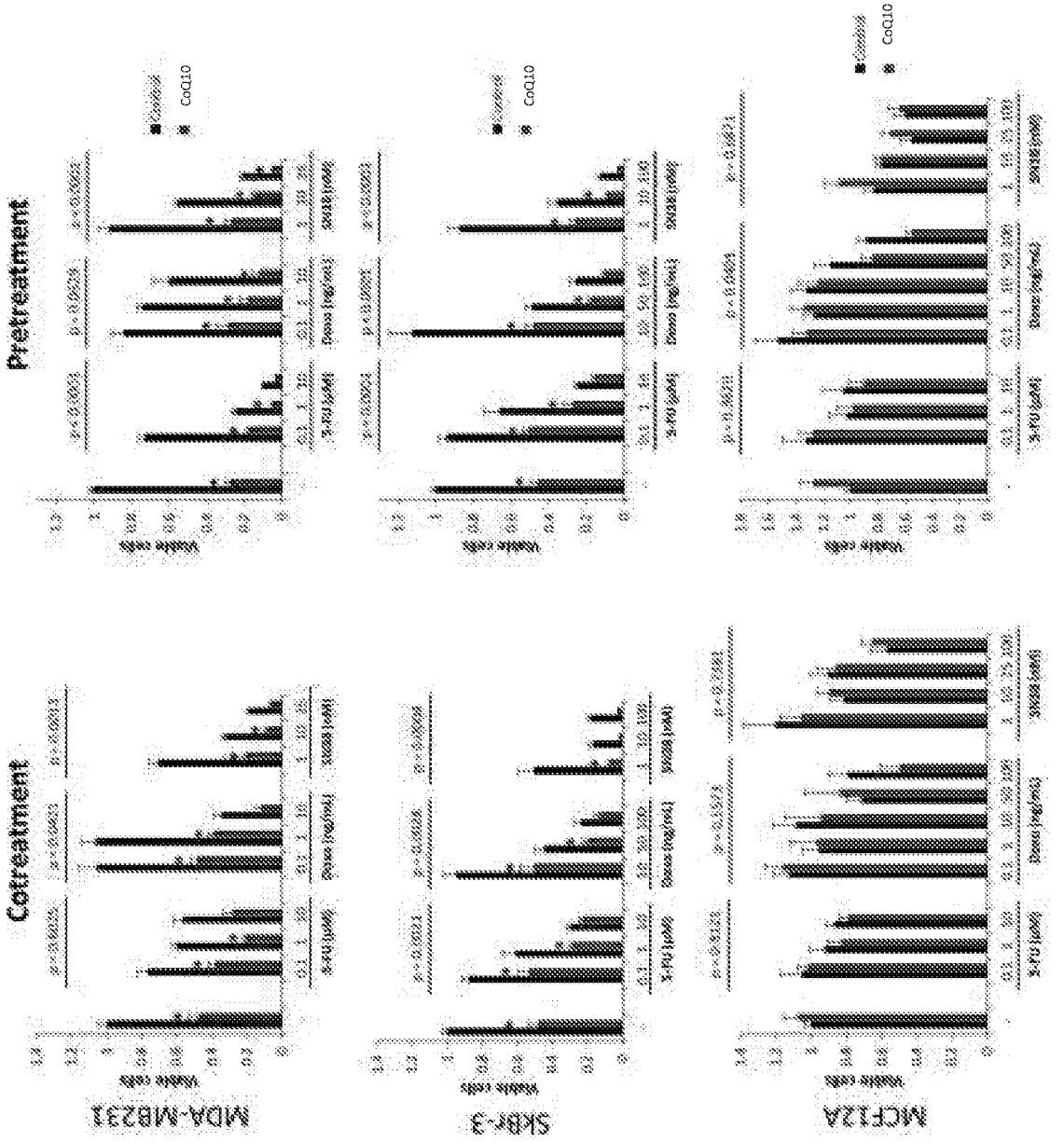


Figure 20

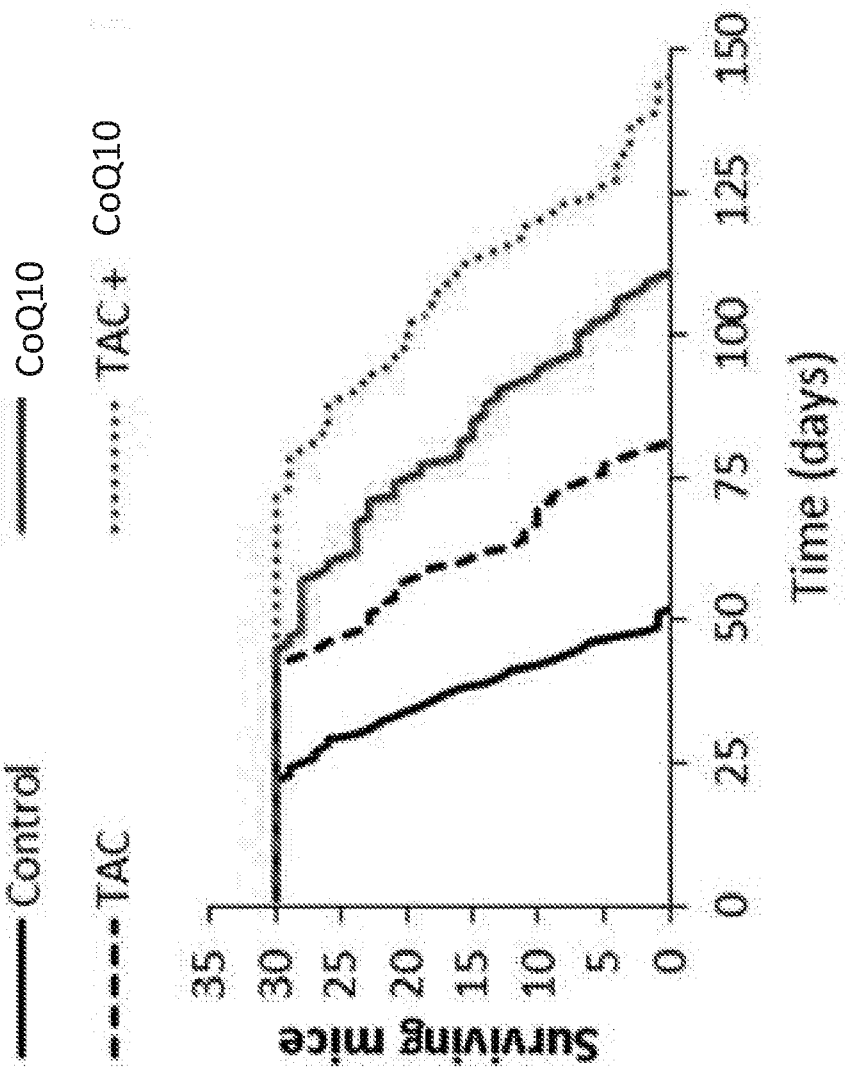

Control
CoQ10
TAC
TAC + CoQ10
Surviving mice
0
5
10
15
20
25
30
35
0
25
50
75
100
125
150
Time (days)

Figure 21

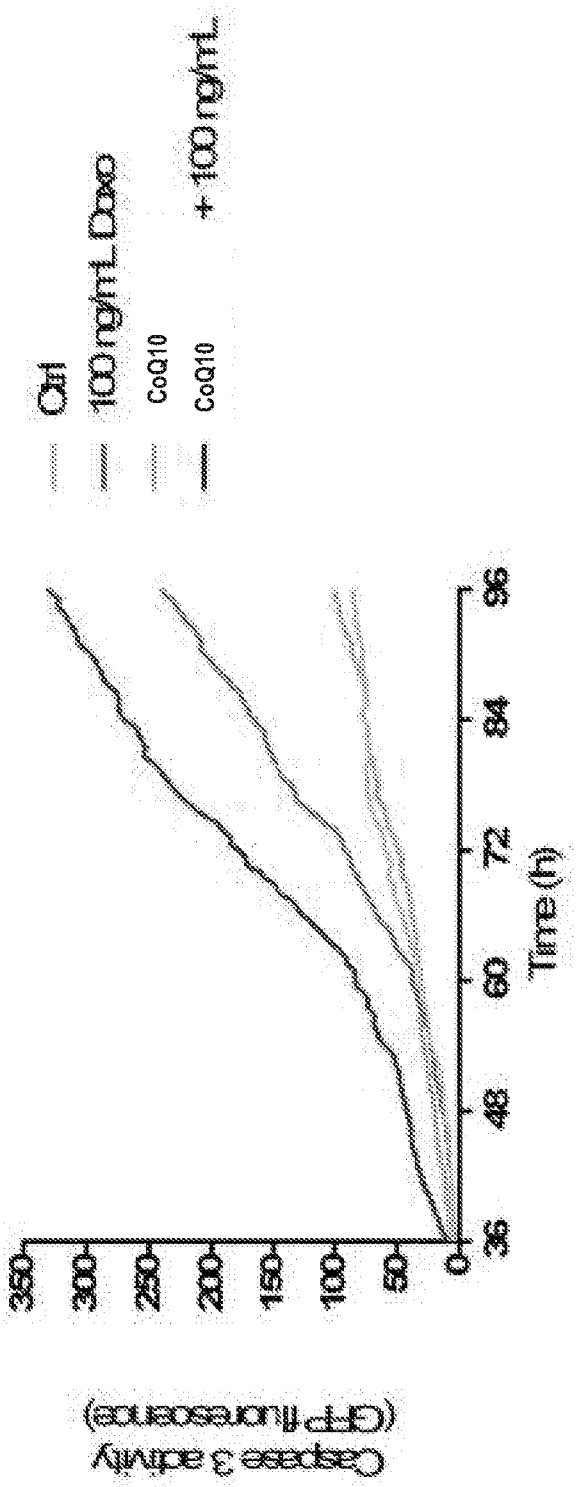

Ctrl
100 ng/mL Doxo
CoQ10
CoQ10 + 100 ng/mL
Caspase 3 activity (GFP fluorescence)
350
300
250
200
150
100
50
0
36
48
60
72
84
96
Time (h)

Figure 22

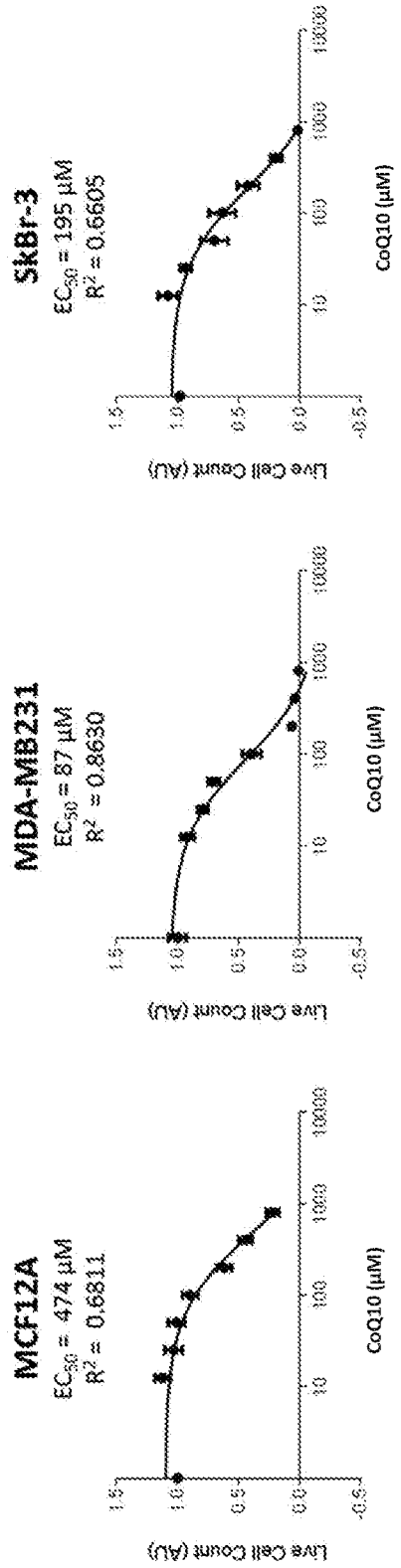

MCF12A
EC50 = 474 µM
R2 = 0.6811
MDA-MB231
EC50 = 87 µM
R2 = 0.8630
SkBr-3
EC50 = 195 µM
R2 = 0.6605
Live Cell Count (AU)
CoQ10 (µM)

Figure 23

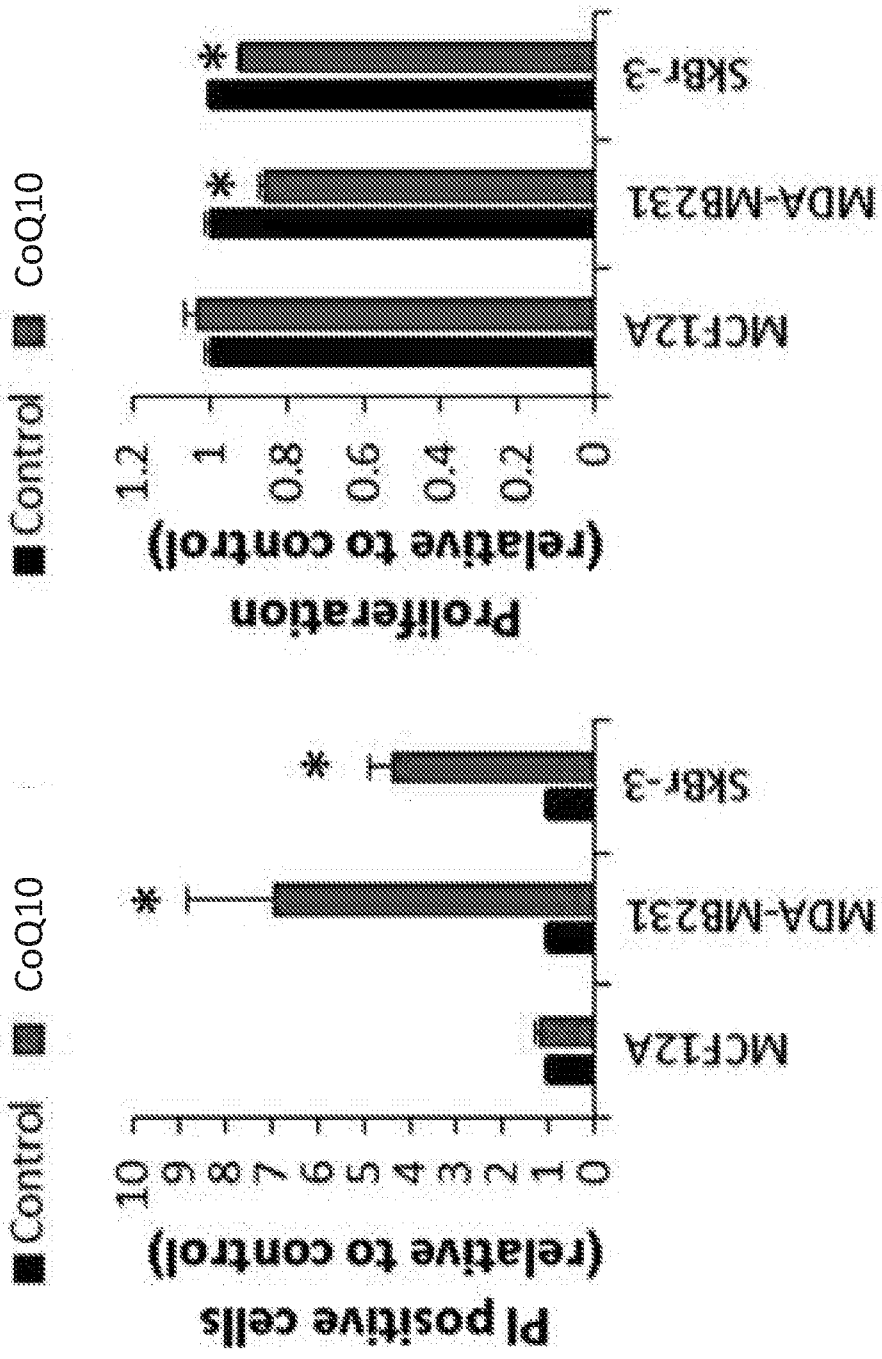

Control
CoQ10
Proliferation
(relative to control)
1.2
1
0.8
0.6
0.4
0.2
0
MCF12A
MDA-MB231
SkBr-3
*
Control
CoQ10
PI positive cells
(relative to control)
10
9
8
7
6
5
4
3
2
1
0
MCF12A
MDA-MB231
SkBr-3
*

Figure 24

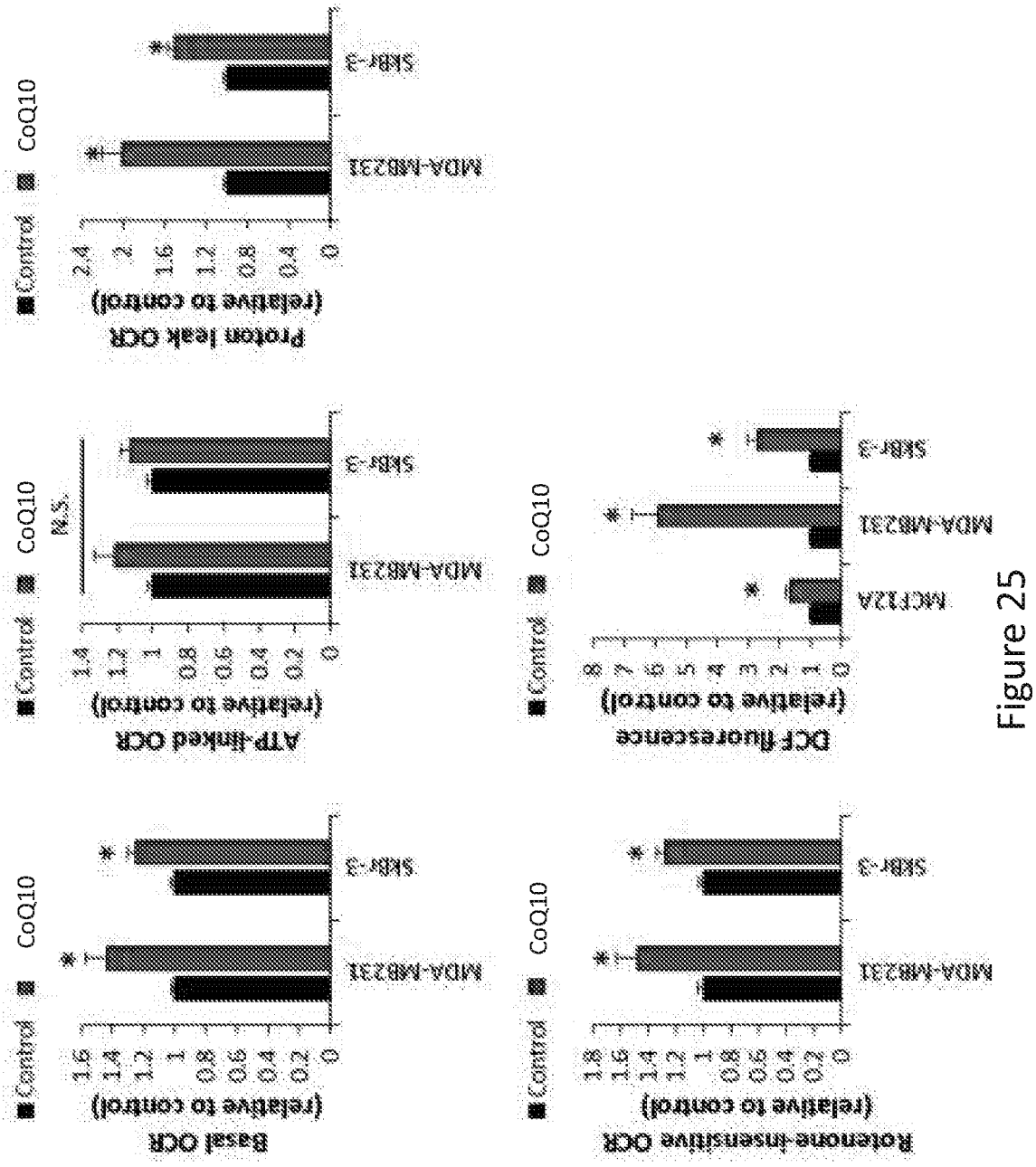

Control
CoQ10
Basal OCR
(relative to control)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
MDA-MB231
SkBr-3
*
ATP-linked OCR
(relative to control)
N.S.
Proton leak OCR
(relative to control)
2.4
2
1.6
1.2
0.8
0.4
0
Rotenone-insensitive OCR
(relative to control)
1.8
DCF fluorescence
(relative to control)
8
7
6
5
4
3
2
MCF12A

Figure 25

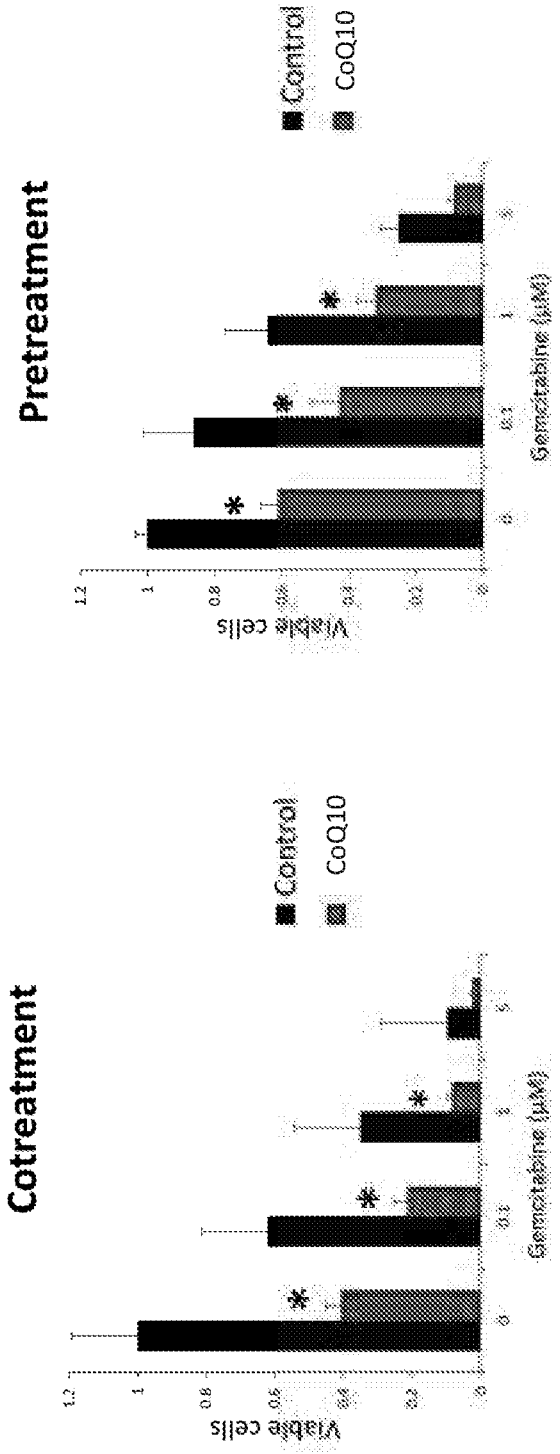

Pretreatment
Control
CoQ10
Viable cells
Gemcitabine (μM)
Cotreatment
Control
CoQ10
Viable cells
Gemcitabine (μM)

Figure 26

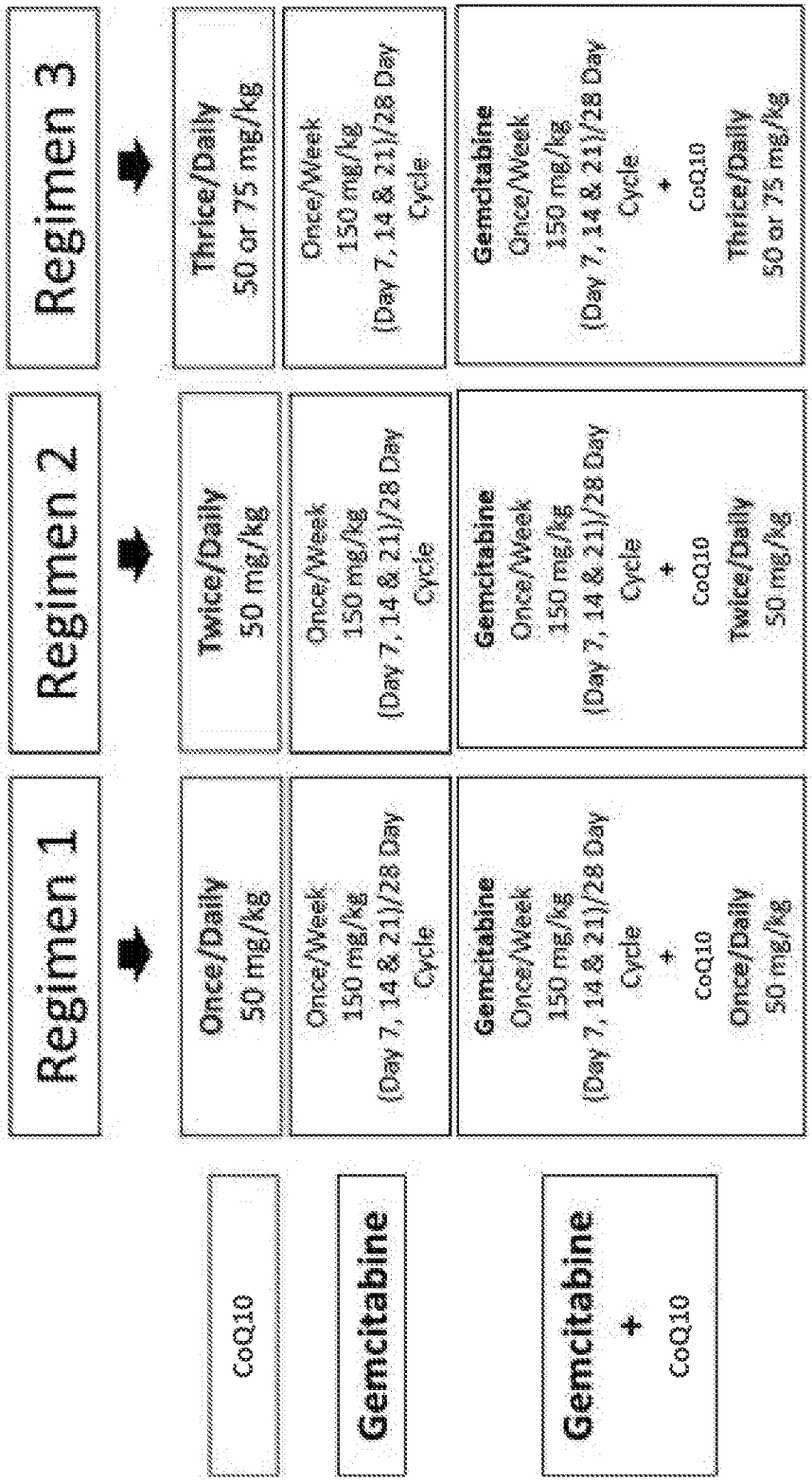

Regimen 1
Regimen 2
Regimen 3
CoQ10
Once/Daily 50 mg/kg
Twice/Daily 50 mg/kg
Thrice/Daily 50 or 75 mg/kg
Gemcitabine
Once/Week 150 mg/kg (Day 7, 14 & 21)/28 Day Cycle
Once/Week 150 mg/kg (Day 7, 14 & 21)/28 Day Cycle
Once/Week 150 mg/kg (Day 7, 14 & 21)/28 Day Cycle
Gemcitabine + CoQ10
Gemcitabine Once/Week 150 mg/kg (Day 7, 14 & 21)/28 Day Cycle + CoQ10 Once/Daily 50 mg/kg
Gemcitabine Once/Week 150 mg/kg (Day 7, 14 & 21)/28 Day Cycle + CoQ10 Twice/Daily 50 mg/kg
Gemcitabine Once/Week 150 mg/kg (Day 7, 14 & 21)/28 Day Cycle + CoQ10 Thrice/Daily 50 or 75 mg/kg

Figure 27

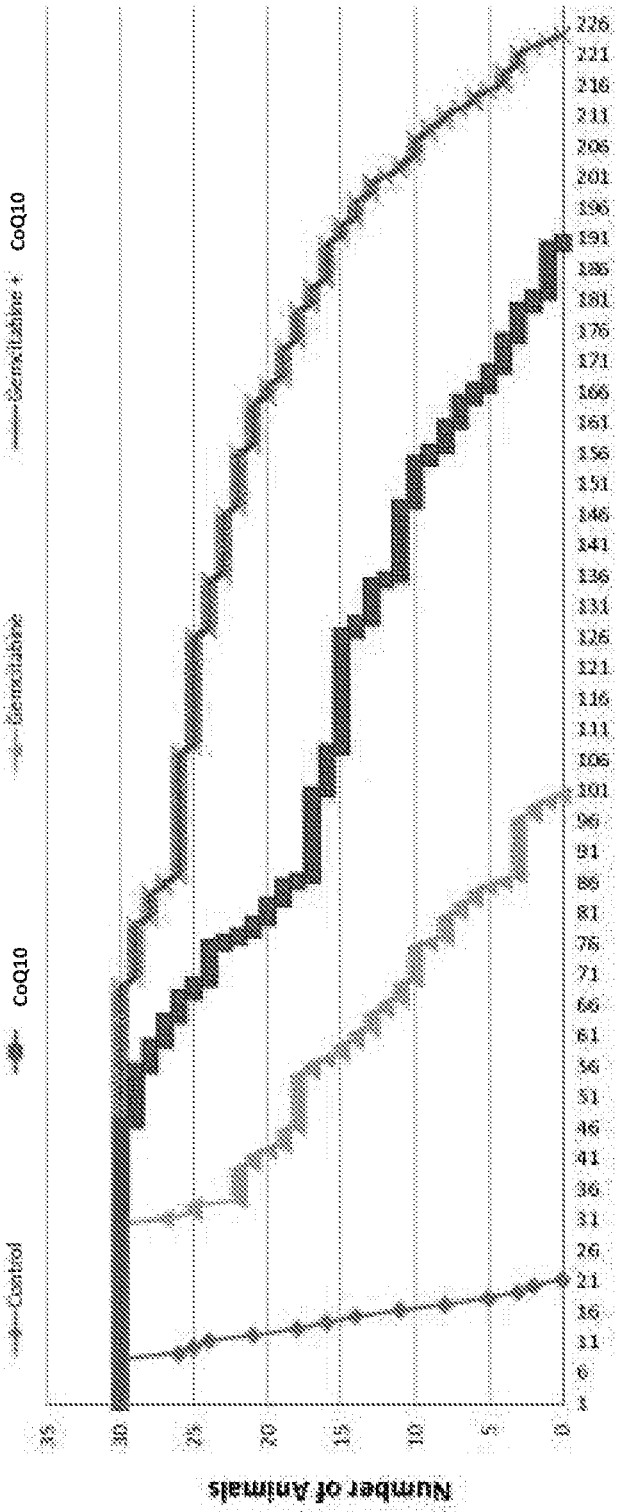

Number of Animals
Control
CoQ10
Gemcitabine
Gemcitabine + CoQ10

Figure 28

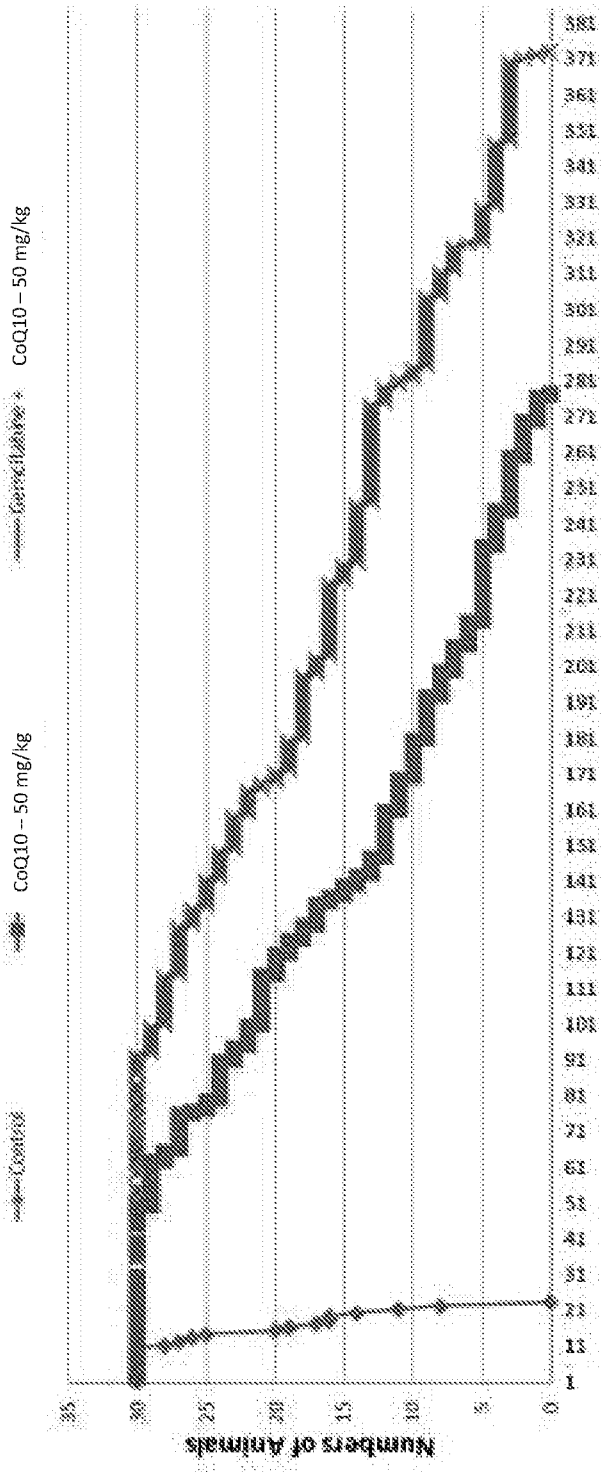

Control
CoQ10 – 50 mg/kg
Ferrostatin +
CoQ10 – 50 mg/kg
Numbers of Animals
0
5
10
15
20
25
30
35
1
11
21
31
41
51
61
71
81
91
101
111
121
131
141
151
161
171
181
191
201
211
221
231
241
251
261
271
281
291
301
311
321
331
341
351
361
371
381

Figure 29

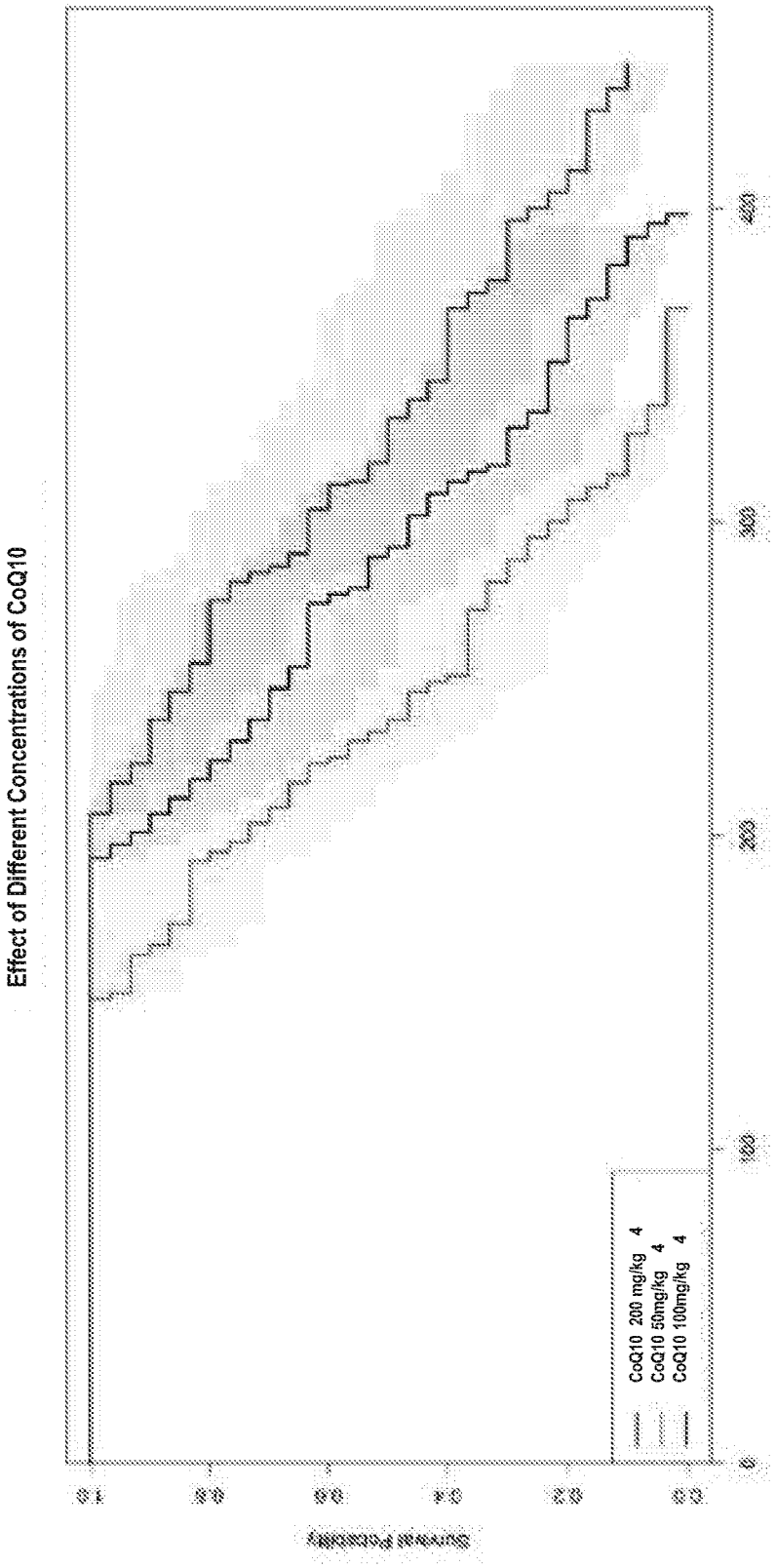

Effect of Different Concentrations of CoQ10
CoQ10 200 mg/kg 4
CoQ10 50mg/kg 4
CoQ10 100mg/kg 4
0
100
200
300
400
0.0
0.2
0.4
0.6
0.8
1.0

Figure 30

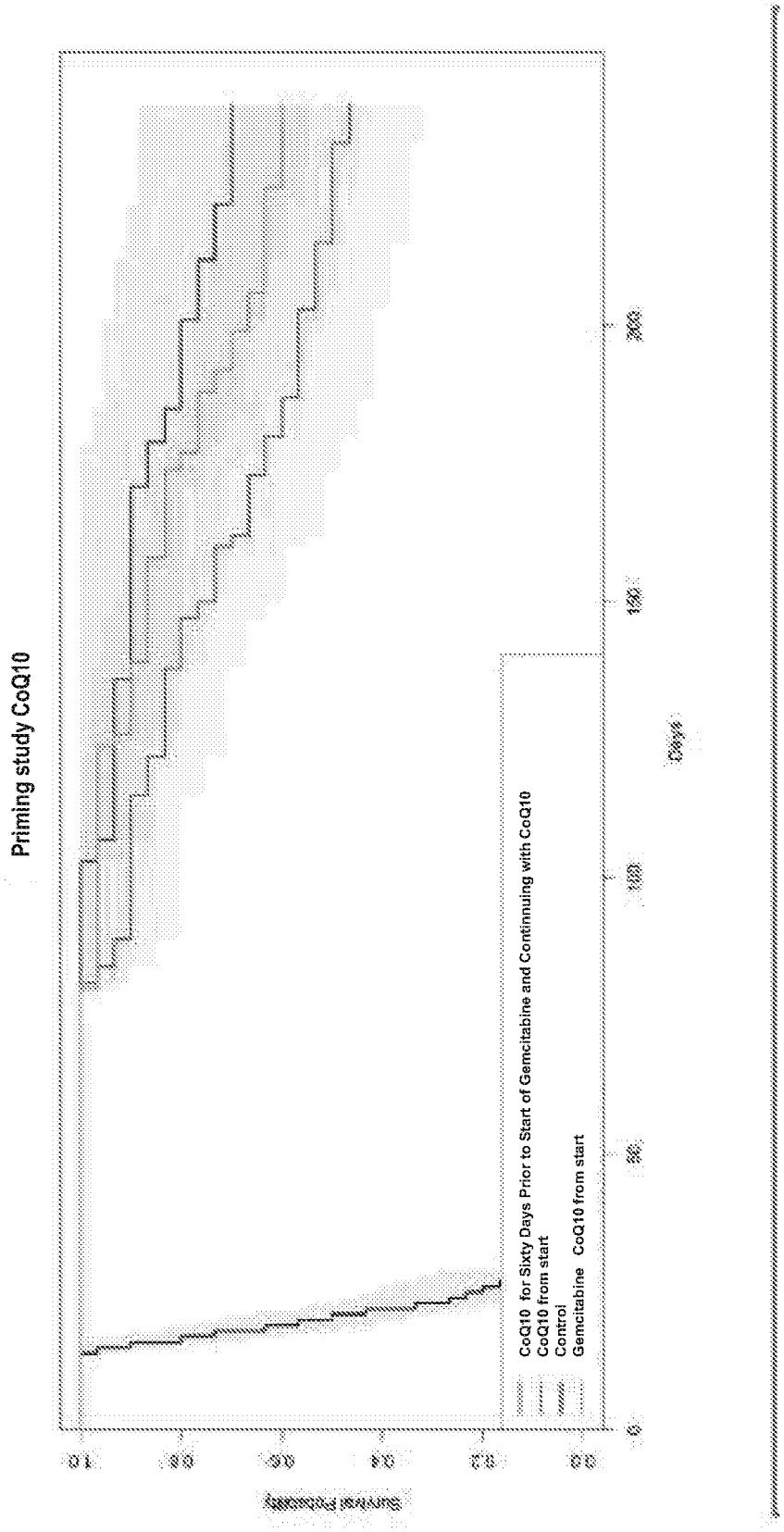

Priming study CoQ10
CoQ10 for Sixty Days Prior to Start of Gemcitabine and Continuing with CoQ10
CoQ10 from start
Control
Gemcitabine CoQ10 from start
Days

Figure 31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/33402

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/122; A61P 35/02; G01N 33/53 (2014.01)
USPC - 424/93.7, 94.1; 435/375
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)
IPC(8) - A61K 9/127, 31/122, 35/12, 38/43, 39/395; A61P 35/00, 35/02; G01N 33/00, 33/53 (2014.01)
USPC - 424/93.7, 94.1, 174.1, 450; 435/4, 7.92, 375; 514/690; 977/773

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)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google Scholar; PubMed; IP.com; Proquest; Coenzyme Q10, CoQ10, ubiquinone, ubidecarenone, vitamin Q10, Q10, chemotherapeutic, anti-cancer, topical, intravenous, infusion, injection, inhalation, transdermal, cancer, oncology, subject, human, combination, pretreatment, administration, lower dose,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/0201801 A1 (HSIA, SL et al.) August 9, 2012; paragraphs [0003], [0068], [0077]-[0077], [0084], [0116], [0118], [0120]-[0121]	1-2, 3/1-2, 4/1-2, 5/1-2, 6/1-2, 7/1-2, 8, 9/1-2, 10/1-2, 13/1-2, 14/1-2, 15/1-2, 16/1-2, 17/1-2, 20-22, 25-29
---		---
Y		11/10/1-2,18/17/1-2, 23/10/1-2, 30, 31/27-30, 32-42, 43/39-42
Y	US 2011/0229554 A1 (NARAIN, NR et al.) September 22, 2011; paragraphs [0003], [0005], [0041], [0122], [0182]-[0183], [0202], [0258]-[0259]	11/10/1-2, 18/17/1-2, 23/10/1-2, 30, 31/27-30, 42, 43/39-42
Y	US 2012/0183621 A1 (SINKO, PJ et al.) July 19, 2012; paragraphs [0057], [0075]; page 13, claims 1, 5	32-42, 43/39-42

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"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)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"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
"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2014 (24.07.2014)	15 AUG 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/33402

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:

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.: 12, 19, 24, 44-66
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:

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.

(19)中华人民共和国国家知识产权局

(12)发明专利申请

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(71)申请人 博格有限责任公司
地址 美国田纳西州
(72)发明人 N·R·纳莱恩 R·萨兰加拉简
(74)专利代理机构 北京市金杜律师事务所 11256
代理人 陈文平
(51)Int.Cl.
A61K 31/122(2006.01)
A61P 35/02(2006.01)
G01N 33/53(2006.01)

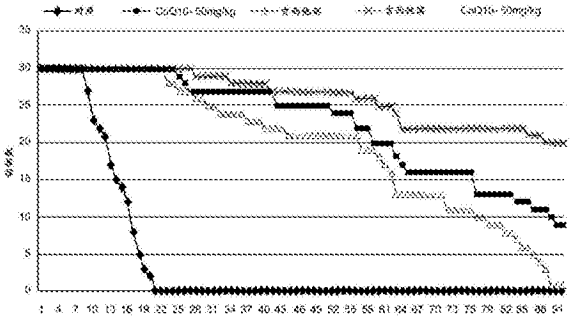
权利要求书5页 说明书75页 附图33页

(54)发明名称

使用辅酶Q10联合疗法治疗癌症

(57)摘要

本文提供了通过共同施用CoQ10制剂与化疗剂和/或外科手术来治疗肿瘤疾病的方法。CoQ10制剂可以是静脉内制剂、局部制剂或通过吸入的制剂中的至少一种。化疗剂可以是抗代谢物或蒽环类中的至少一种。可在施用化疗之前、与施用化疗同时或基本同时、与化疗的施用间隔或在施用化疗之后共同施用CoQ10制剂。



CN 105338973 A

1. 一种治疗受试者的肿瘤疾病的方法，所述方法包括：

(a) 向所述受试者施用辅酶 Q10(CoQ10)；

(b) 中断 CoQ10 的施用；和

(c) 在已中断 CoQ10 的施用后，向所述受试者施用至少一种化疗剂，

使得所述肿瘤疾病被治疗。

2. 一种治疗受试者的肿瘤疾病的方法，所述方法包括：

(a) 向所述受试者施用辅酶 Q10(CoQ10)；

(b) 在开始 CoQ10 的施用后，向所述受试者施用至少一种化疗剂；和

(c) 在开始所述至少一种化疗剂的施用后，继续使用 CoQ10 治疗，

使得所述肿瘤疾病被治疗。

3. 根据权利要求 1 或 2 所述的方法，其中所述 CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 24 小时。

4. 根据权利要求 1 或 2 所述的方法，其中所述 CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 48 小时。

5. 根据权利要求 1 或 2 所述的方法，其中所述 CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 1 周。

6. 根据权利要求 1 或 2 所述的方法，其中所述 CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 2 周。

7. 根据权利要求 1 或 2 所述的方法，其中所述 CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 3 周。

8. 根据权利要求 1 所述的方法，其中所述 CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 4 周。

9. 根据权利要求 1 或 2 所述的方法，其中在 CoQ10 施用开始后至少 24 小时、在 CoQ10 施用开始后一周或多周、在 CoQ10 施用开始后两周或更多周、在 CoQ10 施用开始后三周或更多周、在 CoQ10 施用开始后四周或更多周、在 CoQ10 施用开始后五周或更多周、在 CoQ10 施用开始后六周或更多周、在 CoQ10 施用开始后七周或更多周或者在 CoQ10 施用开始后八周或更多周，开始施用所述至少一种化疗剂。

10. 根据权利要求 1 或 2 所述的方法，其中相对于单独使用所述至少一种化疗剂的治疗 [SPEC：即在不存在向所述受试者的 CoQ10 施用的情况下]，所述肿瘤疾病对治疗的反应被改善。

11. 根据权利要求 10 所述的方法，其中相对于单独使用所述至少一种化疗剂的治疗，所述反应改善至少 5%、至少 10%、至少 15%、至少 20%、至少 30%、至少 40%或至少 50%。

12. 根据权利要求 10 或 11 所述的方法，其中所述反应包括减小肿瘤负荷、减小肿瘤大小、抑制肿瘤生长、在治疗前患有进行性肿瘤疾病的受试者中实现稳定的肿瘤疾病、延长到肿瘤疾病进展的时间和增加存活时间中的任意一种或多种。

13. 根据权利要求 1 或 2 所述的方法，其中所述 CoQ10 局部施用。

14. 根据权利要求 1 或 2 所述的方法，其中所述 CoQ10 通过吸入施用。

15. 根据权利要求 1 或 2 所述的方法，其中所述 CoQ10 通过注射或输注施用。

16. 根据权利要求 1 或 2 所述的方法，其中所述 CoQ10 通过静脉内给药施用。

17. 根据权利要求 1 或 2 所述的方法，其中所述 CoQ10 通过连续静脉内输注施用。

18. 根据权利要求 17 所述的方法，其中所述剂量通过经 24 小时连续输注施用。

19. 根据权利要求 15-18 中任一项所述的方法，其中所述 CoQ10 以约 5mg/kg、约 10mg/kg、约 12.5mg/kg、约 20mg/kg、约 25mg/kg、约 30mg/kg、约 35mg/kg、约 40mg/kg、约 45mg/kg、约 50mg/kg、约 55mg/kg、约 58mg/kg、约 58.6mg/kg、约 60mgkg、约 75mg/kg、约 78mg/kg、约 100mg/kg、约 104mg/kg、约 125mg/kg、约 150mg/kg、约 175mg/kg、约 200mg/kg、约 300mg/kg 或约 400mg/kg 的剂量施用。

20. 一种改进针对受试者的肿瘤疾病的化疗治疗方案的方法，所述方法包括在开始化疗治疗方案之前使用辅酶 Q10(CoQ10) 对患有肿瘤疾病的受试者预治疗足够的时间，其中所述化疗治疗方案包括施用一种或多种化疗剂，使得相对于单独使用所述化疗治疗方案的治疗，所述肿瘤疾病的反应被改善。

21. 根据权利要求 20 所述的方法，其中在开始所述化疗治疗方案之前，所述受试者使用 CoQ10 预治疗至少 24 小时、至少 48 小时、至少 1 周、至少 2 周、至少 3 周或至少 4 周。

22. 根据权利要求 20 所述的方法，其中在 CoQ10 预治疗开始后至少 24 小时、在 CoQ10 预治疗开始后一周或多周、在 CoQ10 预治疗开始后两周或更多周、在 CoQ10 预治疗开始后三周或更多周、在 CoQ10 预治疗开始后四周或更多周、在 CoQ10 预治疗开始后五周或更多周、在 CoQ10 预治疗开始后六周或更多周、在 CoQ10 预治疗开始后七周或更多周或者在 CoQ10 预治疗开始后八周或更多周，开始所述化疗治疗方案。

23. 根据权利要求 10 所述的方法，其中相对于单独使用所述化疗治疗方案的治疗，所述反应改善至少 5%、至少 10%、至少 15%、至少 20%、至少 30%、至少 40%或至少 50%。

24. 根据权利要求 20-23 中任一项所述的方法，其中所述反应包括减小肿瘤负荷、减小肿瘤大小、抑制肿瘤生长、在治疗前患有进行性肿瘤疾病的受试者中实现肿瘤疾病稳定、延长到肿瘤疾病进展的时间和增加存活时间中的任意一种或多种。

25. 根据权利要求 20 所述的方法，其中所述 CoQ10 局部施用。

26. 根据权利要求 20 所述的方法，其中所述 CoQ10 通过吸入施用。

27. 根据权利要求 20 所述的方法，其中所述 CoQ10 通过注射或输注施用。

28. 根据权利要求 20 所述的方法，其中所述 CoQ10 通过静脉内给药施用。

29. 根据权利要求 20 所述的方法，其中所述 CoQ10 通过连续静脉内输注施用。

30. 根据权利要求 20 所述的方法，其中所述 CoQ10 通过经 24 小时连续输注施用。

31. 根据权利要求 27-30 中任一项所述的方法，其中所述 CoQ10 以约 5mg/kg、约 10mg/kg、约 12.5mg/kg、约 20mg/kg、约 25mg/kg、约 30mg/kg、约 35mg/kg、约 40mg/kg、约 45mg/kg、约 50mg/kg、约 55mg/kg、约 58mg/kg、约 58.6mg/kg、约 60mgkg、约 75mg/kg、约 78mg/kg、约 100mg/kg、约 104mg/kg、约 125mg/kg、约 150mg/kg、约 175mg/kg、约 200mg/kg、约 300mg/kg 或约 400mg/kg 的剂量施用。

32. 一种治疗受试者的肿瘤疾病的方法，所述方法包括：

(a) 向所述受试者施用辅酶 Q10(CoQ10)；和

(b) 以比用来治疗所述肿瘤疾病的化疗剂的标准剂量低的剂量向所述受试者施用至少一种化疗剂，

使得所述肿瘤疾病被治疗。

33. 根据权利要求 32 所述的方法，其中在向所述受试者施用所述至少一种化疗剂之前中断 CoQ10 的施用。

34. 根据权利要求 32 所述的方法，其中在向所述受试者施用所述至少一种化疗剂之后继续 CoQ10 的施用。

35. 根据权利要求 32 所述的方法，其中所述 CoQ10 在施用所述至少一种化疗剂之前施用至少 24 小时、至少 48 小时、至少 1 周、至少 2 周、至少 3 周或至少 4 周。

36. 根据权利要求 32 所述的方法，其中在 CoQ10 施用开始后至少 24 小时、在 CoQ10 施用开始后一周或多周、在 CoQ10 施用开始后两周或更多周、在 CoQ10 施用开始后三周或更多周、在 CoQ10 施用开始后四周或更多周、在 CoQ10 施用开始后五周或更多周、在 CoQ10 施用开始后六周或更多周、在 CoQ10 施用开始后七周或更多周或者在 CoQ10 施用开始后八周或更多周，施用所述至少一种化疗剂。

37. 根据权利要求 32 所述的方法，其中所述 CoQ10 局部施用。

38. 根据权利要求 32 所述的方法，其中所述 CoQ10 通过吸入施用。

39. 根据权利要求 32 所述的方法，其中所述 CoQ10 通过注射或输注施用。

40. 根据权利要求 32 所述的方法，其中所述 CoQ10 通过静脉内给药施用。

41. 根据权利要求 32 所述的方法，其中所述 CoQ10 通过连续静脉内输注施用。

42. 根据权利要求 32 所述的方法，其中所述 CoQ10 通过经 24 小时连续输注施用。

43. 根据权利要求 39-42 中任一项所述的方法，其中所述 CoQ10 以约 5mg/kg、约 10mg/kg、约 12.5mg/kg、约 20mg/kg、约 25mg/kg、约 30mg/kg、约 35mg/kg、约 40mg/kg、约 45mg/kg、约 50mg/kg、约 55mg/kg、约 58mg/kg、约 58.6mg/kg、约 60mgkg、约 75mg/kg、约 78mg/kg、约 100mg/kg、约 104mg/kg、约 125mg/kg、约 150mg/kg、约 175mg/kg、约 200mg/kg、约 300mg/kg 或约 400mg/kg 的剂量施用。

44. 根据前述权利要求中任一项所述的方法，其中所述至少一种化疗剂包含选自拓扑异构酶 I 抑制剂、拓扑异构酶 II 抑制剂、有丝分裂抑制剂、烷化剂、铂化合物和抗代谢物的化疗剂。

45. 根据权利要求 44 所述的方法，其中所述至少一种化疗剂包含拓扑异构酶 II 抑制剂。

46. 根据权利要求 45 所述的方法，其中所述拓扑异构酶 II 抑制剂包含多柔比星、表柔比星、伊达比星、米托蒽醌、洛索蒽醌、依托泊苷和替尼泊苷中的至少一种。

47. 根据权利要求 44 所述的方法，其中所述至少一种化疗剂包含拓扑异构酶 I 抑制剂。

48. 根据权利要求 47 所述的方法，其中所述拓扑异构酶 I 抑制剂包含伊立替康、托泊替康、9- 硝基喜树碱、喜树碱和喜树碱衍生物中的至少一种。

49. 根据权利要求 44 所述的方法，其中所述至少一种化疗剂包含抗代谢物。

50. 根据权利要求 49 所述的方法，其中所述抗代谢物包含 5- 氟尿嘧啶、卡培他滨、吉西他滨、甲氨喋呤和依达曲沙中的至少一种。

51. 根据权利要求 44 所述的方法，其中所述至少一种化疗剂包含烷化剂。

52. 根据权利要求 51 所述的方法，其中所述烷化剂包含氮芥、亚乙基亚胺化合物、烷基磺酸盐、亚硝基脲、达卡巴嗪、环磷酰胺、异环磷酰胺和美法仑中的至少一种。

53. 根据权利要求 44 所述的方法，其中所述至少一种化疗剂包含铂化合物。

54. 根据权利要求 53 所述的方法，其中所述铂化合物包含顺铂、奥沙利铂和卡铂中的至少一种。

55. 根据权利要求 44 所述的方法，其中所述至少一种化疗剂包含有丝分裂抑制剂。

56. 根据权利要求 55 所述的方法，其中所述有丝分裂抑制剂包含紫杉醇、多西紫杉醇、长春碱、长春新碱、长春瑞滨和鬼臼毒素衍生物中的至少一种。

57. 根据前述权利要求中任一项所述的方法，其中所述至少一种化疗剂包含选自以下的化疗剂：阿米福汀（氨磷汀）、顺铂、达卡巴嗪 (DTIC)、放线菌素、二氯甲基二乙胺（氮芥）、链脲佐菌素、环磷酰胺、卡莫司汀 (BCNU)、洛莫司汀 (CCNU)、多柔比星（阿霉素）、多柔比星脂质体（阿霉素脂质体）、吉西他滨（健择）、柔红霉素、柔红霉素脂质体、甲基苄肼、丝裂霉素、阿糖胞苷、依托泊苷、甲氨喋呤、5- 氟尿嘧啶 (5-FU)、长春碱、长春新碱、博来霉素、紫杉醇（泰素）、多西紫杉醇（泰素帝）、阿地白介素、天冬酰胺酶、白消安、卡铂、克拉屈滨、喜树碱、CPT-11、10- 羟基 -7- 乙基 - 喜树碱 (SN38)、达卡巴嗪、S-I 卡培他滨、替加氟、5'- 脱氧氟尿苷、UFT、恩尿嘧啶、脱氧胞苷、5- 氮杂胞嘧啶、5- 氮杂脱氧胞嘧啶、别嘌呤醇、2- 氯腺苷、三甲曲沙、氨喋呤、亚甲基 -10- 脱氮杂氨喋呤 (MDAM)、奥沙利铂、吡铂、四铂、沙铂、铂 -DACH、奥马铂、CI-973、JM-216 和它们的类似物、表柔比星、依托泊苷磷酸盐、9- 氨基喜树碱、10,11- 亚甲基二氧喜树碱、karenitecin、9- 硝基喜树碱、TAS 103、长春地辛、L- 苯丙氨酸氮芥、异环磷酰胺、培磷酰胺、氯乙环磷酰胺卡莫司汀、司莫司汀、埃博霉素 A-E、拓优得、6- 巯基嘌呤、6- 硫鸟嘌呤、安吖啶、依托泊苷磷酸盐、karenitecin、阿昔洛韦、伐昔洛韦、更昔洛韦、金刚烷胺、金刚乙胺、拉米夫定、齐多夫定、贝伐单抗、曲妥珠单抗、利妥昔单抗、5- 氟尿嘧啶、卡培他滨、喷司他汀、三甲曲沙、克拉屈滨、氟尿苷、氟达拉滨、羟基脲、异环磷酰胺、伊达比星、美司钠、伊立替康、米托蒽醌、拓扑替康、亮丙瑞林、甲地孕酮、美法仑、巯基嘌呤、普卡霉素、米托坦、培门冬酶、喷司他汀、哌泊溴烷、普卡霉素、链脲佐菌素、他莫昔芬、替尼泊苷、睾内酯、硫鸟嘌呤、塞替派、尿嘧啶氮芥、长春瑞滨、苯丁酸氮芥、顺铂、多柔比星、紫杉醇（泰素）、博莱霉素、mTor、表皮生长因子受体 (EGFR) 和成纤维细胞生长因子 (FGF) 及其组合。

58. 根据前述权利要求中任一项所述的方法，其中所述至少一种化疗剂包含吉西他滨、5- 氟尿嘧啶、顺铂、卡培他滨、甲氨蝶呤、依达曲沙、多西紫杉醇、环磷酰胺、多柔比星和伊立替康中的至少一种。

59. 根据前述权利要求中任一项所述的方法，其中所述肿瘤疾病选自癌瘤、肉瘤、淋巴瘤、黑素瘤和白血病。

60. 根据前述权利要求中任一项所述的方法，其中所述肿瘤疾病选自胰腺癌、乳腺癌、肝癌、皮肤癌、肺癌、结肠癌、前列腺癌、甲状腺癌、膀胱癌、直肠癌、子宫内膜癌、肾癌、骨癌、脑癌、子宫颈癌、胃癌、口癌和口腔癌、成神经细胞瘤、睾丸癌、子宫癌和外阴癌。

61. 根据权利要求 60 所述的方法，其中所述皮肤癌选自黑素瘤、鳞状细胞癌、基底细胞癌和皮肤 T- 细胞淋巴瘤 (CTCL)。

62. 根据前述权利要求中任一项所述的方法，其中所述肿瘤疾病为三阴性乳腺癌。

63. 根据前述权利要求中任一项所述的方法，其中所述受试者为人。

64. 根据前述权利要求中任一项所述的方法，其中所述至少一种化疗剂包含吉西他滨、顺铂、多西紫杉醇、环磷酰胺、多柔比星、伊立替康和 5- 氟尿嘧啶中的至少一种。

65. 根据权利要求 64 所述的方法，其中所述方法包括每周一次施用约 100mg/kg 的吉西他滨至约 10mg/kg 的吉西他滨，施用 3 周，休止一周。

66. 根据权利要求 64 所述的方法，其中所述方法包括每三周向所述受试者施用 5mg/kg 多西紫杉醇、1mg/kg 多柔比星和 35mg/kg 环磷酰胺，施用六个周期。

使用辅酶 Q10 联合疗法治疗癌症

[0001] 相关申请

[0002] 本申请要求 2013 年 4 月 8 日提交的美国临时专利申请第 61/809,840 号的优先权，该临时专利申请的内容全文并入本文中。

技术领域

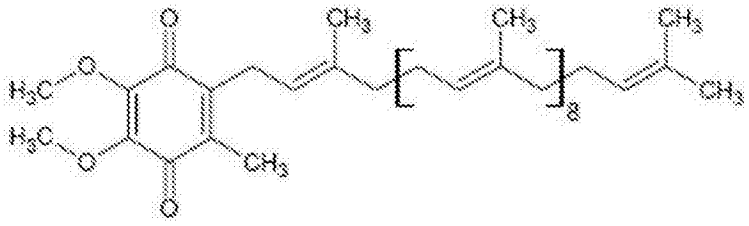
[0003] 本发明总体涉及治疗肿瘤疾病的方法，其包括施用辅酶 Q10(CoQ10) 和化疗剂。

背景技术

[0004] 癌症是目前发达国家中的主要死亡原因之一。癌症的诊断传统上涉及严重的健康并发症。癌症可以引起毁容、慢性或急性疼痛、病变、器官衰竭或者甚至死亡。常被诊断出的癌症包括胰腺癌、乳腺癌、肺癌、黑素瘤、淋巴瘤、癌瘤、肉瘤、非霍奇金淋巴瘤、白血病、子宫内膜癌、结肠和直肠癌、前列腺癌和膀胱癌。传统上，许多癌症（例如，乳腺癌、白血病、肺癌等）用外科手术、化疗、放射或其组合来治疗。已知癌症治疗中使用的化疗剂在患者中产生若干严重且使人不快的副作用。例如，一些化疗剂导致神经病、肾毒性（例如，高血脂、蛋白尿、低蛋白血症、它们的组合等）、口腔炎、粘膜炎、呕吐、脱发、厌食、食道炎、闭经、免疫力下降、贫血、高音听力损失、心脏毒性、疲劳、神经病或其组合。仍然期望用于治疗包括癌症在内的肿瘤疾病的改进方法和能够递送生物活性剂以帮助治疗疾病及其它病症的组合物。

[0005] 辅酶 Q10（本文中也称 CoQ10）、泛醌或泛癸利酮是一种流行的营养补充剂并可以作为维生素样补充剂以胶囊形式见于营养品商店、保健食品商店、药店等中，从而通过泛醇 (CoQ10 的还原形式）的抗氧化剂性能帮助保护免疫系统。CoQ10 广泛存在于大多数人体组织及其它哺乳动物的组织中，并聚集在线粒体中。CoQ10 是非常亲脂性的且大多不溶于水。该不溶性与具有如以下 CoQ10 的结构中所示烃性质的 50 个碳原子的类异戊二烯侧链有关。

[0006]



发明内容

[0007] 本发明提供了通过向受试者施用 CoQ10 和至少一种化疗剂来治疗受试者的肿瘤疾病的方法，以便肿瘤疾病得到治疗。

[0008] 在一些实施方式中，所述方法包括 (a) 向受试者施用辅酶 Q10(CoQ10)；(b) 中断 CoQ10 的施用；和 (c) 在中断 CoQ10 的施用后，向受试者施用至少一种化疗剂，使得肿瘤疾病被治疗。在其它实施方式中，所述方法包括 (a) 向受试者施用辅酶 Q10(CoQ10)；(b) 在开始施用 CoQ10 后，向受试者施用至少一种化疗剂；和 (c) 在开始施用所述至少一种化疗剂

后，继续使用 CoQ10 治疗，使得肿瘤疾病被治疗。

[0009] 在某些实施方式中，CoQ10 在施用第一剂的所述至少一种化疗剂之前施用。在一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 24 小时。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 48 小时。在进一步的优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 1 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 2 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 3 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 4 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 5 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 6 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 7 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用至少 8 周。

[0010] 在其它优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用约 24 小时。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用约 48 小时。在进一步的优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用约 1 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用约 2 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用约 3 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用约 4 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用约 5 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用约 6 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用约 7 周。在另一个优选实施方式中，CoQ10 在施用一剂所述至少一种化疗剂之前施用约 8 周。

[0011] 在某些实施方式中，在 CoQ10 施用开始后至少 24 小时、在 CoQ10 施用开始后一周或多周、在 CoQ10 施用开始后两周或更多周、在 CoQ10 施用开始后三周或更多周、在 CoQ10 施用开始后四周或更多周、在 CoQ10 施用开始后五周或更多周、在 CoQ10 施用开始后六周或更多周、在 CoQ10 施用开始后七周或更多周或在 CoQ10 的施用开始后八周或更多周，开始施用所述至少一种化疗剂。

[0012] 在前述方法的一个优选实施方式中，相对于单独使用所述至少一种化疗剂的治疗，即在不存在向受试者施用 CoQ10 的情况下，肿瘤疾病对治疗的反应被改善。在进一步的优选实施方式中，相对于单独使用所述至少一种化疗剂的治疗，所述反应改善至少 2%、至少 3%、至少 4%、至少 5%、至少 6%、至少 7%、至少 8%、至少 9%、至少 10%、至少 11%、至少 12%、至少 13%、至少 14%、至少 15%、至少 16%、至少 17%、至少 18%、至少 19%、至少 20%、至少 21%、至少 22%、至少 23%、至少 24%、至少 25%、至少 26%、至少 27%、至少 28%、至少 29%、至少 30%、至少 31%、至少 32%、至少 33%、至少 34%、至少 35%、至少 36%、至少 37%、至少 38%、至少 39%、至少 40%、至少 41%、至少 42%、至少 43%、至少 44%、至少 45%、至少 46%、至少 47%、至少 48%、至少 49%、至少 50%、至少 55%、至少 60%、至少 65%、至少 70%、至少 75%、至少 80%、至少 85%、至少 90%、至少 95%或至少 100%。

[0013] 在某些实施方式中，所述反应包括减小肿瘤负荷、减小肿瘤大小、抑制肿瘤生长、

减慢肿瘤生长、按照 RECIST 标准的改善、在治疗前患有进行性肿瘤疾病的受试者中实现肿瘤疾病稳定、延长到肿瘤疾病进展的时间和增加存活时间中的任意一种或多种。

[0014] 在前述方法的一个优选实施方式中，CoQ10 局部施用。在另一个优选实施方式中，CoQ10 通过吸入施用。在另一个优选实施方式中，CoQ10 通过注射或输注施用。在另一个优选实施方式中，CoQ10 通过静脉内给药施用。在进一步的优选实施方式中，CoQ10 通过连续静脉内输注施用。在又进一步的优选实施方式中，CoQ10 的剂量通过经 24 小时连续输注施用。

[0015] 在某些实施方式中，CoQ10 以约 5mg/kg、约 10mg/kg、约 12.5mg/kg、约 20mg/kg、约 25mg/kg、约 30mg/kg、约 35mg/kg、约 40mg/kg、约 45mg/kg、约 50mg/kg、约 55mg/kg、约 58mg/kg、约 58.6mg/kg、约 60mgkg、约 75mg/kg、约 78mg/kg、约 100mg/kg、约 104mg/kg、约 125mg/kg、约 150mg/kg、约 175mg/kg、约 200mg/kg、约 300mg/kg 或约 400mg/kg 的剂量施用。

[0016] 本发明还提供了一种改进针对受试者的肿瘤疾病的化疗治疗方案的方法，其包括在开始化疗治疗方案之前使用辅酶 Q10(CoQ10) 对患肿瘤疾病的受试者预治疗足够的时间，其中所述化疗治疗方案包括施用一种或多种化疗剂，使得相对于单独使用化疗治疗方案的治疗，肿瘤疾病的反应被改善。在前述方法的某些实施方式中，化疗治疗方案不包括施用 CoQ10。在前述方法的一些实施方式中，在开始化疗治疗方案之前停止 CoQ10 的预治疗。

[0017] 在前述方法的一个优选实施方式中，受试者在开始化疗治疗方案之前使用 CoQ10 预治疗至少 24 小时、至少 48 小时、至少 1 周、至少 2 周、至少 3 周、至少 4 周、至少 5 周、至少 6 周、至少 7 周或至少 8 周。在另一个优选实施方式中，受试者在开始化疗治疗方案之前使用 CoQ10 预治疗约 24 小时、约 48 小时、约 1 周、约 2 周、约 3 周、约 4 周、约 5 周、约 6 周、约 7 周或约 8 周。

[0018] 在前述方法的另一个优选实施方式中，在 CoQ10 预治疗开始后至少 24 小时、在 CoQ10 预治疗开始后一周或多周、在 CoQ10 预治疗开始后两周或更多周、在 CoQ10 预治疗开始后三周或更多周、在 CoQ10 预治疗开始后四周或更多周、在 CoQ10 预治疗开始后五周或更多周、在 CoQ10 预治疗开始后六周或更多周、在 CoQ10 预治疗开始后七周或更多周或者在 CoQ10 预治疗开始后八周或更多周，开始化疗治疗方案。

[0019] 在前述方法的某些实施方式中，相对于单独使用化疗治疗方案的治疗，所述反应改善至少 2%、至少 3%、至少 4%、至少 5%、至少 6%、至少 7%、至少 8%、至少 9%、至少 10%、至少 11%、至少 12%、至少 13%、至少 14%、至少 15%、至少 16%、至少 17%、至少 18%、至少 19%、至少 20%、至少 21%、至少 22%、至少 23%、至少 24%、至少 25%、至少 26%、至少 27%、至少 28%、至少 29%、至少 30%、至少 31%、至少 32%、至少 33%、至少 34%、至少 35%、至少 36%、至少 37%、至少 38%、至少 39%、至少 40%、至少 41%、至少 42%、至少 43%、至少 44%、至少 45%、至少 46%、至少 47%、至少 48%、至少 49%、至少 50%、至少 55%、至少 60%、至少 65%、至少 70%、至少 75%、至少 80%、至少 85%、至少 90%、至少 95%或至少 100%。

[0020] 在前述方法的某些实施方式中，反应包括减小肿瘤负荷、减小肿瘤大小、抑制肿瘤生长、减慢肿瘤生长、按照 RECIST 标准的改善、在治疗前患有进行性肿瘤疾病的受试者中实现肿瘤疾病稳定、延长到肿瘤疾病进展的时间和增加存活时间中的任意一种或多种。

[0021] 在一些实施方式中，CoQ10 局部施用。在其它实施方式中，CoQ10 通过吸入施用。

在其它实施方式中，CoQ10 通过注射或输注施用。在另一个实施方式中，CoQ10 通过静脉内给药施用。

[0022] 在进一步的实施方式中，CoQ10 通过连续静脉内输注施用。在更进一步的实施方式中，CoQ10 的剂量通过经 24 小时连续静脉内输注施用。

[0023] 在某些实施方式中，CoQ10 以约 5mg/kg、约 10mg/kg、约 12.5mg/kg、约 20mg/kg、约 25mg/kg、约 30mg/kg、约 35mg/kg、约 40mg/kg、约 45mg/kg、约 50mg/kg、约 55mg/kg、约 58mg/kg、约 58.6mg/kg、约 60mgkg、约 75mg/kg、约 78mg/kg、约 100mg/kg、约 104mg/kg、约 125mg/kg、约 150mg/kg、约 175mg/kg、约 200mg/kg、约 300mg/kg 或约 400mg/kg 的剂量施用。

[0024] 本发明还提供了一种治疗受试者的肿瘤疾病的方法，其包括：(a) 向受试者施用 CoQ10；和 (b) 以比用来治疗肿瘤疾病的化疗剂的标准剂量低的剂量向受试者施用至少一种化疗剂，使得肿瘤疾病被治疗。在某些实施方式中，在向受试者施用所述至少一种化疗剂之前中断 CoQ10 的施用。在其它实施方式中，在向受试者施用所述至少一种化疗剂之后继续施用 CoQ10。

[0025] 在前述方法的某些实施方式中，CoQ10 在施用所述至少一种化疗剂之前施用至少 24 小时、至少 48 小时、至少 1 周、至少 2 周、至少 3 周、至少 4 周、至少 5 周、至少 6 周、至少 7 周或至少 8 周。在前述方法的其它实施方式中，CoQ10 在施用所述至少一种化疗剂之前施用约 24 小时、约 48 小时、约 1 周、约 2 周、约 3 周、约 4 周、约 5 周、约 6 周、约 7 周或约 8 周。

[0026] 在前述方法的其它实施方式中，在 CoQ10 施用开始后至少 24 小时、在 CoQ10 施用开始后一周或多周、在 CoQ10 施用开始后两周或更多周、在 CoQ10 施用开始后三周或更多周、在 CoQ10 施用开始后四周或更多周、在 CoQ10 施用开始后五周或更多周、在 CoQ10 施用开始后六周或更多周、在 CoQ10 施用开始后七周或更多周或在 CoQ10 施用开始后八周或更多周，施用所述至少一种化疗剂。

[0027] 在前述方法的某些实施方式中，CoQ10 局部施用。在其它实施方式中，CoQ10 通过吸入施用。在其它实施方式中，CoQ10 通过注射或输注施用。在其它实施方式中，CoQ10 通过静脉内给药施用。在其它实施方式中，CoQ10 通过连续静脉内输注施用。在其它实施方式中，CoQ10 通过经 24 小时连续输注施用。

[0028] 在前述方法的某些实施方式中，CoQ10 以约 5mg/kg、约 10mg/kg、约 12.5mg/kg、约 20mg/kg、约 25mg/kg、约 30mg/kg、约 35mg/kg、约 40mg/kg、约 45mg/kg、约 50mg/kg、约 55mg/kg、约 58mg/kg、约 58.6mg/kg、约 60mgkg、约 75mg/kg、约 78mg/kg、约 100mg/kg、约 104mg/kg、约 125mg/kg、约 150mg/kg、约 175mg/kg、约 200mg/kg、约 300mg/kg 或约 400mg/kg 的剂量施用。

[0029] 在前述方法的某些实施方式中，所述至少一种化疗剂包含选自拓扑异构酶 I 抑制剂、拓扑异构酶 II 抑制剂、有丝分裂抑制剂、烷化剂、铂化合物和抗代谢物的化疗剂。在一些实施方式中，所述至少一种化疗剂包含拓扑异构酶 II 抑制剂。在一个优选实施方式中，拓扑异构酶 II 抑制剂包含多柔比星、表柔比星、伊达比星、米托蒽醌、洛索蒽醌、依托泊苷和替尼泊苷中的至少一种。在其它实施方式中，所述至少一种化疗剂包含拓扑异构酶 I 抑制剂。

[0030] 在一个优选实施方式中，拓扑异构酶 I 抑制剂包含伊立替康、托泊替康、9- 硝基喜

树碱、喜树碱和喜树碱衍生物中的至少一种。在其它实施方式中，所述至少一种化疗剂包含抗代谢物。在一个优选实施方式中，抗代谢物包含 5- 氟尿嘧啶、卡培他滨、吉西他滨、甲氨喋呤和依达曲沙中的至少一种。在其它实施方式中，所述至少一种化疗剂包含烷化剂。

[0031] 在一个优选实施方式中，烷化剂包含氮芥、亚乙基亚胺化合物、烷基磺酸盐、亚硝基脲、达卡巴嗪、环磷酰胺、异环磷酰胺和美法仑中的至少一种。在其它实施方式中，所述至少一种化疗剂包含铂化合物。在一个优选实施方式中，铂化合物包含顺铂、奥沙利铂和卡铂中的至少一种。在其它实施方式中，所述至少一种化疗剂包含有丝分裂抑制剂。在一个优选实施方式中，有丝分裂抑制剂包含紫杉醇、多西紫杉醇、长春碱、长春新碱、长春瑞滨和鬼臼毒素衍生物中的至少一种。

[0032] 在前述方法的某些实施方式中，所述至少一种化疗剂包含选自以下的化疗剂：阿米福汀（氨磷汀）、顺铂、达卡巴嗪 (DTIC)、放线菌素、二氯甲基二乙胺（氮芥）、链脲佐菌素、环磷酰胺、卡莫司汀 (BCNU)、洛莫司汀 (CCNU)、多柔比星（阿霉素）、多柔比星脂质体（阿霉素脂质体）、吉西他滨（健择）、柔红霉素、柔红霉素脂质体 (daunoxome)、甲基苄肼、丝裂霉素、阿糖胞苷、依托泊苷、氨甲喋呤、5- 氟尿嘧啶 (5-FU)、长春碱、长春新碱、博来霉素、紫杉醇（泰素）、多西紫杉醇（泰索帝）、阿地白介素、天冬酰胺酶、白消安、卡铂、克拉屈滨、喜树碱、CPT-11、10- 羟基 -7- 乙基 - 喜树碱 (SN38)、达卡巴嗪、S-I 卡培他滨、替加氟、5'- 脱氧氟尿苷、UFT、恩尿嘧啶、脱氧胞苷、5- 氮杂胞嘧啶、5- 氮杂脱氧胞嘧啶、别嘌呤醇、2- 氯腺苷、三甲曲沙、氨喋呤、亚甲基 -10- 脱氮杂 - 氨喋呤 (MDAM)、奥沙利铂 (oxaplatin)、吡铂、四铂、沙铂、铂 -DACH、奥马铂、CI-973、JM-216 和它们的类似物、表柔比星、依托泊苷磷酸盐、9- 氨基喜树碱、10,11- 亚甲基二氧喜树碱、karenitecin、9- 硝基喜树碱、TAS 103、长春地辛、L- 苯丙氨酸氮芥、异环磷酰胺 (ifosphamidemefosphamide)、培磷酰胺、氯乙环磷酰胺、卡莫司汀、司莫司汀、埃博霉素 A-E、拓优得、6- 巯基嘌呤、6- 硫鸟嘌呤、安吖啶、依托泊苷磷酸盐、karenitecin、阿昔洛韦、伐昔洛韦、更昔洛韦、金刚烷胺、金刚乙胺、拉米夫定、齐多夫定、贝伐单抗、曲妥珠单抗、利妥昔单抗、5- 氟尿嘧啶、卡培他滨、喷司他汀、三甲曲沙、克拉屈滨、氟尿苷、氟达拉滨、羟基脲、异环磷酰胺、伊达比星、美司钠、伊立替康、米托蒽醌、拓扑替康、亮丙瑞林、甲地孕酮、美法仑、巯基嘌呤、普卡霉素、米托坦、培门冬酶、喷司他汀、哌泊溴烷、普卡霉素、链脲佐菌素、他莫昔芬、替尼泊苷、睾内酯、硫鸟嘌呤、塞替派、尿嘧啶氮芥、长春瑞滨、苯丁酸氮芥、顺铂、多柔比星、紫杉醇（泰素）、博莱霉素、mTor、表皮生长因子受体 (EGFR) 和成纤维细胞生长因子 (FGF) 及其组合。

[0033] 在前述方法的一个优选实施方式中，所述至少一种化疗剂包含吉西他滨、5- 氟尿嘧啶、顺铂、卡培他滨、甲氨喋呤、依达曲沙、多西紫杉醇、环磷酰胺、多柔比星和伊立替康中的至少一种。

[0034] 在前述方法的某些实施方式中，肿瘤疾病选自癌瘤、肉瘤、淋巴瘤、黑素瘤和白血病。在一个优选实施方式中，肿瘤疾病选自胰腺癌、乳腺癌、肝癌、皮肤癌、肺癌、结肠癌、前列腺癌、甲状腺癌、膀胱癌、直肠癌、子宫内膜癌、肾癌、骨癌、脑癌、子宫颈癌、胃癌、口癌和口腔癌、成神经细胞瘤、睾丸癌、子宫癌和外阴癌。在进一步的优选实施方式中，皮肤癌选自黑素瘤、鳞状细胞癌、基底细胞癌和皮肤 T- 细胞淋巴瘤 (CTCL)。在另一个优选的实施方式中，肿瘤疾病为三阴性乳腺癌。

[0035] 在前述方法的某些实施方式中，肿瘤疾病是难治性疾病。在前述方法的某些实施

方式中，肿瘤疾病未能响应至少一种、两种、三种、四种、五种、六种、七种、八种或更多种既往的治疗。在前述方法的某些实施方式中，肿瘤疾病是晚期癌症。在前述方法的某些实施方式中，所述方法还包括选择患有难治性肿瘤疾病的受试者来进行治疗。在前述方法的某些实施方式中，所述方法还包括选择患有未响应至少一种、两种、三种、四种、五种、六种、七种、八种或更多种既往治疗的肿瘤疾病的受试者来进行治疗。在前述方法的某些实施方式中，所述方法还包括选择患有晚期癌症的受试者来进行治疗。

[0036] 在前述方法的优选实施方式中，受试者为人。

[0037] 在前述方法的某些实施方式中，化疗剂包含吉西他滨、顺铂、多西紫杉醇、环磷酰胺、多柔比星、伊立替康和 5- 氟尿嘧啶中的至少一种。

[0038] 在前述方法的一个优选实施方式中，所述方法包括每周一次施用约 100mg/kg 的吉西他滨至约 10mg/kg 的吉西他滨，施用 3 周，休止一周。

[0039] 在前述方法的另一个优选实施方式中，所述方法包括每三周向受试者施用 5mg/kg 多西紫杉醇、1mg/kg 多柔比星和 35mg/kg 环磷酰胺，施用六个周期。

[0040] 在前述方法的某些实施方式中，化疗剂为 SN38 且肿瘤疾病为前列腺癌，化疗剂为 SN38 且肿瘤疾病为肝癌，化疗剂为多柔比星且肿瘤疾病为乳腺癌，化疗剂为多柔比星且肿瘤疾病为胰腺癌，化疗剂为多柔比星且肿瘤疾病为肝癌，化疗剂为 5- 氟尿嘧啶且肿瘤疾病为乳腺癌，化疗剂为 5- 氟尿嘧啶且肿瘤疾病为三阴性乳腺癌，化疗剂为 5- 氟尿嘧啶且肿瘤疾病为肝癌，化疗剂为顺铂且肿瘤疾病为肺癌，化疗剂为 4-HCP 且肿瘤疾病为乳腺癌，化疗剂为 4-HCP 且肿瘤疾病为三阴性乳腺癌，化疗剂为 4-HCP 且肿瘤疾病为乳腺癌，化疗剂为 4-HCP 且肿瘤疾病为卵巢癌，化疗剂为他莫昔芬且肿瘤疾病为乳腺癌，化疗剂为吉西他滨且肿瘤疾病为肺癌，化疗剂为氟他胺且肿瘤疾病为前列腺癌，或者化疗剂为戈舍瑞林且肿瘤疾病为前列腺癌。

[0041] 在其中 CoQ10 以静脉内 CoQ10 制剂提供的一些实施方式中，静脉内 CoQ10 制剂包含 (1) 水性溶液、(2) 分散成颗粒的纳米分散体的 CoQ10 和 (3) 分散稳定剂与调理作用缩减剂中的至少一种，其中 CoQ10 的纳米分散体分散成平均粒度小于 200nm 的纳米颗粒。

[0042] 在一些实施方式中，分散稳定剂选自聚乙二醇化蓖麻油、Cremophor EL、Cremophor RH 40、聚乙二醇化维生素 E、维生素 E TPGS 和二肉豆蔻酰基磷脂酰基胆碱 (DMPC)。在一些实施方式中，分散稳定剂优选是 DMPC。

[0043] 在一些实施方式中，调理作用缩减剂选自泊洛沙姆类和泊洛沙胺类 (poloxamines)。在一些优选实施方式中，调理作用缩减剂为泊洛沙姆 188。在一些优选实施方式中，调理作用缩减剂为泊洛沙姆 188 且分散稳定剂为 DMPC。

[0044] 在一些实施方式中，CoQ10 制剂分别具有 4%、3% 和 1.5% 重量 / 体积比的 CoQ10、DMPC 和泊洛沙姆 188。

[0045] 在一些实施方式中，CoQ10 以局部 CoQ10 制剂提供，其中所述局部 CoQ10 制剂为 3% 的 CoQ10 乳膏剂，其包含 :(1) 相 A，其具有组合物的约 4.0 重量 / 重量 % 的 C12-15 烷基苯甲酸酯、组合物的约 2.00 重量 / 重量 % 的鲸蜡醇、约 1.5 重量 / 重量 % 的硬脂醇、硬脂酸甘油酯和约 4.5 重量 / 重量 % 的 PEG-100 ;(2) 相 B，其具有约 2.00 重量 / 重量 % 的甘油、约 1.5 重量 / 重量 % 的丙二醇、约 5.0 重量 / 重量 % 的乙氧基二甘醇、约 0.475 重量 / 重量 % 的苯氧乙醇、约 40 重量 / 重量 % 的卡波姆分散体、约 16.7 重量 / 重量 % 的纯化水 ;(3) 相

C，其具有约 1.3 重量 / 重量％的三乙醇胺、约 0.5 重量 / 重量％的乳酸、约 2.0 重量 / 重量％的乳酸钠溶液、约 2.5 重量 / 重量％的水；(4) 相 D，其具有约 1.0 重量 / 重量％的二氧化钛；和 (5) 相 E，其具有约 15.0 重量 / 重量％的 CoQ1021％浓缩物。

[0046] 在某些实施方式中，CoQ10 以用于吸入的制剂提供，其中所述制剂包含含有适于连续雾化的脂质体颗粒分散体的药物组合物，所述组合物包含：平均直径在约 30 和 500nm 之间的脂质体颗粒分散体，每个脂质体颗粒包含疏水性生物活性剂、磷脂和水性分散介质，其中疏水性生物活性剂：磷脂的比率在约 5:1 和约 1:5 之间，疏水性生物活性剂在组合物的约 0.1 和 30 重量 / 重量％之间，磷脂在组合物的约 0.1 和 30 重量 / 重量％之间，并且脂质体颗粒分散在水性分散介质中，并且其中在对受试者施用时，组合物特征在于足以向受试者提供治疗剂量的疏水性生物活性剂的连续雾化。在某些实施方式中，水性分散介质包含水或水性盐溶液。在某些实施方式中，脂质体颗粒分散体为连续可吸入气雾剂的形式，其包含多个含有脂质体颗粒的分散体并具有在约 1 和 5μm 之间的质量中值气体动力学直径 (MMAD) 的水性液滴。在某些实施方式中，组合物特征在于经过至少 15 分钟连续雾化，约 50 和 100％之间的平均百分传输率 (APT)。在某些实施方式中，经过至少 15 分钟连续雾化，所述多个液滴具有约 1 和 5μm 之间的 MMAD。

[0047] 化疗剂包括但不限于环磷酰胺、紫杉烷类 (例如，紫杉醇或多西紫杉醇)、白消安、顺铂、甲氨喋呤、柔红霉素、多柔比星、美法仑、克拉屈滨、长春新碱、长春碱、苯丁酸氮芥、他莫昔芬、泰素、依托泊苷 (VP-16)、多柔比星、5- 氟尿嘧啶 (5FU)、喜树碱、放线菌素 -D、丝裂霉素 C、顺铂 (CDDP)、考布他汀和伊立替康；以及它们的衍生物和前药。化疗剂包括抗血管生成剂。抗血管生成剂包括但不限于血管抑素；内皮抑素；16kDa 催乳素片段；层粘连蛋白肽；纤连蛋白肽；组织金属蛋白酶抑制剂 (TIMP 1、2、3、4)；纤溶酶原激活物抑制剂 (PAI-1、-2)；肿瘤坏死因子 α；TGF-β1；干扰素 (IFN-α、-β、-γ)；ELR-CXC 趋化因子：IL-12；SDF-1；MIG；血小板因子 4(PF-4)；IP-10；血小板反应蛋白 (TSP)；SPARC；2- 甲氧基雌二醇增殖蛋白相关蛋白；苏拉明；沙利度胺；可的松；烟曲霉素 (AGM-1470、TNP-470)；他莫昔芬；韩国槲寄生提取物 (白果槲寄生 (Viscum album coloratum))；类视黄醇；CM101；地塞米松和白血病抑制因子 (LIF)。本文中还提供了其它化疗剂。

[0048] 在一些实施方式中，抗代谢物包括嘌呤或嘧啶类似物中的至少一种。在一些实施方式中，抗代谢物包括吉西他滨、5- 氟尿嘧啶、卡培他滨、甲氨喋呤和依达曲沙中的至少一种。在一些优选实施方式中，抗代谢物为吉西他滨。

[0049] 在一些实施方式中，蒽环类抗生素为拓扑异构酶 II 抑制剂。在一些实施方式中，拓扑异构酶 II 抑制剂包括多柔比星、表柔比星、伊达比星、米托蒽醌、洛索蒽醌、依托泊苷和替尼泊苷中的至少一种。在一些优选实施方式中，拓扑异构酶 II 抑制剂为多柔比星。

[0050] 在一些实施方式中，化疗剂为拓扑异构酶 I 抑制剂。在一些实施方式中，拓扑异构酶 I 抑制剂包括伊立替康、托泊替康、9- 硝基喜树碱、喜树碱和喜树碱衍生物中的至少一种。

[0051] 施用化疗剂的途径和方法是本领域已知的。

[0052] 在一些实施方式中，所述方法包括其中对受试者每天一次静脉内施用至少约 50mg/kg/ 剂的静脉内 CoQ10 制剂，施用 3 周，休止一周，与化疗剂共施用一个周期的方案。

[0053] 在一些实施方式中，所述方法包括其中对受试者每天两次静脉内施用至少约

50mg/kg/ 剂的静脉内 CoQ10 制剂，施用 3 周，休止一周，与化疗剂共施用一个周期的方案。

[0054] 在一些实施方式中，所述方法包括其中对受试者每天三次静脉内施用至少约 50mg/kg/ 剂的静脉内 CoQ10 制剂，施用 3 周，休止一周，与化疗剂共施用一个周期的方案。

[0055] 在一些实施方式中，所述方法包括其中对受试者每天一次静脉内施用至少约 75mg/kg/ 剂的静脉内 CoQ10 制剂，施用 3 周，休止一周，与化疗剂共施用一个周期的方案。

[0056] 在一些实施方式中，所述方法包括其中对受试者每天两次静脉内施用至少约 75mg/kg/ 剂的静脉内 CoQ10 制剂，施用 3 周，休止一周，与化疗剂共施用一个周期的方案。

[0057] 在一些实施方式中，所述方法包括其中对受试者每天三次静脉内施用至少约 75mg/kg/ 剂的静脉内 CoQ10 制剂，施用 3 周，休止一周，与化疗剂共施用一个周期的方案。

[0058] 在一些实施方式中，所述方法包括其中对受试者每天一次静脉内施用至少约 50mg/kg/ 剂的静脉内 CoQ10 制剂，施用 3 周，休止一周，并随后施用化疗剂一个周期的方案。

[0059] 在一些实施方式中，所述方法包括其中对受试者每天两次静脉内施用至少约 50mg/kg/ 剂的静脉内 CoQ10 制剂，施用 3 周，休止一周，并随后施用化疗剂一个周期的方案。

[0060] 在一些实施方式中，所述方法包括其中对受试者每天三次静脉内施用至少约 50mg/kg/ 剂的静脉内 CoQ10 制剂，施用 3 周，休止一周，并随后施用化疗剂一个周期的方案。

[0061] 在一些实施方式中，所述方法包括其中对受试者每天一次静脉内施用至少约 75mg/kg/ 剂的静脉内 CoQ10 制剂，施用 3 周，休止一周，并随后施用化疗剂一个周期的方案。

[0062] 在一些实施方式中，所述方法包括其中对受试者每天两次静脉内施用至少约 75mg/kg/ 剂的静脉内 CoQ10 制剂，施用 3 周，休止一周，并随后施用化疗剂一个周期的方案。

[0063] 在一些实施方式中，所述方法包括其中对受试者每天三次静脉内施用至少约 75mg/kg/ 剂的静脉内 CoQ10 制剂，施用 3 周，休止一周，并随后施用化疗剂一个周期的方案。

[0064] 在某些实施方式中，每天施用 CoQ10 而没有三周间隔处的一周休止。在某些实施方式中，每天施用 CoQ10 直至观察到限制性毒性。

[0065] 在一些实施方式中，所述方法包括其中在施用化疗剂之前通过连续输注对受试者静脉内施用 CoQ10 的方案。在一些实施方式中，在施用化疗剂之前连续输注 24 小时。

[0066] 在某些实施方式中，在一剂 CoQ10 施用完成 24 小时内开始施用化疗剂。在某些实施方式中，在一剂 CoQ10 施用完成 18 小时内开始施用化疗剂。在某些实施方式中，在一剂 CoQ10 施用完成 12 小时内开始施用化疗剂。在某些实施方式中，在一剂 CoQ10 施用完成 6 小时内开始施用化疗剂。在某些实施方式中，在一剂 CoQ10 施用完成 4 小时内开始施用化疗剂。在某些实施方式中，在一剂 CoQ10 施用完成 3 小时内开始施用化疗剂。在某些实施方式中，在一剂 CoQ10 施用完成 2 小时内开始施用化疗剂。在某些实施方式中，在一剂 CoQ10 施用完成 1 小时内开始施用化疗剂。

[0067] 在某些实施方式中，在 CoQ10 预治疗后，在化疗剂治疗过程中继续 CoQ10 的治疗。

[0068] 在其中在化疗剂之前施用 CoQ10 的一些实施方式中，在施用两个或更多个（例如，2、3、4、5、6、7、8 个等）周期的化疗剂之前施用两个或更多个周期的 CoQ10（例如，2、3、4、5、6、7、8 个周期等）。

[0069] 在某些实施方式中，在施用化疗剂之前施用足够时间和量的 CoQ10 以达到 CoQ10 的稳态。

[0070] 在某些实施方式中，在化疗剂治疗开始之前施用负荷剂量的 CoQ10。

[0071] 在其中在化疗剂之前施用 CoQ10 的一些实施方式中，在施用一个周期的化疗剂之前施用一个周期的CoQ10。在某些实施方式中，在每个治疗周期中在每个剂量的化疗剂之前施用 CoQ10。在某些实施方式中，与化疗剂周期交替地施用多个周期的 CoQ10。在某些实施方式中，在每个治疗周期中在每个剂量的化疗剂之前施用 CoQ10。在某些实施方式中，在每个剂量的化疗剂之前和与每个剂量的化疗剂同时施用CoQ10。在某些实施方式中，在每个周期的化疗剂施用之前和与每个周期的化疗剂施用同时施用 CoQ10。

[0072] 在其中在化疗剂之前施用 CoQ10 的一些实施方式中，在施用两个或更多个（例如，2、3、4、5、6、7、8 个等）周期的化疗剂之前施用一个周期的 CoQ10。

[0073] 应理解，化疗剂常常以混合物 (cocktail) 形式施用。如本文所用，化疗剂应理解为一种或多种（例如，1、2、3、4、5、6、7、8 种等）化疗剂。此外，应理解，在施用多个周期的化疗剂时，每个周期中使用的具体给药方案和 / 或化疗剂不必相同。然而，在某些实施方式中，化疗剂及其给药方案对所有周期都是相同的。

[0074] 在某些实施方式中，CoQ10 通过与化疗剂相同的施用途径施用。在某些实施方式中，CoQ10 通过与化疗剂不同的施用途径施用。

[0075] 在一些实施方式中，治疗受试者的肿瘤疾病，其包括胰腺癌、乳腺癌、皮肤癌、肝癌、癌瘤、肉瘤、淋巴瘤、黑素瘤或白血病中的至少一种。在某些实施方式中，治疗受试者的肿瘤疾病，其包括实体肿瘤。在某些实施方式中，治疗受试者的肿瘤疾病，其包括非实体肿瘤。

附图说明

[0076] 图 1 为示出在使用人胰腺肿瘤 MIAPaCa-2 细胞的胰腺癌异种小鼠模型中，单独或与吉西他滨联合的每天一次静脉内 CoQ10 给药对存活时间（天）的影响的曲线图。在该图中，第 1 天指开始治疗的那天。

[0077] 图 2 为示出在使用人胰腺肿瘤 MIAPaCa-2 细胞的胰腺癌异种小鼠模型中，单独或与吉西他滨联合的每天一次静脉内 CoQ10 给药对死亡时肿瘤大小的影响的照片。组 1 中的肿瘤在治疗开始后 20 天时采集。组 2 中的肿瘤在治疗开始后 50-60 天时采集。组 3 中的肿瘤在治疗开始后 40-50 天时采集。组 4 中的肿瘤在治疗开始后 50-60 天时采集。

[0078] 图 3 为示出在使用人胰腺肿瘤 MIAPaCa-2 细胞的胰腺癌异种小鼠模型中，单独或与吉西他滨联合的每天一次静脉内 CoQ10 给药对死亡时肿瘤大小的影响的曲线图。组 1 中的肿瘤在治疗开始后 20 天时采集。组 2 中的肿瘤在治疗开始后 50-60 天时采集。组 3 中的肿瘤在治疗开始后 40-50 天时采集。组 4 中的肿瘤在治疗开始后 50-60 天时采集。

[0079] 图 4 为示出在使用人胰腺肿瘤 MIAPaCa-2 细胞的胰腺癌异种小鼠模型中，单独或与吉西他滨联合的每天两次静脉内 CoQ10 给药对存活时间（天）的影响的曲线图。在该图中，第 1 天指开始治疗的那天。

[0080] 图 5A 为示出使用吉西他滨、CoQ10、CoQ10 静脉内制剂或与吉西他滨联合的 CoQ10 静脉内制剂处理 6 小时对体外 MIAPaCa-2 胰腺癌细胞存活力的影响的图表。

[0081] 图 5B 为示出使用吉西他滨、CoQ10、CoQ10 静脉内制剂或与吉西他滨联合的 CoQ10 静脉内制剂处理 6 小时对体外 SK-Br3 乳腺癌细胞存活力的影响的图表。

[0082] 图 6A 为示出使用多柔比星、CoQ10、CoQ10 静脉内制剂或与多柔比星联合的 CoQ10

静脉内制剂处理 6 小时对体外 MIAPaCa-2 胰腺癌细胞存活力的影响的图表。

[0083] 图 6B 为示出使用多柔比星、CoQ10、CoQ10 静脉内制剂或与多柔比星联合的 CoQ10 静脉内制剂处理 6 小时对体外 SK-Br3 乳腺癌细胞存活力的影响的图表。

[0084] 图 7 为示出在使用人胰腺肿瘤 MIAPaCa-2 胰腺癌细胞的胰腺癌异种小鼠模型中，每天一次静脉内 CoQ10 与多柔比星或单独的多柔比星给药对存活时间的影响的曲线图。

[0085] 图 8 为示出在使用人胰腺肿瘤 MIAPaCa-2 细胞的胰腺癌异种小鼠模型中，单独或与吉西他滨联合地每天三次以指定剂量腹膜内给药 CoQ10 静脉内制剂对存活时间的影响的曲线图。在该图中，第 1 天指开始治疗的那天。

[0086] 图 9A 为示出单独或与 CoQ10(100 μM) 联合使用化疗剂伊立替康 (SN38) 处理对体外 Hep3B 肝癌细胞存活力的影响的图表。存活力通过活细胞计数来评估。值相对于既未用 CoQ10 又未用化疗剂处理的细胞数归一化。

[0087] 图 9B 为示出单独或与 CoQ10(100 μM) 联合使用化疗剂顺铂处理对体外 Hep3B 肝癌细胞存活力的影响的图表。存活力通过活细胞计数来评估。值相对于既未用 CoQ10 又未用化疗剂处理的细胞数归一化。

[0088] 图 9C 为示出单独或与 CoQ10(100 μM) 联合使用化疗剂 5- 氟尿嘧啶处理对体外 Hep3B 肝癌细胞存活力的影响的图表。存活力通过活细胞计数来评估。值相对于既未用 CoQ10 又未用化疗剂处理的细胞数归一化。

[0089] 图 10 为示出单独或与 CoQ10(100 μM) 联合使用化疗剂多柔比星处理对体外 Hep3B 肝癌细胞存活力的影响的图表。存活力通过活细胞计数来评估。值相对于既未用 CoQ10 又未用化疗剂处理的细胞数归一化。

[0090] 图 11A-11B 示出了用单独或与 CoQ10(100 μM) 联合的吉西他滨处理的 Mia-PaCa2 胰腺癌细胞的图像。(A) 辅酶 Q10 在加入化疗之前 6 小时添加，或 (B) 辅酶 Q10 与化疗同时添加。

[0091] 图 12A-12B 为示出其中 MIAPaCa2 胰腺癌细胞用单独或与 CoQ10(100 μM) 联合的吉西他滨处理的生长抑制 / 细胞死亡促进分析的结果的图表。(A) 辅酶 Q10 在加入化疗之前 6 小时添加，或 (B) 辅酶 Q10 与化疗同时添加。生长抑制 / 细胞死亡促进通过活细胞计数来评估。值相对于既未用 CoQ10 又未用化疗剂处理的细胞数归一化。

[0092] 图 13 为示出其中在通过使用染色活细胞的细胞示踪染料 CFSE 的流式细胞分析来评估增殖之前，MIAPaCa2 胰腺癌细胞用单独或与 CoQ10 联合的吉西他滨处理的增殖分析结果的图表。值相对于既未用 CoQ10 又未用化疗剂处理的细胞数归一化。

[0093] 图 14 为示出其中在通过使用染色死细胞的碘化丙啶的流式细胞分析来评估剩余粘附细胞的凋亡之前，MIAPaCa2 胰腺癌细胞用单独或与 CoQ10 联合的吉西他滨处理的分析的结果的图表。值相对于既未用 CoQ10 又未用化疗剂处理的细胞数归一化。

[0094] 图 15 为示出在使用人胰腺肿瘤 MIAPaCa-2 胰腺癌细胞的胰腺癌异种小鼠模型中，与吉西他滨 (150mg/kg/ 剂，每 3 周 1 次) 联合的 CoQ10 静脉内制剂 (75mg/kg/ 剂) 每天三次腹膜内给药对存活时间的影响的曲线图。在吉西他滨治疗开始前 0、1、2 或 3 周开始施用 CoQ10。在该图中，第 1 天指开始治疗的那天。

[0095] 图 16 示出了 CoQ10 处理对体外各种肿瘤细胞系存活力的影响。细胞用 100 μM CoQ10 处理 48-72 小时。

[0096] 图 17 示出了 CoQ10 处理对体外乳腺癌细胞 (MDA-MB231 和 SKBR-3) 和非致瘤性对照细胞 (MCF12A) 中的基础耗氧率 (OCR)、细胞外酸化率 (ECAR) 和活性氧物质 (ROS) 的影响。细胞用 100μM CoQ10 处理 24 小时。

[0097] 图 18 示出了 CoQ10 处理对乳腺癌细胞 (MDA-MB231 和 SKBR-3) 中的半胱天冬酶 3 活性的影响。

[0098] 图 19 示出了在 A549、PC3 和 SKOV3 癌细胞中，使用 CoQ10 与各种化疗剂的组合的共处理与预处理的效果。

[0099] 图 20 示出了经受 CoQ10(100μM) 与化疗剂 (5- 氟尿嘧啶，5-FU；多柔比星，Doxo；SN38，伊立替康活性代谢物）共处理或 CoQ10 预处理 (6 小时）接着与化疗剂共孵育的 MDA-MB231 和 SkBr-3 乳腺癌细胞及 MCF12A 对照细胞。在 48 小时后评估活细胞的数量。p 值表示双因素方差分析的交互作用。与单独的化疗剂相比，*p<0.05。

[0100] 图 21 示出了携带三阴性乳腺癌 (TNBC) 异种移植物并用具有和不具有 75mg/kg 体重的 CoQ10(BPM 31510) 的 TAC 方案 (5mg/kg 多西紫杉醇、1mg/kg 多柔比星和 35mg/kg 环磷酰胺）治疗的小鼠的存活曲线。TAC 每三周给予，共六个周期。

[0101] 图 22 示出了用 100μM CoQ10(BPM 31510) 和 100ng/ml 多柔比星共处理的 SkBr-3 乳腺癌细胞。使用可裂解的荧光底物随时间监测半胱天冬酶 3 活性。

[0102] 图 23 示出了用增加剂量的 CoQ10(BPM 31510) 处理的 MDA-MB231 和 SkBr-3 乳腺癌细胞及 MCF12A 非致瘤性对照细胞。在 48 小时后评估活细胞数量。使用非线性回归分析计算 EC_{50} 值。

[0103] 图 24 示出了用 100μM CoQ10(BPM 31510) 处理 48 小时的 MDA-MB231 和 SkBr-3 乳腺癌细胞及 MCF12A 非致瘤性对照细胞。分别使用碘化丙啶 (PI) 和 CFSE 细胞示踪剂测量经 CoQ10 处理的细胞中的细胞死亡和增殖。

[0104] 图 25 示出了用 100μM CoQ10(BPM 31510) 处理 24 小时的 MDA-MB231 和 SkBr-3 乳腺癌细胞及 MCF12A 非致瘤性对照细胞。在 Seahorse XF96 分析仪中使用线粒体毒素（寡霉素、CCCP 和鱼藤酮）顺序注射来评估线粒体功能。还测量 DCF 荧光作为以相同方式处理的细胞中活性氧物质产生的指示。与对照相比，*P<0.05，N.S. 表示无统计学显著性。

[0105] 图 26 示出了使用 100μM CoQ10(BPM31510) 的人胰腺癌细胞 (PcCa2) 预处理，接着使用吉西他滨 (0.1、1 和 5μM) 处理，或者这些细胞使用 CoQ10 和吉西他滨共处理。与单独的吉西他滨相比，预处理和共处理均显著减少活细胞的数量 (*P<0.05)。

[0106] 图 27 示出了在人胰腺癌异种移植小鼠模型中，用于评价单独或与吉西他滨联合的 CoQ10(BPM 31510) 对动物存活的影响的三个治疗方案。

[0107] 图 28 示出了在人胰腺癌异种移植小鼠模型中，CoQ10(API 31510) 和吉西他滨的方案 2（图 27 中描述）治疗对动物存活的影响。单独的吉西他滨对比吉西他滨 +CoQ10(50mg/kg)，p = 7.3E-8

[0108] 图 29 示出了在人胰腺癌异种移植小鼠模型中，CoQ10(API 31510) 和吉西他滨的方案 3（图 27 中描述）治疗对动物存活的影响。单独的吉西他滨对比吉西他滨 +CoQ10(50mg/kg)，p = 7.3E-8

[0109] 图 30 示出了在人胰腺癌异种移植小鼠模型中，各种浓度的 CoQ10(BPM 31510) 随时间（天）对动物存活的影响。与 50mg/kg CoQ10 相比，以 200mg/kg 连续输注 CoQ10 显著

改善存活（$p<0.00001$）。例如，200mg/kg CoQ10 治疗的小鼠在 300 天时具有最高的存活率（存活概率），50mg/kg CoQ10 治疗的小鼠在 300 天时具有最低的存活率（存活概率），和 100mg/kg CoQ10 治疗的小鼠在 300 天时具有介于其它两个治疗组之间的存活率（存活概率）。

[0110] 图 31 示出了在人胰腺癌小鼠异种移植模型中，CoQ10 和吉西他滨随时间（天）对动物存活的影响。在人胰腺癌小鼠异种移植模型中，在吉西他滨 +CoQ10 治疗开始之前六十天使用 CoQ10(200mg/kg) 预治疗与在治疗方案开始时使用吉西他滨 +CoQ10 治疗相比改善了存活。例如，在 200 天时，在吉西他滨开始之前使用 CoQ10 治疗 60 天并持续使用 CoQ10 治疗的小鼠具有最高的存活率（存活概率），从开始使用吉西他滨和 CoQ10 治疗的小鼠具有第二高的存活率，从开始使用 CoQ10 治疗的小鼠具有第三高的存活率，而对照小鼠具有最低的存活率。

具体实施方式

[0111] I. 定义

[0112] 根据本公开并如本文所用，除明确指出以外，以下术语定义为具有以下含义。

[0113] 如本文所用，“药学上可接受的”组分是适用于人和 / 或动物而无过度的不良副作用（如毒性、刺激和过敏反应）并具有合理的收益 / 风险比的那些。

[0114] “治疗”是意图防止疾病发展或改变疾病的病理、症状或体征而进行的干预。因此，“治疗”指治疗性治疗及预防性或防止性措施。需要治疗的那些包括已经患有疾病的那些以及要预防疾病的那些。如本文所用，“治疗”指的是接近于标准化值（例如在健康患者或个体中获得的值）的症状或体征，例如，如使用常规统计检验测定的，与标准化值的差异小于 50%，在一些实施方案中与标准化值的差异小于约 25%，在其它实施方案中与标准化值的差异小于 10%，和在再其它的实施方案中存在与标准化值无明显差异的症状。如本文所用，治疗可包括减小肿瘤负荷、抑制肿瘤生长，包括在治疗前患有进行性疾病的受试者中诱导稳定的疾病、延长到进展的时间或增加存活时间。增加可相对于合适的对照或预期的结果来确定。如本文所用，治疗可包括与合适的对照相比，在肿瘤负荷减小或不减小的情况下增加受试者的存活。治疗不必是治愈性的。

[0115] 如本文所用，“周期”应理解为用于施用 CoQ10 或化疗剂的方案。通常，化疗剂不作为单一治疗或以连续的固定间隔（例如，每天、每周）的治疗施用。周期包括化疗治疗的时间及之后在下次治疗之前的间隔。例如，周期持续 4 周，可具有第 1 天、第 2 天和第 3 天的治疗及然后从第 4 天到第 28 天不进行治疗。然后周期再次开始。或者，作为另一实例，3 周的周期可在第 1 和第 8 天进行治疗，而在第 2 至 7 天和第 9 至 21 天不进行治疗。在某些实施方式中，周期可包括按照相同或不同时间表的化疗剂组合的治疗，然后是非治疗窗口以允许恢复。

[0116] 在某些实施方式中，在施用至少一个周期的至少一种化疗剂之前施用一个周期的 CoQ10。在其它实施方式中，在施用至少一个周期的至少一种化疗剂之前施用两个或更多个周期的 CoQ10。在进一步的实施方式中，在施用至少一个周期的化疗剂之前施用三个或更多个周期的 CoQ10。在又进一步的实施方式中，在施用至少一个周期的化疗剂之前施用四个或更多个周期的 CoQ10。

[0117] 如本文所用，“连续输注”应理解为连续地施用治疗剂至少 24 小时的时间。连续输注通常通过使用泵、任选地使用可植入泵来实现。连续输注可在治疗周期的背景下施用。例如，一剂治疗剂可通过各周的每周一次 24 小时的连续输注来施用。使用连续输注的治疗不需要在整个治疗期间向受试者输注治疗剂。

[0118] 应理解，连续输注可包括短暂的施用中断，例如以更换被施用的辅酶 Q10 的储器。连续施用通常通过泵的使用来促进。连续输注的进行不包括故意的任何明显给药中断。如本文所用，中断以评估生命体征和 / 或进行实验室评估以确保患者的安全和不发生不可接受的不良事件不被认为是明显的中断。因设备故障如泵故障导致的中断不是故意的中断。

[0119] 术语“肿瘤疾病”、“癌症”或“肿瘤”是本领域公知的，且指的是在例如受试者中存在具有致癌细胞典型特性（例如失控的增殖、永生性、转移可能性、快速的生长和增殖速率、减少的细胞死亡 / 凋亡以及某些特征性形态特征）的细胞。

[0120] 如本文所用，“肿瘤疾病”、“癌症”或“肿瘤”指在人类中发现的所有类型的癌症或赘生物或恶性肿瘤，包括但不限于 :白血病、淋巴瘤、黑素瘤、癌瘤和肉瘤。如本文所用，术语或语言“肿瘤疾病”、“癌症”、“赘生物”和“肿瘤”可互换地使用并以单数或复数形式指的是已经经历恶性转化的细胞，所述恶性转化使得它们对于宿主生物体是病理性的。原发性癌细胞（即，从恶性转化部位附近获得的细胞）可通过已建立的技术特别是组织学检查容易地与非癌细胞区分开来。如本文所用，癌细胞的定义不仅包括原发性癌细胞，而且包括癌干细胞，以及癌祖细胞或源自癌细胞祖先的任意细胞。这包括转移的癌细胞以及源自癌细胞的体外培养物和细胞系。

[0121] “实体肿瘤”是可基于肿瘤团块检测的肿瘤，例如通过如 CAT 扫描、MR 成像、X- 射线、超声或触诊的程序 ;和 / 或其因为在可获自患者的样品中一种或多种癌症特异性抗原的表达而可检测。肿瘤不必具有可测量的维度。

[0122] 在提及通常表现为实体肿瘤的癌症类型时，“临床可检测的”肿瘤是基于肿瘤团块可检测的肿瘤，例如通过如 CAT 扫描、MR 成像、X- 射线、超声或触诊的程序 ;和 / 或其因为在可获自患者的样品中一种或多种癌症特异性抗原的表达而可检测。

[0123] 如本文所用，“可检测的肿瘤”是在实体肿瘤的情况中，可例如使用成像方法（例如，X- 射线、CT 扫描、有或无造影剂的磁共振成像、超声）、触诊或其它物理检查方法，和 / 或通过外科手术方法或活检的直接观察（通常与组织学分析结合）;或者在非实体肿瘤例如白血病的情况中，通过血液样品的分析如全血计数或组织学分析，确认存在于受试者中的肿瘤。在某些实施方式中，肿瘤可基于某些标志物的存在来检测。应理解，肿瘤的诊断和检测可包括多种试验和诊断方法。

[0124] 术语“肉瘤”通常指由如胚性结缔组织的物质构成并通常由包埋在纤维性或均质物质中的紧密包装的细胞组成的肿瘤。可用 IV 制剂中的 CoQ10 胶状分散体治疗的肉瘤实例包括例如软骨肉瘤、纤维肉瘤、淋巴肉瘤、黑素肉瘤、粘液肉瘤、骨肉瘤、Abemethy 肉瘤、脂肉瘤、脂肪肉瘤、腺泡状软组织肉瘤、成釉细胞肉瘤、葡萄状肉瘤、绿色瘤肉瘤、绒毛膜癌、胚胎性肉瘤、维尔姆斯肿瘤肉瘤、子宫内膜肉瘤、间质肉瘤、尤因氏肉瘤、筋膜肉瘤、纤维母细胞肉瘤、巨细胞肉瘤、粒细胞肉瘤、霍奇金肉瘤、特发性多发性色素沉着出血性肉瘤、B 细胞免疫母细胞肉瘤、淋巴瘤、T 细胞免疫母细胞肉瘤、詹森肉瘤、卡波西肉瘤、库普弗细胞肉瘤、血管肉瘤、白色肉瘤、恶性间叶瘤肉瘤、骨膜外肉瘤、网状细胞肉瘤、劳斯肉瘤、浆液囊性肉瘤、

滑膜肉瘤和毛细血管扩张性肉瘤。

[0125] 术语“黑素瘤”用来指从皮肤及其它器官的黑素细胞系统产生的肿瘤。可用 IV 制剂中的 CoQ10 胶状分散体治疗的黑素瘤包括例如肢端 - 雀斑样痣性黑素瘤、无黑色素性黑素瘤、良性幼年黑素瘤、Cloudman 黑素瘤、S91 黑素瘤、Harding-Passey 黑素瘤、幼年黑素瘤、恶性雀斑样痣黑素瘤、恶性黑素瘤、结节性黑素瘤、甲下黑素瘤和浅表扩散黑素瘤。

[0126] 术语“癌瘤”是指由倾向于浸润周围组织并引起转移的上皮细胞构成的恶性新生长。可用如本文所述的 IV 制剂中的 CoQ10 胶状分散体治疗的癌瘤包括例如腺泡癌 (acinar carcinoma)、腺泡状癌 (acinous carcinoma)、腺囊性癌 (adenocystic carcinoma)、腺样囊性癌 (adenoid cystic carcinoma)、腺瘤癌 (carcinoma adenomatosum)、肾上腺皮质癌 (carcinoma of adrenal cortex)、肺泡癌 (alveolar carcinoma)、肺泡细胞癌 (alveolar cell carcinoma)、基底细胞癌 (basal cell carcinoma)、基底细胞性癌 (carcinoma basocellulare)、基底细胞样癌 (basaloid carcinoma)、基底鳞状细胞癌 (basosquamous cell carcinoma)、细支气管肺泡癌 (bronchioalveolar carcinoma)、细支气管癌 (bronchiolar carcinoma)、支气管原癌 (bronchogenic carcinoma)、髓状癌 (cerebriform carcinoma)、胆管细胞癌 (cholangiocellular carcinoma)、绒毛膜癌 (chorionic carcinoma)、胶样癌 (colloid carcinoma)、粉刺状癌 (comedo carcinoma)、子宫体癌 (corpus carcinoma)、筛状癌、铠甲状癌、皮肤癌 (carcinoma cutaneum)、圆柱细胞癌、柱状细胞癌、导管癌、硬癌 (carcinoma durum)、胚胎性癌、髓样癌 (encephaloid carcinoma)、表皮样癌、腺样上皮癌、外植癌、溃疡性癌、纤维癌 (carcinoma fibrosum)、胶样癌 (gelatiniform carcinoma)、胶状癌 (gelatinous carcinoma)、巨大细胞癌 (giant cell carcinoma)、巨细胞癌 (carcinoma gigantocellulare)、腺癌、颗粒细胞癌、发基质癌、血样癌、肝细胞癌、许特耳细胞癌、透明癌 (hyaline carcinoma)、肾透明细胞样癌 (hypemephroid carcinoma)、幼稚型胚胎性癌、原位癌、表皮内癌、上皮内癌、Krompecher 癌、支气管 K 细胞癌 (Kulchitzky-cell carcinoma)、大细胞癌、豆状癌 (lenticular carcinoma)、豆状癌 (carcinoma lenticulare)、脂瘤癌、淋巴上皮癌、髓样癌 (carcinoma medullare)、髓样癌 (medullary carcinoma)、黑色素癌、软癌 (carcinoma molle)、梅克尔细胞癌、粘液癌、胶样癌、粘液细胞癌、粘液表皮样癌、粘液癌、粘液性癌 (mucinous carcinoma)、粘液癌 (carcinoma muciparum)、粘液细胞癌 (carcinoma mucocellulare)、粘液表皮样癌 (mucoepidermoid carcinoma)、粘液癌 (carcinoma mucosum)、粘液癌 (mucous carcinoma)、粘液瘤样癌、鼻咽癌、燕麦细胞癌、骨化性癌、骨样癌、乳头状癌、门脉周围癌、浸润前癌 (preinvasive carcinoma)、棘细胞癌、软糊状癌 (pultaceous carcinoma)、肾脏的肾细胞癌、储备细胞癌、肉瘤样癌、施奈德癌、硬癌 (scirrhous carcinoma)、阴囊癌、印戒细胞癌、单纯癌、小细胞癌、马铃薯样癌、球样细胞癌、梭形细胞癌、海绵样癌、鳞状癌、鳞状细胞癌、绳捆癌 (string carcinoma)、血管扩张性癌 (carcinoma telangiectaticum)、毛细管扩张性癌 (carcinoma telangiectodes)、移行细胞癌、结节性皮癌 (carcinoma tuberosum)、结节性癌、疣状癌和绒毛状癌 (carcinoma villosum)。

[0127] 癌症分期的具体标准取决于具体的癌症类型，其基于肿瘤大小、组织学特征、肿瘤标志物及本领域技术人员已知的其它标准。通常，癌症分期可描述如下：

[0128] 0 期：原位癌

[0129] I 期、II 期和 III 期：数越高表示疾病越广泛：较大的肿瘤大小和 / 或癌症扩散超出其最先在其中出现的器官到附近的淋巴结和 / 或邻近原发性肿瘤位置的组织或器官

[0130] IV 期：癌症已扩散到远处的组织或器官

[0131] 如本文所用，术语“治疗 (treat)”、“处理 (treating)”或“疗法 (treatment)”优选指获得有利或期望的临床结果的行为，所述有利或期望的临床结果包括但不限于减轻或改善疾病或病症的一个或多个体征或症状（例如，部分或完全退化）、减轻疾病程度、疾病的稳定状态（即，不恶化，获得稳定的疾病）、改善或缓和疾病状态、减小进展率或时间以及缓解（无论是部分的还是完全的）。癌症的“治疗”也可指与在不存在治疗的情况下与预期的存活相比延长的存活。治疗不必是治愈性的。在某些实施方式中，治疗包括如由有资质的个体如治疗医生使用例如公认的疼痛和生活质量 (QOL) 评估工具判断的疼痛减轻或生活质量 QOL 提高中的一种或多种。在某些实施方式中，治疗不包括如由有资质的个体如治疗医生使用例如公认的疼痛和生活质量 (QOL) 评估工具判断的疼痛减少或 QOL 提高中的一种或多种。

[0132] RECIST 标准为临床上公认的用来提供实体肿瘤测量的标准方法，并为肿瘤大小变化的客观评估提供定义的用于临床试验中的评估标准。这样的标准也可用来监测经受实体肿瘤的治疗的个体的反应。RECIST 1.1 标准在 Eisenhauer 等，New response evaluation criteria in solid tumors:Revised RECIST guideline(version 1.1).Eur. J.Cancer.45:228-247,2009 中详细讨论，其以引用方式并入本文中。靶病灶的反应标准包括：

[0133] 完全反应 (CR)：所有靶病灶均消失。任意病理性淋巴结（无论是靶标还是非靶标）必须在短轴上减小到 <10mm。

[0134] 部分反应 (PR)：以基线直径总和为参照，靶病灶的直径总和减小至少 30％。

[0135] 进行性疾病 (PD)：以研究中的最小总和（这包括基线总和，如果其在研究中是最小的）为参照，靶病灶的直径总和增大至少 20％。除 20％的相对增大外，总和必须还显示至少 5mm 的绝对增大。（注：一个或多个新病灶的出现也被视为是进展。）

[0136] 稳定的疾病 (SD)：以研究时的最小直径总和为参照，既不充分缩小至达到 PR 标准又不充分增大至达到 PD 标准。

[0137] RECIST 1.1 标准还考虑非靶病灶，其被定义为可能可测量但不必被测量，且仅应当在期望时间点定性评估的病灶。非靶病灶的反应标准包括：

[0138] 完全反应 (CR)：所有非靶病灶消失并且肿瘤标志物水平正常化。所有淋巴结在大小上都必须是非病理性的（短轴 <10mm）。

[0139] 非 CR/ 非 PD：一个或多个非靶病灶留存和 / 或肿瘤标志物水平保持高于正常限度。

[0140] 进行性疾病 (PD)：现存非靶病灶的明确进展（强调原初）。一个或多个新病灶的出现也被视为进展。为在非靶疾病的基础上取得“明确进展”，必须有非靶疾病整体水平的实质性恶化，使得即便在靶疾病中存在 SD 或 PR 的情况下，总体肿瘤负荷也充分增大至应当中断治疗。一个或多个非靶病灶尺寸的适度“增大”通常不足以作为明确进展状态。因此面对靶疾病中的 SD 或 PR，仅仅基于非靶疾病中的变化而称为总体进展是极其少见的。

[0141] 在急性白血病中治疗反应的临床可接受标准如下：

[0142] 完全缓解 (CR) :患者必须无白血病相关的所有症状并具有嗜绝对中性粒细胞计数≥ 1.0x10^9/L、血小板计数≥ 100x10^9/L 以及具有<5%胚细胞且无 Auer 小体的正常骨髓。

[0143] 血细胞计数恢复不完全的完全缓解 (Cri) :按照 CE,但具有残余的血小板减少症(血小板计数<100x10^9/L) 或残余的嗜中性粒细胞减少症 (绝对嗜中性细胞计数<1.0x10^9/L)。

[0144] 部分缓解 (PR) :骨髓胚细胞减少≥ 50%至骨髓中 5 至 25%异常细胞 ;或若存在 Auer 小体,胚细胞≤ 5%的 CR。

[0145] 治疗失败 :治疗未能实现 CR、Cri 或 PR。复发。

[0146] 确认的 CR 后复发 :白血病胚细胞在外周血中重现,或者不可归因于任意其它原因(例如,巩固治疗后的骨髓再生) 的骨髓中≥ 5%的胚细胞,或者出现新的发育异常的变化。

[0147] “化疗剂”是指用于治疗癌症的药物。化疗剂包括但不限于小分子、激素和激素类似物以及生物制剂 (例如,抗体、肽药物、核酸药物)。在某些实施方式中,化疗不包括激素和激素类似物。

[0148] “化疗方案”是用于治疗癌症的临床上接受的给药方案,其包括依照特定时间表以特定量向受试者施用一种或多种化疗剂。在某些实施方式中,化疗剂可以是临床试验中的药剂。

[0149] 如本文所用,“共施用”或“联合疗法”应理解为使用单独的制剂或单一药物制剂施用两种或更多种活性剂,或者以任意顺序相继施用,使得存在两种 (或全部) 活性剂同时发挥其生物活性的时间段。本文中预想一种活性剂 (例如, CoQ10) 可改善第二药剂的活性,例如,可使靶细胞如癌细胞对第二药剂的活性敏感。共施用不要求药剂在相同时间、以相同频率或通过相同给药途径施用。如本文所用,“共施用”或“联合疗法”包括施用 CoQ10 化合物与一种或多种另外的抗癌剂如化疗剂,或者施用两种或更多种 CoQ10 化合物。本文中提供了抗癌剂 (包括化疗剂) 的实例。

[0150] 在优选实施方式中,在本文中提供的治疗方法中与 CoQ10 联合施用的另外的抗癌剂例如化疗剂或化疗方案不包括 CoQ10,排除 CoQ10。

[0151] 化疗方案可包括依照预定“周期”施用药物,所述“周期”包括施用和不施用一种或多种用于治疗癌症的药剂的时间间隔。例如,可以连续三周每周一次或多次施用药剂,然后一周不施用药剂,以提供四周的周期。可以重复该周期以使得受试者经受三个治疗周、一个非治疗周、三个治疗周、一个非治疗周,等等,持续期望数量的周期。在某些实施方式中,在每个周期结束时或每隔一个周期评估治疗疗效和实验室值 (例如,肝酶、血计数、肾功能)。

[0152] “化疗方案失败的受试者”是根据 RECIST 1.1 标准 (参见 Eisenhauer 等 , 2009 和如上文讨论的) 患有对使用化疗方案的治疗无反应或停止反应的癌症的受试者,即在单独的或与在可能的情况下通常临床上指定与化疗结合的外科手术和 / 或放疗相结合的化疗方案过程中或结束后,未在靶病灶中获得至少稳定的疾病 (即,稳定的疾病、部分反应或完全反应) ;或未实现至少非靶病灶的非 CR/ 非 PD(即,非 CR/ 非 PD 或完全反应) 的受试者。失败的化疗方案导致例如肿瘤生长、增大的肿瘤负荷和 / 或肿瘤转移。在一些实施方式中,如本文所用,失败的化疗方案包括由于剂量限制性毒性如 III 级或 IV 级毒性而终止的治疗方案,所述剂量限制性毒性不能被解决以允许继续或恢复使用引起毒性的化疗剂或方案的治疗。在一些实施方式中,失败的化疗方案包括在延长的时间段内,如至少 1 个月、至少 2 个

月、至少 3 个月、至少 4 个月、至少 5 个月、至少 6 个月、至少 12 个月、至少 18 个月或低于临床定义的治愈的任意时间段，对于所有靶和非靶病灶不导致至少稳定疾病的治疗方案。在一些实施方式中，失败的化疗方案包括在化疗剂治疗过程中导致至少一个靶病灶的进行性疾病，或在治疗方案结束后不到 2 周、不到 1 个月、不到两个月、不到 3 个月、不到 4 个月、不到 5 个月、不到 6 个月、不到 12 个月或不到 18 个月或者不到低于临床定义的治愈的任意时间段导致进行性疾病的治疗方案。

[0153] 失败的化疗方案不包括其中经癌症治疗的受试者达到临床定义的治愈，例如在治疗方案结束后 5 年的完全反应，以及其中受试者随后例如在治疗方案结束后超过 5 年、超过 6 年、超过 7 年、超过 8 年、超过 9 年、超过 10 年、超过 11 年、超过 12 年、超过 13 年、超过 14 年或超过 15 年诊断出不同癌症的治疗方案。例如，患有儿科癌症的受试者可能在该儿科癌症治愈后的生活中发生癌症。在这样的受试者中，治疗儿科癌症的化疗方案被认为已成功。

[0154] “难治性癌症”是外科手术无效的恶性肿瘤，其在开始对化疗或放疗无反应，或者其随时间变得对化疗或放疗无反应。

[0155] “治疗有效量”是足以治疗受试者的疾病的量。治疗有效量可以一次或多次施用来施用。

[0156] 术语“施用 (administer)”、“给药 (administering)”或“用药 (administration)”包括向受试者的系统中或向受试者中或受试者上的特定区域递送药物组合物或药剂的任意方法。在某些实施方式中，药剂经口递送。在某些实施方式中，药剂肠胃外施用。在某些实施方式中，药剂通过注射或输注递送。在某些实施方式中，药剂局部递送，包括经粘膜递送。在某些实施方式中，药剂通过吸入递送。在本发明的某些实施方式中，药剂通过肠胃外递送来施用，包括静脉内、肌内、皮下、髓内注射以及鞘内、直接心室内、腹膜内、鼻内或眼内注射。在一个实施方式中，本文提供的组合物可通过直接注射到肿瘤来施用。在一些实施方式中，本发明的制剂可通过静脉内注射或静脉内输注来施用。在某些实施方式中，本发明的制剂可通过连续输注来施用。在某些实施方式中，施用不是口服的。在某些实施方式中，施用是全身性的。在某些实施方式中，施用是局部的。在一些实施方式中，可组合一种或多种给药途径，如静脉内和肿瘤内、或者静脉内和经口、或者静脉内和口服、静脉内和局部、或者静脉内和经皮或经粘膜。施用药剂可通过多人协同工作来进行。施用药剂包括例如向受试者开具待施用药剂的处方和 / 或直接或通过他人提供通过自身递送 (如通过口服递送)、皮下递送、通过中心导管的静脉内递送等来服用特定药剂的指导 ；或者由受过训练的专业人员递送，如静脉内递送、肌内递送、肿瘤内递送等。

[0157] “不良事件”或“AE”由取决于严重度的等级表征。一些 AE (例如，恶心、低血液计数、疼痛、降低的血液凝结) 可以被治疗，使得可以继续或恢复特定化疗方案。一些不良事件 (例如，心脏、肝脏或肾脏功能的损失 ；恶心) 可能不是可治疗的，从而需要终止药物治疗。AE 等级的确定和适当的干预可由本领域技术人员确定。不良事件的通用术语标准 (CTCAE) 第 4.0 版 (出版日期 ：2009 年 5 月 28 日) 提供了如下的不良事件分级量表 ：

[0158] 1 级 ：轻度 ；无症状或轻微症状 ；仅有临床或诊断观察 ；不需要干预。

[0159] 2 级 ：中等 ；需要最低限度的、局部的或非侵入性的干预 ；限制适龄的日常器械活动 (ADL)。

[0160] 3 级 ：严重或医学上显著但不直接威胁生命的 ；需要住院治疗或延长住院治疗 ；致

残，限制自我护理的 ADL。

[0161] 4 级 ：威胁生命的后果 ；需要紧急干预。

[0162] 5 级 ：与不良事件相关的死亡。

[0163] 如本文所用，术语“存活”是指已经治疗疾病或病症如癌症的受试者的生命的延续。存活时间可从任意点如进入临床试验的时间、早前治疗方案完成或失败的时间、诊断的时间等定义。

[0164] 如本文所用，“调理作用”是指如本文所述的亲脂性生物活性剂经标记以由吞噬细胞摄取和破坏的过程。调理作用包括调理素结合到生物活性剂。在调理素结合到膜后，吞噬细胞被吸引到活性剂。调理素是充当吞噬过程的结合增强剂的任意分子。

[0165] 如本文所用，术语“调理作用缩减剂”是指与活性剂结合地作用以降低调理素充当吞噬过程的结合增强剂的能力的任意药剂。

[0166] 如本文所用，“分散体”是指其中任意性质（例如，固体、液体或气体）的胶体尺寸的颗粒分散在不同组成或状态的连续相中的体系。在静脉内药物递送中，连续相基本上是水而分散的颗粒可以是固体（混悬液）或不混溶的液体（乳液）。

[0167] 待通过本发明方法治疗的“受试者”可以是指人或非人动物，优选哺乳动物，更优选人。在某些实施方式中，受试者在开始使用本发明方法治疗之前具有可检测的肿瘤。在某些实施方式中，受试者在使用本发明方法开始治疗时具有可检测的肿瘤。

[0168] 如本文所用，术语“安全和治疗有效量”是指当以本公开的方式使用时，足以产生期望的治疗反应而无过度的不良副作用（如毒性、刺激或过敏反应）并具有合理的收益 / 风险比的组分量。

[0169] “治疗有效量”是指在施用于患者以治疗疾病时，足以使这样的疾病治疗生效的化合物量。在施用以预防疾病时，该量足以避免或延迟疾病发作。“治疗有效量”将根据化合物、疾病及其严重度以及待治疗的患者的年龄、体重等而发生变化。治疗有效量不必是治愈性的。治疗有效量不必一起防止疾病或病症发生。相反，治疗有效量是至少延迟或减少疾病或病症的发作、严重度或进展的量。疾病进展可例如通过肿瘤负荷、到进展的时间、存活时间或本领域中使用的其它临床测量中的一种或多种来监测。

[0170] 术语“治疗效果”指由药理活性物质在动物、特别是哺乳动物和更特别是人中引起的局部或全身性效果。该术语因此是指预期用在疾病的诊断、治愈、缓解、治疗或预防中或者用在增强动物或人中的期望身体或精神发育和状况中的任意物质。短语“治疗有效量”是指以可适用于任意治疗的合理收益 / 风险比产生一些期望的局部或全身性效果的这种物质的量。在某些实施方式中，化合物的治疗有效量将取决于其治疗指数、溶解度等。

[0171] “预防 (preventing)”或“防止 (prevention)”是指降低获得疾病或病症的风险（即，使得疾病的临床体征或症状中的至少之一不在可能暴露于或易患该疾病但尚未经历或显示出该疾病症状的受试者中发生）。预防不要求疾病或病症在受试者中从未发生或复发。

[0172] 术语“病症 (disorders)”和“疾病 (diseases)”被包涵性地使用并且指的是与身体的任意部位、器官或系统（或其任意组合）的正常结构或功能的任意偏离。特定的疾病由特征性的症状和体征表现，包括生物学、化学和物理学变化，并常常与多种其它因素相关联，包括但不限于人口统计学、环境、职业、遗传和医疗史因素。某些特征性的体征、症状和

相关因素可通过多种方法量化以给出重要的诊断信息。

[0173] 在本申请中出现一系列列举数值的所有地方，应理解任意所列举的数值可以是数值范围的上限或下限。还应理解本发明涵盖所有这样的数值范围，即具有数值上限和数值下限的组合的一个范围，其中上限和下限各自的数值都可以是本文中列举的任意数值。本文提供的范围应理解为包括该范围内的所有值。例如，1-10 应理解为包括值 1、2、3、4、5、6、7、8、9 和 10 中的全部，并视情况包括分数值。表达为“高达”某个值（例如高达 5）的范围应理解为所有值（包括该范围的上限），例如 0、1、2、3、4 和 5，并视情况包括分数值。至多一周或在一周内应理解为包括 0.5、1、2、3、4、5、6 或 7 天。类似地，由“至少”限定的范围应理解为包括所提供的较低值和所有更高的值。

[0174] 除非另有指出，所有百分比形式是重量 / 重量。

[0175] 如本文所用，“约”应理解为包括在平均值的三个标准偏差内或特定领域中的标准公差范围内。在某些实施方式中，约应理解为不超过 0.5 的变异。

[0176] 冠词“一 (a)”和“一个 (an)”在本文中用以指一个或超过一个（即，至少一个）该冠词的语法客体。举例来说，“一个元素”指一个元素或超过一个元素。

[0177] 术语“包括”在本文中用以指短语“包括但不限于”并可与其互换地使用。

[0178] 除非上下文另有明确指出，术语“或”在本文中包含性地用以指术语“和 / 或”并可与其互换地使用。

[0179] 术语“例如”在本文中用以指短语“例如但不限于”并可与其互换地使用。

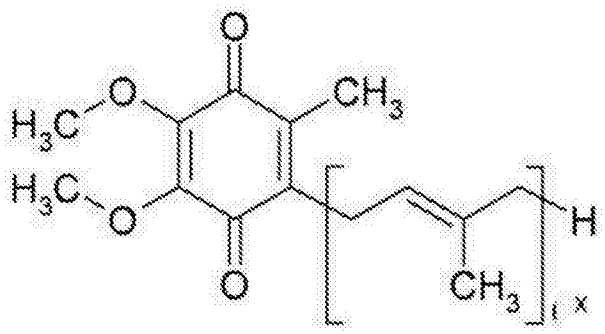
[0180] 如本文所用，术语“标准剂量”是指常用于治疗病症的治疗剂剂量。例如，治疗剂生产商在产品说明书中描述的治疗剂推荐剂量应视为标准剂量。化疗剂的标准剂量实例在表 3 中提供。

[0181] 例如，如表 3 中所示，用于静脉内使用以治疗卵巢癌的吉西他滨的标准剂量为在每个 21 天周期的第 1 和 8 天，30 分钟的 1000mg/m^2；用于静脉内使用以治疗乳腺癌的吉西他滨标准剂量为在每个 21 天周期的第 1 和 8 天，30 分钟的 1250mg/m^2；用于静脉内使用以治疗非小细胞肺癌的吉西他滨标准剂量为在每个 28 天周期的第 1、8 和 15 天，30 分钟的 1000mg/m^2 或在每个 21 天周期的第 1 和 8 天，30 分钟的 1250mg/m^2；以及用于静脉内使用以治疗胰腺癌的吉西他滨标准剂量为前 7 周内每周一次，然后休止一周，然后在在每个 28 天周期的 3 周内每周一次 30 分钟的 1000mg/m^2。

[0182] II. 辅酶 Q10 化合物

[0183] 应理解，本发明中提供的所有方法可涉及施用任意其它的辅酶 Q10 化合物或其组合来代替辅酶 Q10。辅酶 Q10 化合物旨在包括一类 CoQ10 化合物。对本文所述方法有效的辅酶 Q10 化合物包括 CoQ10、CoQ10 代谢物、CoQ10 的生物合成前体、CoQ10 类似物、CoQ10 衍生物和 CoQ10 相关化合物。CoQ10 类似物包括不具有或具有至少一个异戊二烯基重复的类似物。CoQ10 具有以下结构：

[0184]



[0185] 其中，x 为 10。在本发明中，CoQ10 化合物可包括 CoQ10 衍生物，其中 x 为 4-10 的任意数量的异戊二烯基单元、或 6-10 的任意数量的异戊二烯基单元或 8-10 的任意数量的异戊二烯基单元、或 9-10 个异戊二烯基单元。CoQ10 包括完全氧化的型式（也称泛醌）、部分氧化的型式（也称半醌或泛半醌）或者完全还原的型式（也称泛醇）或其任意混合物或组合。在某些实施方式中，用于治疗癌症的 CoQ10 化合物为泛醌。在某些实施方式中，用于治疗癌症的 CoQ10 化合物为泛醇。

[0186] 在本发明的某些实施方式中，治疗剂为辅酶 Q10(CoQ10)。辅酶 Q10，在本文中也称 CoQ10，还被称为泛醌或泛癸利酮。CoQ10 是公知的并且还被描述于国际公布号 WO 2005/069916(申请号 PCT/US2005/001581)、WO 2008/116135(申请号 PCT/US08/57786)、WO2010/132507(申请号 PCT/US2010/034453)、WO 2011/112900(申请号 PCT/US2011/028042) 和 WO2012/174559(申请号 PCT/US2012/043001) 中，它们中每一者的全文通过引用明确并入本文。CoQ10 是存在于真核细胞线粒体电子传递系统中的一系列聚戊二烯基 2,3- 二甲氧基 -5- 甲基苯醌（泛醌）中的一种。人类细胞仅产生 CoQ10 并且其见于所有人类细胞的细胞和线粒体膜中，并在具有高能量需求的器官如肝脏和心脏中具有最高水平。已估计 CoQ10 的身体库为约 2 克，其中超过 50％是内源性的。每天需要来自饮食或生物合成的大约 0.5 克 CoQ10。CoQ10 在全球补充剂市场以成吨的量生产并可获自 Kaneka，其工厂在德克萨斯州的 Pasadena 和日本的 Takasagoshi。

[0187] 辅酶 Q10 相关化合物包括但不限于苯醌类、类异戊二烯类、法尼醇类、乙酸法尼基酯、焦磷酸法尼基酯、1- 苯丙氨酸、d- 苯丙氨酸、dl- 苯丙氨酸、1- 酪氨酸、d- 酪氨酸、dl- 酪氨酸、4- 羟基 - 苯基丙酮酸酯、4- 羟基 - 苯基乳酸酯、4- 羟基 - 肉桂酸酯、酪氨酸或苯丙氨酸的二肽和三肽、3,4- 二羟基扁桃酸酯、3- 甲氧基 -4- 羟基苯基乙二醇、3- 甲氧基 -4- 羟基扁桃酸酯、香草酸、乙酸苯酯、吡哆醇、S- 腺苷基甲硫氨酸、泛醇、甲羟戊酸、焦磷酸异戊酯、丁酸苯酯、4- 羟基 - 苯甲酸酯、焦磷酸十异戊二烯基酯、β - 羟基丁酸酯、3- 羟基 -3- 甲基 - 戊二酸酯、乙酰肉毒碱、乙酰乙酰肉毒碱、乙酰甘氨酸、乙酰乙酰甘氨酸、肉毒碱、乙酸、丙酮酸、3- 羟基 -3- 甲基戊二酰肉毒碱；丝氨酸、丙氨酸、半胱氨酸、甘氨酸、苏氨酸、羟脯氨酸、赖氨酸、异亮氨酸和亮氨酸的所有异构体形式；甚至是肉毒碱和甘氨酸的 C4 至 C8 脂肪酸（丁酸、己酸、辛酸、癸酸、月桂酸、肉豆蔻酸、棕榈酸和硬脂酸）盐，如棕榈酰肉毒碱和棕榈酰甘氨酸，和 4- 羟基 - 苯甲酸酯聚异戊烯基转移酶、这些化合物的任意盐及其任意组合等。在某些实施方式中，该类药剂可根据本文提供的方法用于癌症治疗。

[0188] CoQ10 的代谢物和生物合成前体包括但不限于在酪氨酸和乙酰 -CoA 化学 / 生物转化为泛醇之间形成的那些化合物。辅酶生物合成途径的中间体包括酪氨酸、乙酰 -CoA、3- 六异戊二烯基 -4- 羟基苯甲酸酯、3- 六异戊二烯基 -4,5- 二羟基苯甲酸酯、3- 六异戊二

烯基-4-羟基-5-甲氧基苯甲酸酯、2-六异戊二烯基-6-甲氧基-1,4-苯醌、2-六异戊二烯基-3-甲基-6-甲氧基-1,4-苯醌、2-六异戊二烯基-3-甲基-5-羟基-6-甲氧基-1,4-苯醌、3-八异戊二烯基-4-羟基苯甲酸酯、2-八异戊二烯基苯酚、2-八异戊二烯基-6-甲氧基苯酚、2-八异戊二烯基-3-甲基-6-甲氧基-1,4-苯醌、2-八异戊二烯基-3-甲基-5-羟基-6-甲氧基-1,4-苯醌、2-十异戊二烯基-3-甲基-5-羟基-6-甲氧基-1,4-苯醌、2-十异戊二烯基-3-甲基-6-甲氧基-1,4-苯醌、2-十异戊二烯基-6-甲氧基-1,4-苯醌、2-十异戊二烯基-6-甲氧基苯酚、3-十异戊二烯基-4-羟基-5-甲氧基苯甲酸酯、3-十异戊二烯基-4,5-二羟基苯甲酸酯、3-十异戊二烯基-4-羟基苯甲酸酯、4-羟基苯基丙酮酸酯、4-羟基苯基乳酸酯、4-羟基-苯甲酸酯、4-羟基肉桂酸酯和六异戊二烯基二磷酸酯。在某些实施方式中，该类药剂可根据本文提供的方法用于癌症治疗。

[0189] III. 组合物

[0190] 本公开提供了含CoQ10化合物如辅酶Q10的组合物以治疗和预防癌症。本公开的组合物可以其自身或以其中其与适合的载体或赋形剂混合的药物组合物施用于患者。在治疗表现出肿瘤病症的患者时，施用治疗有效量的CoQ10化合物。

[0191] 本发明组合物的适合给药途径可包括肠胃外递送，仅举数例来说，包括静脉内、肌内、皮下、髓内注射以及鞘内、直接心室内、腹膜内、鼻内或眼内注射。在一个实施方式中，本文提供的组合物可通过直接注射到肿瘤来施用。在一些实施方式中，本发明的制剂可通过静脉内注射或静脉内输注来施用。在一些实施方式中，制剂通过连续输注来施用。在一个实施方式中，本发明的组合物通过静脉内注射来施用。在一个实施方式中，本发明的组合物通过静脉内输注来施用。当施用途径为例如静脉内输注时，本文提供了其中IV输注包含大约40mg/mL的浓度的活性剂如CoQ10的实施方式。当组合物通过IV输注施用时，可将其在药学上可接受的水性溶液如磷酸盐缓冲盐水或生理盐水中稀释。在一些实施方式中，可组合一种或多种施用途径，如静脉内和肿瘤内、或者静脉内和经口、或者静脉内和口服、或者静脉内和局部、经皮或经粘膜。

[0192] 本文描述的组合物可以以任何适合的制剂施用于受试者。这些包括例如液体、半固体和固体剂型，如液体溶液（例如，可注射和可输注溶液）、分散体或混悬液、片剂、丸剂、粉剂、乳膏剂、洗剂、搽剂、软膏剂或糊剂、用于施用于眼、耳或鼻的滴剂、脂质体和栓剂。优选的剂型取决于预期的施用方式和治疗应用。

[0193] 在某些实施方式中，CoQ10化合物如CoQ10可用防止快速释放的载体制备，如控释制剂，包括植入物、经皮贴剂和微胶囊化递送系统。可使用可生物降解的、生物相容性聚合物，如乙烯乙酸乙烯酯、聚酸酐类、聚乙醇酸、胶原、聚原酸酯类和聚乳酸。制备该类制剂的许多方法已获专利或是本领域技术人员周知的。参见例如Sustained and Controlled Release Drug Delivery Systems, J.R.Robinson, ed., Marcel Dekker, Inc., New York, 1978。

[0194] 例如，CoQ10化合物如CoQ10可配制用于肠胃外递送，例如用于皮下、静脉内、肌内或肿瘤内注射。组合物可以以单次浓注、多次注射或者通过连续输注（例如，静脉内或通过腹膜透析）施用。对于肠胃外给药，可将组合物配制为无菌的无热原形式。

[0195] 为了实施本发明，使用药学上可接受的载体将本文中所公开的化合物配制成适于全身施用的剂型是在本发明的范围之内。通过适当选择载体和适合的制造实施方法，本公

开的组合物，特别是配制为溶液的那些，可以肠胃外施用，如通过静脉内注射。

[0196] 该类化合物的毒性和疗效可通过标准药物程序在细胞培养物或实验动物中测定，例如，用于测定LD50（群体50％致死的剂量）和ED50(50％群体中治疗有效的剂量）。毒性与治疗效果之间的剂量比为治疗指数，且其可表示为比率LD50/ED50。显示出大的治疗指数的化合物可能是合乎需要的。从这些细胞培养物分析和动物研究获得的数据可用于制定人用的剂量范围。该类化合物的剂量可在具有很少或无毒性的包括ED50的循环浓度范围内。剂量可在该范围内根据所采用的剂型和所使用的给药途径变化。

[0197] 适用于本发明的药物组合物包括其中以有效量包含活性成分以实现其预期目的的组合物。有效量的确定完全在本领域技术人员的能力之内，尤其是参照本文提供的详细公开。除活性成分外，这些药物组合物可含有帮助将活性化合物加工成可以药用的制剂的合适的药学上可接受载体，包括赋形剂和辅剂。针对静脉内施用配制的制剂可以是胶状分散剂的溶液的形式。

[0198] 用于肠胃外给药的药物组合物包括水溶性形式的活性化合物的水性溶液。另外，活性化合物的混悬液可制备为适宜的油性注射混悬剂。适合的亲脂性溶剂或媒介包括脂肪油如芝麻油或者合成脂肪酸酯（如油酸乙酯或甘油三酯类）或者脂质体。水性注射混悬剂可含有增加混悬液粘度的物质如羧甲基纤维素钠、山梨糖醇或葡聚糖。任选地，混悬液还可含有适合的稳定剂或提高化合物溶解度以允许制备高度浓缩溶液的试剂。

[0199] IV. 制剂

[0200] 活性剂（例如CoQ10化合物，如CoQ10）可在用于所需的给药途径的任意药学上可接受的载体中递送。如本文所用，包含CoQ10化合物的制剂被配制用于任意给药途径，另有明确指示除外。在优选的实施方式中，所述制剂用于通过注射、输注或局部给药来施用。在某些实施方式中，CoQ10化合物不经口递送。

[0201] 用于本发明方法的优选治疗制剂包含微粒形式的活性剂（例如，CoQ10化合物，例如CoQ10）以用于例如静脉内施用。这样的静脉内制剂在例如WO2011/112900（申请号PCT/US2011/028042）中提供，其全文通过引用明确并入本文，并且如WO2011/112900（申请号PCT/US2011/028042）中所述的示例性静脉内制剂被用于下文所述的实施例。通过高压均质化，活性剂（例如，CoQ10化合物，例如CoQ10）颗粒被缩小以产生小到足以通过200nm除菌过滤器的颗粒。小到足以通过200nm除菌过滤器的颗粒可静脉内注射。这些颗粒远小于血细胞并因此将不栓塞毛细血管。红细胞例如为6微米×2微米的圆盘。颗粒被分散并通过稳定剂包裹或包围。虽然不希望受到任何理论的束缚，但据信稳定剂被吸引到疏水性治疗剂，使得疏水性治疗剂的分散颗粒被稳定剂包围，而形成混悬剂或乳剂。混悬剂或乳剂中的分散颗粒包含稳定剂表面和由固体微粒形式（混悬剂）或不可混溶的液体形式（乳剂）的疏水性治疗剂（例如CoQ10化合物如CoQ10）组成的核心。分散颗粒可被确立在脂质体的亲脂性区域中。

[0202] 分散的胶体体系允许在不使用助溶剂的情况下制剂的高载药量。此外，在不依赖于内源性低密度脂蛋白载体的情况下实现高且相对可再现的血浆水平。更重要的是，由于疏水性治疗剂的胶体颗粒的被动积累，制剂允许在实体肿瘤中维持高药物水平。

[0203] 优选的静脉内制剂基本上包含连续的水相和分散的固体（混悬剂）或分散的不可混溶液体（乳剂）。其中颗粒大部分由活性剂（药物）自身组成的分散胶体体系可以通常

递送比连续溶解体系更多的每单位体积的药物，如果该体系可制备为充分稳定的话。

[0204] 作为制剂介质，水性溶液可包括 Hank 溶液、Ringer 溶液、磷酸盐缓冲盐水 (PBS)、生理盐水缓冲液或其它适合的盐或组合，以达到用于肠胃外递送制剂的适宜 pH 和渗透压。可使用水性溶液来将用于施用的制剂稀释至期望浓度。例如，可使用水性溶液来将用于静脉内施用的制剂从约 4 重量 / 体积％的浓度稀释至较低浓度以便于施用较低剂量的 CoQ10。该水性溶液可含有增大溶液粘度的物质，如羧甲基纤维素钠、山梨糖醇或葡聚糖。

[0205] 活性剂 (例如，CoQ10 化合物，例如 CoQ10) 被分散在水性溶液中以使得形成胶状分散体，其中疏水性治疗剂的纳米分散颗粒被分散稳定剂覆盖或包裹或围绕而形成活性剂 (例如，CoQ10 化合物，例如 CoQ10) 颗粒的纳米分散体。纳米分散的活性剂 (例如，CoQ10 化合物，例如 CoQ10) 颗粒具有由被稳定剂包围的疏水性治疗剂形成的核心。类似地，在某些方面，稳定剂为具有亲水性部分和亲脂性部分的磷脂。在均质化时，磷脂形成脂质体或其它纳米颗粒。在某些方面，这些脂质体是双层的单片层脂质体，而在其它实施方式中，脂质体是双层的多片层脂质体。分散的活性剂 (例如，CoQ10 化合物，例如 CoQ10) 颗粒被分散到由磷脂形成的脂质体的双层结构的亲脂性部分中。在某些其它方面，脂质体的核心，如活性剂 (例如，CoQ10 化合物，例如 CoQ10) 颗粒的纳米分散体的核心，由疏水性治疗剂形成，且外层由磷脂的双层结构形成。在某些实施方式中，胶状分散体通过冻干工艺处理，从而纳米颗粒分散体被转化为干粉。

[0206] 在一些实施方式中，所用注射或输注用制剂是如 WO2011/112900 中制备的纳米混悬液形式的含 CoQ10 的 4％无菌水性胶状分散体。在某些实施方式中，制剂包含水性溶液 ；分散以形成颗粒的胶状纳米分散体的疏水性活性剂，例如 CoQ10、CoQ10 前体或代谢物或 CoQ10 相关化合物 ；以及分散稳定剂和调理作用缩减剂中的至少一种 ；其中活性剂的胶状纳米分散体被分散成平均粒度小于 200nm 的纳米分散颗粒。

[0207] 在某些实施方式中，分散稳定剂包括但不限于聚乙二醇化蓖麻油、Cremphor® EL、Cremophor® RH 40、聚乙二醇化维生素 E、维生素 E TPGS 和二肉豆蔻酰基磷脂酰基胆碱 (DMPC)。

[0208] 在某些实施方式中，调理作用缩减剂是泊洛沙姆和泊洛沙胺。

[0209] 在某些实施方式中，胶状纳米分散体是混悬液或乳液。任选地，胶状纳米分散体是晶体形式或过冷熔体形式。

[0210] 在某些实施方式中，注射或输注用制剂包含冻干保护剂如营养性糖，包括但不限于乳糖、甘露糖、麦芽糖、半乳糖、果糖、山梨糖、棉子糖、神经氨酸、葡糖胺、半乳糖胺、N- 甲基葡糖胺、甘露糖醇、山梨糖醇、精氨酸、甘氨酸和蔗糖或其任意组合。

[0211] 在某些实施方式中，注射或输注用制剂包含水性溶液 ；分散以形成颗粒的胶状纳米分散体的疏水活性剂 ；以及分散稳定剂和调理作用缩减剂中的至少一种。活性剂的胶状纳米分散体分散成粒度小于 200nm 的纳米分散颗粒。在一些实施方式中，分散稳定剂选自天然或半合成的磷脂。例如，适合的稳定剂包括聚乙氧基化 (又称聚乙二醇化) 蓖麻油 (Cremophor® EL)、聚乙氧基化氢化蓖麻油 (Cremophor® RH 40)、生育酚聚乙二醇琥珀酸酯 (聚乙二醇化维生素 E、维生素 E TPGS)、失水山梨糖醇脂肪酸酯 (Spans®)、胆汁酸和胆汁酸盐或二肉豆蔻酰基磷脂酰基胆碱 (DMPC)。在一些实施方式中，稳定剂是

DMPC。

[0212] 在某些实施方式中，制剂适合于肠胃外施用，包括静脉内、腹膜内、原位、颅内、肌内、皮下、髓内注射以及鞘内、直接心室内、鼻内或眼内注射。在某些实施方式中，制剂以设计为稳定颗粒的纳米混悬液的 4:3:1.5 的比率分别含有 CoQ10、二肉豆蔻酰基磷脂酰基胆碱和泊洛沙姆 188。在一些实施方式中，制剂包含磷酸盐缓冲盐水溶液，其含有磷酸氢二钠、磷酸二氢钾、氯化钾、氯化钠和注射用水。在某些实施方式中，纳米混悬液形式的含 CoQ10 的 4％无菌水性胶状分散体以例如 1:1、1:2、1:3、1:4、1:5、1:6、1:7、1:8、1:9、1:10、1:11、1:12、1:13、1:14、1:15、1:16、1:17、1:18、1:19、1:20 或由该值中的任意两个所包括的其它适宜比率提供的磷酸盐缓冲盐水溶液中稀释。

[0213] 在一些实施方式中，制剂为局部制剂。CoQ10 化合物的局部制剂在例如 WO2010/132507(PCT 申请号 PCT/US2010/034453)、WO2008116135(PCT 申请号 PCT/US2008/116135) 和 WO2005/069916(PCT 申请号 PC/US2005/001581) 中提供，其每一篇的全文通过引用明确并入本文。

[0214] 适于局部施用的制剂包括适于渗透通过皮肤的液体或半液体制剂，如搽剂、洗剂、乳膏剂、软膏剂或糊剂，以及适于施用于眼、耳或鼻的滴剂。根据本公开的滴剂可包括无菌水性或油性溶液或混悬液，并可通过将活性成分溶解至杀细菌剂和 / 或杀真菌剂和 / 或其它任何适合的防腐剂的合适水溶液中来制备，并且在一些实施方式中包括表面活性剂。然后可通过过滤使所得溶液澄清化和除菌，并通过无菌技术转移到容器中。适于包含在滴剂中的杀细菌和杀真菌剂的实例是硝酸或乙酸苯汞 (0.002％)、苯扎氯铵 (0.01％) 和醋酸氯己定 (0.01％)。用于制备油性溶液的适合溶剂包括甘油、稀酒精和丙二醇。

[0215] 根据本公开的洗剂包括适于应用到皮肤或眼的那些。洗眼剂可包括任选地含有杀细菌剂的无菌水性溶液并可通过与制备滴剂的方法类似的方法制备。应用到皮肤的洗剂或搽剂还可包含加快干燥和冷却皮肤的试剂 (如醇) 和 / 或保湿剂 (如甘油) 或油 (如蓖麻油或花生油)。

[0216] 可用于本发明方法的乳膏剂、软膏剂或糊剂是供外用的活性成分的半固体制剂。它们可在合适机器的帮助下通过将单独的或以水性或非水性流体的溶液或混悬液中的细碎或粉末形式的活性成分与油脂或非油脂基质混合来制得。基质可包括烃如硬、软或液体石蜡、甘油、蜂蜡、金属皂 ;粘胶 ;天然来源的油如杏仁油、玉米油、花生油、蓖麻油或橄榄油 ;羊毛脂或其衍生物，或者脂肪酸 (如硬脂酸或油酸) 及醇 (如丙二醇) 或大粒凝胶。制剂中可引入任何适合的表面活性试剂，例如阴离子、阳离子或非离子表面活性试剂，如失水山梨糖醇酯或其聚氧乙烯衍生物。也可包含悬浮剂如天然树胶、纤维素衍生物或无机材料 (如硅质二氧化硅) 及其它成分如羊毛脂。

[0217] 在一些实施方式中，局部递送媒介的其余组分可以是水或水相，在某些实施方式中是纯化的 (如去离子的) 水、甘油、丙二醇、乙氧基二甘醇、苯氧基乙醇和交联的丙烯酸聚合物。这样的递送媒介组合物可含有基于组合物总重量约 50 至约 95％的量的水或水相。存在的水的具体量不是关键性的，而是可调节的，以获得期望粘度 (通常为约 50cps 至约 10,000cps) 和 / 或其它组分的浓度。局部递送媒介可具有至少约 30 厘泊的粘度。

[0218] 局部制剂还可包含油相，包括例如可进而包含润肤剂、脂肪醇、乳化剂、它们的组合等的油相。例如，油相可包含润肤剂如 C12-15 烷基苯甲酸酯 (可商购自 Finetex Inc.

(Edison,N.J.)的FINSOLV™ TN)、癸酸-辛酸甘油三酯(可商购自Huls的MIGLYOL™ 812)等。其它可采用的适合的润肤剂包括植物衍生油(玉米油、红花油、橄榄油、澳洲坚果油等);各种合成酯,包括癸酸酯、亚油酸酯、二亚油酸酯、异硬脂酸酯、富马酸酯、癸二酸酯、乳酸酯、柠檬酸酯、硬脂酸酯、棕榈酸酯等;合成的中链甘油三酯、硅油或聚合物;脂肪醇,如鲸蜡醇、硬脂醇、鲸蜡硬脂醇、月桂醇、它们的组合等;和乳化剂,包括硬脂酸甘油酯、PEG-100硬脂酸酯、硬脂酸甘油酯、硬脂酸甘油酯SE、中和的或部分中和的脂肪酸,包括硬脂酸、棕榈酸、油酸等;含有脂肪酸的植物油提取物、Ceteareth®-20、Ceteth®-20、PEG-150硬脂酸酯、PEG-8月桂酸酯、PEG-8油酸酯、PEG-8硬脂酸酯、PEG-20硬脂酸酯、PEG-40硬脂酸酯、PEG-150二硬脂酸酯、PEG-8二硬脂酸酯、它们的组合等;或在本领域技术人员技能范围内的用于润肤的其它非极性化妆品或药学上可接受的材料、它们的组合等。

[0219] 局部制剂还可包含脂质体浓缩物,其包含例如磷脂,如卵磷脂、溶血卵磷脂、磷脂酰胆碱、磷脂酰乙醇胺、磷脂酰肌醇、磷脂酰甘油、磷脂酸、磷脂酰丝氨酸、溶血磷脂酰胆碱、溶血磷脂酰乙醇胺、溶血磷脂酰甘油、溶血磷脂酸、溶血磷脂酰丝氨酸、PEG-磷脂酰乙醇胺、PVP-磷脂酰乙醇胺及其组合、至少一种亲脂性生物活性剂和至少一种增溶剂。脂质体浓缩物可以以组合物的约0.5重量%至约20重量%的量与具有至少一种渗透促进剂的至少一种药学上可接受的载体组合。磷脂可以以组合物的约2重量%至约20重量%的量存在于组合物中,且生物活性剂可以以组合物的约0.5重量%至约20重量%的量存在。

[0220] 也可使用经皮渗透促进剂来促进CoQ10的递送。示例的是亚砜类如乙氧基二甘醇、1,3-丁二醇、异戊二醇、1,2-戊二醇、丙二醇、2-甲基丙-2-醇、丙-2-醇、乙基-2-羟基丙酸酯、己-2,5-二醇、二(2-羟丙基)醚、戊-2,4-二醇、丙酮、聚氧乙烯(2)甲醚、2-羟基丙酸、2-羟基辛酸、丙-1-醇、1,4-二氧六环、四氢呋喃、丁-1,4-二醇、丙二醇二壬酸酯、聚氧丙烯15硬脂基醚、辛醇、油醇的聚氧乙烯酯、油醇、月桂醇、己二酸二辛酯、己二酸二癸酯、己二酸二异丙酯、癸二酸二异丙酯、癸二酸二丁酯、癸二酸二乙酯、癸二酸二甲酯、癸二酸二辛酯、辛二酸二丁酯、壬二酸二辛酯、癸二酸二苄酯、邻苯二甲酸二丁酯、壬二酸二丁酯、肉豆蔻酸乙酯、壬二酸二甲酯、肉豆蔻酸丁酯、琥珀酸二丁酯、邻苯二甲酸二癸酯、油酸癸酯、己酸乙酯、水杨酸乙酯、棕榈酸异丙酯、月桂酸乙酯、壬酸2-乙基己基酯、异硬脂酸异丙酯、月桂酸丁酯、苯甲酸苄酯、苯甲酸丁酯、月桂酸己酯、癸酸乙酯、辛酸乙酯、硬脂酸丁酯、水杨酸苄酯、2-羟基辛酸、二甲亚砜、甲基磺酰甲烷、N,N-二甲基乙酰胺、N,N-二甲基甲酰胺、2-吡咯烷酮、1-甲基-2-吡咯烷酮、5-甲基-2-吡咯烷酮、1,5-二甲基-2-吡咯烷酮、1-乙基-2-吡咯烷酮、膦氧化物、糖酯、四氢糠醇、脲、二乙基-间-甲苯酰胺、1-十二烷基氮杂环庚-2-酮及其组合。

[0221] 增溶剂,特别是用于局部施用的增溶剂,可包括但不限于聚氧化烯葡聚糖、蔗糖的脂肪酸酯、寡葡糖苷的脂肪醇酯、甘油的脂肪酸酯、聚氧乙烯的脂肪酸酯、失水山梨糖醇的聚乙氧基化脂肪酸酯、聚(环氧乙烷)的脂肪酸酯、聚(环氧乙烷)的脂肪醇醚、聚(环氧乙烷)的烷基酚醚、聚氧乙烯-聚氧丙烯嵌段共聚物、乙氧基化油及其组合。

[0222] 局部制剂可包含润肤剂,包括但不限于苯甲酸C12-15烷基酯、癸酸-辛酸甘油三酯、植物衍生油、癸酸酯、亚油酸酯、二亚油酸酯、异硬脂酸酯、富马酸酯、癸二酸酯、乳酸酯、柠檬酸酯、硬脂酸酯、棕榈酸酯、合成中链甘油三酯、硅油、聚合物及其组合;脂肪醇选自鲸蜡醇、硬脂醇、鲸蜡硬脂醇、月桂醇及其组合;和乳化剂选自硬脂酸甘油酯、聚乙二醇100硬

脂酸酯、中和的脂肪酸、部分中和的脂肪酸、聚乙二醇 150 硬脂酸酯、聚乙二醇 8 月桂酸酯、聚乙二醇油酸酯、聚乙二醇 8 硬脂酸酯、聚乙二醇 20 硬脂酸酯、聚乙二醇 40 硬脂酸酯、聚乙二醇 150 二硬脂酸酯、聚乙二醇 8 二硬脂酸酯及其组合。

[0223] 局部制剂可包含中和相，所述中和相包含水、胺、乳酸钠和乳酸中的一种或多种。

[0224] 水相可进一步任选地包含一种或多种水相，其包含与粘度调节剂任选地组合的渗透促进剂，所述粘度调节剂选自交联的丙烯酸聚合物、短梗霉多糖、甘露聚糖、硬化葡聚糖、聚乙烯吡咯烷酮、聚乙烯醇、瓜耳胶、羟丙基瓜耳胶、黄原胶、阿拉伯树胶 (acacia gum)、阿拉伯胶 (arabia gum)、黄蓍胶、半乳聚糖、角豆胶、刺梧桐树胶、刺槐豆胶、角叉菜胶、果胶、支链淀粉、琼脂、槐柽籽、大米淀粉、玉米淀粉、马铃薯淀粉、小麦淀粉、藻类提取物、葡聚糖、琥珀酰葡聚糖、羧甲基淀粉、甲基羟丙基淀粉、藻酸钠、藻酸丙二醇酯、聚丙烯酸钠、聚乙基丙烯酸酯、聚丙烯酰胺、聚乙烯亚胺、膨润土、硅酸铝镁、锂皂石、水辉石和无水硅酸。

[0225] 局部制剂还可包含颜料如二氧化钛。

[0226] 在实施方式中，用于本发明方法的局部制剂包含量为组合物的约 5 重量％至约 20 重量％的油相，所述油相包含苯甲酸 C12-15 烷基酯或癸酸 / 辛酸甘油三酯、鲸蜡醇、硬脂醇、硬脂酸甘油酯和聚乙二醇 100 硬脂酸酯；量为组合物的约 60 重量％至约 80 重量％的水相，所述水相包含甘油、丙二醇、乙氧基二甘醇、苯氧乙醇、水和交联的丙烯酸聚合物；量为组合物的约 0.1 重量％至约 15 重量％的中和相，所述中和相包含水、三乙醇胺、乳酸钠和乳酸；量为组合物的约 0.2 重量％至约 2 重量％的颜料，所述颜料包含二氧化钛；和量为组合物的约 0.1 重量％至约 30 重量％的脂质体浓缩物，所述脂质体浓缩物包含失水山梨糖醇的聚乙氧基化脂肪酸酯、辅酶 Q10、磷脂酰胆碱卵磷脂、苯氧乙醇、丙二醇和水，其中丙二醇和乙氧基二甘醇以组合物的 3 重量％至约 15 重量％的合并量存在，并且辅酶 Q10 以组合物的约 0.75 重量％至约 10 重量％的量存在。用于本发明方法的其它制剂在例如 WO2008/116135(PCT 申请号 PCT/US08/57786) 和 WO2010/132507(PCT/US2010/034453) 中提供，其每一篇的全文通过引用方式明确并入本文。

[0227] 在一个实施方式中，用于本发明方法的局部制剂为如 US 2011/0027247 所述的 3％ CoQ10 乳膏剂，其全文通过引用并入本文。在一个实施方式中，3％的 CoQ10 包含：

[0228] (1) 相 A，其含有组合物的约 4.0 重量 / 重量％的苯甲酸 C12-15 烷基酯或癸酸 / 辛酸甘油三酯、组合物的约 2.00 重量 / 重量％的鲸蜡醇、约 1.5 重量 / 重量％的硬脂醇、约 4.5 重量 / 重量％的硬脂酸甘油酯和 PEG-100；

[0229] (2) 相 B，其含有约 2.00 重量 / 重量％的甘油、约 1.5 重量 / 重量％的丙二醇、约 5.0 重量 / 重量％的乙氧基二甘醇、约 0.475 重量 / 重量％的苯氧乙醇、约 40 重量 / 重量％的卡波姆分散体、约 16.7 重量 / 重量％的纯化水；

[0230] (3) 相 C，其含有约 1.3 重量 / 重量％的三乙醇胺、约 0.5 重量 / 重量％的乳酸、约 2.0 重量 / 重量％的乳酸钠溶液、约 2.5 重量 / 重量％的水；

[0231] (4) 相 D，其含有约 1.0 重量 / 重量％的二氧化钛；和

[0232] (5) 相 E，其含有约 15.0 重量 / 重量％的 CoQ1021％浓缩物。

[0233] CoQ1021％浓缩物组合物 (上述 3％乳膏剂中的相 E) 可通过如下所述组合相 A 和 B 制备。相 A 包含 21 重量 / 重量％的泛癸利酮 USP(CoQ10) 和 25 重量 / 重量％的聚山梨酸酯 80NF。相 B 包含 10.00 重量 / 重量％的丙二醇 USP、0.50 重量 / 重量％的苯氧乙醇 NF、

8.00 重量 / 重量%的卵磷脂 NF(PHOSPHOLIPON 85G) 和 35.50 重量 / 重量%的纯化水 USP。所有重量百分数都是相对于整个 CoQ1021%浓缩物组合物的重量。百分数和进一步的详情列于下表中。

[0234] 表 1

[0235]

相	商品名	INCI 名称	百分数
A	RITABATE 80	聚山梨酸酯 80	25.000
A	UBIDECARENONE	泛醌	21.000
B	PURIFIED WATER	水	35.500
B	PROPYLENE GLYCOL	丙二醇	10.000
B	PHENOXYETHANOL	苯氧乙醇	0.500
B	PHOSPHOLIPON 85G	卵磷脂	8.000
总计			100.000

[0236] 将苯氧乙醇和丙二醇置于适合的容器中并混合直至澄清。向第二容器 (混合罐 1) 中加入要求量的水。在混合的同时加热混合罐 1 至 45 和 55℃之间。向水中加入苯氧乙醇 / 丙二醇溶液并混合至其澄清且均匀。当混合罐 1 中的水相内容物在 45 至 55℃范围内时，在低到中度混合下加入 Phospholipon G。在避免任何起泡的同时，混合混合罐 1 的内容物直至 Phospholipon 85G 均匀分散。向适合的容器 (混合罐 2) 中加入聚山梨酸酯 89 并加热至 50 和 60℃之间。然后向混合罐 2 中加入泛癸利酮。在使温度保持在 50 和 60℃之间的同时，混合混合罐 2 直至全部泛癸利酮溶解。在全部泛癸利酮都已溶解后，将水相缓慢转移至混合罐 2。当所有材料都已合并时，使内容物均质化直至分散体平滑且均匀。在小心不要过热的同时使温度保持在 50 和 60℃之间。然后停止均质化并将混合罐 2 的内容物转移到适合的容器以进行贮存。

[0237] 在一些实施方式中，用于本发明的任何施用途径的制剂可包含约 0.001 至约 20%(重量 / 重量) 的 CoQ10，更优选地约 0.01%和约 15%之间、甚至更优选地约 0.1%至约 10%(重量 / 重量) 之间的 CoQ10。在某些实施方式中，用于本发明的任何施用途径的制剂可包含约 1%至约 10%(重量 / 重量) 的 CoQ10。在某些实施方式中，用于本发明的任何施用途径的制剂可包含约 2%至约 8%(重量 / 重量) 的 CoQ10。在某些实施方式中，用于本发明的任何施用途径的制剂可包含约 2%至约 7%(重量 / 重量) 的 CoQ10。在某些实施方式中，用于本发明的任何施用途径的制剂可包含约 3%至约 6%(重量 / 重量) 的 CoQ10。在某些实施方式中，用于本发明的任何施用途径的制剂可包含约 3%至约 5%(重量 / 重量) 的 CoQ10。在某些实施方式中，用于本发明的任何施用途径的制剂可包含约 3.5%至约 4.5%(重量 / 重量) 的 CoQ10。在某些实施方式中，用于本发明的任何施用途径的制剂可包含约 3.5%至约 5%(重量 / 重量) 的 CoQ10。在一个实施方式中，制剂包含约 4%(重

量 / 重量）的 CoQ10。在一个实施方式中，制剂包含约 8%（重量 / 重量）的 CoQ10。在各种实施方式中，制剂包含约 0.1%、0.2%、0.3%、0.4%、0.5%、1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、11%、12%、13%、14%、15%、16%、17%、18%、19%或 20%（重量 / 重量）的 CoQ10 或由所列举的任意两个值所包括的任意范围。在某些实施方式中，制剂可按照重量 / 体积百分比而不是重量 / 重量百分比制备。取决于制剂，CoQ10 的浓度在重量 / 重量和重量 / 体积百分比形式中可以相同或大致相同。CoQ10 可从 Kaneka Q10 以粉末形式的 Kaneka Q10(USP 泛癸利酮）获得 (Pasadena, Texas, USA)。本文示例的方法中使用的 CoQ10 具有以下特性：残余溶剂满足 USP 467 要求；水含量低于 0.0%、低于 0.05%或低于 0.2%；炽灼残渣为 0.0%、低于 0.05%或低于 0.2%低于；重金属含量低于 0.002%或低于 0.001%；纯度介于 98-100%之间或为 99.9%或 99.5%。

[0238] 在某些实施方式中，制剂中 CoQ10 的浓度为 1mg/mL 至 150mg/mL。在一个实施方式中，制剂中 CoQ10 的浓度为 5mg/mL 至 125mg/mL。在一个实施方式中，制剂中 CoQ10 的浓度为 10mg/mL 至 100mg/mL。在一个实施方式中，制剂中 CoQ10 的浓度为 20mg/mL 至 90mg/mL。在一个实施方式中，CoQ10 的浓度为 30mg/mL 至 80mg/mL。在一个实施方式中，CoQ10 的浓度为 30mg/mL 至 70mg/mL。在一个实施方式中，CoQ10 的浓度为 30mg/mL 至 60mg/mL。在一个实施方式中，CoQ10 的浓度为 30mg/mL 至 50mg/mL。在一个实施方式中，CoQ10 的浓度为 35mg/mL 至 45mg/mL。应理解，具有前述值的任意之一作为上限或下限的其它范围也旨在作为本发明的部分，例如，10mg/mL 至 50mg/mL 或 20mg/mL 至 60mg/mL。

[0239] 在某些实施方式中，制剂中 CoQ10 的浓度为约 10、15、20、25、30、31、32、33、34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49、50、55、60、65、70、75、80、85、90 或 95mg/mL。在一个实施方式中，制剂中 CoQ10 的浓度为约 50mg/mL。在一个实施方式中，制剂中 CoQ10 的浓度为约 60mg/mL。在一个实施方式中，制剂中 CoQ10 的浓度为约 30mg/mL。在优选实施方式中，制剂中 CoQ10 的浓度为约 40mg/mL。应理解，具有这些值的任意之一作为上限或下限的范围也旨在作为本发明的部分，例如，37mg/mL 和 47mg/mL 之间或 31mg/mL 和 49mg/mL 之间。

[0240] 应理解，可类似地制备含有 CoQ10 前体、代谢物和相关化合物的制剂。

[0241] IV. 联合疗法

[0242] 本文提供了通过向有需要的受试者共施用 CoQ10 和至少一种化疗剂来治疗受试者的肿瘤病症的方法。如本文所用，术语“共施用”是指在化疗剂施用之前、与化疗剂施用同时或基本同时、在化疗剂施用之后或与化疗剂施用间隔地施用 CoQ10。在某些实施方式中，CoQ10 在化疗剂之前和与化疗剂同时施用。在某些实施方式中，CoQ10 在化疗剂之前但不与化疗剂同时施用，即，CoQ10 施用在开始化疗剂治疗或开始化疗剂施用之前中断。在一个实施方式中，可根据本发明方法在联合疗法中使用静脉内 (IV)CoQ10 制剂与至少一种其它化疗剂。在一个实施方式中，可根据本发明方法在联合疗法中使用局部 CoQ10 制剂与至少一种其它化疗剂。在一个实施方式中，可根据本发明方法在联合疗法中使用可吸入 CoQ10 制剂与至少一种其它化疗剂。CoQ10 和 / 或其药物制剂及其它化疗剂可加和地或更优选协同地起作用。在一个实施方式中，CoQ10 和 / 或其制剂与另一化疗剂的施用同时施用。在另一个实施方式中，CoQ10 和 / 或其药物制剂在另一化疗剂的施用之前或之后施用。在一个实施方式中，CoQ10 和另外的化疗剂协同地起作用。在一些实施方式中，协同结果是在肿瘤

病症的治疗中。在其它实施方式中，协同结果是在与化疗剂相关毒性的调节中。在一个实施方式中，CoQ10 和另外的化疗剂加和地起作用。在一个实施方式中，CoQ10 使肿瘤病症、癌症或癌细胞对另一化疗剂的治疗敏感。在一个实施方式中，在化疗剂治疗之前的 CoQ10 预治疗使肿瘤病症、癌症或癌细胞对另一化疗剂的治疗敏感。在一个实施方式中，CoQ10 预治疗以及在化疗剂治疗之前所述治疗的中断使肿瘤病症、癌症或癌细胞对另一化疗剂的治疗敏感。

[0243] 在一些实施方式中，CoQ10 是静脉内 CoQ10 制剂、吸入 CoQ10 制剂或局部 CoQ10 制剂的形式。静脉内 CoQ10 制剂在 2011 年 3 月 11 日提交的 WO2011/112900 中公开。WO2011/112900 的公开内容全文并入本文。局部 CoQ10 制剂在 2010 年 5 月 11 日提交的美国专利申请公开第 US2011/0027247 号中公开。US2011/0027247 的公开内容全文并入本文。吸入 CoQ10 制剂在 2012 年 6 月 8 日提交的美国专利公开第 20120321698 号和 2008 年 12 月 5 日提交的美国专利公开第 20110142914 号中公开。CoQ10 和化疗剂不必通过相同施用途径递送。在某些实施方式中，CoQ10 不经口施用。

[0244] 在一些实施方式中，提供了通过共施用静脉内 CoQ10 制剂与化疗剂来治疗肿瘤病症的方法。在某些实施方式中，化疗剂为吉西他滨、多柔比星、顺铂、5- 氟尿嘧啶和伊立替康。在一些实施方式中，化疗剂为抗代谢物或蒽环类药物。化疗剂通常属于各种不同类别，包括例如 :1. 拓扑异构酶 II 抑制剂（细胞毒性抗生素），如蒽环类 / 蒽二酮类，例如多柔比星、表柔比星、伊达比星和奈莫柔比星，蒽醌类，例如米托蒽醌和洛索蒽醌，及鬼臼毒素类，例如依托泊苷和替尼泊苷 ;2. 影响微管形成的药剂（有丝分裂抑制剂），如植物生物碱类（例如，属于源自植物的生物活性且细胞毒性的碱性含氮分子家族的化合物），例如紫杉烷类，如紫杉醇和多西紫杉醇，和长春花生物碱类，例如长春碱、长春新碱和长春瑞滨，以及鬼臼毒素的衍生物 ;3. 烷化剂，如氮芥、亚乙基亚胺化合物、烷基磺酸酯和其它具有烷化作用的化合物如亚硝基脲、达卡巴嗪、环磷酰胺、异环磷酰胺和美法仑 ;4. 抗代谢物（核苷抑制剂），例如叶酸类，如叶酸、氟嘧啶、嘌呤或嘧啶类似物如 5- 氟尿嘧啶、卡培他滨、吉西他滨、甲氨喋呤和依达曲沙 ;5. 拓扑异构酶 I 抑制剂，如托泊替康、伊立替康和 9- 硝基喜树碱及喜树碱衍生物 ;和 6. 铂化合物 / 络合物，如顺铂、奥沙利铂和卡铂。

[0245] 用于本发明方法的示例性化疗剂包括但不限于阿米福汀（氨磷汀）、顺铂、达卡巴嗪 (DTIC)、放线菌素、二氯甲基二乙胺（氮芥）、链脲佐菌素、环磷酰胺、卡莫司汀 (BCNU)、洛莫司汀 (CCNU)、多柔比星（阿霉素）、多柔比星脂质体（阿霉素脂质体）、吉西他滨（健择）、柔红霉素、柔红霉素脂质体 (daunoxome)、甲基苄肼、丝裂霉素、阿糖胞苷、依托泊苷、氨甲喋呤、5- 氟尿嘧啶 (5-FU)、长春碱、长春新碱、博来霉素、紫杉醇（泰素）、多西紫杉醇（泰索帝）、阿地白介素、天冬酰胺酶、白消安、卡铂、克拉屈滨、喜树碱、CPT-11、10- 羟基 -7- 乙基 - 喜树碱 (SN38)、达卡巴嗪、S-I 卡培他滨、替加氟、5'- 脱氧氟尿苷、UFT、恩尿嘧啶、脱氧胞苷、5- 氮杂胞嘧啶、5- 氮杂脱氧胞嘧啶、别嘌呤醇、2- 氯腺苷、三甲曲沙、氨喋呤、亚甲基 -10- 脱氮杂氨喋呤 (MDAM)、奥沙利铂、吡铂、四铂、沙铂、铂 -DACH、奥马铂、CI-973、JM-216 及其类似物、表柔比星、依托泊苷磷酸盐、9- 氨基喜树碱、10,11- 亚甲基二氧喜树碱、karenitecin、9- 硝基喜树碱、TAS 103、长春地辛、L- 苯丙氨酸氮芥、异环磷酰胺、培磷酰胺、氯乙环磷酰胺、卡莫司汀、司莫司汀、埃博霉素 A-E、拓优得、6- 巯基嘌呤、6- 硫鸟嘌呤、安吖啶、依托泊苷磷酸盐、karenitecin、阿昔洛韦、伐昔洛韦、更昔洛韦、金刚烷胺、金刚

乙胺、拉米夫定、齐多夫定、贝伐单抗、曲妥珠单抗、利妥昔单抗、5- 氟尿嘧啶、卡培他滨、喷司他汀、三甲曲沙、克拉屈滨、氟尿苷、氟达拉滨、羟基脲、异环磷酰胺、伊达比星、美司钠、伊立替康、米托蒽醌、拓扑替康、亮丙瑞林、甲地孕酮、美法仑、巯基嘌呤、普卡霉素、米托坦、培门冬酶、喷司他汀、哌泊溴烷、普卡霉素、链脲佐菌素、他莫昔芬、替尼泊苷、睾内酯、硫鸟嘌呤、塞替派、尿嘧啶氮芥、长春瑞滨、苯丁酸氮芥、顺铂、多柔比星、紫杉醇（泰素）、博莱霉素、mTor、表皮生长因子受体 (EGFR) 和成纤维细胞生长因子 (FGF) 及其基于特定肿瘤或癌症的适宜治疗标准对于本领域技术人员来说显而易见的组合。

[0246] 在某些实施方式中，用于本发明的联合疗法的另外的化疗剂为生物剂。生物剂（也称生物制剂）为生物系统如生物体、细胞或重组系统的产物。该类生物剂的实例包括核酸分子（例如，反义核酸分子）、干扰素、白细胞介素、集落刺激因子、抗体（例如，单克隆抗体）、抗血管生成剂和细胞因子。示例性的生物剂在下文更详细地讨论并通常属于各种不同类别，包括例如 :1. 激素、激素类似物和激素复合物，例如雌激素和雌激素类似物、孕酮、孕酮类似物和孕激素、雄激素、肾上腺皮质类固醇、抗雌激素、抗雄激素、抗睾酮、肾上腺类固醇抑制剂和抗促黄体生成激素 ;和 2. 酶、蛋白、肽、多克隆和 / 或单克隆抗体，如白细胞介素、干扰素、集落刺激因子等。

[0247] 在一个实施方式中，生物制剂是干扰素。干扰素 (IFN) 是身体中天然存在的一种类型的生物剂。干扰素也在实验室中产生并在生物疗法中给予癌症患者。它们已被证实改善了癌症患者的免疫系统对抗癌细胞的方式。

[0248] 干扰素可直接作用于癌细胞以减慢其生长，或者它们可使癌细胞变为具有更正常的行为的细胞。一些干扰素还可刺激自然杀伤细胞 (NK)、T 细胞和巨噬细胞，其是血流中帮助对抗癌细胞的白血细胞类型。

[0249] 在一个实施方式中，生物制剂是白细胞介素。白细胞介素 (IL) 刺激许多免疫细胞的生长和活性。它们是身体内天然存在的蛋白（细胞因子和趋化因子），但也可在实验室中制备。一些白细胞介素刺激起到破坏癌细胞作用的免疫细胞如淋巴细胞的生长和活性。

[0250] 在另一个实施方式中，生物制剂是集落刺激因子。集落刺激因子 (CSF) 是给予患者以激励骨髓内的干细胞产生更多血细胞的蛋白。身体持续地需要新的白细胞、红细胞和血小板，尤其是在存在癌症时。CSF 与化疗一起提供以帮助增强免疫系统。当癌症患者接受化疗时，骨髓产生新的血细胞的能力被抑制，使得患者更易于发生感染。免疫系统的一些部分在没有血细胞的情况下不能起作用，因此集落刺激因子激励骨髓干细胞产生白细胞、血小板和红细胞。在具有适当的细胞生成的情况下，可以继续其它癌症治疗，从而允许患者安全地接受更高剂量的化疗。

[0251] 在另一个实施方式中，生物制剂是抗体。抗体，如单克隆抗体，是结合于癌细胞的在实验室中产生的药剂。

[0252] 单克隆抗体药剂不会破坏健康细胞。单克隆抗体通过各种不同的机制实现其治疗效果。它们可在产生细胞凋亡或程序性细胞死亡中具有直接作用。它们可阻断生长因子受体，从而有效地抑止肿瘤细胞增殖。在表达单克隆抗体的细胞中，它们可导致抗独特型抗体形成。

[0253] 可用于本发明的联合治疗的抗体的实例包括抗 -CD20 抗体，例如但不限于西妥昔单抗、托西莫单抗、利妥昔单抗和替伊莫单抗。抗 -HER2 抗体也可与辅酶 Q10 联合使用来治

疗癌症。在一个实施方式中，抗 -HER2 抗体为曲妥珠单抗（赫赛汀）。可与辅酶 Q10 联合使用来治疗癌症的抗体的其它实例包括抗 -CD52 抗体（例如，阿仑单抗）、抗 -CD-22 抗体（例如，依帕珠单抗）和抗 -CD33 抗体（例如，吉妥单抗奥佐米星）。抗 -VEGF 抗体也可与辅酶 Q10 联合使用来治疗癌症。在一个实施方式中，抗 -VEGF 抗体为贝伐单抗。在其它实施方式中，生物剂为抗体，其为抗 -EGFR 抗体，例如西妥昔单抗。另一个实例为抗糖蛋白 17-1A 抗体依决洛单抗。许多其它的抗肿瘤抗体是本领域已知的并且本领域技术人员将理解其为本发明所涵盖。

[0254] 在另一个实施方式中，生物制剂为细胞因子。细胞因子疗法使用蛋白（细胞因子）来帮助受试者的免疫系统识别和破坏癌性的那些细胞。细胞因子在身体中由免疫系统天然产生，但也可在实验室中产生。该疗法用于晚期黑素瘤并与辅助疗法（在主要癌症治疗之后或之外给予的疗法）一起使用。细胞因子疗法到达身体的所有部分来杀灭癌细胞并防止肿瘤生长。

[0255] 在另一个实施方式中，生物制剂为融合蛋白。例如，可在联合疗法中使用重组人 Apo2L/TRAIL(GENETECH)。Apo2L/TRAIL 为设计以激活促凋亡受体 DR4 和 DR5 二者的第一种双重促凋亡受体激动剂，促凋亡受体 DR4 和 DR5 参与细胞凋亡（程序性细胞死亡）的调控。

[0256] 在一个实施方式中，生物制剂为治疗性核酸分子。核酸治疗剂是本领域熟知的。核酸治疗剂包括与细胞中的靶序列互补的单链和双链（即，具有长度为至少 15 个核苷酸的互补区的核酸治疗剂）核酸二者。治疗性核酸可针对基本上细胞中的任意靶核酸序列。在某些实施方式中，核酸治疗剂靶向于编码血管生成刺激剂如 VEGF、FGF 或肿瘤生长刺激剂如 EGFR 的核酸序列。

[0257] 反义核酸治疗剂为单链核酸治疗剂，通常长度为约 16 至 30 个核苷酸，并且与靶细胞中的靶核酸序列互补，无论是在培养物中还是在生物体中。

[0258] 在另一个方面，药剂为单链反义 RNA 分子。反义 RNA 分子与靶 mRNA 内的序列互补。反义 RNA 可通过与 mRNA 碱基配对并物理地阻碍翻译机制来以化学计量方式抑制翻译，参见 Dias,N. 等，(2002)Mol Cancer Ther 1:347-355。反义 RNA 分子可具有约 15-30 个与靶 mRNA 互补的核苷酸。涉及反义核酸、化学修饰和治疗用途的专利在例如涉及含化学修饰 RNA 的治疗化合物的美国专利第 5,898,031 号，涉及使用这些化合物作为治疗剂的方法的美国专利第 6,107,094 号，涉及通过施用单链化学修饰 RNA 样化合物治疗患者的方法的美国专利第 7,432,250 号，和涉及含单链化学修饰 RNA 样化合物的药物组合物的美国专利号 7,432,249 中提供。美国专利第 7,629,321 号涉及使用具有多个 RNA 核苷酸和至少一个化学修饰的单链寡核苷酸裂解靶 mRNA 的方法。本段中列出的专利中的每一个的整个内容以引用方式并入本文。

[0259] 用于本发明的方法中的核酸治疗剂还包括双链核酸治疗剂。在本文中可互换地使用的“RNAi 剂”、“双链 RNAi 剂”、双链 RNA(dsRNA) 分子（也称“dsRNA 剂”、“dsRNA”、“siRNA”、“iRNA 剂”）是指核糖核酸分子的复合物，其具有包含两个反向平行的且基本上互补（如下文所定义）的核酸链的双链体结构。如本文所用，RNAi 剂还可包括 dsiRNA（参见例如美国专利公开第 20070104688 号，其以引用方式并入本文中）。通常，每条链的大多数核苷酸为核糖核苷酸，但如本文中所述，各条链或全部两条链还可包含一个或多个非核糖核苷酸，例如脱氧核糖核苷酸和 / 或修饰的核苷酸。另外，如本说明书中所用，“RNAi 剂”可包括具有

化学修饰的核糖核苷酸；RNAi 剂可在多个核苷酸处包含实质性修饰。该类修饰可包括本文中公开的或本领域中已知的所有修饰类型。就本说明书和权利要求书的目的而言，如 siRNA 型分子中所用的任何该类修饰都涵盖在“RNAi 剂”内。在本发明的方法中使用的 RNAi 剂包括具有例如 2011 年 11 月 18 日提交的美国临时申请第 61/561,710 号、2010 年 9 月 15 日提交的国际申请第 PCT/US2011/051597 号和 PCT 公布 WO 2009/073809 中公开的化学修饰的药剂，它们中的每一者的整个内容以引用方式并入本文中。

[0260] 用于本发明的方法中的其它示例性生物剂包括但不限于吉非替尼（易瑞沙）、阿那曲唑、二乙基己烯雌酚、雌二醇、普力马林、雷洛昔芬、孕酮、异炔诺酮 (norethynodrel)、炔孕酮 (esthisterone)、地美炔酮 (dimesthisterone)、醋酸甲地孕酮、醋酸甲羟孕酮、己酸羟孕酮、炔诺酮、甲睾酮、睾酮、地塞米松、强的松、氢化可的松、甲强龙 (solumedrol)、他莫昔芬、氟维司群、托瑞米芬、氨鲁米特、睾内酯、屈洛昔芬、阿那曲唑、比卡鲁胺、氟他胺、尼鲁米特、戈舍瑞林、氟他胺、亮丙瑞林、曲普瑞林、氨鲁米特、米托坦、戈舍瑞林、西妥昔单抗、厄洛替尼、伊马替尼、托西莫单抗、阿仑单抗、曲妥珠单抗、吉妥单抗、利妥昔单抗、替伊莫单抗 (Ibritumomab tiuxetan)、贝伐单抗、地尼白介素 (Denileukin diftitox)、达利珠单抗、干扰素 α、干扰素 β、抗 -4-1BB、抗 -4-1BBL、抗 -CD40、抗 -CD154、抗 -OX40、抗 -OX40L、抗 -CD28、抗 -CD80、抗 -CD86、抗 -CD70、抗 -CD27、抗 -HVEM、抗 -LIGHT、抗 -GITR、抗 -GITRL、抗 -CTLA-4、可溶性 OX40L、可溶性 4-IBBL、可溶性 CD154、可溶性 GITRL、可溶性 LIGHT、可溶性 CD70、可溶性 CD80、可溶性 CD86、可溶性 CTLA4-Ig、GVAX®及其基于特定肿瘤或癌症的适宜治疗标准对于本领域技术人员来说显而易见的组合。药剂的可溶性形式可通过操作性地连接药剂与例如 Ig-Fc 区而制备为例如融合蛋白。

[0261] 应注意，可与本文提供的辅酶 Q10 和辅酶 Q10 制剂联合地施用不止一种另外的抗癌化疗剂，例如 2、3、4、5 或更多种。例如，在一个实施方式中，可与辅酶 Q10 联合地施用两种另外的化疗剂。在一个实施方式中，可与辅酶 Q10 联合地施用三种另外的化疗剂。在一个实施方式中，可与辅酶 Q10 联合地施用四种另外的化疗剂。在一个实施方式中，可与辅酶 Q10 联合地施用五种另外的化疗剂。本文中提供的化疗剂的适宜剂量和施用途径是本领域已知的。

[0262] 在某些实施方式中，本发明的方法包括通过连续输注所提供的辅酶 Q10 和与另外的抗癌剂或干预（例如，放射、外科手术、骨髓移植）的联合疗法来治疗癌症。在某些实施方式中，“联合疗法”包括用辅酶 Q10 治疗来减小肿瘤负荷和 / 或改善临床反应。与姑息治疗或减轻药物副作用（例如，减轻恶心、疼痛、焦虑或炎症，使凝血正常化）的治疗一并施用辅酶 Q10 不视为是癌症的联合治疗。

[0263] 在某些实施方式中，通过连续输注用辅酶 Q10 治疗与待治疗的特定癌症的标准治疗联合，例如施用标准剂量的一种或多种化疗剂。特定癌症类型的标准治疗可由本领域技术人员基于例如癌症的类型和严重度、受试者的年龄、体重、性别和 / 或病史，以及既往治疗的成功或失败来决定。

[0264] 在某些实施方式中，对患有白血病，特别是 ALL 或 AML 的受试者的治疗，辅酶 Q10 的施用（例如，静脉内，例如连续输注）与以下治疗中的一者或优选二者联合。

[0265] 1、氟达拉滨，优选地以 15mg/m^2 的剂量静脉内施用 15-30 分钟 ±15 分钟，每 12 小时施用一次，施用 5 天（或在 65 岁以上或 ECOG 行为状态 3 的患者中持续 4 天）。

[0266] 2、阿糖胞苷，优选地以0.5g/m^{2}在250ml生理盐水中静脉内施用2小时±20分钟，每12小时±2小时施用一次，施用5天（或在65岁以上或ECOG行为状态3的患者中持续4天）。

[0267] 在某些实施方式中，向受试者施用1、2、3、4或5个周期的联合治疗。在每一个周期结束时评估受试者的反应标准。还在每一周期的整个过程中监测受试者的不良事件（例如，凝血、贫血、肝和肾功能等）以确保治疗方案充分耐受。

[0268] 在某些实施方式中，通过连续输注辅酶Q10对患有实体瘤的受试者的治疗与以下治疗中的一种或多种联合。

[0269] 1、吉西他滨，优选地通过静脉内施用，每周剂量以600mg/m^{2}开始，并基于受试者对药物的耐受性调节剂量。

[0270] 2、5-氟尿嘧啶(5-FU)，优选地通过静脉内施用，每周剂量以350mg/m^{2}起始，并基于受试者对药物的耐受性调节剂量，其与100mg/m^{2}的亚叶酸联合施用。

[0271] 3、多西紫杉醇，优选通过静脉内施用，每周一次，起始剂量为20mg/m^2，并基于受试者对药物的耐受性调节剂量。

[0272] 在某些实施方式中，向受试者施用1、2、3、4或5个周期的联合治疗。在每一个周期结束时评估受试者的反应标准。还在每一周期的整个过程中监测受试者的不良事件（例如，凝血、贫血、肝和肾功能等）以确保治疗方案充分耐受。

[0273] 在其它实施方式中，以比在特定肿瘤疾病的标准治疗下用来治疗肿瘤疾病的化疗剂的标准剂量低的剂量施用化疗剂。化疗剂的标准剂量是本领域技术人员已知的，并可例如从化疗剂生产商提供的产品说明书获得。化疗剂的标准剂量的实例在表3中提供。在某些实施方式中，化疗剂的施用剂量比该化疗剂针对特定肿瘤疾病的标准剂量低5％、10％、20％、30％、40％、50％、60％、70％、80％或90％。在某些实施方式中，化疗剂的施用剂量为该化疗剂针对特定肿瘤疾病的标准剂量的95％、90％、85％、80％、75％、70％、65％、60％、55％、50％、45％、40％、35％、30％、25％、20％、15％、10％或5％。在其中施用非CoQ10化疗剂的组合的一个实施方式中，化疗剂中的至少之一以比该化疗剂针对特定肿瘤疾病的标准剂量低的剂量施用。在其中施用化疗剂（例如，非CoQ10）的组合的一个实施方式中，化疗剂中的至少两者以比该化疗剂针对特定肿瘤疾病的标准剂量低的剂量施用。在其中施用化疗剂（例如，非CoQ10）的组合的一个实施方式中，化疗剂中的至少三者以比该化疗剂针对特定肿瘤疾病的标准剂量低的剂量施用。在其中施用化疗剂（例如，非CoQ10）的组合的一个实施方式中，所有的化疗剂均以比该化疗剂针对特定肿瘤疾病的标准剂量低的剂量施用。

[0274] 在某些实施方式中，辅酶Q10以在单独递送时治疗有效的量施用，即辅酶Q10作为治疗性抗癌剂施用和/或发挥作用，而不是主要作为减轻其它化疗或其它癌症治疗的副作用的药剂。

[0275] V.肿瘤疾病的治疗

[0276] 可采用本发明的联合疗法来治疗肿瘤疾病。相应地，本发明提供了治疗或预防受试者的肿瘤疾病的方法，其包括以足以治疗或预防肿瘤疾病的量向受试者施用本发明的制剂，从而治疗或预防肿瘤疾病。也可采用本发明的制剂来抑制肿瘤细胞生长。相应地，本发明还提供了抑制受试者中肿瘤细胞生长的方法，其包括向受试者静脉内施用本发明的制

剂，以便肿瘤细胞生长被抑制。在某些实施方式中，治疗癌症包括与对照如群体对照相比，延长存活或延长到达肿瘤进展的时间。在某些实施方式中，受试者是人类受试者。在优选实施方式中，受试者在施用第一剂 CoQ10 之前被确定为患有肿瘤。在某些实施方式中，受试者在第一次施用 CoQ10 之时患有肿瘤。

[0277] 这样的联合疗法包括例如与本文中描述或引入的化疗剂共施用的 CoQ10 制剂。在某些实施方式中，治疗受试者的肿瘤疾病的方法包括：(a) 向受试者施用辅酶 Q10(CoQ10)；(b) 中断 CoQ10 的治疗；和 (c) 在已中断施用 CoQ10 后，向受试者施用至少一种化疗剂，其中肿瘤疾病被治疗。

[0278] 在其它实施方式中，治疗受试者的肿瘤疾病的方法包括：(a) 向受试者施用辅酶 Q10(CoQ10)；(b) 在开始施用 CoQ10 后，向受试者施用至少一种化疗剂；和 (c) 在开始施用所述至少一种化疗剂后，继续 CoQ10 的治疗，其中肿瘤疾病被治疗。

[0279] 在其它实施方式中，治疗受试者的肿瘤疾病的方法包括：在开始化疗治疗方案之前使用辅酶 Q10(CoQ10) 对患肿瘤疾病的受试者预治疗足够的时间，其中所述化疗治疗方案包括施用一种或多种化疗剂，使得与单独使用化疗治疗方案的治疗相比，肿瘤疾病的反应被改善。

[0280] 还在其它的实施方式中，治疗受试者的肿瘤疾病的方法包括：(a) 向受试者施用辅酶 Q10(CoQ10)；和 (b) 以比用来治疗肿瘤疾病的化疗剂的标准剂量低的剂量向受试者施用至少一种化疗剂，使得肿瘤疾病被治疗。

[0281] 在前述各个实施方式中，可在 CoQ10 施用开始后至少 24 小时、在 CoQ10 施用开始后一周或多周、在 CoQ10 施用开始后两周或更多周、在 CoQ10 施用开始后三周或更多周、在 CoQ10 施用开始后四周或更多周、在 CoQ10 施用开始后五周或更多周、在 CoQ10 施用开始后六周或更多周、在 CoQ10 施用开始后七周或更多周或在 CoQ10 施用开始后八周或更多周开始施用所述至少一种化疗剂。

[0282] 在一个优选的实施方式中，在 CoQ10 施用开始后至少 24 小时开始施用所述至少一种化疗剂。在另一个优选的实施方式中，在 CoQ10 施用开始后 24 小时至 4 周开始施用所述至少一种化疗剂。在进一步优选的实施方式中，在 CoQ10 施用开始后 2 至 4 周开始施用所述至少一种化疗剂。在又进一步优选的实施方式中，在 CoQ10 施用开始后 2 周开始施用所述至少一种化疗剂。在又进一步优选的实施方式中，在 CoQ10 施用开始后 1 周开始施用所述至少一种化疗剂。在又进一步优选的实施方式中，在 CoQ10 施用开始后 3 周开始施用所述至少一种化疗剂。在又进一步优选的实施方式中，在 CoQ10 施用开始后 4 周开始施用所述至少一种化疗剂。在又进一步优选的实施方式中，在 CoQ10 施用开始后 5 周开始施用所述至少一种化疗剂。在又进一步优选的实施方式中，在 CoQ10 施用开始后 6 周开始施用所述至少一种化疗剂。在又进一步优选的实施方式中，在 CoQ10 施用开始后 7 周，开始施用所述至少一种化疗剂。在又进一步优选的实施方式中，在 CoQ10 施用开始后 8 周开始施用所述至少一种化疗剂。

[0283] CoQ10 制剂可以是吸入制剂、静脉内制剂或局部制剂。在某些实施方式中，CoQ10 制剂不是口服制剂。例如，静脉内制剂可在药学上可接受的载体中包含 CoQ10 或其代谢物。在一些实施方式中，这样的制剂可包含约 0.001％至约 20％（重量 / 重量）的 CoQ10，更优选地约 0.01％和约 15％之间、甚至更优选地约 0.1％至约 10％（重量 / 重量）之间的 CoQ10，

更优选地约3%至约5%（重量/重量）的CoQ10。在一个实施方式中，制剂包含约4%（重量/重量）的CoQ10。在一个实施方式中，制剂包含约8%（重量/重量）的CoQ10。在各种实施方式中，制剂包含约0.5%、1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、11%、12%、13%、14%、15%、16%、17%、18%、19%或20%（重量/重量）的CoQ10。如本文中还指出的，本公开的组合物可以是液体形式，能够通过本领域技术人员能力范围内的任意施用方式或途径引入到受试者中。例如，组合物可通过包括但不限于静脉内、瘤内、腹膜内、它们的组合等等的施用途径施用。

[0284] 在一些实施方式中，化疗方案与CoQ10制剂共施用以治疗肿瘤疾病。可以在化疗方案施用之前、与化疗方案施用同时或基本同时、在化疗方案施用之前并与化疗方案施用同时、与化疗方案施用间隔或在化疗方案施用之后施用CoQ10制剂。在某些实施方式中，在化疗剂施用之前施用负荷剂量的CoQ10。在某些实施方式中，在化疗剂施用之前施用CoQ10以达到CoQ10的稳态水平。当联合疗法包括静脉内CoQ10制剂时，对受试者静脉内施用CoQ10以使得肿瘤疾病被治疗或预防。在一个实施方式中，对受试者静脉内施用CoQ10以使得对化疗剂的反应被改善，例如相对于单独使用化疗剂的治疗。

[0285] 对受试者施用在约0.5mg/kg至约10,000mg/kg、约5mg/kg至约5,000mg/kg、约10mg/kg至约3,000mg/kg范围内的一剂CoQ10。在一个实施方式中，施用在约10mg/kg至约1,400mg/kg范围内的辅酶Q10。在一个实施方式中，施用在约10mg/kg至约650mg/kg范围内的辅酶Q10。在一个实施方式中，施用在约10mg/kg至约200mg/kg范围内的辅酶Q10。在各种实施方式中，以约2mg/kg、5mg/kg、10mg/kg、15mg/kg、20mg/kg、25mg/kg、30mg/kg、35mg/kg、40mg/kg、45mg/kg、50mg/kg、55mg/kg、58mg/kg、58.6mg/kg、60mg/kg、65mg/kg、70mg/kg、75mg/kg、78mg/kg、80mg/kg、85mg/kg、90mg/kg、95mg/kg、100mg/kg、104mg/kg、110mg/kg、120mg/kg、130mg/kg、140mg/kg、150mg/kg、160mg/kg、170mg/kg、180mg/kg、190mg/kg或200mg/kg的剂量施用辅酶Q10。还应理解，具有这些值中的任意之一作为上限或下限的范围也旨在作为本发明的部分，例如，约50mg/kg至约200mg/kg或约650mg/kg至约1400mg/kg。在一个实施方式中，施用的剂量为至少约1mg/kg、至少约5mg/kg、至少约10mg/kg、至少约12.5mg/kg、至少约20mg/kg、至少约25mg/kg、至少约30mg/kg、至少约35mg/kg、至少约40mg/kg、至少约45mg/kg、至少约50mg/kg、至少约55mg/kg、至少约58mg/kg、至少约58.6mg/kg、至少约60mg/kg、至少约75mg/kg、至少约78mg/kg、至少约100mg/kg、至少约104mg/kg、至少约125mg/kg、至少约150mg/kg、至少约175mg/kg、至少约200mg/kg、至少约300mg/kg或至少约400mg/kg。

[0286] 在某些实施方式中，以每天至少一剂施用CoQ10。在某些实施方式中，以每天至少两剂施用CoQ10。在某些实施方式中，以每天至少三剂施用CoQ10。在某些实施方式中，以每天一剂施用CoQ10。在某些实施方式中，以每天两剂施用CoQ10。在某些实施方式中，以每天三剂施用CoQ10。在某些实施方式中，CoQ10通过连续输注施用。

[0287] 例如，在一些实施方式中，前述方法包括静脉内施用CoQ10的方案，例如至少约50mg/kg的CoQ10，每天一次，施用3周，任选地休止一周，并随后施用化疗剂。在其它实施方式中，所述方法包括静脉内施用CoQ10的方案，例如至少约75mg/kg的CoQ10，每天一次，施用3周，任选地休止一周，并随后施用化疗剂。

[0288] CoQ10吸入制剂的剂量范围可与供注射施用的那些相似。应理解，用于通过吸入递

送的喷雾器或其它装置是本领域已知的并可与本发明的方法结合使用。

[0289] 局部 CoQ10 的剂量通常取决于待治疗的区域的大小。例如，局部施用的 CoQ10 可用于皮肤癌的治疗。CoQ10 以足以覆盖病变的量通常每天一次或两次局部施加到癌性病变部位，例如，像向丘疹施加痤疮药物一样。如果受试者有许多治疗的病变，则将 CoQ10 施加到多个部位，从而增大施用于受试者的总剂量。如果受试者具有单一病变，则将 CoQ10 施加到该单一部位。

[0290] 在一个实施方式中，联合疗法的化疗剂为吉西他滨。当联合疗法包括施用 CoQ10 制剂和吉西他滨时，对受试者施用 CoQ10 制剂和吉西他滨（例如，二者均静脉内施用）使得肿瘤疾病被治疗或预防。对受试者施用在约 10mg/m^2至约 10,000mg/m^2、约 10mg/m^2至约 5,000mg/m^2、约 10mg/m^2至约 3,000mg/m^2范围内的一剂吉西他滨。在一个实施方式中，施用在约 10mg/m^2至约 1,500mg/m^2范围内的吉西他滨。在一个实施方式中，施用在约 10mg/m^2至约 1000mg/m^2范围内的吉西他滨。在一个实施方式中，施用在约 10mg/m^2至约 750mg/m^2范围内的吉西他滨。在一个实施方式中，施用在约 10mg/m^2至约 500mg/m^2范围内的吉西他滨。在一个实施方式中，施用在约 10mg/m^2至约 400mg/m^2范围内的吉西他滨。在一个实施方式中，施用在约 10mg/m^2至约 300mg/m^2范围内的吉西他滨。在一个实施方式中，施用在约 10mg/m^2至约 200mg/m^2范围内的吉西他滨。在一个实施方式中，施用在约 10mg/m^2至约 100mg/m^2范围内的吉西他滨。在一个实施方式中，施用在约 10mg/m^2至约 70mg/m^2范围内的吉西他滨。在各种实施方式中，以约 10mg/m^2、20mg/m^2、30mg/m^2、40mg/m^2、50mg/m^2、60mg/m^2、65mg/m^2、70mg/m^2、80mg/m^2、90mg/m^2、100mg/m^2、100mg/m^2、200mg/m^2、300mg/m^2、400mg/m^2、500mg/m^2、600mg/m^2、700mg/m^2、800mg/m^2、900mg/m^2、1000mg/m^2、1500mg/m^2、2000mg/m^2、3000mg/m^2的 剂量施用吉西他滨。应理解，具有这些值中的任意之一作为上限或下限的范围也旨在作为本发明的部分。在一个实施方式中，吉西他滨的施用剂量为至少约 10mg/m^2、至少约 30mg/m^2、至少约 50mg/m^2、至少约 65mg/m^2、至少约 100mg/m^2、至少约 150mg/m^2、至少约 200mg/m^2、至少约 300mg/m^2、至少约 400mg/m^2、至少约 500mg/m^2、至少约 600mg/m^2、至少约 700mg/m^2、至少约 750mg/m^2、至少约 800mg/m^2、至少约 900mg/m^2、至少约 1000mg/m^2或至少约 1500mg/m^2。在一些实施方式中，方案包括共施用静脉内 CoQ10 制剂和化疗剂如吉西他滨。

[0291] 在第一示例性方案（每天一次方案）中，每天一次施用剂量为至少约 50mg/kg/ 剂或至少约 75mg/kg/ 剂的静脉内 CoQ10 制剂，连续 3 周，然后休止一周，同时每周一次施用 150mg/kg/ 剂的吉西他滨，连续 3 周，然后休止一周。图 1 示出了根据第一方案共施用静脉内 CoQ10 制剂和静脉内吉西他滨的联合疗法方案的结果。

[0292] 在第二示例性方案（每天两次方案）中，每天两次施用剂量为至少约 50mg/kg/ 剂或至少约 75mg/kg 的静脉内 CoQ10 制剂，连续 3 周，然后休止一周，同时每周一次施用 150mg/kg/ 剂的吉西他滨，施用 3 周，休止一周。图 4 示出了根据第二方案共施用静脉内 CoQ10 制剂和静脉内吉西他滨的联合疗法方案的结果。

[0293] 在第三示例性方案（每天三次方案）中，每天施用三次剂量为至少约 50mg/kg/ 剂或至少约 75mg/kg/ 剂的静脉内 CoQ10 制剂，连续 3 周，然后休止一周，同时每周一次施用 150mg/kg/ 剂的吉西他滨，施用 3 周，休止一周。图 8 示出了根据第三方案共施用静脉内 CoQ10 制剂和静脉内吉西他滨的联合疗法方案的结果。

[0294] 在第四示例性方案（预治疗方案）中，每天三次施用剂量为至少约 75mg/kg/ 剂的

静脉内 CoQ10 制剂，施用至少 24 小时、1 天、2 天、3 天、4 天、5 天、6 天、1 周、2 周、3 周或更多。在某些实施方式中，在施用第一剂化疗剂之前使用预治疗方案。在某些实施方式中，在施用每一剂化疗之前使用预治疗方案。在某些实施方式中，在施用每个周期的化疗之前使用预治疗方案。

[0295] 在修改的方案 1 至 4 中，CoQ10 每天以指定的剂量通过连续输注施用而不是每天以 1、2 或 3 个分开的剂量施用。

[0296] 例如，在某些实施方式中，前述方法包括静脉施用至少约 50mg/kg 的静脉内 CoQ10 制剂的方案，每天一次，施用 3 周，休止一周，并施用约 100mg/kg 的吉西他滨和约 10mg/kg 的吉西他滨之间的吉西他滨，每周一次，施用 3 周，休止一周。

[0297] 在其它实施方式中，所述方法包括静脉内施用至少约 50mg/kg 的静脉内 CoQ10 制剂的方案，每天两次，施用 3 周，休止一周，并施用约 100mg/kg 的吉西他滨和约 10mg/kg 的吉西他滨之间的吉西他滨，每周一次，施用 3 周，休止一周。在其它实施方式中，所述方法包括静脉内施用至少约 50mg/kg 的静脉内 CoQ10 制剂的方案，每天三次，施用 3 周，休止一周，并施用约 100mg/kg 的吉西他滨和约 10mg/kg 的吉西他滨之间的吉西他滨，每周一次，施用 3 周，休止一周。在进一步实施方式中，所述方法包括静脉内施用至少约 75mg/kg 的静脉内 CoQ10 制剂的方案，每天一次，施用 3 周，休止一周，并施用约 100mg/kg 的吉西他滨和约 10mg/kg 的吉西他滨之间的吉西他滨，每周一次，施用 3 周，休止一周。在进一步实施方式中，所述方法包括静脉内施用至少约 75mg/kg 的静脉内 CoQ10 制剂的方案，每天两次，施用 3 周，休止一周，并施用约 100mg/kg 的吉西他滨和约 10mg/kg 的吉西他滨之间的吉西他滨，每周一次，施用 3 周，休止一周。还在其它的实施方式中，所述方法包括静脉内施用至少约 75mg/kg 的静脉内 CoQ10 制剂的方案，每天三次，施用 3 周，休止一周，并施用约 100mg/kg 的吉西他滨和约 10mg/kg 的吉西他滨之间的吉西他滨，每周一次，施用 3 周，休止一周。

[0298] 在某些实施方式中，前述方法包括每三周向受试者施用 5mg/kg 的多西紫杉醇、1mg/kg 的多柔比星和 35mg/kg 的环磷酰胺，施用六个周期。

[0299] 在一些实施方式中，联合疗法方案包括向有需要的受试者共施用静脉内 CoQ10 制剂和化疗剂如吉西他滨。在一个实施方式中，联合疗法的吉西他滨通过静脉输注以约 1000mg/m^2的剂量施用，每周一次，至多 7 周（或直至毒性使得有必要减小或暂停剂量），然后治疗休止一周，作为第一治疗周期。在某些实施方式中，在不存在剂量限制性毒性的情况下，以期望剂量和频率每天施用 CoQ10。在一个实施方式中，第一施用周期后接着由每 4 周中连续 3 周的每周一次输注组成的后续周期。在一个实施方式中，基于患者经受的血液学毒性的程度调节吉西他滨的剂量。在一个实施方式中，当患者的绝对粒细胞计数大于或等于 1000×10^6/L 并且患者的血小板计数大于或等于 $100,000\times10^6$/L 时，可每周一次向患者施用 1000mg/m^2的全剂量。在一个实施方式中，当患者的绝对粒细胞计数介于约 500-999×10^6/L 之间或患者的血小板计数介于约 50,000-$99,000\times10^6$/L 之间时，可每周一次向患者施用全剂量的 75%，例如 750mg/m^2。在一个实施方式中，当患者的绝对粒细胞计数小于 500×10^6/L 或患者的血小板计数小于 $50,000\times10^6$/L 时，应暂停施用吉西他滨直至患者的绝对粒细胞计数大于或等于 500×10^6/L 或患者的血小板计数大于或等于 $50,000\times10^6$/L。

[0300] 批准用于各种癌症类型中的化疗剂的适宜给药方案的指导是本领域已知的。本文

提供的 CoQ10 治疗方案可基于本文提供的示例性教导而与其它已知治疗方案结合。

[0301] 在一些实施方式中，方案包括共施用静脉内 CoQ10 制剂和化疗剂如吉西他滨。在第一方案（一天一次方案）中，每天一次施用剂量为至少约 58mg/kg、至少约 58.6mg/kg、至少约 78mg/kg 或至少约 104mg/kg 的静脉内 CoQ10 制剂，至多 7 周（或直至毒性使得有必要减少或暂停剂量），任选地接着由每 4 周中连续 3 周的每天一次输注组成的后续周期；同时每周一次施用至少约 1000mg/m^2或至少约 750mg/m^2的吉西他滨，至多 7 周（或直至毒性使得有必要减少或暂停剂量），任选地接着由每 4 周中连续 3 周的每天一次输注组成的后续周期。在第二方案（每天两次方案）中，每天两次施用剂量为至少约 58mg/kg、至少约 58.6mg/kg、至少约 78mg/kg 或至少约 104mg/kg 的静脉内 CoQ10 制剂，至多 7 周（或直至毒性使得有必要减少或暂停剂量），任选地接着由每 4 周中连续 3 周的每天一次输注组成的后续周期；同时每周一次施用至少约 1000mg/m^2或至少约 750mg/m^2的吉西他滨，至多 7 周（或直至毒性使得有必要减少或暂停剂量），任选地接着由每 4 周中连续 3 周的每天一次输注组成的后续周期。在第三方案（每天三次方案）中，每天三次施用剂量为至少约 58mg/kg、至少约 58.6mg/kg、至少约 78mg/kg 或至少约 104mg/kg 的静脉内 CoQ10 制剂，至多 7 周（或直至毒性使得有必要减少或暂停剂量），任选地接着由每 4 周中连续 3 周的每天一次输注组成的后续周期；同时每周一次施用至少约 1000mg/m^2或至少约 750mg/m^2的吉西他滨，至多 7 周（或直至毒性使得有必要减少或暂停剂量），任选地接着由每 4 周中连续 3 周的每天一次输注组成的后续周期。在某些实施方式中，CoQ10 通过连续输注施用，总日剂量基于上面方案 1-3 中提供的那些。在某些实施方式中，在不存在剂量限制性毒性的情况下，以期望剂量和频率每天施用 CoQ10。

[0302] 在一个实施方式中，基于患者经受的血液学毒性程度调节吉西他滨的剂量。在一个实施方式中，当患者的绝对粒细胞计数大于或等于 1000×10^6/L 并且患者的血小板计数大于或等于 $100,000\times10^6$/L 时，可每周一次向患者施用 1000mg/m^2的全剂量。在一个实施方式中，当患者的绝对粒细胞计数介于约 $500\text{-}999\times10^6$/L 之间或患者的血小板计数介于约 $50,000\text{-}99,000\times10^6$/L 之间时，可每周一次向患者施用全剂量的 75％，例如 750mg/m^2。在一个实施方式中，当患者的绝对粒细胞计数小于 500×10^6/L 或患者的血小板计数小于 $50,000\times10^6$/L 时，应暂停施用吉西他滨直至患者的绝对粒细胞计数大于或等于 500×10^6/L 或患者的血小板计数大于或等于 $50,000\times10^6$/L。

[0303] 在本文提供的联合治疗方法的一个实施方式中，每周一次施用 CoQ10 制剂。在一个实施方式中，每周 2 次施用 CoQ10 制剂。在一个实施方式中，每周 3 次施用 CoQ10 制剂。在另一个实施方式中，每周 5 次施用 CoQ10 制剂。在一个实施方式中，每天一次施用 CoQ10 制剂。在一个实施方式中，每天两次施用 CoQ10 制剂。在一个实施方式中，每天三次施用 CoQ10 制剂。在其中通过输注施用 IV 制剂的一些实施方式中，剂量通过约 1 小时、2 小时、3 小时、4 小时或更长输注施用。在一个实施方式中，IV CoQ10 制剂通过约 4 小时输注施用。在某些实施方式中，IV CoQ10 制剂通过约 6、8、10、12、14、16、18、20、22 或 24 小时输注施用。

[0304] 在另一个实施方式中，CoQ10 以约 10mg/kg 和约 10,000mg/kg 之间、约 20mg/kg 至约 5000mg/kg、约 50mg/kg 至约 3000mg/kg、约 100mg/kg 至约 2000mg/kg、约 200mg/kg 至约 1000mg/kg 或约 300mg/kg 至约 500mg/kg 的剂量以静脉内 CoQ10 制剂的形式施用，其中所述 CoQ10 制剂包含约 1％和 10％之间的辅酶 Q10。在一个实施方式中，CoQ10 制剂包含约 3％

至约 5％的辅酶 Q10。在一个实施方式中，CoQ10 制剂包含约 4％的辅酶 Q10。在一个实施方式中，CoQ10 制剂包含约 8％的辅酶 Q10。在其它实施方式中，CoQ10IV 制剂包含约 1％、1.5％、2％、2.5％、3％、3.5％、4％、4.5％、5％、5.5％、6％、6.5％、7％、7.5％、8％、8.5％、9％、9.5％或 10％的辅酶 Q10。应理解，具有这些值中的任意之一作为上限或下限的范围也旨在作为本发明的部分。

[0305] 在某些实施方式中，在施用第一剂化疗剂或化疗方案之前至少 8 小时、至少 12 小时、至少 18 小时、至少 24 小时、至少 36 小时、至少 48 小时、至少 3 天、至少 4 天、至少 5 天、至少 6 天、至少 1 周、至少 2 周、至少 3 周、至少 4 周、至少 5 周、至少 6 周、至少 7 周或至少 8 周开始施用 CoQ10。在一个实施方式中，在开始使用化疗剂或化疗方案治疗之前中断施用 CoQ10，即，化疗剂的治疗排除了 CoQ10 的治疗。在一个实施方式中，在开始使用化疗剂或化疗方案治疗之后继续或恢复施用 CoQ10，使得 CoQ10 和化疗剂被同时施用例如至少一个周期。

[0306] 当用在联合疗法中以治疗癌症时，静脉内 CoQ10 制剂可在药学上可接受的载体中，其可作为单一疗法、与针对给定适应症的至少一种其它化疗剂联合、在手术干预以彻底移除肿瘤后与放疗联合、与其它针对癌症的替代性和 / 或补充性的可接受疗法联合等，以治疗有效量施用于肿瘤发生区域。在某些实施方式中，本公开还提供了通过向患者的肿瘤发生区域施用本公开的组合物来重新激活突变的 / 灭活的 p53 蛋白的方法。

[0307] 一般来说，可使用包括本文描述的 CoQ10 制剂和化疗剂中任一的联合疗法来预防性地或治疗性地治疗任何肿瘤。在一个特别的实施方式中，使用联合疗法来治疗实体肿瘤。在本发明的各种实施方式中，使用联合疗法来治疗或预防以下癌症：脑癌、中枢神经系统癌、头颈癌、前列腺癌、乳腺癌、睾丸癌、胰腺癌、肝癌、结肠癌、膀胱癌、尿道癌、胆囊癌、肾癌、肺癌、非小细胞肺癌、黑素瘤、间皮瘤、子宫癌、子宫颈癌、卵巢癌、肉瘤、骨癌、胃癌、皮肤癌和髓母细胞瘤。在优选实施方式中，使用联合疗法来治疗三阴性乳腺癌 (TNBC)。在一个实施方式中，可使用包括本文描述的 CoQ10 的联合疗法来治疗绿色白血病，例如原发性绿色白血病或者继发性或转移性绿色白血病，例如其存在于、迁移到或转移到特定器官如肺、肝脏或中枢神经系统。

[0308] 然而，使用本发明的联合疗法的治疗不限于前述癌症类型。适合于联合疗法治疗的癌症实例包括但不限于例如霍奇金病、非霍奇金淋巴瘤、多发性骨髓瘤、成神经细胞瘤、乳腺癌、卵巢癌、肺癌、横纹肌肉瘤、原发性血小板增多症、原发性巨球蛋白血症、小细胞肺肿瘤、原发性脑肿瘤、胃癌、结肠癌、恶性胰腺胰岛瘤、恶性类癌瘤、膀胱癌、恶化前皮肤病变、皮肤癌、睾丸癌、淋巴瘤、甲状腺癌、成神经细胞瘤、食道癌、泌尿生殖道癌、恶性高钙血症、宫颈癌、子宫内膜癌、肾上腺皮质癌和前列腺癌。在一个实施方式中，可与化疗剂联合使用本文描述的 CoQ10IV 制剂来治疗或预防各种类型的皮肤癌（例如，鳞状细胞癌或基底细胞癌）、胰腺癌、乳腺癌、前列腺癌、肝癌或骨癌。在一个实施方式中，使用包括 CoQ10 的联合疗法来治疗皮肤肿瘤疾病，包括但不限于鳞状细胞癌（包括 SCCIS（原位）和更侵袭性的鳞状细胞癌）、基底细胞癌（包括浅表、结节性和浸润性基底细胞癌）、黑素瘤和光化性角化病。在一个实施方式中，可用包括 CoQ10 的联合疗法治疗的肿瘤疾病或癌症不是黑素瘤。在一个实施方式中，肿瘤疾病是梅克尔细胞癌 (MCC)。在一个实施方式中，可用包括 CoQ10 的联合疗法治疗的肿瘤疾病或癌症不是皮肤癌。

[0309] 在某些实施方式中，包括 CoQ10 的联合疗法对癌细胞可具有的效果可以部分地取决于癌细胞显示的代谢和氧化流的各种状态。可利用 CoQ10 来打断和 / 或干扰致癌细胞糖酵解依赖性的转化和增加的乳酸利用。由于其与癌症状态相关，这种对肿瘤微环境的糖酵解和氧化流的干扰可以以减少癌细胞发展的方式影响细胞凋亡和血管生成。在一些实施方式中，CoQ10 与糖酵解和氧化流因子的相互作用可增强 CoQ10 在癌症中发挥其恢复性凋亡作用的能力，同时建立用于药物发现和开发的可行药物靶点。

[0310] 在一个实施方式中，施用本文中所述或引入的 CoQ10 和化疗剂减小了患有肿瘤疾病的受试者的肿瘤大小、重量或体积，延长了到进展的时间，抑制了肿瘤生长和 / 或延长了存活时间。在优选实施方式中，CoQ10 通过注射，例如通过静脉内施用如本文中所述或引入的静脉内 CoQ10 制剂来施用。在某些实施方式中，相对于施用单独的 CoQ10 或单独的化疗剂的相应对照受试者，施用 CoQ10 和化疗剂减小受试者的肿瘤大小、重量或体积，延长到进展的时间，抑制肿瘤生长和 / 或延长存活时间至少 1％、2％、3％、4％、5％、10％、20％、30％、40％、50％、60％、70％、80％、90％、100％、200％、300％、400％或 500％。在其它实施方式中，施用 CoQ10 和化疗剂使在治疗前患有进行性肿瘤疾病的受试者的肿瘤疾病稳定化。

[0311] 本发明还涉及通过向人或其它动物静脉内施用有效的、非毒性量的 CoQ10 来治疗这样的人或动物中的肿瘤的方法。本领域技术人员将能够通过常规实验确定对于治疗恶性肿瘤的目的而言有效的、非毒性量的 CoQ10。例如，CoQ10 的治疗有效量可随如受试者的疾病分期（例如，I 期对 IV 期）、年龄、性别、医学并发症（例如，免疫抑制病症或疾病）和体重以及 CoQ10 在受试者中引起期望反应的能力的因素而变化。可以调整剂量方案以提供最佳治疗反应。例如，可以每天施用若干分开的剂量或通过连续输注施用，或者可以根据治疗情况的迫切性需要按比例降低剂量。

[0312] 在另一个方面，本发明还提供了治疗或预防人的侵袭性肿瘤疾病的方法。这些方法包括以治疗有效剂量向人静脉内施用 CoQ10，同时共施用化疗剂，以便发生侵袭性肿瘤疾病的治疗或预防。在一个实施方式中，这些方法包括以比针对较低侵袭性或非侵袭性肿瘤疾病使用或选择的剂量方案低的所选定剂量向受试者静脉内施用 CoQ10，以便发生侵袭性肿瘤疾病的治疗或预防。在某些实施方式中，侵袭性肿瘤疾病包括胰腺癌、肝细胞癌、尤因氏肉瘤、转移性乳腺癌、转移性黑素瘤、脑癌（星形细胞瘤、胶质母细胞瘤）、神经内分泌癌、结肠癌、肝癌、肺癌、骨肉瘤、非雄激素依赖性前列腺癌、卵巢癌、皮肤癌和非霍奇金淋巴瘤。

[0313] 在另一个方面，本发明提供了尤其是在皮肤癌治疗中与通过任意施用路径施用的化疗剂联合的局部施用 CoQ10 的方法。这样的方法包括在第一次施用化疗剂之前用 CoQ10 预治疗。

[0314] 在相关的方面，本发明提供了治疗或预防人的非侵袭性肿瘤疾病的方法。这些方法包括以治疗有效剂量向受试者静脉内共施用 CoQ10 和化疗剂，以便发生非侵袭性肿瘤疾病的治疗或预防。在一个实施方式中，这些方法包括以比针对侵袭性肿瘤疾病使用或选择的剂量方案高的所选定剂量向受试者施用 CoQ10，以便发生非侵袭性肿瘤疾病的治疗或预防。在某些实施方式中，非侵袭性肿瘤疾病包括非转移性乳腺癌、雄激素依赖性前列腺癌、小细胞肺癌和急性淋巴细胞性白血病。

[0315] 在本发明的一些实施方式中，肿瘤疾病的治疗或预防经由 CoQ10 与蛋白质或选自以下的其它细胞组分的相互作用发生：HNF4-α、Bcl-xl、Bcl-xS、BNIP-2、Bcl-2、Birc6、

Bcl-2-L11(Bim)、XIAP、BRAF、Bax、c-Jun、Bmf、PUMA、cMyc、转醛醇酶 1、CoQ1、CoQ3、CoQ6、异戊二烯基转移酶、4- 羟苯甲酸酯、嗜中性粒细胞胞质因子 2、一氧化氮合成酶 2A、超氧化物岐化酶 2、VDAC、Bax 通道、ANT、细胞色素 c、复合物 1、复合物 II、复合物 III、复合物 IV、Foxo 3a、DJ-1、IDH-1、Cpt1C 和 Cam 激酶 II。在一些实施方式中，肿瘤疾病选自白血病、淋巴瘤、黑素瘤、癌瘤和肉瘤。

[0316] 在一些实施方式中，化疗剂（例如吉西他滨）通过损伤指示癌细胞如何在有丝分裂中复制自身的 RNA 或 DNA 而起作用。如果细胞不能分裂，那么它们将会死亡。在一些情况下，化疗剂诱导细胞凋亡。吉西他滨将自身引入到癌性细胞中并防止它们分裂。与氟尿嘧啶和其它嘧啶一样，吉西他滨的三磷酸盐类似物在 DNA 复制过程中替代核酸的构建块之一（即，胞苷）。这使肿瘤生长停止，因为只有一个另外的核苷可连接到错误的核苷上，这导致细胞凋亡。吉西他滨还靶向于核糖核苷酸还原酶 (RNR)。二磷酸盐类似物结合到 RNR 活性位点并使该酶不可逆地失活。一旦 RNA 被抑制，细胞不能产生 DNA 复制和修复所需要的脱氧核糖核苷酸，且发生细胞凋亡。在一些实施方式中，吉西他滨通过 GemCarbo 方案施用，其中吉西他滨与卡铂在 21 天周期内联合施用。

[0317] 2009 年 4 月 9 日提交的国际专利申请公开 WO/2009/126764 号公开了用 CoQ10 治疗癌症，和 2011 年 3 月 11 日提交的国际专利申请公开 WO2011/11290 号公开了 CoQ10 的静脉内制剂。2010 年 5 月 11 日提交的美国专利申请公开第 US2011/0027247 号公开了使用局部施用的 CoQ10 治疗肿瘤疾病的方法。2009 年 6 月 11 日提交的国际专利申请第 WO2009073843 号和 2012 年 6 月 18 日提交的国际专利申请第 WO2012174559 号公开了通过吸入施用的 CoQ10 制剂。这些申请各以引用方式全文并入本文中。在本发明的某些实施方式中，所述方法还包括治疗方案，其包括外科手术、放疗、激素疗法、抗体疗法、使用生长因子、细胞因子的疗法和化疗中的任意一种或组合。

[0318] 现在将详细论及本发明的优选实施方式。虽然本发明将结合优选实施方式描述，但将理解其非旨在将本发明限制于这些优选实施方式。相反，意图的是涵盖可包含在由附随权利要求书限定的本发明的精神和范围内的替代方案、变型和等同物。

[0319] 实施例

[0320] 以下实施例提供了非限制性的示例性方法和用 CoQ10 与化疗剂的联合疗法治疗肿瘤疾病的结果。

[0321] 方法

[0322] 实施例 1- 方案 1-- 每天一次 IV CoQ10 和每周一次吉西他滨组合

[0323] 胰腺癌是最致命的癌症类型之一，并且由于大多数诊断发生在疾病晚期，其无疑是临床上最难对付的一种。吉西他滨是少数几种 FDA 批准单独和与其它抗肿瘤剂联合用于胰腺癌的药物之一。CoQ10 的静脉内 4％制剂在基于细胞的体外分析中和在人胰腺癌异种小鼠模型中单独或与吉西他滨联合使用，以证实 CoQ10 与吉西他滨的组合在胰腺癌治疗中提高的效力。所用的具体制剂在 2011 年 3 月 11 日提交的国际专利公布第 WO2011/112900 号中提供，其以引用方式全文并入本文中。

[0324] 人胰腺癌小鼠异种模型

[0325] 将相等数量的 MIAPaCa-2 人胰腺肿瘤细胞悬浮在 MATRIGEL® 中并注射到 NOD scid γ (NSG) 小鼠中。NSG 小鼠模型缺乏先天免疫系统和适应性免疫系统，并提供了适

合人肿瘤在体内生长的生物环境。MIAPaCa-2 是良好确认的人源胰腺癌细胞系，其可用来在免疫抑制动物中建立胰腺肿瘤。在开始治疗之前让 MIAPaca-2 肿瘤在小鼠中发展平均至少 3 周。将具有可触知肿瘤的动物随机分成治疗组。图中示出的结果表明研究中从治疗的第一天起的存活天数。

[0326] 使用上面提供的方法将 MIAPaca-2 细胞（1×10^7个细胞每动物）注射到 NSG 小鼠中。将具有可触知肿瘤的小鼠随机分成如下的 4 个组，每组 30 只小鼠：

[0327] i. 组 1- 无治疗。

[0328] ii. 组 2- 静脉内施用 4％辅酶 Q10，50mg/kg/ 天。

[0329] iii. 组 3- 每周静脉内单次施用吉西他滨，150mg/kg/ 周，施用 3 周，休止一周。以四周时间间隔重复该周期。

[0330] iv. 组 4- 静脉内施用 4％辅酶 Q10（50mg/kg/ 天）和每周静脉内单次施用吉西他滨（150mg/kg，施用 3 周，休止一周）的联合。以四周时间间隔重复该周期。

[0331] 观察小鼠的活力和二次症状，并通过触诊监测肿瘤生长。在死亡时，从小鼠采集肿瘤并测量、称重和分析肿瘤血管的存在。

[0332] 存活曲线示于图 1 中。如所示出的，未治疗组显示出急剧上升的死亡率，而单独的 CoQ10、吉西他滨及 CoQ10 的组合产生了与未治疗的对照相比寿命的延长。单独的 CoQ10 比单独的吉西他滨对存活具有显著更高的影响。用吉西他滨与 CoQ10 的组合治疗的动物显示出与其它组相比统计学显著的存活延长和长期缓解。

[0333] 死亡时从动物采集的肿瘤示于图 2 中。治疗开始后第 20 天从组 1（对照）动物采集肿瘤。治疗开始后第 50-60 天从组 2（单独辅酶 Q10）动物采集肿瘤。治疗开始后第 40-50 天从组 3（单独吉西他滨）动物采集肿瘤。治疗开始后第 50-60 天从组 4（吉西他滨 + 辅酶 Q10）动物采集肿瘤。图 2 中示出的肿瘤大小代表在所示时间段时每组中总体上观察到的肿瘤大小。

[0334] 虽然在从治疗组（组 2-4）采集肿瘤的日期之前 20-40 天从对照组（组 1）中的动物采集肿瘤，但从图 2 很明显，在死亡之时，对照组中的肿瘤平均而言显著大于任何治疗组中的那些。这些结果表明辅酶 Q10 和吉西他滨二者均抑制了人肿瘤异种小鼠模型中胰腺肿瘤的生长。

[0335] 另外，对肿瘤称重以定量测定大小。这些结果示于图 3 中。平均而言，来自单独用辅酶 Q10 治疗（组 2）的小鼠的肿瘤显著小于来自对照组中小鼠的肿瘤（组 2 对比组 1，$p<0.001$）或来自吉西他滨治疗组中小鼠的肿瘤（组 2 对比组 3，$p<0.001$）。发现来自用辅酶 Q10 和吉西他滨联合治疗（组 4）的小鼠的肿瘤平均而言显著小于来自单独用辅酶 Q10 治疗的小鼠的肿瘤（组 2 对比组 4，$p = 0.01$）或单独用吉西他滨治疗的小鼠的肿瘤（组 3 对比组 4，$p<0.0001$）。

[0336] 类似地，注意到与对照组中的肿瘤相比，可触知肿瘤在治疗组中减小。此外，肿瘤的组织学分析揭示出与至少来自未治疗的对照小鼠的肿瘤相比，来自用辅酶 Q10 治疗的小鼠肿瘤中的肿瘤血管减少（数据未示出）。未进行肿瘤血管的定量分析。

[0337] 这些数据证实，与未治疗的对照小鼠相比和与单独用吉西他滨（一种批准用于治疗人胰腺肿瘤的药剂）治疗的小鼠相比，向携带胰腺肿瘤的小鼠静脉内施用辅酶 Q10 抑制了胰腺肿瘤生长。此外，静脉内施用的辅酶 Q10 与吉西他滨组合比单独用任一药剂的治疗

更有效地抑制了小鼠中胰腺肿瘤的生长。

[0338] 还观察到，静脉内施用的辅酶 Q10 导致胰腺肿瘤中的血管量至少比来自未治疗对照小鼠的肿瘤减少，进一步证实辅酶 Q10 在癌症治疗中的有效性。

[0339] 这些数据还证实，与未治疗的对照动物相比和与单独用吉西他滨（一种批准用于治疗人的胰腺肿瘤的药剂）治疗的动物相比，向携带胰腺肿瘤的小鼠静脉内施用辅酶 Q10 增加了小鼠的存活时间。此外，辅酶 Q10 与吉西他滨组合比单独用任一药剂的治疗更有效地增加了携带胰腺肿瘤的小鼠的存活时间。

[0340] 实施例 2- 方案 2-- 一天两次 IV CoQ10 和每周一次吉西他滨组合用于治疗胰腺癌

[0341] 使用上面提供的方法将 MIAPaca-2 细胞（1×10^7个细胞每动物）注射到 NSG 小鼠中。将具有可触知肿瘤的小鼠随机分成如下 4 个组，每组 30 只小鼠：

[0342] 在第二方案中，给药

[0343] i. 对照，无治疗。

[0344] ii. 腹膜内施用 50mg/kg 的静脉 4% CoQ10 静脉内制剂，每天两次，施用 3 周，休止一周。

[0345] iii. 每周一次 150mg/kg 的吉西他滨，施用 3 周，休止一周。

[0346] iv. 腹膜内施用 50mg/kg 的静脉 4% CoQ10 静脉内制剂，每天两次，施用 3 周，休止一周，以及 150mg/kg 剂量的吉西他滨，每周一次，施用 3 周，休止一周。

[0347] 在该实施例中，腹膜内施用 CoQ10 静脉内制剂以避免因施用频率导致的血管损伤。

[0348] 监测小鼠的存活。如图 4 中所示，结果证实与未治疗的小鼠或单独用吉西他滨治疗的小鼠相比，单独或与吉西他滨联合使用 CoQ10 治疗的小鼠的存活增加。这些数据证实，单独或与吉西他滨组合的 CoQ10 比单独的吉西他滨在胰腺癌治疗中更有效。

[0349] 实施例 3- 胰腺癌和乳腺癌的体外联合疗法 (CoQ10+ 吉西他滨）

[0350] 体外细胞存活力分析

[0351] 使用各细胞系的标准培养条件将细胞系（例如，MIAPaCa-2、Hep3B 和 / 或 SK-Br3 细胞系）保持在培养物中。用 CoQ10 或指定化疗剂在指定浓度下处理细胞达指定时间。在预定的孵育时间后，使用常规方法染色细胞以区分活细胞和非活细胞。通过显微镜或流式细胞仪对细胞计数。将处理后的细胞数针对未处理样品中的细胞数归一化。

[0352] 具体而言，为体外评估与吉西他滨联合的 CoQ10 的疗效，将 MIAPaCa-2 胰腺癌细胞保持在培养物中并暴露于增加浓度的与 CoQ10、4% CoQ10 静脉内制剂或 CoQ10 静脉内制剂的赋形剂组合的吉西他滨。图 5A 示出了用单独或与吉西他滨组合的 CoQ10 或 4% CoQ10 静脉内制剂处理 6 小时对 MIAPaCa-2 胰腺癌细胞的影响。图 5B 示出了用单独或与吉西他滨联合的 CoQ10 或 4% CoQ10 静脉内制剂处理 6 小时对 SK-Br3 乳腺癌细胞的影响。结果证实，在暴露于与吉西他滨组合的 4% CoQ10 静脉内制剂之后，在 6 小时处胰腺癌和乳腺癌细胞中的细胞死亡均增加。与单独用吉西他滨处理相比，用吉西他滨和 4% CoQ10 静脉内制剂联合处理导致细胞死亡增加。

[0353] 实施例 4- 胰腺癌和乳腺癌的体外联合疗法 (CoQ10+ 多柔比星）

[0354] 为体外评估与多柔比星组合的 CoQ10 的疗效，将 MIAPaCa-2 胰腺癌细胞保持在培养物中并暴露于增加浓度的与 CoQ10、4% CoQ10 静脉内制剂或 CoQ10 静脉内制剂的赋形剂

组合的吉西他滨。图 6A 示出了用单独或与多柔比星组合的 CoQ10 或 CoQ10 静脉内制剂处理 6 小时对 MIAPaCa-2 胰腺癌细胞的影响。图 6B 示出了用单独或与多柔比星组合的 CoQ10 或 4% CoQ10 静脉内制剂处理 6 小时对 SK-Br3 乳腺癌细胞的影响。结果证实，在暴露于与多柔比星组合的 CoQ10 的 4% CoQ10 静脉内制剂之后，在 6 小时时胰腺癌和乳腺癌细胞均诱发了增加的细胞死亡。与单独用多柔比星处理相比，用多柔比星和 4% CoQ10 静脉内制剂联合处理导致细胞死亡的增加。

[0355] 为确认体外观察到的结果，使用上述 MIAPaCa-2 小鼠异种模型来评估单独或与 CoQ10 静脉内制剂联合的多柔比星增加小鼠存活的活性。如图 7 中所示，与单独用多柔比星治疗相比，CoQ10 静脉内制剂与多柔比星联合提高了生存力。

[0356] 发现在胰腺癌的治疗中，单独的 CoQ10 或与多柔比星联合的 CoQ10 比吉西他滨或多柔比星在实现与有益的治疗终点相关的反应中更有效，最显著的是增加存活。静脉内 CoQ10 还在乳腺癌的治疗中具有潜在效用。在至多 42 天的胰腺癌异种小鼠模型中，单独或与吉西他滨联合的 CoQ10 制剂将生存力延长至 42 天。与单独用多柔比星的治疗相比，联合施用 CoQ10 与多柔比星降低了胰腺癌异种小鼠模型中观察到的死亡率。

[0357] 实施例 5- 方案 3- 每天三次 IV CoQ10 和每周一次吉西他滨组合

[0358] 将相等数量的 MIAPaca2 人胰腺肿瘤细胞（1×10^7 个）悬浮在 MATRIGEL® 中并注射到小鼠中。在开始治疗之前让肿瘤发展平均至少 3 周。

[0359] 将具有可触知肿瘤的小鼠随机分成如下 5 个组，每组 30 只小鼠：

[0360] i. 组 1- 无治疗。

[0361] ii. 组 2- 腹膜内施用 4% CoQ10 静脉内制剂，50mg/kg/ 剂，每天 3 次（150mg/kg/ 天）。

[0362] iii. 组 3- 腹膜内施用 4% 辅酶 Q10 静脉内制剂，75mg/kg/ 剂，每天 3 次（225mg/kg/ 天）。

[0363] iv. 组 4- 腹膜内施用 4% 辅酶 Q10 静脉内制剂（50mg/kg/ 剂，每天 3 次（150mg/kg/ 天））和每周一次静脉内施用吉西他滨（150mg/kg，施用 3 周，休止一周）的组合。以四周时间间隔重复该周期。

[0364] v. 组 5- 腹膜内施用 4% 辅酶 Q10 静脉内制剂（75mg/kg/ 剂，每天 3 次（225mg/kg/ 天））和每周一次静脉内施用吉西他滨（150mg/kg，施用 3 周，休止一周）的组合。以四周时间间隔重复该周期。

[0365] 辅酶 Q10 的高频率施用阻止了静脉内施用辅酶 Q10，因为由高频率静脉内注射导致血管损伤。观察动物的存活力并通过触诊监测肿瘤生长。

[0366] 图 8 中示出了到第 417 天收集的存活结果。未治疗的对照组（组 1）中的所有小鼠到开始向组 2-5 中的小鼠施用治疗剂后第 23 天全部死亡。相比之下，在每个治疗组（组 2-5）中，至少 50% 的动物在治疗开始后第 130 天存活。在两个治疗剂量中单独用辅酶 Q10 治疗的动物比对照动物显示出显著增加的存活。此外，在治疗过程中，用辅酶 Q10 和吉西他滨的组合治疗的动物与单独用相同剂量的辅酶 Q10 治疗的小鼠相比显示出增加的存活。

[0367] 实施例 6- 致癌细胞和正常细胞对辅酶 Q10 的相对敏感性

[0368] 研究并比较辅酶 Q10 处理对各种致癌和正常细胞系的影响。通过监测细胞凋亡的诱导评估细胞对辅酶 Q10 的敏感性。细胞的 CoQ10 处理如下文“材料和方法”中所详细描

述的那样进行。如下文所述，通过监测早期凋亡的指示（例如，Bcl-2 表达、半胱天冬酶激活和通过使用膜联蛋白分析）评估处理细胞中凋亡的诱导。从这些研究确定在细胞系组中诱导凋亡所需的最小 CoQ10 剂量（例如，CoQ10 浓度）和处理时间。

[0369] 数据证实辅酶 Q10 处理在表现出增加的致癌性和 / 或更高的转移潜能的细胞类型（即源自更高侵袭性的癌症或肿瘤的细胞类型）中的功效更高。这些研究的结果汇总在表中。数据证实 CoQ10 以时间和浓度依赖性的方式对呈更高侵袭性癌症状态的细胞更有效。此外，对正常细胞观察到与致癌细胞相比令人惊异的相异结果。具体而言，出乎意料地发现辅酶 Q10 在正常组织环境中表现出略微支持性的作用，其中在包括角质形成细胞和真皮成纤维细胞的正常细胞中观察到增加的增殖和迁移。

[0370] 辅酶 Q10 在癌症中对基因调节和蛋白质机制的影响不同于在正常细胞中。关键的细胞机构和组分如细胞骨架结构、膜流动性、运输机制、免疫调节、血管生成、细胞周期控制、基因组稳定性、氧化控制、糖酵解流、代谢控制和细胞外基质蛋白完整性调节异常，且因此细胞的遗传和分子指纹被改变。疾病环境有利于细胞控制过程的管理。本文提供的数据表明，CoQ10 通过以允许恢复凋亡潜能的方式使一些关键的前述过程正常化而发挥更高水平的功效（例如，在癌细胞中对比在正常细胞中，以及在更高侵袭性的癌症状态的细胞中对比在较低侵袭性或非侵袭性的癌症状态的细胞中）。

[0371] 在各种细胞类型中诱导早期凋亡所需的最小 CoQ10 浓度和处理时间

[0372]

组织起源（细胞类型）	**早期凋亡指征（Bcl-2、膜联蛋白 V 或半胱天冬酶激活）**	**浓度（μM）**	**时间（小时）**	**侵袭性水平：1 = 正常组织 2 = 恶性 3 = 转移性**
皮肤：				
角质形成细胞（*Heka, Hekn*）	无	N/A	N/A	1
成纤维细胞（*nFib*）	无	N/A	N/A	1
黑素细胞（*Hema, LP*）	无	N/A	N/A	1
黑素瘤（*Skmel 28*）	强	20	24	2
黑素瘤（Skmel 2）	非常强	25	24	3
SCC，鳞状细胞癌	非常强	25	24	3

[0373]

乳腺:				
MCF-7	强	50	48	2
SkBr-3	非常强	50	24	3
BT-20	强	100	48	2
ZR-75	轻微	200	72	2
MDA MB 468	强	100	48	2
乳腺成纤维细胞: 184A1 和 184B5) (Lawrence Berkeley)	无	N/A		1
前列腺:				
PC3	非常强	25	24	3
肝脏:				
HepG2	非常强	50	24	3
Hep3B	非常强	50	24	3
骨:				
骨肉瘤 (143b)	非常强	50	48	2
尤因氏肉瘤 (NCI)	极强	5	1	3
胰腺:				3
PaCa2	非常强	25	24	
心脏:				
主动脉平滑肌(HASMC)	无	N/A	N/A	1

[0374] 材料和方法

[0375] 细胞制备与处理

[0376] 在皿或瓶中制备的细胞

[0377] 在含 5% CO_2水平的 37℃孵育箱中于 T-75 培养瓶中用补充了 10%胎牛血清(FBS)、1% PSA(青霉素、链霉素、两性霉素 B)(Invitrogen and Cellgro)的相关培养基培养细胞直至达到 70-80%的汇合。为收获细胞用于处理,向瓶中加入 1mL 胰蛋白酶,吸出,用另外 3mL 进行胰蛋白酶化并于 37℃下孵育 3-5 分钟。然后用等体积的培养基使细胞中和,并随后将溶液于 10,000rpm 下离心 8 分钟。吸出上清液并用 8.5ml 培养基再悬浮细胞。用库尔特计数器对 500ul 重悬液和 9.5ml 异丙醇的混合物读取两次,并确定待接种到每个皿中的细胞的适宜数量。一式三份对对照组和浓度范围 0 至 200 μM 的组进行检验。从 500 μM CoQ-10 储备溶液进行连续稀释以在适宜的皿中获得期望实验浓度。取决于细胞类型和实验

方案，将皿于含 5% CO_2水平的 37℃孵育箱中孵育 0-72 小时。

[0378] 蛋白质分离和定量

[0379] 在皿中制备的细胞

[0380] 在细胞处理孵育期结束后，进行蛋白质分离。用 2ml 冰冷 1x 磷酸盐缓冲盐水 (PBS) 将所有处理组的皿洗涤两次，并用 1ml 冰冷 1x 磷酸盐缓冲盐水 (PBS) 洗涤一次。仅在最初 2 次洗涤后从皿中吸出 PBS。使用来自第三次洗涤的最终体积，将细胞轻轻刮下并收集到微量离心管中，且于 10,000rpm 下离心 10 分钟。离心后，吸出上清液并用 50uL 裂解缓冲液（每 100uL 裂解缓冲液中 1uL 蛋白酶和磷酸酶抑制剂）裂解球粒。然后将样品于 -20℃下冷冻过夜。

[0381] 在瓶中制备的细胞

[0382] 在细胞处理孵育期结束后，进行蛋白质分离。用 5ml 冰冷 1x PBS 将所有处理组的烧瓶洗涤两次，并用 3ml 冰冷 1x PBS 洗涤一次。仅在最初 2 次洗涤后从瓶中吸出 PBS。使用来自第三次洗涤的最终体积，将细胞轻轻刮下并收集到 15mL 离心管中，且于 10,000rpm 下离心 10 分钟。离心后，吸出上清液并用适宜量的裂解缓冲液（每 100uL 裂解缓冲液中 1uL 蛋白酶和磷酸酶抑制剂）裂解球粒。裂解缓冲液体积取决于球粒尺寸。将样品转移到微量离心管中并于 -20℃下冷冻过夜。

[0383] 蛋白质定量

[0384] 在蛋白质分离的第二天将样品于 -4℃解冻并超声处理以确保均质化。使用 micro BCA 蛋白分析试剂盒 (Pierce) 进行蛋白质定量。为制备用于免疫印迹法的样品，制备 β-巯基乙醇 (Sigma) 对样品缓冲液 (Bio-Rad) 的 1:19 溶液。用 β-巯基乙醇 - 样品缓冲溶液将样品 1:1 稀释，在 95℃下沸腾 5 分钟，并于 -20℃下冷冻过夜。

[0385] 免疫印迹法

[0386] Bcl-2、半胱天冬酶 -9、细胞色素 c

[0387] 使用自 BCA 蛋白分析获得的蛋白质原始平均浓度确定每孔加载的样品体积。对于每一处理时间点，加载大约 30-60μg 蛋白质。使蛋白质一式三份在 12% Tris-HCl 预制凝胶（Bio-Rad®）或手铸凝胶上于 1x 运行缓冲液中 85 和 100 伏下跑胶。然后于 100 伏下使蛋白质转移到硝酸纤维素纸上 1 小时，并在 5% 牛奶溶液中再封闭 1 小时。将膜放置在一抗 (1uL Ab:1000uL TBST)(Cell Signaling) 中于 -4℃下过夜。第二天，用 Tris- 缓冲盐水 Tween®-20 (TBST) 洗涤膜三次，每次十分钟，然后于 -4℃下施加二抗（抗 - 兔 ;1uL Ab:1000uL TBST) 一小时。再用 TBST 洗涤膜三次，每次十分钟，并完成使用 Pico 或 Femto 底物的化学发光（Pierce®）。然后将膜于产生最佳视觉效果的时间间隔显影。显影后，将膜保持在 -4℃下的 TBST 中直至可测量肌动蛋白水平。

[0388] 肌动蛋白

[0389] 将膜在肌动蛋白一抗 (1uL Ab:5000uL TBST)(Cell Signaling 公司）中于 -4℃下放置 1 小时，用 TBST 洗涤三次，每次十分钟，然后于 -4℃下施加二抗（抗 - 小鼠 ;1uL Ab:1000uL TBST) 一小时。再用 TBST 洗涤膜三次，每次十分钟，并完成使用 Pico 底物的化学发光 (Pierce)。然后将膜于产生最佳视觉效果的时间间隔显影。

[0390] 膜联蛋白 V 分析

[0391] 将细胞在PBS中洗涤两次并再悬浮于结合缓冲液(0.1M HEPES,pH 7.4;1.4M NaCl;25mM $CaCl_2$)中。将100μl样品加到含5μl膜联蛋白-PE染料或7-ADD的培养管中。混合细胞并在室温下无光孵育15分钟。其后,向每一样品中加入400μl 1X结合缓冲液并通过流式细胞仪对它们进行分析。

[0392] 实施例7-CoQ10处理在体内使肿瘤对化疗剂敏感

[0393] 使用实施例6中的方法测试细胞以确定用CoQ10和化疗剂处理细胞的相对时机是否对细胞杀灭有影响,例如通过促进细胞凋亡、诱导肿瘤裂解、抑制细胞增殖。

[0394] 简言之,如实施例6中那样培养细胞。单独地或联合地用CoQ10和化疗剂或者用适宜的媒介对照处理细胞。对于用CoQ10和化疗剂二者处理的细胞,使细胞以各种顺序接触CoQ10和化疗剂。使用CoQ10和化疗剂的各种浓度。还使用各种处理时间。示例性的条件在下表中提供。

[0395]

	治疗#1		治疗#2	
	CoQ10	化疗	CoQ10	化疗
1	+	+	+	+
2	+	--	+	--
3	--	+	--	+
4	+	--	+	+
5	+	—	—	+

[0396] 对各CoQ10和化疗剂使用适宜的媒介对照。

[0397] 在如所示用CoQ10和化疗处理后,采集细胞并使用上文提供的方法分析存活力和细胞凋亡。经证实,在用化疗处理之前用CoQ10预处理比用CoQ10和化疗共同处理或在化疗之后用CoQ10处理在细胞杀灭中更有效。具体而言,用CoQ10预处理,然后用CoQ10和化疗同时处理在细胞杀灭中有效。用CoQ10预处理和中断CoQ10,接着用化疗处理在细胞杀灭中也有效。不受理论束缚,据认为CoQ10通过改变磷酸戊糖旁路、糖酵解和氧化磷酸化中关键调控酶的表达而“再教育”依赖于糖酵解的癌症(glycolysis addicted cancers)利用线粒体呼吸链作为能量源。CoQ10在癌细胞中实现的代谢切换与导致凋亡途径重演的涉及TP53、Bcl-2/Bax和VEGF的新型集成信号传导交互的诱导相关。数据表明CoQ10在使癌细胞对化疗剂的细胞毒性作用敏感而同时对正常细胞提供保护方面直接影响线粒体中心途径。

[0398] 实施例8-CoQ10处理在体内使肿瘤对化疗剂敏感

[0399] 在体内肿瘤异种移植模型中,对小鼠移植肿瘤。例如,向NSG小鼠中注射悬浮在MATRIGEL中的MIAPaCa-2胰腺癌细胞。或者,在异种移植小鼠模型中使用其它肿瘤细胞系,例如三阴性乳腺癌、肝癌、前列腺癌、黑素瘤、肉瘤、癌瘤细胞系。也可使用化学诱导的肿瘤和其它癌症动物模型。在所有动物中,于治疗开始之前确认肿瘤的存在。

[0400] 测试各种序列方案和CoQ10与化疗剂的组合减小肿瘤负荷和/或减少肿瘤转移的能力。例如,使用实施例7中的表中提供的示例性方案。如实施例7中的表中所示治疗#1

和治疗 #2 各自可以是使用该药剂的一个或多个周期治疗。例如，在一些动物中，在治疗 2 中的一个或多个周期的化疗剂之前施用在治疗 1 中的 2 个或更多个周期的 CoQ10。在一些动物中，在施用治疗 2 中的多个周期的化疗之前施用治疗 1 中的一个周期的 CoQ10。

[0401] 使用常规方法如卡尺、成像分析来监测肿瘤体积。在研究结束时，切除肿瘤并使用常规方法分析例如大小（例如，重量和体积）、组织学特征、分级和血管形成。在用化疗剂治疗之前用一个或多个周期的 CoQ10 治疗证明比共施用 CoQ10 和化疗剂或单独施用化疗剂更有效。

[0402] 实施例 9-CoQ10 处理增强化疗剂在体外肝癌细胞处理中的功效

[0403] 在标准条件下培养 Hep3B 肝癌细胞。用化疗剂伊立替康 (SN38)、顺铂、5- 氟尿嘧啶或多柔比星在指定的浓度下单独或与 CoQ10(100 μM) 联合地处理细胞预定的时间段。

[0404] 通过活细胞计数评估生长抑制 / 促进细胞死亡。结果示于图 9A-9C 和 10 中。CoQ10 证明提高了所有化疗剂的功效，增加细胞死亡并减少活细胞数量。这些数据表明这些治疗剂的组合比单独的化疗剂在肝癌治疗中更有效。

[0405] 实施例 10-CoQ10 对胰腺癌中细胞凋亡机构的线粒体启动 (Mitochondrial priming) 以增强化疗功效

[0406] 不受机理的束缚，据认为，CoQ10 实现从糖酵解向增强的线粒体氧化磷酸化的代谢切换，导致癌症中细胞凋亡的重演。研究 CoQ10 的作用以确定用 CoQ10 预处理是否导致线粒体启动，从而增强标准治疗化疗剂的细胞毒性作用。将 MIAPaCa-2 人胰腺癌细胞 (a) 在用吉西他滨处理之前用 CoQ10 预处理或 (b) 用 CoQ10 和吉西他滨共同处理。监测处理对细胞存活力的影响并将结果示于图 10-14 中。

[0407] 与单独用吉西他滨处理相比，CoQ10 处理导致 MIAPaca-2 细胞增殖减少。用 CoQ10 处理 MIAPaca-2 细胞在预处理和共同处理方案中均增强了吉西他滨的细胞毒性潜能。

[0408] 实施例 11-CoQ10 对胰腺癌中细胞凋亡机构的线粒体启动以增强化疗功效

[0409] 将相等数量的 MIAPaCa2 人胰腺肿瘤细胞 (1×10^7 个）悬浮在 MATRIGEL® 中并注射到小鼠中。在开始治疗之前让肿瘤发展平均至少 3 周。

[0410] 将具有可触知肿瘤的小鼠如下随机分成 5 个组，每组 30 只小鼠：

[0411] i. 组 1- 无治疗。

[0412] ii. 组 2- 腹膜内施用 4％辅酶 Q10 静脉内制剂 (75mg/kg/ 剂，每天 3 次 (225mg/kg/ 天)) 并在同一天开始每周一次静脉内施用吉西他滨 (150mg/kg，施用 3 周，休止一周）。

[0413] iii. 组 3- 腹膜内施用 4％辅酶 Q10 静脉内制剂 (75mg/kg/ 剂，每天 3 次 (225mg/kg/ 天)) 并于 CoQ10 治疗开始后一周开始每周一次静脉内施用吉西他滨 (150mg/kg，施用 3 周，休止一周）。

[0414] iv. 组 4- 腹膜内施用 4％辅酶 Q10 静脉内制剂 (75mg/kg/ 剂，每天 3 次 (225mg/kg/ 天)) 并于 CoQ10 治疗开始后两周开始每周一次静脉内施用吉西他滨 (150mg/kg，施用 3 周，休止一周）。

[0415] v. 组 5- 腹膜内施用 4％辅酶 Q10 静脉内制剂 (75mg/kg/ 剂，每天 3 次 (225mg/kg/ 天)) 并于 CoQ10 治疗开始后三周开始每周一次静脉内施用吉西他滨 (150mg/kg，施用 3 周，休止一周）。

[0416] 高频率施用辅酶 Q10 阻止了静脉内施用辅酶 Q10，因为高频率静脉内注射导致血

管损伤。通过触诊观察动物的存活和肿瘤生长。

[0417] 早期时间点表明在静脉内 CoQ10 预治疗之后使用吉西他滨在胰腺癌模型中产生与共同治疗方案相比改善的存活（图 15A）。不受机理的束缚，数据表明 CoQ10 可以是可行的线粒体启动剂以在胰腺癌中使癌细胞对吉西他滨的细胞毒性作用敏感。数据证实，CoQ10 的加入提高了吉西他滨在胰腺癌中的细胞毒性作用，并与未治疗的对照相比在最后的时间点以统计学显著的方式增加存活（参见下文）。另外，CoQ10 治疗接着吉西他滨治疗与改善的存活相关（参见，例如，与化疗同时开始的 CoQ10 75mg/kg，对比 CoQ10 75mg/kg×3 周然后化疗）。

[0418]

条件 1	条件 2	p- 值
对照	CoQ10 75mg/kg，与化疗同时开始	<0.00001
对照	CoQ10 75mg/kg×1 周然后化疗	<0.00001
对照	CoQ10 75mg/kg×2 周然后化疗	<0.00001
对照	CoQ10 75mg/kg×3 周然后化疗	<0.00001
CoQ10 75mg/kg，与化疗同时开始	CoQ10 75mg/kg×1 周然后化疗	0.26503
CoQ10 75mg/kg，与化疗同时开始	CoQ10 75mg/kg×2 周然后化疗	0.45960
CoQ10 75mg/kg，与化疗同时开始	CoQ10 75mg/kg×3 周然后化疗	0.02724*

[0419]

CoQ10 75mg/kg×1 周然后化疗	CoQ10 75mg/kg×2 周然后化疗	0.82980
CoQ10 75mg/kg×1 周然后化疗	CoQ10 75mg/kg×3 周然后化疗	0.20885
CoQ10 75mg/kg×2 周然后化疗	CoQ10 75mg/kg×3 周然后化疗	0.15515

[0420] 实施例 12- 各种癌细胞类型的体外 CoQ10 单一疗法

[0421] 为评估 CoQ10 的体外功效，将各种癌细胞（MIAPaCa-2 胰腺癌细胞、SKOV-3 卵巢癌细胞、PC-3 前列腺癌细胞、HT-29 结肠癌细胞、MCF7 乳腺癌细胞、MDA-MB231 乳腺癌细胞、SKBR-3 乳腺癌细胞、A549 肺癌细胞、Hep3B 肝癌细胞）保持在培养物中并暴露于 100μM CoQ10 48-72 小时。图 16 示出了 CoQ10 处理对各种癌细胞的影响。结果证实在暴露于 CoQ10 后癌细胞中的细胞死亡增加。

[0422] 实施例 13-CoQ10 对细胞代谢和半胱天冬酶 3 活性的影响

[0423] 在用 100μM CoQ10 处理 24 小时的 MDA-MB213 和 SKBR-3 乳腺癌细胞中测量基础耗氧率（OCR）和细胞外酸化率（ECAR）。图 17 示出了 CoQ10 处理对乳腺癌细胞中 OCR 和 ECAR 的影响。用 CoQ10 处理的乳腺癌细胞中较高 OCR-ECAR 比率表明 CoQ10 在乳腺癌细胞中增加了氧化磷酸化（OXPHOS）而减少了糖酵解。还在经 100μM CoQ10 处理 24 小时的 MDA-MB213

和 SKBR-3 乳腺癌细胞及非致瘤性对照细胞 (MCF12A) 中测量活性氧物质 (ROS) 的产生。线粒体代表已知参与细胞死亡途径激活的 ROS 的重要来源。图 17 显示 CoQ10 处理在乳腺癌细胞和对照细胞二者中增加了 ROS 的产生。

[0424] 在经 100 μM CoQ10 处理 72-96 小时的 MDA-MB213 和 SKBR-3 乳腺癌细胞及未处理的对照 MDA-MB213 和 SKBR-3 乳腺癌细胞中比较半胱天冬酶 3 活性。半胱天冬酶 3 是内在（线粒体）和外在凋亡途径都需要的执行者 (executioner) 半胱天冬酶。图 18 显示 CoQ10 处理在 MDA-MB213 和 SKBR-3 乳腺癌细胞中提高了半胱天冬酶 3 活性。

[0425] 实施例 14- 在各种癌细胞中 CoQ10 预处理和共处理的体外分析

[0426] 用 CoQ10 及分别化疗剂顺铂、多西紫杉醇和环磷酰胺预处理或共处理 A549 肺癌细胞、PC3 前列腺癌细胞和 SKOV3 卵巢癌细胞。对于预处理，将细胞用 CoQ10 处理 6 小时，然后向培养基中加入指定的化疗剂。因此，对于预处理组，CoQ10 处理在化疗剂处理过程中持续。化疗剂处理的时间长度随细胞类型而异。A549 细胞用顺铂处理 48 小时，PC3 细胞用多西紫杉醇处理 48 小时，和 SKOV3 细胞用环磷酰胺处理 72 小时。共处理和预处理的细胞用化疗剂处理相同的时间长度。图 19 示出了用 CoQ10 和化疗剂共处理或预处理的影响。

[0427] 实施例 15- 三阴性乳腺癌 (TNBC) 动物模型对单独的或与标准方案化疗联合的 CoQ10 的反应的评价

[0428] 在用和不用 CoQ10 的情况下，用 TAC 方案 (5mg/kg 多西紫杉醇、1mg/kg 多柔比星和 35mg/kg 环磷酰胺）治疗携带三阴性乳腺癌 (TNBC) 异种移植物的小鼠。TAC 每三周施用，施用六个周期。也用单独的 CoQ10 治疗小鼠。单独或与 TAC 方案联合的 CoQ10 显著改善了存活。参见图 21。

[0429] 实施例 16-CoQ10 和化疗剂处理的乳腺癌细胞的体外研究

[0430] 使不同受体状态的人乳腺癌细胞 (SKBR3、MDA-MB231) 经受 (a)CoQ10 预处理 (6 小时）然后与化疗剂 (5- 氟尿嘧啶，5-FU ；多柔比星，Doxo ；SN38，伊立替康活性代谢物）共孵育 48 小时或 (b) 用 CoQ10 与化疗剂共处理。与非致瘤性乳腺细胞 (MCF12A) 比较癌细胞反应。48 小时后评估活细胞的数量。分别使用碘化丙啶 (PI) 和 CFSE 细胞示踪物来测量处理的细胞中的细胞死亡和增殖。当与化疗剂比较时，单独的 CoQ10 或者 CoQ10 加标准治疗的预处理和共处理策略都导致活乳腺癌细胞的显著减少 ；然而，在非致瘤性 MCF12A 细胞中观察到最低的影响。参见图 20、23 和 24。

[0431] 此外，CoQ10 与化疗剂联合放大了半胱天冬酶 3 活化和凋亡细胞死亡，这表明 CoQ10 增强凋亡信号传导。参见图 22。合在一起，这些数据证实 CoQ10 是与恶性肿瘤的基础遗传构成无关地重新啮合癌细胞的细胞代谢和凋亡机构的新型药剂。此外，CoQ10 通过调节线粒体代谢和氧化应激增强标准治疗化疗剂在乳腺癌细胞中的细胞毒性。这些发现确认 CoQ10 是在包括 TNBC 的乳腺癌（其否则将具有差预后且治疗选择有限）中具有多种效用（作为单一药剂或联合）的新型药剂。

[0432] 为确定线粒体生物能学的作用及活性氧物质的产生，将 MDA-MB231 和 SkBr-3 乳腺癌细胞及 MCF12A 对照细胞用 100 μM CoQ10(BPM 31510) 处理 24 小时。在 Seahorse XF96 分析仪中使用线粒体毒素（寡霉素、CCCP 和鱼藤酮）的顺序注射评估线粒体功能。还测量 DCF 荧光作为在以相同方式处理的细胞中活性氧物质产生的指标。细胞生物能学分析揭示出 CoQ10 使细胞代谢从糖酵解转换至线粒体代谢，并且该代谢转换与活性氧物质 (ROS) 的

显著增加相关。参见图 25。

[0433] 实施例 17- 单独的或与吉西他滨联合的 CoQ10 的预治疗、剂量和施用途径在人胰腺癌异种移植小鼠模型中的影响

[0434] 在人胰腺癌的异种移植小鼠模型中评价图 27 中示出的三个治疗方案（方案 1、方案 2 和方案 3）以确定单独的或与吉西他滨联合的 CoQ10 对动物存活的影响。方案 1 的治疗的效果在上面的实施例 1 中描述。以三个不同的静脉内剂量（50mg/kg 或 75mg/kg 体重每天，方案 3）施用的 CoQ10 与存活的剂量依赖性增加相关，并且具有对吉西他滨的加和作用。参见图 29。连续输注 CoQ10 与三剂（50mg/kg 或 75mg/kg）的 CoQ10 相比显著改善了存活率，最好结果出现在 200mg/kg 处。参见图 30。单独用 CoQ10 预治疗六十天然后与吉西他滨联合也和与单独的吉西他滨或 CoQ10 相比改善的存活结果相关。参见图 31。数据表明单独或与标准治疗化疗剂联合的 CoQ10 的剂量和施用途径影响并改善胰腺癌动物模型中的存活。

[0435] 实施例 18-CoQ10 预处理接着吉西他滨处理对体外人胰腺癌细胞的存活的影响

[0436] 将人胰腺癌细胞（PcCa2）用 100μM CoQ10 预处理接着用吉西他滨（0.1、1 和 5μM）处理或者用 CoQ10 与吉西他滨共同处理。与单独的吉西他滨相比，预处理和共同处理均显著减少活细胞数量（*p<0.05）。参见图 26。

[0437] 实施例 19- 在众多癌细胞中与各种化疗联合的 CoQ10 的体外分析

[0438] 用 CoQ10 与不同的癌症治疗剂的联合处理各种癌细胞以确定联合疗法对细胞存活和细胞代谢的影响。癌细胞和相应的对照细胞示于下表中。

[0439]

乳腺	SKBR-3
	MDA-231
	BT549
	MCF-7
	MCF12A（对照）
胰腺	PaCa2
	PL-45
	Panc1
肺	A549
结肠	CaCo2
	HT29
肝脏	Hep3B
	THLE-2（对照）
子宫颈	Scc25
前列腺	PC-3
	LnCap
	PNT2（对照）
卵巢	SKOV-3

[0440] 测试了以下癌症治疗剂：

[0441]

药物	作用模式	靶标
赫赛汀	结合 HER2 的抗体	大多数乳腺癌/HER2+
伊立替康	抑制拓扑异构酶 I	所有分裂细胞
顺铂	连接和交联 DNA（Inter and Crosslinks DNA）	所有分裂细胞
5-氟尿嘧啶	抑制胸苷形成	所有分裂细胞
多西紫杉醇	阻止微管解聚	所有分裂细胞
4-羟基环磷酰胺	烷化剂	所有分裂细胞
吉西他滨	具有氟的核苷	所有分裂细胞
多柔比星	拓扑异构酶 II 抑制剂并诱导氧化应激。抑制线粒体复合物 1	所有分裂细胞
紫杉醇	微管稳定剂	所有分裂细胞
氟他胺	雄激素（DHT）受体阻滞剂	含雄激素受体的细胞
雌莫司汀	烷化剂，雌激素衍生物	雌激素诱导细胞
依托泊苷	拓扑异构酶 II 抑制剂	所有分裂细胞
奥沙利铂	交联 DNA 的双齿铂板	所有分裂细胞
戈舍瑞林	GnRH 和 LHRH 激动剂	
他莫昔芬	雌激素受体拮抗剂	含 ER 的细胞

[0442] 使用以下分析来测量细胞存活和代谢。

[0443]

分析	方法	仪器
细胞计数	台盼蓝	Nexcelon 细胞计数仪
增殖	固定细胞中的碘丙啶	流式细胞仪
细胞死亡	碘丙啶	流式细胞仪
凋亡（半胱天冬酶 3）	半胱天冬酶 3 染料	荧光显微镜

ROS	CM-DCFDA 染料	流式细胞仪

[0444]

耗氧量	线粒体应激	Seahorse 胞外分析仪
细胞外酸化	糖酵解途径	Seahorse 胞外分析仪

[0445] 细胞在以下生长培养基中培养：

[0446]

	培养基	来源	血清	抗生素
PaCa2	DMEM（不含丙酮酸钠）	Lonza	5% FBS; 2.5% HS	1x 青霉素/链霉素/两性霉素 B
PC-3	DMEM（不含丙酮酸钠）	Lonza	5% FBS	1x 青霉素/链霉素/两性霉素 B
MDA231	RPMI 1640	Lonza	5% FBS	庆大霉素（GA-1000）
SKBR-3	McCoy's 5A	Lonza	5% FBS	1x 青霉素/链霉素/两性霉素 B
Hep3B	EMEM	Lonza	5% FBS	1x 青霉素/链霉素/两性霉素 B
A549	KF-12	Invitrogen	5% FBS	1x 青霉素/链霉素/两性霉素 B
HT-29	McCoy's 5A	Lonza	5% FBS	1x 青霉素/链霉素/两性霉素 B
SKOV-3	McCoy's 5A	Lonza	5% FBS	1x 青霉素/链霉素/两性霉素 B
MCF-7	MEM + NEEA	Invitrogen	5% FBS	1x 青霉素/链霉素/两性霉素 B
HUMEC	HUMEC 培养基	Invitrogen	-	1x 青霉素/链霉素/两性霉素 B
PNT2	RPMI 1640	Lonza	10% FBS	1x 青霉素/链霉素/两性霉素 B
Panc1	DMEM	Lonza	5% FBS	1x 青霉素/链霉素/两性霉素 B
MCF-12A	HAM/F-12	Lonza	5%马血清	1x 青霉素/链霉素/两性霉素 B
BT-549	RPMI 1640	Lonza	10% FBS	1x 青霉素/链霉素/两性霉素 B

[0447] 补充剂

[0448]

	补充剂		
Hep3B	1x Glutamax		
MCF-7	1x Glutamax		
MCF-12A	20ng/ml hEGF	10ug/ml 胰岛素	500ng/ml 氢化可的松
BT-549	0.5ug/ml 胰岛素		

[0449] 接种细胞的方法

[0450] 对于细胞计数、增殖和活性氧物质 (ROS) 测量，细胞量及接种和处理方法相同。在添加处理剂的同时接种细胞。如下将细胞接种在 24- 孔板中 ：

[0451]

样品	细胞 / 孔	样品	细胞 / 孔	样品	细胞 / 孔
SKBR-3	60k	PC3	60k	HT-29	100k
MDA231	60k	PaCa2	50K	BT549	30K
MCF-7	50K	Panc-1	50K	Hep3B	60K
MCF12A	60k	A-549	100k	SKOV-3	60k

[0452] 对于测量细胞凋亡的半胱天冬酶 3 分析，将细胞接种在玻璃 12 孔板中，其中细胞处于 110k/ 孔的比率下并让其粘附 5 小时至 18 小时，然后添加处理。为测量耗氧量和细胞外酸化，将细胞接种在 Seahorse XF-96 板中。各种细胞系的细胞数实例示于下表中 ：

[0453]

样品	细胞 / 孔
SKBR-3	10k
MDA231	10k
MCF12A	30k

[0454] 化疗剂的来源、溶剂和原液浓度示于下表中 ：

[0455]

原液制剂	目录编号#	溶剂	小瓶	原液[]
SN38	Sigma H0165-10mg	255ul DMSO	10mg	100mM
顺铂***	Enzo ALX-400-040-M050	33ml 0.9%盐水	50mg	5mM
Doxo	Sigma D-1515	1ml DMSO	10mg	10mg/ml
5FU	Amresco 0597-5G	1ml DMSO	重 13mg	100mM
赫赛汀	Thermo Fisher	20ml，提供的 H2O	400mg	20mg/ml
环磷酰胺	Santa Cruz sc-219703	500ul H2O + 硫代硫酸盐	25mg	4.4mM
吉西他滨	Sigma G6423-10mg	3.3ml H2O	10mg	10mM
紫杉醇	Sigma T7402-1mg	118ul DMSO	1mg	10mM
多西紫杉醇	Sigma 01885-5mg-F	618ul DMSO	5mg	10mM
他莫昔芬	Sigma H7904	1290ul EtOH	5mg	10mM
阿瓦斯汀	Myoderm Medical 提供			
雌莫司汀	Sigma#SLBD7083V	1ml DMSO	5.6mg	100mM
依托泊苷	Sigma lot#	425ul DMSO	25mg	100mM

[0456]

原液制剂	目录编号#	溶剂	小瓶	原液[]
	BCBH0586V			
奥沙利铂	Sigma lot# SLBD0630V	1.25ml DMSO	5mg	100mM

[0457] 对于每项化疗，测试的浓度范围可源从本领域已知的浓度范围。针对如下表中所示的每种化疗剂生成剂量反应曲线：

[0458]

药物	剂量反应曲线浓度				
SN38	0.1nM	1nM	10nM	100nM	1000nM
顺铂	1uM	6uM	12uM	25uM	50uM
Doxo	1ng/ml	10ng/ml	100ng/ml	1ug/ml	10ug/ml
5FU	0.1uM	1uM	10uM	100uM	1000uM
	1uM	5uM	10uM	25uM	50uM
赫赛汀	10ug/ml	25ug/ml	50ug/ml	100ug/ml	250ug/ml
	1ug/ml	5ug/ml	10ug/ml	25ug/ml	50ug/ml
环磷酰胺	0.05uM	0.25uM	1uM	4uM	12.5uM
吉西他滨	0.1uM	1uM	10uM	100uM	1000uM
紫杉醇	5nM	10nM	25nM	50nM	100nM
多西紫杉醇	0.1nM	1nM	10nM	100nM	1000nM
他莫昔芬	0.3uM	0.62uM	1.25uM	2.5uM	5uM
氟他胺	0.01uM	0.1uM	1uM	10uM	100uM
雌莫司汀	0.01uM	0.1uM	1uM	10uM	100uM
依托泊苷	0.01uM	0.1uM	1uM	10uM	100uM
奥沙利铂	0.1uM	1uM	10uM	100uM	1000uM

[0459] 对于共处理实验，对每种细胞系选择以下剂量：

[0460]

	组合浓度									
药物	SKBR-3	Hep3B	MDA231	Paca2	A549	PC-3	THL E-2	SKOV-3	HT-29	MCF-7
SN38	1, 10, 100 nM	10, 100 nM	1, 10, 25 nM			25, 100, 250 nM	1, 10 nM		0.5, 1, 10 nM	1, 5, 10 nM
顺铂	1, 5, 10 μM	1, 5, 10 μM			0.1, 1, 10 μM			0.5, 2.5, 5 μM		1.5, 3, 6 μM
多柔比星	10, 50, 100 ng/ml	10, 25, 50 ng/ml	0.1, 1, 10 ng/ml	10, 50, 100 μg/ml						2, 4, 8 ng/ml

[0461]

5-氟尿嘧啶	0.1, 1, 10 μM	0.1, 1, 10 μM	0.1, 1, 10 μM						0.1, 1, 10 nM	
赫赛汀	10, 25, 50 μg/ml									
环磷酰胺	0.5, 1, 2 μM		1, 2, 4 μM, 0.5, 1, 2 μM					0.25, 4, 8 μM		0.5, 1, 2 μM
吉西他滨				0.1, 1, 5 μM	0.01, 0.1, 1 μM	25, 100, 200 nM				
紫杉醇			10, 50, 100 nM, 10, 25, 50 nM		5, 10, 25 nM	25, 100, 200 nM				
多西紫杉醇	0.01, 0.1, 1 nM				0.1, 1, 10 nM	1, 10, 100 μM				
他莫昔芬										2, 4, 6 μM
氟他胺						0.01, 0.1, 1 μM				
雌莫司汀						1, 10 100 μM				
依托泊苷						0.01, 0.1, 1 μM				
奥沙利铂				1, 10, 50 μM				10, 50, 100 μM		

[0462] 根据端点分析优化处理时间，例如：对于代谢分析，使用较短的孵育时间；对于细胞计数，使用较长的孵育时间。基于细胞倍增时间即细胞生长的速度有多快来选择涉及增殖和细胞计数的孵育。下表提供了各种细胞类型和分析的孵育时间。

[0463]

	细胞计数、ROS、细胞增殖（碘丙啶）	OCR、ECAR	半胱天冬酶 3
SKBR-3	48h	24h	96h
MDA-231	48h	24h	96h
BT549	48h	24h	96h
MCF-7	72h	24h	96h
MCF12A	48h	24h	96h
PaCa2	72h	24h	96h
PL-45	48h	24h	96h
Panc1	48h	24h	96h

[0464]

A549	48h	24h	96h
CaCo2	48h	24h	96h
HT29	48h	24h	96h
Hep3B	48h	24h	96h
THLE-2	48h	24h	96h
Scc25	48h	24h	96h
PC-3	48h	24h	96h
LnCap	48h	24h	96h
PNT2	48h	24h	96h
SKOV-3	72h	24h	96h

[0465] 实施例 20-CoQ10 预治疗然后化疗剂治疗在体内对各种肿瘤的影响

[0466] 使用在水中 4:3:1.5 比率的 CoQ10(4 重量 / 体积%):DMPC(3 重量 / 体积%):泊洛沙姆 188(1.5 重量 / 体积%)的 CoQ10 浓缩水性纳米分散体;该纳米分散体浓缩物含有 40mg/mL 粒度为 30-50nm 的 CoQ10。单一媒介对照组接受以最高耐受剂量(1000mg API 当量)给药的 3 重量 / 体积% DMPC 和 1.5 重量 / 体积%泊洛沙姆 188 的无菌溶液。单一阴性对照组接受无菌缓冲生理盐水。CoQ10 纳米分散体在研究开始的 2 周内制备并在整个研究中贮存于 4-25℃下。在研究的开始和结束时分析试验样品的 CoQ10 活性和粒度分布。

[0467] 纳米分散体中使用的赋形剂 DMPC 和泊洛沙姆 188 用于配制 CoQ10 水性纳米分散体。在使用时,将浓缩纳米分散体用无菌缓冲生理盐水 (PBS) 稀释。媒介含有 PBS 作为稀释剂并且 PBS 不经稀释用作盐水对照。使用来自 Jackson 实验室和 Harlan 实验室的免疫低下小鼠。免疫低下小鼠缺乏先天和适应性免疫系统。这提供了适于人肿瘤体内生长的生物环境。这些动物特别适于移植不同的人类癌症。

[0468] 4 周龄小鼠抵达机构并于 48 小时后进行实验。将小鼠安置单一识别号的每笼 5 只的窝中。动物在抵达时及整个实验过程中称重以得到响应于不同配方的另一个参数。采用的饮食为 PMI Nutrition International,LLC 生产的配方 Lab Diet® 5001 啮齿动物饮食。该生产商为 ISO 9001:2000 认证的机构。该饮食每 6 个月购买一次,且批号可追溯到每个房间并将由技术员记录。施用于 NSG 小鼠的食物在放置于动物笼中之前必须经过高压灭菌。全部小鼠都自由进食。水得自佛罗里达水利部并由动物技术员在干净的瓶中分发到每个笼。每天检查水中是否存在碎屑并用干净的水替换。施用于 NSG 小鼠的水在施用于小鼠之前必须是无菌的。到 20 日龄时通过 CO_2 吸入处死小鼠。为确保死亡,对每只动物施以颈椎脱臼法并刺破隔膜。

[0469] 静脉内施用无菌 CoQ10 制剂和适合的无菌对照。基于不断发展的结果施用 CoQ10 剂量。在以至多 50mg/kg 每周三次施用 CoQ10 时,先前的实验未显示出毒性迹象,而以 250mg/kg 每周三次给药 4 周建立大鼠中的 MTD。将 CoQ10 的作用与其它特别针对每种癌系的化疗方案相比较。该研究的另一分支评价 CoQ10 与其它化疗剂之间的协同作用。

[0470] 评价以下癌细胞:

[0471]

		细胞名称
乳腺	三阴性	MDA-MB-231
肺	小细胞	H522
	非小细胞	A549
卵巢		SK-OV-3
肝脏		HepG2
前列腺		LnCap
急性白血病		Kg1, K562
结肠		HT29, CaCo
胶质母细胞瘤		LN229

[0472] 所有细胞在 5% CO_2、100%湿度的孵育箱中于 37℃下培养。基础培养基随每种细胞而异。为制备完全生长培养基，向基础培养基中添加以下组分：胎牛血清至 10%的最终浓度。在向动物中注射细胞之前，让细胞生长至50%汇合，其后根据细胞实验方案粘附或离心。采集以下器官：肾、胰、肺、心脏和肝脏。对器官称重并记录。进行常规瑞氏染色或苏木精 / 伊红染色的病理报告。腹膜内或静脉内施用 CoQ10 制剂和化疗剂。

[0473] 观察缺乳、嗜睡和体重减轻的存在。该类濒死迹象为早期处死的基础并在动物中进行尸检（即，器官重量、病理切片）。

[0474] 在无菌条件下，如上所述向动物进行注射。将窝根据笼卡号识别符随机化并记录每只动物的重量。然后让小鼠返回到它们的笼子。其后，每天向小鼠进行腹膜内注射直至它们因肿瘤负荷或其存活而被处死。

[0475] 如所示出的，对各种癌细胞测试以下化疗方案：

[0476] 乳腺癌（非转移性）

[0477]

联合化疗
多柔比星/环磷酰胺
环磷酰胺/多柔比星/5-氟尿嘧啶

[0478] 肺癌（小细胞）

[0479]

联合化疗
环磷酰胺/多柔比星/长春新碱
环磷酰胺/多柔比星/依托泊苷

[0480] 肺癌（非小细胞）

[0481]

联合化疗

顺铂/紫杉醇
多西紫杉醇/顺铂
吉西他滨/顺铂

[0482] 卵巢癌

[0483]

联合化疗

顺铂/环磷酰胺
顺铂/紫杉醇

[0484] 肝细胞癌

[0485]

单药

[0486]

多柔比星
顺铂
卡培他滨

[0487] 前列腺癌

[0488]

联合化疗

紫杉醇/雌莫司汀
多西紫杉醇/雌莫司汀

[0489] 急性白血病

[0490]

联合化疗

阿糖胞苷/柔红霉素
阿糖胞苷/伊达比星
阿糖胞苷/多柔比星

[0491] 结肠癌

[0492]

单药

卡培他滨

[0493] 胶质母细胞瘤

[0494]

单药

贝伐单抗

缬更昔洛韦

[0495] 实施例 21- 用 CoQ10 和化疗剂处理的各种癌细胞系的体外分析

[0496] 如上面实施例 14 中所述，用 CoQ10 和各种化疗剂共处理或预处理各种癌细胞系。显著减少活细胞数的细胞 / 化疗剂组合示于下表 2 中。

[0497] 表 2 :CoQ10 和各种化疗剂处理的各种癌细胞系的体外研究汇总。

[0498] Co :共处理 ;Pre :预处理。

[0499]

	PC3	SkBr-3	MB231	MCF-7	MiaPaCa2	BT549	Hep3B	A549	SKOV3
	前列腺	乳腺	TNBC	乳腺	胰腺	乳腺	肝脏	肺	卵巢
SN38		Co					Co 和 Pre		
Doxo		Pre		Pre	Pre	Pre	Co		
5-FU		Co	Co				Co		
顺铂								Pre	
4-HCP		Co	Co	Co					Co
紫杉醇								Co	
他莫昔芬				Pre					
吉西他滨								Pre	
氟他胺	Pre								
戈舍瑞林	Pre								

[0500] 表 3 :化疗剂的标准剂量。标准剂量得自化疗剂生产商的产品说明书。

[0501]

化疗剂	**推荐剂量**
多柔比星	以 1mg/min 的初始速率施用多柔比星以使输注反应的风险最小化。如果无输注相关反应发生，则增大输注速率至 1 小时完成施用。 不以浓注注射或未稀释溶液施用。 **卵巢癌：** 50mg/m^2，IV，每 4 周，最少 4 个疗程 **艾滋病相关卡波西肉瘤：** 20mg/m^2，IV，每 3 周一次 **多发性骨髓瘤：** 30mg/m^2，在施用硼替佐米（以 1.3mg/m^2 在第 1、4、8 和 11 天浓注）后第 4 天 IV，每 3 周
环磷酰胺	**治疗恶性疾病 - 成人和儿童：** 当用作唯一的溶瘤药物疗法时，无血液缺陷的患者的 CYTOXAN 初始疗程通常由在 2 至 5 天期间以分次剂量静脉内施用 40 至 50mg/kg 组成。其它静脉内方案包括每 7 至 10 天 10 至 15mg/kg 或每周两次 3 至 5mg/kg。 对于初始和维持给药，口服 CYTOXAN 给药通常在 1 至 5mg/kg/天的范围内。 当 CYTOXAN 被包含在联合细胞毒性方案中时，可能有必要减少 CYTOXAN 的剂量以及其它药物的剂量。 **治疗非恶性疾病 - 儿童中活检证实的“微小变化”肾病综合征：**

[0502]

	推荐 60 至 90 天期间每天 2.5 至 3mg/kg 的口服剂量。在男性中，如果 CYTOXAN 治疗持续时间超过 60 天，则少精子症和无精子症的发生率增加。超过 90 天的治疗增加不育可能性。在 CYTOXAN 疗法的疗程中，可逐渐减少和中断肾上腺皮质类固醇疗法。
5-氟尿嘧啶	氟尿嘧啶注射应仅静脉内施用。 **剂量:** 连续 4 天每天一次静脉内施用 12mg/kg。日剂量应不超过 800mg。如果未观察到毒性，则在第 6 天、第 8 天、第 10 天和第 12 天施用 6mg/kg，除非毒性出现。在第 5 天、第 7 天、第 9 天或第 11 天不施用治疗。在第 12 天结束时中断治疗，即便没有毒性变得明显。 风险承受能力低的患者（poor risk patients）或未处于适当营养状态的患者应接受 6mg/kg/天，施用 3 天。如果未观察到毒性，则可在第 5 天、第 7 天和第 9 天施用 3mg/kg，除非毒性出现。在第 4 天、第 6 天或第 8 天不施用治疗。日剂量应不超过 400mg。 **维持疗法:** 在毒性尚未成问题的情况下，推荐用任一以下时间表继续治疗: 1. 在早先疗程的最后一天之后每 30 天重复第一疗程的剂量。 2. 当因初始疗程所致的毒性迹象已消退时，以单剂量施用 10 至 15mg/kg/周的维持剂量。不超过 1gm 每周。
长春新碱	该药以每周的时间间隔静脉内施用。 对于**儿科患者**，硫酸长春新碱的常用剂量为 2mg/m^2。对于体重 10kg 或以下的儿科患者，起始剂量应为 0.05mg/kg，一周施用一次。 对于**成人**，硫酸长春新碱的常用剂量为 1.4mg/m^2。对于直接血清胆红素值高于 3mg/100mL 的患者，建议将硫酸长春新碱的剂量降低 50%。
依托泊苷	在**睾丸癌**中，与其它批准的化疗剂联合的依托泊苷注射剂的常用剂量在第 1 至 5 天在 50 至 100mg/m^2/天的范围内，至在第 1、3 和 5 天为 100mg/m^2/天。 在**小细胞肺癌**中，与其它批准的化疗药物联合的依托泊苷注射剂剂量从 35mg/m^2/天施用四天至 50mg/m^2/天施用 5 天。 在从任意毒性充分恢复后，以 3 至 4 周时间间隔重复化疗疗程。
顺铂	顺铂通过缓慢静脉内输注施用。 **转移性睾丸肿瘤:** 对于与其它批准的化疗剂联合治疗睾丸癌，常用的顺铂（顺铂注射剂）剂量为每天 20 mg/m^2 IV，每周期 5 天。 **转移性卵巢肿瘤:** 对于与环磷酰胺联合治疗转移性卵巢肿瘤，常用的顺铂（顺铂注射剂）剂量为每 4 周一次（第 1 天），每周期 75 至 100mg/m^2 IV。 当与顺铂（顺铂注射剂）联合使用时，环磷酰胺的剂量为每 4 周一次（第 1 天）600mg/m^2 IV。在联合疗法中，顺铂（顺铂注射剂）和环磷酰胺依次施用。 作为单药，顺铂（顺铂注射剂）应以每 4 周一次，每周期 100mg/m^2 IV 的剂量施

[0503]

	用。 **晚期膀胱癌：**顺铂（顺铂注射剂）应以单药方式每 3 至 4 周一次，每周期 50 至 70mg/m^2 IV 的剂量施用，取决于既往暴露于放疗和/或既往化疗的程度。对于重度预治疗患者，推荐每 4 周重复的每周期 50mg/m^2 的初始剂量。
紫杉醇	在施用紫杉醇之前应对所有患者前驱用药，以防止严重的超敏反应。这样的前驱用药可由在紫杉醇之前大约 12 和 6 小时经口施用地塞米松 20mg、在紫杉醇之前 30 至 60 分钟静脉内施用苯海拉明（或其等同物）50mg 和在紫杉醇之前 30 至 60 分钟静脉内施用西咪替丁（300mg）或雷尼替丁（50mg）组成。 **卵巢癌：** 1）对于此前未治疗的患有卵巢癌的患者，可每 3 周施用以下推荐方案之一： 静脉内施用紫杉醇 3 小时，剂量为 175mg/m^2，接着施用顺铂，剂量为 75mg/m^2；或 静脉内施用紫杉醇 24 小时，剂量为 135mg/m^2，接着施用顺铂，剂量为 75mg/m^2。 2）在此前用化疗治疗卵巢癌的患者中，紫杉醇已经以若干剂量和时间表使用；然而，最佳方案尚不清楚。推荐方案为每 3 周 3 小时静脉内施用紫杉醇 135mg/m^2 或 175mg/m^2。 **乳腺癌：** 1）对于淋巴结阳性乳腺癌的辅助治疗，推荐方案为与含多柔比星的联合化疗依次地每 3 周静脉内施用紫杉醇 3 小时，剂量为 175mg/m^2，4 个疗程。 2）在针对转移性疾病的初始化疗失败后或在辅助化疗的 6 个月内复发后，每 3 周以 175mg/m^2 的剂量静脉内施用紫杉醇 3 小时已证明是有效的。 **非小细胞肺癌：** 每 3 周给予的推荐方案为以 135mg/m^2 的剂量静脉内施用紫杉醇 24 小时，接着施用 75mg/m^2 的顺铂。 **艾滋病相关卡波西肉瘤：** 推荐每 3 周以 135mg/m^2 的剂量静脉内施用紫杉醇 3 小时或每 2 周以 100mg/m^2 的剂量静脉内施用紫杉醇 3 小时（剂量强度为 45-50mg/m^2/周）。 **晚期 HIV 疾病：** 1）将作为 3 种前驱用药药物之一的地塞米松的剂量减少至 10mg PO（代替 20mg PO）； 2）仅在中性粒细胞计数为至少 1000 个细胞/mm^3 时，开始或重复紫杉醇的治疗； 3）对于遭遇严重中性粒细胞减少（中性粒细胞< 500 细胞/mm^3 达一周或更久）的患者，将后续紫杉醇疗程的剂量降低 20%；和 4）根据临床指示开始伴随的造血生长因子（G-CSF）。 **肝损伤：** 下表中针对 3 小时和 24 小时输注示出了第一疗程的剂量调整建议。后续疗程中进

[0504]

<table>
<tr><td></td><td>一步的剂量减少应基于个体耐受性。

在肝损伤患者中基于临床试验数据的给药建议 [a]

<table>
<tr><th colspan="3">肝损伤程度</th><th rowspan="2">推荐紫杉醇剂量 [c]</th></tr>
<tr><th>转氨酶水平</th><th></th><th>胆红素水平 [b]</th></tr>
<tr><td colspan="4">24-小时输注</td></tr>
<tr><td>< 2 × ULN</td><td>和</td><td>≤1.5mg/dL</td><td>135mg/m^2</td></tr>
<tr><td>2 至 10 × ULN</td><td>和</td><td>≤1.5mg/dL</td><td>100mg/m^2</td></tr>
<tr><td>< 10 × ULN</td><td>和</td><td>1.6-7.5mg/dL</td><td>50mg/m^2</td></tr>
<tr><td>≥10 × ULN</td><td>或</td><td>> 7.5mg/dL</td><td>不建议</td></tr>
<tr><td colspan="4">3-小时输注</td></tr>
<tr><td>< 10 × ULN</td><td>和</td><td>≤1.25 × ULN</td><td>175mg/m^2</td></tr>
<tr><td>< 10 × ULN</td><td>和</td><td>1.26-2.0 × ULN</td><td>135mg/m^2</td></tr>
<tr><td>< 10 × ULN</td><td>和</td><td>2.01-5.0 × ULN</td><td>90mg/m^2</td></tr>
<tr><td>≥10 × ULN</td><td>或</td><td>> 5.0 × ULN</td><td>不建议</td></tr>
</table>
[a] 这些建议是基于无肝损伤的患者 135mg/m^2 24 小时或 175mg/m^2 3 小时的剂量；数据不可用做其它方案的剂量调整建议（例如，AIDS 相关卡波西肉瘤）。
[b] 3 小时和 24 小时输注之间的胆红素水平标准的不同是由于临床试验设计的不同。
[c] 剂量建议针对的是第一疗程；后续疗程中进一步的剂量减少应基于个体耐受性。</td></tr>
<tr><td>多西紫杉醇</td><td>在为应对可能的并发症（例如，过敏性反应）而配备的设施中施用。每 3 周静脉内(IV)施用 1 小时。不建议 PVC 设备。只使用 21 号针头从药瓶吸取 TAXOTERE。

BC 局部晚期或转移性： 60mg/m^2 至 100mg/m^2 单药

BC 辅助：在 50mg/m^2 多柔比星和 500mg/m^2 环磷酰胺后每 3 周施用 75mg/m^2 1 小时一次，6 个周期

NSCLC：在铂疗法失败后：75mg/m^2 单药

NSCLC：初始化疗：75mg/m^2，接着顺铂 75mg/m^2

HRPC：75mg/m^2 与 5mg 泼尼松，连续每天两次

GC：75mg/m^2，接着顺铂 75mg/m^2（均仅在第 1 天），接着在顺铂输注结束时开始每天氟尿嘧啶 750mg/m^2 24 小时 IV（第 1-5 天）

SCCHN：75mg/m^2，接着静脉内顺铂 75mg/m^2（第 1 天），接着在顺铂输注结束时开始每天静脉内氟尿嘧啶 750mg/m^2 24 小时（第 1-5 天）；4 个周期

SCCHN：75mg/m^2，接着静脉内顺铂 100mg/m^2（第 1 天），接着每天静脉内施用氟尿嘧啶 1000mg/m^2 24 小时（第 1-4 天）；3 个周期

对于所有患者：前驱用药口服皮质类固醇，且必要时调节剂量</td></tr>
<tr><td>吉西他滨</td><td>健择仅供静脉内使用。

卵巢癌： 1000mg/m^2 30 分钟，各 21 天周期的第 1 和 8 天。

乳腺癌： 1250mg/m^2 30 分钟，各 21 天周期的第 1 和 8 天。</td></tr>
</table>

[0505]

	非小细胞肺癌： 1000mg/m^2 30 分钟，每 28 天周期的第 1、8 和 15 天施用，或者 1250mg/m^2 30 分钟，各 21 天周期的第 1 和 8 天。 **胰腺癌：** 1000mg/m^2 30 分钟，前 7 周每周一次，然后休止一周，然后每周一次，各 28 天周期的 3 周。
卡培他滨	饭后 30 分钟内用水服用 XELODA。 **单一疗法：** 经口施用 1250mg/m^2，每天两次（早上和晚上；等同于 2500mg/m^2 总日剂量），施用 2 周，然后休止一周，以 3 周周期施用。 辅助治疗**推荐总共 6 个月（8 个周期）** **在与多西紫杉醇联合时，XELODA 的推荐剂量为 1250mg/m^2，每天两次，2 周，然后是 1 周休止时段，与每 3 周以 75mg/m^2 静脉内输注 1 小时的多西紫杉醇联合。** XELODA 剂量可能需要个体化以优化患者管理。 在中度肾损伤的患者中将 XELODA 剂量降低 25%。
雌莫司汀	推荐的日剂量为 14mg 每 kg 体重（即，对于每 10kg 或 22lb 体重为一粒 140mg 的胶囊），分 3 或 4 个分剂量施用。在美国，研究中的大多数患者已经用 10 至 16mg 每 kg 每天的剂量范围进行治疗。 应指导患者在饭前至少 1 小时或饭后 2 小时服用 EMCYT 胶囊。EMCYT 应当用水吞服，且牛奶、奶制品和富含钙的食物或药物（如含钙的抗酸剂）不得与 EMCYT 同时服用。 在医生确定继续治疗的可能益处之前，应治疗患者 30 至 90 天。只要有利的反应持续，则应继续治疗。一些患者已经以 10 至 16mg 每 kg 体重每天的范围内的剂量保持治疗超过 3 年。
阿糖胞苷	阿糖胞苷口服是没有活性的。施用的时间表和方法随待使用的治疗程序而异。阿糖胞苷可通过静脉内输注或注射，皮下或鞘内施用。 在**急性非淋巴细胞性白血病**的诱导治疗中，与其它抗癌药物联合的常用阿糖胞苷剂量为连续静脉内输注 100mg/m^2/天（第 1 至 7 天）或每 12 小时静脉内 100mg/m^2（第 1 至 7 天）。 **脑膜白血病**中的鞘内使用：阿糖胞苷已被鞘内用于急性白血病，剂量范围为 5 至 75mg/m^2 体表面积。施用频率从每天一次、施用 4 天变化至每 4 天一次。
柔红霉素	**成人急性非淋巴细胞性白血病：** 组合地： 对于年龄在 60 岁以下的患者，在第一疗程的第 1、2 和 3 天和在后续疗程的第 1、2 天静脉内施用盐酸柔红霉素 45mg/m^2/天，并在第一疗程施用 7 天和在后续疗程施用 5 天每天静脉内输注胞嘧啶阿拉伯糖苷 100mg/m^2/天。 对于年龄在 60 岁及以上的患者，在第一疗程的第 1、2 和 3 天和在后续疗程的第 1、2 天静脉内施用盐酸柔红霉素 30mg/m^2/天，并在第一疗程施用 7 天和在后续疗程施用 5 天每天静脉内输注胞嘧啶阿拉伯糖苷 100mg/m^2/天。

[0506]

	小儿急性淋巴细胞性白血病: 组合地: 在每周第 1 天静脉内施用盐酸柔红霉素 25mg/m^2、每周第 1 天静脉内施用长春新碱 1.5mg/m^2、每天经口施用泼尼松 40mg/m^2。 在年龄不到 2 岁或体表面积小于 0.5m^2 的儿童中，已建议盐酸柔红霉素剂量计算应基于体重（1mg/kg）而不是体表面积。 **成人急性淋巴细胞性白血病:** 组合地: 在第 1、2 和 3 天静脉内施用盐酸柔红霉素 45mg/m^2/天并在第 1、8 和 15 天静脉内施用长春新碱 2mg；在第 1 到 22 天经口施用泼尼松 40mg/m^2/天，然后在第 22 至 29 天之间逐渐减少；在第 22 到 32 天静脉内施用 L-天冬酰胺酶 500IU/kg/天×10 天。
伊达比星	对于在患有 **AML** 的成年患者中的诱导疗法，推荐以下剂量时间表: 与阿糖胞苷联合，通过缓慢（10 至 15 分钟）静脉内注射盐酸伊达比星注射剂 12mg/m^2 每天，施用 3 天。阿糖胞苷可按照通过连续输注 7 天，每天 100mg/m^2 施用，或者按照静脉内浓注阿糖胞苷 25mg/m^2，接着连续输注 5 天，每天 200mg/m^2 阿糖胞苷施用。 在第一诱导疗程之后有明确的白血病迹象的患者中，可施用第二疗程。在遭遇严重的粘膜炎的患者中，应延迟施用第二疗程直至已出现该毒性的恢复，并建议将剂量降低 25%。 在患有肝和/或肾损伤的患者中，应考虑减少盐酸伊达比星注射剂的剂量。如果胆红素水平超过 5mg%，则不应施用盐酸伊达比星注射剂。
贝伐单抗	不以静脉推注或浓注施用。 不在大手术后 28 天内开始阿瓦斯汀，且直至手术伤口完全愈合。 **转移性结肠直肠癌** • 每 2 周静脉内施用 5mg/kg，并浓注 IFL • 每 2 周静脉内施用 10mg/kg，并施用 FOLFOX4 • 每 2 周静脉内施用 5mg/kg，或者每 3 周静脉内施用 7.5mg/kg，并在含阿瓦斯汀的一线方案进展后施用基于氟嘧啶-伊立替康或氟嘧啶-奥沙利铂的化疗 **非鳞状非小细胞肺癌** • 每 3 周静脉内施用 15mg/kg，并施用卡铂/紫杉醇 **胶质母细胞瘤** • 每 2 周静脉内施用 10mg/kg **转移性肾细胞癌**（mRCC） • 每 2 周静脉内施用 10mg/kg，并施用干扰素 α
缬更昔洛韦	**具有正常肾功能的成年患者** **CMV 视网膜炎的治疗** 诱导：推荐剂量为 900mg（两片 450mg 片剂），每天两次，施用 21 天。 维持：在诱导治疗后，或在患有非活动性 CMV 视网膜炎的成年患者中，推荐剂

[0507]

	量为 900mg（两片 450mg 片剂），每天一次。 **CMV 疾病的预防** 对于已接受心脏或肾-胰腺移植的成年患者，推荐剂量为 900mg（两片 450mg 片剂），每天一次，从移植的 10 天内开始，直至移植后 100 天。 对于已接受肾移植的成年患者，推荐剂量为 900mg（两片 450mg 片剂），每天一次，从移植的 10 天内开始，直至移植后 200 天。 **儿科患者** **CMV 疾病的预防** 对于已接受肾或心脏移植的 4 个月到 16 岁年龄的儿科患者，从移植的 10 天内开始直至移植后 100 天，推荐的万赛维每日一次剂量是基于体表面积（BSA）和从修正的 Schwartz 公式得出的肌酐清除率（CrCl），并使用下式计算： 儿科剂量（mg）= 7 × BSA × CrCl（使用修正的 Schwartz 公式计算）。如果计算出的 Schwartz 肌酐清除率超过 150mL/min/1.73m²，则应在该公式中使用 150mL/min/1.73m²的最大值。 Mosteller BSA (m²) = √身高(cm) x 体重(kg)/ 3600 Schwartz 肌酐清除率 mL/min/1.73m²) = k×身高(cm)/血清肌酐(mg/dL) 其中，k = 0.45（对于 4 月至小于 1 岁年龄的患者）、0.45（对于 1 岁至小于 2 岁年龄的患者，注意，k 值为 0.45 而不是 0.55 的典型值）、0.55（对于 2 岁至小于 13 岁年龄的男童和 2 至 16 岁年龄的女童）和 0.7（对于 13 至 16 岁年龄的男童）。 对于实际可递送剂量，所有计算剂量应四舍五入到最接近的 25mg 增量。如果计算剂量超过 900mg，则应施用 900mg 的最大剂量。万赛维口服溶液是优选的制剂，因为其提供了施用根据上式计算的剂量的能力；然而，如果计算剂量在可用片剂强度（450mg）的 10%内，则可使用万赛维片剂。例如，如果计算剂量介于 405mg 和 495mg 之间，则可服用一片 450mg 片剂。
甲氨喋呤	**肿瘤性疾病：**在施用低剂量时，常优选以片剂形式口服施用，因为吸收快并获得有效血清水平。甲氨喋呤注射剂可通过肌内、静脉内或动脉内途径施用。 **绒毛膜癌及类似的滋养细胞疾病：**以 15 至 30mg 每天的剂量经口或肌内施用甲氨喋呤，五天一个疗程。这样的疗程常根据需要重复 3 至 5 次，疗程之间插入一周或多周的休止期，直至任意显现出的毒性症状消退。治疗的有效性通常通过尿绒毛膜促性腺激素（hCG）的 24 小时定量分析来评价，通常在第三或第四个疗程后 hCG 应返回到正常或低于 50IU/24 小时，并且之后通常在 4 至 6 周内可测量病灶完全消退。通常建议在 hCG 正常化后一至两个疗程的甲氨喋呤。在药物的每一个疗程之前，进行仔细的临床评估是必不可少的。甲氨喋呤与其它抗肿瘤药物的周期性联合疗法已经报告为有用的。 **白血病：**最初单独使用甲氨喋呤或与类固醇联合使用甲氨喋呤来诱导急性淋巴母细胞性白血病的缓解。近来皮质类固醇疗法与其它抗白血病药物联合或与包括甲氨喋呤的周期性联合已显现为产生快速且有效的缓解。当用于诱导时，与 60mg/m² 泼尼松联合，每日施用 33mg/m² 剂量的甲氨喋呤通常在 4 至 6 周的期间内在 50%的治疗患者中产生缓解。甲氨喋呤与其它药剂联合显现为是实现药物诱导缓解的维持的药物选择。当实现缓解并且支持性治疗已产生总体的临床改善时，如下开

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	始维持疗法：以 30mg/m^2 的每周总剂量经口或肌内每周施用 2 次甲氨喋呤。还已经每 14 天以 2.5mg/kg 的剂量静脉内施用。如果确实出现复发和在复发时，通常可再次通过重复初始诱导方案获得缓解的再次诱导。 **淋巴瘤：**在 I-II 期伯基特氏肿瘤中，甲氨喋呤已在一些病例中产生长时间的缓解。推荐剂量为 4 至 8 天经口 10 至 25mg/天。在 III 期中，甲氨喋呤通常伴随其它抗肿瘤剂施用。在所有分期中的治疗常常由若干个药物疗程组成，其间插入 7 至 10 天的休止期。III 期淋巴肉瘤可响应于含甲氨喋呤的联合药物疗法，其中甲氨喋呤以每天 0.625 至 2.5mg/kg 剂量施用。 **蕈样肉芽肿（皮肤 T 细胞淋巴瘤）：**使用甲氨喋呤作为单药的疗法显现为在至多 50%的治疗患者中产生临床反应。早期阶段的剂量通常为 5 至 50mg，每周一次。剂量减少或停止是由患者反应和血液学监测来指导。还已在对每周治疗反应不佳的患者中以 15 至 37.5mg 范围内的剂量每周两次施用甲氨喋呤。包括以较高剂量静脉内施用的甲氨喋呤和亚叶酸解救（leucovorin rescue）的联合化疗方案已被用在该疾病的晚期阶段中。 **骨肉瘤：**有效的辅助化疗方案需要施用若干种细胞毒性化疗剂。除高剂量甲氨喋呤与亚叶酸解救外，这些药剂可包括下表中所示剂量和时间表的多柔比星、顺铂，以及博莱霉素、环磷酰胺和放线菌素（BCD）的组合：高剂量甲氨喋呤治疗的起始剂量为 12 克/m^2。如果该剂量在甲氨喋呤输注结束时不足以产生 1,000 微摩尔的峰值血清甲氨喋呤浓度，则可在后续治疗中将剂量逐渐增加至 15 克/m^2。如果患者呕吐或不能耐受口服药物治疗，则以相同的剂量和时间表静脉内或肌内施用亚叶酸。 **成人类风湿性关节炎：**推荐的起始剂量时间表 1. 单次口服剂量 7.5mg，每周一次。 2. 分次口服剂量 2.5mg，以 12 小时时间间隔，3 剂一疗程，每周一次。 **多关节型（Polyarticular Course）青少年类风湿性关节炎：**推荐的起始剂量为 10mg/m^2，每周一次施用。 **牛皮癣：**推荐的起始剂量时间表： 1. 每周单次口服、肌内或静脉剂量时间表：10 至 25mg 每周，直至获得足够的反应 2. 分次口服剂量时间表：2.5mg，以 12 小时时间间隔服用三剂
表柔比星	以重复的 3 至 4 周周期静脉内施用，在每个周期的第 1 天施用总剂量或每个周期的第 1 和第 8 天均分施用 盐酸表柔比星注射剂的推荐起始剂量为 100 至 120mg/m^2。 推荐以下方案： CEF-120：在第 1 至 14 天经口施用环磷酰胺 75mg/m^2、在第 1 和第 8 天静脉内施用盐酸表柔比星注射剂 60mg/m^2、在第 1 和第 8 天静脉内施用 5-氟尿嘧啶 500mg/m^2，每 28 天重复，施用 6 个周期 FEC-100：5-氟尿嘧啶 500mg/m^2、盐酸表柔比星注射剂 100mg/m^2、环磷酰胺 500mg/m^2

[0509]

	所有药物都在第 1 天静脉内施用并且每 21 天重复，施用 6 个周期。 当以某些组合施用时可能减少剂量。 在第一治疗周期后的剂量调整应基于血液学和非血液学毒性而进行。 在肝损伤患者中减少剂量。 在严重肾损伤患者中考虑更低的剂量。
米托蒽醌	**多发性硬化症：** NOVANTRONE 的推荐剂量为每 3 个月 12mg/m^2，以短时（大约 5 至 15 分钟）静脉输注施用。 **激素难治性前列腺癌：** NOVANTRONE 的推荐剂量为每 21 天 12 至 14mg/m^2，以短时静脉输注施用 **成人中 ANLL 的联合初始治疗：** 对于诱导，推荐剂量为在第 1-3 天以静脉内输注每天施用 NOVANTRONE 12mg/m^2，并在第 1-7 天连续 24 小时输注施用阿糖胞苷 100mg/m^2，施用 7 天。
替尼泊苷	在一项研究中，使用 VUMON 165mg/m^2 和阿糖胞苷 300mg/m^2 的组合静脉内治疗用含阿糖胞苷的方案进行诱导疗法失败的儿童 ALL 患者，每周两次，施用 8 至 9 剂。 在另一项研究中，使用 VUMON 250mg/m^2 和长春新碱 1.5mg/m^2，每周一次，4 至 8 周，与经口施用泼尼松 40mg/m^2， 28 天的组合静脉内治疗含长春新碱/泼尼松的方案难治的儿童 ALL 患者。
伊立替康	结肠直肠癌联合方案 1：在第 1、8、15、22 天静脉内输注 CAMPTOSAR 125mg/m^2 90 分钟，并在第 1、8、15、22 天静脉内浓注输注 LV 20mg/m^2，接着在第 1、8、15、22 天静脉内浓注输注 5-FU，每 6 周一次。 结肠直肠癌联合方案 2：在第 1、15、29 天静脉内输注 CAMPTOSAR 180mg/m^2 90 分钟，并在第 1、2、15、16、29、20 天静脉内输注 LV 200mg/m^2 2 小时，接着在第 1、2、15、16、29、30 天静脉内浓注输注 5-FU 400mg/m^2 和在第 1、2、15、16、29、30 天静脉内输注 5-FU 600mg/m^2 22 小时。 结肠直肠癌单药方案 1：在第 1、8、15、22 天静脉内输注 CAMPTOSAR 125mg/m^2 90 分钟，然后休止 2 周。 结直肠癌单药方案 2：在每 3 周的第 1 天静脉内输注 CAMPTOSAR 350mg/m^2 90 分钟。
拓扑替康	HYCAMTIN 胶囊的推荐剂量为 2.3mg/m^2/天，每天一次，连续 5 天，每 21 天重复。 HYCAMTIN 的推荐剂量为每天 1.5mg/m^2 静脉内输注 30 分钟，连续 5 天，从 21 天疗程的第 1 天开始。在不存在肿瘤进展的情况下，推荐至少 4 个疗程，因为肿瘤反应可能延迟。 肾功能损伤：对中度肾损伤患者（20 至 39mL/min），建议剂量调整至 0.75mg/m^2。

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白消安	**白消安经口施用。***诱导缓解*的常用成人剂量范围为每天总剂量 4 至 8mg。基于体重的剂量对于儿科患者和成人是相同的，大约为每天 60mcg/kg 体重或 1.8mg/m^2 体表面积。 **BUSULFEX® (白消安)注射剂**作为 BuCy 调理方案的成分在骨髓或外周血祖细胞置换之前施用，推荐剂量如下： 常用成人剂量为 0.8mg/kg 理想体重或实际体重中较低者，每六小时施用一次，施用四天（总共 16 剂）。对于肥胖或严重肥胖患者，BUSULFEX 应基于调整的理想体重施用。理想体重（IBW）应计算如下（身高 cm，体重 kg）：IBW（kg；男）=50+0.91×(身高 cm-152)；IBW（kg；女）=45+0.91×(身高 cm-152)。调整的理想体重（AIBW）应计算如下：AIBW =IBW+0.25×(实际体重-IBW)。环磷酰胺作为一小时输注以 60mg/kg 的剂量在两天中的每一天施用，从 BMT 前 3 天开始，不早于第 16 剂 BUSULFEX 后六小时。
美法仑	**美法仑注射剂：** 常用静脉内剂量为 16mg/m^2。药物作为单一输注施用 15 至 20 分钟。ALKERAN 以 2 周时间间隔施用四剂，然后，在从毒性充分恢复后，以 4 周时间间隔施用。基于经大约每周时间间隔所做的血细胞计数，根据需要调节剂量。在 2 至 3 周的治疗后，应中断药物至多 4 周，在该期间应仔细监测血细胞计数。 **美法仑片剂：** **多发性骨髓瘤：**常用口服剂量为每天 6mg（3 片）。 **上皮性卵巢癌：**治疗卵巢癌的一种常用方案是以每天 0.2mg/kg 的剂量施用 ALKERAN，5 天一个疗程。每 4 至 5 周重复疗程，取决于血液学耐受性。
克拉屈滨	**毛细胞白血病：** LEUSTATIN 注射剂的推荐剂量和时间表是通过连续 7 天以 0.09mg/kg/天的剂量连续输注施用作为一个疗程。 **慢性淋巴细胞性白血病：**推荐的治疗由在 28 天周期的第 1 至 5 天以 0.12mg/kg/天（4.8mg/m^2/天）的剂量连续输注 LEUSTATIN 注射剂 2 小时组成。建议 LEUSTATIN 注射剂在有反应的患者中施用至多 6 个月周期而无反应的患者接受不超过 2 个周期的治疗。
长春碱	该制剂仅供静脉内使用。 **成年患者：** 对于成年人，以每周时间间隔的简化和保守剂量递增方法可概述如下： 首次剂量.....3.7mg/m^2 体表面积 二次剂量.....5.5mg/m^2 体表面积 三次剂量.....7.4mg/m^2 体表面积 四次剂量.....9.25mg/m^2 体表面积 五次剂量.....11.1mg/m^2 体表面积 可使用上面提到的增加直至对于成年人达到不超过 18.5mg/m^2 体表面积的最大剂量。 **儿科患者：** 作为用于勒-雪病（组织细胞增多症 X）的单药，硫酸长春碱的初始剂量据报道为

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	6.5mg/m^2。 当与其它化疗剂联合使用硫酸长春碱来治疗霍奇金病时，初始剂量据报道为6mg/m^2。对于睾丸生殖细胞癌，硫酸长春碱在联合方案中的初始剂量据报道为3mg/m^2。 **肾或肝损伤患者** 对于直接血清胆红素值高于 3mg/100mL 的患者，推荐将硫酸长春碱的剂量降低50%。由于代谢和排泄主要在肝，故对于肾功能受损患者不建议修改。
苯丁酸氮芥	常用口服剂量为每天 0.1 至 0.2mg/kg 体重，根据需要施用 3 至 6 周。对于普通患者，这通常等同于成 4 至 10mg 每天。全日剂量可一次施用。 患有**霍奇金病**的患者通常需要 0.2mg/kg 每天，而患有其它**淋巴瘤或慢性淋巴细胞性白血病**的患者通常仅需要 0.1mg/kg 每天。当存在**骨髓的淋巴细胞浸润**时，或当骨髓发育不全时，日剂量应不超过 0.1mg/kg（对于普通患者，约 6mg）。 采用苯丁酸氮芥的间歇性的、两周的或每月一次的脉冲式剂量的**慢性淋巴细胞性白血病**治疗的替代时间表已见报道。苯丁酸氮芥的间歇性时间表从 0.4mg/kg 的初始单剂量开始。剂量一般以 0.1mg/kg 增加，直至观察到淋巴细胞增多的控制或毒性。改变后续剂量以产生轻度血液学毒性。 如果使用维持剂量，则应不超过 0.1mg/kg 每天并也可能低至 0.03mg/kg 每天。典型的维持剂量为 2mg 至 4mg 每天或更少，取决于血细胞计数状态。
他莫昔芬	对于患有**乳腺癌**的患者，推荐的日剂量为 20-40mg。大于 20mg 每天的剂量应以分次剂量施用（早上和晚上）。 **原位导管癌**（DCIS）：推荐剂量为 20mg 每天，施用 5 年。 减少高风险妇女中的乳腺癌发病率：推荐剂量为 20mg 每天，施用 5 年。
放线菌素-D	不用于口服施用 对于成人或儿童，每 2 周周期的剂量强度应不超过静脉内 15mcg/kg/天或400-600mcg/m^2/天，5 天。 **肾母细胞瘤、儿童横纹肌肉瘤和尤因氏肉瘤：**以与其它化疗剂的各种组合和时间表每天静脉内施用 15mcg/kg、施用五天的方案已被用在肾母细胞瘤、横纹肌肉瘤和尤因氏肉瘤的治疗中。 **转移性非精原细胞（Nonseminomatous）睾丸癌：**于第 1 天静脉内施用 1000mcg/m^{2}作为与环磷酰胺、博来霉素、长春碱和顺铂的联合方案的部分。 **妊娠滋养细胞肿瘤：**作为单药每天静脉内施用 12mcg/kg，施用五天。在第 1 和 2 天静脉内施用 500mcg 作为与依托泊苷、氨甲喋呤、亚叶酸、长春新碱、环磷酰胺和顺铂的联合方案的部分。 **在局部复发和局部实体恶性肿瘤中区域性灌注：**一般来说，建议以下剂量： 对于下肢或骨盆，50mcg（0.05mg）每千克体重。

[0512]

	对于上肢，35mcg（0.035mg）每千克体重。 在肥胖患者中或是当已采用在先化疗或放疗时使用较低剂量可能是明智的。
丝裂霉素 C	丝裂霉素仅应静脉内施用。 可以 6 至 8 周时间间隔使用以下剂量时间表：经由功能性静脉导管以单剂量静脉内施用 20mg/m^2。 在丝裂霉素与其它骨髓抑制剂联用时，剂量应相应地调节。如果在两个疗程的丝裂霉素后疾病继续进展，则应停止药物，因为反应的可能性极低。
维拉帕米	**盐酸维拉帕米延释片：** 用早上施用的 180mg 盐酸维拉帕米延释片开始治疗。在可能对维拉帕米有更强反应的患者（例如，老人和小孩）中，120mg 一天的较低初始剂量可能是保险的。 如果使用 180mg 盐酸维拉帕米延释片未获得足够的反应，则可以以如下方式向上滴定剂量： 1. 每个早上 240mg， 2. 每个早上 180mg 加每个晚上 180mg；或每个早上 240mg 加每个晚上 120mg， 3. 每 12 小时 240mg。 **盐酸维拉帕米-注射剂：** 推荐的维拉帕米静脉内剂量如下： **成人：** 初始剂量：5 至 10mg（0.075 至 0.15mg/kg 体重），以静脉浓注施用至少 2 分钟。 重复剂量：如果初始反应不够，则在首次剂量后 30 分钟施用 10mg（0.15mg/kg 体重）。后续静脉内剂量的最佳时间间隔尚未确定，且应针对每个患者个体化。 老年患者：剂量应施用至少 3 分钟以最大限度地减小不良药物反应的风险。 **儿科：** 初始剂量： 0-1 岁：0.1 至 0.2mg/kg 体重（常用单剂量范围 0.75 至 2mg）应在持续 ECG 监控下静脉浓注施用至少 2 分钟。 1-15 岁：0.1 至 0.3mg/kg 体重（常用单剂量范围 2 至 5mg）应作为静脉内浓注施用至少 2 分钟。不超过 5mg。 重复剂量： 0-1 岁：如果初始反应不够，则在首次剂量后 30 分钟施用 0.1 至 0.2mg/kg 体重（常用单剂量范围 0.75 至 2mg）（在持续 ECG 监控下）。 1-15 岁：如果初始反应不够，则在初始剂量后 30 分钟施用 0.1 至 0.3mg/kg 体重（常用单剂量范围 2 至 5mg）。作为单剂量，不超过 10mg。
鬼臼毒素	每天早上和晚上施用两次（每 12 小时），连续 3 天，然后连续 4 天撤药。可重复

[0513]

	该一周周期的治疗至多四次，直至无可见疾组织。

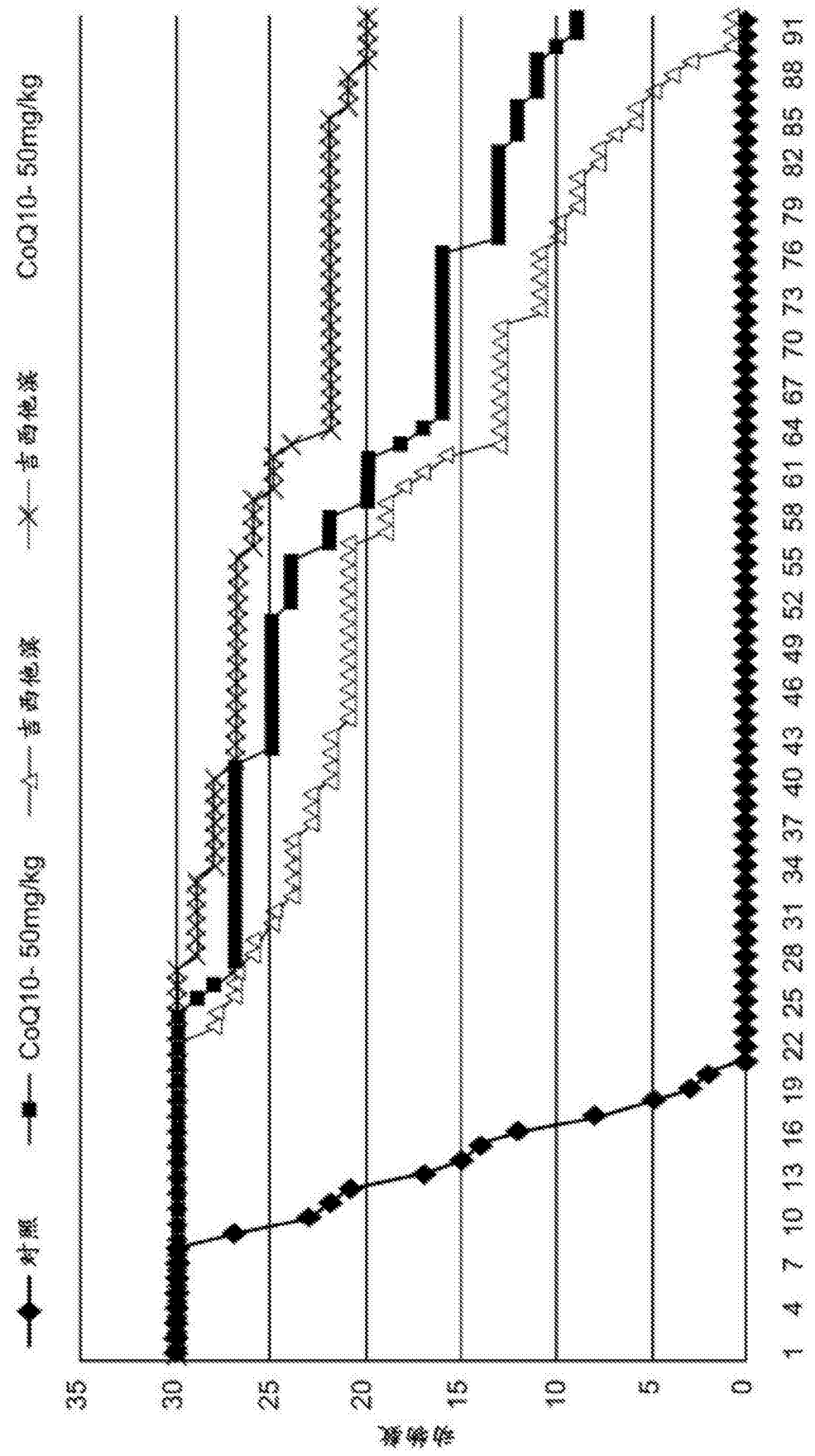

对照
CoQ10- 50mg/kg
吉西他滨
CoQ10- 50mg/kg
吉西他滨
0
5
10
15
20
25
30
35
1 4 7 10 13 16 19 22 25 28 31 34 37 40 43 46 49 52 55 58 61 64 67 70 73 76 79 82 85 88 91

图 1

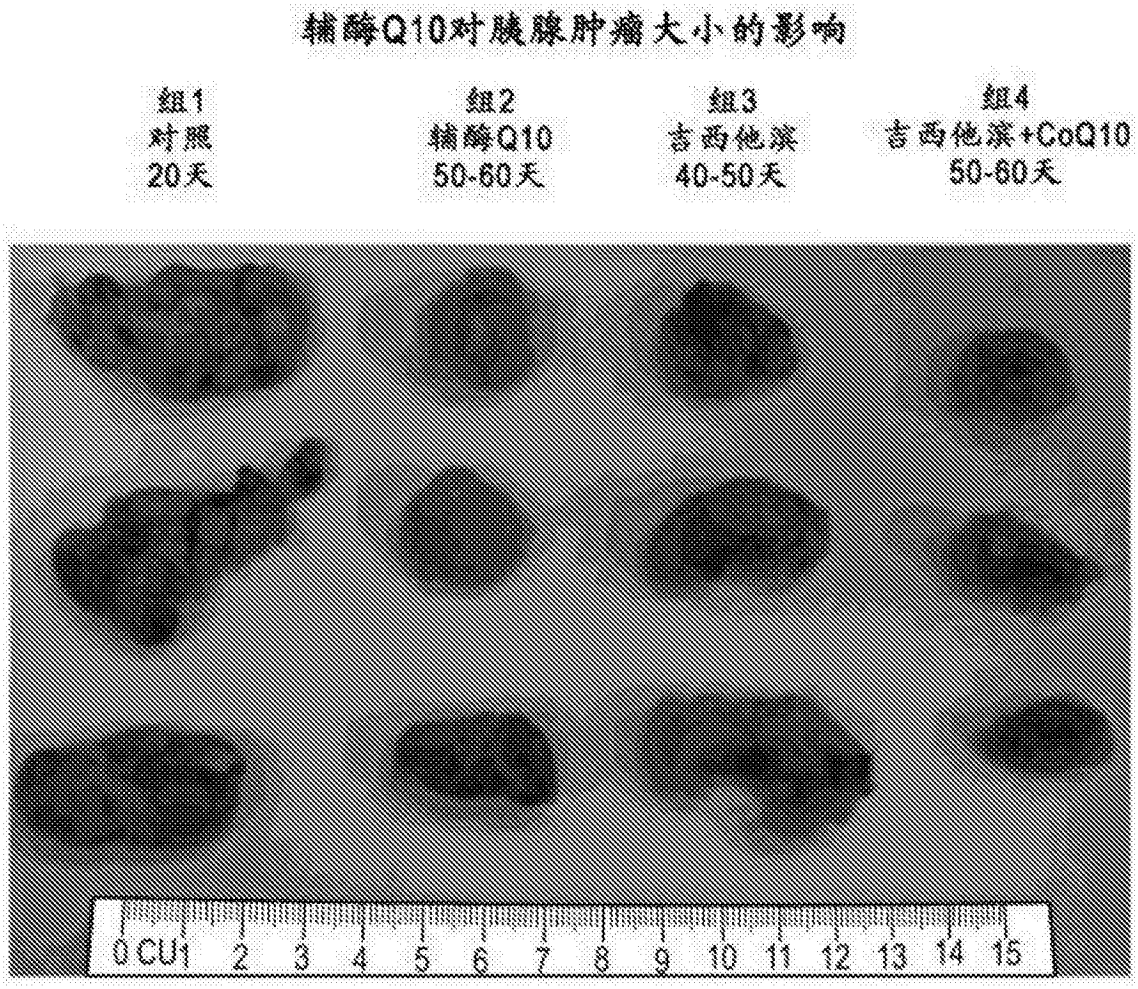

辅酶Q10对胰腺肿瘤大小的影响
组1
对照
20天
组2
辅酶Q10
50-60天
组3
吉西他滨
40-50天
组4
吉西他滨+CoQ10
50-60天
0 CU1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

图 2

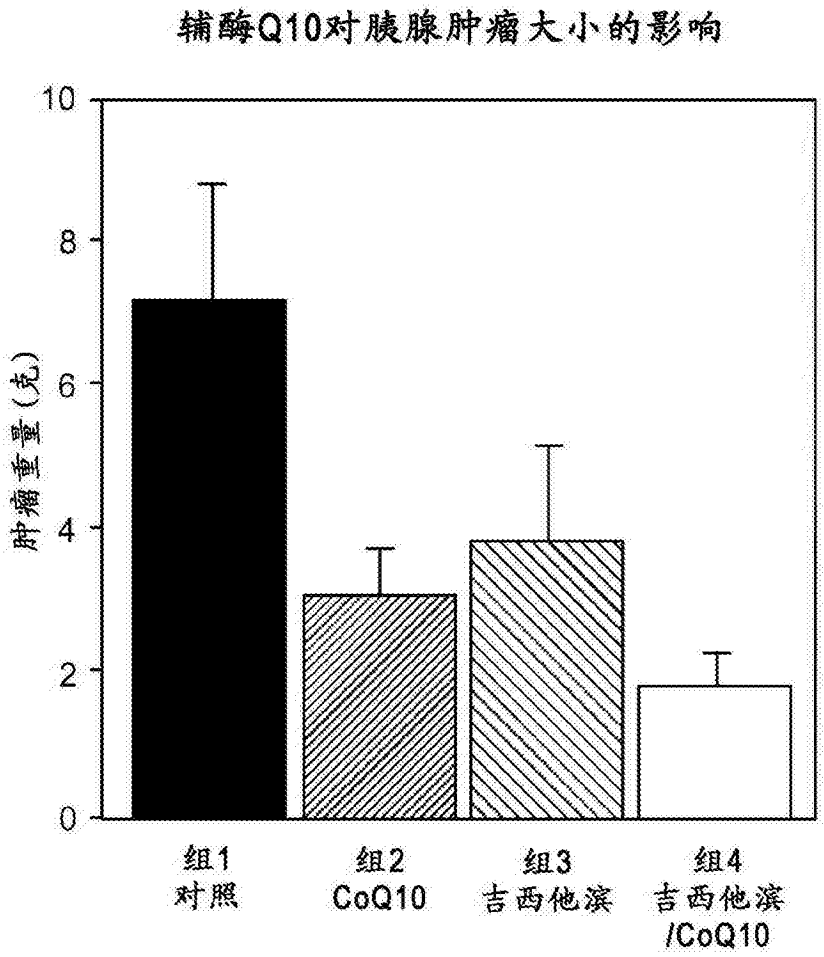

辅酶Q10对胰腺肿瘤大小的影响
肿瘤重量(克)
10
8
6
4
2
0
组1
对照
组2
CoQ10
组3
吉西他滨
组4
吉西他滨
/CoQ10

图 3

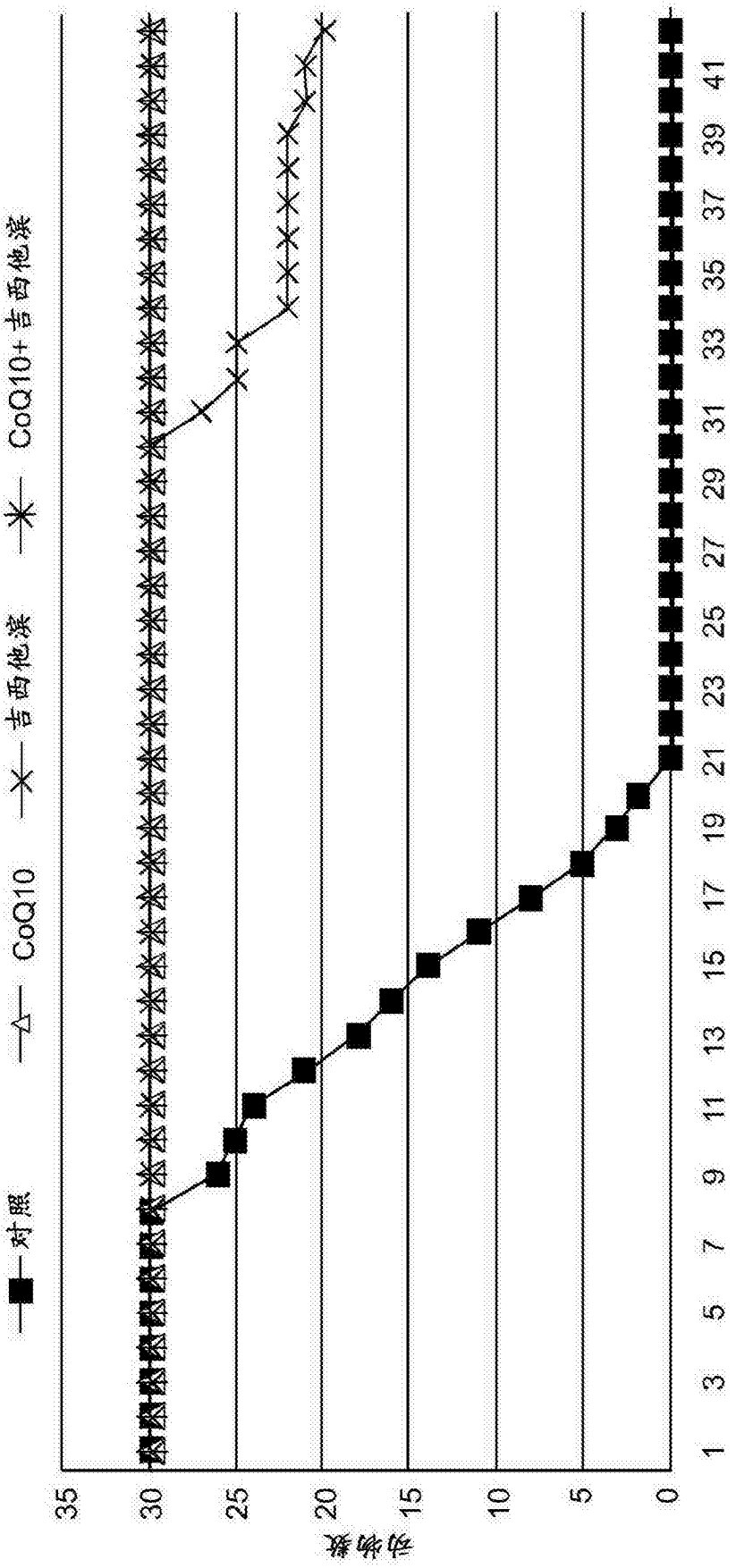

对照
CoQ10
吉西他滨
CoQ10+吉西他滨
动物数
0
5
10
15
20
25
30
35
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
41

图 4

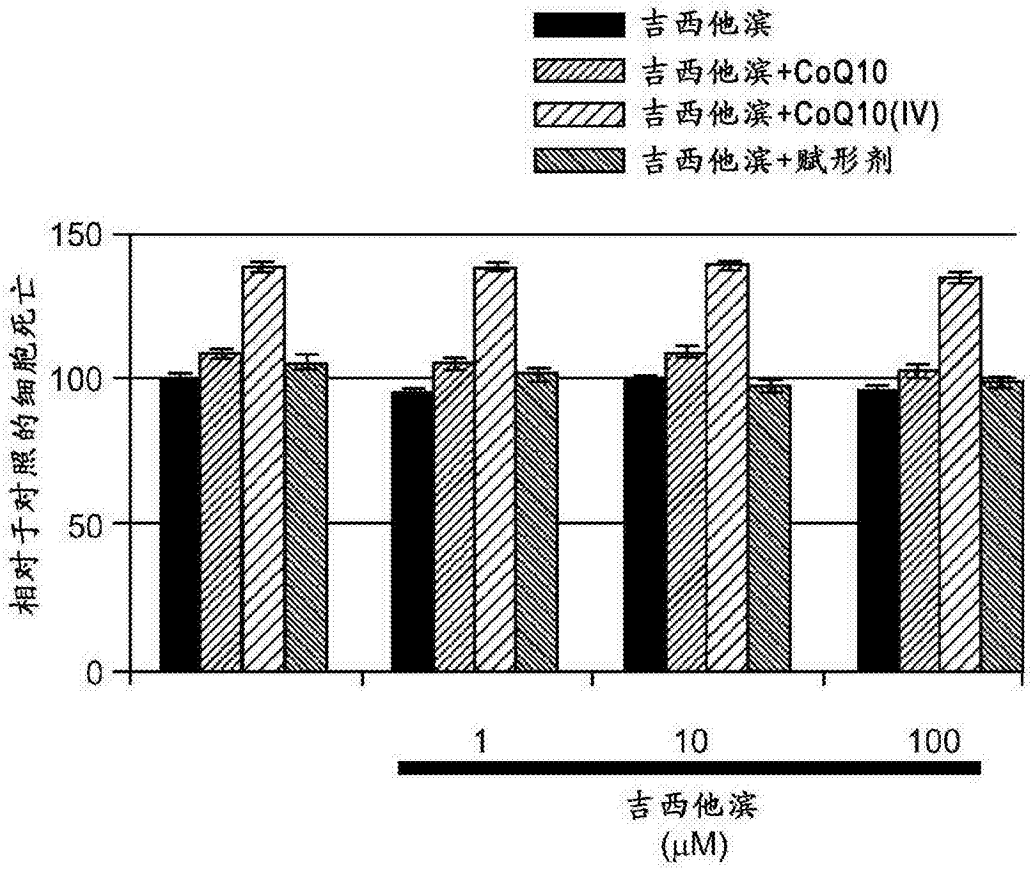

吉西他滨
吉西他滨+CoQ10
吉西他滨+CoQ10(IV)
吉西他滨+赋形剂
相对于对照的细胞死亡
150
100
50
0
1
10
100
吉西他滨
(μM)

图 5A

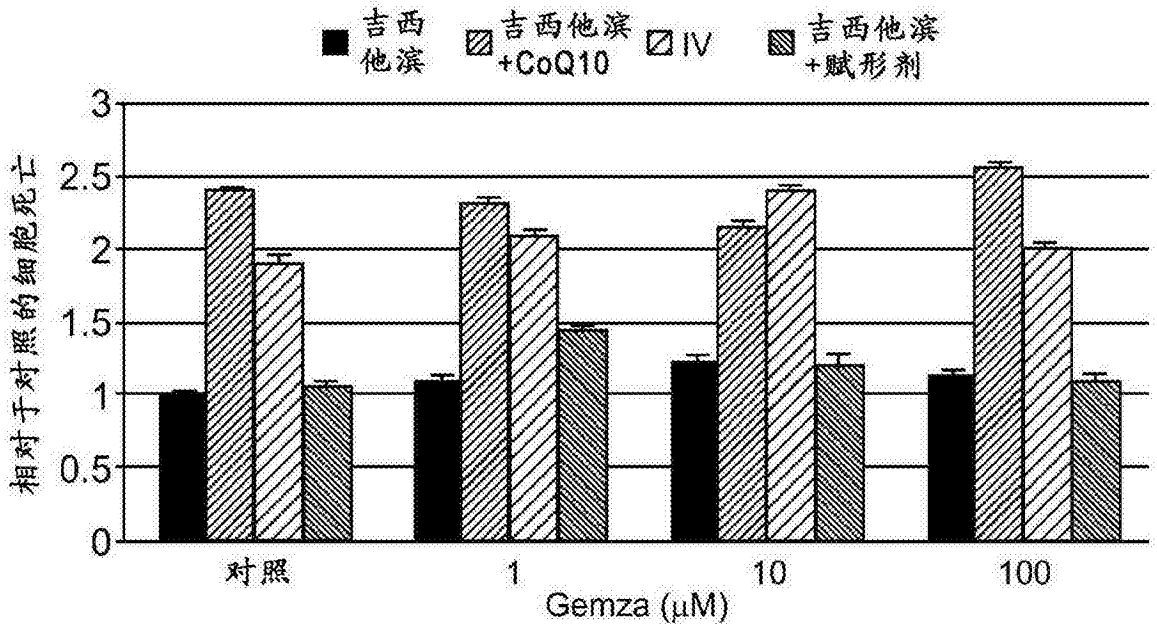

吉西他滨
吉西他滨+CoQ10
IV
吉西他滨+赋形剂
相对于对照的细胞死亡
3
2.5
2
1.5
1
0.5
0
对照
1
10
100
Gemza (μM)

图 5B

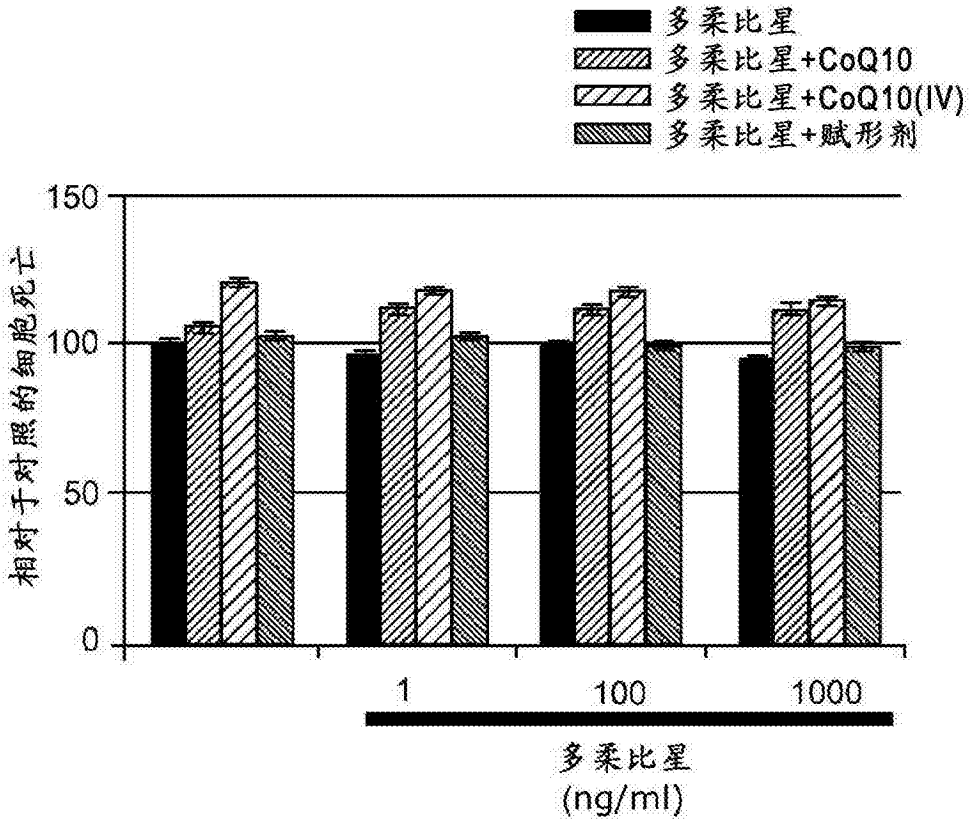

多柔比星
多柔比星+CoQ10
多柔比星+CoQ10(IV)
多柔比星+赋形剂
相对于对照的细胞死亡
150
100
50
0
1
100
1000
多柔比星
(ng/ml)

图 6A

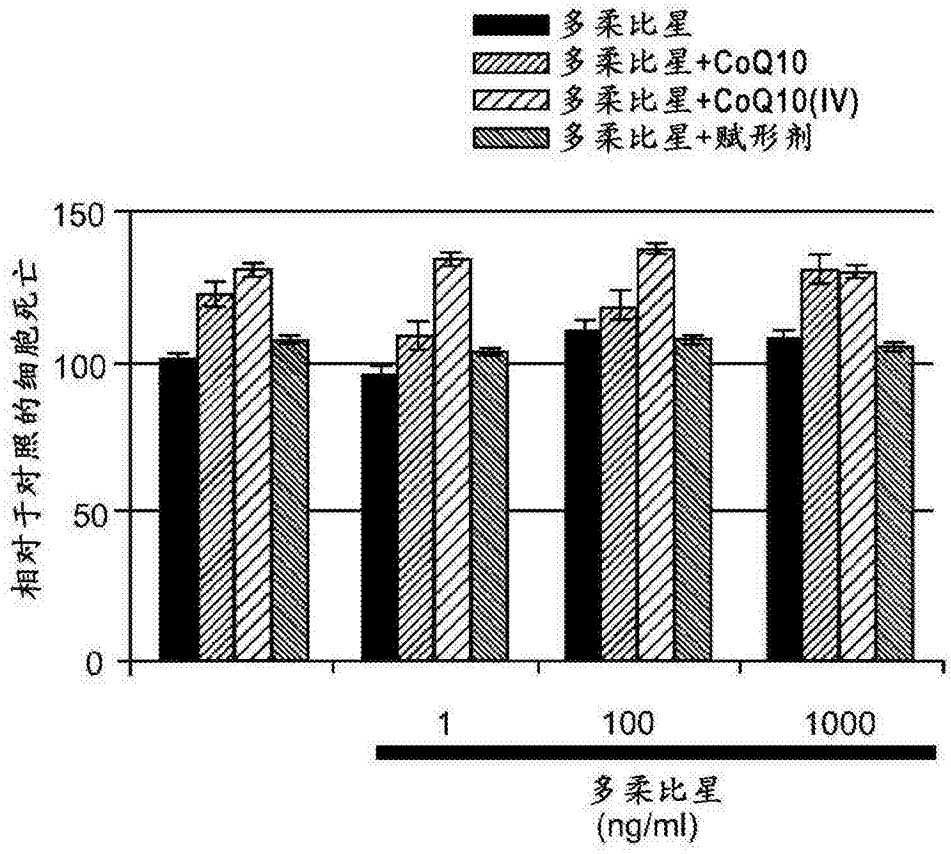

多柔比星
多柔比星+CoQ10
多柔比星+CoQ10(IV)
多柔比星+赋形剂
相对于对照的细胞死亡
150
100
50
0
1
100
1000
多柔比星
(ng/ml)

图 6B

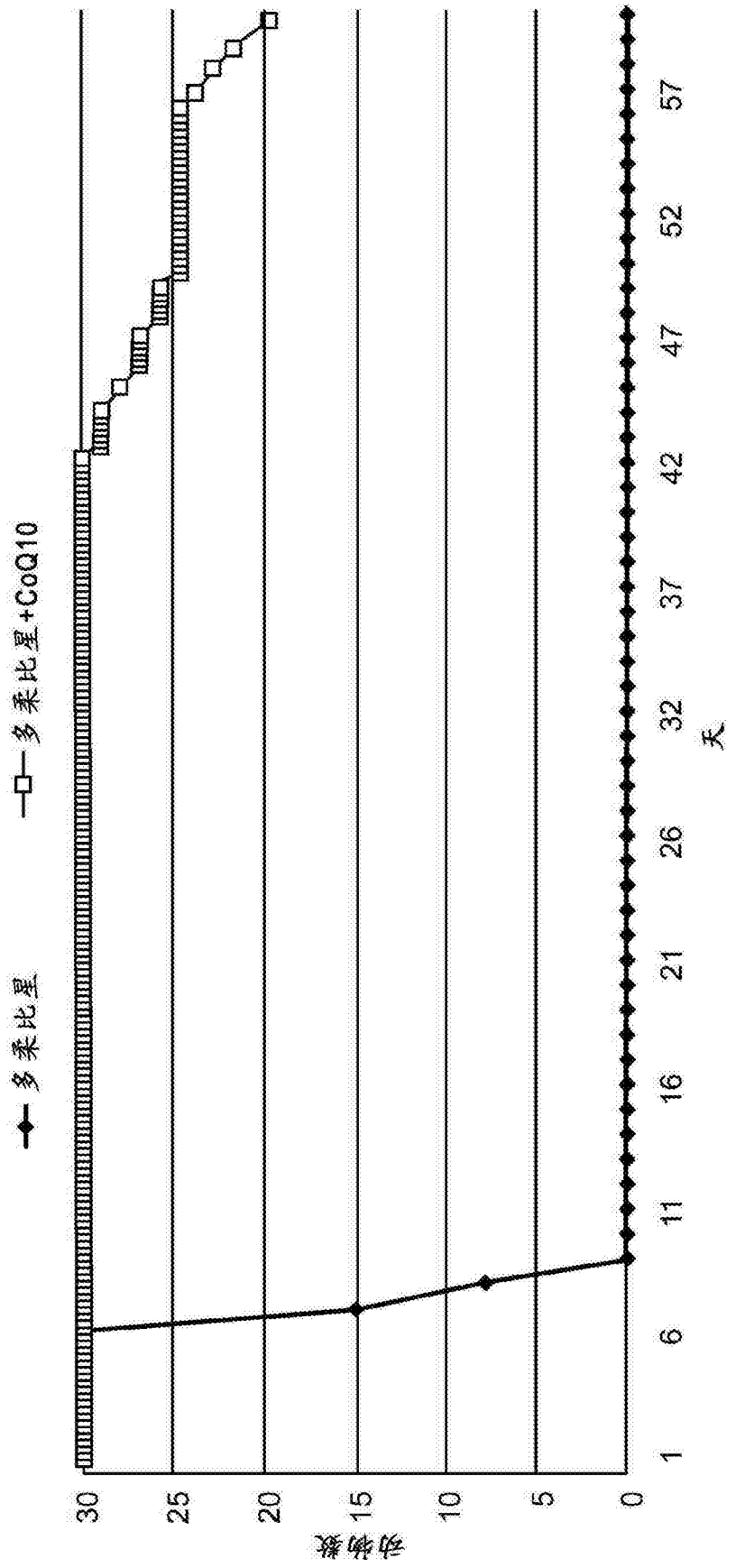

多柔比星
多柔比星+CoQ10
动物数
天
0
5
10
15
20
25
30
1
6
11
16
21
26
32
37
42
47
52
57

图 7

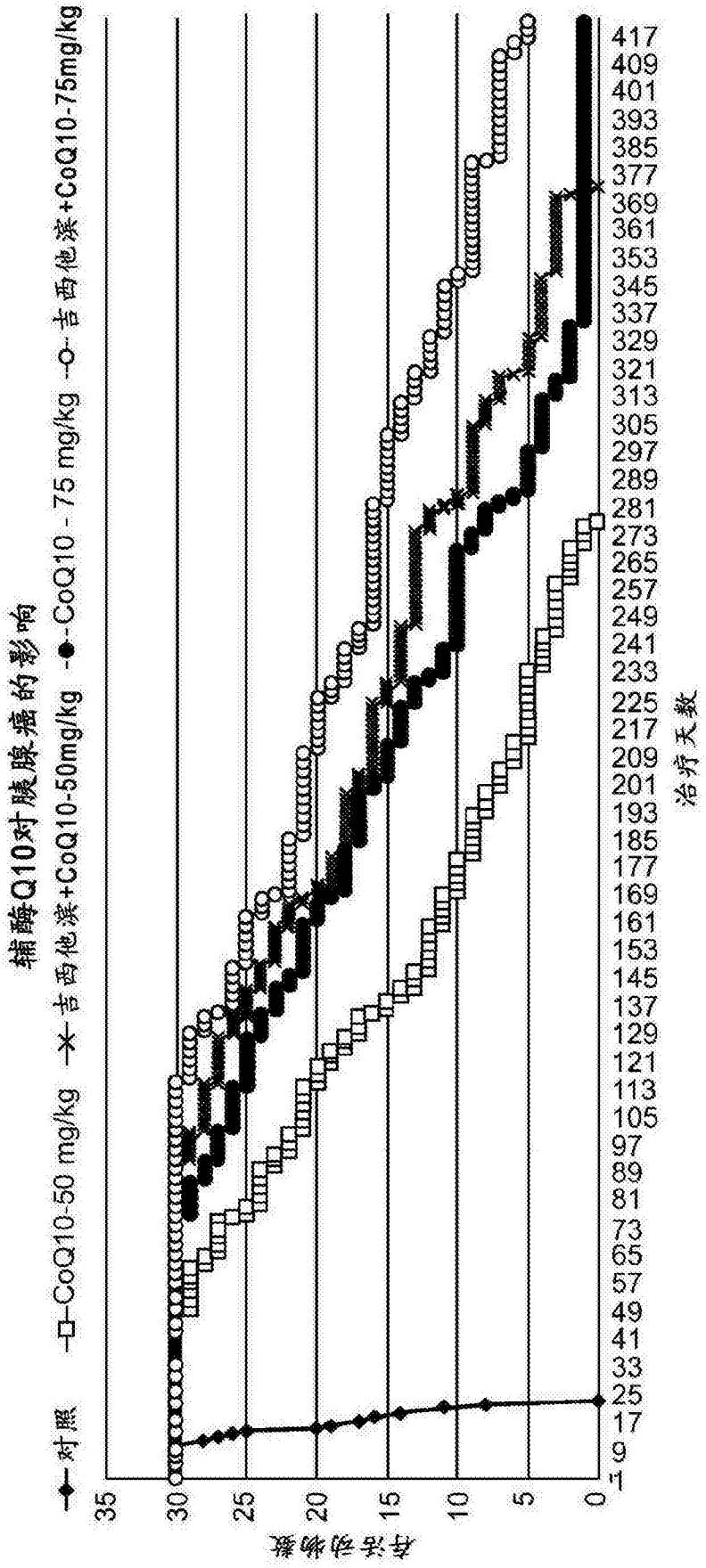

辅酶Q10对胰腺癌的影响
对照
CoQ10-50 mg/kg
吉西他滨+CoQ10-50mg/kg
CoQ10 - 75 mg/kg
吉西他滨+CoQ10-75mg/kg
存活动物数
治疗天数
35
30
25
20
15
10
5
0
417
409
401
393
385
377
369
361
353
345
337
329
321
313
305
297
289
281
273
265
257
249
241
233
225
217
209
201
193
185
177
169
161
153
145
137
129
121
113
105
97
89
81
73
65
57
49
41
33
25
17
9
1

图 8

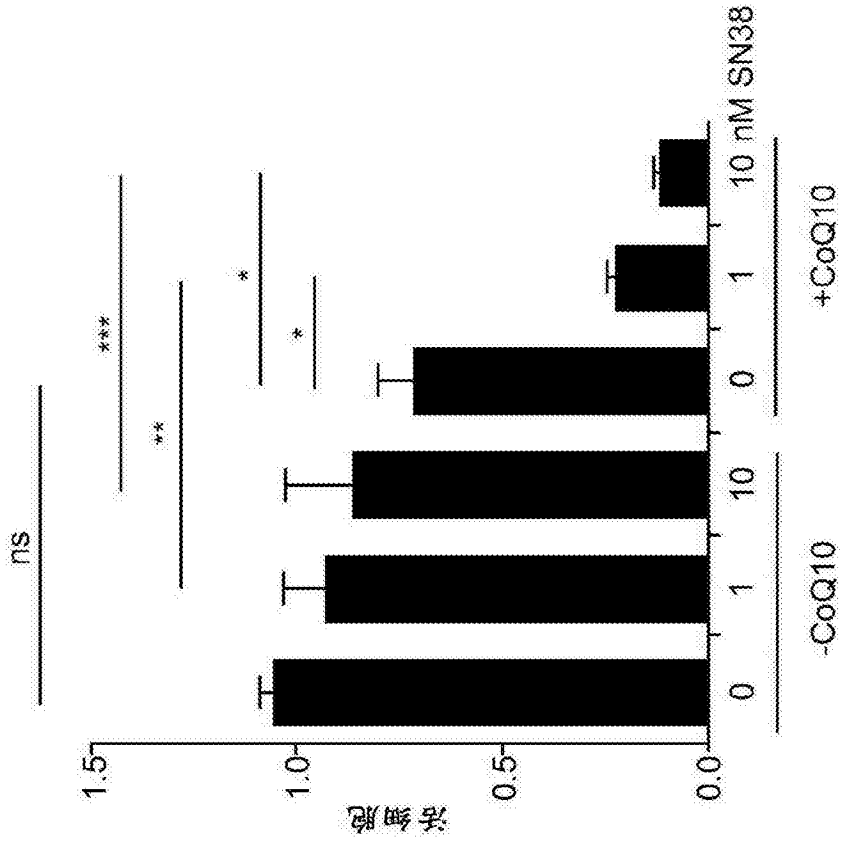


图 9A

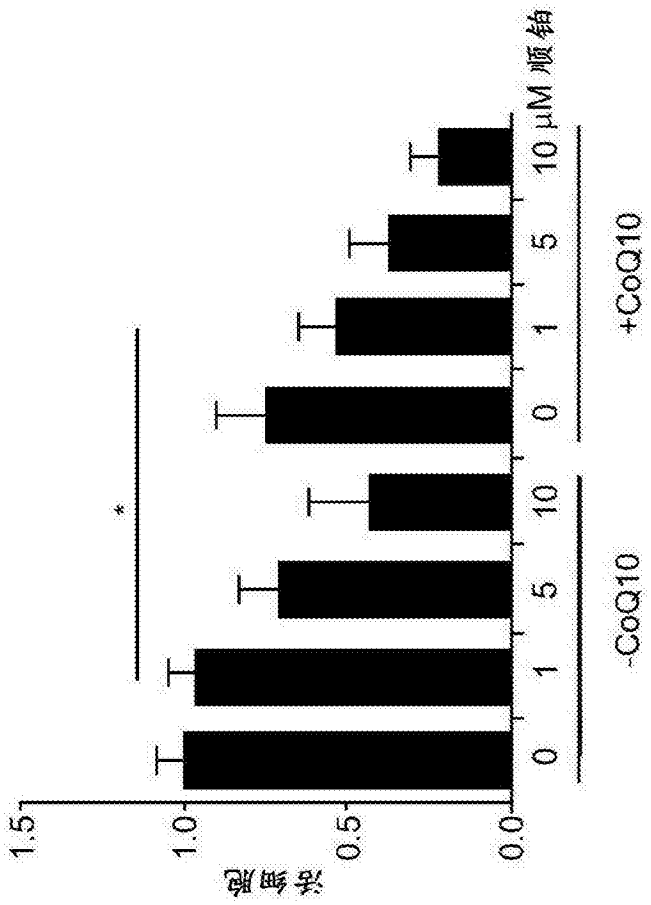


图 9B

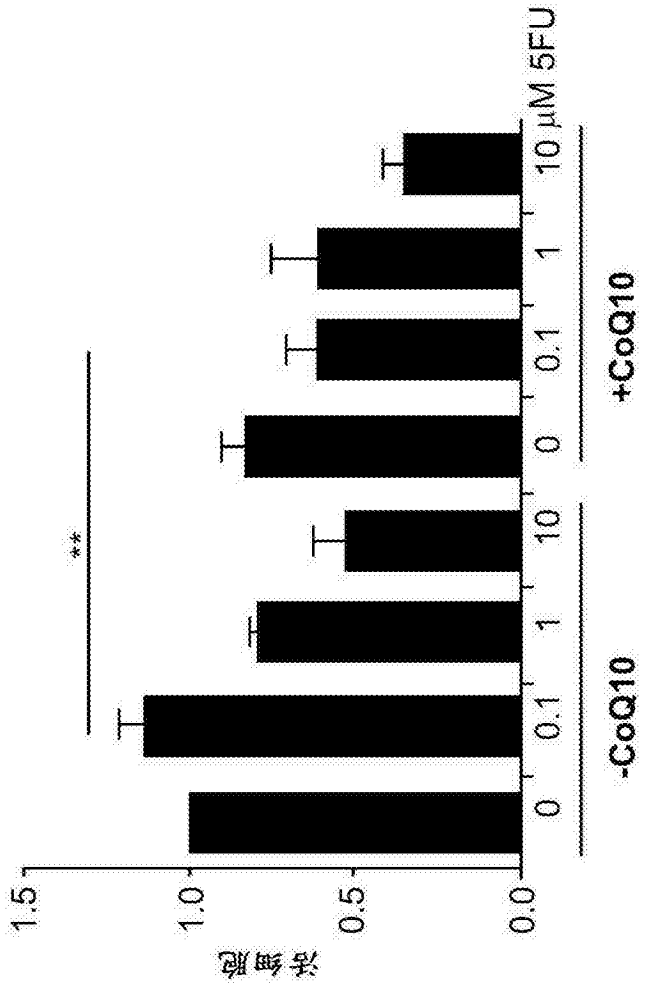


图 9C

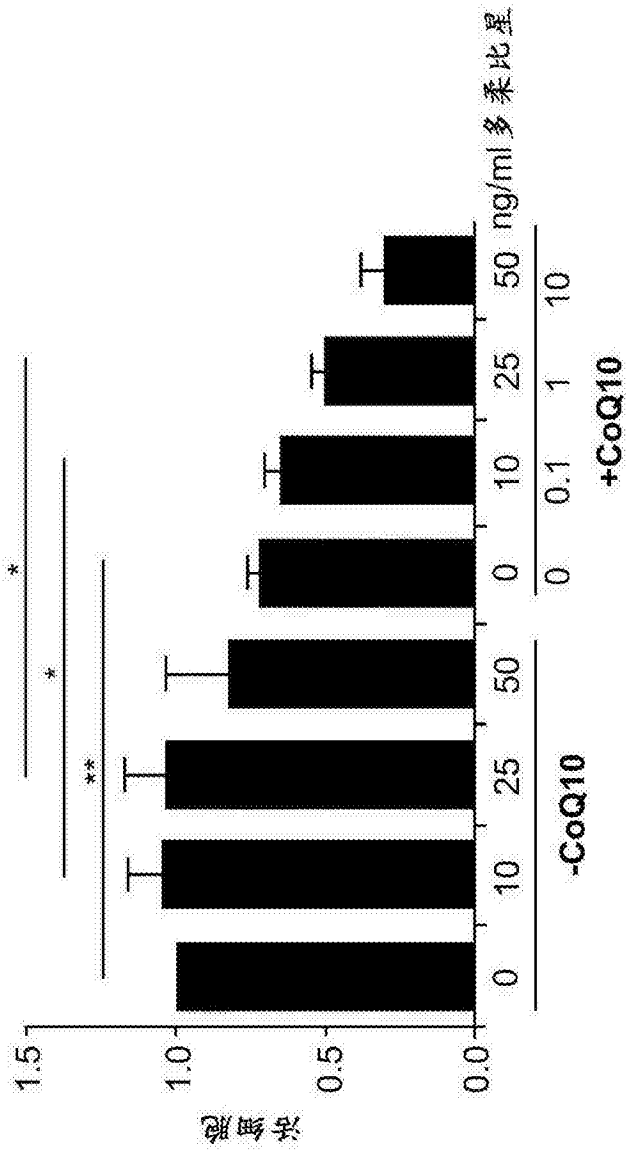


图 10

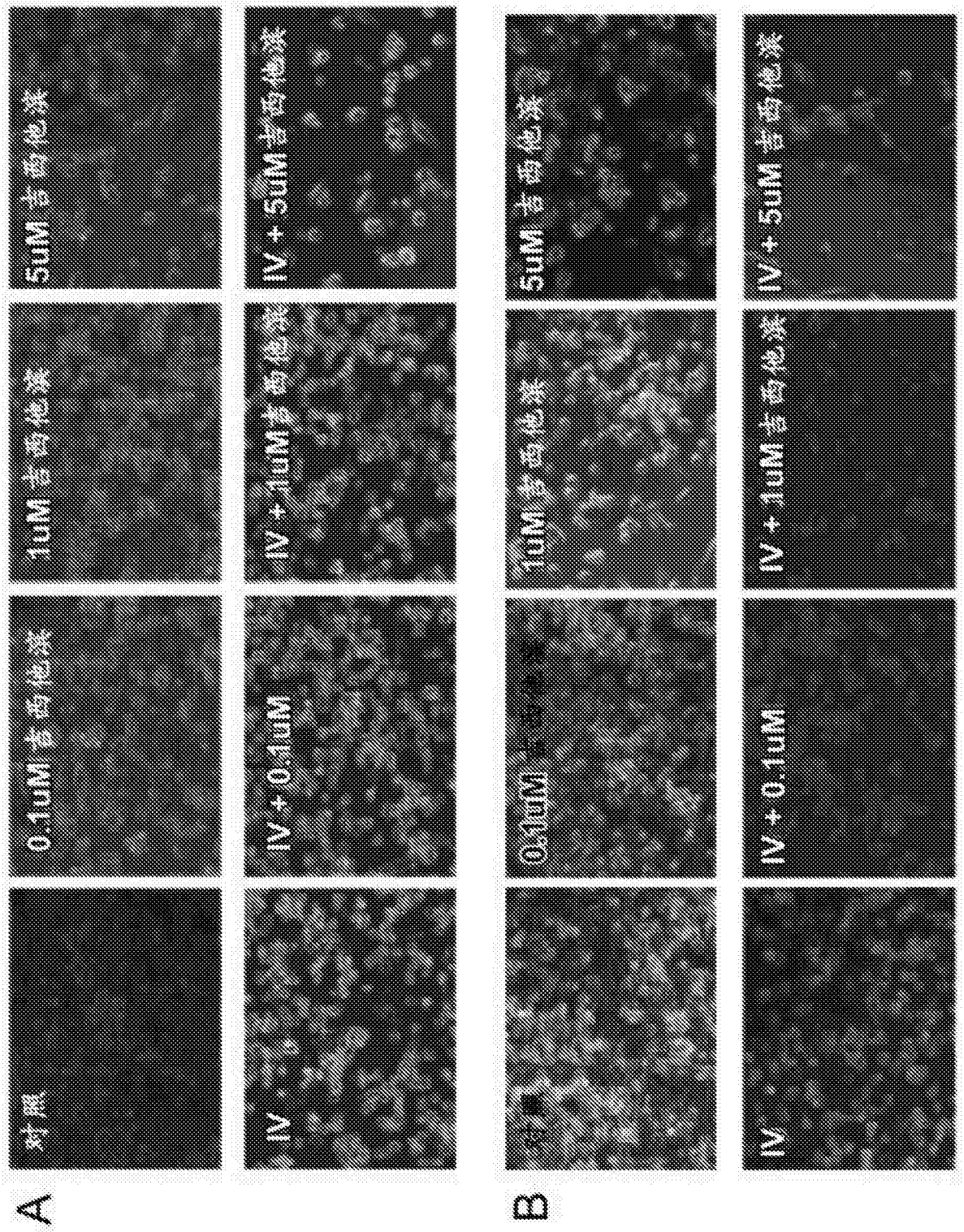

A
对照
0.1uM卡奇霉素
1uM卡奇霉素
5uM卡奇霉素
IV
IV + 0.1uM
IV + 1uM卡奇霉素
IV + 5uM卡奇霉素
B
对照
0.1uM
10uM卡奇霉素
5uM卡奇霉素
IV
IV + 0.1uM
IV + 1uM卡奇霉素
IV + 5uM卡奇霉素

图 11

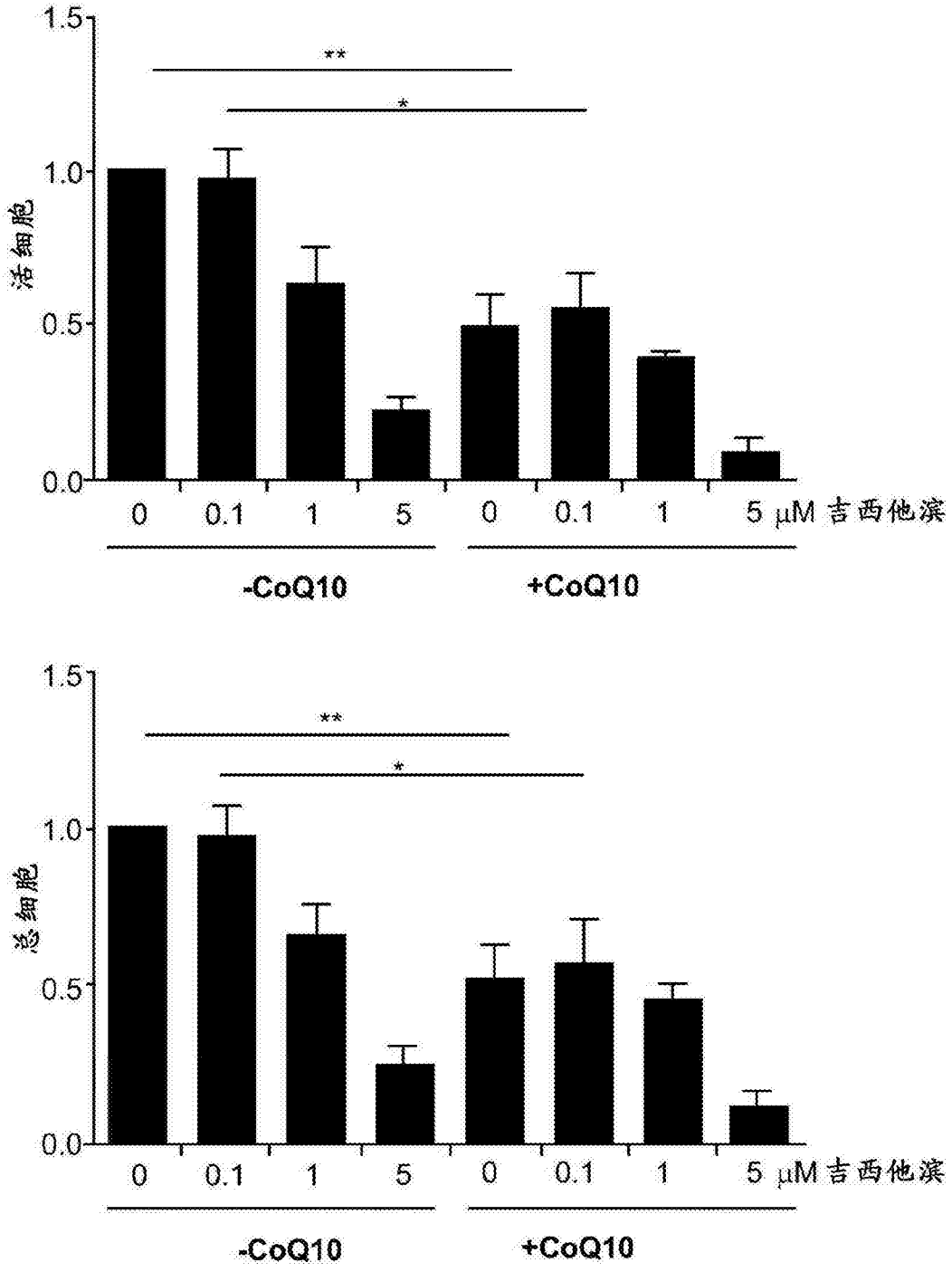

1.5
1.0
0.5
0.0
活细胞
**
*
0
0.1
1
5
0
0.1
1
5 μM 吉西他滨
-CoQ10
+CoQ10
1.5
1.0
0.5
0.0
总细胞
**
*
0
0.1
1
5
0
0.1
1
5 μM 吉西他滨
-CoQ10
+CoQ10

图 12A

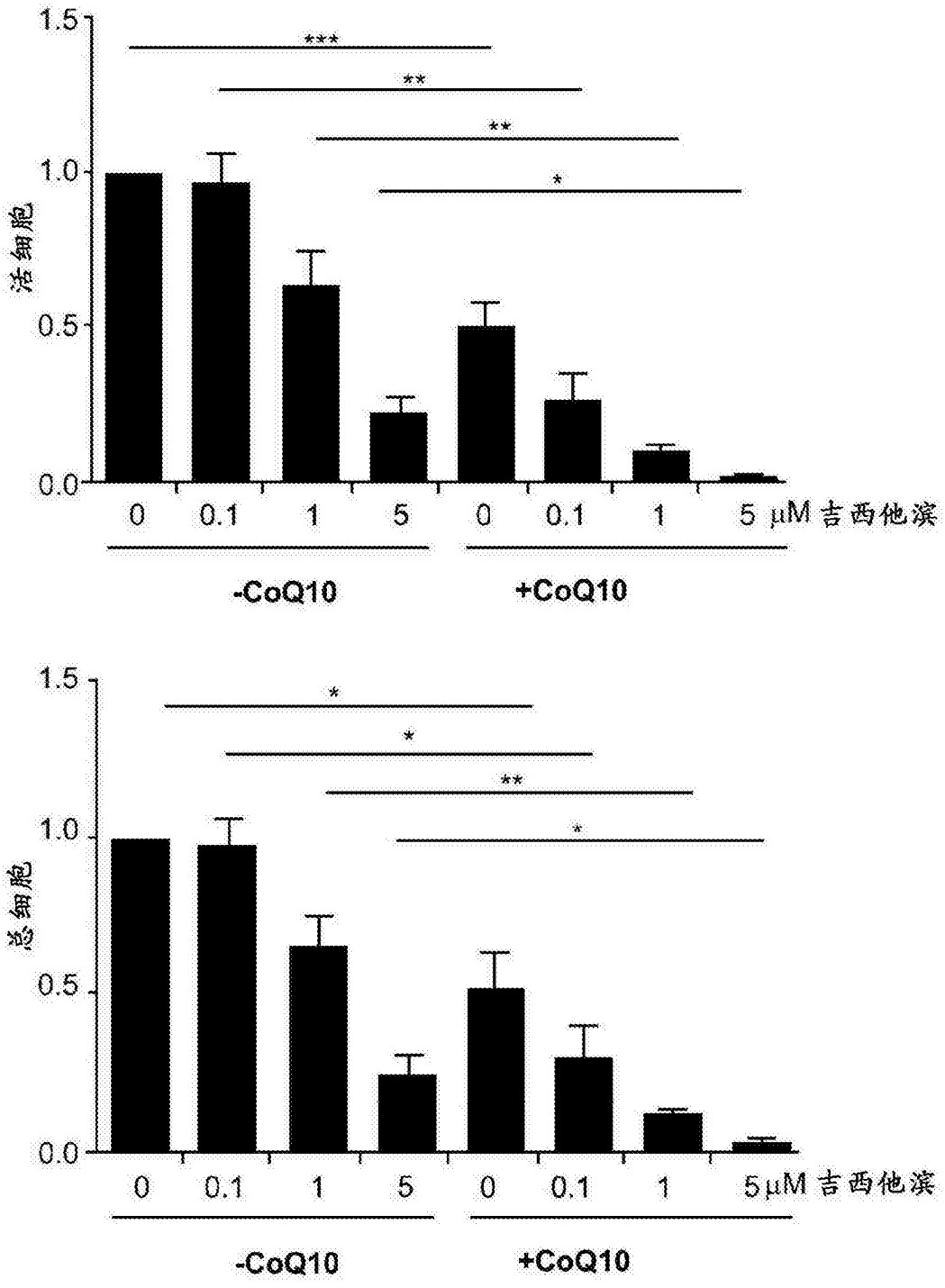

1.5
1.0
0.5
0.0
活细胞
***
**
**
*
0
0.1
1
5
0
0.1
1
5 μM 吉西他滨
-CoQ10
+CoQ10
1.5
1.0
0.5
0.0
总细胞
*
*
**
*
0
0.1
1
5
0
0.1
1
5μM 吉西他滨
-CoQ10
+CoQ10

图 12B

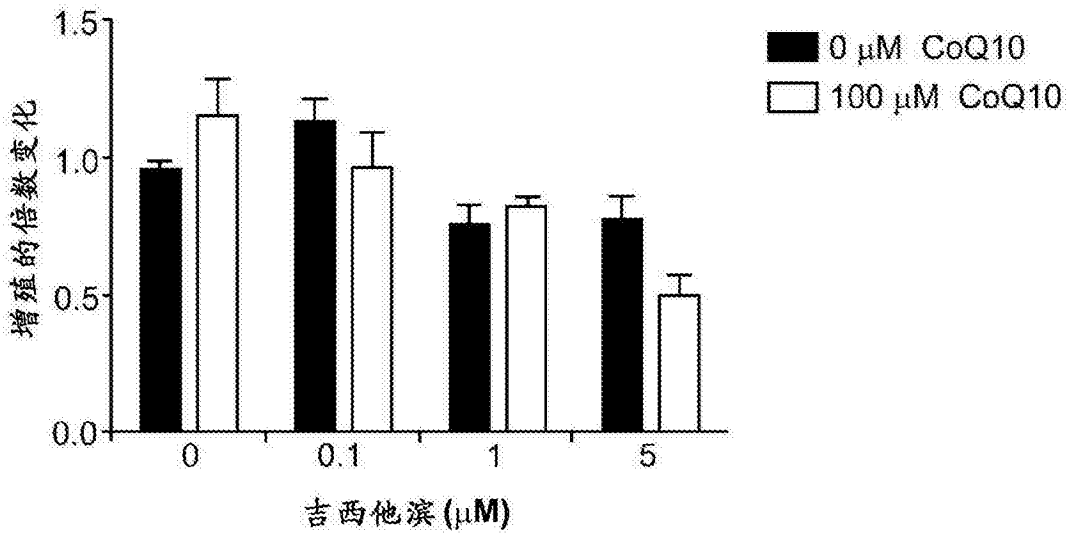

1.5
1.0
0.5
0.0
增殖的倍数变化
0 μM CoQ10
100 μM CoQ10
0
0.1
1
5
吉西他滨 (μM)

图 13

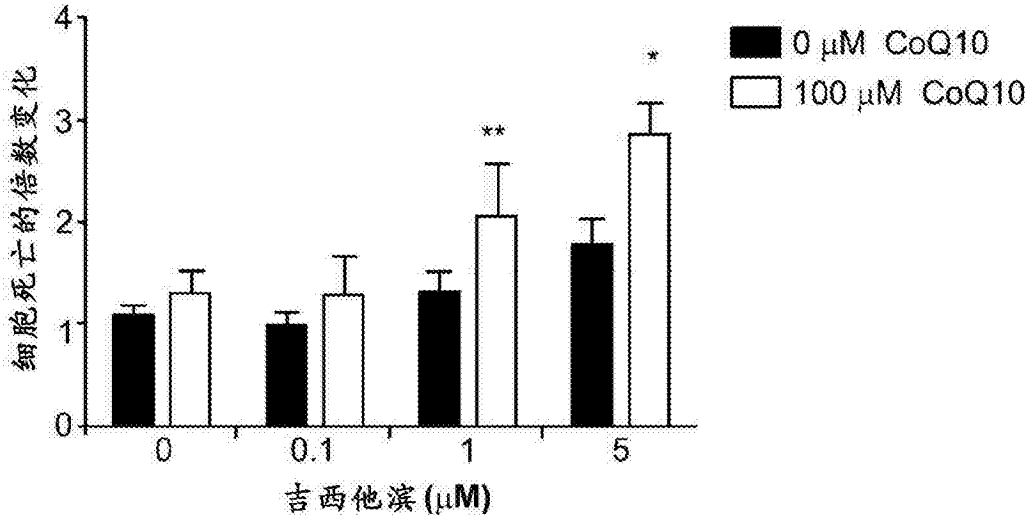

4
3
2
1
0
细胞死亡的倍数变化
0 μM CoQ10
100 μM CoQ10
**
*
0
0.1
1
5
吉西他滨 (μM)

图 14

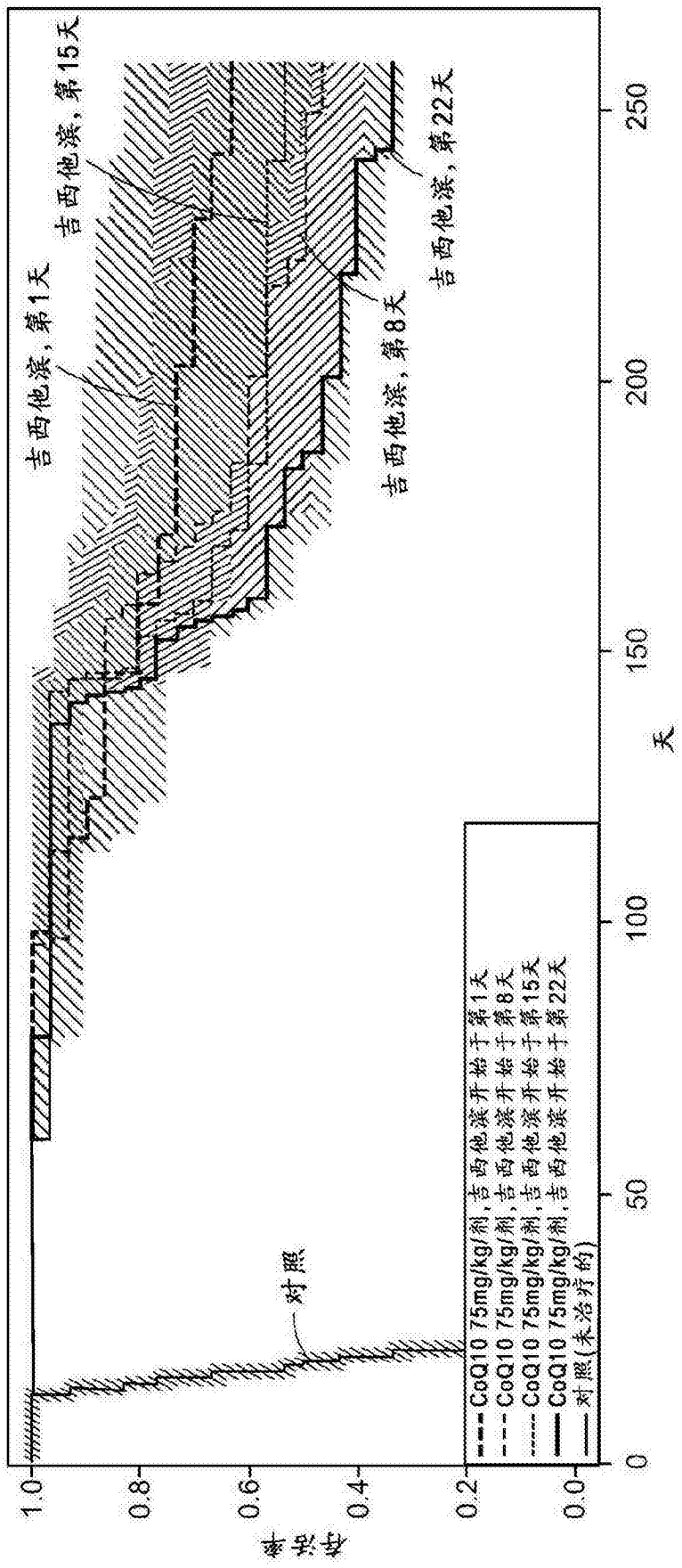

吉西他滨，第1天
吉西他滨，第15天
吉西他滨，第8天
吉西他滨，第22天
对照
CoQ10 75mg/kg/剂，吉西他滨开始于第1天
CoQ10 75mg/kg/剂，吉西他滨开始于第8天
CoQ10 75mg/kg/剂，吉西他滨开始于第15天
CoQ10 75mg/kg/剂，吉西他滨开始于第22天
对照(未治疗的)
存活率
天
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
200
250

图 15

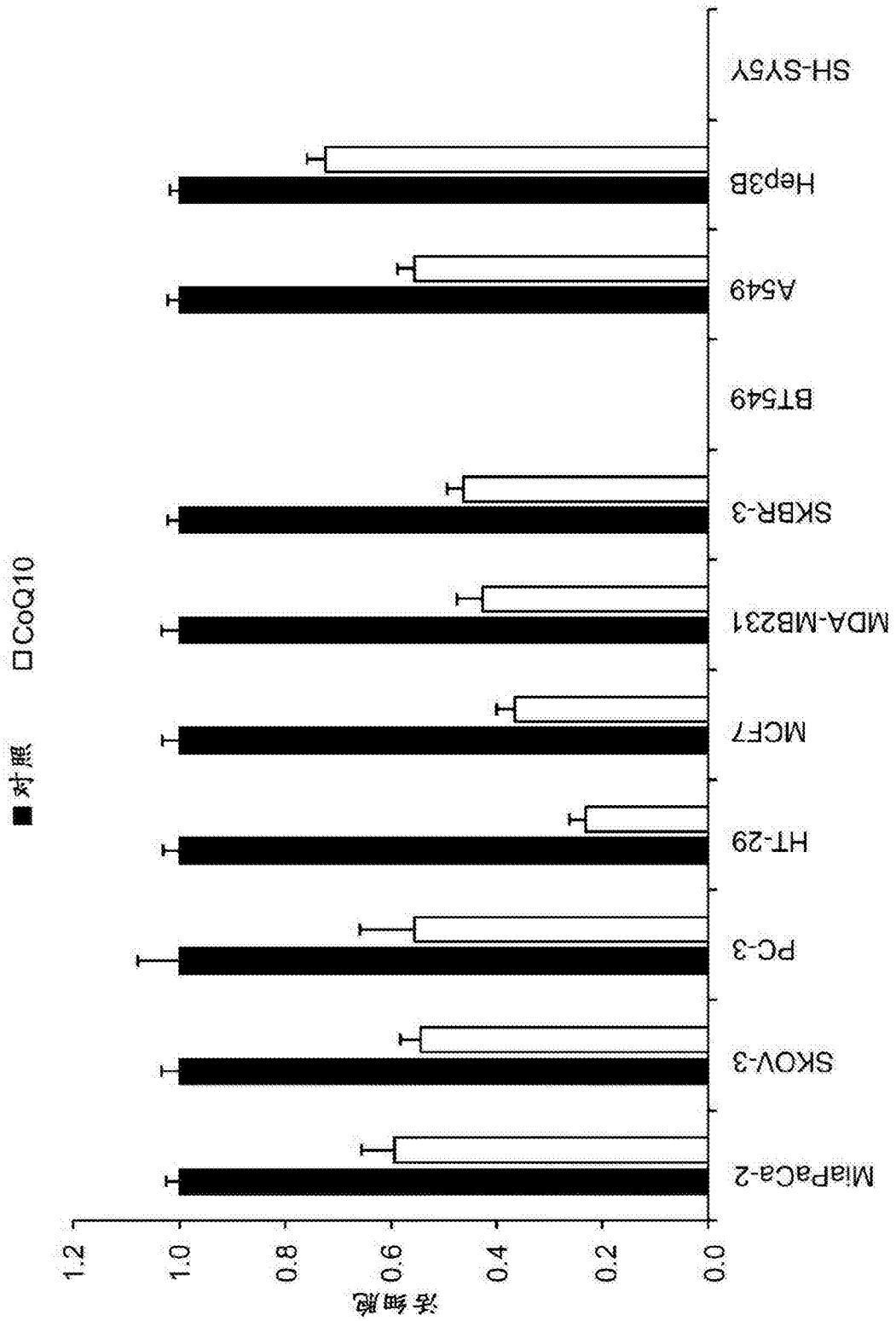

SH-SY5Y
Hep3B
A549
BT549
SKBR-3
MDA-MB231
MCF7
HT-29
PC-3
SKOV-3
MiaPaCa-2
1.2
1.0
0.8
0.6
0.4
0.2
0.0
活细胞
■对照 □CoQ10

图 16

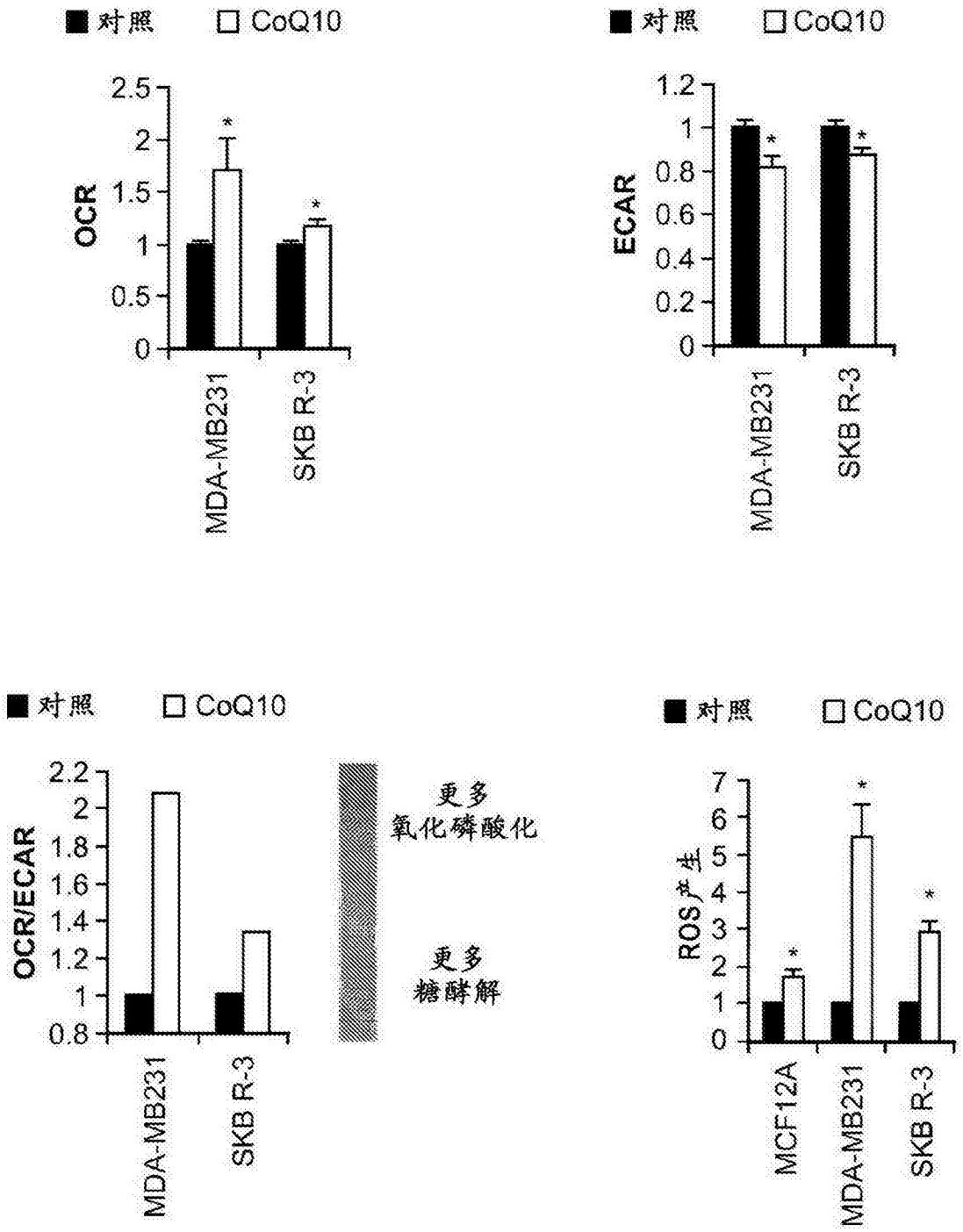

对照
CoQ10
OCR
2.5
2
1.5
1
0.5
0
MDA-MB231
SKB R-3
对照
CoQ10
ECAR
1.2
1
0.8
0.6
0.4
0.2
0
MDA-MB231
SKB R-3
对照
CoQ10
OCR/ECAR
2.2
2
1.8
1.6
1.4
1.2
1
0.8
MDA-MB231
SKB R-3
更多
氧化磷酸化
更多
糖酵解
对照
CoQ10
ROS产生
7
6
5
4
3
2
1
0
MCF12A
MDA-MB231
SKB R-3

图 17

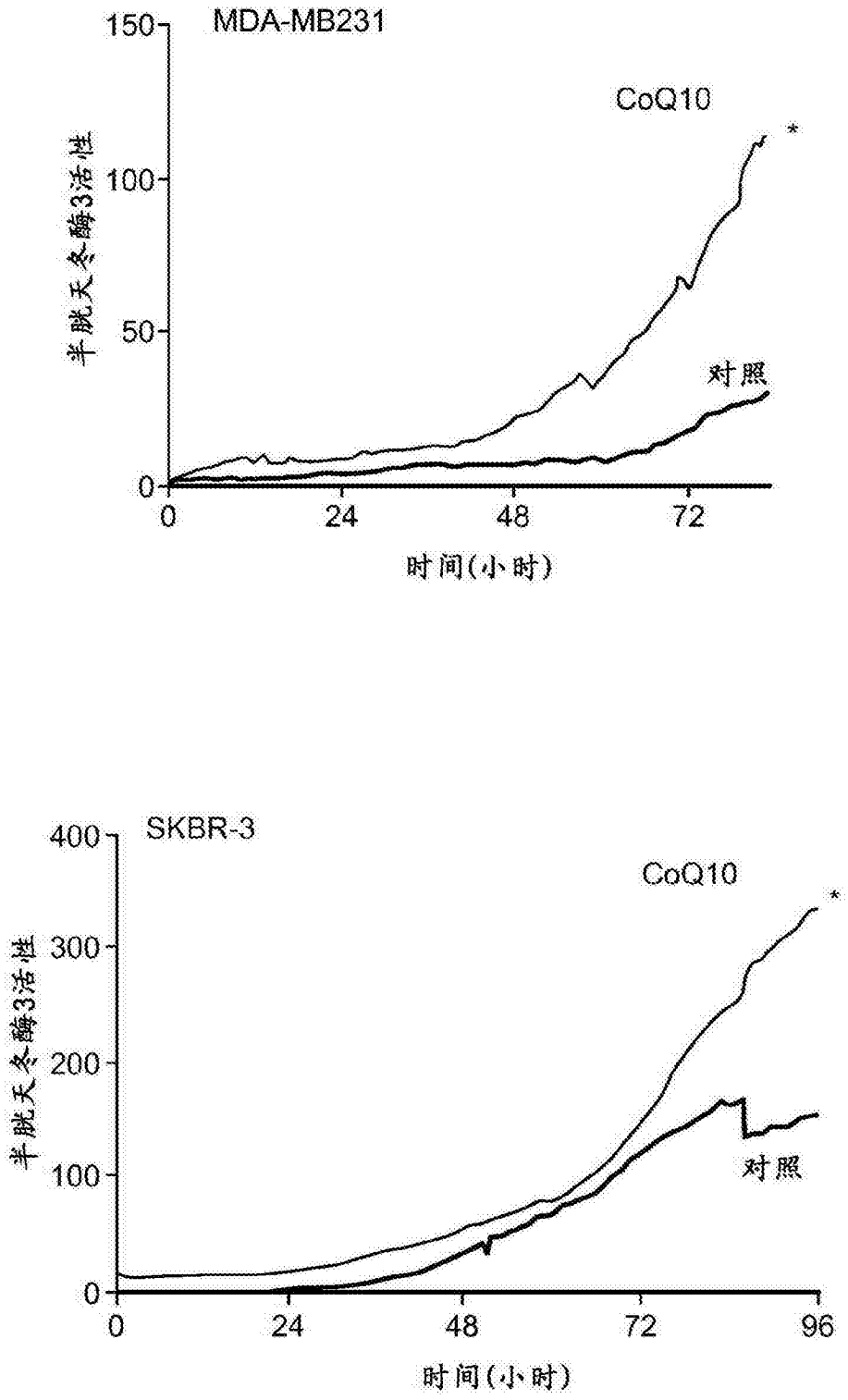

MDA-MB231
CoQ10
*
对照
半胱天冬酶3活性
150
100
50
0
0
24
48
72
时间(小时)
SKBR-3
CoQ10
*
对照
半胱天冬酶3活性
400
300
200
100
0
0
24
48
72
96
时间(小时)

图 18

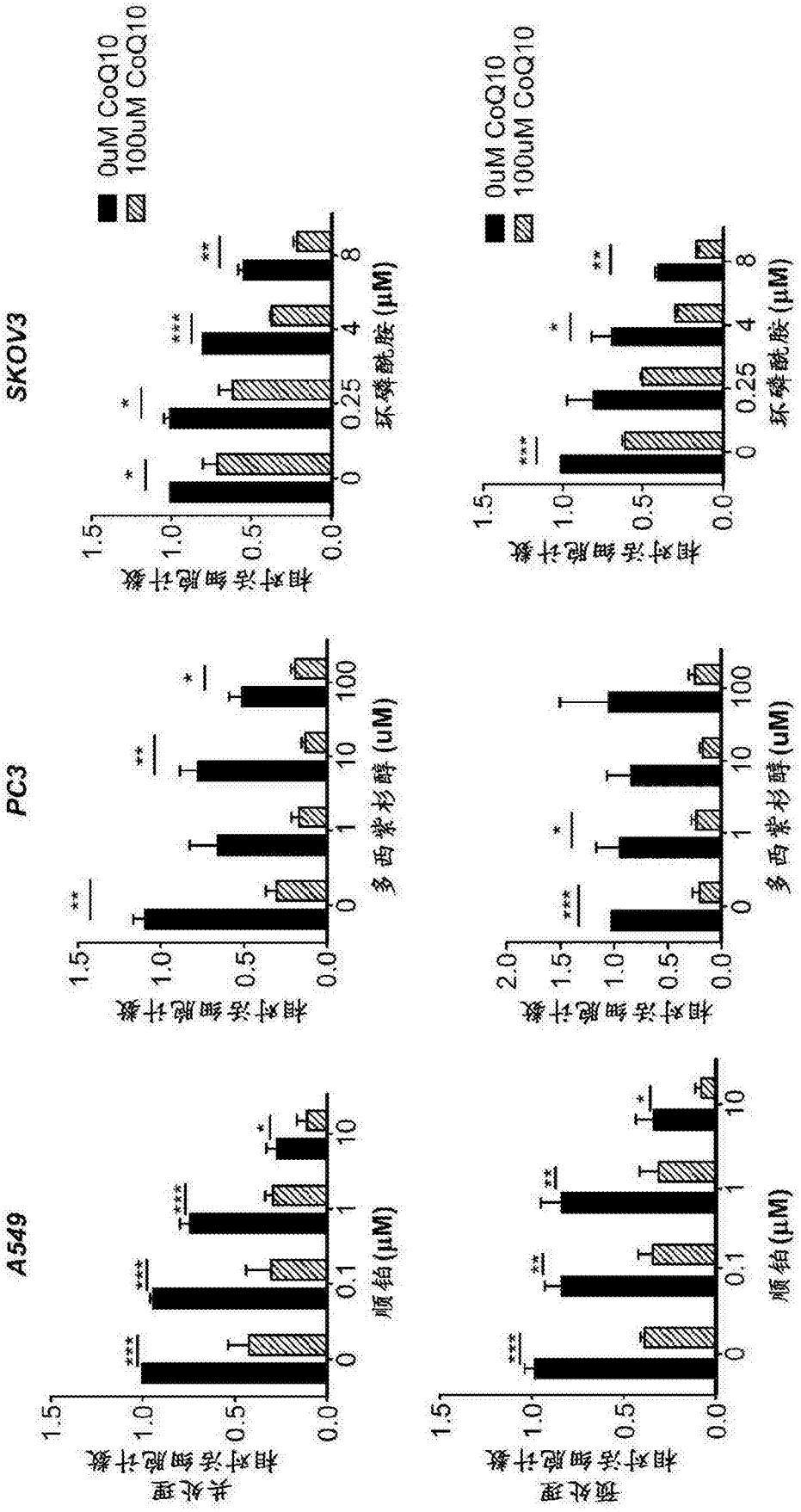

0uM CoQ10
100uM CoQ10
SKOV3
PC3
A549
相对活细胞计数
环磷酰胺 (μM)
多西紫杉醇 (uM)
顺铂 (μM)
预处理
共处理

图 19

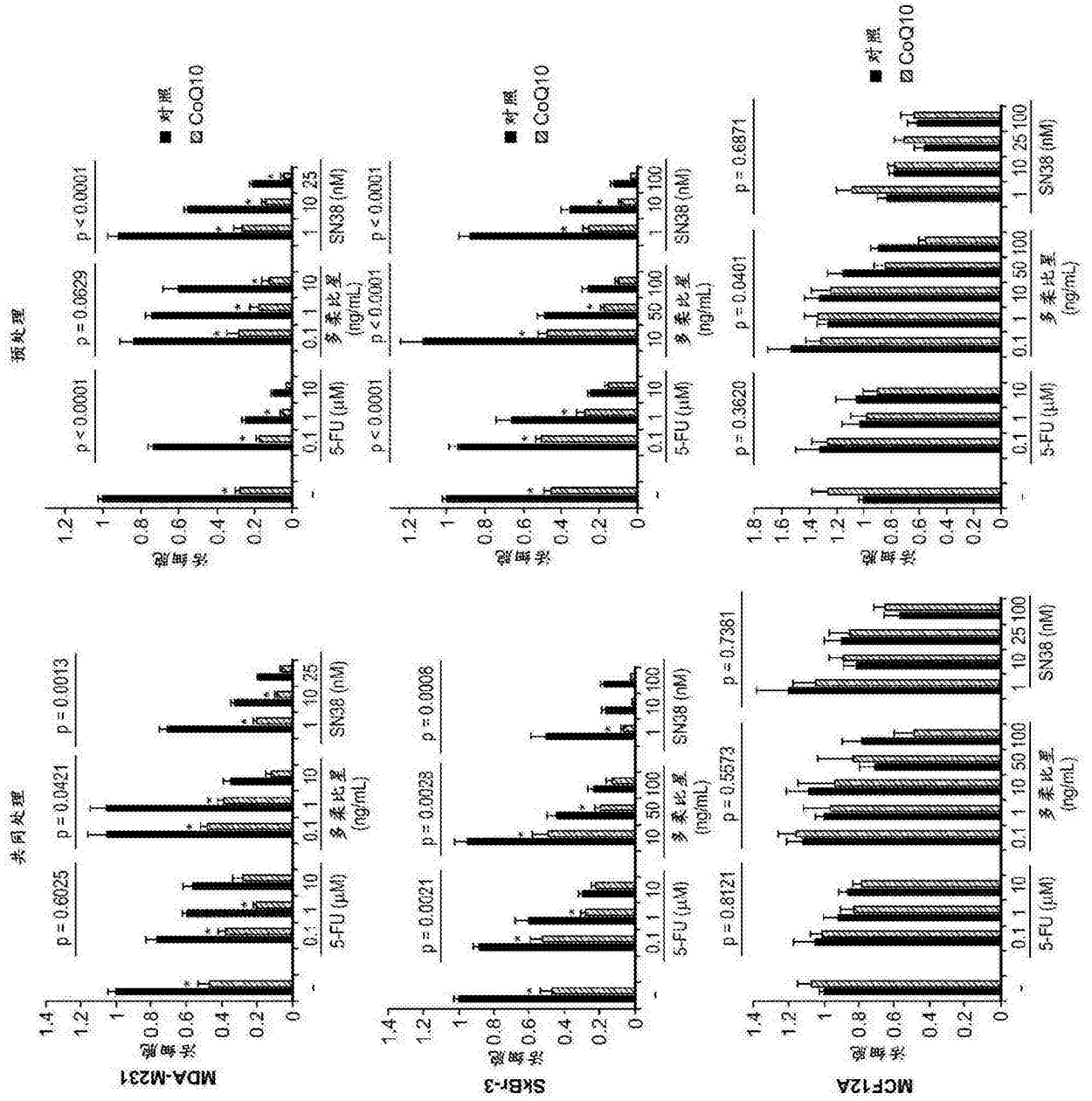

预处理
共同处理
对照
CoQ10
活细胞
5-FU (μM)
多柔比星 (ng/mL)
SN38 (nM)
MDA-MB231
SkBr-3
MCF12A
p < 0.0001
p = 0.0629
p < 0.0001
p = 0.6025
p = 0.0421
p = 0.0013
p = 0.0021
p = 0.0028
p = 0.0006
p = 0.8121
p = 0.5573
p = 0.7381
p = 0.3620
p = 0.0401
p = 0.6871

图 20

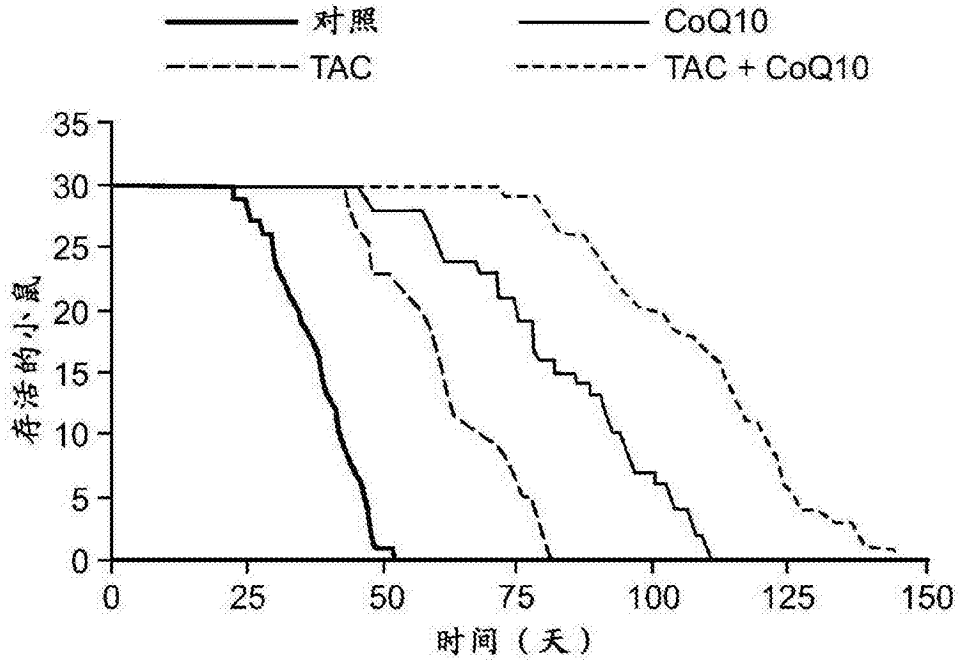

对照
CoQ10
TAC
TAC + CoQ10
存活的小鼠
35
30
25
20
15
10
5
0
0
25
50
75
100
125
150
时间（天）

图 21

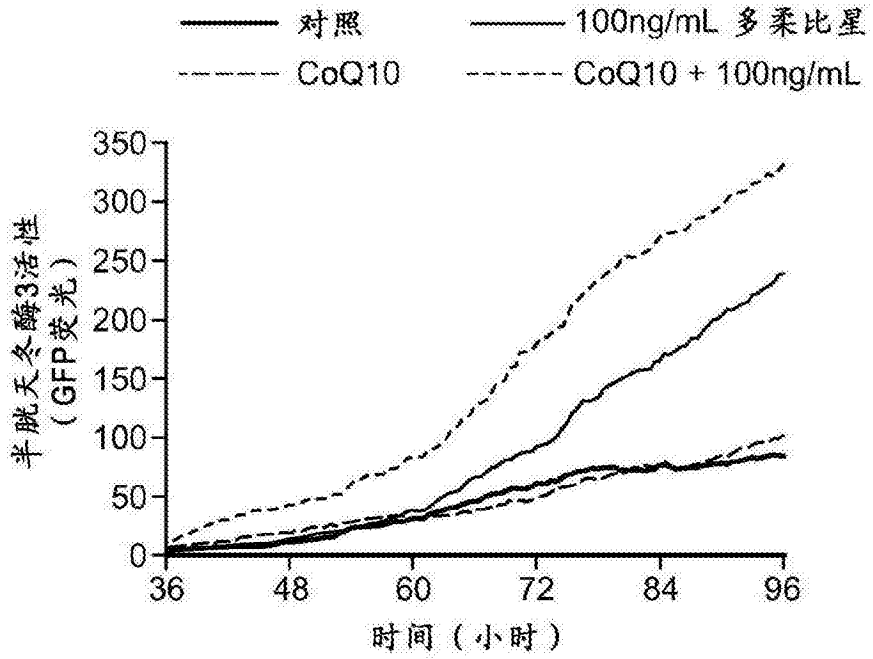

对照
100ng/mL 多柔比星
CoQ10
CoQ10 + 100ng/mL
半胱天冬酶3活性
（GFP荧光）
350
300
250
200
150
100
50
0
36
48
60
72
84
96
时间（小时）

图 22

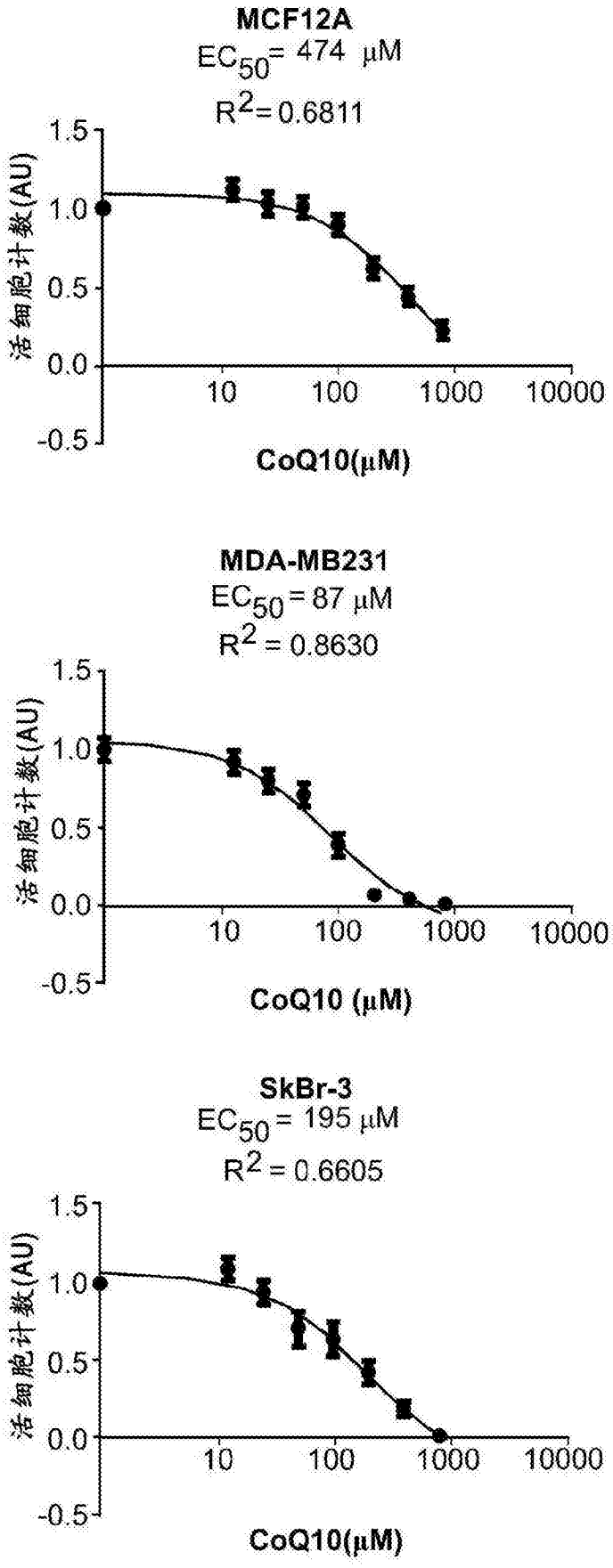
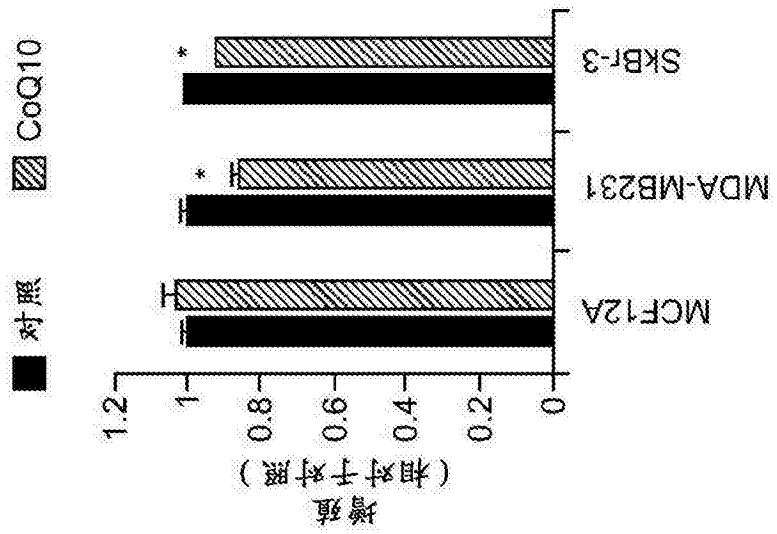

MCF12A
EC50= 474 μM
R2= 0.6811
活细胞计数(AU)
1.5
1.0
0.5
0.0
-0.5
10
100
1000
10000
CoQ10(μM)
MDA-MB231
EC50 = 87 μM
R2 = 0.8630
活细胞计数(AU)
1.5
1.0
0.5
0.0
-0.5
10
100
1000
10000
CoQ10 (μM)
SkBr-3
EC50 = 195 μM
R2 = 0.6605
活细胞计数(AU)
1.5
1.0
0.5
0.0
-0.5
10
100
1000
10000
CoQ10(μM)

图 23


CoQ10
对照
MCF12A
MDA-MB231
SkBr-3
0
0.2
0.4
0.6
0.8
1
1.2
*
*
*
增殖
（相对于对照）

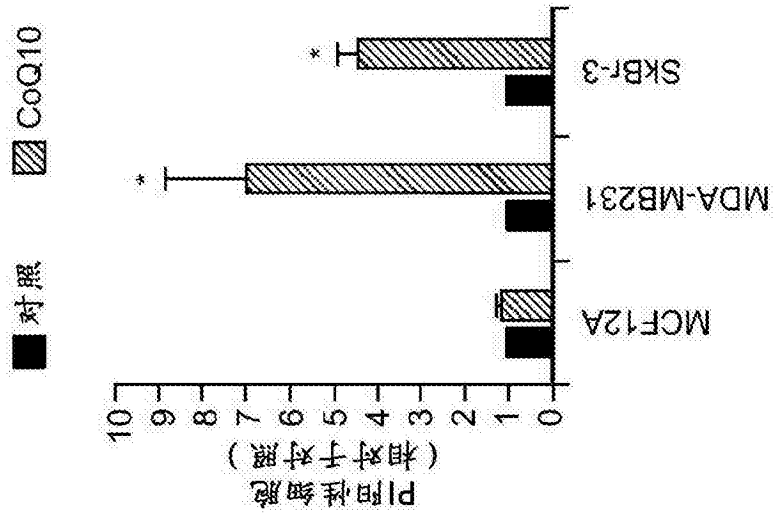

CoQ10
对照
MCF12A
MDA-MB231
SkBr-3
0
1
2
3
4
5
6
7
8
9
10
*
*
*
pI阳性细胞
（相对于对照）

图 24

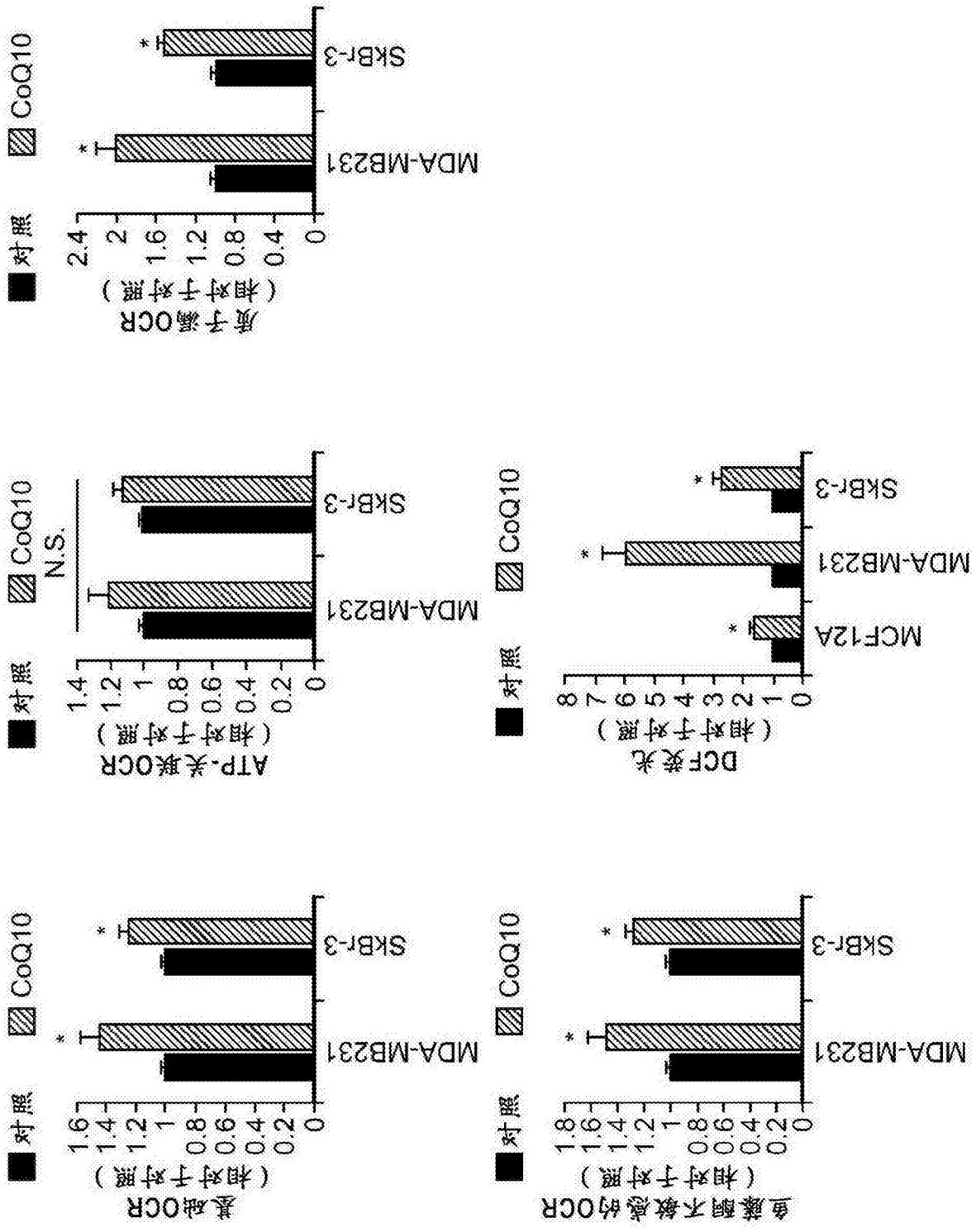

对照
CoQ10
N.S.
*
MDA-MB231
SkBr-3
MCF12A
(相对于对照)
DCF荧光
ATP-关联OCR
基础OCR
线粒体不偶联的OCR
残余OCR

图 25

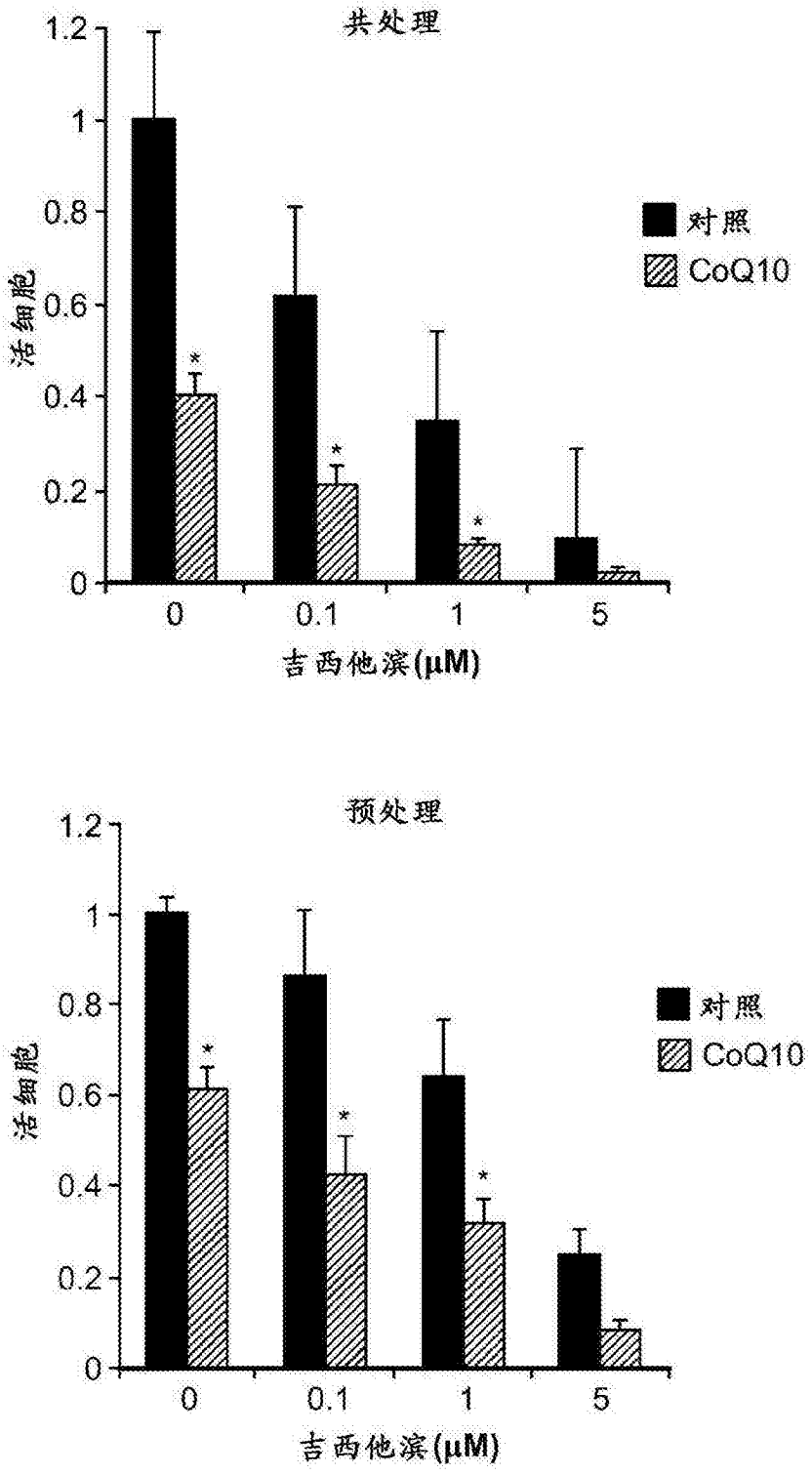

共处理
1.2
1
0.8
0.6
0.4
0.2
0
活细胞
对照
CoQ10
*
*
*
0
0.1
1
5
吉西他滨(μM)
预处理
1.2
1
0.8
0.6
0.4
0.2
0
活细胞
对照
CoQ10
*
*
*
0
0.1
1
5
吉西他滨(μM)

图 26

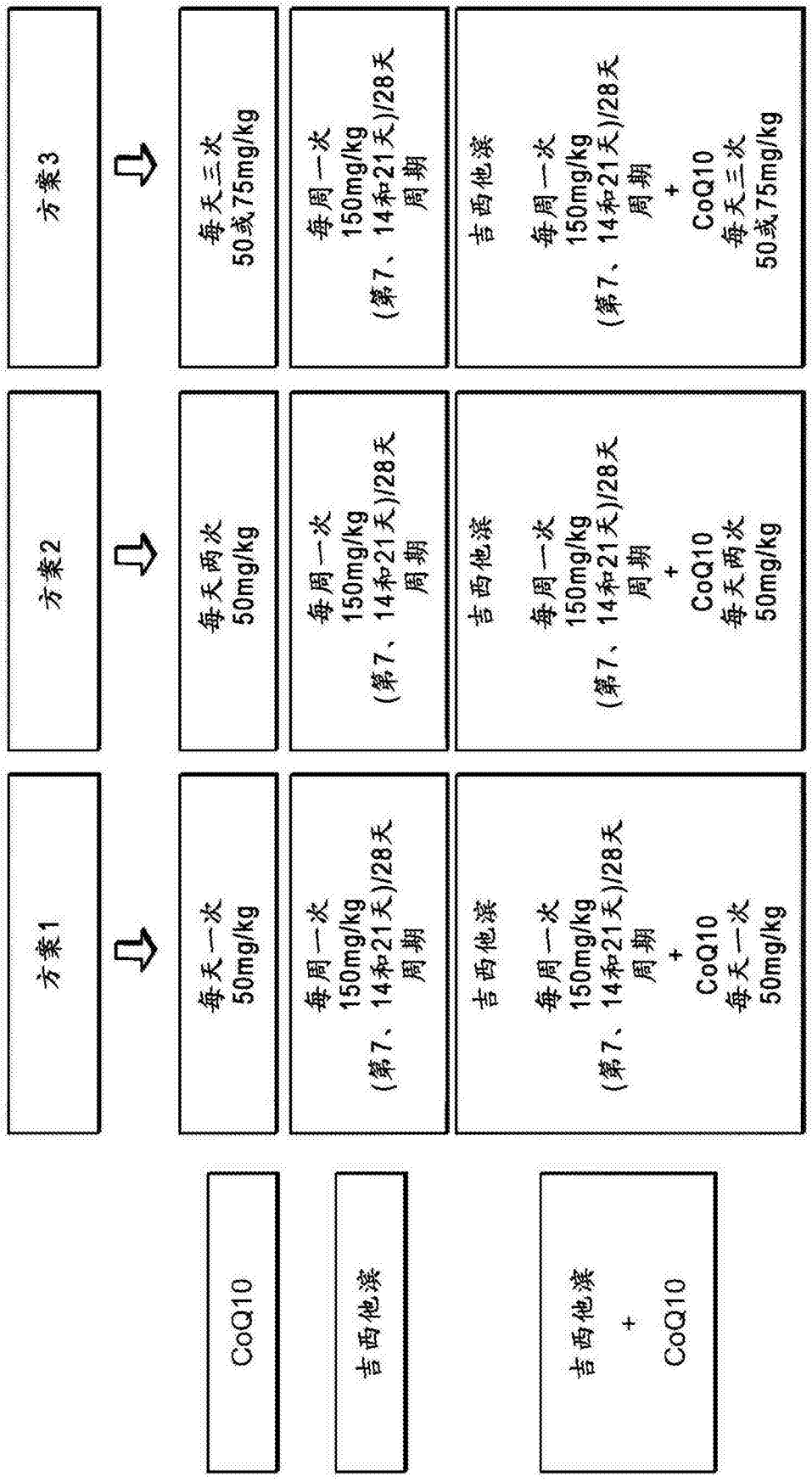

方案1
每天一次
50mg/kg
每周一次
150mg/kg
(第7、14和21天)/28天
周期
吉西他滨
每周一次
150mg/kg
(第7、14和21天)/28天
周期
+
CoQ10
每天一次
50mg/kg
方案2
每天两次
50mg/kg
每周一次
150mg/kg
(第7、14和21天)/28天
周期
吉西他滨
每周一次
150mg/kg
(第7、14和21天)/28天
周期
+
CoQ10
每天两次
50mg/kg
方案3
每天三次
50或75mg/kg
每周一次
150mg/kg
(第7、14和21天)/28天
周期
吉西他滨
每周一次
150mg/kg
(第7、14和21天)/28天
周期
+
CoQ10
每天三次
50或75mg/kg
CoQ10
吉西他滨
吉西他滨
+
CoQ10

图 27

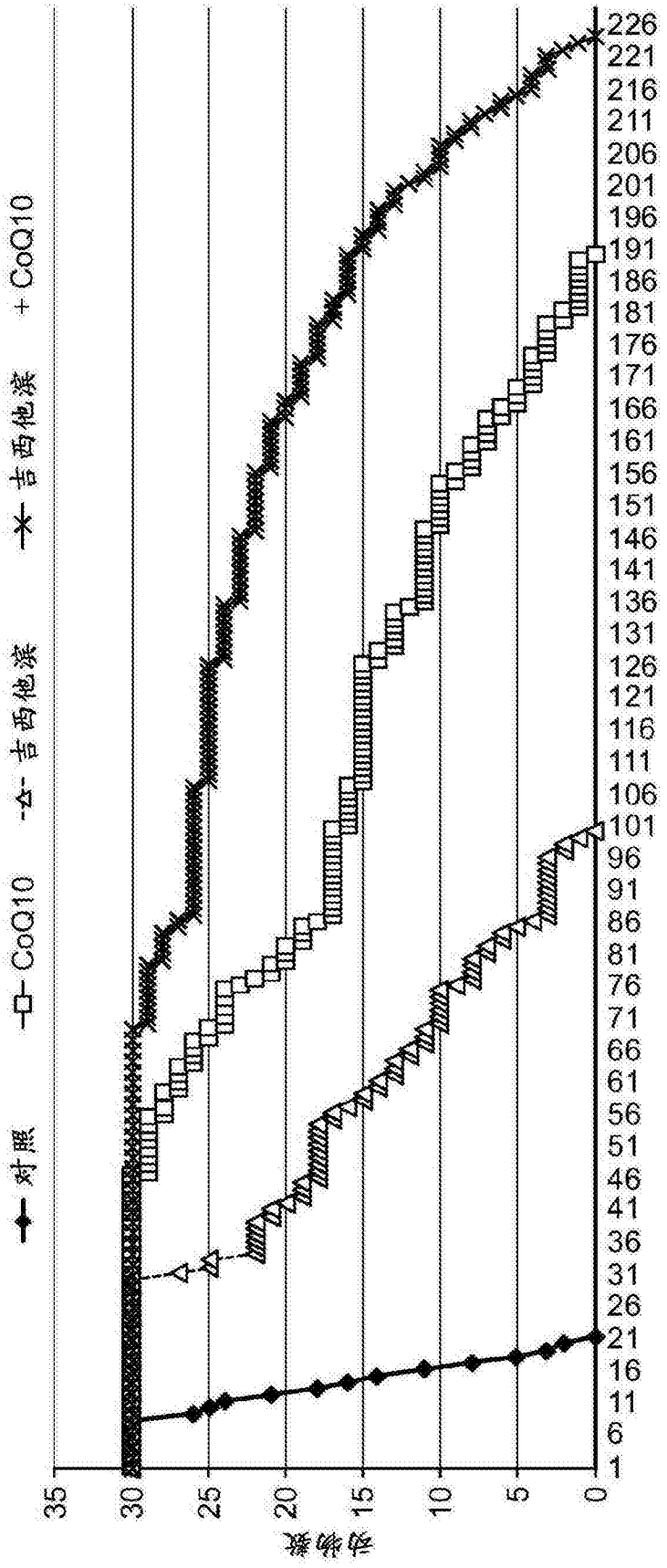

对照
CoQ10
吉西他滨
+ CoQ10
吉西他滨
动物数
35
30
25
20
15
10
5
0
226
221
216
211
206
201
196
191
186
181
176
171
166
161
156
151
146
141
136
131
126
121
116
111
106
101
96
91
86
81
76
71
66
61
56
51
46
41
36
31
26
21
16
11
6
1

图 28

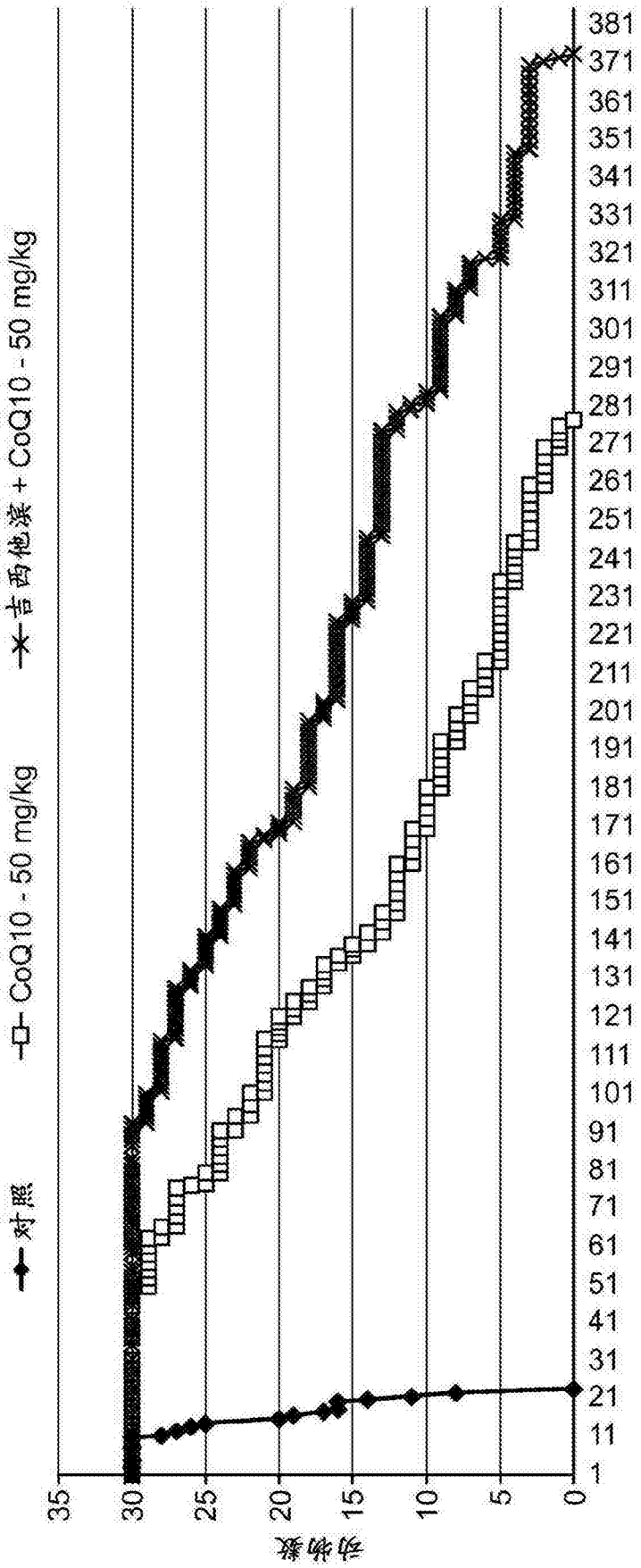

对照
CoQ10 - 50 mg/kg
吉西他滨 + CoQ10 - 50 mg/kg
动物数
0
5
10
15
20
25
30
35
1
11
21
31
41
51
61
71
81
91
101
111
121
131
141
151
161
171
181
191
201
211
221
231
241
251
261
271
281
291
301
311
321
331
341
351
361
371
381

图 29

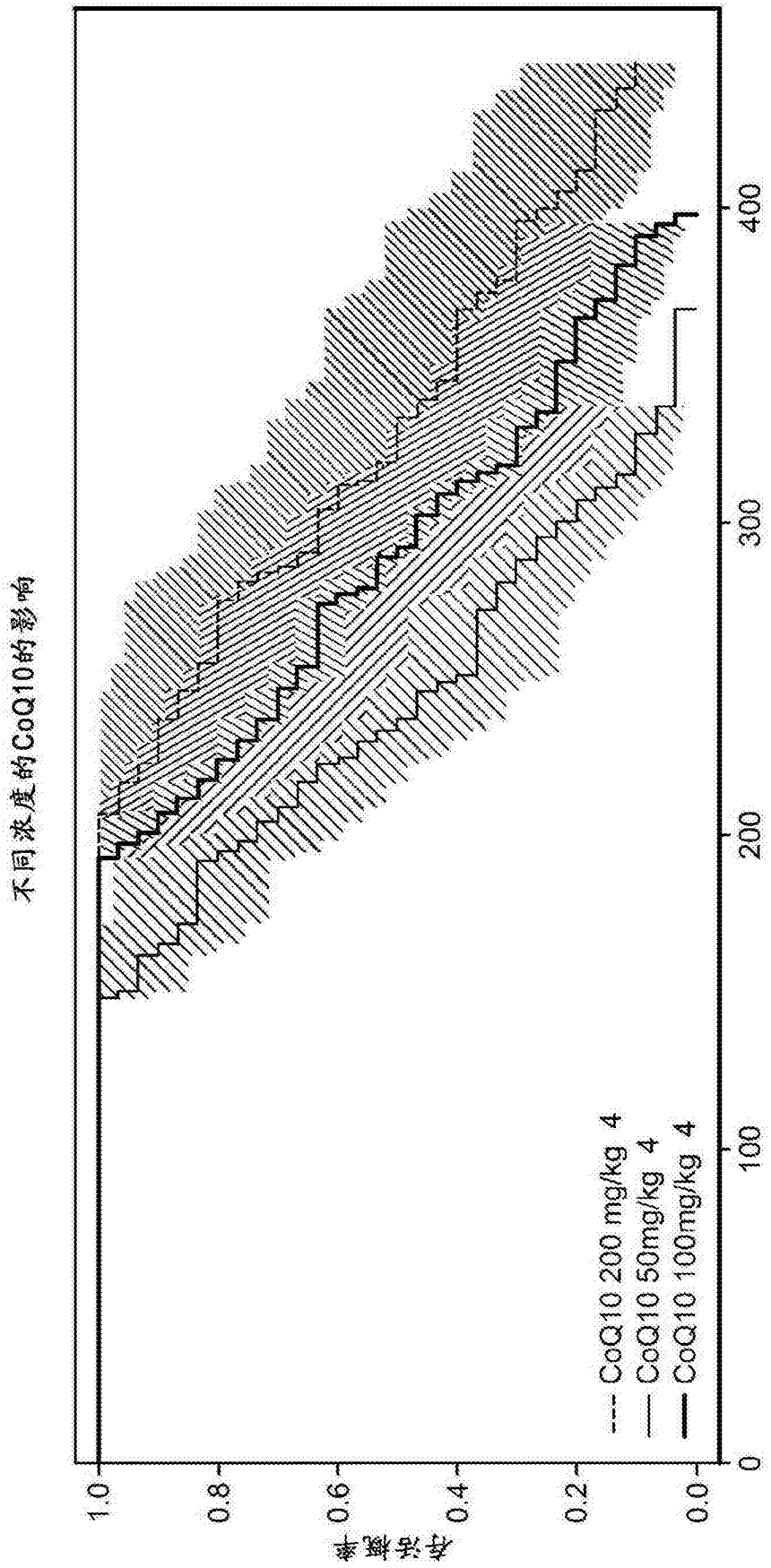

不同浓度的CoQ10的影响
存活概率
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
CoQ10 200 mg/kg 4
CoQ10 50mg/kg 4
CoQ10 100mg/kg 4

图 30

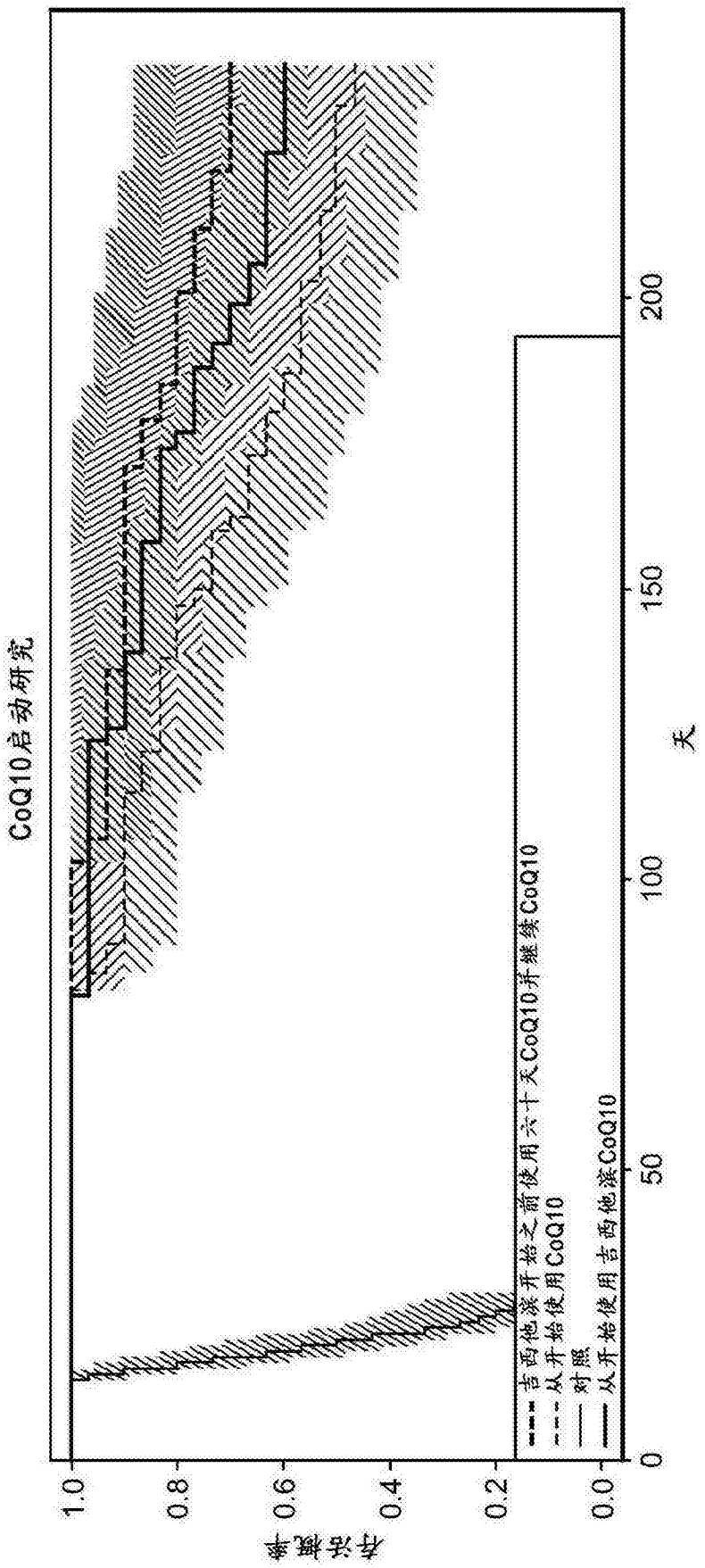

CoQ10启动研究
存活概率
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
天
吉西他滨开始之前使用六十天CoQ10并继续CoQ10
从开始使用CoQ10
对照
从开始使用吉西他滨CoQ10

图 31