Summary

[0013] It has now been found that by supplying two or more therapeutic agents, each as a prodrug conjugate of a hydrophobic moiety coupled through a linker to said therapeutic agent and encapsulating said prodrugs in nanoparticles of appropriate size by mixing said prodrugs with a copolymer of a hydrophobic portion and a hydrophilic portion of an appropriate ratio and forming said nanoparticles by mixing said mixture with an aqueous phase, compositions are obtained such that a wide variety of therapeutic agents can be provided to subjects, wherein the maximum tolerated dose is increased and plasma concentrations are maintained at a desirable level for long periods of time.

[0014] Thus, in one example, the disclosure is directed to a pharmaceutical composition comprising nanoparticles wherein said nanoparticles have an average diameter of less than 80 nm, or preferably 20-80 nm, or even more preferably 40-80 nm, and comprise at least two therapeutic agents, each therapeutic agent coupled through a linker to a hydrophobic moiety to form a prodrug, said nanoparticles also comprising a copolymer of a hydrophobic portion and a hydrophilic portion wherein the weight ratio of the hydrophobic portion to the hydrophilic portion is in the range of 8:5 to 12:5 and wherein the hydrophobic portion has a molecular weight of 8 kD to 15 kD.

[0014a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising nanoparticles, wherein said nanoparticles have an average diameter of less than 80 nm and said nanoparticles comprise: a) at least two different therapeutic agents, each said therapeutic agent couple through a linker to cholesterol or to a hydrophobic natural product to form a prodrug, and b) an amphiphilic copolymer stabilizer comprising a hydrophobic portion and a hydrophilic portion wherein the weight ratio of the hydrophobic portion to the hydrophilic portion is in the range of 8:5 to 12:5 and wherein the hydrophobic portion has a molecular weight of 8 kD to 15 kD and wherein the prodrugs of said two different therapeutic agents are contained in the same nanoparticles or are contained in separate nanoparticles.

[0014b] In another aspect, the present disclosure refers to a method to prepare the composition as described herein which method comprises rapidly mixing an aqueous phase with an organic phase comprising said copolymer and said prodrug.

[0015] The prodrugs may be encapsulated in the same nanoparticle, or in separate nanoparticles. A single composition can be administered as a combination of said agents either encapsulated in the same nanoparticle or in separate nanoparticles or separate compositions of nanoparticles containing each of the prodrugs may be administered. Thus, as used herein, a "composition" includes not only a single composition *per se,* but also a "set" of compositions wherein the set provides nanoparticles comprising the prodrugs of the therapeutic agents used in combination. Thus, the "set" is simply an alternative way to supply the combination of agents without necessarily premixing individual compositions each including nanoparticles comprising prodrugs of a therapeutic agent. Thus, "a composition" includes this possibility of providing to a subject the combination in separate formulations without mixing them prior to administration. When provided as a "set" of compositions, the administration may be simultaneous or sequential.

[0016] Combinations of taxane with heat shock inhibitors or combinations of inhibitors of various kinase pathways are used as examples, but the compositions of the disclosure can readily include any desired combination of therapeutic agents, and may include more than two therapeutic agents.

[0017] In one illustrative example, the disclosure relates to compositions and methods for administering effective and less-toxic amounts of taxane/HSP90i drug combinations using nanoparticles that are stably associated with at least one taxane and one HSP90i. These compositions allow the two or more agents to be delivered to the disease site in a coordinated fashion, thereby assuring that the agents are present at the disease site at therapeutically active concentrations in order to enhance efficacy. This result will be achieved whether the agents are coencapsulated in nanoparticle or micelle-based delivery vehicles, or are each separately encapsulated in nanoparticle or micelle-based delivery vehicles administered such that therapeutically active concentrations of each are provided at the disease site. The pharmacokinetics (PK) of the composition are controlled by the delivery vehicles themselves such that coordinated delivery is achieved (provided that the PK of the delivery systems are comparable). In one example, the taxane and HSP90i are formulated as drug conjugates.

[0018] In this specific example, the disclosure is directed to a method to deliver a therapeutically effective amount of a taxane/HSP90i drug combination to a desired target by administering the compositions of the disclosure.

[0019] The disclosure is also directed to a method to reduce the side effect profile of a taxane/HSP90i drug combination by administering the compositions of the disclosure. The "reduced side effect profile" may be measured by a reduction in gastrointestinal, ocular and/or other side effects associated with a taxane or taxane/HSP90i drug combination products which are not associated with nanoparticles of the disclosure. Side effects associated with either free drug cocktails of taxane/HSP90i combinations or nanoparticle-encapsulated taxanes themselves are known by those of ordinary skill and an improved side effect profile using formulations of the disclosure are readily measured. Thus, provided herein are safer and/or less-toxic compositions comprising a taxane/HSP90i drug combination.

[0020] The disclosure is also directed to a method to reduce drug resistance by administering the taxane/HSP90i drug combination compositions of the disclosure. Thus, provided herein are compositions comprising a taxane/HSP90i drug combination with reduced drug resistance. Preferably, said drug resistance is taxane-specific drug resistance.

[0021] The disclosure is also directed to a method to deliver a therapeutically effective amount of a taxane/HSP90i drug combination by administering an HSP90i either before, concurrent or after delivery of a taxane stably associated with a delivery vehicle. In preferred examples, the taxane and/or HSP90i are each conjugated to a hydrophobic moiety.

[0022] In another illustrative example of the disclosure compositions and methods for administering effective and less-toxic amounts of combinations of inhibitors of the RAS/RAF/MEK/ERK ("ERK") pathway and/or the PI3K/AKT/mTOR ("AKT") pathway using

nanoparticles that are stably associated with at least two of these inhibitors are disclosed. These compositions allow the two or more agents to be delivered to the disease site in a coordinated fashion, thereby assuring that the agents are present at the disease site at therapeutically active concentrations in order to enhance efficacy. This result will be achieved whether the agents are coencapsulated in nanoparticle (including micelle)-based delivery vehicles, or are each separately encapsulated in nanoparticle or micelle-based delivery vehicles administered such that therapeutically active concentrations of each are provided at the disease site. The pharmacokinetics (PK) of the composition are controlled by the delivery vehicles themselves such that coordinated delivery is achieved (provided that the PK of the delivery systems are comparable). In one example, the ERK and/or AKT inhibitors are formulated as drug conjugates.

[0023] In this illustrative example, the disclosure is directed to a method to deliver a therapeutically effective amount of an ERK/AKT inhibitor drug combination to a desired target by administering the compositions of the disclosure.

[0024] The disclosure is also directed to a method to reduce the side effect profile of an ERK/AKT inhibitor drug combination by administering the compositions of the disclosure. The "reduced side effect profile" may be measured by a reduction in papulopustular rash, gastrointestinal, ocular and/or other side effects associated with an ERK/AKT inhibitor drug combination product which is not associated with nanoparticles of the disclosure. Side effects associated with either free drug cocktails of ERK/AKT inhibitor drug combinations or of each individual inhibitors are known by those of ordinary skill and an improved side effect profile using formulations of the disclosure is readily measured. Thus, provided herein are safer and/or less toxic compositions comprising an ERK/AKT inhibitor drug combination.

[0025] The disclosure also includes a method to reduce drug resistance by administering the ERK/AKT inhibitor drug combination compositions of the disclosure. Thus, provided herein are compositions comprising an ERK/AKT inhibitor drug combination with reduced drug resistance.

[0026] The disclosure also includes a method to deliver a therapeutically effective amount of an ERK/AKT inhibitor drug combination by administering an ERK inhibitor either before, concurrent or after delivery of an AKT inhibitor stably associated with a delivery vehicle. In preferred examples, the ERK inhibitor and/or AKT inhibitor are each conjugated to a hydrophobic moiety.

[0027] In some examples, an additional therapeutic agent is administered with compositions of the disclosure.

[0028] Some of the combinations of the present disclosure are useful for treating proliferative diseases. A proliferative disease is mainly a tumor disease (or cancer) (and/or any metastases). The inventive combinations are particularly useful for treating a tumor which is a solid tumor.

Brief Description of the Drawings

[0029] FIGURE 1 is a graph of the plasma concentrations (measured as percent of injected dose) of free docetaxel (inverted triangles), free AUY922 (triangles) in comparison to nanoparticle-encapsulated docetaxel (circles) and nanoparticle-encapsulated AUY922 (squares) when administered *in vivo*.

[0030] FIGURE 2 is a graph of the relative tolerability of docetaxel and AUY922 administered as a nanoparticle combination compared to the maximum tolerated dose (MTD) of the free drugs administered individually and in combination.

[0031] FIGURE 3 is a graph of the efficacy of a combination of docetaxel and AUY922 coencapsulated in nanoparticles of the invention and administered at a 1:2 docetaxel:AUY922 wt/wt ratio at either a 10 mg docetaxel dose (squares) or a 20 mg docetaxel dose (triangles) when administered to mice bearing the ST996 PDX tumor model which is characterized as being taxane-resistant.

[0032] FIGURE 4 is a graph of the efficacy of a combination of docetaxel and AUY922 coencapsulated in nanoparticles of the invention in comparison to the free drug combination at its MTD when administered to mice bearing the HCT15 tumor model which is characterized as being taxane-resistant.

[0033] FIGURE 5A is a graph of the efficacy of a combination of selumetinib and ipatasertib coencapsulated in nanoparticles of the invention in comparison to the free drug combination (circles) when administered to mice bearing the HCT116 tumor model. Selumetinib is administered as a 10 mg/kg dose in the free drug combination and a 50 mg/kg dose when encapsulated. Ipatasertib is administered at a 20 mg/kg dose in the free drug combination and a 50 mg/kg dose (inverted triangles) or 100 mg/kg dose (diamonds) when coencapsulated in nanoparticles of the invention.

[0034] FIGURE 5B is a graph of the efficacy of a combination of selumetinib and ipatasertib coencapsulated in nanoparticles of the invention in comparison to the free drug combination (circles) when administered to mice bearing the HCT116 tumor model. Selumetinib is administered as a 20 mg/kg dose in the free drug combination and a 50 mg/kg dose when encapsulated. Ipatasertib is administered at a 40 mg dose in the free drug

Claims

1. A pharmaceutical composition comprising nanoparticles, wherein said nanoparticles have an average diameter of less than 80 nm and said nanoparticles comprise:

a) at least two different therapeutic agents, each said therapeutic agent couple through a linker to cholesterol or to a hydrophobic natural product to form a prodrug, and

b) an amphiphilic copolymer stabilizer comprising a hydrophobic portion and a hydrophilic portion wherein the weight ratio of the hydrophobic portion to the hydrophilic portion is in the range of 8:5 to 12:5 and wherein the hydrophobic portion has a molecular weight of 8 kD to 15 kD and wherein the prodrugs of said two different therapeutic agents are contained in the same nanoparticles or are contained in separate nanoparticles.

2. The composition of claim 1 wherein said amphiphilic stabilizer is a diblock copolymer.

3. The composition of claim 1 wherein in said amphiphilic stabilizer, the hydrophobic portion comprises polylactic acid (PLA) or poly(lactic-co-glycolic acid (PLGA) and the hydrophilic portion comprises polyethylene glycol (PEG).

4. The composition of claim 1 wherein said prodrugs of said at least two therapeutic agents are included in the same nanoparticle.

5. The composition of claim 1 wherein one therapeutic agent is a taxane and the other therapeutic agent is an HSP inhibitor or wherein one therapeutic agent is a PI3K/AKT/mTOR inhibitor and the other therapeutic agent is an RAS/RAF/MEK/ERK inhibitor.

6. The composition of claim 1 wherein in each of said prodrugs the hydrophobic moiety is cholesterol and/or the linker is diglycolic acid.

7. The composition of claim 1 wherein said nanoparticles are formed by mixing an aqueous phase and an organic phase, said organic phase comprising said copolymer and said prodrug.

8. The composition of claim 7 wherein said mixing is conducted by rapid mixing of jet streams one of which comprises the aqueous phase and the other of which comprises the organic phase.

9. The composition of claim 1 wherein said nanoparticles have an average diameter of 20-80 nm.

10. The composition of claim 1 which further comprises a third therapeutic agent.

11. The composition of claim 10 wherein said third therapeutic agent is supplied as a prodrug and encapsulated in said nanoparticles.

12. A method to prepare the composition of claim 1 which method comprises rapidly mixing an aqueous phase with an organic phase comprising said copolymer and said prodrug.