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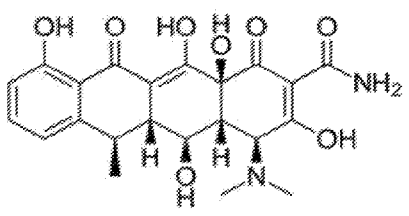
(54) Title: COMPANION DIAGNOSTICS FOR MITOCHONDRIAL INHIBITORS

(57) Abstract: The present disclosure relates to methods of identifying patients that may be responsive to mitochondrial inhibitor therapies to target and eradicate cancer stem cells. Also described are diagnostic kits that may be used to identify patients responsive to mitochondrial inhibitor therapies.

FIG. 1A



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COMPANION DIAGNOSTICS FOR MITOCHONDRIAL INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/508,799, filed May 19, 2017, U.S. Provisional Application No. 62/508,788, filed May 19, 2017, U.S. Provisional Application No. 62/508,769, filed May 19, 2017, U.S. Provisional Application No. 62/508,750, filed May 19, 2017, U.S. Provisional Application No. 62/529,871, filed July 7, 2017, U.S. Provisional Application No. 62/524,829, filed June 26, 2017, U.S. Provisional Application No. 62/576,287, filed October 24, 2017, U.S. Provisional Application No. 62/590,432, filed November 24, 2017, and Patent Cooperation Treaty Application No. PCT/US2018/022403, filed March 14, 2018, the contents of which are incorporated by reference in their entireties. U.S. Provisional Application No. 62/471,688, filed March 15, 2017, is also incorporated by reference in its entirety.

FIELD

[0002] The present disclosure relates to diagnostic kits and methods for identifying patients that may be responsive to mitochondrial inhibitor therapies to target and eradicate cancer stem cells.

BACKGROUND

[0003] Researchers have struggled to develop new anti-cancer treatments. Conventional cancer therapies (e.g. irradiation, alkylating agents such as cyclophosphamide, and anti-metabolites such as 5-Fluorouracil) have attempted to selectively detect and eradicate fast-growing cancer cells by interfering with cellular mechanisms involved in cell growth and DNA replication. Other cancer therapies have used immunotherapies that selectively bind mutant tumor antigens on fast-growing cancer cells (e.g., monoclonal antibodies). Unfortunately, tumors often recur

following these therapies at the same or different site(s), indicating that not all cancer cells have been eradicated. Relapse may be due to insufficient chemotherapeutic dosage and/or emergence of cancer clones resistant to therapy. Hence, novel cancer treatment strategies are needed.

[0004] Advances in mutational analysis have allowed in-depth study of the genetic mutations that occur during cancer development. Despite having knowledge of the genomic landscape, modern oncology has had difficulty with identifying primary driver mutations across cancer subtypes. The harsh reality appears to be that each patient's tumor is unique, and a single tumor may contain multiple divergent clone cells. What is needed, then, is a new approach that emphasizes commonalities between different cancer types. Targeting the metabolic differences between tumor and normal cells holds promise as a novel cancer treatment strategy. An analysis of transcriptional profiling data from human breast cancer samples revealed more than 95 elevated mRNA transcripts associated with mitochondrial biogenesis and/or mitochondrial translation. Sotgia et al., *Cell Cycle*, 11(23):4390-4401 (2012). Additionally, more than 35 of the 95 upregulated mRNAs encode mitochondrial ribosomal proteins (MRPs). Proteomic analysis of human breast cancer stem cells likewise revealed the significant overexpression of several mitoribosomal proteins as well as other proteins associated with mitochondrial biogenesis. Lamb et al., *Oncotarget*, 5(22):11029-11037 (2014).

[0005] Functional inhibition of mitochondrial biogenesis using the off-target effects of certain bacteriostatic antibiotics or OXPHOS inhibitors provides additional evidence that functional mitochondria are required for the propagation of cancer stem cells. The inventors recently showed that a mitochondrial fluorescent dye (MitoTracker) could be effectively used to enrich and purify cancer stem-like cells (CSCs) from a heterogeneous population of living cells. Farnie et al., *Oncotarget*, 6:30272-30486 (2015). Cancer cells with the highest mitochondrial mass

had the strongest functional ability to undergo anchorage-independent growth, a characteristic normally associated with metastatic potential. The 'Mito-high' cell sub-population also had the highest tumor-initiating activity in vivo, as shown using pre-clinical models. The inventors also demonstrated that several classes of non-toxic antibiotics could be used to halt CSC propagation. Lamb et al., *Oncotarget*, 6:4569-4584 (2015). Because of the conserved evolutionary similarities between aerobic bacteria and mitochondria, certain classes of antibiotics or compounds having antibiotic activity can inhibit mitochondrial protein translation as an off-target side-effect.

SUMMARY

[0006] In view of the foregoing background, it is an object of this disclosure to demonstrate methods for identifying a patient for anti-mitochondrial therapy. Methods may include obtaining a sample from the patient; determining the level of at least one mitochondrial marker in the sample; classifying the patient as a candidate for therapy with an anti-mitochondrial therapy if the sample is determined to have an increased level of the at least one mitochondrial marker relative to a threshold level. Methods include collecting samples from lung, breast, ovarian, gastric, skin, kidney, pancreas, rectum, colon, prostate, bladder, epithelial, and non-epithelial tissue sample. In some embodiments, the sample is a body fluid such as blood, serum, plasma, saliva, sputum, milk, tears, urine, ascites, cyst fluid, pleural fluid, and cerebral spinal fluid. In some embodiments, the sample includes circulating tumor cells isolated from at least one of serum, plasma, and blood.

[0007] The present disclosure includes using mitochondrial protein, RNA, and/or DNA as a mitochondrial marker. The mitochondrial marker may relate to or regulate beta-oxidation and/or ketone metabolism. Such markers include HSD17B10, BDH1, ACAT1, ACADVL, ACACA, ACLY, HADHB, SUCLG2, ACAD9, HADHA, ECHS1, and ACADSB.

[0008] In some embodiments, the mitochondrial marker relates to or regulates at least one of mitochondrial biogenesis, electron transport, metabolism, ATP synthesis, ADP/ATP exchange/transport, CoQ synthesis, ROS production, and suppression of glycolysis, autophagy and/or mitophagy. Such markers include HSPA9, TIMM8A, GFM1, MRPL45, MRPL17, HSPD1(HSP60), TSFM, TUFM, NDUFB10, COX6B1, PMPCA, COX5B, SDHA, UQCRC1, CHCHD2, ATP5B, ATPIF1, ATP5A1, ATP5F1, ATP5H, ATP5O, SLC25A5, COQ9, GPD2, SOGA1, and LRPPRC. In some embodiments, the mitochondrial marker regulates at least one enzymes ACAT1/2 and/or OXCT1/2.

[0009] The present disclosure further relates to methods of administering to the patient having an increased level of at least one mitochondrial marker at least mitochondrial inhibitor. The mitochondrial inhibitor may be a mitoriboscin, a mitoketoscin, a antimitoscin, metformin, a tetracycline family member, a erythromycin family member, atovaquone, bedaquiline, vitamin c, caffeic acid phenyl ester, and berberine. In some embodiments, the tetracycline family member is doxycycline. In some embodiments, the erythromycin family member is azithromycin.

[0010] The present disclosure also relates to methods of administering to the patient an anti-angiogenic agent. Anti-angiogenic agents include angiostatin, bevacizumab, arresten, canstatin, combretastatin, endostatin, NM-3, thrombospondin, tumstatin, 2-methoxyestradiol, Vitaxin, Getfitinib, ZD6474, erlotinib, CI1033, PKI1666, cetuximab, PTK787, SU6668, SUl 1248, trastuzumab, Marimastat, COL-3, Neovastat, 2-ME, SU6668, anti-VEGF antibody, Medi-522 (Vitaxin E), tumstatin, arrestin, recombinant EPO, troponin I, EMD121974, IFN-α celecoxib, PD0332991, tamoxifen, paclitaxel (taxol) and thalidomide. In some embodiments, the anti-angiogenic agent is administered simultaneously or sequentially with a mitochondrial inhibitor.

[0011] The present disclosure also relates to diagnostic kits for measuring one or more mitochondrial markers (companion diagnostics) to identify a high-risk cancer patient population that is most likely to benefit from anti-mitochondrial therapy. In some embodiments, the kit may include a component for measuring for measuring levels of mitochondrial marker RNA, DNA, and/or protein relative to a normal control. In some embodiments, the mitochondrial marker is measured by any number of ways known in the art for measuring RNA, DNA, and or protein, including quantitative PCR and/or RT-PCR kits, microarrays, Northern blots, and Western blots. In some embodiments, the kit may include an antibody specific to a mitochondrial marker. The antibody may be a monoclonal or a polyclonal antibody. In some embodiments, the kit may include a molecule that binds to at least one of a mitochondrial ribosomal protein (MRP), an OXPHOS complex, and a mitochondrial membrane protein/chaperone.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIGs. 1A-E illustrate the structures of antibiotics that may be used inhibit the propagation of cancer stem cells (CSCs).

[0013] FIGs. 2A-D illustrate the structures of naturally occurring compounds that may be used to inhibit the propagation of CSCs.

[0014] FIGs. 3A-C illustrate the structures of experimental compounds that may be used to inhibit the propagation of CSCs.

[0015] FIGs. 4A-D illustrate the structure of exemplary mitoriboscins.

[0016] FIG. 5 illustrates an exemplary pharmacophore for a mitoketoscin.

[0017] FIG. 6A shows a docking image of Compound 2 docking at a succinyl-CoA binding site of 3-oxoacid CoA-transferase 1 (OXCT1). FIG. 6B shows a docking image of Compound 8 docking at a CoA binding site of human acetyl-CoA acetyltransferase (ACAT1).

[0018] FIG. 7 shows the structures of diphenyleneiodium chloride (DPI) and 2-butene-1,4-bis-triphenylphosphonium (TPP).

[0019] FIGs. 8A-C show the structures of brutieridin, melitidin, and mDIVI1, respectively.

[0020] FIG. 9 provides a summary for personalized cancer diagnosis and treatment based on mitochondrial-based diagnostics.

[0021] FIGs. 10A-B show the probability of recurrence and distant metastasis, respectively, of patients having specific Mito-Signatures.

[0022] FIGs. 11A-B show the probability of overall survival in patients having a specific Mito-Signature and undergoing platin or taxol treatment, respectively.

[0023] FIG. 12 shows the basic components of a mitochondrial-based oncology platform.

DESCRIPTION

[0024] The following description illustrates embodiments of the present approach in sufficient detail to enable practice of the present approach. Although the present approach is described with reference to these specific embodiments, it should be appreciated that the present approach can be embodied in different forms, and this description should not be construed as limiting any appended claims to the specific embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the present approach to those skilled in the art.

[0025] Tumors and their microenvironment are heterogeneous structures that behave like metabolic ecosystems. It is well accepted that more than a single type of cancer cell exists. For example, within a given epithelial cancer cell line (such as MCF7 cells), there are "bulk" cancer cells (~85-95%; the majority of the population), as well as various types of progenitor cells (less than 5%), and cancer stem cells (CSCs; less than 1%). CSCs and progenitor cells are thought to be the most dangerous as they behave as tumor-initiating cells (TICs) in vivo and can undergo metastasis. In contrast, "bulk" cancer cells are largely non-tumorigenic.

[0026] Because CSCs are relatively "rare", little is known about their metabolic properties. The inventors previously showed that cells may be functionally enriched for CSCs by trypsinizing the entire cell population and seeding it as a single-cell suspension onto low-attachment plates. Under such conditions, the majority (more than 90%) of "bulk" cancer cells die via apoptosis, while only the CSCs survive and propagate, ultimately resulting in the formation of 3D spheroid structures after about 5 days. Each 3D spheroid is clonally formed from a single CSC. For breast CSCs, these 3D spheroids are also known as tumor-spheres or mammospheres. The generation of these 3D spheroids is thought to mimic the process of tumor formation and/or metastasis, thus providing a model for drug discovery and functional validation.

[0027] To understand the metabolic differences between "bulk" cancer cells and CSCs, the inventors previously compared cultured breast cancer cells grown either as monolayers or 3D spheroids. These cells were subjected to profiling via unbiased label-free proteomics analysis. The inventors found that over 60 nuclear-encoded mitochondrial proteins were specifically up-regulated in 3D spheroid structures relative to monolayer cells processed in parallel. Virtually identical results were obtained with two distinct ER(+) breast cancer cell lines (MCF7 and T47D; more than 40 overlapping mitochondrial proteins). Informatics analysis of the list of up-regulated

mitochondrial proteins was consistent with an increase in mitochondrial mass, due either to i) increased mitochondrial biogenesis or ii) a shut down in mitophagy, or both. These results indicate that high mitochondrial mass is a characteristic feature of the CSC phenotype. These results also suggest that CSCs are dependent on OXPHOS and/or new mitochondrial biogenesis (protein translation) for survival and propagation. While testing this hypothesis, inventors showed that 3D spheroid formation is effectively blocked using specific mitochondrial inhibitors, such as oligomycin, which targets mitochondrial Complex V and shuts off ATP synthesis. However, oligomycin is toxic and cannot be used as an anti-cancer therapeutic. Thus, these results highlight the need for compounds that can target mitochondria in CSCs without inducing deleterious side effects in normal cells.

[0028] To further validate the functional relationship between high mitochondrial mass and "stemness", inventors employed staining with MitoTracker to metabolically fractionate an MCF7 cell line into "Mito-high" and "Mito-low" cell sub-populations. MitoTracker is a non-toxic fluorescent probe that can be used to directly measure mitochondrial mass in live cells by flow cytometry. As predicted, the "Mito-high" cell population, with increased mitochondrial mass, showed the greatest capacity for i) 3D spheroid formation and ii) tumor initiation in a pre-clinical animal model in vivo. Therefore, mitochondrial mass may be a critical determinant of stemness in cancer cells. Similarly, elevated telomerase activity (hTERT), a functional marker of proliferation and immortality in CSCs, was also specifically associated with high mitochondrial mass. The inventors hypothesized that a targeted reduction in mitochondrial mass or OXPHOS may be used to eradicate CSCs.

[0029] The inventors have recently focused efforts on the identification and repurposing of FDA-approved drugs that may be used to inhibit the propagation of CSCs. These antibiotics

include members of the tetracycline family (doxycycline/tigecycline), the erythromycin family (azithromycin), anti-parasitic drugs (pyrvinium pamoate and atovaquone), and antimicrobials targeting drug-resistant mycobacterium (bedaquiline; TB, tuberculosis). FIG. 1 provides exemplary structures of these antibiotics (FIGs. 1A-E show the structures of doxycycline, azithromycin, pyrvinium (pamoate salt; not shown), atovaquone, and bedaquiline, respectively). Table 1 lists exemplary antibiotics and shows which mitochondrial structure or process is targeted. For example, doxycycline and azithromycin inhibit mitochondrial protein translation, thereby inhibiting mitochondrial biogenesis as an off-target side effect. Pyrvinium pamoate and atovaquone inhibit OXPHOS (related to mitochondrial complex II/III) as a side effect. Bedaquiline inhibits ATP-synthase (mitochondrial complex V). Each of these antibiotics has been shown to inhibit anchorage-independent propagation of CSCs by targeting mitochondrial function.

Drug Name	**Inhibition of**	**FDA-approved**
Doxycycline	Mito Biogenesis	Yes
Tigecycline	Mito Biogenesis	Yes
Azithromycin	Mito Biogenesis	Yes
Pyrvinium pamoate	OXPHOS/Complex II	Yes
Atovaquone	OXPHOS/Complex III	Yes
Bedaquiline	Complex V	Yes
Palbociclib	CDK4/6	Yes

Table 1. Exemplary FDA-approved drugs that may be used to eradicate CSCs.

[0030] Inventors have also previously identified experimental and natural compounds that target CSCs, including glycolysis inhibitors (Vitamin C and Silibinin), mitochondrial inhibitors (Actinonin; CAPE, from Honey bee propolis), and inhibitors of protein synthesis (puromycin) and NAD(+) recycling (FK-866). As CSCs appear to be highly proliferative, due to their over-expression of telomerase (hTERT), they are sensitive to Palbociclib, an FDA-approved CDK4/6 inhibitor, with an IC-50 of ~100 nM. Therefore, inhibition of CSC proliferation is an alternative or could be used in conjunction with other cancer therapies.

[0031] Doxycycline shows many other anti-cancer properties that may be further explored. For example, Doxycycline behaves as a radio-sensitizer, making CSCs approximately 3 to 5 times more sensitive to radiation treatment. In addition, Doxycycline effectively targets hypoxic CSCs and overcomes Paclitaxel-resistance under conditions of hypoxia; this may have important implications for achieving more effective anti-angiogenic therapy. Doxycycline appears to be effective as a mutation-independent approach for targeting CSCs as it inhibits both activated H-Ras (G12V) and c-Myc oncogenes as well as other environmental oncogenic stimuli (mitochondrial oxidative stress/ROS), via the specific targeting of mitochondrial biogenesis.

[0032] One concern with doxycycline therapy is the potential for the development of drug-resistance in CSCs. To investigate this issue, the inventors developed and characterized the phenotypic behavior of Doxy-resistant (DoxyR)-MCF7 cells. The inventors found that DoxyR-CSCs show a significant shift towards aerobic glycolysis due to a loss of mitochondrial function, which ultimately results in metabolic inflexibility. (DoxyR)-MCF7 cells showed an up to 35-fold loss of mitochondrial-DNA encoded proteins (mt-DNA) that are required for OXPHOS activity, such as MT-ND3, MT-CO2, MT-ATP6 and MT-ATP8. DoxyR-CSCs appeared to be more "quiescent", with greater than 50% reductions in proliferation and cell migration, as well as a significantly impaired ability to form 3D spheroids. The inventors showed that DoxyR-CSCs are sensitive to other metabolic therapies, including inhibitors of i) OXPHOS (Atovaquone, Irinotecan, Sorafenib, Niclosamide), ii) glycolysis (Vitamin C and Stiripentol) and iii) autophagy (Chloroquine). A listing of these drugs and their targets is provided in Table 2. Therefore, the efficacy of doxycycline treatment may be improved by developing combination therapies with other metabolic inhibitors, based on the concepts of metabolic inflexibility and synthetic lethality in cancer cells.

Drug Name	Target	FDA-approved
Atovaquone	OXPHOS	Yes
Irinotecan	OXPHOS	Yes
Sorafenib	OXPHOS	Yes
Niclosamide	OXPHOS	Yes
Berberine	OXPHOS	Natural supplement
2-deoxy-glucose (2-DG)	Glycolysis	Experimental
Vitamin C	Glycolysis	Natural supplement
Stiripentol	Glycolysis	Clinically-approved (EU/CA/JP)
Chloroquine	Autophagy	Yes

Table 2. Exemplary drugs used in conjugation with doxycycline to eradicate CSCs.

[0033] The inventors have also focused efforts on the development of therapeutics that focus on specific mitochondrial targets. Exemplary therapeutics are listed in Table 3.

Drug Name	Target	Metabolic Process/Mechanism
Mitoriboscins	Mitochondrial Ribosome	Mitochondrial Protein Synthesis
Mitoketoscins	OXCT1/ACAT1	Mitochondrial Ketone Metabolism
Mitoflavoscins	Mito Complex I/II	Flavin-containing proteins (Vit-B2)
Tri-phenyl-phosphonium (TPP)	Mitochondria	Mitochondrial-targeting-signal (MTS)

Table 3. Exemplary therapeutics that focus on mitochondrial targets.

[0034] One family of therapeutics, coined "mitoriboscins," are mito-ribosome inhibitors that inhibit mitochondrial protein synthesis. FIG. 4A-D illustrates examples of mitoriboscins. The inventors identified these compounds by combining computational chemistry (in silico drug design in which the target used was the 3D structure of the large mitochondrial ribosome, as determined by cryo-electron microscopy) with phenotypic library screening to detect ATP depletion.

[0035] By targeting the mitochondrial enzymes OXCT1 and ACAT1, inventors also developed mitochondrial inhibitors that interfere with ketone metabolism (these compounds mimic the structure of CoA). These compounds are known as "mitoketoscins." FIG. 5 illustrates a pharmacophore for a mitoketoscin. FIG. 6A illustrates the docking of Compound 2 (a hit for an OXCT1 screen) at the succinyl-CoA binding site of OXCT1. FIG. 6B illustrates the docking of Compound 8 (a hit for an ACAT1 screen) at the CoA binding site of human ACAT1.

[0036] Inventors also identified compounds named "mitoflavoscins," compounds that bind to flavin-containing enzymes and inhibit mitochondrial function. Such compounds may be designed to target and deplete FMN, FAD, and/or riboflavin. The inventors identified an approach to acutely induce a Vitamin B2 (riboflavin) deficiency that potently inhibits CSC propagation, with an IC-50 of ~3 nM. This drug is approximately 30 times more potent than Palbociclib for targeting CSCs. FIG. 7 illustrates the structure of DPI, one embodiment of a mitoflavoscin.

[0037] Inventors also identified the use of tri-phenyl-phosphonium (TPP) to eradicate CSCs. TPP behaves as a mitochondrial targeting signal. FIG. 7 illustrates the structure of TPP. TPP compounds appear to be able to metabolically distinguish between "normal cell" mitochondria and "malignant" mitochondria of bulk cancer cells and CSCs, as the TPP compounds are non-toxic in normal human fibroblasts and yet block CSC propagation.

[0038] Inventors also investigated naturally-occurring mitochondrial inhibitors that may be used to more effectively target CSCs. A list of exemplary naturally-occurring mitochondrial inhibitors is provided in Table 4. The inventors found that brutieridin and melitidin, two compounds found in bergamot, act as statin-like drugs and inhibit mevolonate metabolism as well as CSC propagation. FIGs. 8A-B illustrate the structures of brutieridin and melitidin, respectively. FIG. 8C illustrates the structure of mDIVI1 for comparison. Interference with the normal process of mitochondrial fission-fusion cycles, such as by targeting the DRP1 protein, may represent a viable strategy for eradicating CSCs.

Drug Name	**Target**	**Metabolic Process Inhibited**
mDIVI1	DRP1*	Mitochondrial Fission/Fusion
Brutieridin	HMGR**	Mevalonate Metabolism
Melitidin	HMGR**	Mevalonate Metabolism

*Dynamin-related protein 1
**3-hydroxy-3-methylglutaryl-CoA-reductase.

Table 4. Naturally-occurring mitochondrial inhibitors that target CSCs.

[0039] The identification and design of new mitochondrial inhibitors may have other medical applications and benefits such as the development of new anti-bacterial and anti-fungal agents and combating antibiotic-resistance. According to the ndo-symbiotic Theory of Mitochondrial Evolution", mitochondria first originated historically from the engulfment of aerobic bacteria, an event that occurred ~1.45 billion years ago. As a result, mitochondria share strong structural and functional similarities with bacteria, explaining the off-target effects of antibiotics, which often show manageable mitochondrial side-effects. Conversely, it would be predicted that mitochondrial inhibitors may also show some moderate anti-bacterial and anti-fungal side effects.

[0040] To directly test this hypothesis, the inventors evaluated the anti-bacterial and anti-fungal activity of exemplary mitoriboscins. Several mitoriboscins showed anti-bacterial activity towards both gram-positive and gram-negative organism(s), pathogenic yeast (Candida albicans) and Methicillin-resistant Staphylococcus aureus (MRSA). Therefore, using cancer cells for initial drug screening may also be useful for developing new antibiotics to combat drug-resistant micro-organisms.

[0041] Over one thousand mitochondrial proteins are encoded by the nuclear genome. The inventors have begun to assess their potential prognostic value as biomarkers and companion diagnostics. The inventors hypothesize that the over-expression of a given mitochondrial protein in cancer cells and CSCs may be associated with tumor recurrence and metastasis, due to the emergence of drug resistance, and ultimately resulting in treatment failure. To test this hypothesis, the inventors used an online survival-analysis tool to perform Kaplan-Meier (K-M) studies on more than 400 nuclear mitochondrial gene transcripts to interrogate publicly available microarray data from patients with four distinct epithelial cancer types: i) breast, ii) ovarian, iii) lung and iv)

gastric. In all four anatomic cancer types, the inventors observed that the over-expression of mitochondrial gene transcripts is associated with poor clinical outcome. For example, this approach effectively predicted tamoxifen-resistance in ER(+) breast cancer patients (represented as recurrence and distant metastasis in FIGs. 10A-B, respectively), as well as Taxol and Platin resistance in ovarian cancer patients (represented as overall survival in FIGs. 11A-B, respectively). These results are functionally supported by further experimental observations demonstrating that Tamoxifen-resistant MCF7 cells (TAMR) show a significant increase in mitochondrial oxygen consumption and ATP production.

[0042] The present disclosure therefore relates to methods of predicting the sensitivity of neoplastic cell growth to anti-mitochondrial agents. The methods may include obtaining a sample of a neoplasm from a patient, determining the level of mitochondrial markers in the sample and comparing the level of mitochondrial markers to a control, and predicting the sensitivity of the neoplastic cell growth to inhibition by an anti-mitochondrial agent based on relative marker levels. High expression levels of mitochondrial markers correlate with high sensitivity to inhibition by an anti-mitochondrial agent. Mitochondrial markers may be obtained from tumor biopsy samples and/or by isolating circulating tumor cells from serum, plasma, and/or blood samples. Mitochondrial markers may include mitochondrial RNAs, proteins, and/or mitochondrial DNA. In some embodiments, mitochondrial DNA may be obtained from body fluids (e.g., blood, serum, plasma, saliva, sputum, milk, tears, urine, ascites, cyst fluid, pleural fluid, and/or cerebral spinal fluid). Mitochondrial marker levels may be measured by any number of ways known in the art, including quantitative PCR and/or RT-PCR, microarrays, Northern blots, Western blots, etc.

[0043] In some embodiments, mitochondrial markers may include mitochondrial proteins, RNA, and/or DNA that are associated with or regulate beta-oxidation and/or ketone metabolism,

such as HSD17B10, BDH1, ACAT1, ACADVL, ACACA, ACLY, HADHB, SUCLG2, ACAD9, HADHA, ECHS1, ACADSB. In some embodiments, mitochondrial markers may include mitochondrial proteins, RNA, and/or DNA that are involved in: mitochondrial biogenesis, such as HSPA9, TIMM8A, GFM1, MRPL45, MRPL17, HSPD1(HSP60), TSFM, TUFM; electron transport, such as NDUFB10, COX6B1, PMPCA, COX5B, SDHA, UQCRC1; metabolism, such as CHCHD2, ATP synthesis, such as ATP5B, ATPIF1, ATP5A1, ATP5F1, ATP5H, ATP5O; ADP/ATP exchange/transport, such as SLC25A5; CoQ synthesis, such as COQ9; ROS production, such as GPD2; and/or suppression of glycolysis, autophagy and mitophagy, such as SOGA1 and LRPPRC. In some embodiments, the mitochondrial markers may include mitochondrial proteins, RNA, and/or DNA related to the enzymes ACAT1/2 and/or OXCT1/2.

[0044] In some embodiments, the mitochondrial markers may include mitochondrial proteins, RNA, and/or DNA that are upregulated or increased in certain cancer types. For example, Table 5, adapted from U.S. Provisional Application No. 62/508,799, the contents of which is incorporated by reference in its entirety, shows exemplary proteins that may be used as mitochondrial biomarkers in gastric cancers. As is shown in Table 5, mitochondrial biomarkers may include mitochondrial proteins, RNA, and/or DNA associated with heat shock proteins and chaperones, membrane proteins, mitochondrial antioxidants, mitochondrial genome maintenance, large and/or small ribosomal subunits, and OXPHOS complexes. In some embodiments, two or

more mitochondrial biomarkers may be used to create a "Mito-Signature", a predictor for clinical outcomes. An exemplary Mito-Signature for gastric cancer is shown in Table 6.

Gene Probe ID	Symbol	Hazard-Ratio	Log-Rank Test
Heat Shock Proteins and Chaperones (4 probes)			
200807_s_at	HSPD1	1.83	1.9e-06
200806_s_at	HSPD1	1.56	0.003
200691_s_at	HSPA9	1.61	0.0002
205565_s_at	FXN	1.38	0.01
Membrane Proteins (9 probes)			
208844_at	VDAC3	2.22	1.4e-09
211662_s_at	VDAC2	1.51	0.002
200955_at	IMMT	2.20	2.4e-09
218118_s_at	TIMM23	1.91	4.2e-07
218408_at	TIMM10	1.88	1.4e-06
218357_s_at	TIMM8B	1.49	0.002
201821_s_at	TIMM17A	1.33	0.025
201870_at	TOMM34	1.95	5.1e-07
202264_s_at	TOMM40	1.44	0.009
Mitochondrial Anti-Oxidants (2 probes)			
215223_s_at	SOD2	1.72	2.1e-05
215078_at	SOD2	1.70	2.9e-05
Mitochondrial Genome Maintenance (3 probes)			
208694_at	PRKDC	2.05	1.2e-07
210543_s_at	PRKDC	1.78	6.9e-06
215757_at	PRKDC	1.47	0.003
Large Ribosomal Subunit (12 probes)			
204599_s_at	MRPL28	2.17	1.2e-08
221997_s_at	MRPL52	2.12	3.2e-09
222216_s_at	MRPL17	1.68	0.0001
220527_at	MRPL20	1.67	0.0002
217907_at	MRPL18	1.62	0.0004
218887_at	MRPL2	1.60	0.0002
203931_s_at	MRPL12	1.56	0.001
208787_at	MRPL3	1.53	0.0007
217919_s_at	MRPL42	1.52	0.002
218049_s_at	MRPL13	1.47	0.008
218281_at	MRPL48	1.40	0.009
213897_s_at	MRPL23	1.29	0.049
Small Ribosomal Subunit (8 probes)			
215919_s_at	MRPS11	1.89	5.1e-07
213840_s_at	MRPS12	1.84	1.5e-06
210008_s_at	MRPS12	1.47	0.004
204330_s_at	MRPS12	1.37	0.015
204331_s_at	MRPS12	1.37	0.037

203800_s_at	MRPS14	1.53	0.002
219220_x_at	MRPS22	1.44	0.005
219819_s_at	MRPS28	1.42	0.01
218112_at	MRPS34	1.36	0.02
Complex I (11 probes)			
201757_at	NDUFS5	2.27	6e-10
215850_s_at	NDUFA5	1.93	2.1e-07
208969_at	NDUFA9	1.92	1.5e-06
203606_at	NDUFS6	1.74	7.9e-05
214241_at	NDUFB8	1.67	5.7e-05
203371_s_at	NDUFB3	1.51	0.002
218226_s_at	NDUFB4	1.49	0.003
202001_s_at	NDUFA6	1.37	0.02
218160_at	NDUFA8	1.31	0.04
202785_at	NDUFA7	1.31	0.04
218563_at	NDUFA3	1.30	0.04
Complex II (1 probe)			
214166_at	SDHB	1.40	0.009
Complex III (2 probes)			
207618_s_at	BCS1L	1.76	7.1e-06
202233_s_at	UQCR8	1.51	0.001
Complex IV (10 probes)			
213736_at	COX5B	2.14	1.4e-08
218057_x_at	COX4NB	1.94	7.7e-07
201754_at	COX6C	1.74	7.1e-05
201441_at	COX6B1	1.67	0.0001
200925_at	COX6A1	1.64	8.8e-05
203880_at	COX17	1.60	0.0003
217451_at	COX5A	1.49	0.006
202110_at	COX7B	1.42	0.01
217249_x_at	COX7A2	1.33	0.035
216003_at	COX10	1.33	0.046
Complex V (13 probes)			
221677_s_at	ATP5O	2.22	2.1e-10
207552_at	ATP5G2	1.90	7.5e-06
207335_x_at	ATP5I	1.84	8.4e-06
217801_at	ATP5E	1.64	0.0002
208972_s_at	ATP5G1	1.51	0.002
210149_s_at	ATP5H	1.49	0.003
202961_s_at	ATP5J2	1.47	0.004
210453_x_at	ATP5L	1.45	0.006
207573_x_at	ATP5L	1.44	0.01
208746_x_at	ATP5L	1.40	0.009
213366_x_at	ATP5C	1.33	0.03
206993_at	ATP5S	1.29	0.04
213366_x_at	ATP5C1	1.33	0.03

Table 5. Prognostic value of mitochondrial markers in gastric cancers.

Gene Probe ID	Symbol	Hazard-Ratio	Log-Rank Test
201757_at	NDUFS5	2.27	6e-10
208844_at	VDAC3	2.22	1.4e-09
221677_s_at	ATP5O	2.22	2.1e-10
200955_at	IMMT	2.20	2.4e-09
204599_s_at	MRPL28	2.17	1.2e-08
213736_at	COX5B	2.14	1.4e-08
221997_s_at	MRPL52	2.12	3.2e-09
208694_at	PRKDC	2.05	1.2e-07
Combined		**2.77**	**1.4e-14**

Table 6. Exemplary compact gastric cancer Mito-Signature for predicting clinical outcome.

[0045] In some embodiments, the mitochondrial markers may include mitochondrial proteins, RNA, and/or DNA that are upregulated or increased in ovarian cancers. Table 7, adapted from U.S. Provisional Application No. 62/508,788, the contents of which is incorporated by reference in its entirety, shows exemplary proteins that may be used as mitochondrial biomarkers in ovarian cancers. As is shown in Table 7, mitochondrial biomarkers may include mitochondrial proteins, RNA, and/or DNA associated with heat shock proteins and chaperones, membrane proteins, mitochondrial antioxidants, mitochondrial creatine kinases, large and/or small ribosomal subunits, and OXPHOS complexes. Exemplary Mito-Signatures for ovarian cancer are shown in Table 8.

Gene Probe ID	Symbol	Hazard-Ratio	Log-Rank Test
Chaperones/HSPs			
200691_s_at	HSPA9	1.77	0.047
Membrane Proteins			
200955_at	IMMT	2.61	0.002
218408_at	TIMM10	2.63	0.0008
201821_s_at	TIMM17A	2.46	0.003
217981_s_at	TIMM10B	1.94	0.05
218118_s_at	TIMM23	1.79	0.05
201519_at	TOMM70A	2.28	0.005
211662_s_at	VDAC2	2.32	0.01
208845_at	VDAC3	2.07	0.01
208846_s_at	VDAC3	1.96	0.048

200657_at	SLC25A5	2.67	0.0008
221020_s_at	SLC25A32	1.98	0.05
Anti-Oxidant Proteins			
201468_s_at	NQO1	3.48	0.001
210519_s_at	NQO1	2.37	0.006
215223_s_at	SOD2	1.82	0.048
Mitochondrial Creatine Kinase			
205295_at	CKMT2	2.27	0.0035
Large Ribosomal Subunit			
201717_at	MRPL49	3.56	4.3e-05
221692_s_at	MRPL34	2.99	0.001
218890_x_at	MRPL35	2.48	0.002
213897_s_at	MRPL23	2.48	0.01
217907_at	MRPL18	2.36	0.006
218281_at	MRPL48	2.29	0.007
222216_s_at	MRPL17	2.17	0.007
217980_s_at	MRPL16	2.17	0.008
219162_s_at	MRPL11	2.14	0.02
218105_s_at	MRPL4	1.90	0.03
Small Ribosomal Subunit			
203800_s_at	MRPS14	2.97	0.0002
204331_s_at	MRPS12	2.90	9e-04
210008_s_at	MRPS12	2.46	0.0035
221688_s_at	MRPS4	2.88	0.002
219819_s_at	MRPS28	2.64	0.0008
218001_at	MRPS2	2.15	0.01
219220_x_at	MRPS22	2.13	0.025
218654_s_at	MRPS33	2.05	0.02
217942_at	MRPS35	2.05	0.03
212604_at	MRPS31	2.02	0.02
221437_s_at	MRPS15	1.88	0.05
Complex I			
218563_at	NDUFA3	3.55	2.3e-05
218320_s_at	NDUFB11	3.12	7e-05
201740_at	NDUFS3	2.93	0.001
218200_s_at	NDUFB2	2.60	0.001
203371_s_at	NDUFB3	2.56	0.0008
203189_s_at	NDUFS8	2.43	0.002
218201_at	NDUFB2	2.43	0.002
203613_s_at	NDUFB6	2.43	0.008
202000_at	NDUFA6	2.43	0.0015
202785_at	NDUFA7	2.30	0.01
220864_s_at	NDUFA13	2.25	0.006
209303_at	NDUFS4	2.20	0.009
218160_at	NDUFA8	2.16	0.008
203190_at	NDUFS8	2.15	0.01

202941_at	NDUFV2	2.13	0.02
208714_at	NDUFV1	2.07	0.03
209224_s_at	NDUFA2	2.03	0.044
211752_s_at	NDUFS7	1.98	0.02
217860_at	NDUFA10	1.95	0.037
202298_at	NDUFA1	1.91	0.03
208969_at	NDUFA9	1.89	0.26
201966_at	NDUFS2	1.86	0.035
Complex II			
210131_x_at	SDHC	2.97	0.0005
202004_x_at	SDHC	2.78	0.0005
202675_at	SDHB	1.83	0.04
Complex III			
208909_at	UQCRFS1	3.68	9.8e-05
201568_at	UQCR7	2.28	0.004
209065_at	UQCR6	2.12	0.04
202090_s_at	UQCR	1.86	0.04
212600_s_at	UQCR2	1.76	0.047
Complex IV			
201441_at	COX6B	2.64	0.0009
203880_at	COX17	2.49	0.004
203858_s_at	COX10	2.47	0.002
211025_x_at	COX5B	2.34	0.004
202343_x_at	COX5B	2.32	0.004
202110_at	COX7B	2.30	0.02
218057_x_at	COX4NB	2.08	0.01
202698_x_at	COX4I1	1.89	0.03
201119_s_at	COX8A	1.87	0.04
204570_at	COX7A	1.76	0.05
Complex V			
208870_x_at	ATP5C	2.57	0.0008
213366_x_at	ATP5C	2.44	0.002
205711_x_at	ATP5C	2.08	0.01
207507_s_at	ATP5G3	2.40	0.002
210453_x_at	ATP5L	2.35	0.003
208746_x_at	ATP5L	2.24	0.005
207573_x_at	ATP5L	2.20	0.006
208972_s_at	ATP5G	2.15	0.007
207508_at	ATP5G3	2.12	0.01
202961_s_at	ATP5J2	1.91	0.02
217848_s_at	PPA1	1.89	0.03
202325_s_at	ATP5J	1.78	0.05

Table 7. Prognostic value of mitochondrial markers in ovarian cancers.

Mito-Signature 1			
Gene Probe ID	**Symbol**	**Hazard-Ratio**	**Log-Rank Test**
208909_at	UQCRFS1	3.68	9.8e-05
201717_at	MRPL49	3.56	4.3e-05
Combination		**4.59**	**3.1e-05**
Mito-Signature 2			
Gene Probe ID	**Symbol**	**Hazard-Ratio**	**Log-Rank Test**
208909_at	UQCRFS1	3.68	9.8e-05
218563_at	NDUFA3	3.55	2.3e-05
Combination		**5.03**	**1.2e-05**
Mito-Signature 3			
Gene Probe ID	**Symbol**	**Hazard-Ratio**	**Log-Rank Test**
208909_at	UQCRFS1	3.68	9.8e-05
218563_at	NDUFA3	3.55	2.3e-05
201202_at	PCNA	2.85	0.0003
Combination		**5.63**	**7.6e-06**

Table 8. Exemplary compact ovarian cancer Mito-Signatures for predicting clinical outcome.

[0046] In some embodiments, the mitochondrial markers may include mitochondrial proteins, RNA, and/or DNA that are upregulated or increased in breast cancers. Table 9, adapted from U.S. Provisional Application No. 62/508,750, the contents of which is incorporated by reference in its entirety, shows exemplary proteins that may be used as mitochondrial biomarkers in breast cancers. As is shown in Table 9, mitochondrial biomarkers may include mitochondrial proteins, RNA, and/or DNA associated mitochondrial chaperones, membrane proteins, mitochondrial carrier families, mitochondrial antioxidants, mitochondrial creatine kinases, large and/or small ribosomal subunits, and OXPHOS complexes. Exemplary Mito-Signatures for breast cancer are shown in Table 10.

Gene Probe ID	**Symbol**	**Hazard-Ratio**	**Log-Rank Test**
Mito Chaperones			
200807_s_at	HSPD1	3.61	5.9e-06
200806_s_at	HSPD1	2.30	0.006
200691_s_at	HSPA9	2.04	0.01
205565_s_at	FXN	1.83	0.038
221235_s_at	TRAP1	1.79	0.047
Mito Membrane Proteins			
211662_s_at	VDAC2	4.17	2.2e-07
210626_at	AKAP1	2.15	0.01

200955_at	IMMT	1.81	0.04
201519_at	TOMM70A	2.78	0.0003
201512_s_at	TOMM70A	2.15	0.01
203093_s_at	TIMM44	2.23	0.01
218188_s_at	TIMM13	2.23	0.02
201822_at	TIMM17A	2.01	0.01
215171_s_at	TIMM17A	1.85	0.04
203342_at	TIMM17B	1.78	0.04
Mito Carrier Family			
217961_at	SLC25A38	2.77	0.0003
210010_s_at	SLC25A1	2.38	0.002
200657_at	SLC25A5	2.04	0.01
221020_s_at	SLC25A32	1.98	0.02
Mito Anti-Oxidants			
215223_s_at	SOD2	2.94	0.0001
215078_at	SOD2	2.81	0.008
Mito Creatine Kinase			
205295_at	CKMT2	2.18	0.04
202712_s_at	CKMT1A	2.03	0.02
Large Ribosomal Subunit			
218027_at	MRPL15	3.28	1.6e-05
217907_at	MRPL18	2.91	0.0001
219244_s_at	MRPL46	2.89	0.02
218270_at	MRPL24	2.38	0.002
218049_s_at	MRPL13	2.14	0.01
218281_at	MRPL48	2.11	0.01
208787_at	MRPL3	2.07	0.03
213897_s_at	MRPL23	2.02	0.04
218105_s_at	MRPL4	1.99	0.02
222216_s_at	MRPL17	1.97	0.02
217919_s_at	MRPL42	1.88	0.05
218202_x_at	MRPL44	1.78	0.04
Small Ribosomal Subunit			
204330_s_at	MRPS12	2.35	0.03
211595_s_at	MRPS11	2.26	0.01
219819_s_at	MRPS28	1.88	0.03
217919_s_at	MRPL42	1.88	0.05
219220_x_at	MRPS22	1.85	0.04
218654_s_at	MRPS33	1.84	0.04
Complex I			
218160_at	NDUFA8	2.45	0.002
202000_at	NDUFA6	2.41	0.002
202001_s_at	NDUFA6	2.23	0.006
203039_s_at	NDUFS1	2.40	0.003
201740_at	NDUFS3	2.17	0.006
203613_s_at	NDUFB6	1.99	0.02

208714_at	NDUFV1	1.96	0.03
203606_at	NDUFS6	1.92	0.04
202298_at	NDUFA1	1.89	0.03
Complex III			
209065_at	UQCRB	3.42	1.9e-05
209066_x_at	UQCRB	2.12	0.01
205849_s_at	UQCR6	2.53	0.002
201066_at	UQCR4	1.96	0.02
212600_s_at	UQCRC2	1.92	0.04
Complex IV			
203880_at	COX17	2.99	7.6e-05
213735_s_at	COX5B	2.51	0.001
202343_x_at	COX5B	2.10	0.01
211025_x_at	COX5B	2.08	0.01
202698_x_at	COX4I1	2.36	0.02
200925_at	COX6A1	2.14	0.01
218057_x_at	COX4NB	1.99	0.04
217249_x_at	COX7A2	1.90	0.03
Complex V			
202325_s_at	ATP5J	2.65	0.01
202961_s_at	ATP5J2	2.44	0.035
213366_x_at	ATP5C1	2.19	0.01
208870_x_at	ATP5C1	2.08	0.01
205711_x_at	ATP5C1	2.00	0.02
217848_s_at	PPA1	2.07	0.01
221677_s_at	ATP5O	2.03	0.02
217801_at	ATP5E	1.99	0.02
207508_at	ATP5G3	1.93	0.02

Table 9. Prognostic value of mitochondrial markers in breast cancers.

Mito-Signature 1			
Gene Probe ID	**Symbol**	**Hazard-Ratio**	**Log-Rank Test**
200807_s_at	HSPD1	3.61	5.9e-06
209065_at	UQCRB	3.42	1.9e-05
218027_at	MRPL15	3.28	1.6e-05
203880_at	COX17	2.99	7.6e-05
Combined		**5.34**	**1e-09**
Mito-Signature 2			
Gene Probe ID	**Symbol**	**Hazard-Ratio**	**Log-Rank Test**
211662_s_at	VDAC2	4.17	2.2e-07
200807_s_at	HSPD1	3.61	5.9e-06
Combined		**5.19**	**6e-09**

Table 10. Exemplary compact breast cancer Mito-Signatures for predicting clinical outcome.

[0047] In some embodiments, the mitochondrial markers may include mitochondrial proteins, RNA, and/or DNA that are upregulated or increased in lung cancers. Table 11, adapted from U.S. Provisional Application No. 62/508,769, the contents of which is incorporated by reference in its entirety, shows exemplary proteins that may be used as mitochondrial biomarkers in lung cancers. As is shown in Table 11, mitochondrial biomarkers may include mitochondrial proteins, RNA, and/or DNA associated with mitochondrial heat shock proteins and membrane proteins, mitochondrial creatine kinases, mitochondrial genome maintenance proteins, large and/or small ribosomal subunits, and OXPHOS complexes.

Gene Probe ID	Symbol	Hazard-Ratio	Log-Rank Test
HSPs and Membrane Proteins (28 probes in total)			
200806_s_at	HSPD1	4.89	<1.0e-16
218119_at	TIMM23	4.68	1.1e-16
218357_s_at	TIMM8B	4.26	7.8e-16
203342_at	TIMM17B	3.31	2.5e-11
203093_s_at	TIMM44	2.29	1.1e-09
217981_s_at	TIMM10B	2.15	1.2e-06
218316_at	TIMM9	2.06	4.3e-08
201821_s_at	TIMM17A	2.04	1.7e-09
218188_s_at	TIMM13	1.94	8.5e-09
218118_s_at	TIMM23	1.83	1.8e-07
218408_at	TIMM10	1.79	4e-05
202264_s_at	TOMM40	4.29	1.1e-14
217960_s_at	TOMM22	3.19	1.3e-13
201870_at	TOMM34	2.83	9.8e-12
201812_s_at	TOMM7	2.84	5.4e-13
201512_s_at	TOMM70A	1.90	3.1e-08
212773_s_at	TOMM20	1.54	0.0006
217139_at	VDAC1	3.74	1.9e-14
217140_s_at	VDAC1	2.58	1.1e-16
212038_s_at	VDAC1	1.63	7.8e-05
208844_at	VDAC3	3.64	3.9e-14
211662_s_at	VDAC2	2.36	6e-14
210625_s_at	AKAP1	1.88	1.3e-06
200657_at	SLC25A5	1.54	0.0001
Mitochondrial Creatine Kinase (2 probes in total)			
202712_s_at	CKMT1A	2.88	7.8e-10
205295_at	CKMT2	1.51	0.0005
Mitochondrial Genome Maintenance (3 probes in total)			

210543_s_at	PRKDC	4.69	1.1e-16
208694_at	PRKDC	2.23	4.3e-12
215757_at	PRKDC	1.65	4.0e-05
Large Ribosomal Subunit (21 probes in total)			
218281_at	MRPL48	4.36	1.9e-15
213897_s_at	MRPL23	3.55	5.4e-13
219162_s_at	MRPL11	3.29	2.5e-13
221997_s_at	MRPL52	3.20	3.6e-14
221692_s_at	MRPL34	3.08	1.6e-11
203931_s_at	MRPL12	2.82	3.3e-12
218887_at	MRPL2	2.81	4.4e-11
217919_s_at	MRPL42	2.54	1.6e-13
218270_at	MRPL24	2.35	1.8e-09
218105_s_at	MRPL4	2.32	1.6e-09
218202_x_at	MRPL44	2.19	2.5e-10
222216_s_at	MRPL17	2.02	1.4e-08
218890_x_at	MRPL35	1.96	5.7e-09
204599_s_at	MRPL28	1.91	1.4e-07
220527_at	MRPL20	1.84	9.1e-05
201717_at	MRPL49	1.68	8.7e-06
218049_s_at	MRPL13	1.68	8.1e-06
217980_s_at	MRPL16	1.66	1.5e-05
203152_at	MRPL40	1.62	0.0001
218027_at	MRPL15	1.59	0.0001
203781_at	MRPL33	1.47	0.001
Small Ribosomal Subunit (19 probes in total)			
204331_s_at	MRPS12	4.10	1.1e-16
210008_s_at	MRPS12	3.93	4.9e-14
204330_s_at	MRPS12	3.27	1e-13
213840_s_at	MRPS12	2.99	2.3e-12
217932_at	MRPS7	3.55	2.3e-12
218001_at	MRPS2	3.28	1e-11
221688_s_at	MRPS4	3.09	7.7e-11
211595_s_at	MRPS11	2.96	9.1e-12
215919_s_at	MRPS11	1.55	0.0002
218112_at	MRPS34	2.43	7.6e-08
212604_at	MRPS31	2.29	2.7e-07
219819_s_at	MRPS28	1.74	2.7e-06
217942_at	MRPS35	1.70	8.4e-06
221437_s_at	MRPS15	1.59	0.0001
12145_at	MRPS27	1.61	7.4e-05
218398_at	MRPS30	1.47	0.003
218654_s_at	MRPS33	1.35	0.01
203800_s_at	MRPS14	1.27	0.05
Complex I (27 probes in total)			
203371_s_at	NDUFB3	4.30	3.6e-15

203189_s_at	NDUFS8	4.15	4.4e-16
203190_at	NDUFS8	2.94	2.1e-11
209303_at	NDUFS4	3.83	1.1e-15
218484_at	NDUFA4L2	3.33	2.1e-13
218226_s_at	NDUFB4	3.21	1.8e-14
220864_s_at	NDUFA13	3.00	9.5e-11
202941_at	NDUFV2	3.00	1.3e-13
201740_at	NDUFS3	2.92	1.2e-11
217860_at	NDUFA10	2.77	3e-14
218563_at	NDUFA3	2.23	1.9e-10
214241_at	NDUFB8	2.23	1.5e-09
218201_at	NDUFB2	2.21	1.2e-08
215850_s_at	NDUFA5	1.83	3.6e-07
202785_at	NDUFA7	1.81	3e-07
202298_at	NDUFA1	1.72	3e-06
201966_at	NDUFS2	1.70	6.6e-06
202839_s_at	NDUFB7	1.64	0.0009
201757_at	NDUFS5	1.64	4.3e-05
209224_s_at	NDUFA2	1.59	6.6e-05
208969_at	NDUFA9	1.56	0.0002
211752_s_at	NDUFS7	1.50	0.0007
203613_s_at	NDUFB6	1.49	0.0009
209223_at	NDUFA2	1.49	0.0009
218320_s_at	NDUFB11	1.48	0.001
218200_s_at	NDUFB2	1.48	0.001
208714_at	NDUFV1	1.44	0.002
Complex II (5 probes in total)			
216591_s_at	SDHC	4.27	7.8e-16
202004_x_at	SDHC	3.64	4e-14
210131_x_at	SDHC	3.45	4.2e-14
202675_at	SDHB	2.06	7.4e-07
214166_at	SDHB	1.94	2.5e-08
Complex III (8 probes in total)			
201568_at	UQCR7	3.34	3.7e-13
209066_x_at	UQCR6	2.96	2.5e-10
202233_s_at	UQCR8	2.09	5.9e-07
208909_at	UQCRFS1	1.69	2.6e-05
201066_at	UQCR4/CYC1	1.54	0.0006
207618_s_at	BCS1L	1.54	0.0003
205849_s_at	UQCR6	1.48	0.0008
202090_s_at	UQCR	1.45	0.004
Complex IV (19 probes in total)			
211025_x_at	COX5B	4.46	5.3e-15
202343_x_at	COX5B	3.97	1.1e-16
213735_s_at	COX5B	2.15	9.6e-10
213736_at	COX5B	1.51	0.0015

200925_at	COX6A	3.94	1.1e-16
201119_s_at	COX8A	3.78	2.4e-15
203880_at	COX17	3.55	3.9e-15
201754_at	COX6C	3.24	1.8e-14
217249_x_at	COX7A2	3.05	3.3e-13
201441_at	COX6B	2.93	3.8e-12
206353_at	COX6A2	2.77	1.8e-11
203858_s_at	COX10	2.44	1.3e-09
202110_at	COX7B	2.29	2.5e-12
216003_at	COX10	2.18	1.8e-07
221550_at	COX15	2.09	1.5e-10
217451_at	COX5A	2.01	9e-06
218057_x_at	COX4NB	1.54	0.0008
204570_at	COX7A	1.51	0.0015
202698_x_at	COX4I1	1.39	0.01
Complex V (23 probes in total)			
202961_s_at	ATP5J2	4.38	1.3e-14
207507_s_at	ATP5G3	4.14	<1e-17
207508_at	ATP5G3	2.34	1.6e-13
210149_s_at	ATP5H	3.70	3.7e-15
209492_x_at	ATP5I	3.33	7.7e-13
207335_x_at	ATP5I	2.14	2e-08
203926_x_at	ATP5D	3.02	2.7e-11
213041_s_at	ATP5D	2.41	3.1e-10
208764_s_at	ATP5G2	2.75	2.9e-10
207552_at	ATP5G2	2.55	4.3e-09
217368_at	ATP5G2	1.85	4.9e-07
217801_at	ATP5E	2.62	2e-09
210453_x_at	ATP5L	2.56	1.8e-11
207573_x_at	ATP5L	2.25	1.9e-10
208746_x_at	ATP5L	2.10	7.4e-10
201322_at	ATP5B	1.88	1.5e-07
206992_s_at	ATP5S	1.88	2.9e-07
206993_at	ATP5S	1.85	2.1e-07
208972_s_at	ATP5G	1.87	5.4e-08
221677_s_at	ATP5O	1.71	6.8e-06
208870_x_at	ATP5C	1.54	0.0008
205711_x_at	ATP5C	1.42	0.004
213366_x_at	ATP5C	1.40	0.007

Table 11. Prognostic value of mitochondrial markers in lung cancers.

[0048] The present disclosure also relates to methods of treating a neoplastic disease in a patient. Such treatment may occur following the determination of increased expression levels of one or more mitochondrial markers. Methods may include obtaining a sample of a neoplasm from

a neoplastic disease patient, determining the expression level of one or more mitochondrial markers in the CSCs (*e.g.*, Mito-signature) of the neoplasm sample relative to a control sample, and, if the higher expression levels of one or more mitochondrial markers is detected, administering to the patient a therapeutically effective amount of an anti-mitochondrial agent. The anti-mitochondrial agent may include one or more mitoriboscins, mitoketoscins, and/or antimitoscins. The anti-mitochondrial agent may include compounds that inhibit mitochondrial function as an off-target effect, such as metformin, tetracycline family members (such as doxycycline), erythromycin family members (such as azithromycin), atovaquone, bedaquiline. In some embodiments, the anti-mitochondrial agent comprises a lactate transporter inhibitor or a glycolysis inhibitor. In some embodiments, the glycolysis inhibitor comprises an agent which inhibits triose-phosphate isomerase, fructose 1,6 bisphosphate aldolase, glycero-3-phosphate dehydrogenase, phosphoglycerate kinase, phosphoglycerate mutase, enolase, pyruvate kinase, and/or lactate dehydrogenase.

[0049] In some embodiments, the neoplastic disease is a breast neoplasm subtype such as ER(+), PR(+), HER2(+), triple-negative (ER(-)/PR(-)/HER2(-)), ER(-), PR(-), any neoplasm and nodal stages, and any neoplasm grades. The neoplasm may include Luminal A, Luminal B, and Basal breast cancers. In some embodiments, wherein the neoplasm is a pre-malignant lesion such as a ductal carcinoma in situ (DCIS) of the breast or myelodysplastic syndrome of the bone marrow. In some embodiments, the neoplasm may be from a tissue including breast, skin, kidney, lung, pancreas, gastric, rectum and colon, prostate, ovarian, and bladder, and may include epithelial cells, non-epithelial cells, lymphomas, sarcomas, and melanomas.

[0050] In some embodiments, a patient may be treated with an anti-mitochondrial agent concurrently with an anti-angiogenic agent and/or an anti-neoplastic agent. For example, patients

may be treated with an anti-mitochondrial agent in addition to treatment with a conventional cancer therapy, as is outline in FIG. 9. In some embodiments, one or more anti-neoplastic agents and/ or anti-angiogenic agents may be administered simultaneously to or sequentially with the anti-mitochondrial agent. Anti-angiogenic agents may include one or more of angiostatin, bevacizumab, arresten, canstatin, combretastatin, endostatin, NM-3, thrombospondin, tumstatin, 2-methoxyestradiol, Vitaxin, Getfitinib, ZD6474, erlotinib, CI1033, PKI1666, cetuximab, PTK787, SU6668, SUl 1248, trastuzumab, Marimastat, COL-3, Neovastat, 2-ME, SU6668, anti-VEGF antibody, Medi-522 (Vitaxin E), tumstatin, arrestin, recombinant EPO, troponin I, EMD121974, IFN-α celecoxib, PD0332991, tamoxifen, paclitaxel (taxol) and thalidomide. Anti-neoplastic agents may include natural products such as vitamin C, caffeic acid phenyl ester (CAPE), and/or berberine. The anti-neoplastic agent may include one or more of 17-AAG, Apatinib, Ascomycin, Axitinib, Bexarotene, Bortezomib, Bosutinib, Bryostatin 1, Bryostatin 2, Canertinib, Carboplatin, Cediranib, Cisplatin, Cyclopamine, Dasatinib, 17-DMAG, Docetaxel, Doramapimod, Dovitinib, Erlotinib, Everolimus, Gefitinib, Geldanamycin, Gemcitabine, Imatinib, Imiquimod, Ingenol 3-Angelate, Ingenol 3-Angelate 20-Acetate, Irinotecan, Lapatinib, Lestaurtinib, Nedaplatin, Masitinib, Mubritinib, Nilotinib, NVP-BEZ235, OSU-03012, Oxaliplatin, Paclitaxel, Palbociclib (and other CDK4/6 inhibitors), Pazopanib, Picoplatin, Pimecrolimus, PKC412, Rapamycin, Satraplatin, Sorafenib, Sunitinib, Tandutinib, Tivozanib, Thalidomide, Temsirolimus, Tozasertib, Vandetanib, Vargatef, Vatalanib, Zotarolimus, ZSTK474, Bevacizumab (Avasti), Cetuximab, Herceptin, Rituximab, Tamoxifen, Trastuzumab, Apatinib, Axitinib, Bisindolylmaleimide I, Bisindolylmaleimide I, Bosutinib, Canertinib, Cediranib, Chelerythrine, CP690550, Dasatinib, Dovitinib, Erlotinib, Fasudil, Gefitinib, Genistein, Go 6976, H-89, HA-1077, Imatinib, K252a, K252c, Lapatinib, Di-p- Toluenesulfonate,

Lestaurtinib, LY 294002, Masitinib, Mubritinib, Nilotinib, OSU-03012, Pazopanib, PD 98059, PKC412, Roscovitine, SB 202190, SB 203580, Sorafenib, SP600125, Staurosporine, Sunitinib, Tandutinib, Tivozanib, Tozasertib, Tyrphostin AG 490, Tyrphostin AG 1478, U0126, Vandetanib, Vargatef, Vatalanib, Wortmannin, ZSTK474, Cyclopamine, Carboplatin, Cisplatin, Eptaplatin, Nedaplatin, Oxaliplatin, Picoplatin, Satraplatin, Bortezomib (Velcade), Metformin, Halofuginone. Metformin, N-acetyl -cysteine (NAC), RTA 402 (Bardoxolone methyl), Auranofin, BMS-345541, IMD-0354, PS-1145, TPCA-I, Wedelolactone, Echinomycin, 2-deoxy-D-glucose (2-DG), 2-bromo-D-glucose, 2-fluoro-D-glucose, and 2-iodo- D-glucose, dichloro-acetate (DCA), 3-chloro-pyruvate, 3-Bromo-pyruvate (3-BrPA), 3-Bromo- 2-oxopropionate, Oxamate, LY 294002, NVP-BEZ235, Rapamycin, Wortmannin, Quercetin, Resveratrol, N-acetyl-cysteine (NAC), N-acetyl -cysteine amide (NACA), Ascomycin, CP690550, Cyclosporin A, Everolimus, Fingolimod, FK-506, Mycophenolic Acid, Pimecrolimus, Rapamycin, Temsirolimus, Zotarolimus, Roscovitine, PD 0332991 (CDK4/6 inhibitor), Chloroquine, BSI-201 , Olaparib, DR 2313, and NU 1025.

[0051] The present disclosure relates to diagnostic kits that may be used to assay a cancer sample for sensitivity to mitochondrial inhibitor therapy. In some embodiments, this kit or platform, known as MITO-ONC-RX, includes both therapeutic and diagnostic modalities (FIG. 12). In some embodiments, the present disclosure includes a kit for measuring one or more mitochondrial markers (companion diagnostics) to identify a high-risk cancer patient population that is most likely to benefit from anti-mitochondrial therapy. In some embodiments, the kit may include a component for measuring for measuring levels of mitochondrial marker RNA, DNA, and/or protein relative to a normal control. In some embodiments, the mitochondrial marker is measured by any number of ways known in the art for measuring RNA, DNA, and or protein, including quantitative PCR and/or RT-PCR kits, microarrays, Northern blots, and Western blots.

In some embodiments, the kit may include an antibody specific to a mitochondrial marker. The antibody may be a monoclonal or a polyclonal antibody. In some embodiments, the kit may include a molecule that binds to at least one of a mitochondrial ribosomal protein (MRP), an OXPHOS complex, and a mitochondrial membrane protein/chaperone.

[0052] The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used in the description of the invention and the appended claims, the singular forms "a," "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. The invention includes numerous alternatives, modifications, and equivalents as will become apparent from consideration of the following detailed description.

[0053] It will be understood that although the terms "first," "second," "third," "a)," "b)," and "c)," etc. may be used herein to describe various elements of the invention should not be limited by these terms. These terms are only used to distinguish one element of the invention from another. Thus, a first element discussed below could be termed an element aspect, and similarly, a third without departing from the teachings of the present invention. Thus, the terms "first," "second," "third," "a)," "b)," and "c)," etc. are not intended to necessarily convey a sequence or other hierarchy to the associated elements but are used for identification purposes only. The sequence of operations (or steps) is not limited to the order presented in the claims.

[0054] Unless otherwise defined, all terms (including technical and scientific terms) used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. It will be further understood that terms, such as those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the present application and relevant art and should not be interpreted in an

idealized or overly formal sense unless expressly so defined herein. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. In case of a conflict in terminology, the present specification is controlling.

[0055] Also, as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

[0056] Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination. Moreover, the present invention also contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted. To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed.

[0057] As used herein, the transitional phrase "consisting essentially of" (and grammatical variants) is to be interpreted as encompassing the recited materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. Thus, the term "consisting essentially of" as used herein should not be interpreted as equivalent to "comprising."

[0058] The term "about," as used herein when referring to a measurable value, such as, for example, an amount or concentration and the like, is meant to encompass variations of ± 20%, ± 10%, ± 5%, ± 1%, ± 0.5%, or even ± 0.1% of the specified amount. A range provided herein for a measurable value may include any other range and/or individual value therein.

[0059] Having thus described certain embodiments of the present invention, it is to be understood that the invention defined by the appended claims is not to be limited by particular details set forth in the above description as many apparent variations thereof are possible without departing from the spirit or scope thereof as hereinafter claimed.

CLAIMS

What is claimed is:

1. A method for identifying a patient for anti-mitochondrial therapy, the method comprising:

obtaining a sample from the patient;

determining the level of at least one mitochondrial marker in the sample; and

classifying the patient as a candidate for therapy with an anti-mitochondrial therapy, wherein a patient is classified as a candidate for therapy with an anti-mitochondrial therapy if the sample is determined to have an increased level of the at least one mitochondrial marker relative to a threshold level.

2. The method of claim 1, wherein the sample is at one of a lung, breast, ovarian, gastric, skin, kidney, pancreas, rectum, colon, prostate, bladder, epithelial, and non-epithelial tissue sample.

3. The method of clam 1, wherein the sample is a body fluid comprising at least one of blood, serum, plasma, saliva, sputum, milk, tears, urine, ascites, cyst fluid, pleural fluid, and cerebral spinal fluid.

4. The method of claim 1, wherein the sample comprises circulating tumor cells isolated from at least one of serum, plasma, and blood.

5. The method of claim 1, wherein the mitochondrial marker is at least one of a mitochondrial protein, a mitochondrial RNA, and a mitochondrial DNA.

6. The method of claim 5, wherein the mitochondrial marker regulates at least one of beta-oxidation and ketone metabolism.

7. The method of claim 6, wherein the mitochondrial marker is at least one of HSD17B10, BDH1, ACAT1, ACADVL, ACACA, ACLY, HADHB, SUCLG2, ACAD9, HADHA, ECHS1, and ACADSB.

8. The method of claim 5, wherein the mitochondrial marker regulates at least one of mitochondrial biogenesis, electron transport, metabolism, ATP synthesis, ADP/ATP exchange/transport, CoQ synthesis, ROS production, and suppression of glycolysis, autophagy and/or mitophagy.

9. The method of claim 8, wherein the mitochondrial marker is at least one of HSPA9, TIMM8A, GFM1, MRPL45, MRPL17, HSPD1(HSP60), TSFM, TUFM, NDUFB10, COX6B1, PMPCA, COX5B, SDHA, UQCRC1, CHCHD2, ATP5B, ATPIF1, ATP5A1, ATP5F1, ATP5H, ATP5O, SLC25A5, COQ9, GPD2, SOGA1, and LRPPRC.

10. The method of claim 5, wherein the mitochondrial marker regulates at least one of ACAT1/2 and/or OXCT1/2.

11. The method of claim 1, further comprising administering to the patient having an increased level of at least one mitochondrial marker a mitochondrial inhibitor.

12. The method of claim 11, wherein the mitochondrial inhibitor is at least one of a mitoriboscin, a mitoketoscin, a antimitoscin, metformin, a tetracycline family member, a erythromycin family member, atovaquone, bedaquiline, vitamin c, caffeic acid phenyl ester, and berberine.

13. The method of claim 12, wherein the tetracycline family member is doxycycline.

14. The method of claim 12, wherein the erythromycin family member is azithromycin.

15. The method of claim 1, further comprising administering to the patient an anti-angiogenic agent.

16. The method of claim 15, wherein the anti-angiogenic agent is at least one of angiostatin, bevacizumab, arresten, canstatin, combretastatin, endostatin, NM-3, thrombospondin, tumstatin, 2-methoxyestradiol, Vitaxin, Getfitinib, ZD6474, erlotinib, CI1033, PKI1666, cetuximab, PTK787, SU6668, SUl 1248, trastuzumab, Marimastat, COL-3, Neovastat, 2-ME, SU6668, anti-VEGF antibody, Medi-522 (Vitaxin E), tumstatin, arrestin, recombinant EPO, troponin I, EMD121974, IFN-α celecoxib, PD0332991, tamoxifen, paclitaxel (taxol) and thalidomide.

17. The method of claim 15, wherein the anti-angiogenic agent is administered simultaneously or sequentially with a mitochondrial inhibitor.

18. A diagnostic kit for identifying a patient for an anti-mitochondrial therapy, the kit comprising a component for measuring for measuring levels of at least one of a mitochondrial marker RNA, a mitochondrial marker DNA, and a mitochondrial marker protein relative to a threshold level.

19. The kit of claim 18, wherein the component for measuring levels of at least one of a mitochondrial marker RNA, a mitochondrial marker DNA, and a mitochondrial marker protein is at least one of a PCR kit, a microarray, a Northern blot, and a Western blot.

20. The kit of claim 18, wherein the kit comprises an antibody specific to a mitochondrial marker.

21. The kit of claim 20, wherein the antibody is at least one of a monoclonal antibody and a polyclonal antibody.

FIG. 1B

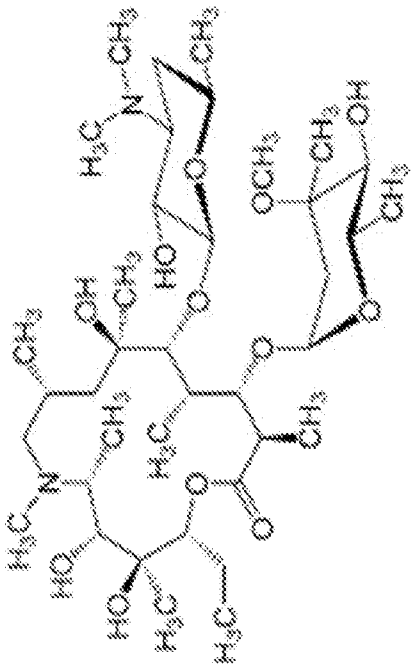


FIG. 1D

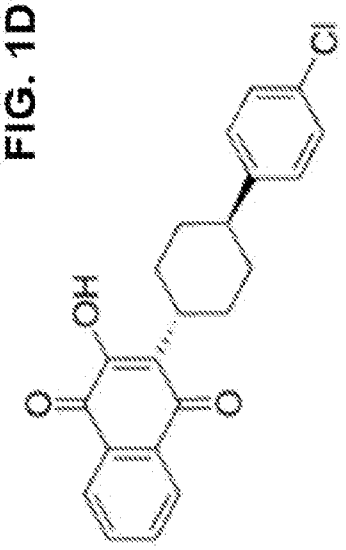


FIG. 1A

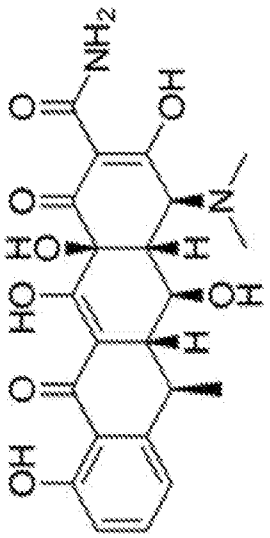
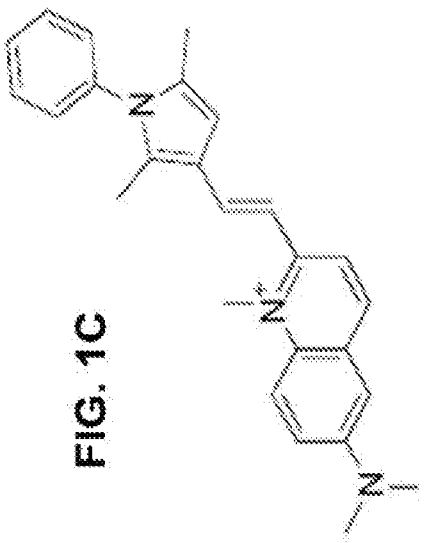


FIG. 1C



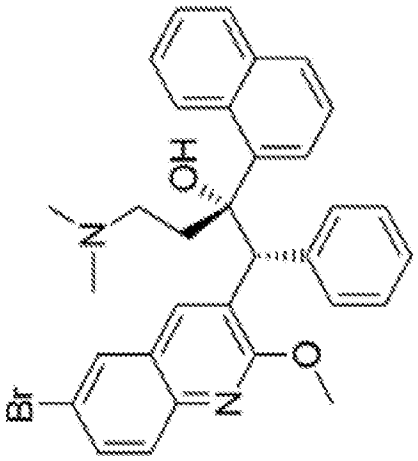


FIG. 1E

FIG. 2A

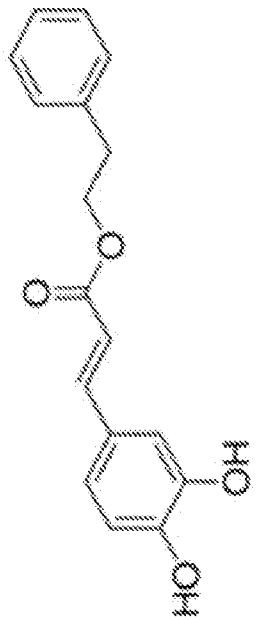


FIG. 2B

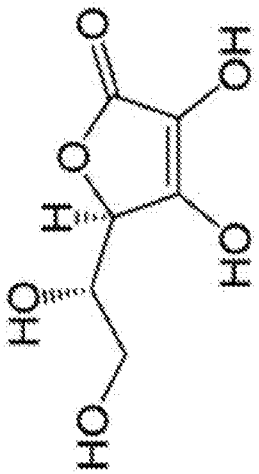


FIG. 2C

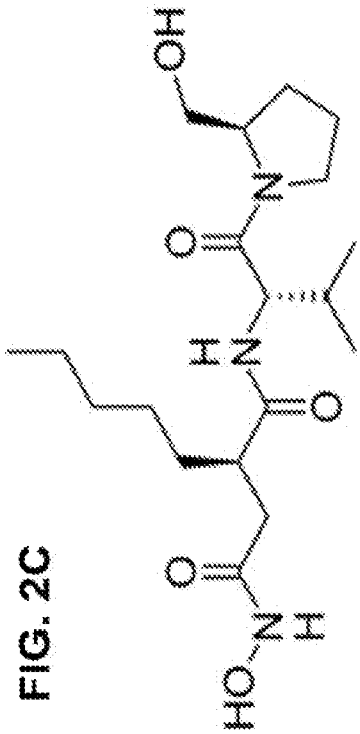


FIG. 2D

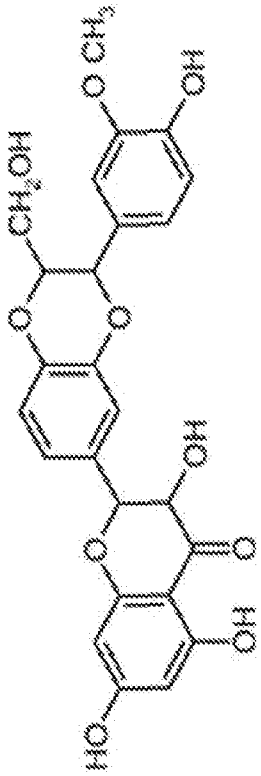


FIG. 3B

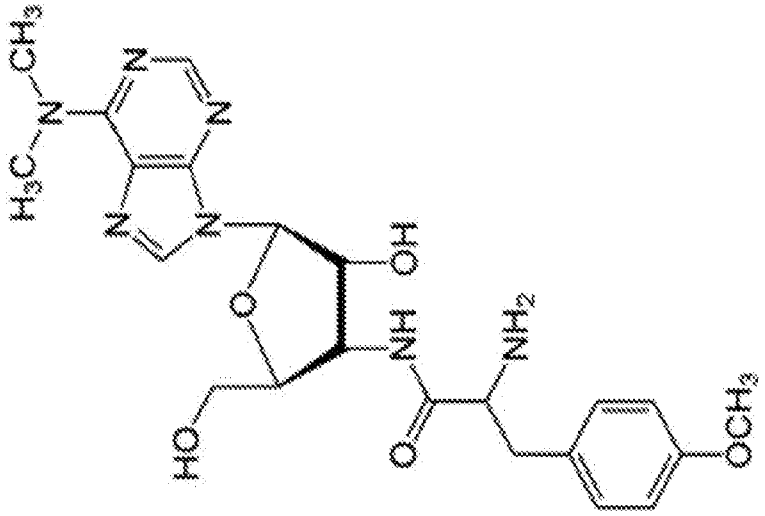


FIG. 3A

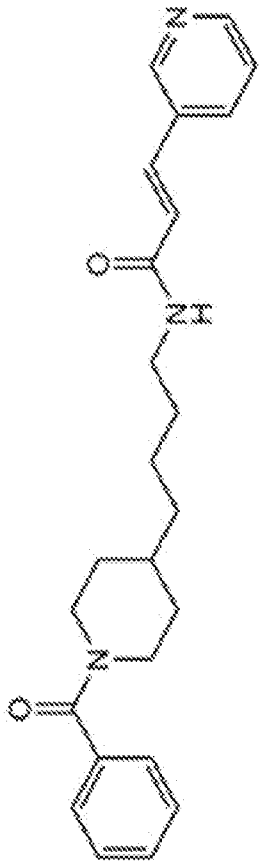
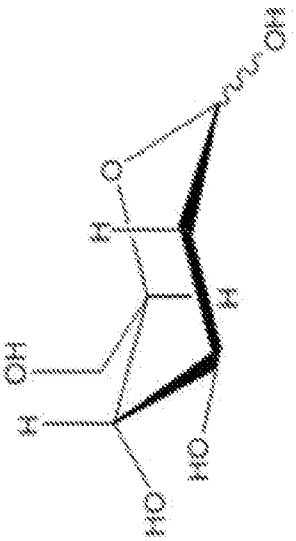


FIG. 3C



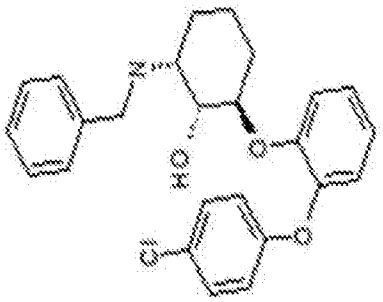


FIG. 4A

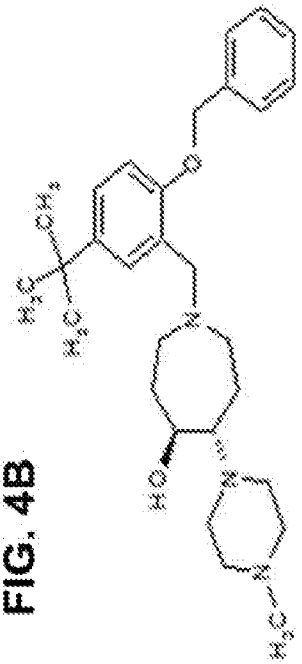


FIG. 4B

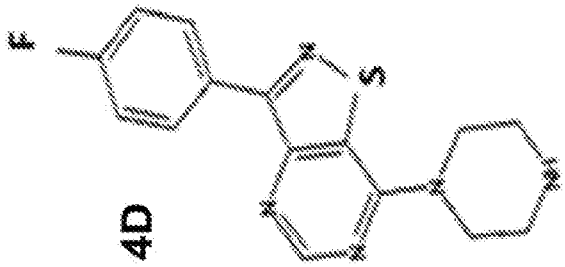


FIG. 4D

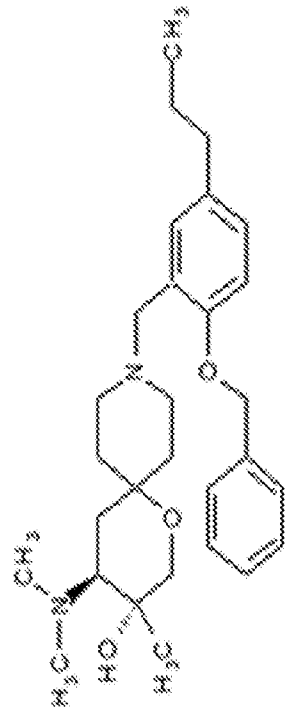
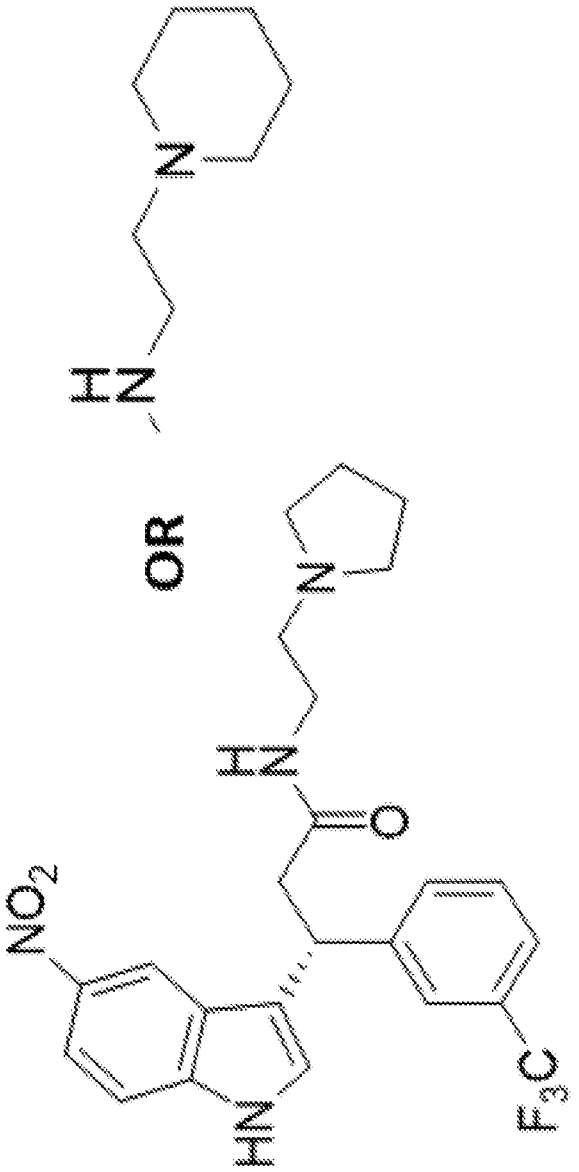


FIG. 4C

FIG. 5



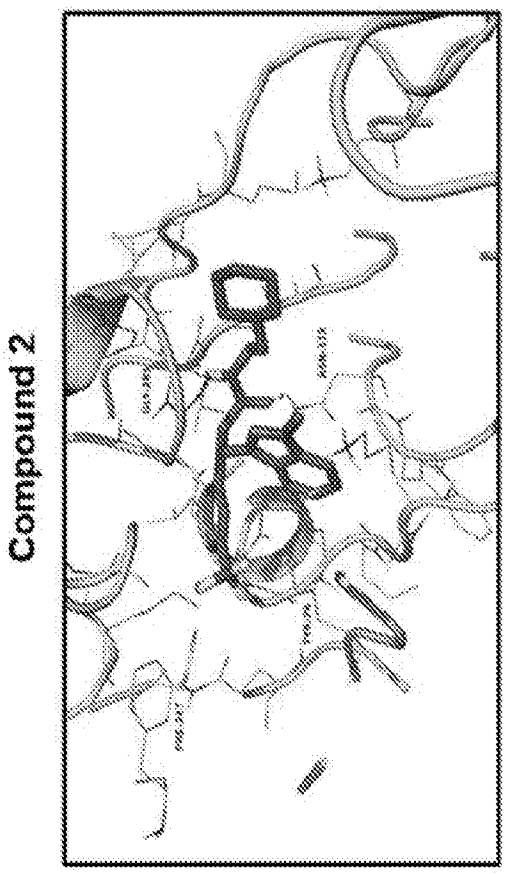


FIG. 6A

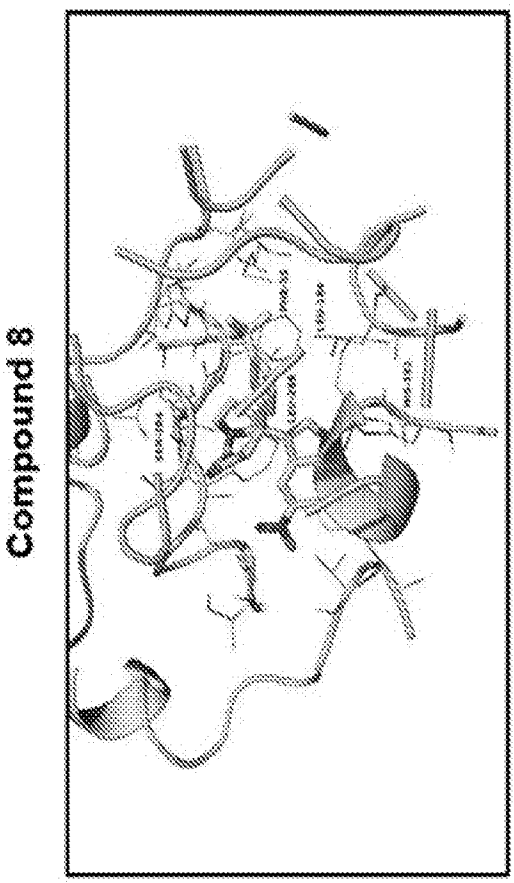
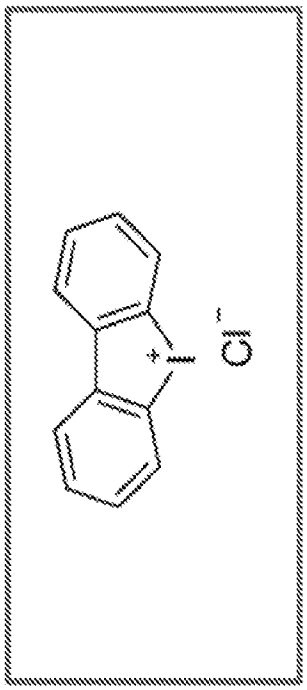


FIG. 6B

Mitoflavoscins (DPI)



Tri-phenyl-phosphonium (TPP)

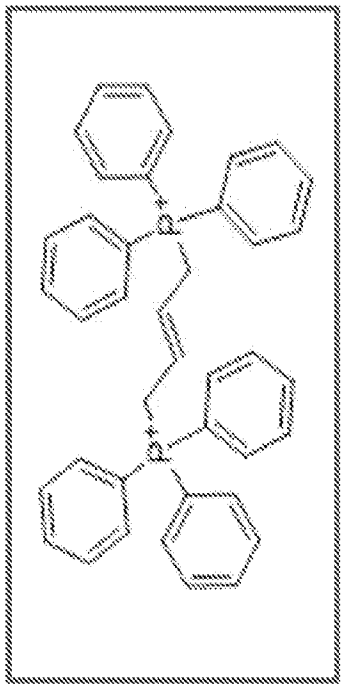


FIG. 7

FIG. 8B

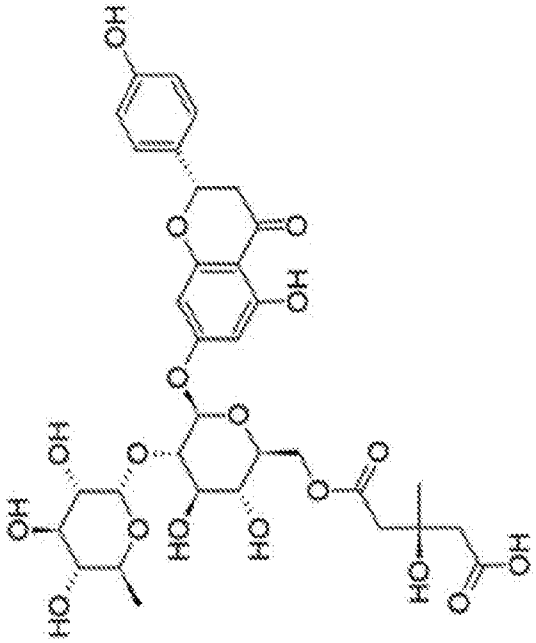


FIG. 8A

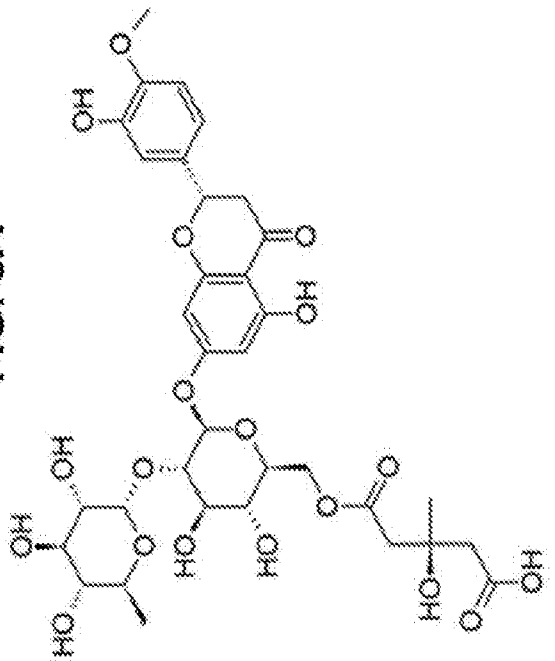


FIG. 8C

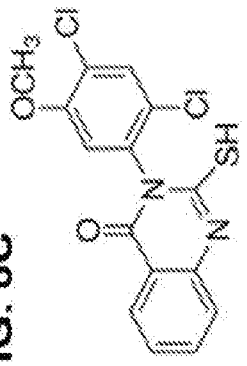
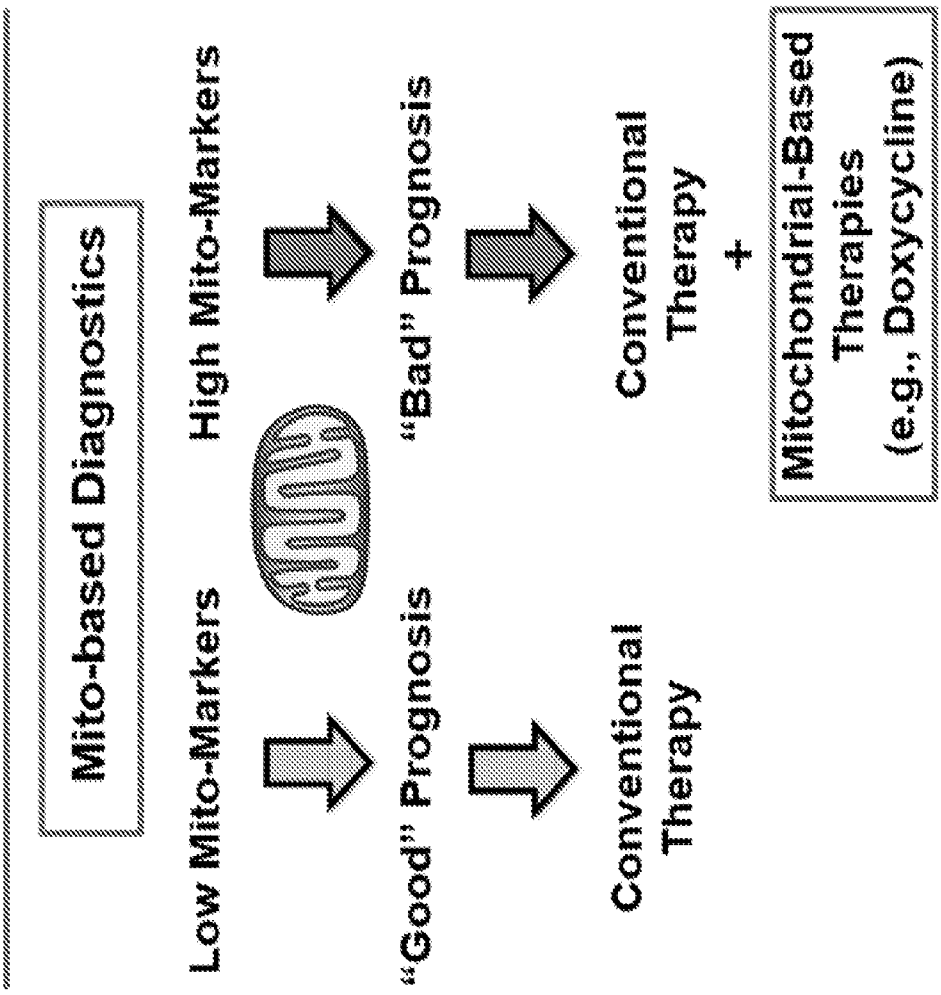


FIG. 9


Personalized Cancer
Diagnosis and Treatment
Mito-based Diagnostics
Low Mito-Markers
"Good" Prognosis
Conventional
Therapy
High Mito-Markers
"Bad" Prognosis
Conventional
Therapy
+
Mitochondrial-Based
Therapies
(e.g., Doxycycline)

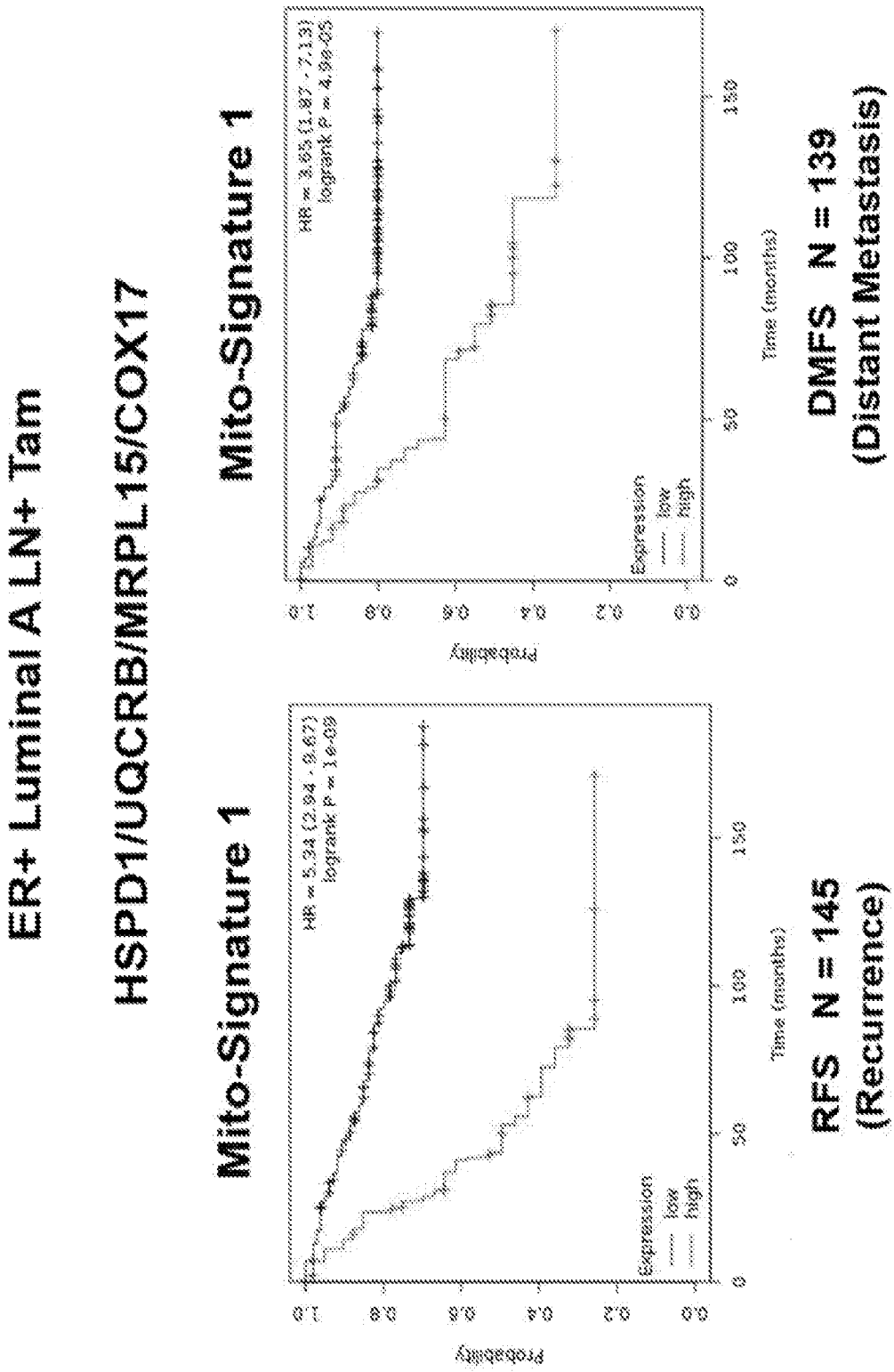


FIG. 10A

FIG. 10B

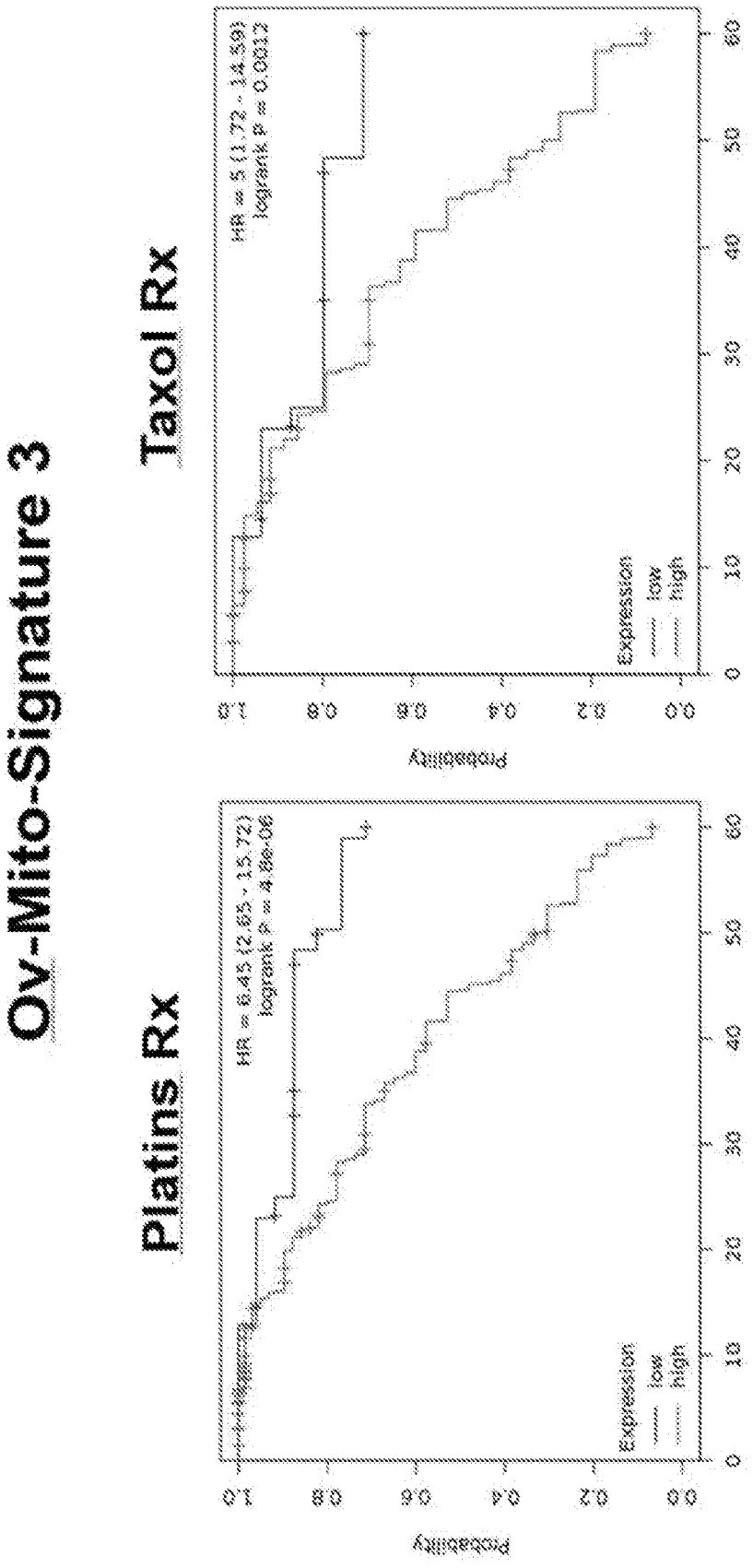
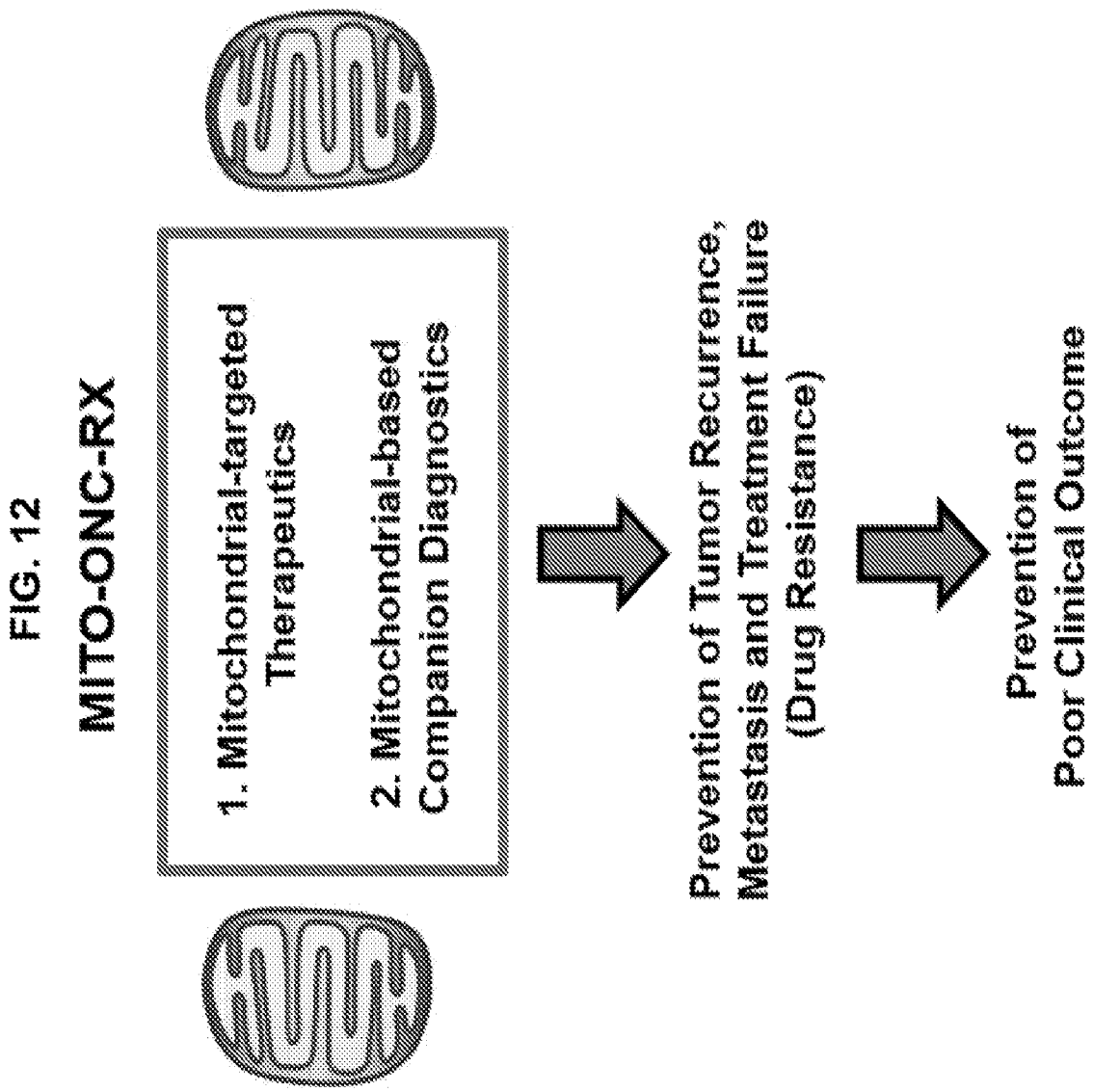


FIG. 11B

FIG. 11A

FIG. 12


MITO-ONC-RX
1. Mitochondrial-targeted Therapeutics
2. Mitochondrial-based Companion Diagnostics
Prevention of Tumor Recurrence, Metastasis and Treatment Failure (Drug Resistance)
Prevention of Poor Clinical Outcome

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/033488

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 35/00; C12Q 1/00; G01N 33/48; G01N 33/50; G01N 33/569; G01N 33/574 (2018.01)

CPC - A61K 45/00; A61P 35/00; C12Q 2600/158; G01N 33/48; G01N 33/50; G01N 33/5011; G01N 33/5079; G01N 33/569; G01N 33/574; G01N 33/57407; G01N 2500/10 (2018.05)

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)

See Search History document

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

USPC - 435/29; 514/19.3; 514/19.4 (keyword delimited)

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	DELUCA et al. "Mitochondrial biogenesis is required for the anchorage-independent survival and propagation of stem-like cancer cells," Oncotarget, 20 July 2015 (20.07.2015), Vol. 6, No. 17, Pgs. 14777-14795. entire document	1, 2, 5-9, 11-13, 18-21 ---------- 3, 4, 10, 14-17
Y	US 2011/0008418 A1 (KO) 13 January 2011 (13.01.2011) entire document	3, 4
Y	LAMB et al. "Mitochondria as new therapeutic targets for eradicating cancer stem cells: Quantitative proteomics and functional validation via MCT1/2 inhibition," Oncotarget, 30 November 2014 (30.11.2014), Vol. 5, No. 22, Pgs. 11029-11037. entire document	10
Y	LAMB et al. "Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: treating cancer like an infectious disease," Oncotarget, 10 March 2015 (10.03.2015), Vol. 6, No. 7, Pgs. 4569-4584. entire document	14
Y	US 2012/0071465 A1 (CLEMENT et al) 22 March 2012 (22.03.2012) entire document	15-17
A	WO 2001/051923 A2 (MITOKOR) 19 July 2001 (19.07.2001) entire document	1-21
A	WO 2010/111208 A1 (UNIVERSITY OF MIAMI) 30 September 2010 (30.09.2010) entire document	1-21
A	WO 2012/166700 A2 (LISANTI et al) 06 December 2012 (06.12.2012) entire document	1-21
A	WO 2014/052305 A2 (THOMAS JEFFERSON UNIVERSITY) 03 April 2014 (03.04.2014) entire document	1-21

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"E" earlier application or patent but published on or after the international filing date

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 July 2018	08 AUG 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/033488

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2017/024207 A1 (WISTAR INSTITUTE) 09 February 2017 (09.02.2017) entire document	1-21