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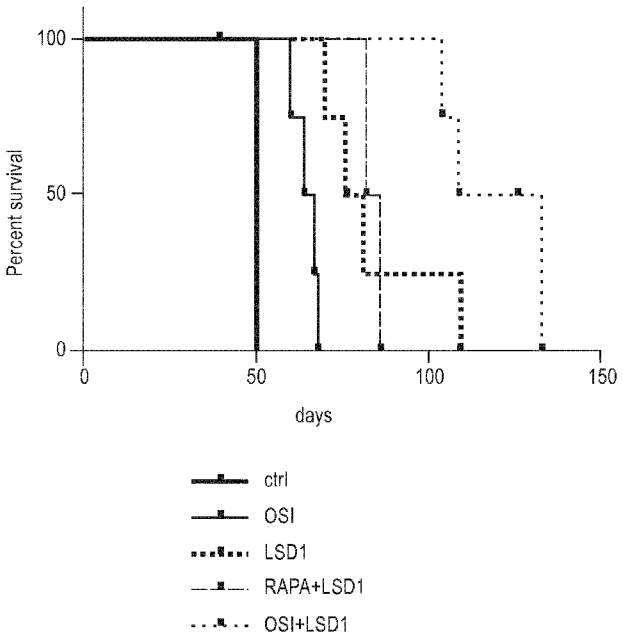
[Continued on next page]

(54) Title: COMBINATION OF CALORIC RESTRICTION (CR) OR IGF1/INSULIN RECEPTOR INHIBITOR WITH LSD1 INHIBITOR

(57) Abstract: The present application relates to the use of an LSD1 inhibitor in combination with a caloric restricted diet, a calorie restriction mimetic and/or an IGF1/Insulin receptor inhibitor for the treatment of cancer, e.g., a leukemia, such as acute myeloid leukemia, acute promyelocytic leukemia.

Figure 7



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Combination of Caloric Restriction (CR) or IGF1/insulin receptor inhibitor with LSD1 inhibitor

RELATED APPLICATION

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 62/263,849 filed December 7, 2016. This document is incorporated by reference herein in its entirety for all purposes.

TECHNICAL FIELD OF THE APPLICATION

[0002] The present application relates to the use of an LSD1 inhibitor in combination with a caloric restricted diet, a calorie restriction mimetic and/or an IGF1/Insulin receptor inhibitor for the treatment of cancer, e.g., a leukemia, such as acute myeloid leukemia, acute promyelocytic leukemia.

BACKGROUND

[0003] There is increasing interest in therapeutic modulation of metabolic pathways in cancer. Tumor cells preferentially use aerobic glycolysis to meet their energetic demands. However, glycolysis inhibition alone is unable to bring durable responses because of limited therapeutic index and because of previously underappreciated metabolic adaptability in tumor cells, which can switch to alternative substrate usage when specific nutrients are limiting. The molecular basis of metabolic adaptation is poorly understood. Caloric restriction (CR) is associated with extensive metabolic changes. The effects of CR on metabolism and the underlying mechanisms are diverse and only partially understood.

SUMMARY

[0004] In one aspect, the application is based on the data disclosed herein which show that the combination of LSD1 inhibition (also known as KDM1) and insulin/IGF1 signaling reduction by pharmacological or dietary intervention is a highly effective therapeutic strategy for the treatment of cancer.

[0005] In one aspect, this application pertains to methods of treating and/or preventing cancer in subject in need thereof.

[0006] In one aspect, this application pertains to a method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject an effective amount of an LSD1 inhibitor, wherein the method further comprises:

a. administration of at least one calorie restriction mimetic; or

b. administration of at least one IGF1/insulin inhibitor; or

c. administration of at least one calorie restriction mimetic and at least one IGF1/insulin inhibitor, wherein the subject is optionally on a calorie restricted diet.

[0007] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of an LSD1 inhibitor and a calorie restriction mimetic, wherein the subject is optionally on a calorie restricted diet.

[0008] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of an LSD1 inhibitor and a calorie restriction mimetic, wherein the subject is on a calorie restricted diet.

[0009] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of an LSD1 inhibitor and a calorie restriction mimetic, wherein the subject is on a standard diet.

[0010] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of an LSD1 inhibitor and an IGF1/insulin inhibitor, wherein the subject is optionally on a calorie restricted diet.

[0011] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of an LSD1 inhibitor and an IGF1/insulin inhibitor, wherein the subject is on a calorie restricted diet.

[0012] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of an LSD1 inhibitor and an IGF1/insulin inhibitor, wherein the subject is on a standard diet.

[0013] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of an LSD1 inhibitor, a calorie restriction mimetic, and an IGF1/insulin inhibitor, wherein the subject is optionally on a calorie restricted diet.

[0014] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of an LSD1 inhibitor, a calorie restriction mimetic, and an IGF1/insulin inhibitor, wherein the subject is on a calorie restricted diet.

[0015] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of an LSD1 inhibitor, a calorie restriction mimetic, and an IGF1/insulin inhibitor, wherein the subject is on a standard diet.

[0016] In one aspect, this application pertains to a method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject an effective amount of an LSD1 inhibitor, wherein the method further comprises:

a. administration of at least one calorie restriction mimetic; or

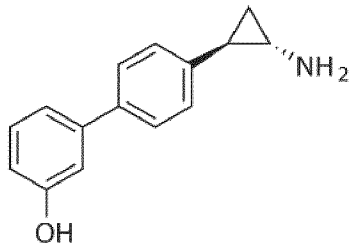
b. administration of at least one IGF1/insulin inhibitor; or

c. administration of at least one calorie restriction mimetic and at least one IGF1/insulin inhibitor, wherein the subject is optionally on a calorie restricted diet;

and wherein the LSD1 inhibitor is selected from any compound of Formula (I), Formula (Ia), Formula (II), Formula (III), any other compound indicated as an LSD1 inhibitor, or a stereoisomer or pharmaceutically acceptable salt thereof.

[0017] In one embodiment, the LSD1 inhibitor is selected from the group consisting of:

tranylcypromine;



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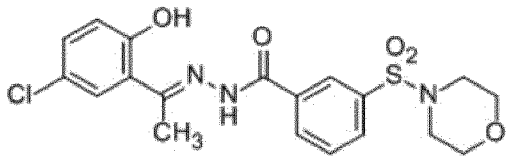
(*R*)-4-[5-(Pyrrolidin-3-ylmethoxy)-2-p-tolyl-pyridin-3-yl]-benzonitrile;

1-(4-methyl-1-piperazinyl)-2-[[(1*R**,2*S**)-2-[4-phenylmethoxy)phenyl]cyclopropyl]amino]ethanone dihydrochloride;



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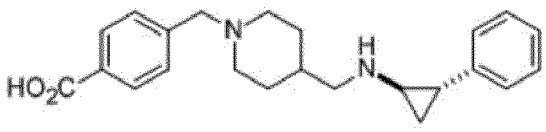

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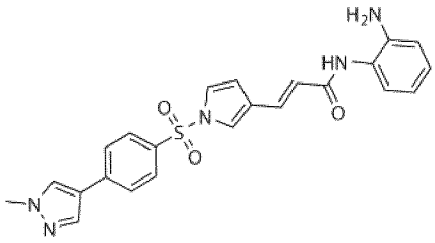

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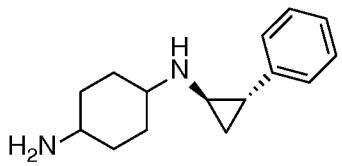

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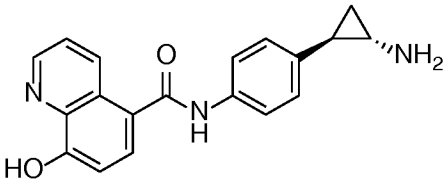

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N-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide; and a pharmaceutically acceptable salt thereof.

[0018] In one embodiment, the LSD1 inhibitor is *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride.

[0019] In one embodiment, the IGF1/insulin inhibitor is selected from the group consisting of: inhibitor of IGF1 receptor, inhibitor of insulin receptor, and inhibitor of both IGF1 receptor and insulin receptor.

[0020] In one embodiment, the IGF1/insulin inhibitor is 3-[8-Amino-1-(2-phenyl-7-quinolyl)imidazo[1,5-a]pyrazin-3-yl]-1-methyl-cyclobutanol.

[0021] In one embodiment, the calorie restriction mimetic is a sirtuin-activating compound.

[0022] In one aspect, this application pertains to a method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject an effective amount of an *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride, wherein the method further comprises:

a. administration of at least one calorie restriction mimetic; or

b. administration of at least one IGF1/insulin inhibitor; or

c. administration of at least one calorie restriction mimetic and at least one IGF1/insulin inhibitor, wherein the subject is optionally on a calorie restricted diet.

[0023] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride and a calorie restriction mimetic, wherein the subject is optionally on a calorie restricted diet.

[0024] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride and a calorie restriction mimetic, wherein the subject is on a calorie restricted diet.

[0025] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride and a calorie restriction mimetic, wherein the subject is on a standard diet.

[0026] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride and an IGF1/insulin inhibitor, wherein the subject is optionally on a calorie restricted diet.

[0027] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride and an IGF1/insulin inhibitor, wherein the subject is on a calorie restricted diet.

[0028] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride and an IGF1/insulin inhibitor, wherein the subject is on a standard diet.

[0029] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride, a calorie restriction mimetic, and an IGF1/insulin inhibitor, wherein the subject is optionally on a calorie restricted diet.

[0030] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride, a calorie restriction mimetic, and an IGF1/insulin inhibitor, wherein the subject is on a calorie restricted diet.

[0031] In one embodiment, the method comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride, a calorie restriction mimetic, and an IGF1/insulin inhibitor, wherein the subject is on a standard diet.

[0032] In one aspect, for any of the methods described herein, the cancer is a tumor of the hematopoietic and lymphoid tissues.

[0033] In one embodiment, the tumor of the hematopoietic and lymphoid tissues is a leukemia.

[0034] In one embodiment, the leukemia is acute myeloid leukemia or acute promyelocytic leukemia.

[0035] In one aspect, for any of the methods described herein, the cancer is characterized in that the cancer cells have features of cancer stem cells

[0036] In one aspect, for any of the methods described herein, the cancer is a drug resistant cancer.

[0037] In one embodiment, the drug resistant cancer is drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia.

[0038] In one aspect, for any of the methods described herein, this application pertains to a method of treating or preventing drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia in a subject in need thereof, comprising administering to the subject an effective amount of an *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride, wherein the method further comprises:

a. administration of at least one calorie restriction mimetic; or

b. administration of at least one IGF1/insulin inhibitor; or

c. administration of at least one calorie restriction mimetic and at least one IGF1/insulin inhibitor, wherein the subject is optionally on a calorie restricted diet.

[0039] In one embodiment, the method of treating or preventing drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride and a calorie restriction mimetic, wherein the subject is optionally on a calorie restricted diet.

[0040] In one embodiment, the method of treating or preventing drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride and a calorie restriction mimetic, wherein the subject is on a calorie restricted diet.

[0041] In one embodiment, the method of treating or preventing drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride and a calorie restriction mimetic, wherein the subject is on a standard diet.

[0042] In one embodiment, the method of treating or preventing drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride and an IGF1/insulin inhibitor, wherein the subject is optionally on a calorie restricted diet.

[0043] In one embodiment, the method of treating or preventing drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-

methylpiperazin-1-yl)benzamide dihydrochloride and an IGF1/insulin inhibitor, wherein the subject is on a calorie restricted diet.

[0044] In one embodiment, the method of treating or preventing drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride and an IGF1/insulin inhibitor, wherein the subject is on a standard diet.

[0045] In one embodiment, the method of treating or preventing drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride, a calorie restriction mimetic, and an IGF1/insulin inhibitor, wherein the subject is optionally on a calorie restricted diet.

[0046] In one embodiment, the method of treating or preventing drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride, a calorie restriction mimetic, and an IGF1/insulin inhibitor, wherein the subject is on a calorie restricted diet.

[0047] In one embodiment, the method of treating or preventing drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia comprises administering to the subject in need thereof an effective amount of *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride, a calorie restriction mimetic, and an IGF1/insulin inhibitor, wherein the subject is on a standard diet.

[0048] In one aspect, this application pertains to an LSD1 inhibitor, a calorie restricted diet, at least one caloric restriction mimetic, at least one IGF1/insulin inhibit, or any combination thereof for use in the treatment or prevention of cancer

[0049] In one embodiment, the application pertains to an LSD1 inhibitor and

(i) a calorie restricted diet and/or

(ii) at least one caloric restriction mimetic and/or

(iii) at least one IGF1/insulin inhibitor

for use in the treatment and/or in the prevention of cancer.

[0050] In one embodiment, the application pertains to an LSD1 inhibitor and

(i) at least one caloric restriction mimetic and/or

(ii) at least one IGF1/insulin inhibitor

for use in the treatment and/or in the prevention of cancer.

[0051] In one embodiment, the application pertains to a combination of an LSD1 inhibitor and

(i) a calorie restricted diet and/or

(ii) a caloric restriction mimetic

for use in the treatment and/or in the prevention of cancer.

[0052] The application also pertains to a combination of an LSD1 inhibitor and at least one IGF1/insulin inhibitor for use in the treatment and/or in the prevention of cancer.

[0053] In one embodiment, the application pertains to a combination of an LSD1 inhibitor and

(i) a calorie restricted diet and/or

(ii) a caloric restriction mimetic and at least one IGF1/insulin inhibitor

for use in the treatment and/or in the prevention of cancer.

[0054] In one embodiment, the application pertains to a pharmaceutical composition comprising an LSD1 inhibitor and

(i) at least one caloric restriction mimetic, and/or

(ii) at least one IGF1/insulin inhibitor

for use in the treatment and/or in the prevention of cancer.

[0055] In one embodiment, the application pertains to an LSD1 inhibitor for use in the treatment and/or in the prevention of cancer, or any of the combinations for use disclosed herein in the treatment and/or in the prevention of cancer, or any of the pharmaceutical compositions for use disclosed herein in the treatment and/or in the prevention of cancer, wherein the caloric restriction mimetic is a sirtuin-activating compound.

[0056] In one embodiment, the application pertains to an LSD1 inhibitor for use in the treatment and/or in the prevention of cancer, or any of the combinations for use disclosed herein in the treatment and/or in the prevention of cancer, or any of the pharmaceutical compositions for use disclosed herein in the treatment and/or in the prevention of cancer, wherein the IGF1/insulin inhibitor is selected from the group consisting of: inhibitor of IGF1 receptor, inhibitor of insulin receptor, and inhibitor of both IGF1 receptor and insulin receptor.

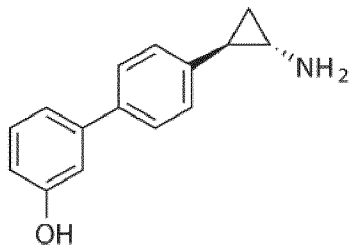
[0057] In one embodiment, the application pertains to an LSD1 inhibitor for use in the treatment and/or in the prevention of cancer, or any of the combinations for use disclosed herein in the treatment and/or in the prevention of cancer, or any of the pharmaceutical compositions for use disclosed herein in the treatment and/or in the prevention of cancer, wherein the IGF1/insulin inhibitor is 3-[8-Amino-1-(2-phenyl-7-quinolyl)imidazo[1,5-a]pyrazin-3-yl]-1-methyl-cyclobutanol.

[0058] In one embodiment, the application pertains to an LSD1 inhibitor for use in the treatment and/or in the prevention of cancer, or any of the combinations for use disclosed herein in the

treatment and/or in the prevention of cancer, or any of the pharmaceutical compositions for use disclosed herein in the treatment and/or in the prevention of cancer, wherein the LSD1 inhibitor is selected from a compound as described in WO2013057322, WO2011131576, WO2014086790, WO2012135113, or WO 2015/181380.

[0059] In one embodiment, the application pertains to an LSD1 inhibitor for use in the treatment and/or in the prevention of cancer, or any of the combinations for use disclosed herein in the treatment and/or in the prevention of cancer, or any of the pharmaceutical compositions for use disclosed herein in the treatment and/or in the prevention of cancer, wherein the LSD1 inhibitor is selected from the group consisting of:

tranylcypromine;



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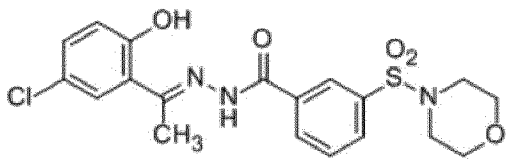
(*R*)-4-[5-(Pyrrolidin-3-ylmethoxy)-2-p-tolyl-pyridin-3-yl]-benzonitrile;

1-(4-methyl-1-piperazinyl)-2-[[(1*R**,2*S**)-2-[4-phenylmethoxy)phenyl]cyclopropyl]amino]ethanone dihydrochloride;



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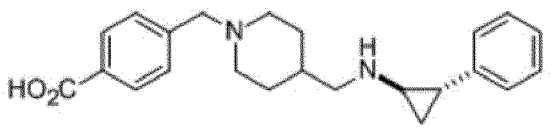

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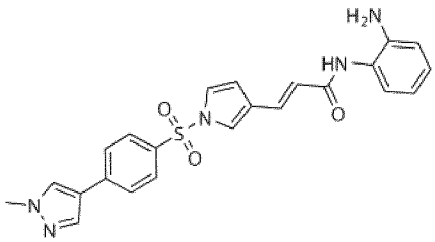

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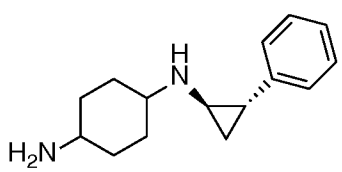

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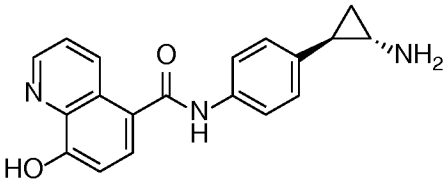

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N-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide; and a pharmaceutically acceptable salt thereof.

[0060] In one embodiment, the application pertains to an LSD1 inhibitor for use in the treatment and/or in the prevention of cancer, or any of the combinations for use disclosed herein in the treatment and/or in the prevention of cancer, or any of the pharmaceutical compositions for use disclosed herein in the treatment and/or in the prevention of cancer, wherein the LSD1 inhibitor is *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride.

[0061] In one embodiment, the application pertains to an LSD1 inhibitor for use in the treatment and/or in the prevention of cancer, or any of the combinations for use disclosed herein in the treatment and/or in the prevention of cancer, or any of the pharmaceutical compositions for use disclosed herein in the treatment and/or in the prevention of cancer, wherein the cancer is a tumor of the hematopoietic and lymphoid tissues.

[0062] In one embodiment, the application pertains to an LSD1 inhibitor for use in the treatment and/or in the prevention of cancer, or any of the combinations for use disclosed herein in the treatment and/or in the prevention of cancer, or any of the pharmaceutical compositions for use disclosed herein in the treatment and/or in the prevention of cancer, wherein the cancer is a tumor of the hematopoietic and lymphoid tissues and the tumor of the hematopoietic and lymphoid tissues is a leukemia.

[0063] In one embodiment, the application pertains to an LSD1 inhibitor for use in the treatment and/or in the prevention of cancer, or any of the combinations for use disclosed herein in the treatment and/or in the prevention of cancer, or any of the pharmaceutical compositions for use disclosed herein in the treatment and/or in the prevention of cancer, wherein the cancer is a tumor of the hematopoietic and lymphoid tissues, the tumor of the hematopoietic and lymphoid tissues is a leukemia, and the leukemia is acute myeloid leukemia (AML) or acute promyelocytic leukemia (APL).

[0064] In one embodiment, the application pertains to an LSD1 inhibitor for use in the treatment and/or in the prevention of cancer, or any of the combinations for use disclosed herein in the treatment and/or in the prevention of cancer, or any of the pharmaceutical compositions for use disclosed herein in the treatment and/or in the prevention of cancer, wherein the cancer is characterized in that the cancer cells have features of cancer stem cells.

[0065] In one embodiment, the application pertains to an LSD1 inhibitor for use in the treatment and/or in the prevention of cancer, or any of the combinations for use disclosed herein in the treatment and/or in the prevention of cancer, or any of the pharmaceutical compositions for use disclosed herein in the treatment and/or in the prevention of cancer, wherein the cancer is a drug resistant cancer, for example, drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia.

[0066] The application also pertains to the use of an LSD1 inhibitor, any of the combinations disclosed herein or any of the pharmaceutical compositions disclosed herein in the manufacture of a medicament for the treatment and/or in the prevention of cancer. In one embodiment, the cancer is a tumor of the hematopoietic and lymphoid tissues. In one embodiment, the tumor of the hematopoietic and lymphoid tissues is a leukemia. In one embodiment, the leukemia is acute myeloid leukemia (AML) or acute promyelocytic leukemia (APL). In one embodiment, the cancer is characterized in that the cancer cells have features of cancer stem cells. In one embodiment, the LSD1 inhibitor is *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride.

[0067] The application also pertains to a method of treatment of cancer comprising administering to a subject in need thereof

(i) an LSD1 inhibitor, or

(ii) any of the combinations disclosed herein, or

(iii) any of the pharmaceutical compositions disclosed herein.

[0068] The application also pertains to a kit comprising an LSD1 inhibitor and

(i) a caloric restriction mimetic, or

(ii) an IGF1/insulin inhibitor, or

(iii) a caloric restriction mimetic and an IGF1/insulin inhibitor.

[0069] In one embodiment, the kit comprising an LSD1 inhibitor further comprises a caloric restriction mimetic that is a sirtuin-activating compound.

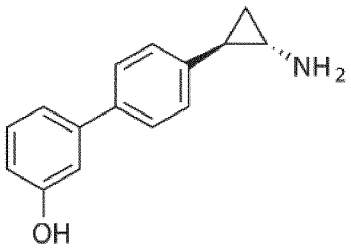
[0070] In one embodiment, the kit comprising an LSD1 inhibitor further comprises an IGF1/insulin inhibitor that is selected from the group consisting of: inhibitor of IGF1 receptor, inhibitor of insulin receptor, and inhibitor of both IGF1 receptor and insulin receptor.

[0071] In one embodiment, the kit comprising an LSD1 inhibitor further comprises an IGF1/insulin inhibitor that is 3-[8-Amino-1-(2-phenyl-7-quinolyl)imidazo[1,5-a]pyrazin-3-yl]-1-methyl-cyclobutanol.

[0072] In one embodiment, the kit comprises an LSD1 inhibitor that is selected from a compound as described in WO2013057322, WO2011131576, WO2014086790, WO2012135113, or WO2015/181380.

[0073] In one embodiment, the kit comprises an LSD1 inhibitor that is selected from the group consisting of:

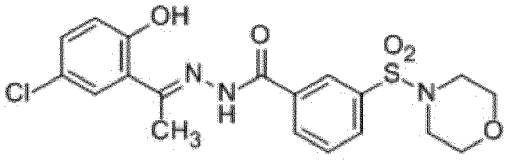
tranylcypromine;



;

(*R*)-4-[5-(Pyrrolidin-3-ylmethoxy)-2-p-tolyl-pyridin-3-yl]-benzonitrile;

1-(4-methyl-1-piperazinyl)-2-[[(1*R**,2*S**)-2-[4-phenylmethoxy)phenyl]cyclopropyl]amino]ethanone dihydrochloride;



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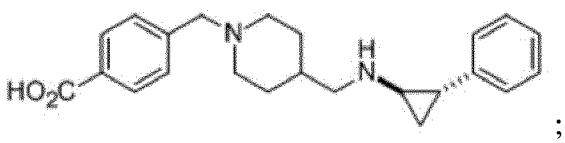

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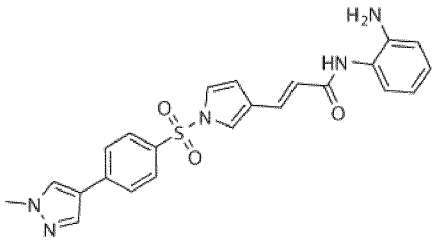

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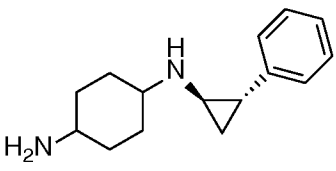

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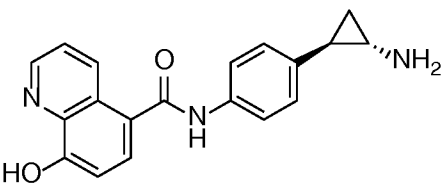


;

N-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide; and a pharmaceutically acceptable salt thereof.

[0074] In one embodiment, the kit comprises an LSD1 inhibitor that is *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride.

[0075] The present application also provides a combination of at least one LSD1 inhibitor and a calorie restricted diet and/or a caloric restriction mimetic for use in the treatment and/or in the prevention of cancer.

[0076] The application also pertains to a combination of at least one LSD1 inhibitor and at least one IGF1/insulin inhibitor for use in the treatment and/or in the prevention of cancer.

[0077] The application also pertains to a combination of at least one LSD1 inhibitor and a calorie restricted diet and/or a caloric restriction mimetic and at least one IGF1/insulin inhibitor for use in the treatment and/or in the prevention of cancer.

[0078] The application also pertains to a pharmaceutical composition comprising an LSD1 inhibitor and at least one caloric restriction mimetic and/or at least one IGF1/insulin inhibitor as defined above for use in the treatment and/or in the prevention of cancer.

[0079] In one embodiment, the cancer is a tumor of the hematopoietic and lymphoid tissues.

[0080] In one embodiment, the tumor of the hematopoietic and lymphoid tissues is a leukemia.

[0081] In one embodiment, the leukemia is acute myeloid leukemia (AML) or acute promyelocytic leukemia (APL).

[0082] In one embodiment, the cancer is characterized in that the cancer cells have features of cancer stem cells.

[0083] In one embodiment, the cancer is a drug resistant cancer, for example, drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia.

[0084] The application also pertains to a kit comprising an LSD1 inhibitor and at least one caloric restriction mimetic and/or at least one IGF1/insulin inhibitor as defined above.

[0085] The application also pertains to a method of treatment of cancer comprising administering to a subject in need thereof at least one LSD1 inhibitor and a calorie restricted diet and/or at least one caloric restriction mimetic and/or at least one IGF1/insulin inhibitor.

[0086] The application also pertains to a pharmaceutical composition comprising an LSD1 inhibitor of the disclosure, or a pharmaceutically acceptable salt, solvate, or prodrug thereof and a pharmaceutically acceptable carrier and/or diluent.

[0087] The application also pertains to the use of a compound of the disclosure, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, or a pharmaceutical composition of the disclosure for preventing or treating a disease or disorder in a subject in need thereof. In

one embodiment, the disease or disorder is cancer.

[0088] The application also pertains to the use of a compound of the disclosure, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, or a pharmaceutical composition of the disclosure in the manufacture of a medicament for preventing or treating a disease or disorder in a subject in need thereof.

[0089] Although methods and materials similar to or equivalent to those described herein can be used in the practice and testing of the application, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference.

[0090] The references cited herein are not admitted to be prior art to the claimed application. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[0091] Other features and advantages of the application will become apparent from the following detailed description in conjunction with the examples.

[0092] The application will be illustrated by means of non-limiting examples in reference to the following figures.

BRIEF DESCRIPTION OF THE FIGURES

[0093] Figure 1A-1D: Graphs showing the effect of caloric restriction (CR) on leukemic blasts.

[0094] Figure 2A-2B: Graphs showing the effect of CR on survival of mice with APL.

[0095] Figure 3A-3B: Graphs showing the effect of CR on leukemia initiating cells in tertiary recipients.

[0096] Figure 4A-4F: Charts and Graphs Transcriptional analysis, gene set enrichment of leukemia in CR vs SD by RNAseq. Analysis.

[0097] Figure 5: Graph showing change in transcription of 104 superenhancer-associated genes compared to all genes for CR versus SD.

[0098] Figure 6A-6C: Graphs and charts showing synergy between CR and LSD1 inhibition by compound 1.

[0099] Figure 7: Graph showing synergy between OSI906 and LSD1 inhibition by compound 1.

[00100] Figure 8A-8B: Graph and picture describing *in vitro* system to mimic CR/LSD1 inhibition synergy.

[00101] Figure 9: Graph summarizing screening for additional leukemia cell lines.

[00102] Figure 10: Graph displaying cell cycle analysis using propidium iodide and Ki67.

[00103] Figure 11: Graphs displaying analysis of TCGA data expression.

[00104] Figure 12: Graphs displaying analysis of tumor growth data in NB4 cells wild-type (WT) and knockout (KO) for LSD1 expression.

[00105] Figures 13A-C: Charts and graphs showing that LSD1 inhibitor significantly alters gene expression in APL cells.

[00106] Figures 14A-D: Graphs summarizing experiments with OSI906 and LSD1 inhibitor on a mouse model of NPMc/FLT3ITD (AML).

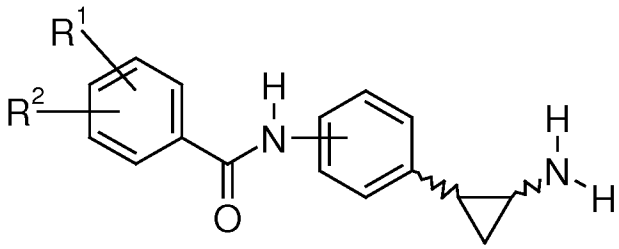
DETAILED DESCRIPTION

[00107] The present application is based on the finding disclosed herein that LSD1 regulates metabolic adaptability and is a therapeutic target upon metabolic modulation through caloric restriction (CR) in cancer. In one aspect, the cancer is selected from acute myeloid leukemia (AML) or acute promyelocytic leukemia (APL).

[00108] In the present application the LSD1 inhibitor is any known LSD1 inhibitor, for instance an LSD1 inhibitor as described in WO2013057322, WO2011131576, WO2014086790, WO2012135113, WO 2015/181380 and WO 2016/34946, each of which are incorporated herein by reference in their entireties.

[00109] In one embodiment, the LSD1 inhibitor may also be an antisense, an antibody, or a monoclonal antibody.

[00110] In one embodiment the LSD1 inhibitor is selected from a compound of Formula (I)



(I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

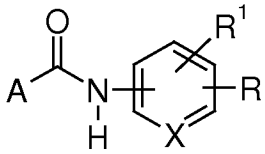
R^1 is heterocyclyl or heterocyclyl substituted by oxo, wherein the heterocyclyl is unsubstituted or substituted by one or more C_1-C_6 alkyl;

R^2 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, or benzyloxycarbonylamino.

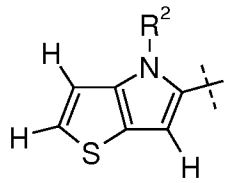
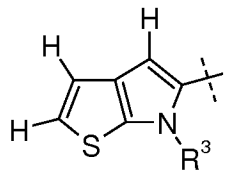
[00111] In one embodiment, the LSD1 inhibitor is selected from a compound of Formula (I) that is: *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide; *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(1-methyl-4-piperidyl)benzamide; *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-3-(2-oxooxazolidin-3-yl)benzamide; *N*-[4-[*trans*-2-

aminocyclopropyl]phenyl]-4-morpholino-benzamide; *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(2-oxooxazolidin-3-yl)benzamide; benzyl *N*-[5-[[4-[(*trans*-2-aminocyclopropyl]phenyl]carbamoyl]-2-(4-methylpiperazin-1-yl)phenyl]carbamate; benzyl *N*-[4-[[4-[*trans*-2-aminocyclopropyl]phenyl]carbamoyl]-2-(4-methylpiperazin-1-yl)phenyl]carbamate; benzyl *N*-[5-[[4-[*trans*-2-aminocyclopropyl]phenyl]carbamoyl]-2-(1-piperidyl)phenyl]carbamate; benzyl *N*-[5-[[4-[*trans*-2-aminocyclopropyl]phenyl]carbamoyl]-2-morpholino-phenyl]carbamate; *N*-[4-[(1S,2R)-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide; *N*-[4-[(1S,2R)-2-aminocyclopropyl]phenyl]-3-(2-oxooxazolidin-3-yl)benzamide; *N*-[4-[(1R,2S)-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide; *N*-[4-[(1R,2S)-2-aminocyclopropyl]phenyl]-3-(2-oxooxazolidin-3-yl)benzamide; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00112] In one embodiment the LSD1 inhibitor is selected from a compound of Formula (Ia)



(**Ia**) , or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

A is  or  ;

X is CH or N;

R is L1-R^4;

R^1 is H, halogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, -CH_2-Z-R^5, or -Z-CH_2-R^6;

R^2 and R^3 are C_1-C_4-alkyl;

L1 is -(CH_2)j-Y-, -Y-$(CH_2)_k$-, -CH_2-CH_2- or -CO-NH-;

j and k are, independently, each an integer from 1 to 6;

Y is oxygen, sulphur, NH or N(C_1-C_6-alkyl);

Z is a bond, oxygen, sulphur, NH or N(C_1-C_6-alkyl);

R^4, R^5, and R^6 are, independently, C_1-C_6-alkyl, aryl, heteroaryl, wherein the aryl or heteroaryl are optionally substituted by halogen, C_1-C_6-alkyl, or L2-R^7; or heterocyclyl, wherein the heterocyclyl is optionally substituted by C_1-C_6-alkyl;

L2 is -$(CH_2)_m$- or -$(CH_2)_n$-W-$(CH_2)_o$-;

R^7 is C_1-C_6-alkylamino, C_3-C_7 cycloalkyl or heterocyclyl, wherein the C_3-C_7 cycloalkyl or

heterocyclyl are optionally substituted by C_1-C_6-alkyl, or NH_2; or guanidine;

m, n, o are, independently, each zero or an integer from 1 to 6;

W is oxygen, sulphur, NH, or CH_2;

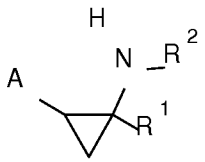
wherein aryl is a mono or bicyclic aromatic ring system of 6 or 9 or 10 atoms; heteroaryl is a mono or bicyclic heteroaromatic ring system of 5 to 10 members, which contains one, two, three or four heteroatoms selected from nitrogen, oxygen and sulphur, and one to nine carbon atoms; and heterocyclyl is a mono, bicyclic or a spirocyclic saturated or partially saturated non-aromatic ring system of 4 to 12 members, which contains one, two, or three heteroatoms selected from nitrogen, oxygen, and sulphur, and three to eleven carbon atoms;

[00113] In one embodiment, the LSD1 inhibitor is selected from a compound of Formula (Ia) that is: 4-methyl-N-[2-[[4-(4-piperidyloxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[4-(4-piperidylmethoxy)phenoxy]methyl]phenyl]thieno-[3,2-b]pyrrole-5-carboxamide; N-[2-[[4-[(1-ethyl-4-piperidyl)oxy]phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[4-[[(3R)-pyrrolidin-3-yl]methoxy]phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[4-(pyrrolidin-3-ylmethoxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-ethyl-N-[3-[[4-(4-piperidyloxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; N-[2-[[4-(azepan-4-yloxy)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; 4-ethyl-N-[2-[[4-(4-piperidyloxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; N-[2-[[4-(cis-4-aminocyclohexoxy)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[3-[[4-(4-piperidyloxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[4-[[(3S)-pyrrolidin-3-yl]methoxy]phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-ethyl-N-[2-[[4-[(1-methyl-4-piperidyl)oxy]phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[4-[(1-methyl-4-piperidyl)oxy]phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; N-[2-[[4-(trans-4-aminocyclohexoxy)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[3-[[4-[(1-methyl-4-piperidyl)oxy]phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[(4-pyrrolidin-3-yloxyphenoxy)methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[3-[(1-methyl-4-piperidyl)oxy]phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[3-(4-piperidyloxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[3-[(1-methyl-3-piperidyl)methoxy]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[4-[(4-methylpiperazin-1-yl)methyl]phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[3-(4-

pyridylmethoxy)phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[3-(4-pyridyloxymethyl)phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[4-[[4-[(1-methyl-4-piperidyl)oxy]phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; N-[2-[[4-[[(1S,5R)-8-azabicyclo[3.2.1]octan-3-yl]oxy]phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; N-[3-[[4-[[(1S,5R)-8-azabicyclo[3.2.1]octan-3-yl]oxy]phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[3-[[4-(4-piperidylmethoxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[4-(3-piperidyloxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[3-[[4-(3-piperidyloxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; N-[3-[[4-(trans-4-aminocyclohexoxy)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; N-[3-[[4-(azetidin-3-ylmethoxy)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[4-(3-methylaminopropoxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[3-[(4-pyrrolidin-3-yloxyphenoxy)methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; N-[3-[[4-(azepan-4-yloxy)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; N-[3-[[4-(cis-4-aminocyclohexoxy)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[3-[[4-(pyrrolidin-3-ylmethoxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[4-(4-piperidyloxy)phenyl]carbamoyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[(4-piperazin-1-ylphenoxy)methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[4-[(1-methyl-4-piperidyl)oxy]phenyl]methoxy]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[4-(4-piperidylamino)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; N-[2-[[4-(azetidin-3-ylmethoxy)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; N-[2-[[4-(2,8-diazaspiro[4.5]decan-2-ylmethyl)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; N-[3-(methoxymethyl)-2-[[4-[[(3R)-pyrrolidin-3-yl]methoxy]phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; N-[3-(methoxymethyl)-2-[[4-(4-piperidyloxy)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; N-[2-[[4-(azepan-4-yloxy)phenoxy]methyl]-3-(methoxymethyl)phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; N-[3-(methoxymethyl)-2-[[4-[[(3S)-pyrrolidin-3-yl]methoxy]phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; N-[3-(ethoxymethyl)-2-[[4-(4-piperidyloxy)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; N-[3-(isopropoxymethyl)-2-[[4-(4-piperidyloxy)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; N-[3-(ethoxymethyl)-2-[[4-[[(3R)-pyrrolidin-3-

yl]methoxy]phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; 4-ethyl-N-[3-(methoxymethyl)-2-[[4-[[(3R)-pyrrolidin-3-yl]methoxy]phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[3-(morpholinomethyl)-2-[[4-(4-piperidyloxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[5-methyl-2-[[4-(pyrrolidin-3-ylmethoxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[5-(4-piperidyloxy)-2-pyridyl]oxymethyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-(4-piperidylmethoxy)phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[3-[[3-(4-piperidyloxy)phenoxy]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; N-[3-[[4-(guanidinomethyl)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; N-[2-[[4-(guanidinomethyl)phenoxy]methyl]phenyl]-4-methyl-thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[2-[4-(4-piperidyloxy)phenyl]ethyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[3-[2-[4-(4-piperidyloxy)phenyl]ethyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 4-methyl-N-[2-[[4-(4-piperidyloxy)anilino]methyl]phenyl]thieno[3,2-b]pyrrole-5-carboxamide; 6-methyl-N-[2-[[3-(4-piperidyloxy)phenoxy]methyl]phenyl]thieno[2,3-b]pyrrole-5-carboxamide; 6-ethyl-N-[2-[[3-(4-piperidyloxy)phenoxy]methyl]phenyl]thieno[2,3-b]pyrrole-5-carboxamide; 6-ethyl-N-[2-[[4-(4-piperidyloxy)phenoxy]methyl]phenyl]thieno[2,3-b]pyrrole-5-carboxamide; 6-methyl-N-[2-[[4-(4-piperidyloxy)phenoxy]methyl]phenyl]thieno[2,3-b]pyrrole-5-carboxamide; 6-methyl-N-[2-[[4-(pyrrolidin-3-ylmethoxy)phenoxy]methyl]phenyl]thieno[2,3-b]pyrrole-5-carboxamide; 4-methyl-N-[4-[[4-(4-piperidyloxy)phenyl]carbamoyl]-2-pyridyl]thieno[3,2-b]pyrrole-5-carboxamide; or a stereoisomer or pharmaceutically acceptable salt thereof.

[00114] In one embodiment, the LSD1 inhibitor is selected from a compound of Formula (II)



(**II**), wherein:

A is aryl or heteroaryl, wherein the aryl or heteroaryl may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, nitro, NH_2, azide, OH, C_1-C_6 alkylamino, and **R**-**L**-;

R is aryl, wherein the aryl may be optionally substituted by one, two or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, nitro, NH_2, azide, C_1-C_6 alkylamino optionally substituted by OH, heterocyclylamino optionally substituted by C_1-C_6 alkyl, OH, phenyl, heterocyclyl

optionally substituted by C_1-C_6 alkyl, heterocyclyl substituted by oxo, heteroaryl, and benzyloxycarbonylamino; or heteroaryl;

L is a single bond; C_1-C_6 alkylene; C_2-C_6 alkenylene; $-(CH_2)_mX-(CH_2)_n-$; $-(CH_2)_o(SO_2)NH-$; $-(CH_2)_p(CO)NR^3-$; $-(CH_2)_qNR^4(CO)-$; heterocyclyl substituted by oxo; or heteroaryl;

R^1 is C_1-C_6 alkyl, optionally substituted by aryl or heteroaryl; aryl; heteroaryl; or $-(CH_2)_r-Y-R^5$; and wherein the aryl or heteroaryl group may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, nitro, acetamido, and phenyl;

R^2 is hydrogen; C_1-C_6 alkyl, optionally substituted by aryl, heteroaryl, or by heterocyclyl and wherein the aryl or heteroaryl may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and NH_2; or $-CH_2(CO)NR^6R^7$;

m, n, o, p, q are, independently, zero or an integer from 1 to 6;

r is an integer from 1 to 6;

X and Y are, independently, NR^8; O; or S;

R^3 and R^4 are, independently, hydrogen; or C_1-C_6 alkyl;

R^5 is hydrogen, aryl or heteroaryl, wherein the aryl or heteroaryl may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and phenyl;

R^6 and R^7 are, independently, hydrogen; C_1-C_6 alkyl; or R^6 and R^7 together with the nitrogen to which they are bound form a C_4-C_{10}-heterocyclic ring, optionally containing one or more further heteroatoms in the ring independently selected from NR^9, O or S and being optionally substituted by NH_2;

R^8 is hydrogen; C_1-C_6 alkyl, optionally substituted by aryl or heterocyclyl; or C_{3-6} cycloalkyl;

R^9 is hydrogen or C_1-C_6 alkyl;

or stereoisomers or pharmaceutically acceptable salts thereof.

[00115] In one embodiment, the LSD1 inhibitor is selected from a compound of Formula (II) that is: (1S,2R)-1-ethyl-2-phenyl-cyclopropanamine; (1R,2S)-1-ethyl-2-phenyl-cyclopropanamine; trans-1-methyl-2-phenyl-cyclopropanamine; (1R,2S)-1-methyl-2-phenyl-cyclopropanamine; (1S,2R)-1-methyl-2-phenyl-cyclopropanamine; trans-1-propyl-2-phenyl-cyclopropanamine; trans-1-isopropyl-2-phenyl-cyclopropanamine; trans-1-benzyl-2-phenyl-cyclopropanamine; (1S,2S)-1-benzyl-2-phenyl-cyclopropanamine; (1R,2R)-1-benzyl-2-phenyl-cyclopropanamine; trans-1-phenethyl-2-phenyl-cyclopropanamine; trans-2-(4-bromophenyl)-1-ethyl-cyclopropanamine; trans-1-benzyl-2-(4-bromophenyl)cyclopropanamine; trans-1-ethyl-2-

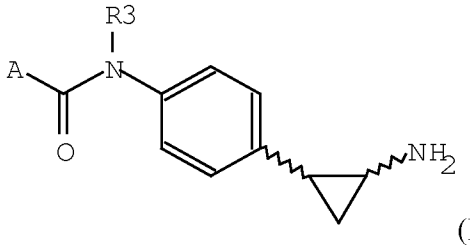
(6-quinolyl)cyclopropanamine; trans-1-(2-naphthylmethyl)-2-phenyl-cyclopropanamine; trans-1-ethyl-2-(4-fluorophenyl)cyclopropanamine; trans-1-ethyl-2-(4-chlorophenyl)cyclopropanamine; trans-1-ethyl-2-[3-(trifluoromethyl)phenyl]cyclopropanamine; trans-1-ethyl-2-[4-(trifluoromethyl)phenyl]cyclopropanamine; trans-1-ethyl-2-(3-fluorophenyl)cyclopropanamine; trans-1-ethyl-2-(3-chlorophenyl)-cyclopropanamine; trans-1-ethyl-2-(3-bromophenyl)-cyclopropanamine; trans-1-ethyl-2-[3-methoxyphenyl]cyclopropanamine; 1-ethyl-(trans)-2-[4-(trifluoromethoxy)phenyl]cyclopropanamine; trans-1-ethyl-2-(2-fluorophenyl)cyclopropanamine; trans-1-ethyl-2-(2-chlorophenyl)-cyclopropanamine; trans-1-ethyl-2-(2-bromophenyl)-cyclopropanamine; trans-1-(1-naphthylmethyl)-2-phenyl-cyclopropanamine; trans-2-(4-bromophenyl)-1-(2-naphthylmethyl)cyclopropanamine; trans-N-[4-[2-amino-2-ethyl-cyclopropyl]phenyl]naphthalene-2-carboxamide; N-[2-[(trans)-2-amino-2-ethyl-cyclopropyl]phenyl]benzamide; benzyl N-[3-[[2-[(trans)-2-amino-2-ethyl-cyclopropyl]phenyl]carbamoyl]phenyl]carba-mate; benzyl N-[3-[[3-[(trans)-2-amino-2-ethyl-cyclopropyl]phenyl]carbamoyl]phenyl]carba-mate; N-[4-[(trans)-2-amino-2-ethyl-cyclopropyl]phenyl]-3-chloro-benzamide N-[4-[(trans)-2-amino-2-ethyl-cyclopropyl]phenyl]-3-phenyl-benzamide; N-[4-[(trans)-2-amino-2-ethyl-cyclopropyl]phenyl]-4-phenyl-benzamide; benzyl N-[3-[[4-[(trans)-2-amino-2-ethyl-cyclopropyl]phenyl]carbamoyl]phenyl]carba-mate; benzyl N-[4-[[4-[(trans)-2-amino-2-ethyl-cyclopropyl]phenyl]carbamoyl]phenyl]carba-mate; N-[4-[(trans)-2-amino-2-ethyl-cyclopropyl]phenyl]-2-phenyl-acetamide; N-[4-[(trans)-2-amino-2-ethyl-cyclopropyl]phenyl]-3-phenyl-propanamide; 2-(4-benzyloxyphenyl)-trans-1-ethyl-cyclopropanamine; N-[4-[(2-amino-trans-2-ethyl-cyclopropyl]phenyl]benzenesulfonamide; trans-1-benzyl-2-(4-benzyloxyphenyl)cyclopropanamine; N-[4-[trans-2-amino-2-(2-naphthylmethyl)cyclopropyl]phenyl]benzamide; benzyl-N-[3-[[4-[(trans)-2-amino-2-(2-naphthylmethyl)cyclopropyl]phenyl]carbamoyl]phenyl]carbamate; N-[4-[(trans)-2-amino-2-(2-naphthylmethyl)cyclopropyl]phenyl]-2-phenyl-acetamide; N-[4-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]benzamide; trans-4-(2-amino-2-ethyl-cyclopropyl)aniline; trans-2-(3-azidophenyl)-1-ethyl-cyclopropanamine; 1-amino-(trans)-2-phenyl-cyclopropyl]methanol; 1-amino-(cis)-2-phenyl-cyclopropyl]methanol; (1R,2S)-1-ethyl-N-[(2-methoxyphenyl)methyl]-2-phenyl-cyclopropanamine; (1R,2S)-1-ethyl-N-[(2-methoxy-1-naphthyl)methyl]-2-phenyl-cyclopropanamine; 2-[[(1S,2R)-1-methyl-2-phenyl-cyclopropyl]amino]-1-(4-methylpiperazin-1-yl)ethanone; 2-[[(1S,2S)-1-methyl-2-phenyl-cyclopropyl]amino]-1-(4-methylpiperazin-1-yl)ethanone; 1-[(3S)-3-aminopyrrolidin-1-yl]-2-[[(1S,2R)-1-methyl-2-phenyl-cyclopropyl]amino]ethanone; trans-2-[[(1-ethyl-2-phenyl-cyclopropyl]amino]-1-(4-

methylpiperazin-1-yl)ethanone; cis-2-[[(1-ethyl-2-phenyl-cyclopropyl]amino]-1-(4-methylpiperazin-1-yl)ethanone; trans-1-ethyl-N-methyl-2-phenyl-cyclopropanamine; cis-1-ethyl-N-methyl-2-phenyl-cyclopropanamine; trans-1-ethyl-N-ethyl-2-phenyl-cyclopropanamine; cis-1-ethyl-N-ethyl-2-phenyl-cyclopropanamine; trans-2-[[1-ethyl-2-phenyl-cyclopropyl]amino]acetamide; trans-N-benzyl-1-ethyl-2-phenyl-cyclopropanamine; trans-N-[(3,4-dimethoxyphenyl)methyl]-1-ethyl-2-phenyl-cyclopropanamine; trans-N-[(4,7-dimethoxy-1-naphthyl)methyl]-1-ethyl-2-phenyl-cyclopropanamine; trans-N-[(2-chloro-3-pyridyl)methyl]-1-ethyl-2-phenyl-cyclopropanamine; trans-N-[(2,2-dimethylchroman-6-yl)methyl]-1-ethyl-2-phenyl-cyclopropanamine; cis-1,2-diphenylcyclopropanamine; trans-1,2-diphenylcyclopropanamine; trans-1-ethyl-2-phenyl-cyclopropanamine; trans-2-(4-bromo-3-fluoro-phenyl)-1-ethyl-cyclopropanamine; trans 2-(3-bromophenyl)-1-phenethyl-cyclopropanamine; (1R,2S)-1,2-diphenylcyclopropanamine; (1S,2R)-1,2-diphenylcyclopropanamine; trans-2-(4-fluorophenyl)-1-(2-naphthylmethyl)cyclopropanamine; trans-2-(4-chlorophenyl)-1-(2-naphthylmethyl)cyclopropanamine; trans-2-(3-chlorophenyl)-1-(2-naphthylmethyl)cyclopropanamine; trans-2-(3-bromophenyl)-1-(2-naphthylmethyl)cyclopropanamine; trans-2-(4-chlorophenyl)-1-phenethyl-cyclopropanamine; trans-2-(4-fluorophenyl)-1-phenethyl-cyclopropanamine; trans-1-benzyl-2-(4-fluorophenyl)cyclopropanamine; trans-1-benzyl-2-(4-chlorophenyl)cyclopropanamine; trans 2-(4-bromophenyl)-1-phenethyl-cyclopropanamine; cis-1-ethyl-2-phenyl-cyclopropanamine; N-[4-(trans-2-amino-2-ethyl-cyclopropyl)phenyl]-3-[(1-methyl-4-piperidyl)amino]-4-phenyl-benzamide; 2-(4-benzyloxyphenyl)-1-(2-naphthylmethyl)cyclopropanamine; N-[4-trans-[2-amino-2-ethyl-cyclopropyl]phenyl]-2-(1-naphthyl)acetamide; N-[4-trans-[2-amino-2-ethyl-cyclopropyl]phenyl]-2-(4-nitrophenyl)acetamide; benzyl N-[4-[[4-[trans-2-amino-2-(2-naphthylmethyl)cyclopropyl]phenyl]carbamoyl] phenyl]carbamate; N-[4-(trans-2-amino-2-ethyl-cyclopropyl)phenyl]naphthalene-1-carboxamide; N-[4-[trans-2-amino-2-(2-naphthylmethyl)cyclopropyl]phenyl]naphthalene-2-carboxamide; N-[4-[trans-2-amino-2-(2-naphthylmethyl)cyclopropyl]phenyl]-4-phenyl-benzamide; N-[4-trans-2-amino-2-ethyl-cyclopropyl]phenyl]-2-(2-naphthyl)acetamide; N-[4-[trans-2-amino-2-phenyl-cyclopropyl]phenyl]benzamide; N-[4-[trans-2-amino-2-(2-naphthylmethyl)cyclopropyl]phenyl]-2-(1-naphthyl)acetamide; N-[3-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]-2-(1-naphthyl)acetamide; N-[4-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]-4-(3-furyl)benzamide; N-[4-[trans-2-amino-2-(2-naphthylmethyl)cyclopropyl]phenyl]-3-chloro-benzamide; N-[3-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]-3-chloro-benzamide; N-[4-[trans-2-amino-2-(2-

naphthylmethyl)cyclopropyl]phenyl]-3-phenyl-propanamide; N-[4-[trans-2-amino-2-(2-naphthylmethyl)cyclopropyl]phenyl]-3-phenyl-benzamide; N-[4-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]-4-(2-oxooxazolidin-3-yl)benzamide; benzyl N-[3-[(4-[trans-2-amino-2-phenyl-cyclopropyl]phenyl)carbamoyl]phenyl] carbamate; N-[4-[trans-2-amino-2-phenyl-cyclopropyl]phenyl]naphthalene-2-carboxamide; N-[4-[trans-2-amino-2-ethyl-cyclopropyl]-2-fluoro-phenyl]benzamide; N-[4-[trans-2-amino-2-ethyl-cyclopropyl]-2-fluoro-phenyl]-4-phenyl-benzamide; N-[4-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]-4-morpholino-benzamide; N-[4-[trans-2-amino-2-phenyl-cyclopropyl]phenyl]-4-phenyl-benzamide; N-[4-[trans-2-amino-2-phenyl-cyclopropyl]phenyl]naphthalene-1-carboxamide; N-[3-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]-4-phenyl-benzamide; N-[3-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]naphthalene-2-carboxamide; N-[3-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]benzamide; N-[4-[trans-2-amino-2-ethyl-cyclopropyl]-2-fluoro-phenyl]-2-(1-naphthyl)acetamide; benzyl N-[4-[[4-[trans-2-amino-2-ethyl-cyclopropyl]-2-fluoro-phenyl]carbamoyl]phenyl] carbamate; N-[4-[trans-2-amino-2-ethyl-cyclopropyl]-2-fluoro-phenyl]-4-(4-methylpiperazin-1-yl)benzamide; N-[4-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide; N-[4-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]-3-(2-oxooxazolidin-3-yl)benzamide; benzyl N-[5-[[4-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]carbamoyl]-2-morpholino-phenyl]carbamate; N-[4-[trans-2-amino-2-ethyl-cyclopropyl]phenyl]-4-(1-methyl-4-piperidyl)benzamide; N-[4-(trans-2-amino-2-ethyl-cyclopropyl)phenyl]pyridine-4-carboxamide; N-[4-(trans-2-amino-2-ethyl-cyclopropyl]phenyl)-4-(4-pyridyl)benzamide; N-[4-(trans-2-amino-2-phenyl-cyclopropyl]phenyl]-3-chloro-benzamide; N-[4-(trans-2-amino-2-phenyl-cyclopropyl)phenyl]-2-(1-naphthyl)acetamide; N-[4-(trans-2-amino-2-phenyl-cyclopropyl)phenyl]-2-phenyl-acetamide; N-[4-(trans-2-amino-2-phenyl-cyclopropyl)phenyl]-3-phenyl-benzamide; N-[4-(trans-2-amino-2-phenyl-cyclopropyl)phenyl]-2-(2-naphthyl)acetamide; N-[4-(trans-2-amino-2-phenyl-cyclopropyl)phenyl]pyridine-4-carboxamide; N-[4-(trans-2-amino-2-phenyl-cyclopropyl]phenyl)-4-(1-methyl-4-piperidyl)benzamide; N-[4-(trans-2-amino-2-phenyl-cyclopropyl)phenyl]-4-(4-methylpiperazin-1-yl)benzamide; N-[4-(trans-2-amino-2-phenyl-cyclopropyl)phenyl]-3-(2-oxooxazolidin-3-yl)benzamide; N-[4-(trans-2-amino-2-phenethyl-cyclopropyl)phenyl]pyridine-4-carboxamide; N-[4-(trans-2-amino-2-phenethyl-cyclopropyl)phenyl]-4-phenyl-benzamide; N-[4-trans-2-amino-2-phenethyl-cyclopropyl)phenyl]benzamide; N-[4-(trans-2-amino-2-phenethyl-cyclopropyl)phenyl]-4-(1-methyl-4-piperidyl)benzamide; N-[4-(trans-2-amino-2-phenethyl-cyclopropyl)phenyl]-4-(4-methylpiperazin-1-yl)benzamide; benzyl N-[5-[[4-[trans-2-amino-2-ethyl-

cyclopropyl]phenyl]carbamoyl]-2-(4-methylpiperazin-1-yl)phenyl]carbamate; N-[4-(trans-2-amino-2-phenethyl-cyclopropyl)phenyl]-3-(2-oxooxazolidin-3-yl)benzamide; 4-[trans-2-amino-2-(2-naphthylmethyl)cyclopropyl]aniline; N-[4-(trans-2-amino-2-ethyl-cyclopropyl]phenyl)-4-(2-hydroxyethylamino)benzamide; benzyl N-[3-[1-[4-[2-amino-2-ethyl-cyclopropyl]phenyl]triazol-4-yl]phenyl]carbamate; trans-1-ethyl-2-[3-(4-phenyltriazol-1-yl)phenyl]cyclopropanamine; benzyl N-[3-[1-[4-[2-amino-2-(2-naphthylmethyl)cyclopropyl]phenyl]triazol-4-yl]phenyl]carbamate; trans-1-(2-naphthylmethyl)-2-[4-(4-phenyltriazol-1-yl)phenyl]cyclopropanamine; trans 1-ethyl-2-[2-(4-phenyltriazol-1-yl)phenyl]cyclopropanamine; trans-1-benzyl-2-[4-(4-phenyltriazol-1-yl)phenyl]cyclopropanamine; N-[4-[(1S,2R)-2-amino-2-ethyl-cyclopropyl]phenyl]-4-phenyl-benzamide; N-[4-[(1R,2S)-2-amino-2-ethyl-cyclopropyl]phenyl]-4-phenyl-benzamide; trans 1-benzyl-2-(3-methoxyphenyl)cyclopropanamine; 1-[3-[(trans-2-amino-2-ethyl-cyclopropyl]phenyl]-3-phenyl-imidazolidin-2-one; trans-1-ethyl-2-[4-(4-phenyltriazol-1-yl)phenyl]cyclopropanamine; trans 1-[(benzylamino)methyl]-2-phenyl-cyclopropanamine; trans 1-[(cyclopropylamino)methyl]-2-phenyl-cyclopropanamine; trans 1-[(4-methylpiperazin-1-yl)methyl]-2-phenyl-cyclopropanamine; 5-[[[trans-1-methyl-2-phenyl-cyclopropyl]amino]methyl]pyrimidin-2-amine; trans-N-[(2-methoxy-3-pyridyl)methyl]-1-methyl-2-phenyl-cyclopropanamine; trans-N-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-1-methyl-2-phenyl-cyclopropanamine; cis-N,1-dimethyl-2-phenyl-cyclopropanamine;2-[[trans-1,2-diphenylcyclopropyl]amino]-1-(4-methylpiperazin-1-yl)ethanone; 1-(4-methylpiperazin-1-yl)-2-[[trans-1-(2-naphthylmethyl)-2-phenyl-cyclopropyl]amino]ethanone;2-[[(1R,2S)-1-methyl-2-phenyl-cyclopropyl]amino]-1-(4-methylpiperazin-1-yl)ethanone; 2-[[(1R,2R)-1-methyl-2-phenyl-cyclopropyl]amino]-1-(4-methylpiperazin-1-yl)ethanone; 2-[[trans-1-methyl-2-phenyl-cyclopropyl]amino]-1-(4-methylpiperazin-1-yl)ethanone; 2-[[cis-1-methyl-2-phenyl-cyclopropyl]amino]-1-(4-methylpiperazin-1-yl)ethanone; trans-N,1-dimethyl-2-phenyl-cyclopropanamine; 2-[[trans-1-ethyl-2-phenyl-cyclopropyl]amino]-1-(1-piperidyl)ethanone;trans-1-ethyl-2-phenyl-N-[2-(1-piperidyl)ethyl]cyclopropanamine; 5-[[[trans-1-methyl-2-phenyl-cyclopropyl]amino]methyl]-1,3,4-oxadiazol-2-amine; trans-1-(4-nitrophenyl)-2-phenyl-cyclopropanamine; trans-2-(4-chlorophenyl)-1-phenyl-cyclopropanamine; trans-2-(4-bromophenyl)-1-phenyl-cyclopropanamine; N-[4-(trans-1-amino-2-phenyl-cyclopropyl]phenyl]acetamide; or a stereoisomer or pharmaceutically acceptable salt thereof.

[00116] In one embodiment, the LSD1 inhibitor is selected from a compound of Formula (III)



(III)

or an isomer, tautomer, racemic form, enantiomer, diastereomer, epimer, polymorph, solvate, mixtures thereof, pharmaceutically acceptable salt thereof, wherein:

A is R or $CH(R_1)$-NH-CO-R_2;

R and R_2 are selected from: alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, heterocycloalkylalkyloxy, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, cycloalkylalkylamino, arylalkylamino, heteroarylalkylamino, heterocycloalkylalkylamino;

R_1 is selected from: alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl;

R_3 is H, C_1-C_6 alkyl.

[00117] In one embodiment, the LSD1 inhibitor is selected from a compound of Formula (III) that is: trans benzyl 4-(2-aminocyclopropyl)phenylcarbamate; trans N-(4-(2-aminocyclopropyl)phenyl)benzamide; trans N-(4-(2-aminocyclopropyl)phenyl)-1-naphthamide; trans N-(4-(2-aminocyclopropyl)phenyl)-2-naphthamide; trans N-(4-(2-aminocyclopropyl)phenyl)biphenyl-4-carboxamide; trans N-(4-(2-aminocyclopropyl)phenyl)-2-phenylacetamide; trans N-(4-(2-aminocyclopropyl)phenyl)-2-(naphthalen-1-yl)acetamide; trans N-(4-(2-aminocyclopropyl)phenyl)-2-(naphthalen-2-yl)acetamide; trans benzyl 1-(4-(2-aminocyclopropyl)phenylamino)-3-methyl-1-oxobutan-2-ylcarbamate; trans benzyl 1-(4-(2-aminocyclopropyl)phenylamino)-4-methyl-1-oxopentan-2- ylcarbamate; trans benzyl 1-(4-(2-aminocyclopropyl)phenylamino)-3-cyclohexyl-1-oxopropan-2-ylcarbamate; trans benzyl 2-(4-(2-aminocyclopropyl)phenylamino)-2-oxo-1-phenylethylcarbamate; trans benzyl 1-(4-(2-aminocyclopropyl)phenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate; trans benzyl 1-(4-(2-aminocyclopropyl)phenylamino)-3-(4-bromophenyl)-1-oxopropan-2-ylcarbamate; trans benzyl 1-(4-(2-aminocyclopropyl)phenylamino)-3-(4-methoxyphenyl)-1-oxopropan-2-ylcarbamate; trans benzyl 1-(4-(2-aminocyclopropyl)phenylamino)-1-oxo-4-phenylbutan-2-ylcarbamate; trans benzyl 1-(4-(2-aminocyclopropyl)phenylamino)-1-oxo-3,3-diphenylpropan-2-ylcarbamate; trans benzyl 1-(4-(2-aminocyclopropyl)phenylamino)-3-(naphthalen-1-yl)-1-oxopropan-2-ylcarbamate; trans benzyl 1-(4-(2-aminocyclopropyl)phenylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-ylcarbamate; trans benzyl 1-(4-(2-aminocyclopropyl)phenylamino)-4-(1H-indol-3-yl)-1-oxobutan-2-ylcarbamate; trans benzyl 1-

(4-(2-aminocyclopropyl)phenylamino)-4-(benzo[b]thiophen-3-yl)-1-oxobutan-2-ylcarbamate; trans 4-bromobenzyl 1-(4-(2-aminocyclopropyl)phenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate; cis benzyl 1-(4-(2-aminocyclopropyl)phenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate; trans N1-(4-(2-aminocyclopropyl)phenyl)-N8-hydroxyoctanediamide; trans benzyl 1-((4-(2-aminocyclopropyl)phenyl)(methyl)amino)-1-oxo-3-phenylpropan-2-ylcarbamate; trans N-(4-(2-aminocyclopropyl)phenyl)-2-(3-benzylureido)-3-phenylpropanamide or a isomer, tautomer, racemic form, enantiomer, diastereomer, epimer, polymorph, solvate, mixtures thereof, pharmaceutically acceptable salt thereof.

[00118] In one embodiment, the LSD1 inhibitor is selected from: N1-((trans)-2-phenylcyclopropyl)cyciohexane-1,4-diamine; (cis)-N1-((1S,2R)-2-phenylcyclopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1S,2R)-2-phenylcyclopropyl)cyclohexane-1,4-diamine; (cis)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(thiazol-5-yl)cyclopropyl)cyclohexane-1,4-diamine; 1 -((trans)-2-(pyridin-3-yl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(6-(3-(trifluoromethyl)phenyl)pyridin-3-yl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(4-(benzyloxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine; 4-(((trans)-2-(6-(3-(trifluoromethyl)phenyl)pyridin-3-yl)cyclopropyl)amino)cyclohexanol; 4-(((trans)-2-(6-(3-(trifluoromethyl)phenyl)pyridin-3-yl)cyclopropyl)amino)cyclohexanecarboxamide; N-(4-(((trans)-2-(6-(3-(trifluoromethyl)phenyl)pyridin-3-yl)cyclopropyl)amino)cyclohexyl)acetamide; (4-(((trans)-2-(6-(3-(trifiuoromethyl)phenyl)pyrldin-3-yl; (R)-1-(4-(((trans)-2-phenylcyclopropyl)amino)cyclohexyl)pyrrolidin-3-amine; N1-((trans)-2-(4'-chloro-[1,1'-biphenyl]-4-yl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(3'-chloro-[1,1'-biphenyl]-4-yl)cyclopropyl)cyclohexane-1 ,4-diamine; 4'-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-ol; N-(4'-((trans)-2-((4-aminocyciohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)methanesulfonamide; N1-((trans)-2-(4-((2-fluorobenzyl)oxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(4-((3-fluorobenzyl)oxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(4-((4-fluorobenzyl)oxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-methyl-N4-((trans)-2-phenylcyclopropyl)cyclohexane-1,4-diamine; N1-methyl-N4-((trans)-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(4-

(benzyloxy)phenyl)cyciopropyl)-N4-methylcyclohexane-1,4-diamine; N1-((trans)-2-phenylcyclopropyl)cyclobutane-1,3-diamine; N1-((trans)-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)cyclopropyl)cyclobutane-1,3-diamine; N1-((trans)-2-(4-(benzyloxy)phenyl)cyclopropyl)cyclobutane-1,3-diamine; N1-((trans)-2-phenylcyclopropyl)-2,3-dihydro-1H-indene-1 ,3-diamine; N1-((trans)-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)cyclopropyl)-2,3-dihydro-1H-indene-1,3-diamine; N1-((trans)-2-(4-(benzyloxy)phenyl)cyclopropyl)-2,3-dihydro-1H-indene-1,3-diamine; N1-((trans)-2-fluoro-2-phenylcyclopropyl)cyclohexane-1,4-diamine; N1-((1 S,2S)-2-fluoro-2-phenylcyclopropyl)cyclohexane-1,4-diamine; N1-((1 R,2R)-2-fluoro-2-phenylcyclopropyl)cyclohexane-1,4-diamine; 1-methyl-N4-((trans)-2-phenylcyclopropyl)cyclohexane-1 ,4-diamine; 4-(aminomethyl)-N-((trans)-2-phenylcyclopropyl)cyclohexanamine; N1-((trans)-2-phenyicyciopropyl)cyciohexane-1,3-diamine; N1-((cis)-2-phenylcyclopropyl)cyclohexane-1,4-diamine; tert-butyl (4-(((trans)-2-phenylcyclopropyl)amino)cyclohexyl)carbamate; 1-ethyl-3-(4-(((trans)-2-phenylcyclopropyl)amino)cyclohexyl)urea; 4-morpholino-N-((trans)-2-phenylcyclopropyl)cyclohexanamine; N1-((trans)-2-(4-bromophenyl)cyclopropyl)cyclohexane-1 ,4-diamine; N1-{2-(o-tolyl)cyclopropyl)cyclohexane-1,4-diamine; N1-(2-(4-(trifluoromethyl)phenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-(2-(4-methoxyphenyl)cyclopropyl)cyclohexane-1,4-diamine; 4-(2-((4-aminocyclohexyl)amino)cyclopropyl)phenol; N1-(2-(2-fluorophenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-(2-(3,4-difluorophenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-(2-(naphthalen-2-yl)cyclopropyl)cyclohexane-1,4-diamine; N1-(2-methyl-2-phenylcyclopropyl)cyclohexane-1,4-diamine; (R)-1-(4-(((trans)-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)cyclopropyl)amino)cyclohexyl)pyrrolidin-3-amine; (cis)-N1-((1S,2R)-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)cyclopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1S,2R)-2-(3'-(trifiuoromethyl)-[1,1'-biphenyl]-4-yl)cyclo-propyl)cyclohexane-1,4-diamine; (cis)-N1-((1R,2S)-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)cyclo-propyl)cyclohexane-1,4-diamine; (Trans)-N1-({1R,2S)-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-yl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(4-cyclopropylphenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(4-(pyridin-3-yl)phenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(4-(1H-indazol-6-yl)phenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(4-(1H-pyrazol-5-yl)phenyl)cyclopropyl)cyclohexane-1,4-diamine; 3-(5-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)thiophen-2-yl)phenol; 3-(5-((trans)-2-((4-

aminocyciohexyl)amino)cyclopropyl)thiazol-2-yl)phenol; 3-(5-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)pyridin-2-yl)-5-methoxybenzonitrile; 5- 5-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)pyridin-2-yl)-2-methylphenol; N-(4'-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)-6-methoxy-[1,1,-biphenyl]-3-yl)methanesulfonamide; N-(3-(5-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)thiazol-2-yl)phenyl)-2-cyanobenzenesulfonamide; N-(4'-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)-2-cyanobenzenesulfonamide; 6-amino-N-(4'-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)pyridine-3-sulfonamide; N-(4'-((trans)-2-((4-aminocyclohexyl)amino)cyciopropyl)-[1,1'-biphenyi]-3-yl)piperazine-1-sulfonamide; N1-((cis)-2-fluoro-2-phenylcyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(4-((3-(piperazin-1-yl)benzyl)oxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(4-(pyridin-3-ylmethoxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(6-((3-methylbenzyl)amino)pyridin-3-yl)cyclopropyl)cyclohexane-1,4-diamine; 3-((5-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)pyridin-2-yl)aminobenzonitrile; N1-((trans)-2-(naphthalen-2-yl)cyclopropyl)cyclohexane-1 ,4-diamine; N1-((trans)-2-(o-tolyl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(4-(trifluoromethyl)phenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(4-methoxyphenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(2-fluorophenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-(3,4-difluorophenyl)cyclopropyl)cyclohexane-1,4-diamine; N1-((trans)-2-methyl-2-phenylcyclopropyl)cyclohexane-1,4-diamine; (cis)-N1-((1S,2R)-2-(pyridin-3-yl)cyclopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1R,2S)-2-(pyridin-3-yl)cyclopropyl)cyclohexane-1,4-diamine; (cis)-N1-((1R,2S)-2-(pyridin-3-yl)cyclopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1S,2R)-2-(pyridin-3-yl)cyclopropyl)cyclohexane-1,4-diamine; (cis)-N1-((1S,2R)-2-phenylcyclopropyl)cyclobutane-1 ,3-diamine; trans N1-(1R,2S)-2-phenylcyclopropyl)cyclobutane-1.3-diamine; (cis)-N1-((1R,2S)-2-phenylcyclopropyl)cyclobutane-1,3-diamine; (trans)-N1-((1S,2R)-2-phenylcyclopropyl)cyclobutane-1,3-diamine; (cis)-N1-((1S,2R)-2-(3,4-difluorophenyl)cyclopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)cyclohexane-1,4-diamine; (cis)-N1-((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1S,2R)-2-(3,4-difluorophenyl)cyclopropyl)cyclohexane-1,4-diamine; (cis)-N1-((1S,2R)-2-(naphthalen-2-yl)cyclopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1R,2S)-2-(naphthalen-2-yl)cyclopropyl)cyciohexane-1,4-diamine; (cis)- 1-((1R,2S)-2-(naphthalen-2-

yl)cyclopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1S,2R)-2-(naphthalen-2-yl)cyclopropyl)cyclohexane-1,4-diamine; (cis)-N1-((1S,2R)-2-(4-(1H-pyrazol-5-yi)phenyl)cyciopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1R,2S)-2-(4-(1H-pyrazol-5-yl)phenyl)cyclopropyl)cyclohexane-1,4-diamine; (cis)-N1-((1R,2S)-2-(4-(1H-pyrazol-5-yl)phenyl)cyclopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1S,2R)-2-(4-(1H-pyrazol-5-yl)phenyl)cyclopropyl)cyclohexane-1,4-diamine; N-(4'-((1R,2S)-2-(((cis)-4-aminocyclohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)piperazine-1-sulfonamide; N-(4'-((1S,2R)-2-(((trans)-4-aminocyclohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)piperazine-1-sulfonamide; N-(4'-((1S,2R)-2-(((cis)-4-aminocyclohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)piperazine-1-sulfonamide; N-(4'-((1R,2S)-2-(((trans)-4-aminocyciohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)piperazin; (cis)-N1-((1S,2R)-2-(4-((2-fluorobenzyl)oxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1R,2S)-2-(4-((2-fluorobenzyl)oxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine; (cis)-N1-((1R,2S)-2-(4-((2-fluorobenzyl)oxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine; (trans)-N1-((1S,2R)-2-(4-((2-fluorobenzyl)oxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine; or a pharmaceutically acceptable salt or solvate thereof.

[00119] In one embodiment, the LSD1 inhibitor is selected from: 1,1-Dimethylethyl 4-({[trans-2-phenylcyclopropyl]amino}methyl)-1-piperidinecarboxylate; 1,1-Dimethylethyl 4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)-1-piperidinecarboxylate; 1,1-Dimethylethyl 4-({[(1S,2R)-2-phenylcyclopropyl]amino}methyl)-1-piperidinecarboxylate; [trans-2-Phenylcyclopropyl]{[1-(phenylmethyl)-4-piperidinyl]methyl}amine; N-Phenyl-4-(((trans-2-phenylcyclopropyl)amino)methyl)piperidine-1-carboxamide; Phenyl(4-(((trans-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methanone; 1-(4-(((trans-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)ethanone; Benzyl 4-(((trans-2-phenylcyclopropyl)amino)methyl)piperidine-1-carboxylate; 1,1-Dimethylethyl 4-({[trans-2-phenylcyclopropyl]amino}methyl)hexahydro-1H-azepine-1-carboxylate 2-(4-(((trans-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)acetic acid; 4-{[(3R)-3-({[(1R,2S)-2-Phenylcyclopropyl]amino}methyl)-1-pyrrolidinyl]methyl}benzoic acid; 4-{[(3S)-3-({[(1R,2S)-2-Phenylcyclopropyl]amino}methyl)-1-pyrrolidinyl]methyl}benzoic acid; 4-{3-[4-({[(1R,2S)-2-Phenylcyclopropyl]amino}methyl)-1-piperidinyl]propyl}benzoic acid; trans-2-Phenyl-N-((1-(pyridin-4-ylmethyl)piperidin-4-yl)methyl)cyclopropanamine; trans-N-((1-(2-Fluorobenzyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; trans-N-((1-(3-Fluorobenzyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; trans-N-((1-(4-Fluorobenzyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; trans-N-((1-(2,4-

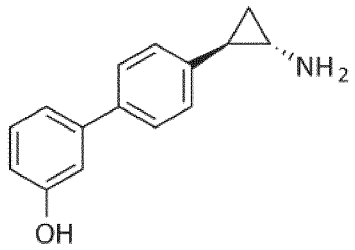
Difluorobenzyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; Ethyl 4-((4-(((trans-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoate; trans-N-((1-(4-(Methylsulfonyl)benzyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; 2-((4-(((trans-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzonitrile; trans-2-Phenyl-N-((1-(2-(trifluoromethyl)benzyl)piperidin-4-yl)methyl)cyclopropanamine; trans-N-((1-((5-Methylisoxazol-3-yl)methyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; trans-N-((1-((1H-Pyrazol-4-yl)methyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; N-(4-((4-(((trans-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)phenyl)acetamide; 4-((4-(((trans-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzo[c][1,2]oxaborol-1(3H)-ol; 5-((4-(((trans-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzo[c][1,2]oxaborol-1(3H)-ol; (4-((4-(((trans-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)phenyl)boronic acid; 2-((4-(((trans-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 3-((4-(((trans-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)-methyl)benzoic acid; 4-((4-(((trans-2-(4-Bromophenyl)cyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 4-((4-(((trans-2-(4-Chlorophenyl)cyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 4-((4-(((trans-2-(3,4-Dichlorophenyl)cyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 4-((4-(((trans-2-(4-(Trifluoromethyl)phenyl)cyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 4-((4-(((trans-2-(3,4-Dimethoxyphenyl)cyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 4-((4-(((trans-2-(4-Acetamidophenyl)cyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 4-((4-(((trans-2-(4-Benzamidophenyl)cyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; trans-2-Phenyl-N-((1-phenylpiperidin-4-yl)methyl)cyclopropanamine; Ethyl 4-(((trans-2-phenylcyclopropyl)amino)methyl)piperidine-1-carboxylate; trans-4-((4-(((trans-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)cyclohexanecarboxylic acid; (trans)-N-((1-(Methylsulfonyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; N-ethyl-4-((((trans)-2-phenylcyclopropyl)amino)methyl)piperidine-1-carboxamide; N-cyclopropyl-4-((((trans)-2-phenylcyclopropyl)amino)methyl)piperidine-1-carboxamide; N,N-dimethyl-4-((((trans)-2-phenylcyclopropyl)amino)methyl)piperidine-1-carboxamide, (4-((((trans)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)(pyrrolidin-1-yl)methanone; trans-N-((1-((cyclopropylsulfonyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; trans-N-((1-((isopropylsulfonyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; trans-N-((1-(3,5-dimethylisoxazol-4-yl)sulfonyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; trans-N-((1-((1,2-dimethyl-1H-imidazol-4-yl)sulfonyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine;

(trans)-2-Phenyl-N-(2-(1-(pyridin-2-yl)piperidin-4-yl)ethyl)cyclopropanamine; 6-(4-(2-(((trans)-2-Phenylcyclopropyl)amino)ethyl)piperidin-1-yl) nicotinic acid; trans-2-phenyl-N-(2-(1-(pyridin-4-yl)piperidin-4-yl)ethyl)cyclopropanamine; trans-2-phenyl-N-(2-(1-(pyrimidin-4-yl)piperidin-4-yl)ethyl)cyclopropanamine; trans-2-phenyl-N-(2-(1-phenylpiperidin-4-yl)ethyl)cyclopropanamine; trans-2-phenyl-N-(2-(1-(pyridin-3-yl)piperidin-4-yl)ethyl)cyclopropanamine; trans-2-phenyl-N-(2-(1-(pyrimidin-2-yl)piperidin-4-yl)ethyl)cyclopropan- amine; 3-Cyano-4-((4-((((trans)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 2-fluoro-4-((4-((((trans)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 3-fluoro-4-((4-((((trans)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl-)methyl)benzoic acid; 3-chloro-4-((4-((((trans)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl-)methyl)benzoic acid; 3-methoxy-4-((4-((((trans)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 2-chloro-4-((4-((((trans)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 4-(3-(4-(Cyano(((1R,2S)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)propyl)benzoic acid; 4-{3-[4-({[(trans))-2-phenylcyclopropyl]amino}methyl)-1-piperidinyl]propyl}benzoic acid; 4-(4-(4-((((1R,2S)-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)butyl)benzoic acid; 4-(4-(4-(Cyano(((1R,2S)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)butyl)benzoic acid; 4-(2-(4-((((trans)-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)ethyl)benzoic acid; 4-(2-(4-((((1R,2S)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)ethyl)benzoic acid; 6-((4-((((trans)-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)-2-naphthoic acid; 6-((4-((((1R,2S)-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)-2-naphthoic acid; (trans)-N-((1-(4-(1H-Tetrazol-5-yl)benzyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; 2-(4-((4-((((trans)-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzamido)acetic acid; N-(4-((4-((((trans)-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)phenyl)methanesulfonamide; (trans)-N-((1-(3-(1H-Tetrazol-5-yl)propyl)piperidin-4-yl)methyl)-2-phenylcyclopropanamine; 4-((4-(2-(((trans)-2-Phenylcyclopropyl)amino)ethyl)piperidin-1-yl)methyl)- benzoic acid; 6-((4-((((trans)-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)nicotinic acid; 2-(4-((4-((((trans)-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)phenyl)acetic acid; 2-((4-((((trans)-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)o- xazole-4-carboxylic acid; 2-(4-((4-((((trans)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)phenoxy)acetic acid; N-(Methylsulfonyl)-4-((4-((((trans)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzamide; 4-((4-((((trans)-2-(4-Iodophenyl)cyclopropyl)amino)methyl)piperidin-1-

yl)methyl)benzoic acid; 4-((trans)-2-(((1-Benzylpiperidin-4-yl)methyl)amino)cyclopropyl)benzoic acid; 4-((4-((((trans)-2-(4-(1-Methyl-1H-pyrazol-4-yl)phenyl)cyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 4-((4-((((trans)-2-(4-Cyclopropylphenyl)cyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 2-Chloro-4-((4-((((1R,2S)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid; 3-(3-(4-((((trans)-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)propyl)benzoic acid; or 2-(4-((4-((((1R,2S)-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)phenyl)acetic acid or a pharmaceutically acceptable salt or solvate thereof.

[00120] In one embodiment, the LSD1 inhibitor, which may also be referred to as a KDM1A inhibitor, is selected from the group consisting of:

tranylcypromine;



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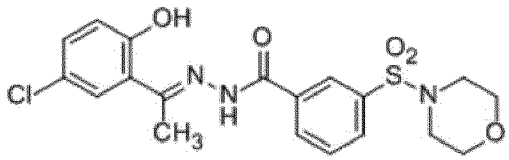

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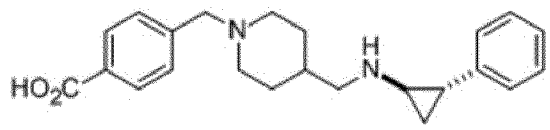

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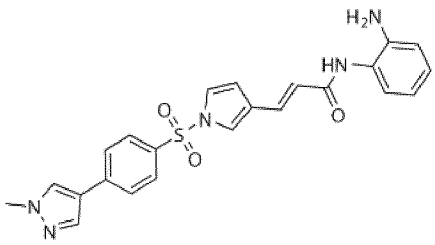

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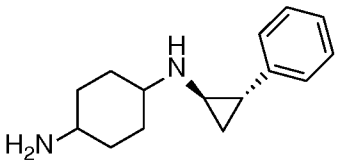

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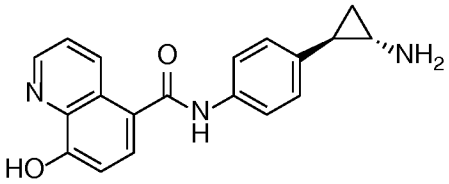

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N-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide; and a pharmaceutically acceptable salt thereof. (Maes, T. *et al.* Current Opinion in Phamacol. 2015, 23:52-60).

[00121] In one embodiment, the LSD1 inhibitor is *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride.

[00122] In one embodiment, the IGF1/insulin inhibitor is selected from inhibitors of IGF1 receptor, inhibitors of insulin receptor, and inhibitors of both IGF1 receptor and insulin receptor.

[00123] In one embodiment, an inhibitor of IGF1 is selected from:

1. Tyrphostins such as AG538 and AG1024. These are in early pre-clinical testing. They are not thought to be ATP-competitive, although they are when used in EGFR as described in QSAR studies;
2. Pyrrolo(2,3-d)-pyrimidine derivatives such as NVP-AEW541;
3. Monoclonal antibodies such as figitumumab.

[00124] In one embodiment, the IGF1/insulin inhibitor is 3-[8-Amino-1-(2-phenyl-7-quinolyl)imidazo[1,5-a]pyrazin-3-yl]-1-methyl-cyclobutanol, which is also known as linsitinib or OSI906.

[00125] Calorie restriction (CR), or caloric restriction, or energy restriction, is a dietary regimen that reduces calorie intake without incurring malnutrition or a reduction in essential nutrients.

[00126] Standard diet (SD), *i.e.*, a normal caloric intake, is dependent upon age, gender and lifestyle (sedentary, moderately active, active), but generally ranges from 1,000 to 2,400 Calories for females and 1,000 to 3,200 Calories for males. In the examples disclosed herein, mice are allowed to eat without restriction and their caloric intake is monitored for a period of time. The average amount of Calories consumed in this period of time is the basis for determining the number of Calories to be fed to mice under Caloric restriction (CR).

[00127] A Calorie restricted (CR) diet is a diet with less than 90 % normal intake, less than 80% normal intake, less than 75% normal intake, less than 70%, normal intake, less than 65%, normal intake, less than 60%, normal intake, less than 55%, normal intake, or less than 50%, normal intake.

[00128] A "caloric restriction mimetic," as used herein, refers to a class of supplements and

drugs that mimic the anti-aging effects of calorie restriction, including, for example, the alteration of key metabolic pathways. Caloric restrictions mimetics are also referred to as energy restriction mimetics.

[00129] Examples of caloric restriction mimetic include, without limitation, sirtuin-activating compounds.

[00130] Specific examples of caloric restriction mimetics include, without limitation, resveratrol, butein, piceatannol, isoliquiritigenin, fisetin, and quercetin. Other examples of caloric restriction mimetics include, without limitation, metformin, oxaloacetate, rimonabant, lipoic acid, 2-deoxy-D-glucose, rapamycin, peroxisome proliferator-activate receptor gamma inhibitors (rosigalitazone, gugulipids), exenatide, adiponectin, acipimox, hydroxycitrate, dipeptidyl peptidase 4 inhibitors, iodoacetate, mannoheptulose, modulators of neuropeptide Y, 4-phenylbutyrate, gymnemoside, and spermidine.

[00131] In one aspect, the pharmaceutical composition comprising an LSD1 inhibitor of the disclosure as defined above, further comprises at least one other therapeutic agent, selected from the group consisting of: histone deacetylase inhibitors, retinoid receptor modulators, anti-proliferative/antineoplastic agents, cytostatic agents, agents which inhibit cancer cell invasion, inhibitors of growth factor function, anti-angiogenic agents, cell cycle inhibitors, proteasome inhibitors, HSP90 inhibitors, selective COX-2 inhibitors or a chemotherapeutic agent.

[00132] As used herein, phrases containing the term "and/or" such as "A, B and/or C" refer to any of the following: A only; B only; C only; A and B; A and C; B and C; A, B and C.

[00133] The term, "subject" as used herein refers to a human or non-human. In one embodiment, the subject is a mammal. In one embodiment, the subject is a human.

[00134] The phrase, "therapeutically effective amount" as used herein indicates an amount necessary to administer to a subject, or to a cell, tissue, or organ of a subject, to achieve a therapeutic effect, such as an ameliorating or alternatively a curative effect.

[00135] In one aspect, the disclosure relates to a pharmaceutical composition in the form of tablets, capsules, oral preparations, powders, granules, pills, injectable or infusible liquid, solutions, suspensions, emulsions, suppositories, ointments, creams, lotions, gels, pastes, or transdermal delivery devices. A reference for the formulations is the book by Remington ("Remington: The Science and Practice of Pharmacy", Lippincott Williams & Wilkins, 2000).

[00136] Compounds of the application may be administered to a patient in a total daily dose of, for example, from 0.001 to 1000 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose. The determination of optimum dosages for a particular patient is well known to one skilled in the art.

[00137] Any of the compounds, combinations, pharmaceutical compositions, and/or dosage forms described herein can be administered to the patient via an oral, topical, intravenous, inhalational, otic, intramucosal, intraarterial, intraocular, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, and/or subcutaneous route of administration.

[00138] Any of the compounds, combinations, pharmaceutical compositions, and/or dosage forms described herein can be administered to the patient on a daily (*e.g.*, 1, 2, or 3 times daily), weekly (*e.g.*, 1, 2, 3, 4, or 5 times weekly), or monthly basis (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times monthly). Determination of the appropriate dosing schedule is within the routine level of skill in the art.

[00139] Any of the compounds, combinations, pharmaceutical compositions, and/or dosage forms described herein may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 21st Edition, 2000, Lippincott Williams & Wilkins, which is incorporated herein in its entirety.

[00140] As is common practice, the compositions are normally accompanied by written or printed instructions for use in the treatment in question.

[00141] Another aspect of the disclosure is a kit comprising an LSD1 inhibitor, combination or pharamaceutical composition as defined herein and at least one therapeutic agent selected from the group consisting of: histone deacetylase inhibitors, retinoid receptor modulators, antiproliferative/ antineoplastic agents, cytostatic agents, agents which inhibit cancer cell invasion, inhibitors of growth factor function, antiangiogenic agents, cell cycle inhibitors, proteasome inhibitors, HSP90 inhibitors, Selective COX-2 inhibitors and chemotherapeutic agents.

[00142] Optionally, the compound of the disclosure and the at least one therapeutic agent are in separated containers.

[00143] In one embodiment, the LSD1 inhibitor and the at least one caloric restriction mimetic and/or the at least one IGF1/insulin inhibitor are administered simultaneously or sequentially. The LSD1 inhibitor may be administered before or after the at least one caloric restriction mimetic and/or the at least one IGF1/insulin inhibitor.

[00144] In the kit, the LSD1 inhibitor and at least one caloric restriction mimetic and/or at least one IGF1/insulin inhibitor are in separated containers or in the same container.

[00145] In any of the methods described herein, if the subject is under a CR diet, then the CR diet may start before the administration of an LSD1 inhibitor, after the administration of an

LSD1 inhibitor, or concurrently with the administration of an LSD1 inhibitor.

[00146] In one embodiment, the CR diet starts before the administration of an LSD1 inhibitor. For example, 1 day, 2 days, 3 day, 4 days, 5 days, 6 days, 14 days, 21 days, 30 days, 60 days, 90 days or any time period in between.

[00147] In one embodiment, the CR diet starts after the administration of an LSD1 inhibitor. For example, 1 day, 2 days, 3 day, 4 days, 5 days, 6 days, 14 days, 21 days, 30 days, 60 days, 90 days or any time period in between.

[00148] In one embodiment, the CR diet starts concurrently with the administration of an LSD1 inhibitor.

Materials and methods

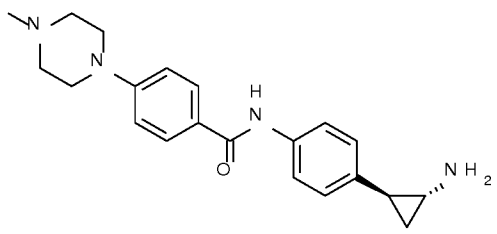
[00149] Mice used in the examples presented herein were either under Caloric-restriction (CR) or a standard diet (SD). Mice were caged individually. Prior to starting the diet (CR), food consumption was monitored for 1 week. Then food was administered daily in doses equal to 70% of the daily intake (30 % caloric restriction). Other mice were under Standard Diet (SD).

[00150] APL cells were generated in mice expressing the PML-RARa fusion under the control of the Cathepsin G promoter (Westervelt et al, Blood. 2003 Sep 1;102(5):1857-65). Primary leukemia cells were transplanted into recipients subjected to 30% CR or Standard Diet (SD). We scored the effect of CR alone or in combination with compound 1 (Varasi et al Eur. J. Cancer Vol 50 suppl. info. 6: 185) on mouse survival, leukemia initiating cell (LIC) frequency and epigenomic, transcriptomic and metabolic parameters.

[00151] Primary leukemia cells isolated from cathepsin G-PML/RARa knockin mice (total spleen cells from moribund mice, >90% infiltrated) were frozen in DMSO, aliquoted and stored in liquid nitrogen. For each experiment, aliquots were thawed and 100,000 live cells (as ascertained by Trypan Blue exclusion) were resuspended in PBS and injected intravenously in the tail vein. Recipient animals were congenic CD45-2 C57Bl/6 male mice aged 8-10 weeks.

Drug preparation and administration

[00152] *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide:



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was prepared as described in WO 2015/181380 and dissolved in 40% poly-ethylene glycol (PEG) in PBS (v/v) at 4.5 μg/ml and administered by gavage at 45 mg/kg per dose. Administration schedule was for 2 or 3 weeks on days 1, 2 or 3, in the evening (6-8 p.m.).

[00153] OSI906 was purchased from Selleck Chemicals and dissolved in DMSO at 100 mM and subsequently dissolved in 40% PEG in PBS (v/v) at 2 μg/ml. It was administered by gavage at 20 mg/kg per dose. Administration schedule was for 3 weeks on days 1, 3 or 5 in the morning (6-8 a.m.).

In vitro conditions for cell line screening

[00154] Growing cell lines were resuspended in their medium at 200,000 cells/mL and OSI906 was added at 1 or 5 μM. Cells were grown for 3 days, harvested and replated in fresh medium containing vehicle or OSI/906 at their prior concentration, plus or minus compound 1 at 500 nM. Cells were grown for 2 additional days, harvested and then plated at 2000 cells/mL in methylcellulose/IMDM. Colonies were scored after 8 days by microscopy.

EXAMPLES

Example 1.

[00155] The effect of CR on an established model of cancer, the murine APL (Westervelt et al Blood 2002), was assessed by transplanting primary leukemia cells into recipient mice subjected to CR or standard diet (SD). We observed initially (3-4 weeks) a dramatic decrease in the total leukemic burden, this was followed by a rapid rise in blast numbers (Figure 1A). Further evidence of the decrease in leukemic burden was found in the bone marrow (Figure 1B – 4 weeks, Figure 1C – 6 weeks) and spleen (Figure 1D of the mice).

[00156] Survival of mice was significantly prolonged by CR, with a median survival of 91 vs 51 days for SD, p=0.038 (Figure 2A). Initiation of CR after leukemia cell injection is equally effective at extending the lifespan of mice injected with APL cells (Figure 2B).

Example 2.

[00157] To evaluate the effect of CR on leukemia initiating, transplanted leukemic cells were isolated after 6 weeks of SD or CR in limiting dilutions into tertiary recipients. This revealed a ~4-fold increase in leukemia initiating cells (LICs) and a more aggressive phenotype of CR-conditioned leukemia. (Figure 3A - limiting dilution analysis, Figure 3B - survival after injection of 50,000 cells from SD or CR secondary recipient). RNAseq analysis showed that CR had induced a dramatic transcriptional reprogramming characterized by: i) upregulation of

genes controlling oxidative phosphorylation, TCA cycle and a number of anabolic pathways, including nucleotide and protein biosynthesis; ii) downregulation of inflammation and monocytic differentiation-associated pathways (Figures 4A-4C). Gene set enrichment analysis of RNAseq data obtained from APL cells sorted after 6 weeks of standard diet or caloric restriction showed transcriptional reprogramming of multiple pathways involved in metabolism and inflammation. (Figure 4D) Caloric restriction leads to increased mitochondrial activity, as shown by upregulation of mitochondrially-transcribed genes coding for respiratory complex subunits (but not mitochondrially encoded tRNAs, Figure 4E) and by increased signal with the vital dye Mitotracker Red (Figure 4F), whose fluorescence intensity is proportional to mitochondrial redox potential.

[00158] Chromatin Immunoprecipitation followed by sequencing (ChIPseq) with antibodies against several histone modifications was performed and, using H3K27ac signal, a group of so-called "super-enhancers" in leukemic cells in SD, characterized by disproportionately high signal and genomic vicinity. Transcription of genes proximal to these super-enhancers was characterized by uniform downregulation upon CR (Figure 5).

[00159] Collectively, these data show that upon CR, leukemic cells undergo an initial phase of adaptation to the new metabolic environment and increased LIC activity, characterized by global transcriptional changes where superenhancer-associated genes play a crucial role.

Example 3.

[00160] Subject mice with leukemia were subjected to CR and then treated with compound 1. Strikingly, the combination of CR and compound 1 resulted in apparent eradication of disease in the majority of tested mice (n=5), as shown by their prolonged survival (all 5 mice were sacrificed in the absence of pathological signs after more than 5 months, Figure 6A). A lack of tertiary leukemia development upon transplantation of whole bone marrow into RAG-/- mice for 4 out of 5 donors was also observed (Figure 6B). Administration of compound 1 on SD-fed mice resulted in 3 out of 5 mice succumbing to disease and subsequent transplantation into RAG-/- mice of the 2 survivors led to leukemia development in 1 case. In an independent experiment, analysis of bone marrow after 2 weeks of treatment with compound 1 revealed complete disappearance of blasts in 4 out of 6 mice and a 1,000-10,000-fold decrease compared to all other groups in the remaining 2 mice (Figure 6C).

[00161] In another series of experiments, APL cells were injected in two cohorts of recipient mice: one that had been subjected to CR for the prior two weeks, some had been fed *ad libitum* with normal food. Two weeks later, each cohort was further randomized into receiving

compound 1 by gavage at 45 mg/kg per dose, on days 1, 2 and 3 of each of the subsequent 3 weeks in the evening (6-8 p.m.). Treatment was then stopped, and mice were kept on their respective diet (CR or SD) and monitored for survival. None of the five mice treated with compound 1 under a CR-diet succumbed to disease, whereas all five mice died under SD. Three out of five mice succumbed to disease when compound 1 was administered without CR.

[00162] In another series of experiments, APL cells were injected in two cohorts of recipient mice: one that had been subjected to CR for the prior two weeks, some had been fed *ad libitum* with normal food. Two weeks later, each cohort was further randomized into receiving compound 1 by gavage at 45 mg/kg per dose, on days 1, 2 and 3 of each of the subsequent 2 weeks in the evening (6-8 p.m.). Mice were then sacrificed and the number of leukemic blasts in the bone marrow scored by flow cytometry as CD45-2+. Treatment with compound 1 in mice under a CR-diet resulted in complete disappearance of blasts in 4 out of 6 mice and a 1,000-10,000 fold decrease compared to all other groups in the remaining 2 mice.

Example 4

[00163] CR mimetics rapamycin and the IGF1R/Insulin receptor inhibitor OSI906 were evaluated as a possible replacement for a CR-diet. APL cells were injected in mice all fed SD, and then subjected to treatment with OSI906 and compound 1 starting from week 2 after injection. OSI906 was administered by gavage at 20 mg/kg per dose, on days 1, 3 and 5 of each week, in the morning (6-8 a.m.). Compound 1 was administered by gavage at 45 mg/kg per dose, on days 1, 2 and 3, of each week, in the evening (6-8 p.m.). Treatment was continued for 3 weeks and then mice were monitored for survival. The combination with OSI906 was synergistic, significantly prolonging survival (median 121 vs 50 days, p=0.0143). (Figure 7). Rapamycin had no effect, neither alone nor in combination (not shown).

Example 5

[00164] In order to identify other types of leukemia where IGF1R/Insulin receptor inhibition could synergize with LSD1 inhibition, we developed an *in vitro* screening system using the established APL cell line NB4. Cells were treated with OSI906 or vehicle for 3 days (to mimic CR conditioning), and then with or without an LSD1 inhibitor (compound 1) for two additional days. After scoring cell viability (reduced by half by OSI906, not shown), cells were plated in a semi-solid medium to score colony-forming ability (Figure 8A, upper panel). Treatment with OSI906 induced a dose-dependent increase in colony formation, but this was entirely abrogated by treatment with the LSD1 inhibitor (compound 1) (Figure 8A, bottom panel). Interestingly,

treatment with OSI906 led to increased LSD1 protein and decreased H3K4me2 levels, suggestive of higher enzymatic activity; this again was abrogated by the LSD1 inhibitor (compound 1) (Figure 8B). Thus, this *in vitro* system reproduces essential features of CR (*e.g.*, increased self-renewal and the mechanistic involvement of LSD1) and can be used to rapidly identify cancer cell lines sensitive to CR plus LSD1 inhibition. Thus, we screened for leukemia cell lines in which: i) IGF1R inhibitor is able to increase colony formation and ii) LSD1 inhibitor (compound 1) abrogates this increase. As can be seen in Figure 9, MV4-11 and, to a minor extent, OCI-AML3 fit this paradigm These cell lines are widely used model for the investigation of common leukemic mutations: MV4-11 bears MLL-AF9 (MLL translocations are present in 21% of AML patients) and FLT3-ITD (present in 27% of AMLs), whereas OCI-AML5 s driven by an NPM mutation (27% of AMLs). These findings indicate that the synergy between CR or IGF1R inhibitor is not limited to the PML/RARa-bearing acute promyelocytic leukemia but occurs also in other leukemias.

[00165] Compared to SD controls, CR-fed mice experienced an initial dramatic decrease in the total leukemic burden accompanied by cell cycle slowdown ("adaptation phase"); this was followed by a delayed disease progression that brought animals to death ("terminal phase") (median survival 91 vs 51 days, $p=0.038$). Limiting-dilution transplantation of CR-conditioned leukemias revealed increased frequency of LICs (estimated frequency 1/3064 cells in SD vs 1/947 in CR, $p=0.003$) and increased aggressiveness (median survival reduced to 49 vs 70.5 days with 5000 cells injected, $p<0.0001$). Thus, CR limits the expansion of leukemic cells but enriches for cells with increased ability to regrow.

Example 6

[00166] Cell cycle analysis using propidium iodide and Ki67 to discriminate cells in G0 (PI-low, Ki67-low), G1 (PI-low, Ki67-high), and S-G2-M (PI-high, Ki67-high or low) shows that caloric restriction induces cell cycle slowdown (increase in the percentage of G0 cells), which is reversed by the use of LSD1 inhibitor (compound 1) (Figure 10).

Example 7

[00167] Analysis of the Cancer Genome Atlas (TCGA) data expression suggests that a subset of AMLs express elevated levels of IGF1 receptor and is a likely candidate for response to the combination of caloric restriction or OSI-906 and LSD1 inhibitor(compound 1) (Figure 11).

Example 8

[00168] RNAseq of leukemic cells purified during the terminal phase (but not earlier) showed that a dramatic transcriptional reprogramming in CR, characterized by upregulation of genes controlling OXPHOS, Krebs cycle and nucleotide and protein biosynthesis, and downregulation of insulin signaling and glucose transporters. Flow cytometry with Mitotracker Red confirmed increased mitochondrial activity. Thus, leukemic cells exposed to CR put in place adaptive transcriptional changes to allow survival in a nutrient/growth factor deprived environment.

[00169] To investigate the basis of these transcriptional changes, we revised ChIPseq analysis of LSD1 binding in human APL cell lines and found a significant enrichment for i) NRF1 consensus binding motif and ii) promoters of genes encoding for OXPHOS and Krebs cycle enzymes. NRF1 binding to OXPHOS/Krebs enzymes was confirmed on mouse leukemias by ChIPseq. These data suggested that the CR-induced adaptive changes could be mediated by LSD1/NRF1.

[00170] Strikingly, co-treatment of leukemic mice with CR and compound 1 resulted in macroscopic and microscopic eradication of disease ($p=0.0018$ compared to SD). In these conditions, leukemic cells completely disappeared in 4/6 mice after 4 weeks. LSD1 inhibition alone was also effective but did not produce bona fide disease eradication. Importantly, some of the features of the CR-LSD1 interaction could be modeled by combining LSD1 and an IGF1/Insulin inhibitor. *In vivo*, this combination was synergistic and led to durable responses (median survival 121 vs 50 days in untreated controls, $p=0.0143$, vs 65.5 and 78.5 days with Insulin/IGF1 Inhibitor and compound 1 respectively).

Example 9

[00171] Experiments involving NB4 cells (an established model for human APL) in which the LSD1 locus was stably knocked out using CRISPR-CAS9 technology were conducted. Equal numbers of NB4 cells wild-type (WT) and knockout (KO) for LSD1 were implanted subcutaneously in the two flanks of immunodeficient NOD-SCID-IL2Rg KO (NSG) mice, and recipient mice were randomized to either standard diet (SD) or caloric restriction (CR). This design allowed to perfectly control the experiment, since both WT and KO cells are exposed to the same metabolic environment. As shown in Figure 12, LSD1 very significantly decreased tumor growth in CR mice, but not in SD mice. (Left panel = tumor volume; right panel = tumor weight). Genetic loss of LSD1 function synergizes with CR, thus the observed effect of the LSD1 inhibitor is in fact due to specific inhibition of LSD1, and not off-target effects.

Example 10

[00172] RNAseq was performed on APL cells collected from SD or CR mice, 18 days after injection and/or 1 day after 3 daily administrations of OSI-906 and/or compound 1. Principal Component Analysis (PCA, Figure 13A) revealed that most variation in transcriptomes (PC1, accounting for ~60% total variance) could be attributed to treatment with an LSD1 inhibitor, and the second strongest component (PC2, accounting for ~20% variance) correlated with metabolic state, with OSI-906 inducing an intermediate state between SD and CR. Importantly, SD and CR-LSD1 were at the two extremes of the PC space, indicating extreme transcriptional variation. CR-LSD1 altered the transcription of 696 genes by at least 2 fold (adjusted p value < 0.01) compared to CR (Figure 13B), and the top differentially expressed gene sets were related to interferon and apoptosis signaling, according to Gene Set Enrichment Analysis (Figure 13C). The same pathways are not activated by CR alone. Thus, the mechanism of CR+LSD1 inhibition-induced death of APL cells is likely to involve interferon signaling and activation of apoptosis, which are both well known to be involved in the eradication of leukemia stem cells. Compound 1 significantly alters gene expression in APL cells, suggesting that lethality is due to specific transcriptional changes involving the interferon and apoptotic pathways.

Example 11

[00173] The efficacy of OSI906 and compound 1 was assessed alone and in combination on a mouse AML cell line derived from an *in vivo* AML mouse model based on the combination of NPM1 and FLT3 mutations (Mallardo M et al, Leukemia. 2013 Nov;27(11):2248-51). NPM1 and FLT3 are the most frequently mutated genes in AML, each occurring in 30-40% of the cases and in combination in 10%. Double mutant AMLs are characterized by a poor prognosis, with approximately 50% survival after 5 years (Papaemmanuil et al, N. Engl. J. Med. 2016 Jun 9;374(23):2209-21).

[00174] Both OSI906 and compound 1 were effective in reducing cell growth as measured after 4 days by Cell Titer Glo assay, with IC_{50} values of 1 μM for OSI906 and 1.8 μM for compound 1. (Figures 14A and 14B) Combining the two had a synergistic effect, as demonstrated by combination analysis using the median-effect method of Chou and Talalay (Chou T, Cancer Res. 2010 Jan 15;70(2):440-6). Combination index was consistently below 1 for a wide range of drug combinations, indicating *bona fide* synergy between the two drugs (Figures 14C and 14D). Thus, OSI-906 and LSD1 inhibitors, *e.g.*, compound 1, have synergistic activity on a mouse model of NPMc/FLT3ITD (AML).

EQUIVALENTS

[00175] The application can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the application described herein. Scope of the application is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

CLAIMS

1. A method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject an effective amount of an LSD1 inhibitor, wherein the method further comprises:

a. administration of at least one calorie restriction mimetic; or

b. administration of at least one IGF1/insulin inhibitor; or

c. administration of at least one calorie restriction mimetic and at least one IGF1/insulin inhibitor,

wherein the subject is optionally on a calorie restricted diet.

2. The method of claim 1, comprising administering to the subject in need thereof an effective amount of an LSD1 inhibitor and a calorie restriction mimetic, wherein the subject is optionally on a calorie restricted diet.

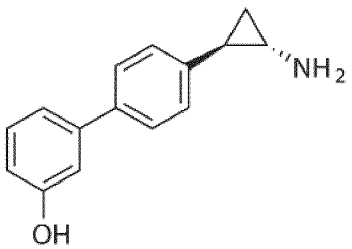
3. The method of claim 1, comprising administering to the subject in need thereof an effective amount of an LSD1 inhibitor and an IGF1/insulin inhibitor, wherein the subject is optionally on a calorie restricted diet.

4. The method of claim 1, comprising administering to the subject in need thereof an effective amount of an LSD1 inhibitor, a calorie restriction mimetic, and an IGF1/insulin inhibitor, wherein the subject is optionally on a calorie restricted diet.

5. The method of any one of claim 1-4, wherein the LSD1 inhibitor is selected from any compound of Formula (I), Formula (Ia), Formula (II), Formula (II), any other compound indicated as an LSD1 inhibitor, or a stereoisomer or pharmaceutically acceptable salt thereof.

6. The method of any one of claim 1-4, wherein the LSD1 inhibitor is selected from the group consisting of:

tranylcypromine;



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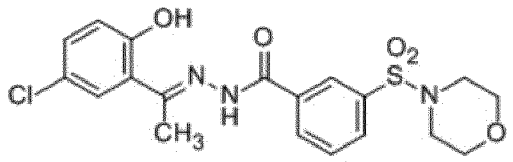
(*R*)-4-[5-(Pyrrolidin-3-ylmethoxy)-2-p-tolyl-pyridin-3-yl]-benzonitrile;

1-(4-methyl-1-piperazinyl)-2-[[(1*R**,2*S**)-2-[4-phenylmethoxy)phenyl]cyclopropyl]amino]ethanone dihydrochloride;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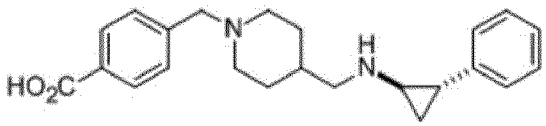
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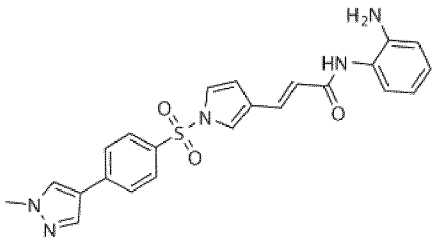
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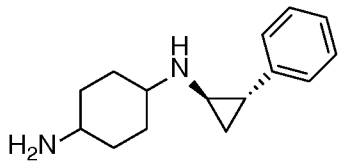
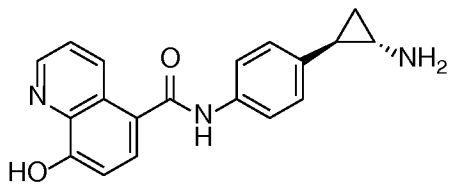

;


;

N-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide; and a pharmaceutically acceptable salt thereof.

7. The method of claim 5, wherein the LSD1 inhibitor is *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride.

8. The method of any one of claims 1, 3 or 4, wherein the IGF1/insulin inhibitor is selected from the group consisting of: inhibitor of IGF1 receptor, inhibitor of insulin receptor, and inhibitor of both IGF1 receptor and insulin receptor.

9. The method of any one of claims 1, 3, 4 or 8, wherein the IGF1/insulin inhibitor is 3-[8-Amino-1-(2-phenyl-7-quinolyl)imidazo[1,5-a]pyrazin-3-yl]-1-methyl-cyclobutanol.

10. The method of any one of claims 1, 2 or 4, wherein the calorie restriction mimetic is a sirtuin-activating compound.

11. The method of any one of claims 1-10, wherein the cancer is a tumor of the hematopoietic and lymphoid tissues.

12. The method of claim 11, wherein the tumor of the hematopoietic and lymphoid tissues is a leukemia.

13. The method of claim 12, wherein the leukemia is acute myeloid leukemia or acute promyelocytic leukemia.

14. The method of any one of claims 1-10, wherein the cancer is characterized in that the cancer cells have features of cancer stem cells.

15. The method of any one of claims 1-10, wherein the cancer is a drug resistant cancer.

16. The method of claim 15, where in the drug resistant cancer is drug resistant relapsed acute promyelocytic leukemia or drug resistant acute myeloid leukemia.

17. An LSD1 inhibitor and

(i) a calorie restricted diet and/or

(ii) at least one caloric restriction mimetic and/or

(iii) at least one IGF1/insulin inhibitor

for use in the treatment and/or in the prevention of cancer.

18. An LSD1 inhibitor and

(i) at least one caloric restriction mimetic and/or

(ii) at least one IGF1/insulin inhibitor

for use in the treatment and/or in the prevention of cancer.

19. A combination of an LSD1 inhibitor and

(i) a calorie restricted diet and/or

(ii) a caloric restriction mimetic

for use in the treatment and/or in the prevention of cancer.

20. A combination of an LSD1 inhibitor and at least one IGF1/insulin inhibitor for use in the treatment and/or in the prevention of cancer.

21. A combination of an LSD1 inhibitor and

(i) a calorie restricted diet and/or

(ii) a caloric restriction mimetic and at least one IGF1/insulin inhibitor

for use in the treatment and/or in the prevention of cancer.

22. A pharmaceutical composition comprising an LSD1 inhibitor and

(i) at least one caloric restriction mimetic, and/or

(ii) at least one IGF1/insulin inhibitor

for use in the treatment and/or in the prevention of cancer.

23. The LSD1 inhibitor for use according to any one of claims 17 or 18, or the combination for use according to any one of claims 19 to 21, or the pharmaceutical composition for use according to claim 22, wherein the caloric restriction mimetic is a sirtuin-activating compound.

24. The LSD1 inhibitor, the combination, or the pharmaceutical composition for use according to any one of claims 16 to 23 wherein the IGF1/insulin inhibitor is selected from the group consisting of: inhibitor of IGF1 receptor, inhibitor of insulin receptor, and inhibitor of both IGF1 receptor and insulin receptor.

25. The LSD1 inhibitor, the combination, or the pharmaceutical composition for use according to any one of claims 16 to 24 wherein the IGF1/insulin inhibitor is 3-[8-Amino-1-(2-phenyl-7-quinolyl)imidazo[1,5-a]pyrazin-3-yl]-1-methyl-cyclobutanol.

26. The LSD1 inhibitor, the combination, or the pharmaceutical composition for use according to any one of claims 16 to 25 wherein the LSD1 inhibitor is selected from a compound as described in WO2013057322, WO2011131576, WO2014086790, WO2012135113, or WO2015/181380.

27. The LSD1 inhibitor, the combination, or the pharmaceutical composition for use according to any one of claims 16 to 26 wherein the LSD1 inhibitor is *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride.

28. The LSD1 inhibitor, the combination, or the pharmaceutical composition for use according to any one of claims 16 to 27 wherein the cancer is a tumor of the hematopoietic and lymphoid tissues.

29. The LSD1 inhibitor, the combination, or the pharmaceutical composition for use according to claim 28 wherein the tumor of the hematopoietic and lymphoid tissues is a leukemia.

30. The LSD1 inhibitor, the combination, or the pharmaceutical composition for use according to claim 29 wherein the leukemia is acute myeloid leukemia (AML), preferably APL (acute promyelocytic leukemia).

31. The LSD1 inhibitor, the combination, or the pharmaceutical composition for use according to any one of claims 17-30 wherein the cancer is characterized in that the cancer cells have features of cancer stem cells.

32. The LSD1 inhibitor, the combination, or the pharmaceutical composition for use according to any one of claims 17-31 wherein the cancer is a drug resistant cancer, preferably drug resistant relapsed acute promyelocytic leukemia and drug resistant acute myeloid leukemia.

33. Use of the LSD1 inhibitor according to any one of claims 17-18 or 23-32, or the combination according to any one of claims 18-20 or 23-32, or the pharmaceutical composition according to any one of claims 22-32 in the manufacture of a medicament for the treatment and/or in the prevention of cancer.

34. A method of treatment of cancer comprising administering to a subject in need thereof

(i) the LSD1 inhibitor according to any one of claims 17-18 or 23-32, or

(ii) the combination according to any one of claims 18-20 or 23-32, or

(iii) the pharmaceutical composition according to any one of claims 22-32.

35. A kit comprising an LSD1 inhibitor and

(i) a caloric restriction mimetic, or

(ii) an IGF1/insulin inhibitor, or

(iii) a caloric restriction mimetic and an IGF1/insulin inhibitor.

36. The kit according to claim 35, wherein the caloric restriction mimetic is a sirtuin-activating compound.

37. The kit according to any one of claims 35 or 36, wherein the IGF1/insulin inhibitor is selected from the group consisting of: inhibitor of IGF1 receptor, inhibitor of insulin receptor, and inhibitor of both IGF1 receptor and insulin receptor.

38. The kit according to any one of claims 35 to 37, wherein the IGF1/insulin inhibitor is 3-[8-Amino-1-(2-phenyl-7-quinolyl)imidazo[1,5-a]pyrazin-3-yl]-1-methyl-cyclobutanol.

39. The kit according to any one of claims 35 to 38, wherein the LSD1 inhibitor is selected from a compound as described in WO2013057322, WO2011131576, WO2014086790, WO2012135113, or WO2015/181380.

40. The kit according to any one of claims 35 to 39, wherein the LSD1 inhibitor is *N*-[4-[*trans*-2-aminocyclopropyl]phenyl]-4-(4-methylpiperazin-1-yl)benzamide dihydrochloride.

Figure 1A

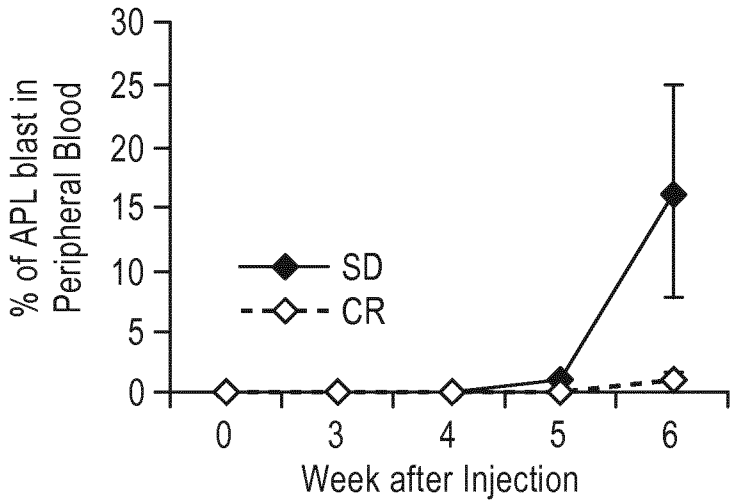

30
25
20
15
10
5
0
% of APL blast in Peripheral Blood
SD
CR
0
3
4
5
6
Week after Injection

Figure 1B

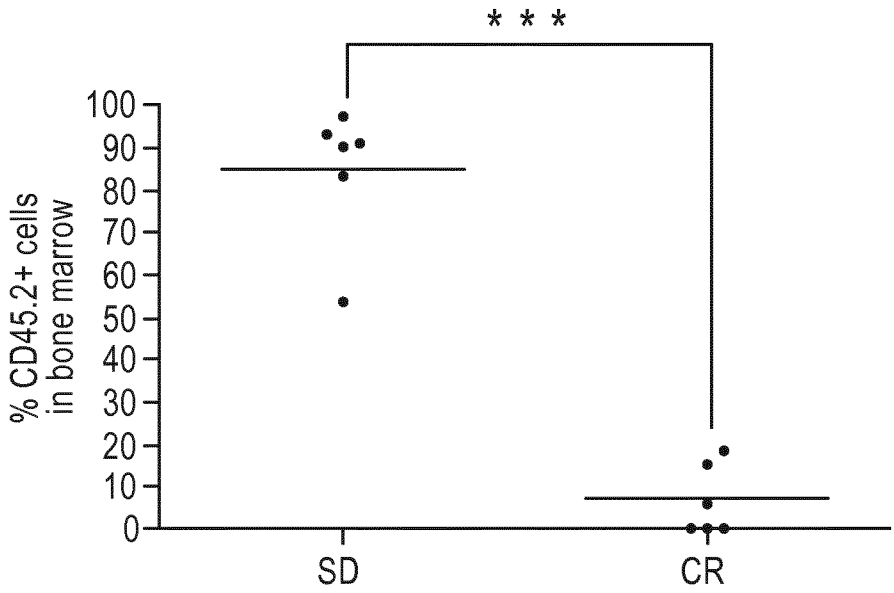


Figure 1C

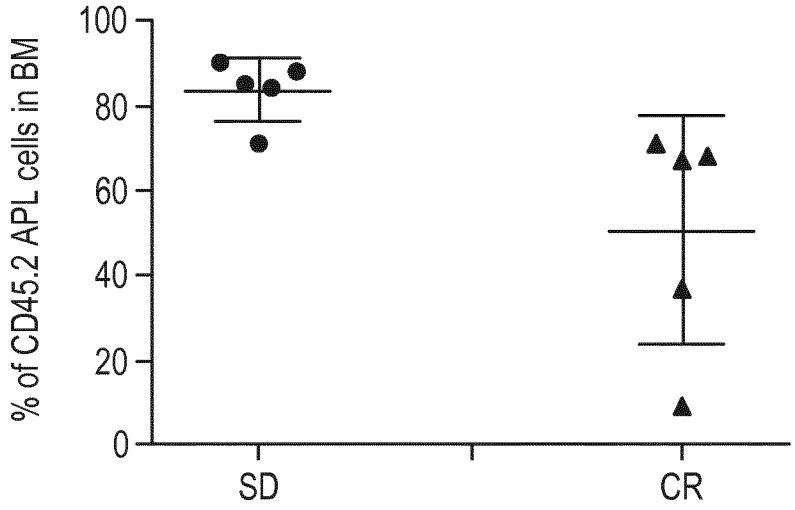


Figure 1D

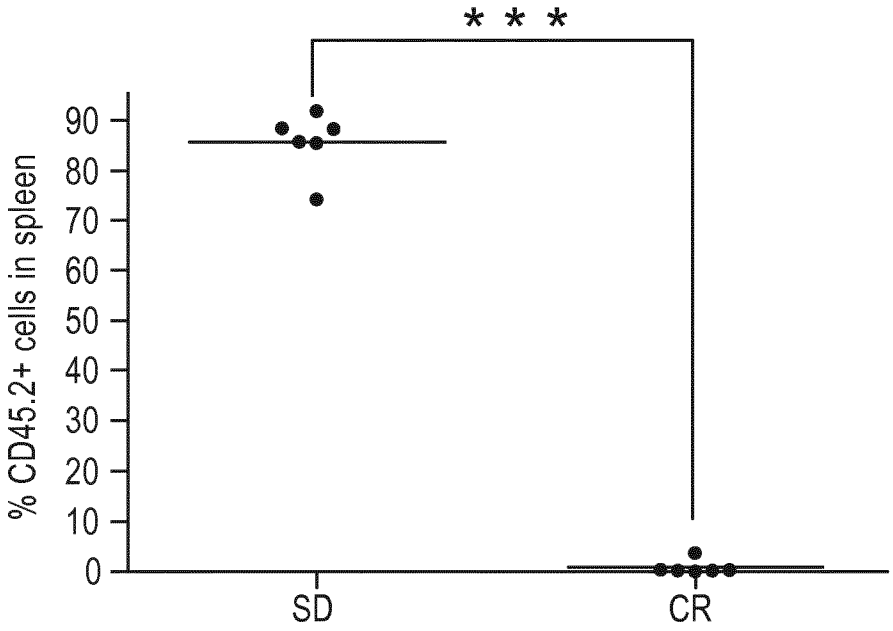


Figure 2A

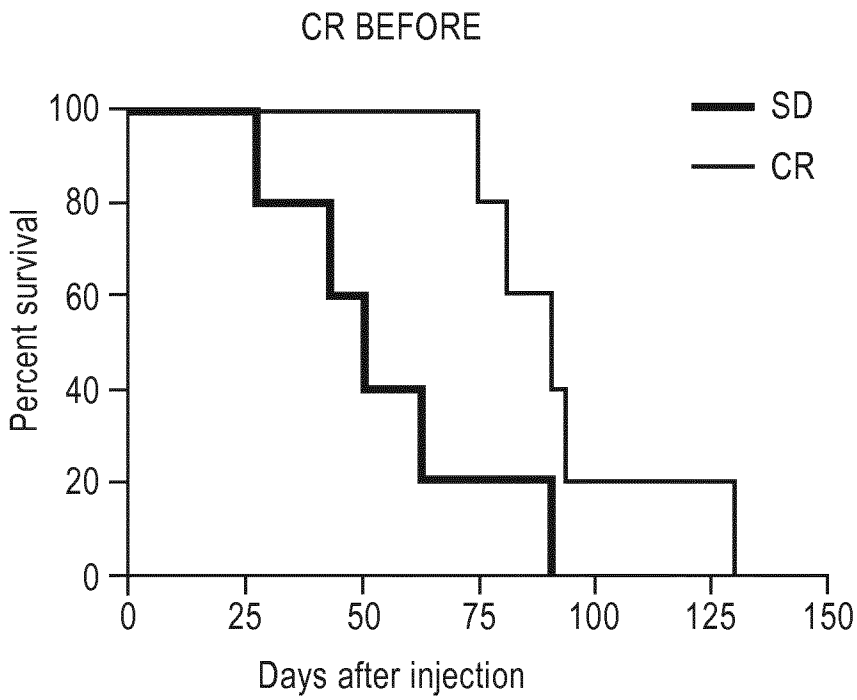

CR BEFORE
SD
CR
Percent survival
100
80
60
40
20
0
0
25
50
75
100
125
150
Days after injection

Figure 2B

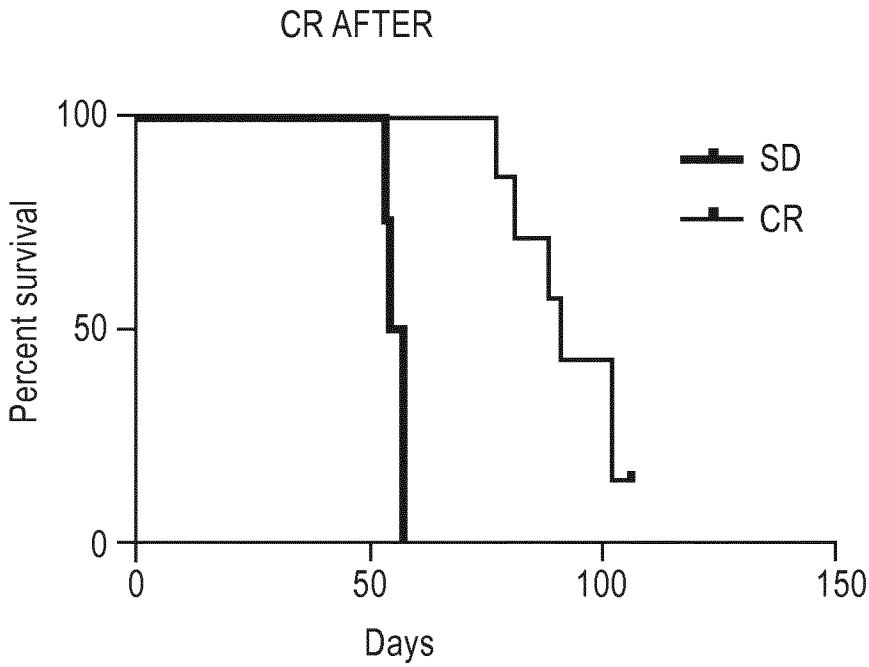


Figure 3A

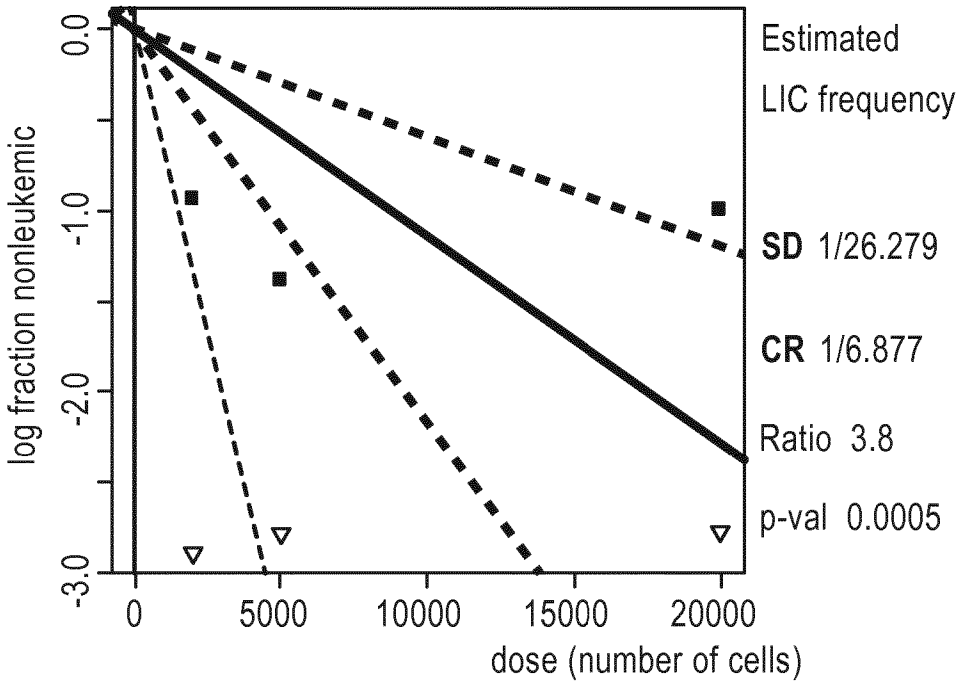

log fraction nonleukemic
0.0
-1.0
-2.0
-3.0
0
5000
10000
15000
20000
dose (number of cells)
Estimated
LIC frequency
SD 1/26.279
CR 1/6.877
Ratio 3.8
p-val 0.0005

Figure 3B

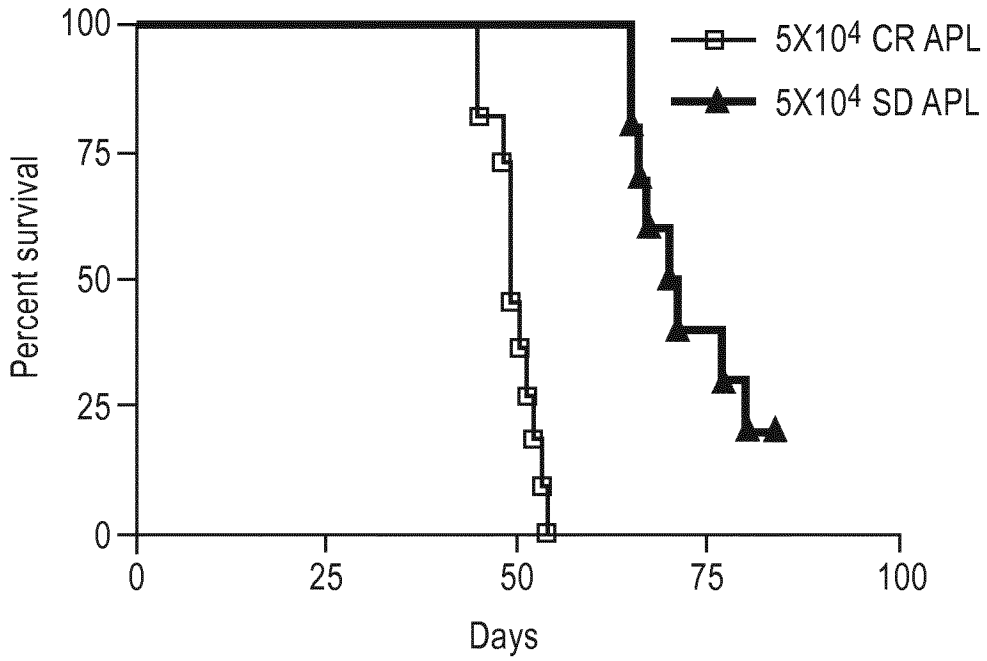

100
75
50
25
0
Percent survival
0
25
50
75
100
Days
5X10^4 CR APL
5X10^4 SD APL

Figure 4A

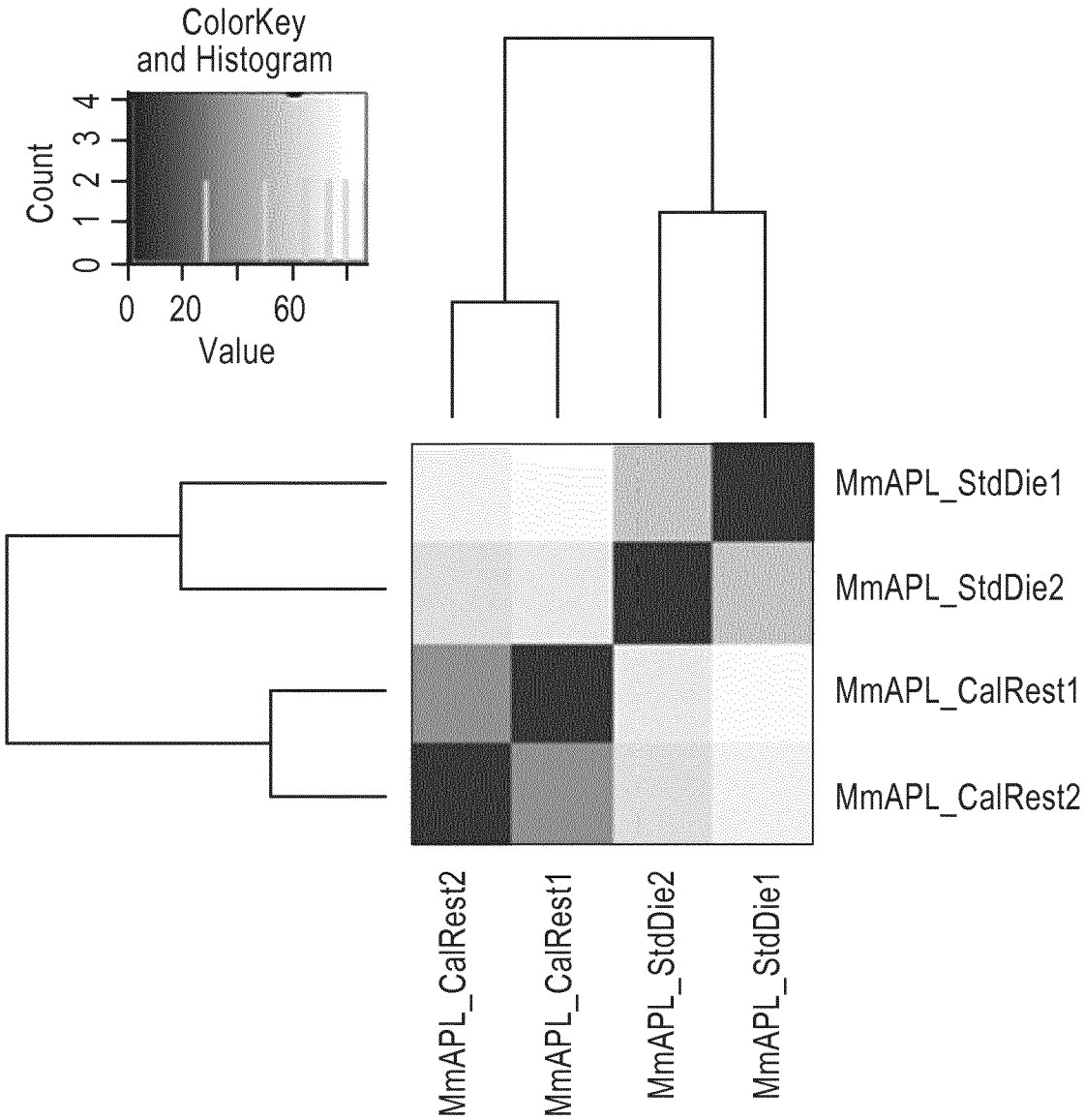
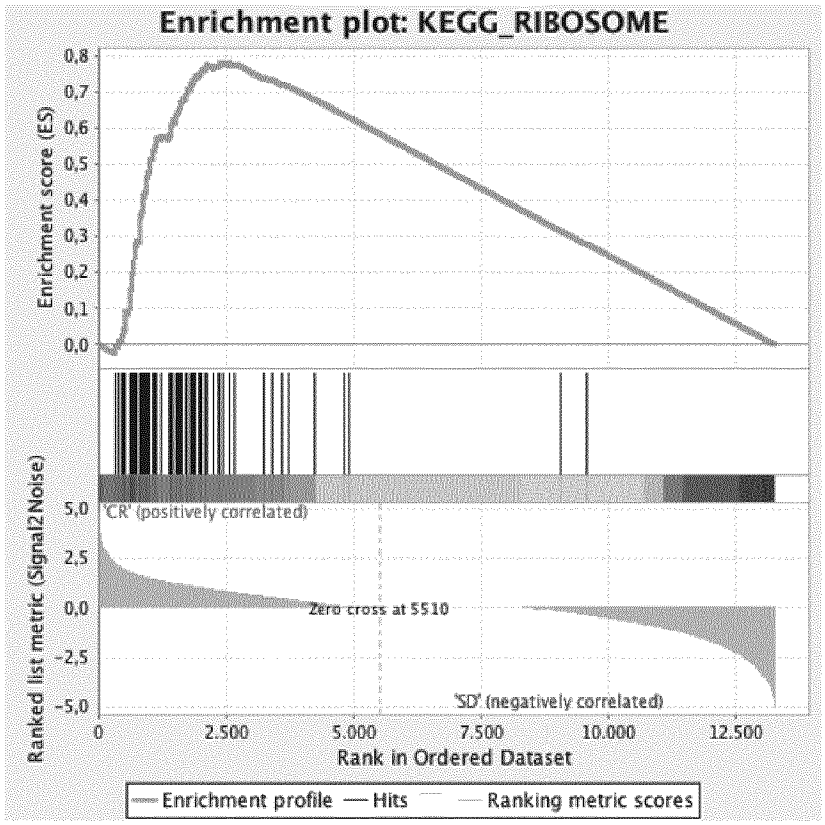

ColorKey
and Histogram
Count
0 1 2 3 4
0 20 60
Value
MmAPL_StdDie1
MmAPL_StdDie2
MmAPL_CalRest1
MmAPL_CalRest2
MmAPL_CalRest2
MmAPL_CalRest1
MmAPL_StdDie2
MmAPL_StdDie1

Figure 4B


Enrichment plot: KEGG_RIBOSOME
Enrichment score (ES)
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
'CR' (positively correlated)
Zero cross at 5510
'SD' (negatively correlated)
Ranked list metric (Signal2Noise)
5,0
2,5
0,0
-2,5
-5,0
0
2.500
5.000
7.500
10.000
12.500
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

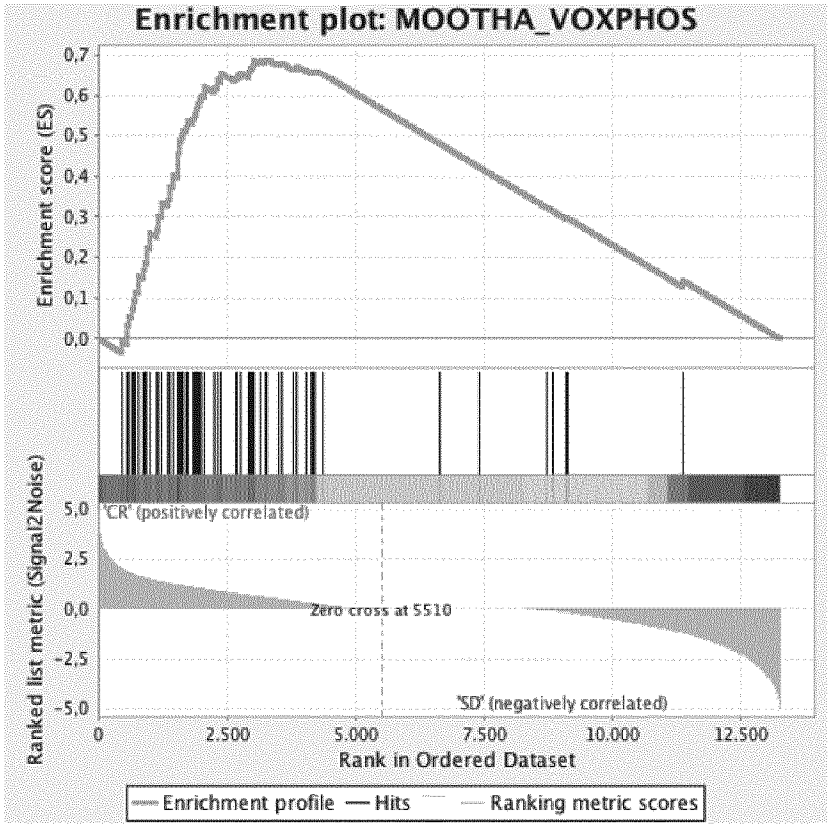
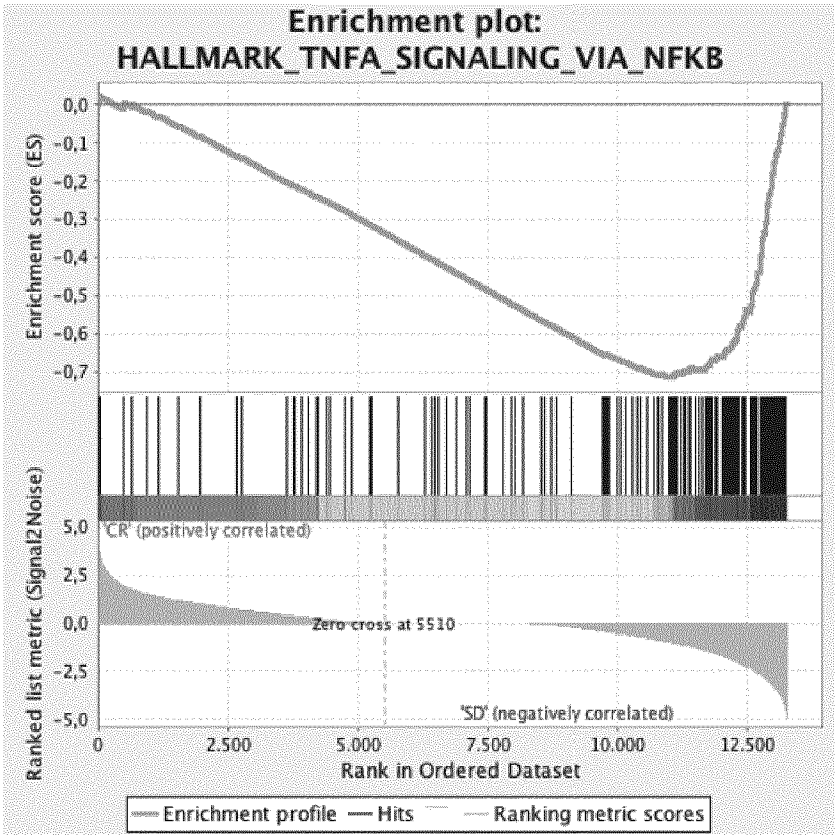

Enrichment plot: MOOTHA_VOXPHOS
Enrichment score (ES)
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
'CR' (positively correlated)
Zero cross at 5510
'SD' (negatively correlated)
Ranked list metric (Signal2Noise)
5,0
2,5
0,0
-2,5
-5,0
0
2.500
5.000
7.500
10.000
12.500
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

Figure 4C


Enrichment plot:
HALLMARK_TNFA_SIGNALING_VIA_NFKB
Enrichment score (ES)
0,0
-0,1
-0,2
-0,3
-0,4
-0,5
-0,6
-0,7
Ranked list metric (Signal2Noise)
5,0
2,5
0,0
-2,5
-5,0
'CR' (positively correlated)
Zero cross at 5510
'SD' (negatively correlated)
0
2.500
5.000
7.500
10.000
12.500
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

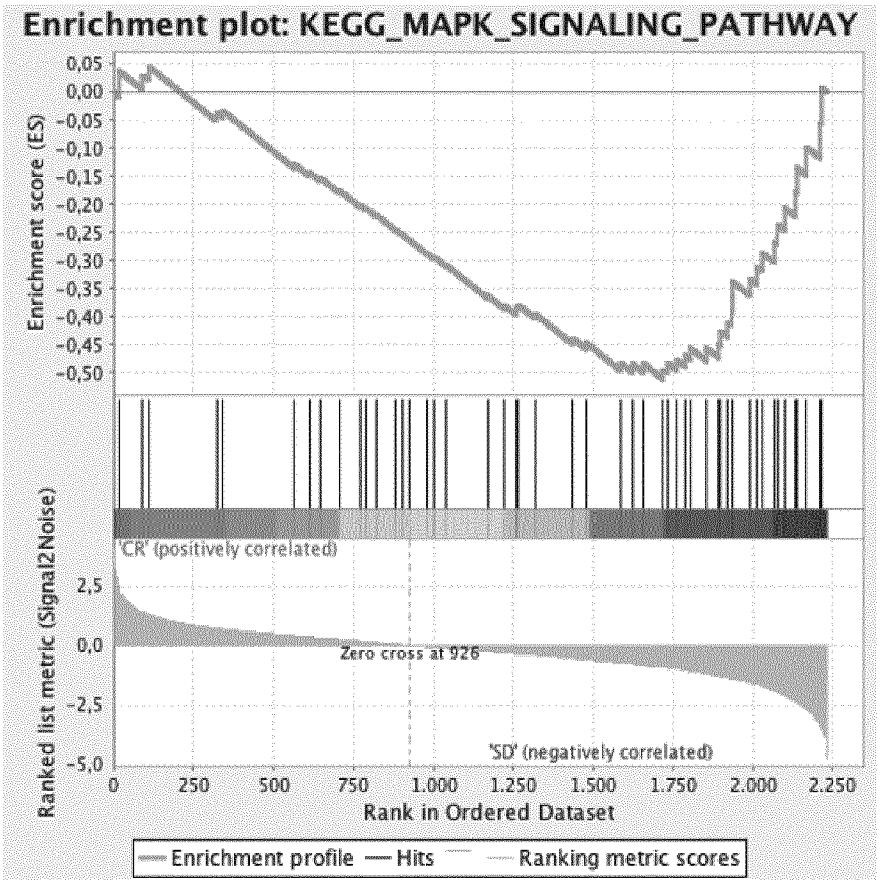

Enrichment plot: KEGG_MAPK_SIGNALING_PATHWAY
Enrichment score (ES)
0,05
0,00
-0,05
-0,10
-0,15
-0,20
-0,25
-0,30
-0,35
-0,40
-0,45
-0,50
Ranked list metric (Signal2Noise)
'CR' (positively correlated)
2,5
0,0
-2,5
-5,0
Zero cross at 926
'SD' (negatively correlated)
0
250
500
750
1.000
1.250
1.500
1.750
2.000
2.250
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

Figure 4D

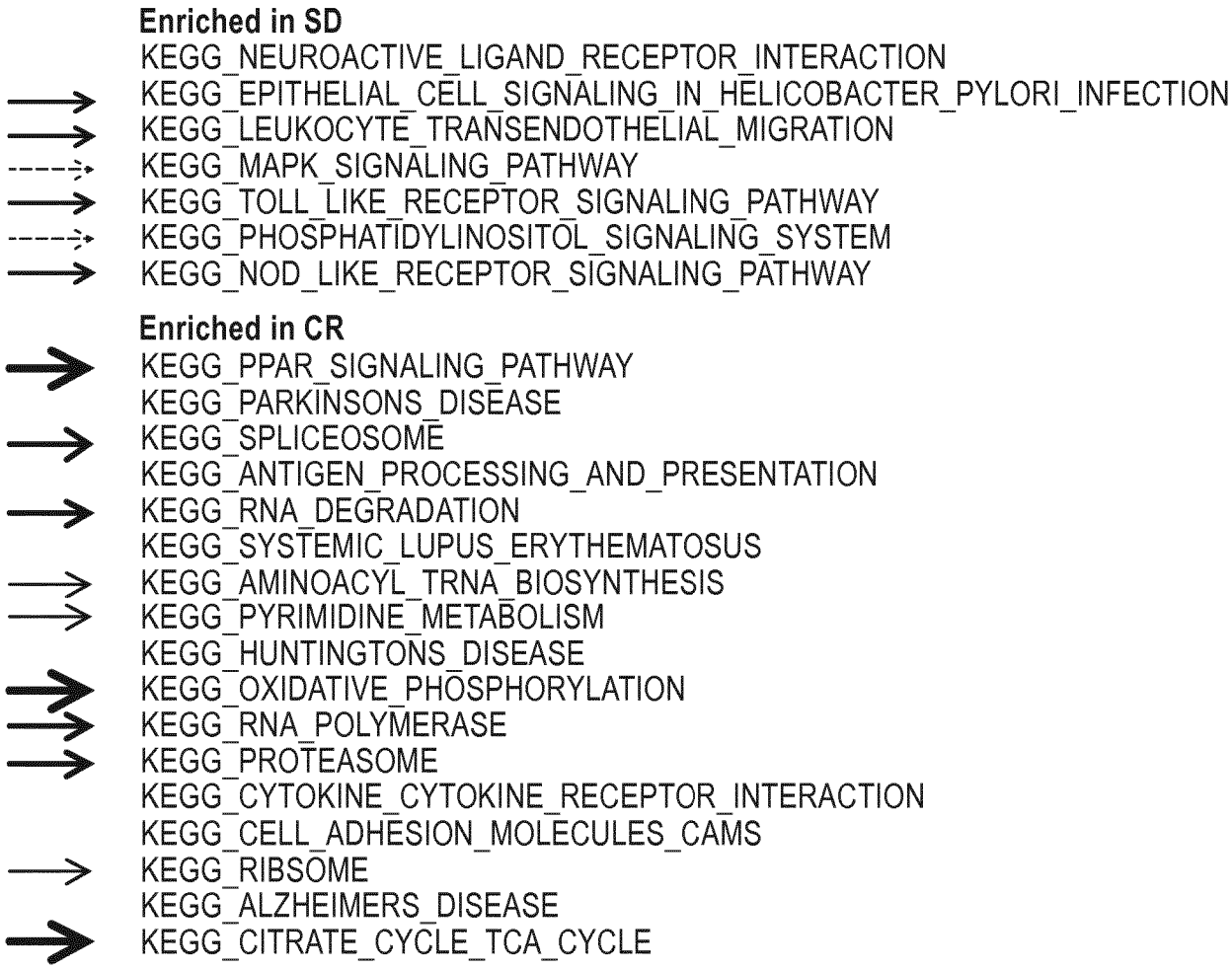

Enriched in SD
KEGG_NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION
KEGG_EPITHELIAL_CELL_SIGNALING_IN_HELICOBACTER_PYLORI_INFECTION
KEGG_LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION
KEGG_MAPK_SIGNALING_PATHWAY
KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY
KEGG_PHOSPHATIDYLINOSITOL_SIGNALING_SYSTEM
KEGG_NOD_LIKE_RECEPTOR_SIGNALING_PATHWAY
Enriched in CR
KEGG_PPAR_SIGNALING_PATHWAY
KEGG_PARKINSONS_DISEASE
KEGG_SPLICEOSOME
KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION
KEGG_RNA_DEGRADATION
KEGG_SYSTEMIC_LUPUS_ERYTHEMATOSUS
KEGG_AMINOACYL_TRNA_BIOSYNTHESIS
KEGG_PYRIMIDINE_METABOLISM
KEGG_HUNTINGTONS_DISEASE
KEGG_OXIDATIVE_PHOSPHORYLATION
KEGG_RNA_POLYMERASE
KEGG_PROTEASOME
KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION
KEGG_CELL_ADHESION_MOLECULES_CAMS
KEGG_RIBSOME
KEGG_ALZHEIMERS_DISEASE
KEGG_CITRATE_CYCLE_TCA_CYCLE

Figure 4E

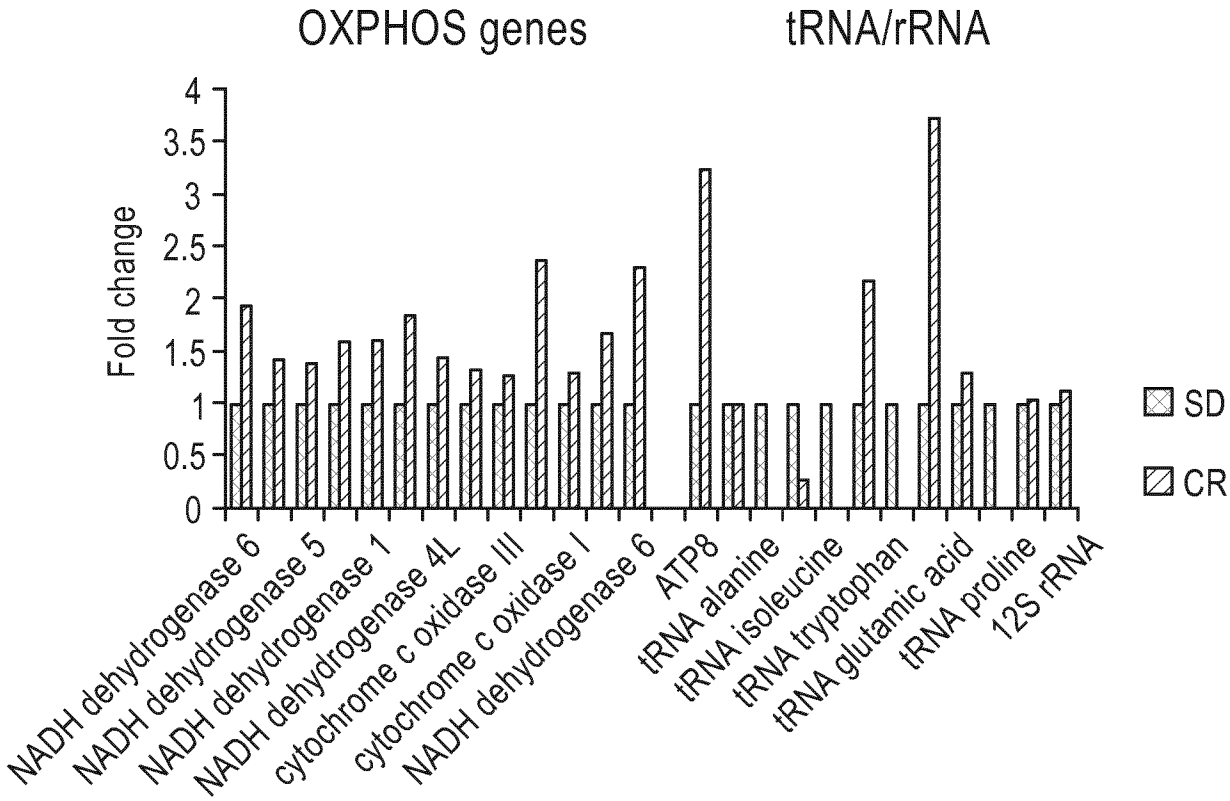

OXPHOS genes
tRNA/rRNA
Fold change
4
3.5
3
2.5
2
1.5
1
0.5
0
SD
CR
NADH dehydrogenase 6
NADH dehydrogenase 5
NADH dehydrogenase 1
NADH dehydrogenase 4L
cytochrome c oxidase III
cytochrome c oxidase I
NADH dehydrogenase 6
ATP8
tRNA alanine
tRNA isoleucine
tRNA tryptophan
tRNA glutamic acid
tRNA proline
12S rRNA

Figure 4F

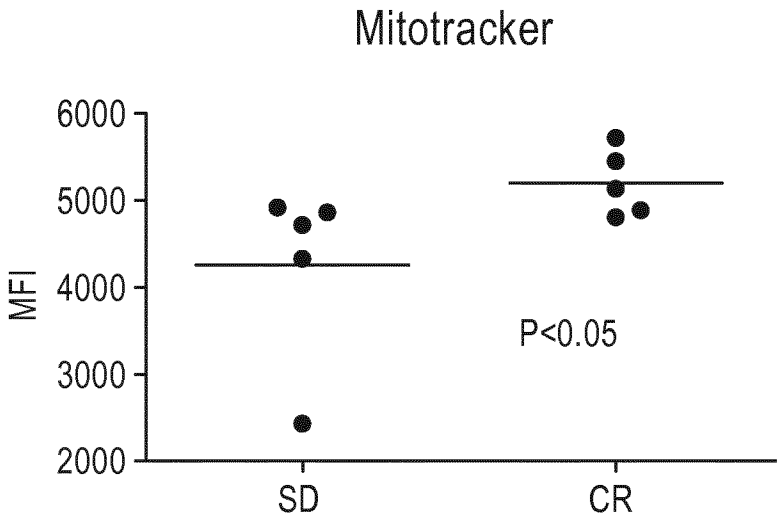


Figure 5

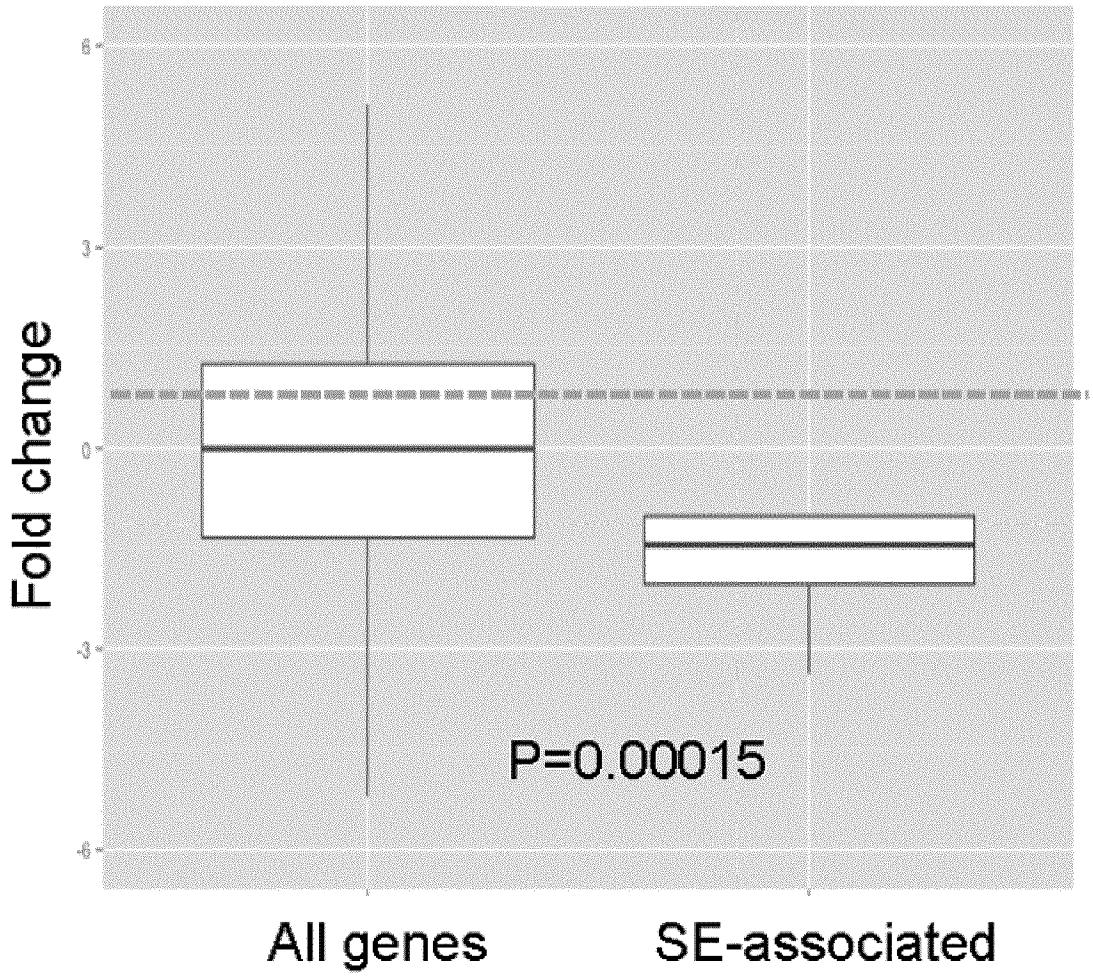


Figure 6A

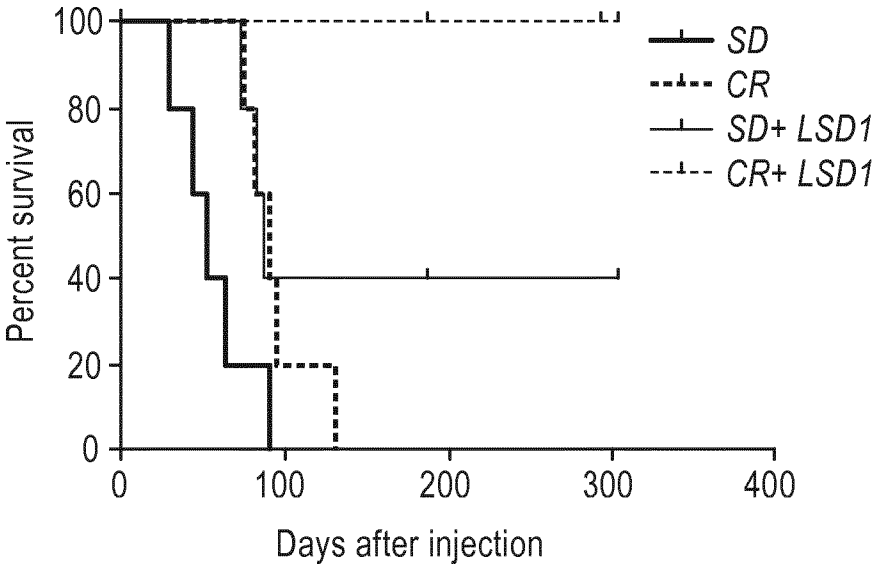
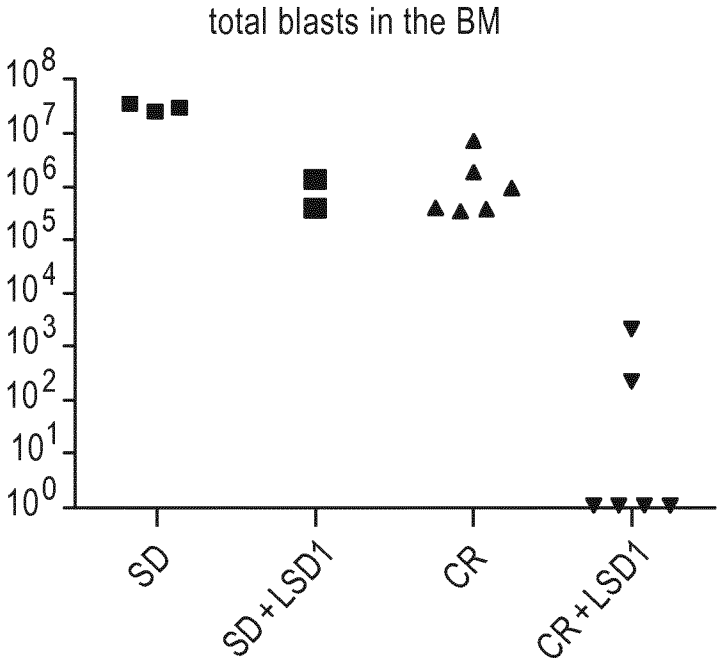

100
80
60
40
20
0
Percent survival
0
100
200
300
400
Days after injection
SD
CR
SD+ LSD1
CR+ LSD1

Figure 6B

Donors	RAG-/- recipients	dead
SD+LSD1	5	5
SD+LSD1	5	0
CR+LSD1	5	4
CR+LSD1	5	0
CR+LSD1	5	0
CR+LSD1	5	0
CR+LSD1	5	0

Figure 6C


total blasts in the BM
10^8
10^7
10^6
10^5
10^4
10^3
10^2
10^1
10^0
SD
SD+LSD1
CR
CR+LSD1

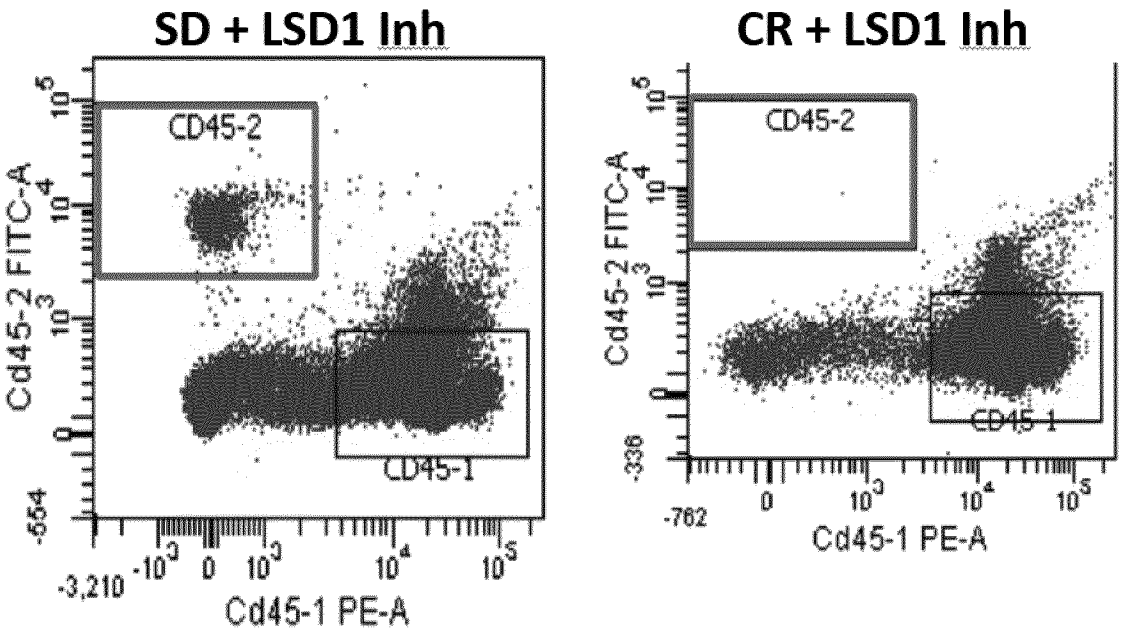

SD + LSD1 Inh
CD45-2
CD45-1
Cd45-2 FITC-A
Cd45-1 PE-A
-554
-3,210
CR + LSD1 Inh
CD45-2
CD45-1
Cd45-2 FITC-A
Cd45-1 PE-A
-336
-762

Figure 7

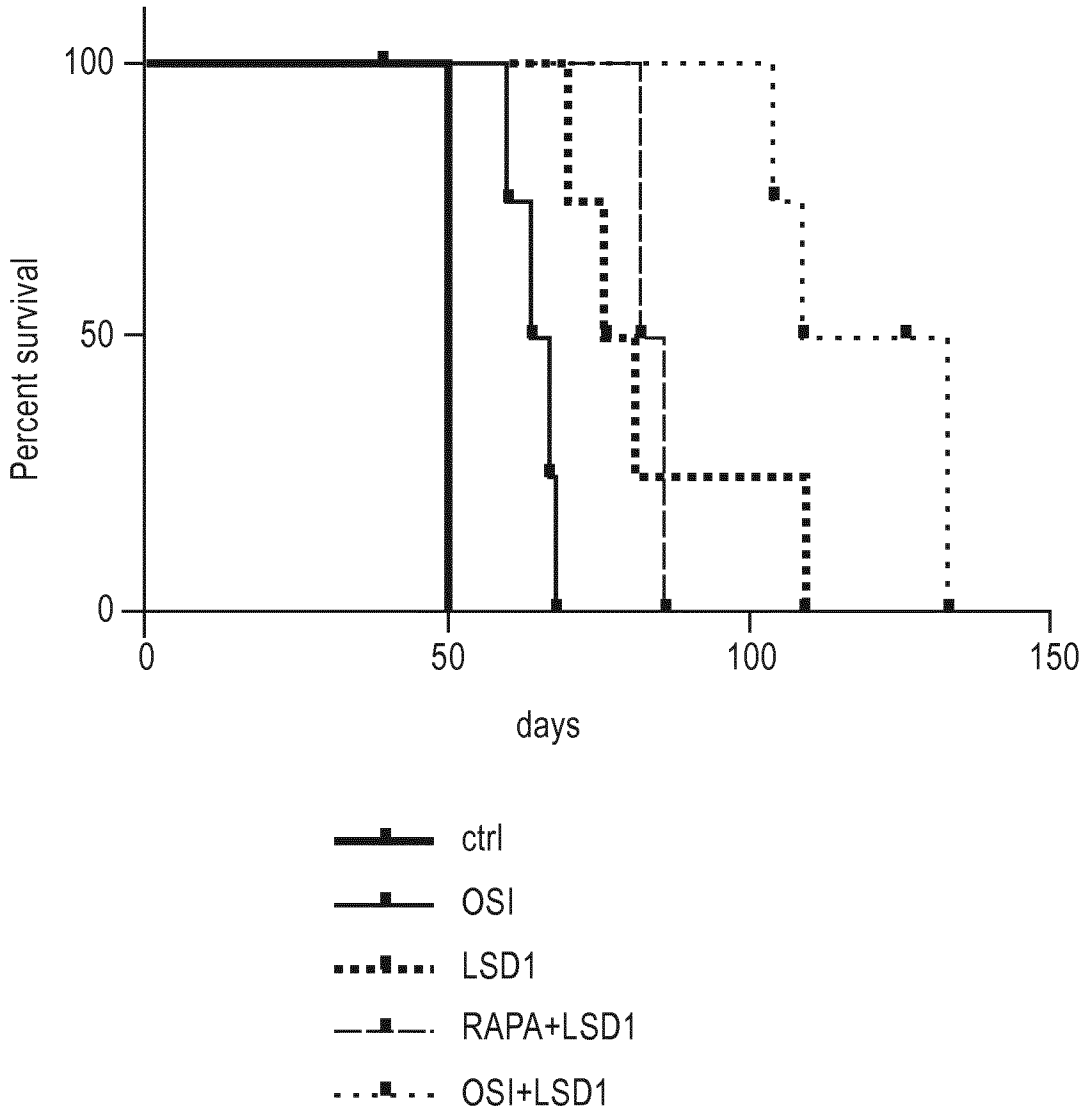

100
50
0
Percent survival
0
50
100
150
days
ctrl
OSI
LSD1
RAPA+LSD1
OSI+LSD1

Figure 8A

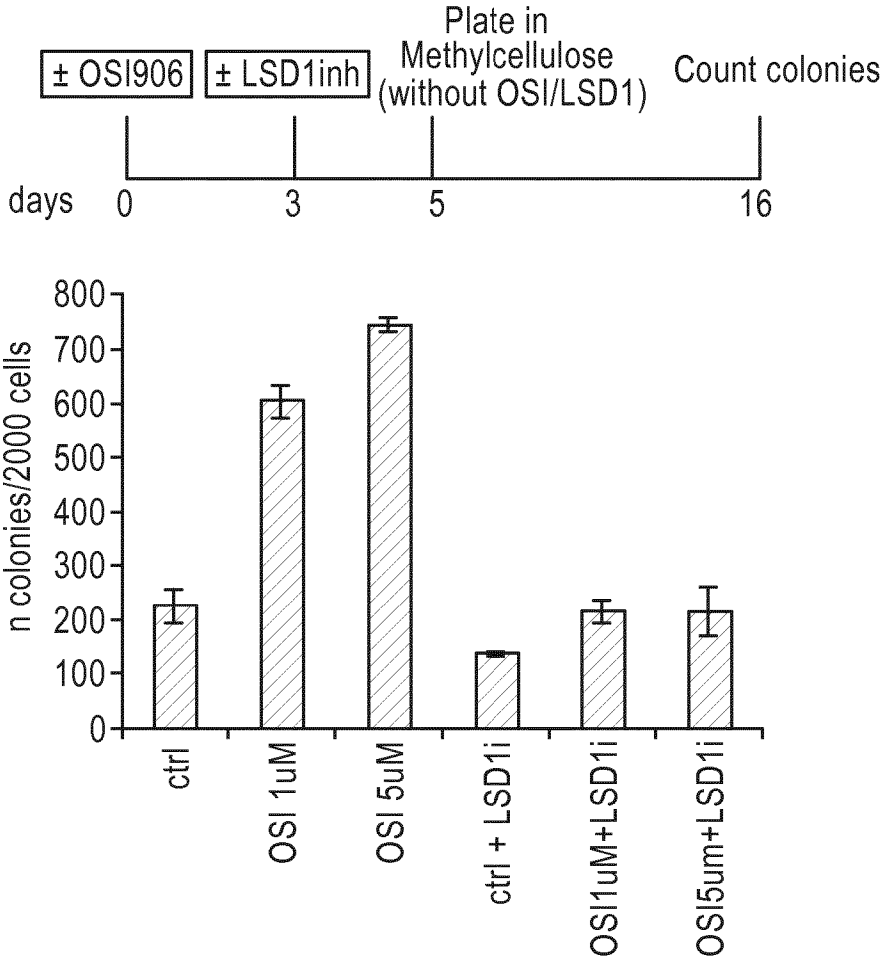

± OSI906
± LSD1inh
Plate in Methylcellulose (without OSI/LSD1)
Count colonies
days
0
3
5
16
n colonies/2000 cells
800
700
600
500
400
300
200
100
0
ctrl
OSI 1uM
OSI 5uM
ctrl + LSD1i
OSI1uM+LSD1i
OSI5um+LSD1i

Figure 8B

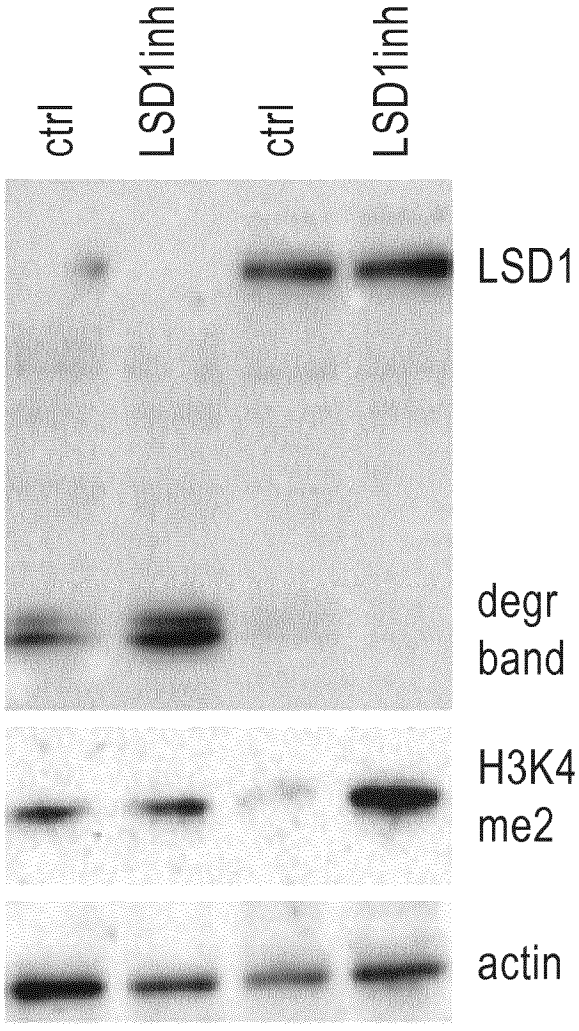

OSI-906
ctrl
LSD1inh
ctrl
LSD1inh
LSD1
degr band
H3K4 me2
actin

Figure 9

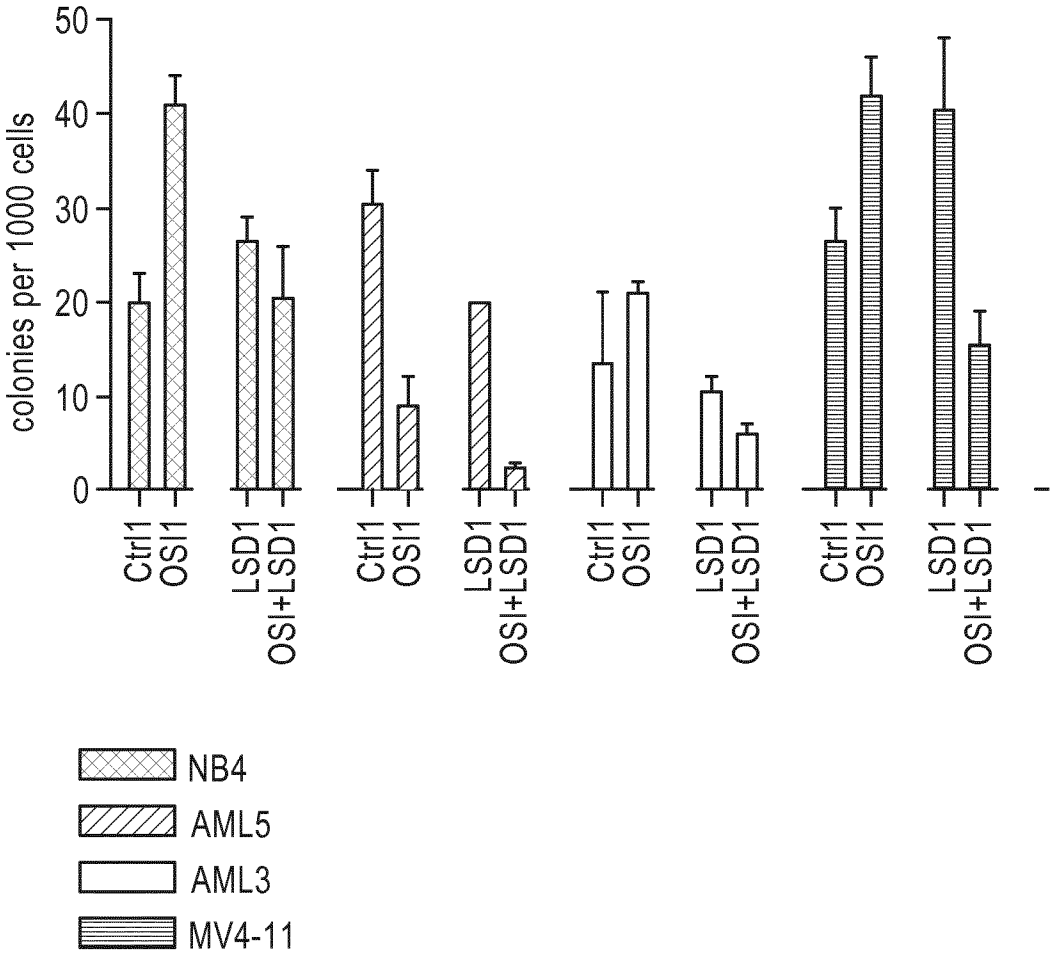

colonies per 1000 cells
50
40
30
20
10
0
Ctrl1
OSI1
LSD1
OSI+LSD1
Ctrl1
OSI1
LSD1
OSI+LSD1
Ctrl1
OSI1
LSD1
OSI+LSD1
Ctrl1
OSI1
LSD1
OSI+LSD1
NB4
AML5
AML3
MV4-11

Figure 10

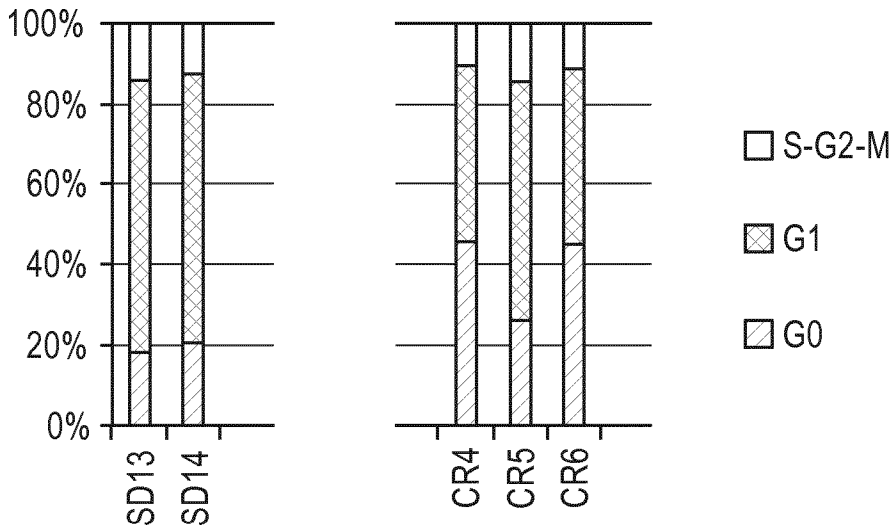


Figure 11

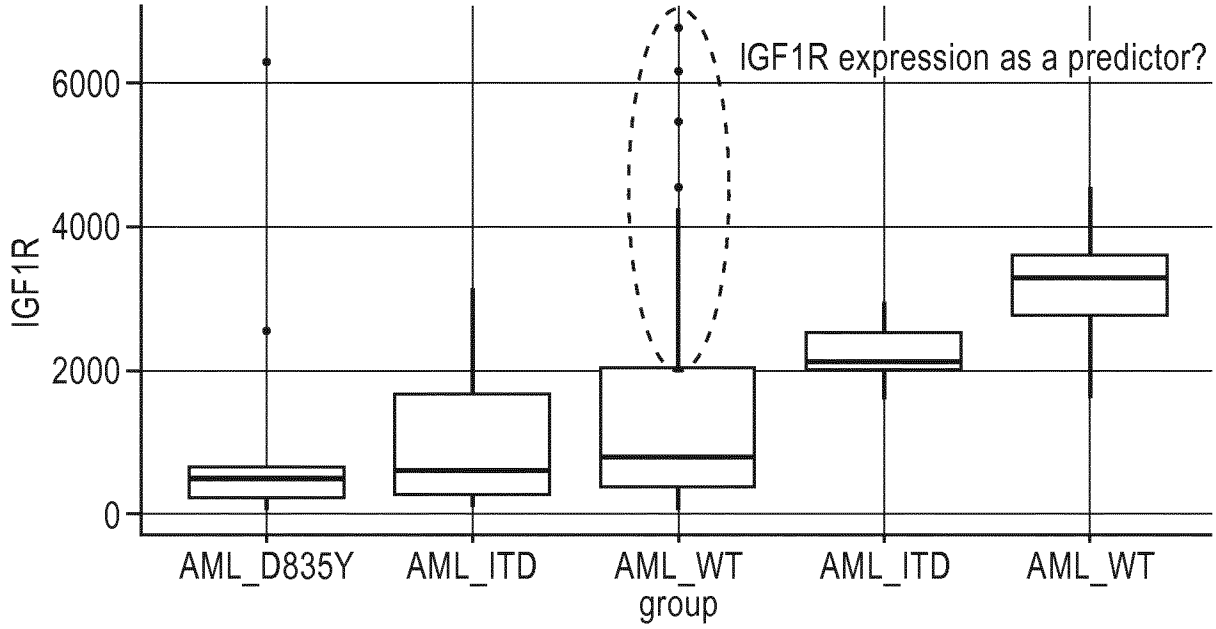

IGF1R expression as a predictor?
IGF1R
6000
4000
2000
0
AML_D835Y
AML_ITD
AML_WT
AML_ITD
AML_WT
group

Figure 12

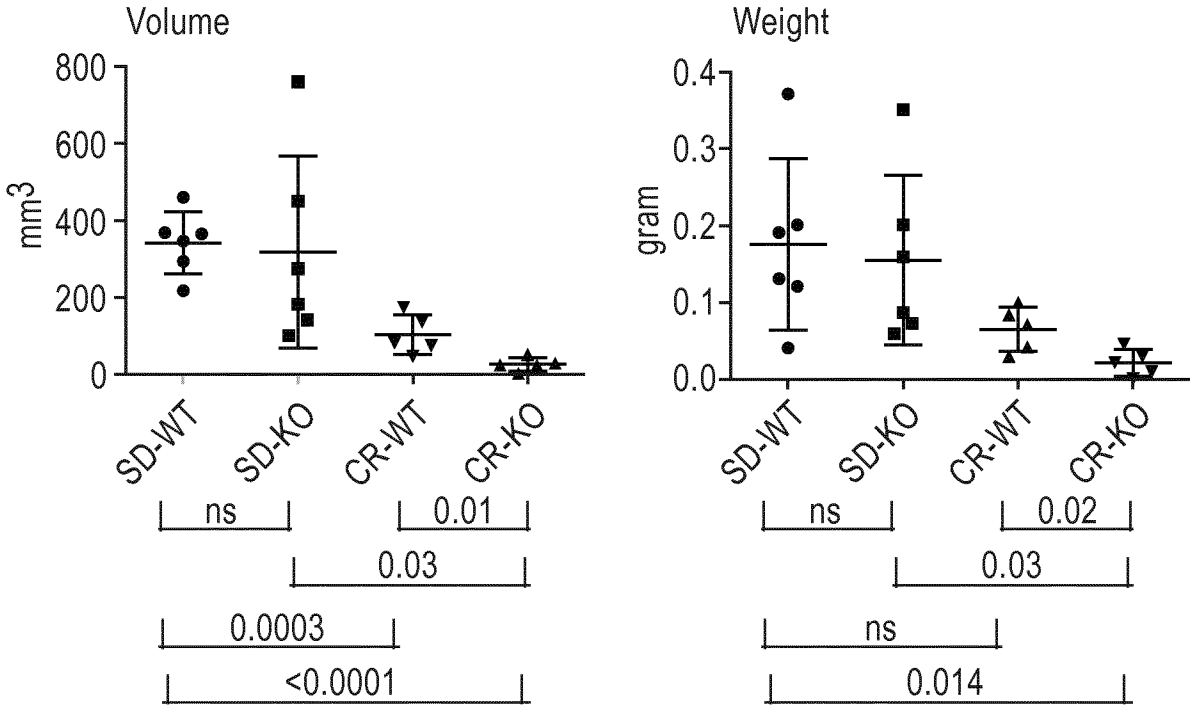

Volume
mm3
800
600
400
200
0
SD-WT
SD-KO
CR-WT
CR-KO
ns
0.01
0.03
0.0003
<0.0001
Weight
gram
0.4
0.3
0.2
0.1
0.0
SD-WT
SD-KO
CR-WT
CR-KO
ns
0.02
0.03
ns
0.014

Figure 13A

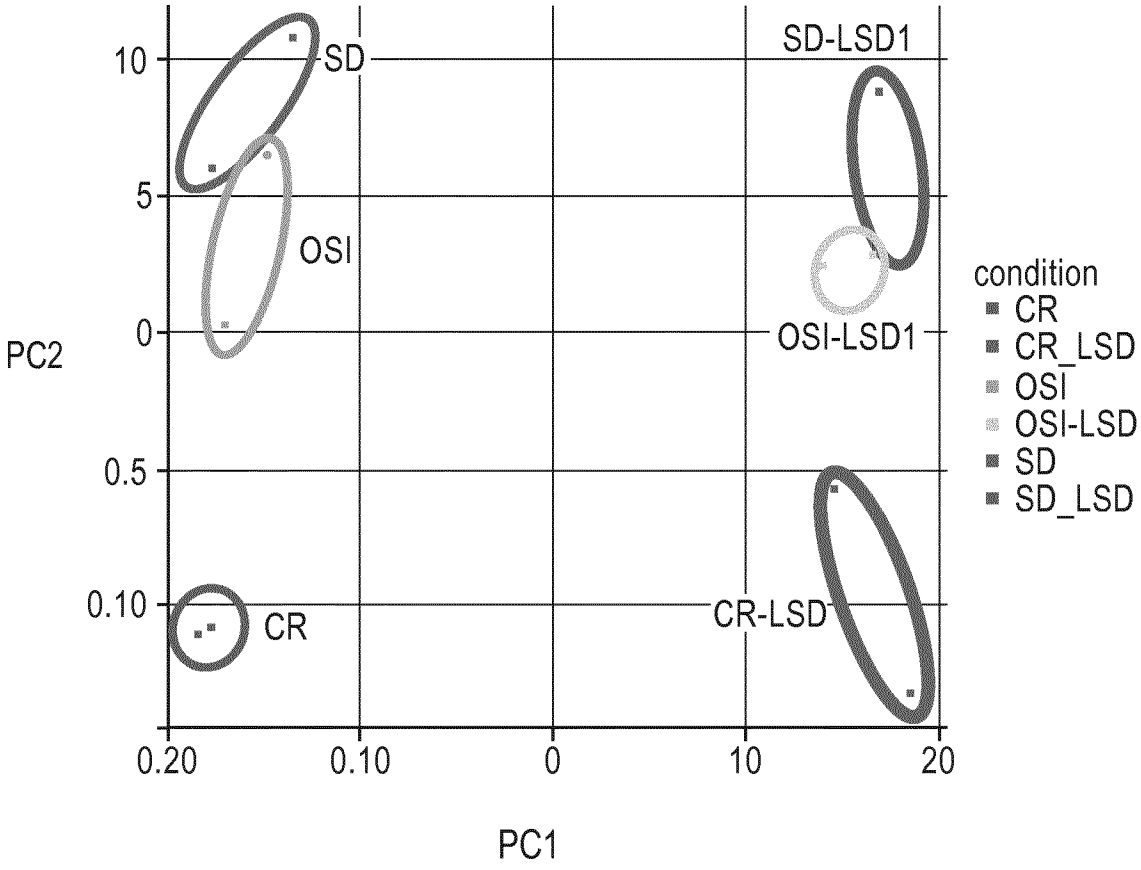

SD
SD-LSD1
OSI
OSI-LSD1
CR
CR-LSD
10
5
0
0.5
0.10
0.20
0.10
0
10
20
PC2
PC1
condition
CR
CR_LSD
OSI
OSI-LSD
SD
SD_LSD

Figure 13B

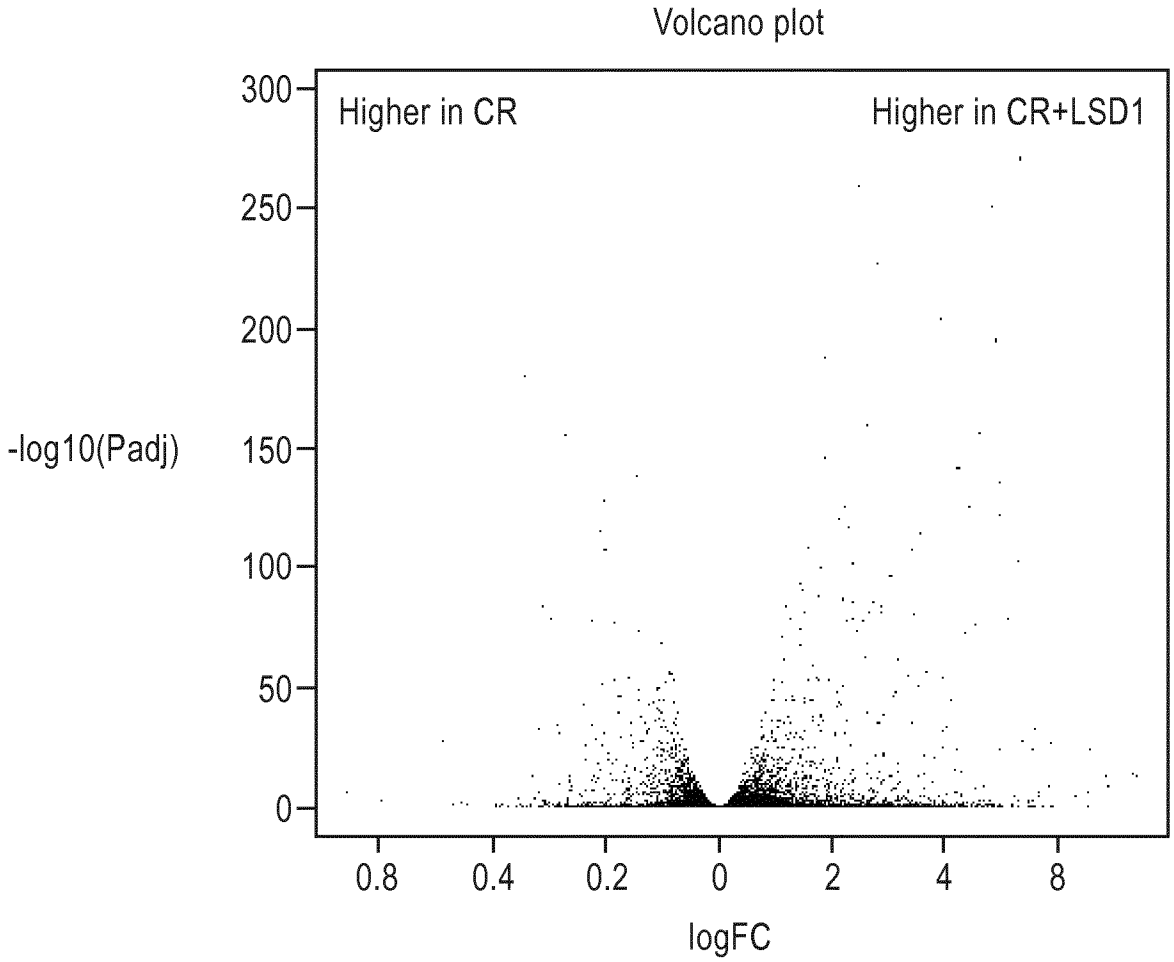

Volcano plot
Higher in CR
Higher in CR+LSD1
-log10(Padj)
300
250
200
150
100
50
0
0.8
0.4
0.2
0
2
4
8
logFC

Figure 13C

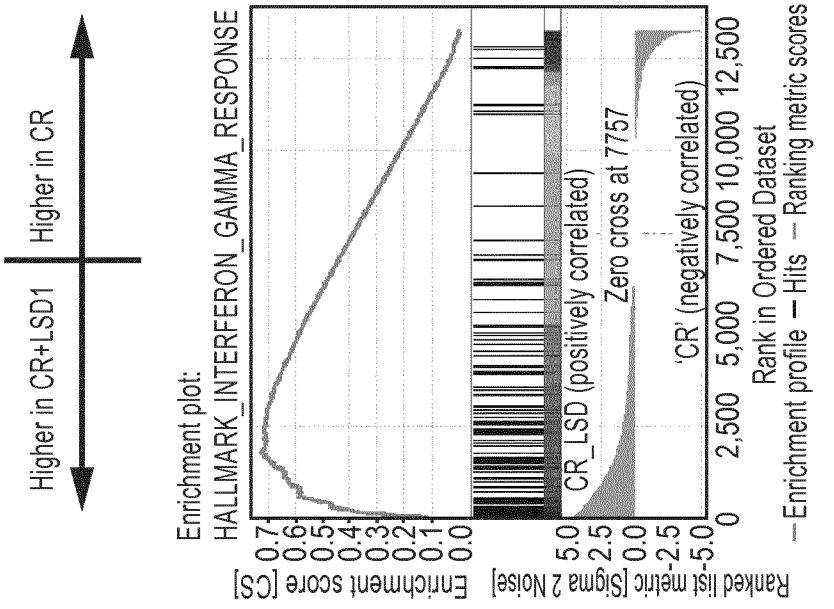

Higher in CR+LSD1
Higher in CR
Enrichment plot:
HALLMARK_INTERFERON_GAMMA_RESPONSE
Enrichment score [CS]
Ranked list metric [Signal 2 Noise]
CR_LSD (positively correlated)
Zero cross at 7757
'CR' (negatively correlated)
Rank in Ordered Dataset
Enrichment profile Hits Ranking metric scores
Enrichment plot:
HALLMARK_INTERFERON_ALPHA_RESPONSE
Enrichment plot:HALLMARK_APOPTOSIS

Figure 14A

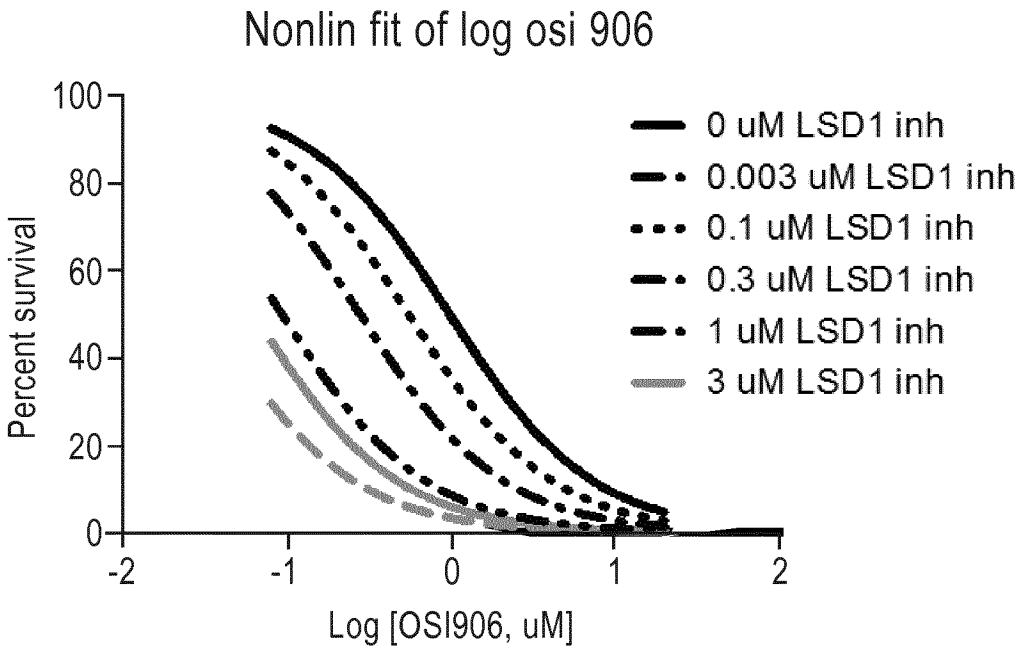

Nonlin fit of log osi 906
Percent survival
100
80
60
40
20
0
-2
-1
0
1
2
Log [OSI906, uM]
0 uM LSD1 inh
0.003 uM LSD1 inh
0.1 uM LSD1 inh
0.3 uM LSD1 inh
1 uM LSD1 inh
3 uM LSD1 inh

Figure 14B

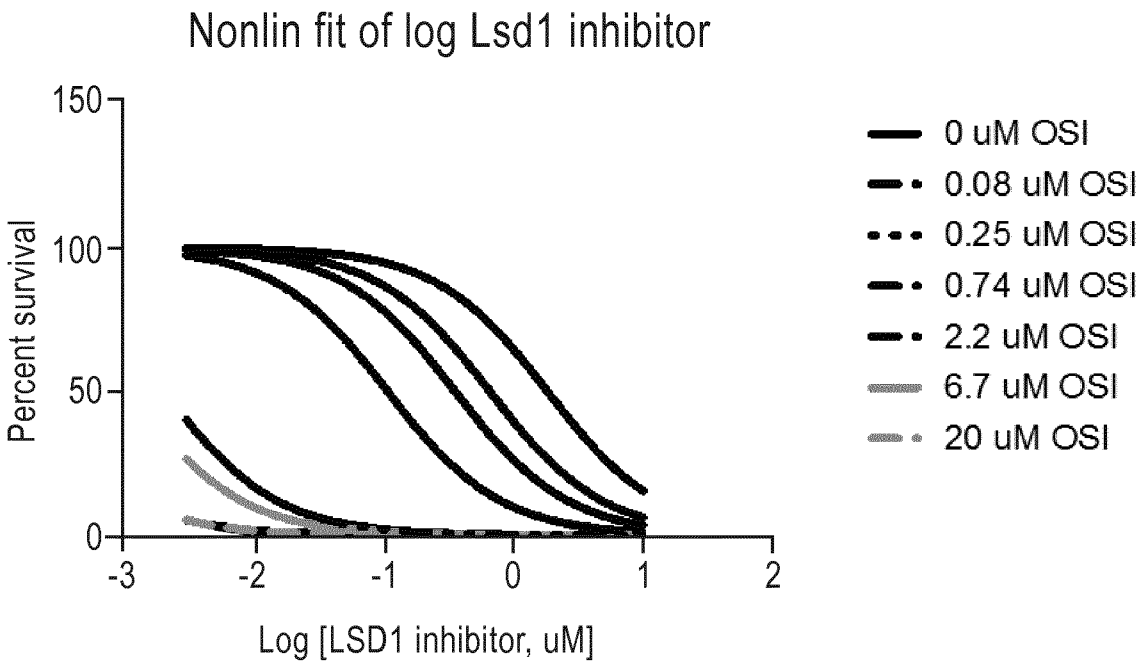

Nonlin fit of log Lsd1 inhibitor
Percent survival
150
100
50
0
-3
-2
-1
0
1
2
Log [LSD1 inhibitor, uM]
0 uM OSI
0.08 uM OSI
0.25 uM OSI
0.74 uM OSI
2.2 uM OSI
6.7 uM OSI
20 uM OSI

Figure 14C

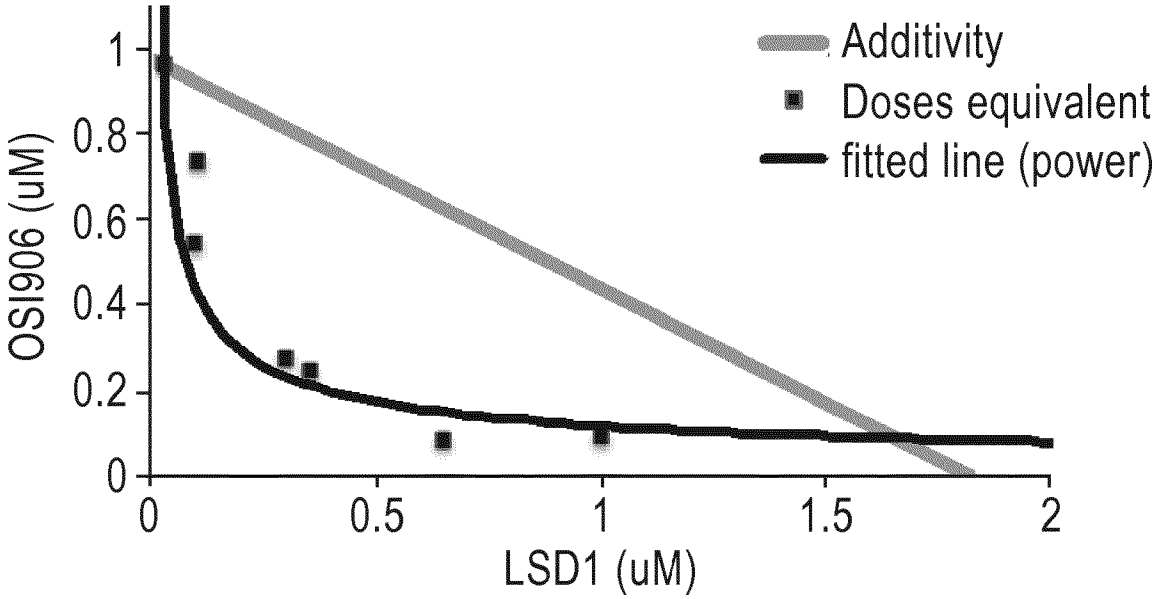
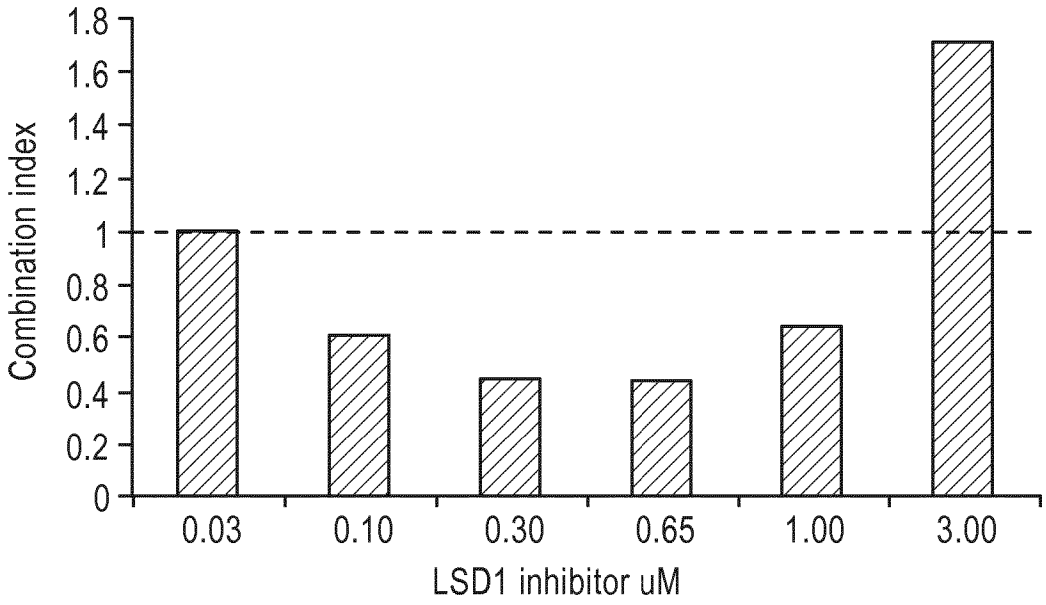

Additivity
Doses equivalent
fitted line (power)
OSI906 (uM)
LSD1 (uM)
0
0.2
0.4
0.6
0.8
1
0
0.5
1
1.5
2

Figure 14D


Combination index
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.03
0.10
0.30
0.65
1.00
3.00
LSD1 inhibitor uM

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/080156

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4155 A61K31/4465 A61K31/4704 A61K31/5375 A61P35/00
ADD.

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)
A61K

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)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 949 648 A1 (IEO ISTITUTO EUROP DI ONCOLOGIA SRL [IT]) 2 December 2015 (2015-12-02) abstract page 3, paragraph 12 - page 4, paragraph 24 page 10, paragraph 55 page 21; table 3 claims 8, 9 ----- -/--	1,3,5-8, 11,12, 17,18, 20,22, 24, 26-29, 33,34

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2017	21/02/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Damiani, Federica

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	MICHAEL J. CHEN ET AL: "Running exercise- and antidepressant-induced increases in growth and survival-associated signaling molecules are IGF-dependent", GROWTH FACTORS., vol. 25, no. 2, 11 January 2007 (2007-01-11), pages 118-131, XP055343817, XX ISSN: 0897-7194, DOI: 10.1080/08977190701602329 the whole document	1-40
Y	US 2014/163017 A1 (VANKAYALAPATI HARIPRASAD [US] ET AL) 12 June 2014 (2014-06-12) abstract page 29; compound 12 claims 1-16	1-40
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Information on patent family members

International application No
PCT/EP2016/080156

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		EP 2956776 A2	23-12-2015
		HK 1212028 A1	03-06-2016
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