~~What is Claimed:~~CLAIMS

1. Use of ~~A~~a copper ionophore ~~method~~ in the manufacture of a medicament ~~of~~ for inhibiting growth or proliferation of a tumor and/or immune cell, comprising:

(a) determining whether the tumor and/or immune cell comprises a level of protein lipoylation above a threshold level; and

(b) if the level of protein lipoylation is above the threshold level, contacting the tumor and/or immune cell with ~~a~~ the copper ionophore.

~~2. The method of claim 1, wherein the copper ionophore induces tumor cell death and/or immune cell death.~~

~~3~~2. The ~~method~~use of claim 1~~ or 2~~, wherein the lipoylated protein is lipoyl-DLAT (lipoyl-dihydrolipoamide acetyltransferase), lipoyl-DLST (lipoyl-dihydrolipoyl succinyltransferase), lipoyl-GCSH (lipoyl-Glycine Cleavage System Protein H), or lipoyl-DBT (lipoyl-dihydrolipoamide branched chain transacylase E2).

~~4~~3. The ~~method~~use of ~~any one of claims 1-3~~claim 1 or 2, wherein determining whether the tumor and/or immune cell is characterized by a level of protein lipoylation above a threshold level comprises measuring the level of protein lipoylation in cells of the tumor and/or the immune cell.

~~5~~4. The ~~method~~use of any one of claims 1-~~4~~3, further comprising determining whether the tumor and/or immune cell is characterized by a level of a mitochondrial protein and/or a nucleic acid encoding a mitochondrial protein above a threshold level.

~~6~~5. The ~~method~~use of claim ~~5~~4, wherein determining whether the tumor and/or immune cell is characterized by a level of a mitochondrial protein and/or a nucleic acid encoding a mitochondrial protein above a threshold level comprises measuring the level of the mitochondrial protein and/or the nucleic acid encoding the mitochondrial protein in cells of the tumor and/or the immune cell.

~~7~~6. The ~~method~~use of claim ~~5~~ 4 or ~~6~~5, wherein the mitochondrial protein binds the copper ionophore.

87. The methoduse of any one of claims 1-76, wherein the copper ionophore is a dithiocarbamate.

9. The method of any one of claims 1-7, wherein the copper ionophore is , Pyrithione Zinc.

10. The method of any one of claims 1-7, wherein the copper ionophore is, Tetramethylthiuram−monosulfide.

11. The method of any one of claims 1-7, wherein the copper ionophore is, Oxyquinoline (8HQ).

12. The method of any one of claims 1-7, wherein the copper ionophore is , Thiram.

13. The method of any one of claims 1-7, wherein the copper ionophore is , Cu(GTSM).

14. The method of any one of claims 1-7, wherein the copper ionophore is , NSC-319726.

15. The method of any one of claims 1-7, wherein the copper ionophore is , FR-122047.

16. The method of any one of claims 1-7, wherein the copper ionophore is, Cu(isapn).

17. The method of any one of claims 1-7, wherein the copper ionophore is, a Paullone-based complex.

18. The method of any one of claims 1-7, wherein the copper ionophore is, a Casiopeína-based complex.

19. The method of any one of claims 1-7, wherein the copper ionophore is, a Bis(thiosemicarbazone) Cu complex.

20. The method of any one of claims 1-7, wherein the copper ionophore is, a Isatin-Schiff-based complex.

21. The method of any one of claims 1-7, wherein the copper ionophore is, a (D-glucopyranose)-4-phenylthiosemicarbazide Cu complex.

22. The method of any one of claims 1-7, wherein the copper ionophore is, a $BCANa_2$.

~~23. The method of any one of claims 1-7, wherein the copper ionophore is,~~ a $BCSNa_2$~~.~~

~~24. The method of any one of claims 1-7, wherein the copper ionophore is,~~ a $BCSANa_2$~~.~~

~~25. The method of any one of claims 1-7, wherein the copper ionophore is,~~ PTA~~.~~

~~26. The method of any one of claims 1-7, wherein the copper ionophore is,~~ DAPTA~~.~~

~~27. The method of any one of claims 1-7, wherein the copper ionophore is,~~ a soluble thiosemicarbazone complex~~.~~

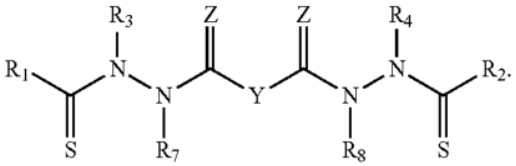
~~28. The method of any one of claims 1-7, wherein the copper ionophore is,~~ a Schiff base complex~~.~~

~~29. The method of any one of claims 1-7, wherein the copper ionophore is a dithiocarbamate~~

~~30. The method of any one of claims 1-7, wherein the copper ionophore is,~~ or a bis(thio-hydrazide amide).

~~3~~18. The ~~method~~use of any one of claims 1-~~7~~76, wherein the copper ionophore is:

(a) a compound of Formula A or a salt thereof:



wherein:

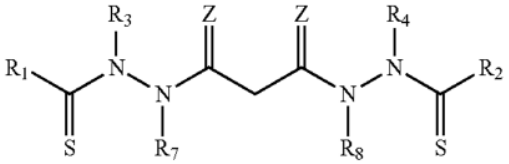
Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic ring optionally fused to an aromatic ring;

R_7 and R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

32. The method of any one of claims 1-7, wherein the copper ionophore is(b) a compound of Formula B1 or a salt thereof:



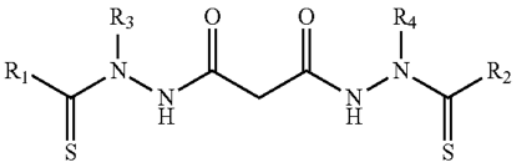
wherein:

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic ring optionally fused to an aromatic ring;

R_7 and R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

33. The method of any one of claims 1-7, wherein the copper ionophore is(c) a compound of Formula B2 or a salt thereof:



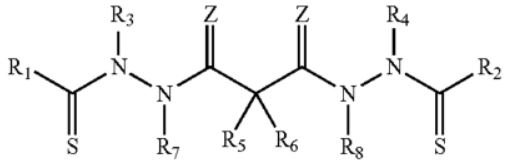
wherein:

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they

are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic ring optionally fused to an aromatic ring.

~~34. The method of any one of claims 1-7, wherein the copper ionophore is,~~

(d) a compound of Formula C or a salt thereof:



wherein:

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic ring optionally fused to an aromatic ring;

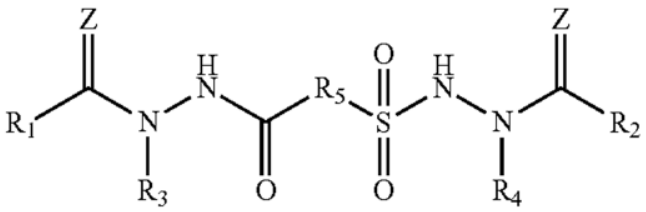
R_5 and R_6 are independently --H or lower alkyl;

R_7 and R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

~~35. The method of any one of claims 1-7, wherein the copper ionophore is,~~

(e) a compound of Formula D or a salt thereof:



wherein:

each Z is independently S, O or Se, provided that Z cannot both be O;

R_1 and R_2 are each independently selected from the group consisting of an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl; an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted

heterocyclic group wherein the heterocyclic group is bonded to the thiocarbonyl carbon via a carbon-carbon linkage, an optionally substituted phenyl, an optionally substituted bicyclic aryl, an optionally substituted five to seven-membered monocyclic heteroaryl, an optionally substituted nine to fourteen-membered bicyclic heteroaryl wherein the heteroaryl group is bonded to the thiocarbonyl carbon via a carbon-carbon linkage, —$NR_{12}R_{13}$, —OR_{14}, —SR_{14} and —$S(O)_pR_{15}$;

R_3 and R_4 are each independently selected from the group consisting of hydrogen, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclic group, and an optionally substituted five to six-membered aryl or heteroaryl group; or

R_1 and R_3 and/or R_2 and R_4, taken together with the atoms to which they are attached, form an optionally substituted heterocyclic group or an optionally substituted heteroaryl group;

R_5 is —CR_6R_7—, —$C(=CHR_8)$— or —$C(=NR_8)$—;

R_6 and R_7 are both —H or an optionally substituted lower alkyl;

R_8 is selected from the group consisting of —OH, an alkyl, an alkenyl, an alkynyl, an alkoxy, an alkenoxy, an alkynoxyl, a hydroxyalkyl, a hydroxyalkenyl, a hydroxyalkynyl, a haloalkyl, a haloalkenyl, a haloalkynyl, an optionally substituted phenyl, an optionally substituted bicyclic aryl, an optionally substituted five to six-membered monocyclic heteroaryl, an optionally substituted nine to fourteen-membered bicyclic heteroaryl, an optionally substituted cycloalkyl or an optionally substituted heterocyclic group; —$NR_{10}R_{11}$, and —COR_9;

R_9 is an optionally substituted phenyl, an optionally substituted bicyclic aryl, an optionally substituted five or six-membered monocyclic heteroaryl, an optionally substituted nine to fourteen-membered bicyclic heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl or an optionally substituted heterocyclic group;

R_{10} and R_{11} are each independently selected from the group consisting of —H, —OH, amino, (di)alkylamino, an alkyl, an alkenyl, an alkynyl, an alkoxy, an alkenoxy, an alkynoxyl, a hydroxyalkyl, a hydroxyalkenyl, a hydroxyalkynyl, a haloalkyl, a haloalkenyl, a haloalkynyl, an optionally substituted phenyl, an optionally substituted bicyclic aryl, an optionally substituted five to six-membered monocyclic heteroaryl, an optionally

substituted nine to fourteen-membered bicyclic heteroaryl, an optionally substituted cycloalkyl or an optionally substituted heterocyclic group and —COR_9, or R_{10} and R_{11}, taken together with the nitrogen atom to which they are attached, form a five to six-membered heteroaryl group; and

R_{12}, R_{13} and R_{14} are each independently —H, an optionally substituted alkyl, an optionally substituted phenyl or an optionally substituted benzyl, or R_{12} and R_{13}, taken together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclic group or an optionally substituted heteroaryl group;

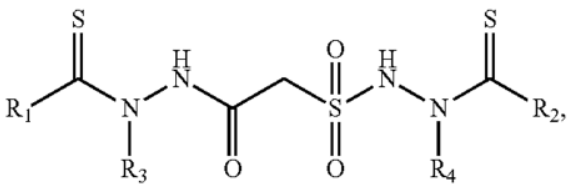
R_{15} is an optionally substituted alkyl, an optionally substituted aryl or an optionally substituted heteroaryl, and

p is 1 or 2;

provided that when both Z are S and R_3 and R_4 are both methyl, then R_1 and R_2 are not both unsubstituted phenyl.

~~36. The method of any one of claims 1-7, wherein the copper ionophore is,~~

(f) a compound of Formula E or a salt thereof:

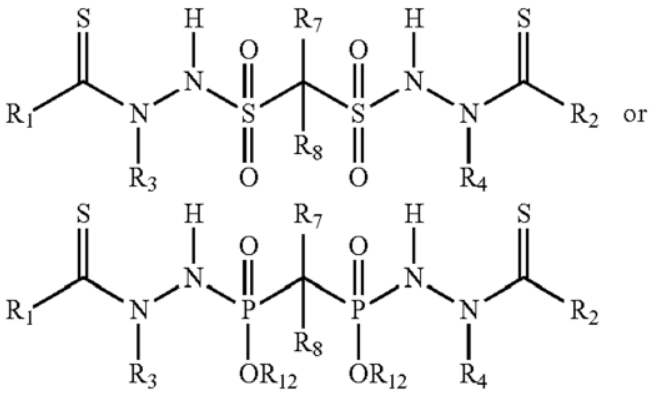


wherein:

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic ring optionally fused to an aromatic ring;

~~37. The method of any one of claims 1-7, wherein the copper ionophore is,~~ or

(g) a compound of the following formula or a salt thereof:



wherein:

R_1 and R_2 are independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, halo, nitro, cyano, guanidino, —OR_{17}, —$NR_{19}R_{20}$, —$C(O)R_{17}$, —$C(O)OR_{17}$, —$OC(O)R_{17}$, —$C(O)NR_{19}R_{20}$, —$NR_{18}C(O)R_{17}$, —$OP(O)(OR_{17})_2$, —$SP(O)(OR_{17})_2$, —SR_{17}, —$S(O)_pR_{17}$, —$OS(O)_pR_{17}$, —$S(O)_pOR_{17}$, —$NR_{18}S(O)_pR_{17}$, or —$S(O)_pNR_{19}R_{20}$;

R_3 and R_4 are independently —H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl or an optionally substituted heteroaryl;

R_7 and R_8 are each independently —H or an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, or R_7 is —H and R_8 is an optionally substituted aryl or an optionally substituted heteroaryl; and R_1, R_2, $R_{3;\ and}$

R_{12} is independently —H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, or halo.

~~38~~9. The ~~method~~use of any one of claims 1-~~7~~6, wherein the copper ionophore is an ALDH inhibitor, elesclomol, or disulfiram.

~~39. The method of any one of claims 1-7, wherein the copper ionophore is elesclomol.~~

~~4~~10. The ~~method~~use of any one of claims 5~~-~~, ~~7~~ 6 or ~~3~~9, wherein the mitochondrial protein is FDX1 (ferredoxin 1), ~~.~~

~~41. The method of any one of claims 1-7, wherein the copper ionophore is disulfiram.~~

~~42. The method of any one of claims 1-7 or 10, wherein the mitochondrial protein is~~ ALDHA1 (aldehyde dehydrogenase A1), ~~or~~ ALDH2 (aldehyde dehydrogenase 2)~~.~~

~~43. The method of claim 5 or 6, wherein the mitochondrial protein is~~ , or a protein involved in lipoic acid biosynthesis~~.~~

~~44. The method~~use ~~of claims 5, 6, or 43, wherein the protein involved in lipoic acid biosynthesis is~~ , e.g., LIAS (lipoic acid synthetase), LIPT1 (lipoyltransferase 1), or LIPT2 (lipoyltransferase 2), or DLD (Dihydrolipoamide Dehydrogenase).

~~45~~11. The ~~method~~use of any one of claims 1-~~44~~10, wherein contacting the tumor and/or immune cell with the copper ionophore inhibits Pyruvate dehydrogenase complex, 2-oxoglutarate dehydrogenase complex, Branched-Chain Alpha-Keto Acid Dehydrogenase Complex, and/or glycine cleavage.

~~46~~12. The ~~method~~use of any one of claims 1-~~45~~11, further comprising treating the tumor and/or immune cell with another anti-cancer agent conjointly with the copper ionophore.

~~47. The method of claim 46, whereby the copper ionophore enhances the effects of the anti-cancer agent relative to the anti-cancer agent alone.~~

~~48~~13. The ~~method~~use of claim ~~46 or 47~~12, wherein the anti-cancer agent is a chemotherapeutic agent, an immune checkpoint inhibitor, an EGFR inhibitor, or a proteasome inhibitor.

~~49~~14. The ~~method~~use of claim ~~48~~13, wherein the anti-cancer agent is a chemotherapeutic agent~~.~~

~~50. The methoduse of claim 49, wherein the chemotherapeutic agent is, e.g.,~~ cytarabine~~.~~

~~51. The method of claim 49, wherein the chemotherapeutic agent is,~~ a b-raf inhibitor~~.~~

~~52. The method of claim 49, wherein the chemotherapeutic agent is,~~ docetaxel~~.~~

~~53. The method of claim 49, wherein the chemotherapeutic agent is,~~ or imatinib.

~~54~~15. The ~~method~~use of claim ~~48~~14, wherein the anti-cancer agent is an EGFR inhibitor~~.~~

~~55. The methoduse of claim 54, wherein the EGFR inhibitor is, e.g.,~~ a tyrosine kinase inhibitor~~.~~

~~56. The method of claim 54, wherein the EGFR inhibitor is,~~ gefitinib~~.~~

~~57. The method of claim 54, wherein the EGFR inhibitor is,~~ or osimertinib.

~~58. The method of any one of claims 46-27, wherein the copper ionophore enhances tumor cell death and/or immune cell death of the anti-cancer agent relative to the anti-cancer agent alone.~~

~~59~~16. The ~~method~~use of any one of claims 1-~~58~~15, wherein the copper ionophore is pre-loaded with copper(II).

~~60. The method of claim 59, wherein the copper ionophore is elesclomol.~~

~~61. The method of claim 59, wherein the copper ionophore is disulfiram.~~

~~62~~17. Use of a copper ionophore in the manufacture of a medicament for ~~A method of~~ treating cancer refractory to treatment with an anti-cancer agent in a subject, comprising the steps of:

(a) determining whether the cancer is characterized by a level of protein lipoylation above a threshold level; and

(b) if the cancer is characterized by a level of protein lipoylation above the threshold level, conjointly administering ~~a~~ the copper ionophore and the anti-cancer agent to the subject.

~~63~~18. The ~~method~~use of claim ~~62~~17, wherein the anti-cancer agent is a chemotherapeutic agent, an immune checkpoint inhibitor, an EGFR inhibitor, or a proteasome inhibitor.

6419. The methoduse of claim 6318, wherein the anti-cancer agent is a chemotherapeutic agent.

65. The methoduse of claim 64 wherein the chemotherapeutic agent is, e.g., cytarabine.

66. The method of claim 64, wherein the chemotherapeutic agent is, a b-raf inhibitor.

67. The method of claim 64, wherein the chemotherapeutic agent is, docetaxel.

68. The method of claim 64, wherein the chemotherapeutic agent is, or imatinib.

6920. The methoduse of claim 6318, wherein the anti-cancer agent is an EGFR inhibitor.

70. The methoduse of claim 69, wherein the EGFR inhibitor is, e.g., a tyrosine kinase inhibitor.

71. The method of claim 69, wherein the EGFR inhibitor is, gefitinib.

72. The method of claim 69, wherein the EGFR inhibitor is, or osimertinib.

7321. The methoduse of any one of claims 6217-7220, wherein the lipoylated protein is lipoyl-DLAT, lipoyl-DLST, lipoyl-GCSH, or lipoyl-DBT.

7422. The methoduse of any one of claims 6217-7321, wherein determining whether the cancer is characterized by a level of protein lipoylation above a threshold level comprises measuring the level of protein lipoylation in cells of the cancer.

7523. The methoduse of any one of claims 6217-7422, further comprising determining whether the cancer is characterized by a level of a mitochondrial protein and/or a nucleic acid encoding a mitochondrial protein above a threshold level.

7624. The methoduse of any one of claims 7523, wherein determining whether the cancer is characterized by a level of a mitochondrial protein and/or a nucleic acid encoding a mitochondrial protein above a threshold level comprises measuring the level of the mitochondrial protein and/or the nucleic acid encoding the mitochondrial protein in the cells of the cancer.

7725. The methoduse of claim 42 23 or 4324, wherein the copper ionophore binds the mitochondrial protein.

7826. The methoduse of any one of claims 6217-7725, wherein the copper ionophore is a dithiocarbamate.

79. The method of any one of claims 62-77, wherein the copper ionophore is, Pyrithione Zinc.

80. The method of any one of claims 62-77, wherein the copper ionophore is, Tetramethylthiuram−monosulfide.

81. The method of any one of claims 62-77, wherein the copper ionophore is, Oxyquinoline (8HQ).

82. The method of any one of claims 62-77, wherein the copper ionophore is , Thiram.

83. The method of any one of claims 62-77, wherein the copper ionophore is , Cu(GTSM).

84. The method of any one of claims 62-77, wherein the copper ionophore is, NSC-319726.

85. The method of any one of claims 62-77, wherein the copper ionophore is, FR-122047.

86. The method of any one of claims 62-77, wherein the copper ionophore is , Cu(isapn).

87. The method of any one of claims 62-77, wherein the copper ionophore is , a Paullone-based complex.

88. The method of any one of claims 62-77, wherein the copper ionophore is, a Casiopeína-based complex.

89. The method of any one of claims 62-77, wherein the copper ionophore is, a Bis(thiosemicarbazone) Cu complex.

90. The method of any one of claims 62-77, wherein the copper ionophore is, a Isatin-Schiff-based complex.

91. The method of any one of claims 62-77, wherein the copper ionophore is, a (D-glucopyranose)-4-phenylthiosemicarbazide Cu complex.

~~92. The method of any one of claims 62-77, wherein the copper ionophore is,~~ a $BCANa_2$~~.~~

~~93. The method of any one of claims 62-77, wherein the copper ionophore is ,~~ a $BCSNa_2$~~.~~

~~94. The method of any one of claims 62-77, wherein the copper ionophore is,~~ a $BCSANa_2$~~.~~

~~95. The method of any one of claims 62-77, wherein the copper ionophore is,~~ PTA~~.~~

~~96. The method of any one of claims 62-77, wherein the copper ionophore is,~~ DAPTA~~.~~

~~97. The method of any one of claims 62-77, wherein the copper ionophore is,~~ a soluble thiosemicarbazone complex~~.~~

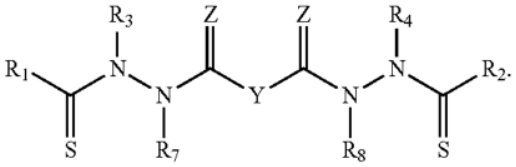
~~98. The method of any one of claims 62-77, wherein the copper ionophore is,~~ a Schiff base complex~~.~~

~~99. The method of any one of claims 62-77, wherein the copper ionophore is a dithiocarbamate~~

~~100. The method of any one of claims 62-77, wherein the copper ionophore is,~~ a bis(thio-hydrazide amide).

~~101~~27. The ~~method~~use of any one of claims ~~62~~17-~~77~~25, wherein the copper ionophore is:

(a) a compound of Formula A or a salt thereof:



wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they

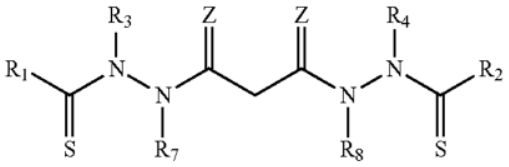
are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic ring optionally fused to an aromatic ring;

R_7 and R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

~~102. The method of any one of claims 62-77, wherein the copper ionophore is,~~

(b) a compound of Formula B1 or a salt thereof:



wherein:

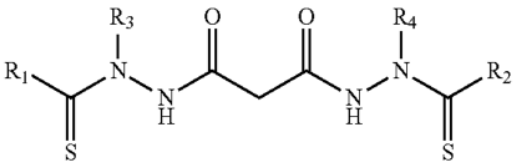
R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic ring optionally fused to an aromatic ring;

R_7 and R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

~~103. The method of any one of claims 62-77, wherein the copper ionophore is,~~

(c) a compound of Formula B2 or a salt thereof:



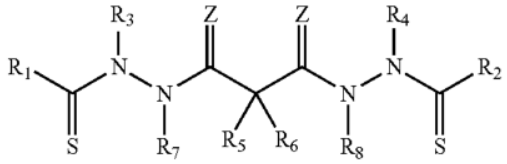
wherein:

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they

are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic ring optionally fused to an aromatic ring.

~~104. The method of any one of claims 62-77, wherein the copper ionophore is,~~

(d) a compound of Formula C or a salt thereof:



wherein:

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic ring optionally fused to an aromatic ring;

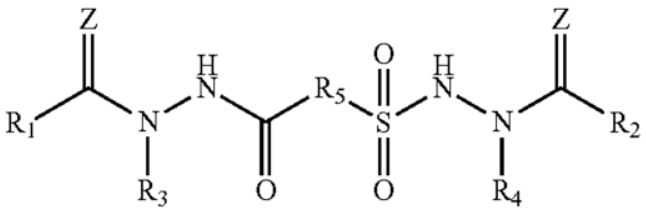
R_5 and R_6 are independently --H or lower alkyl;

R_7 and R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

~~105. The method of any one of claims 62-77, wherein the copper ionophore is,~~

(e) a compound of Formula D or a salt thereof:



wherein:

each Z is independently S, O or Se, provided that Z cannot both be O;

R_1 and R_2 are each independently selected from the group consisting of an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl; an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted

heterocyclic group wherein the heterocyclic group is bonded to the thiocarbonyl carbon via a carbon-carbon linkage, an optionally substituted phenyl, an optionally substituted bicyclic aryl, an optionally substituted five to seven-membered monocyclic heteroaryl, an optionally substituted nine to fourteen-membered bicyclic heteroaryl wherein the heteroaryl group is bonded to the thiocarbonyl carbon via a carbon-carbon linkage, —$NR_{12}R_{13}$, —OR_{14}, —SR_{14} and —$S(O)_pR_{15}$;

R_3 and R_4 are each independently selected from the group consisting of hydrogen, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclic group, and an optionally substituted five to six-membered aryl or heteroaryl group; or

R_1 and R_3 and/or R_2 and R_4, taken together with the atoms to which they are attached, form an optionally substituted heterocyclic group or an optionally substituted heteroaryl group;

R_5 is —CR_6R_7—, —$C(=CHR_8)$— or —$C(=NR_8)$—;

R_6 and R_7 are both —H or an optionally substituted lower alkyl;

R_8 is selected from the group consisting of —OH, an alkyl, an alkenyl, an alkynyl, an alkoxy, an alkenoxy, an alkynoxyl, a hydroxyalkyl, a hydroxyalkenyl, a hydroxyalkynyl, a haloalkyl, a haloalkenyl, a haloalkynyl, an optionally substituted phenyl, an optionally substituted bicyclic aryl, an optionally substituted five to six-membered monocyclic heteroaryl, an optionally substituted nine to fourteen-membered bicyclic heteroaryl, an optionally substituted cycloalkyl or an optionally substituted heterocyclic group; —$NR_{10}R_{11}$, and —COR_9;

R_9 is an optionally substituted phenyl, an optionally substituted bicyclic aryl, an optionally substituted five or six-membered monocyclic heteroaryl, an optionally substituted nine to fourteen-membered bicyclic heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl or an optionally substituted heterocyclic group;

R_{10} and R_{11} are each independently selected from the group consisting of —H, —OH, amino, (di)alkylamino, an alkyl, an alkenyl, an alkynyl, an alkoxy, an alkenoxy, an alkynoxyl, a hydroxyalkyl, a hydroxyalkenyl, a hydroxyalkynyl, a haloalkyl, a haloalkenyl, a haloalkynyl, an optionally substituted phenyl, an optionally substituted bicyclic aryl, an optionally substituted five to six-membered monocyclic heteroaryl, an optionally

substituted nine to fourteen-membered bicyclic heteroaryl, an optionally substituted cycloalkyl or an optionally substituted heterocyclic group and —COR_9, or R_{10} and R_{11}, taken together with the nitrogen atom to which they are attached, form a five to six-membered heteroaryl group; and

R_{12}, R_{13} and R_{14} are each independently —H, an optionally substituted alkyl, an optionally substituted phenyl or an optionally substituted benzyl, or R_{12} and R_{13}, taken together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclic group or an optionally substituted heteroaryl group;

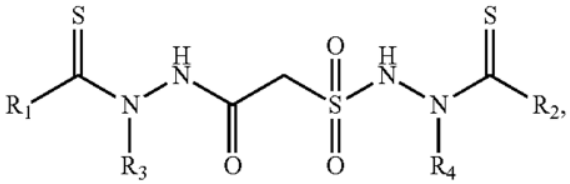
R_{15} is an optionally substituted alkyl, an optionally substituted aryl or an optionally substituted heteroaryl, and

p is 1 or 2;

provided that when both Z are S and R_3 and R_4 are both methyl, then R_1 and R_2 are not both unsubstituted phenyl.

~~106. The method of any one of claims 62-77, wherein the copper ionophore is,~~

(f) a compound of Formula E or a salt thereof:

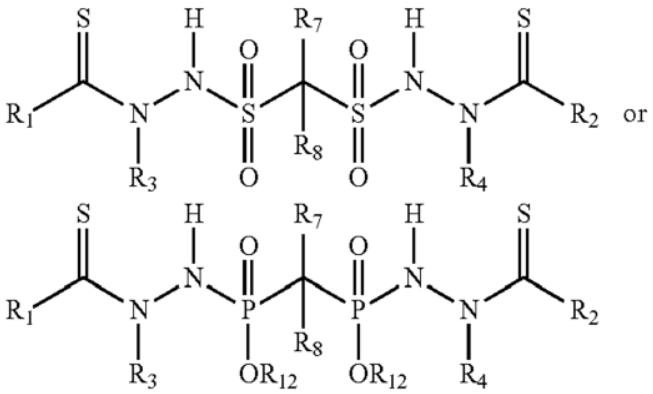


wherein:

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic ring optionally fused to an aromatic ring;

~~107. The method of any one of claims 62-77, wherein the copper ionophore is,~~

(g) a compound of the following formula or a salt thereof:



wherein:

R_1 and R_2 are independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, halo, nitro, cyano, guanidino, —OR_{17}, —$NR_{19}R_{20}$, —$C(O)R_{17}$, —$C(O)OR_{17}$, —$OC(O)R_{17}$, —$C(O)NR_{19}R_{20}$, —$NR_{18}C(O)R_{17}$, —$OP(O)(OR_{17})_2$, —$SP(O)(OR_{17})_2$, —SR_{17}, —$S(O)_pR_{17}$, —$OS(O)_pR_{17}$, —$S(O)_pOR_{17}$, —$NR_{18}S(O)_pR_{17}$, or —$S(O)_pNR_{19}R_{20}$;

R_3 and R_4 are independently —H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl or an optionally substituted heteroaryl;

R_7 and R_8 are each independently —H or an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, or R_7 is —H and R_8 is an optionally substituted aryl or an optionally substituted heteroaryl; and R_1, R_2, $R_{3;\ and}$

R_{12} is independently —H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, or halo.

~~108~~28. The ~~method~~use of any one of claims ~~62~~17-~~77~~25, wherein the copper ionophore is an ALDH inhibitor~~.~~

~~109. The method of any one of claims 62-77, wherein the copper ionophore is,~~ elesclomol, or disulfiram.

~~110~~29. The ~~method~~use of any one of claims ~~75~~17-~~77~~ 25 or ~~109~~28, wherein the mitochondrial protein is FDX1~~.~~

~~111. The method of any one of claims 62-77, wherein the copper ionophore is disulfiram.~~

~~112. The method of any one of claims 75-77 or 111, wherein the mitochondrial protein is,~~ ALDHA1 ~~or,~~ ALDH2~~.~~

~~113. The method of claim 75 or 76, wherein the mitochondrial protein is,~~ or a protein involved in lipoic acid biosynthesis~~.~~

~~114. The method of claims 75, 76, or 113, wherein the protein involved in lipoic acid biosynthesis is,~~ e.g., LIAS, LIPT1, LIPT2, or DLD.

~~115~~30. The ~~method~~use of any one of claims ~~62~~17-~~114~~29, wherein contacting the tumor and/or immune cell with the copper ionophore inhibits Pyruvate dehydrogenase complex, 2-oxoglutarate dehydrogenase complex, Branched-Chain Alpha-Keto Acid Dehydrogenase Complex, and/or glycine cleavage.

~~116~~31. The ~~method~~use of any one of claims ~~62~~17-~~115~~30, wherein the copper ionophore is pre-loaded with copper(II).

~~117. The method of claim 116, wherein the copper ionophore is elesclomol.~~

~~118. The method of claim 116, wherein the copper ionophore is disulfiram.~~

~~119~~32. A method of identifying a candidate anti-cancer agent, comprising the steps of:

(a) contacting a cell sample with a test agent;

(b) measuring a level of cellular protein lipoylation of the cell sample; and

(c) identifying the test agent as a candidate anti-cancer agent if the level of cellular protein lipoylation is decreased as compared to a level of cellular protein lipoylation of a cell sample not contacted with the test agent.

~~120. The method of claim 119, wherein the level of cellular protein lipoylation of a cell sample not contacted with the test agent is the level of cellular protein lipoylation in the cell sample prior to contact with the test agent.~~

~~121. The method of claim 119 or 120, wherein the level of cellular protein lipoylation of a cell sample not contacted with the test agent is the level of cellular protein lipoylation of a corresponding control cell sample.~~

~~122. The method of any one of claims 119-121, wherein the level of cellular protein lipoylation of a cell sample not contacted with the test agent is the level of cellular protein lipoylation of one or more reference samples representative of the cell sample contacted with the test agent.~~

~~123. The method of any one of claims 119-122, wherein the lipoylated protein is lipoyl-DLAT, lipoyl-DLST, lipoyl-GCSH, or lipoyl-DBT.~~

~~124. The method of any one of claims 119-123, further comprising measuring a level or activity of a mitochondrial protein and/or a nucleic acid encoding a mitochondrial protein in the cell sample and determining if the level or activity of the mitochondrial protein and/or the nucleic acid encoding the mitochondrial protein is decreased as compared to a level or activity of the mitochondrial protein and/or the nucleic acid encoding the mitochondrial protein of a cell sample not contacted with the test agent.~~

~~125. The method of claim 124, wherein the mitochondrial protein is FDX1, ALDHA1, ALDH2, LIAS, LIPT1, LIPT2, DLD, or Pyruvate dehydrogenase complex, 2-oxoglutarate dehydrogenase complex, Branched-Chain Alpha-Keto Acid Dehydrogenase Complex, and/or glycine cleavage.~~

~~126. The method of any one of claims 119-125, further comprising measuring a level of cell death in the cell sample and determining if the level of cell death is increased as compared to a level of cell death of a cell sample not contacted with the test agent.~~

~~127. A method of determining increased mitochondrial metabolism in a tumor and/or immune cell, comprising staining for lipoic acid in the tumor and/or immune cell.~~

~~128. A method of identifying a candidate anti-cancer agent, comprising the steps of:~~

~~(a) incubating a cell sample with copper-supplemented media;~~

~~(b) contacting a cell sample with a test agent;~~

~~(c) measuring cell viability of the cell sample; and~~

~~(d) identifying the test agent as a candidate anti-cancer agent if the level of cell viability is decreased as compared to a level of cell viability of a cell sample incubated with copper-supplemented media and not contacted with the test agent.~~

~~129. A method of identifying a candidate anti-cancer agent, comprising the steps of:~~

~~(a) incubating a cell sample with a copper chelator;~~

~~(b) contacting a cell sample with a test agent;~~

~~(c) measuring cell death of the cell sample; and~~

~~(d) identifying the test agent as a candidate anti-cancer agent if the level of cell death is decreased as compared to a level of cell death of a cell sample incubated a copper chelator and not contacted with the test agent.~~

~~130. A kit for identifying a candidate anti-cancer agent comprising a test agent and an assay for measuring cellular protein lipoylation.~~

~~131. A kit for identifying a candidate anti-cancer agent comprising copper-supplemented media, a test agent, and an assay for measuring cell viability.~~

~~132. A kit for identifying a candidate anti-cancer agent comprising a copper chelator, a test agent, and an assay for measuring cell death.~~