

CLAIMS

1. A method for identifying a modulator of a biological system, the method comprising:
 - establishing a model for the biological system, using cells associated with the biological system, to represents a characteristic aspect of the biological system;
 - obtaining a first data set from the model, wherein the first data set represents global proteomic changes in the cells associated with the biological system;
 - obtaining a second data set from the model, wherein the second data set represents one or more functional activities or cellular responses of the cells associated with the biological system, wherein said one or more functional activities or cellular responses of the cells comprises global enzymatic activity and/or an effect of the global enzyme activity on the enzyme metabolites or substrates in the cells associated with the biological system;
 - generating a consensus causal relationship network among the global proteomic changes and the one or more functional activities or cellular responses based solely on the first and second data sets using a programmed computing device, wherein the generation of the consensus causal relationship network is not based on any known biological relationships other than the first and second data sets; and
 - identifying, from the consensus causal relationship network, a causal relationship unique in the biological system, wherein at least one enzyme associated with the unique causal relationship is identified as a modulator of the biological system.
2. The method of claim 1, wherein the first data set further represents lipidomic data characterizing the cells associated with the biological system.
3. The method of claim 2, wherein the consensus causal relationship network is generated among the global proteomic changes, lipidomic data, and the one or more functional activities or cellular responses of the cells, wherein said one or more functional activities or cellular responses of the cells comprises global enzymatic activity and/or the effect of the global enzymatic activity on at least one enzyme metabolite or substrate.

4. The method of claim 1, wherein the first data set further represents one or more of lipidomic, metabolomic, transcriptomic, genomic and SNP data characterizing the cells associated with the biological system.
5. The method of claim 1, wherein the first data set further represents two or more of lipidomic, metabolomic, transcriptomic, genomic and SNP data characterizing the cells associated with the biological system.
6. The method of claims 4 or 5, wherein the consensus causal relationship network is generated among the global proteomic changes, the one or more of lipidomic, metabolomic, transcriptomic, genomic, and SNP data, and the one or more functional activities or cellular responses of the cells, wherein said one or more functional activities or cellular responses of the cells comprises global enzymatic activity and/or the effect of the global enzymatic activity on at least one enzyme metabolite or substrate.
7. The method of any one of claims 1-6, wherein the global enzyme activity comprises global kinase activity.
8. The method of any one of claims 1-7, wherein the effect of the global enzyme activity on the enzyme metabolites or substrates comprises the phospho proteome of the cells.
9. The method of any one of claims 1-8, wherein the second data set representing one or more functional activities or cellular responses of the cell further comprises one or more of bioenergetics, cell proliferation, apoptosis, organellar function, cell migration, tube formation, chemotaxis, extracellular matrix degradation, sprouting, and a genotype-phenotype associate actualized by functional models selected from ATP, ROS, OXPHOS, and Seahorse assays.
10. The method of claim 1-8, wherein the consensus causal relationship network is generated among the global proteomic changes, the one or more of lipidomic, metabolomic, transcriptomic, genomic, and SNP data, and the one or more functional activities or cellular responses of the cells, wherein said one or more functional activities or cellular responses of the cells comprises global enzymatic activity and/or the effect of the global enzymatic activity on at least one enzyme metabolite or substrate and further comprises one or more of bioenergetics, cell proliferation, apoptosis, organellar

function, cell migration, tube formation, chemotaxis, extracellular matrix degradation, sprouting, and a genotype-phenotype associate actualized by functional models selected from ATP, ROS, OXPHOS, and Seahorse assays.

11. The method of any one of claims 1-10, wherein the model of the biological system comprises an *in vitro* culture of cells associated with the biological system, optionally further comprising a matching *in vitro* culture of control cells.

12. The method of claim 11, wherein the *in vitro* culture of the cells is subject to an environmental perturbation, and the *in vitro* culture of the matching control cells is identical cells not subject to the environmental perturbation.

13. The method of claim 12, wherein the environmental perturbation comprises one or more of contact with a bioactive agent, a change in culture condition, introduction of a genetic modification / mutation, and introduction of a vehicle that causes a genetic modification / mutation.

14. The method of claim 13, wherein the environmental perturbation comprises contacting the cells with an enzymatic activity inhibitor.

15. The method of claim 14, wherein the enzymatic activity inhibitor is a kinase inhibitor.

16. The method of claim 13, wherein the environmental perturbation comprises contacting the cells with CoQ10.

17. The method of claim 14, wherein the environmental perturbation further comprises contacting the cells with CoQ10.

18. The method of claim 1, wherein the generating step is carried out by an artificial intelligence (AI) -based informatics platform.

19. The method of claim 18, wherein the AI-based informatics platform receives all data input from the first and second data sets without applying a statistical cut-off point.

20. The method of claim 1, wherein the consensus causal relationship network established in the generating step is further refined to a simulation causal relationship

network, before the identifying step, by *in silico* simulation based on input data, to provide a confidence level of prediction for one or more causal relationships within the consensus causal relationship network.

21. The method of claim 11, wherein the unique causal relationship is identified as part of a differential causal relationship network that is uniquely present in cells associated with the biological system, and absent in the matching control cells.

22. The method of claim 12, wherein the unique causal relationship is identified as part of a differential causal relationship network that is uniquely present in cells subject to the environmental perturbation, and absent in the matching control cells.

23. The method of any one of claims 1 to 22, wherein the unique causal relationship identified is a relationship between at least one pair selected from the group consisting of expression of a gene and level of a lipid; expression of a gene and level of a transcript; expression of a gene and level of a metabolite; expression of a first gene and expression of a second gene; expression of a gene and presence of a SNP; expression of a gene and a functional activity; level of a lipid and level of a transcript; level of a lipid and level of a metabolite; level of a first lipid and level of a second lipid; level of a lipid and presence of a SNP; level of a lipid and a functional activity; level of a first transcript and level of a second transcript; level of a transcript and level of a metabolite; level of a transcript and presence of a SNP; level of a first transcript and level of a functional activity; level of a first metabolite and level of a second metabolite; level of a metabolite and presence of a SNP; level of a metabolite and a functional activity; presence of a first SNP and presence of a second SNP; and presence of a SNP and a functional activity.

24. The method of any one of claims 1 to 23, wherein the unique causal relationship identified is a relationship between at least a level of a lipid, expression of a gene, and one or more functional activities wherein the functional activity is a global kinase activity.

25. A method for identifying a modulator of a disease process, the method comprising:

establishing a model for the disease process, using disease related cells, to represents a characteristic aspect of the disease process;

obtaining a first data set from the model, wherein the first data set represents global proteomic changes in the disease related cells;

obtaining a second data set from the model, wherein the second data set represents one or more functional activities or cellular responses of the cells associated with the biological system, wherein said one or more functional activities or cellular responses of the cells comprises global enzyme activity and/or an effect of the global enzyme activity on the enzyme metabolites or substrates in the disease related cells;

generating a consensus causal relationship network among the global proteomic changes and the one or more functional activities or cellular responses of the cells based solely on the first and second data sets using a programmed computing device, wherein the generation of the consensus causal relationship network is not based on any known biological relationships other than the first and second data sets; and

identifying, from the consensus causal relationship network, a causal relationship unique in the disease process, wherein at least one enzyme associated with the unique causal relationship is identified as a modulator of the disease process.

26. The method of claim 25, wherein the first data set further represents lipidomic data characterizing the cells associated with the biological system.

27. The method of claim 26, wherein the consensus causal relationship network is generated among the global proteomic changes, lipidomic data, and the one or more functional activities or cellular responses of the cells, wherein said one or more functional activities or cellular responses of the cells comprises global enzymatic activity and/or an effect of the global enzyme activity on the enzyme metabolites or substrates in the disease related cells.

28. The method of claim 25, wherein the first data set further represents one or more of lipidomic, metabolomic, transcriptomic, genomic and SNP data characterizing the cells associated with the biological system.

29. The method of claim 28, wherein the first data set further represents two or more of lipidomic, metabolomic, transcriptomic, genomic and SNP data characterizing the cells associated with the biological system.

30. The method of claim 28 or 29, wherein the consensus causal relationship network is generated among the global proteomic changes, the one or more of lipidomic, metabolomic, transcriptomic, genomic and SNP data, and the one or more functional activities or cellular responses of the cells, wherein said one or more functional activities or cellular responses of the cells comprises global enzymatic activity and/or the effect of the global enzymatic activity on at least one enzyme metabolite or substrate in the disease related cells.

31. The method of any one of claims 25 to 30, wherein the global enzyme activity comprises global kinase activity, and wherein the effect of the global enzyme activity on the enzyme metabolites or substrates comprises the phospho proteome of the cells.

32. The method of any one of claims 25 to 31, wherein the second data set representing one or more functional activities or cellular responses of the cell further comprises one or more of bioenergetics, cell proliferation, apoptosis, organellar function, cell migration, tube formation, chemotaxis, extracellular matrix degradation, sprouting, and a genotype-phenotype associate actualized by functional models selected from ATP, ROS, OXPHOS, and Seahorse assays.

33. The method of claim 32, wherein the consensus causal relationship network is generated among the global proteomic changes, the one or more of lipidomic, metabolomic, transcriptomic, genomic and SNP data, and the one or more functional activities or cellular responses of the cells, wherein said one or more functional activities or cellular responses of the cells comprises one or more of bioenergetics, cell proliferation, apoptosis, organellar function, cell migration, tube formation, chemotaxis, extracellular matrix degradation, sprouting, and a genotype-phenotype associate actualized by functional models selected from ATP, ROS, OXPHOS, and Seahorse assays.

34. The method of any of claims 25 to 33, wherein the disease process is cancer, diabetes, obesity, cardiovascular disease, age related macular degeneration, diabetic retinopathy, or inflammatory disease.
35. The method of any of claims 25 to 33, wherein the disease process comprises angiogenesis.
36. The method of any of claims 25 to 33, wherein the disease process comprises hepatocellular carcinoma, lung cancer, breast cancer, prostate cancer, melanoma, carcinoma, sarcoma, lymphoma, leukemia, squamous cell carcinoma, colorectal cancer, pancreatic cancer, thyroid cancer, endometrial cancer, bladder cancer, kidney cancer, a solid tumor, leukemia, non-Hodgkin lymphoma, or a drug-resistant cancer.
37. The method of any of claims 25 to 33, wherein the disease model comprises an *in vitro* culture of disease cells, optionally further comprising a matching *in vitro* culture of control or normal cells.
38. The method of claim 37, wherein the *in vitro* culture of the disease cells is subject to an environmental perturbation, and the *in vitro* culture of the matching control cells is identical disease cells not subject to the environmental perturbation.
39. The method of claim 38, wherein the environmental perturbation comprises one or more of contact with a bioactive agent, a change in culture condition, introduction of a genetic modification / mutation, and introduction of a vehicle that causes a genetic modification / mutation.
40. The method of claim 39, wherein the environmental perturbation comprises contacting the cells with an enzymatic activity inhibitor.
41. The method of claim 40, wherein the enzymatic activity inhibitor is a kinase inhibitor.
42. The method of claim 39, wherein the environmental perturbation comprises contacting the cells with CoQ10.

43. The method of claim 25, wherein the characteristic aspect of the disease process comprises a hypoxia condition, a hyperglycemic condition, a lactic acid rich culture condition, or combinations thereof.

44. The method of claim 25, wherein the generating step is carried out by an artificial intelligence (AI) -based informatics platform.

45. The method of claim 25, wherein the AI-based informatics platform receives all data input from the first and second data sets without applying a statistical cut-off point.

46. The method of claim 25, wherein the consensus causal relationship network established in the generating step is further refined to a simulation causal relationship network, before the identifying step, by *in silico* simulation based on input data, to provide a confidence level of prediction for one or more causal relationships within the consensus causal relationship network.

47. The method of claim 37, wherein the unique causal relationship is identified as part of a differential causal relationship network that is uniquely present in model of disease cells, and absent in the matching control cells.

48. The method of claim 38, wherein the unique causal relationship is identified as part of a differential causal relationship network that is uniquely present in cells subject to environmental perturbation, and absent in the matching control cells.

49. A method for identifying a modulator of a biological system, the method comprising:

establishing a model for the biological system, using cells associated with the biological system, to represent a characteristic aspect of the biological system ;

obtaining a first data set from the model, wherein the first data set represents global proteomic changes in the cells and one or more of lipidomic, metabolomic, transcriptomic, genomic, and SNP data characterizing the cells associated with the biological system;

obtaining a second data set from the model, wherein the second data set represents one or more functional activities or cellular responses of the cells associated

with the biological system, wherein said one or more functional activities or cellular responses of the cells comprises global kinase activity and/or an effect of the global kinase activity on the kinase metabolites or substrates in the cells associated with the biological system;

generating a consensus causal relationship network among the global proteomic changes, the one or more of lipidomic, metabolomic, transcriptomic, genomic, and SNP data, and the one or more functional activities or cellular responses based solely on the first and second data sets using a programmed computing device, wherein the generation of the consensus causal relationship network is not based on any known biological relationships other than the first and second data sets; and

identifying, from the consensus causal relationship network, a causal relationship unique in the biological system, wherein at least one kinase associated with the unique causal relationship is identified as a modulator of the biological system.

50. A method for treating, alleviating a symptom of, inhibiting progression of, preventing, diagnosing, or prognosing a disease in a mammalian subject, the method comprising:

administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a biologically active substance that affects the modulator identified by any one of claims 1-48, thereby treating, alleviating a symptom of, inhibiting progression of, preventing, diagnosing, or prognosing the disease.

51. A method of diagnosing or prognosing a disease in a mammalian subject, the method comprising:

determining an expression or activity level, in a biological sample obtained from the subject, of one or more modulators identified by any one of claims 1-48; and

comparing the level in the subject with the level of expression or activity of the one or more modulators in a control sample,

wherein a difference between the level in the subject and the level of expression or activity of the one or more modulators in the control sample is an indication that the

subject is afflicted with a disease, or predisposed to developing a disease, or responding favorably to a therapy for a disease, thereby diagnosing or prognosing the disease in the mammalian subject.

52. A method of identifying a therapeutic compound for treating, alleviating a symptom of, inhibiting progression of, or preventing a disease in a mammalian subject, the method comprising:

contacting a biological sample from a mammalian subject with a test compound;

determining the level of expression, in the biological sample, of one or more modulators identified by any one of claims 1-48;

comparing the level of expression of the one or more modulators in the biological sample with a control sample not contacted by the test compound; and

selecting the test compound that modulates the level of expression of the one or more modulators in the biological sample,

thereby identifying a therapeutic compound for treating, alleviating a symptom of, inhibiting progression of, or preventing a disease in a mammalian subject.

53. A method for treating, alleviating a symptom of, inhibiting progression of, or preventing a disease in a mammalian subject, the method comprising:

administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition comprising the therapeutic compound of claim 52, thereby treating, alleviating a symptom of, inhibiting progression of, or preventing the disease.

54. A method for treating, alleviating a symptom of, inhibiting progression of, or preventing a disease in a mammalian subject, the method comprising:

administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a biologically active substance that affects expression or activity of any one or more of TCOF1, TOP2A, CAMK2A, CDK1, CLTCL1, EIF4G1, ENO1, FBL, GSK3B, HDLBP, HIST1H2BA, HMGB2, HNRNPK,

HNRPDL, HSPA9, MAP2K2, LDHA, MAP4, MAPK1, MARCKS, NME1, NME2, PGK1, PGK2, RAB7A, RPL17, RPL28, RPS5, RPS6, SLTM, TMED4, TNRCBA, TUBB, and UBE21,

thereby treating, alleviating a symptom of, inhibiting progression of, or preventing the disease.

55. The method of claim 54, wherein the disease is hepatocellular carcinoma.

56. A method of diagnosing or prognosing a disease in a mammalian subject, the method comprising:

determining an expression or activity level, in a biological sample obtained from the subject, of any one or more proteins of TCOF1, TOP2A, CAMK2A, CDK1, CLTCL1, EIF4G1, ENO1, FBL, GSK3B, HDLBP, HIST1H2BA, HMGB2, HNRNPK, HNRPDL, HSPA9, MAP2K2, LDHA, MAP4, MAPK1, MARCKS, NME1, NME2, PGK1, PGK2, RAB7A, RPL17, RPL28, RPS5, RPS6, SLTM, TMED4, TNRCBA, TUBB, and UBE21; and

comparing the level in the subject with the level of expression or activity of the one or more proteins in a control sample,

wherein a difference between the level in the subject and the level of expression or activity of the one or more proteins in the control sample is an indication that the subject is afflicted with a disease, or predisposed to developing a disease, or responding favorably to a therapy for a disease, thereby diagnosing or prognosing the disease in the mammalian subject.

57. The method of claim 56, wherein the disease is hepatocellular carcinoma.

58. A method of identifying a therapeutic compound for treating, alleviating a symptom of, inhibiting progression of, or preventing a disease in a mammalian subject, the method comprising:

contacting a biological sample from a mammalian subject with a test compound;

determining the level of expression, in the biological sample, of any one or more proteins of TCOF1, TOP2A, CAMK2A, CDK1, CLTCL1, EIF4G1, ENO1, FBL, GSK3B, HDLBP, HIST1H2BA, HMGB2, HNRNPK, HNRPDL, HSPA9, MAP2K2, LDHA, MAP4, MAPK1, MARCKS, NME1, NME2, PGK1, PGK2, RAB7A, RPL17, RPL28, RPS5, RPS6, SLTM, TMED4, TNRCBA, TUBB, and UBE21;

comparing the level of expression of the one or more proteins in the biological sample with a control sample not contacted by the test compound; and

selecting the test compound that modulates the level of expression of the one or more proteins in the biological sample,

thereby identifying a therapeutic compound for treating, alleviating a symptom of, inhibiting progression of, or preventing a disease in a mammalian subject.

59. The method of claim 58, wherein the disease is hepatocellular carcinoma.

60. A method for treating, alleviating a symptom of, inhibiting progression of, or preventing a disease in a mammalian subject, the method comprising:

administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition comprising the therapeutic compound of claim 58, thereby treating, alleviating a symptom of, inhibiting progression of, or preventing the disease.

61. A method for identifying a modulator of angiogenesis, said method comprising:

- (1) establishing a model for angiogenesis, using cells associated with angiogenesis, to represents a characteristic aspect of angiogenesis;
- (2) obtaining a first data set from the model for angiogenesis, wherein the first data set represents one or more of genomic data, lipidomic data, proteomic data, metabolomic data, transcriptomic data, and single nucleotide polymorphism (SNP) data characterizing the cells associated with angiogenesis;
- (3) obtaining a second data set from the model for angiogenesis, wherein the second data set represents one or more functional activities or cellular responses of the

cells associated with angiogenesis;

(4) generating a consensus causal relationship network among the one or more of genomic data, lipidomic data, proteomic data, metabolic data, transcriptomic data, and single nucleotide polymorphism (SNP) data characterizing the cells associated with angiogenesis, and the one or more functional activities or cellular responses of the cells associated with angiogenesis based solely on the first data set and the second data set using a programmed computing device, wherein the generation of the consensus causal relationship network is not based on any known biological relationships other than the first data set and the second data set;

(5) identifying, from the consensus causal relationship network, a causal relationship unique in angiogenesis, wherein a gene, lipid, protein, metabolite, transcript, or SNP associated with the unique causal relationship is identified as a modulator of angiogenesis.

62. A method for identifying a modulator of angiogenesis, said method comprising:

(1) establishing a model for angiogenesis, using cells associated with angiogenesis, to represents a characteristic aspect of angiogenesis;

(2) obtaining a first data set from the model for angiogenesis, wherein the first data set represents lipidomic data;

(3) obtaining a second data set from the model for angiogenesis, wherein the second data set represents one or more functional activities or a cellular responses of the cells associated with angiogenesis;

(4) generating a consensus causal relationship network among the lipidomics data and the one or more functional activities or cellular responses based solely on the first data set and the second data set using a programmed computing device, wherein the generation of the consensus causal relationship network is not based on any known biological relationships other than the first data set and the second data set;

(5) identifying, from the consensus causal relationship network, a causal relationship unique in angiogenesis, wherein a lipid associated with the unique causal relationship is identified as a modulator of angiogenesis.

63. The method of claim 61 or 62, wherein the second data set representing one or more functional activities or cellular responses of the cells associated with angiogenesis comprises global enzymatic activity and/or an effect of the global enzymatic activity on the enzyme metabolites or substrates in the cells associated with angiogenesis.

64. A method for identifying a modulator of angiogenesis, said method comprising:

- (1) establishing a model for angiogenesis, using cells associated with angiogenesis, to represent a characteristic aspect of angiogenesis;
- (2) obtaining a first data set from the model for angiogenesis, wherein the first data set represents one or more of genomic data, lipidomic data, proteomic data, metabolic data, transcriptomic data, and single nucleotide polymorphism (SNP) data characterizing the cells associated with angiogenesis;
- (3) obtaining a second data set from the model for angiogenesis, wherein the second data set represents one or more functional activities or cellular responses of the cells associated with angiogenesis, wherein the one or more functional activities or cellular responses comprises global enzymatic activity and/or an effect of the global enzymatic activity on the enzyme metabolites or substrates in the cells associated with angiogenesis;
- (4) generating a consensus causal relationship network among the one or more of genomic data, lipidomic data, proteomic data, metabolic data, transcriptomic data, and single nucleotide polymorphism (SNP) data characterizing the cells associated with angiogenesis and the one or more functional activities or cellular responses of the cells associated with angiogenesis based solely on the first data set and the second data set using a programmed computing device, wherein the generation of the consensus causal relationship network is not based on any known biological relationships other than the first data set and the second data set;
- (5) identifying, from the consensus causal relationship network, a causal relationship unique in angiogenesis, wherein an enzyme associated with the unique causal relationship is identified as a modulator of angiogenesis.

65. The method of claim 63 or 64, wherein the global enzyme activity comprises global kinase activity and an effect of the global enzymatic activity on the enzyme metabolites or substrates in the cells associated with angiogenesis comprises the phosphoproteome of the cell.
66. The method of claim 63 or 64, wherein the global enzyme activity comprises global protease activity.
67. The method of any one of claims 61 to 66, wherein the modulator stimulates or promotes angiogenesis.
68. The method of any one of claims 61 to 66, wherein the modulator inhibits angiogenesis.
69. The method of any one of claims 61 to 68, wherein the model for angiogenesis comprising cells associated with angiogenesis is selected from the group consisting of an *in vitro* cell culture angiogenesis model, rat aorta microvessel model, newborn mouse retina model, chick chorioallantoic membrane (CAM) model, corneal angiogenic growth factor pocket model, subcutaneous sponge angiogenic growth factor implantation model, MATRIGEL® angiogenic growth factor implantation model, and tumor implantation model; and wherein the model of angiogenesis optionally further comprises a matching control model of angiogenesis comprising control cells.
70. The method of claim 69, wherein the *in vitro* culture angiogenesis model is selected from the group consisting of MATRIGEL® tube formation assay, migration assay, Boyden chamber assay, scratch assay.
71. The method of claim 69 or 70, wherein the cells associated with angiogenesis in the *in vitro* culture model are human endothelial vessel cells (HUVEC).
72. The method of claim 69, wherein the angiogenic growth factor in the corneal angiogenic growth factor pocket model, subcutaneous sponge angiogenic growth factor implantation model, or MATRIGEL® angiogenic growth factor implantation model is selected from the group consisting of FGF-2 and VEGF.
73. The method of claim 69, wherein the cells in the model of angiogenesis are subject to an environmental perturbation, and the cells in the matching model of

angiogenesis are identical cells not subject to the environmental perturbation.

74. The method of claim 73, wherein the environmental perturbation comprises one or more of a contact with an agent, a change in culture condition, an introduced genetic modification or mutation, a vehicle that causes a genetic modification or mutation, and induction of ischemia.

75. The method of claim 74, wherein the agent is a pro-angiogenic agent or an anti-angiogenic agent.

76. The method of claim 75, wherein the pro-angiogenic agent is selected from the group consisting of FGF-2 and VEGF.

77. The method of claim 75, wherein the anti-angiogenic agent is selected from the group consisting of VEGF inhibitors, integrin antagonists, angiostatin, endostatin, tumstatin, Avastin, sorafenib, sunitinib, pazopanib, and everolimus, soluble VEGF-receptor, angiopoietin 2, thrombospondin1, thrombospondin 2, vasostatin, calreticulin, prothrombin (kringle domain-2), antithrombin III fragment, vascular endothelial growth inhibitor (VEGI), Secreted Protein Acidic and Rich in Cysteine (SPARC) and a SPARC peptide corresponding to the follistatin domain of the protein (FS-E), and coenzyme Q10.

78. The method of claim 74, wherein the agent is an enzymatic activity inhibitor.

79. The method of claim 74, wherein the agent is a kinase activity inhibitor.

80. The method of claim 61 or 64, wherein the first data set comprises protein and/or mRNA expression levels of a plurality of genes in the genomic data set.

81. The method of claim 61 or 64, wherein the first data set comprises two or more of genomic data, lipidomic data, proteomic data, metabolic data, transcriptomic data, and single nucleotide polymorphism (SNP) data.

82. The method of claim 61 or 64, wherein the first data set comprises three or more of genomic data, lipidomic data, proteomic data, metabolic data, transcriptomic data, and single nucleotide polymorphism (SNP) data.

83. The method of any one of claims 61 to 64, wherein the second data set representing one or more functional activities or a cellular responses of the cells associated with angiogenesis further comprises one or more of bioenergetics, cell proliferation, apoptosis, organellar function, cell migration, tube formation, enzyme activity, chemotaxis, extracellular matrix degradation, sprouting, and a genotype-phenotype association actualized by functional models selected from ATP, ROS, OXPHOS, and Seahorse assays.
84. The method of claim 83, wherein the enzyme activity is kinase activity.
85. The method of claim 83, wherein the enzyme activity is protease activity.
86. The method of any one of claims 61 to 64, wherein step (4) is carried out by an artificial intelligence (AI) -based informatics platform.
87. The method of claim 86, wherein the AI-based informatics platform comprises REFS(TM).
88. The method of claim 86, wherein the AI-based informatics platform receives all data input from the first data set and the second data set without applying a statistical cut-off point.
89. The method of any one of claims 61 to 64, wherein the consensus causal relationship network established in step (4) is further refined to a simulation causal relationship network, before step (5), by *in silico* simulation based on input data, to provide a confidence level of prediction for one or more causal relationships within the consensus causal relationship network.
90. The method of any one of claims 61 to 64, wherein the unique causal relationship is identified as part of a differential causal relationship network that is uniquely present in cells, and absent in the matching control cells.
91. The method of any one of claims 61 to 90, wherein the unique causal relationship identified is a relationship between at least one pair selected from the group consisting of expression of a gene and level of a lipid; expression of a gene and level of a transcript; expression of a gene and level of a metabolite; expression of a first gene and expression of a second gene; expression of a gene and presence of a SNP; expression of

a gene and a functional activity; level of a lipid and level of a transcript; level of a lipid and level of a metabolite; level of a first lipid and level of a second lipid; level of a lipid and presence of a SNP; level of a lipid and a functional activity; level of a first transcript and level of a second transcript; level of a transcript and level of a metabolite; level of a transcript and presence of a SNP; level of a first transcript and level of a functional activity; level of a first metabolite and level of a second metabolite; level of a metabolite and presence of a SNP; level of a metabolite and a functional activity; presence of a first SNP and presence of a second SNP; and presence of a SNP and a functional activity.

92. The method of claim 91, wherein the functional activity is selected from the group consisting of bioenergetics, cell proliferation, apoptosis, organellar function, cell migration, tube formation, enzyme activity, chemotaxis, extracellular matrix degradation, and sprouting, , and a genotype-phenotype association actualized by functional models selected from ATP, ROS, OXPHOS, and Seahorse assays.

93. The method of claim 91 or 92, wherein the functional activity is kinase activity.

94. The method of claim 91 or 92, wherein the functional activity is protease activity.

95. The method of any one of claims 61 to 93, wherein the unique causal relationship identified is a relationship between at least a level of a lipid, expression of a gene, and one or more functional activities wherein the functional activity is a kinase activity.

96. The method of any one of claims 61 to 95, further comprising validating the identified unique causal relationship in angiogenesis.

97. A method for providing a model for angiogenesis for use in a platform method, comprising:

establishing a model for angiogenesis, using cells associated with angiogenesis, to represent a characteristic aspect of angiogenesis, wherein the model for angiogenesis is useful for generating data sets used in the platform method;

thereby providing a model for angiogenesis for use in a platform method.

98. A method for obtaining a first data set and second data set from a model for angiogenesis for use in a platform method, comprising:

(1) obtaining a first data set from the model for angiogenesis for use in a platform method, wherein the model for angiogenesis comprises cells associated with angiogenesis, and wherein the first data set represents one or more of genomic data, lipidomic data, proteomic data, metabolic data, transcriptomic data, and single nucleotide polymorphism (SNP) data characterizing the cells associated with angiogenesis;

(2) obtaining a second data set from the model for angiogenesis for use in the platform method, wherein the second data set represents one or more functional activities or cellular responses of the cells associated with angiogenesis;

thereby obtaining a first data set and second data set from the model for angiogenesis for use in a platform method.

99. A method for identifying a modulator of angiogenesis, said method comprising:

(1) generating a consensus causal relationship network among a first data set and second data set obtained from a model for angiogenesis, wherein the model comprises cells associated with angiogenesis, and wherein the first data set represents one or more of genomic data, lipidomic data, proteomic data, metabolic data, transcriptomic data, and single nucleotide polymorphism (SNP) data characterizing the cells associated with angiogenesis; and the second data set represents one or more functional activities or cellular responses of the cells associated with angiogenesis, using a programmed computing device, wherein the generation of the consensus causal relationship network is not based on any known biological relationships other than the first data set and the second data set;

(2) identifying, from the consensus causal relationship network, a causal relationship unique in angiogenesis, wherein at least one of a gene, a lipid, a protein, a metabolite, a transcript, or a SNP associated with the unique causal relationship is identified as a modulator of angiogenesis;

thereby identifying a modulator of angiogenesis.

100. A method for identifying a modulator of angiogenesis, said method comprising:

- (1) providing a consensus causal relationship network generated from a model for angiogenesis;
- (2) identifying, from the consensus causal relationship network, a causal relationship unique in angiogenesis, wherein at least one of a gene, a lipid, a protein, a metabolite, a transcript, or a SNP associated with the unique causal relationship is identified as a modulator of angiogenesis;

thereby identifying a modulator of angiogenesis.

101. The method of claim 90, wherein the consensus causal relationship network is generated among a first data set and second data set obtained from the model for angiogenesis, wherein the model comprises cells associated with angiogenesis, and wherein the first data set represents one or more of genomic data, lipidomic data, proteomic data, metabolic data, transcriptomic data, and single nucleotide polymorphism (SNP) data characterizing the cells associated with angiogenesis; and

the second data set represents one or more functional activities or cellular responses of the cells associated with angiogenesis, using a programmed computing device, wherein the generation of the consensus causal relationship network is not based on any known biological relationships other than the first data set and the second data set.

102. The method of any one of claims 97 to 101, wherein the model for angiogenesis is selected from the group consisting of *in vitro* cell culture angiogenesis model, rat aorta microvessel model, newborn mouse retina model, chick chorioallantoic membrane (CAM) model, corneal angiogenic growth factor pocket model, subcutaneous sponge angiogenic growth factor implantation model, MATRIGEL® angiogenic growth factor implantation model, and tumor implantation model; and wherein the model of angiogenesis optionally further comprises a matching control model of angiogenesis comprising control cells.

103. The method of any one of claims 97 to 102, wherein the first data set comprises lipidomics data.

104. The method of any one of claims 97 to 103, wherein the second data set representing one or more functional activities or cellular responses of the cells associated with angiogenesis comprises global enzymatic activity, and/or an effect of the global enzymatic activity on the enzyme metabolites or substrates in the cells associated with angiogenesis.

105. The method of claim 104, wherein the second data set comprises kinase activity or protease activity.

106. The method of any one of claims 97 to 103, wherein the second data set representing one or more functional activities or cellular responses of the cells associated with angiogenesis comprises one or more of bioenergetics profiling, cell proliferation, apoptosis, organellar function, cell migration, tube formation, kinase activity, and protease activity; and a genotype-phenotype association actualized by functional models selected from ATP, ROS, OXPHOS, and Seahorse assays.

107. The method of any one of claims 61 to 106, wherein the angiogenesis is related to a disease state.

108. A method for modulating angiogenesis in a mammalian subject, the method comprising:

administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a biologically active substance that affects the modulator identified by any one of claims 61-107, thereby modulating angiogenesis.

109. A method of detecting modulated angiogenesis in a mammalian subject, the method comprising:

determining a level, activity, or presence, in a biological sample obtained from the subject, of one or more modulators identified by any one of claims 61-107; and

comparing the level, activity, or presence in the subject with the level, activity, or presence of the one or more modulators in a control sample,

wherein a difference between the level, activity, or presence in the subject and the level, activity, or presence of the one or more modulators in the control sample is an

indication that angiogenesis is modulated in the mammalian subject.

110. A method of identifying a therapeutic compound for modulating angiogenesis in a mammalian subject, the method comprising:

contacting a biological sample from a mammalian subject with a test compound;

determining the level, activity or presence, in the biological sample, of one or more modulators identified by any one of claims 61-107;

comparing the level, activity, or presence of the one or more modulators in the biological sample with a control sample not contacted by the test compound; and

selecting the test compound that modulates the level, activity, or presence of the one or more modulators in the biological sample,

thereby identifying a therapeutic compound for modulating angiogenesis in a mammalian subject.

111. A method for modulating angiogenesis in a mammalian subject, the method comprising:

administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition comprising the therapeutic compound of claim 110, thereby treating, alleviating a symptom of, inhibiting progression of, preventing, diagnosing, or prognosing the disease.

CLAIMS

1. An invention not claimed in any divisional application.