CLAIMS

We claim:

1. A method for identifying a drug that causes or is at risk for causing drug-induced cardiotoxicity, comprising: comparing (i) a level of expression of one or more biomarkers present in a first cell sample obtained prior to the treatment with the drug; with (ii) a level of expression of the one or more biomarkers present in a second cell sample obtained following the treatment with the drug; wherein the one or more biomarkers is selected from the markers listed in table 2; wherein a modulation in the level of expression of the one or more biomarkers in the second sample as compared to the first sample is an indication that the drug causes or is at risk for causing drug-induced cardiotoxicity.

2. A method for identifying a rescue agent that can reduce or prevent drug-induced cardiotoxicity comprising: (i) determining a normal level of expression of one or more biomarkers present in a first cell sample obtained prior to the treatment with a cardiotoxicity inducing drug; (ii) determining a treated level of expression of the one or more biomarkers present in a second cell sample obtained following the treatment with the cardiotoxicity inducing drug to identify one or more biomarkers with a change of expression in the treated cell sample; (iii) determining the level of expression of the one or more biomarkers with a changed level of expression in the cardiotoxicity inducing drug treated sample present in a third cell sample obtained following the treatment with the cardiotoxicity inducing drug and the rescue agent; and (iv) comparing the level of expression of the one or more biomarkers determined in the third sample with the level of expression of the one or more biomarkers present in the first sample; wherein the one or more biomarkers is selected from the markers listed in table 2; and wherein a normalized level of expression of the one or more biomarkers in the third sample as compared to the first sample is an indication that the rescue agent can reduce or prevent drug-induced cardiotoxicity.

3. A method for alleviating, reducing or preventing drug-induced cardiotoxicity, comprising administering to a subject a rescue agent identified by the method of claim 2, thereby reducing or preventing drug-induced cardiotoxicity in the subject.

4. The method of any one of claims 1-3, wherein the one or more biomarkers is selected from the group consisting TIMP1, PTX3, HSP76, FINC, CYB5, PAI1, IBP7 (IGFBP7), 1C17, EDIL3, HMOX1, NUCB1, CS010, and HSPA4.

5. The method of claim 4, wherein the drug-induced cardiotoxicity is cardiomyopathy, heart failure, atrial fibrillation, cardiomyopathy and heart failure, heart failure and LV dysfunction, atrial flutter and fibrillation, or heart valve damage and heart failure.

6. The method of any one of claims 1-5, wherein the cell samples are cardiomyocytes or diabetic cardiomyocytes.

7. The method of any one of claims 1-3, wherein the drug is a cancer drug, diabetic drug, neurological drug, or anti-inflammatory drug.

8. The method of any one of claims 1-7, wherein the drug is Anthracyclines, 5-Fluorouracil, Cisplatin, Trastuzumab, Gemcitabine, Rosiglitazone, Pioglitazone, Troglitazone, Cabergoline, Pergolide, Sumatriptan, Bisphosphonates, or TNF antagonists.

9. The method of claim 3, wherein the subject is a mammal, a human, or a non-human animal.

10. The method of claim 3, wherein the rescue agent is administered to a subject that has already been treated with a cardiotoxicity-inducing drug.

11. The method of claim 3, wherein the rescue agent is administered to a subject at the same time as treatment of the subject with a cardiotoxicity-inducing drug.

12. The method of claim 3, wherein the rescue agent is administered to a subject prior to treatment of the subject with a cardiotoxicity-inducing drug.

13. The method of claim 3, wherein the rescue agent is Coenzyme Q10.

14. The method of claim 3, wherein the rescue agent is not Coenzyme Q10.

15. The method of claim 3, further comprising monitoring the subject for drug induced cardiotoxicity.

16. A method for identifying a modulator of drug-induced toxicity, said method comprising:

(1) establishing a model for drug-induced toxicity, using cells associated with drug-induced toxicity, to represents a characteristic aspect of drug-induced toxicity;

(2) obtaining a first data set from the model for drug-induced toxicity, wherein the first data set represents one or more of genomics, lipidomics, proteomics, metabolomics, transcriptomics, and single nucleotide polymorphism (SNP) data characterizing the cells associated with drug-induced toxicity;

(3) obtaining a second data set from the model for drug-induced toxicity, wherein the second data set represents a functional activity or a cellular response of the cells associated with drug-induced toxicity;

(4) generating a consensus causal relationship network among the expression levels of the one or more of genomics, lipidomics, proteomics, metabolomics, transcriptomics, and single nucleotide polymorphism (SNP) data and the functional activity or cellular response 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 drug-induced toxicity, wherein a gene, lipid, protein, metabolite, transcript, or SNP associated with the unique causal relationship is identified as a modulator of drug-induced toxicity.

17. The method of claim 16, wherein second data set representing the functional activity or cellular response of the cells comprises one or more of bioenergetics, cell proliferation, apoptosis, organellar function, a genotype-phenotype association actualized by functional models selected from ATP, ROS, OXPHOS, and Seahorse assays, global enzyme activity, and an effect of global enzyme activity on the enzyme metabolic substrates of cells associated with drug-induced toxicity.

18. The method of claim 17, wherein the global enzyme activity is global kinase activity, and wherein the effect of global enzyme activity on the enzyme metabolic substrates is the phospho proteome.

19. The method of any one of claims 1 to 3 and 16, wherein the first data set comprises two or more of genomics, lipidomics, proteomics, metabolomics, transcriptomics, and single nucleotide polymorphism (SNP) data.

20. The method of claim 16, wherein step (4) is carried out by an artificial intelligence (AI) -based informatics platform.

21. The method of claim 20, wherein the AI-based informatics platform comprises REFS(TM).

22. The method of claim 21, 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.

23. The method of claim 16, 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.

24. The method of claim 16, 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.

25. The method of claim 16, 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 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 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 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; level of a first SNP and presence of a second SNP; and presence of a SNP and a functional activity.

26. The method of claim 25, wherein the functional activity is selected from the group consisting of bioenergetics, cell proliferation, apoptosis, organellar function, kinase activity, protease activity, and a genotype-phenotype association actualized by functional models selected from ATP, ROS, OXPHOS, and Seahorse assays.

27. The method of claim 16, further comprising validating the identified unique causal relationship in drug-induced toxicity.

28. The method of claim 16, wherein the drug-induced toxicity is drug-induced cardiotoxicity, hepatotoxicity, nephrotoxicity, neurotoxicity, renaltoxicity, or myotoxicity.

29. The method of claim 28, wherein the drug-induced cardiotoxicity is cardiomyopathy, heart failure, atrial fibrillation, cardiomyopathy and heart failure, heart failure and LV dysfunction, atrial flutter and fibrillation, or, heart valve damage and heart failure.

30. The method of claim 16, wherein the model for drug-induced toxicity comprises cell cardiomyocytes, diabetic cardiomyocytes, hepatocytes, kidney cells, neuronal cells, renal cells, or myoblasts.

31. The method of claim 16, wherein the model for drug-induced toxicity comprises a toxicity inducing drug, cancer drug, diabetic drug, neurological drug, or anti-inflammatory drug.

32. The method of claim 16, wherein the drug is Anthracyclines, 5-Fluorouracil, Cisplatin, Trastuzumab, Gemcitabine, Rosiglitazone, Pioglitazone, Troglitazone, Cabergoline, Pergolide, Sumatriptan, Bisphosphonates, or TNF antagonists.

33. A method for identifying a drug that causes or is at risk for causing drug-induced toxicity, comprising: comparing (i) a level of one or more biomarkers present in a first

cell sample obtained prior to the treatment with the drug; with (ii) a level of the one or more biomarkers present in a second cell sample obtained following the treatment with the drug; wherein the one or more biomarkers is selected from the modulators identified by the methods of any one of claims 16-32; wherein a modulation in the level of the one or more biomarkers in the second sample as compared to the first sample is an indication that the drug causes or is at risk for causing drug-induced toxicity.

34. A method for identifying a rescue agent that can reduce or prevent drug-induced toxicity comprising: (i) determining a normal level of one or more biomarkers present in a first cell sample obtained prior to the treatment with a toxicity inducing drug; (ii) determining a treated level of the one or more biomarkers present in a second cell sample obtained following the treatment with the toxicity inducing drug to identify one or more biomarkers with a change of level in the treated cell sample; (iii) determining the level of the one or more biomarkers with a changed level in the toxicity inducing drug treated sample present in a third cell sample obtained following the treatment with the toxicity inducing drug and the rescue agent; and (iv) comparing the level of the one or more biomarkers determined in the third sample with the level of the one or more biomarkers present in the first sample, wherein the one or more biomarkers is selected from the modulators identified by the methods of any one of claims 16-32 and wherein a normalized level of the one or more biomarkers in the third sample as compared to the first sample is an indication that the rescue agent can reduce or prevent drug-induced toxicity.

35. A method for alleviating, reducing or preventing drug-induced toxicity, comprising administering to a subject the rescue agent of claim 34, thereby reducing or preventing drug-induced toxicity in the subject.

CLAIMS

1. A method for identifying a modulator of drug-induced toxicity, said method comprising:

(1) establishing a model for drug-induced toxicity, using cells associated with drug-induced toxicity, to represents a characteristic aspect of drug-induced toxicity;

(2) obtaining a first data set from the model for drug-induced toxicity, wherein the first data set represents one or more of genomics, lipidomics, proteomics, metabolomics, transcriptomics, and single nucleotide polymorphism (SNP) data characterizing the cells associated with drug-induced toxicity;

(3) obtaining a second data set from the model for drug-induced toxicity, wherein the second data set represents a functional activity or a cellular response of the cells associated with drug-induced toxicity;

(4) generating a consensus causal relationship network among the expression levels of the one or more of genomics, lipidomics, proteomics, metabolomics, transcriptomics, and single nucleotide polymorphism (SNP) data and the functional activity or cellular response 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 drug-induced toxicity, wherein a gene, lipid, protein, metabolite, transcript, or SNP associated with the unique causal relationship is identified as a modulator of drug-induced toxicity;

wherein step (4) is carried out by an artificial intelligence (AI) -based informatics platform;

wherein the AI-based informatics platform comprises REFS(TM); and

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.