METHODS, SYSTEMS AND COMPOSITIONS RELATING TO CELL CONVERSION VIA PROTEIN-INDUCED IN-VIVO CELL REPROGRAMMING

GRANT REFERENCE

[0001] This invention was made with government support under Grant No. 1 R01 CA172480-01A1, awarded by the National Institutes of Health/National Cancer Institute. The Government has certain rights in the invention.

FIELD OF THE INVENTION

[0002] The present invention relates generally to methods, systems and compositions for treatment of a pathological condition in a subject in need thereof. In specific aspects, the present invention relates to methods, systems and compositions for protein-induction of cell conversion in vivo for treatment of a pathological condition in a subject in need thereof.

BACKGROUND OF THE INVENTION

[0003] Despite recent medical progress, there is a continuing need for methods and compositions for treatment of disease and injury.

SUMMARY ~~OF THE INVENTION~~

[0004] Methods of treating a subject in need thereof are provided according to embodiments ~~aspects~~ of the present ~~invention~~ disclosure which include administering a pharmaceutical composition comprising a protein transduction reagent-modified reprogramming protein to the subject, wherein the protein transduction reagent is non-covalently bound to the reprogramming protein and wherein the protein transduction reagent comprises a cation reagent and a lipid.

[0004a] A pharmaceutical composition is provided according to one aspect of the present disclosure comprising a protein transduction reagent-modified reprogramming protein, wherein the protein transduction reagent is non-covalently bound to the reprogramming protein and wherein the protein transduction reagent comprises a cation reagent and a lipid for use in therapy.

[0004b] Use of a protein transduction reagent-modified reprogramming protein as disclosed above is provided according to another aspect of the present disclosure in the

manufacture of a medicament for the treatment of a condition characterized by damaged, and/or defective cells in a subject.

[0005] Methods of treating a subject in need thereof are provided according to embodimentsaspects of the present disclosure ~~invention~~ which include administering a pharmaceutical composition comprising a protein transduction reagent-modified reprogramming protein to the subject, wherein the protein transduction reagent is non-covalently bound to the reprogramming protein and wherein the protein transduction reagent comprises a cation reagent and a lipid, wherein the subject has a disease selected from the group consisting of: cancer; pancreatic disease or injury; heart disease or heart injury such as acute myocardial infarction, chronic myocardial infarction and heart failure; liver injury or liver disease such as familial hyper-cholesterolaemia (FH), Crigler-Najjar syndrome and hereditary tryosinemia I; atherosclerosis; neurological disease or injury such as spinal cord

injury, traumatic brain injury, amyotrophic lateral sclerosis, spinal muscular atrophy and Parkinson's disease; arthritis; joint disease or injury; blood disease; diabetes; obesity; muscle disease or injury; cartilage disease or injury; breast disease or injury; and vascular disease or injury.

[0006] Methods of treating a subject having a condition characterized by damaged and/or defective cells are provided according to embodiments ~~aspects~~ of the present disclosure ~~invention~~ including: administering a pharmaceutical composition including a protein transduction reagent-modified reprogramming protein to the subject, wherein the protein transduction reagent is non-covalently bound to the reprogramming protein and wherein the protein transduction reagent comprises a cation reagent and a lipid.

[0007] Methods of treating a subject having cancer including: administering a pharmaceutical composition including a protein transduction reagent-modified reprogramming protein to the subject, wherein the protein transduction reagent is non-covalently bound to the reprogramming protein and wherein the protein transduction reagent comprises a cation reagent and a lipid.

[0008] Methods of treating a subject having cancer are provided according to embodiments ~~aspects~~ of the present disclosure ~~invention~~ which include administering a pharmaceutical composition including a protein transduction reagent-modified reprogramming protein selected from the group consisting of: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog.

[0009] Methods of treating a subject having cancer are provided according to embodiments ~~aspects~~ of the present disclosure ~~invention~~ which include administering a pharmaceutical composition including protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog.

[0010] Methods of treating a subject having a brain tumor or breast cancer and are provided according to embodiments ~~aspects~~ of the present disclosure ~~invention~~ which include administering a pharmaceutical composition including a protein transduction reagent-modified reprogramming protein selected from the group consisting of: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog.

[0011] Methods of treating a subject having a brain tumor or breast cancer and are provided according to embodiments ~~aspects~~ of the present disclosure ~~invention~~ which include administering a pharmaceutical composition including protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog.

[0012] Methods of treating a subject having a condition characterized by damaged and/or defective cells are provided according to embodiments ~~aspects~~ of the present disclosure ~~invention~~ including: administering a pharmaceutical composition including a protein transduction reagent-modified reprogramming protein to the subject, wherein the protein transduction reagent is non-covalently bound to the reprogramming protein and wherein the protein transduction reagent comprises a cation reagent and a lipid, wherein the condition is a heart disease or heart damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hand2, protein transduction reagent-modified MEF2c and protein transduction reagent-modified Tbox5; wherein the condition is a liver disease or liver damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Hnf1a, protein transduction reagent-modified Foxa1, protein transduction reagent-modified Foxa2 and protein transduction reagent-modified Foxa3; wherein the condition is a liver disease or liver damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hnf1a and protein transduction reagent-modified Foxa3; wherein the condition is atherosclerosis and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified CEBPα, protein transduction reagent-modified CEBPβ and protein transduction reagent-modified PU.1; wherein the condition is a neurodegenerative disease or neuronal tissue damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Sox2 and protein transduction reagent-modified Foxg1; one or more of: protein transduction reagent-modified Ascl, protein transduction reagent-modified Lmx1a, protein transduction reagent-modified Nurr1, protein transduction reagent-modified Brn2 and protein transduction reagent-modified Mytl1; one or more of: protein transduction reagent-modified Ascl, protein transduction reagent-modified Brn2, protein transduction reagent-modified Mytl1 and protein transduction reagent-modified NeuroD1; protein transduction reagent-modified Ngn2; one or both of: protein transduction reagent-modified Sox2 and protein transduction reagent-modified NeuroD1; one or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Ascl1, protein transduction reagent-modified Mytl1, protein transduction reagent-modified Lhx3 and protein transduction reagent-modified Hb9; one or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Ascl1, protein transduction reagent-modified Mytl1, protein transduction reagent-modified Lhx3, protein transduction reagent-modified Hb9, protein transduction reagent-modified Lsl1 and protein transduction reagent-modified Ngn2; protein transduction reagent-modified Dlx2; protein

transduction reagent-modified Dlx2 and protein transduction reagent-modified Ascl1; one or more of: protein transduction reagent-modified Ascl, protein transduction reagent-modified Brn2, protein transduction reagent-modified Mytl1, protein transduction reagent-modified Lmx1a and protein transduction reagent-modified Foxa2; or one or more of: protein transduction reagent-modified Ascl, protein transduction reagent-modified Lmx1a and protein transduction reagent-modified Nurr1; wherein the condition is a disease or disorder of the blood and the pharmaceutical composition comprises: protein transduction reagent-modified Oct4; wherein the condition is diabetes, a pancreatic disease or pancreatic tissue damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified Pax4 or one or more of: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified MafA; wherein the condition is obesity and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Prdm16 and protein transduction reagent-modified C/EBPb; wherein the condition is a muscle disease or muscle damage and the pharmaceutical composition comprises protein transduction reagent-modified MyoD; wherein the condition is arthritis or joint disease or injury and the pharmaceutical composition comprises or one or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Runx2, protein transduction reagent-modified Sox5 and protein transduction reagent-modified Sox6; wherein the condition is a breast disease or breast tissue damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Slug, protein transduction reagent-modified Stat5a, protein transduction reagent-modified Gata3 and protein transduction reagent-modified Brca-1l; wherein the condition is a vascular disease or blood vessel damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Erg1, protein transduction reagent-modified Er71, protein transduction reagent-modified Fli1 and protein transduction reagent-modified Gata2 or one or more of: protein transduction reagent-modified Hey1, protein transduction reagent-modified Hey2, protein transduction reagent-modified FoxC1 and protein transduction reagent-modified FoxC2 or one or both of: protein transduction reagent-modified Sox7 and protein transduction reagent-modified Sox18.

[0012a] A pharmaceutical composition is provided according to another aspect of the present disclosure, comprising a protein transduction reagent-modified reprogramming protein.

[0013] Pharmaceutical compositions are provided according to embodiments ~~aspects~~ of the present disclosure ~~invention~~ which include one or more protein transduction reagent-reprogramming proteins selected from the group consisting of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hand2, protein transduction reagent-modified MEF2c, protein transduction

reagent-modified Tbox, protein transduction reagent-modified Hnf1a, protein transduction reagent-modified Foxa1, protein transduction reagent-modified Foxa2 and protein transduction reagent-modified Foxa3, protein transduction reagent-modified Hnf1a, protein transduction reagent-modified CEBPα, protein transduction reagent-modified CEBPβ, protein transduction reagent-modified PU.1, protein transduction reagent-modified Brn2, protein transduction reagent-modified Sox2 and protein transduction reagent-modified Foxg1, protein transduction reagent-modified Ascl, protein transduction reagent-modified Lmx1a, protein transduction reagent-modified Nurr1, protein transduction reagent-modified Mytl1, protein transduction reagent-modified NeuroD1, protein transduction reagent-modified Ngn2, protein transduction reagent-modified Lhx3, protein transduction reagent-modified Hb9, protein transduction reagent-modified Lsl1, protein transduction reagent-modified Dlx2, protein transduction reagent-modified Ascl, protein transduction reagent-modified Oct4, protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1, protein transduction reagent-modified Pax4, protein transduction reagent-modified MafA, protein transduction reagent-modified Prdm16, protein transduction reagent-modified MyoD, protein transduction reagent-modified Sox9, protein transduction reagent-modified Runx2, protein transduction reagent-modified Sox5 and protein transduction reagent-modified Sox6, protein transduction reagent-modified Slug, protein transduction reagent-modified Stat5a, protein transduction reagent-modified Gata3, protein transduction reagent-modified Brca-1l, protein transduction reagent-modified Erg1, protein transduction reagent-modified Er71, protein transduction reagent-modified Fli1, protein transduction reagent-modified Gata2,protein transduction reagent-modified Hey1, protein transduction reagent-modified Hey2, protein transduction reagent-modified FoxC1 and protein transduction reagent-modified FoxC2, protein transduction reagent-modified Sox7 and protein transduction reagent-modified Sox18.

[0014] Pharmaceutical compositions are provided according to embodiments ~~aspects~~ of the present disclosure ~~invention~~ which include two or more protein transduction reagent-modified reprogramming proteins selected from the group consisting of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hand2, protein transduction reagent-modified MEF2c and protein transduction reagent-modified Tbox5; two or more of: protein transduction reagent-modified Hnf1a, protein transduction reagent-modified Foxa1, protein transduction reagent-modified Foxa2 and protein transduction reagent-modified Foxa3; two or more of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hnf1a and protein transduction reagent-modified Foxa3; protein transduction reagent-modified CEBPα, protein

modified FoxC1 and protein transduction reagent-modified FoxC2; or protein transduction reagent-modified Sox7 and protein transduction reagent-modified Sox18.

[0015] Methods according to the present disclosure ~~invention~~ allow of delivery of protein-transduction reagent-modified reprogramming proteins to cancer cells, such as tumor cells, as well as diseased cells of diseased tissues.

[0016] Methods according to embodiments ~~aspects~~ of the present disclosure ~~invention~~ provide in vivo conversion of diseased cells into normal cells via protein-induced in situ cell reprogramming. Methods according to embodiments ~~aspects~~ of the present disclosure ~~invention~~ provide in vivo conversion of cancer cells into normal cells via protein-induced in situ cell reprogramming.

[0017] Use of protein-transduction reagent-modified reprogramming proteins to reprogram cancer cells or diseased cells in situ into stem cells or transient protein-induced multipotent stem cells that are then induced to differentiate into normal cells in the tissue where the cancer cells or diseased cells were located is provided according to embodiments ~~aspects~~ of the present disclosure~~invention~~.

[0018] Methods of treating cancer are provided according to embodiments ~~aspects~~ of the present disclosure ~~invention~~ which treat the cancer in vivo not by killing the cancer cells but instead by converting the cancer cells into non-cancerous cells by administration, such as systemic or local administration, of one or more protein transduction reagent-modified reprogramming proteins.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Figure 1A is a representative MRI image of a 9L-intracranial tumor bearing rat brain showing enhanced permeability and retention effect in a 9L brain tumor for QQ-ferritin showing that the intravenous (i.v.) injected QQ-ferritin was delivered into 9L brain tumor via enhanced permeability and retention effect, causing an enhanced negative MRI image of brain tumor in the 9L-brain tumor bearing rat;

[0020] Figure 1B is a representative MRI image of a 9L-intracranial tumor bearing rat brain showing no enhanced permeability and retention effect in a 9L brain tumor for ferritin without QQ modification showing that the i.v. injected ferritin did not reach into 9L brain tumor and no enhanced negative MRI image of brain tumor was observed in the 9L-brain tumor bearing rat;

[0021] Figure 2A is a representative MRI image of a mouse bearing a 4T1 breast tumor prior to a tail-vein injection of QQ-ferritin;

[0022] Figure 2B is a representative MRI image of a mouse bearing a 4T1 breast tumor 0.5 hours after a tail-vein injection of QQ-ferritin;

[0023] Figure 2C is a representative MRI image of a mouse bearing a 4T1 breast tumor 2

CLAIMS

1. ~~A method of treating a subject in need thereof, comprising: administering a~~ A pharmaceutical composition comprising a protein transduction reagent-modified reprogramming protein ~~to the subject~~, wherein the protein transduction reagent is non-covalently bound to the reprogramming protein and wherein the protein transduction reagent comprises a cation reagent and a lipid for use in therapy.

2. The composition ~~method~~ of claim 1, wherein the cation reagent comprises polyethylenimine.

3. Use of a protein transduction reagent-modified reprogramming protein of claim 1 or 2 in the manufacture of a medicament for the treatment of a condition characterized by damaged, and/or defective cells in a subject.

~~3. The method of claim 1 or 2, wherein the subject has a condition characterized by damaged, and/or defective cells.~~

4. The use ~~method~~ of ~~any one of~~ claim~~s 1~~-3, wherein the subject has cancer.

5. The ~~method~~ use of ~~any one of~~ claims ~~3~~1 or 4, wherein the subject has cancer and the pharmaceutical composition comprises a protein transduction reagent-modified reprogramming protein selected from the group consisting of: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog.

6. The use ~~method~~ of ~~any one of~~ claims ~~3~~1- or 4, wherein the subject has cancer and the pharmaceutical composition comprises protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog.

7. The use ~~method~~ of any one of claims ~~3~~1-5, wherein the subject has a brain tumor or breast cancer and the pharmaceutical composition comprises a protein transduction reagent-modified reprogramming protein selected from the group consisting of: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog.

8. The ~~method~~ use of ~~any one of~~ claims ~~3,1~~- 4 or 6, wherein the subject has a brain tumor or breast cancer and the pharmaceutical composition comprises protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog.

9. The ~~method~~ use of ~~any one of~~ claims 3 or ~~1~~-4, wherein the subject has a disease selected from the group consisting of: heart disease, liver disease, atherosclerosis, neurological disease, neurodegenerative disease, blood disease, diabetes, pancreatic disease obesity, muscle disease, breast disease and vascular disease.

10. The use ~~method~~ of claim 9, wherein the liver disease is selected from the group consisting of: familial hyper-cholesterolaemia (FH), Crigler-Najjar syndrome and hereditary tryosinemia I.

11. The use~~method~~ of claim 9, wherein the neurological or neurodegenerative disease is selected from the group consisting of: spinal cord injury, traumatic brain injury, amyotrophic lateral sclerosis, spinal muscular atrophy and Parkinson's.

12. The use~~method~~ of ~~any one of~~ claims 3 or ~~1~~ 4, wherein the condition is a heart disease or heart damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hand2, protein transduction reagent-modified MEF2c and protein transduction reagent-modified Tbox5; wherein the condition is a liver disease or liver damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Hnf1a, protein transduction reagent-modified Foxa1, protein transduction reagent-modified Foxa2 and protein transduction reagent-modified Foxa3; wherein the condition is a liver disease or liver damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hnf1a and protein transduction reagent-modified Foxa3; wherein the condition is atherosclerosis and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified CEBPα, protein transduction reagent-modified CEBPβ and protein transduction reagent-modified PU.1; wherein the condition is a neurodegenerative disease or neuronal tissue damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Sox2 and protein transduction reagent-modified Foxg1; one or more of: protein transduction reagent-modified Ascl, protein transduction reagent-modified Lmx1a, protein transduction reagent-modified Nurr1, protein transduction reagent-modified Brn2 and protein transduction reagent-modified Mytl1; one or more of: protein transduction reagent-modified Ascl, protein transduction reagent-modified Brn2, protein transduction reagent-modified Mytl1 and protein transduction reagent-modified NeuroD1; protein transduction reagent-modified Ngn2; one or both of: protein transduction reagent-modified Sox2 and protein transduction reagent-modified NeuroD1; one or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Ascl1, protein transduction reagent-modified Mytl1, protein transduction reagent-modified Lhx3 and protein transduction reagent-modified Hb9; one or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Ascl1, protein transduction reagent-modified Mytl1, protein transduction reagent-modified Lhx3, protein transduction reagent-modified Hb9, protein transduction reagent-modified

Lsl1 and protein transduction reagent-modified Ngn2; protein transduction reagent-modified Dlx2; protein transduction reagent-modified Dlx2 and protein transduction reagent-modified Ascl1; one or more of: protein transduction reagent-modified Asc1, protein transduction reagent-modified Brn2, protein transduction reagent-modified Mytl1, protein transduction reagent-modified Lmx1a and protein transduction reagent-modified Foxa2; or one or more of: protein transduction reagent-modified Asc1, protein transduction reagent-modified Lmx1a and protein transduction reagent-modified Nurr1; wherein the condition is a disease or disorder of the blood and the pharmaceutical composition comprises: protein transduction reagent-modified Oct4; wherein the condition is diabetes, a pancreatic disease or pancreatic tissue damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified Pax4 or one or more of: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified MafA; wherein the condition is obesity and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Prdm16 and protein transduction reagent-modified C/EBPb; wherein the condition is a muscle disease or muscle damage and the pharmaceutical composition comprises protein transduction reagent-modified MyoD; wherein the condition is arthritis or joint disease or injury and the pharmaceutical composition comprises or one or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Runx2, protein transduction reagent-modified Sox5 and protein transduction reagent-modified Sox6; wherein the condition is a breast disease or breast tissue damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Slug, protein transduction reagent-modified Stat5a, protein transduction reagent-modified Gata3 and protein transduction reagent-modified Brca-1l; wherein the condition is a vascular disease or blood vessel damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Erg1, protein transduction reagent-modified Er71, protein transduction reagent-modified Fli1 and protein transduction reagent-modified Gata2 or one or more of: protein transduction reagent-modified Hey1, protein transduction reagent-modified Hey2, protein transduction reagent-modified FoxC1 and protein transduction reagent-modified FoxC2 or one or both of: protein transduction reagent-modified Sox7 and protein transduction reagent-modified Sox18.

13. The use~~method~~ of claim 12, wherein the heart disease or heart damage is selected from the group consisting of: acute myocardial infarction, chronic myocardial infarction and heart failure.

~~14. Use of a protein transduction reagent-modified reprogramming protein to treat a disease or condition in a subject in need thereof.~~

~~15. The use of claim 13, wherein the subject has a condition characterized by damaged, and/or defective cells.~~

~~16. The use of claim 13 or 14, wherein the subject has cancer.~~

~~17. The use of any one of claims 13-16, wherein the subject has cancer and the one or more protein transduction reagent-modified reprogramming proteins comprise a reprogramming protein selected from the group consisting of: Sox2, Oct4 and Nanog.~~

~~18. The use of any one of claims 13-16, wherein the subject has cancer and the one or more protein transduction reagent-modified reprogramming proteins comprise Sox2, Oct4 and Nanog.~~

~~19. The use of any one of claims 13-17, wherein the subject has a brain tumor or breast cancer and the one or more protein transduction reagent-modified reprogramming proteins comprise a reprogramming protein selected from the group consisting of: Sox2, Oct4 and Nanog.~~

~~20. The use of any one of claims 13-16 and 18, wherein the subject has a brain tumor or breast cancer and the one or more protein transduction reagent-modified reprogramming proteins comprise Sox2, Oct4 and Nanog.~~

~~21. The use any one of claims 13-16, wherein the subject has a disease selected from the group consisting of: heart disease, liver disease, atherosclerosis, neurological disease, neurodegenerative disease, blood disease, diabetes, obesity, muscle disease, breast disease arthritis, joint disease and vascular disease.~~

~~22. The use of claim 21, wherein the liver disease is selected from the group consisting of: familial hyper-cholesterolaemia, Crigler-Najjar syndrome and hereditary tryosinemia I.~~

~~23. The use of any one of claims 13-16, wherein the condition is a heart disease or heart damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hand2, protein transduction reagent-modified MEF2c and protein transduction reagent-modified Tbox5 or one or more of: protein transduction reagent-modified Hnf1a, protein transduction reagent-modified Foxa1, protein transduction reagent-modified Foxa2 and protein transduction reagent-modified Foxa3; wherein the condition is a liver disease or liver damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hnf1a and protein transduction reagent-modified Foxa3; wherein the condition is atherosclerosis and the pharmaceutical composition comprises one or more of: protein transduction reagent-~~

modified CEBPα, protein transduction reagent-modified CEBPβ, and protein transduction reagent-modified PU.1; wherein the condition is a neurodegenerative disease or neuronal tissue damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Sox2 and protein transduction reagent-modified Foxg1; one or more of: protein transduction reagent-modified Asc1, protein transduction reagent-modified Lmx1a, protein transduction reagent-modified Nurr1, protein transduction reagent-modified Brn2 and protein transduction reagent-modified Mytl1; one or more of: protein transduction reagent-modified Asc1, protein transduction reagent-modified Brn2, protein transduction reagent-modified Mytl1 and protein transduction reagent-modified NeuroD1; protein transduction reagent-modified Ngn2; one or both of: protein transduction reagent-modified Sox2 and protein transduction reagent-modified NeuroD1; one or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Ascl1, protein transduction reagent-modified Mytl1, protein transduction reagent-modified Lhx3 and protein transduction reagent-modified Hb9; one or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Ascl1, protein transduction reagent-modified Mytl1, protein transduction reagent-modified Lhx3, protein transduction reagent-modified Hb9, protein transduction reagent-modified Lsl1 and protein transduction reagent-modified Ngn2; protein transduction reagent-modified Dlx2; protein transduction reagent-modified Dlx2 and protein transduction reagent-modified Ascl1; one or more of: protein transduction reagent-modified Asc1, protein transduction reagent-modified Brn2, protein transduction reagent-modified Mytl1, protein transduction reagent-modified Lmx1a and protein transduction reagent-modified Foxa2; or one or more of: protein transduction reagent-modified Asc1, protein transduction reagent-modified Lmx1a and protein transduction reagent-modified Nurr1; wherein the condition is a disease or disorder of the blood and the pharmaceutical composition comprises: protein transduction reagent-modified Oct4; wherein the condition is diabetes, a pancreatic disease or pancreatic tissue damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified Pax4 or one or more of: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified MafA; wherein the condition is obesity and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Prdm16 and protein transduction reagent-modified C/EBPβ; wherein the condition is a muscle disease or muscle damage and the pharmaceutical composition comprises protein transduction reagent-modified MyoD; wherein the condition is arthritis or joint disease or injury and the pharmaceutical

~~composition comprises or one or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Runx2, protein transduction reagent-modified Sox5 and protein transduction reagent-modified Sox6; wherein the condition is a breast disease or breast tissue damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Slug, protein transduction reagent-modified Stat5a, protein transduction reagent-modified Gata3 and protein transduction reagent-modified Brca 1l; wherein the condition is a vascular disease or blood vessel damage and the pharmaceutical composition comprises one or more of: protein transduction reagent-modified Erg1, protein transduction reagent-modified Er71, protein transduction reagent-modified Fli1 and protein transduction reagent-modified Gata2 or one or more of: protein transduction reagent-modified Hey1, protein transduction reagent-modified Hey2, protein transduction reagent-modified FoxC1 and protein transduction reagent-modified FoxC2 or one or both of: protein transduction reagent-modified Sox7 and protein transduction reagent-modified Sox18.~~

~~24. The use of claim 22, wherein the heart disease or heart damage is acute or chronic myocardial infarction.~~

~~25.~~14. ~~A~~ pharmaceutical composition, comprising a protein transduction reagent-modified reprogramming protein.

~~26.~~15. The pharmaceutical composition of claim 14~~25~~, wherein the pharmaceutical composition comprises one or more protein transduction reagent-modified reprogramming proteins selected from the group consisting of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hand2, protein transduction reagent-modified MEF2c, protein transduction reagent-modified Tbox, protein transduction reagent-modified Hnf1a, protein transduction reagent-modified Foxa1, protein transduction reagent-modified Foxa2 and protein transduction reagent-modified Foxa3, protein transduction reagent-modified Hnf1a, protein transduction reagent-modified CEBPα, protein transduction reagent-modified CEBPβ, protein transduction reagent-modified PU.1, protein transduction reagent-modified Brn2, protein transduction reagent-modified Sox2 and protein transduction reagent-modified Foxg1, protein transduction reagent-modified Ascl, protein transduction reagent-modified Lmx1a, protein transduction reagent-modified Nurr1, protein transduction reagent-modified Mytl1, protein transduction reagent-modified NeuroD1, protein transduction reagent-modified Ngn2, protein transduction reagent-modified Lhx3, protein transduction reagent-modified Hb9, protein transduction reagent-modified Lsl1, protein transduction reagent-modified Dlx2, protein transduction reagent-modified Asc1, protein transduction reagent-modified Oct4, protein

transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1, protein transduction reagent-modified Pax4, protein transduction reagent-modified MafA, protein transduction reagent-modified Prdm16, protein transduction reagent-modified MyoD, protein transduction reagent-modified Sox9, protein transduction reagent-modified Runx2, protein transduction reagent-modified Sox5 and protein transduction reagent-modified Sox6, protein transduction reagent-modified Slug, protein transduction reagent-modified Stat5a, protein transduction reagent-modified Gata3, protein transduction reagent-modified Brca-1l, protein transduction reagent-modified Erg1, protein transduction reagent-modified Er71, protein transduction reagent-modified Fli1, protein transduction reagent-modified Gata2,protein transduction reagent-modified Hey1, protein transduction reagent-modified Hey2, protein transduction reagent-modified FoxC1 and protein transduction reagent-modified FoxC2, protein transduction reagent-modified Sox7 and protein transduction reagent-modified Sox18.

~~27.~~16. The pharmaceutical composition of claim 14~~25~~ or 15~~26~~, wherein the pharmaceutical composition comprises two or more protein transduction reagent-modified reprogramming proteins selected from the group consisting of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hand2, protein transduction reagent-modified MEF2c and protein transduction reagent-modified Tbox5; two or more of: protein transduction reagent-modified Hnf1a, protein transduction reagent-modified Foxa1, protein transduction reagent-modified Foxa2 and protein transduction reagent-modified Foxa3; two or more of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hnf1a and protein transduction reagent-modified Foxa3; protein transduction reagent-modified CEBPα, protein transduction reagent-modified CEBPβ, and protein transduction reagent-modified PU.1; two or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Sox2 and protein transduction reagent-modified Foxg1; two or more of: protein transduction reagent-modified Ascl, protein transduction reagent-modified Lmx1a, protein transduction reagent-modified Nurr1, protein transduction reagent-modified Brn2 and protein transduction reagent-modified Mytl1; two or more of: protein transduction reagent-modified Ascl, protein transduction reagent-modified Brn2, protein transduction reagent-modified Mytl1 and protein transduction reagent-modified NeuroD1; protein transduction reagent-modified Ngn2; protein transduction reagent-modified Sox2 and protein transduction reagent-modified NeuroD1; two or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Ascl1, protein transduction reagent-modified Mytl1, protein transduction reagent-modified Lhx3 and protein transduction reagent-modified Hb9; two or more of: protein transduction reagent-modified Brn2, protein transduction

reagent-modified Ascl1, protein transduction reagent-modified Mytl1, protein transduction reagent-modified Lhx3, protein transduction reagent-modified Hb9, protein transduction reagent-modified Lsl1 and protein transduction reagent-modified Ngn2; protein transduction reagent-modified Dlx2; protein transduction reagent-modified Dlx2 and protein transduction reagent-modified Ascl1; two or more of: protein transduction reagent-modified Asc1, protein transduction reagent-modified Brn2, protein transduction reagent-modified Mytl1, protein transduction reagent-modified Lmx1a and protein transduction reagent-modified Foxa2; two or more of: protein transduction reagent-modified Asc1, protein transduction reagent-modified Lmx1a and protein transduction reagent-modified Nurr1; protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified Pax4; two or more of: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified MafA; protein transduction reagent-modified Prdm16 and protein transduction reagent-modified C/EBPβ; two or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Runx2, protein transduction reagent-modified Sox5 and protein transduction reagent-modified Sox6; two or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Slug, protein transduction reagent-modified Stat5a, protein transduction reagent-modified Gata3 and protein transduction reagent-modified Brca-1l; two or more of: protein transduction reagent-modified Erg1, protein transduction reagent-modified Er71, protein transduction reagent-modified Fli1 and protein transduction reagent-modified Gata2; two or more of: protein transduction reagent-modified Hey1, protein transduction reagent-modified Hey2, protein transduction reagent-modified FoxC1 and protein transduction reagent-modified FoxC2; or protein transduction reagent-modified Sox7 and protein transduction reagent-modified Sox18.

~~28.~~17. The protein transduction reagent-modified reprogramming protein~~method~~ of ~~any one of~~ claims 1 or 2~~-13~~ wherein the protein transduction reagent is selected from the group consisting of: QQ1a, QQ2a, QQ3a, QQ4a, QQ5a, QQ6a, QQ7a, QQ8a and QQ9a.

~~29.~~18. The use of any one of claims ~~14-24~~3-13 wherein the protein transduction reagent-modified reprogramming protein is a reprogramming protein treated with a protein transduction reagent is selected from the group consisting of: QQ1a, QQ2a, QQ3a, QQ4a, QQ5a, QQ6a, QQ7a, QQ8a and QQ9a.

~~30.~~19. The pharmaceutical composition of any one of claims ~~25-27~~14-16 wherein the protein transduction reagent-modified reprogramming protein is a reprogramming protein treated with a

protein transduction reagent is selected from the group consisting of: QQ1a, QQ2a, QQ3a, QQ4a, QQ5a, QQ6a, QQ7a, QQ8a and QQ9a.

~~31. A method of reprogramming a cell of a subject in need thereof substantially as described herein.~~

~~32. Use of a protein transduction reagent modified reprogramming protein to treat a disease or condition in a subject in need thereof substantially as described herein.~~

~~33. A pharmaceutical composition substantially as described herein.~~