[0004b] In another aspect, there is provided use of a protein transduction reagent-modified reprogramming protein in the manufacture of a medicament for the treatment of a condition characterized by damaged, and/or defective cells in a 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 cation reagent is a polyethylenimine (PEI); and wherein the lipid is selected from the group consisting of DOTMA, (N-1(-(2,3-dioleyloxy)propyl-N,N,N-trimethyl-ammonium chloride; DOGS, (dioctadecylamido-glycylspermine); DOTAP, 1,2-dioleoyl-3-trimethylammonium-propane; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; POPC, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; DMPE 1,2-dimyristoyl-sn-glycero-3-phosphocholine and combinations thereof; and

wherein the condition is selected from the group consisting of cancer, heart disease, liver disease, atherosclerosis, neurological disease, neurodegenerative disease, blood disease, diabetes, pancreatic disease, obesity, muscle disease, breast disease and vascular disease.

[0005] Methods of treating a subject in need thereof are provided according to embodiments of the present 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, 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

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 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 of the present disclosure provide in vivo conversion of diseased cells into normal cells via protein-induced in situ cell reprogramming. Methods according to embodiments of the present disclosure 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 of the present disclosure.

[0018] Methods of treating cancer are provided according to embodiments of the present disclosure 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 pharmaceutical composition comprising a protein transduction reagent-modified reprogramming protein for use in therapy, 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 cation reagent is a polyethylenimine (PEI); and wherein the lipid is selected from the group consisting of DOTMA, (N-1(-(2,3-dioleyloxy)propyl-N,N,N-trimethyl-ammonium chloride; DOGS, (dioctadecylamido-glycylspermine); DOTAP, 1,2-dioleoyl-3-trimethylammonium-propane; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; POPC, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; DMPE 1,2-dimyristoyl-sn-glycero-3-phosphocholine and combinations thereof.

2. The composition of claim 1, wherein the polyethylenimine (PEI) is selected from the group consisting of PEI Mw 1,200 (PEI 1.2K), PEI Mw 2000 (PEI 2K), PEI Mw 4000 (PEI 4K) and PEI Mw 8000 (PEI 8K).

3. Use of a protein transduction reagent-modified reprogramming protein in the manufacture of a medicament for the treatment of a condition characterized by damaged, and/or defective cells in a 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 cation reagent is a polyethylenimine (PEI); and wherein the lipid is selected from the group consisting of DOTMA, (N-1(-(2,3-dioleyloxy)propyl-N,N,N-trimethyl-ammonium chloride; DOGS, (dioctadecylamido-glycylspermine); DOTAP, 1,2-dioleoyl-3-trimethylammonium-propane; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; POPC, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; DMPE 1,2-dimyristoyl-sn-glycero-3-phosphocholine and combinations thereof; and

wherein the condition is selected from the group consisting of cancer, heart disease, liver disease, atherosclerosis, neurological disease, neurodegenerative disease, blood disease, diabetes, pancreatic disease, obesity, muscle disease, breast disease and vascular disease.

4. The use of claim 3, wherein the condition is cancer.

5. The use of claims 3 or 4, wherein the condition is cancer and the protein transduction reagent-modified reprogramming protein is 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 of claims 3 or 4, wherein the condition is cancer and the protein transduction reagent-modified reprogramming protein comprises protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog.

7. The use of any one of claims 3-5, wherein the cancer is a brain tumor or breast cancer or pancreatic cancer and the protein transduction reagent-modified reprogramming protein is selected from the group consisting of:

protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog.

8. The use of claims 3, 4 or 6, wherein the cancer is a brain tumor or breast cancer or pancreatic cancer and the protein transduction reagent-modified reprogramming protein comprises protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog.

9. The use of claim 3, wherein the condition is 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 of claim 9, wherein the heart disease is selected from the group consisting of: atherosclerosis, myocardial infarction, and chronic heart failure.

16. The use of any one of claims 3-15 wherein the protein transduction reagent-modified reprogramming protein is a reprogramming protein treated with a protein transduction reagent selected from the group consisting of: QQ1a, QQ2a, QQ3a, QQ4a, QQ5a, QQ6a, QQ7a, QQ8a and QQ9a as defined in the table below

Protein transduction reagent (QQ reagent)	PEI 1.2K	PEI 2K	PEI 4K	PEI 8K	DOTAP or DOTMA	DOPE or DOGS	POPC	DMPE
QQ1a	10-200µl	-	-	-	25-100µl	25-100µl	-	-
QQ2a	10-200µl	-	10-100µl	-	25-100µl	25-100µl	-	-
QQ3a	10-200µl	-	10-100µl	10-100µl	25-100µl	25-100µl	-	-
QQ4a	10-200µl	10-100µl	-	10-100µl	25-100µl	25-100µl	-	-
QQ5a	10-200µl	10-100µl	10-100µl	10-100µl	25-100µl	25-100µl	-	-
QQ6a	10-200µl	10-100µl	10-100µl	10-100µl	-	--	25-100µl	25-100µl
QQ7a	10-200µl	10-100µl	10-100µl	10-100µl	25-100µl	25-100µl	25-100µl	25-100µl
QQ8a	10-200µl	-	-	10-100µl	25-100µl	25-100µl	25-100µl	25-100µl
QQ9a	10-200µl	-	10-100µl	10-100µl	-	-	25-100µl	25-100µl

* PEI: polyethylenimine
DOTMA: (N-1(-(2,3-dioleyloxy)propyl-N,N,N-trimethyl-ammonium chloride;
DOGS: (dioctadecylamido-glycylspermine);
DOTAP: 1,2-dioleoyl-3-trimethylammonium-propane;
DOPE: 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine;
POPC: 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine;
DMPE: 1,2-dimyristoyl-sn-glycero-3-phosphocholine.