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(72) Inventeurs/Inventors:
WANG, JIANJUN, US;
LI, QIANQIAN, US;
CHOPP, MICHAEL, US;
JIANG, FENG, US;
WU, GUOJUN, US

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(54) Titre : PROCEDES, SYSTEMES ET COMPOSITIONS ASSOCIES A UNE CONVERSION DE CELLULES PAR L'INTERMEDIAIRE D'UNE REPROGRAMMATION CELLULAIRE IN-VIVO INDUITE PAR PROTEINES

(54) Title: METHODS, SYSTEMS AND COMPOSITIONS RELATING TO CELL CONVERSION VIA PROTEIN-INDUCED IN-VIVO CELL REPROGRAMMING

(57) Abrégé/Abstract:
Methods for treating a subject in need thereof are provided 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. According to aspects, such methods provide delivery of protein-transduction reagent- modified reprogramming proteins to cancer cells, such as tumor cells, as well as diseased cells of diseased tissues and provide in vivo conversion of diseased cells into normal cells via protein- induced in situ cell reprogramming without administration of nucleic acids to the subject.

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(74) Agent: RIDOUT & MAYBEE LLP

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(71) Applicants: **WAYNE STATE UNIVERSITY** [US/US]; 5057 Woodward, Suite 6306, Detroit, MI 48202 (US). **HENRY FORD HEALTH SYSTEM** [US/US]; 1 Ford Place, Detroit, MI 48202 (US).

(72) Inventors: **WANG, Jianjun**; 246 Candace Court, Troy, MI 48098 (US). **LI, Qianqian**; 246 Candace Court, Troy, MI 48098 (US). **CHOPP, Michael**; 28415 Brooks Lane, Southfield, MI 48034 (US). **JIANG, Feng**; 4895 Somerton Dr., Troy, MI 48085 (US). **WU, Guojun**; 17126 Orchard Ridge Road, Northville, MI 48168 (US).

(74) Agents: **STAPLE, Julie, K.** et al.; Gifford, Krass, Sprinkle, Anderson & Citkowski,P.C., 2701 Troy Center Drive, Suite 330, Post Office Box 7021, Troy, MI 48007-7021 (US).

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(54) **Title**: METHODS, SYSTEMS AND COMPOSITIONS RELATING TO CELL CONVERSION VIA PROTEIN INDUCED IN-VIVO CELL REPROGRAMMING

(57) **Abstract**: Methods for treating a subject in need thereof are provided 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. According to aspects, such methods provide delivery of protein-transduction reagent- modified reprogramming proteins to cancer cells, such as tumor cells, as well as diseased cells of diseased tissues and provide in vivo conversion of diseased cells into normal cells via protein- induced in situ cell reprogramming without administration of nucleic acids to the subject.

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

[0001]

## 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 aspects of the present 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.

[0005] Methods of treating a subject in need thereof are provided according to aspects of the present 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 aspects of the present 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 aspects of the present 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 aspects of the present 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 aspects of the present 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 aspects of the present 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 aspects of the present 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 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/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.

**[0013]** Pharmaceutical compositions are provided according to aspects of the present 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 Asc1, 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.

**[0014]** Pharmaceutical compositions are provided according to aspects of the present 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

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 Asc1, 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 Asc1, 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.

**[0015]** Methods according to the present 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 aspects of the present invention provide in vivo conversion of diseased cells into normal cells via protein-induced in situ cell reprogramming. Methods according to aspects of the present 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 aspects of the present invention.

**[0018]** Methods of treating cancer are provided according to aspects of the present 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

hours after a tail-vein injection of QQ-ferritin;

**[0024]** Figure 2D is a representative MRI image of a mouse bearing a 4T1 breast tumor 3.5 hours after a tail-vein injection of QQ-ferritin;

**[0025]** Figure 2E is a representative MRI image of a mouse bearing a 4T1 breast tumor 8 hours after a tail-vein injection of QQ-ferritin;

**[0026]** Figure 2F is a representative MRI image of a mouse bearing a 4T1 breast tumor 18 hours after a tail-vein injection of QQ-ferritin;

**[0027]** Figure 3A is a graph showing proliferation of U251 cells and U251-piPSCs monitored by Ki67 assay;

**[0028]** Figure 3B is a graph showing dose-dependent chemotherapeutic drug sensitivity of patient-derived primary human GBM (12-14) cells (squares) and GBM (12-14)-piPSCs (circles) against the alkylating agent temozolomide;

**[0029]** Figure 3C is a graph showing dose-dependent chemotherapeutic drug sensitivity of 9L-cells (squares) and 9L-piPSCs (circles) against carboplatin;

**[0030]** Figure 4A is an image showing Western blots of several epithelial and mesenchymal markers of U251 cells and U251-piPSCs, including E-cadherin (E-cad), β-catenin (β-cat), vimentin (VMT), indicating a mesenchymal-to-epithelial transition (MET) during cell reprogramming. In addition, cell reprogramming of 9L-cells into 9L-piPSCs also caused an enhanced expression of glial fibrillary acidic protein (GFAP), a marker for astrocytes;

**[0031]** Figure 4B is a graph showing that the tumorigenicity reduction of U251 cells after cell reprogramming according to aspects of the present invention is confirmed by in vitro assays for cell migration of U251-cells and U251-piPSCs, indicating significantly reduced migration of U251-piPSCs ($p < 0.01$) in vitro;

**[0032]** Figure 4C is a graph showing that the tumorigenicity reduction of U251 cells after cell reprogramming according to aspects of the present invention is confirmed by in vitro assays for invasion of U251-cells and U251-piPSCs, indicating significantly reduced invasion by U251-piPSCs ($p < 0.01$) in vitro;

**[0033]** Figure 4D is a graph showing reduced proliferation of 4T1-piPSCs and 67NR-piPSCs as compared to those properties of the parental 4T1 cells and 67NR cells, indicating a significantly reduced tumorigenicity of 4T1 cells and 67NR cells after cell reprogramming into 4T1-piPSCs and 67NR-piPSCs in vitro;

**[0034]** Figure 4E is a graph showing reduced mammary sphere formation of 4T1-piPSCs as compared to those properties of the parental 4T1 cells, indicating a significantly reduced

tumorigenicity of 4T1 cells after cell reprogramming into 4T1-piPSCs in vitro;

**[0035]** Figure 4F is a graph showing reduced migration of 4T1-piPSCs as compared to those properties of the parental 4T1 cells, indicating a significantly reduced tumorigenicity of 4T1 cells after cell reprogramming into 4T1-piPSCs in vitro;

**[0036]** Figure 4G is a graph showing reduced invasion of 4T1-piPSCs as compared to those properties of the parental 4T1 cells, indicating a significantly reduced tumorigenicity of 4T1 cells after cell reprogramming into 4T1-piPSCs in vitro;

**[0037]** Figure 5A is an image showing cell morphology of U251 cells;

**[0038]** Figure 5B is an image showing changes in cell morphology of U251 cells indirectly co-cultured with U251-piPSCs for 40-64 hours, indicative of mesenchymal-to-epithelial transition and demonstrating a bystander effect of the U251-piPSCs on U251 cells;

**[0039]** Figure 5C is a graph showing significantly reduced proliferation of U251-piPSCs and U251 cells indirectly co-cultured with U251-piPSCs at a 1:1 ratio of the U251-piPSCs and U251 cells, indicating a significantly reduced tumorigenicity of the co-cultured U251 cells and supporting the observation of a bystander effect;

**[0040]** Figure 5D is a graph showing significantly reduced migration of U251-piPSCs and U251 cells indirectly co-cultured with U251-piPSCs at 1:1 and 8:1 ratios (U251:U251-piPSCs), ($p < 0.005$), indicating a significantly reduced tumorigenicity of the co-cultured U251 cells and supporting the observation of a bystander effect;

**[0041]** Figure 5E is a graph showing significantly reduced invasion of U251-piPSCs and U251 cells indirectly co-cultured with U251-piPSCs at 1:1 and 8:1 ratios (U251:U251-piPSCs), ($p < 0.005$), indicating a significantly reduced tumorigenicity of the co-cultured U251 cells and supporting the observation of a bystander effect;

**[0042]** Figure 5F is a graph showing significantly reduced proliferation of 4T1 cells co-cultured with 4T1-piPSCs for 40 hours, indicating a significantly reduced tumorigenicity of the co-cultured 4T1 cells and supporting the observation of a bystander effect;

**[0043]** Figure 5G is a graph showing significantly reduced migration of 4T1 cells co-cultured with 4T1-piPSCs for 40 hours, indicating a significantly reduced tumorigenicity of the co-cultured 4T1 cells and supporting the observation of a bystander effect;

**[0044]** Figure 5H is a graph showing significantly reduced invasion of 4T1 cells co-cultured with 4T1-piPSCs for 40 hours, indicating a significantly reduced tumorigenicity of the co-cultured 4T1 cells and supporting the observation of a bystander effect;

**[0045]** Figure 6A is a graph showing tumor volume (mm3) in rats intracranially-implanted

with either 9L cells or 9L-piPSCs (n = 10) at day 14 and showing significantly reduced volume of the intracranial 9L-piPSC tumors as compared with those of 9L-tumors, indicating a significantly reduced tumorigenicity of 9L-cells after cell reprogramming into 9L-piPSCs in vivo;

**[0046]** Figure 6B is a graph showing tumor weight (grams) in rats subcutaneously-implanted with 9L cells and 9L-piPSCs at day 25 after implantation (n = 6) and showing significantly reduced weight of the subcutaneous 9L-piPSC tumors as compared with those of 9L-tumors, indicating a significantly reduced in vivo tumorigenicity of 9L-cells after cell reprogramming into 9L-piPSCs in vivo;

**[0047]** Figure 6C is a graph showing 4T1- and 4T1-piPSC tumor growth curve as measured using tumor volume over 25 days after 4T1- and 4T1-piPSC implantation, indicating a significant in vivo tumor stasis of 4T1 cells after cell reprogrammed into 4T1-piPSCs in vivo;

**[0048]** Figure 6D is a graph showing 4T1- and 4T1-piPSC tumor growth curve as measured using tumor weight at day 25 after 4T1- and 4T1-piPSC implantation, indicating a significant in vivo tumor stasis of 4T1 cells after cell reprogrammed into 4T1-piPSCs in vivo;

**[0049]** Figure 6E is a graph showing lung metastases in mice implanted with 4T1 cells or 4T1-piPSCs at day 25 after cell implantation, indicating a major in vivo metastasis inhibition caused by cell reprogramming of 4T1 cells into 4T1-piPSCs in vivo; the lung was divided into 200 fields and number of metastases was counted and reported in the y-axis;

**[0050]** Figure 6F is a Kaplan-Meier survival curve of mice implanted with 4T1 cells and 4T1-piPSCs in the #4 fat pads, demonstrating a significantly prolonged survival of the 4T1-piPSCs during this 250-day survival experiment, indicating that cell reprogramming of malignant cancer cells into piPSCs significantly reduces tumorigenicity and metastatic properties of the parental cancer cells;

**[0051]** Figure 7A is a graph showing dose-dependent 9L tumor growth curves measured by tumor volume in rats treated with QQ-reagent in PBS buffer (n = 10), QQ-SON proteins 1 μg/day (n = 5), QQ-SON proteins 5 μg/day (n = 5), and QQ-SON proteins 10 μg/day (n = 10) for 18 daily treatments where the treatment started at day 5 after 9L cell implantation and the rats were sacrificed at day 23;

**[0052]** Figure 7B is a graph showing 9L tumor weight in rats treated with QQ-reagent in PBS buffer (n = 10), QQ-SON proteins 1 μg/day (n = 5), QQ-SON proteins 5 μg/day (n = 5), and QQ-SON proteins 10 μg/day (n = 10) for 18 daily treatments where the treatment started at day 5 after 9L cell implantation and the rats were sacrificed at day 23;

**[0053]** Figure 7C is a Kaplan–Meier survival curve (130-days) of rats having subcutaneous

9L tumors treated with QQ-reagents in PBS (solid line, n = 6; median survival = 21 days) or QQ-SON proteins (dashed line, 10μg/day, n = 8; median survival = 127 days) for 30 daily treatments, the endpoint is when tumor volume reaches 12 $cm^3$;

**[0054]** Figure 7D is a graph showing effects of various QQ-SON protein dosages on 4T1-tumor growth monitored by tumor volume in the breast over a 25-day time course;

**[0055]** Figure 7E is a graph showing effects of various QQ-SON protein dosages on 4T1-tumor weight in the breast at day 25;

**[0056]** Figure 7F is a graph showing changes of tumor volumes at different time points, determined by MRI imaging, of 4T1-tumor bearing mice treated either with QQ-SON proteins (n = 8) or QQ-PBS as a control (n = 8), showing major tumor stasis without primary tumor removal;

**[0057]** Figure 7G is a graph showing tumor weight of 4T1-tumor bearing mice treated either with QQ-SON proteins (n = 8) or QQ-PBS as the control (n = 8) at day 35, showing major tumor stasis without primary tumor removal;

**[0058]** Figure 7H is a Kaplan-Meier survival curve of 4T1-breast cancer bearing mice treated with QQ-PBS (Control, dotted line) and QQ-SON proteins (Treatment, solid line) during a 60-day survival experiment without primary 4T1 breast cancer removed as shown in Figure 7H. The treatment started at day 5 after 4T1-cell implantation. Mice that met the endpoint, including tumor size burden, labored breath, uncontrollable pain, etc. were sacrificed;

**[0059]** Figure 7I is a graph showing the percentage of QQ-SON or QQ-PBS treated 4T1 tumor-bearing mice having metastatic lesions in the lung, without primary tumor removal, as observed by MRI at indicated days, indicating a major metastasis inhibition in the 4T1-bearing mice caused by QQ-SON protein treatment without primary tumor removal;

**[0060]** Figure 7J is a graph showing the percentage of QQ-SON or QQ-PBS treated 4T1 tumor-bearing mice having metastatic lesions in lymph nodes, without primary tumor removal, as observed by MRI at indicated days, indicating a major metastasis inhibition in the 4T1-bearing mice caused by QQ-SON protein treatment without primary tumor removal;

**[0061]** Figure 7K is a graph showing the percentage of QQ-SON or QQ-PBS treated 4T1 tumor-bearing mice having metastatic lesions in the liver, without primary tumor removal, as observed by MRI at indicated days, indicating a major metastasis inhibition in the 4T1-bearing mice caused by QQ-SON protein treatment without primary tumor removal;

**[0062]** Figure 7L is a graph showing the percentage of QQ-SON or QQ-PBS treated 4T1 tumor-bearing mice having metastatic lesions in the spleen, without primary tumor removal, as observed by MRI at indicated days, indicating a major metastasis inhibition in the 4T1-bearing

mice caused by QQ-SON protein treatment without primary tumor removal;

**[0063]** Figure 7M is a graph showing the average number per mouse of QQ-SON or QQ-PBS treated 4T1 tumor -bearing mice having metastatic lesions in the lung, without primary tumor removal, as observed by MRI at indicated days, indicating a major metastasis inhibition in the 4T1-bearing mice caused by QQ-SON protein treatment without primary tumor removal;

**[0064]** Figure 7N is a graph showing the average number per mouse of QQ-SON or QQ-PBS treated 4T1 tumor-bearing mice having metastatic lesions in the lymph nodes, without primary tumor removal, as observed by MRI at indicated days, indicating a major metastasis inhibition in the 4T1-bearing mice caused by QQ-SON protein treatment without primary tumor removal;

**[0065]** Figure 7O is a graph showing the average number per mouse of QQ-SON or QQ-PBS treated 4T1 tumor-bearing mice having metastatic lesions in the liver, without primary tumor removal, as observed by MRI at indicated days, indicating a major metastasis inhibition in the 4T1-bearing mice caused by QQ-SON protein treatment without primary tumor removal;

**[0066]** Figure 7P is a graph showing the average number per mouse of QQ-SON or QQ-PBS treated 4T1 tumor-bearing mice having metastatic lesions in the spleen, without primary tumor removal, as observed by MRI at indicated days, indicating a major metastasis inhibition in the 4T1-bearing mice caused by QQ-SON protein treatment without primary tumor removal; and

**[0067]** Figure 8 is a Kaplan-Meier survival curve (250-day survival) of 4T1-breast cancer bearing mice after surgical removal of the primary 4T1-breast cancer at day 18 and QQ-SON protein treatment started at day 6.

## DETAILED DESCRIPTION

**[0068]** Scientific and technical terms used herein are intended to have the meanings commonly understood by those of ordinary skill in the art. Such terms are found defined and used in context in various standard references illustratively including J. Sambrook and D.W. Russell, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press; 3rd Ed., 2001; F.M. Ausubel, Ed., Short Protocols in Molecular Biology, Current Protocols; 5th Ed., 2002; B. Alberts et al., Molecular Biology of the Cell, 4th Ed., Garland, 2002; D.L. Nelson and M.M. Cox, Lehninger Principles of Biochemistry, 4th Ed., W.H. Freeman & Company, 2004; Engelke, D.R., RNA Interference (RNAi): Nuts and Bolts of RNAi Technology, DNA Press LLC, Eagleville, PA, 2003; Herdewijn, P. (Ed.), Oligonucleotide Synthesis: Methods and Applications, Methods in Molecular Biology, Humana Press, 2004; A. Nagy, M. Gertsenstein, K. Vintersten, R. Behringer, Manipulating the Mouse Embryo: A Laboratory Manual, 3rd edition, Cold Spring Harbor Laboratory Press; December 15, 2002, ISBN-10: 0879695919; Kursad Turksen (Ed.), Embryonic

stem cells: methods and protocols in Methods Mol Biol. 2002;185, Humana Press; Current Protocols in Stem Cell Biology, ISBN: 9780470151808.

**[0069]** The singular terms "a," "an," and "the" are not intended to be limiting and include plural referents unless explicitly stated otherwise or the context clearly indicates otherwise.

**[0070]** Methods, systems and compositions according to aspects of the present invention provide protein-induced cell reprogramming in vivo to treat a subject in need thereof.

**[0071]** Methods, systems and compositions according to aspects of the present invention provide for conversion of diseased or injured cells into normal cells by introducing one or more QQ-modified reprogramming proteins into the diseased or injured cells in vivo without introduction of nucleic acids encoding the one or more reprogramming proteins.

**[0072]** Methods, systems and compositions according to aspects of the present invention provide for conversion of cancer cells into non-cancerous cells by introducing one or more QQ-modified reprogramming proteins into the cancer cells in vivo without introduction of nucleic acids encoding the one or more reprogramming proteins.

**[0073]** Methods of treating a subject in need thereof are provided according to aspects of the present invention which include systemically and/or locally 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.

**[0074]** Pharmaceutical compositions which include a protein transduction reagent-modified reprogramming protein are provided according to aspects of the present invention.

**[0075]** A "protein transduction reagent-modified reprogramming protein" is a reprogramming protein that has been treated with the protein transduction reagent, also termed a “QQ reagent” herein. The term “protein transduction reagent” refers to a composition effective to enable a protein non-covalently bound to the protein transduction reagent to be delivered into mammalian cells and once present in mammalian cells, to dissociate from the protein to allow proper delivery of the protein to its proper subcellular location. The protein transduction reagent, also termed a “QQ reagent” herein, includes at least one cation reagent, at least one lipid, and optionally an enhancer. The term “QQ modified reprogramming protein” and grammatical variants thereof as used herein is equivalent to “protein transduction reagent-modified reprogramming protein” and grammatical variants thereof as used herein. Similarly, one or more proteins termed “QQ” protein signifies that the proteins is modified by treatment with a protein transduction reagent and is a “protein transduction reagent-modified reprogramming protein. For example, the term “QQ-SON”

refers to a mixture of Sox2, Oct4 and Nanog proteins modified by treatment with a protein transduction reagent as described herein to produce protein transduction reagent-modified reprogramming Sox2, Oct4 and Nanog proteins.

**[0076]** One example of an appropriate cation reagent is polyethylenimine (PEI), such as, but not limited to, PEI Mw 1,200 (PEI 1.2K), PEI Mw 2000 (PEI 2K), PEI Mw 4000 (PEI 4K) and PEI Mw 8000 (PEI 8K). The lipid can be any lipid known to those of skill in the art to have the same general properties as those listed herein. Examples of such lipids include, but are not limited to, 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; and DMPE 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine.

**[0077]** Optionally, the protein transduction reagent includes polyethylenimine as a cation reagent and the lipid is DOTAP or DOTMA and DOPE or DOGS; POPC and DMPE; or DOTAP or DOTMA, DOPE or DOGS, POPC and DMPE. Optionally, the protein transduction reagent is QQ1a, QQ2a, QQ3a, QQ4a, QQ5a, QQ6a, QQ7a, QQ8a, QQ9a as described in Table 1.

**[0078]** The optional enhancer can be any enhancer that significantly enhances cell loading of cationized proteins. Examples of such enhancers in cell cultures include, but are not limited to MG132, protease inhibitor, $CaCl_2$, DMSO and growth factors. Other enhancers can also be used, including, but not limited to, cell membrane surfactants. The reagent can also include stabilizers and other inert carriers that do not affect the function of the reagent. As shown in Table 1, the concentrations and specific compounds utilized can vary.

**[0079]** The term "reprogramming protein" as used herein refers to a DNA binding transcription factor protein, or effective portion thereof, which affects transcription of a gene and which induces a change from a first differentiated cell type to a second, different, differentiated cell type. The change from a first differentiated cell type to a second, different, differentiated cell type typically proceeds through an intermediate, less differentiated, cell type, such as a transient stem cell including protein-induced pluripotent stem cells. Reprogramming proteins and nucleic acids that encode them have been isolated from humans and other species. Reprogramming proteins include, but are not limited to, Asc1, Ascl1, Brca-1l, Brn2, C/EBPα, CEBPβ , c-MYC, Dlx2, EKLF, Erg1, Er71, Fli1, Foxa1, Foxa2, Foxa3, FoxC1, FoxC2, FOXG1, FOXP3, Gata1, Gata2, Gata3, Gata4, Gata6, GFI1, Hand2, Hb9, Hey1, Hey2, HNF4A, Hnf1a, Klf4, Lhx3, LIN28A, Lmx1a, Lsl1, MafA, MEF2c, Mytl1, MYF5, MyoD, NAB2, Nanog, NeuroD1, NEUROG2, NEUROG3, Nurr1, Oct4, Pdx1, Pax4, PAX5, Pax6, Prdm16, PU.1, ROR gamma, Runx2,

SLC7A10, Slug, Sox2, Sox5, Sox6, Sox7, Sox9, Sox18, Stat5a, T-bet and Tbox5. Amino acid sequences for such reprogramming proteins are known, as exemplified by the sequences shown herein as SEQ ID NOs:1-63, along with nucleic acids encoding them shown herein as SEQ ID NOs: 65-127.

**[0080]** A reprogramming protein to be QQ-modified is obtained by methods such as isolation, synthesis, or recombinant expression of a nucleic acid encoding the reprogramming protein. Such proteins may also be obtained commercially.

**[0081]** The term "nucleic acid" refers to RNA or DNA molecules having more than one nucleotide in any form including single-stranded, double-stranded, oligonucleotide or polynucleotide. The term "nucleotide sequence" refers to the ordering of nucleotides in an oligonucleotide or polynucleotide in a single-stranded form of nucleic acid.

**[0082]** Recombinant expression of a reprogramming protein to be QQ-modified includes expression of a nucleic acid encoding the protein wherein the nucleic acid is included in an expression construct.

**[0083]** A host cell may be transfected with the expression construct encoding the desired reprogramming protein such that the reprogramming protein is expressed in the cell.

**[0084]** The terms "expression construct" and "expression cassette" are used herein to refer to a double-stranded recombinant DNA molecule containing a desired nucleic acid coding sequence for a reprogramming factor to be expressed and containing one or more regulatory elements necessary or desirable for the expression of the operably linked coding sequence.

**[0085]** Expression constructs operable to express a desired protein include, for example, in operable linkage: a promoter, a DNA sequence encoding a desired protein and a transcription termination site.

**[0086]** The term "regulatory element" as used herein refers to a nucleotide sequence which controls some aspect of the expression of nucleic acid sequences. Exemplary regulatory elements illustratively include an enhancer, an internal ribosome entry site (IRES), an intron; an origin of replication, a polyadenylation signal (polyA), a promoter, a transcription termination sequence, and an upstream regulatory domain, which contribute to the replication, transcription, post-transcriptional processing of a nucleic acid sequence. Those of ordinary skill in the art are capable of selecting and using these and other regulatory elements in an expression construct with no more than routine experimentation. Expression constructs can be generated recombinantly or synthetically using well-known methodology.

**[0087]** The term "operably linked" as used herein refers to a nucleic acid in functional relationship with a second nucleic acid.

**[0088]** A regulatory element included in an expression cassette is a promoter in particular aspects.

**[0089]** The term "promoter" is well-known in the art and refers to one or more DNA sequences operably linked to a nucleic acid sequence to be transcribed and which bind an RNA polymerase and allow for initiation of transcription. A promoter is typically positioned upstream (5') of a nucleic acid encoding a peptide or protein to be expressed.

**[0090]** An included promoter can be a constitutive promoter or can provide inducible expression. One of skill in the art is familiar with various well-known promoters and is able to select a promoter suitable for use in expressing a peptide or protein in a particular environment, such as in a specified cell type.

**[0091]** For expression in a yeast host cell, suitable promoters include, but are not limited to, an ADH1 promoter, a PGK1 promoter, an ENO promoter, a PYK1 promoter and the like; or a regulatable promoter such as a GAL1 promoter, a GAL 10 promoter, an ADH2 promoter, a PH05 promoter, a CUP1 promoter, a GAL7 promoter, a MET25 promoter, a MET3 promoter, a CYC1 promoter, a HIS 3 promoter, an ADH1 promoter, a PGK promoter, a GAPDH promoter, an ADC1 promoter, a TRP1 promoter, a URA3 promoter, a LEU2 promoter, an ENO promoter, a TP1 promoter, and AOX1.

**[0092]** For expression in a prokaryotic host cell include, suitable promoters include, but are not limited to, a bacteriophage T7 RNA polymerase promoter; a trp promoter; a lac operon promoter; a trc promoter; a tac promoter,; an araBAD promoter; an ssaG promoter; a pagC promoter, a sigma70 promoter, a dps promoter, an spv promoter, an SPI-2 promoter; an actA promoter, an rps M promoter; a tetracycline promoter, an SP6 promoter, a bacteriophage T3 promoter, a gpt promoter and a bacteriophage lambda P promoter.

**[0093]** Additional suitable bacterial and eukaryotic promoters are well-known, for example as described in Sambrook et al., Molecular Cloning, A Laboratory Manual, 2nd ed. 1989; and 3rd ed., 2001; Kriegler, Gene Transfer and Expression: A Laboratory Manual (1990); and Ausubel et al., Current Protocols in Molecular Biology, 2014.

**[0094]** For expression in an eukaryotic cell, promoters that can be included in an expression construct include, but are not limited to, cytomegalovirus immediate early promoter; herpes simplex virus thymidine kinase promoter; early and late SV40 promoters; a phosphoglycerate kinase (PGK) promoter; a promoter present in long terminal repeats from a retrovirus; and a mouse

metallothionein-I promoter, a beta-actin promoter, a ROSA26 promoter, a heat shock protein 70 (Hsp70) promoter, an EF-1 alpha gene encoding elongation factor 1 alpha (EF1) promoter, an eukaryotic initiation factor 4A (eIF-4A1) promoter, a chloramphenicol acetyltransferase (CAT) promoter and the long terminal repeat region of Rous Sarcoma virus (RSV promoter).

**[0095]** In addition to a promoter, one or more enhancer sequences may be included such as, but not limited to, cytomegalovirus (CMV) early enhancer element and an SV40 enhancer element.

**[0096]** Additional included sequences include an intron sequence such as the beta globin intron or a generic intron, a transcription termination sequence, and an mRNA polyadenylation (pA) sequence such as, but not limited to SV40-pA, beta-globin-pA and SCF-pA.

**[0097]** An expression construct may include sequences necessary for amplification in bacterial cells, such as a selection marker (e.g. kanamycin or ampicillin resistance gene) and a replicon.

**[0098]** An internal ribosome entry site (IRES) is an optionally included nucleic acid sequence that permits translation initiation at an internal site in an mRNA. IRES are well-known in the art, for example as described in Pelletier, J. et al., Nature, 334:320-325, 1988; Vagner, S. et al., EMBO Rep., 2:893-898, 2001; and Hellen, C. U. et al, Genes Dev. 15:1593-1612, 2001.

**[0099]** The term "transcription termination site" refers to a DNA sequence operable to terminate transcription by an RNA polymerase. A transcription termination site is generally positioned downstream (3') of a nucleic acid encoding a peptide or protein to be expressed.

**[00100]** A leader sequence is optionally included in an expression construct.

**[00101]** Codon optimization of a nucleic acid encoding a desired protein may be used to improve expression in a particular expression system, for example by improving the efficiency of translation. A selected nucleic acid encoding a desired protein may be codon optimized for expression in any designated host cell, prokaryotic or eukaryotic, such as, but not limited to, bacteria, insect cells, yeast, fungus, bird eggs and mammalian cells.

**[00102]** An expressed protein optionally includes an N-terminal element such as a leader sequence and/or N-terminal methionine.

**[00103]** In addition to one or more nucleic acids encoding a desired reprogramming protein, one or more nucleic acid sequences encoding additional proteins can be included in an expression vector. For example, a nucleic acid sequence encoding a reporter, including, but not limited to, beta-galactosidase, green fluorescent protein and antibiotic resistance reporters is optionally included. In a further example, a his-tag, GST-tag or MBP-tag is optionally included.

**[00104]** A nucleic acid encoding a reprogramming protein can be cloned into an expression vector for transformation into prokaryotic or eukaryotic cells and expression of the encoded peptides and/or protein(s). As used herein, "expression vectors" are defined as polynucleotides which, when introduced into an appropriate host cell, an expression system, can be transcribed and translated, producing the encoded polypeptide(s).

**[00105]** Expression vectors are known in the art and include plasmids, cosmids, viruses and bacteriophages, for example. Expression vectors can be prokaryotic vectors, insect vectors, or eukaryotic vectors, for example.

**[00106]** For example, an expression construct including, in operable linkage: a promoter, a DNA sequence encoding a desired protein and a transcription termination site, is included in a plasmid, cosmid, virus or bacteriophage expression vector.

**[00107]** Particular vectors are known in the art and one of skill in the art will recognize an appropriate vector for a specific purpose.

**[00108]** Any suitable expression vector/host cell system can be used for expression of a transcription factor for administration to a subject according to aspects of the present invention.

**[00109]** Expression of a reprogramming protein using a recombinant expression vector is accomplished by introduction of the expression vector into an eukaryotic or prokaryotic host cell expression system such as an insect cell, mammalian cell, yeast cell, fungus, bird egg, bacterial cell or any other single or multicellular organism recognized in the art.

**[00110]** Host cells containing the recombinant expression vector are maintained under conditions wherein the desired protein is produced. Host cells may be cultured and maintained using known cell culture techniques such as described in Celis, Julio, ed., 1994, Cell Biology Laboratory Handbook, Academic Press, N.Y. Various culturing conditions for these cells, including media formulations with regard to specific nutrients, oxygen, tension, carbon dioxide and reduced serum levels, can be selected and optimized by one of skill in the art.

**[00111]** Bacterial cells can be used as the host cells to produce reprogramming proteins. Recombinant protein expression in bacterial cells and purification of the produced protein may be performed using known protocols, such as described in Paulina Balbás, Argelia Lorence ed., 2004, Recombinant Gene Expression: Reviews and Protocols, Humana Press, New Jersey; Peter E. Vaillancourt, 2003, E. Coli Gene Expression Protocols, Springer Science & Business Media.

**[00112]** Optionally, recombinantly produced reprogramming proteins are purified to remove endotoxin when an endotoxin producing host cell type is used. For example, an additional washing

step can be added during protein purification stage using 10 column volume of 0.2% of Triton X114 to remove endotoxin from bacterially expressed recombinant reprogramming proteins.

**[00113]** Alternatively, in order to produce recombinant reprogramming proteins which do not trigger endotoxic response in human cells, a genetically modified bacterial strain, ClearColi™ BL21(DE3) can be used as host cells such that no endotoxin removal is required.

**[00114]** For expression in a host cell, any of the well-known procedures for introducing recombinant nucleic acids into host cells may be used, such as calcium phosphate transfection, polybrene, protoplast fusion, electroporation, sonoporation, liposomes and microinjection, examples of which are described in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, 2001; and Ausubel, F. et al., (Eds.), Current Protocols in Molecular Biology, 2014.

**[00115]** Cell free expression systems is optionally used to express a reprogramming protein, such as described in Ausubel, F. et al., (Eds.), Current Protocols in Molecular Biology, 2014.

**[0001]** Human reprogramming proteins shown herein as SEQ ID NOs: 1-63, and encoded by the nucleic acid sequences of SEQ ID NOs:65-127, and variants thereof, can be used in methods according to aspects described herein.

**[00116]** As used herein, the term "variant" refers to a variation of a nucleic acid sequence encoding a reprogramming protein or a variation of a reprogramming protein in which one or more nucleotides or amino acid residues have been modified by nucleotide or amino acid substitution, addition, or deletion while retaining the function of the reference nucleic acid sequence or reprogramming protein. Variants of a nucleic acid sequence or reprogramming protein described herein are characterized by conserved functional properties compared to the corresponding nucleic acid sequence or reprogramming protein.

**[00117]** Mutations can be introduced using standard molecular biology techniques, such as chemical synthesis, site-directed mutagenesis and PCR-mediated mutagenesis.

**[00118]** One of skill in the art will recognize that one or more amino acid mutations can be introduced without altering the functional properties of a desired reprogramming protein. For example, one or more amino acid substitutions, additions, or deletions can be made without altering the functional properties of a desired reprogramming protein.

**[00119]** Biological activity of a reprogramming protein variant is readily determined by one of skill in the art, for instance using any of the functional assays described herein or other functional assays known in the art.

**[00120]** Variants of a reprogramming protein described herein are characterized by conserved

functional properties compared to the corresponding reprogramming protein and have 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or greater identity to the amino acid sequence of a reference reprogramming protein.

**[00121]** When comparing a reference reprogramming protein to a variant, amino acid similarity may be considered in addition to identity of amino acids at corresponding positions in an amino acid sequence. "Amino acid similarity" refers to amino acid identity and conservative amino acid substitutions in a putative homologue compared to the corresponding amino acid positions in a reference protein.

**[00122]** Variants of a reprogramming protein described herein are characterized by conserved functional properties compared to the corresponding reprogramming protein and have 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or greater similarity to the amino acid sequence of a reference reprogramming protein.

**[00123]** Conservative amino acid substitutions can be made in reference proteins to produce variants.

**[00124]** Conservative amino acid substitutions are art recognized substitutions of one amino acid for another amino acid having similar characteristics. For example, each amino acid may be described as having one or more of the following characteristics: electropositive, electronegative, aliphatic, aromatic, polar, hydrophobic and hydrophilic. A conservative substitution is a substitution of one amino acid having a specified structural or functional characteristic for another amino acid having the same characteristic. Acidic amino acids include aspartate, glutamate; basic amino acids include histidine, lysine, arginine; aliphatic amino acids include isoleucine, leucine and valine; aromatic amino acids include phenylalanine, glycine, tyrosine and tryptophan; polar amino acids include aspartate, glutamate, histidine, lysine, asparagine, glutamine, arginine, serine, threonine and tyrosine; and hydrophobic amino acids include alanine, cysteine, phenylalanine, glycine, isoleucine, leucine, methionine, proline, valine and tryptophan; and conservative substitutions include substitution among amino acids within each group. Amino acids may also be described in terms of relative size, alanine, cysteine, aspartate, glycine, asparagine, proline, threonine, serine, valine, all typically considered to be small.

**[00125]** A variant can include synthetic amino acid analogs, amino acid derivatives and/or non-standard amino acids, illustratively including, without limitation, alpha-aminobutyric acid, citrulline, canavanine, cyanoalanine, diaminobutyric acid, diaminopimelic acid, dihydroxy-phenylalanine, djenkolic acid, homoarginine, hydroxyproline, norleucine, norvaline, 3-

phosphoserine, homoserine, 5-hydroxytryptophan, 1-methylhistidine, 3-methylhistidine, and ornithine.

**[00126]** Percent identity is determined by comparison of amino acid or nucleic acid sequences, including a reference amino acid or nucleic acid sequence and a putative homologue amino acid or nucleic acid sequence. To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity=number of identical overlapping positions/total number of positions X 100%). The two sequences compared are generally the same length or nearly the same length.

**[00127]** The determination of percent identity between two sequences can also be accomplished using a mathematical algorithm. Algorithms used for determination of percent identity illustratively include the algorithms of S. Karlin and S. Altshul, PNAS, 90:5873-5877, 1993; T. Smith and M. Waterman, Adv. Appl. Math. 2:482-489, 1981, S. Needleman and C. Wunsch, J. Mol. Biol., 48:443-453, 1970, W. Pearson and D. Lipman, PNAS, 85:2444-2448, 1988 and others incorporated into computerized implementations such as, but not limited to, GAP, BESTFIT, FASTA, TFASTA; and BLAST, for example incorporated in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Drive, Madison, Wis.) and publicly available from the National Center for Biotechnology Information.

**[00128]** A non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, PNAS 87:2264-2268, modified as in Karlin and Altschul, 1993, PNAS. 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al., 1990, J. Mol. Biol. 215:403. BLAST nucleotide searches are performed with the NBLAST nucleotide program parameters set, e.g., for score=100, word length=12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the present invention. BLAST protein searches are performed with the XBLAST program parameters set, e.g., to score 50, word length=3 to obtain amino acid sequences homologous to a protein molecule of the present invention. To obtain gapped alignments for comparison purposes, Gapped BLAST are utilized as described in Altschul et al., 1997, Nucleic

Acids Res. 25:3389-3402. Alternatively, PSI BLAST is used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (e.g., of XBLAST and NBLAST) are used. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11-17. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 is used.

**[00129]** The percent identity between two sequences is determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted.

**[00130]** One of skill in the art will recognize that one or more nucleic acid or amino acid mutations can be introduced without altering the functional properties of a given nucleic acid or protein, respectively.

**[00131]** As noted, human reprogramming proteins shown herein as SEQ ID NOs: 1-63, are encoded by the nucleic acid sequences of SEQ ID NOs:65-127. It is appreciated that due to the degenerate nature of the genetic code, alternate nucleic acid sequences encode a particular reprogramming protein, and that such alternate nucleic acids may be expressed to produce the desired reprogramming protein.

**[00132]** The term "complementary" refers to Watson-Crick base pairing between nucleotides and specifically refers to nucleotides hydrogen bonded to one another with thymine or uracil residues linked to adenine residues by two hydrogen bonds and cytosine and guanine residues linked by three hydrogen bonds. In general, a nucleic acid includes a nucleotide sequence described as having a "percent complementarity" to a specified second nucleotide sequence. For example, a nucleotide sequence may have 80%, 90%, or 100% complementarity to a specified second nucleotide sequence, indicating that 8 of 10, 9 of 10 or 10 of 10 nucleotides of a sequence are complementary to the specified second nucleotide sequence. For instance, the nucleotide sequence 3'-TCGA-5' is 100% complementary to the nucleotide sequence 5'-AGCT-3'. Further, the nucleotide sequence 3'-TCGA-5' is 100% complementary to a region of the nucleotide sequence 5'-TTAGCTGG-3'.

**[00133]** The terms "hybridization" and "hybridizes" refer to pairing and binding of complementary nucleic acids. Hybridization occurs to varying extents between two nucleic acids

depending on factors such as the degree of complementarity of the nucleic acids, the melting temperature, Tm, of the nucleic acids and the stringency of hybridization conditions, as is well known in the art. The term "stringency of hybridization conditions" refers to conditions of temperature, ionic strength, and composition of a hybridization medium with respect to particular common additives such as formamide and Denhardt's solution. Determination of particular hybridization conditions relating to a specified nucleic acid is routine and is well known in the art, for instance, as described in J. Sambrook and D.W. Russell, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press; 3rd Ed., 2001; and F.M. Ausubel, Ed., Short Protocols in Molecular Biology, Current Protocols; 5th Ed., 2002. High stringency hybridization conditions are those which only allow hybridization of substantially complementary nucleic acids. Typically, nucleic acids having about 85-100% complementarity are considered highly complementary and hybridize under high stringency conditions. Intermediate stringency conditions are exemplified by conditions under which nucleic acids having intermediate complementarity, about 50-84% complementarity, as well as those having a high degree of complementarity, hybridize. In contrast, low stringency hybridization conditions are those in which nucleic acids having a low degree of complementarity hybridize.

**[00134]** The terms "specific hybridization" and "specifically hybridizes" refer to hybridization of a particular nucleic acid to a target nucleic acid without substantial hybridization to nucleic acids other than the target nucleic acid in a sample.

**[00135]** Stringency of hybridization and washing conditions depends on several factors, including the Tm of the probe and target and ionic strength of the hybridization and wash conditions, as is well-known to the skilled artisan. Hybridization and conditions to achieve a desired hybridization stringency are described, for example, in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, 2001; and Ausubel, F. et al., (Eds.), Short Protocols in Molecular Biology, Wiley, 2002.

**[00136]** An example of high stringency hybridization conditions is hybridization of nucleic acids over about 100 nucleotides in length in a solution containing 6X SSC, 5X Denhardt's solution, 30% formamide, and 100 micrograms/ml denatured salmon sperm at 37°C overnight followed by washing in a solution of 0.1X SSC and 0.1% SDS at 60°C for 15 minutes. SSC is 0.15M NaCl/0.015M Na citrate. Denhardt's solution is 0.02% bovine serum albumin/0.02% FICOLL/0.02% polyvinylpyrrolidone.

**[00137]** A reprogramming protein modified by QQ is an isolated protein according to aspects of the present invention. The term "isolated protein" indicates that the protein has been separated

from biological materials, such as cells, cellular debris and other proteins, which may be present in the system in which the protein is produced. The term "isolated protein" may, but does not necessarily, indicate that the protein is purified. Purified protein included in methods and compositions of the present invention contains least about 1 – 100% of the mass, by weight, such as about 25%, 50%, 75%, 85%, 95%, 99% or greater than about 99% of the mass, by weight, of the protein included.

**[00138]** The term "subject" refers to an individual in need of treatment for a disease or injury responsive to the beneficial effects of cell reprogramming, and generally includes mammals and birds, such as, but not limited to, humans, other primates, cats, dogs, sheep, cows, goats, horses, pigs, poultry, rabbits and rodents, such as rats, mice and guinea pigs. According to aspects of the present invention, the subject is human.

**[00139]** Condition characterized by damaged, and/or defective cells.

**[00140]** The terms "treating" and "treatment" used to refer to treatment of a condition characterized by damaged, and/or defective cells such as a disease or injury of a subject include: inhibiting or ameliorating the disease or injury in the subject, such as slowing progression of the disease and/or reducing or ameliorating a sign or symptom of the disease or injury.

**[00141]** Conditions characterized by angiogenesis are treated according to aspects of methods of the present invention and are characterized by effective delivery of QQ-modified reprogramming proteins via the enhanced permeability and retention effect (EPR effect) of the angiogenic blood vessels.

**[00142]** Conditions characterized by damaged, and/or defective cells treated according to aspects of the present invention are various human conditions, including, but not limited to, cancer; cardiovascular disease or injury such as acute and chronic myocardial infarction, ischemia, heart injury, coronary artery disease, congenital heart disease, cardiomyopathies such as alcoholic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, hypertensive cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, inflammatory cardiomyopathy, ischemic cardiomyopathy, cardiomyopathy secondary to a systemic metabolic disease, myocardiodystrophy, noncompaction cardiomyopathy, restrictive cardiomyopathy, and valvular cardiomyopathy; vascular disease or blood vessel damage; anemias; ischemic and hemorrhagic stroke; metabolic diseases or conditions, such as diabetes, type I and type II, and obesity; neurological diseases and injuries such as spinal cord injury, traumatic brain injury, Huntington's disease, schizophrenia, Alzheimer's disease, amyotrophic lateral sclerosis, ataxias, autism, Lyme disease, meningitis, migraine, motor neuron diseases, movement disorders such as Parkinson's disease, neuropathy,

pain, neuropathic pain, spinal cord disorders, peripheral and central nerve disorders, autonomic nervous system disorders, seizure disorders such as epilepsy, sleep disorders, dementias such as Alzheimer's disease, muscular dystrophy, Charcot-Marie-Tooth Neuropathy Type 1A and demyelinating diseases such as acute disseminated encephalomyelitis, adrenoleukodystrophy, adrenomyeloneuropathy, multiple sclerosis, neuromyelitis optica, optic neuritis, and transverse myelitis; wounds; inflammatory conditions; liver diseases and injuries such as liver disease such as familial hyper-cholesterolaemia (FH), Crigler-Najjar syndrome, hereditary tryosinemia I, fulminant hepatic failure, viral hepatitis, drug-induced liver injury, cirrhosis, inherited hepatic insufficiency such as due to Wilson's disease, Gilbert's syndrome, or a1-antitrypsin deficiency, hepatobiliary carcinoma, autoimmune liver disease, such as autoimmune chronic hepatitis or primary biliary cirrhosis; autoimmune diseases; osteoarthritis; rheumatoid arthritis; cartilage disease or injury such as due to joint disorder, osteoarthritis, cartilage injury, traumatic rupture or detachment, achondroplasia, costochondritis, spinal disc herniation, relapsing polychonritis, tumor, chondroma, chondrosarcoma, and pleomorphic adenoma; Crohn's disease and genetic abnormalities.

**[00143]** Particular cancers treated using methods and compositions described herein are characterized by abnormal cell proliferation including, but not limited to, pre-neoplastic hyperproliferation, cancer in-situ, neoplasms and metastasis. The terms “treating” and “treatment” used to refer to treatment of a cancer in a subject include: inhibiting or ameliorating the cancer in the subject, such as slowing progression of the cancer and/or reducing or ameliorating a sign or symptom of the cancer.

**[00144]** A therapeutically effective amount of a composition including an anti-cancer composition of the present invention is an amount which has a beneficial effect in a subject being treated. In subjects having cancer, such as a condition characterized by abnormal cell proliferation including, but not limited to, pre-neoplastic hyperproliferation, cancer in-situ, neoplasms, metastasis, a tumor, a benign growth or other condition responsive to an inventive composition, a therapeutically effective amount of a QQ-modified protein is effective to ameliorate one or more signs and/or symptoms of the cancer. For example, a therapeutically effective amount of a composition is effective to detectably decrease proliferation of cells of a cancer characterized by abnormal cell proliferation including, but not limited to, pre-neoplastic hyperproliferation, cancer in-situ, neoplasms, metastasis, a tumor, a benign growth or other condition responsive to an administered QQ-modified protein.

**[00145]** Such cancers include solid and non-solid cancers such as cancer of the bladder; breast; colorectal; cervical; esophagus; head and neck; kidney; lung; cancers of the nervous system such as

glioblastoma, astrocytoma, ependymoma, neuroblastoma, retinoblastoma, meningiomas, granular cell tumors and nerve sheath tumors; ovary; pancreas; prostate; skin; stomach; testicle; throat cancer; urachus; or vagina.

**[00146]** A pharmaceutical composition according to aspects of the present invention includes a QQ-modified reprogramming protein and a pharmaceutically acceptable carrier.

**[00147]** The term "pharmaceutically acceptable carrier" as used herein refers to a carrier or diluent that is generally non-toxic to an intended recipient and which does not significantly inhibit activity of a QQ-modified protein or other active agent included in the composition.

**[00148]** A composition according to the present invention generally includes about 0.1-99% of a QQ-modified reprogramming protein.

**[00149]** Pharmaceutical compositions suitable for delivery to a subject may be prepared in various forms illustratively including physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions.

**[00150]** Pharmaceutical compositions optionally include a buffer, a solvent, or a diluent.

**[00151]** Examples of suitable aqueous and nonaqueous carriers include water, ethanol, polyols such as propylene glycol, polyethylene glycol and glycerol; vegetable oils such as olive oil; and injectable organic esters such as ethyloleate; and suitable mixtures of any two or more thereof.

**[00152]** Such formulations are administered by a suitable route including parenteral administration. Optionally, administration includes systemic or local administration.

**[00153]** These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. One or more isotonic agents is optionally included, for example, sugars and or salts such as sodium chloride.

**[00154]** In particular aspects, QQ-modified proteins are administered by topical application.

**[00155]** A topical formulation can be an ointment, lotion, cream or gel in particular aspects. Topical dosage forms such as ointment, lotion, cream or gel bases are described in Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins, 2006, p.880-882 and p.886-888; and in Allen, L. V. et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th Ed., Lippincott Williams & Wilkins, 2005, p.277-297.

**[00156]** Pharmaceutically acceptable carriers and formulation of pharmaceutical compositions are known in the art, illustratively including, but not limited to, as described in Remington: The

Science and Practice of Pharmacy, 21st Ed., Lippincott, Williams & Wilkins, Philadelphia, PA, 2006; and Allen, L.V. et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th Ed., Lippincott, Williams & Wilkins, Philadelphia, PA, 2005.

**[00157]** A pharmaceutical composition including a QQ-modified protein is suitable for administration to a subject by a variety of systemic and/or local routes including, but not limited to, parenteral, oral, rectal, nasal, pulmonary, epidural, ocular, otic, intraarterial, intracardiac, intracerebroventricular, intracranial, intradermal, intravenous, intramuscular, intraperitoneal, intraosseous, intrathecal, intratumoral, intravesical, subcutaneous, topical, transdermal, and transmucosal, such as by sublingual, buccal, vaginal, and inhalational routes of administration.

**[00158]** Administration of pharmaceutical composition

**[00159]** An inventive composition may be administered acutely or chronically. For example, a composition as described herein may be administered as a unitary dose or in multiple doses over a relatively limited period of time, such as seconds – hours. In a further embodiment, administration may include multiple doses administered over a period of days – years, such as for chronic treatment of cancer.

**[00160]** A therapeutically effective amount of a QQ-modified protein will vary depending on the route of administration and form of the composition being administered and the particular composition administered, the severity and type of condition being treated in the subject, the species of the subject, the age and sex of the subject and the general physical characteristics of the subject to be treated. One of skill in the art could determine a therapeutically effective amount in view of these and other considerations typical in medical practice without undue experimentation in view of the present disclosure and what is known in the art. In general it is contemplated that a therapeutically effective amount would be in the range of about 0.001 ng/kg – 100 mg/kg body weight, optionally in the range of about 0.01 ng/kg – 1 mg/kg, and further optionally in the range of about 0.1 ng/kg – 0.1 mg/kg. Further, dosage may be adjusted depending on whether treatment is to be acute or continuing.

**[00161]** Usually between 1 and 100 doses of a QQ-modified protein are administered to treat a subject in need thereof, although more doses can be given. A QQ-modified protein can be administered twice a day, daily, biweekly, weekly, every other week, monthly or at some other interval, for a treatment course extending one day, 1 week, 2 weeks, 4 weeks, 1 month, 2 months, 3-6 months or longer. A course of treatment is optionally repeated and may extend to chronic treatment if necessary.

**[00162]** Administration of a QQ-modified protein according to aspects of a method of the present invention includes administration according to a dosage regimen to produce a desired response. A suitable schedule for administration of doses depends on several factors including age, weight, gender, medical history and health status of the subject, type of composition used and route of administration, for example. One of skill in the art is able to readily determine a dose and schedule of administration for a particular subject.

**[00163]** Methods according to embodiments of the present invention include administration of a QQ-modified protein as a pharmaceutical formulation, such as by systemic or local administration. Exemplary routes of administration include, but are not limited to, parenteral, oral, rectal, nasal, pulmonary, epidural, ocular, otic, intraarterial, intracardiac, intracerebroventricular, intracranial, intradermal, intravenous, intramuscular, intraperitoneal, intraosseous, intrathecal, intratumoral, intravesical, subcutaneous, topical, transdermal, and transmucosal, such as by sublingual, buccal, vaginal, and inhalational routes of administration.

**[00164]** The QQ-modified protein may be administered parenterally, for example, by injection such as intravenous injection, intramuscular injection, intraperitoneal injection, subcutaneous injection, transdermal injection, intrathecal injection, intracranial injection, intracerebrospinal injection, and/or continuous infusion such as by an intravenous or intracerebrospinal continuous infusion device.

**[00165]** According to aspects, a protein transduction reagent-modified reprogramming protein is a DNA binding transcription factor. Administration of a protein transduction reagent-modified reprogramming protein is effective to reprogram one or more cell types in situ at the site of disease or damage to treat the disease or damage in vivo according to aspects described herein. Administration of a protein transduction reagent-modified reprogramming protein is effective to reprogram one or more cell types in situ at the site of disease or damage, generating transient stem cells which then differentiate into normal cells in situ at the site of disease or damage in vivo to treat the disease or damage according to aspects described herein.

**[00166]** Methods of treating cancer according to aspects of the present invention include administering one or more of: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog. Methods of treating cancer according to aspects of the present invention include administering two or more of: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog. Methods of treating cancer according to aspects of the present invention include administering: protein transduction reagent-modified Sox2, protein

transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog. Such methods produce new normal cells at the site of the cancer by reprogramming cancer cells at the site.

**[00167]** Methods of treating brain tumor according to aspects of the present invention include administering one or more of: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog. Methods of treating brain tumor according to aspects of the present invention include administering two or more of: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog. Methods of treating brain tumor according to aspects of the present invention include administering: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog. Such methods produce new normal cells at the site of the brain tumor by reprogramming brain tumor cells at the site.

**[00168]** Methods of treating brain tumor according to aspects of the present invention including administrating one or more of: protein transduction reagent-modified Sox2 and protein transduction reagent-modified NeuroD. Methods of treating pancreatic cancer according to aspects of the present invention including administrating: protein transduction reagent-modified Sox2 and protein transduction reagent-modified NeuroD. Such methods produce new normal cells at the site of pancreatic cancer by reprogramming brain tumor cells at the site.

**[00169]** Methods of treating breast cancer according to aspects of the present invention include administering one or more of: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog. Methods of treating breast cancer according to aspects of the present invention include administering two or more of: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog. Methods of treating breast cancer according to aspects of the present invention include administering: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog. Such methods produce new normal cells at the site of the breast cancer by reprogramming breast cancer cells at the site.

**[00170]** Methods of treating breast cancer according to aspects of the present invention including administrating one or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Slug, protein transduction reagent-modified Gata3, protein transduction reagent-modified Brca-1 and protein transduction reagent-modified State5a. Methods

of treating breast cancer according to aspects of the present invention including administrating two or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Slug, protein transduction reagent-modified Gata3, protein transduction reagent-modified Brca-1 and protein transduction reagent-modified State5a. Methods of treating breast cancer according to aspects of the present invention including administrating three or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Slug, protein transduction reagent-modified Gata3, protein transduction reagent-modified Brca-1 and protein transduction reagent-modified State5a. Methods of treating breast cancer according to aspects of the present invention including administrating four or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Slug, protein transduction reagent-modified Gata3, protein transduction reagent-modified Brca-1 and protein transduction reagent-modified State5a. Methods of treating breast cancer according to aspects of the present invention including administrating: protein transduction reagent-modified Sox9, protein transduction reagent-modified Slug, protein transduction reagent-modified Gata3, protein transduction reagent-modified Brca-1 and protein transduction reagent-modified State5a. Such methods produce new normal cells at the site of breast cancer by reprogramming breast cancer cells at the site.

**[00171]** Methods of treating pancreatic cancer according to aspects of the present invention including administrating one or more of: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog. Methods of treating pancreatic cancer according to aspects of the present invention including administrating two or more of: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog. Methods of treating pancreatic cancer according to aspects of the present invention including administrating: protein transduction reagent-modified Sox2, protein transduction reagent-modified Oct4 and protein transduction reagent-modified Nanog. Such methods produce new normal cells at the site of pancreatic cancer by reprogramming pancreatic cancer cells at the site.

**[00172]** Methods of treating pancreatic cancer according to aspects of the present invention including administrating one or more of: protein transduction reagent-modified PDX1, protein transduction reagent-modified PAX4, protein transduction reagent-modified MafA and protein transduction reagent-modified Ngn3. Methods of treating pancreatic cancer according to aspects of the present invention including administrating two or more of: protein transduction reagent-modified PDX1, protein transduction reagent-modified PAX4, protein transduction reagent-modified MafA and protein transduction reagent-modified Ngn3. Methods of treating pancreatic

cancer according to aspects of the present invention including administrating three or more of: protein transduction reagent-modified PDX1, protein transduction reagent-modified PAX4, protein transduction reagent-modified MafA and protein transduction reagent-modified Ngn3. Methods of treating pancreatic cancer according to aspects of the present invention including administrating: protein transduction reagent-modified PDX1, protein transduction reagent-modified PAX4, protein transduction reagent-modified MafA and protein transduction reagent-modified Ngn3. Such methods produce new normal cells at the site of pancreatic cancer by reprogramming pancreatic cancer cells at the site.

**[00173]** Methods of treating a heart disease or heart damage, such as damage due to acute or chronic myocardial infarction, according to aspects of the present invention include administering 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. Methods of treating a heart disease or heart damage according to aspects of the present invention include administering two or more of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hand2, protein transduction reagent-modified MEF2c and protein transduction reagent-modified Tbox5. Methods of treating a heart disease or heart damage according to aspects of the present invention include administering three or more of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hand2, protein transduction reagent-modified MEF2c and protein transduction reagent-modified Tbox5. Methods of treating a heart disease or heart damage according to aspects of the present invention include administering: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hand2, protein transduction reagent-modified MEF2c and protein transduction reagent-modified Tbox5. Such methods produce new cardiomyocytes, smooth muscle cells and endothelial cells at the site of the disease or damage by reprogramming fibroblasts at the site.

**[00174]** Methods of treating a liver disease or liver damage according to aspects of the present invention include administering one or more of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hnf1a and protein transduction reagent-modified Foxa3. Methods of treating a liver disease or liver damage according to aspects of the present invention include administering two or more of: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hnf1a and protein transduction reagent-modified Foxa3. Methods of treating a liver disease or liver damage according to aspects of the present invention include administering: protein transduction reagent-modified Gata4, protein transduction reagent-modified Hnf1a and protein transduction reagent-modified Foxa3. Such methods produce new hepatocytes

at the site of the disease or damage by reprogramming fibroblasts at the site. Examples of such liver disease or liver damage include familial hyper-cholesterolaemia (FH), Crigler-Najjar syndrome and hereditary tryosinaemica I.

**[00175]** Methods of treating a liver disease or liver damage according to aspects of the present invention include administering 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. Methods of treating a liver disease or liver damage according to aspects of the present invention include administering 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. Methods of treating a liver disease or liver damage according to aspects of the present invention include administering: protein transduction reagent-modified Hnf1a, protein transduction reagent-modified Foxa1, protein transduction reagent-modified Foxa2 and protein transduction reagent-modified Foxa3. Such methods produce new hepatocytes at the site of the disease or damage by reprogramming fibroblasts at the site. Examples of such liver disease or liver damage include familial hyper-cholesterolaemia (FH), Crigler-Najjar syndrome and hereditary tryosinaemica I.

**[00176]** Methods of treating atherosclerosis according to aspects of the present invention include administering one or more of: protein transduction reagent-modified CEBP/α/β and protein transduction reagent-modified PU.1. Methods of treating atherosclerosis according to aspects of the present invention include administering both of: CEBP/α/β and protein transduction reagent-modified PU.1. Such methods produce new foam cells and macrophages at the site of the atherosclosis by reprogramming fibroblasts at the site.

**[00177]** Methods of treating a neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering one or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Sox2 and protein transduction reagent-modified Foxg1. Methods of treating a neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering two or more of: protein transduction reagent-modified Brn2, protein transduction reagent-modified Sox2 and protein transduction reagent-modified Foxg1. Methods of treating neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering: protein transduction reagent-modified Brn2, protein transduction reagent-modified Sox2 and protein transduction reagent-modified Foxg1. Such methods produce new neurons at the site of the disease or damage by reprogramming fibroblasts at the site.

**[00178]** Methods of treating a neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering 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. Methods of treating neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering 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. Methods of treating neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering three 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. Methods of treating neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering four 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. Methods of treating neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering: 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. Such methods produce new glutamatergic neurons at the site of the disease or damage by reprogramming fibroblasts at the site.

**[00179]** Methods of treating a neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering 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. Methods of treating neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering 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. Methods of treating neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering three or more of: protein transduction reagent-modified Ascl, protein transduction reagent-modified Brn2, protein transduction reagent-modified Mytl1 and protein transduction reagent-modified NeuroD1.

Methods of treating neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering: protein transduction reagent-modified Asc1, protein transduction reagent-modified Brn2 , protein transduction reagent-modified Mytl1 and protein transduction reagent-modified NeuroD1. Such methods produce new glutamatergic neurons at the site of the disease or damage by reprogramming fibroblasts at the site.

**[00180]** Methods of treating a neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering: protein transduction reagent-modified Ngn2. Such methods produce new glutamatergic neurons at the site of the disease or damage by reprogramming astrocytes at the site.

**[00181]** Methods of treating a neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering one or more of: protein transduction reagent-modified Sox2 and protein transduction reagent-modified NeuroD1. Methods of treating neurodegenerative disease or neuronal tissue damage according to aspects of the present invention include administering: protein transduction reagent-modified Sox2 and protein transduction reagent-modified NeuroD1. Such methods produce new neural stem cells at the site of the disease or damage.

**[00182]** Methods of treating a neurological disease or neuronal tissue damage according to aspects of the present invention include administering 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering three 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering four 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the

present invention include administering: 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. Such methods produce new motor neurons at the site of the disease or damage by reprogramming fibroblasts at the site. Examples of such neurological diseases include amyotrophic lateral sclerosis (ALS).

**[00183]** Methods of treating a neurological disease or neuronal tissue damage according to aspects of the present invention include administering 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering three 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering four 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering five 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering six 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering: 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. Such methods produce new motor neurons at the site of the disease or damage by reprogramming fibroblasts at the site. Examples of such neurological diseases include amyotrophic lateral sclerosis (ALS).

**[00184]** Methods of treating a neurological disease or neuronal tissue damage according to aspects of the present invention include administering: protein transduction reagent-modified. Such methods produce new GABA neurons at the site of the disease or damage by reprogramming fibroblasts at the site. Examples of such neurological diseases include spinal muscular atrophy (SMA).

**[00185]** Methods of treating a neurological disease or neuronal tissue damage according to aspects of the present invention include administering: protein transduction reagent-modified Dlx2. Such methods produce new GABA neurons at the site of the disease or damage by reprogramming fibroblasts at the site. Examples of such neurological diseases include amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA) and Parkinson's disease.

**[00186]** Methods of treating a neurological disease or neuronal tissue damage according to aspects of the present invention include administering: protein transduction reagent-modified Dlx2 and protein transduction reagent-modified Ascl1. Such methods produce new GABA neurons at the site of the disease or damage by reprogramming astrocytes at the site. Examples of such neurological diseases include spinal muscular atrophy (SMA).

**[00187]** Methods of treating a neurological disease or neuronal tissue damage according to aspects of the present invention include administering 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the

present invention include administering three 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering four 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. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering: 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. Such methods produce new dopamine neurons at the site of the disease or damage by reprogramming fibroblasts at the site. Examples of such neurological diseases include Parkinson's disease.

**[00188]** Methods of treating a neurological disease or neuronal tissue damage according to aspects of the present invention include administering one or more of: protein transduction reagent-modified Ascl, protein transduction reagent-modified Lmx1a and protein transduction reagent-modified Nurr1. Methods of treating a neurological disease or neuronal tissue damage according to aspects of the present invention include administering two or more of: protein transduction reagent-modified Ascl, protein transduction reagent-modified Lmx1a and protein transduction reagent-modified Nurr1. Methods of treating neurological disease or neuronal tissue damage according to aspects of the present invention include administering: protein transduction reagent-modified Ascl, protein transduction reagent-modified Lmx1a and protein transduction reagent-modified Nurr1. Such methods produce new neurons at the site of the disease or damage by reprogramming fibroblasts at the site. Examples of such neurological diseases include Parkinson's disease.

**[00189]** Methods of treating a disease or disorder of the blood according to aspects of the present invention include administering: protein transduction reagent-modified Oct4. Such methods produce new hematopoietic cells at the site of the disease or damage by reprogramming fibroblasts at the site.

**[00190]** Methods of treating diabetes, a pancreatic disease or pancreatic tissue damage according to aspects of the present invention include administering one or more of: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified Pax4. Methods of treating diabetes, a pancreatic disease or

pancreatic tissue damage according to aspects of the present invention include administering two or more of: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified Pax4. Methods of treating diabetes, a pancreatic disease or pancreatic tissue damage according to aspects of the present invention include administering: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified Pax4. Such methods produce new pancreatic beta-cells at the site of the disease or damage by reprogramming fibroblasts at the site.

**[00191]** Methods of treating diabetes, a pancreatic disease or pancreatic tissue damage according to aspects of the present invention include administering one or more of: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified MafA. Methods of treating diabetes, a pancreatic disease or pancreatic tissue damage according to aspects of the present invention include administering two or more of: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified MafA. Methods of treating diabetes, a pancreatic disease or pancreatic tissue damage according to aspects of the present invention include administering: protein transduction reagent-modified Ngn3, protein transduction reagent-modified Pdx1 and protein transduction reagent-modified MafA. Such methods produce new pancreatic beta-cells at the site of the disease or damage by reprogramming pancreatic exocrine cells at the site.

**[00192]** Methods of treating obesity according to aspects of the present invention include administering one or both of: protein transduction reagent-modified Prdm16 and protein transduction reagent-modified C/EBPb. Methods of treating obesity according to aspects of the present invention include administering both: protein transduction reagent-modified Prdm16 and protein transduction reagent-modified C/EBPb. Such methods produce new brown adipocytes at the site of the disease or damage by reprogramming white adipocytes at the site.

**[00193]** Methods of treating a muscle disease or muscle damage according to aspects of the present invention include administering: protein transduction reagent-modified MyoD. Such methods produce new muscle cells at the site of the disease or damage by reprogramming fibroblasts at the site.

**[00194]** Methods of treating arthritis, osteoarthritis, cartilage degeneration and/or cartilage injury according to aspects of the present invention include administering 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. Methods of

treating arthritis, osteoarthritis, cartilage degeneration and/or cartilage injury according to aspects of the present invention include administering 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. Methods of treating arthritis, osteoarthritis, cartilage degeneration and/or cartilage injury according to aspects of the present invention include administering three or more of: protein transduction reagent-modified Sox9, protein transduction reagent-modified Runx2, protein transduction reagent-modified Sox5 and protein transduction reagent-modified Sox6. Methods of treating arthritis, osteoarthritis, cartilage degeneration and/or cartilage injury according to aspects of the present invention include administering: protein transduction reagent-modified Sox9, protein transduction reagent-modified Runx2, protein transduction reagent-modified Sox5 and protein transduction reagent-modified Sox6. Such methods produce new chondrocytes at the site of the disease or damage by reprogramming fibroblasts at the site.

**[00195]** Methods of treating a breast disease or breast tissue damage according to aspects of the present invention include administering 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-1. Methods of treating a breast disease or breast tissue damage according to aspects of the present invention include administering protein transduction reagent-modified Brca-1. Methods of treating a breast disease or breast tissue damage according to aspects of the present invention include administering 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-1. Methods of treating a breast disease or breast tissue damage according to aspects of the present invention include administering both: protein transduction reagent-modified Sox9 and protein transduction reagent-modified Slug. Methods of treating a breast disease or breast tissue damage according to aspects of the present invention include administering both: protein transduction reagent-modified Stat5a and protein transduction reagent-modified Gata3. Methods of treating a breast disease or breast tissue damage according to aspects of the present invention include administering three 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-1. Methods of treating a breast disease or breast tissue damage according to aspects of the present invention include administering four 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-1. Methods of treating a breast disease or breast tissue damage according to aspects of the present invention include administering: 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-1. Such methods produce new mammary duct cells at the site of the disease or damage by reprogramming fibroblasts at the site.

**[00196]** Methods of treating a vascular disease or blood vessel damage according to aspects of the present invention include administering 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. Methods of treating a vascular disease or blood vessel damage according to aspects of the present invention include administering 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. Methods of treating a vascular disease or blood vessel damage according to aspects of the present invention include administering three or more of: protein transduction reagent-modified Erg1, protein transduction reagent-modified Er71, protein transduction reagent-modified Fli1 and protein transduction reagent-modified Gata2. Methods of treating a vascular disease or blood vessel damage according to aspects of the present invention include administering: protein transduction reagent-modified Erg1, protein transduction reagent-modified Er71, protein transduction reagent-modified Fli1 and protein transduction reagent-modified Gata2. Such methods produce new endothelial cells at the site of the disease or damage by reprogramming cells at the site.

**[00197]** Methods of treating a vascular disease or blood vessel damage according to aspects of the present invention include administering 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. Methods of treating a vascular disease or blood vessel damage according to aspects of the present invention include administering 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. Methods of treating a vascular disease or blood vessel damage according to aspects of the present invention include administering three or more of: protein transduction reagent-modified Hey1, protein transduction reagent-modified Hey2, protein transduction reagent-modified FoxC1 and protein

transduction reagent-modified FoxC2. Methods of treating a vascular disease or blood vessel damage according to aspects of the present invention include administering: protein transduction reagent-modified Hey1, protein transduction reagent-modified Hey2, protein transduction reagent-modified FoxC1 and protein transduction reagent-modified FoxC2. Such methods produce new arterial endothelial cells at the site of the disease or damage by reprogramming cells at the site.

**[00198]** Methods of treating a vascular disease or blood vessel damage according to aspects of the present invention include administering one or both of: protein transduction reagent-modified Sox7 and protein transduction reagent-modified Sox18. Methods of treating a vascular disease or blood vessel damage according to aspects of the present invention include administering both: protein transduction reagent-modified Sox7 and protein transduction reagent-modified Sox18. Such methods produce new venous endothelial cells at the site of the disease or damage by reprogramming cells at the site.

**[00199]** Combination Treatments

**[00200]** Combinations of therapeutic agents are administered according to aspects of the present invention.

**[00201]** In some aspects, two or more QQ-modified proteins are administered to a subject to treat a disorder in a subject in need thereof.

**[00202]** In further aspects, at least one QQ-modified protein and at least one additional therapeutic agent are administered to a subject to treat a disorder in a subject in need thereof.

**[00203]** In still further aspects, at least one QQ-modified protein and at least two additional therapeutic agents are administered to a subject to treat a disorder in a subject in need thereof.

**[00204]** In some aspects, two or more QQ-modified proteins are administered to a subject to treat cancer in a subject in need thereof. In further aspects, at least one QQ-modified protein and at least one additional therapeutic agent are administered to a subject to treat cancer in a subject in need thereof. In still further aspects, at least one QQ-modified protein and at least two additional therapeutic agents are administered to a subject to treat cancer in a subject in need thereof.

**[00205]** The term "additional therapeutic agent" is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule (such as a nucleic acid, an antibody, a protein or portion thereof, e.g., a peptide), or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues which is a biologically, physiologically, or pharmacologically active substance (or substances) that acts locally or systemically in a subject.

**[00206]** Additional therapeutic agents included in aspects of methods and compositions of the present invention include, but are not limited to, antibiotics, antivirals, antineoplastic agents, analgesics, antipyretics, antidepressants, antipsychotics, anti-cancer agents, antihistamines, anti-osteoporosis agents, anti-osteonecrosis agents, antiinflammatory agents, anxiolytics, chemotherapeutic agents, diuretics, growth factors, hormones, non-steroidal anti-inflammatory agents, steroids and vasoactive agents.

**[00207]** Combination therapies utilizing one or more QQ-modified proteins and one or more additional therapeutic agents may show synergistic effects, e.g., a greater therapeutic effect than would be observed using either the one or more QQ-modified proteins or one or more additional therapeutic agents alone as a monotherapy.

**[00208]** According to aspects, combination therapies include: (1) pharmaceutical compositions that include one or more QQ-modified proteins in combination with one or more additional therapeutic agents; and (2) co-administration of one or more QQ-modified proteins with one or more additional therapeutic agents wherein the one or more QQ-modified proteins and the one or more additional therapeutic agents have not been formulated in the same composition. When using separate formulations, the one or more QQ-modified proteins may be administered at the same time, intermittent times, staggered times, prior to, subsequent to, or combinations thereof, with reference to the administration of the one or more additional therapeutic agents.

**[00209]** Combination treatments can allow for reduced effective dosage and increased therapeutic index of the one or more QQ-modified proteins and the one or more additional therapeutic agents used in methods of the present invention.

**[00210]** Optionally, a method of treating a subject having cancer or at risk of having cancer further includes an adjunct anti-cancer treatment. An adjunct anti-cancer treatment can be administration of an anti-cancer agent.

**[00211]** Anti-cancer agents are described, for example, in Goodman et al., Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th Ed., Macmillan Publishing Co., 1990.

**[00212]** Anti-cancer agents illustratively include acivicin, aclarubicin, acodazole, acronine, adozelesin, aldesleukin, alitretinoin, allopurinol, altretamine, ambomycin, ametantrone, amifostine, aminoglutethimide, amsacrine, anastrozole, anthramycin, arsenic trioxide, asparaginase, asperlin, azacitidine, azetepa, azotomycin, batimastat, benzodepa, bicalutamide, bisantrene, bisnafide dimesylate, bizelesin, bleomycin, brequinar, bropirimine, busulfan, cactinomycin, calusterone, capecitabine, caracemide, carbetimer, carboplatin, carmustine, carubicin, carzelesin, cedefingol, celecoxib, chlorambucil, cirolemycin, cisplatin, cladribine, crisnatol mesylate, cyclophosphamide,

cytarabine, dacarbazine, dactinomycin, daunorubicin, decitabine, dexormaplatin, dezaguanine, dezaguanine mesylate, diaziquone, docetaxel, doxorubicin, droloxifene, dromostanolone, duazomycin, edatrexate, eflomithine, elsamitrucin, enloplatin, enpromate, epipropidine, epirubicin, erbulozole, esorubicin, estramustine, etanidazole, etoposide, etoprine, fadrozole, fazarabine, fenretinide, floxuridine, fludarabine, fluorouracil, flurocitabine, fosquidone, fostriecin, fulvestrant, gemcitabine, hydroxyurea, idarubicin, ifosfamide, ilmofosine, interleukin II (IL-2, including recombinant interleukin II or rIL2), interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon beta-Ia, interferon gamma-Ib, iproplatin, irinotecan, lanreotide, letrozole, leuprolide, liarozole, lometrexol, lomustine, losoxantrone, masoprocol, maytansine, mechlorethamine hydrochlride, megestrol, melengestrol acetate, melphalan, menogaril, mercaptopurine, methotrexate, metoprine, meturedepa, mitindomide, mitocarcin, mitocromin, mitogillin, mitomalcin, mitomycin, mitosper, mitotane, mitoxantrone, mycophenolic acid, nelarabine, nocodazole, nogalamycin, ormnaplatin, oxisuran, paclitaxel, pegaspargase, peliomycin, pentamustine, peplomycin, perfosfamide, pipobroman, piposulfan, piroxantrone hydrochloride, plicamycin, plomestane, porfimer, porfiromycin, prednimustine, procarbazine, puromycin, pyrazofurin, riboprine, rogletimide, safingol, semustine, simtrazene, sparfosate, sparsomycin, spirogermanium, spiromustine, spiroplatin, streptonigrin, streptozocin, sulofenur, talisomycin, tamoxifen, tecogalan, tegafur, teloxantrone, temoporfin, teniposide, teroxirone, testolactone, thiamiprine, thioguanine, thiotepa, tiazofurin, tirapazamine, topotecan, toremifene, trestolone, triciribine, trimetrexate, triptorelin, tubulozole, uracil mustard, uredepa, vapreotide, verteporfin, vinblastine, vincristine sulfate, vindesine, vinepidine, vinglycinate, vinleurosine, vinorelbine, vinrosidine, vinzolidine, vorozole, zeniplatin, zinostatin, zoledronate, and zorubicin.

**[00213]** An adjunct anti-cancer treatment can be a radiation treatment of a subject or an affected area of a subject's body.

**[00214]** Embodiments of inventive compositions and methods are illustrated in the following examples. These examples are provided for illustrative purposes and are not considered limitations on the scope of inventive compositions and methods.

**[00215]** Examples

**[00216]** Example 1

**[00217]** Reprogramming protein expression and preparation

**[00218]** Plasmid construction

**[00219]** DNA encoding each of Oct4, Sox2, Klf4, and c-Myc, Nanog, GATA4, Hand2, Mef2c and Tbox5 reprogramming proteins were separately subcloned into an sHT-pET30a bacterial

expression vector, in which a short his-tag: 'HHHHHHSS' (SEQ ID NO:64) replaced the long his-tag in the pET30a expression vector from Novagen. A factor Xa (IEGR) cleavage site is placed between the short his-tag and the coding genes. The sequences of the bacterial expression vectors were confirmed by DNA sequencing.

**[00220]** Protein expression and purification

**[00221]** The DNA constructs of reprogramming proteins were transformed into E.Coli strain BL-21(DE3) or ClearColi™ BL21(DE3) bacterial cells individually. The ClearColi™ BL21(DE3) bacterial cells were used for production of recombinant reprogramming proteins which are endotoxin-free. A single colony was selected for bacterial protein expression. After brief optimization, protein expression was induced by 0.5-1.2 mM IPTG depending on different proteins and continued to culture at 18 C° for 12-16 hours. The cells were harvested in the binding buffer containing 6M urea and sonicated several times to extract proteins. The recombinant reprogramming proteins were purified using a His-Bind Resin column (Novagen) according to the manual with modifications. Usually the protein extraction supernatant was loaded on the column twice, washed with 5 x column volume of the binding buffers. When using regular bacterial strain, BL21(DE3) to produce recombinant reprogramming proteins, an additional washing step can be added during protein purification stage using 10 column volume of 0.2% of Triton X-114 to remove endotoxin from bacterially expressed recombinant reprogramming proteins. The column loaded with recombinant proteins is washed again using 10 x column volume washing buffer containing 15-50 mM imidazole. The purified proteins were eluted from the column using elusion buffer containing 500 mM imidazole. The purified proteins were dialyzed extensively against water and lyophilized into protein powders.

**[00222]** Example 2

**[00223]** QQ-modification: Modification of expressed reprogramming proteins with protein transduction reagent to produce protein transduction reagent-modified reprogramming proteins

**[00224]** The protein transduction reagent (QQ reagent) can be adjusted by altering the composition to include reagents as shown in Table 1 to obtain the best protein transduction efficiency for the particular reprogramming protein and cell type.

**[00225]** For in vivo applications, to make total volume 1ml:

Table 1

| 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 |

The polyethylenimine (PEI) concentration for the stock solution:

| 1.2K | 2K | 4K | 8K |
|---|---|---|---|
| 5mg/ml | 2mg/ml | 2mg/ml | 2mg/ml |

Lipid concentration for the stock solution:

| DOTAP | DOTMA | DOPE | DOGS | POPC | DMPE |
|---|---|---|---|---|---|
| 1mg/ml | 1mg/ml | 1mg/ml | 1mg/ml | 1mg/ml | 1mg/ml |

PBS buffer containing reprogramming proteins in 1-6 M urea and specified PEI, lipids is used to make 1 ml total volume.

**[00226]** The reprogramming protein(s) is first dissolved in sodium phosphate buffer (pH7.0, NaCl 50 mM) at concentrations of 0.5-10 mg/ml, depending on protein solubility. Protein solubility was found to influence cationization efficiency. To completely dissolve proteins, an overnight stir of the protein solution at room temperature is performed (with or without DTT at 3 mM for overnight, depending on if the reprogramming protein has cysteine residues). Proteins can also be dissolved in 1-6 M urea to improve protein solubility.

**[00227]** A lipid DOTAP/DOPE (1:1) emulsion was prepared using a method as the following: 1 mg of DOTAP/DOPE (0.5 mg:0.5 mg=1:1) mixture was dissolved in chloroform and dried under N2 gas. The dried lipid film was then dissolved in PBS buffer, pH7.0 and the lipid solution was

sonicated for 3x30 seconds using a power of 7-8 on a sonicator from Fisher Scientific (Sonic Dismembrator, Model 100) with micro probe. The lipid solution was further incubated at 37°C for 2 hours until the suspension becomes semi-clear. The prepared emulsion was stored at 4°C and is stable for one month.

**[00228]** The other ingredients of the QQ reagents (not including the lipid emulsion or the optional Ca or DMSO) were mixed in a tube, according to the recipe described above. The QQ reagent is then titrated into the protein solution very slowly, drop by drop, while stirring and then add the lipid emulsion. Once this is completed, the resulting protein solution is left at room temperature for 4 hours before use. During this period, gentle stirring is necessary to mix the QQ reagent with protein solution and also to allow the protein modification reaction to complete. If precipitation is observed, the protein solution can be centrifuged at 14,000 rpm for 15 minutes to remove the precipitate. If the precipitate occurs, a BCA protein assay will be carried out using the supernatant to check the amount of protein remaining in solution. To ensure the efficiency of protein transfer into the cells, the concentration of modified protein has to be high enough at >0.1 mg/ml.

**[00229]** Typically, QQ-modified proteins are prepared at 0.5-1.5 mg/ml concentration, depending on protein solubility, for in vivo administration.

**[00230]** QQ modification may be performed on each protein individually or on a mixture of proteins to be administered together to a subject.

**[00231]** Optionally, the QQ modification is performed on each protein individually, the QQ-modified proteins mixed together for several hours and then aliquoted into small tubes at 1ml/tube and stored at -20°C where they are stable for several months.

**[00232]** If the majority of the reprogramming protein is precipitated, another QQ reagent can be used for protein modification. The QQ series reagents cover a wide range of cationization reagents along with different lipids and enhancers, thus any precipitation problem is solved. The above procedure can be repeated to prepare higher concentrations of protein transduction reagent-modified reprogramming protein.

**[00233]** The protein transduction reagent-modified reprogramming protein is passed through a desalting column to separate the protein transduction reagent-modified reprogramming protein from remaining unreacted materials. The purified proteins are passed through a filter (0.22 μm cutoff, for sterilization before in vivo administration. The purified protein fractions can be concentrated before or after sterilization, such as by using a spin column, and are stable and can be stored at -20°C for between a few weeks to a few months.

**[00234]** Different QQ reagents can also be used for the best efficiency of protein transfer as well as the least cell toxicity. In addition, different proteins are modified with different QQ reagents for best efficiency of protein transfer into cells. In general, for better in vivo delivery efficiency, QQ5a-QQ9a are used. However, this may cause larger in vivo toxicity. When using QQ5a-QQ9a, use of lower concentrations of larger PEI and lipids is emphasized.

**[00235]** For good in vivo delivery efficiency, QQ1a-QQ4a is used with less in vivo toxicity. QQ1-QQ4 can be used with higher lipid concentrations.

**[00236]** Example 3

**[00237]** The reprogramming proteins were dissolved in 50 mM sodium phosphate pH 7.4 with 2 M urea. Protein transduction reagents (QQ-reagents) were freshly prepared based on the recipe. QQ-reagent used in this example is a cocktail of polyethylenimine (PEI) 1,200 (1.2K, 0.05-1.0 mg/ml) and DOTAP/DOPE (25-100μg/ml). The QQ-modification of reprogramming proteins was performed by mixing the QQ-reagent with one or more reprogramming proteins, such as Oct4/Sox2/Nanog: 1 mg/ml, for 4-hours at room temperature or overnight in a cold room.

**[00238]** Example 4

**[00239]** QQ-Protein delivery into brain tumors in rats by an intravenous injection

**[00240]** Ferritin is a ubiquitous iron-containing protein useful as a negative contrast reagent for magnetic resonance imaging (MRI).

**[00241]** In this example, ferritin or ferritin treated with QQ reagent to produce QQ-ferritin is intravenously injected into rats having brain tumors generated by implantation of rat gliosarcoma cell line 9L cells.

**[00242]** Cells of a rat gliosarcoma cell line 9L were freshly prepared and adjusted to $1x10^6$ cells/ml before implantation. The intracranial xenografts were performed according to standard protocols. Fisher rats were anesthetized and placed in a stereotactic frame, and the skull was exposed. A hole was made 3 mm to the right and 1 mm anterior of the bregma, and 9L cells (5 x $10^4$ cells in 5 μl) were injected using a 10-μl Hamilton syringe with a 26s-gauge needle mounted in a stereotactic holder (Bonaduz, GR, Switzerland). The syringe was lowered to a depth of 3.5 mm and then raised to a depth of 3.0 mm. The tumor cells were injected at a rate of 0.5 μl/10 s, and the craniotomy covered with Horsley's bone wax. 12-days after 9L-cell implantation, QQ-modified ferritin or ferritin alone, 100μg/100μl/rat, was injected via the rat tail vein. Four hours after injection, the rats were anesthetized and the rat brains were imaged by MRI. After MRI, the animals were sacrificed. The extracted brains were fixed in 4% paraformaldehyde overnight and then embedded in paraffin for further analysis. Six micrometer thin sections were cut from each of

the blocks and were stained with hematoxylin and eosin. The sizes of brain tumors were microscopically determined.

**[00243]** Figures 1A and 1B show MRI evidence of targeted delivery of QQ-ferritin into 9L-brain tumor in rats and no detectable ferritin in 9L-brain tumor of rats injected with ferritin alone. Figure 1A is a representative MRI image of a rat with 9L-brain tumor injected with QQ-ferritin via tail-vein. The arrow points to a 9L-brain tumor and the black color is indicative of ferritin delivered to the tumor. Figure 1B: A representative MRI image of a rat with 9L-brain tumor injected with ferritin without QQ modification. No ferritin is observed in the brain tumor in this case although the rat was sacrificed and confirmed to have a large 9L-brain tumor.

**[00244]** Double immunostains of the QQ-ferritin injected 9L-brain tumor tissue sections were performed using an antibody for a blood vessel marker, CD31, and an antibody for ferritin. The nuclei of the 9L-cancer cells in the sections were stained with DAPI. Overlapping immunostaining for the CD31 and ferritin were observed in blood vessels of the brain tumors, indicating that QQ-ferritin leaked out from the blood vessels by the enhanced permeability and retention effect (EPR effect) of the angiogenic blood vessels associated with brain tumor. In the QQ-ferritin treated animal, immunostaining for ferritin was observed inside the cytosol of the tumor cells near or next to the blood vessels, indicating that the QQ-ferritin penetrated into tumor cells. In contrast, ferritin immunostaining in the 9L-tumor sections treated with ferritin without QQ-modification showed that the ferritin without QQ modification did not penetrate into tumor cells, although immunostaining indicated that this unmodified ferritin also leaked out of the tumor-associated angiogenic blood vessels. These unmodified ferritin nanoparticles were observed between cells and likely did not accumulate due to the fluid between cells inside the tissues so that no tumor was observed by MRI without QQ-modification of the ferritin.

**[00245]** These data provide MRI evidence of the targeted delivery of ferritin to brain tumor in rats by the QQ-protein delivery technology, which is confirmed by histology analysis and immunostaining of the brain tissue sections.

**[00246]** Example 5

**[00247]** QQ-protein delivery into breast cancer in mice by an intravenous injection.

**[00248]** In this example, ferritin or ferritin treated with QQ reagent to produce QQ-ferritin is intravenously injected into mice having orthotopic breast tumors generated by implantation of mouse metastatic breast cancer cell line 4T1 cells. Implantation of mouse metastatic breast cancer cell line 4T1 cells in mice is a mouse model for spontaneous metastatic breast cancer.

**[00249]** 4T1 cells were implanted into the breast (#4 fat pad) of 2 month old female BALB/c mice (20,000 4T1 cells in 50 µl/mouse). At day 18 after 4T1 cell implantation, 4T1 tumors had grown in the mouse breast to a size of ~1.0-1.5 cm in diameter. QQ-modified ferritin (100µg/50µl/mouse) was injected via tail-vein. The mice were anesthetized and subjected to MRI imaging before injection of the QQ-modified ferritin and at 0.5 hours, 2 hours, 3.5 hours, 8 hours and 18 hours following the injection.

**[00250]** Figures 2A-F are representative MRI images from this time course showing QQ-delivered ferritin in the primary tumor of breast cancer bearing mouse as darkened areas in the primary tumor. This primary tumor darkness was time-dependent and reached a maximum at 8-hours, then started to decrease in intensity.

**[00251]** MRI results were confirmed by histology analysis using Prussian blue stain and ferritin immunostaining. Immunohistochemical stain and Prussian blue stain of the primary tumor tissue sections of 4T1-breast cancer bearing mouse at 18-hour after QQ-ferritin injection showed positive ferritin and Prussian blue stains inside the primary tumor. This histological result confirmed the MRI observation of QQ-delivered ferritin inside the primary tumor of 4T1-tumor bearing mice.

**[00252]** Example 6

**[00253]** QQ-protein delivery of Oct4 and Klf4 protein into the nuclei of 4T1-breast cancer cells of the primary tumor of 4T1 breast cancer bearing mice

**[00254]** 4T1 cells (2 x $10^4$ cells/50µl/mouse) were implanted into female BALB/c mice. 15-days after tumor cell implantation Alexa Fluor594 labeled Klf4 was prepared. QQ-modified unlabeled Oct4 (QQ-Oct4) and QQ-modified Alexa Fluor594 labeled Klf4 were then prepared. Intra-tumoral injection of 50 µg QQ-Oct4 and QQ-Alexa Fluor594 labeled Klf4 proteins was performed. The mice were sacrificed 5 hours after injection and tumor tissue sections were prepared for immunostaining and fluorescence microscopy. Immunostaining for Oct4 in the primary 4T1-breast cancer tissue sections demonstrated nuclear localization of Oct4 in the 4T1-cancer cells and co-localization with DAPI. Fluorescence microscopic imaging also showed nuclear localization of Klf4 in the primary 4T1-breast cancer tissue sections and co-localization with DAPI.

**[00255]** Example 7

**[00256]** QQ-protein delivery of GATA4, OCT4 and SOX2 to the injured hearts of rats after acute myocardial infarction

**[00257]** QQ-modified and fluorescence labeled GATA4, Sox2 and Oct4 are administered by an intraperitoneal injection to rats after myocardial infarction and the QQ-modified proteins and fluorescence labeled were delivered to injured heart tissues in the animals.

**[00258]** GATA4, Sox2 and Oct4 are each labeled with Alexa Fluor488 according to methods specified by the manufacturer. The labeled GATA4, Sox2 and Oct4 proteins were purified with small spin columns. The Alexa Fluor488-GATA4, Alexa Fluor488-Sox2 and Alexa Fluor488-Oct4 are then QQ-modified to generate QQ-modified Alexa Fluor488-GATA4, QQ-modified Alexa Fluor488-Sox2 and QQ-modified Alexa Fluor488-Oct4.

**[00259]** Lewis rats were anesthetized and coronary artery ligation surgery was performed to create myocardial infarction in the Lewis rats. 24-hours after coronary artery ligation surgery, QQ-modified Alexa Fluor488-labeled GATA4, QQ-modified Alexa Fluor488-labeled Sox2 and QQ-modified Alexa Fluor488-labeled Oct4 (200 μg/100 μl/rat) were intraperitoneally injected into Lewis rats. 7-hours after fluorescence labeled protein injections, the rats were sacrificed and heart tissue sections were prepared for either Trichrome staining for infarction sizes or for immunostaining with an α-actinin antibody, which is a heart muscle marker indicative of mature cardiomyocytes.

**[00260]** Fluorescence microscopic analysis showed colocalization of Alexa Fluor488-GATA4 protein with α-actinin immunofluorescence, indicating that intraperitoneal injection of QQ-fluorescence labeled GATA4 resulted in delivery of the GATA4 protein into the scar zone of the injured heart tissue after coronary artery ligation. Similarly, fluorescence microscopic analysis of Alexa Fluor488-Sox2 and α-actinin immunofluorescence indicated that intraperitoneal injection of QQ- modified Alexa Fluor488 labeled-Sox2 resulted in location of the Sox2 protein in the border zone of the injured heart tissue after coronary artery ligation. Finally, fluorescence images of Alexa Fluor488-Oct4 showed localization of injected QQ-modified Alexa Fluor488-Oct4 in the remote normal heart tissue zone. These results indicate that fluorescence labeled and QQ-modified GATA4, Sox2 and Oct4 administered by intraperitoneal injection reached injured heart tissues in the scar zone, the border zone and the normal heart tissue zones. These data demonstrate that QQ-protein delivery targeted deliver these proteins into the injured heart tissues.

**[00261]** Example 8

**[00262]** Malignant glioma cells including 9L-, U251-, U87- and a primary GBM cell line from a patient were reprogrammed into protein induced pluripotent stem cells (piPSCs) using QQ-modified Sox2, Oct4 and Nanog (SON) proteins as follows: At day 0, glioma cells were seeded for 24-hours to allow them to grow in a 50 mm petri dish. At day 2, QQ-SON proteins were added to

the culture medium at 0.5-2.0 μg/ml and cultured for 24 hours. Next day, fresh QQ-SON proteins were added into new culture medium and cultured for 24 hours. Such cycles were repeated for 5-7 cycles depending on glioma cells used for cell reprogramming. At the end of cell reprogramming, the culture media were changed to maintaining medium for 2 days. During cell reprogramming, piPSC colonies appeared. At day 8, whole dish passage was performed to expand the generated piPSCs. Immunostaining of the whole dish passaged glioma-piPSCs including both monolayer and colony of the 9L-piPSCs using pluripotency markers including nuclear markers Oct4, Nanog, Rex-1 and surface markers ALP, Tra1-60, and Tra1-81 showed nearly all cells were positive for these pluripotency markers. In contrast, immunostains of 9L-cells showed negative stains for these markers. These data indicate high conversion efficiency of cell reprogramming of 9L-cells into 9L-piPSCs using the QQ-SON proteins.

**[00263]** This is confirmed by immunostaining of whole well (96-well) of 9L-piPSCs using Nanog and Oct4. When counting positive 9L-piPSC clones compared with negative clones, an average of 96±2% conversion efficiency is found, see Table 2. A control immunostaining of 9L cells showed negative stains for these two pluripotency markers Nanog and Oct4. The conversion efficiency of 9L-piPSCs from 9L cells was calculated by positively stained colonies and monolayer 9L-piPSCs versus total colonies and monolayer cells as stained with DAPI using the software provided by EVOS Auto fluorescence microscope. Immunostaining of the 9L-piPSCs of duplicated 96-wells were used to calculate average conversion efficiency and standard deviation.

Table 2: Conversion efficiency of QQ-SON protein-induced cell reprogramming of 9L-gliosacoma cells

| Marker | Oct4 | Nanog | Average |
|---|---|---|---|
| Whole Wells Counted | 2 | 2 | 2 |
| Conversion Efficiency (%) | 94.0±1.0 | 98.0±0.1 | 96.0±2.0 |

Cell reprogramming of 9L cells to generate 9L-piPSCs using the QQ-SON proteins (0.5ug/ml. Sox2:Oct4:Nanog=1:1:1, 5 continue cycles).

**[00264]** Using a similar cell reprogramming protocol, 4T1-piPSCs were generated from 4T1 mouse breast cancer cells. The reprogramming conversion efficiency of 4T1 cells into 4T1-piPSCs is 96±1.3% using the same whole well counting method (96-wells), see Table 3.

Table 3: Conversion efficiency of QQ-SON protein-induced cell reprogramming of 4T1-breast cancer cells

| Pluripotent Marker | Number of Wells | Number of Colonies/Well | Conversion Efficiency (%) |
|---|---|---|---|
| Nanog | 2 | 1344±200 | 98±1 |
| Rex 1 | 2 | 1943±234 | 96±1 |
| Sox 2 | 2 | 1862±198 | 94±2 |
| Average | | | 96±1.3 |

**[00265]** Example 9

**[00266]** Cells of human glioblastoma cell line U251 are reprogrammed into U251-piPSCs using QQ-modified Sox2, Oct4 and Nanog (SON) proteins as follows: At day 0, U251glioblastoma cells were seeded for 24-hours to allow them to grow in a 50 mm petri dish. At day 2, QQ-SON proteins were added to the culture medium at 0.5-2.0 μg/ml and cultured for 24 hours. Next day, fresh QQ-SON proteins were added into new culture medium and cultured for 24 hours. Such cycles were repeated for 5-7 cycles. At the end of cell reprogramming, the culture media were changed to maintaining medium for 2 days. During cell reprogramming, U251-piPSCs colonies appeared. At day 8, whole dish passage was performed to expand the generated U251-piPSCs.

**[00267]** Proliferative activity of U251 and U251-piPSCs was assayed by determining the number of Ki67-positive cells. Figure 3A is a graph showing results of this assay indicating that cell reprogramming of glioma cells into piPSCs significantly reduces their proliferation, error Bar represents standard error of three independent experiments.

**[00268]** Example 10

**[00269]** Cells of a patient-derived primary human glioblastoma multiforme (GBM) cell line, GBM (12-14), is reprogrammed into GBM-piPSCs using QQ-modified Sox2, Oct4 and Nanog (SON) proteins as follows: At day 0, GBM cells were seeded for 24-hours to allow them to grow in a 50 mm petri dish. At day 2, QQ-SON proteins were added to the culture medium at 0.5-2.0 μg/ml and cultured for 24 hours. Next day, fresh QQ-SON proteins were added into new culture medium and cultured for 24 hours. Such cycles were repeated for 5-7 cycles. At the end of cell reprogramming, the culture media were changed to maintaining medium for 2 days. During cell reprogramming, GBM1-piPSCs colonies appeared. At day 8, whole dish passage was performed to expand the generated GBM-piPSCs.

**[00270]** Dose-dependent chemotherapeutic drug sensitivity of patient-derived primary human GBM (12-14) cells (squares) and GBM (12-14)-piPSCs (circles) against the alkylating agent temozolomide was determined and results are shown in Figure 3B. Experiments were done in

triplicate, mean ± SD, $p < 0.01$. Drug sensitivity of the GBM-piPSCs was significantly enhanced to temozolomide as compared with the parental glioblastoma cells.

**[00271]** Example 11

**[00272]** Cells of rat gliosarcoma cell line 9L are reprogrammed into 9L-piPSCs using QQ-modified Sox2, Oct4 and Nanog (SON) proteins as follows: At day 0, 9L glioma cells were seeded for 24-hours to allow them to grow in a 50 mm petri dish. At day 2, QQ-SON proteins were added to the culture medium at 0.5-2.0 μg/ml and cultured for 24 hours. Next day, fresh QQ-SON proteins were added into new culture medium and cultured for 24 hours. Such cycles were repeated for 5-7 cycles. At the end of cell reprogramming, the culture media were changed to maintaining medium for 2 days. During cell reprogramming, 9L-piPSCs colonies appeared. At day 8, whole dish passage was performed to expand the generated 9L-piPSCs.

**[00273]** Dose-dependent chemotherapeutic drug sensitivity of 9L-cells (squares) and 9L-piPSCs (circles) against carboplatin was determined by an MTT assay and results are shown in Figure 3C. Experiments were done in triplicate, mean ± SD, $p < 0.01$. Drug sensitivity of the 9L-piPSCs was significantly enhanced to carboplatin as compared with the parental 9L cells.

**[00274]** Example 12

**[00275]** Cells of mouse mammary tumor cell line 4T1 are reprogrammed into 4T1-piPSCs using QQ-modified Sox2, Oct4 and Nanog (SON) proteins as follows: At day 0, 4T1 cells were seeded for 24-hours to allow them to grow in a 50 mm petri dish. At day 2, QQ-SON proteins were added to the culture medium at 0.5-2.0 μg/ml and cultured for 24 hours. Next day, fresh QQ-SON proteins were added into new culture medium and cultured for 24 hours. Such cycles were repeated for 5-7 cycles. At the end of cell reprogramming, the culture media were changed to maintaining medium for 2 days. During cell reprogramming, 4T1-piPSCs colonies appeared. At day 8, whole dish passage was performed to expand the generated 4T1-piPSCs.

**[00276]** Proliferative activity of 4T1-cells and 4T1-piPSCs was assayed by determining the number of Ki67-positive cells and it was found that cell reprogramming of 4T1 mammary tumor cells into 4T1-piPSCs significantly reduces their proliferation.

**[00277]** Mammary sphere formation of 4T1-piPSCs was reduced as compared with that of 4T1-cells.

**[00278]** Dose-dependent chemotherapeutic drug sensitivity of 4T1-cells and 4T1-piPSCs against doxorubicin and paclitaxel was determined using an MTT assay. Drug sensitivity of the 4T1-piPSCs was significantly enhanced to doxorubicin and paclitaxel as compared with the parental 4T1 cells.

**[00279]** Example 13

**[00280]** Glioma cell-derived piPSC differentiation into three germ layers in vitro

**[00281]** Embryonic bodies (EBs) were prepared for glioma-piPSCs using the hanging-drop method. The glioma-piPSCs EBs were placed into a spontaneous differentiation medium for 10-days, followed by immunostaining with markers of ectoderm, mesoderm and endoderm, showing positive immunostains of PAX6 for ectoderm, positive immunostains of desmin for mesoderm and positive immunostains of α-fetoprotein (AFP) for endoderm. Immunostaining of control 9L cells was negative for these markers. Similar results have been also obtained for 4T1-piPSCs, indicating that the 4T1-piPSCs also differentiated into three germ layers.

**[00282]** Example 14

**[00283]** Glioma cell-derived piPSC differentiation into neural-lineage in vitro

**[00284]** Glioma-piPSCs EBs were placed into a specific neural-lineage inducing differentiation medium for 14-days, followed by immunostaining with neural lineage markers, showing positive immunostains of Tuj I for neurons, positive immunostains of GFAP for astrocytes and positive immunostains of nestin for neural stem cells. These neural-specifically differentiated cells also displayed neural cell morphology. Immunostaining of control 9L cells was negative for these markers.

**[00285]** Example 15

**[00286]** Cell reprogramming causes a mesenchymal-to-epithelial transition (MET) and reduction of tumorigenicity in vitro.

**[00287]** Results of Western blot analysis of several epithelial and mesenchymal markers of U251 cells and U251-piPSCs, including E-cadherin (E-cad), β-catenin (β-cat), vimentin (VMT), see Figure 4A, indicate an MET during cell reprogramming which is confirmed by cell morphology changes and qRT-PCR results. GFAP protein level is also significantly enhanced after cell reprogramming into U251-piPSCs from U251 cells, indicating that cell reprogramming caused a significant reduction of tumorigenicity of U251 cells in vitro during cell reprogramming. Actin protein expression was used as an internal control. Immunostaining of U251 cells and U251-piPSCs using an anti-GFAP antibody, confirmed up-regulated protein expression of GFAP in U251-piPSCs as shown in Western blot. In addition, the GFAP-expressing cells displayed morphologies of neural cells.

**[00288]** The tumorigenicity reduction of U251 cells after cell reprogramming has been confirmed by in vitro assays for cell migration, Figure 4B, and invasion, Figure 4C, of U251-cells

and U251-piPSCs, indicating significantly reduced migration and invasion of U251-piPSCs ($p < 0.01$).

**[00289]** Similarly, immunostainings of 41-piPSCs and 4T1 cells using an epithelial marker: E-cadherin and a mesenchymal marker fibronectin were compared and showed that while 4T1 cells display positive E-cadherin immunostaining, 4T1-piPSCs showed much stronger E-cadherin immunostaining. In contrast, 4T1 cells displayed stronger fibronectin immunostaining and 4T1-piPSCs exhibited nearly negative fibronectin immunostaining. This results confirm a MET of 4T1 cells during cell reprogramming into 4T1-piPSCs. In addition, 4T1-piPSCs also exhibited reduced proliferation, Figure 4D, reduced mammary sphere formation, Figure 4E, reduced migration, Figure 4F, and reduced invasion, Figure 4G, as compared to those properties of the parental 4T1 cells, indicating a significantly reduced tumorigenicity of 4T1 cells after cell reprogramming into 4T1-piPSCs in vitro.

**[00290]** Example 16

**[00291]** Co-culture between glioma cells and glioma-piPSCs indicated that glioma-piPSCs displayed a bystander effect to change the phenotypes of their surrounding glioma cells and reduced tumorigenicity in vitro.

**[00292]** Cell morphology changes of U251 cells indirectly co-cultured with U251-piPSCs for 40-64 hours are observed indicating a mesenchymal-to-epithelial transition (MET) of the co-cultured glioma cells. Figure 5A is an image showing cell morphology of U251 cells and Figure 5B is an image showing changes in cell morphology of U251 cells indirectly co-cultured with U251-piPSCs for 40-64 hours.

**[00293]** This MET was confirmed by immunostaining of U251 cells, U251-piPSCs, first ($1^{st}$) co-cultured U251 cells and second ($2^{nd}$) co-cultured U251 cells using an anti-pan-cadherin antibody, showing cytosol/nuclear localization of pan-cadherin in U251 cells and membrane/nuclear localization of U251-piPSCs and $1^{st}/2^{nd}$ co-cultured U251 cells, suggesting a major enhancement of cell-cell adhesion among U251-piPSCs as well as among the $1^{st}/2^{nd}$ co-cultured U251 cells. This is an indication of MET during cell reprogramming and the $1^{st}/2^{nd}$ co-cultured U251 cells. A $2^{nd}$ co-culture is the indirect co-culture experiment that places the $1^{st}$ co-cultured cells into the transwell insert and fresh U251 cells in the basolateral chamber. Double immunostains of the U251 cells and indirectly co-cultured U251 cells using distinctly labeled anti-GFAP and anti-Tuj1 antibodies, showing significant GFAP protein expression in the co-cultured U251 cells with neural morphology whereas U251 cells (spindle morphology) do not express GFAP.

**[00294]** Results of proliferation assay of U251 cells, U251-piPSCs and indirectly co-cultured U251 cells by Ki-67 immunostaining show significantly reduced proliferation of U251-piPSCs and the co-cultured U251 cells, Figure 5C. Results of migration assays, Figure 5D, and invasion assays, Figure 5E, of U251 cells, U251-piPSCs, directly co-cultured U251 cells at 1:1 and 8:1 ratios (U251:U251-piPSCs), show significantly reduced migration and invasion of the U251 cells after co-cultures with U251-piPSCs ($p < 0.005$).

**[00295]** Following a similar co-culture experiment, MET of co-cultured 4T1 cells with 4T1-piPSCs was observed. Immunostains of co-cultured 4T1 cells and 4T1-piPSCs showed that both cells had high protein expression of E-cadherin and lower protein expression of fibronectin, confirming a MET of the co-cultured 4T1 cells. In addition, the co-cultured 4T1 cells also displayed a significantly reduced proliferation, Figure 5F, migration, Figure 5G, and invasion, Figure 5H, indicating a significantly reduced tumorigenicity of the 4T1 cells after co-cultured with 4T1-piPSCs for 40-hours.

**[00296]** Co-culture of patient-derived primary brain tumor cells, GBM (12-14), with U251-piPSCs also causes a mesenchymal-to-epithelial transition and reduced tumorigenicity of the co-cultured patient-derived primary brain tumor cells – a bystander effect of U251-piPSCs.

**[00297]** These results indicate that a bystander effect of piPSCs changes the phenotypes of surrounding cancer cells for tumorigenicity and malignancy reduction. This bystander effect indicates that a smaller number of piPSCs can change malignant phenotype of a large numbers of surrounding tumor cells via this bystander effect, serving a cellular mechanism of a cell-converting cancer therapy.

**[00298]** Example 17

**[00299]** Significantly reduced tumorigenicity and metastasis/infiltration inhibition in vivo of piPSCs generated from malignant cancer cells.

**[00300]** In a first set of animals, equal numbers of 9L cells or 9L-piPSCs ( $5x10^4$ cells/5μl) were implanted into Fisher rats intracranially. In a second set of animals, equal numbers of 9L cells or 9L-piPSCs ($1x10^6$ cells/100μl) were implanted into Fisher rats subcutaneously.

**[00301]** Tumor volume ($mm^3$) of intracranial-implanted rats with either 9L cells or 9L-piPSCs, n = 10 was measured at day 14, see Figure 6A. Tumor weight in grams of subcutaneously-implanted rats with 9L cells and 9L-piPSCs was measured at day 25 after 4T1-cell implantation, n = 6, see Figure 6B. Results showed a significantly reduced volume of the intracranial 9L-piPSC tumors and a significantly reduced weight of the subcutaneous 9L-piPSC tumors as compared with those of 9L-tumors, indicating a significantly reduced tumorigenicity of 9L-cells after cell

reprogramming into 9L-piPSCs. This result is also confirmed by hematoxylin and eosin (H&E) staining of the tumors from 9L-cell and 9L-piPSC implanted animals, indicating a major inhibition of 9L-cell infiltration, since the 9L-piPSC intracranial tumor showed a clear intact border, whereas 9L-intracranial tumor showed a broken border with a major infiltration of the 9L-tumor cells into normal brain tissues.

**[00302]** Example 18

**[00303]** Significantly reduced tumorigenicity and metastasis/infiltration inhibition in vivo of piPSCs generated from malignant breast cancer cells.

**[00304]** Equal numbers of 4T1 cells and 4T1-piPSCs ($2 \times 10^4$ cells/50μl) were implanted into the #4 fat pads of 2-3 month old female BALB/c mice (20 grams). 4T1 breast tumors were observed at day 5-7 after cell implantation. The tumor volume and body weight of the mice were monitored every day. At day 25, the mice were sacrificed and the tumors were weighed. For the survival experiment, animals were sacrificed once they reached tumor burden.

**[00305]** 4T1 and 4T1-piPSC tumor growth were measured by tumor volume, Figure 6C, and tumor weight, Figure 6D, at day 25 after 4T1- and 4T1-piPSC implantation, indicating a significant tumor stasis of 4T1 cells after cell reprogrammed into 4T1-piPSCs.

**[00306]** Lung metastases of the mice that were implanted with 4T1 cells and 4T1-piPSCs were analyzed at day 25 after cell implantation. While all the mice implanted with 4T1 cells displayed many metastatic lesions, no lung metastases were observed in the mice implanted with 4T1-piPSCs at day 25 after cell implantation, Figure 6E, indicating a major metastasis inhibition caused by cell reprogramming of 4T1 cells into 4T1-piPSCs. This result was confirmed by H&E stain of the lung tissue sections of 4T1-bearing mice and 4T1-piPSC bearing mice, showing no lung metastasis in the mice implanted with 4T1-piPSCs.

**[00307]** A Kaplan-Meier survival curve of the mice implanted with 4T1 cells and 4T1-piPSCs in the #4 fat pads, Figure 6F, demonstrates a significantly prolonged survival of the 4T1-piPSC bearing mice during this 250-day survival experiment. These results demonstrate that cell preprogramming of malignant cancer cells into piPSCs significantly reduces tumorigenicity and metastatic property of the parental cancer cells, thus significantly prolonging the survival of the mice implanted with 4T1-piPSCs.

**[00308]** Example 19

**[00309]** Tumor cell derived piPSCs differentiate into different normal tissues in vivo depending on different differentiating tissue environments.

**[00310]** H&E stains of the brain tissue sections of 9L-intracranial implanted rats showed major glioma angiogenesis into normal brain tissues and severe bleeding inside brain tumors, whereas much less angiogenesis and bleeding were observed in the 9L-piPSC-intracranial implanted rats. In addition, 9L-piPSC-intracranial implanted rats also showed newly differentiated neural rosettes near the tumors in the brain. Further, H&E stain of the tumor tissue slides of subcutaneously-implanted rats with 9L-piPSCs, showed immature sweat glands with cuboidal and low columnar epithelial cells and melanocytes with brown color of melanin within the tumors. H&E stains of tumor tissue slides of rats subcutaneously implanted with 9L-piPSCs also showed skin epithelium with two layers of epidermis and early simple columnar epithelial cells with longer shape and nuclei in the base of the cells.

**[00311]** Similarly, H&E staining of the tumor masses of the 4T1-piPSC-bearing mice showed in vivo differentiation of the implanted 4T1-piPSCs into normal breast tissues including adipocytes including both brown and white adipocytes and mature and immature mammary ducts.

**[00312]** These results indicate that tumor cell derived-piPSCs differentiate into different normal tissue cells in vivo depending on different differentiating tissue environments.

**[00313]** Example 20

**[00314]** Lineage tracing shows tumor cell derived piPSCs differentiate into normal tissues.

**[00315]** To ensure that tumor cell derived piPSCs differentiate into normal tissues, GFP-expressing 9L- and 4T1-cells were prepared.

**[00316]** GFP-9L-piPSCs and GFP-4T1-piPSCs were prepared.

**[00317]** Lineage-tracing experiments were performed using both cell types. For GFP-9L-piPSCs, the cells were subcutaneously implanted into left flanks of Fisher rats. For GFP-4T1-piPSCs, the cells were implanted into the #4 fat pad of female BALB/c mice. Small tumor mass were observed at day 10-15 for GFP-9L-piPSC-implanted rats and at day 20-25 days for GFP-4T1-piPSC-implanted mice. The animals were sacrificed at different days after cell implantation and tumor masses were collected and used to make tissue sections for H&E stains and immunostaining. Immunostaining with Tuj I and Nestin neural marker antibodies, adiponectin (an adipocytes marker), cytokeratin 8, 14, 18 (CK8, 14, 18) or cytokeratin 5,8 (CK5,8) (mammary duct markers) were performed using differentially detectable labels.

**[00318]** H&E stain of both the center and edges of tumor mass of the 4T1-piPSC-bearing mice showed appearance of potential adipocytes and immature mammary ducts in the tumor mass.

**[00319]** Immunostains of the tissue section of the GFP-9L-piPSCs tumor mass obtained from the lineage tracing experiment using an anti-Tuj I antibody showed positive Tuj I immunostaining

that overlapped with GFP fluorescence of GFP-expressing cells of the same tissue sections. Only overlapping Tuj I and GFP fluorescence images were observed in the tissue sections, indicating that these Tuj I-positive cells originated from the GFP-expressing 9L-piPSCs. The Tuj I/GFP-positive cells displayed neuronal cell morphology. This data demonstrates that the GFP-expressing 9L-piPSCs differentiated in vivo into Tuj I-positive neuronal lineage cells.

**[00320]** Immunostains of the tissue section of the GFP-9L-piPSCs tumor mass obtained from the lineage tracing experiment using an anti-nestin antibody showed positive nestin immunostaining that overlapped with GFP fluorescence of GFP-expressing cells of the same tissue sections. Only overlapping nestin and GFP fluorescence images were observed in the tissue sections, indicating that these nestin-positive cells originated from the GFP-expressing 9L-piPSCs. This data demonstrates that the GFP-expressing 9L-piPSCs differentiated in vivo into nestin-positive neural lineage cells.

**[00321]** Immunostains of the tumor tissue sections of the 4T1-piPSC-bearing mice with an anti-adiponectin antibody showed adiponectin-positive immunostaining that overlapped with green fluorescence from the GFP-expressing cells. Only overlapping adiponectin and GFP fluorescence were observed in the tissue sections in cells with adipocyte morphology, indicating presence of adipocytes in the middle of the tumor mass of the 4T1-piPSC-bearing mice and these adipocytes originated from differentiation of the implanted GFP-4T1-piPSCs, since these adipocytes expressed GFP.

**[00322]** Immunostains of the tumor tissue sections of the 4T1-piPSC-bearing mice with anti-CK8,18,14 and anti-CK5,8 antibodies showed CK8,18,14- and anti-CK5,8-positive immunostaining that overlapped with green fluorescence from the GFP-expressing cells. Only overlapping CK8,18,14- or anti-CK5,8-positive and GFP fluorescence were observed in the tissue sections in cells with morphology of mammary ducts, indicating presence of immature mammary ducts that originated from differentiation of the implanted GFP-4T1-piPSCs, since these mammary ducts expressed GFP.

**[00323]** Example 21

**[00324]** QQ-SON protein-induced cell reprogramming treatment of tumors in vivo

**[00325]** To generate 9L-tumor bearing rats, 9L cells (1 x $10^6$ cells/100µl) were implanted into Fisher rats subcutaneously. 5-days after 9L-implantation, QQ-SON protein was administered by intra-tumor injection every day at 1 µg/day (n = 5), 5 µg/day (n = 5), or 10 µg/day (n = 10) for 18 daily treatments. QQ-reagent in PBS buffer was administered by intra-tumor injection to control

rats (n = 10). The tumor volume and body weight of the rats were monitored every day. At day 23, the rats were sacrificed and the tumors were weighed.

**[00326]** Tumor growth was measured by volume, see Figure 7A and tumor weight in grams, see Figure 7B. The rats were sacrificed at day 23 and tumors were weighed. This data indicates that QQ-SON treatment induced in situ cell reprogramming that results in tumor stasis.

**[00327]** To determine the effect of QQ-SON protein treatment on the survival of the rats subcutaneously implanted with 9L-cells, at day 5 after 9L cell implantation rats were treated with QQ-reagents in PBS (n = 8; median survival = 21 days) or QQ-SON proteins (10μg/day, n = 8; median survival = 127 days) for 30 daily treatments. Animals were sacrificed once they reached tumor burden (< 12 $cm^3$). Kaplan–Meier survival curve (130-days) is shown in Figure 7C. This data indicated that QQ-SON protein treatment significantly prolonged the survival of 9L-tumor bearing rats.

**[00328]** Example 22

**[00329]** QQ-SON protein-induced cell reprogramming treatment of tumors in vivo

**[00330]** To generate orthotopic 4T1 breast cancer-bearing mice, 4T1 cells (2 x $10^4$ cells/50μl) were implanted into the #4 fat pads of 2-3 month old female BALB/c mice (20 grams). 4T1 breast tumors were observed at day 5-7 after cell implantation. The tumor volume and body weight of the mice were monitored every day. At day 25, the mice were sacrificed and the tumors were weighed. For the survival experiment, animals were sacrificed once they reached endpoints including tumor burden (< 2 gram), metastasis causing labored breath, uncontrollable pain, etc.

**[00331]** Various dosages of QQ-SON proteins were administered, 0.5 μg QQ-modified SON proteins/mouse, 1.25 μg QQ-modified SON proteins/mouse, or 2.5 μg QQ-modified SON proteins/mouse, and compared with QQ-PBS control. Efficacy was determined by measurement of tumor volume over a 25-day time course, Figure 7D, and measurement of tumor weight in grams, Figure 7E, at day 25.

**[00332]** In a further experiment, tumor volume of the mice treated either with QQ-SON proteins (n = 8) or QQ-PBS as the control (n = 8) during a 35-day time course was determined by MRI, see Figure 7F, and tumor weights of both groups were determined by weighing at day 35, see Figure 7G. QQ-SON protein treatment caused major tumor stasis without primary tumor removal.

**[00333]** Mice were analyzed to determine number and percentage of metastases in the lung, Figures 7I and 7M, lymph nodes, Figures 7J and 7N, liver, Figures 7K and 7O, and spleen, Figures 7L and 7P, of the QQ-SON and QQ-PBS treated 4T1-bearing mice without primary tumor removal as observed by MRI at indicated days. These results demonstrate that, as compared to QQ-PBS

treated mice, QQ-SON treated mice displayed metastasis at much later dates after 4T1-cell implantation and much less metastatic lesions in the lung, lymph nodes and no metastasis lesion was observed in the liver and spleen. This data indicates a major metastasis inhibition in the 4T1-bearing mice caused by QQ-SON protein treatment without primary tumor removal.

**[00334]** Example 23

**[00335]** Histological analysis of the tumor tissue sections treated with QQ-PBS and QQ-SON proteins without primary tumor removed.

**[00336]** H&E stains of a 9L-tumor tissue slides of a rat treated with QQ-reagents in PBS buffer for 18 daily treatments, showing uniform tumor cells with extensive angiogenesis. Immunostains of a nearby tissue slide with anti-VE-cadherin antibody confirmed angiogenesis. This rat was sacrificed at day 26 after subcutaneous 9L cell implantation with a tumor of 13.5 $cm^3$ (around 15.5 g). In contrast, H&E stains of a tumor tissue slide of a rat treated with QQ-SON protein for 18 daily treatments showed different cell zones including tumor cell zone, connective tissue zone and fibroblast zone. This rat was sacrificed at day 49 after subcutaneous 9L cell implantation and its tumor was significantly reduced in size to 0.2 $cm^3$ (around 0.6 g). Immunostain of the fibroblast zone of a nearby tumor tissue slide of the same rat using an anti-a-procollagen, a fibroblast marker, antibody, confirmed the fibroblast zoon (positively stained) and tumor cell zone (negatively stained). Immunostains of the tumor tissue slides of the same rat treated with QQ-SON proteins for 18 daily treatments using anti-GFAP and anti-Tuj1 antibodies showed positive stains of both markers with neuronal cell morphology and neural rosette formation. This data indicates that the injected QQ-SON proteins induced in situ generation of transient 9L-piPSCs that differentiate into non-cancerous cells including neuronal lineage cells.

**[00337]** Similarly, H&E stains of 4T1-tumor tissue slides of the mice treated with QQ-SON protein also showed adipocytes and mammary duct, which were immunostained positive with adiponectin and cytokaratin 5/8/14, indicating that the injected QQ-SON protein also induced in situ 4T1-tumor cell reprogramming inside the primary tumor into 4T1-piPSCs that differentiate into breast tissue.

**[00338]** Example 24

**[00339]** QQ-SON treatment significantly enhances the genome stability of the treated 9L-cells in vivo.

**[00340]** SKY genome analysis of explanted cells of two subcutaneous 9L-tumor-bearing rats, both treated with QQ-SON protein for 18-days was performed. One rat (#12) displayed major response to the QQ-SON treatment and tumor started to shrink. Before the tumor disappeared, this

rat was sacrificed and the tumor collected for both explants and tumor tissue slides. Another rat (#15) displayed no response to the QQ-SON protein treatment and tumor continued to grow to reach the ending point (> 12 $cm^3$). This rat was also sacrificed and explants and tumor tissue slides were prepared.

**[00341]** The cells from the explant of #15 rat grew rapidly and reached confluency in 3-days. The cells displayed typical 9L-cell spindle morphology. However, the cells from the explant of #12 rat grew very slowly and only two-weeks later some cells with neural morphology with some colonies were observed. Immunostains of the tumor tissue slides with GFAP and Tuj 1 showed positive stains for both markers for those cells that displayed neural morphology in #12 rat, but negative stains for these two markers for #15 rat. Additional immunostains with β-catenin, CK5/6, E-cadherin, Lefty, Nodal and Cripto-1 showed opposite results for #12 and #15 rats. While the tumor tissue slides of #12 rat showed positive stains of CK5/6, E-cadherin, Lefty and β-catenin, a negative stain was observed in the tumor tissue slides of #15 rat. Interestingly, Lefty and E-cadherin co-stained in the same areas of the tumor tissue sections as well as CK5/6 and E-cadherin. In contrast, the tumor tissue slides of #15 rat showed positive stains for Nodal and Cripto-1, but those tissue sections of #12 showed negative stains for these two markers. These results indicate tumor cell conversion into non-cancerous cells in the tissue section of #12 rat, whereas the tissue sections of #15 rat remained 9L-tumor cells.

**[00342]** To assess genome stability of the explant cells, molecular cytogenetic analyses were performed. 20 mitotic images were collected for each explant of rat #15 and rat #12 and the average number of chromosomes for rat #15 and for rat #12 were analyzed. Table 4 shows a comparison of chromosomal aberrations of rat #15 and rat #12. Molecular cytogenetic analyses indicated 35% non-clonal chromosomal aberrations (NCCAs) and 20% of clonal chromosomal aberrations (CCAs) for rat #12 and 70% NCCAs and 15% CCAs for rat #15 (Table 4). Since the frequencies of NCCAs represent the level of genome instability while CCAs represent relative stability, these data suggest that the tumor that did not respond to QQ-SON protein treatment (rat #15) displayed higher levels of genome heterogeneity than those of the tumor (rat #12) that showed a good response to the QQ-SON treatment. This result indicates that the protein-induced *in situ* cell reprogramming significantly enhances genome stability of the treated cancer cells, indicating cell conversion of malignant cancer cells into non-cancerous cells.

Table 4: tumors that respond to the QQ-SON protein treatment (#12) display higher genome stability than a tumor that did not respond (#15); NCCA: non-clonal chromosomal aberrations; CCA: clonal chromosomal aberrations

| Rat | #mitotic images | # chromosomes | # NCCAs | % NCCAs | # CCAs | % CCAs |
|---|---|---|---|---|---|---|
| #12 | 20 | 64 | 7 | 35 | 4 | 20 |
| #15 | 20 | 60 | 14 | 70 | 3 | 15 |

**[00343]** Example 25

**[00344]** QQ-SON induced cell-converting cancer therapy mediated by protein-induced in situ cell reprogramming caused cancer cure of subcutaneous 9L-tumor bearing rats and late stage 4T1-bearing mice after surgical removal of primary tumors.

**[00345]** Subcutaneous implantation of 9L-cells into Fisher rats was performed to generate tumor-bearing rats. Five days after tumor cell implantation, daily intratumor injections of QQ-modified SON (QQ-SON) proteins were performed. A proper control of QQ-reagents in PBS (QQ-PBS) was also performed. A 90-day survival experiment was performed following a 18 daily intratumoral treatment regimen using QQ-SON proteins at 10 μg/mouse/day. During treatments, significantly reduced tumor growth in all treated rats was observed. After 18 daily treatments, 50% of the treated rats displayed diminished tumor volume over time, and no palpable tumor was present in these animals. The remaining treated rats displayed significantly slower tumor growth. The median survival of the treated group was 49±20 days (n = 8) whereas survival in the control group was 21±4 days (n = 6). Tumor recurrence was observed in three treated rats at day 32, 43 and 62, with a median recurrence of 45±13 days. The recurrent tumors grew very aggressively and reached a volume of > 12 $cm^3$ in 5-7 days (Table 5, Treatment 1). The fourth glioma-cured rat remained tumor-free for more than 30 months without evidence of teratoma formation.

**[00346]** When the daily intratumor treatment regimen was expanded to 30 days, 100% glioma-cured rats within the first 73 days during a 400-day survival experiment (n = 8) were obtained. Again, tumor recurrence for three treated rats at day 73, 78, and 92 (median recurrence: 81±8 days) was observed, which was much later than the tumor recurrence observed in rats treated for only 18 days. The remaining 5 rats remained tumor-free for 400-days. The three rats with recurrent tumors were treated for an additional 30 days (daily intra-tumor injection, 10μg/day QQ-SON). Of the three rats, two had very slow progression and survived for an additional 66 days (tumor occurrence on day 78) or 68 days (tumor reoccurrence on day 92). Only one rat displayed slow tumor growth and was sacrificed at day 109 (36 days after tumor recurrence was identified) when the tumor reached 12 $cm^3$ in volume. The median survival of the treated rats was 280±155 days (n = 8) compared to 21±4 days for the control group (n = 6) (Table 5, Treatment 2).

**[00347]** To ensure that this result was reproducible, the above 30 daily treatment experiment was repeated and achieved 80% glioma-cured rats within the first 79-days. Two rats displayed slow tumor growth but had reached a tumor volume of 12 $cm^3$ at day 29 and 48, respectively (Table 5, Treatment 3). However, two glioma-cured rats displayed tumor recurrence at day 79 and 111 (median recurrence: 95±16 days). These two rats were treated with the QQ-SON proteins (10 μg/day) for an additional 30 days. One of the two rats displayed a slow tumor growth and reached a volume of 12 $cm^3$ in 30 days after the tumor recurred on day 79. The other rat survived for an additional 69-days. The median survival of the treated rats was 276±156 days (n = 10), whereas the control rats treated with QQ-PBS only survived for 23±3 days after tumor implantation (n = 6). The tumor-cured rats from both treatments 2 and 3 survived for more than 15-months so far without tumor recurrence and without teratoma formation.

Table 5

| Group | # of Rats | # injections | 9L-Glioma Cured (%) | Mean Survival (Day) | Mean Recurrence (day / Recurrence %) | Recurrence day |
|---|---|---|---|---|---|---|
| Control | 6 | 18 or 30 (QQ-PBS) | 0 | 21±4 | - | - |
| Treatment 1 | 8 | 18 (QQ-SON) | 13 (90 day survival) | 49±20 | 45±13 / 37.5 | 32/42/62 |
| Treatment 2 | 8 | 30 (QQ-SON) | 70 (400 day survival) | 280±155 | 81±8 / 30 | 72/78/92 |
| Treatment 3 | 10 | 30 (QQ-SON) | 60 (400 day survival) | 276±156 | 95±16 / 20 | 79/111 |

**[00348]** A similar result was observed for late stage of 4T1-breast cancer bearing mice after surgical removal of the primary tumors at day 18 after 4T1-cell implantation for both QQ-PBS and QQ-SON treated mice. The daily intra-tumor QQ-SON protein treatment was performed at day 5 and continued for 40-days. Previously, it was shown that lung metastasis started at day 7. At day 18, MRI observable lung metastatic lesions for every mouse were observed. A 250-day survival experiment was performed. The resultant data, Table 6, indicated that while the QQ-PBS control mice died between days 25-47, the QQ-SON treated mice survived much longer and 61% (n=11) of QQ-SON treated mice survived entire 250-days without tumor recurrence and teratoma formation (n=18), see Figure 8. MRI results showed disappearance of lung metastatic lesions. These data demonstrate high treatment efficacy of this QQ-SON-induced cell-converting cancer therapy.

Table 6

| Mice | Group | Tumor size at surgery ($mm^3$) | Primary Tumor Recurrence | Day detecting lung lesion | Day of lung lesions disappeared or cause of death | Survival Day | Alive 10-23-2014) |
|---|---|---|---|---|---|---|---|
| Red 1 | Control | 114 | No | 16 | Metastasis | 46 | |
| Red 2 | Control | 125 | No | 16 | Metastasis | 46 | |
| Red 3 | Control | 60.5 | No | 16 | Metastasis | 44 | |
| Red 4 | Control | 25.5 | No | 16 | Metastasis | 44 | |
| Blue 1 | Treatment | 6.5 | No | 16 | Inflammation | 47 | |
| Blue 2 | Treatment | 20.5 | No | 16 | Stasis | | 110 |
| Blue 3 | Treatment | 3.5 | No | 16 | 74 | | 267 |
| Blue 4 | Treatment | 60.5 | No | 16 | Metastasis | 49 | |
| Blue 5 | Treatment | 33.5 | No | 16 | 59 | | 267 |
| Green 1 | Treatment | 20 | No | 16 | 60 | | 267 |
| Green 2 | Treatment | 18.5 | No | 16 | Inflammation | 75 | |
| Green 3 | Treatment | 15.5 | No | 16 | 60 | | 267 |
| Green 4 | Treatment | 54 | No | 16 | Metastasis position | 45 | |
| Green 5 | Treatment | 53 | No | 16 | Inflammation | 54 | |

**[00349]** Figure 8 is a Kaplan-Meier survival curve (250-day survival) of 4T1-breast cancer bearing mice after surgical removal of the primary 4T1-breast cancer at day 18. These 4T1 breast cancer bearing mice were treated with QQ-PBS (Control) and QQ-SON proteins (Treatment) at day 6 after 4T1-cell implantation into the #4 fat pad of female BALB/c mice. The primary tumors were palpable around day 5 and surgically removed at day 18. The QQ-PBS/QQ-SON treatment was performed daily by both intra-tumoral (5µg/mouse/day) and intraperitoneal injections (25µg/mouse/day).

**[00350]** Day 0 in the Kaplan-Meier survival curve of Figure 8 is the day when the surgery was performed at day 18. A small population of mice displayed tumor recurrence due to incomplete tumor removal. These mice were treated with QQ-SON protein or QQ-PBS via intra-tumoral injections and their survival were also compared (dotted survival curves). For those mice without tumor recurrence, their survival curves are shown in solid lines. Mice that survived for this entire 250-day survival experiment without tumor recurrence are considered tumor-cured mice. Tumor-cure has been achieved in 61% of population of treated mice.

**[00351]** Thus, QQ-SON-induced in situ cell reprogramming of the cancer cells inside the tumor to generate transient piPSCs that differentiate into different non-cancerous cells within that tissue is demonstrated. The types of the differentiated non-cancerous cells depend on specific tissue environment. This inter-play between QQ-SON-induced in situ cell reprogramming and tissue environment induced differentiation precisely regulates generation of transient piPSCs inside tumor and induced differentiation, preventing tumor and teratoma formation. This safe protein-induced in situ cell reprogramming technology in situ generates stem cells and which then differentiate into normal cells induced by tissue environment to replace diseased cells for treatment of many diseases and injuries.

**[00352]** Sequences

**[00353]** Homo sapiens SRY (sex determining region Y)-box 2 (SOX2) (NM_003106) SEQ ID NO:1 (protein) and SEQ ID NO:65 (DNA)

MYNMMETELKPPGPQQTSGGGGGNSTAAAAGGNQKNSPDRVKRPMNAFMVWSRGQRRKMAQENPK
MHNSEISKRLGAEWKLLSETEKRPFIDEAKRLRALHMKEHPDYKYRPRRKTKTLMKKDKYTLPGG
LLAPGGNSMASGVGVGAGLGAGVNQRMDSYAHMNGWSNGSYSMMQDQLGYPQHPGLNAHGAAQMQ
PMHRYDVSALQYNSMTSSQTYMNGSPTYSMSYSQQGTPGMALGSMGSVVKSEASSSPPVVTSSSH
SRAPCQAGDLRDMISMYLPGAEVPEPAAPSRLHMSQHYQSGPVPGTAINGTLPLSHM (SEQ ID NO:1)

atgtacaacatgatggagacggagctgaagccgccgggcccgcagcaaacttcgggggcggcgg
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ggtgccggaacccgccgccccccagcagacttcacatgtcccagcactaccagagcggcccggtgc
ccggcacggccattaacggcacactgcccctctcacacatgtga (SEQ ID NO:65)

**[00354]** Homo sapiens POU class 5 homeobox 1 (POU5F1) also known as Oct4 (NM_002701) SEQ ID NO:2 (protein) and SEQ ID NO:66 (DNA)

MAGHLASDFAFSPPPGGGGDGPGGPEPGWVDPRTWLSFQGPPGGPGIGPGVGPGSEVWGIPPCPP
PYEFCGGMAYCGPQVGVGLVPQGGLETSQPEGEAGVGVESNSDGASPEPCTVTPGAVKLEKEKLE
QNPEESQDIKALQKELEQFAKLLKQKRITLGYTQADVGLTLGVLFGKVFSQTTICRFEALQLSFK
NMCKLRPLLQKWVEEADNNENLQEICKAETLVQARKRKRTSIENRVRGNLENLFLQCPKPTLQQI
SHIAQQLGLEKDVVRVWFCNRRQKGKRSSSDYAQREDFEAAGSPFSGGPVSFPLAPGPHFGTPGY
GSPHFTALYSSVPFPEGEAFPPVSVTTLGSPMHSN (SEQ ID NO:2)

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gggagccctcacttcactgcactgtactcctcggtccctttccctgaggggaagcctttccccc
tgtctccgtcaccactctgggctctcccatgcattcaaactga (SEQ ID NO:66)

**[00355]** Homo sapiens Nanog homeobox (NANOG) (NM_024865) SEQ ID NO:3 (protein) and SEQ ID NO:67 (DNA)

MSVDPACPQSLPCFEASDCKESSPMPVICGPEENYPSLQMSSAEMPHTETVSPLPSSMDLLIQDS
PDSSTSPKGKQPTSAEKSVAKKEDKVPVKKQKTRTVFSSTQLCVLNDRFQRQKYLSLQQMQELSN
ILNLSYKQVKTWFQNQRMKSKRWQKNNWPKNSNGVTQKASAPTYPSLYSSYHQGCLVNPTGNLPM
WSNQTWNNSTWSNQTQNIQSWSNHSWNTQTWCTQSWNNQAWNSPFYNCGEESLQSCMQFQPNSPA
SDLEAALEAAGEGLNVIQQTTRYFSTPQTMDLFLNYSMNMQPEDV (SEQ ID NO:3)

atgagtgtggatccagcttgtccccaaagcttgccttgctttgaagcatccgactgtaaagaatc
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gtattttagtactccacaaaccatggatttattcctaaactactccatgaacatgcaacctgaag
acgtgtga (SEQ ID NO:67)

**[00356]** Homo sapiens lin-28 homolog A (C. elegans) (LIN28A) (NM_024674) SEQ ID NO:4 (protein) and SEQ ID NO:68 (DNA)

MGSVSNQQFAGGCAKAAEEAPEEAPEDAARAADEPQLLHGAGICKWFNVRMGFGFLSMTARAGVA
LDPPVDVFVHQSKLHMEGFRSLKEGEAVEFTFKKSAKGLESIRVTGPGGVFCIGSERRPKGKSMQ
KRRSKGDRCYNCGGLDHHAKECKLPPQPKKCHFCQSISHMVASCPLKAQQGPSAQGKPTYFREEE
EEIHSPTLLPEAQN (SEQ ID NO:4)

atgggctccgtgtccaaccagcagtttgcaggtggctgcgccaaggcggcagaagaggcgcccga
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gtccgctgaaggcccagcagggccctagtgcacagggaaagccaacctactttcgagaggaagaa
gaagaaatccacagccctaccctgctcccggaggcacagaattga (SEQ ID NO:68)

**[00357]** Homo sapiens Krueppel-like factor 4 (Klf4) (NP_004226) SEQ ID NO:5 (protein) and SEQ ID NO:69 (DNA)

MRQPPGESDMAVSDALLPSFSTFASGPAGREKTLRQAGAPNNRWREELSHMKRLPPVLPGRPYDL
AAATVATDLESGGAGAACGGSNLAPLPRRETEEFNDLLDLDFILSNSLTHPPESVAATVSSSASA
SSSSSPSSSGPASAPSTCSFTYPIRAGNDPGVAPGGTGGGLLYGRESAPPPTAPFNLADINDVSP
SGGFVAELLRPELDPVYIPPQQPQPPGGGLMGKFVLKASLSAPGSEYGSPSVISVSKGSPDGSHP
VVVAPYNGGPPRTCPKIKQEAVSSCTHLGAGPPLSNGHRPAAHDFPLGRQLPSRTTPTLGLEEVL
SSRDCHPALPLPPGFHPHPGPNYPSFLPDQMQPQVPPLHYQELMPPGSCMPEEPKPKRGRRSWPR
KRTATHTCDYAGCGKTYTKSSHLKAHLRTHTGEKPYHCDWDGCGWKFARSDELTRHYRKHTGHRP
FQCQKCDRAFSRSDHLALHMKRHF (SEQ ID NO:5)

atgaggcagccacctggcgagtctgacatggctgtcagcgacgcgctgctcccatctttctccac
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ttccagtgccaaaaatgcgaccgagcattttccaggtcggaccacctcgccttacacatgaagag
gcatttttaa (SEQ ID NO:69)

**[00358]** Homo sapiens c-MYC (NP_002458) SEQ ID NO:6 (protein) and SEQ ID NO:70 (DNA)

MDFFRVVENQQPPATMPLNVSFTNRNYDLDYDSVQPYFYCDEEENFYQQQQQSELQPPAPSEDIW
KKFELLPTPPLSPSRRSGLCSPSYVAVTPFSLRGDNDGGGGSFSTADQLEMVTELLGGDMVNQSF
ICDPDDETFIKNIIIQDCMWSGFSAAAKLVSEKLASYQAARKDSGSPNPARGHSVCSTSSLYLQD
LSAAASECIDPSVVFPYPLNDSSSPKSCASQDSSAFSPSSDSLLSSTESSPQGSPEPLVLHEETP
PTTSSDSEEEQEDEEEIDVVSVEKRQAPGKRSESGSPSAGGHSKPPHSPLVLKRCHVSTHQHNYA
APPSTRKDYPAAKRVKLDSVRVLRQISNNRKCTSPRSSDTEENVKRRTHNVLERQRRNELKRSFF
ALRDQIPELENNEKAPKVVILKKATAYILSVQAEEQKLISEEDLLRKRREQLKHKLEQLRNSCA
(SEQ ID NO:6)

atggatttttttcgggtagtggaaaaccagcagcctcccgcgacgatgcccctcaacgttagctt
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cccaccaccagcagcgactctgaggaggaacaagaagatgaggaagaaatcgatgttgtttctgt
ggaaaagaggcaggctcctggcaaaaggtcagagtctggatcaccttctgctggaggccacagca
aacctcctcacagcccactggtcctcaagaggtgccacgtctccacacatcagcacaactacgca
gcgcctccctccactcggaaggactatcctgctgccaagagggtcaagttggacagtgtcagagt
cctgagacagatcagcaacaaccgaaaatgcaccagccccaggtcctcggacaccgaggagaatg
tcaagaggcgaacacacaacgtcttggagcgccagaggaggaacgagctaaaacggagctttttt
gccctgcgtgaccagatcccggagttggaaaacaatgaaaaggcccccaaggtagttatccttaa
aaaagccacagcatacatcctgtccgtccaagcagaggagcaaaagctcatttctgaagaggact
tgttgcggaaacgacgagaacagttgaaacacaaacttgaacagctacggaactcttgtgcgtaa
(SEQ ID NO:70

**[00359]** Homo sapiens GATA binding protein 4 (GATA4) (NM_002052) SEQ ID NO:7 (protein) and SEQ ID NO:71 (DNA)

MYQSLAMAANHGPPPGAYEAGGPGAFMHGAGAASSPVYVPTPRVPSSVLGLSYLQGGGAGSASGG
ASGGSSGGAASGAGPGTQQGSPGWSQAGADGAAYTPPPVSPRFSFPGTTGSLAAAAAAAAAREAA
AYSSGGGAAGAGLAGREQYGRAGFAGSYSSPYPAYMADVGASWAAAAAASAGPFDSPVLHSLPGR
ANPAARHPNLDMFDDFSEGRECVNCGAMSTPLWRRDGTGHYLCNACGLYHKMNGINRPLIKPQRR
LSASRRVGLSCANCQTTTTTLWRRNAEGEPVCNACGLYMKLHGVPRPLAMRKEGIQTRKRKPKNL
NKSKTPAAPSGSESLPPASGASSNSSNATTSSSEEMRPIKTEPGLSSHYGHSSSVSQTFSVSAMS
GHGPSIHPVLSALKLSPQGYASPVSQSPQTSSKQDSWNSLVLADSHGDIITA (SEQ ID
NO:7)

atgtatcagagcttggccatggccgccaaccacgggccgccccccggtgcctacgaggcgggcgg
ccccggcgccttcatgcacggcgcgggcgccgcgtcctcgccagtctacgtgcccacaccgcggg
tgccctcctccgtgctgggcctgtcctacctccagggcggaggcgcgggctctgcgtccggaggc
gcctcgggcggcagctccggtggggccgcgtctggtgcggggcccgggacccagcagggcagccc
gggatggagccaggcgggagccgacggagccgcttacaccccgccgccggtgtcgccgcgcttct
ccttcccggggaccaccgggtccctggcggccgccgccgccgctgccgcggcccgggaagctgcg
gcctacagcagtggcggcggagcggcgggtgcgggcctggcgggccgcgagcagtacgggcgcgc
cggcttcgcgggctcctactccagcccctacccggcttacatggccgacgtgggcgcgtcctggg
ccgcagccgccgccgcctccgccggcccccttcgacagcccggtcctgcacagcctgcccggccgg
gccaacccggccgcccgacaccccaatctcgatatgtttgacgacttctcagaaggcagagagtg

tgtcaactgtggggctatgtccaccccgctctggaggcgagatgggacgggtcactatctgtgca
acgcctgcggcctctaccacaagatgaacggcatcaaccggccgctcatcaagcctcagcgccgg
ctgtccgcctcccgccgagtgggcctctcctgtgccaactgccagaccaccaccaccacgctgtg
gcgccgcaatgcggagggcgagcctgtgtgcaatgcctgcggcctctacatgaagctccacgggg
tccccaggcctcttgcaatgcggaaagaggggatccaaaccagaaaacggaagcccaagaacctg
aataaatctaagacaccagcagctccttcaggcagtgagagccttcctcccgccagcggtgcttc
cagcaactccagcaacgccaccaccagcagcagcgaggagatgcgtcccatcaagacggagcctg
gcctgtcatctcactacgggcacagcagctccgtgtcccagacgttctcagtcagtgcgatgtct
ggccatgggccctccatccaccctgtcctctcggccctgaagctctccccacaaggctatgcgtc
tcccgtcagccagtctccacagaccagctccaagcaggactcttggaacagcctggtcttggccg
acagtcacggggacataatcactgcgtaa (SEQ ID NO:71)

**[00360]** Homo sapiens heart and neural crest derivatives expressed 2 (HAND2) (NM_021973) SEQ ID NO:8 (protein) and SEQ ID NO:72 (DNA)

MSLVGGFPHHPVVHHEGYPFAAAAAAAAAAAASRCSHEENPYFHGWLIGHPEMSPPDYSMALSYS
PEYASGAAGLDHSHYGGVPPGAGPPGLGGPRPVKRRGTANRKERRRTQSINSAFAELRECIPNVP
ADTKLSKIKTLRLATSYIAYLMDLLAKDDQNGEAEAFKAEIKKTDVKEEKRKKELNEILKSTVSS
NDKKTKGRTGWPQHVWALELKQ (SEQ ID NO:8)

atgagtctggtaggtggttttccccaccacccggtggtgcaccacgagggctacccgtttgccgc
cgccgccgccgcagctgccgccgccgccgccagccgctgcagccatgaggagaacccctacttcc
atggctggctcatcggccaccccgagatgtcgcccccgactacagcatggccctgtcctacagc
cccgagtatgccagcggcgccgccggcctggaccactcccattacgggggggtgccgccgggcgc
cgggcccccgggcctgggggggccgcgcccggtgaagcgccgaggcaccgccaaccgcaaggagc
ggcgcaggactcagagcatcaacagcgccttcgccgaactgcgcgagtgcatccccaacgtaccc
gccgacaccaaactctccaaaatcaagaccctgcgcctggccaccagctacatcgcctacctcat
ggacctgctggccaaggacgaccagaatggcgaggcggaggccttcaaggcagagatcaagaaga
ccgacgtgaaagaggagaagaggaagaaggagctgaacgaaatcttgaaaagcacagtgagcagc
aacgacaagaaaaccaaaggccggacgggctggccgcagcacgtctgggccctggagctcaagca
gtga (SEQ ID NO:72)

**[00361]** Homo sapiens myocyte enhancer factor 2C (MEF2C) (NM_001193350) SEQ ID NO:9 (protein) and SEQ ID NO:73 (DNA)

MGRKKIQITRIMDERNRQVTFTKRKFGLMKKAYELSVLCDCEIALIIFNSTNKLFQYASTDMDKV
LLKYTEYNEPHESRTNSDIVETLRKKGLNGCDSPDPDADDSVGHSPESEDKYRKINEDIDLMISR
QRLCAVPPPNFEMPVSIPVSSHNSLVYSNPVSSLGNPNLLPLAHPSLQRNSMSPGVTHRPPSAGN
TGGLMGGDLTSGAGTSAGNGYGNPRNSPGLLVSPGNLNKNMQAKSPPPMNLGMNNRKPDLRVLIP
PGSKNTMPSVSEDVDLLLNQRINNSQSAQSLATPVVSVATPTLPGQGMGGYPSAISTTYGTEYSL
SSADLSSLSGFNTASALHLGSVTGWQQQHLHNMPPSALSQLGACTSTHLSQSSNLSLPSTQSLNI
KSEPVSPPRDRTTTPSRYPQHTRHEAGRSPVDSLSSCSSSYDGSDREDHRNEFHSPIGLTRPSPD
ERESPSVKRMRLSEGWAT (SEQ ID NO:9)

atggggagaaaaaagattcagattacgaggattatggatgaacgtaacagacaggtgacatttac
aaagaggaaatttgggttgatgaagaaggcttatgagctgagcgtgctgtgtgactgtgagattg
cgctgatcatcttcaacagcaccaacaagctgttccagtatgccagcaccgacatggacaaagtg
cttctcaagtacacggagtacaacgagccgcatgagagccggacaaactcagacatcgtggagac
gttgagaaagaagggccttaatggctgtgacagcccagaccccgatgcggacgattccgtaggtc
acagccctgagtctgaggacaagtacaggaaaattaacgaagatattgatctaatgatcagcagg
caaagattgtgtgctgttccacctcccaacttcgagatgccagtctccatcccagtgtccagcca
caacagtttggtgtacagcaaccctgtcagctcactgggaaaccccaacctattgccactggctc
acccttctctgcagaggaatagtatgtctcctggtgtaacacatcgacctccaagtgcaggtaac
acaggtggtctgatgggtggagacctcacgtctggtgcaggcaccagtgcagggaacgggtatgg
caatccccgaaactcaccaggtctgctggtctcacctggtaacttgaacaagaatatgcaagcaa
aatctcctcccccaatgaatttaggaatgaataaccgtaaaccagatctccgagttcttattcca

ccaggcagcaagaatacgatgccatcagtgtctgaggatgtcgacctgcttttgaatcaaaggat
aaataactcccagtcggctcagtcattggctaccccagtggtttccgtagcaactcctactttac
caggacaaggaatgggaggatatccatcagccatttcaacaacatatggtaccgagtactctctg
agtagtgcagacctgtcatctctgtctgggtttaacaccgccagcgctcttcaccttggttcagt
aactggctggcaacagcaacacctacataacatgccaccatctgccctcagtcagttgggagctt
gcactagcactcatttatctcagagttcaaatctctccctgccttctactcaaagcctcaacatc
aagtcagaacctgtttctcctcctagagaccgtaccaccacccctttcgagatacccacaacacac
gcgccacgaggcggggagatctcctgttgacagcttgagcagctgtagcagttcgtacgacggga
gcgaccgagaggatcaccggaacgaattccactcccccattggactcaccagaccttcgccggac
gaaagggaaagtccctcagtcaagcgcatgcgactttctgaaggatgggcaacatga (SEQ ID NO:73)

**[00362]** Human transcription factor TBX5 (U80987) SEQ ID NO:10 (protein) and SEQ ID NO:74 (DNA)

MADADEGFGLAHTPLEPDAKDLPCDSKPESALGAPSKSPSSPQAAFTQQGMEGIKVFLHERELWL
KFHEVGTEMIITKAGRRMFPSYKVKVTGLNPKTKYILLMDIVPADDHRYKFADNKWSVTGKAEPA
MPGRLYVHPDSPATGAHWMRQLVSFQKLKLTNNHLDPFGHIILNSMHKYQPRLHIVKADENNGFG
SKNTAFCTHVFPETAFIAVTSYQNHKITQLKIENNPFAKGFRGSDDMELHRMSRMQSKEYPVVPR
STVRQKVASNHSPFSSESRALSTSSNLGSQYQCENGVSGPSQDLLPPPNPYPLPQEHSQIYHCTK
RKGECDHPWSICFLSYLFLSLGWG (SEQ ID NO:10)

atggccgacgcagacgagggctttggcctggcgcacacgcctctggagcctgacgcaaaagacct
gccctgcgattcgaaacccgagagcgcgctcggggccccagcaagtccccgtcgtccccgcagg
ccgccttcacccagcagggcatggagggaatcaaagtgtttctccatgaaagagaactgtggcta
aaattccacgaagtgggcacggaaatgatcataaccaaggctggaaggcggatgtttcccagtta
caaagtgaaggtgacgggccttaatcccaaaacgaagtacattcttctcatggacattgtacctg
ccgacgatcacagatacaaattcgcagataataaatggtctgtgacgggcaaagctgagcccgcc
atgcctggccgcctgtacgtgcacccagactcccccgccaccggggcgcattggatgaggcagct
cgtctccttccagaaactcaagctcaccaacaaccacctggacccatttgggcatattattctaa
attccatgcacaaataccagcctagattacacatcgtgaaagcggatgaaaataatggatttggc
tcaaaaaatacagcgttctgcactcacgtctttcctgagactgcgtttatagcagtgacttccta
ccagaaccacaagatcacgcaattaaagattgagaataatccctttgccaaaggatttcggggca
gtgatgacatggagctgcacagaatgtcaagaatgcaaagtaaagaatatcccgtggtccccagg
agcaccgtgaggcaaaaagtggcctccaaccacagtcctttcagcagcgagtctcgagctctctc
cacctcatccaatttggggtcccaataccagtgtgagaatggtgtttccggcccctcccaggacc
tcctgcctccacccaacccatacccactgccccaggagcatagccaaatttaccattgtaccaag
aggaaaggtgagtgtgatcacccctggtcaatttgctttctttcttacctttttcctttccttggg
ttgggggtga (SEQ ID NO:74)

**[00363]** Homo sapiens neurogenin 3 (NEUROG3) (NM_020999.3) SEQ ID NO:11 (protein) and SEQ ID NO:75 (DNA)

MTPQPSGAPTVQVTRETERSFPRASEDEVTCPTSAPPSPTRTRGNCAEAEEGGCRGAPRKLRARR
GGRSRPKSELALSKQRRSRRKKANDRERNRMHNLNSALDALRGVLPTFPDDAKLTKIETLRFAHN
YIWALTQTLRIADHSLYALEPPAPHCGELGSPGGSPGDWGSLYSPVSQAGSLSPAASLEERPGLL
GATFSACLSPGSLAFSDFL (SEQ ID NO:11)

atgacgcctcaaccctcgggtgcgcccactgtccaagtgacccgtgagacggagcggtccttccc
cagagcctcggaagacgaagtgacctgccccacgtccgccccgcccagccccactcgcacacggg
ggaactgcgcagaggcggaagagggaggctgccgaggggccccgaggaagctccgggcacggcgc
gggggacgcagccggcctaagagcgagttggcactgagcaagcagcgacggagtcggcgaaagaa
ggccaacgaccgcgagcgcaatcgaatgcacaacctcaactcggcactggacgccctgcgcggtg
tcctgcccaccttcccagacgacgcgaagctcaccaagatcgagacgctgcgcttcgcccacaac
tacatctgggcgctgactcaaacgctgcgcatagcggaccacagcttgtacgcgctggagccgcc
ggcgccgcactgcggggagctgggcagcccaggcggttcccccggggactgggggtccctctact

ccccagtctcccaggctggcagcctgagtcccgccgcgtcgctggaggagcgacccgggctgctg
ggggccacctttccgcctgcttgagcccaggcagtctggctttctcagattttctgtga (SEQ ID NO:75)

**[00364]** Homo sapiens paired box 4 (PAX4) (NM_006193.2) SEQ ID NO:12 (protein) and SEQ ID NO:76 (DNA)

MNQLGGLFVNGRPLPLDTRQQIVRLAVSGMRPCDISRILKVSNGCVSKILGRYYRTGVLEPKGIG
GSKPRLATPPVVARIAQLKGECPALFAWEIQRQLCAEGLCTQDKTPSVSSINRVLRALQEDQGLP
CTRLRSPAVLAPAVLTPHSGSETPRGTHPGTGHRNRTIFSPSQAEALEKEFQRGQYPDSVARGKL
ATATSLPEDTVRVWFSNRRAKWRRQEKLKWEMQLPGASQGLTVPRVAPGIISAQQSPGSVPTAAL
PALEPLGPSCYQLCWATAPERCLSDTPPKACLKPCWGHLPPQPNSLDSGLLCLPCPSSHCHLASL
SGSQALLWPGCPLLYGLE (SEQ ID NO:12)

atgaaccagcttgggggctctttgtgaatggccggcccctgcctctggatacccggcagcagat
tgtgcggctagcagtcagtggaatgcggccctgtgacatctcacggatccttaaggtatctaatg
gctgtgtgagcaagatcctagggcgttactaccgcacaggtgtcttggagccaaagggcattggg
ggaagcaagccacggctggctacacccccctgtggtggctcgaattgcccagctgaagggtgagtg
tccagccctctttgcctgggaaatccaacgccagctttgtgctgaagggctttgcacccaggaca
agactcccagtgtctcctccatcaaccgagtcctgcgggcattacaggaggaccagggactaccg
tgcacacggctcaggtcaccagctgttttggctccagctgtcctcactccccatagtggctctga
gactccccggggtacccacccagggaccggccaccggaatcggactatcttctccccaagccaag
cagaggcactggagaaagagttccagcgtgggcagtatcctgattcagtggcccgtggaaagctg
gctactgccacctctctgcctgaggacacggtgagggtctggttttccaacagaagagccaaatg
gcgtcggcaagagaagctcaagtgggaaatgcagctgccaggtgcttcccaggggctgactgtac
caagggttgccccaggaatcatctctgcacagcagtcccctggcagtgtgcccacagcagccctg
cctgccctggaaccactgggtccctcctgctatcagctgtgctgggcaacagcaccagaaaggtg
tctgagtgacaccccacctaaagcctgtctcaagccctgctggggccacttgcccccacagccga
attccctggactcaggactgctttgccttccttgcccttcctcccactgtcacctggccagtctt
agtggctctcaggccctgctctggcctggctgcccactactgtatggcttggaatga (SEQ ID NO:76)

**[00365]** Homo sapiens pancreatic and duodenal homeobox 1 (PDX1) (NM_000209.3) SEQ ID NO:13 (protein) and SEQ ID NO:77 (DNA)

MNGEEQYYAATQLYKDPCAFQRGPAPEFSASPPACLYMGRQPPPPPPHPFPGALGALEQGSPPDI
SPYEVPPLADDPAVAHLHHHLPAQLALPHPPAGPFPEGAEPGVLEEPNRVQLPFPWMKSTKAHAW
KGQWAGGAYAAEPEENKRTRTAYTRAQLLELEKEFLFNKYISRPRRVELAVMLNLTERHIKIWFQ
NRRMKWKKEEDKKRGGGTAVGGGGVAEPEQDCAVTSGEELLALPPPPPPGGAVPPAAPVAAREGR
LPPGLSASPQPSSVAPRRPQEPR (SEQ ID NO:13)

atgaacggcgaggagcagtactacgcggccacgcagctttacaaggacccatgcgcgttccagcg
aggcccggcgccggagttcagcgccagccccctgcgtgcctgtacatgggccgccagcccccgc
cgccgccgccgcacccgttccctggcgccctgggcgcgctggagcagggcagccccccggacatc
tccccgtacgaggtgcccccctcgccgacgaccccgcggtggcgcaccttcaccaccacctccc
ggctcagctcgcgctcccccacccgcccgccgggcccttcccggagggagccgagccgggcgtcc
tggaggagcccaaccgcgtccagctgcctttcccatggatgaagtctaccaaagctcacgcgtgg
aaaggccagtgggcaggcggcgcctacgctgcggagccggaggagaacaagcggacgcgcacggc
ctacacgcgcgcacagctgctagagctggagaaggagttcctattcaacaagtacatctcacggc
cgcgccgggtggagctggctgtcatgttgaacttgaccgagagacacatcaagatctggttccaa
aaccgccgcatgaagtggaaaaaggaggaggacaagaagcgcggcggcgggacagctgtcggggg
tggcggggtcgcggagcctgagcaggactgcgccgtgacctccggcgaggagcttctggcgctgc
cgccgccgccgccccccggaggtgctgtgccgcccgctgcccccgttgccgcccgagagggccgc
ctgccgcctggccttagcgcgtcgccacagccctccagcgtcgcgcctcggcggccgcaggaacc
acgatga (SEQ ID NO:77)

**[00366]** Human SOX9 protein (1-509) (Z46629.1) SEQ ID NO:14 (protein) and SEQ ID NO:78 (DNA)

MNLLDPFMKMTDEQEKGLSGAPSPTMSEDSAGSPCPSGSGSDTENTRPQENTFPKGEPDLKKESE
EDKFPVCIREAVSQVLKGYDWTLVPMPVRVNGSSKNKPHVKRPMNAFMVWAQAARRKLADQYPHL
HNAELSKTLGKLWRLLNESEKRPFVEEAERLRVQHKKDHPDYKYQPRRRKSVKNGQAEAEEATEQ
THISPNAIFKALQADSPHSSSGMSEVHSPGEHSGQSQGPPTPPTTPKTDVQPGKADLKREGRPLP
EGGRQPPIDFRDVDIGELSSDVISNIETFDVNEFDQYLPPNGHPGVPATHGQVTYTGSYGISSTA
ATPASAGHVWMSKQQAPPPPQQPPQAPPAPQAPPQPQAAPPQQPAAPPQQPQAHTLTTLSSEPG
QSQRTHIKTEQLSPSHYSEQQQHSPQQIAYSPFNLPHYSPSYPPITRSQYDYTDHQNSSSYYSHA
AGQGTGLYSTFTYMNPAQRPMYTPIADTSGVPSIPQTHSPQHWEQPVYTQLTRP (SEQ ID NO:14)

atgaatctcctggacccttcatgaagatgaccgacgagcaggagaagggcctgtccggcgcccc
cagccccaccatgtccgaggactccgcgggctcgccctgcccgtcgggctccggctcggacaccg
agaacacgcggccccaggagaacacgttccccaagggcgagcccgatctgaagaaggagagcgag
gaggacaagttccccgtgtgcatccgcgaggcggtcagccaggtgctcaaaggctacgactggac
gctggtgcccatgccggtgcgcgtcaacggctccagcaagaacaagccgcacgtcaagcggccca
tgaacgccttcatggtgtgggcgcaggcggcgcgcaggaagctcgcggaccagtacccgcacttg
cacaacgccgagctcagcaagacgctgggcaagctctggagacttctgaacgagagcgagaagcg
gcccttcgtggaggaggcggagcggctgcgcgtgcagcacaagaaggaccacccggattacaagt
accagccgcggcggaggaagtcggtgaagaacgggcaggcggaggcagaggaggccacggagcag
acgcacatctcccccaacgccatcttcaaggcgctgcaggccgactcgccacactcctcctccgg
catgagcgaggtgcactcccccggcgagcactcggggcaatcccagggcccaccgaccccaccca
ccacccccaaaaccgacgtgcagccgggcaaggctgacctgaagcgagaggggcgccccttgcca
gaggggggcagacagccccctatcgacttccgcgacgtggacatcggcgagctgagcagcgacgt
catctccaacatcgagaccttcgatgtcaacgagtttgaccagtacctgccgcccaacggccacc
cgggggtgccggccacgcacggccaggtcacctacacgggcagctacggcatcagcagcaccgcg
gccaccccggcgagcgcgggccacgtgtggatgtccaagcagcaggcgccgccgccacccccgca
gcagcccccacaggccccgccggccccgcaggcgcccccgcagccgcaggcggcgcccccacagc
agccggcggcacccccgcagcagccacaggcgcacacgctgaccacgctgagcagcgagccgggc
cagtcccagcgaacgcacatcaagacggagcagctgagccccagccactacagcgagcagcagca
gcactcgccccaacagatcgcctacagccccttcaacctcccacactacagcccctcctacccgc
ccatcacccgctcacagtacgactacaccgaccaccagaactccagctcctactacagccacgcg
gcaggccagggcaccggcctctactccaccttcacctacatgaaccccgctcagcgccccatgta
cacccccatcgccgacacctctggggtcccttccatcccgcagacccacagcccccagcactggg
aacaacccgtctacacacagctcactcgaccttga (SEQ ID NO:78)

**[00367]** Homo sapiens zinc finger protein SLUG (SLUG) gene (AF084243.1) SEQ ID NO:15 (protein) and SEQ ID NO:79 (DNA)

MPRSFLVKKHFNASKKPNYSELDTHTVIISPYLYESYSMPVIPQPEILSSGAYSPITVWTTAAPF
HAQLPNGLSPLSGYSSSLGRVSPPPPSDTSSKDHSGSESPISDEEERLQSKLSDPHAIEAEKFQC
NLCNKTYSTFSGLAKHKQLHCDAQSRKSFSCKYCDKEYVSLGALKMHIRTHTLPCVCKICGKAFS
RPWLLQGHIRTHTGEKPFSCPHCNRAFADRSNLRAHLQTHSDVKKYQCKNCSKTFSRMSLLHKHE
ESGCCVAH (SEQ ID NO:15)

atgccgcgctccttcctggtcaagaagcatttcaacgcctccaaaaagccaaactacagcgaact
ggacacacatacagtgattatttccccgtatctctatgagagttactccatgcctgtcataccac
aaccagagatcctcagctcaggagcatacagccccatcactgtgtggactaccgctgctccattc
cacgcccagctacccaatggcctctctcctctttccggatactcctcatctttggggcgagtgag
tccccctcctccatctgacacctcctccaaggaccacagtggctcagaaagccccattagtgatg
aagaggaaagactacagtccaagctttcagacccccatgccattgaagctgaaaagtttcagtgc
aatttatgcaataagacctattcaacttttctgggctggccaaacataagcagctgcactgcga
tgcccagtctagaaaatctttcagctgtaaatactgtgacaaggaatatgtgagcctgggcgccc

tgaagatgcatattcggacccacacattaccttgtgtttgcaagatctgcggcaaggcgttttcc
agaccctggttgcttcaaggacacattagaactcacacgggggagaagccttttttcttgccctca
ctgcaacagagcatttgcagacaggtcaaatctgagggctcatctgcagacccattctgatgtaa
agaaataccagtgcaaaaactgctccaaaaccttctccagaatgtctctcctgcacaaacatgag
gaatctggctgctgtgtagcacactga (SEQ ID NO:79)

**[00368]** Homo sapiens v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog A (MafA) (NM_201589.3) SEQ ID NO:16 (protein) and SEQ ID NO:80 (DNA)

MAAELAMGAELPSSPLAIEYVNDFDLMKFEVKKEPPEAERFCHRLPPGSLSSTPLSTPCSSVPSS
PSFCAPSPGTGGGGGAGGGGGSSQAGGAPGPPSGGPGAVGGTSGKPALEDLYWMSGYQHHLNPEA
LNLTPEDAVEALIGSGHHGAHHGAHHPAAAAAYEAFRGPGFAGGGGADDMGAGHHHGAHHAAHHH
HAAHHHHHHHHHHGGAGHGGGAGHHVRLEERFSDDQLVSMSVRELNRQLRGFSKEEVIRLKQKRR
TLKNRGYAQSCRFKRVQQRHILESEKCQLQSQVEQLKLEVGRLAKERDLYKEKYEKLAGRGGPGS
AGGAGFPREPSPPQAGPGGAKGTADFFL (SEQ ID NO:16)

atggccgcggagctggcgatgggcgccgagctgcccagcagcccgctggccatcgagtacgtcaa
cgacttcgacctgatgaagttcgaggtgaagaaggagcctcccgaggccgagcgcttctgccacc
gcctgccgccaggctcgctgtcctcgacgccgctcagcacgccctgctcctccgtgccctcctcg
cccagcttctgcgcgcccagcccgggcaccggcggcggcggcggcgcgggggggcggcggcggctc
gtctcaggccgggggcgcccccgggccgccgagcgggggccccggcgccgtcgggggcacctcgg
ggaagccggcgctggaggatctgtactggatgagcggctaccagcatcacctcaaccccgaggcg
ctcaacctgacgcccgaggacgcggtggaggcgctcatcggcagcggccaccacggcgcgcacca
cggcgcgcaccacccggcggccgccgcagcctacgaggctttccgcggcccgggcttcgcgggcg
gcggcggagcggacgacatgggcgccggccaccaccacggcgcgcaccacgccgcccaccatcac
cacgccgcccaccaccaccaccaccaccaccaccaccatggcggcgcgggacacggcggtggcgc
gggccaccacgtgcgcctggaggagcgcttctccgacgaccagctggtgtccatgtcggtgcgcg
agctgaaccggcagctccgcggcttcagcaaggaggaggtcatccggctcaagcagaagcggcgc
acgctcaagaaccgcggctacgcgcagtcctgccgcttcaagcgggtgcagcagcggcacattct
ggagagcgagaagtgccaactccagagccaggtggagcagctgaagctggaggtggggcgcctgg
ccaaagagcgggacctgtacaaggagaaatacgagaagctggcgggccggggcggccccgggagc
gcgggcggggccggtttcccgcgggagccttcgccgccgcaggccggtcccggcggggccaaggg
cacggccgacttcttcctgtag (SEQ ID NO:80)

**[00369]** Homo sapiens neuronal differentiation 1 (NEUROD1)(NM_002500.4) SEQ ID NO:17 (protein) and SEQ ID NO:81 (DNA)

MTKSYSESGLMGEPQPQGPPSWTDECLSSQDEEHEADKKEDDLEAMNAEEDSLRNGGEEEDEDED
LEEEEEEEEEDDDQKPKRRGPKKKKMTKARLERFKLRRMKANARERNRMHGLNAALDNLRKVVPC
YSKTQKLSKIETLRLAKNYIWALSEILRSGKSPDLVSFVQTLCKGLSQPTTNLVAGCLQLNPRTF
LPEQNQDMPPHLPTASASFPVHPYSYQSPGLPSPPYGTMDSSHVFHVKPPPHAYSAALEPFFESP
LTDCTSPSFDGPLSPPLSINGNFSFKHEPSAEFEKNYAFTMHYPAATLAGAQSHGSIFSGTAAPR
CEIPIDNIMSFDSHSHHERVMSAQLNAIFHD (SEQ ID NO:17)

atgaccaaatcgtacagcgagagtgggctgatgggcgagcctcagccccaaggtcctccaagctg
gacagacgagtgtctcagttctcaggacgaggagcacgaggcagacaagaaggaggacgacctcg
aagccatgaacgcagaggaggactcactgaggaacgggggagaggaggaggacgaagatgaggac
ctggaagaggaggaagaagaggaagaggaggatgacgatcaaaagcccaagagacgcggccccaa
aaagaagaagatgactaaggctcgcctggagcgttttaaattgagacgcatgaaggctaacgccc
gggagcggaaccgcatgcacggactgaacgcggcgctagacaacctgcgcaaggtggtgccttgc
tattctaagacgcagaagctgtccaaaatcgagactctgcgcttggccaagaactacatctgggc
tctgtcggagatcctgcgctcaggcaaaagcccagacctggtctccttcgttcagacgctttgca
agggcttatcccaacccaccaccaacctggttgcgggctgcctgcaactcaatcctcggacttttt
ctgcctgagcagaaccaggacatgccccccacctgccgacggccagcgcttccttccctgtaca
cccctactcctaccagtcgcctgggctgcccagtccgccttacggtaccatggacagctcccatg
tcttccacgttaagcctccgccgcacgcctacagcgcagcgctggagcccttctttgaaagccct

ctgactgattgcaccagcccttcctttgatggacccctcagcccgccgctcagcatcaatggcaa
cttctctttcaaacacgaaccgtccgccgagtttgagaaaaattatgcctttaccatgcactatc
ctgcagcgacactggcaggggcccaaagccacggatcaatcttctcaggcaccgctgcccctcgc
tgcgagatccccatagacaatattatgtccttcgatagccattcacatcatgagcgagtcatgag
tgcccagctcaatgccatatttcatgattag (SEQ ID NO:81)

**[00370]** Homo sapiens myogenic factor 5 (MYF5) (NM_005593.2) SEQ ID NO:18 (protein) and SEQ ID NO:82 (DNA)

MDVMDGCQFSPSEYFYDGSCIPSPEGEFGDEFVPRVAAFGAHKAELQGSDEDEHVRAPTGHHQAG
HCLMWACKACKRKSTTMDRRKAATMRERRRLKKVNQAFETLKRCTTTNPNQRLPKVEILRNAIRY
IESLQELLREQVENYYSLPGQSCSEPTSPTSNCSDGMPECNSPVWSRKSSTFDSIYCPDVSNVYA
TDKNSLSSLDCLSNIVDRITSSEQPGLPLQDLASLSPVASTDSQPATPGASSSRLIYHVL (SEQ ID NO:18)

atggacgtgatggatggctgccagttctcaccttctgagtacttctacgacggctcctgcatacc
gtcccccgagggtgaatttggggacgagtttgtgccgcgagtggctgccttcggagcgcacaaag
cagagctgcagggctcagatgaggacgagcacgtgcgagcgcctaccggccaccaccaggctggt
cactgcctcatgtgggcctgcaaagcctgcaagaggaagtccaccaccatggatcggcggaaggc
agccactatgcgcgagcggaggcgcctgaagaaggtcaaccaggctttcgaaaccctcaagaggt
gtaccacgaccaaccccaaccagaggctgcccaaggtggagatcctcaggaatgccatccgctac
atcgagagcctgcaggagttgctgagagagcaggtggagaactactatagcctgccgggacagag
ctgctcggagcccaccagccccacctccaactgctctgatggcatgcccgaatgtaacagtcctg
tctggtccagaaagagcagtacttttgacagcatctactgtcctgatgtatcaaatgtatatgcc
acagataaaaactccttatccagcttggattgcttatccaacatagtggaccggatcacctcctc
agagcaacctgggttgcctctccaggatctggcttctctctctccagttgccagcaccgattcac
agcctgcaactccaggggcttctagttccaggcttatctatcatgtgctatga (SEQ ID NO:82)

**[00371]** Homo sapiens PR-domain-containing protein 16 (PRDM16)(AF294278.1) SEQ ID NO:19 (protein) and SEQ ID NO:83 (DNA)

MRSKARARKLAKSDGDVVNNMYEPNRDLLASHSAEDEAEDSAMSPIPVGSPPPFPTSEDFTPKEG
SPYEAPVYIPEDIPIPADFELRESSIPGAGLGVWAKRKMEAGERLGPCVVVPRAAAKETDFGWEQ
ILTDVEVSPQEGCITKISEDLGSEKFCVDANQAGAGSWLKYIRVACSCDDQNLTMCQISEQVIYY
KVIKDIEPGEELLVHVKEGVYPLGTVPPGLDEEPTFRCDECDELFQSKLDLRRHKKYTCGSVGAA
LYEGLAEELKPEGLGGGSGQAHECKDCERMFPNKYSLEQHMVIHTEEREYKCDQCPKAFNWKSNF
IRHQMSHDSGKRFECENCVKVFTDPSNLQRHIRSQHVGARAHACPDCGKTFATSSGLKQHKHIHS
TVKPFICEVCHKSYTQFSNLCRHKRMHADCRTQIKCKDCGQMFSTTSSLNKHRRFCEGKNHYTPG
GIFAPGLPLTPSPMMDKAKPSPSLNHASLGFNEYFPYRPHPGSLPFSTAPPTFPALTPGFPGIFP
PSLYPRPPLLPPTSLLKSPLNHTQDAKLPSPLGNPALPLVSAVSNSSQGTTAAAGPEEKFESRLE
DSCVEKLKTRSSDMSDGSDFEDVNTTTGTDLDTTTGTGSDLDSDVDSDPDKDKGKGKSAEGQPKF
GGGLAPPGAPNSVAEVPVFYSQHSFFPPPDEQLLTATGAAGDSIKAIASIAEKYFGPGFMGMQEK
KLGSLPYHSAFPFQFLPNFPHSLYPFTDRALAHNLLVKAEPKSPRDALKVGGPSAECPFDLTTKP
KDVKPILPMPKGPSAPASGEEQPLDLSIGSRARASQNGGGREPRKNHVYGERKLGAGEGLPQVCP
ARMPQQPPLHYAKPSPFFMDPIYRVEKRKVTDPVGALKEKYLRPSPLLFHPQMSAIETMTEKLES
FAAMKADSGSSLQPLPHHPFNFRSPPPTLSDPILRKGKERYTCRYCGKIFPRSANLTRHLRTHTG
EQPYRCKYCDRSFSISSNLQRHVRNIHNKEKPFKCHLCNRCFGQQTNLDRHLKKHEHENAPVSQH
PGVLTNHLGTSASSPTSESDNHALLDEKEDSYFSEIRNFIANSEMNQASTRTEKRADMQIVDGSA
QCPGLASEKQEDVEEEDDDDLEEDDEDSLAGKSQDDTVSPAPEPQAAYEDEEDEEPAASLAVGFD
HTRRCAEDHEGGLLALEPMPTFGKGLDLRRAAEEAFEVKDVLNSTLDSEALKHTLCRQAKNQAYA
MMLSLSEDTPLHTPSQGSLDAWLKVTGATSESGAFHPINHL (SEQ ID NO:19)

atgcgatccaaggcgagggcgaggaagctagccaaaagtgacggtgacgttgtaaataatatgta
tgagcccaaccgggacctgctggccagccacagcgcggaggacgaggccgaggacagtgccatgt
cgcccatccccgtggggtcaccgcccccttccccaccagcgaggacttcacccccaaggagggc

tcgccgtacgaggcccctgtctacattcctgaagacattccgatcccagcagacttcgagctccg
agagtcctccatcccaggggctggcctgggggtctgggccaagaggaagatggaagccggggaga
ggctgggcccctgcgtggtggtgccccgggcggcggcaaaggagacagacttcggatgggagcaa
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cagtgagaagttctgcgtggatgcaaatcaggcgggggctggcagctggctcaagtacatccgtg
tggcgtgctcctgcgatgaccagaacctcaccatgtgtcagatcagtgagcaggtaatttactat
aaagtcattaaggacattgagccaggtgaggagctgctggtgcacgtgaaggaaggcgtctaccc
cctgggcacagtgccgcccggcctggacgaggagcccacgttccgctgtgacgagtgtgacgaac
tcttccagtccaagctggacctgcggcgccataagaagtacacgtgtggctcagtgggggctgcg
ctctacgagggcctggctgaggagctcaagcccgagggccttggcggtggcagcggccaagccca
cgagtgcaaggactgcgagcggatgttccccaacaagtacagcctggagcagcacatggtcatcc
acacggaggagcgcgagtacaaatgcgaccagtgtcccaaggccttcaactggaagtccaacttc
atccgccaccagatgtcccacgacagcggcaaacgcttcgaatgtgaaaactgcgtgaaggtgtt
cacggaccccagcaaccttcagcggcacatccgctcgcagcacgtgggcgctcgggcccacgcct
gccccgactgcgggaagaccttcgccacgtcctccggcctcaagcagcacaagcatatccacagc
acggtgaagcctttcatatgtgaggtctgccacaagtcctacacgcagttctccaacctgtgccg
gcacaagcggatgcacgccgactgccgcacgcagatcaagtgcaaggactgtggccagatgttca
gcactacctcctccctcaacaagcaccggcgcttctgcgagggcaagaaccattacacgccgggc
ggcatctttgccccgggcctgcccttgacccccagccccatgatggacaaggcaaaaccctcccc
cagcctcaatcacgccagcctgggcttcaacgagtactttccctacaggccgcacccggggagcc
tgcccttctccacggcgcctcccacgttccccgcactcacccccggcttcccgggcatcttccct
ccatccttgtaccccccggccgcctctgctacctcccacatcgctgctcaagagccccctgaacca
cacccaggacgccaagctccccagtcccctggggaacccagccctgcccctggtctccgccgtca
gcaacagcagccagggcacgacggcagctgcggggcccgaggagaagttcgagagccgcctggag
gactcctgtgtggagaagctgaagaccaggagcagcgacatgtcggacggcagtgactttgagga
cgtcaacaccaccacggggaccgacctggacacgaccacggggacgggctcggacctggacagcg
acgtggacagcgaccctgacaaggacaagggcaagggcaagtccgccgagggccagcccaagttt
gggggcggcttggcgcccccgggggccccgaacagcgtggccgaggtgcctgtcttctattccca
gcactcattcttcccgccacccgacgagcagctgctgactgcaacgggcgccgccggggactcca
tcaaggccatcgcatccattgccgagaagtactttggccccggcttcatggggatgcaggagaag
aagctgggctcgctcccctaccactcggcgttccccttccagttcctgcccaacttcccccactc
cctttacccccttcacggaccgagccctcgcccacaacttgctggtcaaggccgagccaaagtcac
cccgggacgccctcaaggtgggcggccccagtgccgagtgcccctttgatctcaccaccaagccc
aaagacgtgaagcccatcctgcccatgcccaagggcccctcggcccccgcatccggcgaggagca
gccgctggacctgagcatcggcagccgggcccgtgccagccaaaacggcggcgggcgggagcccc
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gcgcggatgccccagcagcccccgctccactacgccaagccctcgcccttcttcatggaccccat
ctacagggtagaaaagcggaaggtcacagaccccgtgggagccctgaaggagaagtacctgcggc
cgtccccgctgctcttccacccccagatgtcagccatagagaccatgacagagaagctggagagc
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ccggtccccacccccaacgctctccgaccccatcctcaggaagggcaaggagcgatacacgtgca
ggtactgtgggaagatcttccccagatcagccaatctcaccagacacctgaggacgcacactggg
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cgtccggaacatccacaacaaggagaagcctttcaagtgccacctgtgcaaccgctgcttcgggc
agcagaccaacctggaccggcacctcaagaagcacgagcacgagaacgcaccagtgagccagcac
cccggggtcctcacgaaccacctggggaccagcgcgtcctctcccacctcagagtcggacaacca
cgcacttttagacgagaaagaagactcttatttctcggaaatcagaaactttattgccaatagtg
agatgaaccaagcatcaacgcgaacagagaaacgggcggacatgcagatcgtggacggcagtgcc
cagtgtccaggcctagccagtgagaagcaggaggacgtggaggaggaggacgacgatgacctgga
ggaggacgatgaggacagcctggccgggaagtcgcaggatgacaccgtgtcccccgcacccgagc

cccaggccgcctacgaggatgaggaggatgaggagccagccgcctccctggccgtgggctttgac
cacacccgaaggtgtgctgaggaccacgaaggcggtctgttagctttggagccgatgccgacttt
tgggaaggggctggacctccgcagagcagctgaggaagcatttgaagttaaagatgtgcttaatt
ccaccttagattctgaggctttaaaacatacactgtgcaggcaggctaagaaccaggcatatgca
atgatgctgtccctttccgaagacactcctctccacacccccctcccagggttctctggacgcttg
gttgaaggtcactggagccacgtcggagtctggagcatttcaccccatcaaccacctctga
(SEQ ID NO:83)

**[00372]** Homo sapiens paired box 6 (PAX6) (NM_001604.5) SEQ ID NO:20 (protein) and SEQ ID NO:84 (DNA)

MQNSHSGVNQLGGVFVNGRPLPDSTRQKIVELAHSGARPCDISRILQTHADAKVQVLDNQNVSNG
CVSKILGRYYETGSIRPRAIGGSKPRVATPEVVSKIAQYKRECPSIFAWEIRDRLLSEGVCTNDN
IPSVSSINRVLRNLASEKQQMGADGMYDKLRMLNGQTGSWGTRPGWYPGTSVPGQPTQDGCQQQE
GGGENTNSISSNGEDSDEAQMRLQLKRKLQRNRTSFTQEQIEALEKEFERTHYPDVFARERLAAK
IDLPEARIQVWFSNRRAKWRREEKLRNQRRQASNTPSHIPISSSFSTSVYQPIPQPTTPVSSFTS
GSMLGRTDTALTNTYSALPPMPSFTMANNLPMQPPVPSQTSSYSCMLPTSPSVNGRSYDTYTPPH
MQTHMNSQPMGTSGTTSTGLISPGVSVPVQVPGSEPDMSQYWPRLQ (SEQ ID NO:20)
atgcagaacagtcacagcggagtgaatcagctcggtggtgtctttgtcaacgggcggccactgcc
ggactccacccggcagaagattgtagagctagctcacagcggggcccggccgtgcgacatttccc
gaattctgcagacccatgcagatgcaaaagtccaagtgctggacaatcaaaacgtgtccaacgga
tgtgtgagtaaaattctgggcaggtattacgagactggctccatcagacccagggcaatcggtgg
tagtaaaccgagagtagcgactccagaagttgtaagcaaaatagcccagtataagcgggagtgcc
cgtccatctttgcttgggaaatccgagacagattactgtccgaggggtctgtaccaacgataac
ataccaagcgtgtcatcaataaacagagttcttcgcaacctggctagcgaaaagcaacagatggg
cgcagacggcatgtatgataaactaaggatgttgaacgggcagaccggaagctggggcacccgcc
ctggttggtatccggggacttcggtgccagggcaacctacgcaagatggctgccagcaacaggaa
ggaggggagagaataccaactccatcagttccaacggagaagattcagatgaggctcaaatgcg
acttcagctgaagcggaagctgcaaagaaatagaacatcctttacccaagagcaaattgaggccc
tggagaaagagtttgagagaacccattatccagatgtgtttgcccgagaaagactagcagccaaa
atagatctacctgaagcaagaatacaggtatggttttctaatcgaagggccaaatggagaagaga
agaaaaactgaggaatcagagaagacaggccagcaacacacctagtcatattcctatcagcagta
gtttcagcaccagtgtctaccaaccaattccacaacccaccacaccggtttcctccttcacatct
ggctccatgttgggccgaacagacacagccctcacaaacacctacagcgctctgccgcctatgcc
cagcttcaccatggcaaataacctgcctatgcaacccccagtccccagccagacctcctcatact
cctgcatgctgcccaccagcccttcggtgaatgggcggagttatgatacctacacccccccacat
atgcagacacacatgaacagtcagccaatgggcacctcgggcaccacttcaacaggactcatttc
ccctggtgtgtcagttccagttcaagttcccggaagtgaacctgatatgtctcaatactggccaa
gattacagtaa (SEQ ID NO:84)

**[00373]** SEQ ID NO:21: Homo sapiens HNF1 homeobox A (HNF1A) (NM_000545.5) SEQ ID NO:21 (protein) and SEQ ID NO:85 (DNA)

MVSKLSQLQTELLAALLESGLSKEALIQALGEPGPYLLAGEGPLDKGESCGGGRGELAELPNGLG
ETRGSEDETDDDGEDFTPPILKELENLSPEEAAHQKAVVETLLQEDPWRVAKMVKSYLQQHNIPQ
REVVDTTGLNQSHLSQHLNKGTPMKTQKRAALYTWYVRKQREVAQQFTHAGQGGLIEEPTGDELP
TKKGRRNRFKWGPASQQILFQAYERQKNPSKEERETLVEECNRAECIQRGVSPSQAQGLGSNLVT
EVRVYNWFANRRKEEAFRHKLAMDTYSGPPPGPGPGPALPAHSSPGLPPPALSPSKVHGVRYGQP
ATSETAEVPSSSGGPLVTVSTPLHQVSPTGLEPSHSLLSTEAKLVSAAGGPLPPVSTLTALHSLE
QTSPGLNQQPQNLIMASLPGVMTIGPGEPASLGPTFTNTGASTLVIGLASTQAQSVPVINSMGSS
LTTLQPVQFSQPLHPSYQQPLMPPVQSHVTQSPFMATMAQLQSPHALYSHKPEVAQYTHTGLLPQ
TMLITDTTNLSALASLTPTKQVFTSDTEASSESGLHTPASQATTLHVPSQDPAGIQHLQPAHRLS
ASPTVSSSSLVLYQSSDSSNGQSHLLPSNHSVIETFISTQMASSSQ (SEQ ID NO:21)

atggtttctaaactgagccagctgcagacggagctcctggcggccctgctcgagtcagggctgag
caaagaggcactgatccaggcactgggtgagccggggccctacctcctggctggagaaggccccc
tggacaaggggagtcctgcggcggcggtcgaggggagctggctgagctgcccaatgggctgggg
gagactcggggctccgaggacgagacggacgacgatggggaagacttcacgccacccatcctcaa
agagctggagaacctcagccctgaggaggcggcccaccagaaagccgtggtggagacccttctgc
aggaggacccgtggcgtgtggcgaagatggtcaagtcctacctgcagcagcacaacatcccacag
cgggaggtggtcgataccactggcctcaaccagtcccacctgtcccaacacctcaacaagggcac
tcccatgaagacgcagaagcgggccgccctgtacacctggtacgtccgcaagcagcgagaggtgg
cgcagcagttcacccatgcagggcagggagggctgattgaagagcccacaggtgatgagctacca
accaagaaggggcggaggaaccgtttcaagtggggcccagcatcccagcagatcctgttccaggc
ctatgagaggcagaagaaccctagcaaggaggagcgagagacgctagtggaggagtgcaataggg
cggaatgcatccagagaggggtgtccccatcacaggcacaggggctgggctccaacctcgtcacg
gaggtgcgtgtctacaactggtttgccaaccggcgcaaagaagaagccttccggcacaagctggc
catggacacgtacagcgggccccccccagggccaggcccgggacctgcgctgcccgctcacagct
cccctggcctgcctccacctgccctctcccccagtaaggtccacggtgtgcgctatggacagcct
gcgaccagtgagactgcagaagtaccctcaagcagcggcggtcccttagtgacagtgtctacacc
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tggtctcagcagctgggggccccctcccccctgtcagcaccctgacagcactgcacagcttggag
cagacatccccaggcctcaaccagcagccccagaacctcatcatggcctcacttcctggggtcat
gaccatcgggcctggtgagcctgcctccctgggtcctacgttcaccaacacaggtgcctccaccc
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cccacgccctctacagccacaagcccgaggtggcccagtacacccacacgggcctgctcccgcag
actatgctcatcaccgacaccaccaacctgagcgccctggccagcctcacgcccaccaagcaggt
cttcacctcagacactgaggcctccagtgagtccgggcttcacacgccggcatctcaggccacca
ccctccacgtccccagccaggaccctgccggcatccagcacctgcagccggcccaccggctcagc
gccagccccacagtgtcctccagcagcctggtgctgtaccagagctcagactccagcaatggcca
gagccacctgctgccatccaaccacagcgtcatcgagaccttcatctccacccagatggcctctt
cctcccagtaa (SEQ ID NO:85)

**[00374]** Homo sapiens forkhead box A3 (FOXA3) (NM_004497.2) SEQ ID NO:22 (protein) and SEQ ID NO:86 (DNA)

MLGSVKMEAHDLAEWSYYPEAGEVYSPVTPVPTMAPLNSYMTLNPLSSPYPPGGLPASPLPSGPL
APPAPAAPLGPTFPGLGVSGGSSSSGYGAPGPGLVHGKEMPKGYRRPLAHAKPPYSYISLITMAI
QQAPGKMLTLSEIYQWIMDLFPYYRENQQRWQNSIRHSLSFNDCFVKVARSPDKPGKGSYWALHP
SSGNMFENGCYLRRQKRFKLEEKVKKGGSGAATTTRNGTGSAASTTTPAATVTSPPQPPPPAPEP
EAQGGEDVGALDCGSPASSTPYFTGLELPGELKLDAPYNFNHPFSINNLMSEQTPAPPKLDVGFG
GYGAEGGEPGVYYQGLYSRSLLNAS (SEQ ID NO:22)

atgctgggctcagtgaagatggaggcccatgacctggccgagtggagctactacccggaggcggg
cgaggtctactcgccggtgaccccagtgcccaccatggcccccctcaactcctacatgaccctga
atcctctaagctctccctatccccctgggggctccctgcctccccactgccctcaggacccctg
gcacccccagcacctgcagcccccctggggcccactttcccaggcctgggtgtcagcggtggcag
cagcagctccgggtacggggccccgggtcctgggctggtgcacgggaaggagatgccgaaggggt
atcggcggcccctggcacacgccaagccaccgtattcctatatctcactcatcaccatggccatc
cagcaggcgccgggcaagatgctgaccttgagtgaaatctaccagtggatcatggacctcttccc
ttactaccgggagaatcagcagcgctggcagaactccattcgccactcgctgtctttcaacgact
gcttcgtcaaggtggcgcgttccccagacaagcctggcaagggctcctactgggccctacacccc
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gaaggtgaaaaaaggggcagcggggctgccaccaccaccaggaacgggacagggtctgctgcct
cgaccaccacccccgcggccacagtcacctccccgccccagcccccgcctccagcccctgagcct

gaggcccagggcggggaagatgtgggggctctggactgtggctcacccgcttcctccacacccta
tttcactggcctggagctcccaggggagctgaagctggacgcgccctacaacttcaaccacccctt
tctccatcaacaacctaatgtcagaacagacaccagcacctcccaaactggacgtggggtttggg
ggctacggggctgaaggtggggagcctggagtctactaccagggcctctattcccgctctttgct
taatgcatcctag (SEQ ID NO:86)

**[00375]** Homo sapiens forkhead box A1 (FOXA1) (NM_004496.3) SEQ ID NO:23 (protein) and SEQ ID NO:87 (DNA)

MLGTVKMEGHETSDWNSYYADTQEAYSSVPVSNMNSGLGSMNSMNTYMTMNTMTTSGNMTPASFN
MSYANPGLGAGLSPGAVAGMPGGSAGAMNSMTAAGVTAMGTALSPSGMGAMGAQQAASMNGLGPY
AAAMNPCMSPMAYAPSNLGRSRAGGGGDAKTFKRSYPHAKPPYSYISLITMAIQQAPSKMLTLSE
IYQWIMDLFPYYRQNQQRWQNSIRHSLSFNDCFVKVARSPDKPGKGSYWTLHPDSGNMFENGCYL
RRQKRFKCEKQPGAGGGGGSGSGGSGAKGGPESRKDPSGASNPSADSPLHRGVHGKTGQLEGAPA
PGPAASPQTLDHSGATATGGASELKTPASSTAPPISSGPGALASVPASHPAHGLAPHESQLHLKG
DPHYSFNHPFSINNLMSSSEQQHKLDFKAYEQALQYSPYGSTLPASLPLGSASVTTRSPIEPSAL
EPAYYQGVYSRPVLNTS (SEQ ID NO:23)

atgctgggctcagtgaagatggaggcccatgacctggccgagtggagctactacccggaggcggg
cgaggtctactcgccggtgaccccagtgcccaccatggcccccctcaactcctacatgaccctga
atcctctaagctctccctatccccctgggggctccctgcctccccactgccctcaggacccctg
gcacccccagcacctgcagcccccctggggcccactttcccaggcctgggtgtcagcggtggcag
cagcagctccgggtacggggccccgggtcctgggctggtgcacgggaaggagatgccgaaggggt
atcggcggcccctggcacacgccaagccaccgtattcctatatctcactcatcaccatggccatc
cagcaggcgccgggcaagatgctgaccttgagtgaaatctaccagtggatcatggacctcttccc
ttactaccgggagaatcagcagcgctggcagaactccattcgccactcgctgtctttcaacgact
gcttcgtcaaggtggcgcgttccccagacaagcctggcaagggctcctactgggccctacacccc
agctcagggaacatgtttgagaatggctgctacctgcgccgccagaaacgcttcaagctggagga
gaaggtgaaaaaaggggcagcggggctgccaccaccaccaggaacgggacagggtctgctgcct
cgaccaccacccccgcggccacagtcacctccccgccccagcccccgcctccagcccctgagcct
gaggcccagggcggggaagatgtgggggctctggactgtggctcacccgcttcctccacacccta
tttcactggcctggagctcccaggggagctgaagctggacgcgccctacaacttcaaccacccctt
tctccatcaacaacctaatgtcagaacagacaccagcacctcccaaactggacgtggggtttggg
ggctacggggctgaaggtggggagcctggagtctactaccagggcctctattcccgctctttgct
taatgcatcctag(SEQ ID NO:87)

**[00376]** Homo sapiens forkhead box A2 (FOXA2) (NM_021784.4) SEQ ID NO:24 (protein) and SEQ ID NO:88 (DNA)

MHSASSMLGAVKMEGHEPSDWSSYYAEPEGYSSVSNMNAGLGMNGMNTYMSMSAAAMGSGSGNMS
AGSMNMSSYVGAGMSPSLAGMSPGAGAMAGMGGSAGAAGVAGMGPHLSPSLSPLGGQAAGAMGGL
APYANMNSMSPMYGQAGLSRARDPKTYRRSYTHAKPPYSYISLITMAIQQSPNKMLTLSEIYQWI
MDLFPFYRQNQQRWQNSIRHSLSFNDCFLKVPRSPDKPGKGSFWTLHPDSGNMFENGCYLRRQKR
FKCEKQLALKEAAGAAGSGKKAAAGAQASQAQLGEAAGPASETPAGTESPHSSASPCQEHKRGGL
GELKGTPAAALSPPEPAPSPGQQQQAAAHLLGPPHHPGLPPEAHLKPEHHYAFNHPFSINNLMSS
EQQHHHSHHHHQPHKMDLKAYEQVMHYPGYGSPMPGSLAMGPVTNKTGLDASPLAADTSYYQGVY
SRPIMNSS (SEQ ID NO:24)

atgcactcggcttccagtatgctgggagcggtgaagatggaagggcacgagccgtccgactggag
cagctactatgcagagcccgagggctactcctccgtgagcaacatgaacgccggcctggggatga
acggcatgaacacgtacatgagcatgtcggcggccgccatgggcagcggctcgggcaacatgagc
gcgggctccatgaacatgtcgtcgtacgtgggcgctggcatgagcccgtccctggcggggatgtc
ccccggcgcgggcgccatggcgggcatgggcggctcggccggggcggccggcgtggcgggcatgg
ggccgcacttgagtcccagcctgagcccgctcgggggggcaggcggccggggccatgggcggcctg
gcccccctacgccaacatgaactccatgagccccatgtacgggcaggcgggcctgagccgcgcccg
cgaccccaagacctacaggcgcagctacacgcacgcaaagccgccctactcgtacatctcgctca

tcaccatggccatccagcagagccccaacaagatgctgacgctgagcgagatctaccagtggatc
atggacctcttccccttctaccggcagaaccagcagcgctggcagaactccatccgccactcgct
ctccttcaacgactgtttcctgaaggtgccccgctcgcccgacaagcccggcaagggctccttct
ggaccctgcaccctgactcgggcaacatgttcgagaacggctgctacctgcgccgccagaagcgc
ttcaagtgcgagaagcagctggcgctgaaggaggccgcaggcgccgccggcagcggcaagaaggc
ggccgccggagcccaggcctcacaggctcaactcggggaggccgccgggccggcctccgagactc
cggcgggcaccgagtcgcctcactcgagcgcctccccgtgccaggagcacaagcgaggggcctg
ggagagctgaaggggacgccggctgcggcgctgagccccccagagccggcgccctctcccgggca
gcagcagcaggccgcggcccacctgctgggcccgccccaccacccgggcctgccgcctgaggccc
acctgaagccggaacaccactacgccttcaaccacccgttctccatcaacaacctcatgtcctcg
gagcagcagcaccaccacagccaccaccaccaccaaccccacaaaatggacctcaaggcctacga
acaggtgatgcactaccccggctacggttcccccatgcctggcagcttggccatgggcccggtca
cgaacaaaacgggcctggacgcctcgcccctggccgcagatacctcctactaccagggggtgtac
tcccggcccattatgaactcctcttaa (SEQ ID NO:88)

**[00377]** SEQ ID NO:25: Homo sapiens CCAAT/enhancer binding protein (C/EBP), alpha (CEBPA) (NM_001287435.1) SEQ ID NO:25 (protein) and SEQ ID NO:89 (DNA)

MSSHLQSPPHAPSSAAFGFPRGAGPAQPPAPPAAPEPLGGICEHETSIDISAYIDPAAFNDEFLA
DLFQHSRQQEKAKAAVGPTGGGGGGDFDYPGAPAGPGGAVMPGGAHGPPPGYGCAAAGYLDGRLE
PLYERVGAPALRPLVIKQEPREEDEAKQLALAGLFPYQPPPPPPPSHPHPHPPPAHLAAPHLQFQ
IAHCGQTTMHLQPGHPTPPPTPVPSPHPAPALGAAGLPGPGSALKGLGAAHPDLRASGGSGAGKA
KKSVDKNSNEYRVRRERNNIAVRKSRDKAKQRNVETQQKVLELTSDNDRLRKRVEQLSRELDTLR
GIFRQLPESSLVKAMGNCA (SEQ ID NO:25)

atgagcagccacctgcagagccccccgcacgcgcccagcagcgccgccttcggctttccccgggg
cgcgggccccgcgcagcctcccgccccacctgccgccccggagccgctgggcggcatctgcgagc
acgagacgtccatcgacatcagcgcctacatcgacccggccgccttcaacgacgagttcctggcc
gacctgttccagcacagccggcagcaggagaaggccaaggcggccgtgggccccacgggcggcgg
cggcggcggcgactttgactacccgggcgcgcccgcgggccccggcggcgccgtcatgcccgggg
gagcgcacgggcccccgcccggctacggctgcgcggccgccggctacctggacggcaggctggag
cccctgtacgagcgcgtcggggcgccggcgctgcggccgctggtgatcaagcaggagccccgcga
ggaggatgaagccaagcagctggcgctggccggcctcttcccttaccagccgccgccgccgccgc
cgccctcgcacccgcacccgcacccgccgcccgcgcacctggccgccccgcacctgcagttccag
atcgcgcactgcggccagaccaccatgcacctgcagcccggtcaccccacgccgccgcccacgcc
cgtgcccagcccgcaccccgcgcccgcgctcggtgccgccggcctgccgggccctggcagcgcgc
tcaaggggctgggcgccgcgcaccccgacctccgcgcgagtggcggcagcggcgcgggcaaggcc
aagaagtcggtggacaagaacagcaacgagtaccgggtgcggcgcgagcgcaacaacatcgcggt
gcgcaagagccgcgacaaggccaagcagcgcaacgtggagacgcagcagaaggtgctggagctga
ccagtgacaatgaccgcctgcgcaagcgggtggaacagctgagccgcgaactggacacgctgcgg
ggcatcttccgccagctgccagagagctccttggtcaaggccatgggcaactgcgcgtga (SEQ
ID NO:89)

**[00378]** Homo sapiens Spi-1 proto-oncogene (SPI1) (PU.1) (NM_001080547.1) SEQ ID NO:26 (protein) and SEQ ID NO:90 (DNA)

MLQACKMEGFPLVPPQPSEDLVPYDTDLYQRQTHEYYPYLSSDGESHSDHYWDFHPHHVHSEFES
FAENNFTELQSVQPPQLQQLYRHMELEQMHVLDTPMVPPHPSLGHQVSYLPRMCLQYPSLSPAQP
SSDEEEGERQSPPLEVSDGEADGLEPGPGLLPGETGSKKKIRLYQFLLDLLRSGDMKDSIWWVDK
DKGTFQFSSKHKEALAHRWGIQKGNRKKMTYQKMARALRNYGKTGEVKKVKKKLTYQFSGEVLGR
GGLAERRHPPH (SEQ ID NO:26)

atgttacaggcgtgcaaaatggaagggtttcccctcgtccccctcagccatcagaagacctggt
gccctatgacacggatctataccaacgccaaacgcacgagtattacccctatctcagcagtgatg
gggagagccatagcgaccattactgggacttccacccccaccacgtgcacagcgagttcgagagc
ttcgccgagaacaacttcacggagctccagagcgtgcagcccccgcagctgcagcagctctaccg

ccacatggagctggagcagatgcacgtcctcgatacccccatggtgccaccccatcccagtcttg
gccaccaggtctcctacctgccccggatgtgcctccagtacccatccctgtccccagcccagccc
agctcagatgaggaggagggcgagcggcagagccccccactggaggtgtctgacggcgaggcgga
tggcctggagccccgggcctgggctcctgcctggggagacaggcagcaagaagaagatccgcctgt
accagttcctgttggacctgctccgcagcggcgacatgaaggacagcatctggtgggtggacaag
gacaagggcaccttccagttctcgtccaagcacaaggaggcgctggcgcaccgctggggcatcca
gaagggcaaccgcaagaagatgacctaccagaagatggcgcgcgcgctgcgcaactacggcaaga
cgggcgaggtcaagaaggtgaagaagaagctcacctaccagttcagcggcgaagtgctgggccgc
gggggcctggccgagcggcgccacccgccccactga (SEQ ID NO:90)

**[00379]** Homo sapiens POU class 3 homeobox 2 (POU3F2) (Brn2) (NM_005604.3) SEQ ID NO:27 (protein) and SEQ ID NO:91 (DNA)

MATAASNHYSLLTSSASIVHAEPPGGMQQGAGGYREAQSLVQGDYGALQSNGHPLSHAHQWITAL
SHGGGGGGGGGGGGGGGGGGGGDGSPWSTSPLGQPDIKPSVVVQQGGRGDELHGPGALQQQHQQ
QQQQQQQQQQQQQQQQQQQRPPHLVHHAANHHPGPGAWRSAAAAAHLPPSMGASNGGLLYSQPSF
TVNGMLGAGGQPAGLHHHGLRDAHDEPHHADHHPHPHSHPHQQPPPPPPPQGPPGHPGAHHDPHS
DEDTPTSDDLEQFAKQFKQRRIKLGFTQADVGLALGTLYGNVFSQTTICRFEALQLSFKNMCKLK
PLLNKWLEEADSSSGSPTSIDKIAAQGRKRKKRTSIEVSVKGALESHFLKCPKPSAQEITSLADS
LQLEKEVVRVWFCNRRQKEKRMTPPGGTLPGAEDVYGGSRDTPPHHGVQTPVQ (SEQ ID NO:27)

atggcgaccgcagcgtctaaccactacagcctgctcacctccagcgcctccatcgtgcacgccga
gccgcccggcggcatgcagcagggcgcgggggctaccgcgaagcgcagagcctggtgcagggcg
actacggcgctctgcagagcaacggacacccgctcagccacgctcaccagtggatcaccgcgctg
tcccacggcggcggcggcgggggcggtggcggcggcgggggggcgggggcggcggcgggggcgg
cggcgacggctccccgtggtccaccagccccctgggccagccggacatcaagccctcggtggtgg
tgcagcagggcggccgcggagacgagctgcacgggccaggcgccctgcagcagcagcatcagcag
cagcaacagcaacagcagcagcaacagcagcaacagcagcagcagcagcagcaacagcggccgcc
gcatctggtgcaccacgccgctaaccaccacccgggacccggggcatggcggagcgcggcggctg
cagcgcacctcccaccctccatgggagcgtccaacggcggcttgctctactcgcagcccagcttc
acggtgaacggcatgctgggcgccggcgggcagccggccggtctgcaccaccacggcctgcggga
cgcgcacgacgagccacaccatgccgaccaccacccgcacccgcactcgcacccacaccagcagc
cgccgcccccgccgcccccgcagggtccgcctggccacccaggcgcgcaccacgacccgcactcg
gacgaggacacgccgacctcggacgacctggagcagttcgccaagcagttcaagcagcggcggat
caaactgggatttacccaagcggacgtggggctggctctgggcaccctgtatggcaacgtgttct
cgcagaccaccatctgcaggtttgaggccctgcagctgagcttcaagaacatgtgcaagctgaag
cctttgttgaacaagtggttggaggaggcggactcgtcctcgggcagccccacgagcatagacaa
gatcgcagcgcaagggcgcaagcggaaaaagcggacctccatcgaggtgagcgtcaaggggctc
tggagagccatttcctcaaatgccccaagccctcggcccaggagatcacctccctcgcggacagc
ttacagctggagaaggaggtggtgagagtttggttttgtaacaggagacagaaagagaaaaggat
gacccctcccggagggactctgccgggcgccgaggatgtgtacgggggagtagggacactccac
cacaccacggggtgcagacgcccgtccagtga (SEQ ID NO:91)

**[00380]** Homo sapiens forkhead box G1 (FOXG1) (NM_005249.4) SEQ ID NO:28 (protein) and SEQ ID NO:92 (DNA)

MLDMGDRKEVKMIPKSSFSINSLVPEAVQNDNHHASHGHHNSHHPQHHHHHHHHHHHPPPPAPQP
PPPPQQQQPPPPPPPAPQPPQTRGAPAADDDKGPQQLLLPPPPPPPPAAALDGAKADGLGGKGEP
GGGPGELAPVGPDEKEKGAGAGGEEKKGAGEGGKDGEGGKEGEKKNGKYEKPPFSYNALIMMAIR
QSPEKRLTLNGIYEFIMKNFPYYRENKQGWQNSIRHNLSLNKCFVKVPRHYDDPGKGNYWMLDPS
SDDVFIGGTTGKLRRRSTTSRAKLAFKRGARLTSTGLTFMDRAGSLYWPMSPFLSLHHPRASSTL
SYNGTTSAYPSHPMPYSSVLTQNSLGNNHSFSTANGLSVDRLVNGEIPYATHHLTAAALAASVPC
GLSVPCSGTYSLNPCSVNLLAGQTSYFFPHVPHPSMTSQSSTSMSARAASSSTSPQAPSTLPCES
LRPSLPSFTTGLSGGLSDYFTHQNQGSSSNPLIH (SEQ ID NO:28)

atgctggacatgggagataggaaagaggtgaaaatgatccccaagtcctcgttcagcatcaacag
cctggtgcccgaggcggtccagaacgacaaccaccacgcgagccacggccaccacaacagccacc
acccccagcaccaccaccaccaccaccaccatcaccaccacccgccgccgcccgccccgcaaccg
ccgccgccgccgcagcagcagcagccgccgccgccgccgccccggcaccgcagccccccagac
gcggggcgccccggccgccgacgacgacaagggcccccagcagctgctgctcccgccgccgccac
cgccaccaccggccgccgccctggacggggctaaagcggacgggctgggcggcaagggcgagccg
ggcggcgggccgggggagctggcgcccgtcgggccggacgagaaggagaagggcgccggcgccgg
gggggaggagaagaaggggcgggcgagggcggcaaggacggggagggggcaaggagggcgaga
agaagaacggcaagtacgagaagccgccgttcagctacaacgcgctcatcatgatggccatccgg
cagagccccgagaagcggctcacgctcaacggcatctacgagttcatcatgaagaacttccctta
ctaccgcgagaacaagcagggctggcagaactccatccgccacaatctgtccctcaacaagtgct
tcgtgaaggtgccgcgccactacgacgacccgggcaagggcaactactggatgctggacccgtcg
agcgacgacgtgttcatcggcggcaccacgggcaagctgcggcgccgctccaccacctcgcgggc
caagctggccttcaagcgcggtgcgcgcctcacctccaccggcctcaccttcatggaccgcgccg
gctccctctactggcccatgtcgcccttcctgtccctgcaccacccccgcgccagcagcactttg
agttacaacggcaccacgtcggcctaccccagccaccccatgccctacagctccgtgttgactca
gaactcgctgggcaacaaccactccttctccaccgccaacggcctgagcgtggaccggctggtca
acggggagatcccgtacgccacgcaccacctcacggccgccgcgctagccgcctcggtgccctgc
ggcctgtcggtgccctgctctgggacctactccctcaacccctgctccgtcaacctgctcgcggg
ccagaccagttacttttttcccccacgtcccgcacccgtcaatgacttcgcagagcagcacgtcca
tgagcgccagggccgcgtcctcctccacgtcgccgcaggcccccctcgaccctgccctgtgagtct
ttaagaccctctttgccaagttttacgacgggactgtctgggggactgtctgattatttcacaca
tcaaaatcaggggtcttcttccaacccttaatacattaa (SEQ ID NO:92)

**[00381]** Homo sapiens mRNA for ASC1 protein (SLC7A10 gene) (AJ277731.1) SEQ ID NO:29 (protein) and SEQ ID NO:93 (DNA)

MAGHTQQPSGRGNPRPAPSPSPVPGTVPGASERVALKKEIGLLSACTIIIGNIIGSGIFISPKGV
LEHSGSVGLALFVWVLGGGVTALGSLCYAELGVAIPKSGGDYAYVTEIFGGLAGFLLLWSAVLIM
YPTSLAVISMTFSNYVLQPVFPNCIPPTTASRVLSMACLMLLTWVNSSSVRWATRIQDMFTGGKL
LALSLIIGVGLLQIFQGHFEELRPSNAFAFWMTPSVGHLALAFLQGSFAFSGWNFLNYVTEEMVD
ARKNLPRAIFISIPLVTFVYTFTNIAYFTAMSPQELLSSNAVAVTFGEKLLGYFSWVMPVSVALS
TFGGINGYLFTYSRLCFSGAREGHLPSLLAMIHVRHCTPIPALLVCCGATAVIMLVGDTYTLINY
VSFINYLCYGVTILGLLLLRWRRPALHRPIKVNLLIPVAYLVFWAFLLVFSFISEPMVCGVGVII
ILTGVPIFFLGVFWRSKPKCVHRLTESMTHWGQELCFVVYPQDAPEEEENGPCPPSLLPATDKPS
KPQ (SEQ ID NO:29)

atggccggccacacgcagcagccgagcgggcgcgggaaccccaggcctgcgccctcgccctcccc
agtcccagggaccgtccccggcgcctcggagcgggtggcgctcaagaaggagatcgggctgctga
gcgcctgcaccatcatcatcgggaacatcatcggctcgggcatcttcatctcgcccaaggggtc
ctggagcactcaggctccgtgggtctggccctgttcgtctgggtcctgggtgggggcgtgacggc
tctgggctccctctgctatgcagagctgggagtcgccatccccaagtctggcggggactacgcct
acgtcacagagatcttcgggggcctggctggctttctgctgctctggagcgccgtcctcatcatg
taccccaccagccttgctgtcatctccatgaccttctccaactacgtgctgcagcccgtgttccc
caactgcatccccccccaccacagcctcccgggtgctgtccatggcctgcctgatgctcctgacat
gggtgaacagctccagtgtgcgctgggccacgcgcatccaggacatgttcacaggcgggaagctg
ctggccttgtccctcatcatcggcgtgggccttctccagatcttccaaggacacttcgaggagct
gaggcccagcaatgcctttgctttctggatgacgccctccgtgggacacctggccctggccttcc
tccagggctccttcgccttcagtggctggaacttcctcaactatgtcaccgaggagatggttgac
gcccgaaagaacctacctcgcgccatcttcatctccatcccactggtgaccttcgtgtacacgtt
caccaacattgcctacttcacggccatgtccccccaggagctgctctcctccaatgcggtggctg
tgaccttcggggagaagctgctgggctacttttcttgggtcatgcctgtctccgtggctctgtca
accttcggagggatcaatggttacctgttcacctactccaggctgtgcttctctggagcccgcga

ggggcacctgcccagcctgctggccatgatccacgtcagacactgcacccccatccccgccctcc
tcgtctgttgcggggccacagccgtcatcatgctcgtgggcgacacgtacacgctcatcaactat
gtgtccttcatcaactacctctgctacggcgtcaccatcctgggcctgctgctgctgcgctggag
gcggcctgcactccacaggcccatcaaggtgaaccttctcatccccgtggcgtacttggtcttct
gggccttcctgctggtcttcagcttcatctcagagcctatggtctgtggggtcggcgtcatcatc
atccttacgggggtgcccatttttctttctgggagtgttctggagaagcaaaccaaagtgtgtgca
cagactcacagagtccatgacacactggggccaggagctgtgtttcgtggtctacccccaggacg
cccccgaagaggaggagaatggcccctgcccaccctccctgctgcctgccacagacaagccctcg
aagccacaatga (SEQ ID NO:93)

**[00382]** Homo sapiens achaete-scute family bHLH transcription factor 1 (ASCL1) (NM_004316.3) SEQ ID NO:30 (protein) and SEQ ID NO:94 (DNA)

MESSAKMESGGAGQQPQPQPQQPFLPPAACFFATAAAAAAAAAAAAAQSAQQQQQQQQQQQQAPQ
LRPAADGQPSGGGHKSAPKQVKRQRSSSPELMRCKRRLNFSGFGYSLPQQQPAAVARRNERERNR
VKLVNLGFATLREHVPNGAANKKMSKVETLRSAVEYIRALQQLLDEHDAVSAAFQAGVLSPTISP
NYSNDLNSMAGSPVSSYSSDEGSYDPLSPEEQELLDFTNWF (SEQ ID NO:30)

atggaaagctctgccaagatggagagcggcggcgccggccagcagccccagccgcagccccagca
gcccttcctgccgcccgcagcctgtttctttgccacggccgcagccgcggcggccgcagccgccg
cagcggcagcgcagagcgcgcagcagcagcagcagcagcagcagcagcagcagcaggcgccgcag
ctgagaccggcggccgacggccagccctcaggggggcggtcacaagtcagcgcccaagcaagtcaa
gcgacagcgctcgtcttcgcccgaactgatgcgctgcaaacgccggctcaacttcagcggctttg
gctacagcctgccgcagcagcagccggccgccgtggcgcgccgcaacgagcgcgagcgcaaccgc
gtcaagttggtcaacctgggctttgccacccttcgggagcacgtccccaacggcgcggccaacaa
gaagatgagtaaggtggagacactgcgctcggcggtcgagtacatccgcgcgctgcagcagctgc
tggacgagcatgacgcggtgagcgccgccttccaggcaggcgtcctgtcgcccaccatctccccc
aactactccaacgacttgaactccatggccggctcgccggtctcatcctactcgtcggacgaggg
ctcttacgacccgctcagccccgaggagcaggagcttctcgacttcaccaactggttctga
(SEQ ID NO:94)

**[00383]** Homo sapiens Nurr1 gene (AB017586) SEQ ID NO:31 (protein) and SEQ ID NO:95 (DNA)

MPCVQAQYGSSPQGASPASQSYSYHSSGEYSSDFLTPEFVKFSMDLTNTEITATTSLPSFSTFMD
NYSTGYDVKPPCLYQMPLSGQQSSIKVEDIQMHNYQQHSHLPPQSEEMMPHSGSVYYKPSSPPTP
TTPGFQVQHSPMWDDPGSLHNFHQNYVATTHMIEQRKTPVSRLSLFSFKQSPPGTPVSSCQMRFD
GPLHVPMNPEPAGSHHVVDGQTFAVPNPIRKPASMGFPGLQIGHASQLLDTQVPSPPSRGSPSNE
GLCAVCGDNAACQHYGVRTCEGCKGFFKRTVQKNAKYVCLANKNCPVDKRRRNRCQYCRFQKCLA
VGMVKEVVRTDSLKGRRGRLPSKPKSPQEPSPPSPPVSLISALVRAHVDSNPAMTSLDYSRFQAN
PDYQMSGDDTQHIQQFYDLLTGSMEIIRGWAEKIPGFADLPKADQDLLFESAFLELFVLRLAYRS
NPVEGKLIFCNGVVLHRLQCVRGFGEWIDSIVEFSSNLQNMNIDISAFSCIAALAMVTERHGLKE
PKRVEELQNKIVNCLKDHVTFNNGGLNRPNYLSKLLGKLPELRTLCTQGLQRIFYLKLEDLVPPP
AIIDKLFLDTLPF(SEQ ID NO:31)

atgccttgtgttcaggcgcagtatgggtcctcgcctcaaggagccagccccgcttctcagagcta
cagttaccactcttcgggagaatacagctccgatttcttaactccagagtttgtcaagtttagca
tggacctcaccaacactgaaatcactgccaccacttctctccccagcttcagtacctttatggac
aactacagcacaggctacgacgtcaagccaccttgcttgtaccaaatgcccctgtccggacagca
gtcctccattaaggtagaagacattcagatgcacaactaccagcaacacagccacctgccccccc
agtctgaggagatgatgccgcactccgggtcggtttactacaagccctcctcgcccccgacgccc
accaccccgggcttccaggtgcagcacagccccatgtgggacgacccgggatctctccacaactt
ccaccagaactacgtggccactacgcacatgatcgagcagaggaaaacgccagtctcccgcctct
ccctcttctcctttaagcaatcgccccctggcaccccggtgtctagttgccagatgcgcttcgac
gggcccctgcacgtccccatgaacccggagcccgccggcagccaccacgtggtggacgggcagac
cttcgctgtgcccaaccccattcgcaagcccgcgtccatgggcttcccgggcctgcagatcggcc

acgcgtctcagctgctcgacacgcaggtgccctcaccgccgtcgcggggctccccctccaacgag
gggctgtgcgctgtgtgtggggacaacgcggcctgccaacactacggcgtgcgcacctgtgaggg
ctgcaaaggcttctttaagcgcacagtgcaaaaaaatgcaaaatacgtgtgtttagcaaataaaa
actgcccagtggacaagcgtcgccggaatcgctgtcagtactgccgatttcagaagtgcctggct
gttgggatggtcaaagaagtggttcgcacagacagtttaaaaggccggagaggtcgtttgccctc
gaaaccgaagagcccacaggagccctctccccttcgcccccggtgagtctgatcagtgccctcg
tcagggcccatgtcgactccaacccggctatgaccagcctggactattccaggttccaggcgaac
cctgactatcaaatgagtggagatgacacccagcatatccagcaattctatgatctcctgactgg
ctccatggagatcatccggggctgggcagagaagatccctggcttcgcagacctgcccaaagccg
accaagacctgctttttgaatcagctttcttagaactgtttgtccttcgattagcatacaggtcc
aacccagtggagggtaaactcatcttttgcaatggggtggtcttgcacaggttgcaatgcgttcg
tggctttggggaatggattgattccattgttgaattctcctccaacttgcagaatatgaacatcg
acatttctgccttctcctgcattgctgccctggctatggtcacagagagacacgggctcaaggaa
cccaagagagtggaagaactgcaaaacaagattgtaaattgtctcaaagaccacgtgactttcaa
caatgggggttgaaccgccccaattatttgtccaaactgttggggaagctcccagaacttcgta
ccctttgcacacaggggctacagcgcattttctacctgaaattggaagacttggtgccaccgcca
gcaataattgacaaacttttcctggacactttacctttctaa(SEQ ID NO:95)

**[00384]** SEQ ID NO:32: Homo sapiens neurogenin 2 (NEUROG2) (NM_024019) SEQ ID NO:32 (protein) and SEQ ID NO:96 (DNA)

MFVKSETLELKEEEDVLVLLGSASPALAALTPLSSSADEEEEEEPGASGGARRQRGAEAGQGARG
GVAAGAEGCRPARLLGLVHDCKRRPSRARAVSRGAKTAETVQRIKKTRRLKANNRERNRMHNLNA
ALDALREVLPTFPEDAKLTKIETLRFAHNYIWALTETLRLADHCGGGGGLPGALFSEAVLLSPG
GASAALSSSGDSPSPASTWSCTNSPAPSSSVSSNSTSPYSCTLSPASPAGSDMDYWQPPPPDKHR
YAPHLPIARDCI(SEQ ID NO:32)

atgttcgtcaaatccgagaccttggagttgaaggaggaagaggacgtgttagtgctgctcggatc
ggcctcccccgccttggcggccctgaccccgctgtcatccagcgccgacgaagaagaggaggagg
agccgggcgcgtcaggcggggcgcgtcggcagcgcggggctgaggccgggcaggggggcgcgggc
ggcgtggctgcgggtgcggagggctgccggcccgcacggctgctgggtctggtacacgattgcaa
acggcgcccttcccgggcgcgggccgtctcccgaggcgccaagacggccgagacggtgcagcgca
tcaagaagacccgtagactgaaggccaacaaccgcgagcgaaaccgcatgcacaacctcaacgcg
gcactggacgcgctgcgcgaggtgctccccacgttccccgaggacgccaagctcaccaagatcga
gaccctgcgcttcgcccacaactacatctgggcactcaccgagaccctgcgcctggcggatcact
gcgggggcggcggcgggggcctgccgggggcgctcttctccgaggcagtgttgctgagcccggga
ggagccagcgccgccctgagcagcagcggagacagcccctcgcccgcctccacgtggagttgcac
caacagccccgcgccgtcctcctccgtgtcctccaattccacctcccctacagctgcactttat
cgcccgccagcccggccgggtcagacatggactattggcagcccccacctcccgacaagcaccgc
tatgcacctcacctccccatagccagggattgtatctag(SEQ ID NO:96)

**[00385]** Homo sapiens LIM homeobox transcription factor 1, alpha (LMX1A) (NM_177398) SEQ ID NO:33 (protein) and SEQ ID NO:97 (DNA)

MLDGLKMEENFQSAIDTSASFSSLLGRAVSPKSVCEGCQRVILDRFLLRLNDSFWHEQCVQCASC
KEPLETTCFYRDKKLYCKYDYEKLFAVKCGGCFEAIAPNEFVMRAQKSVYHLSCFCCCVCERQLQ
KGDEFVLKEGQLLCKGDYEKERELLSLVSPAASDSGKSDDEESLCKSAHGAGKGTAEEGKDHKRP
KRPRTILTTQQRRAFKASFEVSSKPCRKVRETLAAETGLSVRVVQVWFQNQRAKMKKLARRQQQQ
QQDQQNTQRLSSAQTNGGGSAGMEGIMNPYTALPTPQQLLAIEQSVYSSDPFRQGLTPPQMPGDH
MHPYGAEPLFHDLDSDDTSLSNLGDCFLATSEAGPLQSRVGNPIDHLYSMQNSYFTS (SEQ ID NO:33)

atgctggacggcctaaagatggaggagaacttccaaagcgcgatcgacacctcggcctccttctc
ctcgctgctgggcagagcggtgagccccaagtctgtctgcgagggctgtcagcgggtcatcttgg
acaggtttctgctgcggctcaacgacagcttctggcatgagcagtgcgtgcagtgcgcctcctgc
aaagagcccctggagaccacctgcttctaccgggacaagaagctgtactgcaagtatgactacga

gaagctgtttgctgttaaatgtgggggctgcttcgaggccatcgctcccaatgagtttgttatgc
gggcccagaagagtgtataccacctgagctgcttctgctgctgtgtctgcgagcgacagcttcag
aagggtgatgagtttgtcctgaaggaggggcagctgctctgcaaaggggactatgagaaggagcg
ggagctgctcagcctggtgagcccagcagcctcagactcaggtaaaagtgatgatgaagaaagtc
tctgcaagtcagcccatggggcagggaaaggaactgctgaggaaggcaaggaccataagcgcccc
aaacgtccgagaaccatcttgacaactcaacagaggcgagcattcaaggcctcatttgaagtatc
ctccaagccctgcaggaaggtgagagagactctggctgcagagacagggctgagtgtccgtgtcg
tccaggtgtggttccaaaaccagagagcgaagatgaagaagctggccaggcgacagcagcagcag
cagcaagatcagcagaacacccagaggctgagctctgctcagacaaacggtggtgggagtgctgg
gatggaaggaatcatgaacccctacacggctctgcccaccccacagcagctcctggccatcgagc
agagtgtctacagctcagatcccttccgacagggtctcaccccaccccagatgcctggagaccac
atgcacccttatggtgccgagccccttttccatgacctggatagcgacgacacctccctcagtaa
cctgggtgattgtttcctagcaacctcagaagctgggcctctgcagtccagagtgggaaacccca
ttgaccatctgtactccatgcagaattcttacttcacatcttga (SEQ ID NO:97)

**[00386]** Homo sapiens HB9 homeobox gene, (U07663) SEQ ID NO:34 (protein) and SEQ ID NO:98 (DNA)

MEKSKNFRIEPCWRWTPHEPPLAERALAKVTSPPVPASGTGGGGGGGGASGGTSGSCSPASSEPP
AAPADRLRAESPSPPRLLAAHCALLPKPGFLGAGGGGGGTGGGHGGPHHHAHPGAAAAAAAAAAA
AAAAAGGLALGLHPGGAQGGAGLPAQAALYGHPVYGYSAAAAAAALAGQHPALSYSYPQVQGAHP
AHPADPIKLGAGTFQLDQWLRATAGMILPKMPDFNSQAQSNLLGKCRRPRTAFTSQQLLELEHQF
KFNKYLSRPKRFEVATSLMLTETQVKIWFQNRRMKWKRSKKAKEQAAQEAEKQKGGGGGAGKGGA
EEPGAEELLGPPAPRDKGSGPPADLRDSDPEEDEDEDDEDHFPYSNGASVHAASSDCSSEDDSPP
PRPSHQPAPQ (SEQ ID NO:34)

atggaaaaatccaaaaatttccgcatcgagccctgctggcggtggacccccacgagccgcctct
cgcagagcgcgcgctggccaaggtcacgtcgccgcccgtgcccgcatctggcaccggaggtggcg
gcggcggcggcggggcgagcggcgggactagcggcagctgcagccccgcgtcctcggagccgccg
gctgcgcccgccgaccgcctgcgcgccgagagcccgtcgccgccgcgcctgctggccgcgcactg
cgcgctgctgcccaagccgggcttcctgggcgcgggcggcggcggcggcggcacgggcggcgggc
acgggggggccccaccaccacgcgcatccgggcgcagcggccgctgccgccgccgccgccgccgcc
gccgccgccgccgctgggggcctggcgctggggctgcaccctgggggcgcgcagggcggcgcggg
cctcccggcgcaggcggcgctctacggccacccggtctacggctactccgcggcggcggcggcgg
ctgcgctggcgggccagcacccggcgctctcctactcgtacccgcaggtgcaaggcgcgcacccc
gcgcaccccgccgaccccatcaagctgggcgccggcaccttccagctggaccagtggctgcgcgc
gtccaccgcgggcatgatcctgcctaagatgcccgacttcaact (SEQ ID NO:98)

**[00387]** Homo sapiens LIM homeobox 3 (LHX3) (NM_178138) SEQ ID NO:35 (protein) and SEQ ID NO:99 (DNA)

MLLETGLERDRARPGAAAVCTLGGTREIPLCAGCDQHILDRFILKALDRHWHSKCLKCSDCHTPL
AERCFSRGESVYCKDDFFKRFGTKCAACQLGIPPTQVVRRAQDFVYHLHCFACVVCKRQLATGDE
FYLMEDSRLVCKADYETAKQREAEATAKRPRTTITAKQLETLKSAYNTSPKPARHVREQLSSETG
LDMRVVQVWFQNRRAKEKRLKKDAGRQRWGQYFRNMKRSRGGSKSDKDSVQEGQDSDAEVSFPDE
PSLAEMGPANGLYGSLGEPTQALGRPSGALGNFSLEHGGLAGPEQYRELRPGSPYGVPPSPAAPQ
SLPGPQPLLSSLVYPDTSLGLVPSGAPGGPPPMRVLAGNGPSSDLSTGSSGGYPDFPASPASWLD
EVDHAQF (SEQ ID NO:35)

atgctgctggaaacgggctcgagcgcgaccgagcgaggcccggggccgccgccgtctgcacctt
gggcgggactcgggagatcccgctgtgcgctggctgtgaccagcacatcctggaccgcttcatcc
tcaaggctctggaccgccactggcacagcaagtgtctcaagtgcagcgactgccacacgccactg
gccgagcgctgcttcagccgaggggagagcgtttactgcaaggacgacttttttcaagcgcttcgg
gaccaagtgcgccgcgtgccagctgggcatcccgcccacgcaggtggtgcgccgcgcccaggact
tcgtgtaccacctgcactgctttgcctgcgtcgtgtgcaagcggcagctggccacgggcgacgag
ttctacctcatggaggacagccggctcgtgtgcaaggcggactacgaaaccgccaagcagcgaga

ggccgaggccacggccaagcggccgcgcacgaccatcaccgccaagcagctggagacgctgaaga
gcgcttacaacacctcgcccaagccggcgcgccacgtgcgcgagcagctctcgtccgagacgggc
ctggacatgcgcgtggtgcaggtttggttccagaaccgccgggccaaggagaagaggctgaagaa
ggacgccggccggcagcgctgggggcagtatttccgcaacatgaagcgctcccgcggcggctcca
agtcggacaaggacagcgttcaggaggggcaggacagcgacgctgaggtctccttccccgatgag
ccttccttggcggaaatgggcccggccaatggcctctacgggagcttgggggaacccacccaggc
cttgggccggccctcgggagccctgggcaacttctccctggagcatggaggcctggcaggcccag
agcagtaccgagagctgcgtcccggcagcccctacggtgtccccccatcccccgccgccccgcag
agcctccctggcccccagcccctcctctccagcctggtgtacccagacaccagcttgggccttgt
gccctcgggagcccccggcgggcccccacccatgagggtgctggcagggaacggacccagttctg
acctatccacggggagcagcgggggttaccccgacttccctgccagccccgcctcctggctggat
gaggtagaccacgctcagttctga (SEQ ID NO:99)

**[00388]** Homo sapiens distal-less homeobox 2 (DLX2) (NM_004405) SEQ ID NO:36 (protein) and SEQ ID NO:100 (DNA)

MTGVFDSLVADMHSTQIAASSTYHQHQQPPSGGGAGPGGNSSSSSSLHKPQESPTLPVSTATDSS
YYTNQQHPAGGGGGGGSPYAHMGSYQYQASGLNNVPYSAKSSYDLGYTAAYTSYAPYGTSSSPAN
NEPEKEDLEPEIRIVNGKPKKVRKPRTIYSSFQLAALQRRFQKTQYLALPERAELAASLGLTQTQ
VKIWFQNRRSKFKKMWKSGEIPSEQHPGASASPPCASPPVSAPASWDFGVPQRMAGGGGPGSGGS
GAGSSGSSPSSAASAFLGNYPWYHQTSGSASHLQATAPLLHPTQTPQPHHHHHHHGGGGAPVSAG
TIF (SEQ ID NO:36)

atgactggagtctttgacagtctagtggctgatatgcactcgacccagatcgccgcctccagcac
gtaccaccagcaccagcagcccccgagcggcggcggcgccggcccgggtggcaacagcagcagca
gcagcagcctccacaagccccaggagtcgcccacccttccggtgtccaccgccaccgacagcagc
tactacaccaaccagcagcacccggcgggcggcggcggcggcgggggctcgccctacgcgcacat
gggttcctaccagtaccaagccagcggcctcaacaacgtcccttactccgccaagagcagctatg
acctgggctacaccgccgcctacacctcctacgctccctatggaaccagttcgtccccagccaac
aacgagcctgagaaggaggaccttgagcctgaaattcggatagtgaacgggaagccaaagaaagt
ccggaaaccccgcaccatctactccagtttccagctggcggctcttcagcggcgtttccaaaaga
ctcaatacttggccttgccggagcgagccgagctggcggcctctctgggcctcacccagactcag
gtcaaaatctggttccagaaccgccggtccaagttcaagaagatgtggaaaagtggtgagatccc
ctcggagcagcaccctggggccagcgcttctccaccttgtgcttcgccgccagtctcagcgccgg
cctcctgggactttggtgtgccgcagcggatggcgggcggcggtggtccgggcagtggcggcagc
ggcgccggcagctcgggctccagcccgagcagcgcggcctcggcttttctgggcaactacccctg
gtaccaccagacctcgggatccgcctcacacctgcaggccacggcgccgctgctgcaccccactc
agaccccgcagccgcatcaccaccaccaccatcacggcggcgggggcgccccggtgagcgcgggg
acgattttctaa (SEQ ID NO:100)

**[00389]** Homo sapiens runt-related transcription factor 2 (RUNX2)(NM_001024630) SEQ ID NO:37 (protein) and SEQ ID NO:101 (DNA)

MASNSLFSTVTPCQQNFFWDPSTSRRFSPPSSSLQPGKMSDVSPVVAAQQQQQQQQQQQQQQQQ
QQQQQQEAAAAAAAAAAAAAAAAAAVPRLRPPHDNRTMVEIIADHPAELVRTDSPNFLCSVLPSHW
RCNKTLPVAFKVVALGEVPDGTVVTVMAGNDENYSAELRNASAVMKNQVARFNDLRFVGRSGRGK
SFTLTITVFTNPPQVATYHRAIKVTVDGPREPRRHRQKLDDSKPSLFSDRLSDLGRIPHPSMRVG
VPPQNPRPSLNSAPSPFNPQGQSQITDPRQAQSSPPWSYDQSYPSYLSQMTSPSIHSTTPLSSTR
GTGLPAITDVPRRISDDDTATSDFCLWPSTLSKKSQAGASELGPFSDPRQFPSISSLTESRFSNP
RMHYPATFTYTPPVTSGMSLGMSATTHYHTYLPPPYPGSSQSQSGPFQTSSTPYLYYGTSSGSYQ
FPMVPGGDRSPSRMLPPCTTTSNGSTLLNPNLPNQNDGVDADGSHSSSPTVLNSSGRMDESVWRP
Y (SEQ ID NO:37)

atggcatcaaacagcctcttcagcacagtgacaccatgtcagcaaaacttcttttgggatccgag
caccagccggcgcttcagccccccctccagcagcctgcagcccggcaaaatgagcgacgtgagcc
cggtggtggctgcgcaacagcagcagcaacagcagcagcagcaacagcagcagcagcagcagcaa

cagcagcagcagcaggaggcggcggcggctgcggcggcggcggcggctgcggcggcggc
agctgcagtgccccggttgcggccgccccacgacaaccgcaccatggtggagatcatcgccgacc
acccggccgaactcgtccgcaccgacagccccaacttcctgtgctcggtgctgccctcgcactgg
cgctgcaacaagaccctgcccgtggccttcaaggtggtagccctcggagaggtaccagatgggac
tgtggttactgtcatggcgggtaacgatgaaaattattctgctgagctccggaatgcctctgctg
ttatgaaaaaccaagtagcaaggttcaacgatctgagatttgtgggccggagtggacgaggcaag
agtttcaccttgaccataaccgtcttcacaaatcctccccaagtagctacctatcacagagcaat
taaagttacagtagatggacctcgggaacccagaaggcacagacagaagcttgatgactctaaac
ctagtttgttctctgaccgcctcagtgatttagggcgcattcctcatcccagtatgagagtaggt
gtcccgcctcagaacccacggccctccctgaactctgcaccaagtccttttaatccacaaggaca
gagtcagattacagaccccaggcaggcacagtcttccccgccgtggtcctatgaccagtcttacc
cctcctacctgagccagatgacgtccccgtccatccactctaccaccccgctgtcttccacacgg
ggcactgggcttcctgccatcaccgatgtgcctaggcgcatttcagatgatgacactgccacctc
tgacttctgcctctggccttccactctcagtaagaagagccaggcaggtgcttcagaactgggcc
ctttttcagaccccaggcagttcccaagcatttcatccctcactgagagccgcttctccaaccca
cgaatgcactatccagccacctttacttacaccccgccagtcacctcaggcatgtccctcggtat
gtccgccaccactcactaccacacctacctgccaccaccctaccccggctcttcccaaagccaga
gtggacccttccagaccagcagcactccatatctctactatggcacttcgtcaggatcctatcag
tttcccatggtgccgggggggagaccggtctccttccagaatgcttccgccatgcaccaccacctc
gaatggcagcacgctattaaatccaaatttgcctaaccagaatgatggtgttgacgctgatggaa
gccacagcagttccccaactgttttgaattctagtggcagaatggatgaatctgtttggcgaccа
tattga (SEQ ID NO:101)

**[00390]** Homo sapiens SRY (sex determining region Y)-box 5 (SOX5) (NM_006940) SEQ ID NO:38 (protein) and SEQ ID NO:102 (DNA)

MLTDPDLPQEFERMSSKRPASPYGEADGEVAMVTSRQKVEEEESDGLPAFHLPLHVSFPNKPHSE
EFQPVSLLTQETCGHRTPTSQHNTMEVDGNKVMSSFAPHNSSTSPQKAEEGGRQSGESLSSTALG
TPERRKGSLADVVDTLKQRKMEELIKNEPEETPSIEKLLSKDWKDKLLAMGSGNFGEIKGTPESL
AEKERQLMGMINQLTSLREQLLAAHDEQKKLAASQIEKQRQQMELAKQQQEQIARQQQQLLQQQH
KINLLQQQIQVQGQLPPLMIPVFPPDQRTLAAAAQQGFLLPPGFSYKAGCSDPYPVQLIPTTMAA
AAAATPGLGPLQLQQLYAAQLAAMQVSPGGKLPGIPQGNLGAAVSPTSIHTDKSTNSPPPKSKDE
VAQPLNLSAKPKTSDGKSPTSPTSPHMPALRINSGAGPLKASVPAALASPSARVSTIGYLNDHDA
VTKAIQEARQMKEQLRREQQVLDGKVAVVNSLGLNNCRTEKEKTTLESLTQQLAVKQNEEGKFSH
AMMDFNLSGDSDGSAGVSESRIYRESRGRGSNEPHIKRPMNAFMVWAKDERRKILQAFPDMHNSN
ISKILGSRWKAMTNLEKQPYYEEQARLSKQHLEKYPDYKYKPRPKRTCLVDGKKLRIGEYKAIMR
NRRQEMRQYFNVGQQAQIPIATAGVVYPGAIAMAGMPSPHLPSEHSSVSSSPEPGMPVIQSTYGV
KGEEPHIKEEIQAEDINGEIYDEYDEEEDDPDVDYGSDSENHIAGQAN (SEQ ID NO:38)

atgcttactgaccctgatttacctcaggagtttgaaaggatgtcttccaagcgaccagcctctcc
gtatggggaagcagatggagaggtagccatggtgacaagcagacagaaagtggaagaagaggaga
gtgacgggctcccagcctttcaccttcccttgcatgtgagttttcccaacaagcctcactctgag
gaatttcagccagtttctctgctgacgcaagagacttgtggccataggactcccacttctcagca
caatacaatggaagttgatggcaataaagttatgtcttcatttgccccacacaactcatctacct
cacctcagaaggcagaagaaggtgggcgacagagtggcgagtccttgtctagtacagccctggga
actcctgaacggcgcaagggcagtttagctgatgttgttgacaccttgaagcagaggaaaatgga
agagctcatcaaaaacgagccggaagaaaccccccagtattgaaaaactactctcaaaggactgga
aagacaagcttcttgcaatgggatcggggaactttggcgaaataaaagggactcccgagagctta
gctgagaaagaaaggcaactcatgggtatgatcaaccagctgaccagcctccgagagcagctgtt
ggctgcccacgatgagcagaagaaactagctgcctctcagattgagaaacagcgtcagcaaatgg
agctggccaagcagcaacaagaacaaattgcaagacagcagcagcagcttctacagcaacaacac
aaaatcaatttgctccagcaacagatccaggttcaaggtcagctgccgccattaatgattcccgt
attccctcctgatcaacggacactggctgcagctgcccagcaaggattcctcctccctccaggct

tcagctataaggctggatgtagtgacccttaccctgttcagctgatcccaactaccatggcagct
gctgccgcagcaacaccaggcttaggcccactccaactgcagcagttatatgctgcccagctagc
tgcaatgcaggtatctccaggagggaagctgccaggcataccccaaggcaaccttggtgctgctg
tatctcctaccagcattcacacagacaagagcacaaacagcccaccacccaaaagcaaggatgaa
gtggcacagccactgaacctatcagctaaacccaagacctctgatggcaaatcacccacatcacc
cacctctccccatatgccagctctgagaataaacagtggggcaggccccctcaaagcctctgtcc
cagcagcgttagctagtccttcagccagagttagcacaataggttacttaaatgaccatgatgct
gtcaccaaggcaatccaagaagctcggcaaatgaaggagcaactccgacgggaacaacaggtgct
tgatgggaaggtggctgttgtgaatagtctgggtctcaataactgccgaacagaaaaggaaaaaa
caacactggagagtctgactcagcaactggcagttaaacagaatgaagaaggaaaatttagccat
gcaatgatggatttcaatctgagtggagattctgatggaagtgctggagtctcagagtcaagaat
ttatagggaatcccgagggcgtggtagcaatgaaccccacataaagcgtccaatgaatgccttca
tggtgtgggctaaagatgaacggagaaagatccttcaagcctttcctgacatgcacaactccaac
atcagcaagatattgggatctcgctggaaagctatgacaaacctagagaaacagccatattatga
ggagcaagcccgtctcagcaagcagcacctggagaagtaccctgactataagtacaagcccaggc
caaagcgcacctgcctggtggatggcaaaaagctgcgcattggtgaatacaaggcaatcatgcgc
aacaggcggcaggaaatgcggcagtacttcaatgttgggcaacaagcacagatccccattgccac
tgctggtgttgtgtaccctggagccatcgccatggctgggatgccctcccctcacctgccctcgg
agcactcaagcgtgtctagcagcccagagcctgggatgcctgttatccagagcacttacggtgtg
aaaggagaggagccacatatcaaagaagagatacaggccgaggacatcaatggagaaatttatga
tgagtacgacgaggaagaggatgatccagatgtagattatgggagtgacagtgaaaaccatattg
caggacaagccaactga (SEQ ID NO:102)

**[00391]** Homo sapiens SOX6 mRNA (AF309034) SEQ ID NO:39 (protein) and SEQ ID NO:103 (DNA)

MSSKQATSPFACAADGEDAMTQDLTSREKEEGSDQHVASHLPLHPIMHNKPHSEELPTLVSTIQQ
DADWDSVLSSQQRMESENNKLCSLYSFRNTSTSPHKPDEGSRDREIMTSVTFGTPERRKGSLADV
VDTLKQKKLEEMTRTEQEDSSCMEKLLSKDWKEKMERLNTSELLGEIKGTPESLAEKERQLSTMI
TQLISLREQLLAAHDEQKKLAASQIEKQRQQMDLARQQQEQIARQQQQLLQQQHKINLLQQQIQV
QGHMPPLMIPIFPHDQRTLAAAAAAQQGFLFPPGITYKPGDNYPVQFIPSTMAAAAASGLSPLQL
QKGHASHPQINQRLKGLSDRFGRNLDTFEHGGGHSYNHKQIEQLYAAQLASMQVSPGAKMPSTPQ
PPNTAGTVSPTGIKNEKRGTSPVTQVKDEAAAQPLNLSSRPKTAEPVKSPTSPTQNLFPASKTSP
VNLPNKSSIPSPIGGSLGRGSSLDILSSLNSPALFGDQDTVMKAIQEARKMREQIQREQQQQQPH
GVDGKLSSINNMGLNSCRNEKERTRFENLGPQLTGKSNEDGKLGPGVIDLTRPEDAEGGATVAEA
RVYRDARGRASSEPHIKRPMNAFMVWAKDERRKILQAFPDMHNSNISKILGSRWKSMSNQEKQPY
YEEQARLSKIHLEKYPNYKYKPRPKRTCIVDGKKLRIGEYKQLMRSRRQEMRQFFTVGQQPQIPI
TTGTGVVYPGAITMATTTPSPQMTSDCSSTSASPEPSLPVIQSTYGMKTDGGSLAGNEMINGEDE
MEMYDDYEDDPKSDYSSENEAPEAVSAN (SEQ ID NO:39)

atgtcttccaagcaagccacctctccatttgcctgtgcagctgatggagaggatgcaatgaccca
ggatttaacctcaagggaaaaggaagagggcagtgatcaacatgtggcctcccatctgcctctgc
accccataatgcacaacaaacctcactctgaggagctaccaacacttgtcagtaccattcaacaa
gatgctgactgggacagcgttctgtcatctcagcaaagaatggaatcagagaataataagttatg
ttccctatattccttccgaaatacctctacctcaccacataagcctgacgaagggagtcgggacc
gtgagataatgaccagtgttacttttggaaccccagagcgccgcaaagggagtcttgccgatgtg
gtggacacactgaaacagaagaagcttgaggaaatgactcggactgaacaagaggattcctcctg
catggaaaaactactttcaaaagattggaaggaaaaaatggaaagactaaataccagtgaacttc
ttggagaaattaaaggtacacctgagagcctggcagaaaaagaacggcagctctccaccatgatt
acccagctgatcagtttacgggagcagctactggcagcgcatgatgaacagaaaaaactggcagc
gtcacaaattgagaaacaacggcagcaaatggaccttgctcgccaacagcaagaacagattgcga
gacaacagcagcaacttctgcaacagcagcacaaaattaatctcctgcagcaacagatccaggtt
cagggtcacatgcctccgctcatgatcccaatttttccacatgaccagcggactctggcagcagc

tgctgctgcccaacagggattcctcttccccctggaataacatacaaaccaggtgataactacc
ccgtacagttcattccatcaacaatggcagctgctgctgcttctggactcagccctttacagctc
cagaagggtcatgcctcccacccacaaattaaccaaaggctaaagggcctaagtgaccgttttgg
caggaatttggacacctttgaacatggtggtggccactcttacaaccacaaacagattgagcagc
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ccaccaaacacagcagggacggtctcacctactgggataaaaaatgaaaagagagggaccagccc
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cagagcctgtaaagtccccaacgtctcccacccagaacctcttcccagccagcaaaaccagccct
gtcaatctgccaaacaaaagcagcatccctagccccattggaggaagcctgggaagaggatcctc
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ccattcaggaggcgcggaagatgcgagagcagatccagcgggagcaacagcagcaacagccacat
ggtgttgacgggaaactgtcctccataaataatatggggctgaacagctgcaggaatgaaaagga
aagaacgcgctttgagaatttggggccccagttaacgggaaagtcaaatgaagatggaaaactgg
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cgagtctacagggacgcccgcggccgtgccagcagcgagccacacattaagcgaccaatgaatgc
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ccaacattagcaaaatcttaggatctcgctggaaatcaatgtccaaccaggagaagcaaccttat
tatgaagagcaggcccggctaagcaagatccacttagagaagtacccaaactataaatacaaacc
ccgaccgaaacgcacctgcattgttgatggcaaaaagcttcggattggggagtataagcaactga
tgaggtctcggagacaggagatgaggcagttctttactgtggggcaacagcctcagattccaatc
accacaggaacaggtgttgtgtatcctggtgctatcactatggcaactaccacaccatcgcctca
gatgacatctgactgctctagcacctcggccagcccggagcccagcctcccggtcatccagagca
cttatggtatgaagacagatggcggaagcctagctggaaatgaaatgatcaatggagaggatgaa
atggaaatgtatgatgactatgaagatgaccccaaatcagactatagcagtgaaaatgaagcccc
ggaggctgtcagtgccaactga (SEQ ID NO:103)

**[00392]** Homo sapiens GATA binding protein 6 (GATA6) (NM_005257) SEQ ID NO:40 (protein) and SEQ ID NO:104 (DNA)

MALTDGGWCLPKRFGAAGADASDSRAFPAREPSTPPSPISSSSSSCSRGGERGPGGASNCGTPQL
DTEAAAGPPARSLLLSSYASHPFGAPHGPSAPGVAGPGGNLSSWEDLLLFTDLDQAATASKLLWS
SRGAKLSPFAPEQPEEMYQTLAALSSQGPAAYDGAPGGFVHSAAAAAAAAAAASSPVYVPTTRVG
SMLPGLPYHLQGSGSGPANHAGGAGAHPGWPQASADSPPYGSGGGAAGGGAAGPGGAGSAAAHVS
ARFPYSPSPPMANGAAREPGGYAAAGSGGAGGVSGGGSSLAAMGGREPQYSSLSAARPLNGTYHH
HHHHHHHHPSPYSPYVGAPLTPAWPAGPFETPVLHSLQSRAGAPLPVPRGPSADLLEDLSESREC
VNCGSIQTPLWRRDGTGHYLCNACGLYSKMNGLSRPLIKPQKRVPSSRRLGLSCANCHTTTTTLW
RRNAEGEPVCNACGLYMKLHGVPRPLAMKKEGIQTRKRKPKNINKSKTCSGNSNNSIPMTPTSTS
SNSDDCSKNTSPTTQPTASGAGAPVMTGAGESTNPENSELKYSGQDGLYIGVSLASPAEVTSSVR
PDSWCALALA (SEQ ID NO:40)

atggccttgactgacggcggctggtgcttgccgaagcgcttcggggccgcgggtgcggacgccag
cgactccagagcctttccagcgcgggagccctccacgccgccttcccccatctcttcctcgtcct
cctcctgctcccggggcggagagcggggccccggcggcgccagcaactgcgggacgcctcagctc
gacacggaggcggcggccggacccccggcccgctcgctgctgctcagttcctacgcttcgcatcc
cttcggggctccccacggaccttcggcgcctggggtcgcgggccccgggggcaacctgtcgagct
gggaggacttgctgctgttcactgacctcgaccaagccgcgaccgccagcaagctgctgtggtcc
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cgctctctccagccagggtccggccgcctacgacggcgcgcccggcggcttcgtgcactctgcgg
ccgcggcggcagcagccgcggcggcggccagctccccggtctacgtgcccaccacccgcgtgggt
tccatgctgcccggcctaccgtaccacctgcaggggtcgggcagtgggccagccaaccacgcggg
cggcgcgggcgcgcaccccggctggcctcaggcctcggccgacagccctccatacggcagcggag
gcggcgcggctggcggcggggccgcggggcctggcggcgctggctcagccgcggcgcacgtctcg
gcgcgcttcccctactctcccagcccgcccatggccaacggcgccgcgcgggagccgggaggcta

cgcggcggcgggcagtgggggcgcgggaggcgtgagcggcggcggcagtagcctggcggccatgg
gcggccgcgagccccagtacagctcgctgtcggccgcgcggccgctgaacgggacgtaccaccac
caccaccaccaccaccaccatccgagcccctactcgccctacgtgggggcgccactgacgcc
tgcctggcccgccggacccttcgagaccccggtgctgcacagcctgcagagccgcgccggagccc
cgctcccggtgccccggggtcccagtgcagacctgctggaggacctgtccgagagccgcgagtgc
gtgaactgcggctccatccagacgccgctgtggcggcgggacggcaccggccactacctgtgcaa
cgcctgcgggctctacagcaagatgaacggcctcagccggcccctcatcaagccgcagaagcgcg
tgccttcatcacggcggcttggattgtcctgtgccaactgtcacaccacaactaccaccttatgg
cgcagaaacgccgagggtgaacccgtgtgcaatgcttgtggactctacatgaaactccatggggt
gcccagaccacttgctatgaaaaaagagggaattcaaaccaggaaacgaaaacctaagaacataa
ataaatcaaagacttgctctggtaatagcaataattccattcccatgactccaacttccacctct
tctaactcagatgattgcagcaaaaatacttcccccacaacacaacctacagcctcaggggcggg
tgccccggtgatgactggtgcgggagagagcaccaatcccgagaacagcgagctcaagtattcgg
gtcaagatgggctctacataggcgtcagtctcgcctcgccggccgaagtcacgtcctccgtgcga
ccggattcctggtgcgccctggccctggcctga (SEQ ID NO:104)

**[00393]** Homo sapiens GATA binding protein 1(GATA1) (NM_002049) SEQ ID NO:41 (protein) and SEQ ID NO:105 (DNA)

MEFPGLGSLGTSEPLPQFVDPALVSSTPESGVFFPSGPEGLDAAASSTAPSTATAAAAALAYYRD
AEAYRHSPVFQVYPLLNCMEGIPGGSPYAGWAYGKTGLYPASTVCPTREDSPPQAVEDLDGKGST
SFLETLKTERLSPDLLTLGPALPSSLPVPNSAYGGPDFSSTFFSPTGSPLNSAAYSSPKLRGTLP
LPPCEARECVNCGATATPLWRRDRTGHYLCNACGLYHKMNGQNRPLIRPKKRLIVSKRAGTQCTN
CQTTTTTLWRRNASGDPVCNACGLYYKLHQVNRPLTMRKDGIQTRNRKASGKGKKKRGSSLGGTG
AAEGPAGGFMVVAGGSGSGNCGEVASGLTLGPPGTAHLYQGLGPVVLSGPVSHLMPFPGPLLGSP
TGSFPTGPMPPTTSTTVVAPLSS (SEQ ID NO:41)

atggagttccctggcctggggtccctggggacctcagagcccctccccagtttgtggatcctgc
tctggtgtcctccacaccagaatcaggggttttcttcccctctgggcctgagggcttggatgcag
cagcttcctccactgccccgagcacagccaccgctgcagctgcggcactggcctactacagggac
gctgaggcctacagacactccccagtctttcaggtgtacccattgctcaactgtatggaggggat
cccaggggctcaccatatgccggctgggcctacggcaagacggggctctaccctgcctcaactg
tgtgtcccacccgcgaggactctcctccccaggccgtggaagatctggatggaaaaggcagcacc
agcttcctggagactttgaagacagagcggctgagcccagacctcctgaccctgggacctgcact
gccttcatcactccctgtccccaatagtgcttatgggggccctgacttttccagtaccttctttt
ctcccaccgggagccccctcaattcagcagcctattcctctcccaagcttcgtggaactctcccc
ctgcctccctgtgaggccagggagtgtgtgaactgcggagcaacagccactccactgtggcggag
ggacaggacaggccactacctatgcaacgcctgcggcctctatcacaagatgaatgggcagaaca
ggcccctcatccggcccaagaagcgcctgattgtcagtaaacgggcaggtactcagtgcaccaac
tgccagacgaccaccacgacactgtggcggagaaatgccagtggggatcccgtgtgcaatgcctg
cggcctctactacaagctacaccaggtgaaccggccactgaccatgcggaaggatggtattcaga
ctcgaaaccgcaaggcatctggaaaagggaaaaagaaacggggctccagtctgggaggcacagga
gcagccgaaggaccagctggtggctttatggtggtggctgggggcagcggtagcgggaattgtgg
ggaggtggcttcaggcctgacactgggccccccaggtactgcccatctctaccaaggcctgggcc
ctgtggtgctgtcagggcctgttagccacctcatgcctttccctggacccctactgggctcaccc
acgggctccttccccacaggccccatgccccccaccaccagcactactgtggtggctccgctcag
ctcatga (SEQ ID NO:105)

**[00394]** Homo sapiens Fli-1 proto-oncogene, ETS transcription factor (FLI1) (NM_002017) SEQ ID NO:42 (protein) and SEQ ID NO:106 (DNA)

MDGTIKEALSVVSDDQSLFDSAYGAAAHLPKADMTASGSPDYGQPHKINPLPPQQEWINQPVRVN
VKREYDHMNGSRESPVDCSVSKCSKLVGGGESNPMNYNSYMDEKNGPPPPNMTTNERRVIVPADP
TLWTQEHVRQWLEWAIKEYSLMEIDTSFFQNMDGKELCKMNKEDFLRATTLYNTEVLLSHLSYLR
ESSLLAYNTTSHTDQSSRLSVKEDPSYDSVRRGAWGNNMNSGLNKSPPLGGAQTISKNTEQRPQP

DPYQILGPTSSRLANPGSGQIQLWQFLLELLSDSANASCITWEGTNGEFKMTDPDEVARRWGERK
SKPNMNYDKLSRALRYYYDKNIMTKVHGKRYAYKFDFHGIAQALQPHPTESSMYKYPSDISYMPS
YHAHQQKVNFVPPHPSSMPVTSSSFFGAASQYWTSPTGGIYPNPNVPRHPNTHVPSHLGSYY
(SEQ ID NO:42)

atggacgggactattaaggaggctctgtcggtggtgagcgacgaccagtccctctttgactcagc
gtacggagcggcagcccatctccccaaggccgacatgactgcctcggggagtcctgactacgggc
agccccacaagatcaacccctcccaccacagcaggagtggatcaatcagccagtgagggtcaac
gtcaagcgggagtatgaccacatgaatggatccagggagtctccggtggactgcagcgttagcaa
atgcagcaagctggtgggcggaggcgagtccaaccccatgaactacaacagctatatggacgaga
agaatggcccccctcctcccaacatgaccaccaacgagaggagagtcatcgtccccgcagacccc
acactgtggacacaggagcatgtgaggcaatggctggagtgggccataaaggagtacagcttgat
ggagatcgacacatccttttccagaacatggatggcaaggaactgtgtaaaatgaacaaggagg
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agaagacccttcttatgactcagtcagaagaggagcttggggcaataacatgaattctggcctca
acaaaagtcctccccttggaggggcacaaacgatcagtaagaatacagagcaacggccccagcca
gatccgtatcagatcctgggcccgaccagcagtcgcctagccaaccctggaagcgggcagatcca
gctgtggcaattcctcctggagctgctctccgacagcgccaacgccagctgtatcacctgggagg
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agcaagcccaacatgaattacgacaagctgagccgggccctccgttattactatgataaaaacat
tatgaccaaagtgcacggcaaaagatatgcttacaaatttgacttccacggcattgcccaggctc
tgcagccacatccgaccgagtcgtccatgtacaagtacccttctgacatctcctacatgccttcc
taccatgcccaccagcagaaggtgaactttgtccctccccatccatcctccatgcctgtcacttc
ctccagcttctttggagccgcatcacaatactggacctcccccacgggggggaatctaccccaacc
ccaacgtcccccgccatcctaacacccacgtgccttcacacttaggcagctactactag (SEQ
ID NO:106)

**[00395]** Human erythroid Kruppel-like factor EKLF gene (U37106) SEQ ID NO:43 (protein) and SEQ ID NO:107 (DNA)

MATAETALPSISTLTALGPFPDTQDDFLKWWRSEEAQDMGPGPPDPTEPPLHVKSEDQPGEEEDD
ERGADATWDLDLLLTNFSGPEPGGAPQTCALAPSEASGAQYPPPPETLGAYAGGPGLVAGLLGSE
DHSGWVRPALRARAPDAFVGPALAPAPAPEPKALALQPVYPGPGAGSSGGYFPRTGLSVPAASGA
PYGLLSGYPAMYPAPQYQGHFQLFRGLQGPAPGPATSPSFLSCLGPGTVGTGLGGTAEDPGVIAE
TAPSKRGRRSWARKRQAAHTCAHPGCGKSYTKSSHLKAHLRTHTGEKPYACTWEGCGWRFARSDE
LTRHYRKHTGQRPFRCQLCPRAFSRSDHLALHMKRHL (SEQ ID NO:43)

atggccacagccgagaccgccttgccctccatcagcacactgaccgccctgggccccttcccgga
cacacaggatgacttcctcaagtggtggcgctccgaagaggcgcaggacatgggcccgggtcctc
ctgaccccacggagccgcccctccacgtgaagtctgaggaccagcccggggaggaagaggacgat
gagaggggcgcggacgccacctgggacctggatctcctcctcaccaacttctcgggcccggagcc
cggtggcgcgccccagacctgcgctctggcgcccagcgaggcctccggggcgcaatatccgccgc
cgcccgagactctgggcgcatatgctggcggcccggggctggtggctgggcttttgggttcggag
gatcactcgggttgggtgcgccctgccctgcgagcccgggctcccgacgccttcgtgggcccagc
cctggctccagccccggcccccgagcccaaggcgctggcgctgcaaccggtgtacccggggcccg
gcgccggctcctcgggtggctacttcccgcggaccgggctttcagtgcctgcggcgtcgggcgcc
ccctacgggctactgtccgggtaccccgcgatgtacccggcgcctcagtaccaagggcacttcca
gctcttccgcgggctccagggacccgcgcccggtcccgccacgtcccctcctcctgagttgtt
tgggacccgggacggtgggcactggactcgggggactgcagaggatccaggtgtgatagccgag
accgcgccatccaagcgaggccgacgttcgtgggcgcgcaagaggcaggcagcgcacacgtgcgc
gcacccgggttgcggcaagagctacaccaagagctcccacctgaaggcgcatctgcgcacgcaca
caggggagaagccatacgcctgcacgtgggaaggctgcggctggagattcgcgcgctcggacgag

ctgacccgccactaccggaaacacacggggcagcgcccttccgctgccagctctgcccacgtgc
tttttcgcgctctgaccacctggccttgcacatgaagcgccacctttga (SEQ ID NO:107)

**[00396]** Human MyoD (X56677) SEQ ID NO:44 (protein) and SEQ ID NO:108 (DNA)

MELLSPPLRDVDLTAPDGSLCSFATTDDFYDDPCFDSPDLRFFEDLDPRLMHVGALLKPEEHSHF
PAAVHPAPGAREDEHVRAPSGHHQAGRCLLWACKACKRKTTNADRRKAATMRERRRLSKVNEAFE
TLKRCTSSNPNQRLPKVEILRNAIRYIEGLQALLRDQDAAPPGAAAFYAPGPLPPGRGGEHYSGD
SDASSPRSNCSDGMMDYSGPPSGARRRNCYEGAYYNEAPSEPRPGKSAAVSSLDYLSSIVERIST
ESPAAPALLLADVPSESPPRRQEAAAPSEGESSGDPTQSPDAAPQCPAGANPNPIYQVL (SEQ
ID NO:44)

atggagctactgtcgccaccgctccgcgacgtagacctgacggcccccgacggctctctctgctc
ctttgccacaacggacgacttctatgacgacccgtgtttcgactccccggacctgcgcttcttcg
aagacctggacccgcgcctgatgcacgtgggcgcgctcctgaaacccgaagagcactcgcacttc
cccgcggcggtgcacccggccccgggcgcacgtgaggacgagcatgtgcgcgcgcccagcgggca
ccaccaggcgggccgctgcctactgtgggcctgcaaggcgtgcaagcgcaagaccaccaacgccg
accgccgcaaggccgccaccatgcgcgagcggcgccgcctgagcaaagtaaatgaggcctttgag
acactcaagcgctgcacgtcgagcaatccaaaccagcggttgcccaaggtggagatcctgcgcaa
cgccatccgctatatcgagggcctgcaggctctgctgcgcgaccaggacgccgcgccccctggcg
cagccgccttctatgcgccgggcccgctgcccccgggccgcggcggcgagcactacagcggcgac
tccgacgcgtccagcccgcgctccaactgctccgacggcatgatggactacagcggcccccgag
cggcgcccggcggcggaactgctacgaaggcgcctactacaacgaggcgcccagcgaacccaggc
ccgggaagagtgcggcggtgtcgagcctagactacctgtccagcatcgtggagcgcatctccacc
gagagccctgcggcgcccgccctcctgctggcggacgtgccttctgagtcgcctccgcgcaggca
agaggctgccgcccccagcgagggagagagcagcggcgaccccacccagtcaccggacgccgccc
cgcagtgccctgcgggtgcgaaccccaacccgatataccaggtgctctga (SEQ ID
NO:108)

**[00397]** Homo sapiens NGFI-A binding protein 2 (EGR1 binding protein 2)(NAB2) (NM_005967) SEQ ID NO:45 (protein) and SEQ ID NO:109 (DNA)

MHRAPSPTAEQPPGGGDSARRTLQPRLKPSARAMALPRTLGELQLYRVLQRANLLSYYETFIQQG
GDDVQQLCEAGEEEFLEIMALVGMATKPLHVRRLQKALREWATNPGLFSQPVPAVPVSSIPLFKI
SETAGTRKGSMSNGHGSPGEKAGSARSFSPKSPLELGEKLSPLPGGPGAGDPRIWPGRSTPESDV
GAGGEEEAGSPPFSPPAGGGVPEGTGAGGLAAGGTGGGPDRLEPEMVRMVVESVERIFRSFPRGD
AGEVTSLLKLNKKLARSVGHIFEMDDNDSQKEEEIRKYSIIYGRFDSKRREGKQLSLHELTINEA
AAQFCMRDNTLLLRRVELFSLSRQVARESTYLSSLKGSRLHPEELGGPPLKKLKQEVGEQSHPEI
QQPPPGPESYVPPYRPSLEEDSASLSGESLDGHLQAVGSCPRLTPPPADLPLALPAHGLWSRHIL
QQTLMDEGLRLARLVSHDRVGRLSPCVPAKPPLAEFEEGLLDRCPAPGPHPALVEGRRSSVKVEA
EASRQ (SEQ ID NO:45)

atgcacagagcgccttcccccacagccgagcagccgccgggcggaggggacagcgcccgccggac
cctgcagcccagactcaagcccagtgcccgagccatggcactgcctcggacgctgggggagctgc
agctgtaccgggtcctgcagcgcgccaacctcctttcctactatgagaccttcatccagcaggga
ggggacgacgtgcagcagctgtgtgaggcgggtgaggaggagtttctggagatcatggcacttgt
gggcatggccaccaagcccctccatgtccggcgcctgcagaaggcactgagagagtgggccacca
atccagggctcttcagtcaaccagtgcctgctgttcccgtctccagcatcccgctcttcaagatc
tctgagactgcgggtacccggaaagggagcatgagcaatgggcatggcagcccaggggaaaaggc
aggcagtgcccgcagttttagccccaagagccccttgaacttggagagaagctatcaccactgc
ctgggggacctggggcaggggacccccggatctggccaggccggagcactccagagtcggacgtt
ggggcaggaggagaagaggaggctggctcgccccccttctcccccccctgcaggggaggagtccc
tgaggggactggggctgggggctggcagcaggtgggactgggggtggtccagaccgactggagc
cagagatggtacgcatggtggtggaaagtgtggagaggatcttccggagcttcccaaggggggat
gctggggaggtcacatccctgctaaagctgaataagaagctggcacggagcgttgggcacatctt
tgagatggatgataatgacagccagaaggaagaggagatccgcaaatacagcatcatctatggcc

gtttcgactctaagcggcgggagggcaagcagctcagcctgcacgagctcaccatcaacgaggct
gctgcccagttctgcatgagggacaacacgctcttattacggagagtggagctcttctctttgtc
ccgccaagtagcccgagagagcacctacttgtcctccttgaagggctccaggcttcaccctgaag
aactgggaggccctccactgaagaagctgaaacaagaggttggagaacagagtcaccctgaaatc
cagcagcctcccccaggccctgagtcctatgtacccccataccgccccagcctggaggaggacag
cgccagcctgtctggggagagtctggatggacatttgcaggctgtggggtcatgtccaaggctga
cgccgcccccctgctgacctgcctctggcattgccagcccatgggctatggagccgacacatcctg
cagcagacactgatggacgaggggctgcggctcgcccgcctcgtctcccacgaccgcgtgggccg
cctcagcccctgtgtgcctgcgaagccacctctcgcagagttcgaggaagggctgctggacagat
gtcctgccccaggaccccatcccgcgctggtggagggtcgcaggagcagcgtgaaagtggaggct
gaggccagccggcagtga (SEQ ID NO:109)

**[00398]** Homo sapiens early growth response 1 (EGR1) (NM_001964) SEQ ID NO:46 (protein) and SEQ ID NO:110 (DNA)

MAAAKAEMQLMSPLQISDPFGSFPHSPTMDNYPKLEEMMLLSNGAPQFLGAAGAPEGSGSNSSSS
SSGGGGGGGGGSNSSSSSSTFNPQADTGEQPYEHLTAESFPDISLNNEKVLVETSYPSQTTRLPP
ITYTGRFSLEPAPNSGNTLWPEPLFSLVSGLVSMTNPPASSSSAPSPAASSASASQSPPLSCAVP
SNDSSPIYSAAPTFPTPNTDIFPEPQSQAFPGSAGTALQYPPPAYPAAKGGFQVPMIPDYLFPQQ
QGDLGLGTPDQKPFQGLESRTQQPSLTPLSTIKAFATQSGSQDLKALNTSYQSQLIKPSRMRKYP
NRPSKTPPHERPYACPVESCDRRFSRSDELTRHIRIHTGQKPFQCRICMRNFSRSDHLTTHIRTH
TGEKPFACDICGRKFARSDERKRHTKIHLRQKDKKADKSVVASSATSSLSSYPSPVATSYPSPVT
TSYPSPATTSYPSPVPTSFSSPGSSTYPSPVHSGFPSPSVATTYSSVPPAFPAQVSSFPSSAVTN
SFSASTGLSDMTATFSPRTIEIC (SEQ ID NO:46)

atggccgcggccaaggccgagatgcagctgatgtccccgctgcagatctctgacccgttcggatc
ctttcctcactcgcccaccatggacaactaccctaagctggaggagatgatgctgctgagcaacg
gggctccccagttcctcggcgccgccggggccccagagggcagcggcagcaacagcagcagcagc
agcagcgggggcggtggaggcggcggggggcggcagcaacagcagcagcagcagcagcaccttcaa
ccctcaggcggacacgggcgagcagccctacgagcacctgaccgcagagtcttttcctgacatct
ctctgaacaacgagaaggtgctggtggagaccagttaccccagccaaaccactcgactgcccccc
atcacctatactggccgcttttccctggagcctgcacccaacagtggcaacaccttgtggcccga
gcccctcttcagcttggtcagtggcctagtgagcatgaccaacccaccggcctcctcgtcctcag
caccatctccagcggcctcctccgcctccgcctcccagagcccacccctgagctgcgcagtgcca
tccaacgacagcagtcccatttactcagcggcacccaccttccccacgccgaacactgacatttt
ccctgagccacaaagccaggccttcccgggctcggcagggacagcgctccagtacccgcctcctg
cctaccctgccgccaagggtggcttccaggttcccatgatccccgactacctgtttccacagcag
caggggatctgggcctgggcaccccagaccagaagcccttccagggcctggagagccgcaccca
gcagccttcgctaacccctctgtctactattaaggcctttgccactcagtcgggctcccaggacc
tgaaggccctcaataccagctaccagtcccagctcatcaaacccagccgcatgcgcaagtacccc
aaccggcccagcaagacgcccccccacgaacgcccttacgcttgcccagtggagtcctgtgatcg
ccgcttctcccgctccgacgagctcacccgccacatccgcatccacacaggccagaagcccttcc
agtgccgcatctgcatgcgcaacttcagccgcagcgaccacctcaccacccacatccgcacccac
acaggcgaaaagcccttcgcctgcgacatctgtggaagaaagtttgccaggagcgatgaacgcaa
gaggcataccaagatccacttgcggcagaaggacaagaaagcagacaaaagtgttgtggcctctt
cggccacctcctctctctcttcctacccgtccccggttgctacctcttacccgtccccggttact
acctcttatccatccccggccaccacctcatacccatcccctgtgcccacctccttctcctctcc
cggctcctcgacctacccatcccctgtgcacagtggcttcccctccccgtcggtggccaccacgt
actcctctgttcccccctgctttcccggcccaggtcagcagcttcccttcctcagctgtcaccaac
tccttcagcgcctccacagggctttcggacatgacagcaacctttctcccaggacaattgaaat
ttgctaa (SEQ ID NO:110)

**[00399]** Homo sapiens growth factor independent 1 transcription repressor(GFI1) (NM_005263) SEQ ID NO:47 (protein) and SEQ ID NO:111 (DNA)

MPRSFLVKSKKAHSYHQPRSPGPDYSLRLENVPAPSRADSTSNAGGAKAEPRDRLSPESQLTEAP
DRASASPDSCEGSVCERSSEFEDFWRPPSPSASPASEKSMCPSLDEAQPFPLPFKPYSWSGLAGS
DLRHLVQSYRPCGALERGAGLGLFCEPAPEPGHPAALYGPKRAAGGAGAGAPGSCSAGAGATAGP
GLGLYGDFGSAAAGLYERPTAAAGLLYPERGHGLHADKGAGVKVESELLCTRLLLGGGSYKCIKC
SKVFSTPHGLEVHVRRSHSGTRPFACEMCGKTFGHAVSLEQHKAVHSQERSFDCKICGKSFKRSS
TLSTHLLIHSDTRPYPCQYCGKRFHQKSDMKKHTFIHTGEKPHKCQVCGKAFSQSSNLITHSRKH
TGFKPFGCDLCGKGFQRKVDLRRHRETQHGLK (SEQ ID NO:47)

atgccgcgctcatttctcgtcaaaagcaagaaggctcacagctaccaccagccgcgctccccagg
accagactattccctccgtttagagaatgtaccggcgcctagccgagcagacagcacttcaaatg
caggcggggcgaaggcggagccccgggaccgtttgtcccccgaatcgcagctgaccgaagcccca
gacagagcctccgcatccccagacagctgcgaaggcagcgtctgcgaacggagctcggagtttga
ggacttctggaggcccccgtcaccctccgcgtctccagcctcggagaagtcaatgtgcccatcgc
tggacgaagcccagcccttccccctgcctttcaaaccgtactcatggagcggcctggcgggttct
gacctgcggcacctggtgcagagctaccgaccgtgtggggccctggagcgtggcgctggcctggg
cctcttctgcgaacccgccccggagcctggccacccggccgcgctgtacggcccgaagcgggctg
ccggcggcgcgggggccggggcgccagggagctgcagcgcaggggccggtgccaccgctggccct
ggcctagggctctacggcgacttcgggtctgcggcagccgggctgtatgagaggcccacggcagc
ggcgggcttgctgtaccccgagcgtggccacgggctgcacgcagacaagggcgctggcgtcaagg
tggagtcggagctgctgtgcacccgcctgctgctgggcggcggctcctacaagtgcatcaagtgc
agcaaggtgttctccacgccgcacgggctcgaggtgcacgtgcgcaggtcccacagcggtaccag
acccttgcctgcgagatgtgcggcaagaccttcgggcacgcggtgagcctggagcagcacaaag
ccgtgcactcgcaggaacggagctttgactgtaagatctgtgggaagagcttcaagaggtcatcc
acactgtccacacacctgcttatccactcagacactcggccctacccctgtcagtactgtggcaa
gaggttccaccagaagtcagacatgaagaaacacactttcatccacactggtgagaagcctcaca
agtgccaggtgtgcggcaaggcattcagccagagctccaacctcatcacccacagccgcaaacac
acaggcttcaagcccttcggctgcgacctctgtgggaagggtttccagaggaaggtggacctccg
aaggcaccgggagacgcagcatgggctcaaatga (SEQ ID NO:111)

**[00400]** Homo sapiens paired box 5 (PAX5) (NM_016734) SEQ ID NO:48 (protein) and SEQ ID NO:112(DNA)

MDLEKNYPTPRTSRTGHGGVNQLGGVFVNGRPLPDVVRQRIVELAHQGVRPCDISRQLRVSHGCV
SKILGRYYETGSIKPGVIGGSKPKVATPKVVEKIAEYKRQNPTMFAWEIRDRLLAERVCDNDTVP
SVSSINRIIRTKVQQPPNQPVPASSHSIVSTGSVTQVSSVSTDSAGSSYSISGILGITSPSADTN
KRKRDEGIQESPVPNGHSLPGRDFLRKQMRGDLFTQQQLEVLDRVFERQHYSDIFTTTEPIKPEQ
TTEYSAMASLAGGLDDMKANLASPTPADIGSSVPGPQSYPIVTGRDLASTTLPGYPPHVPPAGQG
SYSAPTLTGMVPGSEFSGSPYSHPQYSSYNDSWRFPNPGLLGSPYYYSAAARGAAPPAAATAYDR
H (SEQ ID NO:48)

atggatttagagaaaaattatccgactcctcggaccagcaggacaggacatggaggagtgaatca
gcttgggggggtttttgtgaatggacggccactcccggatgtagtccgccagaggatagtggaac
ttgctcatcaaggtgtcaggccctgcgacatctccaggcagcttcgggtcagccatggttgtgtc
agcaaaattcttggcaggtattatgagacaggaagcatcaagcctggggtaattggaggatccaa
accaaaggtcgccacacccaaagtggtggaaaaaatcgctgaatataaacgccaaaatcccacca
tgtttgcctgggagatcagggaccggctgctggcagagcgggtgtgtgacaatgacaccgtgcct
agcgtcagttccatcaacaggatcatccggacaaaagtacagcagccacccaaccaaccagtccc
agcttccagtcacagcatagtgtccactggctccgtgacgcaggtgtcctcggtgagcacggatt
cggccggctcgtcgtactccatcagcggcatcctgggcatcacgtcccccagcgccgacaccaac
aagcgcaagagagacgaaggtattcaggagtctccggtgccgaacggccactcgcttccgggcag
agacttcctccggaagcagatgcggggagacttgttcacacagcagcagctggaggtgctggacc
gcgtgtttgagaggcagcactactcagacatcttcaccaccacagagcccatcaagcccgagcag
accacagagtattcagccatggcctcgctggctggtgggctggacgacatgaaggccaatctggc
cagccccacccctgctgacatcgggagcagtgtgccaggcccgcagtcctaccccattgtgacag

gccgtgacttggcgagcacgaccctccccgggtaccctccacacgtcccccccgctggacagggc
agctactcagcaccgacgctgacagggatggtgcctgggagtgagttttccgggagtccctacag
ccaccctcagtattcctcgtacaacgactcctggaggttccccaacccggggctgcttggctccc
cctactattatagcgctgccgcccgaggagccgccccacctgcagccgccactgcctatgaccgt
cactga (SEQ ID NO:112)

**[00401]** Homo sapiens T-cell-specific T-box transcription factor T-bet mRNA (AF241243) SEQ ID NO:49 (protein) and SEQ ID NO:113 (DNA)

MGIVEPGCGDMLTGTEPMPGSDEGRAPGADPQHRYFYPEPGAQDADERRGGGSLGSPYPGGALVP
APPSRFLGAYAYPPRPQAAGFPGAGESFPPPADAEGYQPGEGYAAPDPRAGLYPGPREDYALPAG
LEVSGKLRVALNNHLLWSKFNQHQTEMIITKQGRRMFPFLSFTVAGLEPTSHYRMFVDVVLVDQH
HWRYQSGKWVQCGKAEGSMPGNRLYVHPDSPNTGAHWMRQEVSFGKLKLTNNKGASNNVTQMIVL
QSLHKYQPRLHIVEVNDGEPEAACNASNTHIFTFQETQFIAVTAYQNAEITQLKIDNNPFAKGFR
ENFESMYTSVDTSIPSPPGPNCQFLGGDHYSPLLPNQYPVPSRFYPDLPGQAKDVVPQAYWLGAP
RDHSYEAEFRAVSMKPAFLPSAPGPTMSYYRGQEVLAPGAGWPVAPQYPPKMGPASWFRPMRTLP
MEPGPGGSEGRGPEDQGPPLVWTEIAPIRPESSDSGLGEGDSKRRRVSPYPSSGDSSSPAGAPSP
FDKEAEGQFYNYFPN (SEQ ID NO:49)

atgggcatcgtggagccgggttgcggagacatgctgacgggcaccgagccgatgccggggagcga
cgagggccgggcgcctggcgccgacccgcagcaccgctacttctacccggagccgggcgcgcagg
acgcggacgagcgtcgcgggggcggcagcctggggtctccctacccgggggcgccttggtgccc
gccccgccgagccgcttccttggagcctacgcctacccgccgcgaccccaggcggccggcttccc
cggcgcgggcgagtccttcccgccgcccgcggacgccgagggctaccagccgggcgagggctacg
ccgccccggacccgcgcgccgggctctacccggggccgcgtgaggactacgcgctacccgcggga
ctggaggtgtcggggaaactgagggtcgcgctcaacaaccacctgttgtggtccaagtttaatca
gcaccagacagagatgatcatcaccaagcagggacggcggatgttcccattcctgtcatttactg
tggccgggctggagcccaccagccactacaggatgtttgtggacgtggtcttggtggaccagcac
cactggcggtaccagagcggcaagtgggtgcagtgtggaaaggccgagggcagcatgccaggaaa
ccgcctgtacgtccacccggactcccccaacacaggagcgcactggatgcgccaggaagtttcat
ttgggaaactaaagctcacaaacaacaaggggcgtccaacaatgtgacccagatgattgtgctc
cagtccctccataagtaccagccccggctgcatatcgttgaggtgaacgacggagagccagaggc
agcctgcaacgcttccaacacgcatatctttactttccaagaaacccagttcattgccgtgactg
cctaccagaatgccgagattactcagctgaaaattgataataacccctttgccaaaggattccgg
gagaactttgagtccatgtacacatctgttgacaccagcatcccctccccgcctggacccaactg
tcaattccttgggggagatcactactctcctctcctacccaaccagtatcctgttcccagccgct
tctaccccgaccttcctggccaggcgaaggatgtggttccccaggcttactggctgggggccccc
cgggaccacagctatgaggctgagtttcgagcagtcagcatgaagcctgcattcttgccctctgc
ccctgggcccaccatgtcctactaccgaggccaggaggtcctggcacctggagctggctggcctg
tggcaccccagtaccctcccaagatgggcccggccagctggttccgccctatgcggactctgccc
atggaacccggccctggaggctcagagggacggggaccagaggaccagggtccccccttggtgtg
gactgagattgccccccatccggccggaatccagtgattcaggactgggcgaaggagactctaaga
ggaggcgcgtgtccccctatccttccagtggtgacagctcctcccctgctggggccccttctcct
tttgataaggaagctgaaggacagttttataactattttcccaactga (SEQ ID NO:113)

**[00402]** Homo sapiens GATA binding protein 3 (GATA3) (NM_001002295) SEQ ID NO:50 (protein) and SEQ ID NO:114 (DNA)

MEVTADQPRWVSHHHPAVLNGQHPDTHHPGLSHSYMDAAQYPLPEEVDVLFNIDGQGNHVPPYYG
NSVRATVQRYPPTHHGSQVCRPPLLHGSLPWLDGGKALGSHHTASPWNLSPFSKTSIHHGSPGPL
SVYPPASSSSLSGGHASPHLFTFPPTPPKDVSPDPSLSTPGSAGSARQDEKECLKYQVPLPDSMK
LESSHSRGSMTALGGASSSTHHPITTYPPYVPEYSSGLFPPSSLLGGSPTGFGCKSRPKARSSTE
GRECVNCGATSTPLWRRDGTGHYLCNACGLYHKMNGQNRPLIKPKRRLSAARRAGTSCANCQTTT
TTLWRRNANGDPVCNACGLYYKLHNINRPLTMKKEGIQTRNRKMSSKSKKCKKVHDSLEDFPKNS

SFNPAALSRHMSSLSHISPFSHSSHMLTTPTPMHPPSSLSFGPHHPSSMVTAMG (SEQ ID NO:50)

atggaggtgacggcggaccagccgcgctgggtgagccaccaccaccccgccgtgctcaacgggca
gcacccggacacgcaccacccgggcctcagccactcctacatggacgcggcgcagtacccgctgc
cggaggaggtggatgtgctttttaacatcgacggtcaaggcaaccacgtcccgccctactacgga
aactcggtcagggccacggtgcagaggtaccctccgacccaccacgggagccaggtgtgccgccc
gcctctgcttcatggatccctaccctggctggacggcggcaaagccctgggcagccaccacaccg
cctcccccctggaatctcagccccttctccaagacgtccatccaccacggctccccggggcccctc
tccgtctaccccccggcctcgtcctcctccttgtcgggggggccacgccagcccgcacctcttcac
cttcccgcccaccccgccgaaggacgtctccccggacccatcgctgtccaccccaggctcggccg
gctcggcccggcaggacgagaaagagtgcctcaagtaccaggtgcccctgcccgacagcatgaag
ctggagtcgtcccactcccgtggcagcatgaccgccctgggtggagcctcctcgtcgacccacca
ccccatcaccacctacccgccctacgtgcccgagtacagctccggactcttcccccccagcagcc
tgctgggcggctcccccaccggcttcggatgcaagtccaggcccaaggcccggtccagcacagaa
ggcagggagtgtgtgaactgtggggcaacctcgaccccactgtggcggcgagatggcacgggaca
ctacctgtgcaacgcctgcgggctctatcacaaaatgaacggacagaaccggcccctcattaagc
ccaagcgaaggctgtctgcagccaggagagcagggacgtcctgtgcgaactgtcagaccaccaca
accacactctggaggaggaatgccaatggggaccctgtctgcaatgcctgtgggctctactacaa
gcttcacaatattaacagacccctgactatgaagaaggaaggcatccagaccagaaaccgaaaaa
tgtctagcaaatccaaaaagtgcaaaaaagtgcatgactcactggaggacttccccaagaacagc
tcgtttaacccggccgccctctccagacacatgtcctccctgagccacatctcgcccttcagcca
ctccagccacatgctgaccacgcccacgccgatgcacccgccatccagcctgtcctttggaccac
accacccctccagcatggtcaccgccatgggttag (SEQ ID NO:114)

**[00403]** Homo sapiens FOXP3 (EF534714) SEQ ID NO:51 (protein) and SEQ ID NO:115 (DNA)

MPNPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLGARGPGGTFQGRDLRGGAHASSSSLNPMP
PSQLQLPTLPLVMVAPSGARLGPLPHLQALLQDRPHFMHQLSTVDAHARTPVLQVHPLESPAMIS
LTPPTTATGVFSLKARPGLPPGINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQSSYPLLA
NGVCKWPGCEKVFEEPEDFLKHCQADHLLDEKGRAQCLLQREMVQSLEQQLVLEKEKLSAMQAHL
AGKMALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPREAPDSLFAVRRHLWGSHGNSTFPEFL
HNMDYFKFHNMRPPFTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFRNHPATWKNAIRHNLS
LHKCFVRVESEKGAVWTVDELEFRKKRSQRPSRCSNPTPGP (SEQ ID NO:51)

atgcccaaccccaggcctggcaagccctcggcccccttccttggcccttggcccatccccaggagc
ctcgcccagctggagggctgcacccaaagcctcagacctgctgggggcccgggggcccaggggggaa
ccttccagggccgagatcttcgaggcgggggcccatgcctcctcttcttccttgaaccccatgcca
ccatcgcagctgcagctgcccacactgcccctagtcatggtggcaccctccggggcacggctggg
cccccttgccccacttacaggcactcctccaggacaggccacatttcatgcaccagctctcaacgg
tggatgcccacgcccggacccctgtgctgcaggtgcacccccctggagagcccagccatgatcagc
ctcacaccacccaccaccgccactggggtcttctccctcaaggcccggcctggcctcccacctgg
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ccagtgcacccaggaaggacagcacccctttcggctgtgccccagagctcctacccactgctggca
aatggtgtctgcaagtggcccggatgtgagaaggtcttcgaagagccagaggacttcctcaagca
ctgccaggcggaccatcttctggatgagaagggcagggcacaatgtctcctccagagagagatgg
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gctgggaaaatggcactgaccaaggcttcatctgtggcatcatccgacaagggctcctgctgcat
cgtagctgctggcagccaaggccctgtcgtcccagcctggtctggcccccgggaggcccctgaca
gcctgtttgctgtccggaggcacctgtggggtagccatggaaacagcacattcccagagttcctc
cacaacatggactacttcaagttccacaacatgcgacccccctttcacctacgccacgctcatccg
ctgggccatcctggaggctccagagaagcagcggacactcaatgagatctaccactggttcacac
gcatgtttgccttcttcagaaaccatcctgccacctggaagaacgccatccgccacaacctgagt

ctgcacaagtgctttgtgcgggtggagagcgagaaggggctgtgtggaccgtggatgagctgga
gttccgcaagaaacggagccagaggcccagcaggtgttccaaccctacacctggcccctga
(SEQ ID NO:115)

**[00404]** Human orphan receptor ROR gamma (U16997) SEQ ID NO:52 (protein) and SEQ ID NO:116 (DNA)

MDRAPQRQHRASRELLAAKKTHTSQIEVIPCKICGDKSSGIHYGVITCEGCKGFFRRSQRCNAAY
SCTRQQNCPIDRTSRNRCQHCRLQKCLALGMSRDAVKFGRMSKKQRDSLHAEVQKQLQQRQQQQQ
EPVVKTPPAGAQGADTLTYTLGLPDGQLPLGSSPDLPEASACPPGLLKASGSGPSYSNNLAKAGL
NGASCHLEYSPERGKAEGRESFYSTGSQLTPDRCGLRFEEHRHPGLGELGQGPDSYGSPSFRSTP
EAPYASLTEIEHLVQSVCKSYRETCQLRLEDLLRQRSNIFSREEVTGYQRKSMWEMWERCAHHLT
EAIQYVVEFAKRLSGFMELCQNDQIVLLKAGAMEVVLVRMCRAYNADNRTVFFEGKYGGMELFRA
LGCSELISSIFDFSHSLSALHFSEDEIALYTALVLINAHRPGLQEKRKVEQLQYNLELAFHHHLC
KTHRQSILAKLPPKGKLRSLCSQHVERLQIFQHLHPIVVQAAFPPLYKELFSTETESPVGCPSDL
EEGLLASPYGLLATSLDPVPPSPFSFPMNPGGWSPPALWK (SEQ ID NO:52)

atggacagggccccacagagacagcaccgagcctcacgggagctgctggctgcaaagaagaccca
cacctcacaaattgaagtgatcccttgcaaaatctgtggggacaagtcgtctgggatccactacg
gggttatcacctgtgaggggtgcaagggcttcttccgccggagccagcgctgtaacgcggcctac
tcctgcacccgtcagcagaactgccccatcgaccgcaccagccgaaaccgatgccagcactgccg
cctgcagaaatgcctggcgctggggatgtcccgagatgctgtcaagttcggccgcatgtccaaga
agcagagggacagcctgcatgcagaagtgcagaaacagctgcagcagcggcaacagcagcaacag
gaaccagtggtcaagacccctccagcaggggcccaaggagcagataccctcacctacaccttggg
gctcccagacgggcagctgcccctgggctcctcgcctgacctgcctgaggcttctgcctgtcccc
ctggcctcctgaaagcctcaggctctgggccctcatattccaacaacttggccaaggcagggctc
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ctatagcacaggcagccagctgacccctgaccgatgtggacttcgttttgaggaacacaggcatc
ctgggcttggggaactgggacagggcccagacagctacggcagccccagtttccgcagcacaccg
gaggcaccctatgcctccctgacagagatagagcacctggtgcagagcgtctgcaagtcctacag
ggagacatgccagctgcggctggaggacctgctgcggcagcgctccaacatcttctcccgggagg
aagtgactggctaccagaggaagtccatgtgggagatgtgggaacggtgtgcccaccacctcacc
gaggccattcagtacgtggtggagttcgccaagaggctctcaggctttatggagctctgccagaa
tgaccagattgtgcttctcaaagcaggagcaatggaagtggtgctggttaggatgtgccgggcct
acaatgctgacaaccgcacggtctttttgaaggcaaatacggtggcatggagctgttccgagcc
ttgggctgcagcgagctcatcagctccatctttgacttctcccactccctaagtgccttgcactt
ttccgaggatgagattgccctctacacagcccttgttctcatcaatgcccatcggccagggctcc
aagagaaaaggaaagtagaacagctgcagtacaatctggagctggcctttcatcatcatctctgc
aagactcatcgccaaagcatcctggcaaagctgccacccaaggggaagcttcggagcctgtgtag
ccagcatgtggaaaggctgcagatcttccagcacctccaccccatcgtggtccaagccgctttcc
ctccactctacaaggagctcttcagcactgaaaccgagtcacctgtgggctgtccaagtgacctg
gaagagggactccttgcctctccctatggcctgctggccacctccctggaccccgttccaccctc
acccttttcctttcccatgaaccctggagggtggtccccaccagctctttggaagtga (SEQ ID NO:116)

**[00405]** Homo sapiens hepatocyte nuclear factor 4, alpha (HNF4A), (NM_178849) SEQ ID NO:53 (protein) and SEQ ID NO:117 (DNA)

MRLSKTLVDMDMADYSAALDPAYTTLEFENVQVLTMGNDTSPSEGTNLNAPNSLGVSALCAICGD
RATGKHYGASSCDGCKGFFRRSVRKNHMYSCRFSRQCVVDKDKRNQCRYCRLKKCFRAGMKKEAV
QNERDRISTRRSSYEDSSLPSINALLQAEVLSRQITSPVSGINGDIRAKKIASIADVCESMKEQL
LVLVEWAKYIPAFCELPLDDQVALLRAHAGEHLLLGATKRSMVFKDVLLLGNDYIVPRHCPELAE
MSRVSIRILDELVLPFQELQIDDNEYAYLKAIIFFDPDAKGLSDPGKIKRLRSQVQVSLEDYIND
RQYDSRGRFGELLLLLPTLQSITWQMIEQIQFIKLFGMAKIDNLLQEMLLGGSPSDAPHAHHPLH

PHLMQEHMGTNVIVANTMPTHLSNGQMSTPETPQPSPPGGSGSEPYKLLPGAVATIVKPLSAIPQ
PTITKQEVI (SEQ ID NO:53)

atgcgactctccaaaaccctcgtcgacatggacatggccgactacagtgctgcactggacccagc
ctacaccaccctggaatttgagaatgtgcaggtgttgacgatgggcaatgacacgtccccatcag
aaggcaccaacctcaacgcgcccaacagcctgggtgtcagcgccctgtgtgccatctgcggggac
cgggccacgggcaaacactacggtgcctcgagctgtgacggctgcaagggcttcttccggaggag
cgtgcggaagaaccacatgtactcctgcagatttagccggcagtgcgtggtggacaaagacaaga
ggaaccagtgccgctactgcaggctcaagaaatgcttccgggctggcatgaagaaggaagccgtc
cagaatgagcgggaccggatcagcactcgaaggtcaagctatgaggacagcagcctgccctccat
caatgcgctcctgcaggcggaggtcctgtcccgacagatcacctccccgtctccgggatcaacg
gcgacattcgggcgaagaagattgccagcatcgcagatgtgtgtgagtccatgaaggagcagctg
ctggttctcgttgagtgggccaagtacatcccagctttctgcgagctccccctggacgaccaggt
ggccctgctcagagcccatgctggcgagcacctgctgctcggagccaccaagagatccatggtgt
tcaaggacgtgctgctcctaggcaatgactacattgtccctcggcactgcccggagctggcggag
atgagccgggtgtccatacgcatccttgacgagctggtgctgcccttccaggagctgcagatcga
tgacaatgagtatgcctacctcaaagccatcatcttctttgacccagatgccaaggggctgagcg
atccagggaagatcaagcggctgcgttcccaggtgcaggtgagcttggaggactacatcaacgac
cgccagtatgactcgcgtggccgctttggagagctgctgctgctgcccaccttgcagagcat
cacctggcagatgatcgagcagatccagttcatcaagctcttcggcatggccaagattgacaacc
tgttgcaggagatgctgctgggagggtcccccagcgatgcaccccatgcccaccacccctgcac
cctcacctgatgcaggaacatatgggaaccaacgtcatcgttgccaacacaatgcccactcacct
cagcaacggacagatgtccacccctgagaccccacagccctcaccgccaggtggctcagggtctg
agccctataagctcctgccgggagccgtcgccacaatcgtcaagcccctctctgccatcccccag
ccgaccatcaccaagcaggaagttatctag (SEQ ID NO:117)

**[00406]** Human signal transducer and activator of transcription Stat5A (U43185) SEQ ID NO:54 (protein) and SEQ ID NO:118 (DNA)

MAGWIQAQQLQGDALRQMQVLYGQHFPIEVRHYLAQWIESQPWDAIDLDNPQDRAQATQLLEGLV
QELQKKAEHQVGEDGFLLKIKLRHYATQLQKTYDRCPLELVRCIRHILYNEQRLVREANNCSSPA
GILVDAMSQKHLQINQTFEELRLVTQDTENELKKLQQTQEYFIIQYQESLRIQAQFAQLAQLSPQ
ERLSRETALQQKQVSLEAWLQREAQTLQQYRVELAEKHQKTLQLLRKQQTIILDDELIQWKRRQQ
LAGNGGPPEGSLDVLQSWCEKLAEIIWQNRQQIRRAEHLCQQLPIPGPVEEMLAEVNATITDIIS
ALVTSTFIIEKQPPQVLKTQTKFAATVRLLVGGKLNVHMNPPQVKATIISEQQAKSLLKNENTRN
ECSGEILNNCCVMEYHQATGTLSAHFRNMSLKRIKRADRRGAESVTEEKFTVLFESQFSVGSNEL
VFQVKTLSLPVVVIVHGSQDHNATATVLWDNAFAEPGRVPFAVPDKVLWPQLCEALNMKFKAEVQ
SNRGLTKENLVFLAQKLFNNSSSHLEDYSGLSVSWSQFNRENLPGWNYTFWQWFDGVMEVLKKHH
KPHWNDGAILGFVNKQQAHDLLINKPDGTFLLRFSDSEIGGITIAWKFDSPERNLWNLKPFTTRD
FSIRSLADRLGDLSYLIYVFPDRPKDEVFSKYYTPVLAKAVDGYVKPQIKQVVPEFVNASADAGG
SSATYMDQAPSPAVCPQAPYNMYPQNPDHVLDQDGEFDLDETMDVARHVEELLRRPMDSLDSRLS
PPAGLFTSARGSLS (SEQ ID NO:54)

atggcgggctggatccaggcccagcagctgcagggagacgcgctgcgccagatgcaggtgctgta
cggccagcacttccccatcgaggtccggcactacttggcccagtggattgagagccagccatggg
atgccattgacttggacaatccccaggacagagcccaagccacccagctcctggagggcctggtg
caggagctgcagaagaaggcggagcaccaggtgggggaagatgggtttttactgaagatcaagct
gaggcactacgccacgcagctccagaaaacatatgaccgctgccccctggagctggtccgctgca
tccggcacattctgtacaatgaacagaggctggtccgagaagccaacaattgcagctctccggct
gggatcctggttgacgccatgtcccagaagcaccttcagatcaaccagacatttgaggagctgcg
actggtcacgcaggacacagagaatgagctgaagaaactgcagcagactcaggagtacttcatca
tccagtaccaggagagcctgaggatccaagctcagtttgcccagctggcccagctgagcccccag
gagcgtctgagccgggagacggccctccagcagaagcaggtgtctctggaggcctggttgcagcg
tgaggcacagacactgcagcagtaccgcgtggagctggccgagaagcaccagaagaccctgcagc

tgctgcggaagcagcagaccatcatcctggatgacgagctgatccagtggaagcggcggcagcag
ctggccgggaacggcgggccccccgagggcagcctggacgtgctacagtcctggtgtgagaagtt
ggccgagatcatctggcagaaccggcagcagatccgcagggctgagcacctctgccagcagctgc
ccatccccggcccagtggaggagatgctggccgaggtcaacgccaccatcacggacattatctca
gccctggtgaccagcacattcatcattgagaagcagcctcctcaggtcctgaagacccagaccaa
gtttgcagccaccgtacgcctgctggtgggcgggaagctgaacgtgcacatgaatcccccccagg
tgaaggccaccatcatcagtgagcagcaggccaagtctctgcttaaaaatgagaacacccgcaac
gagtgcagtggtgagatcctgaacaactgctgcgtgatggagtaccaccaagccacgggcaccct
cagtgcccacttcaggaacatgtcactgaagaggatcaagcgtgctgaccggcggggtgcagagt
ccgtgacagaggagaagttcacagtcctgtttgagtctcagttcagtgttggcagcaatgagctt
gtgttccaggtgaagactctgtccctacctgtggttgtcatcgtccacggcagccaggaccacaa
tgccacggctactgtgctgtgggacaatgcctttgctgagccgggcagggtgccatttgccgtgc
ctgacaaagtgctgtggccgcagctgtgtgaggcgctcaacatgaaattcaaggccgaagtgcag
agcaaccggggcctgaccaaggagaacctcgtgttcctggcgcagaaactgttcaacaacagcag
cagccacctggaggactacagtggcctgtccgtgtcctggtcccagttcaacagggagaacttgc
cgggctggaactacaccttctggcagtggtttgacggggtgatggaggtgttgaagaagcaccac
aagccccactggaatgatggggccatcctaggttttgtgaataagcaacaggcccacgacctgct
catcaacaagcccgacgggaccttcttgttgcgctttagtgactcagaaatcgggggcatcacca
tcgcctggaagtttgattccccggaacgcaacctgtggaacctgaaaccattcaccacgcgggat
ttctccatcaggtccctggctgaccggctgggggacctgagctatctcatctatgtgtttcctga
ccgccccaaggatgaggtcttctccaagtactacactcctgtgctggctaaagctgttgatggat
atgtgaaaccacagatcaagcaagtggtccctgagtttgtgaatgcatctgcagatgctgggggc
agcagcgccacgtacatggaccaggccccctccccagctgtgtgcccccaggctccctataacat
gtacccacagaaccctgaccatgtactcgatcaggatggagaattcgacctggatgagaccatgg
atgtggccaggcacgtggaggaactcttacgccgaccaatggacagtcttgactcccgcctctcg
ccccctgccggtcttttcacctctgccagaggctccctctcatga (SEQ ID NO:118)

**[00407]** Homo sapiens squalene epoxidase (ERG1) mRNA,(AF098865) SEQ ID NO:55 (protein) and SEQ ID NO:119 (DNA)

MWTFLGIATFTYFYKKFGDFITLANREVLLCVLVFLSLGLVLSYRCRHRNGGLLGRQQSGSQFAL
FSDILSGLPFIGFFWAKSPPESENKEQLEARRRRKGTNISETSLIGTAACTSTSSQNDPEVIIVG
AGVLGSALAAVLSRDGRKVTVIERDLKEPDRIVGEFLQPGGYHVLKDLGLGDTVEGLDAQVVNGY
MIHDQESKSEVQIPYPLSENNQVQSGRAFHHGRFIMSLRKAAMAEPNAKFIEGVVLQLLEEDDVV
MGVQYKDKETGDIKELHAPLTVVADGLFSKFRKSLVSNKVSVSSHFVGFLMKNAPQFKANHAELI
LANPSPVLIYQISSSETRVLVDIRGEMPRNLREYMVEKIYPQIPDHLKEPFLEATDNSHLRSMPA
SFLPPSSVKKRGVLLLGDAYNMRHPLTGGGMTVAFKDIKLWRKLLKGIPDLYDDAAIFEAKKSFY
WARKTSHSFVVNILAQALYELFSATDDSLHQLRKACFLYFKLGGECVAGPVGLLSVLSPNPLVLI
GHFFAVAIYAVYFCFKSEPWITKPRALLSSGAVLYKACSVIFPLIYSEMKYMVH (SEQ ID NO:55)

atgtggacttttctgggcattgccactttcacctatttttataagaagttcggggacttcatcac
tttggccaacagggaggtcctgttgtgcgtgctggtgttcctctcgctgggcctggtgctctcct
accgctgtcgccaccgaaacgggggtctcctcgggcgccagcagagcggctcccagttcgccctc
ttctcggatattctctcaggcctgcctttcattggcttcttctgggccaaatcccccctgaatc
agaaaataaggagcagctcgaggccaggaggcgcagaaaaggaaccaatatttcagaaacaagct
taataggaacagctgcctgtacatcaacatcttctcagaatgacccagaagttatcatcgtggga
gctggcgtgcttggctctgctttggcagctgtgctttccagagatggaagaaaggtgacagtcat
tgagagagacttaaaagagcctgacagaatagttggagaattcctgcagccgggtggttatcatg
ttctcaaagaccttggtcttggagatacagtggaaggtcttgatgcccaggttgtaaatggttac
atgattcatgatcaggaaagcaaatcagaggttcagattccttaccctctgtcagaaaacaatca
agtgcagagtggaagagctttccatcacggaagattcatcatgagtctccggaaagcagctatgg
cagagcccaatgcaaagtttattgaaggtgttgtgttacagttattagaggaagatgatgttgtg

atgggagttcagtacaaggataaagagactggagatatcaaggaactccatgctccactgactgt
tgttgcagatgggcttttctccaagttcaggaaaagcctggtctccaataaagtttctgtatcat
ctcattttgttggctttcttatgaagaatgcaccacagtttaaagcaaatcatgctgaacttatt
ttagctaacccgagtccagttctcatctaccagatttcatccagtgaaactcgagtacttgttga
cattagaggagaaatgccaaggaatttaagagaatacatggttgaaaaaatttacccacaaatac
ctgatcacctgaaagaaccattcttagaagccactgacaattctcatctgaggtccatgccagca
agcttccttcctccttcatcagtgaagaaacgaggtgttcttcttttgggagacgcatataatat
gaggcatccacttactggtggaggaatgactgttgcttttaaagatataaaactatggagaaaac
tgctaaagggtatccctgacctttatgatgatgcagctattttcgaggccaaaaaatcattttac
tgggcaagaaaaacatctcattcctttgtcgtgaatatccttgctcaggctctttatgaattatt
ttctgccacagatgattccctgcatcaactaagaaaagcctgttttctttatttcaaacttggtg
gcgaatgtgttgcgggtcctgttgggctgctttctgtattgtctcctaaccctctagttttaatt
ggacacttctttgctgttgcaatctatgccgtgtatttttgctttaagtcagaaccttggattac
aaaacctcgagcccttctcagtagtggtgctgtattgtacaaagcgtgttctgtaatatttcctc
taatttactcagaaatgaagtatatggttcattaa (SEQ ID NO:119)

**[00408]** Homo sapiens ets variant 2 (ETV2/ER71), (NM_014209) SEQ ID NO:56 (protein) and SEQ ID NO:120 (DNA)

MDLWNWDEASPQEVPPGNKLAGLEGAKLGFCFPDLALQGDTPTATAETCWKGTSSSLASFPQLDW
GSALLHPEVPWGAEPDSQALPWSGDWTDMACTAWDSWSGASQTLGPAPLGPGPIPAAGSEGAAGQ
NCVPVAGEATSWSRAQAAGSNTSWDCSVGPDGDTYWGSGLGGEPRTDCTISWGGPAGPDCTTSWN
PGLHAGGTTSLKRYQSSALTVCSEPSPQSDRASLARCPKTNHRGPIQLWQFLLELLHDGARSSCI
RWTGNSREFQLCDPKEVARLWGERKRKPGMNYEKLSRGLRYYYRRDIVRKSGGRKYTYRFGGRVP
SLAYPDCAGGGRGAETQ (SEQ ID NO:56)

atggacctgtggaactgggatgaggcatccccacaggaagtgcctccagggaacaagctggcagg
gcttgaaggagccaaattaggcttctgtttccctgatctggcactccaaggggacacgccgacag
cgacagcagagacatgctggaaaggtacaagctcatccctggcaagcttcccacagctggactgg
ggctccgcgttactgcacccagaagttccatgggggcggagcccgactctcaggctcttccgtg
gtccggggactggacagacatggcgtgcacagcctgggactcttggagcggcgcctcgcagaccc
tgggccccgcccctctcggcccgggccccatccccgccgccggctccgaaggcgccgcgggccag
aactgcgtccccgtggcgggagaggccacctcgtggtcgcgcgcccaggccgccgggagcaacac
cagctgggactgttctgtggggcccgacggcgatacctactggggcagtggcctgggcggggagc
cgcgcacggactgtaccatttcgtggggcgggcccgcgggcccggactgtaccacctcctggaac
ccggggctgcatgcgggtggcaccacctctttgaagcggtaccagagctcagctctcaccgtttg
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gtcccattcagctgtggcagttcctcctggagctgctccacgacggggcgcgtagcagctgcatc
cgttggactggcaacagccgcgagttccagctgtgcgaccccaaagaggtggctcggctgtgggg
cgagcgcaagagaaagccgggcatgaattacgagaagctgagccggggccttcgctactactatc
gccgcgacatcgtgcgcaagagcgggggcgaaagtacacgtaccgcttcgggggccgcgtgccc
agcctagcctatccggactgtgcgggaggcggacggggagcagagacacaataa (SEQ ID NO:120)

**[00409]** Homo sapiens GATA binding protein 2 (GATA2) (NM_001145661) SEQ ID NO:57 (protein) and SEQ ID NO:121 (DNA)

MEVAPEQPRWMAHPAVLNAQHPDSHHPGLAHNYMEPAQLLPPDEVDVFFNHLDSQGNPYYANPAH
ARARVSYSPAHARLTGGQMCRPHLLHSPGLPWLDGGKAALSAAAAHHHNPWTVSPFSKTPLHPSA
AGGPGGPLSVYPGAGGGSGGGSGSSVASLTPTAAHSGSHLFGFPPTPPKEVSPDPSTTGAASPAS
SSAGGSAARGEDKDGVKYQVSLTESMKMESGSPLRPGLATMGTQPATHHPIPTYPSYVPAAAHDY
SSGLFHPGGFLGGPASSFTPKQRSKARSCSEGRECVNCGATATPLWRRDGTGHYLCNACGLYHKM
NGQNRPLIKPKRRLSAARRAGTCCANCQTTTTTLWRRNANGDPVCNACGLYYKLHNVNRPLTMKK
EGIQTRNRKMSNKSKKSKKGAECFEELSKCMQEKSSPFSAAALAGHMAPVGHLPPFSHSGHILPT
PTPIHPSSSLSFGHPHPSSMVTAMG (SEQ ID NO:57)

atggaggtggcgcccgagcagccgcgctggatggcgcacccggccgtgctgaatgcgcagcaccc
cgactcacaccacccgggcctggcgcacaactacatggaacccgcgcagctgctgcctccagacg
aggtggacgtcttcttcaatcacctcgactcgcagggcaacccctactatgccaaccccgctcac
gcgcgggcgcgcgtctcctacagccccgcgcacgcccgcctgaccggaggccagatgtgccgccc
acacttgttgcacagcccgggtttgccctggctggacgggggcaaagcagccctctctgccgctg
cggcccaccaccacaacccctggaccgtgagccccttctccaagacgccactgcacccctcagct
gctggaggccctggaggcccactctctgtgtacccaggggctgggggtgggagcgggggaggcag
cgggagctcagtggcctccctcacccctacagcagcccactctggctcccacctttcggcttcc
cacccacgccacccaaagaagtgtctcctgaccctagcaccacgggggctgcgtctccagcctca
tcttccgcgggggggtagtgcagcccgaggagaggacaaggacggcgtcaagtaccaggtgtcact
gacggagagcatgaagatggaaagtggcagtcccctgcgcccaggcctagctactatgggcaccc
agcctgctacacaccaccccatccccacctacccctcctatgtgccggcggctgcccacgactac
agcagcggactcttccaccccggaggcttcctgggggggaccggcctccagcttcacccctaagca
gcgcagcaaggctcgttcctgttcagaaggccgggagtgtgtcaactgtggggccacagccaccc
ctctctggcggcgggacggcaccggccactacctgtgcaatgcctgtggcctctaccacaagatg
aatgggcagaaccgaccactcatcaagcccaagcgaagactgtcggccgccagaagagccggcac
ctgttgtgcaaattgtcagacgacaaccaccaccttatggcgccgaaacgccaacggggaccctg
tctgcaacgcctgtggcctctactacaagctgcacaatgttaacaggccactgaccatgaagaag
gaagggatccagactcggaaccggaagatgtccaacaagtccaagaagagcaagaaaggggcgga
gtgcttcgaggagctgtcaaagtgcatgcaggagaagtcatccccttcagtgcagctgccctgg
ctggacacatggcacctgtgggccacctcccgcccttcagccactccggacacatcctgcccact
ccgacgcccatccacccctcctccagcctctccttcggccacccccacccgtccagcatggtgac
cgccatgggctag (SEQ ID NO:121)

**[00410]** Homo sapiens hes-related family bHLH transcription factor with YRPW motif 1 (HEY1) (NM_012258) SEQ ID NO:58 (protein) and SEQ ID NO:122 (DNA)

MKRAHPEYSSSDSELDETIEVEKESADENGNLSSALGSMSPTTSSQILARKRRRGIIEKRRRDRI
NNSLSELRRLVPSAFEKQGSAKLEKAEILQMTVDHLKMLHTAGGKGYFDAHALAMDYRSLGFREC
LAEVARYLSIIEGLDASDPLRVRLVSHLNNYASQREAASGAHAGLGHIPWGTVFGHHPHIAHPLL
LPQNGHGNAGTTASPTEPHHQGRLGSAHPEAPALRAPPSGSLGPVLPVVTSASKLSPPLLSSVAS
LSAFPFSFGSFHLLSPNALSPSAPTQAANLGKPYRPWGTEIGAF (SEQ ID NO:58)

atgaagcgagctcaccccgagtacagctcctcggacagcgagctggacgagaccatcgaggtgga
gaaggagagtgcggacgagaatggaaacttgagttcggctctaggttccatgtccccaactacat
cttcccagattttggccagaaaaagacggagaggaataattgagaagcgccgacgagaccggatc
aataacagtttgtctgagctgagaaggctggtacccagtgcttttgagaagcagggatctgctaa
gctagaaaaagccgagatcctgcagatgaccgtggatcacctgaaaatgctgcatacggcaggag
ggaaaggttactttgacgcgcacgcccttgctatggactatcggagtttgggatttcgggaatgc
ctggcagaagttgcgcgttatctgagcatcattgaaggactagatgcctctgacccgcttcgagt
tcgactggtttcgcatctcaacaactacgcttcccagcgggaagccgcgagcggcgcccacgcgg
gcctcggacacattccctgggggaccgtcttcggacatcacccgcacatcgcgcacccgctgttg
ctgccccagaacggccacgggaacgcgggcaccacggcctcacccacggaaccgcaccaccaggg
caggctgggctcggcacatccggaggcgcctgctttgcgagcgcccccctagcggcagcctcggac
cggtgctccctgtggtcacctccgcctccaaactgtcgccgcctctgctctcctcagtggcctcc
ctgtcggccttcccccttctctttcggctccttccacttactgtctcccaatgcactgagcccttc
agcacccacgcaggctgcaaaccttggcaagccctatagaccttgggggacggagatcggagctt
tttaa (SEQ ID NO:122)

**[00411]** Homo sapiens Hey2 (AB044755) SEQ ID NO:59 (protein) and SEQ ID NO:123 (DNA)

MKRPCEETTSESDMDETIDVGSENNYSGQSTSSVIRLNSPTTTSQIMARKKRRGIIEKRRRDRIN
NSLSELRRLVPTAFEKQGSAKLEKAEILQMTVDHLKMLQATGGKGYFDAHALAMDFMSIGFRECL
TEVARYLSSVEGLDSSDPLRVRLVSHLSTCATQREAAAMTSSMAHHHHPLHPHHWAAAFHHLPAA

LLQPNGLHASESTPCRLSTTSEVPPAHGSALLTATFAHADSALRMPSTGSVAPCVPPLSTSLLSL
SATVHAAAAAATAAAHSFPLSFAGAFPMLPPNAAAAVAAATAISPPLSVSATSSPQQTSSGTNNK
PYRPWGTEVGAF (SEQ ID NO:59)
atgaagcgcccctgcgaggagacgacctccgagagcgacatggacgagaccatcgacgtggggag
cgagaacaattactcggggcaaagtactagctctgtgattagattgaattctccaacaacaacat
ctcagattatggcaagaaagaaaaggagagggattatagagaaaaggcgtcgggatcggataaat
aacagtttatctgagttgagaagacttgtgccaactgcttttgaaaaacaaggatctgcaaagtt
agaaaaagctgaaatattgcaaatgacagtggatcatttgaagatgcttcaggcaacaggggta
aaggctactttgacgcacacgctcttgccatggacttcatgagcataggattccgagagtgccta
acagaagttgcgcggtacctgagctccgtggaaggcctggactcctcggatccgctgcgggtgcg
gcttgtgtctcatctcagcacttgcgccacccagcgggaggcggcggccatgacatcctccatgg
cccaccaccatcatccgctccacccgcatcactgggccgccgccttccaccacctgcccgcagcc
ctgctccagcccaacggcctccatgcctcagagtcaacccctgtcgcctctccacaacttcaga
agtgcctcctgcccacggctctgctctcctcacggccacgtttgcccatgcggattcagccctcc
gaatgccatccacgggcagcgtcgccccctgcgtgccacctctctccacctctctcttgtccctc
tctgccaccgtccacgccgcagccgcagcagccaccgcggctgcacacagcttccctctgtcctt
cgcgggggcattccccatgcttcccccaaacgcagcagcagcagtggccgcggccacagccatca
gcccgcccttgtcagtatcagccacgtccagtcctcagcagaccagcagtggaacaaacaataaa
ccttaccgaccctgggggacagaagttggagctttttaa (SEQ ID NO:123)

**[00412]** Homo sapiens forkhead box C1 (FOXC1) (NM_001453) SEQ ID NO:60 (protein) and SEQ ID NO:124 (DNA)

MQARYSVSSPNSLGVVPYLGGEQSYYRAAAAAAGGGYTAMPAPMSVYSHPAHAEQYPGGMARAYG
PYTPQPQPKDMVKPPYSYIALITMAIQNAPDKKITLNGIYQFIMDRFPFYRDNKQGWQNSIRHNL
SLNECFVKVPRDDKKPGKGSYWTLDPDSYNMFENGSFLRRRRRFKKKDAVKDKEEKDRLHLKEPP
PPGRQPPPAPPEQADGNAPGPQPPPVRIQDIKTENGTCPSPPQPLSPAAALGSGSAAAVPKIESP
DSSSSSLSSGSSPPGSLPSARPLSLDGADSAPPPPAPSAPPPHHSQGFSVDNIMTSLRGSPQSAA
AELSSGLLASAAASSRAGIAPPLALGAYSPGQSSLYSSPCSQTSSAGSSGGGGGGAGAAGGAGGA
GTYHCNLQAMSLYAAGERGGHLQGAPGGAGGSAVDDPLPDYSLPPVTSSSSSSLSHGGGGGGGGG
GQEAGHHPAAHQGRLTSWYLNQAGGDLGHLASAAAAAAAAGYPGQQQNFHSVREMFESQRIGLNN
SPVNGNSSCQMAFPSSQSLYRTSGAFVYDCSKF (SEQ ID NO:60)
atgcaggcgcgctactccgtgtccagccccaactccctgggagtggtgccctacctcggcggcga
gcagagctactaccgcgcggcggccgcggcggccgggggcggctacaccgccatgccggccccca
tgagcgtgtactcgcaccctgcgcacgccgagcagtacccgggcggcatggcccgcgcctacggg
ccctacacgccgcagccgcagcccaaggacatggtgaagccgccctatagctacatcgcgctcat
caccatggccatccagaacgccccggacaagaagatcaccctgaacggcatctaccagttcatca
tggaccgcttcccccttctaccgggacaacaagcagggctggcagaacagcatccgccacaacctc
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gacgctggacccggactcctacaacatgttcgagaacggcagcttcctgcggcggcggcggcgct
tcaagaagaaggacgcggtgaaggacaaggaggagaaggacaggctgcacctcaaggagccgccc
ccgcccggccgccagcccccgcccgcgccgccggagcaggccgacggcaacgcgcccggtccgca
gccgccgcccgtgcgcatccaggacatcaagaccgagaacggtacgtgcccctcgccgccccagc
ccctgtccccggccgccgccctgggcagcggcagcgccgccgcggtgcccaagatcgagagcccc
gacagcagcagcagcagcctgtccagcgggagcagccccccgggcagcctgccgtcggcgcggcc
gctcagcctggacggtgcggattccgcgccgccgccgcccgcgccctccgccccgccgccgcacc
atagccagggcttcagcgtggacaacatcatgacgtcgctgcgggggtcgccgcagagcgcggcc
gcggagctcagctccggccttctggcctcggcggccgcgtcctcgcgcgcggggatcgcacccccc
gctggcgctcggcgcctactcgcccggccagagctccctctacagctccccctgcagccagacct
ccagcgcgggcagctcgggcggcggcggcggcggcgcgggggccgcgggggggcgcgggcggcgcc
gggacctaccactgcaacctgcaagccatgagcctgtacgcggccggcgagcgcgggggccactt
gcagggcgcgcccgggggcgcgggcggctcggccgtggacgacccccctgcccgactactctctgc

ctccggtcaccagcagcagctcgtcgtccctgagtcacggcggcggcggcggcggcgggggga
ggccaggaggccggccaccaccctgcggcccaccaaggccgcctcacctcgtggtacctgaacca
ggcgggcggagacctgggccacttggcgagcgcggcggcggcggcggccgcaggctacccgg
gccagcagcagaacttccactcggtgcgggagatgttcgagtcacagaggatcggcttgaacaac
tctccagtgaacgggaatagtagctgtcaaatggccttcccttccagccagtctctgtaccgcac
gtccggagctttcgtctacgactgtagcaagttttga (SEQ ID NO:124)

**[00413]** Homo sapiens forkhead box C2 (MFH-1, mesenchyme forkhead 1)(FOXC2) (NM_005251) SEQ ID NO:61 (protein) and SEQ ID NO:125 (DNA)

MQARYSVSDPNALGVVPYLSEQNYYRAAGSYGGMASPMGVYSGHPEQYSAGMGRSYAPYHHHQPA
APKDLVKPPYSYIALITMAIQNAPEKKITLNGIYQFIMDRFPFYRENKQGWQNSIRHNLSLNECF
VKVPRDDKKPGKGSYWTLDPDSYNMFENGSFLRRRRFKKKDVSKEKEERAHLKEPPPAASKGAP
ATPHLADAPKEAEKKVVIKSEAASPALPVITKVETLSPESALQGSPRSAASTPAGSPDGSLPEHH
AAAPNGLPGFSVENIMTLRTSPPGGELSPGAGRAGLVVPPLALPYAAAPPAAYGQPCAQGLEAGA
AGGYQCSMRAMSLYTGAERPAHMCVPPALDEALSDHPSGPTSPLSALNLAAGQEGALAATGHHHQ
HHGHHHPQAPPPPPAPQPQPTPQPGAAAAQAASWYLNHSGDLNHLPGHTFAAQQQTFPNVREMFN
SHRLGIENSTLGESQVSGNASCQLPYRSTPPLYRHAAPYSYDCTKY (SEQ ID NO:61)

atgcaggcgcgctactccgtgtccgaccccaacgccctgggagtggtgccctacctgagcgagca
gaattactaccgggctgcgggcagctacggcggcatggccagccccatgggcgtctattccggcc
acccggagcagtacagcgcggggatgggccgctcctacgcgccctaccaccaccaccagcccgcg
gcgcctaaggacctggtgaagccgccctacagctacatcgcgctcatcaccatggccatccagaa
cgcgcccgagaagaagatcaccttgaacggcatctaccagttcatcatggaccgcttcccccttct
accgggagaacaagcagggctggcagaacagcatccgccacaacctctcgctcaacgagtgcttc
gtcaaggtgccccgcgacgacaagaagcccggcaagggcagttactggaccctggacccggactc
ctacaacatgttcgagaacggcagcttcctgcggcgccggcggcgcttcaaaaagaaggacgtgt
ccaaggagaaggaggagcgggcccacctcaaggagccgcccccggcggcgtccaagggcgccccg
gccacccccccacctagcggacgccccaaggaggccgagaagaaggtggtgatcaagagcgaggc
ggcgtccccggcgctgccggtcatcaccaaggtggagacgctgagccccgagagcgcgctgcagg
gcagcccgcgcagcgcggcctccacgcccgccggctcccccgacggctcgctgccggagcaccac
gccgcggcgcccaacgggctgcctggcttcagcgtggagaacatcatgaccctgcgaacgtcgcc
gccgggcggagagctgagcccgggggccggacgcgcgggcctggtggtgccgccgctggcgctgc
cctacgccgccgcgccgcccgccgcctacggccagccgtgcgctcagggcctggaggccgggggcc
gccgggggctaccagtgcagcatgcgagcgatgagcctgtacaccggggccgagcggccggcgca
catgtgcgtcccgcccgccctggacgaggccctctcggaccacccgagcggccccacgtcgcccc
tgagcgctctcaacctcgccgccggccaggagggcgcgctcgccgccacgggccaccaccaccag
caccacggccaccaccacccgcaggcgccgccgccccgccggctccccagccccagccgacgcc
gcagcccggggccgccgcggcgcaggcggcctcctggtatctcaaccacagcggggacctgaacc
acctccccggccacacgttcgcggcccagcagcaaactttccccaacgtgcgggagatgttcaac
tcccaccggctggggattgagaactcgaccctcggggagtcccaggtgagtggcaatgccagctg
ccagctgccctacagatccacgccgcctctctatcgccacgcagcccctactcctacgactgca
cgaaatactga (SEQ ID NO:125)

**[00414]** SEQ ID NO:62: Homo sapiens SRY (sex determining region Y)-box 7 (SOX7) NM_031439 SEQ ID NO:62 (protein) and SEQ ID NO:126 (DNA)

MASLLGAYPWPEGLECPALDAELSDGQSPPAVPRPPGDKGSESRIRRPMNAFMVWAKDERKRLAV
QNPDLHNAELSKMLGKSWKALTLSQKRPYVDEAERLRLQHMQDYPNYKYRPRRKKQAKRLCKRVD
PGFLLSSLSRDQNALPEKRSGSRGALGEKEDRGEYSPGTALPSLRGCYHEGPAGGGGGTPSSVD
TYPYGLPTPPEMSPLDVLEPEQTFFSSPCQEEHGHPRRIPHLPGHPYSPEYAPSPLHCSHPLGSL
ALGQSPGVSMMSPVPGCPPSPAYYSPATYHPLHSNLQAHLGQLSPPPEHPGFDALDQLSQVELLG
DMDRNEFDQYLNTPGHPDSATGAMALSGHVPVSQVTPTGPTETSLISVLADATATYYNSYSVS
(SEQ ID NO:62)

atggcttcgctgctgggagcctacccttggcccgagggtctcgagtgcccggccctggacgccga
gctgtcggatggacaatcgccgccggccgtcccccggccccccgggggacaagggctccgagagcc
gtatccggcggcccatgaacgccttcatggtttgggccaaggacgagaggaaacggctggcagtg
cagaacccggacctgcacaacgccgagctcagcaagatgctgggaaagtcgtggaaggcgctgac
gctgtcccagaagaggccgtacgtggacgaggcggagcggctgcgcctgcagcacatgcaggact
accccaactacaagtaccggccgcgcaggaagaagcaggccaagcggctgtgcaagcgcgtggac
ccgggcttccttctgagctccctctcccgggaccagaacgccctgccggagaagagaagcggcag
ccgggggggcgctgggggagaaggaggacaggggtgagtactcccccggcactgccctgcccagcc
tccggggctgctaccacgaggggccggctggtggtggcggcggcggcaccccgagcagtgtggac
acgtacccgtacgggctgcccacacctcctgaaatgtctcccctggacgtgctggagccggagca
gaccttcttctcctcccccctgccaggaggagcatggccatccccgccgcatcccccacctgccag
ggcacccgtactcaccggagtacgccccaagccctctccactgtagccacccccctgggctccctg
gcccttggccagtcccccggcgtctccatgatgtcccctgtacccggctgtcccccatctcctgc
ctattactccccggccacctaccacccactccactccaacctccaagcccacctgggccagctttt
ccccgcctcctgagcaccctggcttcgacgccctggatcaactgagccaggtggaactcctgggg
gacatggatcgcaatgaattcgaccagtatttgaacactcctggccacccagactccgccacagg
ggccatggccctcagtgggcatgttccggtctcccaggtgacaccaacgggtcccacagagacca
gcctcatctccgtcctggctgatgccacggccacgtactacaacagctacagtgtgtcatag
(SEQ ID NO:126)

**[00415]** Homo sapiens SOX18 (AB033888) SEQ ID NO:63 (protein) and SEQ ID NO:127 (DNA)

MQRSPPGYGAQDDPPARRDCAWAPGHGAAADTRGLAAGPAALAAPAAPASPPSPQRSPPRSPEPG
RYGLSPAGRGERQAADESRIRRPMNAFMVWAKDERKRLAQQNPDLHNAVLSKMLGKAWKELNAAE
KRPFVEEAERLRVQHLRDHPNYKYRPRRKKQARKARRLEPGLLLPGLAPPQPPPEPFPAASGSAR
AFRELPPLGAEFDGLGLPTPERSPLDGLEPGEAAFFPPPAAPEDCALRPFRAPYAPTELSRDPGG
CYGAPLAEALRTAPPAAPLAGLYYGTLGTPGPYPGPLSPPPEAPPLESAEPLGPAADLWADVDLT
EFDQYLNCSRTRPDAPGLPYHVALAKLGPRAMSCPEESSLISALSDASSAVYYSACISG (SEQ
ID NO:63)

atgcagagatcgccgcccggctacggcgcacaggacgacccgcccgcccgccgcgactgtgcatg
ggccccgggacacggggccgccgctgacacgcgcggcctcgccgccggccccgccgccctcgccg
cgcccgccgcgcccgcctcgccgcccagcccgcagcgcagtcccccgcgcagccccgagccgggg

cgctatggcctcagcccggccggccgcggggaacgccaggcggcagacgagtcgcgcatccggcg
gcccatgaacgccttcatggtgtgggcaaaggacgagcgcaagcggctggctcagcagaacccgg
acctgcacaacgcggtgctcagcaagatgctgggcaaagcgtggaaggagctgaacgcggcggag
aagcggcccttcgtggaggaagccgaacggctgcgcgtgcagcacttgcgcgaccaccccaacta
caagtaccggccgcgccgcaagaagcaggcgcgcaaggcccggcggctggagcccggcctcctgc
tcccgggattagcgcccccgcagccaccgcccgagcctttccccgcggcgtctggctcggctcgc
gccttccgcgagctgcccccgctgggcgccgagttcgacggcctggggctgcccacgcccgagcg
ctcgcctctggacggcctggagcccggcgaggctgccttcttcccaccgcccgcggcgcccgagg
actgcgcgctgcggcccttccgcgcgccctacgcgcccaccgagttgtcgcgggaccccggcggt
tgctacggggctcccctggcggaggcgctcaggaccgcgcccccgcggcgccgctcgctggcct
gtactacggcaccctgggcacgcccggcccgtaccccggcccgctgtcgccgccgcccgaggccc
cgccgctggagagcgccgagccgctggggcccgccgccgatctgtgggccgacgtggacctcacc
gagttcgaccagtacctcaactgcagccggactcggcccgacgcccccgggctcccgtaccacgt
ggcactggccaaactgggcccgcgcgccatgtcctgcccagaggagagcagcctgatctccgcgc
tgtcggacgccagcagcgcggtctattacagcgcgtgcatctccggctag (SEQ ID NO:127)

**[00416]** The compositions and methods described herein are presently representative of preferred embodiments, exemplary, and not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art. Such changes and other uses can be made without departing from the scope of the invention as set forth in the claims.

CLAIMS

1. A pharmaceutical composition for use in treating cancer by in vivo administration of the pharmaceutical composition to a subject in need thereof, comprising:
protein transduction reagent-modified reprogramming proteins,-Sox2, Oct4 and Nanog, wherein the protein transduction reagent is non-covalently bound to the reprogramming proteins and wherein the protein transduction reagent comprises polyethylenimine and a lipid, wherein the lipid is selected from the group consisting of: N-1 (-(2,3-dioleyloxy)propyl-N,N,N-trimethyl-ammonium chloride (DOTMA), dioctadecylamido-glycylspermine (DOGS), 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), and 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPE).

2. The pharmaceutical composition for use in treating cancer of claim 1, wherein the subject has a brain tumor or breast cancer.

3. Use of protein transduction reagent-modified reprogramming proteins, Sox2, Oct4 and Nanog, to treat cancer in a subject in need thereof by in vivo administration of the protein transduction reagent-modified reprogramming proteins, wherein the protein transduction reagent is non-covalently bound to the reprogramming proteins, wherein the protein transduction reagent comprises polyethylenimine and a lipid, wherein the lipid is selected from the group consisting of: N-1(-(2,3-dioleyloxy)propyl-N,N,N-trimethyl-ammonium chloride (DOTMA), dioctadecylamido-glycylspermine (DOGS), 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), and 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPE).

4. The use of claim 3, wherein the subject has a brain tumor or breast.

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5. The pharmaceutical composition for use in treating cancer of any one of claims 1 or 2 wherein the protein transduction reagent is selected from the group consisting of: QQ 1 a, QQ2a, QQ3a, QQ4a, QQ5a, QQ6a, QQ7a, QQ8a and QQ9a as shown in Table A:

Table A

| Protein transduction reagent (QQ reagent) | PEI Mw1,200 | PEI Mw2000 | PEI Mw4000 | PEI Mw8000 | DOTAP or DOTMA | DOPE or DOGS | POPC | DMPE |
|---|---|---|---|---|---|---|---|---|
| QQ1a | 50-1000μg/ml | - | - | - | 25-100μg/ml | 25-100μg/ml | - | - |
| QQ2a | 50-1000μg/ml | - | 20-200μg/ml | - | 25-100μg/ml | 25-100μg/ml | - | - |
| QQ3a | 50-1000μg/ml | - | 20-200μg/ml | 20-200μg/ml | 25-100μg/ml | 25-100μg/ml | - | - |
| QQ4a | 50-1000μg/ml | 20-200μg/ml | - | 20-200μg/ml | 25-100μg/ml | 25-100μg/ml | - | - |
| QQ5a | 50-1000μg/ml | 20-200μg/ml | 20-200μg/ml | 20-200μg/ml | 25-100μg/ml | 25-100μg/ml | - | - |
| QQ6a | 50-1000μg/ml | 20-200μg/ml | 20-200μg/ml | 20-200μg/ml | - | -- | 25-100μg/ml | 25-100μg/ml |
| QQ7a | 50-1000μg/ml | 20-200μg/ml | 20-200μg/ml | 20-200μg/ml | 25-100μg/ml | 25-100μg/ml | 25-100μg/ml | 25-100μg/ml |
| QQ8a | 50-1000μg/ml | - | - | 20-200μg/ml | 25-100μg/ml | 25-100μg/ml | 25-100μg/ml | 25-100μg/ml |
| QQ9a | 50-1000μg/ml | - | 20-200μg/ml | 20-200μg/ml | - | - | 25-100μg/ml | 25-100μg/ml |

6. The use of any one of claims 3 or 4, wherein the protein transduction reagent-modified reprogramming protein is a reprogramming protein non-covalently bound to a protein transduction reagent selected from the group consisting of: QQla, QQ2a, QQ3a, QQ4a, QQ5a, QQ6a, QQ7a, QQ8a and QQ9a as shown in Table A:

Table A

| Protein transduction reagent (QQ reagent) | PEI Mw1,200 | PEI Mw2000 | PEI Mw4000 | PEI Mw8000 | DOTAP or DOTMA | DOPE or DOGS | POPC | DMPE |
|---|---|---|---|---|---|---|---|---|
| QQ1a | 50-1000μg/ml | - | - | - | 25-100μg/ml | 25-100μg/ml | - | - |
| QQ2a | 50-1000μg/ml | - | 20-200μg/ml | - | 25-100μg/ml | 25-100μg/ml | - | - |
| QQ3a | 50-1000μg/ml | - | 20-200μg/ml | 20-200μg/ml | 25-100μg/ml | 25-100μg/ml | - | - |
| QQ4a | 50-1000μg/ml | 20-200μg/ml | - | 20-200μg/ml | 25-100μg/ml | 25-100μg/ml | - | - |
| QQ5a | 50-1000μg/ml | 20-200μg/ml | 20-200μg/ml | 20-200μg/ml | 25-100μg/ml | 25-100μg/ml | - | - |
| QQ6a | 50-1000μg/ml | 20-200μg/ml | 20-200μg/ml | 20-200μg/ml | - | -- | 25-100μg/ml | 25-100μg/ml |
| QQ7a | 50-1000μg/ml | 20-200μg/ml | 20-200μg/ml | 20-200μg/ml | 25-100μg/ml | 25-100μg/ml | 25-100μg/ml | 25-100μg/ml |
| QQ8a | 50-1000μg/ml | - | - | 20-200μg/ml | 25-100μg/ml | 25-100μg/ml | 25-100μg/ml | 25-100μg/ml |
| QQ9a | 50-1000μg/ml | - | 20-200μg/ml | 20-200μg/ml | - | - | 25-100μg/ml | 25-100μg/ml |

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7. The pharmaceutical composition according to any one of claims 1, 2 and 5, wherein the pharmaceutical composition is for systemic administration.

8. The pharmaceutical composition according to claim 7, wherein the systemic administration is intravenous injection.

9. The pharmaceutical composition according to any one of claims 1, 2 and 5, wherein the pharmaceutical composition is for local administration.

10. The pharmaceutical composition according to any one of claims 1, 2, 5 and 7, further comprising an additional therapeutic agent.

11. The pharmaceutical composition according to claim 10, wherein the additional therapeutic agent is a chemical compound, a biological macromolecule, an antibody, or a combination thereof.

12. The use according to any one of claims 3, 4 and 6, wherein the protein transduction reagent-modified reprogramming protein is for systemic administration.

13. The use according to claim 12, wherein the systemic administration is intravenous injection.

14. The use according to any one of claims 3, 4 and 6, wherein the protein transduction reagent-modified reprogramming protein is for local administration.

15. The use according to any one of claims 3, 4, 6 and 12-14, further comprising an additional therapeutic agent.

16. The use according to claim 15, wherein the additional therapeutic agent is a chemical compound, a biological macromolecule, an antibody, or a combination thereof.

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17. The pharmaceutical composition or use according to any one of claims 1-16, wherein one or more of Sox2, Oct4 and Nanog is an undenatured protein.

18. The pharmaceutical composition or use according to any one of claims 1-16, wherein one or more of Sox2, Oct4 and Nanog is a denatured protein.

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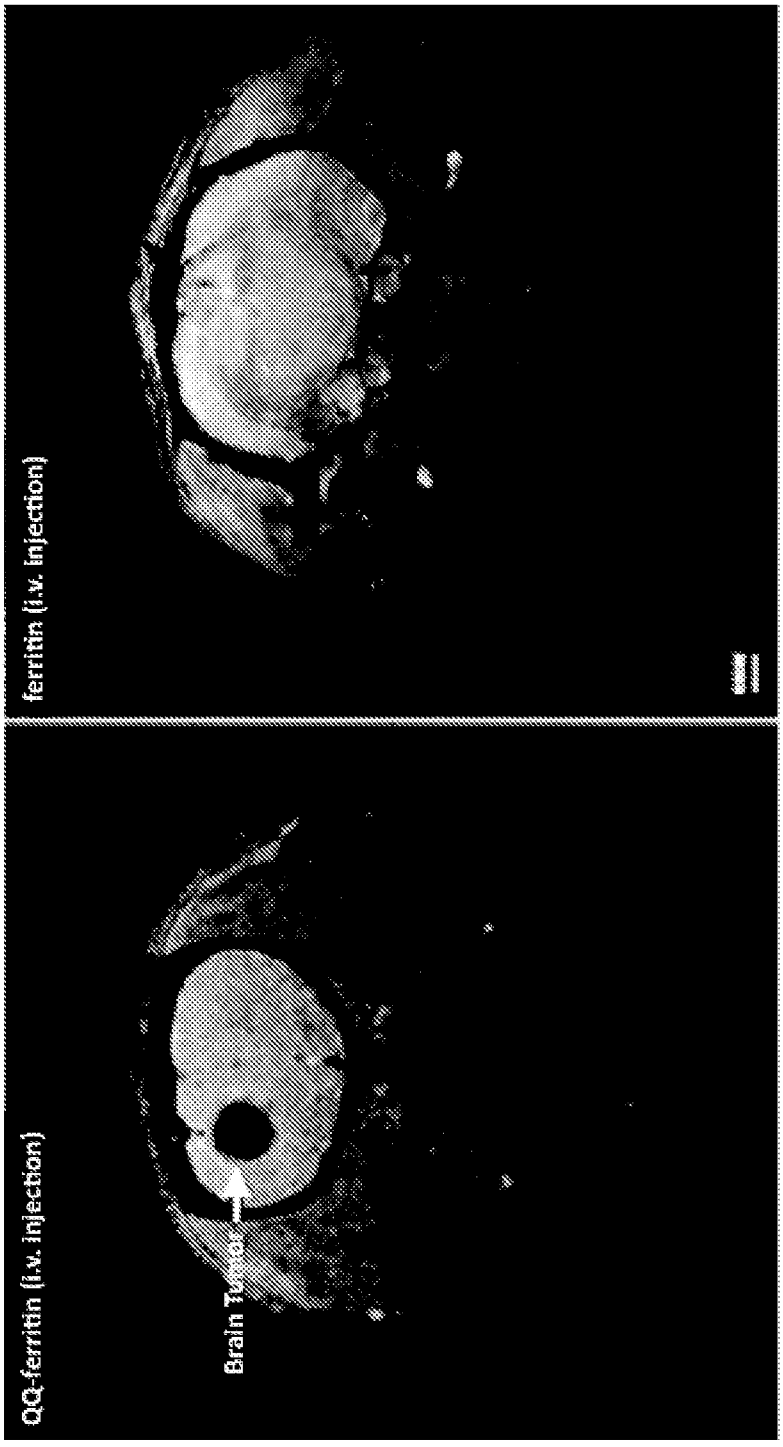
QQ-ferritin (i.v. injection)
Brain Tumor
ferritin (i.v. injection)

FIG. 1A

FIG. 1B

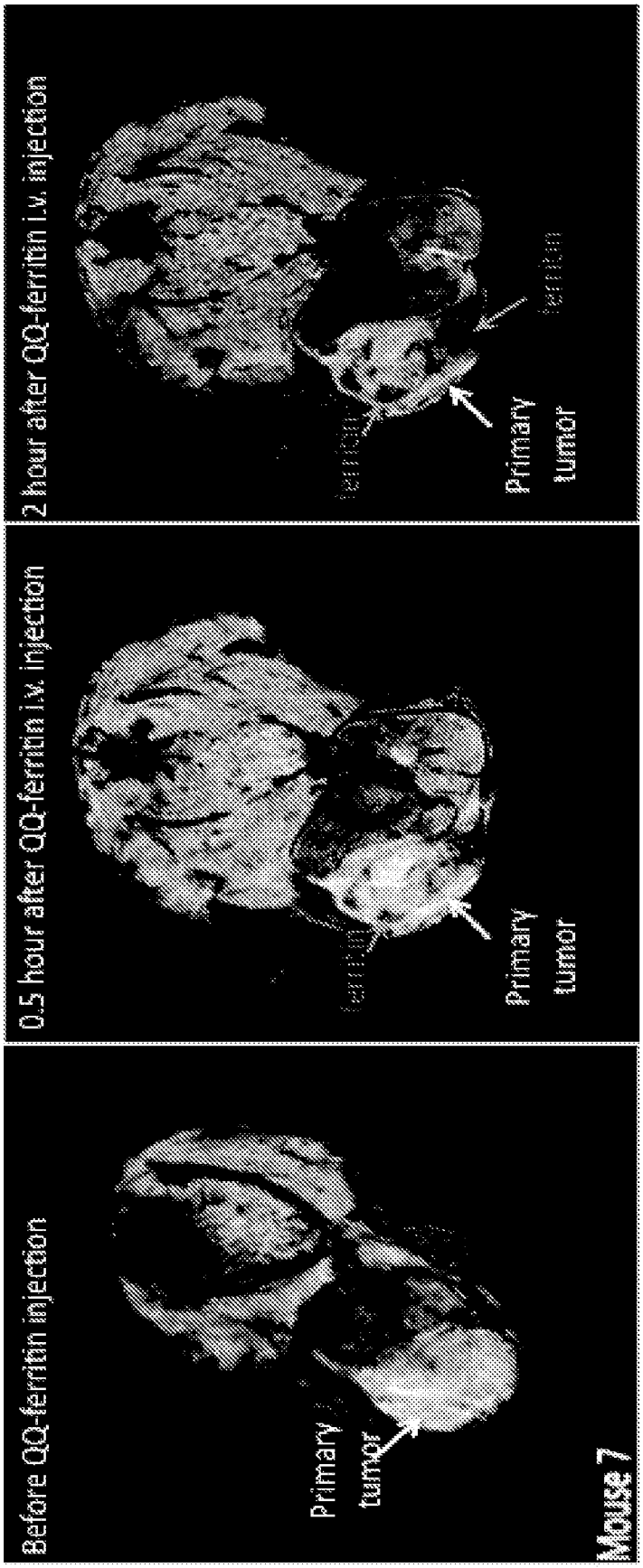


FIG. 2A FIG. 2B FIG. 2C

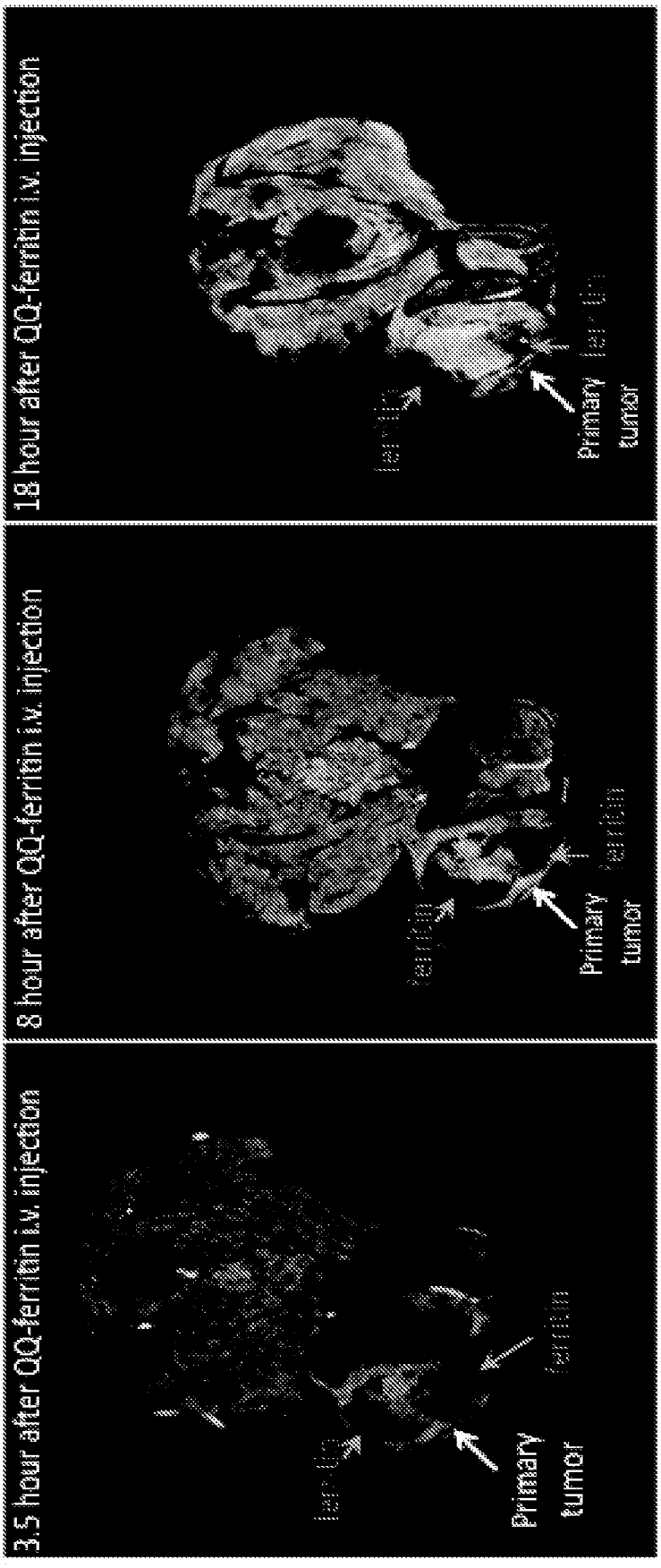


FIG. 2D FIG. 2E FIG. 2F

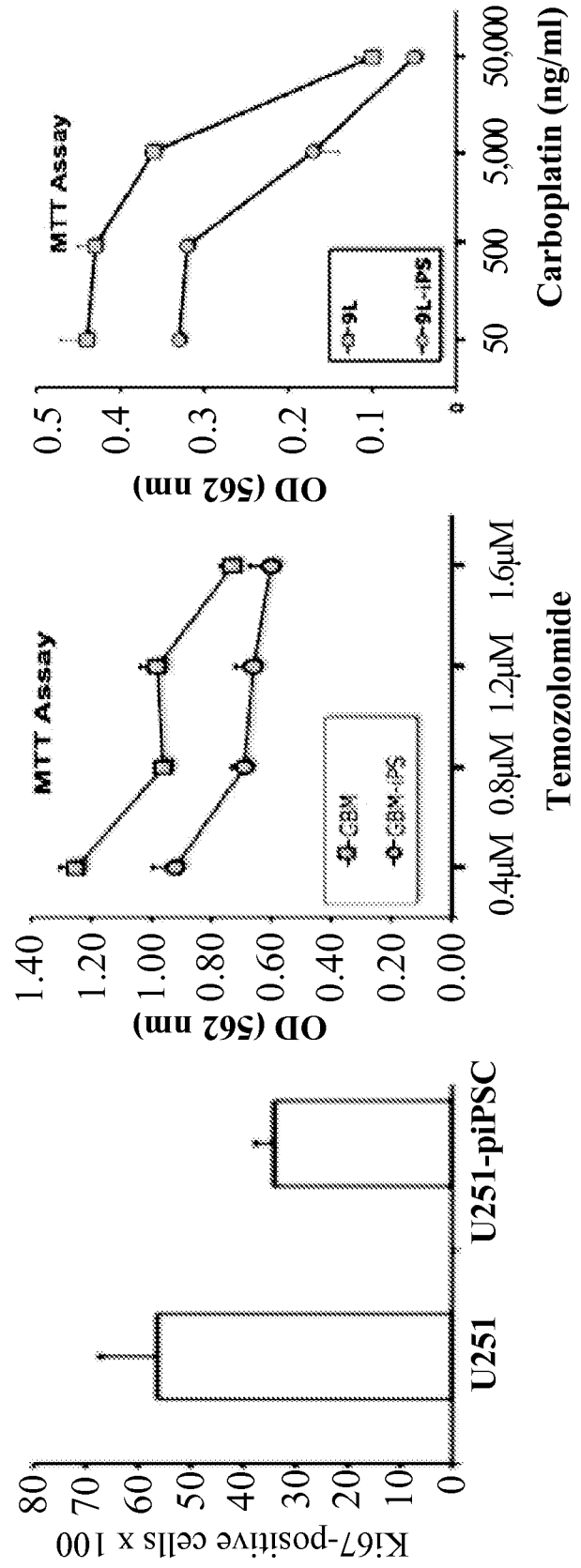


FIG. 3A

FIG. 3B

FIG. 3C

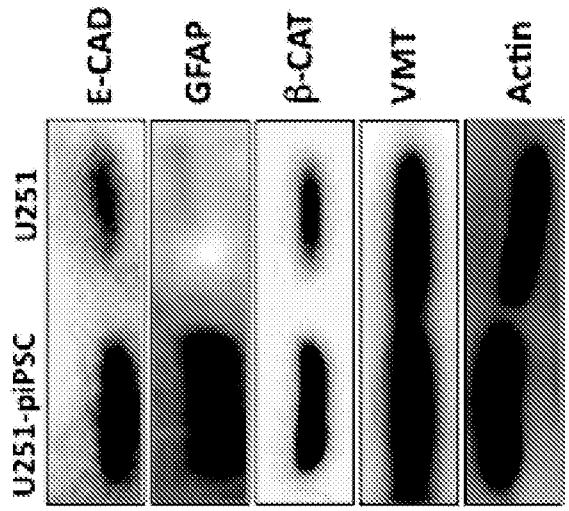


FIG. 4A

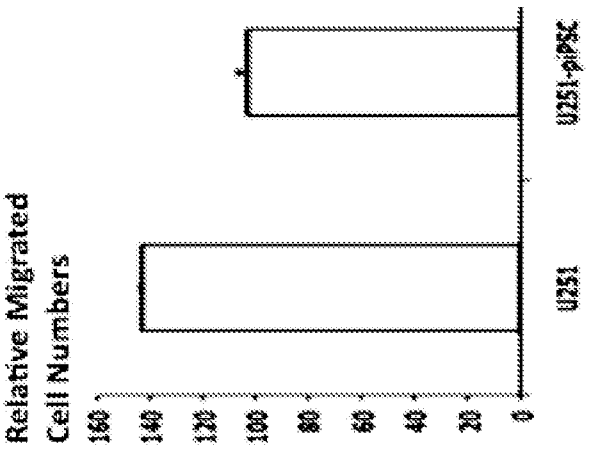


FIG. 4B

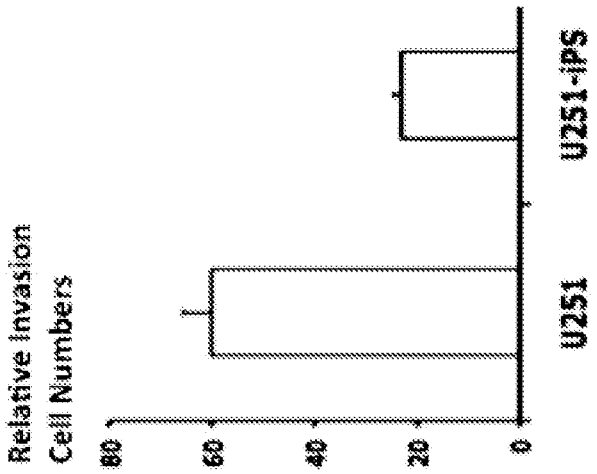


FIG. 4C

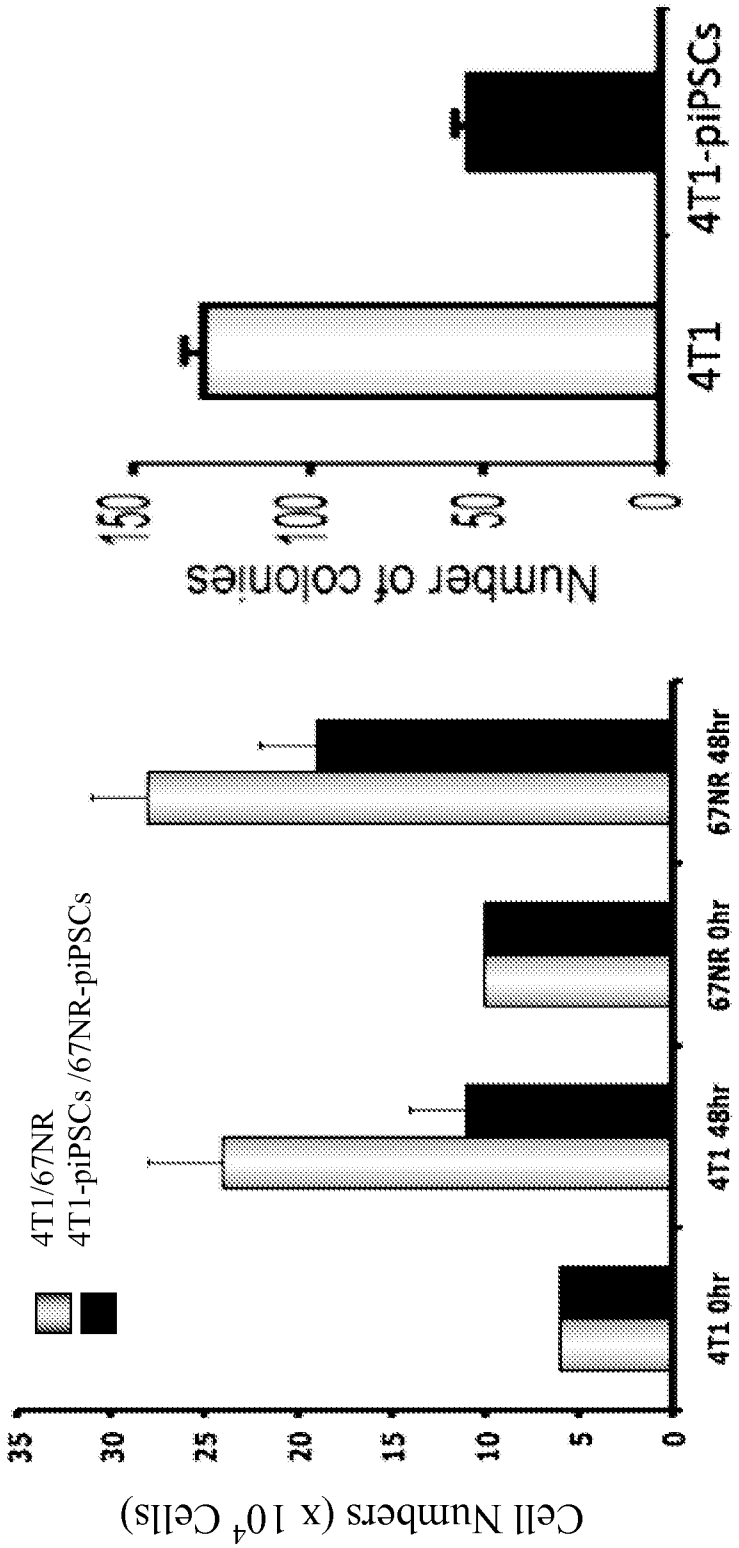
Cell Numbers (x $10^4$ Cells)
35
30
25
20
15
10
5
0
4T1/67NR
4T1-piPSCs /67NR-piPSCs
4T1 0hr
4T1 48hr
67NR 0hr
67NR 48hr

FIG. 4D


Number of colonies
150
100
50
0
4T1
4T1-piPSCs

FIG 4E

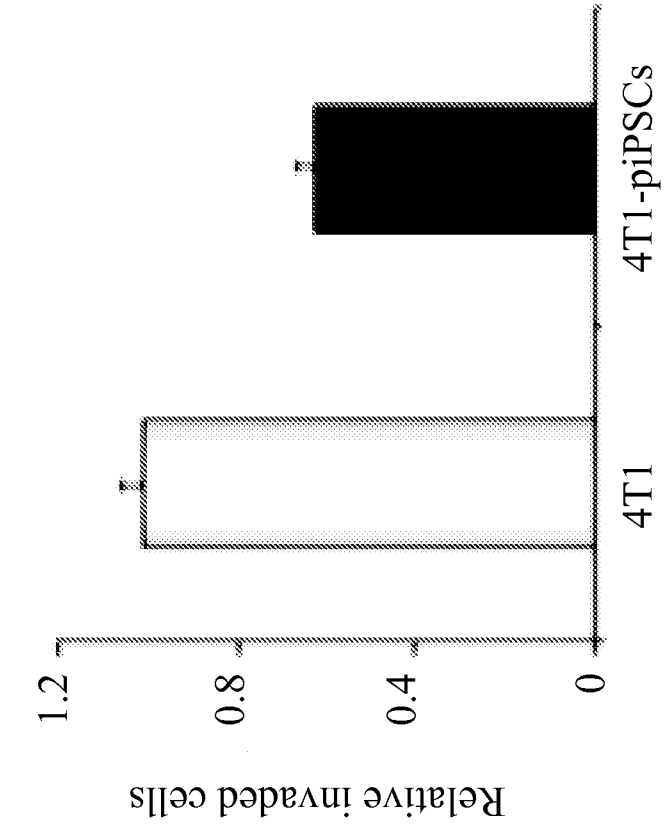
Relative invaded cells
1.2
0.8
0.4
0
4T1
4T1-piPSCs

FIG. 4G

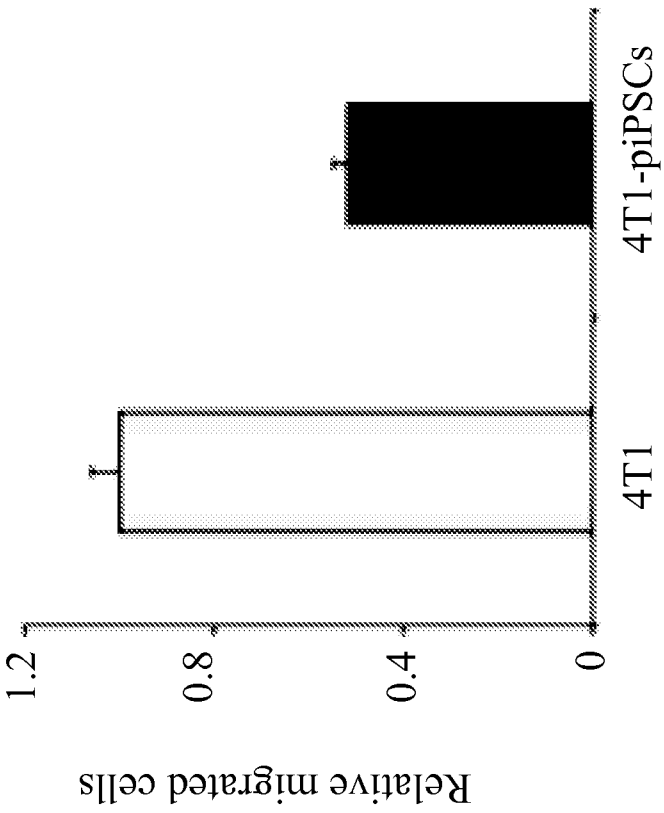
Relative migrated cells
1.2
0.8
0.4
0
4T1
4T1-piPSCs

FIG. 4F


FIG. 5A

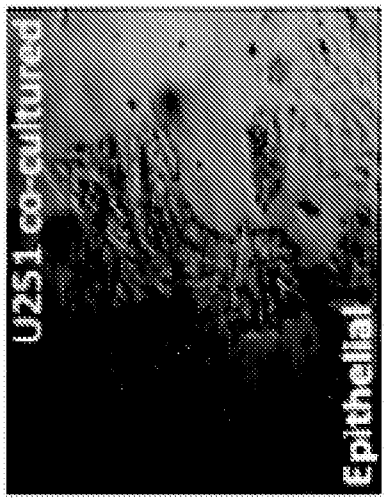


FIG. 5B

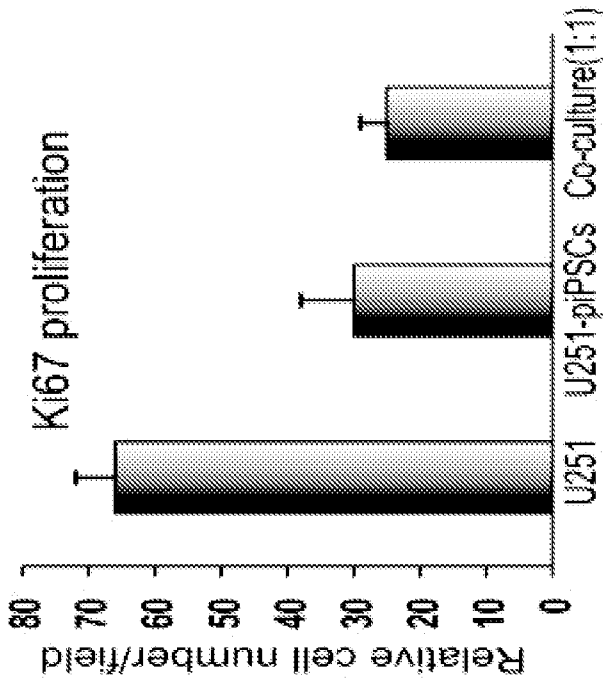


FIG. 5C

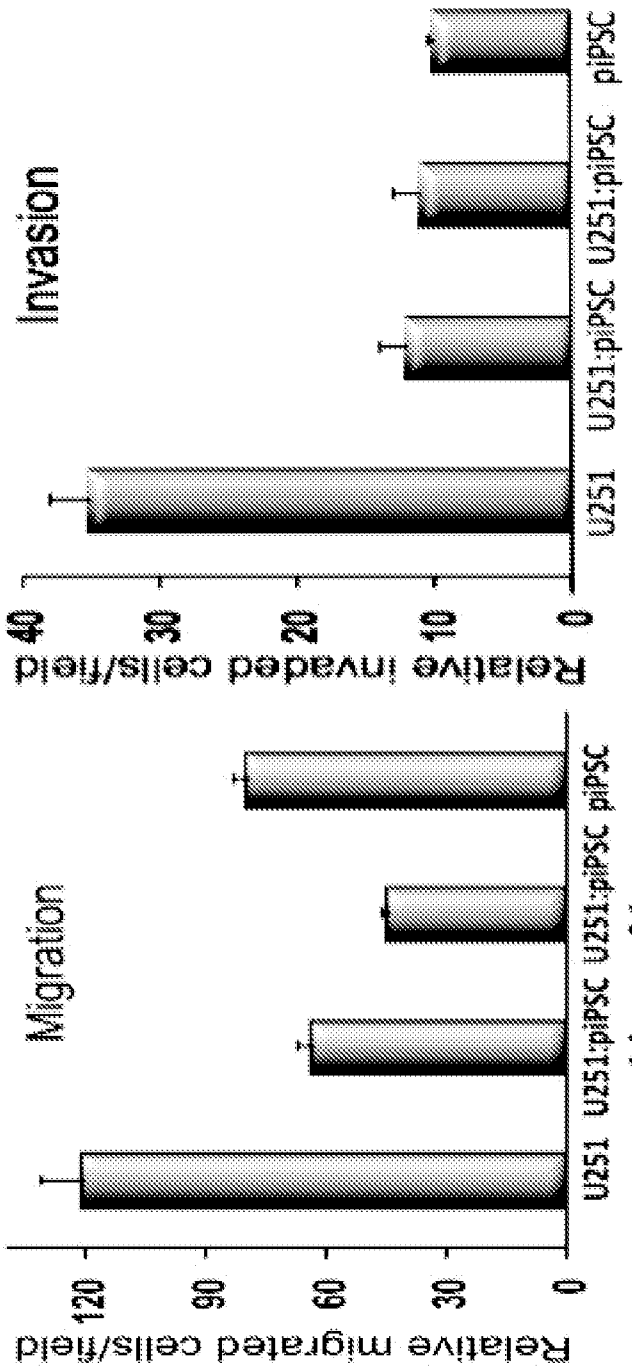
Migration
Relative migrated cells/field
0
30
60
90
120
U251
U251:piPSC 1:1
U251:piPSC 8:1
piPSC
Invasion
Relative invaded cells/field
0
10
20
30
40
U251
U251:piPSC 1:1
U251:piPSC 8:1
piPSC

FIG. 5D

FIG. 5E

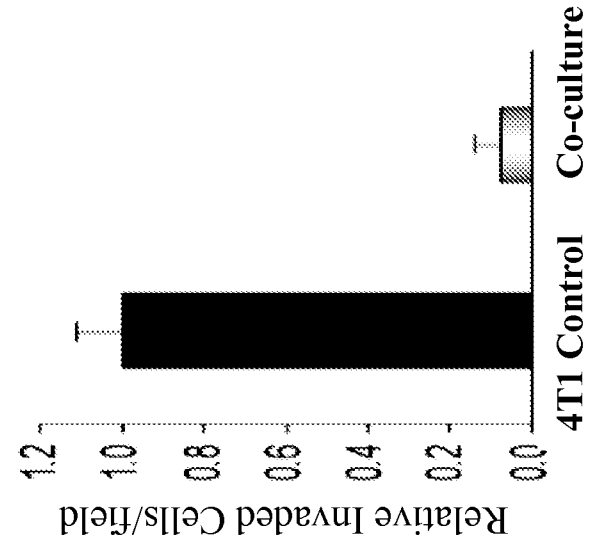


FIG. 5H

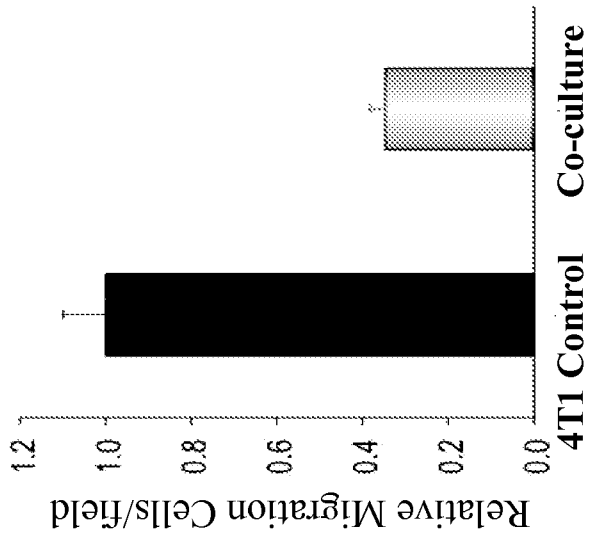


FIG. 5G

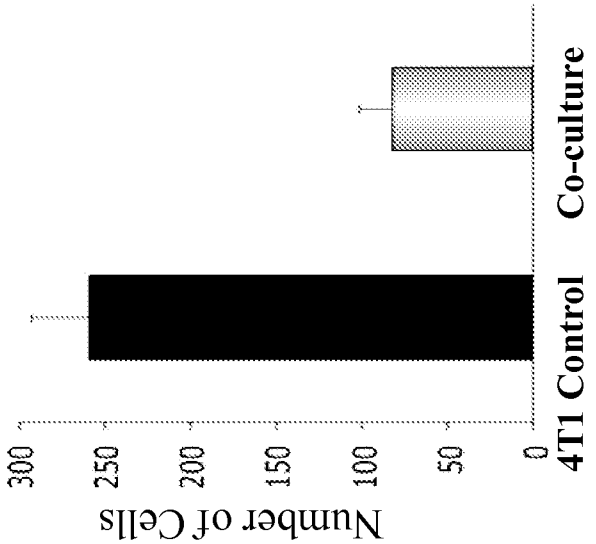


FIG. 5F

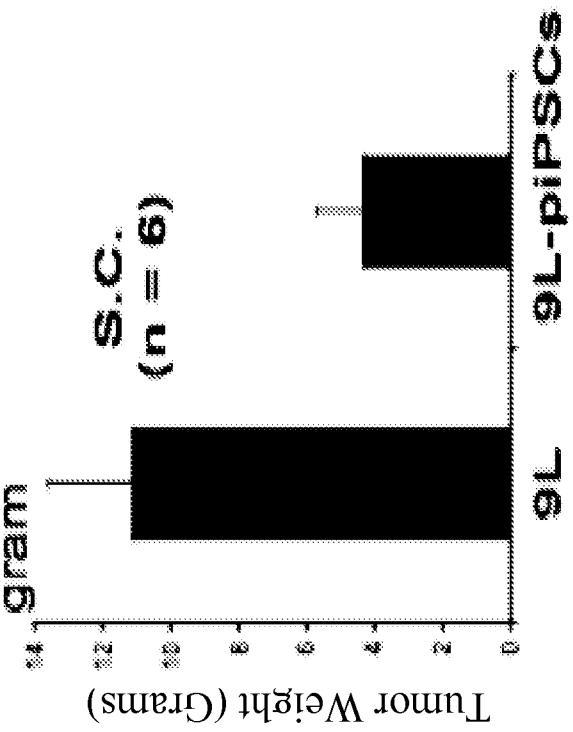
Tumor Weight (Grams)
gram
S.C.
(n = 6)
9L
9L-piPSCs

FIG. 6B

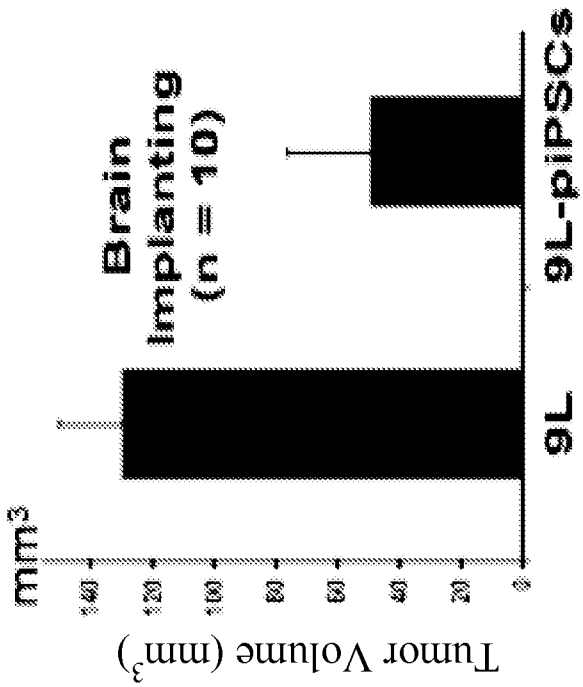
Tumor Volume (mm3)
mm3
Brain
Implanting
(n = 10)
9L
9L-piPSCs

FIG. 6A

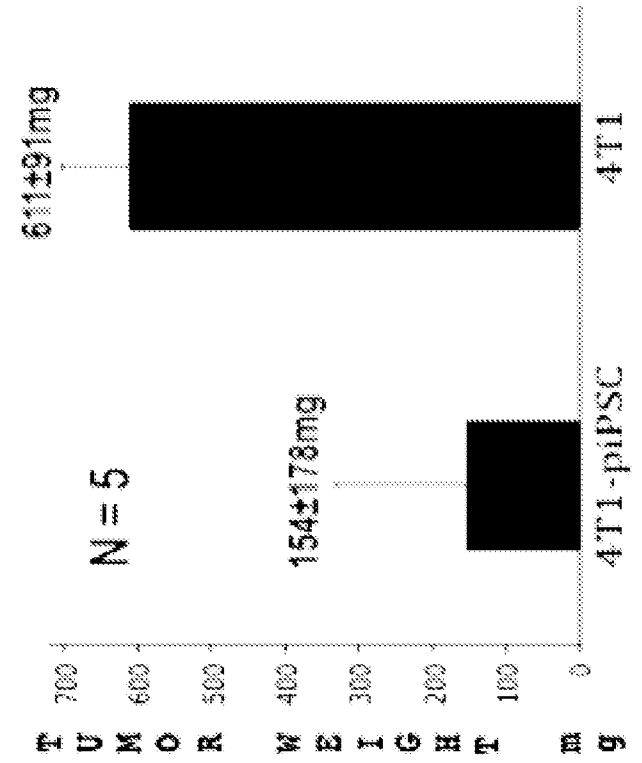
611±91mg
4T1
N = 5
154±178mg
4T1-piPSC
TUMOR WEIGHT mg
700
600
500
400
300
200
100
0

FIG. 6D

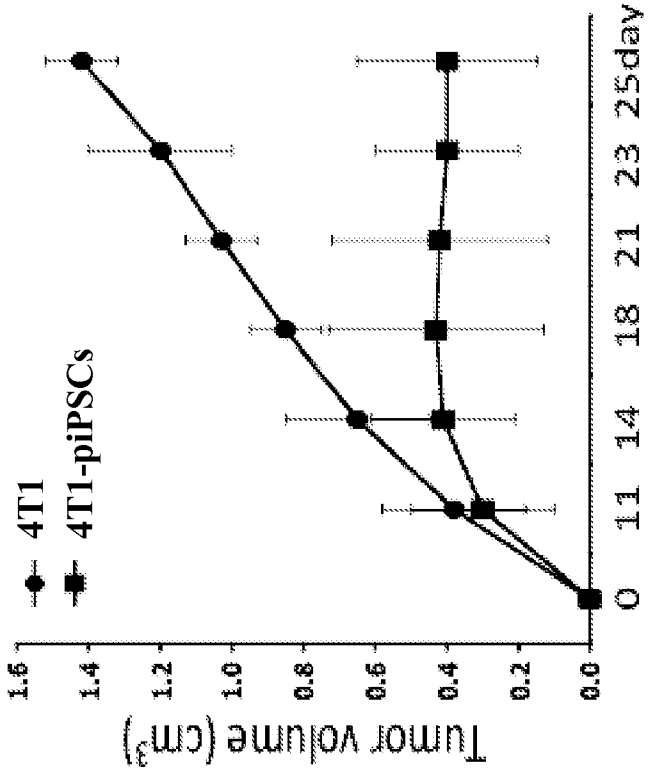
4T1
4T1-piPSCs
Tumor volume (cm³)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
11
14
18
21
23
25day

FIG. 6C

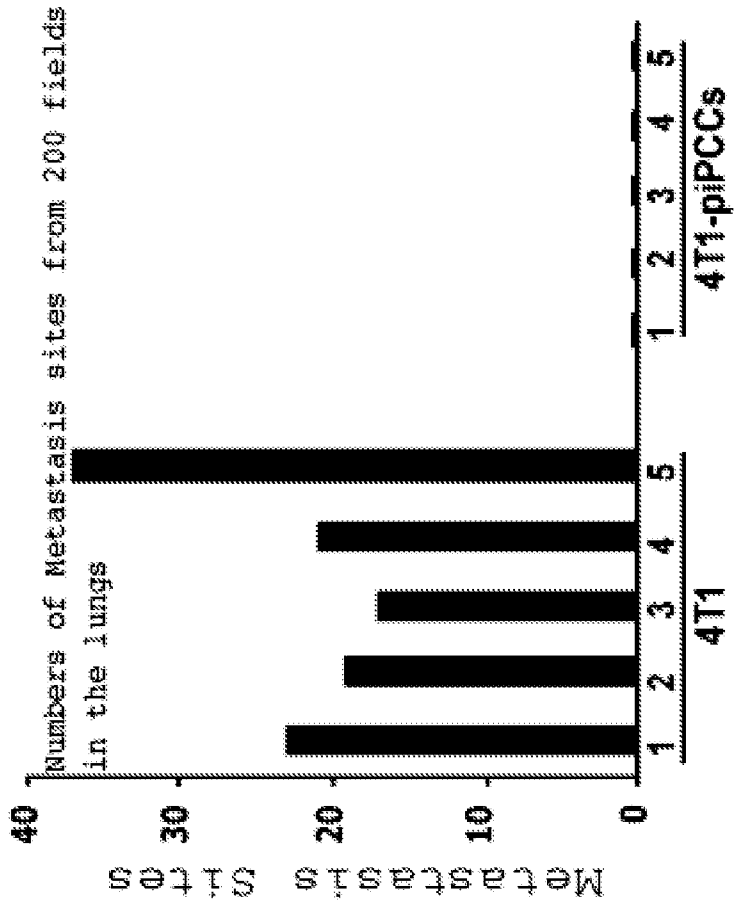
Numbers of Metastasis sites from 200 fields in the lungs
Metastasis Sites
40
30
20
10
0
1 2 3 4 5
4T1
1 2 3 4 5
4T1-piPCCs

FIG. 6E

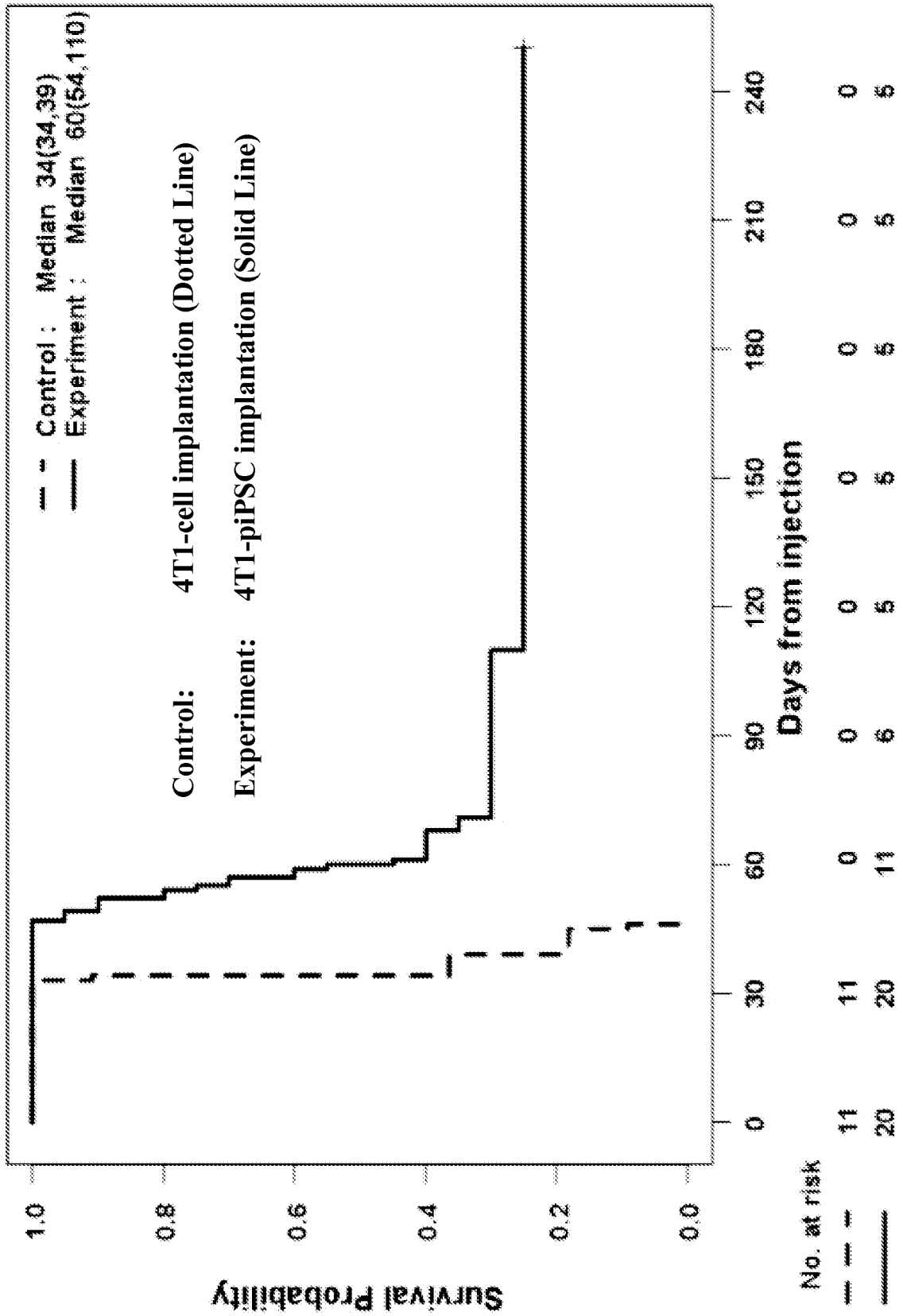
Control : Median 34(34,39)
Experiment : Median 60(54,110)
Control: 4T1-cell implantation (Dotted Line)
Experiment: 4T1-piPSC implantation (Solid Line)
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Days from injection
0 30 60 90 120 150 180 210 240
No. at risk
11 11 0 0 0 0 0 0 0
20 20 11 6 5 5 5 5 5

FIG. 6F

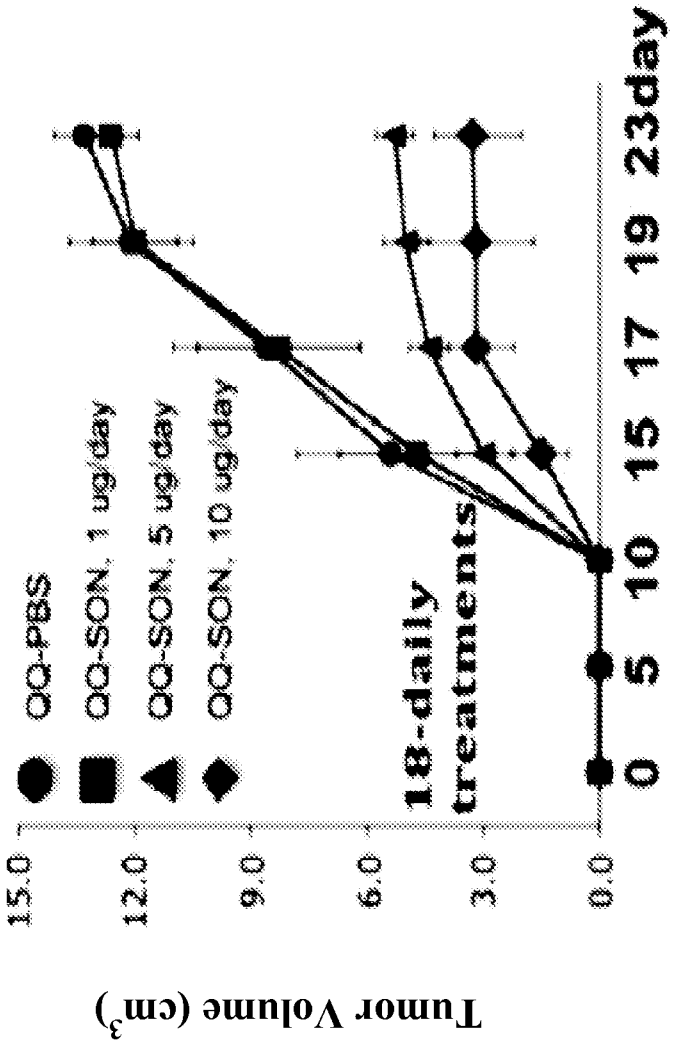
Tumor Volume (cm3)
15.0
12.0
9.0
6.0
3.0
0.0
0 5 10 15 17 19 23day
18-daily treatments
QQ-PBS
QQ-SON, 1 ug/day
QQ-SON, 5 ug/day
QQ-SON, 10 ug/day

FIG. 7A

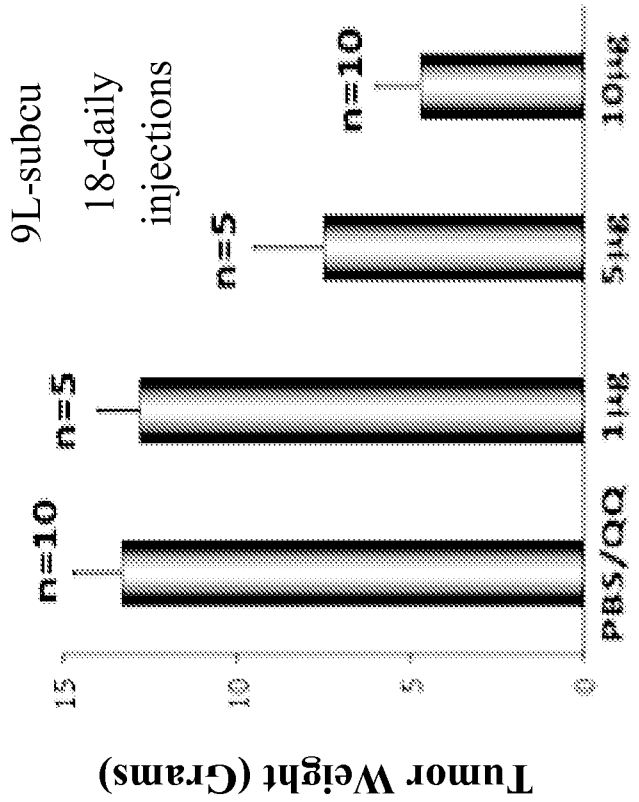
9L-subcu
18-daily
injections
Tumor Weight (Grams)
15
10
5
0
n=10
n=5
n=5
n=10
PBS/QQ
1μg
5μg
10μg

FIG. 7B

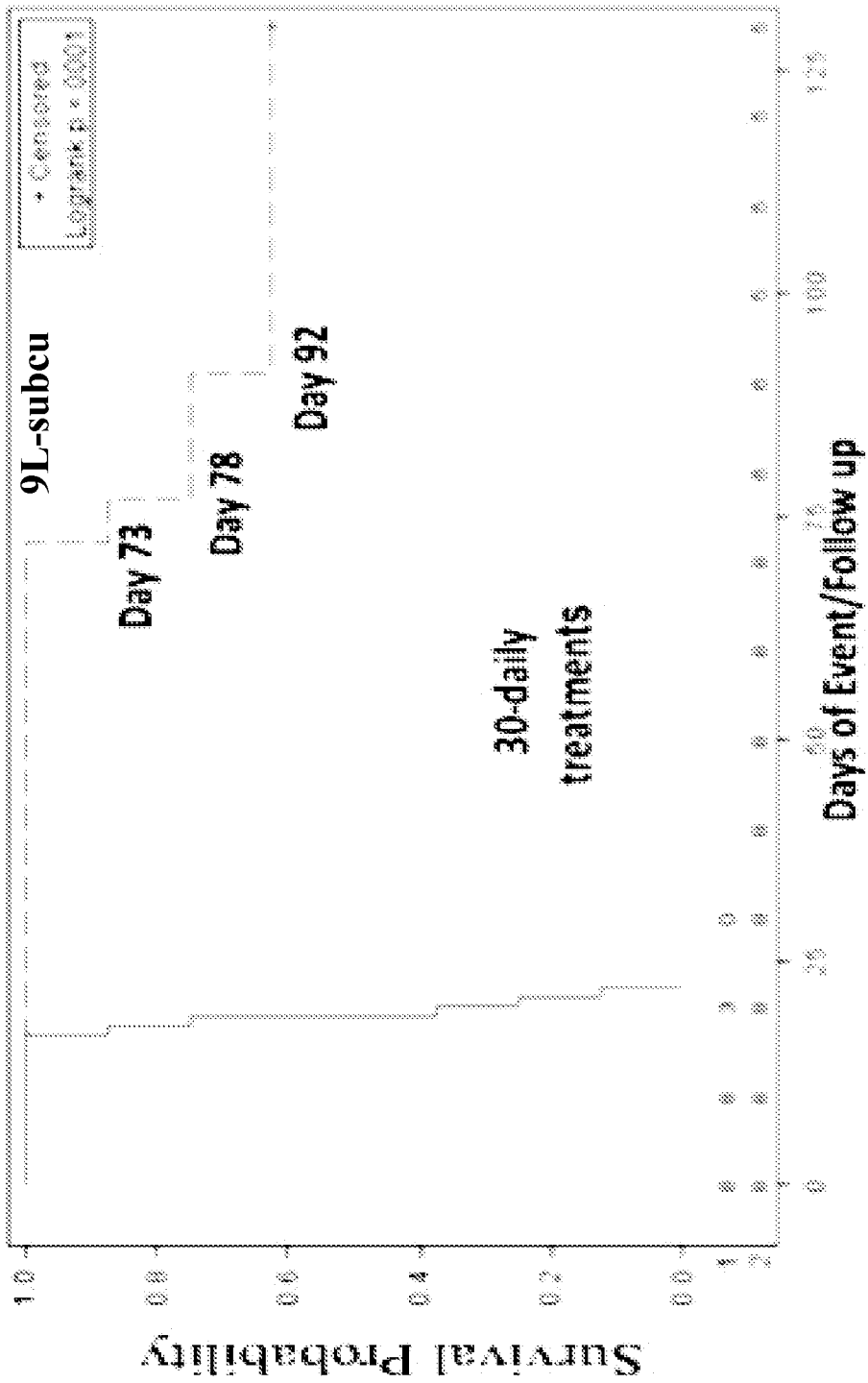
9L-subcu
Day 73
Day 78
Day 92
30-daily
treatments
Survival Probability
Days of Event/Follow up
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120

FIG. 7C

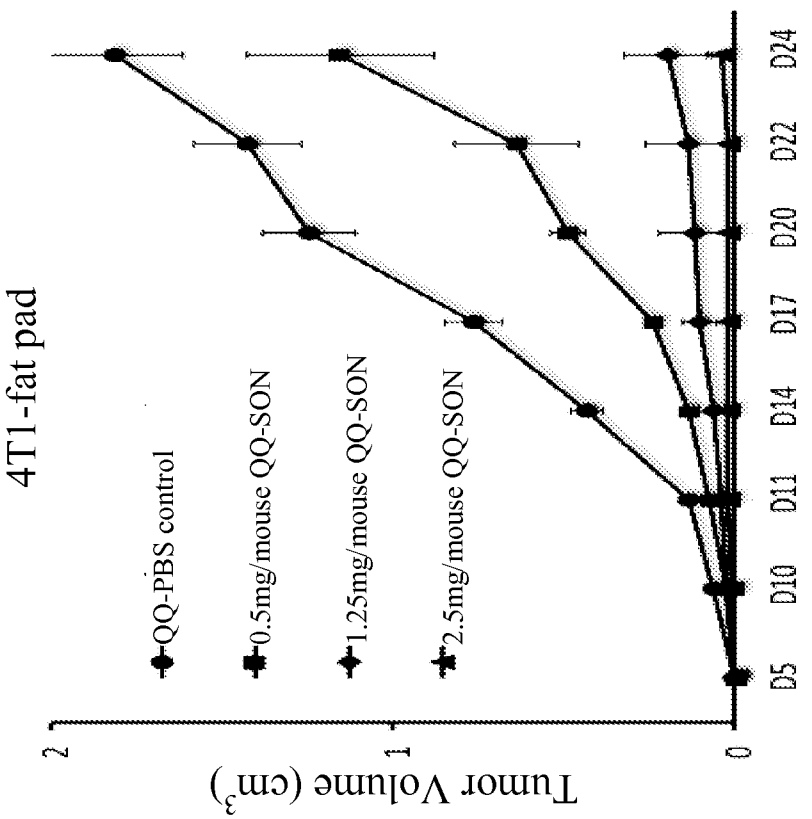
4T1-fat pad
Tumor Volume (cm3)
2
1
0
D5
D10
D11
D14
D17
D20
D22
D24
QQ-PBS control
0.5mg/mouse QQ-SON
1.25mg/mouse QQ-SON
2.5mg/mouse QQ-SON

FIG. 7D

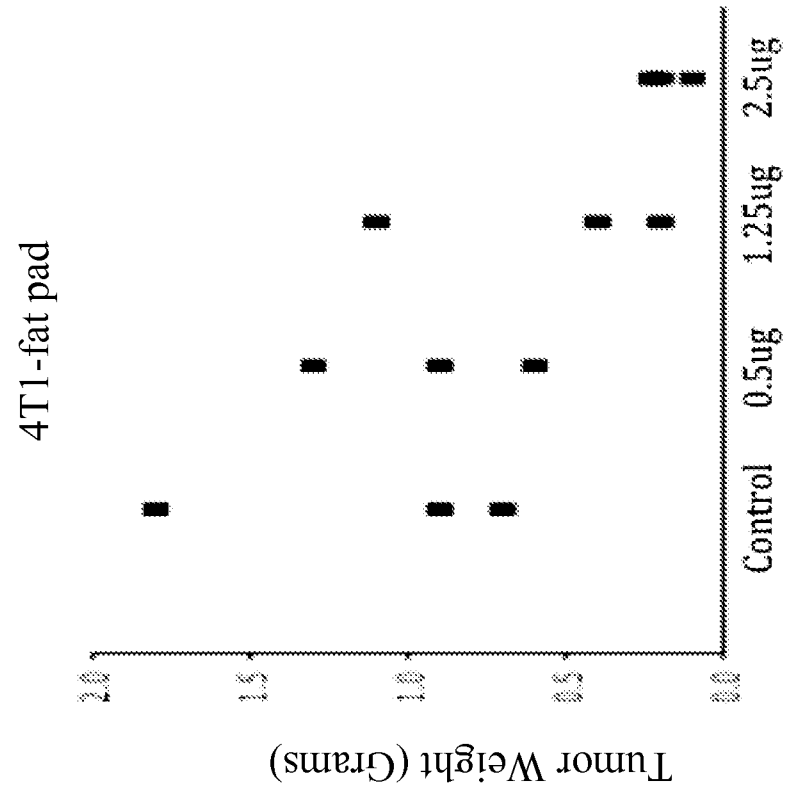
4T1-fat pad
Tumor Weight (Grams)
2.0
1.5
1.0
0.5
0.0
Control
0.5ug
1.25ug
2.5ug

FIG. 7E

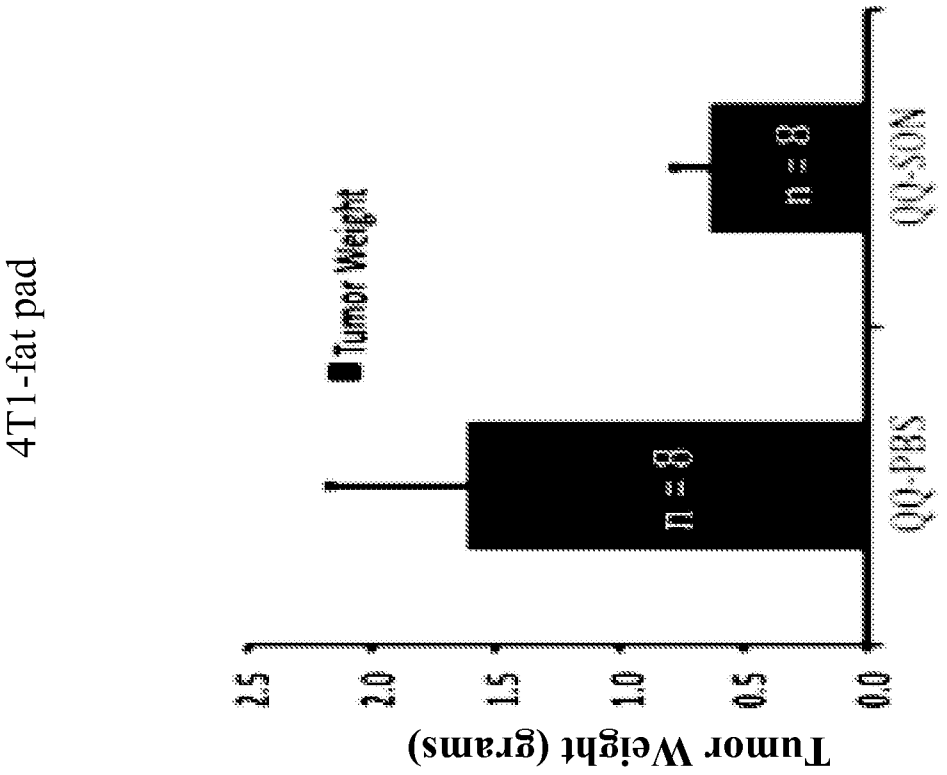
4T1-fat pad
Tumor Weight
n = 8
n = 8
QQ-PBS
QQ-SON
Tumor Weight (grams)
2.5
2.0
1.5
1.0
0.5
0.0

FIG. 7G

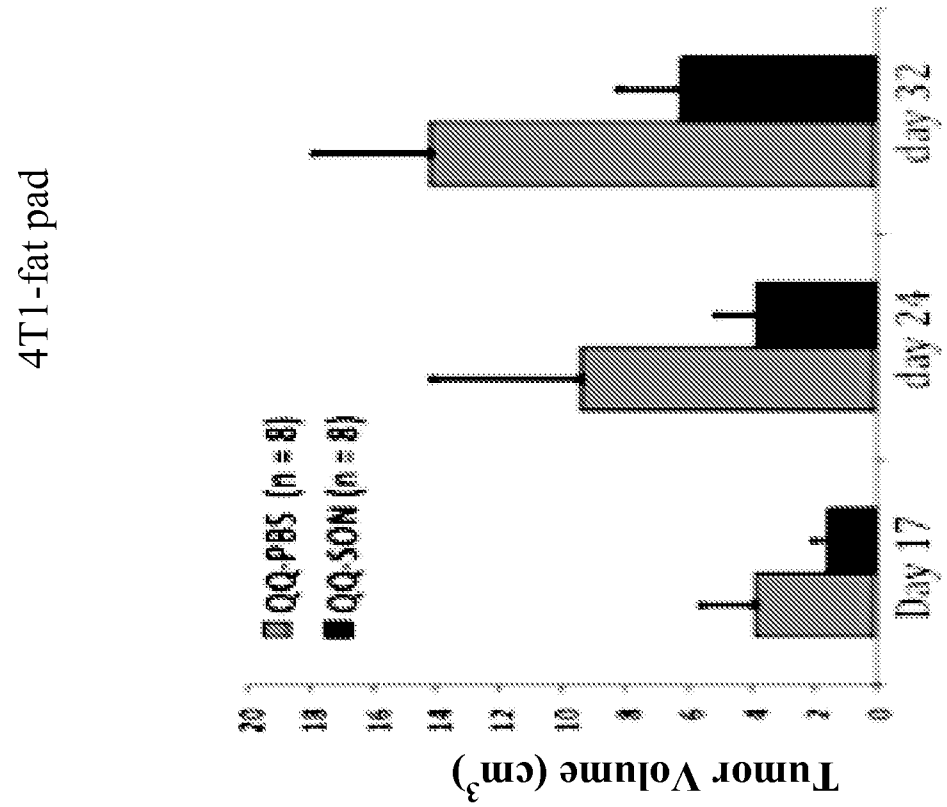
4T1-fat pad
QQ-PBS (n = 8)
QQ-SON (n = 8)
Day 17
day 24
day 32
Tumor Volume (cm3)
20
18
16
14
12
10
8
6
4
2
0

FIG. 7F

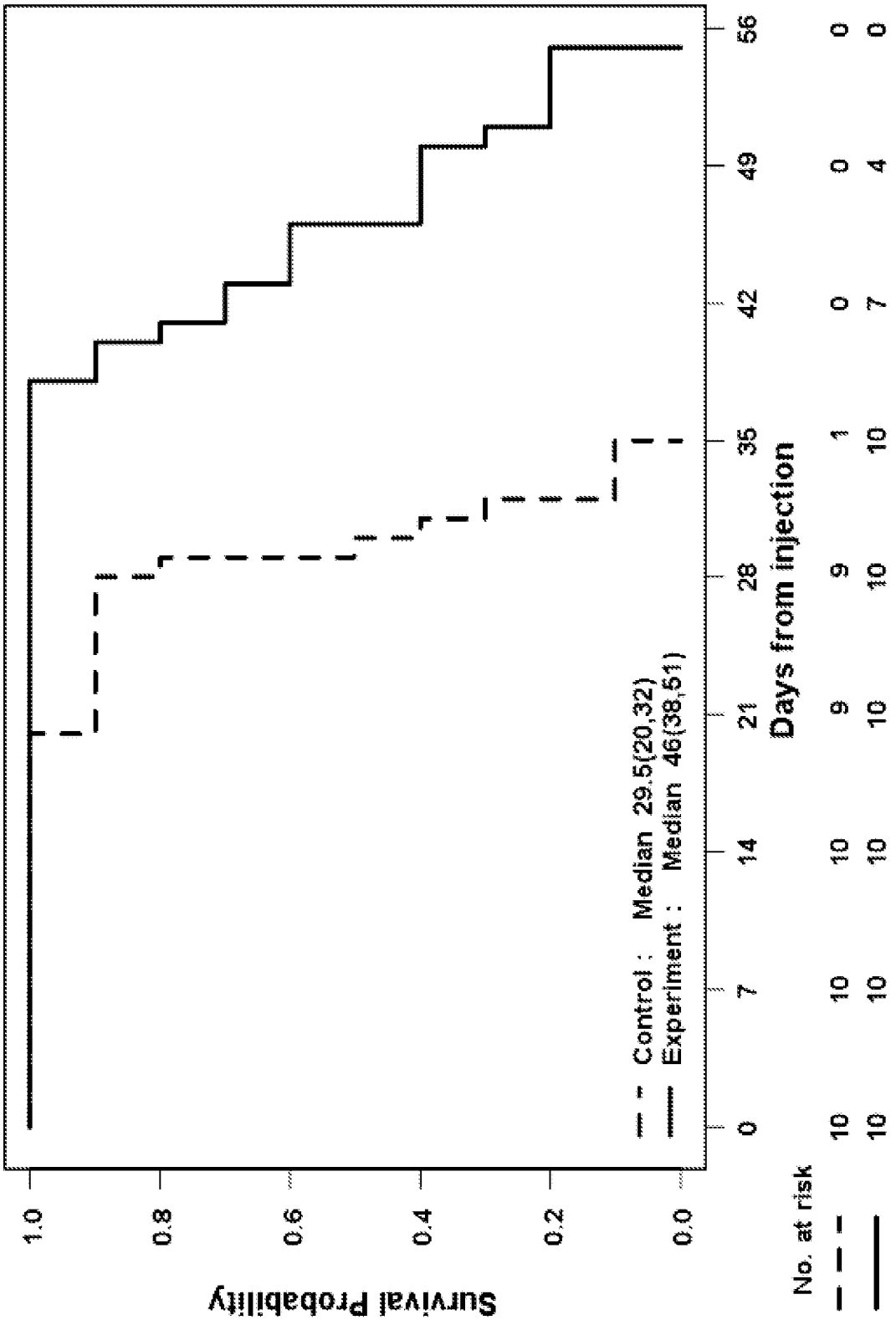
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Control : Median 29.5(20,32)
Experiment : Median 46(38,51)
Days from injection
0 7 14 21 28 35 42 49 56
No. at risk
10 10 10 9 9 1 0 0 0
10 10 10 10 10 10 7 4 0

FIG. 7H

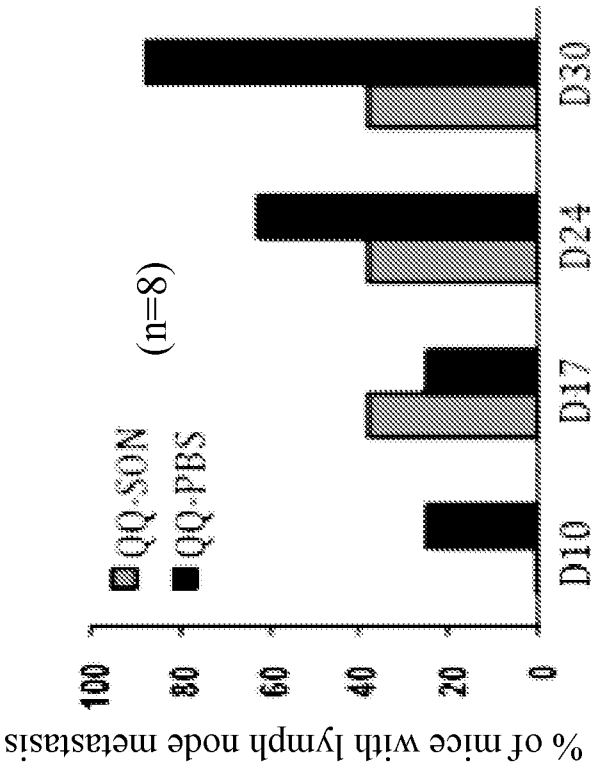
% of mice with lymph node metastasis
100
80
60
40
20
0
QQ-SON
QQ-PBS
(n=8)
D10
D17
D24
D30

FIG. 7J

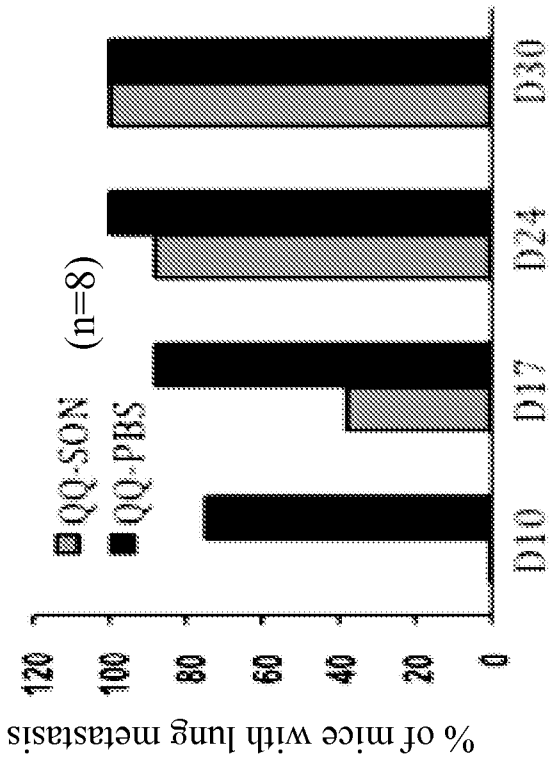
% of mice with lung metastasis
120
100
80
60
40
20
0
QQ-SON
QQ-PBS
(n=8)
D10
D17
D24
D30

FIG. 7I

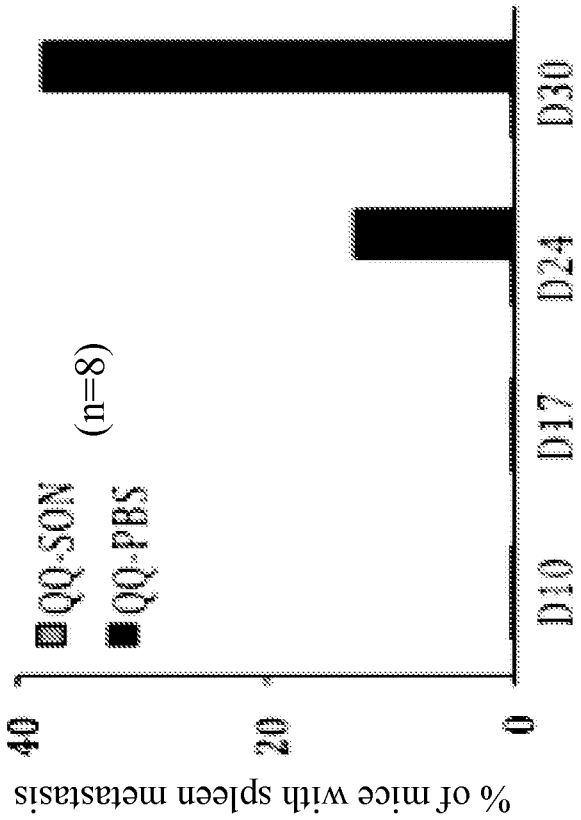
% of mice with spleen metastasis
40
20
0
QQ-SON
QQ-PBS
(n=8)
D10
D17
D24
D30

FIG. 7L

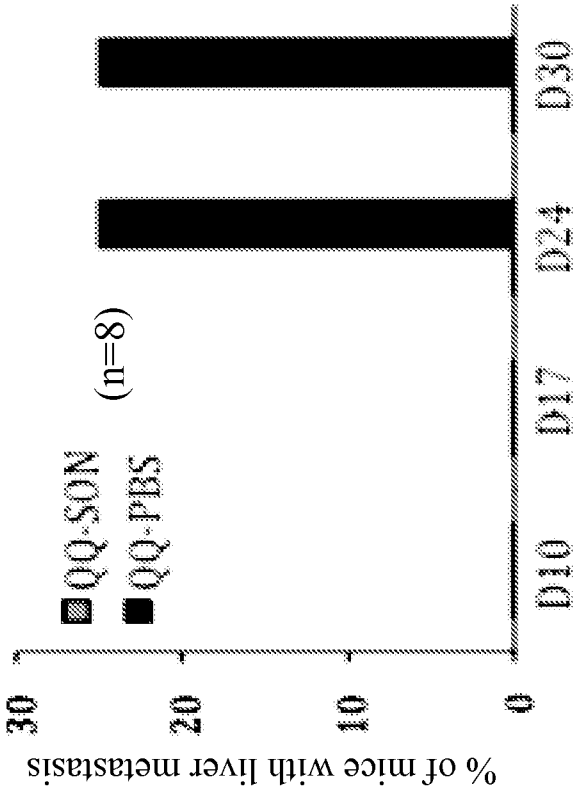
% of mice with liver metastasis
30
20
10
0
QQ-SON
QQ-PBS
(n=8)
D10
D17
D24
D30

FIG. 7K

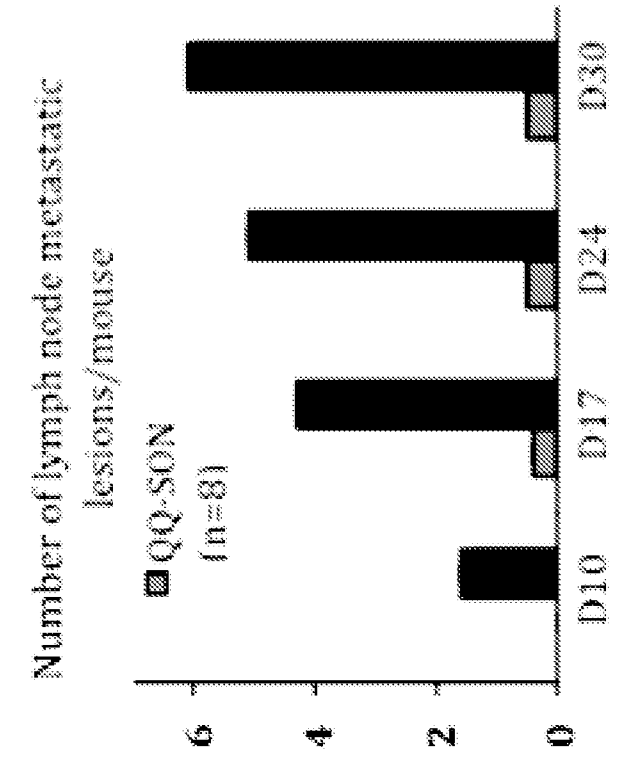
Number of lymph node metastatic lesions/mouse
QQ-SON (n=8)
0
2
4
6
D10
D17
D24
D30

FIG. 7N

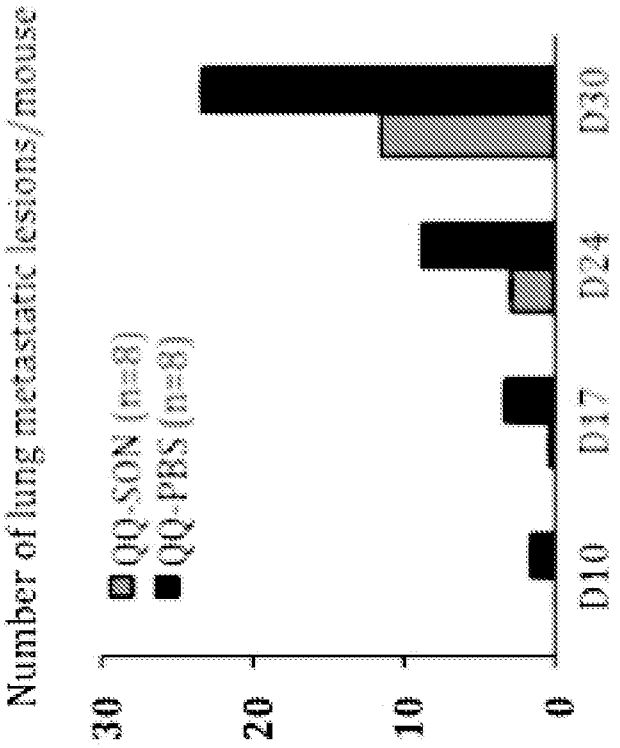
Number of lung metastatic lesions/mouse
QQ-SON (n=8)
QQ-PBS (n=8)
0
10
20
30
D10
D17
D24
D30

FIG. 7M

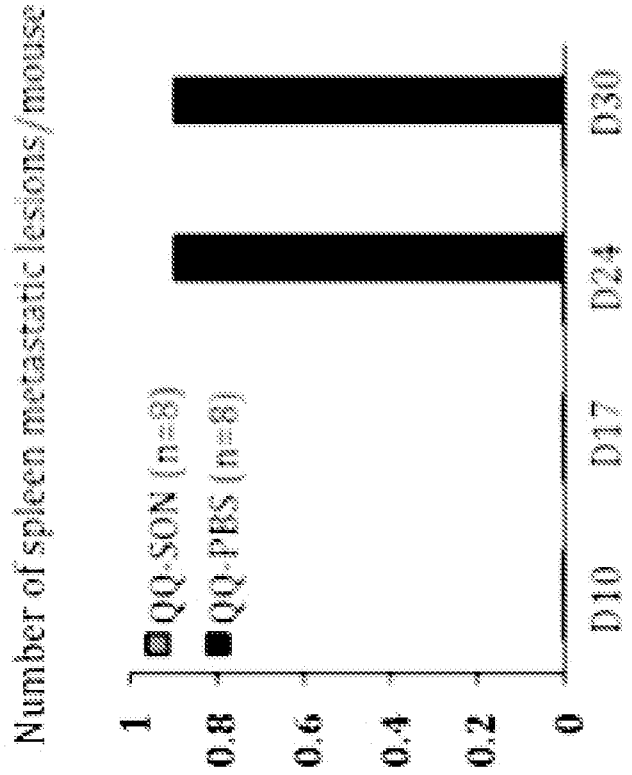
Number of spleen metastatic lesions/mouse
QQ-SON (n=8)
QQ-PBS (n=8)
1
0.8
0.6
0.4
0.2
0
D10
D17
D24
D30

FIG. 7P

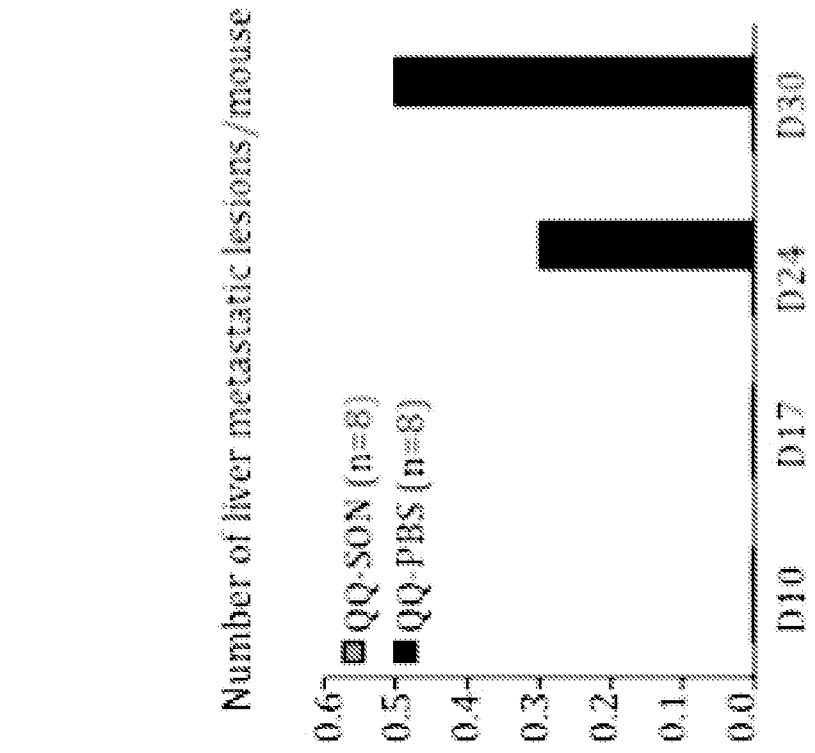
Number of liver metastatic lesions/mouse
QQ-SON (n=8)
QQ-PBS (n=8)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
D10
D17
D24
D30

FIG. 7O

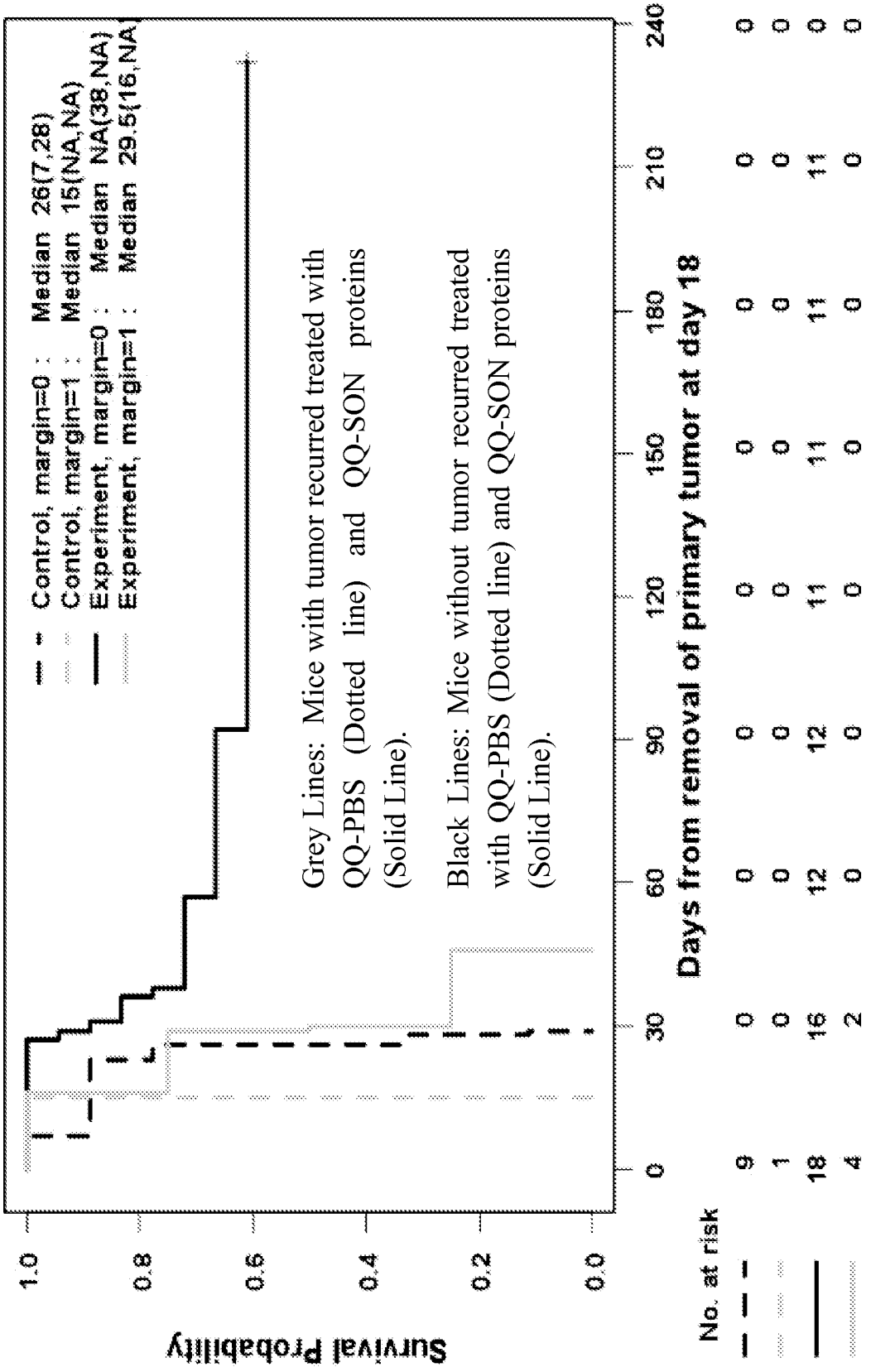
Control, margin=0 : Median 26(7,28)
Control, margin=1 : Median 15(NA,NA)
Experiment, margin=0 : Median NA(38,NA)
Experiment, margin=1 : Median 29.5(16,NA
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Grey Lines: Mice with tumor recurred treated with QQ-PBS (Dotted line) and QQ-SON proteins (Solid Line).
Black Lines: Mice without tumor recurred treated with QQ-PBS (Dotted line) and QQ-SON proteins (Solid Line).
Days from removal of primary tumor at day 18
0 30 60 90 120 150 180 210 240
No. at risk
9 0 0 0 0 0 0 0 0
1 0 0 0 0 0 0 0 0
18 16 12 12 11 11 11 11 0
4 2 0 0 0 0 0 0 0

FIG. 8