COMBINATION IMMUNOTHERAPY APPROACH FOR TREATMENT OF CANCER

BACKGROUND OF THE INVENTION

[0001] Cancer is the second most common cause of death in the United States, exceeded only by heart disease. In the United States, cancer accounts for 1 of every 4 deaths. The 5-year relative survival rate for all cancer patients diagnosed in 1996-2003 is 66%, up from 50% in 1975-1977 (Cancer Facts & Figures American Cancer Society: Atlanta, GA (2008)). Discovering highly effective cancer treatments is a primary goal of cancer research.

[0002] The tumor stem cell hypothesis may explain the resistance of some tumors to conventional therapies. In this model, a certain subset of tumor cells, with characteristics similar to some stem cells, is capable of producing a variety of cell types, which constitute the bulk of the tumor. An effective approach for eradicating these cells is needed.

SUMMARY OF THE INVENTION

[0003] The present invention relates generally to the treatment of human cancer and, more specifically, to use of several treatment modalities in combination to induce effective anti-tumor immune responses.

[0004] Disclosed herein, in some embodiments, is a method for treating a solid tumor or hematologic malignancy in a subject, comprising two or more of the following: (a) sensitizing a tumor by administering to the subject a treatment that will: (i) induce apoptosis in cells within the tumor, (ii) modify the tumor environment, (iii) stimulate tumor-infiltrating immune cells, or (iv) a combination thereof; (b) injecting into the subject: (i) a modified stem cell, wherein the modified stem cell comprises a cytotoxic payload; (ii) a wild-type or genetically modified virus; (iii) a wild-type or genetically modified bacteria; or (iv) a combination thereof; and (c) administering a treatment to the subject that will activate the T-cell response within the subject.

In some embodiments, step (a) is performed before step (b) and step (c). In some embodiments, step (b) is performed after step (c). In some embodiments, step (b) is performed before step (c). In some embodiments, any of the steps are performed concurrently.

[0005] In some embodiments, the treatment that will induce apoptosis in cells within the tumor is selected from the group consisting of: radiation therapy, chemotherapy, immunotherapy, phototherapy, or a combination thereof. In some embodiments, the treatment that will induce apoptosis in cells is immunotherapy. In some embodiments, the immunotherapy is selected from peptide vaccine therapy using tumor antigen peptides; adoptive immunotherapy using lymphocytes such as cytotoxic T cells or natural killer cells; DNA vaccine therapy which involves administration of organisms comprising vectors expressing tumor antigen proteins or tumor antigen peptides ; and dendritic cell vaccine therapy which involves administering dendritic cells displaying tumor antigen peptides. In some embodiments, the treatment that will induce apoptosis in cells is chemotherapy. In some embodiments, the chemotherapy comprises administration of a chemotherapeutic agent is selected from an alkylating drug, an antimetabolite, an antimytotic cytostatic, a topoisomerase inhibitor, antitumor antibiotic, and any other cytostatic, and/or a radiotherapy. In some embodiments, the chemotherapeutic agent is an alkylating agent. In some embodiments, the alkylating agent is selected from cisplatin, oxaliplatin, cyclop hosphamid, ifosfamid, trofosfamid, melphalan, chlorambucil, estramustin, busulfan, treosulfan, carmustin, lomustin, nimustin, streptozocin, procarbazin, dacarbazin, temozolomid, and thiotepa. In some embodiments, the chemotherapeutic agent is an antimetabolite. In some embodiments, the antimetabolite is selected from 5- fluorouracil, methotrexate, azacitidin, capecitabin, doxifluridin, cytarabin, gemcitabin, 6-thioguanin, pentostatin, azathioprin, 6-mercaptopurin, fludarabin, and cladribin. In some embodiments, the chemotherapeutic agent is a topoisomerase inhibitor. In some embodiments, the topoisomerase inhibitor is selected from doxorubicin, camptothecin, topotecan, irinotecan, etoposide, and teniposide. In some embodiments, the chemotherapeutic agent is an antitumor antibiotic. In some embodiments, the antitumor antibiotic is selected from tamoxifen, 5-fluoro-5'-

deoxyuridine, belomycin, actinomycin D, and mitomycin. In some embodiments, the chemotherapeutic agent is a cytostatic. In some embodiments, the cytostatic is L-asparaginase or hydroxycarb amide. In some embodiments, the treatment that will induce apoptosis in cells is phototherapy. In some embodiments, the phototherapy is selected from ultraviolet B radiation (UVB) phototherapy and ultraviolet A photochemotherapy (PUVA). In some embodiments, the phototherapy further comprises the use of psoralen. In some embodiments, sensitizing the tumor comprises administering irradiation to the subject. In some embodiments, the irradiation is ionizing radiation. In some embodiments, the irradiation is high-dose hypofractionation radiation therapy (HDHRT). In some embodiments, step (a) comprises modification of the tumor microenvironment. In some embodiments, modification of the tumor microenvironment comprises administration of a cytokine-blocking agent. In some embodiments, the cytokine-blocking agent is selected from Ustekinumab, Adalimumab, Infliximab, Etanercept, and Golimumab.

[0006] In some embodiments, step (b) comprises injecting into the subject a modified stem cell, wherein the modified stem cell comprises a cytotoxic payload.. In some embodiments, the modified stem cell carries one or more imaging payloads. In some embodiments, the modified stem cell carries one or more of a virus, an antibody, or a cytokine as the cytotoxic payload. In some embodiments, the modified stem cell expresses a cytokine as the cytotoxic payload. In some embodiments, the cytokine is selected from colony-stimulating factor (CSF), interferon (IFN), interleukin (IL), stem cell factor (SCF), tumour growth factors (TGF), and tumour necrosis factor (TNF). In some embodiments, the cytokine is a CSF. In some embodiments, the CSF is G-CSF, M-CSF, or GM-CSF. In some embodiments, the CSF is selected from ancestim, garnocestim, pegacaristim, leridistim, milodistim, filgrastim, lenograstim, nartograstim, pegfilgrastim, pegnartograstim, ecogramostim, molgramostim, regramostim, sargramostim, cilmostim, lanimostim, mirimostim, daniplestim, muplestim, or derivates thereof. . In some embodiments, the cytokine is an interleukin (IL). In some embodiments, the interleukin is selected from IL-1 to IL-35, and derivates thereof. In some embodiments, the interleukin is IL -

2, IL-4, or derivates thereof. In some embodiments, the cytotoxic payload comprises a lytic virus. In some embodiments, the lytic virus is a vaccinia virus. In some embodiments, the cytotoxic payload comprises a chemotherapeutic agent. In some embodiments, step (b) results in *in situ* vaccination of the subject against the tumor.

[0007] In some embodiments, the modified stem cell is an adult stem cell. In some embodiments, the modified stem cell is transformed with a lenti-virus or retrovirus. In some embodiments, the modified stem cell is transiently transfected with an artificial chromosome, virus or plasmid DNA. In some embodiments, the modified stem cell is capable of localizing to the tumor. In some embodiments, the modified stem cell is autologous. In some embodiments, the modified stem cell is allogeneic. In some embodiments, the modified stem cell is selected from the group consisting of adult stem cells, embryonic stem cells, fetal stem cells, mesenchymal stem cells, neural stem cells, totipotent stem cells, pluripotent stem cells, multipotent stem cells, oligopotent stem cells, unipotent stem cells, adipose stromal cells, endothelial stem cells, and combinations thereof. In some embodiments, the modified cell is derived from adipose-derived Stromal Vascular Fraction (SVF), which comprises adult stem cells, monocytes/macrophages, regulatory T cells, endothelial cells, and combinations thereof. In some embodiments, the modified stem cell is injected into the subject in conjunction with adipose-derived SVF. In some embodiments, the modified stem cell is an umbilical cord-derived mesenchymal like cell. In some embodiments, the umbilical cord-derived mesenchymal-like cell is an Immstem™ cell.

[0008] In some embodiments, step (b) further comprises treatment of the modified stem cell with a treatment selected from: a TLR agonist; intravenous immunoglobulin (IVIG); monocyte conditioned media; supernatant from neutrophil extracellular trap-exposed peripheral blood mononuclear cells; co-culture with monocytes; co-culture with monocytes that have been pretreated with IVIG; co-culture with T cells; coculture with T cells that have been exposed to a T cell stimulus; co-culture with natural killer cells; peptidoglycan isolated from gram positive bacteria; lipoarabinomannan isolated from mycobacteria; zymosan isolated from a yeast cell

wall; polyadenylic-polyuridylic acid; poly (IC); lipopolysaccharide; monophosphoryl lipid A; flagellin; Gardiquimod; Imiquimod; R848; oligonucleosides containing CpG motifs; and 23S ribosomal RNA.

[0009] In some embodiments, step (c) comprises injection of a stem cell into the subject. In some embodiments, the stem cell is an adult stem cell. In some embodiments, the stem cell is capable of excreting growth factors. In some embodiments, the stem cell is injected into the site of the tumor. In some embodiments, the stem cell is injected into the tumor. In some embodiments, the stem cell produces antibodies, or growth factors capable of stimulating T-cell growth and expansion. In some embodiments, the stem cell is transformed with a lenti-virus or retrovirus. In some embodiments, the lenti-virus or retrovirus comprise a heterologous nucleic acid encoding a protein involved in T-cell activation.. In some embodiments, the stem cell is transiently transfected with an artificial chromosome, virus or plasmid DNA.

[00010] In some embodiments, step (c) comprises promoting simultaneous signaling through the T cell receptor and a costimulatory molecule. In some embodiments, the costimulatory molecule is CD28.

[00011] In some embodiments, step (c) comprises administering to the tumor one or more T-cells expressing one or more growth factors.

[00012] In some embodiments, step (c) comprises administering agonistic antibodies directed against activating co-stimulatory molecules. In some embodiments, step (c) comprises administration of agonistic antibodies against a co-stimulatory molecule selected from the group consisting of : CD28, OX40, GITR, CD137, CD27 and HVEM.

[00013] In some embodiments, step (c) comprises administering blocking antibodies against negative co-stimulatory molecules. In some embodiments, step (c) comprises administration of blocking antibodies against a negative co-stimulatory molecule selected from the group consisting of: CTLA-1; PD-1, TIM-3, BTLA, VISTA and LAG-3. In some embodiments, step

(c) comprises administration of CTLA-4 blocking antibodies. In some embodiments, step (c) comprises administration of inhibitors of the PD-1 pathway. In some embodiments, the inhibitor of the PD-1 pathway is selected from antibodies against PD-1 and soluble PD-1 ligand. In some embodiments, the inhibitors of the PD-1 pathway are selected from AMP-244, MEDI-4736, MPDL328 OA, and MIH1.

[00014] In some embodiments, the tumor is selected from: glioblastoma, breast carcinoma, lung carcinoma, prostate carcinoma, colon carcinoma, ovarian carcinoma, neuroblastoma, central nervous system tumor, melanoma, and hematologic malignancies.

BRIEF DESCRIPTION OF THE DRAWINGS

[00015] FIG. 1 exemplifies a non-limiting embodiment of a method for combination immunotherapy of cancer, composed of three elements: **S**ensitization of tumor sites; ***In situ*** vaccination or immunization utilizing patient's own tumor cells; **T**-cell induction **[S.I.T.].** In the exemplified embodiment, tumor sensitization is accomplished via irradiation (Step 1) although any other suitable sensitization methodology can be utilized, *in situ* vaccination or immunization is induced by injecting into the tumor healthy stem cells armed with a cytotoxic payload (Step 2), immune checkpoint inhibitors, growth factor inhibitors, etc., can be administered (e.g., simultaneously) as well (Step 2+3), and to induce T-cell activation, the tumor is injected with healthy stem cells containing growth factors which produces a long-lasting anti-tumor and clinical response (Step 3).

[00016] FIG. 2. illustrates non-limiting examples of how one or more embodiments of the present technology can overcome various challenges associated with other approaches to targeting cancer.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[00017] A tumor's escape from immune control (immune evasion) is being increasingly recognized as a vital capability allowing tumor expansion and clinical presentation. Immune evasion mechanisms include antigenic loss, downregulation of MHC molecules, secretion of immune-suppressive cytokines, recruitment of regulatory, tolerogenic and suppressive innate and adaptive immune cells and upregulation of immuno-suppressive receptors, among others. In addition, the paucity of endothelial adhesion molecules in tumor vasculature and abnormal architecture presents significant barriers to T cell infiltration into tumors. Therefore, the tumor microenvironment actively supports tumor growth and prevents tumor rejection.

[00018] Converting the immunosuppressive tumor microenvironment into an immunogenic environment can be a successful immuno-therapeutic strategy against cancer.

[00019] Many of the embodiments described herein are able to overcome one or more of the challenges or limitations typically associated with other approaches to targeting cancer (See Figure 2). For example, sensitization converts a normally immuno-suppressive tumor microenvironment into an immunogenic one. Additionally, an intratumoral injection of armed protective stem cells (payload delivery) prevents the immune system from inactivating the payload. Such a precise transient inactivation of specific host immune components ensures a long-lasting payload presence which is capable of simultaneously killing both tumor cells and cancer stem cells whereas other approaches are limited by inefficient tumor cell lysis and inefficient targeting of cancer stem cells. Finally, checkpoint inhibition and growth factor release leads to an efficient T-cell activation and significant expansion whereas other approaches are hindered by inefficient T-cell induction and limited expansion.

[00020] Accordingly, embodiments of the present invention generally relate to methods for the treatment of human cancer and, more specifically, in some embodiments to the use of multiple treatment modalities in combination to induce effective anti-tumor immune response.

Definitions

[00021] As used herein, a subject includes any animal for which diagnosis, screening, monitoring or treatment is contemplated. Animals include mammals such as primates and domesticated animals. An exemplary primate is human. A patient refers to a subject such as a mammal, primate, human, or livestock subject afflicted with a disease condition or for which a disease condition is to be determined or risk of a disease condition is to be determined.

[00022] As used here, the term "antibody" is used in the broadest sense and specifically covers monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), bi-specific T cell engagers (BiTE) antibodies, and antibody fragments (e.g., single-chain, nanobodies, etc.) so long as they exhibit the desired biological activity.

[00023] As used herein, "virus" refers to any of a large group of entities referred to as viruses. Viruses typically contain a protein coat surrounding an RNA or DNA core of genetic material, but no semipermeable membrane, and are capable of growth and multiplication only in living cells. Viruses for use in the methods provided herein include, but are not limited, to a poxvirus, adenovirus, herpes simplex virus, Newcastle disease virus, vesicular stomatitis virus, mumps virus, influenza virus, measles virus, reovirus, human immunodeficiency virus (HIV), hanta virus, myxoma virus, cytomegalovirus (CMV), lentivirus, and any plant or insect virus.

[00024] As used herein, the term "viral vector" is used according to its art-recognized meaning. It refers to a nucleic acid vector construct that includes at least one element of viral origin and can be packaged into a viral vector particle. The viral vector particles can be used for the purpose of transferring DNA, RNA or other nucleic acids into cells either in vitro or in vivo. Viral vectors include, but are not limited to, retroviral vectors, vaccinia vectors, lentiviral vectors, herpes virus vectors (e.g., HSV), baculoviral vectors, cytomegalovirus (CMV) vectors, papillomavirus vectors, simian virus (SV40) vectors, semliki forest virus vectors, phage vectors, adenoviral vectors, and adeno-associated viral (AAV) vectors.

[00025] As used herein, "hematologic malignancy" refers to tumors of the blood and lymphatic system (e.g. Hodgkin's disease, Non-Hodgkin's lymphoma, Burkitt's lymphoma, AIDS-related lymphomas, malignant immunoproliferative diseases, multiple myeloma and malignant plasma cell neoplasms, lymphoid leukemia, myeloid leukemia, acute or chronic lymphocytic leukemia, monocytic leukemia, other leukemias of specified cell type, leukemia of unspecified cell type, other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissues, for example diffuse large cell lymphoma, T-cell lymphoma or cutaneous T-cell lymphoma).

Combination Immunotherapy

[00026] In one aspect, the invention provides a strategy for combination immunotherapy of cancer, composed of at least three elements: **S**ensitization of tumor sites; ***In situ*** vaccination utilizing patient's own tumor cells; **T**-cell induction (S.I.T. Technology). It should be understood that the elements can be utilized individually, in a two-element combination, and with other treatments and modalities, as well according to some embodiments. In one embodiment, the invention provides methods to sensitize tumor sites in preparation for the subsequent treatment elements. In another embodiment, the invention provides methods for killing tumor cells for *in situ* vaccination. In yet another embodiment, the invention provides methods for designing vehicles for delivery of tumor cell-killing agents ("Trojan Horse" delivery technology). In yet another embodiment, the invention provides methods for induction and expansion of tumor-specific T cells. Such methods can be used together or in any combination. One or more of the described methods can be specifically excluded from some embodiments.

[00027] Growing evidence supports the notion that personalized immunotherapy utilizing multiple antigens and treatment approaches will lead to effective tumor targeting. Importantly, *in situ* vaccinations with patient's own killed tumor cells will provide the entire antigenic diversity of patient's own tumor. This approach, when combined with other immunotherapeutic strategies, will induce broad, long-lasting and potent anti-tumor immune responses that will lead to the eradication of both treated tumors, as well as non-treated distant metastatic tumor deposits.

[00028] The methods disclosed herein can be used to treat any solid tumor or hematologic malignancy. Tumors that can be treated by the methods disclosed herein include, but are not limited to a bladder tumor, breast tumor, prostate tumor, carcinoma, basal cell carcinoma, biliary tract cancer, bladder cancer, bone cancer, brain cancer, CNS cancer, glioma tumor, cervical cancer, choriocarcinoma, colon and rectum cancer, connective tissue cancer, cancer of the digestive system, endometrial cancer, esophageal cancer, eye cancer, cancer of the head and neck, gastric cancer, intra-epithelial neoplasm, kidney cancer, larynx cancer, leukemia, liver cancer, lung cancer, lymphoma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, melanoma, myeloma, neuroblastoma, oral cavity cancer, ovarian cancer, pancreatic cancer, retinoblastoma, rhabdomyosarcoma, rectal cancer, renal cancer, cancer of the respiratory system, sarcoma, skin cancer, stomach cancer, testicular cancer, thyroid cancer, uterine cancer, and cancer of the urinary system, such as lymphosarcoma, osteosarcoma, mammary tumors, mastocytoma, brain tumor, melanoma, adenosquamous carcinoma, carcinoid lung tumor, bronchial gland tumor, bronchiolar adenocarcinoma, small cell lung cancer, non-small cell lung cancers, fibroma, myxochondroma, pulmonary sarcoma, neurosarcoma, osteoma, papilloma, retinoblastoma, Ewing's sarcoma, Wilm's tumor, Burkitt's lymphoma, microglioma, neuroblastoma, osteoclastoma, oral neoplasia, fibrosarcoma, osteosarcoma and rhabdomyosarcoma, genital squamous cell carcinoma, transmissible venereal tumor, testicular tumor, seminoma, Sertoli cell tumor, hemangiopericytoma, histiocytoma, chloroma, granulocytic sarcoma, corneal papilloma, corneal squamous cell carcinoma, hemangiosarcoma, pleural mesothelioma, basal cell tumor, thymoma, stomach tumor, adrenal gland carcinoma, oral papillomatosis, hemangioendothelioma, cystadenoma, follicular lymphoma, intestinal lymphosarcoma, fibrosarcoma, and pulmonary squamous cell carcinoma, leukemia, hemangiopericytoma, ocular neoplasia, preputial fibrosarcoma, ulcerative squamous cell carcinoma, preputial carcinoma, connective tissue neoplasia, mastocytoma, hepatocellular carcinoma, lymphoma, pulmonary adenomatosis, pulmonary sarcoma, Rous sarcoma, reticulo-endotheliosis, fibrosarcoma, nephroblastoma, B-cell lymphoma, lymphoid leukosis, retinoblastoma, hepatic neoplasia, lymphosarcoma, plasmacytoid leukemia, swimbladder sarcoma (in fish), caseous lumphadenitis, lung carcinoma, insulinoma,

lymphoma, sarcoma, neuroma, pancreatic islet cell tumor, gastric MALT lymphoma and gastric adenocarcinoma. In some embodiments, the tumor is selected from: glioblastoma, breast carcinoma, lung carcinoma, prostate carcinoma, colon carcinoma, ovarian carcinoma, neuroblastoma, central nervous system tumor, and melanoma.

Tumor Sensitization

[00029] Disclosed herein in some embodiments, is a method of sensitizing a tumor to subsequent treatment modalities. The sensitization portion of the technology according to some embodiments may be performed using any of the approaches described herein. In some embodiments, a tumor is sensitized by administering to a subject a treatment that will: (i) induce apoptosis in cells within the tumor, (ii) modify the tumor environment, (iii) stimulate tumor-infiltrating immune cells, or (iv) a combination of two or more thereof.

[00030] In some embodiments, the treatment that will induce apoptosis in cells within the tumor is selected from the group consisting of: radiation therapy, chemotherapy, immunotherapy, phototherapy, or a combination thereof.

[00031] In some embodiments, the treatment that will induce apoptosis in cells is immunotherapy. In some embodiments, the immunotherapy is selected from peptide vaccine therapy using tumor antigen peptides; adoptive immunotherapy using lymphocytes such as cytotoxic T cells or natural killer cells; DNA vaccine therapy which involves administration of organisms comprising vectors expressing tumor antigen proteins or tumor antigen peptides ; and dendritic cell vaccine therapy which involves administering dendritic cells displaying tumor antigen peptides.

[00032] In some embodiments, the treatment that will induce apoptosis in cells is phototherapy. In some embodiments, the phototherapy is selected from ultraviolet B radiation (UVB) phototherapy and ultraviolet A photochemotherapy (PUVA). In some embodiments, the phototherapy further comprises the use of psoralen.

[00033] In some embodiments, sensitizing the tumor comprises administering irradiation to the subject. In some embodiments, the irradiation is ionizing radiation. In one embodiment, the sensitization will be achieved with local tumor irradiation, e.g. high-dose hypofractionation radiation therapy (HDHRT).

[00034] Ionizing radiation has a significant potential to modify the tumor microenvironment and facilitate immune-mediated tumor rejection. Specifically, radiation can induce remodeling of the abnormal tumor vessels and up-regulation of vascular cell adhesion molecules (e.g. VCAM-1) and chemokine secretion (e.g. CXCL16), resulting in efficient T-cell infiltration into the tumor. Other important effects of radiation include up-regulation of MHC class-I molecules, NKG2D ligands, and Fas/CD95, thus augmenting T-cell binding to and killing of the cancer cells. However, despite these significant pro-immunogenic effects, radiation by itself is insufficient to induce long-lasting and powerful enough anti-tumor immune responses leading to tumor eradication.

[00035] Radiation therapy includes, but is not limited to, photodynamic therapy, radionuclides, radio immunotherapy and proton beam treatment.

[00036] In some embodiments, the treatment that will induce apoptosis in cells within the tumor comprises administration of a chemotherapeutic compound. Chemotherapeutic compounds include, but are not limited to platinum; platinum analogs (e.g., platinum coordination complexes) such as cisplatin, carboplatin, oxaliplatin, DWA2114R, NK121, IS 3 295, and 254-S; anthracenediones; vinblastine; alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamime nitrogen mustards such as chiorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine,

trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; etoglucid; gallium nitrate; substituted ureas; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; anti-cancer polysaccharides; polysaccharide-K; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; cytosine arabinoside; cyclophosphamide; thiotepa; taxoids, such as paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; XELODA; ibandronate; CPT11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; methylhydrazine derivatives; Erlotinib (TARCEVA); sunitinib malate (SUTENT); and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit

hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone and toremifene (FARESTON); adrenocortical suppressants; and antiandrogens such as flutamide, nilutamide, bicalutamide, leuprolide and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Such chemotherapeutic compounds that can be used herein include compounds whose toxicities preclude use of the compound in general systemic chemotherapeutic methods. In some embodiments, the chemotherapy comprises administration of a chemotherapeutic agent is selected from an alkylating drug, an antimetabolite, an antimytotic cytostatic, a topoisomerase inhibitor, antitumor antibiotic, and any other cytostatic, and/or a radiotherapy. In some embodiments, the chemotherapeutic agent is an alkylating agent. In some embodiments, the alkylating agent is selected from cisplatin, oxaliplatin, cyclop hosphamid, ifosfamid, trofosfamid, melphalan, chlorambucil, estramustin, busulfan, treosulfan, carmustin, lomustin, nimustin, streptozocin, procarbazin, dacarbazin, temozolomid, and thiotepa. In some embodiments, the chemotherapeutic agent is an antimetabolite. In some embodiments, the antimetabolite is selected from 5- fluorouracil, methotrexate, azacitidin, capecitabin, doxifluridin, cytarabin, gemcitabin, 6-thioguanin, pentostatin, azathioprin, 6-mercaptopurin, fludarabin, and cladribin. In some embodiments, the chemotherapeutic agent is a topoisomerase inhibitor. In some embodiments, the topoisomerase inhibitor is selected from doxorubicin, camptothecin, topotecan, irinotecan, etoposide, and teniposide. In some embodiments, the chemotherapeutic agent is an antitumor antibiotic. In some embodiments, the antitumor antibiotic is selected from tamoxifen, 5-fluoro-5'-deoxyuridine, belomycin, actinomycin D, and mitomycin. In some embodiments, the chemotherapeutic agent is a cytostatic. In some embodiments, the cytostatic is L-asparaginase or hydroxycarb amide.

[00037] In some embodiments, the tumor microenvironment is modified by a treatment selected from: local tumor irradiation, cytokine injections, cytokine-blocking agents (e.g.

Ustekinumab, Adalimumab, Infliximab, Etanercept, Golimumab), antibody injections, and injection of stem cells secreting cytokines and/or chemokines.

[00038] In some embodiments, stimulating tumor-infiltrating immune cells in the sensitization phase is accomplished via a treatment selected from: local tumor irradiation, cytokine injections, antibody injections, and injection of stem cells secreting cytokines and/or chemokines.

***In Situ* Vaccination**

[00039] Disclosed herein, in some embodiments, is a method of treating a solid tumor comprising administration of a treatment that will result in *in situ* vaccination of a subject against the tumor by the tumor's own antigens. In some embodiments, the method comprises injecting into the subject: (i) a modified stem cell, wherein the modified stem cell comprises a cytotoxic payload; (ii) a wild-type or genetically modified virus; (iii) a wild-type or genetically modified bacteria; or (iv) a combination of two or more thereof ("Trojan Horse" delivery technology).

[00040] The *in situ* vaccination portion of the invention may be performed using any of the approaches described in the invention, including viruses and specific chemotherapeutic agents used directly, or within adult stem cell delivery vehicles. In some embodiments, the adult stem cells are permanently transformed (e.g. with lenti-virus or retro-virus), or transiently altered with artificial chromosomes, viruses or plasmid DNA, to produce viruses, antibodies, cytokines or other proteins as payloads to kill tumor cells and cancer stem cells.

[00041] The immune system has developed precise sensors to distinguish cell death due to physiological tissue turnover from pathogenic cell death. The innate immune cells have an important class of receptors, the pattern recognition receptors (PRR), dedicated to this function. The PRR bind to pathogen-associated molecular pattern (PAMP) molecules derived from infectious agents and damage-associated molecular pattern (DAMP) molecules derived from cells dying a stressful/immunogenic death.

[00042] The immunogenic cell death (ICD) inducers (e.g. chemotherapeutics and radiation) and viruses induce a similar danger response, leading to anticancer immunity. ICD induced by radiation and specific chemotherapeutic agents results in reactive oxygen species (ROS) production and an endoplasmic reticulum (ER) stress response. Active infection of tumor cells by viruses overwhelms the cellular machinery, resulting in ER stress and tumor cell death. During these sequences of events, tumor cells express calreticulin (CRT) on the cell surface that attracts antigen-presenting cells (APCs). In addition, dying cells release immunomodulatory molecules such as high-mobility group box 1 (HMGB1) and adenosine triphosphate (ATP) into the extracellular tumor microenvironment, leading to potent antigen presentation. APCs that take up tumor-associated antigens migrate to the lymph nodes to present these antigens to naïve T cells for establishment of anticancer immunity. In addition to danger-associated molecular patterns (DAMPs), virus infected tumor cells release pathogen-associated molecular patterns (PAMPs) (foreign viral proteins and viral DNA/RNA) that are potent activators of innate immune cells to secrete cytokines, such as the type I IFN. These cytokines help orchestrate the anticancer adaptive immune response. Therefore, the ICD constitutes a prominent pathway for the activation of the immune system against cancer, which in turn determines the long-term success of all anticancer therapies.

[00043] Development of optimal vehicles for delivery of the ICD inducers to the tumor sites is an essential element of the overall combination immunotherapy strategy. Some ICD inducers, like chemotherapeutic agents and viruses, are subject to significant elimination and/or neutralization following systemic application. Therefore, designing suitable vehicles for their shielding from the elements of the humoral and cellular immunity in the blood stream, as well as methods for their targeted delivery to the tumor sites is of paramount importance. Recent studies have demonstrated extensive homing of stem cells to glioma tumors and the potential of gene loading into stem cells using viral vectors. These studies indicate that the stem cells are a promising candidate as a vehicle for delivery of the ICD inducers to the tumor sites.

[00044] Accordingly, in some embodiments, *in situ* vaccination comprises injecting into the subject a modified stem cell, wherein the modified stem cell comprises a cytotoxic payload ("Trojan Horse" delivery technology). In some embodiments, the modified stem cell carries one or more imaging payloads. In some embodiments, the modified stem cell carries one or more of a virus, an antibody, or a cytokine as the cytotoxic payload. In some embodiments, the modified stem cell expresses a cytokine as the cytotoxic payload. In some embodiments, the cytokine is selected from colony-stimulating factor (CSF), interferon (IFN), interleukin (IL), stem cell factor (SCF), tumour growth factors (TGF), and tumour necrosis factor (TNF). In some embodiments, the cytokine is a CSF. In some embodiments, the CSF is G-CSF, M-CSF, or GM-CSF. In some embodiments, the CSF is selected from ancestim, garnocestim, pegacaristim, leridistim, milodistim, filgrastim, lenograstim, nartograstim, pegfilgrastim, pegnartograstim, ecogramostim, molgramostim, regramostim, sargramostim, cilmostim, lanimostim, mirimostim, daniplestim, muplestim, or derivates thereof. . In some embodiments, the cytokine is an interleukin (IL). In some embodiments, the interleukin is selected from IL-1 to IL-35, and derivates thereof. In some embodiments, the interleukin is IL -2, IL-4, or derivates thereof. In some embodiments, the cytotoxic payload comprises a lytic virus. In some embodiments, the lytic virus is a vaccinia virus. In some embodiments, the cytotoxic payload comprises a chemotherapeutic agent. In some embodiments, step (b) results in *in situ* vaccination of the subject against the tumor.

[00045] In some embodiments, the modified stem cell is an adult stem cell. In some embodiments, the modified stem cell is transformed with a lenti-virus or retrovirus. In some embodiments, the modified stem cell is transiently transfected with an artificial chromosome, virus or plasmid DNA. In some embodiments, the modified stem cell is capable of localizing to the tumor. In some embodiments, the modified stem cell is autologous. In some embodiments, the modified stem cell is allogeneic. In some embodiments, the modified stem cell is selected from the group consisting of adult stem cells, embryonic stem cells, fetal stem cells, mesenchymal stem cells, neural stem cells, totipotent stem cells, pluripotent stem cells, multipotent stem cells, oligopotent stem cells, unipotent stem cells, adipose stromal cells,

endothelial stem cells, and combinations thereof. In some embodiments, the modified cell is derived from adipose-derived Stromal Vascular Fraction (SVF), comprising adult stem cells, monocytes/macrophages, regulatory T cells, endothelial cells, and combinations thereof. In some embodiments, the modified stem cell is injected into the subject in conjunction with adipose-derived SVF. In some embodiments, the modified stem cell is an umbilical cord-derived mesenchymal like cell. In some embodiments, the umbilical cord-derived mesenchymal-like cell is an Immstem™ cell.

[00046] ImmStem are umbilical cord-derived mesenchymal-like cells, which possess pluripotent differentiation capacity and are characterized by unique surface markers and growth factor production. ImmStem possess numerous advantages compared to other stem cell sources, including ease of collection, higher rate of proliferation, very low immunogenicity, and ability to differentiate into tissues representative of all three germ layer components. In comparison to other mesenchymal stem cell (MSC) subtypes, ImmStem has demonstrated upregulated anti-inflammatory and migratory capacity due to a "cytokine priming" step, which is performed prior to administration. ImmStem cells are generated from human umbilical cords, which are obtained from full term women immediately after delivery. To stimulate a stress response, the cells are cultured for 48 hours with interferon gamma.

[00047] Other agents may be used within the practice of the current invention to augment immune modulatory, migratory, or growth factor producing activity of said modified stem cell, which include, a) a TLR agonist; b) intravenous immunoglobulin (IVIG); c) monocyte conditioned media; d) supernatant from neutrophil extracellular trap exposed peripheral blood mononuclear cells; e) co-culture with monocytes; f) co-culture with monocytes that have been pretreated with IVIG; g) co-culture with T cells; h) co-culture with T cells that have been exposed to a T cell stimulus; i) co-culture with NK cells; j) peptidoglycan isolated from gram positive bacteria; k) lipoteichoic acid isolated from gram positive bacteria; l) lipoprotein isolated from gram positive bacteria; m) lipoarabinomannan isolated from mycobacteria, n) zymosan isolated from yeast cell well; o) Polyadenylic-polyuridylic acid; p) poly (IC); q)

lipopolysaccharide; r) monophosphoryl lipid A; s) flagellin; t) Gardiquimod; u) Imiquimod; v) R848; w) oligonucleosides containing CpG motifs; and x) 23S ribosomal RNA.

[00048] In some embodiments, *in situ* vaccination of the subject against a tumor comprises injecting into the subject a wild-type or genetically modified virus.

[00049] In some embodiments, *in situ* vaccination of the subject against a tumor comprises injecting into the subject a wild-type of genetically modified bacteria.

T-Cell Induction

[00050] Disclosed herein, in some embodiments, is the combination of activating the T-cell response within a subject in need thereof in combination with a treatment disclosed herein.

[00051] Cytotoxic T lymphocytes (CTL) are among the most direct and effective elements of the immune system that are capable of generating anti-tumor immune responses. Tumor cells expressing the appropriate tumor-associated antigens can be effectively recognized and destroyed by these immune effector cells, which may result in dramatic clinical responses. Both the adoptive transfer of tumor-reactive CTL and active immunization designed to elicit CTL responses have been reported to lead to significant therapeutic anti-tumor responses in patients with cancer.

[00052] The T-cell induction portion of the invention may be performed using any of the approaches described in the invention, including cytokines and T-cell modulating agents used directly, or within adult stem cell delivery vehicles.

[00053] In some embodiments, induction of the T-cell response within a subject comprises injection of a stem cell in the subject. In some embodiments, the stem cell is an adult stem cell. In some embodiments, the stem cell is capable of excreting growth factors. In some embodiments, the stem cell produces antibodies, or growth factors capable of stimulating T-cell growth and expansion. In some embodiments, the stem cell is transformed with a lenti-virus or

retrovirus. In some embodiments, the stem cell is transiently transfected with an artificial chromosome, virus or plasmid DNA. In some embodiments, the lenti-virus or retrovirus comprise a heterologous nucleic acid encoding a protein involved in T-cell activation.. In some embodiments, the adult stem cells are permanently transformed (e.g. with lenti-virus or retro-virus), or transiently altered with artificial chromosomes, viruses or plasmid DNA, which results in the production of antibodies, growth factors, or other proteins as payloads that stimulate T-cell growth and expansion.

[00054] In some embodiments, the stem cell is injected into site of the tumor. In some embodiments, the stem cell is injected into the tumor.

[00055] Optimal T cell activation requires simultaneous signals through the T cell receptor and costimulatory molecules. The costimulatory molecule CD28, upon interaction with its ligands B7-1 and B7-2, plays a crucial role in initial T cell priming. However, the CD28-mediated T cell expansion is opposed by the B7-1/2 counter receptor, cytotoxic T lymphocyte associated antigen 4 (CTLA-4), which mitigates the proliferation of recently activated T cells. This sequential regulation of CD28 and CTLA-4 expression balances the activating and inhibitory signals and ensures the induction of an effective immune response, while protecting against the development of autoimmunity. Blocking of CTLA-4 with monoclonal antibodies has demonstrated some success in human clinical trials. Additional CD28 and B7 family members have been identified: PD-l (programmed death-1), PD-Ll (programmed death ligand-l or B7-Hl), and PD-L2 (B7-DC). As in the CTLA-4/B7 system, the PD-l interactions with PD-Ll and PD-L2 suppress both central and peripheral immune responses, and therefore, the PD-1 blockade is also being explored in clinical trials. In addition, numerous new agents targeting the inhibitory and activation pathways involved in T-cell modulation such as LAG-3, B7-H3, CD40, OX40, CD137 and others are in active development.

[00056] Accordingly, in some embodiments, T-cell induction comprises administration an agonist of an activating co-stimulatory molecule. In some embodiments, the method comprises administration of agonistic antibodies directed against activating co-stimulatory molecules. In

some embodiments, T-cell induction comprises administration of agonistic antibodies against a co-stimulatory molecule selected from the group consisting of : CD28, OX40, GITR, CD137, CD27 and HVEM.

[00057] In some embodiments, T-cell induction comprises administration of a treatment that antagonizes negative co-stimulatory molecules. In some embodiments, the method comprises administration of blocking antibodies against negative co-stimulatory molecules. In some embodiments, T-cell induction comprises administration of blocking antibodies against a negative co-stimulatory molecule selected from the group consisting of: CTLA-1; PD-1, TIM-3, BTLA, VISTA and LAG-3. In some embodiments, T-cell induction comprises administration of CTLA-4 blocking antibodies. In some embodiments, T-cell induction comprises administration of PD-1 pathway inhibitors. In some embodiments, the inhibitor of the PD-1 pathway is selected from antibodies against PD-1 and soluble PD-1 ligand. In some embodiments, the inhibitors of the PD-1 pathway are selected from AMP-244, MEDI-4736, MPDL328 OA, and MIH1.

[00058] In some embodiments, T-cell induction comprises administration of a treatment that stimulates T-cell expansion. In some embodiments, a treatment that stimulates T-cell expansion comprises administration of cytokines. In some embodiments, a treatment that stimulates T-cell expansion comprises administration of cytokine-expressing stem cells.

Administration of Treatment Modalities

[00059] It is to be understood that the treatment modalities of the invention may be administered in any order. In some embodiments, step (a) is performed before step (b) and step (c). In some embodiments, step (b) is performed after step (c). In some embodiments, step (b) is performed before step (c). In some embodiments, any of the steps are performed concurrently.

[00060] The effective dosage of each of the treatment modalities employed in the combination therapy of the invention may vary depending on the particular treatment, compound or pharmaceutical composition employed, the mode of administration, the condition being treated,

the severity of the condition being treated. Thus, the dosage regimen of the combination of the invention is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the single active ingredients required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of the active ingredients within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the active ingredients' availability to target sites.

[00061] Methods of preparing pharmaceutical compositions comprising the relevant treatments disclosed herein are known in the art and will be apparent from the art, from known standard references, such as Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 18th edition (1990).

[00062] It should be understood that the embodiments described herein are not limited to vaccinations or vaccinating per se, but also relate to generating an immune response or reaction to cancer cells. While the words "vaccine," "vaccination," or other like terms are used for convenience, it should be understood that such embodiments also relate to immune compositions, immunogenic compositions, immune response generation, immunization, etc., where absolute prophylactic immunity is not required or generated. For example, the embodiments referring to vaccination also can relate to generating or to assisting in creating an immunogenic or immune response against a tumor cell or tumor, regardless of whether that response results in absolute eradication or immunization against such tumor cell, tumor or the cancer.

[00063] The disclosures illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising," "including," containing," etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein

have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the disclosure claimed.

[00064] Other embodiments are set forth within the following claims.

WHAT IS CLAIMED IS:

1. Use of (a) modified stem cells, and (b) an agent that comprises a blocking antibody against a negative co-stimulatory molecule or an agonist antibody against a co-stimulatory molecule, in the manufacture of a medicament for combination therapy of a solid tumor or hematologic malignancy in a subject, wherein:

the modified stem cells are adipose stromal stem cells;

the modified stem cells comprise a cytotoxic payload;

the cytotoxic payload comprises a lytic virus that is a vaccinia virus;

the blocking antibody is against a negative co-stimulatory molecule selected from among CTLA-1, CTLA-4, PD-1, PD-L1, TIM-3, BTLA, VISTA and LAG-3; and

the agonist antibody is against a co-stimulatory molecule selected from among CD28, OX40, GITR, CD137, CD27 and HVEM.

2. The use according to claim 1, wherein in (b) the agent comprises a blocking antibody against a negative co-stimulatory molecule.

3. The use according to claim 2, wherein the blocking antibody is against a negative co-stimulatory molecule selected from among CTLA-1, CTLA-4, PD-1, and PD-L1.

4. The use according to any one of claims 1-3, wherein in (b) the agent comprises an inhibitor of the PD-1 pathway selected from among AMP-244, MEDI-4736, MPDL328 OA, and MIH1.

5. The use according to any one of claims 1-3, wherein in (b) the agent comprises an inhibitor of the PD-1 pathway selected from among antibodies against PD-1 and soluble PD-1 ligand.

6. The use according to any one of claims 1-3, wherein in (b) the agent comprises an anti-CTLA-4 antibody, an anti-PD-L1 antibody, or an anti-PD-1 antibody.

7. The use according to claim 1 or claim 2, wherein in (b) the agent comprises a blocking antibody against a negative co-stimulatory molecule selected from among PD-L1 and CTLA-4.

8. The use according to claim 1, wherein in (b) the agent comprises an agonist antibody against a co-stimulatory molecule.

9. The use according to claim 8, wherein the co-stimulatory molecule is selected from among CD28, OX40, GITR, and CD137.

10. The use according to any one of claims 1-9, wherein (a) is for use after (b).

11. The use according to any one of claims 1-9, wherein (a) is for use before (b).

12. The use according to any one of claims 1-11, further comprising a treatment that induces apoptosis in cells within the tumor, wherein the treatment is selected from among radiation therapy, chemotherapy, immunotherapy, phototherapy, and combinations thereof.

13. The use according to claim 12, wherein the treatment that induces apoptosis comprises radiation therapy.

14. The use according to any one of claims 1-13, further comprising a treatment for modification of the tumor microenvironment, wherein the treatment comprises a cytokine-blocking agent selected from among Ustekinumab, Adalimumab, Infliximab, Etanercept, and Golimumab.

15. The use according to any one of claims 1-14, wherein the adipose stromal stem cells are derived from an adipose-derived Stromal Vascular Fraction (SVF).

16. The use according to any one of claims 1-15, wherein in (a):

the modified stem cells are provided in combination with an agent selected from among: a TLR agonist; intravenous immunoglobulin (IVIG); monocyte conditioned media; supernatant from neutrophil extracellular trap-exposed peripheral blood mononuclear cells; peptidoglycan isolated from Gram-positive bacteria; lipoarabinomannan isolated from mycobacteria; zymosan isolated from a yeast cell wall; polyadenylic-polyuridylic acid; poly (IC); lipopolysaccharide;

monophosphoryl lipid A; flagellin; Gardiquimod; Imiquimod; R848; oligonucleosides containing CpG motifs; and 23 S ribosomal RNA; or

the modified stem cells have been co-cultured with: monocytes that have been pretreated with IVIG, T cells, T cells that have been exposed to a T cell stimulus, or natural killer cells.

17. The use according to any one of claims 1-16, wherein the solid tumor or hematologic malignancy is selected from among a bladder tumor, breast tumor, prostate tumor, carcinoma, basal cell carcinoma, biliary tract cancer, bone cancer, brain cancer, CNS cancer, glioma tumor, cervical cancer, choriocarcinoma, colon cancer, connective tissue cancer, cancer of the digestive system, endometrial cancer, esophageal cancer, eye cancer, cancer of the head and neck, gastric cancer, intra-epithelial neoplasm, larynx cancer, leukemia, liver cancer, lung cancer, lymphoma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, melanoma, myeloma, neuroblastoma, oral cavity cancer, ovarian cancer, pancreatic cancer, retinoblastoma, rhabdomyosarcoma, rectal cancer, renal cancer, cancer of the respiratory system, sarcoma, skin cancer, testicular cancer, thyroid cancer, uterine cancer, cancer of the urinary system, lymphosarcoma, osteosarcoma, mammary tumors, mastocytoma, adenosquamous carcinoma, carcinoid lung tumor, bronchial gland tumor, bronchiolar adenocarcinoma, small cell lung cancer, non-small cell lung cancer, fibroma, myxochondroma, pulmonary sarcoma, neurosarcoma, osteoma, papilloma, Ewing's sarcoma, Wilm's tumor, Burkitt's lymphoma, microglioma, osteoclastoma, oral neoplasia, fibrosarcoma, genital squamous cell carcinoma, transmissible venereal tumor, seminoma, Sertoli cell tumor, hemangiopericytoma, histiocytoma, chloroma, granulocytic sarcoma, corneal papilloma, corneal squamous cell carcinoma, hemangiosarcoma, pleural mesothelioma, thymoma, adrenal gland carcinoma, oral papillomatosis, hemangioendothelioma, cystadenoma, follicular lymphoma, intestinal lymphosarcoma, pulmonary squamous cell carcinoma, preputial fibrosarcoma, ulcerative squamous cell carcinoma, preputial carcinoma, hepatocellular carcinoma, pulmonary adenomatosis, Rous sarcoma, reticulo-endotheliosis, nephroblastoma, B-cell lymphoma, lymphoid leukosis, hepatic neoplasia, plasmacytoid leukemia, swimbladder

sarcoma in fish, lung carcinoma, insulinoma, neuroma, pancreatic islet cell tumor, gastric MALT lymphoma and gastric adenocarcinoma.

18. The use according to any one of claims 1-16, wherein the solid tumor is selected from among glioblastoma, breast carcinoma, lung carcinoma, prostate carcinoma, colon carcinoma, ovarian carcinoma, neuroblastoma, central nervous system tumor, and melanoma.

19. The use according to any one of claims 1-18, wherein the modified stem cells are autologous.

20. The use according to any one of claims 1-18, wherein the modified stem cells are allogeneic.