SMALLPOX VACCINE FOR CANCER TREATMENT

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 62/203,835, filed August 11, 2015, U.S. Provisional Application No. 62/216,292, filed September 9, 2015, and U.S. Provisional Application No. 62/317,226, filed April 1, 2016, the entire contents of each of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] 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.

SUMMARY

[0003] Disclosed herein are methods and compositions for treating a solid tumor or hematologic malignancy in a subject. In one aspect, the present invention refers to a combination for use for treating a solid tumor or hematologic malignancy in a subject, wherein the combination comprises a) an adipose-derived stromal vascular fraction (SVF); and b) an oncolytic virus that is a vaccinia virus; the SVF and vaccinia virus are provided as a single composition; and the subject has a solid tumor or a hematologic malignancy. In another aspect, the present invention refers to a combination for use for treating a solid tumor or hematologic malignancy in a subject, wherein the combination comprises a) adipose stromal cells; and b) an oncolytic virus that is a vaccinia virus; the adipose stromal cells and vaccinia virus are provided as a single composition; and the subject has a solid tumor or a hematologic malignancy. In yet another aspect, the present invention refers to the use of a composition for the manufacture of a medicament for treating a solid tumor or hematologic malignancy, wherein the composition comprises a) adipose stromal cells; and b) a smallpox vaccine. In a further aspect, the present invention refers to the use of a composition for the manufacture of a medicament for treating a solid tumor or hematologic malignancy, wherein the composition comprises a) an adipose-derived stromal vascular fraction (SVF); and b) a smallpox vaccine.

[0004] In some examples, disclosed herein is a method for treating a proliferative disease (e.g., solid tumor or hematologic malignancy) in a subject, comprising administering to the subject a smallpox vaccine. In some examples, the smallpox vaccine is a replication competent virus. In some examples, the smallpox vaccine does not comprise heterologous nucleic acid. In some examples, the smallpox vaccine is administered by intratumoral, intravenous, intraperitoneal, intrathecal, intraventricular, intraarticular, or intraocular injection. In some examples, the smallpox vaccine is an attenuated New York City Board of Health (NYCBOH) strain of vaccinia virus. In some examples, the NYCBOH strain of vaccinia virus may be ATCC VR- 118 or CJ-MVB-SPX. In some examples, the smallpox vaccine is selected from Dryvax, ACAM1000, ACAM2000, Lister, EM63, LIVP, Tian Tan, Copenhagen, Western Reserve, or Modified Vaccinia Ankara (MVA). In some examples, the solid tumor is selected from: glioblastoma, breast carcinoma, lung carcinoma, prostate carcinoma, colon carcinoma, ovarian carcinoma, neuroblastoma, central nervous system tumor, or melanoma. In some examples, the subject is human. In some examples, the subject is a pediatric patient. In some examples, the proliferative disease is a childhood or pediatric tumor or cancer.

[0005] In some examples, disclosed herein is a method for treating a solid tumor or hematologic malignancy in a subject, comprising administering to the subject a smallpox vaccine concurrently with a stem cell. In some examples, the stem cell is an autologous stem cell. In some examples, the stem cell is selected from 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, induced pluripotent stem cells, bone marrow stem cells, cord blood stem cells, adult peripheral blood stem cells, myoblast stem cells, small juvenile stem cells, skin fibroblast stem cells, and combinations thereof. In some examples, the stem cell is an adipose stromal cell.

[0006] In some examples, the stem cell is a modified stem cell. In some embodiments, the modified stem cell is an adult stem cell. In some examples, the modified stem cell is transformed with a lenti-virus or retrovirus. In some examples, the modified stem cell is transiently transfected with an artificial chromosome, virus or plasmid DNA. In some examples, the stem cell is autologous. In some examples, the smallpox vaccine does not comprise heterologous nucleic acid. In some examples, the smallpox vaccine is administered by intratumoral, intravenous, intraperitoneal, intrathecal, intraventricular, intraarticular, or intraocular injection. In some examples, the smallpox vaccine is an attenuated New York City Board of Health

(NYCBOH) strain of vaccinia virus. In some examples, the NYCBOH strain of vaccinia virus may be ATCC VR- 118 or CJ-MVB-SPX. In some examples, the smallpox vaccine is selected from Dryvax, ACAM1000, ACAM2000, Lister, EM63, LIVP, Tian Tan, Copenhagen, Western Reserve, or Modified Vaccinia Ankara (MVA). In some examples, the solid tumor is glioblastoma, breast carcinoma, lung carcinoma, prostate carcinoma, colon carcinoma, ovarian carcinoma, neuroblastoma, central nervous system tumor, or melanoma. In some examples, the stem cell and the smallpox vaccine are simultaneously administered to the subject by intratumoral, intravenous, intraperitoneal, intrathecal, intraventricular, intraarticular, or intraocular injection. In some examples, the stem cell and the smallpox vaccine are housed in the same vessel prior to injection into the subject. In some examples, the method further comprises concurrently administering a genetically engineered virus to the subject. In some examples, the subject is human. In some examples, the subject is a pediatric patient. In some examples, the proliferative disease is a childhood or pediatric tumor or cancer.

[0007] In some examples, disclosed herein is a method of treating a proliferative disease in a subject, comprising administering to the subject a smallpox vaccine concurrently with an adipose-derived stromal vascular fraction (SVF). In some examples, the adipose-derived SVF is autologous. In some examples, the adipose-derived SVF is administered to the subject within 24 hours of adipose tissue being taken from the subject. In some examples, the smallpox vaccine is administered by intratumoral, intravenous, intraperitoneal, intrathecal, intraventricular, intraarticular, or intraocular injection. In some examples, the adipose-derived SVF is removed from the subject via the Time Machine^{TM} device. In some examples, the adipose-derived SVF is removed using from the subject with a 2.5 to 3 mM cannula. In some examples, the smallpox vaccine is an attenuated New York City Board of Health (NYCBOH) strain of vaccinia virus. In some examples, the NYCBOH strain of vaccinia virus may be ATCC VR- 118 or CJ-MVB-SPX. In some examples, the smallpox vaccine is selected from Dryvax, ACAM1000, ACAM2000, Lister, EM63, LIVP, Tian Tan, Copenhagen, Western Reserve, or Modified Vaccinia Ankara (MVA). In some examples, the solid tumor is glioblastoma, breast carcinoma, lung carcinoma, prostate carcinoma, colon carcinoma, ovarian carcinoma, neuroblastoma, central nervous system tumor, or melanoma. In some examples, the subject is human. In some examples, the subject is a pediatric patient. In some examples, the proliferative disease is a childhood or pediatric tumor or cancer.

[0008] Disclosed herein, in some examples, is a method of treating a proliferative disease, e.g., solid tumor or a hematological malignancy, in a subject, comprising administering to the subject

a smallpox vaccine concurrently with a carrier cell. In some examples, the carrier cell is an autologous cell from the subject. In some examples, the carrier cell is an immune cell selected from a granulocyte, a mast cell, a monocyte, a dendritic cell, a natural killer cell, and a lymphocyte. In some examples, the immune cell is a lymphocyte. In some examples, the lymphocyte is a T cell. In some examples, the carrier cell comprises heterologous nucleic acid. In some examples, the smallpox vaccine and the carrier cell are cultured together in vitro prior to administration to the subject. In some examples, smallpox vaccine and the carrier cell are housed in the same vessel prior to administration into the subject. In some examples, the subject is human. In some examples, the subject is a pediatric patient. In some examples, the proliferative disease is a childhood or pediatric tumor or cancer.

[0009] Disclosed herein, in some examples, is a composition comprising: (a) smallpox vaccine and (b) a stem cell. In some examples, the composition further includes a pharmaceutically acceptable carrier. In some examples, the stem cell is selected from 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, induced pluripotent stem cells, bone marrow stem cells, cord blood stem cells, adult peripheral blood stem cells, myoblast stem cells, small juvenile stem cells, skin fibroblast stem cells, and combinations thereof. In some examples, the stem cell is an adipose stromal cell. In some examples, the stem cell is a modified stem cell. In some examples, the modified stem cell is an adult stem cell. In some examples, the modified stem cell is transformed with a lenti-virus or retrovirus. In some examples, the modified stem cell is transiently transfected with an artificial chromosome, virus or plasmid DNA. In some examples, the smallpox vaccine does not comprise heterologous nucleic acid. In some examples, the composition further comprises a genetically engineered virus.

[00010] Disclosed herein, in some examples, is a composition comprising: (a) smallpox vaccine; and (b) an immune cell, such as a granulocyte, a mast cell, a monocyte, a dendritic cell, a natural killer cell, or a lymphocyte. In some examples, the composition further includes a pharmaceutically acceptable carrier. In some examples, the immune cell is a lymphocyte. In some embodiments, the lymphocyte is a T cell. In some examples, the immune cell comprises heterologous nucleic acid.

[00011] Disclosed herein, in some examples, is a composition comprising: (a) smallpox vaccine; and (b) isolated adipose stromal vascular fraction (SVF).

[00012] Further disclosed herein, in some examples, is a host cell, or a tumor cell, or a mammalian organism comprising a composition of any of the compositions including smallpox vaccine and a stem cell; or including smallpox vaccine and an immune cell selected from a granulocyte, a mast cell, a monocyte, a dendritic cell, a natural killer cell, and a lymphocyte; or including smallpox vaccine and an isolated adipose stromal vascular fraction (SVF).

BRIEF DESCRIPTION OF THE FIGURES

[00013] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of necessary fee.

[00014] FIGS. 1A and 1B show the oncolysis effect on a panel of human tumor cell lines after infection with Lister and ACAM2000 virus strains, respectively.

CLAIMS:

1. A combination for use for treating a solid tumor or hematologic malignancy in a subject, wherein:

the combination comprises:

a) an adipose-derived stromal vascular fraction (SVF); and

b) an oncolytic virus that is a vaccinia virus;

the SVF and vaccinia virus are provided as a single composition; and

the subject has a solid tumor or a hematologic malignancy.

2. A combination for use for treating a solid tumor or hematologic malignancy in a subject, wherein:

the combination comprises:

a) adipose stromal cells; and

b) an oncolytic virus that is a vaccinia virus;

the adipose stromal cells and vaccinia virus are provided as a single composition; and

the subject has a solid tumor or a hematologic malignancy.

3. The combination of claim 1 or claim 2, wherein the vaccinia virus is a smallpox vaccine.

4. The combination of any of claims 1-3, wherein the SVF or adipose stromal cells are allogeneic to the subject.

5. The combination of any of claims 1-3, wherein the SVF or adipose stromal cells are autologous to the subject.

6. The combination of any of claims 3-5, wherein the smallpox vaccine is an attenuated New York City Board of Health (NYCBOH) strain of vaccinia virus.

7. The combination of claim 6, wherein the NYCBOH strain of vaccinia virus has all of the identifying characteristics of the strain deposited as ATCC VR-118 or CJ-MVB-SPX.

8. The combination of any of claims 3-5, wherein the smallpox vaccine is selected from among Dryvax, ACAM1000, ACAM2000, Lister, EM63, LIVP, Tian Tan, Copenhagen, Western Reserve, Modified Vaccinia Ankara (MVA), New York City Board of

Health, Dairen, Ikeda, LC16M8, Tashkent, Wyeth, IHD-J, IHD-W, Brighton, Dairen I, and Connaught strains.

9. The combination of any of claims 3-5, wherein the smallpox vaccine is Dryvax, ACAM2000 or ACAM1000.

10. The combination of any of claims 3-5, wherein the smallpox vaccine is ACAM2000.

11. The combination of any of claims 1-10, wherein the subject is a human.

12. The combination of any of claims 1-11, wherein the vaccinia virus and the SVF or adipose stromal cells are cultured together *in vitro* prior to use.

13. The combination of claim 12, wherein:

the vaccinia virus is a smallpox vaccine; and

the smallpox vaccine and the SVF or adipose stromal cells are cultured together for 2 to 4 hours.

14. The combination of any of claims 1-13, for use for treating a solid tumor.

15. The combination of any of claims 1-13, wherein the solid tumor or hematologic malignancy is selected from among a bladder tumor, a breast tumor, a prostate tumor, basal cell carcinoma, biliary tract cancer, bone 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, a brain tumor, 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, osteosarcoma, 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, basal cell tumor, thymoma, adrenal gland carcinoma, oral papillomatosis, hemangioendothelioma, cystadenoma, follicular lymphoma, intestinal lymphosarcoma, pulmonary squamous cell carcinoma, ocular neoplasia, preputial fibrosarcoma, ulcerative squamous cell carcinoma, preputial carcinoma, connective tissue neoplasia, hepatocellular carcinoma, pulmonary adenomatosis, pulmonary sarcoma, Rous sarcoma, reticulo-endotheliosis, nephroblastoma, B-cell lymphoma, lymphoid leukosis, hepatic neoplasia, plasmacytoid leukemia, caseous lumphadenitis, lung carcinoma, insulinoma, salivary gland tumors, neuroma, pancreatic islet cell tumor, gastric MALT lymphoma and gastric adenocarcinoma.

16. The combination of any of claims 1-13, wherein the solid tumor is selected from among glioblastoma, breast carcinoma, lung carcinoma, prostate carcinoma, colon carcinoma, pancreatic adenocarcinoma, ovarian carcinoma, neuroblastoma, central nervous system tumor, lung small cell carcinoma, lung non-small cell carcinoma, head and neck squamous cell carcinoma, and melanoma.

17. Use of a composition for the manufacture of a medicament for treating a solid tumor or hematologic malignancy, wherein the composition comprises:

a) adipose stromal cells; and

b) a smallpox vaccine.

18. Use of a composition for the manufacture of a medicament for treating a solid tumor or hematologic malignancy, wherein the composition comprises:

a) an adipose-derived stromal vascular fraction (SVF); and

b) a smallpox vaccine.

19. The use of claim 17 or claim 18, wherein the smallpox vaccine is selected from among Dryvax, ACAM1000, ACAM2000, Lister, EM63, LIVP, Tian Tan, Copenhagen, Western Reserve, Modified Vaccinia Ankara (MVA), New York City Board of Health, Dairen, Ikeda, LC16M8, Tashkent, Wyeth, IHD-J, IHD-W, Brighton, Dairen I, and Connaught strains.