ONCOLYTIC VIRUS COMPRISING IMMUNOMODULATORY TRANSGENES AND USES THEREOF

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/913,658, filed October 10, 2019, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] This disclosure relates to myxoma viruses and their uses for treatment of cancers, for example, treatment of hematological cancers with a myxoma virus that expresses one or more immunomodulatory transgenes.

BACKGROUND

[0003] Current treatments used to treat various types of cancer tend to work by poisoning or killing the cancerous cell. Unfortunately, treatments that are toxic to cancer cells typically tend to be toxic to healthy cells as well. Moreover, effective treatments for cancer remain elusive. Current mainstream therapies such as chemotherapy and radiotherapy can have a narrow therapeutic window (e.g., a concentration high enough to achieve efficacy but low enough to avoid toxicity). These types of therapies are considered blunt tools that have limited applicability due to the varying types of tumor cells and the limited window in which these treatments can be administered.

SUMMARY

[0004] Disclosed herein, in some aspects is an engineered myxoma virus (MYXV) comprising a transgene encoding one or more immunomodulatory proteins.

[0005] In some ~~embodiment~~examples, the one or more immunomodulatory proteins is Stimulator of interferon genes (STING), interleukin-12 (IL-12), Fusion-associated small transmembrane (FAST), an immune checkpoint inhibitor, a tumor necrosis factor (TNF) protein, or a combination thereof. In some ~~embodiment~~examples, the IL-12 is an IL-12A. In some ~~embodiment~~examples, the IL-12 is an IL-12B. In some ~~embodiment~~examples, the immune checkpoint inhibitor is a PD-L1 binding molecule. In some ~~embodiment~~examples, the PD-L1 binding molecule is an anti-PD-L1 antibody or an antigen-binding fragment thereof. In some ~~embodiment~~examples, the one or more immunomodulatory proteins is capable of stimulating a toll like receptor (TLR), activating Nuclear factor-κB (NF-κB), or activating an interferon regulatory factor (IRF). In some ~~embodiment~~examples, the engineered

MYXV comprises a modification at or adjacent to one or more genes selected from the group consisting of M001R, M002R, M003.1R, M003.2R, M004.1R, M004R, M005R, M006R, M007R, M008.1R, M008R, M009L, M013, M036L, M063L, M11L, M128L, M131R, M135R, M136R, M141R, M148R, M151R, M152R, M153R, M154L, M156R, M-T2, M-T4, M-T5, M-T7, and SOD. In some ~~embodiment~~examples, the engineered MYXV comprises a modification at or adjacent to M011L, M063, M135R, M136R, M-T2, M-T4, M-T5, M-T7 or SOD. In some ~~embodiment~~examples, the modification comprises a deletion or an insertion. In some ~~embodiment~~examples, the transgene replaces a portion of M011L, M063, M135R, M136R, M-T2, M-T4, M-T5, M-T7, or SOD. In some ~~embodiment~~examples, the transgene is located between the M135R and M136R genes of the genome of the MYXV. In some ~~embodiment~~examples, the transgene replaces a portion of M135R. In some ~~embodiment~~examples, the engineered MYXV is an M135R knockout. In some ~~embodiment~~examples, the engineered MYXV is a SOD knockout. In some ~~embodiment~~examples, the engineered MYXV further comprises a reporter gene. In some ~~embodiment~~examples, the reporter gene encodes a fluorescent protein, a luminescent substrate or an enzyme. In some ~~embodiment~~examples, the engineered MYXV increases autophagy in infected cells by at least 5% compared to a MYXV that lacks the transgene as determined by an LC3-I to LC3-II conversion assay. In some ~~embodiment~~examples, the engineered MYXV increases killing of infected cancer cells by at least 5% compared to a MYXV that lacks the transgene as determined by an in vitro flow cytometric assay. In some ~~embodiment~~examples, the engineered MYXV increases killing of uninfected cancer cells by at least 5% compared to a MYXV that lacks the transgene as determined by an in vitro flow cytometric assay. In some ~~embodiment~~examples, the engineered MYXV is present in a pharmaceutical composition that comprises the engineered MYXV and a pharmaceutically-acceptable excipient. In some ~~embodiment~~examples, the pharmaceutical composition is formulated for systemic administration. In some ~~embodiment~~examples, the pharmaceutical composition is formulated for local administration. In some ~~embodiment~~examples, the pharmaceutical composition is formulated for parenteral administration. In some ~~embodiment~~examples, a plurality of cells is exposed ex vivo to the engineered MYXV, wherein the plurality of cells comprises a peripheral blood mononuclear cell (PBMC), a bone marrow (BM) cell, or a combination thereof. In some ~~embodiment~~examples, the plurality of cells is derived from a single subject. In some ~~embodiment~~examples, the engineered MYXV, the pharmaceutical composition, or the plurality of cells is administered to a subject in need thereof in a method of treating cancer. In some ~~embodiment~~examples, the engineered MYXV is adsorbed ex vivo onto the surface of at least a portion of the plurality of cells. In some ~~embodiment~~examples, the engineered MYXV is adsorbed by exposing the plurality of cells to the engineered MYXV under a condition that permits binding of the engineered MYXV to a surface of the plurality of cells. In some ~~embodiment~~examples, the engineered MYXV is infected to at least a portion of the plurality of cells. In

some ~~embodiment~~examples, the cancer is a solid tumor. In some ~~embodiment~~examples, the cancer has metastasized to a second location in the subject. In some ~~embodiment~~examples, the second location comprises a lung, a brain, a liver and/or a lymph node of the subject. In some ~~embodiment~~examples, the cancer comprises osteosarcoma, triple negative breast cancer, or melanoma. In some ~~embodiment~~examples, an additional therapeutic agent is administered to the subject. In some ~~embodiment~~examples, the additional therapeutic agent is administered to the subject prior to administering the composition. In some ~~embodiment~~examples, the additional therapeutic agent is administered to the subject after administering the composition. In some ~~embodiment~~examples, the additional therapeutic agent is co-administered to the subject with the composition. In some ~~embodiment~~examples, the subject is a human. In some ~~embodiment~~examples, the subject has or is suspected of having a cancer. In some ~~embodiment~~examples, the engineered MYXV is capable of infecting cells that have a deficient innate anti-viral response. In some ~~embodiment~~examples, the cells that have a deficient innate anti-viral response comprise cancer cells. In some ~~embodiment~~examples, the plurality of cells is obtained or derived from the subject's tissue. In some ~~embodiment~~examples, the plurality of cells are from a donor that is allogeneic to the subject. In some ~~embodiment~~examples, the plurality of cells is obtained or derived from a donor's tissue that is HLA-matched, HLA-mismatched, haploidentical, or a combination thereof relative to the subject. In some ~~embodiment~~examples, the engineered MYXV, the pharmaceutical composition, or the composition is part of a kit.

[0006] Some ~~embodiment~~examples relate to a myxoma virus (MYXV) engineered to express one or more immunomodulatory proteins.

[0007] Some ~~embodiment~~examples relate to a myxoma virus (MYXV) engineered to express one or more immunomodulatory proteins capable of stimulating the toll like receptors (TLR) or activating Nuclear factor-κB (NF-κB) or (interferon regulatory factor) IRF.

[0008] Some ~~embodiment~~examples relate to a pharmaceutical composition comprising a myxoma virus described herein and a pharmaceutically acceptable excipient.

[0009] Some ~~embodiment~~examples relate to a composition comprising peripheral blood mononuclear cells (PBMCs), bone marrow (BM) cells, or a combination thereof treated ex vivo by a myxoma virus (MYXV) engineered to express an immunomodulatory protein.

[0010] Some ~~embodiment~~examples relate to a method of inhibiting or treating a cancer in a subject in need thereof, comprising administering to the subject a myxoma virus (MYXV) engineered to express an immunomodulatory protein.

[0011] Some ~~embodiment~~examples relate to a method of inhibiting or treating a cancer in a subject in need thereof, comprising administering to the subject a composition described herein.

[0012] Some ~~embodiment~~examples relate to a kit comprising a myxoma virus or a pharmaceutical composition described herein.