ONCOLYTIC VIRUSES FOR MODIFIED MHC EXPRESSION

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/182,243 filed April 30, 2021, which is incorporated by reference herein in its entirety.

BACKGROUND

[0002] Cancer is the second leading cause of death in the United States. Challenges for commercially available therapies exists around selective targeting of cancer cells, localized gene expression, and reaching and modifying the tumor microenvironment (TME). Thus, there remains a need for improved compositions and methods of use to address these challenges.

BRIEF SUMMARY

[0002a] In one aspect, provided herein is a composition, wherein the composition comprises: an oncolytic virus, wherein the oncolytic virus comprises a genome modification; wherein the genome modification comprises an exogenous nucleic acid encoding for an MHC I inhibitor, wherein the MHC I inhibitor comprises vIRF3.

[0002b] In another aspect, provided herein is a pharmaceutical composition comprising the composition as described herein and a pharmaceutically acceptable excipient.

[0003] Provided herein are compositions, wherein the composition comprises: an oncolytic virus, wherein the oncolytic virus comprises a genome modification, wherein the genome modification comprises an exogenous nucleic acid encoding for an MHC I inhibitor. Further provided herein are compositions, wherein the genome modification further comprises: a deletion or functional deletion of an endogenous nucleic acid encoding an MHC II inhibitor; or an exogenous nucleic acid that results in activation or enhanced activation of MHC II presentation. Further provided herein are compositions, wherein the genome modification further comprises: a deletion or functional deletion of an endogenous nucleic acid encoding an MHC II inhibitor; and an exogenous nucleic acid that results in activation or enhanced activation of MHC II presentation. Further provided herein are compositions, wherein the deletion or functional deletion of the endogenous nucleic acid encoding the MHC II inhibitor comprises a deletion or functional deletion of a vaccinia virus gene encoding protein A35. Further provided herein are compositions, wherein the deletion or functional deletion of the vaccinia virus gene encoding protein A35 is a deletion or functional deletion of gene WR158. Further provided herein are compositions, wherein the exogenous nucleic acid that results in activation or enhanced activation of the MHC II presentation encodes for a protein selected from: an apoptosis inhibitor protein; a necrotic cell death activator

protein; an autophagy enhancer protein; an asparaginyl endopeptidase; a class II transactivator; an interferon-gamma; a Toll-like receptor activator; or a dendritic cell maturation activator. Further provided herein are compositions, wherein the exogenous nucleic acid encodes for the autophagy enhancer protein, and wherein the autophagy enhancer protein is HMGB1 or a functional domain or a variant thereof. Further provided herein are compositions, wherein the exogenous nucleic acid encodes for the dendritic cell maturation activator, wherein the dendritic cell maturation activator comprises osteopontin, TNF-alpha, or a functional fragment or variant thereof. Further provided

PFU/mL, about 6 x 10^{11} PFU/mL, about 7 x 10^{11} PFU/mL, about 8 x 10^{11} PFU/mL, about 9 x 10^{11} PFU/mL, or about 10^{12} PFU/mL, about 10^{12} PFU/mL to about 10^{13} PFU/mL, about 10^{13} PFU/mL to about 10^{14} PFU/mL, or about 10^{14} PFU/mL to about 10^{15} PFU/mL. In some embodiments, a recombinant vaccinia virus of this disclosure can be administered at a dose that can comprise 5 x 10^{9} PFU/mL. In some embodiments, a recombinant vaccinia virus of this disclosure can be administered at a dose that can comprise up to 5 x 10^{9} PFU/mL.

[0067] In some instances, where the recombinant vaccinia virus can be administered by an injection, the dosage can comprise about 10^{3} viral particles per injection, 10^{4} viral particles per injection, 10^{5} viral particles per injection, 10^{6} viral particles per injection, 10^{7} viral particles per injection, 10^{8} viral particles per injection, 10^{9} viral particles per injection, 10^{10} viral particles per injection, 10^{11} viral particles per injection, 10^{12} viral particles per injection, 2 x 10^{12} viral particles per injection, 10^{13} viral particles per injection, 10^{14} viral particles per injection, or 10^{15} viral particles per injection. In further instances, where the recombinant vaccinia virus is administered by an injection, the dosage can comprise about 10^{3} infectious viral particles per injection, 10^{4} infectious viral particles per injection, 10^{5} infectious viral particles per injection, 10^{6} infectious viral particles per injection, 10^{7} infectious viral particles per injection, 10^{8} infectious viral particles per injection, 10^{9} infectious viral particles per injection, 10^{10} infectious viral particles per injection, 10^{11} infectious viral particles per injection, 10^{12} infectious viral particles per injection, 2 x 10^{12} infectious viral particles per injection, 10^{13} infectious viral particles per injection, 10^{14} infectious viral particles per injection, or 10^{15} infectious viral particles per injection. Note that herein 10^{x} is alternatively expressed as 1 eX. In certain embodiments, the recombinant vaccinia virus can be administered in one or more doses. In certain embodiments, the virus can be administered in an amount sufficient to induce oncolysis in at least about 20% of cells in a tumor, in at least about 30% of cells in a tumor, in at least about 40% of cells in a tumor, in at least about 50% of cells in a tumor, in at least about 60% of cells in a tumor, in at least about 70% of cells in a tumor, in at least about 80% of cells in a tumor, or in at least about 90% of cells in a tumor.

[0068] In certain embodiments, a single dose of recombinant virus can refer to the amount administered to a subject or a tumor over a 1, 2, 5, 10, 15, 20, or 24-hour period. In certain embodiments, the dose can be spread over time or by separate injection. In certain

recombinant oncolytic viruses wherein the modification in the viral genome reduces an immune response targeting a virus-infected tumor cell and increases an immune response targeting cells surrounding the virus-infected tumor cell. Further provided herein are recombinant oncolytic viruses wherein a thymidine kinase gene is deleted from the viral genome. Further provided herein are recombinant oncolytic viruses further comprising an exogenous nucleic acid encoding a hyaluronidase. Further provided herein are recombinant oncolytic viruses wherein the hyaluronidase is PH-20 or HysA. Further provided herein are recombinant oncolytic viruses wherein the oncolytic virus is a vaccinia virus, and the vaccinia virus is a Western Reserve strain Vaccinia virus (ATCC VR-1354), a Copenhagen strain, an IHD strain, a Wyeth strain (ATCC VR-325), a NYCBOH strain, a Tian Tan strain, a Lister strain, an Ankara strain (ATCC VR-1508 or ATTC VR1566), a USSR strain, or an ACAM2000 strain.

[0084] Provided herein are recombinant oncolytic viruses comprising a modification in the viral genome wherein the modification comprises a deletion or functional deletion of a vaccinia virus gene encoding A35 protein and insertion of an exogenous gene encoding cowpox protein CPXV012 or cowpox protein CPXV203. Further provided herein are recombinant oncolytic viruses_wherein the modification is such that insertion of the exogenous gene encoding cowpox protein CPXV012 is at the locus of the gene encoding A35 protein of a vaccinia virus. Further provided herein are recombinant oncolytic viruses wherein the modification is such that insertion of the exogenous gene encoding cowpox protein CPXV203 is at the locus of the gene encoding A35 protein of a vaccinia virus. Further provided herein are recombinant oncolytic viruses further comprising an additional modification in the viral genome. Further provided herein are recombinant oncolytic viruses wherein the additional modification comprises at least one of: an insertion of an exogenous nucleic acid that codes for a chemokine receptor or a functional domain or a variant thereof; or an insertion of an exogenous nucleic acid that codes for cytokine or a functional domain or a variant thereof. Further provided herein are recombinant oncolytic viruses comprising the exogenous nucleic acid that codes for a cytokine or a functional domain or a variant thereof, wherein the cytokine comprises at least one of: interleukin-2 (IL-2), interleukin-15/ interleukin-15Ra (IL15/IL15Ra), interleukin-7 (IL-7), or a functional domain or a variant thereof. Further provided herein are recombinant oncolytic viruses wherein the additional modification comprises an insertion of an exogenous nucleic acid that codes for a fusion protein comprising a cytokine and a metabolic modulator protein. Further provided herein are recombinant oncolytic viruses comprising the exogenous nucleic acid that codes for the chemokine receptor or a functional domain or a variant thereof, wherein the chemokine receptor comprises at least one of: CXCR4, CCR2, or functional domains or variants thereof. Further provided herein are recombinant oncolytic viruses wherein the chemokine receptor comprises the CXCR4 or a functional domain or a variant thereof. Further provided herein are recombinant