genes into the viral genome[6-9], such as T-VEC, a herpes simplex virus type 1 based OV recently approved for treatment of melanoma by the US Food and Drug Administration (FDA) [10-12]. Combinations of OVs and other forms of immunotherapy have now emerged as a promising approach in human patients [5-7].

Fumaric acid esters (FAE), such as dimethylfumarate (DMF), are ester derivatives of fumaric acid [13]. Fumaric acid is an intermediate in the citric acid cycle, which is a basic cellular process that generates energy in the mitochondria. Fumaric acid esters (FAE) are a class of compounds with known anti-inflammatory and neuroprotective effects [14, 15, 17]. The mechanisms involved have yet to be fully elucidated, but is thought to be mediated through the activation of the antioxidative transcription factor nuclear factor (erythroid-derived 2)-like 2 (NRF2) pathway [15], the inhibition of NF-κB [16] as well as functional depletion of glutathione (GSH) [18-19].

[0010] FAEs (marketed as Fumaderm®, Psorinovo®) were first approved as a treatment for psoriasis in Germany. Recently, dimethyl fumarate (DMF), an FAE marketed as Tecfidera®, was approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of relapsing forms of multiple sclerosis and relapsing-remitting multiple sclerosis [20]. Clinical studies on the long-term use of DMF have not revealed any severe long-term adverse effects [20-22]. Recent reports suggest that DMF has anticancer potential, shown to suppress tumor growth and metastasis [23-28]in addition to sensitizing tumors to chemotherapy [26, 29]. Furthermore, DMF is currently under clinical evaluation for the treatment of Chronic Lymphocytic Leukemia and Cutaneous T Cell Lymphoma (e.g. NCT02546440, NCT02784834).

[0011] There is a need in the art to identify compounds and compositions that enhance virus growth and spread. There is also a need in the art to identify compounds and compositions that enhance virotherapy anti-cancer efficacy. Further, there is a need in the art to identify novel methods for treating cancer cells *in vitro* and/or *in vivo*.

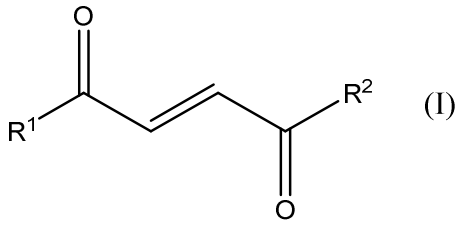
[0012] SUMMARY ~~OF THE INVENTION~~

[0013] The present ~~invention~~disclosure relates to compositions and methods that enhance interferon-sensitive virus production, infection, growth, and/or spread, and/or potentiate the oncolytic and/or immunotherapeutic activity of oncolytic viruses.

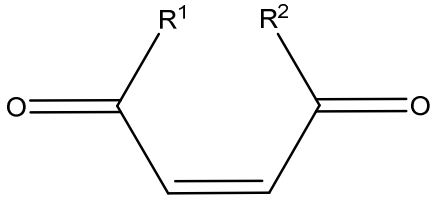
[0014] Results described herein observed one or more previously unreported effects of Fumaric and Maleic Acid Esters (FMAEs): an ability to enhance the production, infection, growth and/or spread of replicating and non-replicating interferon-sensitive viruses; and to increase the therapeutic efficacy of oncolytic viruses, for example in otherwise resistant cancers, which may involve inhibiting the innate antiviral response of cancer cells.

[0014a] In one aspect, the present disclosure refers to a composition for enhancing production, infection, growth, spread, or titer of an interferon-sensitive virus in an immortalized cell, a cancer cell or a tumor cell, the composition comprising:

a compound of formula (I) or (II)



(I)



(II)

wherein R^1 and R^2 are each independently OH or (C_{1-10})alkoxy ;

wherein when one of R^1 and R^2 is OH, the other of R^1 and R^2 is not OH,

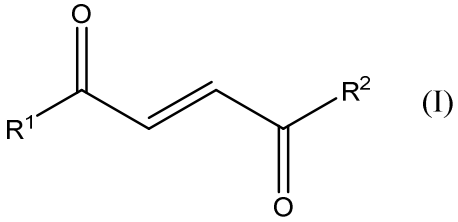
or a pharmaceutically acceptable salt thereof;

wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or an engineered variant thereof.

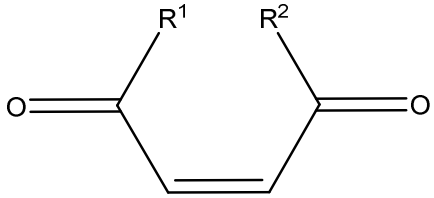
[0014b] In another aspect, the present disclosure refers to a pharmaceutical composition for

treating a tumor or cancer in a subject in need thereof, the composition comprising:

a compound of formula (I) or (II)



(I)



(II)

wherein R^1 and R^2 are each independently OH or (C_{1-10})alkoxy;

wherein when one of R^1 and R^2 is OH, the other of R^1 and R^2 is not OH,

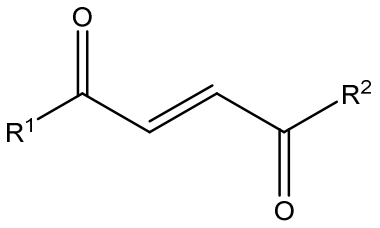
or a pharmaceutically acceptable salt thereof,

for administration before, after, or concurrently with administration of an interferon-sensitive virus to the subject;

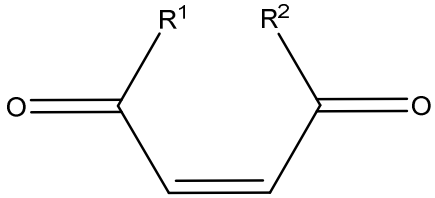
wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or an engineered variant thereof.

[0014c] In another aspect, the present disclosure refers to use of a pharmaceutical composition in the manufacture of a medicament for treating a tumor or cancer in a subject in need thereof, the composition comprising:

a compound of formula (I) or (II)



(I)



(II)

wherein R^1 and R^2 are each independently OH or (C_{1-10})alkoxy;

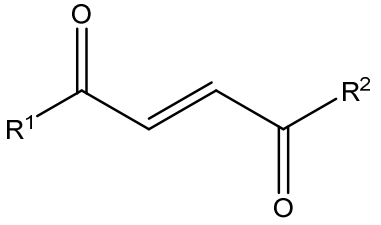
wherein when one of R^1 and R^2 is OH, the other of R^1 and R^2 is not OH,

or a pharmaceutically acceptable salt thereof,

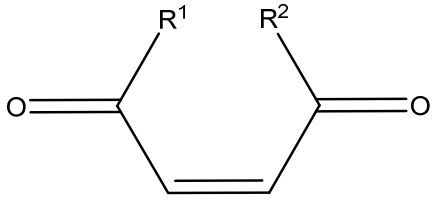
wherein the pharmaceutical composition is to be administered before, after, or concurrently with administration of an interferon-sensitive virus to the subject;

wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or an engineered variant thereof.

[0014d] In another aspect, the present disclosure refers to a composition comprising at least one compound of formula (I) or (II)



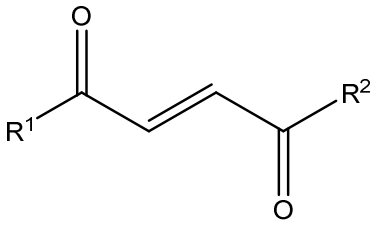
(I)



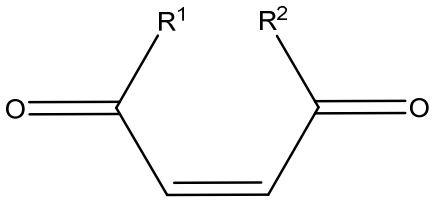
(II)

wherein R^1 and R^2 are each independently OH or (C_{1-10})alkoxy;
wherein when one of R^1 and R^2 is OH, the other of R^1 and R^2 is not OH,
or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient, wherein the composition is for use *in vitro* in viral enhancement of an interferon-sensitive virus;
wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or an engineered variant thereof.

[0014e] In another aspect, the present disclosure refers to a composition comprising an interferon-sensitive virus and at least one compound of formula (I) or (II)



(I)

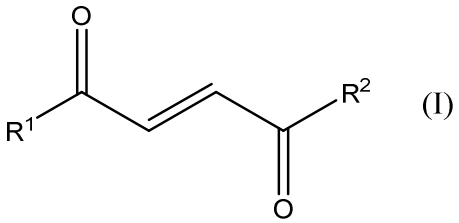


(II)

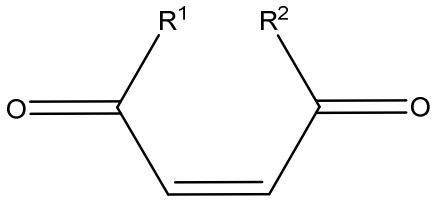
wherein R^1 and R^2 are each independently OH or (C_{1-10})alkoxy;
wherein when one of R^1 and R^2 is OH, the other of R^1 and R^2 is not OH,
or a pharmaceutically acceptable salt thereof, for enhancing production, infection, growth, spread, or titer of the interferon-sensitive virus;
wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or an engineered variant thereof.

[0014f] In another aspect, the present disclosure refers to a method for producing an interferon-sensitive virus comprising:

culturing an immortalized cell, a cancer cell or a tumor cell with the interferon-sensitive virus or a component thereof in an appropriate medium in the presence of at least one compound of formula (I) or (II)



(I)



(II)

wherein R^1 and R^2 are each independently OH or (C_{1-10})alkoxy;

wherein when one of R^1 and R^2 is OH, the other of R^1 and R^2 is not OH, or a pharmaceutically acceptable salt thereof; and producing the interferon-sensitive virus from the immortalized cell, the cancer or the tumor cell;

wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or an engineered variant thereof.

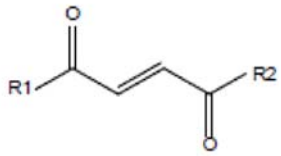
[0015] In an ~~embodiment~~example, there is provided herein a method of enhancing or increasing the production, growth, infection, spread, or titer, of an interferon-sensitive virus in an immortalized cell, cancer cell or tumor cell, comprising administering a FMAE compound to the cell prior to, concurrently with, or after infection of the immortalized, cancer or tumor cell with the interferon-sensitive virus.

[0016] In another ~~embodiment~~example, there is provided herein a method of enhancing, increasing or potentiating the production, infection, spread, titer, or the oncolytic activity of an

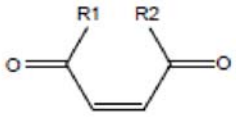
oncolytic virus in cancer or tumor cells, comprising administering one or more FMAE-containing compounds selected from the group consisting of:

Dimethylfumarate (DMF), diethylfumarate (DEF), dimethyl maleate (DMM), diethyl maleate (DEM), monoethyl maleate, monomethyl maleate, monoethyl fumarate, monomethyl fumarate (MMF), and derivatives thereof.

[0017] In certain ~~embodiment~~examples, compounds for viral enhancement may include those defined by formula (I), (II), a combination thereof, fumaric acid esters or maleic acid esters, pharmaceutically acceptable addition salts thereof, or racemic or stereochemically isomeric forms thereof, wherein R1 and R2 may be the same or different and may be independently selected from, for example, OH, O^-, and (C_{1-6})alkoxy, or a pharmaceutically acceptable salt thereof.



[0018] (I)



[0019] (II)

[0020] In another non-limiting ~~embodiment~~example, compounds for viral enhancement may include one or more compounds defined by formula (I) and/or (II), wherein R1 and R2 which may be the same or different and may be independently selected from a linear, branched or cyclic, saturated or unsaturated (C_{1-2})alkoxy, or (C_{3-20})alkoxy, and wherein said radicals may optionally be substituted with halogen, hydroxy, (C_{1-4}) alkyl, nitro or cyano, for example.

[0021] In certain non-limiting ~~embodiment~~examples, compounds of Formulae (I) and/or (II) may also exist in several tautomeric forms including the enol form, the keto form, and mixtures thereof. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms.

[0022] In a non-limiting ~~embodiment~~example, compounds selected from a compound of Formulae (I) and/or (II) may include isotopically labeled compounds, where one or more atoms have an atomic mass different from the atomic mass conventionally found in nature. Examples of isotopes that may be incorporated into the compounds disclosed herein include, but are not limited to, 2H, 3H, 11C, 13C, 14C, 15N, 18O, 17O, etc.

[0023] In another non-limiting ~~embodiment~~example, example compounds may include compounds defined by formula (I) and/or (II), wherein R1 and R2 are both OH, or O^-.

[0024] In certain ~~embodiment~~examples, compounds as described herein, or combinations of one or more compounds as described herein, or compositions comprising at least one compound as described

herein, may be administered to cells prior to, or concurrently with, or following infection of the cells with the virus. Subsequently, the cells, one or more compounds and virus may be grown or cultured.

[0025] In still another ~~embodiment~~example of any one of the method or methods described herein, the FMAE-containing compound or combination of compounds may be present in a composition comprising the compound(s) and one or more of a carrier, diluent or excipient.

[0026] In another ~~embodiment~~example, there is provided herein a composition comprising one or more FMAE-containing compounds, and one or more of a) an interferon-sensitive virus, a genetically modified interferon sensitive virus, an attenuated interferon-sensitive virus, an oncolytic interferon-sensitive virus, an interferon-sensitive virus-based cancer vaccine or cancer gene therapy vector, b) one or more cancer cells, c) a pharmaceutically acceptable carrier, diluent or excipient, d) non-cancer cells; e) cell culture media; f) one or more cancer therapeutics; or any combination of a)-f). The present ~~invention~~disclosure also contemplates ~~embodiment~~examples wherein any one or a combination of a)-f) are specifically excluded from the composition or kit. Any component or group of components may be excluded if desired.

[0027] In yet another ~~embodiment~~example, there is provided herein a kit comprising one or more of FMAE-containing compounds, and one or more of a) an interferon-sensitive virus, a genetically modified interferon-sensitive virus, an attenuated interferon-sensitive virus, an oncolytic interferon-sensitive virus, an interferon-sensitive virus-based cancer vaccine or cancer gene therapy vector, b) one or more cancer cells, c) a pharmaceutically acceptable carrier, diluent or excipient, d) non-cancer cells; e) cell culture media; f) one or more cancer therapeutics, g) a cell culture plate or multi-well dish; h) an apparatus to deliver the compound to a cell, medium or to a subject; i) instructions for using the compound or any component in the kit, of a)-i). The present ~~invention~~disclosure also contemplates kits wherein any one or a combination thereof of a)-i) are specifically excluded.

[0028] In another ~~embodiment~~example, the cells may be cancer cells *in vivo*, or *in vitro*.

[0029] In a further ~~embodiment~~example, the *in vivo* cancer cells may be from a mammalian subject.

[0030] In still a further ~~embodiment~~example, the mammalian subject may be a human subject.

[0031] In another ~~embodiment~~example, the cells may be non-cancer cells *in vitro*.

[0032] In yet another ~~embodiment~~example, there is provided herein a method of increasing the oncolytic activity of an oncolytic interferon-sensitive oncolytic virus in cancer or tumor cells, comprising administering a FMAE-containing compound, or a combination of FMAE containing compounds to said cancer or tumor cells prior to, concurrently with or after the oncolytic virus.

[0033] In another ~~embodiment~~example, the cancer or tumor cells may be *in vivo*, or *in vitro*.

[0034] In still another ~~embodiment~~example, the *in vivo* cancer or tumor cells may be from a mammalian subject.

[0035] In yet another ~~embodiment~~example, the mammalian subject is a human subject.

[0036] In another ~~embodiment~~example, there is provided herein a use of FMAE-containing compounds in the manufacture of a medicament for enhancing or increasing the infection, spread, titer, cytotoxicity or immunotherapeutic activity of an oncolytic interferon-sensitive virus in cancer or tumor cells.

[0037] In yet another ~~embodiment~~example, in any of the compositions or methods described above or herein throughout, the FMAE-containing compound enhances or increases interferon-sensitive virus infection, growth, spread or any combination thereof in infection-resistant cells.

[0038] In yet another ~~embodiment~~example, in any of compositions or methods described above or herein throughout, the FMAE-containing compound enhances or increases interferon-sensitive virus infection, growth, spread or any combination thereof in cancer cells or tumors *in vivo* without inducing virus spread to major organs.

[0039] In a further ~~embodiment~~example, in any of compositions or methods described above or herein throughout, the FMAE-containing compound enhances virally induced cancer cell death *in vivo* and/or *in vitro*.

[0040] In an ~~embodiment~~example of any of the methods as described herein or throughout, the interferon-sensitive virus may be any suitable virus known in the art which is interferon-sensitive or which is rendered interferon-sensitive, examples including, but not limited to, replicating or

non-replicating viruses, such as: newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or a variant or derivative thereof.

[0041] In an ~~embodiment~~example of any method described above or herein, the interferon-sensitive virus is an oncolytic interferon-sensitive virus. Representative example may be any suitable oncolytic virus known in the art which preferentially infects and lyses cancer or tumor cells as compared to non-cancer or normal cells. Examples of viruses known in the art which may be engineered to be used as oncolytic viruses may be employed herein and include, without limitation, reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, rhabdoviruses such as vesicular stomatitis virus, adenovirus, herpes simplex virus and derivatives/variants thereof. In a preferred ~~embodiment~~example, the virus is a Vesicular stomatitis virus (VSV), or a related rhabdovirus variant/derivative thereof for example, selected under specific growth conditions, one that has been subjected to a range of selection pressures, one that has been genetically modified using recombinant techniques known within the art, or a combination thereof. In another preferred ~~embodiment~~example, the virus may be VSVΔ51 [30]. Other derivatives or variants may be based on viruses such as Maraba (MG-1, for example), Rabies, Rotavirus, Influenza, Hepatitis A, Mumps, Measles, Rubella, Reovirus, Dengue Virus, Chikungunya Virus, Respiratory Syncitial Virus, LCMV, lentivirus, or replicating retrovirus, for example.

[0042] In one ~~embodiment~~example of any methods above or described herein throughout, the one or more types of immortalized cells may be immortalized cells *in vitro* or *in vivo* from any cell, cell line, tissue or organism, not limited to, human, rat, mouse, cat, dog, pig, primate, horse and the like, for example, without limitation: Vero, HEK-293 cells, EB-66 cells, EbX cells, PER.C6 cells, AGE1.CR, Age1.CS, Age1.HN, Age1.RO, QOR2/2E11, UMNSAH-DF1, CHO, hybridoma cells, sf9 cells, or R4 cells.

[0043] In another ~~embodiment~~example, the one or more types of cancer or tumor cells may be cancer or tumor cells *in vitro* or *in vivo* from any cell, cell line, tissue or organism, for example, but not limited to human, rat, mouse, cat, dog, pig, primate, horse and the like, for

example tumor forming cells such as, but not limited to 293-T cells, BHK21 cells, or MDCK cells. In a preferred ~~embodiment~~example, the one or more cancer or tumor cells comprise human cancer or tumor cells, for example, but not limited to lymphoblastic leukemia, myeloid leukemia, adrenocortical carcinoma, AIDS-related cancers, AIDS-related lymphoma, anal cancer, appendix cancer, astrocytoma, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, osteosarcoma, malignant fibrous histiocytoma, brain stem glioma, brain tumor, cerebellar astrocytoma, cerebral astrocytoma/malignant glioma, craniopharyngioma, ependymoblastoma, medulloblastoma, pineal parenchymal tumors of intermediate differentiation, supratentorial primitive neuroectodermal tumors and pineoblastoma, visual pathway and hypothalamic glioma, spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, carcinoid tumor, central nervous system lymphoma, cervical cancer, chordoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon cancer, cutaneous T-Cell lymphoma, embryonal tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, intraocular melanoma, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), gastrointestinal stromal cell tumor, germ cell tumors, extracranial, extragonadal, ovarian, gestational trophoblastic tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular (Liver) cancer, histiocytosis, Langerhans cell cancer, Hodgkin lymphoma, hypopharyngeal cancer, islet cell tumors, Kaposi sarcoma, kidney cancer, laryngeal cancer, lymphocytic leukemia, hairy cell leukemia, lip and oral cavity cancer, liver cancer, non-small cell lung cancer, small cell lung cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, malignant fibrous histiocytoma of bone and osteosarcoma, medulloblastoma, medulloepithelioma, melanoma, intraocular melanoma, Merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer, mouth cancer, multiple endocrine neoplasia syndrome, multiple myeloma/plasma cell neoplasm, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oral cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pineal parenchymal tumors, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal

cancer, renal cell (kidney) cancer, renal pelvis and ureter cancer, transitional cell cancer, respiratory tract carcinoma, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, uterine sarcoma, skin cancer, Merkel cell skin carcinoma, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, stomach (Gastric) cancer, supratentorial primitive neuroectodermal tumors, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, trophoblastic tumor, urethral cancer, uterine cancer, endometrial cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or Wilms tumor. However, the compounds and compositions described herein possible may be used to treat other cancers or tumors *in vivo* or *in vitro*.

[0044] The present ~~invention~~disclosure also provides a composition comprising the FMAE-containing compound(s) as described herein, and an acceptable carrier, diluent or excipient. In a further ~~embodiment~~example, the carrier is a pharmaceutically acceptable carrier.

[0045] Also provided is a method of enhancing or increasing the infection, spread and/or titer, and/or cytotoxicity of a virus in cells, the method comprising, administering the FMAE-containing compound(s) as described herein to the cells prior to, after or concurrently with the virus, and culturing the virus and cells to enhance or increase the infection, spread and/or titer, or cytotoxicity of the virus in said cells. Preferably, the cells are cancer cells, tumor cells or cells which have been immortalized. More preferably, the cells are *in vivo* cancer cells from a mammalian, still more preferably a human subject and the method is practiced *in vivo*. In another separate ~~embodiment~~example, the cells are *in vitro* immortalized cells.

[0046] Also provided is a method of enhancing or increasing the oncolytic activity of an oncolytic virus in cancer cells comprising, administering the compound(s) as described herein to the cancer cells or subject prior to, concurrently with or after the oncolytic virus and culturing the oncolytic virus and cancer cells. In a further ~~embodiment~~example, the cancer cells are *in vivo* cancer cells. In a separate ~~embodiment~~example, the cancer cells are *in vitro* cancer cells. The cells may be from a mammalian subject, preferably a human subject.

[0047] In a particular ~~embodiment~~example, which is not meant to be limiting in any manner, there is provided a kit comprising a FMAE-containing compound and a medium for growing, culturing or infecting cells with a virus and optionally, one or more cells which are capable of

being infected by the virus, and/or one or more viruses. The kit may also comprise instructions for using any component or combination of components and/or practicing any method as described herein.

[0048] The present ~~invention~~disclosure also provides a method of enhancing or increasing the infection, spread and/or titer, or oncolytic activity of a virus in cells comprising, administering a FMAE-containing compound as described herein to the cells prior to, after or concurrently with the virus. The method may be practiced *in vivo* or *in vitro.*

[0049] The present ~~invention~~disclosure also provides a method of enhancing or increasing the spread of an oncolytic virus in tumor or cancer cells comprising, administering a compound as described above to the cancer or tumor cells prior to, after or concurrently with the oncolytic virus. The cancer or tumor cells may be *in vivo*, or *in vitro*, preferably *in vivo* from a mammalian subject such as, but not limited to, a human subject.

[0050] Also provided is a method of enhancing or increasing the oncolytic activity of an oncolytic virus in cancer or tumor cells comprising, administering a compound as described above to the cancer or tumor cells prior to, concurrently with or after the oncolytic virus. The cancer or tumor cells may be *in vivo*, or *in vitro*, preferably from a mammalian subject such as, but not limited to a human subject.

[0051] The present ~~invention~~disclosure also contemplates a method of producing a virus by growing the virus in an appropriate medium in the presence of a FMAE-containing compound as described above.

[0052] The present ~~invention~~disclosure also contemplates a method of producing an attenuated interferon-sensitive virus by growing the virus in an appropriate medium in the presence of a FMAE-containing compound as described above.

[0053] The present ~~invention~~disclosure also contemplates a method of producing a genetically modified virus by growing the virus in an appropriate medium in the presence of a FMAE-containing compound as described above.

[0054] The present ~~invention~~disclosure also contemplates a method of producing an oncolytic virus by growing the virus in an appropriate medium in the presence of a FMAE-containing compound as described above.

[0055] The present ~~invention~~disclosure also contemplates a method of producing a live virus vaccine by growing the virus in an appropriate medium in the presence of a FMAE-containing compound as described above.

[0056] The present ~~invention~~disclosure also contemplates a method of producing a virus-based gene therapy vector by growing the virus in an appropriate medium in the presence of a FMAE-containing compound as described above.

[0057] This summary of the ~~invention~~disclosure does not necessarily describe all features of the ~~invention~~disclosure.

[0058] BRIEF DESCRIPTION OF THE DRAWINGS

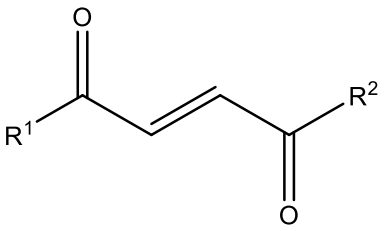
[0059] These and other features of the invention will become more apparent from the following description in which reference is made to the appended drawings wherein:

[0060] **Figure 1** shows that DMF enhanced virus infection and oncolytic activity in cancer cell lines. (**A**) Structure of dimethyl fumarate. (**B-F**) Resistant human renal cancer cell lines 786-0, (**B, D**) and various human and murine cell lines were pretreated with DMF for 4 hours and subsequently infected with (**B-D**) VSVΔ51 (MOI: 0.01), (**E**) HSV (MOI: 0.01), or (**F**) Sindbis (MOI:10). (**B**) 24 hours post infection fluorescent images were taken of the infected cancer cells. (**C-F**) Corresponding viral titer were determined 48 hours post infection from supernatants. (N=3-4; Error bars indicate SD (standard deviation); (**D-F**) 2-tailed t-test; $p<0.05$ as compared to the untreated counterpart for each cell line; (**C**) One-way ANOVA; *$p<0.05$, *** $p<0.001$, as compared to the untreated condition counterpart). (**G**) Human tumor cell line A549 pretreated as in (**B**) and infected with an adenovirus expressing firefly luciferase (Ad5) at an MOI of 1. Luciferase activity was measured over the course of 7 days. Results are represented as relative light units and background is indicated by black line. (N=3; Error bars indicate SD; Significance enhancement for day 2 to 5, $p<0.05$ by two-way ANOVA). (**H**) Multi-step, and single-step growth curve of 786-0 pretreated with DMF and infected with

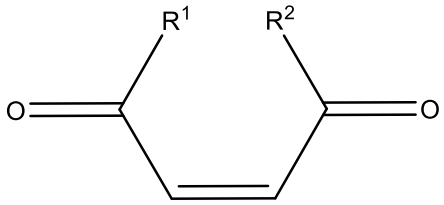
WHAT IS CLAIMED IS:

1. A composition for ~~method of~~ enhancing production, infection, growth, spread, or titer of an interferon-sensitive virus in an immortalized cell, a cancer cell or a tumor cell, the composition ~~method~~ comprising:

a compound of formula (I) or (II)



(I)



(II)

wherein R^1 and R^2 are each independently OH or (C_{1-10})alkoxy ;

wherein when one of R^1 and R^2 is OH, the other of R^1 and R^2 is not OH,

or a pharmaceutically acceptable salt thereof;

wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or an engineered variant thereof.~~administering a Fumaric and Maleic Acid Ester (FMAE) containing compound, or derivative thereof, to the immortalized, cancer or tumor cell before, concurrently with, or after infection of the immortalized, cancer or tumor cell with the interferon-sensitive virus.~~

2. The composition~~method~~ according to claim 1, wherein the interferon-sensitive virus is a non-interferon-sensitive virus genetically rendered interferon-sensitive, an attenuated interferon-sensitive virus, an interferon-sensitive oncolytic virus, or a non-replicating interferon-sensitive virus.

3. The composition~~method~~ according to claim 2, wherein an oncolytic activity, a cell death activity, ~~and/~~or cytotoxic activity of the interferon-sensitive oncolytic virus in the cancer cell or the tumor cell is enhanced or increased.

4. The composition~~method~~ according to claim 2, wherein an immunotherapeutic activity of the interferon-sensitive oncolytic virus in the cancer cell or the tumor cell is enhanced, increased or potentiated, including up-regulation of virus encoded transgenes ~~and/~~or cytokines.

5. The composition~~method~~ according to claim 1, wherein the ~~FMAE-containing~~ compound is~~ or comprises the structure of~~: Dimethylfumarate (DMF), diethylfumarate (DEF), dimethyl maleate (DMM), diethyl maleate (DEM), monoethyl maleate, monomethyl maleate, monoethyl fumarate, or monomethyl fumarate (MMF), or a pharmaceutically acceptable salt, solvate, hydrate~~, prodrug, reduced, or oxidized~~ form thereof.

~~6. The method according to claim 1, wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or a variant or derivative thereof.~~

~~7~~6. The composition~~method~~ according to claim 2, wherein the interferon-sensitive oncolytic virus comprises a rhabdovirus which is vesicular stomatitis virus or ~~a derivative or~~ an engineered variant thereof.

~~8~~7. The composition~~method~~ according to claim 1, wherein the interferon-sensitive virus comprises a virus selected under specific growth conditions, subjected to one or more selection pressures, genetically modified using a recombinant technique, or any combination thereof.

~~9~~8. The composition~~method~~ according to claim 1, wherein the cell is mammalian.

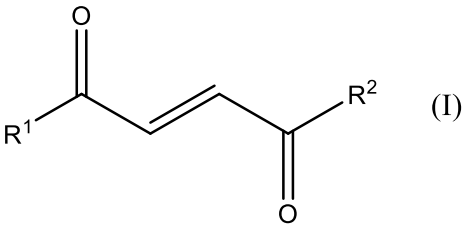
~~10~~9. The composition~~method~~ according to claim ~~9~~8, wherein the cell is human.

~~11~~10. The composition~~method~~ according to claim 1, wherein the immortalized cell, the cancer cell or the tumor cell comprises 293-T cells, BHK21 cells, or MDCK cells, Vero cells, HEK-293 cells, EB-66 cells, EB-bX cells, PER-.C6 cells, AGE1.CR cells, Age1.CS cells, Age1.HN cells, Age1.RO cells, QOR2/2E11 cells, UMNSAH-DF1 cells, CHO cells, hybridoma cells, sf9 cells, or R4 cells. 293-T cells, BHK21 cells, or MDCK cells lymphoblastic leukemia, myeloid leukemia, adrenocortical carcinoma, AIDS-related cancer, AIDS-related lymphoma, anal cancer, appendix cancer, astrocytoma, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, osteosarcoma, malignant fibrous histiocytoma, brain stem glioma, brain tumor, cerebellar astrocytoma, cerebral astrocytoma/malignant glioma, craniopharyngioma, ependymoblastoma, medulloblastoma, pineal parenchymal tumors of intermediate differentiation, supratentorial primitive neuroectodermal tumors and pineoblastoma, visual pathway and hypothalamic glioma, spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, carcinoid tumor, central nervous system lymphoma, cervical cancer, chordoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon cancer, cutaneous T-Cell lymphoma, embryonal tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, intraocular melanoma, retinoblastoma, gallbladder cancer, gastric ~~(stomach)~~ cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor ~~(GIST)~~, gastrointestinal stromal cell tumor, germ cell tumors, extracranial, extragonadal, ovarian, gestational trophoblastic tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular ~~(Liver)~~ cancer, histiocytosis, Langerhans cell cancer, Hodgkin lymphoma, hypopharyngeal cancer, islet cell tumors, Kaposi sarcoma, kidney cancer, laryngeal cancer, lymphocytic leukemia, hairy cell leukemia, lip and oral cavity cancer, liver cancer, non-small cell lung cancer, small cell lung cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, malignant fibrous histiocytoma of bone and osteosarcoma, medulloblastoma, medulloepithelioma, melanoma, intraocular melanoma, Merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer, mouth cancer, multiple endocrine neoplasia syndrome, multiple myeloma/plasma cell neoplasm, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oral cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, penile cancer,

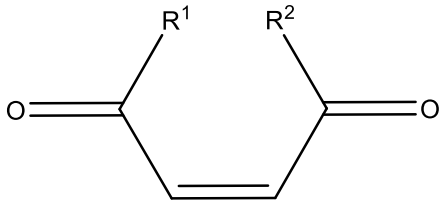
pharyngeal cancer, pheochromocytoma, pineal parenchymal tumors, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell ~~(kidney)~~ cancer, renal pelvis and ureter cancer, transitional cell cancer, respiratory tract carcinoma, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, uterine sarcoma, skin cancer, Merkel cell skin carcinoma, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, stomach ~~(Gastric)~~ cancer, supratentorial primitive neuroectodermal tumors, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, trophoblastic tumor, urethral cancer, uterine cancer, endometrial cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or Wilms tumor.

~~12~~11. A pharmaceutical composition~~method~~ for treating a tumor or cancer in a subject in need thereof, the ~~method~~ composition comprising:

a compound of formula (I) or (II)



(I)



(II)

wherein R^1 and R^2 are each independently OH or (C_{1-10})alkoxy;

wherein when one of R^1 and R^2 is OH, the other of R^1 and R^2 is not OH,

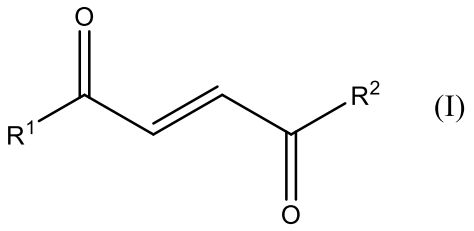
or a pharmaceutically acceptable salt thereof,

for administration before, after, or concurrently with administration of an interferon-sensitive virus to the subject;

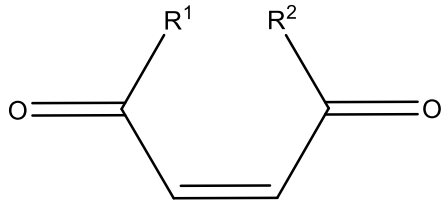
wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory

Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or an engineered variant thereof.~~administering a Fumaric and Maleic Acid Ester (FMAE)-containing compound, or derivative thereof, to the subject before, after, or concurrently with administering an interferon-sensitive virus to the subject.~~

12. Use of a pharmaceutical composition in the manufacture of a medicament for treating a tumor or cancer in a subject in need thereof, the composition comprising:
a compound of formula (I) or (II)



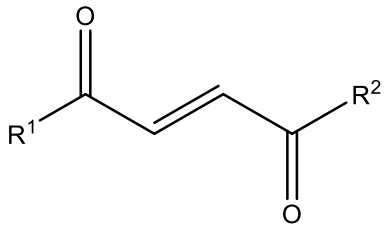
(I)



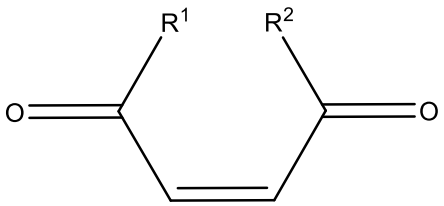
(II)

wherein R^1 and R^2 are each independently OH or (C_{1-10})alkoxy;
wherein when one of R^1 and R^2 is OH, the other of R^1 and R^2 is not OH,
or a pharmaceutically acceptable salt thereof,
wherein the pharmaceutical composition is to be administered before, after, or concurrently with administration of an interferon-sensitive virus to the subject;
wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or an engineered variant thereof.

13. A composition comprising at least one compound of formula (I) or (II)



(I)



(II)

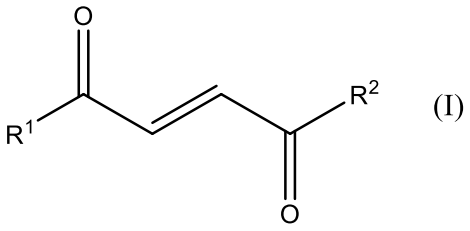
wherein R^1 and R^2 are each independently OH or (C_{1-10})alkoxy;

wherein when one of R^1 and R^2 is OH, the other of R^1 and R^2 is not OH,

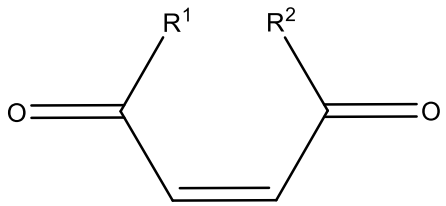
or a pharmaceutically acceptable salt thereof, ~~Fumaric and Maleic Acid Ester (FMAE)-containing compound, or derivative thereof,~~ and a pharmaceutically acceptable carrier or excipient, wherein the composition is for use *in vitro* in viral enhancement of an interferon-sensitive virus;

wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or an engineered variant thereof.

14. A composition comprising an interferon-sensitive virus and at least one compound of formula (I) or (II)



(I)



(II)

wherein R^1 and R^2 are each independently OH or (C_{1-10})alkoxy;

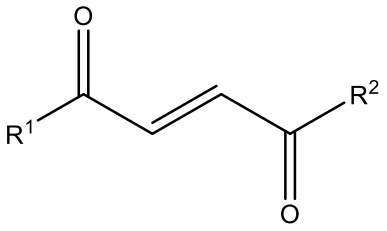
wherein when one of R^1 and R^2 is OH, the other of R^1 and R^2 is not OH,

or a pharmaceutically acceptable salt thereof, for enhancing production, infection, growth, spread, or titer of the interferon-sensitive virus;

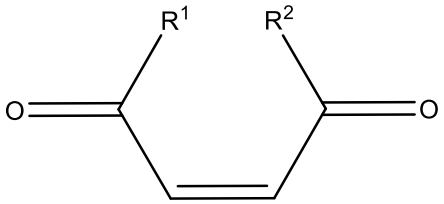
wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or an engineered variant thereof.~~Fumaric and Maleic Acid Ester (FMAE) containing compound, or derivative thereof.~~

15. A method for producing an interferon-sensitive virus comprising:

culturing an immortalized cell, a cancer cell or a tumor cell with the interferon-sensitive virus or a component thereof in an appropriate medium in the presence of at least one compound of formula (I) or (II)



(I)



(II)

wherein R^1 and R^2 are each independently OH or (C_{1-10})alkoxy;

wherein when one of R^1 and R^2 is OH, the other of R^1 and R^2 is not OH, or a pharmaceutically acceptable salt thereof; ~~Fumaric and Maleic Acid Ester (FMAE)-containing compound or derivative thereof;~~ and producing the interferon-sensitive virus from the immortalized cell, the cancer or the tumor cell;

wherein the interferon-sensitive virus is a reovirus, newcastle disease virus, polio virus, mumps virus, measles virus, influenza virus, Maraba virus (such as MG-1), Rabies virus, Rotavirus, Hepatitis A virus, Rubella virus, Dengue virus, Chikungunya virus, Respiratory Syncitial Virus, LCMV, lentivirus, replicating retrovirus, adenovirus, herpes simplex virus or rhabdovirus, or an engineered variant thereof.

16. The method according to claim 15, wherein the interferon-sensitive virus is an attenuated virus, a genetically modified virus, a non-replicating virus, or an oncolytic virus.

17. The method according to claim 16, wherein the interferon-sensitive virus is used to prepare a cancer vaccine, wherein the virus is the vaccine or the vaccine comprises the cell infected with the virus.

18. The method a claim 16, wherein the produced virus is an interferon-sensitive virus-based cancer gene therapy vector.