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(54) Title: METHODS FOR TREATING VIRAL INFECTION

(57) Abstract: The invention also relates to treating and/or preventing a virus infection, and reactions associated with viral vaccination using tyrosine kinase inhibitors and/or epidermal growth factor receptor blockers. Examples of useful tyrosine kinase inhibitors include, quinazoline derivatives, such as 4-quinazolinamine-N-(3chlor-4-fluorophenyl)-7-methosy-6-[3-4-morpholin)propoxy]. The present invention relates to compositions and methods for treating and/or preventing a viral infection with modulators of epidermal growth factor ("EGF") and of the epidermal growth factor receptor ("EGFR") pathway.

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METHODS FOR TREATING VIRAL INFECTION

This application claims the benefit of U.S. Provisional Application Serial No. 60/518,678, filed November 12, 2003.

DESCRIPTION OF THE INVENTION

The present invention provides methods of preventing and/or treating viral infection by any virus that utilizes the epidermal growth factor ("EGF") receptor, either to gain entry into the cell and/or to produce symptoms associated with viral infection.

The present invention also relates to compositions and methods for treating and/or preventing infection associated with poxviruses, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and feline sarcoma virus using modulators of the epidermal growth factor receptor ("EGFR") pathway.

The present invention also relates to treating and/or ameliorating adverse reactions, and other events, associated with viral vaccination, such as poxvirus vaccination, by administering such modulators.

Any agent that modulates the EGFR (epidermal growth factor receptor) pathway can be utilized in accordance with the present invention. The EGF receptor (erbB-1) comprises an extracellular region that contains a binding site for the EGF ligand, a transmembrane domain, and an intracellular tyrosine kinase domain that is responsible for initiating and regulating intracellular signaling. Upon stimulation, it undergoes phosphorylation, initiating a signaling cascade of protein interactions and phosphorylation steps that involve, e.g., Grb2, ras, raf, MEK, MAP kinase, PI-3-kinase, PKB, etc. The EGFR is internalized within the cell via clathrin-dependent endocytosis (clathrin coated pits) of the receptor and its ligand. If the ligand is a virus, it will also be internalized along with the EGFR. Several viruses exploit this mechanism as a means of gaining entry into the target host cell.

The present invention includes preventing and/or treating viral infection by any virus that utilizes the EGF receptor, either to gain entry into the cell and/or to produce symptoms associated with viral infection. As discussed above, viruses can use the receptor molecule as a carrier to be transported into the cells. Additionally, they can produce polypeptides and other products that stimulate the EGFR, leading to deleterious

effects on the host. By blocking the EGFR and/or its activity, these events can be eliminated and/reduced, thereby intervening in the course of the viral disease.

A modulator can modulate any protein and/or step in the signaling pathway, e.g., inhibiting a ligand from stimulating the EGFR, inhibiting EGFR tyrosine kinase activation, inhibiting Grb2, raf or MEK or MAP kinase activity, inhibiting protein/protein interactions, inhibiting internalization of the virus or viral nucleic acid into the cell, etc. Any type of agent can be used, including, e.g., antibodies or other binding molecules (e.g., antibodies to the EGFR or a ligand that interacts with it), small molecules (e.g., chemical compounds that act as direct inhibitors of an enzyme activity or which disrupt protein/protein interactions), etc.

The modulators can also be utilized for all aspects viral treatments, including for poxvirus, EBV and CMV infections and vaccinia immunization, and for any therapeutic, prophylactic, and/or diagnostic use in research, medicine, and veterinary medicine.

Another aspect of the invention relates to treating and/or preventing a viral infection, such as a poxvirus infection, and/or reactions associated with viral (e.g., poxvirus) vaccination (as described above), using a EGFR-blocker or tyrosine kinase inhibitor, such as a quinazoline derivative having a formula as described in U.S. Pat. Nos. 5,770,599, 5,616,582, or 5,457,105 which are hereby incorporated by reference in their entirety and attached as appendices. An example of a useful compound is 4-quinazolinamine-N-(3-chlor-4-fluorophenyl)-7-methoxy-6-[3-4-morpholin)propoxy] ("gefitinib").

As indicated above, methods of the invention can involve treating and/or preventing a viral infection, such as a poxvirus infection, comprising, administering an effective amount of an EGFR blocker or tyrosine kinase inhibitor, such as a quinazoline derivative described in US Pat Nos. 5,770,599, 5,616,582, or 5,457,105, or other compounds as mentioned below. While the compounds in the mentioned patents are described as receptor tyrosine kinase inhibitors or EGFR-blockers, the methods of the present invention are not limited by how the compounds achieve their therapeutic effect, or to any particular mechanism of action.

The term "treating" as it is used herein generally indicates that one or more symptoms of a poxvirus infection are ameliorated, reduced, diminished, improved, etc.

For example, about 7-17 days after exposure to variola virus, an infected subject can begin to experience the first symptoms of smallpox disease. A compound administered during this time period, or at any point during the disease, can prevent or inhibit progression of the disease. The compounds can block, reduce, diminish, alleviate, etc., one or more symptoms of the disease, including, but not limited to, e.g., fever, malaise, head and body aches, vomiting, prodrome phase, typical or atypical rash during all its phases, hemorrhagic rash, hemorrhage, etc. These compounds can reduce the severity of the disease, as well as the degree and period during which it is contagious.

Adverse reactions and other effects of poxvirus vaccination can also be treated in accordance with the present invention, e.g., by administering an effective amount of an EGFR modulator, such as a quinazoline derivative described in U.S. Pat. Nos. 5,770,599, 5,616,582, or 5,457,105, such as gefitinib, or an EGFR specific monoclonal antibody. Adverse reactions to vaccinia vaccination include, but are not limited to, e.g., generalized vaccinia, progressive vaccinia, eczema vaccinatum, post-vaccinal encephalitis, vaccinial myocarditis and/or pericarditis, ocular vaccinia, encephalomyelitis (PVEM), fetal vaccinia, etc.

As mentioned, methods can involve administering an effective amount of a modulator or inhibitor of EGFR-tyrosine kinase activation or activity, or an anti-EGFR antibody or other binding partner that blocks activation of EGFR by binding to an external component effectively blocking ligand binding or producing a conformation change in the EGFR molecule that prevents ligand binding and/or activation (i.e., an EGFR-blocker). EGFR is a polypeptide comprising about 1200 amino acids which contains a single transmembrane spanning domain and a glycosylated ligand-binding domain. Intracellularly, it contains a tyrosine kinase domain which is important in transducing intracellular signals in response to external EGFR binding by a ligand.

By the phrase "tyrosine kinase activity," it is meant a catalytic activity in which a gamma-phosphate from adenosine triphosphate (ATP) is transferred to a tyrosine residue in an appropriate substrate. An agent which inhibits its activity can be referred to as a tyrosine kinase inhibitor of epidermal growth factor receptor.

By the phrase "EGFR-blocker," it is meant an agent that blocks or prevents ligand binding to the receptor and/or receptor activation. It can also be referred to as an EGFR

antagonist, in the classical pharmacological meaning where the blocker antagonizes the effect of the receptor ligand. Examples include, e.g., receptor antibodies (monoclonal, humanized, chimeric, and/or human), and direct receptor binding antagonists (e.g., derivatives of EGF or VGF).

Examples of EGFR modulators, include, but are not limited to, tyrosine kinase inhibitors, quinazoline derivatives described in U.S. Pat. Nos. 5,770,599, 5,616,582, and 5,457,105, such as gefitinib; quinazolines, such as OSI-774 ("Erlotinib"), CI-1033, EKB-569, and PD-0183805; pyridopyrimidines, such as PD-158780 series and PD-180970; pyrrolopyrimidines, such as PKI-166; GW-572016/GW-2016; LFM-A12; Tyrphostins, such as A23 and 25; PD153035; recombinant vaccine, such as EGF-64K; antisense RNA or DNA, such as AS-21; receptor antibodies, such as monoclonal antibodies IMC-C225, ABX-EGF, EMD-72000, TheraCIM-h-R3, and mAB-806; decapeptide antagonists corresponding to the sequence of the third disulphide loop of EGF, VGF or TGF-alpha.

For more tyrosine kinase inhibitors, see also: WO 92/20642; Fry et al., Science, 1994, 265, 1093; 4,5-dianilinophthalimide, Buchdunger et al., Proc. Nat. Acad. Sci., 1994, 91, 2334; various derivatives of styrene, e.g., European Patent Application Nos. 0211363, 0304493 and 0322738; styrene derivatives, Yoneda et al., Cancer Research, 1991, 51, 4430; T. R. Burke Jr., Drugs of the Future, 1992, 17, 119; European Patent Application No. 0635507 disclosing tricyclic compounds which comprise a 5- or 6-membered ring fused to the benzo-ring of a quinazoline; European Patent Application No. 0635498 disclosing quinazoline derivatives which comprise an amino group at the 6-position and a halogeno group at the 7-position.

Quinazoline inhibitors are well known, and include, e.g., 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(2-pyrrolidin-1-ylethoxy)quinazoline; 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(2-morpholinoethoxy)quinazoline; 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-›2-(4-methylpiperazin-1-yl)ethox y!quinazoline; 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-{2-›di-(2-methoxyethyl)aminoethoxy}quinazoline; 4-(3'-chloro-4'-fluoroanilino)-6-(2-dimethylaminoethoxy)-7-methoxyquinazoline; 4-(3'-chloro-4'-fluoroanilino)-6-(2-diethylaminoethoxy)-7-methoxyquinazoline; 4-(2',4'-difluoroanilino)-6-(3-dimethylaminopropoxy)-7-methoxyquinazoline; 4-(3'-chloro-4'-fluoroanilino)-6-(2-hydroxy-3-morpholinopropoxy)-7-methoxyquinazoline; 4-(2',4'-

difluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline; 4-(3'-chloro-4'-fluoroanilino)-6-(2-imidazol-1-ylethoxy)-7-methoxyquinazoline; 4-(3'-chloro-4'-fluoroanilino)-6-(3-diethylaminopropoxy)-7-methoxyquinazoline; 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-pyrrolidin-1-ylpropoxy)quinazoline; 4-(3'-chloro-4'-fluoroanilino)-6-(3-dimethylaminopropoxy)-7-methoxyquinazoline; 4-(3',4'-difluoroanilino)-6-(3-dimethylamninopropoxy)-7-methoxyquinazoline; 4-(3',4'-difluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline; 6-(3-diethylaminopropoxy)-4-(3',4'-difluoroanilino)-7-methoxyquinazoline; 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-piperidinopropoxy)quinazoline ;4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(2-piperidinoethoxy)quinazoline; and 4-(3'-chloro-4'-fluoroanilino)-6-(3-imidazol-1-ylpropoxy)-7-methoxyquinazoline.

Examples of anti-EGR monoclonal antibodies include, e.g., Cetuximab, MDX-447, h-R3, EMD-7200, and ABX-EGF.

Any of the mentioned compounds, or related compounds exerting similar effects, can be utilized in accordance with the present invention, regardless of the mechanism by which they achieve a therapeutic and/or modulatory effect.

In addition to modulating the EGFR tyrosine kinase, a modulator of the present invention can modulate any part of the signaling pathway mediated through or activated by epidermal growth factor receptor, including, e.g., ras, SOS, Grb-2, STAT, raf, MEK, MAPK, and including internalization of the virus or viral nucleic, etc.

The present invention also relates to methods of treating and/or preventing poxvirus infection, comprising administering an inhibitor of a poxvirus epidermal growth factor-like polypeptide. EGF-like polypeptides have been identified in poxviruses. These include, vaccinia growth factor ("VGF") which is expressed as a transmembrane precursor glycoprotein (e.g., Blomquist et al., *Proc. Natl. Acad. Sci.*, 81: 7363-7367, 1984), myxoma growth factor ("MGF") by myxoma, and shope fibroma growth factor (SFGF) by Shope fibroma virus. See, also, Tzahar et al., *EMBO. J.*, 17:5948-5963, 1998. Inhibitors can include, e.g., neutralizing antibodies against the poxvirus growth factor. Antibodies can be produced routinely, e.g., in whole animals or using in vitro technologies.

The term "modulator" is used generally throughout this application to mean an agent that alters or modifies a functional activity changed in comparison to its normal activity in the absence of the compound. This effect includes any quality or degree of modulation, including, increasing, agonizing, augmenting, enhancing, facilitating, stimulating, decreasing, blocking, inhibiting, reducing, diminishing, antagonizing, etc. In preferred embodiments of the present invention, the modulators are inhibitors of kinase activity, e.g., decreasing, blocking, inhibiting, reducing, diminishing, antagonizing, etc.

These methods generally involve administering effective amounts of compounds of the present invention, where an effective amount is the quantity of the compound which is useful to achieve the desired result. Compounds can be administered in any effective form by any effective route, as discussed in more detail below.

Epstein-Barr virus, cytomegalovirus, feline sarcoma virus, and any poxvirus infection can be treated and/or prevented in accordance with the present invention, including, but not limited to, orthopoxvirus, parapoxvirus, avipovirus, capripoxvirus, leporipoxvirus, suipoxvirus, molluscum contagiosum virus fowlpox, etc. Orthopoxvirus, include, e.g., buffalopox, camelpox, cowpox, monkeypox, rabbitpox, raccoon pox, tatera pox, canarypox, vaccinia, variola (smallpox), and vole pox. For other poxvirus, see e.g., *Virology*, Fields et al., Volume 2, Chapters 74-75, Raven Press, 1990.

Viruses that utilize the epidermal growth factor ("EGF") receptor, either to gain entry into the cell and/or to produce symptoms associated with viral infection, can also be treated. For example, viruses can produce polypeptides, such as poxvirus epidermal growth factor-like polypeptide, vaccinia growth factor, myxoma growth factor, and shope fibroma growth factor, that stimulate the EGF receptor upon direct binding, producing deleterious effects on the host.

A compound can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intraperitoneal, topical, transdermal (e.g., using any standard patch, cream, ointment or gel vehicle), ophthalmic, nasally, local, non-oral, such as aerosal, spray, inhalation, subcutaneous, intravenous, intramuscular, buccal, sublingual, rectal, vaginal, intra-arterial, mucosal, and intrathecal, etc. It can be administered alone, or in combination with any ingredient(s), active or inactive.

The present invention provides, e.g., methods of treating and/or preventing poxvirus or other said viral infections, comprising: administering an effective amount of a quinazoline derivative described in US Pat Nos. 5,770,599, 5,616,582, or 5,457,105; methods of treating adverse reactions associated with vaccinia immunization, comprising: administering an effective amount of a quinazoline derivative described in US Pat Nos. 5,770,599, 5,616,582, or 5,457,105, e.g., wherein the adverse reaction is generalized vaccinia, progressive vaccinia, eczema vaccinatum, vaccinia myocarditis and/or pericarditis, and/or post-vaccinal encephalitis; methods of treating and/or preventing poxvirus infection, comprising: administering an effective amount of an inhibitor of epidermal growth factor receptor tyrosine kinase activity; methods of treating and/or preventing poxvirus infection, comprising: administering an inhibitor of the signaling pathway comprising epidermal growth factor receptor; methods of treating and/or preventing poxvirus infection, comprising: administering an inhibitor of a poxvirus epidermal growth factor-like polypeptide.

The amounts of the modulators are administered in effective amounts to achieve the stated purpose. An "effective amount" indicates that the amount of the active agent is useful to achieve the purpose for which it is administered. Effective amounts can be determined routinely, and may vary depending upon the age, health, gender, and weight of a patient, as well as the severity and frequency of the condition (e.g., when an adverse event is being treated). Amounts can be administered once a day, or multiple times per day, e.g., depending upon the subject's physical condition, the severity of the disease, etc. The specific dose level and frequency of dosage may vary, depending upon a variety of factors, including the activity of the specific active agent, its metabolic stability and length of action, rate of excretion, mode and time of administration, the age, body weight, health condition, gender, diet, etc., of the subject.

Modulators in accordance with invention can be administered in combination with other active agents, e.g., other EGFR blockers or modulators, antibiotics, antiviral agents, other receptor blockers or modulators, cytokines which may include, but are not limited to, IL-1, IL-2, IL-6, IL-12, IL-4, IL-10, TNF-alpha, IFN-gamma, GM-CSF, rantes, MIP-1 alpha, MIP-1 beta, corticosteroids, small molecule inhibitors of protein function, etc.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. The entire disclosure of all applications, patents and publications, cited above and in the figures are hereby incorporated by reference in their entirety, including U.S. Provisional Application Serial No. 60/518,678, filed November 12, 2003, and for their disclosures of tyrosine kinase inhibitors, EGFR-blockers, and EGFR modulators.

EXAMPLE

Pure samples of a TKI and cetuximab can be obtained from their manufacturers (gifitinib, AstraZeneca Pharmaceuticals, of Wilmington, Delaware or erlotinib, Genentech of San Francisco, Ca., and cetuximab, Bristol-Meyers Squibb/ImClone, Princeton, NJ) and may be purchased at a pharmacy via a doctor's prescription.

An appropriate strain of vaccinia or other virus can be selected, and a preliminary study performed on each cell type utilized, to determine the most appropriate virus MOI and incubation time. These results can be used to determine how the cultures can be infected with the vaccinia and other viruses.

HeLa cells and human embryonal lung fibroblasts at a concentration of 5×10^5 cells/culture can be cultured separately in 1 ml Dulbecco's modified Eagle's medium (DMEM) or EMEM + 10% FCS (DMEM-10) + penicillin and streptomycin and placed in wells on 24 well plates. Cultures will be pretreated with:

· gifitinib in the following concentrations (3 cultures each): 10 μg/ml, 1 μg/ml, 0.1 μg/ml, and 0.01 μg/ml.

· erlotinib in the following concentrations (3 cultures each): 10 mg/ml, 1000 μg/ml , 100 μg/ml, and 10 μg/ml.

· cetuximab in the following concentrations (3 cultures each) 1000 μg/ml, 100 μg/ml, 10 μg/ml, and 1 μg/ml.

· cetuximab (in the above concentrations) plus erlotinib or gifitinib (in the above corresponding concentrations).

· 6 cultures will not be pretreated.

The cells are incubated for at least 24 hours then washed and lysed.

To measure viral production supernatant can be added to an African green monkey kidney cell culture (BS-C-1 cells) for a plaque reduction assay (see, e.g., Current Protocols in Molecular Biology 1994-2000 vol. 3, FM Ausubel, John Wiley & Sons, Inc.) A significant reduction in viral replication indicates that the compound has anti-poxvirus activity.

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What we claim:

1. A method of treating an infection with Epstein-Barr virus (EBV), cytomegalovirus (CMV), or poxvirus in a subject in need thereof, comprising:

administering an effective amount of a tyrosine kinase inhibitor of epidermal growth factor receptor to said subject infected with said virus, whereby said infection is treated.

2. A method of claim 1, wherein a poxvirus infection is treated.

3. A method of claim 2, wherein said poxvirus is variola.

4. A method of claim 1, wherein said tyrosine kinase inhibitor is 4-quinazolinamine-N-(3-chlor-4-fluorophenyl)-7-methoxy-6-[3-4-morpholin)propoxy] or a pharmaceutically acceptable salt thereof.

5. A method of claim 1, wherein a variola infection is treated with a tyrosine kinase inhibitor.

6. A method of treating an infection with Epstein-Barr virus (EBV), cytomegalovirus (CMV), or poxvirus in a subject in need thereof, comprising:

administering an effective amount of an epidermal growth factor receptor (EGFR) blocker to said subject infected with said virus, whereby said infection is treated.

7. A method of claim 6, wherein a poxvirus infection is treated.

8. A method of claim 6, wherein said poxvirus is variola.

9. A method of claim 6, wherein said EGFR blocker in an anti-EGFR monoclonal antibody.

10. A method of ameliorating adverse reactions associated with poxvirus vaccination, comprising,

administering an effective amount of a tyrosine kinase inhibitor of epidermal growth factor receptor or an anti-EGFR monoclonal antibody, whereby said adverse reaction is ameliorated.

11. A method of claim 10, said tyrosine kinase inhibitor is 4-quinazolinamine-N-(3-chlor-4-fluorophenyl)-7-methoxy-6-[3-4-morpholin)propoxy] or a pharmaceutically acceptable salt thereof.

12. A method of claim 10, wherein said poxvirus vaccination is vaccinia vaccination.

13. A method of treating smallpox infection, comprising: administering an effective amount of a tyrosine kinase inhibitor, or a pharmaceutically acceptable salt thereof.

14. A method of claim 13, wherein said tyrosine kinase inhibitor is 4-quinazolinamine-N-(3-chlor-4-fluorophenyl)-7-methoxy-6-[3-4-morpholin)propoxy], or a pharmaceutically acceptable salt thereof.

15. A method of treating a viral infection in a subject in need thereof, comprising:

administering an effective amount of an EGFR-blocker or tyrosine kinase inhibitor of epidermal growth factor receptor to a host infected with a virus, whereby said infection is treated, and wherein said virus utilizes the epidermal growth factor ("EGF") receptor to gain entry into the cell and/or to produce symptoms associated with viral infection.

16. A method of claim 15, wherein said virus is a poxvirus.

17. A method of claim 16, wherein said virus is variola.