[0005] Despite the efforts to date, there is a need for improved oncolytic viruses for treating cancers and hyperproliferative disorders in human subjects.

SUMMARY OF THE INVENTION

[0005a] In one aspect, provided herein is a recombinant oncolytic adenovirus comprising a first nucleotide sequence encoding a first therapeutic transgene selected from human endostatin and human angiostatin inserted between the start codon of E1b-19K and the start codon of E1b-55K.

[0005b] In another aspect, provided herein is a pharmaceutical composition comprising the recombinant oncolytic adenovirus as described herein and at least one pharmaceutically acceptable carrier or diluent.

[0005c] In another aspect, provided herein is use of the pharmaceutical composition as described herein in the manufacture of a medicament for inhibiting growth of a tumor or treating a cancer in a subject.

[0005d] In another aspect, provided herein is use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the pharmaceutical composition further comprises an anti-angiogenic agent.

[0005e] In another aspect, provided herein is use of the pharmaceutical composition as described herein in the manufacture of a medicament for lowering blood pressure in a subject and/or increasing nitric oxide (NO) production in a subject.

[0005f] In another aspect, provided herein is the pharmaceutical composition as described herein for use in therapy.

[0006] The invention is based, in part, upon the discovery of recombinant adenoviruses that can efficiently express anti-angiogenic factors such as endostatin and/or angiostatin. Additionally, the invention is based, in part, upon the discovery that an anti-cancer treatment using an anti-VEGF antibody, *e.g.*, bevacizumab, can be enhanced when the anti-VEGF antibody is administered in combination with a recombinant adenovirus, *e.g.*, an endostatin and/or angiostatin expressing adenovirus described herein. Surprisingly, it has been discovered that for certain cancers, the recombinant adenoviruses described herein, administered alone or in combination with an anti-VEGF antibody, *e.g.*, bevacizumab, do not merely slow or stop tumor growth but cause a tumor to go in to partial and/or complete remission.

[0007] Accordingly, in one aspect, the invention provides a recombinant adenovirus comprising a first nucleotide sequence encoding a first therapeutic transgene selected from

endostatin and angiostatin inserted into an E1b-19K insertion site; wherein the E1b-19K insertion site is located between the start site of E1b-19K and the start site of E1b-55K.

[0008] In certain embodiments, the recombinant adenovirus is a type 5 adenovirus (Ad5).

[0009] In certain embodiments, the E1b-19K insertion site is located between the start site of E1b-19K and the stop site of E1b-19K. In certain embodiments, the E1b-19K insertion site comprises a deletion of from about 100 to about 305, about 100 to about 300, about 100 to about 250, about 100 to about 200, about 100 to about 150, about 150 to about 305, about 150 to about 300, about 150 to about 250, or about 150 to about 200 nucleotides adjacent the start site of E1b-19K. In certain embodiments, the E1b-19K insertion site comprises a deletion of about 200 nucleotides, *e.g.*, 202 or 203 nucleotides adjacent the start site of E1b-19K. In certain embodiments, the E1b-19K insertion site comprises a deletion corresponding to nucleotides 1714-1916 of the Ad5 genome (SEQ ID NO: 1), or the first therapeutic transgene is inserted between nucleotides corresponding to 1713 and 1917 of the Ad5 genome (SEQ ID NO: 1). In certain embodiments, the first therapeutic transgene is inserted between CTGACCTC (SEQ ID NO: 2) and TCACCAGG (SEQ ID NO: 3), *e.g.*, the recombinant adenovirus comprises, in a 5' to 3' orientation, CTGACCTC (SEQ ID NO: 2), the first therapeutic transgene, and TCACCAGG (SEQ ID NO: 3).