WHAT IS CLAIMED IS:

1. A recombinant adenovirus comprising:

(a) a first nucleotide sequence encoding a first therapeutic transgene 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; and

(b) a second nucleotide sequence encoding a second therapeutic transgene inserted into an E3 insertion site, wherein the E3 insertion site is located between the stop site of pVIII and the start site of Fiber.

2. The recombinant adenovirus of claim 1, wherein the recombinant adenovirus is a type 5 adenovirus (Ad5).

3. The recombinant adenovirus of claims 1 or 2, wherein the E1b-19K insertion site is located between the start site of E1b-19K and the stop site of E1b-19K.

4. The recombinant adenovirus of any one of claims 1-3, wherein 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.

5. The recombinant adenovirus of any one of claims 1-4, wherein the E1b-19K insertion site comprises a deletion of about 200 nucleotides adjacent the start site of E1b-19K.

6. The recombinant adenovirus of any one of claims 1-5, wherein the E1b-19K insertion site comprises a deletion of 202 nucleotides adjacent the start site of E1b-19K.

7 The recombinant adenovirus of any one of claims 1-5, wherein the E1b-19K insertion site comprises a deletion of 203 nucleotides adjacent the start site of E1b-19K.

8. The recombinant adenovirus of any one of claims 1-7, wherein the E1b-19K insertion site comprises a deletion corresponding to nucleotides 1714-1917 of the Ad5 genome (SEQ ID NO: 23).

9. The recombinant adenovirus of any one of claims 1-7, wherein the E1b-19K insertion site comprises a deletion corresponding to nucleotides 1714-1916 of the Ad5 genome (SEQ ID NO: 23).

10. The recombinant adenovirus of any one of claims 1-9, wherein the first therapeutic transgene is inserted between nucleotides corresponding to 1714 and 1917 of the Ad5 genome (SEQ ID NO: 23).

11. The recombinant adenovirus of any one of claims 1-9, wherein the first therapeutic transgene is inserted between nucleotides corresponding to 1714 and 1916 of the Ad5 genome (SEQ ID NO: 23).

12. The recombinant adenovirus of any one of claims 1-11, wherein the first therapeutic transgene is inserted between CTGACCTC (SEQ ID NO: 1) and TCACCAGG (SEQ ID NO: 2).

13. The recombinant adenovirus of any one of claims 1-12, wherein the recombinant adenovirus comprises, in a 5' to 3' orientation, CTGACCTC (SEQ ID NO: 1), the first therapeutic transgene, and TCACCAGG (SEQ ID NO: 2).

14. The recombinant adenovirus of any one of claims 1-13, wherein the E3 insertion site comprises a deletion of from about 500 to about 3185, from about 500 to about 3000, from about 500 to about 2500, from about 500 to about 2000, from about 500 to about 1500, from about 500 to about 1000, from about 1000 to about 3185, from about 1000 to about 3000, from about 1000 to about 2500, from about 1000 to about 2000, from about 1000 to about 1500, from about 1500 to about 3185, from about 1500 to about 3000, from about 1500 to about 2000, from about 2000 to about 3185, from about 2000 to about 3000, from about 2000 to about 2500, from about 2500 to about 3185, from about 2500 to about 3000, or from about 3000 to about 3185 nucleotides.

15. The recombinant adenovirus of any one of claims 1-14, wherein the E3 insertion site is located between the stop site of E3-gp19K and the stop site of E3-14.7K.

16. The recombinant adenovirus of any one of claims 1-15, wherein the E3 insertion site is located between the stop site of E3-10.5K and the stop site of E3-14.7K.

17. The recombinant adenovirus of any one of claims 1-16, wherein the E3 insertion site comprises a deletion of from about 500 to about 1551, from about 500 to about 1500, from about 500 to about 1000, from about 1000 to about 1551, from about 1000 to about 1500, or from about 1500 to about 1551 nucleotides adjacent the stop site of E3-10.5K.

18. The recombinant adenovirus of any one of claims 1-17, wherein the E3 insertion site comprises a deletion of about 1050 nucleotides adjacent the stop site of E3-10.5K.

19. The recombinant adenovirus of any one of claims 1-18, wherein the E3 insertion site comprises a deletion of 1063 nucleotides adjacent the stop site of E3-10.5K.

20. The recombinant adenovirus of any one of claims 1-18, wherein the E3 insertion site comprises a deletion of 1064 nucleotides adjacent the stop site of E3-10.5K

21. The recombinant adenovirus of any one of claims 1-18, wherein the E3 insertion site comprises a deletion corresponding to the Ad5 dl309 E3 deletion.

22. The recombinant adenovirus of any one of claims 1-21, wherein the E3 insertion site comprises a deletion corresponding to nucleotides 29773-30836 of the Ad5 genome (SEQ ID NO: 23).

23. The recombinant adenovirus of any one of claims 1-22, wherein the second therapeutic transgene is inserted between nucleotides corresponding to 29773 and 30836 of the Ad5 genome (SEQ ID NO: 23).

24. The recombinant adenovirus of any one of claims 1-23, wherein the second therapeutic transgene is inserted between CAGTATGA (SEQ ID NO: 3) and TAATAAAAAA (SEQ ID NO: 4).

25. The recombinant adenovirus of any one of claims 1-24, wherein the recombinant adenovirus comprises, in a 5' to 3' orientation, CAGTATGA (SEQ ID NO: 3), the second therapeutic transgene, and TAATAAAAAA (SEQ ID NO: 4).

26. The recombinant adenovirus of claim 15, wherein the E3 insertion site comprises a deletion of from about 500 to about 1824, from about 500 to about 1500, from about 500 to about 1000,

from about 1000 to about 1824, from about 1000 to about 1500, or from about 1500 to about 1824 nucleotides adjacent the stop site of E3-gp19K.

27. The recombinant adenovirus of claim 26, wherein the E3 insertion site comprises a deletion of about 1600 nucleotides adjacent the stop site of E3-gp19K.

28. The recombinant adenovirus of claims 26 or 27, wherein the E3 insertion site comprises a deletion of 1622 nucleotides adjacent the stop site of E3-gp19K.

29. The recombinant adenovirus of any one of claims 26-28, wherein the E3 insertion site comprises a deletion corresponding to nucleotides 29218-30839 of the Ad5 genome (SEQ ID NO: 23).

30. The recombinant adenovirus of any one of claims 26-29, wherein the second therapeutic transgene is inserted between nucleotides corresponding to 29218 and 30839 of the Ad5 genome (SEQ ID NO: 23).

31. The recombinant adenovirus of any one of claims 26-30, wherein the second therapeutic transgene is inserted between TGCCTTAA (SEQ ID NO: 29) and TAAAAAAAAAT (SEQ ID NO: 30).

32. The recombinant adenovirus of any one of claims 26-31, wherein the recombinant adenovirus comprises, in a 5' to 3' orientation, TGCCTTAA (SEQ ID NO: 29), the second therapeutic transgene, and TAAAAAAAAAT (SEQ ID NO: 30).

33. A recombinant adenovirus comprising:

(a) a first nucleotide sequence encoding a first therapeutic transgene inserted into an E1b-19k insertion site; and

(b) a second nucleotide sequence encoding a second therapeutic transgene inserted into the 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, and wherein the first nucleotide sequence and the second nucleotide sequence are separated by a first internal ribosome entry site (IRES).

34. The recombinant adenovirus of claim 33, wherein the adenovirus is a type 5 adenovirus (Ad5).

35. The recombinant adenovirus of claims 33 or 34, wherein the E1b-19K insertion site is located between the start site of E1b-19K and the stop site of E1b-19K.

36. The recombinant adenovirus of any one of claims 33-35, wherein 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.

37. The recombinant adenovirus of any one of claims 33-36, wherein the E1b-19K insertion site comprises a deletion of about 200 nucleotides adjacent the start site of E1b-19K.

38. The recombinant adenovirus of any one of claims 33-37, wherein the E1b-19K insertion site comprises a deletion of 202 nucleotides adjacent the start site of E1b-19K.

39. The recombinant adenovirus of any one of claims 33-37, wherein the E1b-19K insertion site comprises a deletion of 203 nucleotides adjacent the start site of E1b-19K.

40. The recombinant adenovirus of any one of claims 33-39, wherein the E1b-19K insertion site comprises a deletion corresponding to nucleotides 1714-1917 of the Ad5 genome (SEQ ID NO: 23).

41. The recombinant adenovirus of any one of claims 33-39, wherein the E1b-19K insertion site comprises a deletion corresponding to nucleotides 1714-1916 of the Ad5 genome (SEQ ID NO: 23).

42. The recombinant adenovirus of any one of claims 33-41, wherein the first and second therapeutic transgenes are inserted between nucleotides corresponding to 1714 and 1917 of the Ad5 genome (SEQ ID NO: 23).

43. The recombinant adenovirus of any one of claims 33-41, wherein the first and second therapeutic transgenes are inserted between nucleotides corresponding to 1714 and 1916 of the Ad5 genome (SEQ ID NO: 23).

44. The recombinant adenovirus of any one of claims 33-43, wherein the first and second therapeutic transgenes are inserted between CTGACCTC (SEQ ID NO: 1) and TCACCAGG (SEQ ID NO: 2).

45. The recombinant adenovirus of any one of claims 33-44, wherein the recombinant adenovirus comprises, in a 5' to 3' orientation, CTGACCTC (SEQ ID NO: 1), the first therapeutic transgene, the IRES, the second therapeutic transgene, and TCACCAGG (SEQ ID NO: 2).

46. The recombinant adenovirus of any one of claims 33-45, wherein the recombinant adenovirus comprises a third nucleotide sequence encoding a third therapeutic transgene inserted into the E1b-19k insertion site wherein the second nucleotide sequence and the third nucleotide sequence are separated by a second internal ribosome entry site (IRES).

47. The recombinant adenovirus of claim 46, wherein the first, second, and third therapeutic transgenes are inserted between CTGACCTC (SEQ ID NO: 1) and TCACCAGG (SEQ ID NO: 2).

48. The recombinant adenovirus of claims 46 or 47, wherein the recombinant adenovirus comprises, in a 5' to 3' orientation, CTGACCTC (SEQ ID NO: 1), the first therapeutic transgene, the first IRES, the second therapeutic transgene, the second IRES, the third therapeutic transgene, and TCACCAGG (SEQ ID NO: 2).

49. The recombinant adenovirus of any of claims 33-48, wherein the recombinant adenovirus further comprises an E3 deletion, wherein the E3 deletion is located between the stop site of pVIII and the start site of Fiber.

50. The recombinant adenovirus of claim 49, wherein the E3 deletion comprises a deletion of from about 500 to about 3185, from about 500 to about 3000, from about 500 to about 2500, from about 500 to about 2000, from about 500 to about 1500, from about 500 to about 1000, from about 1000 to about 3185, from about 1000 to about 3000, from about 1000 to about 2500, from about 1000 to about 2000, from about 1000 to about 1500, from about 1500 to about 3185, from about 1500 to about 3000, from about 1500 to about 2000, from about 2000 to about 3185, from about 2000 to about 3000, from about 2000 to about 2500, from about 2500 to about 3185, from about 2500 to about 3000, or from about 3000 to about 3185 nucleotides.

51. The recombinant adenovirus of claims 49 or 50, wherein the E3 insertion site is located between the stop site of E3-gp19K and the stop site of E3-14.7K.

52. The recombinant adenovirus of any one of claims 49-51, wherein the E3 deletion is located between the stop site of E3-10.5K and the stop site of E3-14.7K and the start site of Fiber.

53. The recombinant adenovirus of any one of claims 49-52, wherein the E3 deletion comprises a deletion of from about 500 to about 1551, from about 500 to about 1500, from about 500 to about 1000, from about 1000 to about 1551, from about 1000 to about 1500, or from about 1500 to about 1551 nucleotides adjacent the stop site of E3-10.5K.

54. The recombinant adenovirus of any one of claims 49-53, wherein the E3 deletion comprises a deletion of about 1050 nucleotides adjacent the stop site of E3-10.5K.

55. The recombinant adenovirus of any one of claims 49-54, wherein the E3 deletion comprises a deletion of 1063 nucleotides adjacent the stop site of E3-10.5K.

56. The recombinant adenovirus of any one of claims 49-54, wherein the E3 deletion comprises a deletion of 1064 nucleotides adjacent the stop site of E3-10.5K.

57. The recombinant adenovirus of any one of claims 49-54, wherein the E3 deletion comprises a deletion corresponding to the Ad5 dl309 E3 deletion.

58. The recombinant adenovirus of any one of claims 49-57, wherein the E3 deletion comprises a deletion corresponding to nucleotides 29773-30836 of the Ad5 genome (SEQ ID NO: 23).

59. The recombinant adenovirus of any one of claims 49-51, wherein the E3 deletion comprises a deletion of from about 500 to about 1824, from about 500 to about 1500, from about 500 to about 1000, from about 1000 to about 1824, from about 1000 to about 1500, or from about 1500 to about 1824 nucleotides adjacent the stop site of E3-gp19K.

60. The recombinant adenovirus of claim 59, wherein the E3 deletion comprises a deletion of about 1600 nucleotides adjacent the stop site of E3-gp19K.

61. The recombinant adenovirus of claims 59 or 60, wherein the E3 deletion comprises a deletion of 1622 nucleotides adjacent the stop site of E3-gp19K.

62. The recombinant adenovirus of any one of claims 59-61, wherein the E3 deletion comprises a deletion corresponding to nucleotides 29218-30839 of the Ad5 genome (SEQ ID NO: 23).

63. The recombinant adenovirus of any of claims 33-45, wherein the recombinant adenovirus comprises a third nucleotide sequence encoding a third therapeutic transgene inserted into an E3 insertion site, wherein the E3 insertion site is located between the stop site of pVIII and the start site of Fiber.

64. The recombinant adenovirus of claim 63, wherein the E3 insertion site comprises a deletion of from about 500 to about 3185, from about 500 to about 3000, from about 500 to about 2500, from about 500 to about 2000, from about 500 to about 1500, from about 500 to about 1000, from about 1000 to about 3185, from about 1000 to about 3000, from about 1000 to about 2500, from about 1000 to about 2000, from about 1000 to about 1500, from about 1500 to about 3185, from about 1500 to about 3000, from about 1500 to about 2000, from about 2000 to about 3185, from about 2000 to about 3000, from about 2000 to about 2500, from about 2500 to about 3185, from about 2500 to about 3000, or from about 3000 to about 3185 nucleotides.

65. The recombinant adenovirus claims 63 or 64, wherein the E3 insertion site is located between the stop site of E3-gp19K and the stop site of E3-14.7K.

66. The recombinant adenovirus of any one of claims 63-65, wherein the E3 insertion site is located between the stop site of E3-10.5K and the stop site of E3-14.7K.

67. The recombinant adenovirus of any one of claims 63-66, wherein the E3 insertion site comprises a deletion of from about 500 to about 1551, from about 500 to about 1500, from about 500 to about 1000, from about 1000 to about 1551, from about 1000 to about 1500, or from about 1500 to about 1551 nucleotides adjacent the stop site of E3-10.5K.

68. The recombinant adenovirus of any one of claims 63-67, wherein the E3 insertion site comprises a deletion of about 1050 nucleotides adjacent the stop site of E3-10.5K.

69. The recombinant adenovirus of any one of claims 63-68, wherein the E3 insertion site comprises a deletion of 1063 nucleotides adjacent the stop site of E3-10.5K.

70. The recombinant adenovirus of any one of claims 63-68, wherein the E3 insertion site comprises a deletion of 1064 nucleotides adjacent the stop site of E3-10.5K.

71. The recombinant adenovirus of any one of claims 63-68, wherein the E3 insertion site comprises a deletion corresponding to the Ad5 dl309 E3 deletion.

72. The recombinant adenovirus of any one of claims 63-71, wherein the E3 insertion site comprises a deletion corresponding to nucleotides 29773-30836 of the Ad5 genome (SEQ ID NO: 23).

73. The recombinant adenovirus of any one of claims 63-72, wherein the third therapeutic transgene is inserted between nucleotides corresponding to 29773 and 30836 of the Ad5 genome (SEQ ID NO: 23).

74. The recombinant adenovirus of any one of claims 63-73, wherein the third therapeutic transgene is inserted between CAGTATGA (SEQ ID NO: 3) and TAATAAAAAA (SEQ ID NO: 4).

75. The recombinant adenovirus of any one of claims 63-74, wherein the recombinant adenovirus comprises, in a 5' to 3' orientation, CAGTATGA (SEQ ID NO: 3), the third therapeutic transgene, and TAATAAAAAA (SEQ ID NO: 4).

76. The recombinant adenovirus of any one of claims 63-65, wherein the E3 insertion site comprises a deletion of from about 500 to about 1824, from about 500 to about 1500, from about 500 to about 1000, from about 1000 to about 1824, from about 1000 to about 1500, or from about 1500 to about 1824 nucleotides adjacent the stop site of E3-gp19K.

77. The recombinant adenovirus of claim 76, wherein the E3 insertion site comprises a deletion of about 1600 nucleotides adjacent the stop site of E3-gp19K.

78. The recombinant adenovirus of claims 76 or 77, wherein the E3 insertion site comprises a deletion of 1622 nucleotides adjacent the stop site of E3-gp19K.

79. The recombinant adenovirus of any one of claims 76-78, wherein the E3 insertion site comprises a deletion corresponding to nucleotides 29218-30839 of the Ad5 genome (SEQ ID NO: 23).

80. The recombinant adenovirus of any one of claims 76-79, wherein the third therapeutic transgene is inserted between nucleotides corresponding to 29218 and 30839 of the Ad5 genome (SEQ ID NO: 23).

81. The recombinant adenovirus of any one of claims 76-80, wherein the third therapeutic transgene is inserted between TGCCTTAA (SEQ ID NO: 29) and TAAAAAAAAAT (SEQ ID NO: 30).

82. The recombinant adenovirus of any one of claims 76-81, wherein the recombinant adenovirus comprises, in a 5' to 3' orientation, TGCCTTAA (SEQ ID NO: 29), the third therapeutic transgene, and TAAAAAAAAAT (SEQ ID NO: 30).

83. The recombinant adenovirus of any one of claims 33-82, wherein the IRES is selected from the group consisting the encephalomyocarditis virus IRES, the foot-and-mouth disease virus IRES, and the poliovirus IRES.

84. The recombinant adenovirus of any of claims 1-83, wherein the recombinant adenovirus further comprises an E4 deletion, wherein the E4 deletion is located between the start site of E4-ORF6/7 and right inverted terminal repeat (ITR).

85. The recombinant adenovirus of claim 84, wherein the E4 deletion is located between the start site of E4-ORF6/7 and the start site of E4-ORF1.

86. The recombinant adenovirus of claims 84 or 85, wherein the E4 deletion comprises a deletion of from about 500 to about 2500, from about 500 to about 2000, from about 500 to about 1500, from about 500 to about 1000, from about 1000 to about 2500, from about 1000 to about 2000, from about 1000 to about 1500, from about 1500 to about 2500, from about 1500 to about 2000, or from about 2000 to about 2500 nucleotides.

87. The recombinant adenovirus of any one of claims 84-86, wherein the E4 deletion comprises a deletion of from about 250 to about 1500, from about 250 to about 1250, from about 250 to about 1000, from about 250 to about 750, from about 250 to about 500, from 500 to about 1500, from about 500 to about 1250, from about 500 to about 1000, from about 500 to about 750, from 750 to about 1500, from about 750 to about 1250, from about 750 to about 1000, from about 1000 to

about 1500, from about 1000 to about 1250, or from about 1250 to about 1500 nucleotides adjacent the start site of E4-ORF6/7.

88. The recombinant adenovirus of any one of claims 84-87, wherein the E4 deletion comprises a deletion of about 1450 nucleotides adjacent the start site of E4-ORF6/7.

89. The recombinant adenovirus of any one of claims 84-88, wherein the E4 deletion comprises a deletion of 1449 nucleotides adjacent the start site of E4-ORF6/7.

90. The recombinant adenovirus of any one of claims 84-89, wherein the E4 deletion comprises a deletion corresponding to nucleotides 34078-35526 of the Ad5 genome (SEQ ID NO: 23).

91. The recombinant adenovirus of any one of claims 1-90, wherein the first and/or second therapeutic transgenes are not operably linked to an exogenous promoter sequence.

92. The recombinant adenovirus of any one of claims 46-90, wherein the first, second, and/or third therapeutic transgenes are not operably linked to an exogenous promoter sequence.

93. The recombinant adenovirus of any one of claims 1-90, wherein none of the therapeutic transgenes are operably linked to an exogenous promoter sequence.

94. The recombinant adenovirus of any one of claims 1-93, wherein the combined size of the first and second therapeutic transgenes comprises from about 500 to about 5000, from about 500 to about 4000, from about 500 to about 3000, from about 500 to about 2000, from about 500 to about 1000, from about 1000 to about 5000, from about 1000 to about 4000, from about 1000 to about 3000, from about 1000 to about 2000, from about 2000 to about 5000, from about 2000 to about 4000, from about 2000 to about 3000, from about 3000 to about 5000, from about 3000 to about 4000, or from about 4000 to about 5000 nucleotides.

95. The recombinant adenovirus of any one of claims 1-93, wherein the combined size of the first and second therapeutic transgenes comprises from about 500 to about 7000, from about 500 to about 6000, from about 500 to about 5000, from about 500 to about 4000, from about 500 to about 3000, from about 500 to about 2000, from about 500 to about 1000, from about 1000 to about 7000, from about 1000 to about 6000, from about 1000 to about 5000, from about 1000 to about 4000, from about 1000 to about 3000, from about 1000 to about 2000, from about 2000 to about

7000, from about 2000 to about 6000, from about 2000 to about 5000, from about 2000 to about 4000, from about 2000 to about 3000, from about 3000 to about 7000, from about 3000 to about 6000, from about 3000 to about 5000, from about 3000 to about 4000, from about 4000 to about 7000, from about 4000 to about 6000, from about 4000 to about 5000 nucleotides, from about 5000 to about 7000, from about 5000 to about 6000, or from about 6000 to about 7000 nucleotides.

96. The recombinant adenovirus of any one of claims 46-93, wherein the combined size of the first, second, and third therapeutic transgenes comprises from about 500 to about 5000, from about 500 to about 4000, from about 500 to about 3000, from about 500 to about 2000, from about 500 to about 1000, from about 1000 to about 5000, from about 1000 to about 4000, from about 1000 to about 3000, from about 1000 to about 2000, from about 2000 to about 5000, from about 2000 to about 4000, from about 2000 to about 3000, from about 3000 to about 5000, from about 3000 to about 4000, or from about 4000 to about 5000 nucleotides.

97. The recombinant adenovirus of any one of claims 46-93, wherein the combined size of the first, second, and third therapeutic transgenes comprises from about 500 to about 7000, from about 500 to about 6000, from about 500 to about 5000, from about 500 to about 4000, from about 500 to about 3000, from about 500 to about 2000, from about 500 to about 1000, from about 1000 to about 7000, from about 1000 to about 6000, from about 1000 to about 5000, from about 1000 to about 4000, from about 1000 to about 3000, from about 1000 to about 2000, from about 2000 to about 7000, from about 2000 to about 6000, from about 2000 to about 5000, from about 2000 to about 4000, from about 2000 to about 3000, from about 3000 to about 7000, from about 3000 to about 6000, from about 3000 to about 5000, from about 3000 to about 4000, from about 4000 to about 7000, from about 4000 to about 6000, from about 4000 to about 5000 nucleotides, from about 5000 to about 7000, from about 5000 to about 6000, or from about 6000 to about 7000 nucleotides.

98. The recombinant adenovirus of any one of claims 1-97, wherein the combined size of each of the therapeutic transgenes comprises from about 500 to about 5000, from about 500 to about 4000, from about 500 to about 3000, from about 500 to about 2000, from about 500 to about 1000, from about 1000 to about 5000, from about 1000 to about 4000, from about 1000 to about 3000, from about 1000 to about 2000, from about 2000 to about 5000, from about 2000 to about 4000,

from about 2000 to about 3000, from about 3000 to about 5000, from about 3000 to about 4000, or from about 4000 to about 5000 nucleotides.

99. The recombinant adenovirus of any one of claims 1-97, wherein the combined size of each of the therapeutic transgenes comprises from about 500 to about 7000, from about 500 to about 6000, from about 500 to about 5000, from about 500 to about 4000, from about 500 to about 3000, from about 500 to about 2000, from about 500 to about 1000, from about 1000 to about 7000, from about 1000 to about 6000, from about 1000 to about 5000, from about 1000 to about 4000, from about 1000 to about 3000, from about 1000 to about 2000, from about 2000 to about 7000, from about 2000 to about 6000, from about 2000 to about 5000, from about 2000 to about 4000, from about 2000 to about 3000, from about 3000 to about 7000, from about 3000 to about 6000, from about 3000 to about 5000, from about 3000 to about 4000, from about 4000 to about 7000, from about 4000 to about 6000, from about 4000 to about 5000 nucleotides, from about 5000 to about 7000, from about 5000 to about 6000, or from about 6000 to about 7000 nucleotides.

100. The recombinant adenovirus of any one of claims 1-99, wherein the combined size of the first and second therapeutic transgenes comprises at least from about 500 to about 5000, from about 500 to about 4000, from about 500 to about 3000, from about 500 to about 2000, from about 500 to about 1000, from about 1000 to about 5000, from about 1000 to about 4000, from about 1000 to about 3000, from about 1000 to about 2000, from about 2000 to about 5000, from about 2000 to about 4000, from about 2000 to about 3000, from about 3000 to about 5000, from about 3000 to about 4000, or from about 4000 to about 5000 nucleotides.

101. The recombinant adenovirus of any one of claims 1-99, wherein the combined size of the first and second therapeutic transgenes comprises at least from about 500 to about 7000, from about 500 to about 6000, from about 500 to about 5000, from about 500 to about 4000, from about 500 to about 3000, from about 500 to about 2000, from about 500 to about 1000, from about 1000 to about 7000, from about 1000 to about 6000, from about 1000 to about 5000, from about 1000 to about 4000, from about 1000 to about 3000, from about 1000 to about 2000, from about 2000 to about 7000, from about 2000 to about 6000, from about 2000 to about 5000, from about 2000 to about 4000, from about 2000 to about 3000, from about 3000 to about 7000, from about 3000 to about 6000, from about 3000 to about 5000, from about 3000 to about 4000, from about 4000 to

about 7000, from about 4000 to about 6000, from about 4000 to about 5000 nucleotides, from about 5000 to about 7000, from about 5000 to about 6000, or from about 6000 to about 7000 nucleotides.

102. The recombinant adenovirus of any one of claims 46-99, wherein the combined size of the first, second, and third therapeutic transgenes comprises at least from about 500 to about 5000, from about 500 to about 4000, from about 500 to about 3000, from about 500 to about 2000, from about 500 to about 1000, from about 1000 to about 5000, from about 1000 to about 4000, from about 1000 to about 3000, from about 1000 to about 2000, from about 2000 to about 5000, from about 2000 to about 4000, from about 2000 to about 3000, from about 3000 to about 5000, from about 3000 to about 4000, or from about 4000 to about 5000 nucleotides.

103. The recombinant adenovirus of any one of claims 46-99, wherein the combined size of the first, second, and third therapeutic transgenes comprises at least from about 500 to about 7000, from about 500 to about 6000, from about 500 to about 5000, from about 500 to about 4000, from about 500 to about 3000, from about 500 to about 2000, from about 500 to about 1000, from about 1000 to about 7000, from about 1000 to about 6000, from about 1000 to about 5000, from about 1000 to about 4000, from about 1000 to about 3000, from about 1000 to about 2000, from about 2000 to about 7000, from about 2000 to about 6000, from about 2000 to about 5000, from about 2000 to about 4000, from about 2000 to about 3000, from about 3000 to about 7000, from about 3000 to about 6000, from about 3000 to about 5000, from about 3000 to about 4000, from about 4000 to about 7000, from about 4000 to about 6000, from about 4000 to about 5000 nucleotides, from about 5000 to about 7000, from about 5000 to about 6000, or from about 6000 to about 7000 nucleotides.

104. The recombinant adenovirus of any one of claims 1-99, wherein the combined size of each of the therapeutic transgenes comprises at least from about 500 to about 5000, from about 500 to about 4000, from about 500 to about 3000, from about 500 to about 2000, from about 500 to about 1000, from about 1000 to about 5000, from about 1000 to about 4000, from about 1000 to about 3000, from about 1000 to about 2000, from about 2000 to about 5000, from about 2000 to about 4000, from about 2000 to about 3000, from about 3000 to about 5000, from about 3000 to about 4000, or from about 4000 to about 5000 nucleotides.

105. The recombinant adenovirus of any one of claims 1-99, wherein the combined size of each of the therapeutic transgenes comprises at least from about 500 to about 7000, from about 500 to about 6000, from about 500 to about 5000, from about 500 to about 4000, from about 500 to about 3000, from about 500 to about 2000, from about 500 to about 1000, from about 1000 to about 7000, from about 1000 to about 6000, from about 1000 to about 5000, from about 1000 to about 4000, from about 1000 to about 3000, from about 1000 to about 2000, from about 2000 to about 7000, from about 2000 to about 6000, from about 2000 to about 5000, from about 2000 to about 4000, from about 2000 to about 3000, from about 3000 to about 7000, from about 3000 to about 6000, from about 3000 to about 5000, from about 3000 to about 4000, from about 4000 to about 7000, from about 4000 to about 6000, from about 4000 to about 5000 nucleotides, from about 5000 to about 7000, from about 5000 to about 6000, or from about 6000 to about 7000 nucleotides.

106. The recombinant adenovirus of any one of claims 1-105, wherein the combined size of the first and second therapeutic transgenes comprises at least about 500, about 1000, about 2000, about 3000, about 4000, or about 5000 nucleotides.

107. The recombinant adenovirus of any one of claims 1-105, wherein the combined size of the first and second therapeutic transgenes comprises at least about 500, about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, or about 7000 nucleotides.

108. The recombinant adenovirus of any one of claims 46-105, wherein the combined size of the first, second, and third therapeutic transgenes comprises at least about 500, about 1000, about 2000, about 3000, about 4000, or about 5000 nucleotides.

109. The recombinant adenovirus of any one of claims 46-105, wherein the combined size of the first, second, and third therapeutic transgenes comprises at least about 500, about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, or about 7000 nucleotides.

110. The recombinant adenovirus of any one of claims 1-109, wherein the combined size of each of the therapeutic transgenes comprises at least about 500, about 1000, about 2000, about 3000, about 4000, or about 5000 nucleotides.

111. The recombinant adenovirus of any one of claims 1-109, wherein the combined size of each of the therapeutic transgenes comprises at least about 500, about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, or about 7000 nucleotides.

112. The recombinant adenovirus of any one of claims 1-111, wherein the combined size of the first and second therapeutic transgenes comprises about 1650 nucleotides.

113. The recombinant adenovirus of any one of claims 1-111, wherein the combined size of the first and second therapeutic transgenes comprises about 3100 nucleotides.

114. The recombinant adenovirus of any one of claims 46-111, wherein the combined size of the first, second, and third therapeutic transgenes comprises about 1650 nucleotides.

115. The recombinant adenovirus of any one of claims 46-111, wherein the combined size of the first, second, and third therapeutic transgenes comprises about 3100 nucleotides.

116. The recombinant adenovirus of any one of claims 1-115, wherein the combined size of each of the therapeutic transgenes comprises about 1650 nucleotides.

117. The recombinant adenovirus of any one of claims 1-115, wherein the combined size of each of the therapeutic transgenes comprises about 3100 nucleotides.

118. The recombinant adenovirus of any one of claims 1-117, wherein the first and/or second therapeutic transgene encodes a therapeutic polypeptide selected from the group consisting of CD80, CD137L, IL-23A/p19, endostatin, angiostatin, ICAM-1, and a TGF-β trap.

119. The recombinant adenovirus of any one of claims 46-117, wherein the first, second and/or third therapeutic transgene encodes a therapeutic polypeptide selected from the group consisting of CD80, CD137L, IL-23A/p19, endostatin, angiostatin, ICAM-1, and a TGF-β trap.

120. The recombinant adenovirus of any one of claims 1-117, wherein any one of the therapeutic transgenes encode a therapeutic polypeptide selected from the group consisting of CD80, CD137L, IL-23A/p19, endostatin, angiostatin, ICAM-1, and a TGF-β trap.

121. The recombinant adenovirus of any one of claims 1-117, wherein the first and/or second therapeutic transgene encodes a therapeutic polypeptide selected from the group consisting of CD80, CD137L, IL-23A/p19, endostatin, angiostatin, ICAM-1, a TGF-β trap, TGF-β, CD19,

CD20, IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, CD154, CD86, BORIS/CTCFL, FGF, IL-24, MAGE, NY-ESO-1, acetylcholine, interferon-gamma, DKK1/Wnt, p53, thymidine kinase, an anti-PD-1 antibody heavy chain or light chain, and an anti-PD-L1 antibody heavy chain or light chain.

122. The recombinant adenovirus of any one of claims 46-117, wherein the first, second and/or third therapeutic transgene encodes a therapeutic polypeptide selected from the group consisting of CD80, CD137L, IL-23A/p19, endostatin, angiostatin, ICAM-1, a TGF-β trap, TGF-β, CD19, CD20, IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, CD154, CD86, BORIS/CTCFL, FGF, IL-24, MAGE, NY-ESO-1, acetylcholine, interferon-gamma, DKK1/Wnt, p53, thymidine kinase, an anti-PD-1 antibody heavy chain or light chain, and an anti-PD-L1 antibody heavy chain or light chain.

123. The recombinant adenovirus of any one of claims 1-117, wherein any one of the therapeutic transgenes encode a therapeutic polypeptide selected from the group consisting of CD80, CD137L, IL-23A/p19, endostatin, angiostatin, ICAM-1, a TGF-β trap, TGF-β, CD19, CD20, IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, CD154, CD86, BORIS/CTCFL, FGF, IL-24, MAGE, NY-ESO-1, acetylcholine, interferon-gamma, DKK1/Wnt, p53, thymidine kinase, an anti-PD-1 antibody heavy chain or light chain, and an anti-PD-L1 antibody heavy chain or light chain.

124. The recombinant adenovirus of any one of claims 1-117, wherein the first and/or second therapeutic transgene encodes a therapeutic polypeptide selected from the group consisting of CD80, CD137L, IL-23, IL-23A/p19, IL-27, IL-27A/p28, IL-27B/EBI3, endostatin, angiostatin, ICAM-1, a TGF-β trap, TGF-β, CD19, CD20, IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, CD154, CD86, BORIS/CTCFL, FGF, IL-24, MAGE, NY-ESO-1, acetylcholine, interferon-gamma, DKK1/Wnt, p53, thymidine kinase, an anti-PD-1 antibody heavy chain or light chain, and an anti-PD-L1 antibody heavy chain or light chain.

125. The recombinant adenovirus of any one of claims 46-117, wherein the first, second and/or third therapeutic transgene encodes a therapeutic polypeptide selected from the group consisting of CD80, CD137L, IL-23, IL-23A/p19, IL-27, IL-27A/p28, IL-27B/EBI3, endostatin, angiostatin, ICAM-1, a TGF-β trap, TGF-β, CD19, CD20, IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, CD154, CD86, BORIS/CTCFL, FGF, IL-24, MAGE, NY-ESO-1, acetylcholine, interferon-gamma, DKK1/Wnt, p53, thymidine kinase, an anti-PD-1 antibody heavy chain or light chain, and an anti-PD-L1 antibody heavy chain or light chain.

126. The recombinant adenovirus of any one of claims 1-117, wherein any one of the therapeutic transgenes encode a therapeutic polypeptide selected from the group consisting of CD80, CD137L, IL-23, IL-23A/p19, IL-27, IL-27A/p28, IL-27B/EBI3, endostatin, angiostatin, ICAM-1, a TGF-β trap, TGF-β, CD19, CD20, IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, CD154, CD86, BORIS/CTCFL, FGF, IL-24, MAGE, NY-ESO-1, acetylcholine, interferon-gamma, DKK1/Wnt, p53, thymidine kinase, an anti-PD-1 antibody heavy chain or light chain, and an anti-PD-L1 antibody heavy chain or light chain.

127. The recombinant adenovirus of any one of claims 1-126, wherein the first and second therapeutic transgene encode a first and second subunit, respectively, of a heterodimeric cytokine.

128. The recombinant adenovirus of any one of claim 1-126, wherein the first and/or second therapeutic transgenes are selected from the group consisting of CD80 and CD137L.

129. The recombinant adenovirus of any one of claim 46-126, wherein the first, second and/or third therapeutic transgenes are selected from the group consisting of CD80, CD137L, and ICAM-1.

130. The recombinant adenovirus of claims 127 or 128, wherein the first therapeutic transgene encodes CD80.

131. The recombinant adenovirus of any one of claims 127-130, wherein the second therapeutic transgene encodes CD137L.

132. The recombinant adenovirus of any one of claims 128-131, wherein the third therapeutic transgene encodes ICAM-1.

133. The recombinant adenovirus of any one of claims 128-132, wherein the recombinant adenovirus comprises a nucleotide sequence encoding an amino acid sequence that is encoded by SEQ ID NO: 5.

134. The recombinant adenovirus of any one of claims 128-133, wherein the recombinant adenovirus comprises the nucleotide sequence of SEQ ID NO: 6.

135. The recombinant adenovirus of any one of claims 128-134, wherein the recombinant adenovirus comprises a nucleotide sequence encoding an amino acid sequence that is encoded by SEQ ID NO: 7.

136. The recombinant adenovirus of any one of claims 128-135, wherein the recombinant adenovirus comprises the nucleotide sequence of SEQ ID NO: 8.

137. The recombinant adenovirus of any one of claims 128-136, wherein the recombinant adenovirus comprises the nucleotide sequence of SEQ ID NO: 27.

138. The recombinant adenovirus of any one of claims 128-137, wherein the recombinant adenovirus comprises a nucleotide sequence encoding an amino acid sequence that is encoded by SEQ ID NO: 32.

139. The recombinant adenovirus of any one of claims 128-138, wherein the recombinant adenovirus comprises the nucleotide sequence of SEQ ID NO: 31 or SEQ ID NO: 9.

140. The recombinant adenovirus of any one of claims 128-137, wherein the recombinant adenovirus comprises the nucleotide sequence of SEQ ID NO: 31.

141. The recombinant adenovirus of any one of claims 128-137, wherein the recombinant adenovirus comprises the nucleotide sequence of SEQ ID NO: 22.

142. The recombinant adenovirus of any one of claims 1-127, wherein the first and/or second therapeutic transgenes are selected from the group consisting of IL-27A/p28 and IL-27B/EBI3.

143. The recombinant adenovirus of claim 142, wherein the first therapeutic transgene encodes IL-27A/p28.

144. The recombinant adenovirus of claims 142 or 143, wherein the second therapeutic transgene encodes IL-27B/EBI3.

145. The recombinant adenovirus of any one of claims 1-126, wherein the first and/or second therapeutic transgenes are selected from the group consisting of endostatin and angiostatin.

146. The recombinant adenovirus of claim 145, wherein the first therapeutic transgene encodes endostatin.

147. The recombinant adenovirus of claims 145 or 146, wherein the second therapeutic transgene encodes angiostatin

148. The recombinant adenovirus of any one of claims 145-147, wherein the recombinant adenovirus comprises a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 37 or SEQ ID NO: 38.

149. The recombinant adenovirus of any one of claims 145-148, wherein the recombinant adenovirus comprises a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44.

150. The recombinant adenovirus of any one of claims 145-149, wherein the recombinant adenovirus comprises the nucleotide sequence of SEQ ID NO: 11.

151. The recombinant adenovirus of any one of claims 1-150, wherein the recombinant adenovirus further comprises a deletion of a Pea3 binding site, or a functional fragment thereof.

152. The recombinant adenovirus of claim 151, wherein the recombinant adenovirus comprises a deletion of nucleotides corresponding to about -300 to about -250 upstream of the initiation site of E1a.

153. The recombinant adenovirus of claims 151 or 152, wherein the recombinant adenovirus comprises a deletion of nucleotides corresponding to -305 to -255 upstream of the initiation site of E1a.

154. The recombinant adenovirus of claims 151 or 152, wherein the recombinant adenovirus comprises a deletion of nucleotides corresponding to -304 to -255 upstream of the initiation site of E1a.

155. A recombinant adenovirus comprising SEQ ID NO: 14, or a sequence having 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 14.

156. The recombinant adenovirus of any one of claims 1-155, wherein the recombinant adenovirus selectively replicates in a hyperproliferative cell.

157. The recombinant adenovirus of any one of claims 1-156, wherein the recombinant adenovirus selectively expresses the first and/or the second therapeutic transgene in a hyperproliferative cell.

158. The recombinant adenovirus of any one of claims 46-157, wherein the recombinant adenovirus selectively expresses the first, second, and/or third therapeutic transgene in a hyperproliferative cell.

159. The recombinant adenovirus of any one of claims 156-158, wherein the hyperproliferative cell is a cancer cell.

160. The recombinant adenovirus of any one of claims 1-159, wherein the recombinant adenovirus is an oncolytic virus.

161. A pharmaceutical composition comprising the recombinant adenovirus of any one of claims 1-160 and at least one pharmaceutically acceptable carrier or diluent.

162. A method of expressing two therapeutic transgenes in a target cell comprising exposing the cell to an effective amount of the recombinant adenovirus of any one of claims 1-160 to express the two therapeutic transgenes.

163. A method of expressing three therapeutic transgenes in a target cell comprising exposing the cell to an effective amount of the recombinant adenovirus of any one of claims 46-160 to express the two therapeutic transgenes.

164. A method of inhibiting proliferation of a tumor cell comprising exposing the cell to an effective amount of the recombinant adenovirus of any one of claims 1-160 to inhibit proliferation of the tumor cell.

165. A method of inhibiting tumor growth in a subject in need thereof, the method comprising administering to the subject to an effective amount of the recombinant adenovirus of any one of claims 1-160 to inhibit growth of the tumor.

166. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of the recombinant adenovirus of any one of claims 1-160 to treat the cancer in the subject.

167. The method of claim 166, wherein the cancer is selected from the group consisting of melanoma, squamous cell carcinoma of the skin, basal cell carcinoma, head and neck cancer, breast cancer, anal cancer, cervical cancer, non-small cell lung cancer, mesothelioma, small cell lung cancer, renal cell carcinoma, prostate cancer, gastroesophageal cancer, colorectal cancer, testicular cancer, bladder cancer, ovarian cancer, hepatocellular carcinoma, cholangiocarcinoma, brain cancer, endometrial cancer, neuroendocrine cancer, merkel cell carcinoma, gastrointestinal stromal tumors, a sarcoma, and pancreatic cancer.

168. The method of claims 165-167, wherein the recombinant adenovirus is administered in combination with one or more therapies selected from the group consisting of surgery, radiation, chemotherapy, immunotherapy, hormone therapy, and virotherapy.

169. The method of any one of claims 162-168, wherein the effective amount of the recombinant adenovirus is 10^2-10^{15} plaque forming units (pfus).

170. The method of any one of claims 165-169, wherein the subject is a human.

171. The method of claim 170, wherein the subject is a pediatric human.

172. The method of any one of claims 165-171, wherein the method further comprises measuring an immune response to an antigen in the subject.

173. The method of any one of claims 165-172, wherein the effective amount of the recombinant virus is identified by measuring an immune response to an antigen in the subject.

174. The method of claim 172 or 173, wherein the immune response to the antigen is measured by injecting the subject with the antigen at an injection site on the skin of the subject and measuring the size of an induration at the injection site.