

[0017] Such recombinant nucleic acids and viruses are particularly deemed to infect an antigen presenting cell to thereby stimulate T cell activation in a T cell that contacts the antigen presenting cell. Therefore, the inventors also contemplate a method of stimulating an immune response in a mammal that comprises a step of administering the virus (e.g., by subcutaneous or subdermal injection) under a protocol effective to stimulate the immune response. Where desired, such methods will further include administering low-dose chemotherapy or low-dose radiation therapy to the mammal, preferably in metronomical fashion. In another aspect, the present disclosure relates to the use of a virus as disclosed herein in the manufacture of a medicament for stimulating an immune response in a mammal in need thereof, wherein the virus is to be administered under a protocol effective to stimulate the immune response.

[0018] Various objects, features, aspects and advantages of the inventive subject matter will become more apparent from the following detailed description of preferred embodiments.

Detailed Description

[0019] The inventors have discovered that immune therapeutic compositions can be prepared using a viral vector, and most preferably an adenoviral vector, that includes a recombinant nucleic acid encoding a plurality of (co-)stimulatory molecules and at least one inhibitor of an immune checkpoint receptor that is preferably anchored to a cell membrane of an antigen presenting cell. Moreover, such recombinant virus or viral vector will further include one or more human cancer-associated sequences to stimulate an immune reaction against cells presenting proteins encoded by the cancer-associated sequences. Thus, an antigen presenting cell expressing the recombinant proteins will therefore present the antigen in the context of both stimulatory factors and anti-inhibitory factors that promote sufficient interaction for an antigen specific T cell activation.

[0020] It is still further preferred that the virus is non-immunogenic (*i.e.*, can be administered at least two, at least three, at least four or even more times without eliciting a protective immune response against the virus), replication deficient, and administered subcutaneously or subdermally to the patient to thereby preferentially infect dendritic cells. In one particularly preferred example, the viral vector is a recombinant adenovirus that has the E1, E2b, and E3 viral genes deleted to so reduce immunogenicity and increase capacity of payload. Introduced into such modified viral genome is then one or more expression cassettes that encode under

suitable control elements (typically a constitutively active promoter) the co-stimulatory molecules are CD80 (B7.1) and CD86 (B7.2), activator molecules CD54 (ICAM-1/BB2) and CD11 (LFA-1), and an inhibitor for the immune checkpoint receptor CTLA-4 (*e.g.*, a scFv

30. Use of a virus according to any one of claims 22-24 , in the manufacture of a medicament for stimulating an immune response in a mammal in need thereof, wherein the virus is to be administered under a protocol effective to stimulate the immune response.
31. The use of claim 30 wherein the virus is to be administered by subcutaneous or subdermal injection.
32. The use of claim 30, wherein a low-dose chemotherapy or a low-dose radiation therapy is to be administered to the mammal.
33. The use of claim 32 wherein the low-dose chemotherapy or the low-dose radiation therapy is to be metronomically administered.