However, the first generation of vaccine vectors based on the archetypal human adenovirus AdHu5 showed poor efficacy in clinical trials, despite encouraging pre-clinical data[1]. It was subsequently discovered that a large proportion of human adults harbour significant titres of neutralising antibodies to common human serotypes such as AdHu2 and AdHu5, as a result of natural infection. Neutralising antibodies could reduce the potency of viral vector vaccines by blocking viral entry into host cells and hence delivery of the target transgene.

The occurrence of pre-existing anti-vector immunity is being addressed through the development of new adenoviral vectors based on serotypes to which the human population is less likely to have been exposed, including those of chimpanzee origin[2,3]. However, some such chimpanzee adenoviral vectors have limited efficacy on the grounds of unexplained immunity in human populations, varying levels of cross-reactivity with human adenoviruses, and sub-optimal growth in transformed cell lines. In addition, it is advantageous to have a range of different adenoviral vectors available for use in immunising against different diseases, on the grounds that induction of neutralising antibodies against a vector may prevent its re-administration for another indication.

WO2012/172277 describes an adenovirus vector derived from chimpanzee adenovirus AdY25, which addresses some of the above-described problems in the art. This vector is termed ChAdOx1.

However, there continues to be a need in the art for highly immunogenic, non-human adenoviral vectors which effectively deliver the target transgene, minimize the effect of pre-existing immunity to adenovirus serotypes and replicate efficiently in transformed cell lines.

Summary of Invention

In one aspect, the present disclosure refers to an adenoviral vector comprising the genome of chimpanzee adenovirus C68, wherein the genome of the adenovirus has been modified such that the vector lacks the native E4 locus of the adenovirus and comprises heterologous E4Orf4, E4Orf6 and E4Orf6/7 coding regions from AdHu5 in the E4 locus of the adenovirus, wherein the adenoviral vector further comprises heterologous E4Orf1, E4Orf2 and E4Orf3 coding regions from AdY25, wherein the

adenoviral vector lacks a functional E1 locus, and wherein the adenoviral vector lacks an E3 locus.

In another aspect, the present disclosure refers to an immunogenic composition comprising the adenovirus vector as disclosed herein and optionally one or more additional active ingredients, a pharmaceutically acceptable carrier, diluent, excipient or adjuvant. In yet another aspect, the present disclosure refers to the immunogenic composition as disclosed herein for use in medicine.

In still another aspect, the present disclosure refers to the use of the immunogenic composition as disclosed herein in the manufacture of a medicament for treating a disease selected from the group consisting of tuberculosis and other mycobacterial infections including Johne's disease, Crohn's disease, malaria, influenza, Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome, Hepatitis C virus infection, Cytomegalovirus infection, Human papilloma virus infection, adenoviral infection, leishmaniasis, *streptococcus spp*. infection, *staphylococcus spp*. infection, *meningococcus spp*. infection, foot and mouth disease, chikungunya virus infection, Zika virus infection, rabies, Crimean Congo haemorrhagic fever, Ebola virus infection, Marburg, Lassa fever, Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome coronavirus diseases, Nipah and Rift Valley fever, and Chikungunya.

In a further aspect, the present disclosure refers to a polynucleotide sequence encoding the adenoviral vector as disclosed herein. In still another aspect, the present disclosure refers to a host cell transduced with the adenoviral vector as disclosed herein. In yet another aspect, the present disclosure refers to a method of producing the adenoviral vector as disclosed herein, comprising the step of incorporating the polynucleotide as disclosed herein into a Bacterial Artificial Chromosome (BAC) to produce an Ad-BAC vector. In another aspect, the present disclosure refers to a Bacterial Artificial Chromosome (BAC) clone comprising the polynucleotide sequence as disclosed herein. In still a further aspect, the present disclosure refers to a packaging cell line producing the viral vector as disclosed herein. In yet another aspect, the present disclosure refers to a kit comprising: (i) an adenoviral vector as disclosed herein or an immunogenic composition as disclosed herein, and (ii) instructions for use.

Claims

1. An adenoviral vector comprising the genome of chimpanzee adenovirus C68, wherein the genome of the adenovirus has been modified such that the vector lacks the native E4 locus of the adenovirus and comprises heterologous E4Orf4, E4Orf6 and E4Orf6/7 coding regions from AdHu5 in the E4 locus of the adenovirus, wherein the adenoviral vector further comprises heterologous E4Orf1, E4Orf2 and E4Orf3 coding regions from AdY25, wherein the adenoviral vector lacks a functional E1 locus, and wherein the adenoviral vector lacks an E3 locus.

2. The adenoviral vector of claim 1, wherein said adenoviral vector comprises one or more capsid proteins selected from the group consisting of:

   (a) a hexon protein encoded by the coding sequence corresponding to nucleotides 18315 to 21116 of SEQ ID NO. 1 or a sequence having at least 80 % identity thereto;

   (b) a penton protein encoded by the coding sequence corresponding to nucleotides 13884 to 15488 of SEQ ID NO. 1, or a sequence having at least 80 % identity thereto; and

   (c) a fibre protein encoded by the coding sequence corresponding to nucleotides 32134 to 33411 of SEQ ID NO. 1, or a sequence having at least 80 % identity thereto.

3. The adenoviral vector of any of claims 1 to 2, further comprising an exogenous nucleotide sequence of interest that encodes a protein or polypeptide.

4. The adenoviral vector of claim 3, wherein said protein or polypeptide is selected from the group consisting of an antigen, a molecular adjuvant, an immunostimulatory protein or a recombinase.

5. The adenoviral vector of claim 4, wherein the antigen is a pathogen-derived antigen.

6. The adenoviral vector of claim 5, wherein the pathogen is selected from the group consisting of *M. tuberculosis*, *Plasmodium* sp., influenza virus, Human Immunodeficiency Virus, *Hepatitis C virus*, *Cytomegalovirus*, *Human papilloma virus*, rabies virus, measles virus, mumps, rubella, zika virus, leishmania parasites or *Mycobacterium* sp..

7. The adenoviral vector of claim 6, wherein said antigen is from Mycobacterium avium subspecies paratuberculosis (MAP).

8. The adenoviral vector of claim 6, wherein the antigen is rabies virus glycoprotein.

9. The adenoviral vector of claim 3, wherein said exogenous nucleotide sequence of interest is an miRNA or immunostimulatory RNA sequence.

10. An immunogenic composition comprising the adenovirus vector according to any of claims 1 to 9 and optionally one or more additional active ingredients, a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

11. The immunogenic composition of claim 10 for use in medicine.

12. Use of the immunogenic composition according to claim 10 in the manufacture of a medicament for treating a disease selected from the group consisting of tuberculosis and other mycobacterial infections including Johne's disease, Crohn's disease, malaria, influenza, Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome, Hepatitis C virus infection, Cytomegalovirus infection, Human papilloma virus infection, adenoviral infection, leishmaniasis, *streptococcus* spp. infection, *staphylococcus* spp. infection, *meningococcus* spp. infection, foot and mouth disease, chikungunya virus infection, Zika virus infection, rabies, Crimean Congo haemorrhagic fever, Ebola virus infection, Marburg, Lassa fever, Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome coronavirus diseases, Nipah and Rift Valley fever, and Chikungunya.

13. The use according to claim 12, wherein the disease is selected from the group consisting of tuberculosis and other mycobacterial infections, and rabies.

14. The use according to claim 12 or 13 wherein said use comprises that a transgene is to be delivered into a host cell.

15. The use according to claim 12 or 13, wherein said use comprises eliciting an immune response in an animal.

16. The use according to claim 12 or 13, wherein said use comprises boosting an immune response in an animal.

17. The immunogenic composition of claim 11, wherein said use comprises inducing an immune response in an animal that will break tolerance to a self-antigen.

18. The immunogenic composition of claim 11, wherein said use comprises gene therapy.

19. A polynucleotide sequence encoding the adenoviral vector of any of claims 1 to 9.

20. A host cell transduced with the adenoviral vector of any of claims 1 to 9.

21. A method of producing the adenoviral vector of any of claims 1 to 9, comprising the step of incorporating the polynucleotide of claim 19 into a Bacterial Artificial Chromosome (BAC) to produce an Ad-BAC vector.

22. A Bacterial Artificial Chromosome (BAC) clone comprising the polynucleotide sequence of claim 19.

23. A packaging cell line producing the viral vector of any of claims 1 to 7.

24. The packaging cell line of claim 23, wherein said cell comprises the complement of any genes functionally deleted in the viral vector of any of claims 1 to 9.

25. A kit comprising: (i) an adenoviral vector according to any of claims 1 to 9 or an immunogenic composition according to claim 10, and (ii) instructions for use.