Consequently, a need in the art exists for compositions and methods for vaccination of neonates to achieve strong T-cell and antibody responses and protection against pathogens. The invention fulfills this need.

Summary of the invention

The invention encompasses compositions and methods for inducing a protective immune response against a poxvirus in a human neonate or infant of less than 6 months of age. In one embodiment, the invention encompasses administering a dose of at least 10^8 $TCID_{50}$ of an MVA to a human neonate or infant of less than 6 months of age, wherein the administration induces protective T- and B-cell responses against a poxvirus in the human neonate prior to 6 months of age, preferably within 2 weeks of the administration. Most preferably, the immune response is induced in the absence of a second administration of the MVA.

In various embodiments, the administration is administered to a human neonate or infant of less than 2 months of age or within 72 hours after birth.

Preferably, the administration induces protective T- and B-cell responses against a poxvirus. Most preferably, the administration induces protective T- and B-cell responses against smallpox.

In some embodiments, the invention encompasses administering one or more boosting administrations of the MVA.

In some embodiments, the MVA is a recombinant MVA. In some embodiments, the administration induces T- and B-cell responses against a heterologous antigen encoded by the recombinant MVA.

Brief description of the figures

Figures 1a-d show a comparison of the vaccinia-specific immune responses in newborn versus adult mice after a single MVA-BN vaccination. Newborn or adult C57BL/6 mice were immunized with a high dose (1×10^8 $TCID_{50}$) or a low dose (2×10^6 $TCID_{50}$) of MVA. Animals were bled and sacrificed 1, 2, 3, 4 or 7 weeks post-immunization. **(a)** Vaccinia-specific IgG in serum was measured by ELISA. Geometric

after vaccination with a high dose of 1×10^8 $TCID_{50}$ of MVA, a dose that also induces B-cell responses. This was confirmed in T11μMT transgenic mice, in which partial protection showed that B-cells are also required in order to achieve complete protection after a single vaccination with MVA at birth.

The invention encompasses compositions and methods for inducing a protective immune response against a poxvirus in a human neonate or infant. In one embodiment, the invention encompasses administering a dose of at least 10^8 $TCID_{50}$ of an MVA to a human neonate or infant. The MVA can be administered to a human neonate or infant prior to the full maturation of the immune system.

The invention further encompasses MVA for use in inducing a protective immune response against a poxvirus in a human neonate or infant.

The invention also encompasses MVAs for use in vaccinating a human neonate or infant. The invention also encompasses the use of MVAs as vaccines for treating a human neonate or infant and the use of MVAs in the preparation of vaccines or medicaments for treating or vaccinating a human neonate or infant.

Human Neonates and Infants

Within the context of this invention, the term "human neonate" refers to a newborn human less than 1 month of age and the term "human infant" refers to a human between birth and 1 year of age. Preferably, the human neonate is less than 4 weeks of age, less than 3 weeks of age, less than 2 weeks of age, or less than 1 week of age. More preferably, the human neonate is less than 6, 5, 4, 3, 2, or 1 days of age.

In one embodiment, a dose of MVA is administered to a human neonate. In various embodiments, a dose of MVA is administered to a human neonate of less than 4 weeks of age, less than 3 weeks of age, less than 2 weeks of age, or less than 1 week of age. In various embodiments, a dose of MVA is administered to a human neonate of less than 6, 5, 4, 3, 2, or 1 days of age. In preferred embodiments, a dose of MVA is administered to a human neonate within 3, 2, or 1 days of birth.

In one embodiment, a dose of MVA is administered to a human infant of less than 6, 5, 4, 3, 2, or 1 months of age. In various embodiments, a dose of MVA is administered to a human infant of less than 8 weeks of age, less than 7 weeks of

Recombinant MVAs

The invention encompasses recombinant MVA viruses generated with any and all MVA viruses. In one embodiment, the recombinant MVA virus is a recombinant MVA-BN virus. The recombinant MVA virus comprises at least one heterologous nucleic acid sequence. In the context of this invention, the term "heterologous" nucleic acid sequence refers to a nucleic acid sequence that is not naturally found in the MVA.

Preferably, the heterologous nucleic acid sequence is a sequence coding for at least one antigen, antigenic epitope, and/or a therapeutic compound. The antigenic epitopes and/or the antigens can be antigenic epitopes and/or antigens of an infectious agent. The infectious agents can be viruses, fungi, pathogenic unicellular eukaryotic or prokaryotic organisms, and parasitic organisms. In some embodiments, the infectious agent is a virus selected from any of the following: Rotavirus, Rubella virus, Poliovirus, Influenza virus, Flavivirus (particularly Dengue virus and Yellow Fever virus), Paramyxovirus (particularly measles virus, mumps virus, and respiratory syncytial virus (RSV)), Hepatitis virus (particularly Hepatitis A, B, and C viruses), Human immunodeficiency virus (particularly HIV-1), Filovirus (particularly Ebola virus and Marburg virus) or from other viruses causing hemorrhagic fever. In some embodiments, the infectious agent is a bacterium selected from any of the following: Bacillus anthracis, meningococcus, pneumococcus, Haemophilus influenza, Corynebacterium diphtheriae, Clostridium tetani, Burkholderia, Francisella tularensis, Coxiella burnetii, or Bordetella pertussis.

Any antigen, including those that induce a T-cell response, can be expressed by the recombinant MVA of the invention. Viral, bacterial, fungal, and cancer antigens are preferred. Preferred antigens are antigens of any of the viruses or bacteria decribed above. HIV-1 antigens, Dengue virus antigens, anthrax antigens, measles virus antigens, influenza virus antigens, picornavirus antigens, coronavirus antigens and respiratory syncytial virus antigens are particularly preferred antigens. Preferably, the antigen is a foreign antigen or neoantigen. Within the context of this invention, the term "neoantigen" refers to an antigen not naturally expressed by the poxviral vector.

In some embodiments, the administration induces T- and/or B-cell responses against a heterologous antigen encoded by the recombinant MVA. The T-cell response can be an effector and/or long term memory T-cell response. The B-cell response can be a neutralizing antibody response.

Administration

The invention encompasses administration of a dose of an MVA to a human neonate or infant via any route. Preferred routes of administration include subcutaneous (s.c.), intradermal (i.d.), intramuscular (i.m.), in bone marrow (i.bm.) or intravenous (i.v.) injection, oral administration and mucosal administration, especially intranasal administration, or inhalation. The quantity to be administered (dosage) depends on the subject to be treated, considering among other things the condition of the patient, the state of the individual's immune system, the route of administration and the size of the host.

The invention further encompasses MVAs for use as a pharmaceutical composition or vaccine for vaccinating a human neonate or infant, the use of MVAs as pharmaceutical compositions or vaccines for treating a human neonate or infant, and the use of MVAs in the preparation of pharmaceutical compositions or vaccines or medicaments for treating or vaccinating a human neonate or infant.

The pharmaceutical composition, vaccine or medicament can generally include one or more auxiliary substances, such as pharmaceutically acceptable and/or approved carriers, additives, antibiotics, preservatives, adjuvants, diluents and/or stabilizers. Such auxiliary substances can be water, saline, glycerol, ethanol, oil, wetting or emulsifying agents, pH buffering substances, or the like. Suitable carriers are typically large, slowly metabolized molecules such as proteins, polysaccharides, polylactic acids, polyglycollic acids, polymeric amino acids, amino acid copolymers, lipid aggregates, or the like.

For the preparation of pharmaceutical compositions or vaccines or medicaments, the MVA according to the invention can be converted into a physiologically acceptable form. This can be done based on experience in the preparation of poxvirus vaccines used for vaccination against smallpox (as described by Stickl et al. 1974). The purified virus can be stored at -20°C, or -80°C, frozen in a liquid. Preferably, the

virus has a titer of 5×10^8 TCID50/ml, and can be formulated in a buffered solution, for example, in 10 mM Tris, 140 mM NaCl, at pH 7.4.

The virus formulation can contain additional additives such as mannitol, dextran, sugar, glycine, lactose or polyvinylpyrrolidone or other auxiliary substances, such as antioxidants or inert gas, stabilizers or recombinant proteins (*e.g.*, human serum albumin, or HSA) suitable for *in vivo* administration.
Alternatively, the vaccine can be produced by stepwise freeze-drying of the virus in a formulation. For example, 10^8 particles of the virus can be lyophilized in 100 µl to 1 ml of phosphate-buffered saline (PBS) in the presence of 2% peptone and 1% HSA in an ampoule, preferably a glass ampoule. The glass ampoule is then sealed and can be stored between 4°C and room temperature for several months. However, as long as no need exists the ampoule is stored preferably at temperatures below -20°C.

For vaccination or therapy, the virus can administered either systemically or locally, *i.e.*, parenterally, subcutaneously, intravenously, intramuscularly, intranasally, or by any other path of administration known to the skilled practitioner.

Dose

The invention encompasses a dose of at least 10^8 $TCID_{50}$ of an MVA administered to a human neonate or infant. Preferably, the dose is at least 10^8 $TCID_{50}$, 2×10^8 $TCID_{50}$, 3×10^8 $TCID_{50}$, 4×10^8 $TCID_{50}$, 5×10^8 $TCID_{50}$, 6×10^8 $TCID_{50}$, 7×10^8 $TCID_{50}$, 8×10^8 $TCID_{50}$, 9×10^8 $TCID_{50}$, or 10^9 $TCID_{50}$ of an MVA. A particularly preferred dose is 2×10^8 $TCID_{50}$, 3×10^8 $TCID_{50}$, 4×10^8 $TCID_{50}$, 5×10^8 $TCID_{50}$, 6×10^8 $TCID_{50}$, 7×10^8 $TCID_{50}$, 8×10^8 $TCID_{50}$, 9×10^8 $TCID_{50}$, or 10^9 $TCID_{50}$ of an MVA. Especially preferred is a dose of 10^8 $TCID_{50}$.

The human neonate or infant can be vaccinated with a single administration of the MVA in the absence of any additional ("boosting") administrations. In other embodiments, one or more boosting administrations are administered. In one embodiment, a second administration is given four weeks to eight weeks after the first vaccination administration. Preferably, the second administration is given at 2, 4, 6, or 8 weeks after the first administration. In other embodiments, a third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or additional administration is given.

The boosting administration can be administered to increase immune response when the initial response decays or to further increase the initial response. Thus, in some embodiments a boosting administration is provided to augment or reestablish a desired level of immune response.

The time between the first and second administrations and between an administration and a subsequent administration can vary. In one embodiment, the time between administrations is two to six weeks. In various embodiments, the time between administrations is at least 2, 4, 6, 8, 10, 12, 15, 30, or 52 weeks. In various embodiments, the time between administrations is at least 1, 3, 6, 9, 12, 24, 36, or 48 months. In various embodiments, the time between administrations is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 years.

Protective immune response

The invention encompasses the induction of a protective immune response against a poxvirus by administration of a dose of an MVA to a human neonate or infant. Preferably the administration induces protective T- and B-cell responses against the poxvirus in the human neonate or infant prior to 6 months of age. Most preferably, the immune response is induced in the absence of a second administration of the MVA. Within the context of this invention, the phrase "the immune response is induced in the absence of a second administration of the MVA" means that the immune response does not depend on the administration of a second (*i.e.*, boosting) dose of the MVA. The immune response is induced by the first administration. Thus, within the context of this invention, the phrase "the immune response is induced in the absence of a second administration of the MVA" does not mean that a second administration is not administered; it only means that a second administration is not required to induce the protective immune response. In some embodiments, a second or subsequent administration is administered. The second or subsequent administration can increase the level of the immune response and/or the longevity of the immune response.

The protective immune response can protect at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% of the neonates or infants to which the MVA is administered from death and/or disease symptoms.

Claims

1. A method for inducing a protective immune response against a poxvirus in a human neonate or infant of less than 6 months of age comprising administering a dose of at least 10^8 $TCID_{50}$ of an MVA to a human neonate, wherein the administration induces protective T- and B-cell responses against a poxvirus in the human neonate prior to 6 months of age in the absence of a second administration of the MVA.

2. The method of claim 1, wherein the administration is administered to a human infant of less than 2 months of age.

3. The method of claim 1, wherein the administration is administered to a human neonate.

4. The method of claim 1, wherein the administration is administered to a human neonate within 72 hours after birth.

5. The method of claim 1, wherein the administration induces protective T- and B-cell responses against an orthopoxvirus.

6. The method of claim 1, wherein the administration induces protective T- and B-cell responses against a Vaccinia virus.

7. The method of claim 1, wherein the administration induces protective T- and B-cell responses against smallpox.

8. The method of claim 1, further comprising administering one or more boosting administrations of the MVA.

9. The method of claim 1, wherein the MVA is a recombinant MVA.

10. The method of claim 9, wherein the administration induces T- and B-cell responses against a heterologous antigen encoded by the recombinant MVA.

11. A method for inducing a protective immune response against a poxvirus in a human neonate or infant comprising administering a dose of at least 10^8 $TCID_{50}$ of an

MVA to a human neonate or infant of less than 6 months of age, wherein the administration induces protective T- and B-cell responses against a poxvirus in the human neonate or infant within 2 weeks of the administration.

12. The method of claim 11, wherein the administration is administered to a human infant of less than 2 months of age.

13. The method of claim 11, wherein the administration is administered to a human neonate.

14. The method of claim 11, wherein the administration is administered to a human neonate within 72 hours after birth.

15. The method of claim 11, wherein the administration induces protective T- and B-cell responses against an orthopoxvirus.

16. The method of claim 11, wherein the administration induces protective T- and B-cell responses against a Vaccinia virus.

17. The method of claim 11, wherein the administration induces protective T- and B-cell responses against smallpox.

18. The method of claim 11, further comprising administering one or more boosting administrations of the MVA.

19. The method of claim 11, wherein the MVA is a recombinant MVA.

20. The method of claim 19, wherein the administration induces T- and B-cell responses against a heterologous antigen encoded by the recombinant MVA.

21. An MVA for use in inducing a protective immune response against a poxvirus in a human neonate or infant of less than 6 months of age comprising administering a dose of at least 10^8 $TCID_{50}$ of the MVA to a human neonate, wherein the administration induces protective T- and B-cell responses against a poxvirus in the human neonate prior to 6 months of age in the absence of a second administration of the MVA.

22. The MVA of claim 21, wherein the administration is administered to a human infant of less than 2 months of age.

23. The MVA of claim 21, wherein the administration is administered to a human neonate.

24. The MVA of claim 21, wherein the administration is administered to a human neonate within 72 hours after birth.

25. The MVA of claim 21, wherein the administration induces protective T- and B-cell responses against an orthopoxvirus.

26. The MVA of claim 21, wherein the administration induces protective T- and B-cell responses against a Vaccinia virus.

27. The MVA of claim 21, wherein the administration induces protective T- and B-cell responses against smallpox.

28. The MVA of claim 21, further comprising administering one or more boosting administrations of the MVA.

29. The MVA of claim 21, wherein the MVA is a recombinant MVA.

30. The MVA of claim 29, wherein the administration induces T- and B-cell responses against a heterologous antigen encoded by the recombinant MVA.

31. An MVA for use in inducing a protective immune response against a poxvirus in a human neonate or infant comprising administering a dose of at least 10^8 $TCID_{50}$ of the MVA to a human neonate or infant of less than 6 months of age, wherein the administration induces protective T- and B-cell responses against a poxvirus in the human neonate or infant within 2 weeks of the administration.

32. The MVA of claim 31, wherein the administration is administered to a human infant of less than 2 months of age.

33. The MVA of claim 31, wherein the administration is administered to a human neonate.

34. The MVA of claim 31, wherein the administration is administered to a human neonate within 72 hours after birth.

35. The MVA of claim 31, wherein the administration induces protective T- and B-cell responses against an orthopoxvirus.

36. The MVA of claim 31, wherein the administration induces protective T- and B-cell responses against a Vaccinia virus.

37. The MVA of claim 31, wherein the administration induces protective T- and B-cell responses against smallpox.

38. The MVA of claim 31, further comprising administering one or more boosting administrations of the MVA.

39. The MVA of claim 31, wherein the MVA is a recombinant MVA.

40. The MVA of claim 39, wherein the administration induces T- and B-cell responses against a heterologous antigen encoded by the recombinant MVA.

Consequently, a need in the art exists for compositions and methods for vaccination of neonates to achieve strong T-cell and antibody responses and protection against pathogens. The invention fulfills this need.

Summary of the invention

The invention is defined in the independent claims. Some optional features of the invention are defined in the dependent claims. As disclosed herein, there are compositions and methods for inducing a protective immune response against a poxvirus in a human neonate or infant of less than 6 months of age. In one example, this encompasses administering a dose of at least 10^8 $TCID_{50}$ of an MVA to a human neonate or infant of less than 6 months of age, wherein the administration induces protective T- and B-cell responses against a poxvirus in the human neonate prior to 6 months of age, preferably within 2 weeks of the administration. Most preferably, the immune response is induced in the absence of a second administration of the MVA.

In various embodiments, the administration is administered to a human neonate or infant of less than 2 months of age or within 72 hours after birth.

Preferably, the administration induces protective T- and B-cell responses against a poxvirus. Most preferably, the administration induces protective T- and B-cell responses against smallpox.

Some embodiments encompass administering one or more boosting administrations of the MVA.

In some embodiments, the MVA is a recombinant MVA. In some embodiments, the administration induces T- and B-cell responses against a heterologous antigen encoded by the recombinant MVA.

Brief description of the figures

Figures 1a-d show a comparison of the vaccinia-specific immune responses in newborn versus adult mice after a single MVA-BN vaccination. Newborn or adult C57BL/6 mice were immunized with a high dose (1×10^8 $TCID_{50}$) or a low dose (2×10^6 $TCID_{50}$) of MVA. Animals were bled and sacrificed 1, 2, 3, 4 or 7 weeks post-immunization. **(a)** Vaccinia-specific IgG in serum was measured by ELISA. Geometric

after vaccination with a high dose of 1×10^8 $TCID_{50}$ of MVA, a dose that also induces B-cell responses. This was confirmed in T11μMT transgenic mice, in which partial protection showed that B-cells are also required in order to achieve complete protection after a single vaccination with MVA at birth.

There are disclosed compositions and methods for inducing a protective immune response against a poxvirus in a human neonate or infant. One embodiment encompasses administering a dose of at least 10^8 $TCID_{50}$ of an MVA to a human neonate or infant. The MVA can be administered to a human neonate or infant prior to the full maturation of the immune system.

There is also disclosed MVA for use in inducing a protective immune response against a poxvirus in a human neonate or infant.

The method also encompasses MVAs for use in vaccinating a human neonate or infant. The method also encompasses the use of MVAs as vaccines for treating a human neonate or infant and the use of MVAs in the preparation of vaccines or medicaments for treating or vaccinating a human neonate or infant.

Human Neonates and Infants

Within the context as disclosed herein, the term “human neonate” refers to a newborn human less than 1 month of age and the term “human infant” refers to a human between birth and 1 year of age. Preferably, the human neonate is less than 4 weeks of age, less than 3 weeks of age, less than 2 weeks of age, or less than 1 week of age. More preferably, the human neonate is less than 6, 5, 4, 3, 2, or 1 days of age.

In one embodiment, a dose of MVA is administered to a human neonate. In various embodiments, a dose of MVA is administered to a human neonate of less than 4 weeks of age, less than 3 weeks of age, less than 2 weeks of age, or less than 1 week of age. In various embodiments, a dose of MVA is administered to a human neonate of less than 6, 5, 4, 3, 2, or 1 days of age. In preferred embodiments, a dose of MVA is administered to a human neonate within 3, 2, or 1 days of birth.

In one embodiment, a dose of MVA is administered to a human infant of less than 6, 5, 4, 3, 2, or 1 months of age. In various embodiments, a dose of MVA is administered to a human infant of less than 8 weeks of age, less than 7 weeks of

Recombinant MVAs

Recombinant MVA viruses may be generated with any and all MVA viruses. In one embodiment, the recombinant MVA virus is a recombinant MVA-BN virus. The recombinant MVA virus comprises at least one heterologous nucleic acid sequence. In the context as disclosed herein, the term “heterologous” nucleic acid sequence refers to a nucleic acid sequence that is not naturally found in the MVA.

Preferably, the heterologous nucleic acid sequence is a sequence coding for at least one antigen, antigenic epitope, and/or a therapeutic compound. The antigenic epitopes and/or the antigens can be antigenic epitopes and/or antigens of an infectious agent. The infectious agents can be viruses, fungi, pathogenic unicellular eukaryotic or prokaryotic organisms, and parasitic organisms. In some embodiments, the infectious agent is a virus selected from any of the following: Rotavirus, Rubella virus, Poliovirus, Influenza virus, Flavivirus (particularly Dengue virus and Yellow Fever virus), Paramyxovirus (particularly measles virus, mumps virus, and respiratory syncytial virus (RSV)), Hepatitis virus (particularly Hepatitis A, B, and C viruses), Human immunodeficiency virus (particularly HIV-1), Filovirus (particularly Ebola virus and Marburg virus) or from other viruses causing hemorrhagic fever. In some embodiments, the infectious agent is a bacterium selected from any of the following: Bacillus anthracis, meningococcus, pneumococcus, Haemophilus influenza, Corynebacterium diphtheriae, Clostridium tetani, Burkholderia, Francisella tularensis, Coxiella burnetii, or Bordetella pertussis.

Any antigen, including those that induce a T-cell response, can be expressed by the recombinant MVA. Viral, bacterial, fungal, and cancer antigens are preferred. Preferred antigens are antigens of any of the viruses or bacteria decribed above. HIV-1 antigens, Dengue virus antigens, anthrax antigens, measles virus antigens, influenza virus antigens, picornavirus antigens, coronavirus antigens and respiratory syncytial virus antigens are particularly preferred antigens. Preferably, the antigen is a foreign antigen or neoantigen. Within the context as disclosed herein, the term “neoantigen” refers to an antigen not naturally expressed by the poxviral vector.

In some embodiments, the administration induces T- and/or B-cell responses against a heterologous antigen encoded by the recombinant MVA. The T-cell response can be an effector and/or long term memory T-cell response. The B-cell response can be a neutralizing antibody response.

Administration

A dose of an MVA to a human neonate or infant may be administered via any route. Preferred routes of administration include subcutaneous (s.c.), intradermal (i.d.), intramuscular (i.m.), in bone marrow (i.bm.) or intravenous (i.v.) injection, oral administration and mucosal administration, especially intranasal administration, or inhalation. The quantity to be administered (dosage) depends on the subject to be treated, considering among other things the condition of the patient, the state of the individual's immune system, the route of administration and the size of the host.

Also disclosed are MVAs for use as a pharmaceutical composition or vaccine for vaccinating a human neonate or infant, the use of MVAs as pharmaceutical compositions or vaccines for treating a human neonate or infant, and the use of MVAs in the preparation of pharmaceutical compositions or vaccines or medicaments for treating or vaccinating a human neonate or infant.

The pharmaceutical composition, vaccine or medicament can generally include one or more auxiliary substances, such as pharmaceutically acceptable and/or approved carriers, additives, antibiotics, preservatives, adjuvants, diluents and/or stabilizers. Such auxiliary substances can be water, saline, glycerol, ethanol, oil, wetting or emulsifying agents, pH buffering substances, or the like. Suitable carriers are typically large, slowly metabolized molecules such as proteins, polysaccharides, polylactic acids, polyglycollic acids, polymeric amino acids, amino acid copolymers, lipid aggregates, or the like.

For the preparation of pharmaceutical compositions or vaccines or medicaments, the MVA can be converted into a physiologically acceptable form. This can be done based on experience in the preparation of poxvirus vaccines used for vaccination against smallpox (as described by Stickl et al. 1974). The purified virus can be stored at -20°C, or -80°C, frozen in a liquid. Preferably, the

virus has a titer of 5×10^8 TCID50/ml, and can be formulated in a buffered solution, for example, in 10 mM Tris, 140 mM NaCl, at pH 7.4.

The virus formulation can contain additional additives such as mannitol, dextran, sugar, glycine, lactose or polyvinylpyrrolidone or other auxiliary substances, such as antioxidants or inert gas, stabilizers or recombinant proteins (*e.g.*, human serum albumin, or HSA) suitable for *in vivo* administration.

Alternatively, the vaccine can be produced by stepwise freeze-drying of the virus in a formulation. For example, 10^8 particles of the virus can be lyophilized in 100 µl to 1 ml of phosphate-buffered saline (PBS) in the presence of 2% peptone and 1% HSA in an ampoule, preferably a glass ampoule. The glass ampoule is then sealed and can be stored between 4℃ and room temperature for several months. However, as long as no need exists the ampoule is stored preferably at temperatures below -20℃.

For vaccination or therapy, the virus can administered either systemically or locally, *i.e.*, parenterally, subcutaneously, intravenously, intramuscularly, intranasally, or by any other path of administration known to the skilled practitioner.

Dose

A dose of at least 10^8 $TCID_{50}$ of an MVA may be administered to a human neonate or infant. Preferably, the dose is at least 10^8 $TCID_{50}$, 2×10^8 $TCID_{50}$, 3×10^8 $TCID_{50}$, 4×10^8 $TCID_{50}$, 5×10^8 $TCID_{50}$, 6×10^8 $TCID_{50}$, 7×10^8 $TCID_{50}$, 8×10^8 $TCID_{50}$, 9×10^8 $TCID_{50}$, or 10^9 $TCID_{50}$ of an MVA. A particularly preferred dose is 2×10^8 $TCID_{50}$, 3×10^8 $TCID_{50}$, 4×10^8 $TCID_{50}$, 5×10^8 $TCID_{50}$, 6×10^8 $TCID_{50}$, 7×10^8 $TCID_{50}$, 8×10^8 $TCID_{50}$, 9×10^8 $TCID_{50}$, or 10^9 $TCID_{50}$ of an MVA. Especially preferred is a dose of 10^8 $TCID_{50}$.

The human neonate or infant can be vaccinated with a single administration of the MVA in the absence of any additional ("boosting") administrations. In other embodiments, one or more boosting administrations are administered. In one embodiment, a second administration is given four weeks to eight weeks after the first vaccination administration. Preferably, the second administration is given at 2, 4, 6, or 8 weeks after the first administration. In other embodiments, a third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or additional administration is given.

The boosting administration can be administered to increase immune response when the initial response decays or to further increase the initial response. Thus, in some embodiments a boosting administration is provided to augment or reestablish a desired level of immune response.

The time between the first and second administrations and between an administration and a subsequent administration can vary. In one embodiment, the time between administrations is two to six weeks. In various embodiments, the time between administrations is at least 2, 4, 6, 8, 10, 12, 15, 30, or 52 weeks. In various embodiments, the time between administrations is at least 1, 3, 6, 9, 12, 24, 36, or 48 months. In various embodiments, the time between administrations is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 years.

Protective immune response

The invention encompasses the induction of a protective immune response against a poxvirus by administration of a dose of an MVA to a human neonate or infant. Preferably the administration induces protective T- and B-cell responses against the poxvirus in the human neonate or infant prior to 6 months of age. Most preferably, the immune response is induced in the absence of a second administration of the MVA. Within the context as disclosed herein, the phrase “the immune response is induced in the absence of a second administration of the MVA” means that the immune response does not depend on the administration of a second (*i.e.*, boosting) dose of the MVA. The immune response is induced by the first administration. Thus, within the context as disclosed herein, the phrase “the immune response is induced in the absence of a second administration of the MVA” does not mean that a second administration is not administered; it only means that a second administration is not required to induce the protective immune response. In some embodiments, a second or subsequent administration is administered. The second or subsequent administration can increase the level of the immune response and/or the longevity of the immune response.

The protective immune response can protect at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% of the neonates or infants to which the MVA is administered from death and/or disease symptoms.

Claims

1. The use of a dose of at least 10^8 $TCID_{50}$ (50% Tissue Culture Infective Dose) of an Modified Vaccinia virus Ankara (MVA) for the manufacture of a pharmaceutical composition for inducing a protective immune response against a poxvirus in a human neonate or infant of less than 6 months of age, the use comprising administering the dose of at least 10^8 $TCID_{50}$ of the MVA to a human neonate, wherein the administration induces protective T- and B-cell responses against a poxvirus in the human neonate prior to 6 months of age in the absence of a second administration of the MVA.

2. The use of claim 1, wherein the administration is administered to a human infant of less than 2 months of age.

3. The use of claim 1, wherein the administration is administered to a human neonate.

4. The use of claim 1, wherein the administration is administered to a human neonate within 72 hours after birth.

5. The use of claim 1, wherein the administration induces protective T- and B-cell responses against an orthopoxvirus.

6. The use of claim 1, wherein the administration induces protective T- and B-cell responses against a Vaccinia virus.

7. The use of claim 1, wherein the administration induces protective T- and B-cell responses against smallpox.

8. The use of claim 1, further comprising administering one or more boosting administrations of the MVA.

9. The use of claim 1, wherein the MVA is a recombinant MVA.

10. The use of claim 9, wherein the administration induces T- and B-cell responses against a heterologous antigen encoded by the recombinant MVA.

11. The use of a dose of at least 10^8 $TCID_{50}$ (50% Tissue Culture Infective Dose) of an Modified Vaccinia virus Ankara (MVA) for the manufacture of a pharmaceutical composition for inducing a protective immune response against a poxvirus in a human neonate or infant, the use comprising administering the dose of at least 10^8 $TCID_{50}$ of the MVA to a human neonate or infant of less than 6 months of age, wherein the administration induces protective T- and B-cell responses against a poxvirus in the human neonate or infant within 2 weeks of the administration.

12. The use of claim 11, wherein the administration is administered to a human infant of less than 2 months of age.

13. The use of claim 11, wherein the administration is administered to a human neonate.

14. The use of claim 11, wherein the administration is administered to a human neonate within 72 hours after birth.

15. The use of claim 11, wherein the administration induces protective T- and B-cell responses against an orthopoxvirus.

16. The use of claim 11, wherein the administration induces protective T- and B-cell responses against a Vaccinia virus.

17. The use of claim 11, wherein the administration induces protective T- and B-cell responses against smallpox.

18. The use of claim 11, further comprising administering one or more boosting administrations of the MVA.

19. The use of claim 11, wherein the MVA is a recombinant MVA.

20. The use of claim 19, wherein the administration induces T- and B-cell responses against a heterologous antigen encoded by the recombinant MVA.