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(54) **Title:** COMBINATION VACCINE FOR CAMELIDS

(57) **Abstract:** The invention relates to a method for preventing infection with camelpox and MERS coronavirus in camelids, wherein said camelids have been administered an immunogenic composition comprising the MVA virus as a vector comprising an immunogenic element of the MERS coronavirus. Also the use of this immunogenic composition for this purpose is covered. Preferably said immunogenic element is the spike protein or an immunogenic fragment or variant thereof.



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Title: COMBINATION VACCINE FOR CAMELIDS

5 The invention relates to an immunogenic composition that is able to protect camelids, in particular camels and dromedary camels against both camelpox virus and Middle East Respiratory Syndrome (MERS) coronavirus.

BACKGROUND

10 Camelids are prone to infection with camelpox virus and various solutions to prevent infection (spread) have been published.

Camelpox is caused by the *Orthopoxvirus cameli*, which belongs to the genus of Orthopoxviruses within the family Poxviridae. Clinical manifestations range from inapparent and mild local infections, confined to
15 the skin, to moderate and severe systemic infections, which can ultimately lead to the death of the animal. The mortality rate in adult animals is between 5% and 28% and higher in young animals Mayer, A, Czerny C.-P., 1990. Chapter 4; camelpox virus. In: Virus infections of Vertebrates, Vol. 3: Virus Infections of Ruminants, Dinter Z., Morein, B. (eds). Elsevier Science
20 Publ., Amsterdam, The Netherlands, page 19-22).

Currently live attenuated vaccines and inactivated vaccines derived from camelpox strains are commercially available. It has further been established that camelpox virus, like the human pox variant, is closely related to Vaccinia virus, which often is used in vaccines. It has especially
25 been described that the attenuated modified Vaccinia virus Ankara (MVA) can be used as an effective vaccine (Mahy, B.W.J., 2008, The Dictionary of Virology, Elsevier/Academic Press, Amsterdam, The Netherlands, page 74). However, in this reference no data at all are shown nor is it clear how the vaccine has been produced. Similarly, in WO 01/68820 the use of MVA has
30 been indicated as vaccine for camelpox, but also here no enabling disclosure is available. In contrast with these observations, it was recently reported (Abdellatif, M.M. et al., 2014, Rev. sci. tech. Off. Int. Epiz. 33(3):1-19) that

production of one of the original camelpox vaccines (strain Jouf-78) was stopped because it appeared that the Jouf-78 vaccine contained a vaccinia virus rather than a camelpox virus (Yousif, A.A., Ali-Ali, A.M., Biologicals, 40:495-498).

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The Middle East Respiratory Syndrome (MERS) coronavirus was only discovered in 2012 and a team from Erasmus MC (Rotterdam, The Netherlands) including the present inventors was able to characterize the virus as a new type of coronavirus (WO 2014/045254). Currently no commercial
10 vaccines against the disease are available. It has, however, been demonstrated through research from the same group the current inventors come from that an immunogenic composition comprising the coronavirus spike protein delivered by an MVA vector was able to elicit neutralizing antibodies in mice (Song, F. et al., 2013, J. Virol. 87(21):11950-11954).

15

There is some evidence that the virus is transmitted from person to person, but it has also been found recently that the virus is abundantly present in camels (Hemida, M.G. et al., 2013, Euro Surveillance 18(50)).

The inventors have now found that an immunogenic composition
20 comprising the MVA virus as a vector and which also comprises an immunogenic element of the MERS coronavirus is able to prevent infection with both camelpox and MERS virus in camelids.

Next to a direct effect on the health of the animals that are provided with the immunogenic composition there is also an indirect effect on human health
25 because the spread of the MERS coronavirus is inhibited by the present method and further this decreases the risk for human infection with this virus.

DETAILED DESCRIPTION

30 The immunogenic composition comprises both parts of the MVA and the MERS coronavirus. Advantageously this is achieved by using the AMV as a vector for an immunogenic element of the MERS coronavirus.

The term "immunogenic element" includes reference to any part of a MERS CoV protein especially the spike protein, or a functional variant or functional fragment thereof, which is capable of eliciting an immune response in a mammal. Said immunogenic element preferably corresponds to an antigenic determinant of said pathogen.

The term "functional fragment" refers to a shortened version of the protein, which is a functional variant or functional derivative. A "functional variant" or a "functional derivative" of a protein is a protein the amino acid sequence of which can be derived from the amino acid sequence of the original protein by the substitution, deletion and/or addition of one or more amino acid residues in a way that, in spite of the change in the amino acid sequence, the functional variant retains at least a part of at least one of the biological activities of the original protein that is detectable for a person skilled in the art. A functional variant is generally at least 60% homologous (preferably the amino acid sequence is at least 60% identical), advantageously at least 70% homologous and even more advantageously at least 80 or 90% homologous to the protein from which it can be derived. A functional variant may also be any functional part of a protein; the function in the present case being particularly but not exclusively essential activity for respiratory illness. "Functional" as used herein means functional in MERS-Cov and capable of eliciting antibodies which give protection against disease caused by said virus.

The expression "conservative substitutions" as used with respect to amino acids relates to the substitution of a given amino acid by an amino acid having physicochemical characteristics in the same class. Thus where an amino acid of the SP1298 and/or SP2205 proteins has a hydrophobic characterising group, a conservative substitution replaces it by another amino acid also having a hydrophobic characterising group; other such classes are those where the characterising group is hydrophilic, cationic, anionic or contains a thiol or thioether. Such substitutions are well known to those of ordinary skill in the art, i.e. see US 5,380,712. Conservative amino acid substitutions may be made, for example within the group of aliphatic non-polar amino acids (Gly, Ala, Pro, Ile, Leu, Val), the group of polar uncharged amino acids (Cys, Ser, Thr, Met, Asn, Gln),

the group of polar charged amino acids (Asp, Glu, Lys, Arg) or the group of aromatic amino acids (His, Phe, Tyr, Trp).

The term "prophylactic or therapeutic treatment of an infection by MERS" or "prophylactic or therapeutic treatment of a MERS infection" refers to both
5 prophylactic or therapeutic treatments wherein virulence of the pathogen is blocked or diminished, but also to treatments wherein antibodies against the MERS protein(s) recognize the virus and will protect the host against infection, either directly through immune clearance, or indirectly by blocking the activity of the protein or virus, thereby inhibiting the constitution and/or replication of the
10 virus. Also, the term refers to blocking the function of the MERS protein(s) *in vivo* thereby reducing the replication abilities of the pathogen with a concomitant reduction in invasion capabilities. The term thus includes inducing immune responses in subjects using methods of the invention, as well as inhibiting replication of the pathogen *in vivo* by using antibodies generated by methods of the
15 present invention as an active compound in a pharmaceutical composition administered to the subject.

MVA can be used as a production platform for vaccines against respiratory diseases, as has been described in Altenburg, A.F. et al. (2014, Viruses
20 6(7):2735-2761). As has been taught therein, MVA is a replication deficient viral vector that can be used to encode one or more foreign antigens, thereby functioning as a multivalent vaccine. The MVA vectors can be prepared as follows. A DNA construct that contains a DNA sequence that encodes a foreign polypeptide (e.g., any of the MERS antigenic proteins or fragments or functional variants thereof)
25 and that is flanked by MVA DNA sequences adjacent to a naturally occurring deletion with the MVA genome (e.g., deletion III or other non-essential site(s); six major deletions of genomic DNA (designated deletions I, II, III, IV, V, and VI) totaling 31,000 base pairs have been identified (Meyer et al., J. Gen. Virol. 72:1031-1038, 1991)) is introduced into cells infected with MVA under conditions that
30 permit homologous recombination to occur. Once the DNA construct has been introduced into the eukaryotic cell and the foreign DNA has recombined with the viral DNA, the recombinant vaccinia virus can be isolated by methods known in the art (isolation can be facilitated by use of a detectable marker). The DNA

constructed to be inserted can be linear or circular (e.g., a plasmid, linearized plasmid, gene, gene fragment, or modified MERS-CoV genome). The foreign DNA sequence is inserted between the sequences flanking the naturally occurring deletion. For better expression of a DNA sequence, the sequence can include
5 regulatory sequences (e.g., a promoter, such as the vaccinia 11 kDa gene or the 7.5 kDa gene). The DNA construct can be introduced into MVA-infected cells by a variety of methods, including calcium phosphate-assisted transfection (Graham et al., *Virol.* 52:456-467, 1973 and Wigler et al., *Cell* 16:777-785, 1979), electroporation (Neumann et al., *EMBO J.* 1:841-845, 1982) microinjection
10 (Graessmann et al., *Meth. Enzymol.* 101:482-492, 1983), by means of liposomes (Straubinger et al., *Meth. Enzymol.* 101:512-527, 1983), by means of spheroplasts (Schaffner, *Proc. Natl. Acad. Sci. USA* 77:2163-2167, 1980), or by other methods known in the art.

For MERS-CoV this has been shown in Song et al. (2013) where an
15 insert has been introduced into deletion site III of the MVA genome (see Fig. 1 in Song et al.). In this deletion site the coding sequence for the MERS CoV spike protein was inserted and placed under transcriptional control of a vaccinia virus promoter. As is shown in this paper, the S protein is expressed by the recombinant virus particles when administered to mice. This was demonstrated by detection of
20 titers of MERS CoV neutralizing antibodies.

For the present invention the recombinant MVA-MERS virus as described by Song et al. may be used. It is, however, also possible to use recombinant MVA-MERS viruses that are produced in another way. It would, e.g. be feasible to insert an immunogenic element of the MERS CoV in any spot of the
25 MVA viral particle that is not critical for the immunogenicity of the MVA. Accordingly, inserts may be provided at the site of deletions I, II, III, IV, V and VI (as depicted in Fig. 1A of Song et al.), but also, for instance, in intergenic region III (Manuel, E. et al., 2010, *Virology* 403(2): 155–162) and in a site located between the essential I8R and GIL genes in the central conserved region of MVA (Wyatt, I.S. et
30 al., 2009, *J. Virol.* 83(14):7176-7184). Further, in Song et al. the complete sequence coding for the MERS CoV spike protein was inserted. In stead of this spike protein, also other genes that are deemed to yield immunogenic products may be inserted.

As such these sequences do not necessarily need to encode the full protein, but it may be sufficient to encode an antigenic protein from the MERS CoV.

Any viral vector that can be used in methods according to the invention can be tested for expression by transfecting cells, such as chicken embryo
5 fibroblasts (CEF) cells and assessing the level of viral particle formation and (recombinant) antigen expression (by, for example, an antigen-capture ELISA or a Western blot). Viral vectors that express immunogens at a level comparable to, or higher than, the viral vectors described herein are strong therapeutic candidates and are within the scope of the invention (of course, any construct that elicits an
10 effective immune response (e.g., any desirable degree of protection from infection or other therapeutic benefit) is usable in methods according to the invention, regardless of the level of antigen expression it generates). In addition to assessing expression and viral particle formation in cell culture, one can assess candidate vectors in vivo. For example, one can assess immunogenicity in animal models.
15 Plasmids that have substantially the same sequence as the MVA-MERS-S vector described in the experimental part and that express one or more of the antigenic proteins described herein (the MERS CoV spike protein) are within the scope of the invention so long as they are immunogenic enough to induce or enhance a therapeutically beneficial response in a camelid. In tests in animals for
20 immunogenicity, one can perform an intracellular cytokine assay or an ELISPOT assay for IFN-[gamma] production in response to stimulation with an antigenic peptide to evaluate the frequency of responding T cells to that peptide. Proliferation assays can also be carried out. Antigens produced by transient transfection can be used for stimulation, and supernatants from mock-transfected
25 cultures can serve as controls. If desired, the data can be presented as a stimulation index (the growth of cultures in the presence of pathogenic (e.g., viral) antigens divided by the growth of cultures in the presence of mock antigen).

The viral vectors of this invention are administered at a concentration that
30 is therapeutically effective to prevent or treat infections by both camelpox and MERS-CoV. To accomplish this goal, the vaccines may be formulated using a variety of acceptable excipients known in the art. Typically, the vaccines are administered by injection, either intramuscularly, subcutaneously, intredermally,

intravenously, intraperitoneally or mucosally (e.g. intranasally). Methods to accomplish this administration are known to those of ordinary skill in the art.

Preferably the vaccine contains at least 10^6 PFU viral vectors per dose. Any physiologically acceptable medium can be used to introduce a vector comprising a vaccine insert into a subject. For example, suitable pharmaceutically acceptable carriers known in the art include, but are not limited to, sterile water, saline, glucose, dextrose, or buffered solutions. The media may include auxiliary agents such as diluents, stabilizers (i.e., sugars (e.g. glucose and dextrose) and amino acids), preservatives, wetting agents, emulsifying agents, pH buffering agents, additives that enhance viscosity or syringability, colorants, and the like. Preferably, the medium or carrier will not produce adverse effects, or will only produce adverse effects that are far outweighed by the benefit conveyed. Preferably used avec the MVA viral vector are water, saline or PBS buffer.

A vaccine according to the invention may contain a (partially) purified recombinant viral vector, wherein said recombinant viral vector is preferably produced by passaging on chicken embryo fibroblast (CEF) cells..

An immunogenic composition that can be used in a method according to the invention may further comprise a suitable adjuvant. Many adjuvant systems are known in the art, for example commonly used oil in water adjuvant systems. Any suitable oil may be used, for example a mineral oil known in the art for use in adjuvants. The oil phase may also contain a suitable mixture of different oils, either mineral or non-mineral. Suitable adjuvants may also comprise vitamin E, optionally mixed with one or more oils. The water phase of an oil in water adjuvated vaccine will contain the antigenic material. Suitable formulations will usually comprise from about 25-60% oil phase (40-75% water phase). Examples of suitable formulations may comprise 30% water phase and 70% oil phase or 50% of each. The adjuvant used in connection with the vectors described here can be one that slowly releases antigen (e.g., the adjuvant can be a liposome), or it can be an adjuvant that is strongly immunogenic in its own right (these adjuvants are believed to function synergistically). Accordingly, the vaccine compositions described here can include known adjuvants or other substances that promote DNA uptake, recruit immune system cells to the site of the inoculation, or facilitate the

immune activation of responding lymphoid cells. These adjuvants or substances include, next to oil and water emulsions, *Corynebacterium parvum*, *Bacillus Calmette Guerin*, aluminum hydroxide, glucan, dextran sulfate, iron oxide, sodium alginate, Bacto-Adjuvant, certain synthetic polymers such as poly amino acids and
5 co-polymers of amino acids, saponin, REGRESSIN (Vetrepharm, Athens, GA), AVRIDINE (N, N-dioctadecyl-N',N'-bis(2-hydroxyethyl)-propanediamine), paraffin oil, and muramyl dipeptide. Genetic adjuvants, which encode immunomodulatory molecules on the same or a co-inoculated vector, can also be used. For example, GM-CSF, IL-15, IL-2, interferon response factors, and mutated caspase genes can
10 be included on a vector that encodes a pathogenic immunogen (such as a MERS-CoV antigen) or on a separate vector that is administered at or around the same time as the immunogen is administered.

The vaccine formulations of the present invention may be used in prophylactic or therapeutic methods of the invention by immunizing a camelid
15 subject by introducing said formulations into said subject subcutaneously, intramuscularly, intranasally, intradermally, intravenously, transdermally, transmucosally, intranasally, orally, or directly into a lymph node. In another embodiment, the composition may be applied locally, near a local pathogen reservoir against which one would like to vaccinate.

20 The present invention further discloses a method for the manufacture of a vaccine intended for the protection of a subject against MERS and camelpox infection, wherein said vaccine is combined with a pharmaceutically acceptable diluent, carrier, excipient or adjuvant therefore, such that a formulation is provided which can provide a prophylactically or therapeutically effective dose in a
25 single administration event.

A vaccine (prepared by a method) according to the invention can be used in a method to protect a subject against both camelpox and MERS infection.

To provide adequate protection the vaccine is preferably administered in a 2 shot vaccination regimen, whereby the first shot (priming vaccination) and second
30 shot (boosting vaccination) are given to the subject with an interval of at least 2 weeks. In this way the subject will have obtained full protection against the viral infections.

Example 1.

Construction of the viral vector

The viral vector was constructed as essentially described in Song et al.,
5 2013, J. Virol. 87(21):11950-11954. In short, flanking sequences were inserted in
the major deletion site III of the Modified Vaccinia virus Ankara strain. These
sequences were originally prepared by PCR and cloned into MVA transfer plasmids
targeting the deletion III site. In MVA vector plasmids pIIIH5red recombinant
sequences coding for the MERS coV spike protein under control of the vaccine virus
10 promoter pmGH5 and a sequence coding for the fluorescent marker mCherry under
transcriptional control of the vaccinia virus late promoter P11 and placed between
repetitive sequences were inserted. The MVA-MERS-S was isolated in plaque
passages by screening for transient coexpression of the fluorescent marker. The
fluorescent marker was excised through intragenomic homologous recombination
15 using the repetitive sequences. PCR analysis was performed on genomic viral DNA
using oligonucleotide primers to confirm the identity and proper insertion of the
spike protein gene sequence. The recombinant MVA-MERS-S can be efficiently
amplified in chicken embryo fibroblasts.

For vaccination, the MVA-MERS-S virus particles were solved in PBS
20 at a concentration of $5.10e7$ PFU/ml.

Example 2

Animal experiment

Eight dromedaries between 5 to 6 months old, seronegative for MERS-
25 coV and MVA (by ELISA and seroneutralization tests), were selected in the Canary
Islands and brought to continental Spain. They were provided with a primo and
boost vaccination, 4 weeks apart, followed by a MERS-CoV challenge 3 weeks later.
The control groups (MVA, 2 animals; and PBS, 2 animals) were housed in the same
box but physically separated to avoid contact. The remaining four dromedaries
30 (vaccine group) were housed in a separate box. After 5 days adaptation animals
were sampled for sera, blood for PBMC preparation and nasal and rectal swabs (in
PBS). The next day they were simultaneously inoculated by the intramuscular (im)
and intranasal (in) routes as follows:

- PBS, 1.5 ml in each nostril and 3 ml i.m. in the neck, nearby the head.

- MVA, 1.5 ml doses of 1×10^8 pfu in each nostril and 3 ml (2×10^8 pfu) i.m. in the neck, nearby the head.

5 - MVA-MERS-S, 1.5 ml doses of 1×10^8 pfu in each nostril and 3 ml (2×10^8 pfu) i.m. in the neck, nearby the head.

The “in” application is performed with a LMA, MADgic catheter device to ensure spray of the vaccine in the entire nasal mucosa.

Four weeks after, the boost vaccination is performed in the same
 10 schedule. Body temperatures are followed weekly and on the days of inoculations. At 7 weeks after the primary immunization, all animals were challenged with MERS-CoV and at 4 days (half animals of each group) and 14 days after challenge, animals (remaining four) were euthanized to determine viral replication in tissues using different techniques (titration, RT-PCR, immunohistochemistry and in situ
 15 hybridization). The challenge was performed with MERS-CoV EMC isolate 5×10^6 TCID₅₀ per animal via the intranasal route. From the challenge to day 5, body temperatures were taken daily and then every 2 days.

Scheduled sampling:

- 2 weeks after primo vaccination, sera.
- 20 - before boosting vaccination; sera plus rectal and nasal swabs (specific Ig detection).
- before challenge; sera, rectal and nasal swabs plus blood for PBMC. Swabs are from now collected in Transport Media, for virus preservation.
- first four days after challenge (daily); sera plus rectal and
 25 nasal swabs. At day 4th, 2 controls (one of each control group) and 2 vaccinated were euthanized for exhaustive tissue collections.
- from day 5 to day 10 after challenge, every 2 days; sera plus rectal and nasal swabs.
- at day 14 post challenge; sera, rectal and nasal swabs plus
 30 blood for PBMC. Remaining animals (4) were euthanized, 2 controls (one of each control group) and 2 vaccinated for exhaustive tissue collections.

Claims

1. Method for preventing infection with camelpox and MERS coronavirus in camelids, wherein said camelids have been administered an immunogenic composition comprising the MVA virus as a vector comprising an immunogenic element of the MERS coronavirus.
5
2. Method according to claim 1, wherein said camelid is chosen from the group of camel (Bactrian camel or feral camel), dromedary (Arabian camel), llama, alpaca, vucuña and guanaco.
- 10 3. Method according to any of the previous claims, wherein the immunogenic element of the MERS coronavirus is the spike (S) protein.
4. Method for preventing spread of the MERS coronavirus by
15 performing a method according any of claims 1 -3.
5. Method for decreasing the risk of humans being infected by MERS coronavirus by performing a method according to any of claims 1 – 3.
- 20 6. Use of an MVA viral vector in which an immunogenic element of MERS coronavirus has been inserted for the prevention of both camelpox and MERS in camelids.

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2016/050040

A. CLASSIFICATION OF SUBJECT MATTER
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ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, Sequence Search, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	F. SONG ET AL: "Middle East Respiratory Syndrome Coronavirus Spike Protein Delivered by Modified Vaccinia Virus Ankara Efficiently Induces Virus-Neutralizing Antibodies", JOURNAL OF VIROLOGY, vol. 87, no. 21, 1 November 2013 (2013-11-01), pages 11950-11954, XP055157123, ISSN: 0022-538X, DOI: 10.1128/JVI.01672-13 cited in the application the whole document ----- -/--	1-6



Further documents are listed in the continuation of Box C.



See patent family annex.

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Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2016/050040

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ARWEN ALTENBURG ET AL: "Modified Vaccinia Virus Ankara (MVA) as Production Platform for Vaccines against Influenza and Other Viral Respiratory Diseases", VIRUSES, vol. 6, no. 7, 17 July 2014 (2014-07-17), pages 2735-2761, XP055200206, DOI: 10.3390/v6072735 cited in the application the whole document	1-6
X	----- thelonevirologist: "Towards a MERS-CoV vaccine: the importance of S", Virology tidbits 22 May 2014 (2014-05-22), XP002756544, Retrieved from the Internet: URL: http://virologytidbits.blogspot.de/2014/05/towards-mers-cov-vaccine-importance-of-s.html the whole document	1-6
A	----- WO 2014/134439 A1 (NEW YORK BLOOD CT INC [US]; ZHOU YUSEN [CN]; ZHAO GUANGYU [CN]) 4 September 2014 (2014-09-04) the whole document -----	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/NL2016/050040

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014134439 A1	04-09-2014	EP 2961768 A1 WO 2014134439 A1	06-01-2016 04-09-2014
