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(54) Title: VACCINE COMPRISING AN ATTENUATED PESTIVIRUS

(57) Abstract: The present invention relates to attenuated pestiviruses, in particular to attenuated BVDV, wherein at least one mutation is in the coding sequence for glycoprotein Erns and at least another mutation in the coding sequence for Npro which preferably leads to combined inactivation of the RNase activity residing in glycoprotein Erns in addition to the inactivation of the (hypothesized) immunomodulating activity residing in Npro. The invention also relates to methods for attenuating pestiviruses such as BVDV, nucleic acids encoding said pestiviruses, in particular BVDV, compositions and vaccines comprising the attenuated pestiviruses, in particular BVDV of the invention.

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VACCINE COMPRISING AN ATTENUATED PESTIVIRUS

BACKGROUND OF THE INVENTION

TECHNICAL FIELD

5 The present invention relates to the field of animal health and in particular to attenuated pestiviruses such as bovine viral diarrhea virus (BVDV).

BACKGROUND INFORMATION

10 Pestiviruses are causative agents of economically important diseases of animals in many countries worldwide. Presently known virus isolates have been grouped into four different species which together form one genus within the family *Flaviviridae*.

I/II Bovine viral diarrhea virus (BVDV) type 1 (BVDV-1) and type 2 (BVDV-2) cause bovine viral diarrhea (BVD) and mucosal disease (MD) in cattle (Baker, 1987; Moennig and Plagemann, 1992; Thiel et al., 1996). The division of BVDV into 2 species is based on
15 significant differences at the level of genomic sequences (summarized in Heinz et al., 2000) which are also obvious from limited cross neutralizing antibody reactions (Ridpath et al. 1994).

III Classical swine fever virus (CSFV), formerly named hog cholera virus, is responsible for classical swine fever (CSF) or hog cholera (HC) (Moennig and Plagemann, 1992; Thiel et al., 1996).

20 IV Border disease virus (BDV) is typically found in sheep and causes border disease (BD). After intrauterine infection of lambs with BDV persistently infected lambs can be born that are weak and show different abnormalities among which the 'hairy shaker' syndrome is best known (Moennig and Plagemann, 1992; Thiel et al., 1996).

25 Pestiviruses are small enveloped viruses with a single stranded RNA genome of positive polarity lacking both 5' cap and 3' poly(A) sequences. The viral genome codes for a polyprotein of about 4000 amino acids giving rise to final cleavage products by co- and posttranslational processing involving cellular and viral proteases. The viral proteins are arranged in the polyprotein in the order NH₂-N^{pro}-C-E^{ms}-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-NS5B-COOH (Lindenbach and
30 Rice, 2001). Protein C (= core- or capsidprotein) and the glycoproteins E^{ms}, E1 and E2 represent structural components of the pestivirus virion as demonstrated for CSFV (Thiel et al., 1991). This also holds true for BVDV. E2 and to a lesser extent E^{ms} were found to be targets for antibody neutralization (Donis et al., 1988; Paton et al., 1992; van Rijn et al., 1993; Weiland et

al., 1990,1992). E^{ms} lacks a typical membrane anchor and is secreted in considerable amounts from the infected cells; this protein has been reported to exhibit RNase activity (Hulst et al., 1994; Schneider et al., 1993; Windisch et al., 1996). The function of this enzymatic activity for the viral life cycle is presently unknown. The enzymatic activity depends on the presence of two stretches of amino acids conserved between the pestivirus E^{ms} and different known RNases of plant and fungal origin. Both of these conserved sequences contain a histidine residue (Schneider et al., 1993). Exchange of each of these residues against lysine in the E^{ms} protein of a CSFV vaccine strain resulted in the destruction of RNase activity (Hulst et al., 1998). Introduction of these mutations into the genome of the CSFV vaccine strain did not influence viral viability or growth properties but led to a virus exhibiting a cytopathogenic phenotype (Hulst et al., 1998). Similarly, Meyers et al. showed that an RNase negative variant of the virulent CSFV strain Alfort/Tübingen was fully viable. However, the respective virus mutant showed no cytopathogenic phenotype (Meyers et al., 1999).

N^{pro} represents the first protein encoded by the long open reading frame in the pestivirus RNA. N^{pro} represents a nonstructural protein that has protease activity and cleaves itself of the nascent polyprotein (Stark et al., 1993; Wiskerchen et al., 1991) presumably already during translation. N^{pro} is a cysteine protease (Rümenapf et al., 1998) that is not essential for virus replication (Tratschin et al., 1998). Recently, it was shown that N^{pro} somehow interferes with the cellular antiviral defense so that it can be hypothesized to modulate the immune system within an infected host (Rüggli et al., 2003). Mayer and coworkers presented indications for an attenuation of CSFV in consequence of a deletion of the N^{pro} gene (Mayer et al., 2004).

Present BVDV vaccines for the prevention and treatment of BVDV infections still have drawbacks (Oirschot et al. 1999). Vaccines against the classical BVDV-1 provide only partial protection from BVDV-2 infection, and vaccinated dams may produce calves that are persistently infected with virulent BVDV-2 (Bolin et al., 1991, Ridpath et al., 1994). This problem is probably due to the great antigenic diversity between type 1 and type 2 strains which is most pronounced in the glycoprotein E2, the major antigen for virus neutralization (Tijssen et al., 1996). Most monoclonal antibodies against type 1 strains fail to bind to type 2 viruses (Ridpath et al., 1994).

Vaccines comprising attenuated or killed viruses or viral proteins expressed in heterologous expression systems have been generated for CSFV and BVDV and are presently used. Killed

vaccines (inactivated whole virus) or subunit vaccines (conventionally purified or heterologously expressed viral proteins) are most often inferior to live vaccines in their efficacy to produce a full protective immune response even in the presence of adjuvants.

5 The structural basis of the attenuation of BVDV used as live vaccines is not known. These vaccines, although attenuated, are most often associated with safety problems. The vaccine viruses may cross the placenta of pregnant animals, e.g. cows and lead to clinical manifestations in the fetus and/or the induction of persistently infected calves. Therefore, they cannot be applied to breeding herds that contain pregnant cows. Pregnant cows have to be kept separate from
10 vaccinated cattle to protect fetuses and must not be vaccinated themselves. Furthermore, revertants of attenuated live BVDV pose a serious threat to animals. For conventionally derived attenuated viruses wherein the attenuation is achieved by conventional multiple passaging, the molecular origin as well as the genetic stability of the attenuation remains unknown and reversion to the virulent wild-type is unpredictable.

15 Because of the importance of an effective and safe as well as detectable prophylaxis and treatment of pestiviral infections, there is a strong need for improved attenuated pestiviruses, such as BVDV, with a high potential for induction of immunity as well as a defined basis of attenuation which can also be distinguished from pathogenic pestiviruses, such as BVDV, as
20 well as compositions and vaccines comprising said attenuated pestiviruses, such as BVDV.

Therefore, the technical problem underlying the present invention is to provide improved attenuated pestivirus, referably an attenuated BVDV for use as live attenuated vaccines. Such improved attenuated pestivirus, preferably BVDV, should especially (i) not cross the placenta
25 themselves and (ii) induce an immunity that prevents viral transmission across the placenta and thereby prevents pregnancy problems like abortion of the fetus or birth of persistently infected host such calves in the case of BVDV infection.

BRIEF DESCRIPTION OF THE DRAWINGS

30 Fig. 1 Serum neutralisation against NY93/C (BVDV type II)

Fig. 2 Serum neutralisation assay against KE9 (BVDV type I)

Fig. 3 Serum neutralisation assay against NY93/C (BVDV type II)

All subsequent Sequences are the show the deleted regions indicated with dashes (-), which are also numbered, whereas the sequences in the sequence listing attached hereto are continuously numbered without the deleted regions or amino acid codons.

5	SEQ ID NO:1	XIKE-A-cDNA sequence
	SEQ ID NO:2	XIKE-A-NdN-cDNA sequence
	SEQ ID NO:3	XIKE-B-cDNA sequence
	SEQ ID NO:4	XIKE-B-NdN-cDNA
	SEQ ID NO:5	XIKE-A amino acid sequence
10	SEQ ID NO:6	XIKE-A-NdN amino acid sequence
	SEQ ID NO:7	XIKE-B amino acid sequence
	SEQ ID NO:8	XIKE-B-NdN amino acid sequence
	SEQ ID NO:9	XIKE-C-NdN amino acid sequence
	SEQ ID NO:10	XIKE-C-NdN-cDNA sequence
15	SEQ ID NO:11	XIKE-C-cDNA sequence
	SEQ ID NO:12	XIKE-C amino acid sequence

BRIEF SUMMARY OF THE INVENTION

The present invention relates to attenuated pestivirus, preferably to attenuated BVDV, wherein
 20 at least one mutation is in the coding sequence for glycoprotein E^{ms} and at least another mutation in the coding sequence for N^{pro} which preferably leads to combined inactivation of the RNase activity residing in glycoprotein E^{ms} in addition to the inactivation of the (hypothesized) immunomodulating activity residing in N^{pro}. The invention also relates to methods for attenuating pestivirus in such that the attenuation results in an attenuated pestivirus, preferably in
 25 an attenuated BVDV, as described above. The present invention furthermore relates to nucleic acids molecules encoding said attenuated pestiviruses, preferably encoding attenuated BVDV, compositions and vaccines comprising the attenuated pestivirus, preferably BVDV as disclosed herein.

30 DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS OF TERMS USED IN THE DESCRIPTION:

Before the embodiments of the present invention it must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the

context clearly dictates otherwise. Thus, for example, reference to "a BVDV" includes a plurality of such BVDV, reference to the "cell" is a reference to one or more cells and equivalents thereof known to those skilled in the art, and so forth. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are now described. All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing the cell lines, vectors, and methodologies as reported in the publications which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

The term "pestivirus" as used herein refers to all members of the genus *Pestivirus*, including BVDV, CSFV and BDV, within the family *Flaviviridae*.

The term "CSFV" as used herein refers to all viruses belonging to species of classical swine fever virus (CSFV) in the genus *Pestivirus* within the family *Flaviviridae*.

The term "BVDV" as used herein refers to all viruses belonging to species bovine viral diarrhea virus (BVDV) type 1 (BVDV-1) and BVDV type 2 (BVDV-2) in the genus *Pestivirus* within the family *Flaviviridae* (Heinz et al., 2000). The more classical BVDV type 1 strains and the more recently recognized BVDV type 2 strains display some limited but distinctive differences in nucleotide and amino acid sequences.

The term "N^{pro}" as understood herein relates to the first protein encoded by the viral open reading frame and cleaves itself from the rest of the synthesized polyprotein (Stark, et al., J. Virol. 67:7088-7093 (1993); Wiskerchen, et al., Virol. 65:4508-4514 (1991)). Said term, depending on the context, may also relate to the remaining "N^{pro}" amino acids after mutation of the encoding nucleotide sequence or to the coding nucleotide sequence for said protein itself. "Protease activity residing in N^{pro}" relates to the polypeptide cleavage activity of said "N^{pro}".

"E^{ms}" as used herein relates to the glycoprotein E^{ms} which represents a structural component of the pestivirus virion (Thiel et al., 1991). E^{ms} lacks a typical membrane anchor and is secreted in considerable amounts from the infected cells; this protein has been reported to exhibit RNase

activity (Hulst et al., 1994; Schneider et al., 1993; Windisch et al., 1996). It should be noted that the term glycoprotein E0 is often used synonymously to glycoprotein E^{ms} in publications. Said term, depending on the context, may also relate to the mutated "E^{ms}" protein after mutation of the encoding nucleotide sequence or to the coding nucleotide sequence for said protein itself.

5 "RNase activity residing in glycoprotein E^{ms}" relates to the RNA cleavage activity of said glycoprotein, i.e. the ability of the glycoprotein E^{ms} to hydrolyze RNA. The term "inactivation of the RNase activity residing in said glycoprotein" refers to the inability or reduced capability of a modified glycoprotein E^{ms} to hydrolyze RNA as compared to the unmodified wild type of said glycoprotein E^{ms}.

10

Attenuation: "An attenuated pestivirus or BVDV particle" as used herein means that there is a statistically significant difference between the virulence of attenuated pestivirus or BVDV particles of the present invention, wherein said attenuated viral particles being attenuated by a method described herein, and wild-type pestivirus or BVDV isolates from which said attenuated

15 pestivirus or BVDV particles have been derived, for the predominant clinical parameters, in case of BVDV for diarrhea, pyrexia and lethality in animals infected with the same dose, preferably 6×10^6 TCID₅₀. Thus, said attenuated BVDV particles do not cause diarrhea, pyrexia and lethality and thus may be used in a vaccine.

20 Inactivation of E^{ms} as used herein means RNase activity not significantly above the level measured for noninfected control cells in an RNase assay as described in Meyers et al., 1999. "Not significantly above the level measured for noninfected control cells in an RNase assay as described in Meyers et al., 1999, means for example, that the RNase activity is less than 150% compared to the noninfected control cells.

25

Inactivation of N^{pro} as used herein means the prevention or considerable reduction of the probable immunomodulating activity of N^{pro} by mutation. In a preferred embodiment this mutation prevents or considerably reduces the interference of N^{pro} with the induction of an interferon response by the infected cells as described by Rüggli et al., (2003). In this case, the

30 inactivation of N^{pro} would allow the cell to mount a normal interferon response.

"Processing signal" as used herein relates to a substance that ensures the generation of a functional N-terminal of the C protein of the pestivirus, preferably of BVDV, in particular a substance selected from the group of ubiquitin, LC3, SUMO-1, NEDD8, GATE-16 and

GABA(A)RAP. Also proteases selected from the group of Intein, picornavirus 3C, caridovirus 2A and p15 of rabbit hemorrhagic disease virus are understood as "processing signals" as used herein. Any other similar processing signal known to the skilled person that ensures the generation of a functional N-terminal of the C protein shall also be comprised in the term
5 "processing signal".

"Protein C" or "C protein" or "C-protein" as used herein relates to a structural component of the pestivirus virion (Thiel et al., 1991). "Protein C" is the capsid or core protein of pestiviruses. Said term, depending on the context, may also relate to the "Protein C" with one or several
10 amino acids exchanges resulting from mutation of the encoding nucleotide sequence.

A „fragment“ according to the invention is any subunit of a polynucleotide molecule according to the invention, i.e. any subset. For DNA, said fragment is characterized in that it is shorter than the DNA covering the full length viral genome.

15 A „functional variant“ of the nucleotide molecule according to the invention is a nucleotide molecule which possesses a biological activity (either functional or structural) that is substantially similar to the nucleotide molecule according to the invention. The term „functional variant“ also includes „a fragment“, „a functional variant“, „variant based on the degenerative
20 nucleic acid code“ or „chemical derivative“. Such a „functional variant“ e.g. may carry one or several nucleotide exchanges, deletions or insertions. Said functional variant at least partially retains its biological activity, e.g. function as an infectious clone or a vaccine strain, or even exhibits improved biological activity. "Possess a biological activity that is substantially similar" means with respect to the pestiviruses provided herewith, for example, that said pestivirus is
25 attenuated in a manner described herein and result in an non-pathogenic virus suitable for the production of live attenuated virus, which loss ability to pass the placenta but mediates an immune response after vaccination.

30 A „variant based on the degenerative nature of the genetic code“ is a variant resulting from the fact that a certain amino acid may be encoded by several different nucleotide triplets. Said variant at least partially retains its biological activity, or even exhibits improved biological activity.

A molecule is „substantially similar“ to another molecule if both molecules have substantially similar nucleotide sequences or biological activity. Thus, provided that two molecules possess a similar activity, they are considered variants as that term is used herein if the nucleotide sequence is not identical, and two molecules which have a similar nucleotide sequence are
5 considered variants as that term is used herein even if their biological activity is not identical.

A mutation as used herein relates to modifications in the nucleic acid molecules encoding the proteins / amino acids according to the invention. Said mutations relate to, but are not limited to, substitutions (replacement of one or several nucleotides/base pairs), deletions (removal of one or
10 several nucleotides/base pairs), and/or insertions (addition of one or several nucleotides/base pairs). As used herein, mutation may be a single mutation or several mutations, therefore, often the term “mutation(s)” is used and relates to both a single mutation and several mutations. Said mutations include, but are not limited to point mutations (single nucleotide mutations) or larger mutations wherein e.g. parts of the encoding nucleic acid molecules are deleted, substituted
15 and/or additional coding nucleic acid is inserted. Said mutations may result in a modified expressed polypeptide due to the change in the coding sequence. Such modified polypeptides are desired, as set out in the disclosure of the invention as set out below.

The term “vaccine” as used herein refers to a pharmaceutical composition comprising at least
20 one immunologically active component that induces an immunological response in an animal and possibly but not necessarily one or more additional components that enhance the immunological activity of said active component. A vaccine may additionally comprise further components typical to pharmaceutical compositions. The immunologically active component of a vaccine may comprise complete virus particles in either their original form or as attenuated
25 particles in a so called modified live vaccine (MLV) or particles inactivated by appropriate methods in a so called killed vaccine (KV). In another form the immunologically active component of a vaccine may comprise appropriate elements of said organisms (subunit vaccines) whereby these elements are generated either by destroying the whole particle or the growth cultures containing such particles and optionally subsequent purification steps yielding the
30 desired structure(s), or by synthetic processes including an appropriate manipulation by use of a suitable system based on, for example, bacteria, insects, mammalian or other species plus optionally subsequent isolation and purification procedures, or by induction of said synthetic processes in the animal needing a vaccine by direct incorporation of genetic material using suitable pharmaceutical compositions (polynucleotide vaccination). A vaccine may comprise one

or simultaneously more than one of the elements described above. The term "vaccine" as understood herein is a vaccine for veterinary use comprising antigenic substances and is administered for the purpose of inducing a specific and active immunity against a disease provoked by a pestivirus infection, preferably by a BVDV infection. The attenuated pestivirus, in particular the attenuated BVDV as described herein, confer active immunity that may be transferred passively via maternal antibodies against the immunogens it contains and sometimes also against antigenically related organisms. A vaccine of the invention refers to a vaccine as defined above, wherein one immunologically active component is a BVDV or of pestiviral origin or derived from a nucleotide sequence that is more than 70% homologous to any known pestivirus sequence (sense or antisense).

The term "live vaccine" refers to a vaccine comprising a living, in particular, a living viral active component.

Additional components to enhance the immune response are constituents commonly referred to as "adjuvants", like e.g. aluminiumhydroxide, mineral or other oils or ancillary molecules added to the vaccine or generated by the body after the respective induction by such additional components, like but not restricted to interferons, interleukins or growth factors.

A "pharmaceutical composition" essentially consists of one or more ingredients capable of modifying physiological e.g. immunological functions of the organism it is administered to, or of organisms living in or on the organism. The term includes, but is not restricted to, antibiotics or antiparasitics, as well as other constituents commonly used to achieve certain other objectives like, but not limited to, processing traits, sterility, stability, feasibility to administer the composition via enteral or parenteral routes such as oral, intranasal, intravenous, intramuscular, subcutaneous, intradermal or other suitable route, tolerance after administration, controlled release properties. One non-limiting example of such a pharmaceutical composition, solely given for demonstration purposes, could be prepared as follows: Cell culture supernatant of an infected cell culture is mixed with a stabilizer (e.g. spermidine and/or BSA (bovine serum albumin)) and the mixture is subsequently lyophilized or dehydrated by other methods. Prior to vaccination, said mixture is then rehydrated in aqueous (e.g. saline, PBS (phosphate buffered saline)) or non-aqueous solutions (e.g. oil emulsion, aluminum-based adjuvant).

DISCLOSURE OF THE INVENTION

5 It has surprisingly been found that pestiviruses, in particular BVDV can be more effectively attenuated by introducing at least one mutation in the coding sequence for glycoprotein E^{ms} and at least another mutation in the coding sequence for N^{pro} which preferably leads to combined inactivation of the RNase activity residing in glycoprotein E^{ms} in addition to the inactivation of the immunomodulating activity residing in N^{pro}. An immunomodulating effect in one aspect is indicated but not limited to the indicated function for one pestivirus in an exemplary manner by Rüggli et al. (2003).

A pestivirus, in particular BVDV attenuated in accordance with the present invention may be advantageously used in vaccines. Said attenuated pestivirus, in particular said attenuated BVDV now provide live vaccines of high immunogenicity. Surprisingly, the pestivirus, in particular the BVDV according to the invention furthermore are safe for use in pregnant animals as they do not cross the placenta. This is exemplified in a non-limiting manner for BVDV in example 3.

Furthermore, live vaccines with defined mutations as a basis for attenuation will allow to avoid the disadvantages of the present generation of vaccines, e.g. the risk of reversion to an more pathogenic strain. A further advantage of said attenuating mutations lies in their molecular uniqueness which allows to use them as distinctive labels for an attenuated pestivirus, in particular BVDV and to distinguish them from pestivirus, in particular BVDV from the field. Therefore, in one aspect the present invention provides an attenuated pestivirus, in particular an attenuated BVDV having at least one mutation in the coding sequence for glycoprotein E^{ms} and at least another mutation in the coding sequence for N^{pro}. Preferably, in such attenuated pestivirus, preferably in such attenuated BVDV said mutation in the coding sequence for glycoprotein E^{ms} leads to inactivation of the RNase activity residing in E^{ms} and/or said mutation in the coding sequence for N^{pro} leads to inactivation of said N^{pro}. Said inactivation may take place by any mutation known to the person skilled in the art of the E^{ms}- and the N^{pro}-coding sequence, wherein the mutations are any mutation as defined in the "definitions" section, such as deletions, insertion mutations and/or substitution mutations. Most preferably, the mutation(s) are deletions, as the likelihood for reversion to the wild type is the lowest for deletions.

It has been shown that the glycoprotein E^{ms} forms a disulfide-bonded homodimer of about 97 kD, wherein each monomer consists of 227 amino acids corresponding to the amino acids 268 to 494 of the CSFV polyprotein as described by Rümenapf et al. (1993). The genome sequence of the Alfort/Tübingen strain of CSFV is available in the GenBank/EMBL data library under accession number J04358; alternatively, the amino acid sequence for the BVDV strain CP7 can be accessed in the GenBank/EMBL data library (accession number U63479); in the BVDV CP7 polyprotein, the E^{ms} protein corresponds to residues 271 to 497. Two regions of amino acids are highly conserved in glycoprotein E^{ms} as well as in some plant and fungal RNase-active proteins (Schneider et al., 1993). These two regions are of particular importance to the RNase enzymatic activity. The first region consists of the region at the amino acids at position 295 to 307 (298 to 310 for BVDV strain cp7) and the second region consists of the amino acids at position 338 to 357 (341 to 360 for BVDV strain cp7) of said viral polyprotein as exemplified for the Alfort strain of CSFV in Meyers et al., 1999 (numbering according to the published deduced amino acid sequence of CSFV strain Alfort/Tübingen (Meyers et al., 1989). The amino acids of particular importance to the RNase activity as mentioned above are by no means limited to the exact position as defined for the Alfort/Tübingen strain of CSFV but are simply used in an exemplary manner to point out the preferred amino acids being at that position or corresponding to that position in other strains such as found in BVDV, BDV and pestiviruses in general since they are highly conserved. For pestiviruses other than the CSFV Alfort/Tübingen strain the numbering of the positions of the preferred amino acids can be different but an expert in the field of the molecular biology of pestiviruses will easily identify these preferred amino acids by the high degree of conservation of this amino acid sequence and the position of these motifs in the sequence context. In one particular non-limiting example, the position of CSFV Alfort/Tübingen 346 is identical to position 349 of BVDV strain cp7.

As a consequence, the present invention preferably relates to a BVDV according to the invention, wherein said mutation(s) in the coding sequence for glycoprotein E^{ms} are located in the encoding nucleotide sequence corresponding to amino acids at position 298 to 310 and/or position 341 to 360. Preferably, such mutations are (amino acids are given in the one letter symbols; the amino acid before the position number indicates the amino acid to be substituted, the amino acid after the position number the substituting amino acid (del indicates deletion): for example, H300L means histidine 300 was substituted by leucine:

Suitable modification of the glycoprotein E^{ms} are for example, the single substitutions/deletions: S298G, H300K, H300L, H300R, H300del, W303G, P304del, E305A, C308G, R343G, E345del, W346G, K348A, H349K, H349L, H349del, H349Q, H349SV (mutation H349S and insertion of V), K348R, W351P, W351G, W351L, W351K, W351H; the double substitutions/deletions: H300L/H349L, K348del/H349del, H349del/G350del, E345del/H349del, W303G/E305A, H300K/H349K, H300K/H349L and the triple deletions: L299del/H300del/G300del, K348del/H349del/G350del. Numbering is according to the published amino acid sequence of BVDV CP7 for all the mutants listed above (the given numbers minus 3 would correspond to the equivalent residues of the CSFV Alfort/Tübingen amino acid sequence). All the above-listed mutants were at least tested as respective CSFV or BVDV mutants without mutations in the N^{pro} region. Suitable mutants of the pestiviral glycoprotein E^{ms} are provided, for example, by WO 99/64604, which is incorporated herein at its whole. It should be noted, however, that according to the present invention, at least one additional mutation in the N^{pro} region, as disclosed in further detail below, must be present.

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It was particularly found that deletion or substitution of the histidine residue at position 346 (CSFV) or 349 (BVDV) leads to effective inactivation of E^{ms} and therefore leads to particularly useful pestiviral live vaccines. The present invention demonstrates that pestiviruses are viable and code for an E^{ms} protein without RNase activity when the histidine residue at position 346 of the viral polyprotein (numbering according to the published sequence of CSFV Alfort/Tübingen (Meyers et al., 1989)), or at position 349 (numbering according to the published sequence of BVDV CP7 (Meyers et al., 1996b)) if said pestivirus is BVDV, which represents one of the conserved putative active site residues of the E^{ms} RNase, is deleted. Thus, preferably, the invention also relates to a BVDV according to the invention, wherein said mutation in the coding sequence for glycoprotein E^{ms} is a deletion or substitution of the histidine residue at position 349. Even more specifically, the putative active site of the RNase is represented by the conserved E^{ms} sequences SLHGIWPEKICTG and/or LQRHEWNKHGWCNWFHIEPW (sequence of the BVDV-2 New York'93 protein given here in an exemplary manner; minor changes can possibly be found in other pestivirus sequences but the identity of the motif will always be obvious for an expert in the field. As an example, the corresponding amino acid sequences of BVDV-1 CP7 would be SLHGIWPEKICKG and/or LQRHEWNKHGWCNWNIEPW and that of CSFV Alfort/Tübingen SLHGIWPEKICKG and/or LQRHEWNKHGWCNWNIDPW). Thus, preferably, the invention further relates to a BVDV according to the invention, wherein said mutation(s) in the coding sequence for glycoprotein E^{ms} are located in the nucleotide sequence

30

coding for the conserved E^{ms} sequence SLHGIWPEKICTG and/or LQRHEWNKHGWCNWFHIEPW. These sequences are representing the putative active site of the RNase. The sequences SLHGIWPEKIC and RHEWNKHGWCNW of the putative E^{ms} active site are even more conserved across pestiviruses. Thus, preferably, the invention also relates to a pestivirus, in particular to BVDV having at least one mutation in the coding sequence of the N^{pro} protein and the glycoprotein E^{ms}, wherein said mutation(s) in the coding sequence for glycoprotein E^{ms} are located in the nucleotide sequence coding for the conserved E^{ms} sequence SLHGIWPEKIC and/or RHEWNKHGWCNW. Preferably, the mutation is located in only one of said sequences. Thus the invention also relates to a pestivirus, in particular to BVDV having at least one mutation in the coding sequence of the N^{pro} protein and the glycoprotein E^{ms}, wherein said mutation(s) in the coding sequence for glycoprotein E^{ms} are located in the nucleotide sequence coding for the conserved E^{ms} sequence SLHGIWPEKIC or RHEWNKHGWCNW. Preferably, such mutations concern two different amino acids, i.e. are double mutations. Thus, said mutations may be 1 to 3 nucleotide mutations in two different triplets encoding two amino acids. Thus, the invention also relates to a pestivirus, in particular to BVDV having at least one mutation in the coding sequence of the N^{pro} protein and the glycoprotein E^{ms}, wherein said mutation(s) in the coding sequence for glycoprotein E^{ms} are two mutations located in the nucleotide sequence coding for the conserved E^{ms} sequence SLHGIWPEKIC and/or RHEWNKHGWCNW. Preferably, such mutations concern a single amino acid. Thus, said mutation may be 1 to 3 nucleotide mutations in one triplet encoding one amino acid. Thus, the invention also relates to a pestivirus, in particular to BVDV having at least one mutation in the coding sequence of the N^{pro} protein and the glycoprotein E^{ms}, wherein a single mutation is located in the conserved E^{ms} sequence SLHGIWPEKIC or RHEWNKHGWCNW.

As mentioned above, the attenuated pestiviruses provided by the present invention, having at least one mutation in the coding sequence of the glycoprotein E^{ms} and in the coding sequence of the N^{pro} protein, wherein said mutation preferably result in inactivation of the RNase activity residing in the glycoprotein E^{ms} and of the immunomodulating activity residing in N^{pro}. Inactivation of the N^{pro} is achieved in pestiviruses, in particular BVDV of the specified formula described more in detail below, wherein between 0 and all amino acids of N^{pro} are present; ubiquitin or LC3 or another sequence serving as processing signal (e.g. SUMO-1, NEDD8, GATE-16, GABA(A)RAP, or proteases like e.g. Intein, picornavirus 3C, caridovirus 2A, or p15 of rabbit hemorrhagic disease virus) is present or absent. In case a processing signal is present,

the coding sequence of the processing signal is inserted at or close to the C-terminal end of the (remaining part of the) N^{pro}-protein. Only in the case that a processing signal is present, any number of amino acids coding for N^{pro} (=N^{pro} amino acids) may be present. In case no processing signal sequence is inserted, a maximum of 12 amino acids, preferably aminoterminal amino acids, of N^{pro} may be present, the remaining amino acids have to be deleted. Furthermore, other than the E^{ms} mutations as disclosed above (at least one of which has to be present in the pestivirus, in particular in BVDV according to the invention), the remaining sequences of the pestivirus, in particular BVDV may remain unchanged, i.e. are not mutated, or may also have mutations close to the N-terminal end of the C-protein. A number of more specific embodiments as disclosed below exemplify this.

Thus, the invention relates to a pestivirus, in particular to BVDV according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:

$$[N^{pro}]_x-[PS]_y-[C-term]$$

and wherein:

[N^{pro}] relates to the N^{pro} portion of said polyprotein, wherein "x" represents the number of amino acids of the N^{pro} present in the polyprotein;

[PS] relates to a processing signal selected from: ubiquitin, LC3, SUMO-1, NEDD8, GATE-16 or GABA(A)RAP) or proteases like e.g. Intein, picornavirus 3C, caridovirus 2A, or p15 of rabbit hemorrhagic disease virus or any processing signal known to the skilled person that ensures the generation of a functional N-terminal of the C-protein. "Y" may be = 0, which means that no processing signal is present (= PS is absent), or "Y" may be = 1, which means that a processing signal is present (= PS present).

[C-term] relates to the complete pestivirus, in particular the complete BVDV polyprotein except for N^{pro}, but including the capsid (C)-protein and any other protein present in the pestivirus polyprotein, in particular in the BVDV polyprotein including the carboxyterminal NS5B. Preferably, the glycoprotein E^{ms} in said [C-term] is mutated, in such that the RNase activity residing in the glycoprotein E^{ms} is inactivated. The term "any other protein present in the pestivirus polyprotein /BVDV polyprotein" relates to E^{ms}, E1, E2, p7, NS2, NS3, NS4A, NS4B and NS5A, wherein glycoprotein E^{ms} is mutated, preferably as disclosed herein (see above), in such that the RNase activity residing in the glycoprotein E^{ms} is inactivated. Preferably, the pestivirus, in particular the BVDV

according to the invention has a C-protein which is not mutated except for the amino acid at position 2 which is changed from D to N. Therefore, [C-term*] is the same as [C-term] but with a mutation at position 2 of the C-protein (N instead of D);

if "y" is = 0 (means no [PS] present) then "x" is 0 to 12, (means no N^{pro} specific amino acid or 1 to 12 amino acids of N^{pro}, preferably of the N-terminus of N^{pro}, are present);

if "y" is = 1 (means [PS] is present) then "x" is 0 to 168; (means no N^{pro} specific amino acid or 1 to all 168 amino acids of N^{pro}, preferably of the N-terminus of N^{pro}, are present).

Also more preferably, the invention relates to a pestivirus, in particular to BVDV according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:



and wherein the definitions are as defined above.

A specific example thereof is disclosed below, wherein the N-terminal methionine is followed by the C-protein and any other protein present in the polyprotein including the carboxyterminal NS5B. Hence, most preferably, the invention relates to a pestivirus, in particular BVDV according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:



and wherein the definitions are as defined above.

Also more preferably, the invention relates to a pestivirus, in particular to BVDV according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:



and wherein the definitions are as defined above.

A specific example of BVDV is disclosed below, wherein the N-terminal methionine is followed by the N^{pro} sequence EL and the C-protein and any other protein present in the polyprotein including the carboxyterminal NS5B. Hence, most preferably, the invention relates to a BVDV

according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:

$$\text{MEL-}[\text{C-term}]$$

and wherein the definitions are as defined above.

5

Also more preferably, the invention relates to a pestivirus, in particular to BVDV according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:

$$[\text{N}^{\text{pro}}]_4\text{-}[\text{PS}]_0\text{-}[\text{C-term}]$$

10

and wherein the definitions are as defined above.

A specific example of BVDV is disclosed below, wherein the N-terminal methionine is followed by the N^{pro} sequence ELF and the C-protein and any other protein present in the polyprotein including the carboxyterminal NS5B. Hence, most preferably, the invention relates to a BVDV according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:

15

$$\text{MELF-}[\text{C-term}].$$

and wherein the definitions are as defined above.

20

Also more preferably, the invention relates to pestivirus, in particular to BVDV according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:

$$[\text{N}^{\text{pro}}]_6\text{-}[\text{PS}]_0\text{-}[\text{C-term}]$$

and wherein the definitions are as defined above.

25

A specific example of BVDV is disclosed below, wherein the N-terminal methionine is followed by the N^{pro} sequence ELFSN and the C-protein and any other protein present in the polyprotein including the carboxyterminal NS5B. Hence, most preferably, the invention relates to a BVDV according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:

30

$$\text{MELFSN-}[\text{C-term}].$$

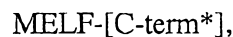
and wherein the definitions are as defined above.

Also more preferably, the invention relates to a pestivirus, in particular to BVDV according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded
5 polypeptide as characterized by the following formula:



and wherein the definitions are as defined above except for the fact that the aminoterminal part of the C-protein is changed.

10 A specific example of BVDV is disclosed below, wherein the N-terminal methionine is followed by the N^{pro} sequence ELF and in the C-protein sequence, the amino acid at position 2 is changed from D to N. Therefore, the aminoterminal C-protein sequence is SNEGSK... instead of SDEGSK. Hence, most preferably, the invention relates to a BVDV according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polypeptide as
15 characterized by the following formula:



wherein in the C-protein the amino acid at position 2 is changed from D to N, and
wherein the definitions are as defined above.

20 Also more preferably, the invention relates to a pestivirus, in particular BVDV according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polypeptide as characterized by the following formula:



wherein the definitions are as defined as above,

25 and wherein PS is any of the PS disclosed above, preferably selected from the group of ubiquitin or LC3.

A specific example of BVDV is disclosed below, wherein the N-terminal methionine is followed by any 21 or 28 N^{pro} amino acids, ubiquitin or LC3 and the C-protein. Hence most preferably,
30 the invention relates to a BVDV according to the invention, wherein said mutation(s) in the

coding sequence for N^{pro} lead to an encoded polypeptide as characterized by the following formula:

$[N^{\text{pro}}]_{22}\text{-[PS]}_1\text{-[C-term]}$, wherein preferably, the PS is ubiquitin or LC3 or

$[N^{\text{pro}}]_{29}\text{-[PS]}_1\text{-[C-term]}$, wherein preferably, the PS is ubiquitin or LC3.

5

Ubiquitin is a well known highly conserved cellular protein of 76 amino acids. Among other functions, ubiquitin is a key player in protein catabolism since conjugation with ubiquitin can mark a protein for degradation via the proteasome. Ubiquitin conjugated with or fused to other proteins via the carboxyterminal glycine can be cleaved off by cellular ubiquitin-specific proteases. Thus, fusion of a protein to the carboxyterminus of ubiquitin will usually result in defined proteolytic cleavage of the fusion protein into its components when expressed within a cell.

10

LC3 (light chain 3 of microtubule associated proteins) represents a cellular protein of 125 amino acids that serves a variety of functions (length given for bovine LC3). Recently, a fundamental role of the protein in autophagy has been defined. During this process, LC3 is activated by carboxyterminal cleavage. Thereby, a new carboxyterminus is generated that consists of glycine. LC3 is then conjugated via the carboxyterminal glycine to phosphatidylethanolamine present in the membranes of autophagic vesicles. Because of this process, a protein fused to the carboxyterminus of LC3 will be cleaved off by a cellular protease at a defined position.

20

Also more preferably, the invention relates to a pestivirus, preferably to BVDV according to the invention, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polypeptide as characterized by the following formula selected from the group of :

25

$[N^{\text{pro}}]_2\text{-[PS]}_y\text{-[C-term]}$ and preferably ME-[PS]_y-[C-term];

$[N^{\text{pro}}]_5\text{-[PS]}_y\text{-[C-term]}$ and preferably MELFS-[PS]_y-[C-term];

$[N^{\text{pro}}]_7\text{-[PS]}_y\text{-[C-term]}$ and preferably MELFSNE-[PS]_y-[C-term];

$[N^{\text{pro}}]_8\text{-[PS]}_y\text{-[C-term]}$ and preferably MELFSNEL-[PS]_y-[C-term];

$[N^{\text{pro}}]_9\text{-[PS]}_y\text{-[C-term]}$ and preferably MELFSNELL-[PS]_y-[C-term];

30

$[N^{\text{pro}}]_{10}\text{-[PS]}_y\text{-[C-term]}$ and preferably MELFSNELLY-[PS]_y-[C-term];

$[N^{\text{pro}}]_{11}\text{-[PS]}_y\text{-[C-term]}$ and preferably MELFSNELLYK-[PS]_y-[C-term]; and

$[N^{\text{pro}}]_{12}\text{-[PS]}_y\text{-[C-term]}$ and preferably MELFSNELLYKT-[PS]_y-[C-term]

and wherein the definitions are as defined as above. The preferably disclosed embodiments refers to BVDV.

Most preferably, y is 0 (no PS present).

5 Also more preferably, said BVDV according to the invention as described *supra* is a BVDV type 1 BVDV. Most preferably, said BVDV according to the invention as described *supra* is a BVDV type 2 BVDV. BVDV-1 and BVDV-2 are differentiated according to features of their genomic sequences (Heinz et al., 2000 and references therein). BVDV-1 as disclosed herein may be used in the manufacture of a composition for use in the prevention and/or treatment of BVDV type 1
10 infections in breeding stocks of cattle, in pregnant cows and in the induction of fetal protection against BVDV type 1 infection in pregnant cows. Surprisingly, a BVDV-2 as disclosed herein may be used in the manufacture of a composition for use in the prevention and/or treatment of BVDV type 1 infections in breeding stocks of cattle. In particular, the invention relates to the use of a BVDV type 2 according to the invention in the manufacture of a composition for use in the
15 prevention and/or treatment of BVDV type 1 infections in pregnant cows. Preferably, the BVDV type 2 according to the invention may be used in the manufacture of a composition for use in the induction of fetal protection against BVDV type 1 infections in pregnant cows. Surprisingly also, a BVDV-1 as disclosed herein may be used in the manufacture of a composition for use in the prevention and/or treatment of BVDV type 2 infections in breeding stocks of cattle. In particular,
20 the invention relates to the use of a BVDV type 1 according to the invention in the manufacture of a composition for use in the prevention and/or treatment of BVDV type 2 infections in pregnant cows. Preferably, the BVDV type 1 according to the invention may be used in the manufacture of a composition for use in the induction of fetal protection against BVDV type 2 infections in pregnant cows. Most preferred is the use of BVDV type 1 and type 2 in
25 combination for the manufacture of a composition for use in the prevention and/or treatment of BVDV type 1 and or type 2 infections in breeding stocks of cattle, in pregnant cows and in the induction of fetal protection against BVDV type 1 and/or type 2 infections in pregnant cows.

Most preferably, the wild type BVDV according to the invention which is to be mutated as
30 disclosed herein corresponds to amino acid sequence SEQ ID No. 5 (termed XIKE A) or is a functional variant thereof. Most preferably also, the BVDV according to the invention has a N^{pro} mutation according to the invention and corresponds to amino acid sequence SEQ ID No. 6 (termed XIKE-A-NdN) or is a functional variant thereof. Preferably, such a functional variant is

at least 65% homologous to the amino acid sequence disclosed herein. On the amino acid level, homologies are very roughly: BVDV-1/-BVDV-1: 93%; BVDV-1/-BVDV-2: 84%; BVDV-2/-BVDV-2: 98%. Therefore, more preferable, such a functional variant is at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89% or 90% homologous to the amino acid sequence disclosed herein. More preferably also, such functional variant is at least 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% homologous to the amino acid sequence disclosed herein. Most preferably, such functional variant is at least 99% or 99.9% homologous to the amino acid sequence disclosed herein.

Most preferably also, the BVDV according to the invention has a E^{ms} mutation according to the invention which has a deletion of the codon coding for histidine 349, and corresponds to amino acid sequence SEQ ID No. 7 (termed XIKE-B) or is a functional variant thereof. Most preferably also, the BVDV according to the invention has both a E^{ms} mutation and a N^{pro} mutation according to the invention, wherein the codon coding for histidine 349 of E^{ms} is deleted and also the complete N^{pro} coding region is deleted, except for codons 1 to 4, thus amino acids MELF of N^{pro} remain. Said mutant corresponds to amino acid sequence SEQ ID No. 8 (termed XIKE-B-NdN) or is a functional variant thereof. Preferably, such a functional variant is at least 65% homologous to the amino acid sequence disclosed herein. More preferable, such a functional variant is at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89% or 90% homologous to the amino acid sequence disclosed herein. More preferably also, such functional variant is at least 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% homologous to the amino acid sequence disclosed herein. Most preferably, such functional variant is at least 99% or 99.9% homologous to the amino acid sequence disclosed herein.

Most preferably also, the BVDV according to the invention has a E^{ms} mutation according to the invention which has a substitution of the codon coding for histidine 300 by the codon coding for leucine and corresponds to amino acid sequence SEQ ID No. 9 (termed XIKE-C) or is a functional variant thereof. Most preferably also, the BVDV according to the invention has both a E^{ms} mutation and a N^{pro} mutation according to the invention, wherein the codon coding for histidine 300 is substituted by the codon coding for leucine and also the complete N^{pro} coding region is deleted, except for codons 1 to 4, thus amino acids MELF of N^{pro} remain. Said mutant corresponds to amino acid sequence SEQ ID No. 10 (termed XIKE-C NdN) or is a functional variant thereof. Preferably, such a functional variant is at least 65% homologous to the amino

acid sequence disclosed herein. More preferable, such a functional variant is at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89% or 90% homologous to the amino acid sequence disclosed herein. More preferably also, such functional variant is at least 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% homologous to the amino acid sequence disclosed herein. Most preferably, such functional variant is at least 99% or 99.9% homologous to the amino acid sequence disclosed herein.

Another important embodiment of the invention described herein is a composition comprising a pestivirus, in particular a BVDV according to the invention and a solution. The skilled person knows additional components which may be comprised in said composition (see also Remington's Pharmaceutical Sciences. (1990). 18th ed. Mack Publ., Easton). The expert may use known injectable, physiologically acceptable sterile solutions. For preparing a ready-to-use solution for parenteral injection or infusion, aqueous isotonic solutions, such as e.g. saline or corresponding plasma protein solutions are readily available. The pharmaceutical compositions may be present as lyophilisates or dry preparations, which can be reconstituted with a known injectable solution directly before use under sterile conditions, e.g. as a kit of parts.

The final preparation of the compositions of the present invention are prepared for e.g. injection by mixing said pestivirus, preferably BVDV according to the invention with a sterile physiologically acceptable solution, that may be supplemented with known carrier substances or/and additives (e.g. serum albumin, dextrose, sodium bisulfite, EDTA). Said solution may be based on a physiologically acceptable solvent, e.g. an aqueous solution between pH 7 and 8. The pH may be stabilised by a pharmaceutically acceptable buffer. The solution may also contain further stabilising agents like a detergent like Tween 20, serum albumin such as BSA (bovine serum albumin), ascorbic acid, and/or spermidine. The composition may also comprise adjuvants, e.g. aluminiumhydroxide, mineral or other oils or ancillary molecules added to the vaccine or generated by the body after the respective induction by such additional components, like but not restricted to interferons, interleukins or growth factors.

For example, in a composition according to the invention, the pestivirus, in particular BVDV may be solved in:

Pestivirus (preferably BVDV)

$10^2 - 10^8$ TCID₅₀

*SGS**

25 % v/v

Cell culture medium

qsp 1 dose

5	* SGS:	<i>Composition per 2 ml</i>
	<i>Sucrose</i>	75 mg
	<i>Gelatine</i>	20 mg
	<i>Potassium hydroxide</i>	0.274 mg
	<i>L- glutamic acid</i>	0.72 mg
10	<i>Potassium dihydrogen phosphate</i>	0.516 mg
	<i>Dipotassium phosphate</i>	1.254 mg
	<i>Water for injection</i>	qsp 2 ml

If the composition is first lyophilized or dehydrated by other methods, then, prior to vaccination, said composition is rehydrated in aqueous (e.g. saline, PBS (phosphate buffered saline)) or non-aqueous solutions (e.g. oil emulsion (mineral oil, or vegetable/metabolizable oil based/single or double emulsion based), aluminum-based, carbomer based adjuvant).

Preferably, the composition according to the invention induces an immunological response in an animal. More preferred, the composition according to the invention is a vaccine. A vaccine as understood herein comprises a pestivirus, in particular BVDV according to the invention and is defined above (section "definitions")

Most preferred, the composition according to the invention further comprises a pharmaceutically acceptable carrier or excipient. Several carriers or excipients are disclosed above. The composition may comprise, if aimed at injections or infusion, substances for preparing isotonic solutions, preservatives such as p-hydroxybenzoates, stabilizers, such as alkalisalts of ethylendiamintetracetic acid, possibly also containing emulsifying and/ or dispersing.

The composition according to the invention may be applied intradermally, intratracheally, or intravaginally. The composition preferably may be applied intramuscularly or intranasally. In an animal body, it can prove advantageous to apply the pharmaceutical compositions as described above via an intravenous or by direct injection into target tissues. For systemic application, the

intravenous, intravascular, intramuscular, intranasal, intraarterial, intraperitoneal, oral, or intrathecal routes are preferred. A more local application can be effected subcutaneously, intradermally, intracutaneously, intracardially, intralobally, intramedullary, intrapulmonarily or directly in or near the tissue to be treated (connective-, bone-, muscle-, nerve-, epithelial tissue).

5 Depending on the desired duration and effectiveness of the treatment, the compositions according to the invention may be administered once or several times, also intermittently, for instance on a daily basis for several days, weeks or months and in different dosages.

The invention also relates to the use of a pestivirus, in particular BVDV according to the
10 invention in the manufacture of a vaccine for the prophylaxis and treatment of pestiviral infections, in particular of BVDV infections.

Another important part of the invention is a polynucleotide molecule comprising the nucleic acid coding for a pestivirus, in particular for a BVDV according to the invention, or a fragment,
15 functional variant, variant based on the degenerative nucleic acid code, fusion molecule or a chemical derivative thereof. Preferably, said polynucleotide molecule is DNA. Also preferably, said polynucleotide molecule is RNA. In a more preferred embodiment, said polynucleotide molecule also comprises the nucleotide sequence of a functional 5'- and/or 3'-non-translated region of a pestivirus, in particular of BVDV.

20 There are several nucleotide sequences known in the art, which represents the basis for the production of a polynucleotide molecule coding for a pestivirus attenuated according to the present invention, having at least one mutation in the coding sequence of N^{pro} and at least one in the coding sequence of glycoprotein E^{ms}, wherein said mutations result in an combined
25 inactivation of the RNase activity residing in glycoprotein E^{ms} and in the inactivation of the immunomodulating activity residing in N^{pro}. Examples of nucleic acid sequences of wild-type sequences of several members of pestiviruses are listed below:

Border disease virus

Strain BD31	NCBI GenBank Accession No. [U70263]
Strain X818	NCBI GenBank Accession No. [AF037405]

Bovine viral diarrhea virus 1

Strain NADL	NCBI GenBank Accession No. [M31182]
Strain Osloss	NCBI GenBank Accession No. [M96687]
Strain SD-1	NCBI GenBank Accession No. [M96751]
Strain CP7	NCBI GenBank Accession No. [U63479]

Bovine viral diarrhea virus 2

Strain 890	NCBI GenBank Accession No. [U18059]
Strain C413	NCBI GenBank Accession No. [AF002227]

Classical swine fever virus

Strain Alfort/187	NCBI GenBank Accession No. [X87939]
Strain Alfort-Tübingen	NCBI GenBank Accession No. [J04358]
Strain Brescia	NCBI GenBank Accession No. [M31768]
Strain C strain	NCBI GenBank Accession No. [Z46258]

The mutations/modifications according to the invention relating to the coding sequence of N^{pro} and E^{ms} are described above more in detail. Having this information, a person skilled in the art is able to realize the manufacture of any polynucleotide/polynucleic acid coding for a pestivirus according to the present invention. Furthermore, this person is able to manufacture an attenuated pestivirus according to the invention. Molecular method for introducing a mutation into a polynucleotide sequence, cloning and amplification of said mutated polynucleotide are for example provided by Sambrook et 1989 or Ausubel et al. 1994.

- Most preferably, the wild type BVDV according to the invention which is to be mutated as disclosed herein is encoded by the nucleic acid sequence SEQ ID No. 1 (termed XIKE A) or a functional variant thereof. Most preferably also, the BVDV according to the invention has a N^{pro} mutation according to the invention and is encoded by nucleic acid sequence SEQ ID No. 2 (termed XIKE-A-NdN) or a functional variant thereof. Preferably, such a functional variant is at least 65% homologous to the nucleic acid sequence disclosed herein. On the nucleic acid level, homologies are very roughly: BVDV-1/-BVDV-1: 80%; BVDV-1/-BVDV-2: 70%; BVDV-2/-BVDV-2: 96%. Therefore, more preferable, such a functional variant is at least 70%, 71%, 72%,

73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89% or 90% homologous to the nucleic acid sequence disclosed herein. More preferably also, such functional variant is at least 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% homologous to the nucleic acid sequence disclosed herein. Most preferably, such functional variant is at least 99% or 99.9% homologous to the nucleic acid sequence disclosed herein.

Most preferably also, the BVDV according to the invention has a E^{ms} mutation according to the invention which has a deletion of codon H349 and is encoded by nucleic acid sequence SEQ ID No. 7 (termed XIKE-B) or by a functional variant thereof. Most preferably also, the BVDV according to the invention has both a E^{ms} mutation and a N^{pro} mutation according to the invention, wherein the codon coding for histidine 349 of E^{ms} is deleted and also the complete N^{pro} coding region is deleted, except for codons 1 to 4, thus amino acids MELF of N^{pro} remain. Said mutant is encoded by nucleic acid sequence SEQ ID No. 8 (termed XIKE-B-NdN) or by a functional variant thereof. Preferably, such a functional variant is at least 65% homologous to the nucleic acid sequence disclosed herein. More preferable, such a functional variant is at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89% or 90% homologous to the nucleic acid sequence disclosed herein. More preferably also, such functional variant is at least 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% homologous to the nucleic acid sequence disclosed herein. Most preferably, such functional variant is at least 99% or 99.9% homologous to the nucleic acid sequence disclosed herein.

Most preferably also, the BVDV according to the invention has a E^{ms} mutation according to the invention which is a substitution of codon "H300" by a leucine codon, and is encoded by nucleic acid sequence SEQ ID No. 11 (termed XIKE-C) or a functional variant thereof. Most preferably also, the BVDV according to the invention has both a E^{ms} mutation and a N^{pro} mutation according to the invention, wherein the codon coding for histidine 300 is substituted by the codon coding for leucine and also the complete N^{pro} coding region is deleted, except for codons 1 to 4, thus amino acids MELF of N^{pro} remain. Said mutant is encoded by nucleic acid sequence SEQ ID No. 12 (termed XIKE-C-NdN) or by a functional variant thereof. Preferably, such a functional variant is at least 65% homologous to the nucleic acid sequence disclosed herein. More preferable, such a functional variant is at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89% or 90% homologous to the nucleic acid sequence disclosed herein. More preferably also, such functional variant is at least 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% homologous to the nucleic acid sequence

disclosed herein. Most preferably, such functional variant is at least 99% or 99.9% homologous to the nucleic acid sequence disclosed herein.

Another important aspect of the invention is a method for attenuating a pestivirus, characterized in that at least one mutation in the coding sequence for glycoprotein E^{ms} and at least another mutation in the coding sequence for N^{pro} is generated in a pestivirus genome. According to a preferred embodiment, said pestivirus is BVDV.

According to a more preferred embodiment, said method comprises the steps:

- 10 a) reverse transcription of a wild-type pestivirus nucleotide sequence into a cDNA;
- b) cloning said cDNA;
- c) introducing mutations selected from the group of deletions, insertion mutations and/or substitution mutations into said cDNA, wherein said mutations are located in the coding sequence encoding glycoprotein E^{ms} and the protease N^{pro},
- 15 d) incorporating the cDNA into a plasmid or into a DNA virus capable of directing the transcription of pestivirus cDNA into RNA in vitro or upon infection of suitable cells.

Regarding the method for attenuating a BVDV according to the invention, said preferred methods comprises the steps:

- 20 a) reverse transcription of a wild-type BVDV nucleotide sequence into a cDNA;
- b) cloning said cDNA;
- c) introducing mutations selected from the group of deletions, insertion mutations and/or substitution mutations into said cDNA, wherein said mutations are located in the coding sequence encoding glycoprotein E^{ms} and the protease N^{pro},
- 25 d) incorporating the cDNA into a plasmid or into a DNA virus capable of directing the transcription of pestivirus cDNA into RNA in vitro or upon infection of suitable cells.

Yet another important embodiment of the invention is a method of treatment of disease caused by a pestivirus, wherein a pestivirus according to the invention or a composition according to the invention, wherein the said pestivirus or said composition is administered to an animal in need thereof at a suitable dosis as known to the skilled person and the reduction of symptoms of said pestivirus infection.

Yet another important embodiment of the invention is a method of treatment of disease caused by BVDV, wherein a BVDV according to the invention or a composition according to the invention, wherein the said BVDV or said composition is administered to an animal in need thereof at a suitable dosis as known to the skilled person and the reduction of symptoms of BVDV infection such as viremia and leukopenia and/or pyrexia and/or diarrhea is monitored.

EXAMPLES

The following examples serve to further illustrate the present invention; but the same should not be construed as limiting the scope of the invention disclosed herein.

EXAMPLE 1

BVDV XIKE-B: foetopathogenicity assessment in pregnant heifers

BVDV XIKE-B, an RNase negative mutant of the highly pathogenic BVDV type 2 isolate NewYork'93/C was recovered from the infectious cDNA clone pKANE40B and showed wild type-like (wt-like) growth characteristics in tissue culture. In animal experiments the mutant virus was found to be considerably attenuated so that it represented a promising candidate for development of a live attenuated vaccine virus (Meyer et al., 2002). To test whether this attenuated virus is still able to cross the placenta and infect the fetus, pregnant heifers were infected with XIKE-B. As a control wild type BVDV recovered from cDNA clone pKANE40A was used. The respective virus named XIKE-A expresses an active E^{rns} RNase in the infected cell.

The study aimed to assess the safety of XIKE-A and XIKE-B in pregnant animals.

EXPERIMENTAL DESIGN

Ten pregnant heifers were selected from a BVDV negative herd. The following groups of 5 heifers were included in the trial:

	No.	Inoculation	Virus
<u>Group 1:</u>	5	One i. n. administration, 3 ml in each nostril	XIKE-A
<u>Group 2:</u>	5	One i. n. administration, 3 ml in each nostril	XIKE-B

Heifers were moved to the experimental facilities 8 days before inoculations. Pregnancy status was confirmed after transport into the experimental facility. Heifers were between days 60 and 90 of gestation on the day of inoculation. Inoculation took place for all animals at one point of
5 time.

Heifers were monitored for the presence of clinical signs of BVDV infection including abortions during the observation period. Blood samples were collected from the animals for serology, antigen detection and white blood cells were counted. The experiment was terminated 9 weeks
10 after infection. Non-aborted cows were slaughtered, the uterus examined and collected. Foetal organ samples were collected during routine necropsy and examined for BVDV infection.

The presence of fetal infection was the main evaluation parameter, composed from the number of BVDV-related cow mortality, the number of BVDV-related abortions and the number of
15 BVDV positive fetuses at termination. In addition to the main parameter, clinical signs characteristic for BVDV infection, viraemia and white blood cell counts in cows and rectal temperature after challenge were evaluated.

Animals

20 Heifers were purchased from a farm free of BVDV.

Only animals, which met the following inclusion criteria, were used.

Inclusion criteria

- 25 - Free of BVD antibodies; each individual will be tested in the serum antibody test prior to transport and at the initiation of the study (at the animal test facility).

- Free of BVDV; plasma and/or buffy-coat preparation from each individual will be tested by a suitable test.

- Clinically healthy at the initiation of the study judged upon physical examination. The health examination of the animals was accomplished in accordance with the current, generally accepted veterinary practice.

- Pregnancy confirmed by physical examination before inoculation. Pregnancy was between 60 - 90 days at the time of inoculation, proven by insemination records.

10 Test Strain A

Description:	XIKE A, live virus BVDV strain
Composition:	Experimental material comprising of cell culture supernatant of low passaged XIKE-A
BVD components:	BVDV type II strain: XIKE-A
Supplied by:	Dr. Gregor Meyers, "Bundesforschungsanstalt für Viruskkrankheiten der Tiere" (BFAV), Paul-Ehrlich-Straße 28, 72076 Tübingen, Germany
Applied BVD virus dose:	Type 1 strain: 10^5 TCID ₅₀ /6ml (TCID = Tissue Culture Infective Dose)
Applied vaccine volume:	3 ml per nostril
Application route:	Intranasal
Preparation of dosage form:	The inoculum was sent in a pre-diluted frozen form in a 50 ml vial on dry ice and was to be stored at -70 °C before inoculation. Immediately before inoculation of Group 1 heifers, the material was thawed avoiding local temperatures above 37 °C. After no ice was visible in the fluid, material was gently stirred and immediately used for inoculation of the animals.
Unused inoculum:	The volume of the unused material was be measured and split on two aliquots before immediate freezing in dry ice or liquid nitrogen and stored for re-titration purposes. Virus and contaminated plastic or glassware were incubated with an appropriate volume of an 8 - 10 % formaldehyde solution for at least 24 hours at room temperature before discarding in order to inactivate viruses.

Test Strain B

Description:	XIKE B, live virus BVDV strain
Composition:	Experimental material comprising of cell culture supernatant of low passaged XIKE B
BVD components:	BVDV type II strain: XIKE-B
Supplied by:	Dr. Gregor Meyers, "Bundesforschungsanstalt für Viruskkrankheiten der Tiere" (BFAV), Paul-Ehrlich-Straße 28, 72076 Tübingen, Germany
Applied BVD virus dose:	Type 1 strain: 10^5 TCID ₅₀ /6ml (TCID = Tissue Culture Infective Dose)
Applied vaccine volume:	3 ml per nostril
Application route:	Intranasal
Preparation of dosage form:	The inoculum was sent in a pre-diluted frozen form in a 50 ml vial on dry ice and was stored at -70 °C before inoculation. Immediately before inoculation of Group 2 heifers, the material was thawed avoiding local temperatures above 37 °C. After no ice was visible in the fluid, material was gently stirred and immediately used for inoculation of the animals.
Unused vaccine:	The volume of the unused material was measured and split on two aliquots before immediate freezing in dry ice or liquid nitrogen and stored for re-titration purposes. Virus and contaminated plastic or glassware was incubated with an appropriate volume of an 8 – 10 % formaldehyde solution for at least 24 hours at room temperature before discarding in order to inactivate viruses.

Pregnancy Control

- 5 Pregnancy was confirmed immediately before inoculation.

Inoculation of Heifers

The inoculation is Day 0 of the experiment.

- 10 In each nostril, 3 ml of the test material was administered intranasally by syringe without needle. Each time a new sterile syringe was taken. Administration was performed during the aspiration phase in order to minimize loss of fluid via expiration of material.

Post-Inoculation Observations

Collection and examination of blood samples

Blood was collected following standard, aseptic procedures (disinfecting the bleeding site). A new sterile syringe and needle was used for each animal.

5 Blood collection to prepare serum

At least 10 ml blood was collected from the heifers immediately before inoculation, then weekly after infection and at the termination of the study. Serum was stored at -20°C until required.

Blood collection for leukocyte counts and buffy coat preparations

- 10 For leukocyte counting, 3 ml blood was transferred immediately after collection to suitable sterile vessels (Venoject, Terumo Europe N.V., Leuven, Belgium), pre-filled with 0.06 ml EDTA (0.235 MOL/L).

- For buffy coat preparations, at least 15 ml blood was transferred immediately after collection to
15 suitable sterile vessels, pre-filled with 0.1 ml Heparin solution (Na-heparin for inj., 5 000 IU/ml lot. A7B163A exp. date: 11/2000: Gedeon Richter RT, Budapest, Hungary) yielding at least 20 IU Heparin per ml blood in the blood sample. The content was carefully mixed thereafter.

For preparation of buffy coats and leukocyte counting, blood was collected from the heifers

- 20
- on every day, between Day 0 and Day 14 after infection;
 - on every second day, between Day 15 and Day 40, or until all animals were negative for virus isolation for three consecutive sampling time points.

Preparation of serum

- 25 Blood was allowed to clot at room temperature, and separated by centrifugation. Each serum sample was divided into two aliquots of at least 2 ml each. One set of aliquots was assayed for BVDV specific antibodies by ELISA. The rest of the sera was frozen and stored at -20°C until required.

30 Leukocyte counts

Leukocyte counts was determined with a coulter-counter semi-automated electronic device (Diatron Minicell-16; Messtechnik GmbH, Wien, Austria) with a claimed accuracy of $0.1 \times 10^9 / \text{l}$, $100 / \mu\text{l}$. The instrument was used (calibration and leukocyte-counts) according to the manufacturer's recommendations.

Preparation of buffy coats

Heparin blood samples was transported to the laboratory as soon as possible. Buffy coat preparation procedure, following a standard laboratory procedure was performed under aseptic conditions (sterile pipettes, handling, clean bench etc.).

The obtained buffy coats were re-suspended in a small volume (2 ml) of RPMI 1640 and frozen at -70°C in two aliquots of 0,5 ml. The residual 1ml buffy coats was immediately used for determination of blood cell associated BVDV by co-cultivation in a permissive cell culture.

BVD serum antibody ELISA-test

Each serum sample was tested for the presence of BVDV-antibodies using a suitable and validated ELISA test (SvanovirTM BVDV antibody test Cat# 10-2200-10). Test was validated and performed according to the manufacturer's recommendations. Positive samples were diluted according to the $\log_2$ scale to determine BVDV antibody titers.

BVD antigen assay(s)

Each buffy coat sample was assayed for the presence of BVDV by co-cultivation of the freshly prepared buffy-coats with susceptible cells or a cell-line. No freezing was allowed before co-cultivation.

Plasma was collected and provided to Man-Gene from each sample.

Clinical observations**Observation of heifers**

Animals were examined daily from Day 0 - 42 post inoculation for the presence of clinical symptoms by a sufficiently trained veterinarian.

All clinical signs were recorded and described by its nature, consistence/touch, severity (mild, medium or severe) location, size of the area affected, and they will be scored according to agreed and standard definitions. Special attention was paid to respiratory signs (respiration, its rate; nasal or ocular discharge; conjunctivitis, sneezing, coughing, etc.) and diarrhea.

Rectal temperatures

Rectal temperatures were measured daily in each heifer, at the same hour of the day (preferably in the morning) from 5 days prior to the inoculation till 21 days post infection.

- 5 Daily measurement of rectal temperature was continued until each animal had rectal temperatures below or equal to 39 °C for at least 3 consecutive days.

Detection of interrupted pregnancy

- 10 Pregnancy was confirmed and suspicion for abortion or resorption of the fetus was established by rectal examination. A trained veterinarian examined all animals at inoculation, 1 and 2 months post-inoculation. The examination was carried out according to the generally accepted veterinary practice.

- 15 Heifers were examined daily for any sign of abortion until termination of the study (8 - 12 weeks post-challenge).

Termination of the Study

- 20 The study was terminated by slaughtering the heifers and extracting the fetuses. Fetuses and fetal material were transferred into closed transport containers marked with the number of the cow and the date/time. Containers were transported to a selected necropsy room.

Necropsy of the heifers was not required. Necropsy will be performed on fetuses, findings recorded and a panel of samples collected as described below.

25 **Post-Mortem Examination**

A detailed necropsy of the experimental animals was done in each case of death.

- 30 Post-mortem examinations were carried out by an experienced veterinary surgeon and the data were recorded on appropriate data sheets. Further laboratory tests were performed according to the clinical signs and lesions observed. If the diagnosis of the necropsy referred to a disease caused by microbial agent the diagnosis was verified by an appropriate test, specific for the agent.

Each tissue sample was collected in at least 2 separate, labeled containers and snap-frozen in liquid nitrogen. Samples were stored at -70°C until required.

Aborted fetuses and study termination

5 At least the following tissue samples were collected from the fetuses:

- exudate from the peritoneal cavity or thorax, if present,
- mesenteric lymph nodes,
- spleen,
- 10 • thymus,
- cerebellum,
- kidney,
- bone marrow from the sternum,
- sample from the placenta, if available.

15

Dead or sacrificed heifers

At least the following tissue samples were collected:

- blood for buffy coat, if available,
- blood for serum, if available,
- 20 • Peyer's patches,
- mesenteric lymph nodes,
- spleen,
- kidney,
- uterus, including a sample from the placenta, if available.

25

Storage and Transport of Samples

Samples:	Storage:
Serum	-20°C
Buffy coat	-70°C
Virus	-70°C
Tissue from heifers	-70°C
Tissue from fetuses	-70°C

30 Samples were sent for laboratory analysis as required by the sponsor. The choice of samples and the timing of transport were agreed with the study monitor or the project manager. As a matter of

general principle, samples coming from aborted material or from new-born calves were investigated as soon as possible.

RESULTS

5 Mortality

Heifer No. 626 (Group 1) died on Day 13 PI (post inoculation). The following table summarises the observed clinical signs and lesions revealed during necropsy:

Heifer	In-life observations	Post mortem findings
No. 626	• signs of disease from 7 DPI • lachrymation, nasal discharge on 7 - 12 DPI • loss of appetite from 8 - 12 DPI • diarrhoea on 11 - 12 DPI • elevated respiratory rate on 9 - 10 and 12 DPI • coughing on 9 DPI • abnormal breathing on 12 DPI	• dehydration • haemorrhages on the serous membranes • hyperaemia of the Peyer's patches • oedema of the lung

- 10 These clinical and gross-pathological findings are consistent with BVDV induced lesions, therefore it may be concluded that the reason of death was the BVDV infection.

Abortions after Infection

- One heifer had clinical abortion in each group. Heifer No. 615 (Group 1) aborted on Day 38 PI,
 15 Heifer No. 469 (Group 2) aborted on Day 39 PI. Both foetuses showed the signs of autolysis, and they were estimated to die at least 3 - 7 days before the abortion (around 32 - 35 DPI).

In Group 1, no foetus was found in Heifer No. 526 during the slaughter examination at termination. Gross-pathology of the uterus revealed the followings:

- the right uterine horn was slightly enlarged,
- 20 • the remains of placenta with progressed autolysis was retained in the lumen.

The findings on the uterus of Heifer No. 526 is consistent with a "silent" abortion, most likely due to the BVD infection.

Clinical Observation of Heifers

- 25 A summary of the clinical observation data and duration of clinical signs in the groups are presented below.

Clinical signs and the days post inoculation (DPI) when they were observed

Group 1 (XIKE-A)

Clinical sign	Animal ID				
	526	598	615	618	626*
	DPI				
Loss of appetite	8 - 13	8 - 18	8 - 18	8 - 16	8 - 12
Lachrymation	7 - 10	7- 8, 10-12	8 - 10	8 - 10	7 - 8
Conjunctivitis	9 - 10	9 - 12	9 - 11	9 - 11	-
Nasal discharge	7 - 13	7-9, 11-12	8 -13	8 - 12	7 - 12
Oral erosion	-	-	-	-	-
Oral haemorrhage	-	-	-	-	-
Diarrhoea	-	11 - 16	10 - 15	11 - 15	11 - 12
Coughing	9	10, 15	9	8 - 9, 13	9
Abnormal breathing	-	11 - 14	12 - 14	12 - 14	12
Elevated respiratory rate	-	10 - 13	9 - 13	8 - 13	9 - 10, 12
Hoof erosion	-	-	-	-	-

*Heifer No. 626 died on Day 13 PI

Group 2 (XIKE-B)

Clinical sign	Animal ID				
	469	588	565	608	619
Loss of appetite	-	-	-	-	-
Lachrymation	-	-	-	-	-
Conjunctivitis	-	-	-	-	-
Nasal discharge	-	-	-	-	-
Oral erosion	-	-	-	-	-
Oral haemorrhage	-	-	-	-	-
Diarrhoea	-	-	-	-	-
Coughing	-	-	-	-	-
Abnormal breathing	-	-	-	-	-
Elevated respiratory rate	-	-	-	-	-
Hoof erosion	-	-	-	-	-

All Group 1 animals infected with XIKE-A exhibited a broad spectrum of clinical signs.

- 10 Respiratory signs appeared first accompanied by loss of appetite, and a few days later heifers developed diarrhoea with the exception of Heifer No. 526. One heifer died and another one aborted (see before) after infection. All these signs are consistent with the symptoms expected after infection with a virulent BVDV strain.

All Group 2 animals infected with XIKE-B were free of clinical signs. At the same time, one heifer had abortion during the observation period.

Rectal Temperatures

5 No abnormal temperature changes were detected before the infection of the animals.

In Group 2, all temperature values remained within the physiological range from Day 0 to Day 21 after infection.

All Group 1 animals showed elevated rectal temperature after infection that were detected between Days 7 - 11 PI.

10

Findings at Study Termination

At study termination, foetuses were examined at slaughter.

No foetus was recovered from Heifer No. 526 (see section 10.2 "Abortions after Infection").

The following findings were observed at the necropsy of the foetuses:

15

Animal No.	Findings	Conclusion
<u>Group 1</u>		
598	Ascites, general oedema, autolysis	Died at least 2 weeks earlier
618	Ascites, general oedema, autolysis	Died at least 3 weeks earlier
<u>Group 2</u>		
565	Ascites, general oedema, liver degeneration	Foetus considered non-viable
588	Normal	-
608	Normal, perirenal oedema	-
619	General autolysis	Died 3 - 6 weeks earlier

The findings suggest that 2 Group 1 animals (Heifers No. 598 and No. 618) and one Group 2 animal (Heifer No. 619) died several weeks before extraction, and so they can be considered abortions.

20

Abortions Modified by Post-Mortem Findings

After the post-mortem examination it was not clear why some of the heifers had not had abortion. Dead foetuses should be considered as abortions, therefore the clinical picture was modified after the termination of the study as follows:

Group 1

Animal No.	Conclusion
526	BVD abortion (uterus with placenta post-mortem)
598	BVD abortion (foetus post-mortem)
615	Clinical BVD abortion
618	BVD abortion (foetus post-mortem)
626	Died due to BVD

Group 2

Animal No.	Conclusion
469	Clinical BVD abortion
565	Expected BVD abortion; non-viable foetus
588	Normal
608	Normal
619	BVD abortion (foetus post-mortem)

5 **Examination of Blood Samples****Leukocyte count**

WBC counting was interrupted on Day 26 PI, as all animals became negative for virus isolation for this time point.

0 DPI values were considered as individual baseline for comparison.

- 10 In Group 2, the leukocyte counts never went to 40 % or more below the baseline value until the end of the observation period (26 DPI).

In Group 1, one animal (Heifer No. 598) had WBC count below the 40 % baseline for one day.

Serology

- 15 None of the selected animals had BVDV specific antibody in their sera before the infection.

After infection, all surviving Group 1 heifers developed BVDV specific antibodies detected from 3 weeks PI and lasted until the end of the observation period in all study animals. In Group 2, 4 out of the 5 heifers had BVDV specific antibodies detected from 4 weeks PI. Measurable antibody response lasted only in 3 animals until the end of the observation period. Titres were

- 20 lower in Group 2 than in Group 1.

Virus Detection by Co-Cultivation**Buffy coats**

BVDV was detected in both groups. The duration of virus detection is summarised below. All samples were co-cultivated immediately after collection, i. e. without freezing.

5

Animal No.	DPI when BVDV was detected
<u>Group 1</u>	
615	5 - 12
526	5 - 9
626	5 - 12
618	5 - 11, 14
598	5 - 11, 13
<u>Group 2</u>	
565	7 - 9
588	8
608	6 - 9
469	8
619	5 - 11

Tissue samples

The presence of BVD virus in the dead heifer and the foetuses is summarised below:

10 Heifer:

Animal No.	BVDV in tissue samples
<u>Group 1</u>	
626	Present [#]

Foetuses:

Animal No.	BVDV in tissue samples
<u>Group 1</u>	
615	Not present [#]
526	NT
626	Present [#]
618	Not present
598	Present

<u>Group 2</u>	
565	Present
588	Not present
608	Present
469	Not present [#]
619	Not present

NT = Not tested

Samples were co-cultivated immediately after collection (i. e. without freezing), except “#” marked ones, from which only frozen samples were available.

5

Summary of BVD related clinical and laboratory data

Group 1

Animal No.	Conclusion	BVD
526	BVD abortion (uterus with placenta post-mortem)	NT (no sample found)
598	BVD abortion (foetus post-mortem)	+ (foetus)*
615	Clinical BVD abortion	- (foetus)*
618	BVD abortion (foetus post-mortem)	- (foetus)*
626	Died due to BVD	+ (foetus) / + (heifer)

NT: not tested

Group 2

Animal No.	Conclusion	BVD
469	Clinical BVD abortion	- (foetus)*
565	Expected BVD abortion; non-viable foetus	+ (foetus)
588	Normal	- (foetus)
608	Normal	+ (foetus)
619	BVD abortion (foetus post-mortem)	- (foetus)*

10

* Foetuses were autolysed at the time of sampling

Conclusion:

The study aimed to assess the safety of XIKE-A and XIKE-B in pregnant animals.

Ten pregnant heifers were selected from a BVDV negative herd. Two groups of 5 heifers were included in the trial: one was inoculated with XIKE-A the other with XIKE-B virus strain. Heifers were between days 60 and 90 of gestation on the day of inoculation.

15

Heifers were monitored for the presence of clinical signs of BVDV infection including abortions during the observation period. Blood samples were collected from the animals for serology, antigen detection and white blood cells were counted. The experiment was terminated 9 weeks after infection. Non-aborted cows were slaughtered, the uterus examined and collected. Foetal
5 organ samples were collected during routine necropsy and examined for BVDV infection.

The presence of fetal infection was the main evaluation parameter, composed from the number of BVDV-related cow mortality, the number of BVDV-related abortions and the number of BVD positive fetuses at termination. In addition to the main parameter, clinical signs characteristic for
10 BVDV infection, viraemia and white blood cell count in cows and rectal temperature after challenge were evaluated.

The XIKE-B virus proved to be less pathogenic than XIKE-A, nevertheless BVD related abortion and infection of the foetus was observed in the XIKE-B group, too. Therefore it can be
15 concluded that the inactivation of the E^{ms} RNase does not prevent fetal infection.

EXAMPLE 2

BVDV XIKE-A-NdN: foetopathogenicity assessment in pregnant heifers

20 The N^{pro} gene has been shown to be nonessential for growth of CSFV in tissue culture (Tratschin et al., 1998). Even though a proof for BVDV attenuation in consequence of N^{pro} deletion is still missing, a role of this protein in the interaction between virus and host seemed to be possible and was actually indicated by recent experiments for CSFV (Mayer et al., 2004; Rüggli et al., 2003).
25 We therefore wanted to investigate, whether the deletion of the major part of the N^{pro} coding sequence leads to a virus that no longer infects the fetus in pregnant heifers. The N^{pro} gene except for the 5' terminal 4 codons was deleted from the full length cDNA clone pKANE40A according to standard procedures. The resulting mutant full length clone was used as template for in vitro transcription and the resulting cRNA was transfected into MDBK cells as described
30 (Meyer et al., 2002). The recovered virus was amplified in tissue culture and then used in the animal experiment described below. BVDV XIKE-B served as a control since it was shown before that it is able to cross the placenta (EXAMPLE 1).

OBJECTIVE(S)/PURPOSE OF THE STUDY

The study aims to assess the safety of a live attenuated BVDV with a genomic deletion of most of the N^{pro} coding region in pregnant animals.

- 5 Material and Methods applied are described in Example 1

STUDY DESIGN

Eight pregnant heifers were assigned at random to two groups. They were treated and observed according to the following schedule:

10

	Group 1	Group 2
N	5	3
Treatments	XIKE-A-NdN	XIKE-B / control
Route	Intramuscular	
Vaccination time	between days 60 and 90 of pregnancy (day 0 of the study)	
Observations Post-vaccination (in life)	• Clinical signs • Serum at days 0, 14, 28, 42 and at termination • WBC at day 0 and then daily for 14 days • Buffy coat at day 0 and then daily for 14 days	
Post-mortem (day 60)	• Gross-pathology • Organ panel for virus isolation	

Type of study:	open controlled clinical study
Experimental unit:	Individual animal
Method of blinding:	Partial blinding. No detailed procedures for blinding and access to treatment schedule were applied. The observing veterinarian at the study location and the pathologist were not be aware of the treatment; they only received a protocol extract relevant to their tasks. Vaccination was performed by the investigator or his assignee. Samples for virus isolation were coded by the investigator until all results are available.

RESULTS

- 15 All heifers were healthy and pregnant at study start. All animals proved to be free of BVDV and BVDV antibodies before the initiation of the.

Preparation and Control of the Virus used for the Infection

- 20 Samples were collected throughout the dilution steps and assayed on the day of preparation, i.e. without freezing by co-cultivation on suitable tissue culture. The results of virus titration are shown in the following table.

Sample ID	Virus strain	Dilution / description	Log ₁₀ titre/ml
VT1a	XIKE-A/NdN (S)	1:2 (at 4 °C)	4.4
VT1b		#2a on ice without opening	4.0
VT1c		Return of #2b	2.8
VT2a	XIKE-B	1:2.2 (at 4 °C)	2.3
VT2b		#3a on ice without opening	2.8
VT2c		Return of #3b	Negative

Clinical Symptoms of BVDV Infection

- 5 The table below gives a summary about the animals that had clinical signs during the observation period.

Clinical signs and the days post inoculation (DPI) when they were observed

Group 1 (XIKE-A NdN)

Clinical sign	Animal ID
	1583
Loss of appetite	8
Lachrymation	-
Conjunctivitis	-
Nasal discharge	-
Oral erosion	-
Oral haemorrhage	-
Diarrhoea	-
Coughing	-
Abnormal breathing	-
Elevated respiratory rate	-
Hoof erosion	-

Group 2 (XIKE-B)

Animal ID	
1438	1585
-	10
-	-
-	-
-	-
-	-
-	-
12	10-13
-	-
-	-
-	-

10 Only mild and transient clinical signs were observed in some of the animals in each group.

In Group 1, one out of the 5 heifers had loss of appetite on day 8 PI. In Group 2, two out of the 3 animals had clinical signs. Both heifers experienced coughing around day 21 PI that was accompanied with loss of appetite in one of the animals.

Rectal Temperatures

15 No abnormal temperature changes were detected before the inoculation of the animals. The few

cases of elevated temperatures measured after the inoculation are summarised in the table below.

Group	Animal ID	Temperature (°C)	PI day
1	1583	39.9	8
	1621	39.0	5
2	1438	39.0	2
	1585	40.8	9

One animal had slightly elevated temperature in each group, and also one animal had fever in each group. Fever was detected on day 8 or 9 PI. Temperature values always returned to normal value on the following day.

Leukocyte Counts

Some leukopenia was observed in all groups between PI days 3 – 8. The number of animals with at least 40 % reduction in white blood cell count was the following:

Group	Number of animals having leukopenia / total
1	3/5 (60%)
2	1/3 (33%)

Serology (BVDV antibodies)

In compliance with the study protocol, all heifers were free of BVDV antibodies before vaccination. In Group 1 (inoculated with XIKE-A NdN) and Group 2 (inoculated with XIKE-B), complete seroconversion was detected only at study termination (2 months after inoculation).

BVD virus isolation from buffy coats

No viremia was detected

BVD virus isolation from foetal tissue samples

	Group 1	Group 2
N	5	3
Treatments	XIKE-A-NdN	XIKE-B / control
Route	Intramuscular	Intramuscular
Number of fetuses in which fetal transmission was detected:	4 out of 5 fetuses infected	2 out of 3 fetuses infected

Conclusion of the virus used for treatment has the potential to be transmitted over the placenta:	Fetal transmission for XIKE-A-NdN observed	Fetal transmission for XIKE – B observed
---	--	--

Conclusion

The N^{pro} deletion resulted in a considerable attenuation of the BVDV in comparison to the parental virus XIKE-A that was shown to be highly pathogenic (Meyer et al., 2002). However, the N^{pro} deletion alone is not preventing transmission of a NY93 based virus recombinant to the foetus after inoculation of pregnant cows.

EXAMPLE 3

BVDV XIKE-B-NdN: foetopathogenicity assessment in pregnant heifers

To be able to test the potential of a combination of RNase inactivation and N^{pro} deletion with regard to BVDV attenuation and fetal transmission, different BVDV-2 mutants with deletions within the N^{pro} coding region were established based on the infectious cDNA clone pKANE40B, the RNase negative mutant of pKANE40A with a deletion of codon 349. The recovered viruses were analyzed with regard to presence of the desired mutations, the absence of second site mutations in the regions flanking the introduced changes and their growth characteristics in tissue culture. XIKE-B-NdN (V-pK88C), a variant containing a deletion of the complete N^{pro} coding region except for codons 1 to 4 in addition to the RNase inactivating deletion of codon 349 was chosen for an animal experiment since it combined the desired mutations with acceptable growth characteristics. The aim of the study was to assess the safety of a live attenuated BVDV isolate in pregnant animals.

Five BVDV-negative, pregnant heifers were inoculated intranasally with an infective dose of 10⁵ TCID₅₀/animal XIKE-B-NdN (back titration data are depicted in Table 3.1). Clinical data were recorded daily. Blood samples were collected for white blood cell counting, for buffy-coat preparation and serology. After termination of the study foetal tissues were collected for virus isolation.

MATERIAL AND METHODS:

As detailed for example 1:

RESULTS

No clinical data were observed (data not shown). Leukocyte counts remained virtually unchanged except for a significant decrease by approx. 40% below the baseline value (day0) in heifer no- 1015 on a single day (day 6 p.i.) (data not shown).

5

Analysis of buffy coat preparations:

Approximately 10^6 leukocytes were cultured in duplicates with MDBK-cells in 24-well tissue culture plates for 5 days. Samples were freeze-thawed twice. One hundred microliter aliquots of thawed samples were inoculated onto freshly seeded 24-well tissue culture plates and tested for virus by indirect immuno-fluorescence staining (mAb Code 4, directed against a conserved epitope in nonstructural protein NS3). No BVDV could be isolated from the buffy coat preparations of animals # 921, 1013, 1015, 1055 and 1075 (Table 3.2) whereas positive controls clearly showed the correct conduction of the test.

15 b) Post-mortem examination of foetal tissues

After termination of the study the following foetal tissues were collected for virus isolation: spleen, kidney, thymus, sternum, cerebellum, placenta, intestine and abdominal fluid. Briefly, tissue suspensions were made in a mortar using sterile sea sand and ice-cold PBS without Ca^{2+} and Mg^{2+} . Mortars were rinsed with 1 ml ice-cold PBS without Ca^{2+} and Mg^{2+} and suspensions were centrifuged for 10 min. at $2000 \times g$ (4°C). The supernatant was first passed through a disposable $0.45 \mu\text{m}$ filter holder, followed by a second filter passage ($0.2 \mu\text{m}$ pore size). Virus isolation was carried out in duplicates ($400 \mu\text{l}$ foetal tissue suspension or $100 \mu\text{l}$ foetal abdominal fluid) on a monolayer of MDBK-cells in a 24 wells tissue culture plate (37°C , 7% CO_2). Tissue samples were controlled daily for cytopathic effects or bacterial contamination, and after an incubation time of 5 days plates were frozen and thawed twice. $100 \mu\text{l}$ of samples were passaged to freshly seeded MDBK-cells. Virus was detected by indirect immuno-fluorescence staining (mAb Code 4). No BVDV could be detected in the tissue samples or foetal abdominal fluid (Table 3.3).

30 c) Serological Findings

Serum neutralization titres were determined before inoculation, 1 month post-inoculation and at termination of the study. Sera from all animals were tested in triplicates for neutralizing antibodies against NY93/C, and the endpoint dilution was read by indirect immunofluorescence staining. Results were expressed as the endpoint dilution, which neutralized approximately 100

TCID₅₀ and calculated by the method of Kaerber. No definite data could be obtained for day 0, and 1 and 2 weeks post infection as the sera were toxic for MBDK-cells in dilutions up to 1:16 and no neutralization could be detected at higher dilutions. Starting with the third week post vaccination all animals developed neutralising antibodies against the homologous BVDV-2 virus NY'93/C lasting till the end of the experiment (Table 3.4 and Fig. 1).

d) Conclusions

The data obtained during the animal study clearly show that BVDV XIKE-B-NdN represents a highly attenuated virus. In contrast to wild type virus or the single mutants XIKE-B or XIKE-A-NdN that show foetal transmission in pregnant heifers at high rates the double mutant did not cross the placenta. BVDV XIKE-B-NdN as well as similar double mutants are extremely suitable for the use in a live attenuated vaccine.

Study No.: B01 BIVI020 and B01 BIVI022

Table 3.1: Back Titration of Viruses

Sample ID	Virus Strain	Dilution	Titre
1a	XIKE-B-NdN	concentrated virus	10 ^{5,44} TCID ₅₀ / ml
1		1:4	10 ^{4,86} TCID ₅₀ / ml
6		residues of infection (#1)	10 ^{4,27} TCID ₅₀ / ml

Table 3.2
Detection of Viremia

Animal ID No.	Days after vaccination														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
0921	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	1. isolation 2. isolation
1013	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	1. isolation 2. isolation
1015	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	1. isolation 2. isolation
1055	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	1. isolation 2. isolation
1075	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	1. isolation 2. isolation
Date	13.12 2001	14.12 2001	15.12 2001	16.12 2001	17.12 2001	18.12 2001	19.12 2001	20.12 2001	21.12 2001	22.12 2001	23.12 2001	24.12 2001	25.12 2001	26.12 2001	27.12 2001

- sample negative

Table 3.3
Analysis of foetus tissue samples for the presence of BVDV

Animal No.	Abdominal fluid	Thoracic Fluid	Mesenteric lymph nodes	Spleen	Kidney	Thymus	Bone marrow (sternum)	Cerebellum	Placenta	Intestine	Date of tissue collection	Isolation
0921	--	NC	NC	--	--	--	--	--	--	--	12.02.02	1. isolation 2. isolation
1013	--	NC	NC	--	--	--	--	--	--	--	12.02.02	1. isolation 2. isolation
1015	--	NC	NC	--	--	--	--	--	--	--	12.02.02	1. isolation 2. isolation
1055	--	NC	NC	--	--	--	--	--	--	--	12.02.02	1. isolation 2. isolation
1075	--	NC	NC	--	--	--	--	--	--	--	12.02.02	1. isolation 2. isolation

NC = Not collected

- = sample negative

**Table 3.4: B01 BIV1022 / BVDV XIKE-B-NdN; foetal protection study
Serum Neutralization Assay**

Animal ID No.	From the heifers									
	at selection	during ACC	1 wPV	2 wPV	3 wPV	4 wPV	5 wPV	6 wPV	7 wPV	8 wPV
0921		*	*	*	1:40 ⁽²⁾	1:161 ⁽¹⁾	1:256 ⁽¹⁾	1:323 ⁽¹⁾	1:128 ⁽¹⁾	1:256 ⁽¹⁾
1013		*	*	*	1:3 ⁽²⁾	NA	1:161 ⁽¹⁾	1:323 ⁽¹⁾	1:406 ⁽¹⁾	1:256 ⁽¹⁾
1015		*	*	*	1:64 ⁽²⁾	1:161 ⁽¹⁾	1:256 ⁽¹⁾	1:323 ⁽¹⁾	1:406 ⁽¹⁾	1:323 ⁽¹⁾
1055		*	*	*	1:32 ⁽²⁾	1:40 ⁽²⁾	1:256 ⁽¹⁾	1:323 ⁽¹⁾	1:406 ⁽¹⁾	1:406 ⁽¹⁾
1075		*	*	*	NA	1:128 ⁽²⁾	1:102 ⁽¹⁾	1:203 ⁽¹⁾	1:161 ⁽¹⁾	1:406 ⁽¹⁾
Date		06.12.2001	20.12.2001	27.12.2001	03.01.2002	10.01.2002	17.01.2002	24.01.2002	31.01.2002	07.02.2002
⁽¹⁾	SNT against 1456 Nase (= NY93/C) 10 ^{2.03} TCID ₅₀ / 50µl * Serum toxic for MBDK-cells in dilutions up to 1:16 ⇒ no data available									
⁽²⁾	SNT against 1456 Nase (= NY93/C) 10 ^{1.57} TCID ₅₀ / 50µl NA data not available									

The Serum Neutralisation Assay against NY93/C is illustrated in Fig. 1.

Efficacy and crossprotection study

Two possible problems have to be faced with regard to vaccination with attenuated virus mutants BVDV XIKE-B or BVDV XIKE-B-NdN. First, there is a general problem concerning cross protection between BVDV-1 and BVDV-2. At least vaccination with inactivated BVDV-1 vaccines did not prevent the transmission of BVDV-2 to the foetus in pregnant animals. Since protection against foetal infection represents the major aim of anti BVDV vaccination, such vaccines cannot be regarded to induce a protective immunity on a broad range. The question therefore was, whether vaccination with live attenuated BVDV-2 can prevent virus transmission to the foetus. Second, the reduced growth rates of BVDV XIKE-B-NdN might result in only a low level of protection not able to prevent transplacental infection of the foetus in pregnant heifers. To address these problems, an animal study was started. The animals (2 groups of 10 animals each) were vaccinated either with BVDV XIKE-B or XIKE-B-NdN (intended dosage: 1ml of supernatant with 10^5 TCID₅₀ of virus; backtitration is shown in Tab. 3.5). None of the animals showed significant clinical signs after the vaccination except for one animal of the nonvaccinated control group with mild coughing for one day. Rectal temperature values were below 39 °C except for one animal of the nonvaccinated control group that had 39.1°C for one day. Buffy coat samples prepared after vaccination were analysed for the presence of virus as described above. The experiments showed that only 5 of the 20 animals contained virus in the blood for 1 or 2 days at 4 to 8 days post infection (Tab. 3.6).

Table 3.5: Back Titration of Viruses used for vaccination

Sample ID	Virus Strain	Dilution	Titre
1a	XIKE-B-NdN	concentrated virus	$10^{5,44}$ TCID ₅₀ / ml
1		1:4	$10^{4,86}$ TCID ₅₀ / ml
6		residues of infection (#1)	$10^{4,27}$ TCID ₅₀ / ml
3	XIKE-B	1:11	$10^{5,76}$ TCID ₅₀ / ml
4		1:110	$10^{4,92}$ TCID ₅₀ / ml
5		residues of infection (#4)	$10^{4,27}$ TCID ₅₀ / ml

Animal	Days after vaccination															
ID No.	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
1134 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1141 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1142 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	+	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	Ø+	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1145 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1149 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	+	ØØ	ØØ	ØØ	Ø+	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1151 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1152 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1156 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1158 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1160 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
Date	13.12 2001	14.12 2001	15.12 2001	16.12 2001	17.12 2001	18.12 2001	19.12 2001	20.12 2001	21.12 2001	22.12 2001	23.12 2001	24.12 2001	25.12 2001	26.12 2001	27.12 2001	

Animal	Days after vaccination															
ID No.	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
1197 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1200 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1206 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	Ø+	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	Ø+	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1210 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1212 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	Ø+	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1214 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1216 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1217 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	Ø+	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1218 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
1225 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	2. isolation
Date	13.12 2001	14.12 2001	15.12 2001	16.12 2001	17.12 2001	18.12 2001	19.12 2001	20.12 2001	21.12 2001	22.12 2001	23.12 2001	24.12 2001	25.12 2001	26.12 2001	27.12 2001	

Code of animal numbers:

(1) vaccination with BVDV XIKE-B (RNase mutant)

(2) vaccination with BVDV XIKE-B-NdN (RNase and N^{pro} double mutant)

Immunofluorescence staining: Code 4

□ sample negative

+ sample positive

B bacterial contamination in well

Four weeks after vaccination, insemination of the animals was carried out. Challenge infections were performed 60 to 90 days later using either a BVDV-1 strain (BVDV KE-9, heterologous challenge, animals vaccinated with XIKE-B) or a heterologous BVDV-2 strain (BVDV KE-13, homologous challenge, animals vaccinated with XIKE-B-NdN) (intended dosage: 10^5 TCID₅₀ in 6ml; backtitration is shown in Tab. 3.7). From each group of vaccinated animals 5 pregnant heifers were randomly selected for the challenge infection. Animals vaccinated with BVDV XIKE-B were challenged with the BVDV-1 strain KE-9, whereas heifers vaccinated with BVDV XIKE-B/NdN were challenged with BVDV-2 KE-13. In addition, 2 nonvaccinated control animals were infected with each of the challenge viruses.

Study No. / Id.: B01 BIVI020 / BVDV Tü XIKE-B-NdN; foetal protection study

Table 3.7: Back titration of challenge viruses

Virus Strain	Sample ID	Titre (TCID ₅₀ / ml)	Mean Titre (TCID ₅₀ / ml)
KE 9	1	$10^{4,44}$	$10^{4,94}$
		$10^{5,10}$	
	2	$10^{4,69*}$	$10^{4,44}$
	3	**	
KE13	1	$10^{4,69}$	$10^{4,76}$
		$10^{4,82}$	
	2	$10^{4,57}$	$10^{4,63}$
		$10^{4,69}$	
	3***	$10^{3,5}$	$10^{3,5}$

Sample 1: stock of inoculate

Sample2: stock of inoculate returned from the stable

Sample3: excess inoculate

* Second inoculation of KE9, sample 2 wasn't interpretable because of cell death.

** KE9, sample 3 wasn't interpretable because of cell death or bacterial contamination.

*** First inoculation of KE13, sample 3 wasn't interpretable because of bacterial contamination.

The vaccinated animals did not show viremia or clinical symptoms upon challenge infection. The challenge was successful as all non-vaccinated controls were BVDV positive (Tab. 3.8). Only mild signs of disease were observed in the control groups. The white blood cell counts were nearly normal (not shown).

Study No. / Id.: B01 BIV1020 / BVDV Tü XIKE-B/XIKE-B-NdN; foetal protection study
Table 3.8: Inoculation with white blood cell (buffy coat) preparations collected after challenge

Animal ID No.	Days after challenge																Isolation
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	
1104 ⁽³⁾	ØØ	ØØ	ØØ	Ø+	++	++	Ø+	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation
	ØØ	ØØ	ØØ	Ø+	++	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	
1108 ⁽³⁾	ØØ	ØØ	ØØ	ØØ	ØØ	Ø+	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation
	ØØ	ØØ	ØØ	Ø+	++	Ø+	ØØ	Ø+	Ø+	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	
1126 ⁽³⁾	ØØ	ØØ	ØØ	ØØ	ØØ	Ø+	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	Ø+	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	
1145 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	
1151 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation 3. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	
1152 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation 3. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	
1156 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation 3. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	
Date	04.22 2002	04.25 2002	04.27 2002	04.29 2002	05.01 2002	05.03 2002	05.05 2002	05.07 2002	05.09 2002	05.11 2002	05.13 2002	05.15 2002	05.17 2002	05.19 2002	05.21 2002	05.23 2002	

Animal ID No.	Days after challenge																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	
1197 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ		ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation 3. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	
1200 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation
1214 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation 3. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	
1216 ⁽²⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation 3. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	
1217 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation 3. isolation
	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	
1218 ⁽¹⁾	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation
	ØØ	ØØ	ØØ	ØØ	++ ++	ØØ +Ø	ØØ ØØ	ØØ ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	1. isolation 2. isolation
Date	04.22 2002	04.25 2002	04.27 2002	04.29 2002	05.01 2002	05.03 2002	05.05 2002	05.07 2002	05.09 2002	05.11 2002	05.13 2002	05.15 2002	05.17 2002	05.19 2002	05.21 2002	05.23 2002	

Code of animal numbers:

(1) vaccination with BVDV XIKE-B (RNase mutant)

(2) vaccination with BVDV XIKE-B-NdN (RNase and N^{pro} double mutant)

(3) nonvaccinated controls

Immunofluorescence staining: Code 4

□ sample negative

+ sample positive

B bacterial contamination in well

Serum neutralization titers were determined before inoculation, 1 month post-inoculation, before challenge, 1 month after challenge and at termination of the study. Sera from all animals were tested in triplicates for neutralizing antibodies against KE9 and NY93/C (1456Nase), and the endpoint dilution was read by indirect immunofluorescence staining.

5 Results were expressed as the endpoint dilution, which neutralized approximately 100 TCID₅₀ and calculated by the method of Kaerber. At some of the higher antibody titres, the used endpoint dilution was not high enough. Against KE9, only animals vaccinated with XIKE-B developed low antibody titres starting about week 4. At challenge, all animals had antibody titres, which increased considerably starting around week 4 post

10 challenge. XIKE-B vaccinated animals had higher antibody titres than those vaccinated with XIKE-B-NdN vaccinated. All animals developed about the same neutralization titre against NY93/C four weeks post vaccination, with marginally lower titres in XIKE-B-NdN vaccinated animals. After challenge all animals had high antibody titres. Fig. 2 shows the serum neutralization assay against KE9 (BVDV-1) and Fig. 3 shows the serum

15 neutralization assay against NY93/C (BVDV-2).

Analysis of tissue samples obtained after termination of the study from the foetuses revealed that the material obtained from the vaccinated animals gave negative results whereas transmission had occurred in all 4 control animals (Tab. 3.9). Thus, it is clear that

20 the established BVDV-2 mutants are well suited as efficient cross protective vaccine viruses .

Study No. / Id.: B01 BIV1020 / BVDV Tü XIKE-B/XIKE-B-NdN; foetal protection study

[illegible]

Animal No.	Abdominal Fluid	Thoracic fluid	Mesenteric lymph nodes	Small intestine	Spleen	Thymus	Kidney	Bone marrow (sternum)	Cerebellum	Placenta	Date
1145⁽²⁾	ØØ	NA	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	21.06.02
1108⁽³⁾	+Ø	NA	++	++	++	++	++	++	++	ØØ	21.06.02
1156⁽²⁾	ØØ	NA	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	21.06.02
1104⁽³⁾	++	NA	++	++	++	++	++	++	++	++	21.06.02
1216⁽²⁾	ØØ	NA	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	21.06.02
1151⁽²⁾	NA	NA	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	21.06.02
1152⁽²⁾	ØØ	NA	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	ØØ	21.06.02

NA = not available

*No foetus was found in the uterus of heifer #1218

**Endometrium (also collected for histology)

*** Sample was not sent to BFA Tübingen

Code of animal numbers:

(1) vaccination with BVDV XIKE-B (RNase mutant)

(2) vaccination with BVDV XIKE-B-NdN (RNase and N^{pro} double mutant)

(3) nonvaccinated controls

Conclusion

The challenge was successful as all non-vaccinated controls were BVDV viraemic and foetuses of all non-vaccinated controls were BVDV positive.

- 5 Both isolates gave full protection under the present test and assay conditions. Isolate XIKE-B, with the single genetic marker was shown to cross-protect against type 1 BVDV challenge in terms of BVD viraemia and transmission to the foetus after challenge. Isolate XIKE-B-NdN with the double genetic marker was able to fully protect against a heterologue type 2 BVDV challenge strain in terms of BVD viraemia and transmission to the foetus after challenge.

10

1. Isolate XIKE-B (type 2 isolate) was shown to cross-protect against type 1 BVDV challenge in terms of BVD viraemia and transmission to the foetus after challenge under the present test and assay conditions (n=4).

2. Isolate XIKE-B-NdN (type 2 isolate) fully protected against a heterologues type 2 BVDV challenge strain in terms of BVD viraemia and transmission to the foetus after challenge under the present test and assay conditions (n=5).

15

EXAMPLE 4

Establishment of N^{pro} mutants

20

Further analyses of BVDV-2 mutants with N^{pro} deletions. Different mutants with deletions in the N^{pro}-coding region of the genome were established. Initially, only true deletions or a deletion accompanied by a point mutation were introduced.

- 25 A: [N^{pro}]₁-[C-term];
 B: [N^{pro}]₃-[C-term];
 C: [N^{pro}]₄-[C-term];
 D: [N^{pro}]₆-[C-term];
 E: [N^{pro}]₄-[C-term*]

- 30 In the formulas [N^{pro}]_x represents the number of residues of the aminotermius of N^{pro} that are left in the mutated polyprotein amino acids, [C-term] is the complete polyprotein except for N^{pro} (starting with the C protein and ending with NS5B), and [C-term*] is the same as [C-term] but with a mutation at position 2 of the C protein (N instead of D).

The growth rates of the recovered viruses were considerably lower than those of wild type XIKE-A or the RNase negative mutant XIKE-B. There are two possible explanations for this finding: (i) dependent on the virus strain, sequences of variable length of the N^{pro}-coding region are necessary for efficient translation initiation (Myers et al., 2001; Tautz et al., 1999) and (ii)
 5 the fusion of additional sequences to the aminotermus of the capsid protein interferes with capsid protein function.

To obtain better growing N^{pro} deletion mutants, a second set of mutants was generated with either a bovine ubiquitin gene or a fragment of the bovine LC3-coding sequence replacing the major part of the N^{pro} gene. These constructs allow efficient translation and generate a capsid
 10 protein with the correct amino terminus.

[N^{pro}]₂₂-[PS]- [C-term]

wherein PS is ubiquitin or LC3, C-term is the complete polyprotein except for N^{pro} (starting with the C protein and ending with NS5B).

The growth rates of these mutants were more similar to what was determined for XIKE-A. It even seemed that the two RNase positive viruses according to the formula [N^{pro}]₂₂-[PS]- [C-term] named V-pK87F and V-pK87G showed no significant growth retardation at all, whereas the RNase negative counterpart V-pK88G once again was somewhat hampered in propagation
 20 but to a lesser extend than the formerly described mutants.

Further examples of N^{pro} deletion mutants may be:

MESDEGSK...

MELFSSDEGSK...

25 MELFSNESDEGSK...

MELFSNELSDEGSK...

MELFSNELLSDEGSK...

MELFSNELLYSDEGSK...

MELFSNELLYKSDEGSK...

30 MELFSNELLYKTSDEGSK...

MELFSNELLYKT represents the aminoterminal sequence of N^{pro} of the BVDV isolate NewYork93/C.

It may also be possible to use variants of this sequence with one or several mutations. Especially the naturally occurring variations as found in other pestiviruses can be expected to be functional. Therefore, the complete list of the tested or proposed variants with the different parts of the aminoterminal end of N^{pro} can be enlarged by equivalent sets with amino acid exchanges. Below, typical examples of the respective sequences are given for several pestiviruses but the possible variations are not limited to these examples.

BVDV NewYork93/C: *MELFSNELLYKT*
BVDV CP13: *MELISNELLYKT*
BVDV SD1: *MELITNELLYKT*____
CSFV Brescia: *MELNHFELLYKT*
BDV X818: *MELNKFELLYKT*

Thus, these variants for example may include: *MELI*-[PS]₀-[C-term];

MELIS-[PS]₀-[C-term];

MELISN-[PS]₀-[C-term];

MELISNE-[PS]₀-[C-term];

MELISNEL-[PS]₀-[C-term];

MELISNELL-[PS]₀-[C-term];

MELISNELLY-[PS]₀-[C-term];

MELISNELLYK-[PS]₀-[C-term];

MELISNELLYKT-[PS]₀-[C-term];

MELIT-[PS]₀-[C-term];

MELITN-[PS]₀-[C-term];

MELITNE-[PS]₀-[C-term];

MELITNEL-[PS]₀-[C-term];

MELITNELL-[PS]₀-[C-term];

MELITNELLY-[PS]₀-[C-term];

MELITNELLYK-[PS]₀-[C-term];

MELITNELLYKT-[PS]₀-[C-term];

These formulas may also have [PS]₁, i.e. PS may also be one of the PS as described herein.

Sequences belonging to the N^{pro} protein are in italics. Amino acid exchanges with regard to the sequence of BVDV NewYork93/C are in bold.

Further examples can be found e.g. by using the GenBank accession numbers given in Becher et al., 2003, Virology 311, 96-104) or by standard sequence data searches.

- 5 A further possibility could be the use of a processing signal (PS) inserted between the (residual) N^{pro} sequence and the aminoterminal of the capsid protein. The PS leads to a cleavage that generates a functional capsid protein. The configuration of such constructs could be as follows:

[N^{pro}]₂₂-PS[C-term]

10

PS: Processing signal. Can either be a target for a protease (e.g. ubiquitin, LC3 as defined herein or a protease or an unstable peptide leading to processing at its own carboxyterminus like e.g. intein (Chong et al. 1998 and references therein) or 3C of picornaviruses, 2A of cardioviruses or aphthoviruses, p15 of rabbit hemorrhagic disease virus or the corresponding protease of other

15 caliciviruses (Proter 1993, and references therein; Meyers et al., 2000 and references therein).

When using a PS, a large number of different variants are possible since the PS ensures the generation of the correct amino terminus of the capsid protein C. Thus, when using a PS construct, all kinds of deletions or mutations of the N^{pro} sequence are expected to result in viable mutants as long as the reading frame is not shifted or translation stopped by an in frame stop

20 codon. As an example we established a viable CSFV N^{pro} deletion mutant according to the formula

[N^{pro}]₂₉-PS[C-term]

Especially interesting could be N^{pro} mutations blocking the proteolytic activity of the protein.

25 R menapf et al. (1998) have published the identification of the active site residues of the protease for CSFV Alfort T bingen. The respective amino acids (glutamic acid at position 22, histidine at position 49 and cysteine at position 69) are conserved for other pestiviruses. Thus, exchanges of any amino acid expect for serine or threonine for the cysteine at position 69 will result in destruction of the protease activity. Similarly, changing the glutamic acid at position 22

30 will most likely result in inactivation of the protease unless the new amino acid is aspartic acid. Similarly most if not all exchanges at position 49 will lead to an inactive protease).

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The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An attenuated pestivirus, having at least one mutation in the coding sequence for glycoprotein E^{ms} and at least another mutation in the coding sequence for N^{pro}, wherein
5 said mutation in the coding sequence for glycoprotein E^{ms} leads to inactivation of RNase activity residing in E^{ms} and said mutation in the coding sequence for N^{pro} leads to inactivation of said N^{pro}.
2. The virus according to claim 1, wherein said mutations are selected from the group
10 of deletions, insertion mutations and/or substitution mutations.
3. The virus according to any one of claims 1 to 2, wherein said mutation(s) are deletions.
- 15 4. The virus according to any one of claims 1 to 3, wherein said pestivirus is a Bovine viral diarrhea virus (BVDV).
5. The virus according to claim 4, wherein said mutation(s) in the coding sequence for glycoprotein E^{ms} are located in the encoding nucleotide sequence corresponding to amino
20 acids at position 298 to 310 and/or position 341 to 360.
6. The virus according to claim 4 or 5, wherein said mutation in the coding sequence for glycoprotein E^{ms} is a deletion or substitution of the histidine at position 349.
- 25 7. The virus according to anyone of claims 1 to 6, wherein said mutation(s) in the coding sequence for glycoprotein E^{ms} are located in the nucleotide sequence coding for the conserved E^{ms} sequence SLHGIWPEKICTG and/or LQRHEWNKHGWCNWFHIEPW.
8. The virus according to any one of claims 1 to 7, wherein said mutation(s) in the
30 coding sequence for glycoprotein E^{ms} located in the nucleotide sequence coding for the conserved E^{ms} sequence SLHGIWPEKIC and/or RHEWNKHGWCNW.

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9. The virus according to anyone of claims 1 to 8, wherein said mutation(s) in the coding sequence for glycoprotein E^{ms} are two mutations located in the nucleotide sequence coding for the conserved E^{ms} sequence SLHGIWPEKIC and/or RHEWNKHGWCNW.

5 10. The virus according to anyone of claims 1 to 9, wherein said mutation in the coding sequence for glycoprotein E^{ms} is a single mutation located in the conserved E^{ms} sequence SLHGIWPEKIC or RHEWNKHGWCNW.

10 11. The virus according to any one of claims 1 to 10, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:

$$[N^{pro}]_x-[PS]_y-[C-term]$$

and wherein:

15 [N^{pro}] relates to the N^{pro} portion of said polyprotein, wherein "x" represents the number of amino acids of the N^{pro} present in the polyprotein; and wherein

[PS] relates to a processing signal selected from the group consisting of: ubiquitin, LC3, SUMO-1, NEDD8, GATE-16 or GABA(A)RAP), Intein, picornavirus 3C, caridovirus 2A, or p15 of rabbit hemorrhagic disease virus; and wherein

20 "Y" may be = 0, which means that no processing signal is present, or "Y" may be = 1, which means that a processing signal is present; and wherein

[C-term] relates to the complete virus polyprotein except for N^{pro}, but including the capsid (C)-protein and any other protein present in the virus polyprotein including the carboxyterminal NS5B; and wherein

25 if "y" is = 0, then "x" is 0 to 12, (means no N^{pro} specific amino acid or 1 to 12 amino acids of N^{pro} are present); and wherein

if "y" is = 1, then "x" is 0 to 168; (means no N^{pro} specific amino acid or 1 to all 168 amino acids of N^{pro} are present).

30 12. The virus according to claim 11, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:

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13. The virus according to claim 11, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:



and wherein the definitions are as defined in claim 11.

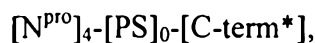
14. The virus according to claim 11, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:



15. The virus according to claim 11, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:



16. The virus according to to claim 11, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:



20 and wherein $[C-term]^*$ is = $[C-term]$ wherein in the C-protein the amino acid at position 2 is changed from D to N.

17. The virus according to claim 11, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the following formula:



and wherein PS is selected from the group of ubiquitin or LC3.

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18. The virus according to claim 11, wherein said virus is BVDV, and wherein mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by a formula selected from the group consisting of :

5 M-[PS]₀-[C-term];
MEL-[PS]₀-[C-term];
MELF-[PS]₀-[C-term];
MELFS-[PS]₀-[C-term];
MELFSN-[PS]₀-[C-term];
MELFSNE-[PS]₀-[C-term];
10 MELFSNEL-[PS]₀-[C-term];
MELFSNELL-[PS]₀-[C-term];
MELFSNELLY-[PS]₀-[C-term];
MELFSNELLYK-[PS]₀-[C-term];
MELFSNELLYKT-[PS]₀-[C-term]

15

19. The virus according to claim 11, wherein said virus is BVDV, and wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by a formula selected from the group consisting of :

20 MELI-[PS]₀-[C-term];
MELIS-[PS]₀-[C-term];
MELISN-[PS]₀-[C-term];
MELISNE-[PS]₀-[C-term];
MELISNEL-[PS]₀-[C-term];
MELISNELL-[PS]₀-[C-term];
25 MELISNELLY-[PS]₀-[C-term];
MELISNELLYK-[PS]₀-[C-term];
MELISNELLYKT-[PS]₀-[C-term];

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20. The virus according to claim 11, wherein said virus is BVDV, and wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by a formula selected from the group consisting of :

MELIT-[PS]₀-[C-term];

MELITN-[PS]₀-[C-term];

MELITNE-[PS]₀-[C-term];

MELITNEL-[PS]₀-[C-term];

MELITNELL-[PS]₀-[C-term];

MELITNELLY-[PS]₀-[C-term];

MELITNELLYK-[PS]₀-[C-term];

MELITNELLYKT-[PS]₀-[C-term];

21. The virus according to claim 11, wherein said virus is BVDV, and wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the formula:

[N^{pro}]_x-[PS]₀-MELF-[PS]₀-[C-term*];

and wherein [C-term]* is = [C-term] wherein in the C-protein the amino acid at position 2 is changed from D to N.

22. The virus according to claim 11, wherein said mutation(s) in the coding sequence for N^{pro} lead to an encoded polyprotein as characterized by the formula:

[N^{pro}]₂₂-[PS]₁-[C-term],

and wherein PS is ubiquitin or LC3.

23. The virus according to any one of claims 18 to 21, wherein the [PS]₀ is replaced by [PS]₁, and wherein said PS is selected from the group of consisting of: ubiquitin, LC3, SUMO-1, NEDD8, GATE-16, GABA(A)RAP, Intein, picornavirus 3C, caridovirus 2A, and p15 of rabbit hemorrhagic disease virus.

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24. The BVDV according to any one of claims 4 to 23, wherein said BVDV is selected from the group of BVDV type 1 or BVDV type 2.
25. The BVDV according to any one of claims 4 to 24, wherein the BVDV has the
5 sequence of SEQ ID No. 8.
26. A composition comprising the virus according to any one of claims 1 to 25 and a solution.
- 10 27. The composition according to claim 26, which induces an immunological response in an animal.
28. The composition according to claim 26 or 27, which is a vaccine.
- 15 29. The composition according to any one of claims 26 to 28, wherein said composition further comprises a pharmaceutically acceptable carrier or excipient.
30. Use of a virus according to any one of claims 1 to 25 in the manufacture of a vaccine for the prophylaxis and treatment of a pestivirus infection.
- 20 31. Use of a BVDV according to any one of claims 4 to 25 in the manufacture of a vaccine for the prophylaxis and treatment of a BVDV infection.
32. A nucleic acid molecule comprising the nucleic acid encoding a live attenuated
25 BVDV according to any one of claims 4 to 25.
33. The nucleic acid molecule according to claim 32, wherein said nucleic acid molecule is DNA.
- 30 34. The nucleic acid molecule according to claim 32, wherein said nucleic acid molecule is RNA.

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35. A method for attenuating a pestivirus, characterized in that at least one mutation in the coding sequence for glycoprotein E^{ms} and at least another mutation in the coding sequence for N^{pro} is generated in a pestivirus.

5 36. The method according to claim 35, comprising the following steps:

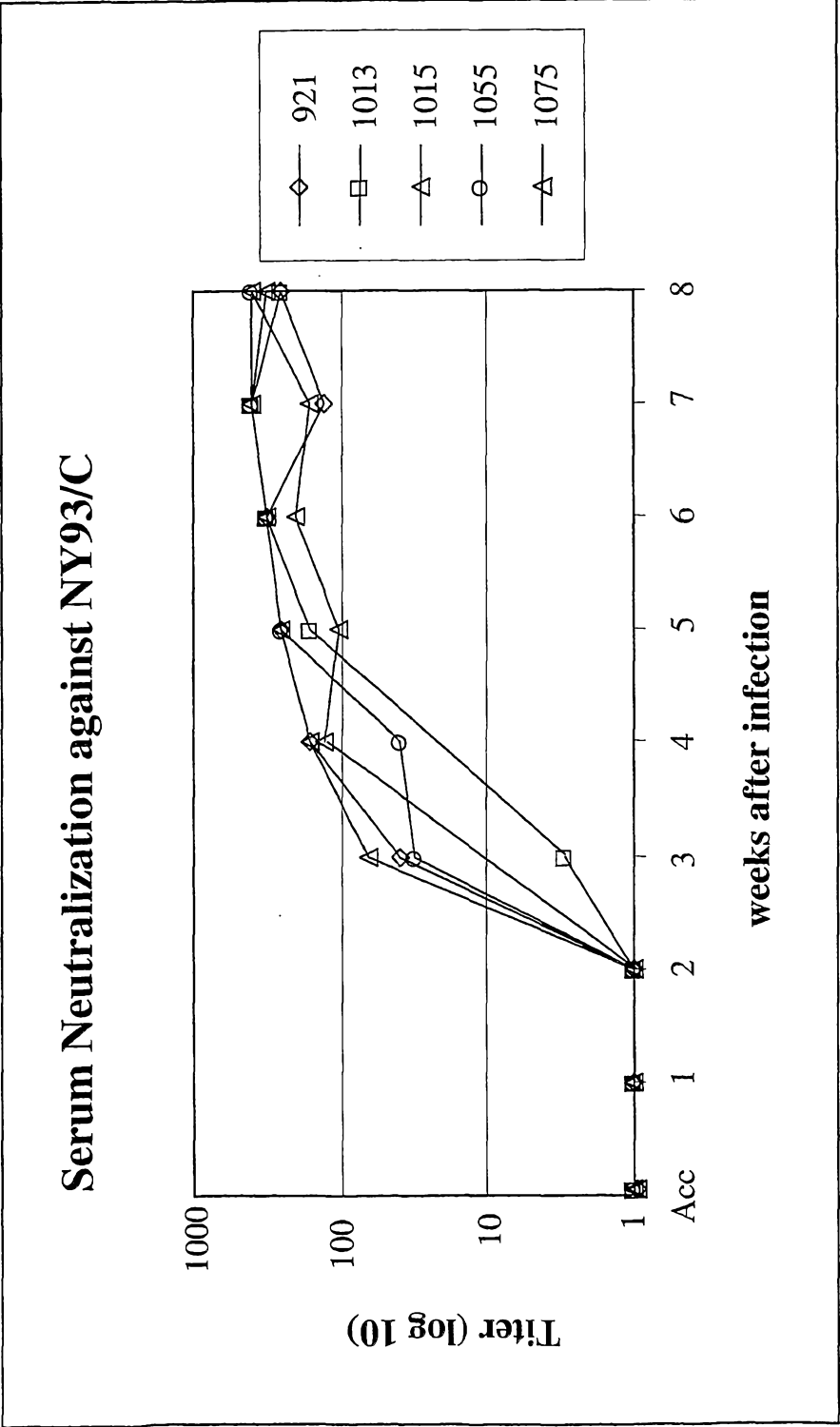
- a) reverse transcription of a wild-type pestivirus nucleotide sequence into a cDNA;
- b) cloning said cDNA;
- c) introducing mutations selected from the group of deletions, insertion mutations and/or substitution mutations into said cDNA, wherein said mutations are located in
10 the coding sequence encoding glycoprotein E^{ms} and the protease N^{pro},
- d) incorporating the cDNA into a plasmid or into a DNA virus capable of directing the transcription of pestivirus cDNA into RNA in vitro or upon infection of suitable cells.

15 37. The method according to claim 35 or 36, wherein said pestivirus is BVDV.

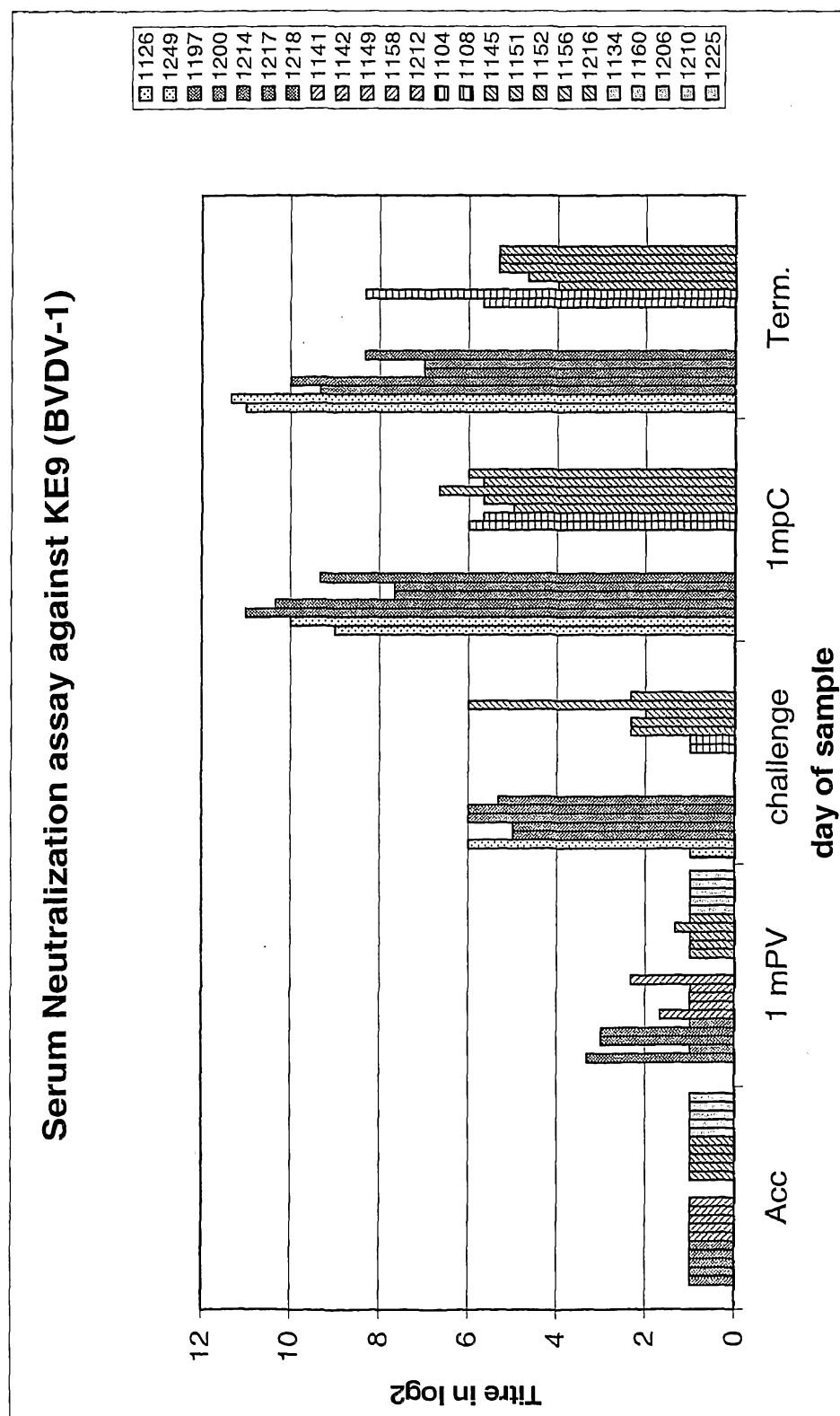
38. Method of treatment of disease caused by BVDV, wherein a BVDV according to any one of claims 4 to 25 or a composition according to claims 26 to 29 is administered to an animal in need thereof at a suitable dose as known to the skilled person and the
20 reduction of symptoms of BVDV infection such as viremia and leukopenia and/or pyrexia and/or diarrhea is monitored.

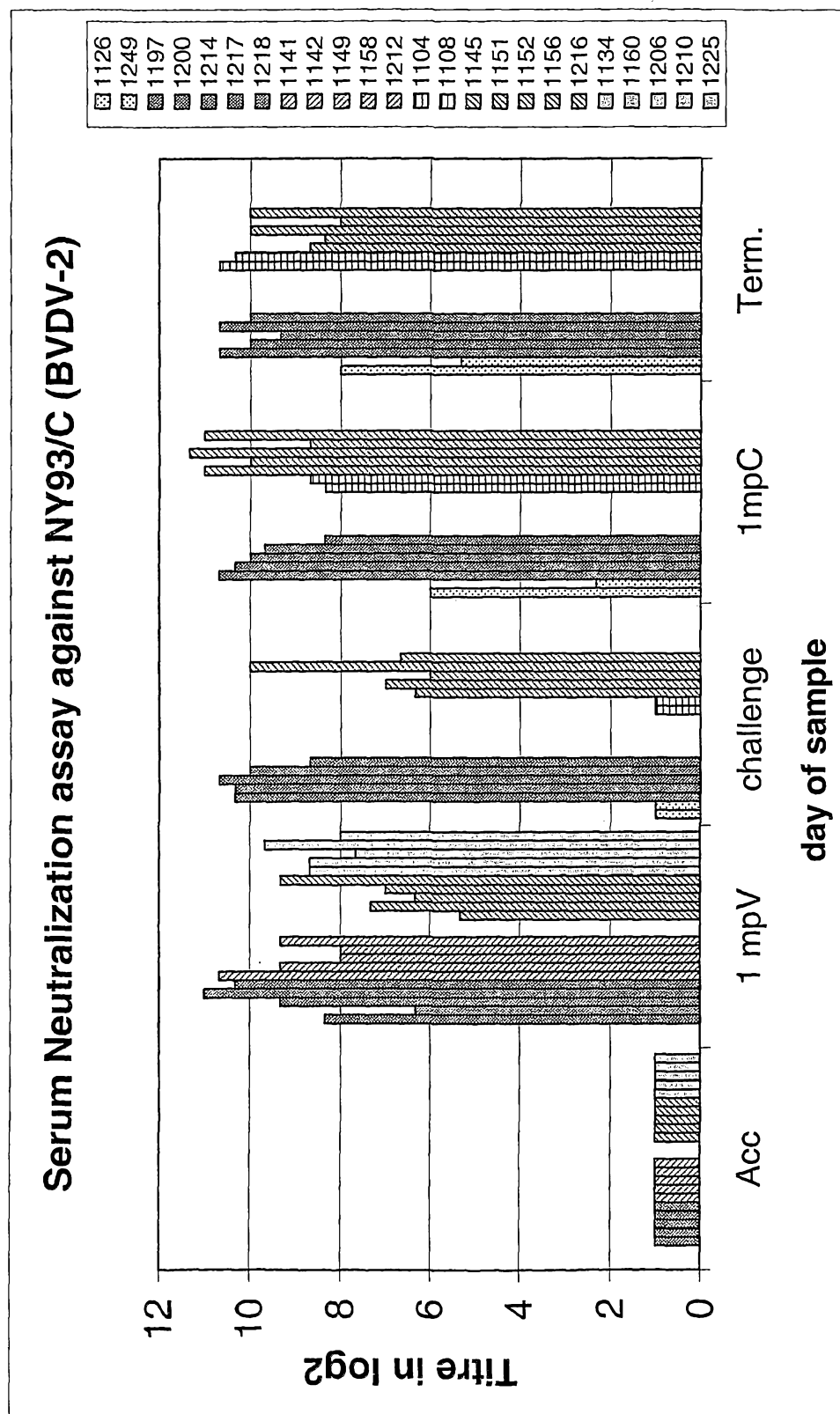
39. An attenuated pestivirus as defined in any one of claims 1 to 25, a composition as defined in any one of claims 26 to 29, a use as defined in claim 30 or 31, a nucleic acid
25 molecule as defined in any one of claims 32 to 34, a method as claimed in any one of claims 35 to 37, or a method as defined in claim 38 substantially as hereinbefore described and with reference to the examples.

Figur 1:



Figur 2:



Figur 3:

SEQUENZPROTOKOLL:

SEQUENCE LISTING

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 20 Ile Tyr Ile Lys Pro Gly Pro Ile Tyr Tyr Gln Asp Tyr Val Gly Pro
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 Val Tyr His Arg Ala Pro Leu Glu Leu Cys Arg Glu Ala Ser Met Cys
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 25 Glu Thr Thr Arg Arg Val Gly Arg Val Thr Gly Ser Asp Gly Lys Leu
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 30 Tyr His Ile Tyr Ile Cys Ile Asp Gly Cys Ile Leu Leu Lys Arg Ala
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	1955						1960					1965			
	Ile	Glu	Glu	Phe	Ile	Ala	Pro	Glu	Val	Met	Lys	Gly	Glu	Asp	Leu
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	1985						1990					1995			
50	Glu	Met	Lys	Gly	Asn	Met	Leu	Val	Phe	Ala	Pro	Thr	Arg	Asn	Met
	2000						2005					2010			
	Ala	Val	Glu	Thr	Ala	Lys	Lys	Leu	Lys	Ala	Lys	Gly	Tyr	Asn	Ser
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55	Gly	Tyr	Tyr	Tyr	Ser	Gly	Glu	Asn	Pro	Glu	Asn	Leu	Arg	Val	Val
	2030						2035					2040			

	Thr	Ser	Gln	Ser	Pro	Tyr	Val	Val	Val	Ala	Thr	Asn	Ala	Ile	Glu
	2045						2050					2055			
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	2060						2065					2070			
	Leu	Lys	Cys	Glu	Lys	Arg	Val	Arg	Ile	Ser	Ser	Lys	Met	Pro	Phe
	2075						2080					2085			
10	Ile	Val	Thr	Gly	Leu	Lys	Arg	Met	Ala	Val	Thr	Ile	Gly	Glu	Gln
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	2135						2140					2145			
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	2690						2695					2700			
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 50 35 40 45
 Val Val Glu Gly Val Lys Tyr Gln Val Lys Lys Lys Gly Lys Val Arg
 50 55 60
 55 Gly Lys Asn Thr Gln Asp Gly Leu Tyr His Asn Lys Asn Lys Pro Pro
 65 70 75 80

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5	Phe	Ala	Pro	Glu	Thr	Ala	Ser	Val	Ile	Tyr	Leu	Val	Leu	His	Phe	Ala
					405					410					415	
	Ile	Pro	Gln	Ser	His	Val	Asp	Val	Asp	Thr	Cys	Asp	Lys	Asn	Gln	Leu
				420					425					430		
10	Asn	Leu	Thr	Val	Ala	Thr	Thr	Val	Ala	Glu	Val	Ile	Pro	Gly	Thr	Val
			435					440					445			
	Trp	Asn	Leu	Gly	Lys	Tyr	Val	Cys	Ile	Arg	Pro	Asp	Trp	Trp	Pro	Tyr
	450						455					460				
15	Glu	Thr	Thr	Thr	Val	Phe	Val	Ile	Glu	Glu	Ala	Gly	Gln	Val	Ile	Lys
	465					470					475					480
	Leu	Met	Leu	Arg	Ala	Ile	Arg	Asp	Leu	Thr	Arg	Ile	Trp	Asn	Ala	Ala
20					485					490					495	
	Thr	Thr	Thr	Ala	Phe	Leu	Ile	Phe	Leu	Val	Lys	Ala	Leu	Arg	Gly	Gln
				500					505					510		
25	Leu	Ile	Gln	Gly	Leu	Leu	Trp	Leu	Met	Leu	Ile	Thr	Gly	Ala	Gln	Gly
			515					520					525			
	Phe	Pro	Glu	Cys	Lys	Glu	Gly	Phe	Gln	Tyr	Ala	Ile	Ser	Lys	Asp	Arg
	530						535					540				
30	Lys	Met	Gly	Leu	Leu	Gly	Pro	Glu	Ser	Leu	Thr	Thr	Thr	Trp	His	Leu
	545					550					555					560
	Pro	Thr	Lys	Lys	Ile	Val	Asp	Ser	Met	Val	His	Val	Trp	Cys	Glu	Gly
35					565					570					575	
	Lys	Asp	Leu	Lys	Ile	Leu	Lys	Met	Cys	Thr	Lys	Glu	Glu	Arg	Tyr	Leu
			580						585					590		
40	Val	Ala	Val	His	Glu	Arg	Ala	Leu	Ser	Thr	Ser	Ala	Glu	Phe	Met	Gln
			595					600					605			
	Ile	Ser	Asp	Gly	Thr	Ile	Gly	Pro	Asp	Val	Ile	Asp	Met	Pro	Asp	Asp
	610						615					620				
45	Phe	Glu	Phe	Gly	Leu	Cys	Pro	Cys	Asp	Ser	Lys	Pro	Val	Ile	Lys	Gly
	625					630					635					640
	Lys	Phe	Asn	Ala	Ser	Leu	Leu	Asn	Gly	Pro	Ala	Phe	Gln	Met	Val	Cys
50					645					650					655	
	Pro	Gln	Gly	Trp	Thr	Gly	Thr	Ile	Glu	Cys	Thr	Leu	Ala	Asn	Gln	Asp
			660						665					670		
55	Thr	Leu	Asp	Thr	Thr	Val	Ile	Arg	Thr	Tyr	Arg	Arg	Thr	Thr	Pro	Phe
			675					680						685		

	Gln	Arg	Arg	Lys	Trp	Cys	Thr	Tyr	Glu	Lys	Ile	Ile	Gly	Glu	Asp	Ile	
	690						695					700					
5	Tyr	Glu	Cys	Ile	Leu	Gly	Gly	Asn	Trp	Thr	Cys	Ile	Thr	Gly	Asp	His	
	705					710					715					720	
	Ser	Arg	Leu	Lys	Asp	Gly	Pro	Ile	Lys	Lys	Cys	Lys	Trp	Cys	Gly	His	
					725					730					735		
10	Asp	Phe	Val	Asn	Ser	Glu	Gly	Leu	Pro	His	Tyr	Pro	Ile	Gly	Lys	Cys	
				740					745					750			
	Met	Leu	Ile	Asn	Glu	Ser	Gly	Tyr	Arg	Tyr	Val	Asp	Asp	Thr	Ser	Cys	
			755					760					765				
15	Asp	Arg	Gly	Gly	Val	Ala	Ile	Val	Pro	Ser	Gly	Thr	Val	Lys	Cys	Arg	
			770				775					780					
20	Ile	Gly	Asn	Val	Thr	Val	Gln	Val	Ile	Ala	Thr	Asn	Asn	Asp	Leu	Gly	
	785					790					795					800	
	Pro	Met	Pro	Cys	Ser	Pro	Ala	Glu	Val	Ile	Ala	Ser	Glu	Gly	Pro	Val	
					805					810					815		
25	Glu	Lys	Thr	Ala	Cys	Thr	Phe	Asn	Tyr	Ser	Arg	Thr	Leu	Pro	Asn	Lys	
				820					825					830			
	Tyr	Tyr	Glu	Pro	Arg	Asp	Arg	Tyr	Phe	Gln	Gln	Tyr	Met	Leu	Lys	Gly	
			835					840					845				
30	Glu	Trp	Gln	Tyr	Trp	Phe	Asp	Leu	Asp	Ser	Val	Asp	His	His	Lys	Asp	
			850				855					860					
35	Tyr	Phe	Ser	Glu	Phe	Ile	Ile	Ile	Ala	Val	Val	Ala	Leu	Leu	Gly	Gly	
	865					870					875					880	
	Lys	Tyr	Val	Leu	Trp	Leu	Leu	Ile	Thr	Tyr	Thr	Ile	Leu	Ser	Glu	Gln	
				885						890					895		
40	Met	Ala	Met	Gly	Ala	Gly	Val	Asn	Thr	Glu	Glu	Ile	Val	Met	Ile	Gly	
				900					905					910			
	Asn	Leu	Leu	Thr	Asp	Ser	Asp	Ile	Glu	Val	Val	Val	Tyr	Phe	Leu	Leu	
			915					920					925				
45	Leu	Tyr	Leu	Ile	Val	Lys	Glu	Glu	Leu	Ala	Arg	Lys	Trp	Ile	Ile	Leu	
			930				935					940					
50	Val	Tyr	His	Ile	Leu	Val	Ala	Asn	Pro	Met	Lys	Thr	Ile	Gly	Val	Val	
	945					950					955					960	
	Leu	Leu	Met	Leu	Gly	Gly	Val	Val	Lys	Ala	Ser	Arg	Ile	Asn	Ala	Asp	
				965						970					975		
55	Asp	Gln	Ser	Ala	Met	Asp	Pro	Cys	Phe	Leu	Leu	Val	Thr	Gly	Val	Val	
				980					985					990			

	Ala	Val	Leu	Met	Ile	Ala	Arg	Arg	Glu	Pro	Ala	Thr	Leu	Pro	Leu	Ile
			995					1000					1005			
5	Val	Ala	Leu	Leu	Ala	Ile	Arg	Thr	Ser	Gly	Phe	Leu	Leu	Pro	Ala	
		1010					1015					1020				
	Ser	Ile	Asp	Val	Thr	Val	Ala	Val	Val	Leu	Ile	Val	Leu	Leu	Leu	
		1025					1030					1035				
10	Ala	Ser	Tyr	Ile	Thr	Asp	Tyr	Phe	Arg	Tyr	Lys	Lys	Trp	Leu	Gln	
		1040					1045					1050				
	Leu	Leu	Phe	Ser	Leu	Ile	Ala	Gly	Ile	Phe	Ile	Ile	Arg	Ser	Leu	
15		1055					1060					1065				
	Lys	His	Ile	Asn	Gln	Met	Glu	Val	Pro	Glu	Ile	Ser	Met	Pro	Ser	
		1070					1075					1080				
20	Trp	Arg	Pro	Leu	Ala	Leu	Val	Leu	Phe	Tyr	Ile	Thr	Ser	Thr	Ala	
		1085					1090					1095				
	Ile	Thr	Thr	Asn	Trp	Asp	Ile	Asp	Leu	Ala	Gly	Phe	Leu	Leu	Gln	
		1100					1105					1110				
25	Trp	Ala	Pro	Ala	Val	Ile	Met	Met	Ala	Thr	Met	Trp	Ala	Asp	Phe	
		1115					1120					1125				
	Leu	Thr	Leu	Ile	Ile	Val	Leu	Pro	Ser	Tyr	Glu	Leu	Ser	Lys	Leu	
30		1130					1135					1140				
	Tyr	Phe	Leu	Lys	Asn	Val	Arg	Thr	Asp	Val	Glu	Lys	Asn	Trp	Leu	
		1145					1150					1155				
35	Gly	Lys	Val	Lys	Tyr	Arg	Gln	Ile	Ser	Ser	Val	Tyr	Asp	Ile	Cys	
		1160					1165					1170				
	Asp	Ser	Glu	Glu	Ala	Val	Tyr	Leu	Phe	Pro	Ser	Arg	His	Lys	Ser	
		1175					1180					1185				
40	Gly	Ser	Arg	Pro	Asp	Phe	Ile	Leu	Pro	Phe	Leu	Lys	Ala	Val	Leu	
		1190					1195					1200				
	Ile	Ser	Cys	Ile	Ser	Ser	Gln	Trp	Gln	Val	Val	Tyr	Ile	Ser	Tyr	
45		1205					1210					1215				
	Leu	Ile	Leu	Glu	Ile	Thr	Tyr	Tyr	Met	His	Arg	Lys	Ile	Ile	Asp	
		1220					1225					1230				
50	Glu	Val	Ser	Gly	Gly	Ala	Asn	Phe	Leu	Ser	Arg	Leu	Ile	Ala	Ala	
		1235					1240					1245				
	Ile	Ile	Glu	Leu	Asn	Trp	Ala	Ile	Asp	Asp	Glu	Glu	Cys	Lys	Gly	
		1250					1255					1260				
55	Leu	Lys	Lys	Leu	Tyr	Leu	Leu	Ser	Gly	Arg	Ala	Lys	Asn	Leu	Ile	
		1265					1270					1275				

	Val	Lys	His	Lys	Val	Arg	Asn	Glu	Ala	Val	His	Arg	Trp	Phe	Gly
	1280						1285					1290			
5	Glu	Glu	Glu	Ile	Tyr	Gly	Ala	Pro	Lys	Val	Ile	Thr	Ile	Ile	Lys
	1295						1300					1305			
	Ala	Ser	Thr	Leu	Ser	Lys	Asn	Arg	His	Cys	Ile	Ile	Cys	Thr	Ile
	1310						1315					1320			
10	Cys	Glu	Gly	Lys	Glu	Trp	Asn	Gly	Ala	Asn	Cys	Pro	Lys	Cys	Gly
	1325						1330					1335			
	Arg	Gln	Gly	Lys	Pro	Ile	Thr	Cys	Gly	Met	Thr	Leu	Ala	Asp	Phe
	1340						1345					1350			
15	Glu	Glu	Lys	His	Tyr	Lys	Lys	Ile	Phe	Ile	Arg	Glu	Glu	Ser	Ser
	1355						1360					1365			
20	Cys	Pro	Val	Pro	Phe	Asp	Pro	Ser	Cys	His	Cys	Asn	Tyr	Phe	Arg
	1370						1375					1380			
	His	Asp	Gly	Pro	Phe	Arg	Lys	Glu	Tyr	Lys	Gly	Tyr	Val	Gln	Tyr
	1385						1390					1395			
25	Thr	Ala	Arg	Gly	Gln	Leu	Phe	Leu	Arg	Asn	Leu	Pro	Ile	Leu	Ala
	1400						1405					1410			
	Thr	Lys	Met	Lys	Leu	Leu	Met	Val	Gly	Asn	Leu	Gly	Ala	Glu	Ile
	1415						1420					1425			
30	Gly	Asp	Leu	Glu	His	Leu	Gly	Trp	Val	Leu	Arg	Gly	Pro	Ala	Val
	1430						1435					1440			
35	Cys	Lys	Lys	Ile	Thr	Asn	His	Glu	Lys	Cys	His	Val	Asn	Ile	Met
	1445						1450					1455			
	Asp	Lys	Leu	Thr	Ala	Phe	Phe	Gly	Ile	Met	Pro	Arg	Gly	Thr	Thr
	1460						1465					1470			
40	Pro	Arg	Ala	Pro	Val	Arg	Phe	Pro	Thr	Ala	Leu	Leu	Lys	Val	Arg
	1475						1480					1485			
	Arg	Gly	Leu	Glu	Thr	Gly	Trp	Ala	Tyr	Thr	His	Gln	Gly	Gly	Ile
	1490						1495					1500			
45	Ser	Ser	Val	Asp	His	Val	Thr	Ala	Gly	Lys	Asp	Leu	Leu	Val	Cys
	1505						1510					1515			
50	Asp	Ser	Met	Gly	Arg	Thr	Arg	Val	Val	Cys	His	Ser	Asn	Asn	Lys
	1520						1525					1530			
	Met	Thr	Asp	Glu	Thr	Glu	Tyr	Gly	Ile	Lys	Thr	Asp	Ser	Gly	Cys
	1535						1540					1545			
55	Pro	Glu	Gly	Ala	Arg	Cys	Tyr	Val	Leu	Asn	Pro	Glu	Ala	Val	Asn
	1550						1555					1560			

	Ile	Ser	Gly	Thr	Lys	Gly	Ala	Met	Val	His	Leu	Gln	Lys	Thr	Gly
	1565						1570					1575			
5	Gly	Glu	Phe	Thr	Cys	Val	Thr	Ala	Ser	Gly	Thr	Pro	Ala	Phe	Phe
	1580						1585					1590			
	Asp	Leu	Lys	Asn	Leu	Lys	Gly	Trp	Ser	Gly	Leu	Pro	Ile	Phe	Glu
	1595						1600					1605			
10	Ala	Ser	Ser	Gly	Arg	Val	Val	Gly	Arg	Val	Lys	Val	Gly	Lys	Asn
	1610						1615					1620			
	Glu	Asp	Ser	Lys	Pro	Thr	Lys	Leu	Met	Ser	Gly	Ile	Gln	Thr	Val
	1625						1630					1635			
15	Ser	Lys	Asn	Gln	Thr	Asp	Leu	Ala	Asp	Ile	Val	Lys	Lys	Leu	Thr
	1640						1645					1650			
20	Ser	Met	Asn	Arg	Gly	Glu	Phe	Lys	Gln	Ile	Thr	Leu	Ala	Thr	Gly
	1655						1660					1665			
	Ala	Gly	Lys	Thr	Thr	Glu	Leu	Pro	Arg	Ser	Val	Ile	Glu	Glu	Ile
	1670						1675					1680			
25	Gly	Arg	His	Lys	Arg	Val	Leu	Val	Leu	Ile	Pro	Leu	Arg	Ala	Ala
	1685						1690					1695			
	Ala	Glu	Ser	Val	Tyr	Gln	Tyr	Met	Arg	Val	Lys	Tyr	Pro	Ser	Ile
	1700						1705					1710			
30	Ser	Phe	Asn	Leu	Arg	Ile	Gly	Asp	Met	Lys	Glu	Gly	Asp	Met	Ala
	1715						1720					1725			
35	Thr	Gly	Ile	Thr	Tyr	Ala	Ser	Tyr	Gly	Tyr	Phe	Cys	Gln	Leu	Pro
	1730						1735					1740			
	Gln	Pro	Lys	Leu	Arg	Ala	Ala	Met	Val	Glu	Tyr	Ser	Tyr	Ile	Phe
	1745						1750					1755			
40	Leu	Asp	Glu	Tyr	His	Cys	Ala	Thr	Pro	Glu	Gln	Leu	Ala	Ile	Ile
	1760						1765					1770			
	Gly	Lys	Ile	His	Arg	Phe	Ala	Glu	Asn	Leu	Arg	Val	Val	Ala	Met
	1775						1780					1785			
45	Thr	Ala	Thr	Pro	Ala	Gly	Thr	Val	Thr	Thr	Thr	Gly	Gln	Lys	His
	1790						1795					1800			
50	Pro	Ile	Glu	Glu	Phe	Ile	Ala	Pro	Glu	Val	Met	Lys	Gly	Glu	Asp
	1805						1810					1815			
	Leu	Gly	Ser	Glu	Tyr	Leu	Asp	Ile	Ala	Gly	Leu	Lys	Ile	Pro	Thr
	1820						1825					1830			
55	Glu	Glu	Met	Lys	Gly	Asn	Met	Leu	Val	Phe	Ala	Pro	Thr	Arg	Asn
	1835						1840					1845			

	Met	Ala	Val	Glu	Thr	Ala	Lys	Lys	Leu	Lys	Ala	Lys	Gly	Tyr	Asn
	1850						1855					1860			
5	Ser	Gly	Tyr	Tyr	Tyr	Ser	Gly	Glu	Asn	Pro	Glu	Asn	Leu	Arg	Val
	1865						1870					1875			
	Val	Thr	Ser	Gln	Ser	Pro	Tyr	Val	Val	Val	Ala	Thr	Asn	Ala	Ile
	1880						1885					1890			
10	Glu	Ser	Gly	Val	Thr	Leu	Pro	Asp	Leu	Asp	Thr	Val	Val	Asp	Thr
	1895						1900					1905			
	Gly	Leu	Lys	Cys	Glu	Lys	Arg	Val	Arg	Ile	Ser	Ser	Lys	Met	Pro
	1910						1915					1920			
15	Phe	Ile	Val	Thr	Gly	Leu	Lys	Arg	Met	Ala	Val	Thr	Ile	Gly	Glu
	1925						1930					1935			
	Gln	Ala	Gln	Arg	Arg	Gly	Arg	Val	Gly	Arg	Val	Lys	Pro	Gly	Arg
20	1940						1945					1950			
	Tyr	Tyr	Arg	Ser	Gln	Glu	Thr	Ala	Ser	Gly	Ser	Lys	Asp	Tyr	His
	1955						1960					1965			
25	Tyr	Asp	Leu	Leu	Gln	Ala	Gln	Arg	Tyr	Gly	Ile	Glu	Asp	Gly	Ile
	1970						1975					1980			
	Asn	Val	Thr	Lys	Ser	Phe	Arg	Glu	Met	Asn	Tyr	Asp	Trp	Ser	Leu
	1985						1990					1995			
30	Tyr	Glu	Glu	Asp	Ser	Leu	Met	Ile	Thr	Gln	Leu	Glu	Val	Leu	Asn
	2000						2005					2010			
	Asn	Leu	Leu	Ile	Ser	Glu	Asp	Leu	Pro	Ala	Ala	Val	Lys	Asn	Ile
35	2015						2020					2025			
	Met	Ala	Arg	Thr	Asp	His	Pro	Glu	Pro	Ile	Gln	Leu	Ala	Tyr	Asn
	2030						2035					2040			
40	Ser	Tyr	Glu	Asn	Gln	Ile	Pro	Val	Leu	Phe	Pro	Lys	Ile	Lys	Asn
	2045						2050					2055			
	Gly	Glu	Val	Thr	Asp	Ser	Tyr	Glu	Asn	Tyr	Thr	Tyr	Leu	Asn	Ala
	2060						2065					2070			
45	Arg	Lys	Leu	Gly	Glu	Asp	Val	Pro	Ala	Tyr	Val	Tyr	Ala	Thr	Glu
	2075						2080					2085			
	Asp	Glu	Asp	Leu	Ala	Val	Asp	Leu	Leu	Gly	Met	Asp	Trp	Pro	Asp
50	2090						2095					2100			
	Pro	Gly	Asn	Gln	Gln	Val	Val	Glu	Thr	Gly	Arg	Ala	Leu	Lys	Gln
	2105						2110					2115			
55	Val	Thr	Gly	Leu	Ser	Thr	Ala	Glu	Asn	Ala	Leu	Leu	Ile	Ala	Leu
	2120						2125					2130			

	Phe Gly Tyr Val Gly Tyr Gln Thr Leu Ser Lys Arg His Ile Pro	
	2135	2140 2145
5	Met Ile Thr Asp Ile Tyr Thr Leu Glu Asp His Arg Leu Glu Asp	
	2150	2155 2160
	Thr Thr His Leu Gln Phe Ala Pro Asn Ala Ile Arg Thr Asp Gly	
	2165	2170 2175
10	Lys Asp Ser Glu Leu Lys Glu Leu Ala Val Gly Asp Leu Asp Lys	
	2180	2185 2190
	Tyr Val Asp Ala Leu Val Asp Tyr Ser Lys Gln Gly Met Lys Phe	
	2195	2200 2205
15	Ile Lys Val Gln Ala Glu Lys Val Arg Asp Ser Gln Ser Thr Lys	
	2210	2215 2220
	Glu Gly Leu Gln Thr Ile Lys Glu Tyr Val Asp Lys Phe Ile Gln	
20	2225	2230 2235
	Ser Leu Thr Glu Asn Lys Glu Glu Ile Ile Arg Tyr Gly Leu Trp	
	2240	2245 2250
25	Gly Val His Thr Ala Leu Tyr Lys Ser Leu Ala Ala Arg Leu Gly	
	2255	2260 2265
	His Glu Thr Ala Phe Ala Thr Leu Val Val Lys Trp Leu Ala Phe	
	2270	2275 2280
30	Gly Gly Glu Thr Val Ser Ala His Ile Lys Gln Val Ala Val Asp	
	2285	2290 2295
	Leu Val Val Tyr Tyr Ile Ile Asn Lys Pro Ser Phe Pro Gly Asp	
35	2300	2305 2310
	Thr Glu Thr Gln Gln Glu Gly Arg Arg Phe Val Ala Ser Leu Phe	
	2315	2320 2325
40	Ile Ser Ala Leu Ala Thr Tyr Thr Tyr Lys Thr Trp Asn Tyr Asn	
	2330	2335 2340
	Asn Leu Gln Arg Val Val Glu Pro Ala Leu Ala Tyr Leu Pro Tyr	
	2345	2350 2355
45	Ala Thr Ser Ala Leu Lys Leu Phe Thr Pro Thr Arg Leu Glu Ser	
	2360	2365 2370
	Val Val Ile Leu Ser Ser Thr Ile Tyr Lys Thr Tyr Leu Ser Ile	
50	2375	2380 2385
	Arg Lys Gly Lys Ser Asp Gly Leu Leu Gly Thr Gly Ile Ser Ala	
	2390	2395 2400
55	Ala Met Glu Ile Leu Asn Gln Asn Pro Ile Ser Val Gly Ile Ser	
	2405	2410 2415

	Val	Met	Leu	Gly	Val	Gly	Ala	Ile	Ala	Ala	His	Asn	Ala	Ile	Glu
	2420						2425					2430			
5	Ser	Ser	Glu	Gln	Lys	Arg	Thr	Leu	Leu	Met	Lys	Val	Phe	Val	Lys
	2435						2440					2445			
	Asn	Phe	Leu	Asp	Gln	Ala	Ala	Thr	Asp	Glu	Leu	Val	Lys	Glu	Asn
	2450						2455					2460			
10	Pro	Glu	Lys	Ile	Ile	Met	Ala	Leu	Phe	Glu	Ala	Val	Gln	Thr	Ile
	2465						2470					2475			
	Gly	Asn	Pro	Leu	Arg	Leu	Ile	Tyr	His	Leu	Tyr	Gly	Val	Tyr	Tyr
	2480						2485					2490			
15	Lys	Gly	Trp	Glu	Ala	Lys	Glu	Leu	Ala	Glu	Lys	Thr	Ala	Gly	Arg
	2495						2500					2505			
	Asn	Leu	Phe	Thr	Leu	Ile	Met	Phe	Glu	Ala	Phe	Glu	Leu	Leu	Gly
20	2510						2515					2520			
	Met	Asp	Ser	Glu	Gly	Lys	Ile	Arg	Asn	Leu	Ser	Gly	Asn	Tyr	Ile
	2525						2530					2535			
25	Leu	Asp	Leu	Ile	Phe	Asn	Leu	His	Asn	Lys	Leu	Asn	Lys	Gly	Leu
	2540						2545					2550			
	Lys	Lys	Leu	Val	Leu	Gly	Trp	Ala	Pro	Ala	Pro	Leu	Ser	Cys	Asp
	2555						2560					2565			
30	Trp	Thr	Pro	Ser	Asp	Glu	Arg	Ile	Ser	Leu	Pro	His	Asn	Asn	Tyr
	2570						2575					2580			
	Leu	Arg	Val	Glu	Thr	Arg	Cys	Pro	Cys	Gly	Tyr	Glu	Met	Lys	Ala
35	2585						2590					2595			
	Ile	Lys	Asn	Val	Ala	Gly	Lys	Leu	Thr	Lys	Val	Glu	Glu	Lys	Gly
	2600						2605					2610			
40	Ser	Phe	Leu	Cys	Arg	Asn	Arg	Leu	Gly	Arg	Gly	Pro	Pro	Asn	Phe
	2615						2620					2625			
	Lys	Val	Thr	Lys	Phe	Tyr	Asp	Asp	Asn	Leu	Ile	Glu	Val	Lys	Pro
	2630						2635					2640			
45	Val	Ala	Arg	Leu	Glu	Gly	Gln	Val	Asp	Leu	Tyr	Tyr	Lys	Gly	Val
	2645						2650					2655			
	Thr	Ala	Lys	Leu	Asp	Tyr	Asn	Asn	Gly	Lys	Val	Leu	Leu	Ala	Thr
50	2660						2665					2670			
	Asn	Lys	Trp	Glu	Val	Asp	His	Ala	Phe	Leu	Thr	Arg	Leu	Val	Lys
	2675						2680					2685			
55	Lys	His	Thr	Gly	Ile	Gly	Phe	Lys	Gly	Ala	Tyr	Leu	Gly	Asp	Arg
	2690						2695					2700			

	Pro	Asp	His	Gln	Asp	Leu	Val	Asp	Arg	Asp	Cys	Ala	Thr	Ile	Thr
	2705						2710					2715			
5	Lys	Asn	Ser	Val	Gln	Phe	Leu	Lys	Met	Lys	Lys	Gly	Cys	Ala	Phe
	2720						2725					2730			
	Thr	Tyr	Asp	Leu	Thr	Ile	Ser	Asn	Leu	Val	Arg	Leu	Ile	Glu	Leu
	2735						2740					2745			
10	Val	His	Lys	Asn	Asn	Leu	Gln	Glu	Arg	Glu	Ile	Pro	Thr	Val	Thr
	2750						2755					2760			
	Val	Thr	Thr	Trp	Leu	Ala	Tyr	Ser	Phe	Val	Asn	Glu	Asp	Leu	Gly
	2765						2770					2775			
15	Thr	Ile	Lys	Pro	Val	Leu	Gly	Glu	Lys	Val	Ile	Pro	Glu	Pro	Pro
	2780						2785					2790			
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 20 25 30
 Phe Gly Glu Ser Ser Asp Leu His Pro Gln Ser Thr Leu Lys Leu Pro
 35 40 45
 55 His Gln Arg Gly Ser Ala Asn Ile Leu Thr Asn Ala Arg Ser Leu Pro

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		2045						2050					2055			
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		2075						2080					2085			
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		2090						2095					2100			
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	Ser Thr Met Ala Ser Ala Gly Ile Arg Leu Glu Lys Leu Pro Val				
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	Glu Lys Ile Asp Lys Thr Glu Asn Lys Gln Thr Pro Glu Leu His				
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	Lys Asp Leu Arg Lys Gly Lys Lys Ile Arg Tyr Tyr Glu Thr Ala				
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	Asp Ala Lys Val Arg Leu Ala Ile Thr Lys Val Met Tyr Lys Trp				
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	Pro Leu Phe Asp Ile Phe Asn Lys Val Lys Lys Glu Trp Asp Ser				
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	Phe Gln Asp Pro Val Ala Val Ser Phe Asp Thr Lys Ala Trp Asp				

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 10 3860 3865 3870
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 35 40 45
 Val Val Glu Gly Val Lys Tyr Gln Val Lys Lys Lys Gly Lys Val Arg
 50 50 55 60
 40 Gly Lys Asn Thr Gln Asp Gly Leu Tyr His Asn Lys Asn Lys Pro Pro
 65 70 75 80
 Glu Ser Arg Lys Lys Leu Glu Lys Ala Leu Leu Ala Trp Ala Ile Leu
 45 85 90 95
 Ala Ala Val Leu Leu Gln Leu Val Thr Gly Glu Asn Ile Thr Gln Trp
 100 105 110
 50 Asn Leu Met Asp Asn Gly Thr Glu Gly Ile Gln Gln Ala Met Phe Leu
 115 120 125
 Arg Gly Val Asn Arg Ser Leu His Gly Ile Trp Pro Glu Lys Ile Cys
 130 135 140
 55 Thr Gly Val Pro Thr His Leu Ala Thr Asp Tyr Glu Leu Lys Glu Ile
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5	Leu	Gln	Arg	His	Glu	Trp	Asn	Lys	Gly	Trp	Cys	Asn	Trp	Phe	His	Ile	
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25	Asp	Gly	Ala	Thr	Asn	Thr	Ile	Glu	Gly	Ala	Arg	Val	Gly	Thr	Ala	Lys	
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35	Cys	Gly	Val	Glu	Arg	Lys	Ile	Gly	Tyr	Val	Trp	Tyr	Thr	Lys	Asn	Cys	
				340					345					350			
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				420				425						430			
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	Asp	Leu	Lys	Ile	Leu	Lys	Met	Cys	Thr	Lys	Glu	Glu	Arg	Tyr	Leu	Val		580		585				590	
25	Ala	Val	His	Glu	Arg	Ala	Leu	Ser	Thr	Ser	Ala	Glu	Phe	Met	Gln	Ile		595		600				605	
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	Ser	Tyr	Ile	Thr	Asp	Tyr	Phe	Arg	Tyr	Lys	Lys	Trp	Leu	Gln	Leu		
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	1085						1090					1095			
	Thr	Thr	Asn	Trp	Asp	Ile	Asp	Leu	Ala	Gly	Phe	Leu	Leu	Gln	Trp
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10	Ala	Arg	Gly	Gln	Leu	Phe	Leu	Arg	Asn	Leu	Pro	Ile	Leu	Ala	Thr
	1400						1405					1410			
	Lys	Met	Lys	Leu	Leu	Met	Val	Gly	Asn	Leu	Gly	Ala	Glu	Ile	Gly
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	Asp	Leu	Glu	His	Leu	Gly	Trp	Val	Leu	Arg	Gly	Pro	Ala	Val	Cys
	1430						1435					1440			
20	Lys	Lys	Ile	Thr	Asn	His	Glu	Lys	Cys	His	Val	Asn	Ile	Met	Asp
	1445						1450					1455			
	Lys	Leu	Thr	Ala	Phe	Phe	Gly	Ile	Met	Pro	Arg	Gly	Thr	Thr	Pro
	1460						1465					1470			
25	Arg	Ala	Pro	Val	Arg	Phe	Pro	Thr	Ala	Leu	Leu	Lys	Val	Arg	Arg
	1475						1480					1485			
	Gly	Leu	Glu	Thr	Gly	Trp	Ala	Tyr	Thr	His	Gln	Gly	Gly	Ile	Ser
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	1505						1510					1515			
35	Ser	Met	Gly	Arg	Thr	Arg	Val	Val	Cys	His	Ser	Asn	Asn	Lys	Met
	1520						1525					1530			
	Thr	Asp	Glu	Thr	Glu	Tyr	Gly	Ile	Lys	Thr	Asp	Ser	Gly	Cys	Pro
	1535						1540					1545			
40	Glu	Gly	Ala	Arg	Cys	Tyr	Val	Leu	Asn	Pro	Glu	Ala	Val	Asn	Ile
	1550						1555					1560			
	Ser	Gly	Thr	Lys	Gly	Ala	Met	Val	His	Leu	Gln	Lys	Thr	Gly	Gly
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	1580						1585					1590			
50	Leu	Lys	Asn	Leu	Lys	Gly	Trp	Ser	Gly	Leu	Pro	Ile	Phe	Glu	Ala
	1595						1600					1605			
	Ser	Ser	Gly	Arg	Val	Val	Gly	Arg	Val	Lys	Val	Gly	Lys	Asn	Glu
	1610						1615					1620			
55	Asp	Ser	Lys	Pro	Thr	Lys	Leu	Met	Ser	Gly	Ile	Gln	Thr	Val	Ser
	1625						1630					1635			

	Lys	Asn	Gln	Thr	Asp	Leu	Ala	Asp	Ile	Val	Lys	Lys	Leu	Thr	Ser
	1640						1645					1650			
5	Met	Asn	Arg	Gly	Glu	Phe	Lys	Gln	Ile	Thr	Leu	Ala	Thr	Gly	Ala
	1655						1660					1665			
	Gly	Lys	Thr	Thr	Glu	Leu	Pro	Arg	Ser	Val	Ile	Glu	Glu	Ile	Gly
	1670						1675					1680			
10	Arg	His	Lys	Arg	Val	Leu	Val	Leu	Ile	Pro	Leu	Arg	Ala	Ala	Ala
	1685						1690					1695			
	Glu	Ser	Val	Tyr	Gln	Tyr	Met	Arg	Val	Lys	Tyr	Pro	Ser	Ile	Ser
15	1700						1705					1710			
	Phe	Asn	Leu	Arg	Ile	Gly	Asp	Met	Lys	Glu	Gly	Asp	Met	Ala	Thr
	1715						1720					1725			
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	1730						1735					1740			
	Pro	Lys	Leu	Arg	Ala	Ala	Met	Val	Glu	Tyr	Ser	Tyr	Ile	Phe	Leu
	1745						1750					1755			
25	Asp	Glu	Tyr	His	Cys	Ala	Thr	Pro	Glu	Gln	Leu	Ala	Ile	Ile	Gly
	1760						1765					1770			
	Lys	Ile	His	Arg	Phe	Ala	Glu	Asn	Leu	Arg	Val	Val	Ala	Met	Thr
30	1775						1780					1785			
	Ala	Thr	Pro	Ala	Gly	Thr	Val	Thr	Thr	Thr	Gly	Gln	Lys	His	Pro
	1790						1795					1800			
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	1835						1840					1845			
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	Gly	Tyr	Tyr	Tyr	Ser	Gly	Glu	Asn	Pro	Glu	Asn	Leu	Arg	Val	Val
	1865						1870					1875			
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	1880						1885					1890			
	Ser	Gly	Val	Thr	Leu	Pro	Asp	Leu	Asp	Thr	Val	Val	Asp	Thr	Gly
	1895						1900					1905			
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	1910						1915					1920			

	Ile Val Thr Gly Leu Lys Arg Met Ala Val Thr Ile Gly Glu Gln	
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5	Ala Gln Arg Arg Gly Arg Val Gly Arg Val Lys Pro Gly Arg Tyr	
	1940 1945 1950	
	Tyr Arg Ser Gln Glu Thr Ala Ser Gly Ser Lys Asp Tyr His Tyr	
	1955 1960 1965	
10	Asp Leu Leu Gln Ala Gln Arg Tyr Gly Ile Glu Asp Gly Ile Asn	
	1970 1975 1980	
	Val Thr Lys Ser Phe Arg Glu Met Asn Tyr Asp Trp Ser Leu Tyr	
15	1985 1990 1995	
	Glu Glu Asp Ser Leu Met Ile Thr Gln Leu Glu Val Leu Asn Asn	
	2000 2005 2010	
20	Leu Leu Ile Ser Glu Asp Leu Pro Ala Ala Val Lys Asn Ile Met	
	2015 2020 2025	
	Ala Arg Thr Asp His Pro Glu Pro Ile Gln Leu Ala Tyr Asn Ser	
	2030 2035 2040	
25	Tyr Glu Asn Gln Ile Pro Val Leu Phe Pro Lys Ile Lys Asn Gly	
	2045 2050 2055	
	Glu Val Thr Asp Ser Tyr Glu Asn Tyr Thr Tyr Leu Asn Ala Arg	
30	2060 2065 2070	
	Lys Leu Gly Glu Asp Val Pro Ala Tyr Val Tyr Ala Thr Glu Asp	
	2075 2080 2085	
35	Glu Asp Leu Ala Val Asp Leu Leu Gly Met Asp Trp Pro Asp Pro	
	2090 2095 2100	
	Gly Asn Gln Gln Val Val Glu Thr Gly Arg Ala Leu Lys Gln Val	
	2105 2110 2115	
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	2120 2125 2130	
	Gly Tyr Val Gly Tyr Gln Thr Leu Ser Lys Arg His Ile Pro Met	
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	Ile Thr Asp Ile Tyr Thr Leu Glu Asp His Arg Leu Glu Asp Thr	
	2150 2155 2160	
50	Thr His Leu Gln Phe Ala Pro Asn Ala Ile Arg Thr Asp Gly Lys	
	2165 2170 2175	
	Asp Ser Glu Leu Lys Glu Leu Ala Val Gly Asp Leu Asp Lys Tyr	
	2180 2185 2190	
55	Val Asp Ala Leu Val Asp Tyr Ser Lys Gln Gly Met Lys Phe Ile	
	2195 2200 2205	

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5	Gly	Leu	Gln	Thr	Ile	Lys	Glu	Tyr	Val	Asp	Lys	Phe	Ile	Gln	Ser
	2225						2230					2235			
	Leu	Thr	Glu	Asn	Lys	Glu	Glu	Ile	Ile	Arg	Tyr	Gly	Leu	Trp	Gly
	2240						2245					2250			
10	Val	His	Thr	Ala	Leu	Tyr	Lys	Ser	Leu	Ala	Ala	Arg	Leu	Gly	His
	2255						2260					2265			
	Glu	Thr	Ala	Phe	Ala	Thr	Leu	Val	Val	Lys	Trp	Leu	Ala	Phe	Gly
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	2285						2290					2295			
20	Val	Val	Tyr	Tyr	Ile	Ile	Asn	Lys	Pro	Ser	Phe	Pro	Gly	Asp	Thr
	2300						2305					2310			
	Glu	Thr	Gln	Gln	Glu	Gly	Arg	Arg	Phe	Val	Ala	Ser	Leu	Phe	Ile
	2315						2320					2325			
25	Ser	Ala	Leu	Ala	Thr	Tyr	Thr	Tyr	Lys	Thr	Trp	Asn	Tyr	Asn	Asn
	2330						2335					2340			
	Leu	Gln	Arg	Val	Val	Glu	Pro	Ala	Leu	Ala	Tyr	Leu	Pro	Tyr	Ala
30	2345						2350					2355			
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	2360						2365					2370			
35	Val	Ile	Leu	Ser	Ser	Thr	Ile	Tyr	Lys	Thr	Tyr	Leu	Ser	Ile	Arg
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	2390						2395					2400			
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	2405						2410					2415			
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	2435						2440					2445			
50	Phe	Leu	Asp	Gln	Ala	Ala	Thr	Asp	Glu	Leu	Val	Lys	Glu	Asn	Pro
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	Asp	Ser	Glu	Gly	Lys	Ile	Arg	Asn	Leu	Ser	Gly	Asn	Tyr	Ile	Leu
	2525						2530					2535			
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	Ala	Arg	Leu	Glu	Gly	Gln	Val	Asp	Leu	Tyr	Tyr	Lys	Gly	Val	Thr
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	2660						2665					2670			
	Lys	Trp	Glu	Val	Asp	His	Ala	Phe	Leu	Thr	Arg	Leu	Val	Lys	Lys
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	2690						2695					2700			
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	2720						2725					2730			
50	Tyr	Asp	Leu	Thr	Ile	Ser	Asn	Leu	Val	Arg	Leu	Ile	Glu	Leu	Val
	2735						2740					2745			
	His	Lys	Asn	Asn	Leu	Gln	Glu	Arg	Glu	Ile	Pro	Thr	Val	Thr	Val
	2750						2755					2760			
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	3050						3055					3060			

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5	Leu Gly Cys Gly Val Tyr Met Gly Thr Ile Pro Ala Arg Arg Leu
	3080 3085 3090
	Lys Ile His Pro Tyr Glu Ala Tyr Leu Lys Leu Lys Glu Leu Val
	3095 3100 3105
10	Glu Val Glu Ser Ser Arg Ala Thr Ala Lys Glu Ser Ile Ile Arg
	3110 3115 3120
	Glu His Asn Thr Trp Ile Leu Arg Lys Val Arg His Glu Gly Asn
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	Leu Arg Thr Lys Ser Met Ile Asn Pro Gly Lys Ile Ser Asp Gln
	3140 3145 3150
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	3155 3160 3165
	Gly Ser Thr Met Ala Ser Ala Gly Ile Arg Leu Glu Lys Leu Pro
	3170 3175 3180
25	Val Val Arg Ala Gln Thr Asp Thr Thr Ser Phe His Gln Ala Ile
	3185 3190 3195
	Arg Glu Lys Ile Asp Lys Thr Glu Asn Lys Gln Thr Pro Glu Leu
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	His Glu Glu Leu Met Lys Val Phe Asp Cys Leu Lys Ile Pro Glu
	3215 3220 3225
35	Leu Lys Glu Ser Tyr Asp Glu Val Ser Trp Glu Gln Leu Glu Ala
	3230 3235 3240
	Gly Ile Asn Arg Lys Gly Ala Ala Gly Tyr Leu Glu Ser Lys Asn
	3245 3250 3255
40	Ile Gly Glu Val Leu Asp Thr Glu Lys His Ile Val Glu Gln Leu
	3260 3265 3270
	Ile Lys Asp Leu Arg Lys Gly Lys Lys Ile Arg Tyr Tyr Glu Thr
45	3275 3280 3285
	Ala Ile Pro Lys Asn Glu Lys Arg Asp Val Ser Asp Asp Trp Glu
	3290 3295 3300
50	Ala Gly Glu Phe Val Asp Glu Lys Lys Pro Arg Val Ile Gln Tyr
	3305 3310 3315
	Pro Asp Ala Lys Val Arg Leu Ala Ile Thr Lys Val Met Tyr Lys
	3320 3325 3330
55	Trp Val Lys Gln Lys Pro Val Val Ile Pro Gly Tyr Glu Gly Lys
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10	Gln	Lys	Tyr	Tyr	Phe	Lys	Arg	Ser	Ile	His	Lys	Phe	Leu	Asp	Thr
	3395						3400					3405			
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	3455						3460					3465			
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	3605						3610					3615			
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Thr Gly Phe Glu Lys Leu Ala Gly Leu Asn Leu Ser Met Thr Thr
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 5 Leu Gly Ile Trp Thr Lys His Thr Ser Lys Arg Leu Ile Gln Ala
 3650 3655 3660
 Cys Val Glu Ile Gly Lys Arg Glu Gly Thr Trp Leu Val Asn Ala
 3665 3670 3675
 10 Asp Arg Leu Ile Ala Gly Lys Thr Gly Lys Phe Tyr Ile Pro Ser
 3680 3685 3690
 Thr Gly Val Thr Leu Leu Gly Lys His Tyr Glu Glu Ile Asn Leu
 15 3695 3700 3705
 Lys Gln Lys Ala Ala Gln Pro Pro Ile Glu Gly Val Asp Arg Tyr
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 Pro Ala Gly Val Val Glu Pro Val Tyr Asp Val Asn Gly Arg Pro Leu
 20 25 30
 40 Phe Gly Glu Ser Ser Asp Leu His Pro Gln Ser Thr Leu Lys Leu Pro
 35 40 45
 His Gln Arg Gly Ser Ala Asn Ile Leu Thr Asn Ala Arg Ser Leu Pro
 50 55 60
 45 Arg Lys Gly Asp Cys Arg Arg Gly Asn Val Tyr Gly Pro Val Ser Gly
 65 70 75 80
 Ile Tyr Ile Lys Pro Gly Pro Ile Tyr Tyr Gln Asp Tyr Val Gly Pro
 50 85 90 95
 Val Tyr His Arg Ala Pro Leu Glu Leu Cys Arg Glu Ala Ser Met Cys
 100 105 110
 55 Glu Thr Thr Arg Arg Val Gly Arg Val Thr Gly Ser Asp Gly Lys Leu
 115 120 125

	Tyr	His	Ile	Tyr	Ile	Cys	Ile	Asp	Gly	Cys	Ile	Leu	Leu	Lys	Arg	Ala	
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	Cys	Pro	Leu	Trp	Val	Thr	Ser	Cys	Ser	Asp	Glu	Gly	Ser	Lys	Gly	Ala	
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				180					185					190			
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			195					200					205				
15	Asp	Ala	Thr	Ile	Val	Val	Glu	Gly	Val	Lys	Tyr	Gln	Val	Lys	Lys	Lys	
	210						215					220					
20	Gly	Lys	Val	Arg	Gly	Lys	Asn	Thr	Gln	Asp	Gly	Leu	Tyr	His	Asn	Lys	
	225					230					235					240	
	Asn	Lys	Pro	Pro	Glu	Ser	Arg	Lys	Lys	Leu	Glu	Lys	Ala	Leu	Leu	Ala	
					245					250						255	
25	Trp	Ala	Ile	Leu	Ala	Ala	Val	Leu	Leu	Gln	Leu	Val	Thr	Gly	Glu	Asn	
				260					265					270			
	Ile	Thr	Gln	Trp	Asn	Leu	Met	Asp	Asn	Gly	Thr	Glu	Gly	Ile	Gln	Gln	
			275					280					285				
30	Ala	Met	Phe	Leu	Arg	Gly	Val	Asn	Arg	Ser	Leu	Leu	Gly	Ile	Trp	Pro	
	290						295					300					
	Glu	Lys	Ile	Cys	Thr	Gly	Val	Pro	Thr	His	Leu	Ala	Thr	Asp	Tyr	Glu	
35	305					310					315					320	
	Leu	Lys	Glu	Ile	Val	Gly	Met	Met	Asp	Ala	Ser	Glu	Lys	Thr	Asn	Tyr	
					325				330						335		
40	Thr	Cys	Cys	Arg	Leu	Gln	Arg	His	Glu	Trp	Asn	Lys	His	Gly	Trp	Cys	
				340					345					350			
	Asn	Trp	Phe	His	Ile	Glu	Pro	Trp	Ile	Trp	Leu	Met	Asn	Lys	Thr	Gln	
			355					360					365				
45	Asn	Asn	Leu	Thr	Glu	Gly	Gln	Pro	Leu	Arg	Glu	Cys	Ala	Val	Thr	Cys	
	370						375					380					
	Arg	Tyr	Asp	Lys	Glu	Thr	Glu	Leu	Asn	Ile	Val	Thr	Gln	Ala	Arg	Asp	
50	385					390					395					400	
	Arg	Pro	Thr	Thr	Leu	Thr	Gly	Cys	Lys	Lys	Gly	Lys	Asn	Phe	Ser	Phe	
					405					410					415		
55	Ala	Gly	Val	Ile	Leu	Asp	Gly	Pro	Cys	Asn	Phe	Lys	Val	Ser	Val	Glu	
				420					425					430			

	Asp	Val	Leu	Phe	Lys	Glu	His	Asp	Cys	Gly	Asn	Met	Leu	Gln	Glu	Thr	
			435					440					445				
5	Ala	Ile	Gln	Leu	Leu	Asp	Gly	Ala	Thr	Asn	Thr	Ile	Glu	Gly	Ala	Arg	
		450					455					460					
	Val	Gly	Thr	Ala	Lys	Leu	Thr	Thr	Trp	Leu	Gly	Lys	Gln	Leu	Gly	Ile	
	465					470					475					480	
10	Leu	Gly	Lys	Lys	Leu	Glu	Asn	Lys	Ser	Lys	Ala	Trp	Phe	Gly	Ala	His	
					485					490					495		
	Ala	Ala	Ser	Pro	Tyr	Cys	Gly	Val	Glu	Arg	Lys	Ile	Gly	Tyr	Val	Trp	
				500					505					510			
15	Tyr	Thr	Lys	Asn	Cys	Thr	Pro	Ala	Cys	Leu	Pro	Arg	Asn	Thr	Arg	Ile	
			515					520					525				
	Ile	Gly	Pro	Gly	Lys	Phe	Asp	Thr	Asn	Ala	Glu	Asp	Gly	Lys	Ile	Leu	
20		530					535					540					
	His	Glu	Met	Gly	Gly	His	Leu	Ser	Glu	Phe	Val	Leu	Leu	Ser	Leu	Val	
	545					550					555					560	
25	Val	Leu	Ser	Asp	Phe	Ala	Pro	Glu	Thr	Ala	Ser	Val	Ile	Tyr	Leu	Val	
					565					570					575		
	Leu	His	Phe	Ala	Ile	Pro	Gln	Ser	His	Val	Asp	Val	Asp	Thr	Cys	Asp	
				580					585					590			
30	Lys	Asn	Gln	Leu	Asn	Leu	Thr	Val	Ala	Thr	Thr	Val	Ala	Glu	Val	Ile	
			595					600					605				
	Pro	Gly	Thr	Val	Trp	Asn	Leu	Gly	Lys	Tyr	Val	Cys	Ile	Arg	Pro	Asp	
35		610					615					620					
	Trp	Trp	Pro	Tyr	Glu	Thr	Thr	Thr	Val	Phe	Val	Ile	Glu	Glu	Ala	Gly	
	625					630					635					640	
40	Gln	Val	Ile	Lys	Leu	Met	Leu	Arg	Ala	Ile	Arg	Asp	Leu	Thr	Arg	Ile	
					645					650					655		
	Trp	Asn	Ala	Ala	Thr	Thr	Thr	Ala	Phe	Leu	Ile	Phe	Leu	Val	Lys	Ala	
				660					665					670			
45	Leu	Arg	Gly	Gln	Leu	Ile	Gln	Gly	Leu	Leu	Trp	Leu	Met	Leu	Ile	Thr	
			675					680					685				
	Gly	Ala	Gln	Gly	Phe	Pro	Glu	Cys	Lys	Glu	Gly	Phe	Gln	Tyr	Ala	Ile	
50		690					695					700					
	Ser	Lys	Asp	Arg	Lys	Met	Gly	Leu	Leu	Gly	Pro	Glu	Ser	Leu	Thr	Thr	
	705					710					715					720	
55	Thr	Trp	His	Leu	Pro	Thr	Lys	Lys	Ile	Val	Asp	Ser	Met	Val	His	Val	
					725					730					735		

	Trp	Cys	Glu	Gly	Lys	Asp	Leu	Lys	Ile	Leu	Lys	Met	Cys	Thr	Lys	Glu	
				740					745					750			
5	Glu	Arg	Tyr	Leu	Val	Ala	Val	His	Glu	Arg	Ala	Leu	Ser	Thr	Ser	Ala	
			755					760					765				
	Glu	Phe	Met	Gln	Ile	Ser	Asp	Gly	Thr	Ile	Gly	Pro	Asp	Val	Ile	Asp	
			770				775					780					
10	Met	Pro	Asp	Asp	Phe	Glu	Phe	Gly	Leu	Cys	Pro	Cys	Asp	Ser	Lys	Pro	
						790					795					800	
	Val	Ile	Lys	Gly	Lys	Phe	Asn	Ala	Ser	Leu	Leu	Asn	Gly	Pro	Ala	Phe	
					805					810					815		
15	Gln	Met	Val	Cys	Pro	Gln	Gly	Trp	Thr	Gly	Thr	Ile	Glu	Cys	Thr	Leu	
				820					825					830			
	Ala	Asn	Gln	Asp	Thr	Leu	Asp	Thr	Thr	Val	Ile	Arg	Thr	Tyr	Arg	Arg	
20			835					840					845				
	Thr	Thr	Pro	Phe	Gln	Arg	Arg	Lys	Trp	Cys	Thr	Tyr	Glu	Lys	Ile	Ile	
			850				855					860					
25	Gly	Glu	Asp	Ile	Tyr	Glu	Cys	Ile	Leu	Gly	Gly	Asn	Trp	Thr	Cys	Ile	
						870					875					880	
	Thr	Gly	Asp	His	Ser	Arg	Leu	Lys	Asp	Gly	Pro	Ile	Lys	Lys	Cys	Lys	
					885					890					895		
30	Trp	Cys	Gly	His	Asp	Phe	Val	Asn	Ser	Glu	Gly	Leu	Pro	His	Tyr	Pro	
				900					905					910			
	Ile	Gly	Lys	Cys	Met	Leu	Ile	Asn	Glu	Ser	Gly	Tyr	Arg	Tyr	Val	Asp	
35			915					920					925				
	Asp	Thr	Ser	Cys	Asp	Arg	Gly	Gly	Val	Ala	Ile	Val	Pro	Ser	Gly	Thr	
			930				935					940					
40	Val	Lys	Cys	Arg	Ile	Gly	Asn	Val	Thr	Val	Gln	Val	Ile	Ala	Thr	Asn	
						950					955					960	
	Asn	Asp	Leu	Gly	Pro	Met	Pro	Cys	Ser	Pro	Ala	Glu	Val	Ile	Ala	Ser	
					965					970					975		
45	Glu	Gly	Pro	Val	Glu	Lys	Thr	Ala	Cys	Thr	Phe	Asn	Tyr	Ser	Arg	Thr	
				980					985					990			
	Leu	Pro	Asn	Lys	Tyr	Tyr	Glu	Pro	Arg	Asp	Arg	Tyr	Phe	Gln	Gln	Tyr	
50			995					1000					1005				
	Met	Leu	Lys	Gly	Glu	Trp	Gln	Tyr	Trp	Phe	Asp	Leu	Asp	Ser	Val		
			1010				1015					1020					
55	Asp	His	His	Lys	Asp	Tyr	Phe	Ser	Glu	Phe	Ile	Ile	Ile	Ala	Val		
							1030					1035					

	Val	Ala	Leu	Leu	Gly	Gly	Lys	Tyr	Val	Leu	Trp	Leu	Leu	Ile	Thr
	1040						1045					1050			
5	Tyr	Thr	Ile	Leu	Ser	Glu	Gln	Met	Ala	Met	Gly	Ala	Gly	Val	Asn
	1055						1060					1065			
	Thr	Glu	Glu	Ile	Val	Met	Ile	Gly	Asn	Leu	Leu	Thr	Asp	Ser	Asp
	1070						1075					1080			
10	Ile	Glu	Val	Val	Val	Tyr	Phe	Leu	Leu	Leu	Tyr	Leu	Ile	Val	Lys
	1085						1090					1095			
	Glu	Glu	Leu	Ala	Arg	Lys	Trp	Ile	Ile	Leu	Val	Tyr	His	Ile	Leu
	1100						1105					1110			
15	Val	Ala	Asn	Pro	Met	Lys	Thr	Ile	Gly	Val	Val	Leu	Leu	Met	Leu
	1115						1120					1125			
	Gly	Gly	Val	Val	Lys	Ala	Ser	Arg	Ile	Asn	Ala	Asp	Asp	Gln	Ser
20	1130						1135					1140			
	Ala	Met	Asp	Pro	Cys	Phe	Leu	Leu	Val	Thr	Gly	Val	Val	Ala	Val
	1145						1150					1155			
25	Leu	Met	Ile	Ala	Arg	Arg	Glu	Pro	Ala	Thr	Leu	Pro	Leu	Ile	Val
	1160						1165					1170			
	Ala	Leu	Leu	Ala	Ile	Arg	Thr	Ser	Gly	Phe	Leu	Leu	Pro	Ala	Ser
	1175						1180					1185			
30	Ile	Asp	Val	Thr	Val	Ala	Val	Val	Leu	Ile	Val	Leu	Leu	Leu	Ala
	1190						1195					1200			
	Ser	Tyr	Ile	Thr	Asp	Tyr	Phe	Arg	Tyr	Lys	Lys	Trp	Leu	Gln	Leu
35	1205						1210					1215			
	Leu	Phe	Ser	Leu	Ile	Ala	Gly	Ile	Phe	Ile	Ile	Arg	Ser	Leu	Lys
	1220						1225					1230			
40	His	Ile	Asn	Gln	Met	Glu	Val	Pro	Glu	Ile	Ser	Met	Pro	Ser	Trp
	1235						1240					1245			
	Arg	Pro	Leu	Ala	Leu	Val	Leu	Phe	Tyr	Ile	Thr	Ser	Thr	Ala	Ile
	1250						1255					1260			
45	Thr	Thr	Asn	Trp	Asp	Ile	Asp	Leu	Ala	Gly	Phe	Leu	Leu	Gln	Trp
	1265						1270					1275			
	Ala	Pro	Ala	Val	Ile	Met	Met	Ala	Thr	Met	Trp	Ala	Asp	Phe	Leu
50	1280						1285					1290			
	Thr	Leu	Ile	Ile	Val	Leu	Pro	Ser	Tyr	Glu	Leu	Ser	Lys	Leu	Tyr
	1295						1300					1305			
55	Phe	Leu	Lys	Asn	Val	Arg	Thr	Asp	Val	Glu	Lys	Asn	Trp	Leu	Gly
	1310						1315					1320			

	Lys Val	Lys Tyr Arg Gln Ile	Ser Ser Val Tyr Asp	Ile Cys Asp
	1325	1330	1335	
5	Ser Glu	Glu Ala Val Tyr Leu	Phe Pro Ser Arg His	Lys Ser Gly
	1340	1345	1350	
	Ser Arg	Pro Asp Phe Ile Leu	Pro Phe Leu Lys Ala	Val Leu Ile
	1355	1360	1365	
10	Ser Cys	Ile Ser Ser Gln Trp	Gln Val Val Tyr Ile	Ser Tyr Leu
	1370	1375	1380	
	Ile Leu	Glu Ile Thr Tyr Tyr	Met His Arg Lys Ile	Ile Asp Glu
	1385	1390	1395	
15	Val Ser	Gly Gly Ala Asn Phe	Leu Ser Arg Leu Ile	Ala Ala Ile
	1400	1405	1410	
	Ile Glu	Leu Asn Trp Ala Ile	Asp Asp Glu Glu Cys	Lys Gly Leu
20	1415	1420	1425	
	Lys Lys	Leu Tyr Leu Leu Ser	Gly Arg Ala Lys Asn	Leu Ile Val
	1430	1435	1440	
25	Lys His	Lys Val Arg Asn Glu	Ala Val His Arg Trp	Phe Gly Glu
	1445	1450	1455	
	Glu Glu	Ile Tyr Gly Ala Pro	Lys Val Ile Thr Ile	Ile Lys Ala
	1460	1465	1470	
30	Ser Thr	Leu Ser Lys Asn Arg	His Cys Ile Ile Cys	Thr Ile Cys
	1475	1480	1485	
	Glu Gly	Lys Glu Trp Asn Gly	Ala Asn Cys Pro Lys	Cys Gly Arg
35	1490	1495	1500	
	Gln Gly	Lys Pro Ile Thr Cys	Gly Met Thr Leu Ala	Asp Phe Glu
	1505	1510	1515	
40	Glu Lys	His Tyr Lys Lys Ile	Phe Ile Arg Glu Glu	Ser Ser Cys
	1520	1525	1530	
	Pro Val	Pro Phe Asp Pro Ser	Cys His Cys Asn Tyr	Phe Arg His
	1535	1540	1545	
45	Asp Gly	Pro Phe Arg Lys Glu	Tyr Lys Gly Tyr Val	Gln Tyr Thr
	1550	1555	1560	
	Ala Arg	Gly Gln Leu Phe Leu	Arg Asn Leu Pro Ile	Leu Ala Thr
50	1565	1570	1575	
	Lys Met	Lys Leu Leu Met Val	Gly Asn Leu Gly Ala	Glu Ile Gly
	1580	1585	1590	
55	Asp Leu	Glu His Leu Gly Trp	Val Leu Arg Gly Pro	Ala Val Cys
	1595	1600	1605	

	Lys	Lys	Ile	Thr	Asn	His	Glu	Lys	Cys	His	Val	Asn	Ile	Met	Asp
	1610						1615					1620			
5	Lys	Leu	Thr	Ala	Phe	Phe	Gly	Ile	Met	Pro	Arg	Gly	Thr	Thr	Pro
	1625						1630					1635			
	Arg	Ala	Pro	Val	Arg	Phe	Pro	Thr	Ala	Leu	Leu	Lys	Val	Arg	Arg
	1640						1645					1650			
10	Gly	Leu	Glu	Thr	Gly	Trp	Ala	Tyr	Thr	His	Gln	Gly	Gly	Ile	Ser
	1655						1660					1665			
	Ser	Val	Asp	His	Val	Thr	Ala	Gly	Lys	Asp	Leu	Leu	Val	Cys	Asp
	1670						1675					1680			
15	Ser	Met	Gly	Arg	Thr	Arg	Val	Val	Cys	His	Ser	Asn	Asn	Lys	Met
	1685						1690					1695			
20	Thr	Asp	Glu	Thr	Glu	Tyr	Gly	Ile	Lys	Thr	Asp	Ser	Gly	Cys	Pro
	1700						1705					1710			
	Glu	Gly	Ala	Arg	Cys	Tyr	Val	Leu	Asn	Pro	Glu	Ala	Val	Asn	Ile
	1715						1720					1725			
25	Ser	Gly	Thr	Lys	Gly	Ala	Met	Val	His	Leu	Gln	Lys	Thr	Gly	Gly
	1730						1735					1740			
	Glu	Phe	Thr	Cys	Val	Thr	Ala	Ser	Gly	Thr	Pro	Ala	Phe	Phe	Asp
	1745						1750					1755			
30	Leu	Lys	Asn	Leu	Lys	Gly	Trp	Ser	Gly	Leu	Pro	Ile	Phe	Glu	Ala
	1760						1765					1770			
35	Ser	Ser	Gly	Arg	Val	Val	Gly	Arg	Val	Lys	Val	Gly	Lys	Asn	Glu
	1775						1780					1785			
	Asp	Ser	Lys	Pro	Thr	Lys	Leu	Met	Ser	Gly	Ile	Gln	Thr	Val	Ser
	1790						1795					1800			
40	Lys	Asn	Gln	Thr	Asp	Leu	Ala	Asp	Ile	Val	Lys	Lys	Leu	Thr	Ser
	1805						1810					1815			
	Met	Asn	Arg	Gly	Glu	Phe	Lys	Gln	Ile	Thr	Leu	Ala	Thr	Gly	Ala
	1820						1825					1830			
45	Gly	Lys	Thr	Thr	Glu	Leu	Pro	Arg	Ser	Val	Ile	Glu	Glu	Ile	Gly
	1835						1840					1845			
50	Arg	His	Lys	Arg	Val	Leu	Val	Leu	Ile	Pro	Leu	Arg	Ala	Ala	Ala
	1850						1855					1860			
	Glu	Ser	Val	Tyr	Gln	Tyr	Met	Arg	Val	Lys	Tyr	Pro	Ser	Ile	Ser
	1865						1870					1875			
55	Phe	Asn	Leu	Arg	Ile	Gly	Asp	Met	Lys	Glu	Gly	Asp	Met	Ala	Thr
	1880						1885					1890			

	Gly	Ile	Thr	Tyr	Ala	Ser	Tyr	Gly	Tyr	Phe	Cys	Gln	Leu	Pro	Gln
	1895						1900					1905			
5	Pro	Lys	Leu	Arg	Ala	Ala	Met	Val	Glu	Tyr	Ser	Tyr	Ile	Phe	Leu
	1910						1915					1920			
	Asp	Glu	Tyr	His	Cys	Ala	Thr	Pro	Glu	Gln	Leu	Ala	Ile	Ile	Gly
	1925						1930					1935			
10	Lys	Ile	His	Arg	Phe	Ala	Glu	Asn	Leu	Arg	Val	Val	Ala	Met	Thr
	1940						1945					1950			
	Ala	Thr	Pro	Ala	Gly	Thr	Val	Thr	Thr	Thr	Gly	Gln	Lys	His	Pro
	1955						1960					1965			
15	Ile	Glu	Glu	Phe	Ile	Ala	Pro	Glu	Val	Met	Lys	Gly	Glu	Asp	Leu
	1970						1975					1980			
20	Gly	Ser	Glu	Tyr	Leu	Asp	Ile	Ala	Gly	Leu	Lys	Ile	Pro	Thr	Glu
	1985						1990					1995			
	Glu	Met	Lys	Gly	Asn	Met	Leu	Val	Phe	Ala	Pro	Thr	Arg	Asn	Met
	2000						2005					2010			
25	Ala	Val	Glu	Thr	Ala	Lys	Lys	Leu	Lys	Ala	Lys	Gly	Tyr	Asn	Ser
	2015						2020					2025			
	Gly	Tyr	Tyr	Tyr	Ser	Gly	Glu	Asn	Pro	Glu	Asn	Leu	Arg	Val	Val
	2030						2035					2040			
30	Thr	Ser	Gln	Ser	Pro	Tyr	Val	Val	Val	Ala	Thr	Asn	Ala	Ile	Glu
	2045						2050					2055			
35	Ser	Gly	Val	Thr	Leu	Pro	Asp	Leu	Asp	Thr	Val	Val	Asp	Thr	Gly
	2060						2065					2070			
	Leu	Lys	Cys	Glu	Lys	Arg	Val	Arg	Ile	Ser	Ser	Lys	Met	Pro	Phe
	2075						2080					2085			
40	Ile	Val	Thr	Gly	Leu	Lys	Arg	Met	Ala	Val	Thr	Ile	Gly	Glu	Gln
	2090						2095					2100			
	Ala	Gln	Arg	Arg	Gly	Arg	Val	Gly	Arg	Val	Lys	Pro	Gly	Arg	Tyr
	2105						2110					2115			
45	Tyr	Arg	Ser	Gln	Glu	Thr	Ala	Ser	Gly	Ser	Lys	Asp	Tyr	His	Tyr
	2120						2125					2130			
50	Asp	Leu	Leu	Gln	Ala	Gln	Arg	Tyr	Gly	Ile	Glu	Asp	Gly	Ile	Asn
	2135						2140					2145			
	Val	Thr	Lys	Ser	Phe	Arg	Glu	Met	Asn	Tyr	Asp	Trp	Ser	Leu	Tyr
	2150						2155					2160			
55	Glu	Glu	Asp	Ser	Leu	Met	Ile	Thr	Gln	Leu	Glu	Val	Leu	Asn	Asn
	2165						2170					2175			

	Leu	Leu	Ile	Ser	Glu	Asp	Leu	Pro	Ala	Ala	Val	Lys	Asn	Ile	Met
	2180						2185					2190			
5	Ala	Arg	Thr	Asp	His	Pro	Glu	Pro	Ile	Gln	Leu	Ala	Tyr	Asn	Ser
	2195						2200					2205			
	Tyr	Glu	Asn	Gln	Ile	Pro	Val	Leu	Phe	Pro	Lys	Ile	Lys	Asn	Gly
	2210						2215					2220			
10	Glu	Val	Thr	Asp	Ser	Tyr	Glu	Asn	Tyr	Thr	Tyr	Leu	Asn	Ala	Arg
	2225						2230					2235			
	Lys	Leu	Gly	Glu	Asp	Val	Pro	Ala	Tyr	Val	Tyr	Ala	Thr	Glu	Asp
	2240						2245					2250			
15	Glu	Asp	Leu	Ala	Val	Asp	Leu	Leu	Gly	Met	Asp	Trp	Pro	Asp	Pro
	2255						2260					2265			
20	Gly	Asn	Gln	Gln	Val	Val	Glu	Thr	Gly	Arg	Ala	Leu	Lys	Gln	Val
	2270						2275					2280			
	Thr	Gly	Leu	Ser	Thr	Ala	Glu	Asn	Ala	Leu	Leu	Ile	Ala	Leu	Phe
	2285						2290					2295			
25	Gly	Tyr	Val	Gly	Tyr	Gln	Thr	Leu	Ser	Lys	Arg	His	Ile	Pro	Met
	2300						2305					2310			
	Ile	Thr	Asp	Ile	Tyr	Thr	Leu	Glu	Asp	His	Arg	Leu	Glu	Asp	Thr
	2315						2320					2325			
30	Thr	His	Leu	Gln	Phe	Ala	Pro	Asn	Ala	Ile	Arg	Thr	Asp	Gly	Lys
	2330						2335					2340			
35	Asp	Ser	Glu	Leu	Lys	Glu	Leu	Ala	Val	Gly	Asp	Leu	Asp	Lys	Tyr
	2345						2350					2355			
	Val	Asp	Ala	Leu	Val	Asp	Tyr	Ser	Lys	Gln	Gly	Met	Lys	Phe	Ile
	2360						2365					2370			
40	Lys	Val	Gln	Ala	Glu	Lys	Val	Arg	Asp	Ser	Gln	Ser	Thr	Lys	Glu
	2375						2380					2385			
	Gly	Leu	Gln	Thr	Ile	Lys	Glu	Tyr	Val	Asp	Lys	Phe	Ile	Gln	Ser
	2390						2395					2400			
45	Leu	Thr	Glu	Asn	Lys	Glu	Glu	Ile	Ile	Arg	Tyr	Gly	Leu	Trp	Gly
	2405						2410					2415			
	Val	His	Thr	Ala	Leu	Tyr	Lys	Ser	Leu	Ala	Ala	Arg	Leu	Gly	His
50	2420						2425					2430			
	Glu	Thr	Ala	Phe	Ala	Thr	Leu	Val	Val	Lys	Trp	Leu	Ala	Phe	Gly
	2435						2440					2445			
55	Gly	Glu	Thr	Val	Ser	Ala	His	Ile	Lys	Gln	Val	Ala	Val	Asp	Leu
	2450						2455					2460			

	Val	Val	Tyr	Tyr	Ile	Ile	Asn	Lys	Pro	Ser	Phe	Pro	Gly	Asp	Thr
	2465						2470					2475			
5	Glu	Thr	Gln	Gln	Glu	Gly	Arg	Arg	Phe	Val	Ala	Ser	Leu	Phe	Ile
	2480						2485					2490			
	Ser	Ala	Leu	Ala	Thr	Tyr	Thr	Tyr	Lys	Thr	Trp	Asn	Tyr	Asn	Asn
	2495						2500					2505			
10	Leu	Gln	Arg	Val	Val	Glu	Pro	Ala	Leu	Ala	Tyr	Leu	Pro	Tyr	Ala
	2510						2515					2520			
	Thr	Ser	Ala	Leu	Lys	Leu	Phe	Thr	Pro	Thr	Arg	Leu	Glu	Ser	Val
	2525						2530					2535			
15	Val	Ile	Leu	Ser	Ser	Thr	Ile	Tyr	Lys	Thr	Tyr	Leu	Ser	Ile	Arg
	2540						2545					2550			
	Lys	Gly	Lys	Ser	Asp	Gly	Leu	Leu	Gly	Thr	Gly	Ile	Ser	Ala	Ala
20	2555						2560					2565			
	Met	Glu	Ile	Leu	Asn	Gln	Asn	Pro	Ile	Ser	Val	Gly	Ile	Ser	Val
	2570						2575					2580			
25	Met	Leu	Gly	Val	Gly	Ala	Ile	Ala	Ala	His	Asn	Ala	Ile	Glu	Ser
	2585						2590					2595			
	Ser	Glu	Gln	Lys	Arg	Thr	Leu	Leu	Met	Lys	Val	Phe	Val	Lys	Asn
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Ala Ala Val Leu Leu Gln Leu Val Thr Gly Glu Asn Ile Thr Gln Trp
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					965					970					975	
	Asp	Gln	Ser	Ala	Met	Asp	Pro	Cys	Phe	Leu	Leu	Val	Thr	Gly	Val	Val
				980					985					990		
50	Ala	Val	Leu	Met	Ile	Ala	Arg	Arg	Glu	Pro	Ala	Thr	Leu	Pro	Leu	Ile
				995				1000					1005			
55	Val	Ala	Leu	Leu	Ala	Ile	Arg	Thr	Ser	Gly	Phe	Leu	Leu	Pro	Ala	
	1010						1015					1020				
	Ser	Ile	Asp	Val	Thr	Val	Ala	Val	Val	Leu	Ile	Val	Leu	Leu	Leu	

	1025		1030		1035														
	Ala	Ser	Tyr	Ile	Thr	Asp	Tyr	Phe	Arg	Tyr	Lys	Lys	Trp	Leu	Gln				
	1040						1045					1050							
5																			
	Leu	Leu	Phe	Ser	Leu	Ile	Ala	Gly	Ile	Phe	Ile	Ile	Arg	Ser	Leu				
	1055						1060					1065							
10	Lys	His	Ile	Asn	Gln	Met	Glu	Val	Pro	Glu	Ile	Ser	Met	Pro	Ser				
	1070						1075					1080							
	Trp	Arg	Pro	Leu	Ala	Leu	Val	Leu	Phe	Tyr	Ile	Thr	Ser	Thr	Ala				
	1085						1090					1095							
15	Ile	Thr	Thr	Asn	Trp	Asp	Ile	Asp	Leu	Ala	Gly	Phe	Leu	Leu	Gln				
	1100						1105					1110							
	Trp	Ala	Pro	Ala	Val	Ile	Met	Met	Ala	Thr	Met	Trp	Ala	Asp	Phe				
	1115						1120					1125							
20																			
	Leu	Thr	Leu	Ile	Ile	Val	Leu	Pro	Ser	Tyr	Glu	Leu	Ser	Lys	Leu				
	1130						1135					1140							
25	Tyr	Phe	Leu	Lys	Asn	Val	Arg	Thr	Asp	Val	Glu	Lys	Asn	Trp	Leu				
	1145						1150					1155							
	Gly	Lys	Val	Lys	Tyr	Arg	Gln	Ile	Ser	Ser	Val	Tyr	Asp	Ile	Cys				
	1160						1165					1170							
30	Asp	Ser	Glu	Glu	Ala	Val	Tyr	Leu	Phe	Pro	Ser	Arg	His	Lys	Ser				
	1175						1180					1185							
	Gly	Ser	Arg	Pro	Asp	Phe	Ile	Leu	Pro	Phe	Leu	Lys	Ala	Val	Leu				
	1190						1195					1200							
35																			
	Ile	Ser	Cys	Ile	Ser	Ser	Gln	Trp	Gln	Val	Val	Tyr	Ile	Ser	Tyr				
	1205						1210					1215							
40	Leu	Ile	Leu	Glu	Ile	Thr	Tyr	Tyr	Met	His	Arg	Lys	Ile	Ile	Asp				
	1220						1225					1230							
	Glu	Val	Ser	Gly	Gly	Ala	Asn	Phe	Leu	Ser	Arg	Leu	Ile	Ala	Ala				
	1235						1240					1245							
45	Ile	Ile	Glu	Leu	Asn	Trp	Ala	Ile	Asp	Asp	Glu	Glu	Cys	Lys	Gly				
	1250						1255					1260							
	Leu	Lys	Lys	Leu	Tyr	Leu	Leu	Ser	Gly	Arg	Ala	Lys	Asn	Leu	Ile				
	1265						1270					1275							
50																			
	Val	Lys	His	Lys	Val	Arg	Asn	Glu	Ala	Val	His	Arg	Trp	Phe	Gly				
	1280						1285					1290							
55	Glu	Glu	Glu	Ile	Tyr	Gly	Ala	Pro	Lys	Val	Ile	Thr	Ile	Ile	Lys				
	1295						1300					1305							
	Ala	Ser	Thr	Leu	Ser	Lys	Asn	Arg	His	Cys	Ile	Ile	Cys	Thr	Ile				

	1310		1315		1320
	Cys Glu Gly Lys Glu Trp Asn Gly Ala Asn Cys Pro Lys Cys Gly				
	1325		1330		1335
5	Arg Gln Gly Lys Pro Ile Thr Cys Gly Met Thr Leu Ala Asp Phe				
	1340		1345		1350
10	Glu Glu Lys His Tyr Lys Lys Ile Phe Ile Arg Glu Glu Ser Ser				
	1355		1360		1365
	Cys Pro Val Pro Phe Asp Pro Ser Cys His Cys Asn Tyr Phe Arg				
	1370		1375		1380
15	His Asp Gly Pro Phe Arg Lys Glu Tyr Lys Gly Tyr Val Gln Tyr				
	1385		1390		1395
	Thr Ala Arg Gly Gln Leu Phe Leu Arg Asn Leu Pro Ile Leu Ala				
	1400		1405		1410
20	Thr Lys Met Lys Leu Leu Met Val Gly Asn Leu Gly Ala Glu Ile				
	1415		1420		1425
	Gly Asp Leu Glu His Leu Gly Trp Val Leu Arg Gly Pro Ala Val				
25	1430		1435		1440
	Cys Lys Lys Ile Thr Asn His Glu Lys Cys His Val Asn Ile Met				
	1445		1450		1455
30	Asp Lys Leu Thr Ala Phe Phe Gly Ile Met Pro Arg Gly Thr Thr				
	1460		1465		1470
	Pro Arg Ala Pro Val Arg Phe Pro Thr Ala Leu Leu Lys Val Arg				
	1475		1480		1485
35	Arg Gly Leu Glu Thr Gly Trp Ala Tyr Thr His Gln Gly Gly Ile				
	1490		1495		1500
	Ser Ser Val Asp His Val Thr Ala Gly Lys Asp Leu Leu Val Cys				
40	1505		1510		1515
	Asp Ser Met Gly Arg Thr Arg Val Val Cys His Ser Asn Asn Lys				
	1520		1525		1530
45	Met Thr Asp Glu Thr Glu Tyr Gly Ile Lys Thr Asp Ser Gly Cys				
	1535		1540		1545
	Pro Glu Gly Ala Arg Cys Tyr Val Leu Asn Pro Glu Ala Val Asn				
	1550		1555		1560
50	Ile Ser Gly Thr Lys Gly Ala Met Val His Leu Gln Lys Thr Gly				
	1565		1570		1575
	Gly Glu Phe Thr Cys Val Thr Ala Ser Gly Thr Pro Ala Phe Phe				
55	1580		1585		1590
	Asp Leu Lys Asn Leu Lys Gly Trp Ser Gly Leu Pro Ile Phe Glu				

		1595					1600					1605				
5	Ala	Ser	Ser	Gly	Arg	Val	Val	Gly	Arg	Val	Lys	Val	Gly	Lys	Asn	
	1610						1615					1620				
	Glu	Asp	Ser	Lys	Pro	Thr	Lys	Leu	Met	Ser	Gly	Ile	Gln	Thr	Val	
	1625						1630					1635				
10	Ser	Lys	Asn	Gln	Thr	Asp	Leu	Ala	Asp	Ile	Val	Lys	Lys	Leu	Thr	
	1640						1645					1650				
	Ser	Met	Asn	Arg	Gly	Glu	Phe	Lys	Gln	Ile	Thr	Leu	Ala	Thr	Gly	
	1655						1660					1665				
15	Ala	Gly	Lys	Thr	Thr	Glu	Leu	Pro	Arg	Ser	Val	Ile	Glu	Glu	Ile	
	1670						1675					1680				
	Gly	Arg	His	Lys	Arg	Val	Leu	Val	Leu	Ile	Pro	Leu	Arg	Ala	Ala	
20	1685						1690					1695				
	Ala	Glu	Ser	Val	Tyr	Gln	Tyr	Met	Arg	Val	Lys	Tyr	Pro	Ser	Ile	
	1700						1705					1710				
25	Ser	Phe	Asn	Leu	Arg	Ile	Gly	Asp	Met	Lys	Glu	Gly	Asp	Met	Ala	
	1715						1720					1725				
	Thr	Gly	Ile	Thr	Tyr	Ala	Ser	Tyr	Gly	Tyr	Phe	Cys	Gln	Leu	Pro	
	1730						1735					1740				
30	Gln	Pro	Lys	Leu	Arg	Ala	Ala	Met	Val	Glu	Tyr	Ser	Tyr	Ile	Phe	
	1745						1750					1755				
	Leu	Asp	Glu	Tyr	His	Cys	Ala	Thr	Pro	Glu	Gln	Leu	Ala	Ile	Ile	
35	1760						1765					1770				
	Gly	Lys	Ile	His	Arg	Phe	Ala	Glu	Asn	Leu	Arg	Val	Val	Ala	Met	
	1775						1780					1785				
40	Thr	Ala	Thr	Pro	Ala	Gly	Thr	Val	Thr	Thr	Thr	Gly	Gln	Lys	His	
	1790						1795					1800				
	Pro	Ile	Glu	Glu	Phe	Ile	Ala	Pro	Glu	Val	Met	Lys	Gly	Glu	Asp	
	1805						1810					1815				
45	Leu	Gly	Ser	Glu	Tyr	Leu	Asp	Ile	Ala	Gly	Leu	Lys	Ile	Pro	Thr	
	1820						1825					1830				
	Glu	Glu	Met	Lys	Gly	Asn	Met	Leu	Val	Phe	Ala	Pro	Thr	Arg	Asn	
50	1835						1840					1845				
	Met	Ala	Val	Glu	Thr	Ala	Lys	Lys	Leu	Lys	Ala	Lys	Gly	Tyr	Asn	
	1850						1855					1860				
55	Ser	Gly	Tyr	Tyr	Tyr	Ser	Gly	Glu	Asn	Pro	Glu	Asn	Leu	Arg	Val	
	1865						1870					1875				
	Val	Thr	Ser	Gln	Ser	Pro	Tyr	Val	Val	Val	Ala	Thr	Asn	Ala	Ile	

	2165		2170		2175									
	Lys Asp Ser Glu Leu Lys Glu	2180	2185	Leu Ala Val Gly Asp	2190	Leu Asp Lys								
5	Tyr Val Asp Ala Leu Val Asp	2195	2200	Tyr Ser Lys Gln Gly	2205	Met Lys Phe								
	Ile Lys Val Gln Ala Glu Lys	2210	2215	Val Arg Asp Ser Gln	2220	Ser Thr Lys								
10	Glu Gly Leu Gln Thr Ile Lys	2225	2230	Glu Tyr Val Asp Lys	2235	Phe Ile Gln								
	Ser Leu Thr Glu Asn Lys Glu	2240	2245	Glu Ile Ile Arg Tyr	2250	Gly Leu Trp								
	Gly Val His Thr Ala Leu Tyr	2255	2260	Lys Ser Leu Ala Ala	2265	Arg Leu Gly								
20	His Glu Thr Ala Phe Ala Thr	2270	2275	Leu Val Val Lys Trp	2280	Leu Ala Phe								
	Gly Gly Glu Thr Val Ser Ala	2285	2290	His Ile Lys Gln Val	2295	Ala Val Asp								
25	Leu Val Val Tyr Tyr Ile Ile	2300	2305	Asn Lys Pro Ser Phe	2310	Pro Gly Asp								
	Thr Glu Thr Gln Gln Glu Gly	2315	2320	Arg Arg Phe Val Ala	2325	Ser Leu Phe								
	Ile Ser Ala Leu Ala Thr Tyr	2330	2335	Thr Tyr Lys Thr Trp	2340	Asn Tyr Asn								
35	Asn Leu Gln Arg Val Val Glu	2345	2350	Pro Ala Leu Ala Tyr	2355	Leu Pro Tyr								
	Ala Thr Ser Ala Leu Lys Leu	2360	2365	Phe Thr Pro Thr Arg	2370	Leu Glu Ser								
40	Val Val Ile Leu Ser Ser Thr	2375	2380	Ile Tyr Lys Thr Tyr	2385	Leu Ser Ile								
	Arg Lys Gly Lys Ser Asp Gly	2390	2395	Leu Leu Gly Thr Gly	2400	Ile Ser Ala								
	Ala Met Glu Ile Leu Asn Gln	2405	2410	Asn Pro Ile Ser Val	2415	Gly Ile Ser								
50	Val Met Leu Gly Val Gly Ala	2420	2425	Ile Ala Ala His Asn	2430	Ala Ile Glu								
	Ser Ser Glu Gln Lys Arg Thr	2435	2440	Leu Leu Met Lys Val	2445	Phe Val Lys								
55	Asn Phe Leu Asp Gln Ala Ala			Thr Asp Glu Leu Val		Lys Glu Asn								

		2735					2740					2745				
5	Val	His	Lys	Asn	Asn	Leu	Gln	Glu	Arg	Glu	Ile	Pro	Thr	Val	Thr	
	2750						2755					2760				
	Val	Thr	Thr	Trp	Leu	Ala	Tyr	Ser	Phe	Val	Asn	Glu	Asp	Leu	Gly	
	2765						2770					2775				
10	Thr	Ile	Lys	Pro	Val	Leu	Gly	Glu	Lys	Val	Ile	Pro	Glu	Pro	Pro	
	2780						2785					2790				
	Glu	Glu	Leu	Ser	Leu	Gln	Pro	Thr	Val	Arg	Leu	Val	Thr	Thr	Glu	
	2795						2800					2805				
15	Thr	Ala	Ile	Thr	Ile	Thr	Gly	Glu	Ala	Glu	Val	Met	Thr	Thr	Gly	
	2810						2815					2820				
	Ile	Thr	Pro	Val	Val	Glu	Met	Lys	Glu	Glu	Pro	Gln	Leu	Asp	His	
20	2825						2830					2835				
	Gln	Ser	Thr	Thr	Leu	Lys	Val	Gly	Leu	Lys	Glu	Gly	Glu	Tyr	Pro	
	2840						2845					2850				
25	Gly	Pro	Gly	Val	Asn	Pro	Asn	His	Leu	Ala	Glu	Val	Ile	Asp	Glu	
	2855						2860					2865				
	Lys	Asp	Asp	Arg	Pro	Phe	Val	Leu	Ile	Ile	Gly	Asn	Lys	Gly	Ser	
	2870						2875					2880				
30	Thr	Ser	Asn	Arg	Ala	Arg	Thr	Ala	Lys	Asn	Ile	Arg	Leu	Tyr	Lys	
	2885						2890					2895				
	Gly	Asn	Asn	Pro	Arg	Glu	Ile	Arg	Asp	Leu	Met	Ser	Gln	Gly	Arg	
35	2900						2905					2910				
	Ile	Leu	Thr	Val	Ala	Leu	Lys	Glu	Leu	Asp	Pro	Glu	Leu	Lys	Glu	
	2915						2920					2925				
40	Leu	Val	Asp	Tyr	Lys	Gly	Thr	Phe	Leu	Asn	Arg	Glu	Ala	Leu	Glu	
	2930						2935					2940				
	Ala	Leu	Ser	Leu	Gly	Lys	Pro	Ile	Lys	Arg	Lys	Thr	Thr	Thr	Ala	
	2945						2950					2955				
45	Met	Ile	Arg	Arg	Leu	Ile	Glu	Pro	Glu	Val	Glu	Glu	Glu	Leu	Pro	
	2960						2965					2970				
	Asp	Trp	Phe	Gln	Ala	Glu	Glu	Pro	Leu	Phe	Leu	Glu	Ala	Lys	Ile	
50	2975						2980					2985				
	Gln	Asn	Asp	Leu	Tyr	His	Leu	Ile	Gly	Ser	Val	Asp	Ser	Ile	Lys	
	2990						2995					3000				
55	Ser	Lys	Ala	Lys	Glu	Leu	Gly	Ala	Thr	Asp	Asn	Thr	Lys	Ile	Val	
	3005						3010					3015				
	Lys	Glu	Val	Gly	Ala	Arg	Thr	Tyr	Thr	Met	Lys	Leu	Ser	Ser	Trp	

	3020					3025					3030				
	Ser	Thr	Gln	Val	Thr	Lys	Lys	Gln	Met	Ser	Leu	Ala	Pro	Leu	Phe
	3035						3040					3045			
5															
	Glu	Glu	Leu	Leu	Leu	Lys	Cys	Pro	Pro	Cys	Ser	Lys	Ile	Ser	Lys
	3050						3055					3060			
10	Gly	His	Met	Val	Ser	Ala	Tyr	Gln	Leu	Ala	Gln	Gly	Asn	Trp	Glu
	3065						3070					3075			
	Pro	Leu	Gly	Cys	Gly	Val	Tyr	Met	Gly	Thr	Ile	Pro	Ala	Arg	Arg
	3080						3085					3090			
15															
	Leu	Lys	Ile	His	Pro	Tyr	Glu	Ala	Tyr	Leu	Lys	Leu	Lys	Glu	Leu
	3095						3100					3105			
	Val	Glu	Val	Glu	Ser	Ser	Arg	Ala	Thr	Ala	Lys	Glu	Ser	Ile	Ile
	3110						3115					3120			
20															
	Arg	Glu	His	Asn	Thr	Trp	Ile	Leu	Arg	Lys	Val	Arg	His	Glu	Gly
	3125						3130					3135			
25	Asn	Leu	Arg	Thr	Lys	Ser	Met	Ile	Asn	Pro	Gly	Lys	Ile	Ser	Asp
	3140						3145					3150			
	Gln	Leu	Cys	Arg	Asp	Gly	His	Lys	Arg	Asn	Ile	Tyr	Asn	Lys	Ile
	3155						3160					3165			
30															
	Ile	Gly	Ser	Thr	Met	Ala	Ser	Ala	Gly	Ile	Arg	Leu	Glu	Lys	Leu
	3170						3175					3180			
	Pro	Val	Val	Arg	Ala	Gln	Thr	Asp	Thr	Thr	Ser	Phe	His	Gln	Ala
	3185						3190					3195			
35															
	Ile	Arg	Glu	Lys	Ile	Asp	Lys	Thr	Glu	Asn	Lys	Gln	Thr	Pro	Glu
	3200						3205					3210			
40	Leu	His	Glu	Glu	Leu	Met	Lys	Val	Phe	Asp	Cys	Leu	Lys	Ile	Pro
	3215						3220					3225			
	Glu	Leu	Lys	Glu	Ser	Tyr	Asp	Glu	Val	Ser	Trp	Glu	Gln	Leu	Glu
	3230						3235					3240			
45															
	Ala	Gly	Ile	Asn	Arg	Lys	Gly	Ala	Ala	Gly	Tyr	Leu	Glu	Ser	Lys
	3245						3250					3255			
	Asn	Ile	Gly	Glu	Val	Leu	Asp	Thr	Glu	Lys	His	Ile	Val	Glu	Gln
	3260						3265					3270			
50															
	Leu	Ile	Lys	Asp	Leu	Arg	Lys	Gly	Lys	Lys	Ile	Arg	Tyr	Tyr	Glu
	3275						3280					3285			
55	Thr	Ala	Ile	Pro	Lys	Asn	Glu	Lys	Arg	Asp	Val	Ser	Asp	Asp	Trp
	3290						3295					3300			
	Glu	Ala	Gly	Glu	Phe	Val	Asp	Glu	Lys	Lys	Pro	Arg	Val	Ile	Gln

		3305					3310					3315							
		Tyr	Pro	Asp	Ala	Lys	Val	Arg	Leu	Ala	Ile	Thr	Lys	Val	Met	Tyr			
		3320						3325					3330						
5		Lys	Trp	Val	Lys	Gln	Lys	Pro	Val	Val	Ile	Pro	Gly	Tyr	Glu	Gly			
		3335						3340					3345						
		Lys	Thr	Pro	Leu	Phe	Asp	Ile	Phe	Asn	Lys	Val	Lys	Lys	Glu	Trp			
10		3350						3355					3360						
		Asp	Ser	Phe	Gln	Asp	Pro	Val	Ala	Val	Ser	Phe	Asp	Thr	Lys	Ala			
		3365						3370					3375						
15		Trp	Asp	Thr	Gln	Val	Thr	Ser	Arg	Asp	Leu	Met	Leu	Ile	Lys	Asp			
		3380						3385					3390						
		Ile	Gln	Lys	Tyr	Tyr	Phe	Lys	Arg	Ser	Ile	His	Lys	Phe	Leu	Asp			
20		3395						3400					3405						
		Thr	Ile	Thr	Glu	His	Met	Val	Glu	Val	Pro	Val	Ile	Thr	Ala	Asp			
		3410						3415					3420						
		Gly	Glu	Val	Tyr	Ile	Arg	Asn	Gly	Gln	Arg	Gly	Ser	Gly	Gln	Pro			
25		3425						3430					3435						
		Asp	Thr	Ser	Ala	Gly	Asn	Ser	Met	Leu	Asn	Val	Leu	Thr	Met	Ile			
		3440						3445					3450						
30		Tyr	Ala	Phe	Cys	Lys	Ser	Thr	Gly	Ile	Pro	Tyr	Arg	Gly	Phe	Ser			
		3455						3460					3465						
		Arg	Val	Ala	Arg	Ile	His	Val	Cys	Gly	Asp	Asp	Gly	Phe	Leu	Ile			
35		3470						3475					3480						
		Thr	Glu	Arg	Gly	Leu	Gly	Leu	Lys	Phe	Ser	Glu	Lys	Gly	Met	Gln			
		3485						3490					3495						
		Ile	Leu	His	Glu	Ala	Gly	Lys	Pro	Gln	Lys	Ile	Thr	Glu	Gly	Asp			
40		3500						3505					3510						
		Lys	Met	Lys	Val	Ala	Tyr	Arg	Phe	Glu	Asp	Ile	Glu	Phe	Cys	Ser			
		3515						3520					3525						
45		His	Thr	Pro	Val	Pro	Val	Arg	Trp	Ala	Asp	Asn	Thr	Ser	Ser	Tyr			
		3530						3535					3540						
		Met	Ala	Gly	Arg	Ser	Thr	Ala	Thr	Ile	Leu	Ala	Lys	Met	Ala	Thr			
50		3545						3550					3555						
		Arg	Leu	Asp	Ser	Ser	Gly	Glu	Arg	Gly	Ser	Thr	Ala	Tyr	Glu	Lys			
		3560						3565					3570						
		Ala	Val	Ala	Phe	Ser	Phe	Leu	Leu	Met	Tyr	Ser	Trp	Asn	Pro	Val			
55		3575						3580					3585						
		Val	Arg	Arg	Ile	Cys	Leu	Leu	Val	Leu	Ser	Gln	Phe	Pro	Glu	Ile			

	3590		3595		3600
	Ser Pro Ser Lys Asn Thr Ile Tyr Tyr Tyr Gln Gly Asp Pro Ile				
	3605		3610		3615
5	Ala Ala Tyr Arg Glu Val Ile Gly Lys Gln Leu Cys Glu Leu Lys				
	3620		3625		3630
	Arg Thr Gly Phe Glu Lys Leu Ala Gly Leu Asn Leu Ser Met Thr				
10	3635		3640		3645
	Thr Leu Gly Ile Trp Thr Lys His Thr Ser Lys Arg Leu Ile Gln				
	3650		3655		3660
15	Ala Cys Val Glu Ile Gly Lys Arg Glu Gly Thr Trp Leu Val Asn				
	3665		3670		3675
	Ala Asp Arg Leu Ile Ala Gly Lys Thr Gly Lys Phe Tyr Ile Pro				
20	3680		3685		3690
	Ser Thr Gly Val Thr Leu Leu Gly Lys His Tyr Glu Glu Ile Asn				
	3695		3700		3705
	Leu Lys Gln Lys Ala Ala Gln Pro Pro Ile Glu Gly Val Asp Arg				
25	3710		3715		3720
	Tyr Lys Leu Gly Pro Ile Val Asn Val Ile Leu Arg Arg Leu Arg				
	3725		3730		3735
30	Val Met Leu Met Thr Val Ala Ser Gly Ser Trp				
	3740		3745		

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