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(54) Titre : LUTTE BIOLOGIQUE CONTRE DES VIRUS DE PLANTES
(54) Title: BIOLOGICAL CONTROL OF PLANT VIRUSES

(57) **Abrégé/Abstract:**

The present disclosure provides new attenuated Pepino mosaic viruses useful in the control of plant disease. Compositions for biological control of plant disease are also provided as well as methods for producing Pepino mosaic virus resistant plants.

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- (57) Abstract: The present disclosure provides new attenuated Pepino mosaic viruses useful in the control of plant disease. Compos-
itions for biological control of plant disease are also provided as well as methods for producing Pepino mosaic virus resistant plants.

Title: Biological control of plant viruses

FIELD OF THE INVENTION

5 The present disclosure provides new attenuated Pepino mosaic viruses useful in the control of plant disease. Compositions for biological control of plant disease are also provided as well as methods for the induction of cross-protection and increased resistance against Pepino mosaic virus in plants.

BACKGROUND OF THE INVENTION

10 The present invention concerns the field of biological control in agriculture and horticulture, in particular, the control of plant pathogens.

Tomato is susceptible to various viral diseases, and one of the causal agents, *Pepino mosaic virus* (PepMV), has recently become a major limiting factor with regard to tomato production. PepMV belongs to the Potexvirus genus of the Alphaflexiviridae family. PepMV has rapidly spread
15 throughout commercial tomato cropping and is currently found throughout Europe and North-America (Jorda *et al.*, 2001; Cotillon *et al.*, 2002; Verhoeven *et al.*, 2003; Ling *et al.*, 2008). The RNA genome of PepMV encompasses approximately 6.4 kb and contains five open reading frames that encode a RNA-dependent polymerase (RdRp), a triple gene block (TGB), a coat protein (CP), and two short untranslated sequences flanking the coding regions (Aguilar *et al.*, 2002; Cotillon *et al.*, 2002). Isolates of PepMV group into four separate strains (genotypes) based on sequence
20 similarity, namely the Peruvian (LP)-strain to which the original PepMV isolate belongs, the European (EU)-strain that was found in Europe in 1999 (Van der Vlugt *et al.*, 2000), the CH2-strain that was discovered in infected tomato seeds in Chile, and the US1-strain that was discovered in diseased tomato plants in the USA (Ling, 2007). Symptom severity varies between different
25 isolates of PepMV (Van der Vlugt *et al.*, 2000) and differences in severity do not necessarily coincide with differences in genotype (Hanssen *et al.*, 2008).

PepMV induces a wide range of symptoms on tomato (Van der Vlugt *et al.*, 2000; Jorda *et al.*, 2001), such as mosaic, leaf distortion, nettle-like heads, single yellow spots, interveinal chlorosis and fruit discoloration. Tomato plants display symptoms shortly after infection with PepMV and, in
30 general, subsequently recover (Van der Vlugt & Stijger, 2008). Symptoms may, however, return later during the growing season. Expression of symptoms may also depend on environmental conditions, such as temperature and light intensity (Jorda *et al.*, 2001; Van der Vlugt & Stijger, 2008). PepMV is sometimes suggested to cause yield losses in tomato, but the highest economic losses are attributed to symptoms that affect the commercial value of tomato fruits, such as

flaming, marbling, blotchy ripening and fruit size reduction (Soler *et al.*, 2000; Spence *et al.*, 2006).

PepMV is transmitted efficiently by contaminated hands, clothing or tools (Van der Vlugt & Stijger, 2008). Direct contact between healthy and infected plants during routine crop handling also suffices to spread PepMV infection. The incidence of PepMV on tomato is very high in some tomato cultivation areas, where the virus may affect up to 90% of the greenhouses (Soler-Aleixandre *et al.*, 2005). To stay free of virus is challenging under such circumstances.

There exists a need in the art to protect plants from PepMV infection and to prevent or reduce plant diseases associated with PepMV infection.

SUMMARY OF THE INVENTION

In one aspect, the disclosure provides an attenuated Pepino mosaic virus comprising a nucleic acid molecule comprising a nucleic acid sequence, wherein the nucleotide at the position corresponding to 2605 of SEQ ID NO:1 is G, the nucleotide at the position corresponding to 3156 of SEQ ID NO:1 is T, and/or the nucleotide at the position corresponding to 3422 SEQ ID NO: 1 is G. Preferably, the nucleic acid sequence is at least 80% identical to SEQ ID NO: 1.

In one aspect, the disclosure provides an attenuated Pepino mosaic virus comprising a nucleic acid molecule comprising a nucleic acid sequence encoding arginine at the position according to 868 of SEQ ID NO:2 and/or encodes phenylalanine at the position according to 1052 of SEQ ID NO:2. Preferably, the nucleic acid sequence is at least 80% identical to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO: 7. More preferably, the nucleic acid sequence is at least 80% identical to SEQ ID NO: 1.

In one aspect, the disclosure provides an isolated nucleic acid molecule comprising a nucleic acid sequence having at least 95% identity to a nucleic acid sequence selected from SEQ ID NO:1, SEQ ID NO: 3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO: 7, wherein the nucleic acid sequence encodes arginine at the position according to 868 of SEQ ID NO:2 and/or encodes phenylalanine at the position according to 1052 of SEQ ID NO:2. In preferred embodiments, the isolated nucleic acid molecule encodes an amino acid sequence having at least 95% identity to any one of the amino acid sequences depicted in Figure 6, wherein the nucleic acid sequence encodes arginine at position 887 of Figure 6 and/or the nucleic acid sequence encodes phenylalanine at position 1071 of Figure 6.

- In one aspect, the disclosure provides an RNA-dependent RNA polymerase wherein the polymerase has an arginine at the position according to 868 of SEQ ID NO:2, a phenylalanine at the position according to 1052 of SEQ ID NO:2, a phenylalanine at the position corresponding to 956 of SEQ ID NO:2, and/or an asparagine at the position corresponding to 1325 of SEQ ID NO:2.
- 5 Preferably said polymerase has an arginine at the position according to 868 of SEQ ID NO:2 and a phenylalanine at the position according to 1052 of SEQ ID NO:2. Preferably said polymerase has a phenylalanine at the position corresponding to 956 of SEQ ID NO:2 and an asparagine at the position corresponding to 1325 of SEQ ID NO:2. Preferably said polymerase has an arginine at the position according to 868 of SEQ ID NO:2 and a phenylalanine at the position corresponding to
- 10 956 of SEQ ID NO:2. In some embodiments the RNA-dependent RNA polymerases has at least 50%, at least 70%, at least 80%, or at least 90% identity to any one of the amino acid sequences depicted in Figure 6. The invention also provides a nucleic acid molecule encoding a polymerase as indicated in this paragraph.
- 15 In one aspect, the disclosure provides an attenuated Pepino mosaic virus comprising a nucleic acid molecule comprising a nucleic acid sequence, wherein the nucleotide at the position corresponding to 2675 of SEQ ID NO:8 is G, the nucleotide at the position corresponding to 3226 of SEQ ID NO:8 is T, and/or the nucleotide at the position corresponding to 3492 SEQ ID NO: 8 is G. Preferably, the nucleic acid sequence is at least 80% identical to SEQ ID NO: 8.
- 20 In one aspect, the disclosure provides an attenuated Pepino mosaic virus comprising a nucleic acid molecule comprising a nucleic acid sequence encoding arginine at the position according to 886 of SEQ ID NO:9 and/or encodes phenylalanine at the position according to 1070 of SEQ ID NO:9. Preferably, the nucleic acid sequence is at least 80% identical to SEQ ID NO: 1, SEQ ID NO: 3,
- 25 SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO: 7. More preferably, the nucleic acid sequence has at least 95%, at least 99%, or 100% identity to. SEQ ID NO: 8.
- In one aspect, the disclosure provides an RNA-dependent RNA polymerase having at least 50%, at least 70%, at least 80%, least 90%, at least 99% or at least 100% identity to SEQ ID NO:9,
- 30 wherein the polymerase has an arginine at the position according to 886 of SEQ ID NO:9 and/or a phenylalanine at the position according to 1070 of SEQ ID NO:9. Preferably said polymerase has an arginine at the position according to 886 of SEQ ID NO: 9 and a phenylalanine at the position according to 1070 of SEQ ID NO:9. Preferably said polymerase has a phenylalanine at the position corresponding to 974 of SEQ ID NO:2 and an asparagine at the position corresponding to 1343 of
- 35 SEQ ID NO:2. Preferably said polymerase has an arginine at the position according to 886 of SEQ

ID NO:2 and a phenylalanine at the position corresponding to 974 of SEQ ID NO:2. The invention also provides a nucleic acid molecule encoding a polymerase as indicated in this paragraph.

5 In one aspect the disclosure provides a vector, preferably an expression vector, comprising a nucleic acid molecule as disclosed herein. In one aspect the disclosure provides an isolated polypeptide encoded by a nucleic acid molecule disclosed herein. In one aspect the disclosure provides an antibody specific for the polypeptide encoded by a nucleic acid molecule as disclosed herein.

10 In one aspect the disclosure provides a composition for biological control of plant disease comprising an attenuated Pepino mosaic virus as disclosed herein, a nucleic acid molecule as disclosed herein or a vector as disclosed herein; and an agriculturally acceptable carrier.

15 In one aspect the disclosure provides a method for identifying a pepino mosaic virus (PepMV)-resistant plant, comprising

- a) exposing a plant or plant part to an attenuated Pepino mosaic virus as disclosed herein, a nucleic acid molecule as disclosed herein, a vector as disclosed herein, or the compositions as disclosed herein;
- b) exposing the plant or plant part to an infective dosage of PepMV, and
- 20 c) identifying said plant as PepMV-resistant plant when, after said exposure, disease-symptoms in said plant or plant part are reduced or delayed and/or PepMV accumulation in said plant or plant parts is reduced or delayed in comparison to a control PepMV infected plant.

25 In one aspect the disclosure provides a method for the detection of a pepino mosaic virus (PepMV) comprising providing a sample suspected of containing PepMV and detecting a PepMV virus as disclosed herein, a nucleic acid molecule as disclosed herein or a vector as disclosed herein. The method is useful among others to determine whether an application of the attenuated virus to a plant has been successful. The method is also useful to determine the extent of infection of a particular patch of crop. Particularly with a PepMV as disclosed herein. The sample is typically

30 prepared from a plant or a part thereof that is susceptible to PepMV infection and/or replication. A sample is suspected of containing PepMV when there is reason to believe that the PepMV is present in the sample. A sample is also suspected of containing PepMV when the sample is from plant of which it needs to be verified that it does or does not contain a PepMV of the invention. Such a sample can be for instance from a plant in a greenhouse in the situation when in a nearby

35 greenhouse a PepMV infection has been reported. It can also be from a plant with one or more

symptoms that point towards a PepMV infection and one wants to confirm this. The invention also provides method for the detection of PepMV as described herein wherein the term “sample suspected of containing PepMV” is replaced by the term “sample of a plant susceptible to PepMV infection”.

5

In one aspect the disclosure provides a method for producing a pepino mosaic virus (PepMV)-resistant plant, comprising exposing a plant or plant part to an attenuated Pepino mosaic virus as disclosed herein, a nucleic acid molecule as disclosed herein, a vector as disclosed herein, or the compositions as disclosed
10 herein.

In one aspect the disclosure provides a PepMV-resistant plant comprising an attenuated Pepino mosaic virus as disclosed herein or a nucleic acid molecule as disclosed herein.

15 In one aspect the disclosure provides a method for controlling infection or disease in a plant comprising applying an effective amount of an attenuated Pepino mosaic virus as disclosed herein, a nucleic acid molecule as disclosed herein, a vector as disclosed herein, or the compositions as disclosed herein to said plant.

20 In one aspect the disclosure provides an attenuated Pepino mosaic virus as disclosed herein, a nucleic acid molecule as disclosed herein, a vector as disclosed herein, or the compositions as disclosed herein for use in controlling infection or disease in a plant. In particular, the use is for inducing resistance to PepMV.

25 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Inoculation of tomato plants with CHD alone resulted in strong necrosis of the leaves and stems, from 3 weeks after inoculation of CHD (Fig 1A). Inoculation of tomato plants with VCA, followed by CHD, protected plants from necrosis (Fig 1B).

Figure 2. Thirty-nine days after inoculation of tomato plants with VC1 (Fig 2A) or VCA (Fig 2B).

30 **Figure 3.** Development of mild symptoms in infected plants; no treatment (Fig. 3A); VCA treatment (Fig. 3B); VC1 treatment (Fig. 3C).

Figure 4. Comparison of symptoms in plants grown under optimal conditions (top row) versus sub-optimal conditions (bottom row); no treatment (Fig. 4A); VC1 treatment (Fig. 4B); VCA treatment (Fig. 4C).

Figure 5. An alignment of the sequence of VCA with closely related sequences identified from BLAST (Basic local alignment search tool) from NCBI. The sequence with the highest identity in the BLAST search was “1906”, having 99.6% identity. The nomenclature listed in Figure 5 corresponds to the annotations of NCBI as follows: 1906: Pepino mosaic virus isolate 1906 replicase, triple gene block protein 1 (TGBp1), triple geneblock protein 2 (TGBp2), triple gene block protein 3 (TGBp3), and coat protein genes,complete cds.
 DQ000985: Pepino mosaic virus isolate Ch2, complete genome.
 FJ212288: Pepino mosaic virus, complete genome.
 Pa: Pepino mosaic virus isolate PepMV-Pa,complete genome.
 10 PK: Pepino mosaic virus isolate PepMV-PK, complete genome.
 220606A1: Pepino mosaic virus isolate 220606A1.
 VFBC12-04: Pepino mosaic virus isolate VFBC12-04.
 VFBC12-08: Pepino mosaic virus isolate VFBC12-08.
 P5: Pepino mosaic virus isolate PepMV-P5, complete genome.
 15 PCH06/104: Pepino mosaic virus isolate PCH 06/104 replicase, triple gene block protein 1 (TGBp1), triple gene block protein 2 (TGBp2), triple gene block protein 3 (TGBp3), and coat protein genes, complete cds

Figure 6. An alignment of the amino acid sequence of RNA-dependent RNA polymerase from VCA and other PepMV viruses.
 20 LE-2002, AJ438767, and Sp-13 are EU isolates. LP-2001 is an LP isolate. US1 is a US isolate.

Figure 7. Sequence listing

Figure 8. Sequence listing

DETAILED DESCRIPTION OF THE DISCLOSED EMBODIMENTS

25 Cross-protection is the phenomenon of protecting crops against virulent isolates of viruses by pre-treatment with closely related attenuated isolates of the virus. In the 1970s, it was first applied successfully against infection of tomato with *Tobacco mosaic virus* in several countries (Burguán & Gáborjányi, 1984). Attenuated isolates may be selected among naturally occurring or be developed by the introduction of mutations into such isolates, for example using random
 30 mutagenesis. A strategy in which attenuated isolates are applied to plants relies on the identification of an isolate that has as little impact on total yield and fruit quality as possible, and effectively protects against more virulent isolates at the same time.

While not wishing to be bound by theory, cross-protection may be due to RNA silencing activity
 35 induced by the protective isolate (Ratcliff *et al.*, 1999; Valkonen *et al.*, 2002). The role of post-

transcriptional gene silencing (PTGS) in cross-protection was demonstrated by the observation that two viral constructs derived from different viruses, but sharing a common sequence, could suppress each other when co-inoculated in plants (Ratcliff *et al.*, 1999). PTGS is an antiviral defence mechanism in plants, which targets double stranded RNA (dsRNA) for degradation in a sequence-specific manner. In cross-protection, it is thought that the mild strain ‘primes’ the defense system of the plant so that it operates against subsequent infection by severe strains.

In the study of Schenk *et al.* (2010), attenuated isolates of PepMV were tested (EU-Att1 and PE-Att1). The attenuated isolates effectively reduced the effects of isolates of PepMV with aggressive symptoms (namely, EU-Ch11 and EU-Nec1). Total virus accumulation, symptom severity and yield losses were significantly reduced in cross-protected plants compared to the single infections by the aggressive isolates. The yields of the cross-protected plants were on a similar level as those of uninfected plants. Although plants cross-protected by the attenuated isolates reduced symptoms, infection by the attenuated isolates alone also produced symptoms (Table 2 of Schenk *et al.*) The attenuated isolates caused symptoms shortly after inoculation, a pattern which has also been observed in other trials (Spence *et al.*, 2006). Overall, the symptom severity correlated to virus accumulation, but accumulation alone did not explain all differences in symptom severity. In turn, symptom severity was negatively correlated to yield. The two symptoms that had the largest effect on yield i.e. leaf deformation and leaf necrosis, affected the leaf area of the plants, which would explain the observed yield losses. One aspect of the present invention is the provision of an attenuated virus that cross-protects plants from further PepMV infection while causing minimal symptoms from exposure to the attenuated virus alone.

Accordingly, one aspect of the disclosure provides Pepino mosaic viruses, in particular attenuated viruses. As is known to a skilled person, an attenuated virus is a virus that has been modified from a wild-type pathogenic virus. An attenuated virus has reduced pathogenicity as compared to the wild-type virus. In addition, an attenuated virus disclosed herein can be used to cross-protect plants against infection from virulent PepMV isolates.

The disclosure identifies several nucleotide positions in PepMV which play a role in the symptoms induced by PepMV infection. Specifically, the disclosure provides PepMV viruses and nucleic acid molecules, wherein the nucleic acid sequence encodes arginine at the position corresponding to 868 of SEQ ID NO:2 (corresponding to position 886 of SEQ ID NO:9) and/or encodes phenylalanine at the position corresponding to 1052 of SEQ ID NO:2 (corresponding to position 1070 of SEQ ID NO:9).

The disclosure provides that the nucleotides at positions 2605 and 3156 of SEQ ID NO: 1 (corresponding to positions 2675 and 3226 of SEQ ID NO: 8), and consequently the amino acids encoded (in part) by these nucleotides, play a role in the pathogenic symptoms. Specifically, an amino acid change from lysine to arginine at position 868 of SEQ ID NO:2 (corresponding to position 886 of SEQ ID NO:9) and an amino acid change from leucine to phenylalanine at position 1052 of SEQ ID NO: 2 (corresponding to position 1070 of SEQ ID NO:9) results in a PepMV attenuated virus. In the pathogenic viruses depicted in Figure 6, as well as the attenuated VC1 virus, the amino acids corresponding to 868 and 1052 of SEQ ID NO:2 (and 886 and 1070 of SEQ ID NO:9) are lysine and leucine, respectively. While not wishing to be bound by theory, these amino acid changes are believed to provide attenuated viruses which demonstrate milder symptoms than the VC1 virus (see Examples).

The disclosure also provides that additional nucleotides- and the amino acids which they encode- also play a role in pathogenic symptoms. Accordingly, in some embodiments the viruses and nucleic acid molecules disclosed herein contain one or more of the following: a C at the nucleotide position corresponding to 191 of SEQ ID NO: 1 (position 261 of SEQ ID NO: 8); a C at the nucleotide position corresponding to 2354 of SEQ ID NO: (position 2424 of SEQ ID NO: 8); a T at the nucleotide position corresponding to 2768 of SEQ ID NO: 1 (position 2838 of SEQ ID NO: 8); a T at position corresponding to 2868 of SEQ ID NO:1 (position 2938 of SEQ ID NO: 8); a G at the nucleotide position corresponding to 3422 of SEQ ID NO: 1 (position 3492 of SEQ ID NO: 8); and/or have an A at the nucleotide position corresponding to 3975 of SEQ ID NO: 1 (position 4045 of SEQ ID NO: 8). In some embodiments the viruses or nucleic acid molecules disclosed herein contain at least two, at least three, at least four, at least five, or all 6 of the nucleotides listed above. These six nucleotides are unique to both the VCA attenuated virus and the VC1 attenuated virus as compared to the virulent CH2 strains depicted in Figure 5. Preferably, the viruses and nucleic acid molecules disclosed herein, in addition to encoding arginine at the position corresponding to 868 of SEQ ID NO:2 (and corresponding to position 886 of SEQ ID NO:9) and/or phenylalanine at the position corresponding to 1052 of SEQ ID NO:2 (and corresponding to position 1070 of SEQ ID NO:9), also encode a phenylalanine at the position corresponding to 956 of SEQ ID NO:2 (and corresponding to position 974 of SEQ ID NO:9) and/or an asparagine at the position corresponding to 1325 of SEQ ID NO:2 (and corresponding to position 1343 of SEQ ID NO:9). As depicted in Figure 6, the wild-type pathogenic viruses encode a leucine and an aspartic acid at these positions. While not wishing to be bound by theory, these amino acids are believed to play a role in reducing the virulence of the viruses.

SEQ ID NO: 1 (herein referred to as the 'VCA' virus) was isolated as an attenuated virus of the CH2 strain. The Examples demonstrate the ability of the VCA virus to cross-protect against wild-type PepMV strains and the reduction of symptoms as compared to another attenuated virus VC1. SEQ ID NO: 1 depicts a partial sequence of the RNA-dependent RNA-polymerase of the VCA virus. SEQ ID NO: 8 depicts the nucleotide sequence of the RNA-dependent RNA-polymerase of the VCA virus, including the complete coding sequence.

See Figures 7 and 8 for the sequence listing. As known to a skilled person, Y indicates a C or T, R indicates A or G; and S indicates G or C. In some embodiments, R is G. In some embodiments, Y1 is C. In some embodiments, Y2 is C. In some embodiments, Y3 is T. In some embodiments, Y4 is T. In some embodiments, S is C. In some embodiments, Y5 is T.. In some embodiments, Y6 is T. Viruses having the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:8 include a single homogenous virus (i.e., having one sequence; for example SEQ ID NO:1 or SEQ ID NO:8 wherein R is G; Y1 is C; Y2 is C; Y3 is T; Y4 is T; S is C; Y5 is T; Y6 is T) as well as mixtures of viruses each having SEQ ID NO:1 or SEQ ID NO:8.

The VCA virus was found to have nucleotide substitutions resulting in amino acid changes in the RNA-dependent RNA polymerase gene of the virus. SEQ ID NO:2 depicts the partial amino acid sequence of the RNA-dependent RNA polymerase from VCA. SEQ ID NO:9 depicts the complete amino acid sequence of the RNA-dependent RNA polymerase from VCA

VCA (SEQ ID NO:1/SEQ ID NO:8) is an exemplary attenuated virus of the CH2 strain. The disclosure also provides attenuated viruses from other PepMV strains. Four amino acids in SEQ ID NO:2 were found to be unique when compared to wild-type EU, LP, CH2, and US1 isolates. Arginine at position 868 of SEQ ID NO:2 (886 of SEQ ID NO:9) corresponds to position 887 in the alignment shown in figure 6. Phenylalanine at position 956 of SEQ ID NO:2 (974 of SEQ ID NO:9) corresponds to position 975 in the alignment shown in figure 6. Phenylalanine at position 1052 of SEQ ID NO:2 (1070 of SEQ ID NO:9) corresponds to position 1071 in the alignment shown in figure 6. Asparagine at position 1325 of SEQ ID NO:2 (1343 of SEQ ID NO:9) corresponds to position 1344 in the alignment shown in figure 6. It is clear to a skilled person that attenuated viruses from any PepMV isolate can be prepared based on these amino acids.

In some embodiments, the virus is an attenuated virus of a EU strain. Exemplary wild-type EU viral sequences are depicted in SEQ ID Nos:3-5. In some embodiments, the virus is an attenuated virus of a US1 strain. An exemplary wild-type US1 viral sequence is depicted in SEQ ID NO:6. In

some embodiments, the virus is an attenuated virus of an LP strain. An exemplary wild-type LP viral sequence is depicted in SEQ ID NO:7.

PepMV viruses have, on the average, around 80% nucleic acid sequence identity. Accordingly, in preferred embodiments the PepMV viruses have a nucleic acid sequence at least 80% identical to SEQ ID NO:1, wherein the nucleic acid sequence encodes arginine at the position corresponding to 868 of SEQ ID NO:2 and/or encodes phenylalanine at the position corresponding to 1052 of SEQ ID NO:2 (or rather, encodes arginine at position 887 of Figure 6 and/or the nucleic acid sequence encodes phenylalanine at position 1071 of Figure 6). In preferred embodiments, the PepMV viruses have a nucleic acid sequence at least 80% identical to SEQ ID NO:8, wherein the nucleic acid sequence encodes arginine at the position corresponding to 886 of SEQ ID NO:9 and/or encodes phenylalanine at the position corresponding to 1070 of SEQ ID NO:9. In a preferred embodiment, the attenuated viruses disclosed herein have a nucleic acid sequence at least 80%, at least 90%, preferably at least 95%, more preferably at least 98%, and most preferably at least 99% identical to SEQ ID NO:1, SEQ ID NO:8, SEQ ID NO: 3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO: 7. The sequences provided herein refer to the bases A, T, C, and G. However, it is clear to a skilled person that when referring to a PepMV virus (an RNA virus), uracil is present instead of thymine.

The disclosure also provides an isolated nucleic acid molecule comprising a nucleic acid sequence at least 80%, at least 90%, preferably at least 95%, more preferably at least 98%, and most preferably at least 99% identical to SEQ ID NO:1, SEQ ID NO:8, SEQ ID NO: 3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO: 7, wherein the nucleic acid sequence encodes arginine at the position corresponding to 868 of SEQ ID NO:2 and/or encodes phenylalanine at the position corresponding to 1052 of SEQ ID NO:2 (or rather, encodes arginine at position 887 of Figure 6 and/or the nucleic acid sequence encodes phenylalanine at position 1071 of Figure 6; or rather encodes arginine at position 886 of SEQ ID NO:9 and/or the nucleic acid sequence encodes phenylalanine at position 1070 of SEQ ID NO:9).

In some embodiments, the nucleotide at the position corresponding to 2605 of SEQ ID NO:1 (2675 of SEQ ID NO:8) is G; the nucleotide at the position corresponding to 3156 of SEQ ID NO: 1 (3226 of SEQ ID NO:8) is T and/or the nucleotide at the position corresponding to 3422 SEQ ID NO: 1 (3492 of SEQ ID NO:8) is G. In preferred embodiments, the nucleotide at the position corresponding to 2605 of SEQ ID NO:1 (2675of SEQ ID NO:8) is G and/or the nucleotide at the position corresponding to 3156 of SEQ ID NO: 1 (3226 of SEQ ID NO:8) is T. In preferred embodiments, the nucleic acid molecules comprise one or more of the following: a C at the

nucleotide position corresponding to 191 of SEQ ID NO: 1 (position 261 of SEQ ID NO: 8); a C at the nucleotide position corresponding to 2354 of SEQ ID NO: 1 (position 2424 of SEQ ID NO: 8); a T at the nucleotide position corresponding to 2768 of SEQ ID NO: 1 (position 2838 of SEQ ID NO: 8); a T at position corresponding to 2868 of SEQ ID NO: 1 (position 2938 of SEQ ID NO: 8);
5 and/or have an A at the nucleotide position corresponding to 3975 of SEQ ID NO: 1 (position 4045 of SEQ ID NO: 8). Such nucleic acid molecules are useful, for example, for producing the viruses disclosed herein.

As used herein, the term "isolated" refers to a protein, peptide or nucleic acid molecule which is
10 substantially separated from other (sub)cellular components. The term includes a nucleic acid molecule or protein which has been removed from its naturally occurring environment, as well as recombinant or cloned DNA isolates and chemically synthesized analogues or analogues biologically synthesized by heterologous systems.

15 A further aspect of the disclosure provides vectors and expression vectors comprising the nucleic acid molecules and viruses disclosed herein. Expression vectors useful in the present disclosure include vaccinia virus, retroviruses, and baculovirus. The expression vector may comprise the nucleic acid sequences disclosed herein or a fragment thereof that is under control of or operatively linked to a regulatory element, such as a promoter. The segment of DNA referred to as the
20 promoter is responsible for the regulation of the transcription of DNA into mRNA. The expression vector may comprise one or more promoters suitable for the expression of the gene in, e.g., plant cells, fungal cells, bacterial cells, yeast cells, insect cells or other eukaryotic cells.

The viruses and nucleic acid molecules disclosed herein can be made by any method known to one
25 of skill in the art. Methods of generating full length cDNA clones of the RNA genome of PepMV have been described, see, e.g., Hasiow-Jaroszewsk et al. Arch Virol (2009) 154:853-856. In addition, the cloning of both EU and CH2 PepMV clones has also been described in Duff-Farrier et al., Molecular Plant Pathology (2015) 16:308-315. Duff-Farrier et al. describes the construction of cDNA from PepMV EU and CH2 isolates and well as the introduction of chimeric sequences into
30 the cDNA. Infectious RNA was synthesized in vitro, which was used to infect plants. Similar methods can be used to generate the viruses and nucleic acid molecules with sequences described herein.

The viruses and nucleic acid molecules disclosed herein are useful for producing plants with
35 increased resistance to PepMV, in particular to disease causing strains of PepMV such as the

Peruvian (LP) strain, the European (EU) strain, the CH2 strain, first identified in Chile, and the US1 strain, identified in the United States. Accordingly, the disclosure provides attenuated viruses and nucleic acid molecules for controlling PepMV infection and/or PepMV disease in a plant. As used herein, controlling PepMV infection includes the reduction, prevention, or delay of PepMV accumulation in a plant. As used herein, controlling PepMV disease includes the reduction, prevention, or delay of PepMV symptoms.

The nucleic acid molecules disclosed herein, the polypeptides encoded by said nucleic acid molecules, as well as antibodies recognizing said polypeptides are all useful for, e.g., detecting infection by the attenuated virus and thereby detecting plants with increased resistance to PepMV.

The viruses and nucleic acid molecules disclosed herein may be provided in compositions comprising an agriculturally acceptable carrier. Such compositions can be used for the biological control of plant disease. Preferably, the composition comprises an anti-oxidant, a phosphate buffer and/or a sulphite (sulphite can help prevent rotting). Preferably, the compositions have a pH range of 6-8.5, more preferably a pH of 7.7 ± 0.5 . Preferably the compositions comprise one or more of the following: mono-basic potassium phosphate, di-basic sodium phosphate dodecahydrate, and/or sodium sulphite. More preferably, the compositions comprises 0.4-1.6 g of mono-basic potassium phosphate per liter, more preferably around 0.8 g/L; 15-60 g of di-basic sodium phosphate dodecahydrate per liter, more preferably around 30g/L; and 1-4 g sodium sulphite per liter, more preferably around 2 g/L.

The viruses may be propagated in a suitable plant host. The tissue from infected plants is ground and the homogenate (the sap) can be used to prepare the compositions disclosed herein. Alternatively, the nucleic acid molecules disclosed herein may be cloned into a vector for replication in another host.

The host range of PepMV is mainly restricted to plant species of the Solanaceae family. Tomato (*Solanum lycopersicum*) is one of the most economically important natural host of PepMV. Pepino plant (*S. muricatum*) is a host in Peru and China (Jones *et al.*, 1980; Soler *et al.*, 2002; Zhang *et al.*, 2003). In surveys in Peru, PepMV has been found to be naturally present in wild *Solanum* species (*S. chilense*, *S. chmielewskii*, *S. parviflorum* and *S. peruvianum*).

Infections, symptomless or with mild symptoms have also been observed in weed species which are member of families of Amaranthaceae, Asteraceae, Boraginaceae, Brassicaceae,

Chenopodiaceae, Compositae, Convolvulaceae, Malvaceae, Plantaginaceae, Polygonaceae and Solanaceae. (Córdoba *et al.*, 2004; Jordá *et al.*, 2001; Kazinczi *et al.*, 2005, Papayiannis *et al.*, 2012; Salomone & Roggero 2002; Soler *et al.*, 2002; Stobbs *et al.*, 2009). Most of these infections were found in the vicinity of tomato greenhouses. PepMV has also been detected in a few potato
 5 cultivars (e.g., *Solanum tuberosum* cv. 'Yungay').

Several species have been found to be experimentally-susceptible to infection by PepMV following artificial inoculation, including eggplant (*Solanum melongena*) which was found to be infected by PepMV by mechanical inoculation (Salomone & Roggero, 2002; Verhoeven *et al.*, 2003).
 10 *Some cultivars of potato (S. tuberosum) can also be experimentally infected by PepMV (Jones et al., 1980). PepMV can infect Datura metel, D. stramonium, Nicotiana debneyi, N. benthamiana systemically (Jones et al., 1980; Verhoeven et al., 2003). Some PepMV isolates can infect N. glutinosa and N. tabacum (LP and some EU isolates; Verhoeven et al., 2003).*

15 Preferably, the term "plant" refers to any plant which is capable of being infected with PepMV. In some embodiments, the plant belongs to the Solanaceae family, in particular the genus Solanum or Lycopersicon. As is known to the skilled person, the nomenclature for tomato plants has recently changed. For example, Solanum juglandifolium is now referred to as Lycopersicon juglandifolium. A preferred plant is a tomato plant.

20 As used herein, the term "plant part" includes, for example, single cells and tissues from pollen, ovules, leaves, embryos, roots, root tips, anthers, flowers, fruits, stems shoots, and seeds; as well as pollen, ovules, leaves, embryos, roots, root tips, anthers, flowers, fruits, stems, shoots, scions, rootstocks, seeds, protoplasts, calli, and the like.

25 PepMV induces a wide range of symptoms on tomato, such as yellow mosaic, leaf distortion, leaf blistering or bubbling, nettle-like heads, single yellow spots, inter-veinal chlorosis, severe leaf mosaics, leaf or stem necrosis and fruit discolouration (Van der Vlugt *et al.*, 2000; Jorda *et al.*, 2001; Roggero *et al.*, 2001; Spence *et al.*, 2006; Hasiów *et al.*, 2008; Hasiów-Jaroszewska *et al.*, 2009a; Hanssen *et al.*, 2009). Tomato
 30 plants display symptoms shortly after infection with PepMV and, in general, symptoms subsequently subside (Van der Vlugt & Stijger, 2008). However, symptoms may return later during the growing season.

Expression of symptoms may depend on environmental conditions, such as temperature and light
 35 intensity. Low environmental temperatures and low light intensity result in more severe damage

(Jorda *et al.*, 2001; Van der Vlugt & Stijger, 2008). PepMV is sometimes suggested to cause yield losses in tomato, but the highest economic losses are attributed to symptoms that affect the commercial value of tomato fruits, such as flaming, marbling, blotchy ripening and fruit size reduction (Soler *et al.*, 2000; Spence *et al.*, 2006; Hanssen & Thomma, 2010). In addition, the so-called ‘tomato collapse’, a sudden and progressive wilt of tomato which can lead to plant death is probably caused by PepMV accumulation in the vascular system (Soler-Alexandre *et al.*, 2005). Striking differences in the severity of symptomatology have been reported (Verhoeven *et al.*, 2003; Hanssen *et al.*, 2008) and not all isolates cause typical PepMV symptoms such as marbled and flamed fruits (Hanssen *et al.*, 2009).

10 Symptoms in plants can be characterized either qualitatively or quantitatively.

The viruses disclosed herein are also useful for inducing resistance in “tolerant plants”, i.e., plants which may become infected with the virus and further its spread but remain symptomless or will have mild symptoms.

15 Several methods have been developed to detect PepMV. A robust method to detect PepMV in plants is DAS-ELISA (Van der Vlugt *et al.*, 2002). Commercially available polyclonal antibodies can be purchased at Prime Diagnostics (Wageningen, The Netherlands). Different PCR-assays have been described to detect PepMV: a general potexvirus detection method (Van der Vlugt & Berendsen, 2002), a real-time immunocapture RT-PCR (Mansilla *et al.*, 2003; Matínez-Culebras *et al.*, 2002; Ling, 2005; Ling *et al.*, 2007) and sensitive real-time PCR assays (Alfaro-Fernández *et al.*, 2009; Johnson & Walcott, 2012; Gutiérrez-Aguirre *et al.*, 2009). Simultaneous detection of multiple plant viruses including PepMV can be performed by using micro-arrays (Boonham *et al.*, 2007) and deep sequencing (Li *et al.*, 2012). Preferably, the accumulation of PepMV in a plant is

20 determined using a quantitative detection method (e.g. an ELISA method or a quantitative reverse transcriptase-polymerase chain reaction [RT-PCR]).

25 A further aspect of the disclosure provides isolated polypeptides expressed by the viruses. In some embodiments the polypeptide is a RNA-dependent polymerase (RdRp) or a coat protein (CP). Preferably, the polypeptide is RdRp.

30 A further aspect of the disclosure provides antibodies specific for the polypeptides disclosed herein, preferably RdRp. In preferred embodiments, the antibody recognizes an antigen specific to VCA, but does not recognize the CH2, the US-1, the EU, or the LP strains. Preferably the antigen comprises the arginine at the position corresponding to 868 of SEQ ID NO:2 and/or the

35 phenylalanine at the position corresponding to 1052 of SEQ ID NO:2 (or rather, the arginine at the

position corresponding to 886 of SEQ ID NO:9 and/or the phenylalanine at the position corresponding to 1070 of SEQ ID NO:9).

A further aspect of the disclosure provides a method for producing said antibodies comprising
 5 immunizing a host (such as a mouse) with the attenuated virus, or a protein or peptide fragment thereof ; harvesting from blood (including serum) or splenocytes of said host antibodies against said virus, protein or peptide fragment. In a preferred embodiment, the method further comprises selecting one antibody-producing splenocyte, fusing said splenocyte to an immortalized hybridoma cell line and allowing said hybridoma fusion to produce monoclonal antibodies. Preferably, the
 10 antigen is in part encoded by a nucleic acid sequence wherein the nucleotide at the position corresponding to 2605 of SEQ ID NO:1 (2675 of SEQ ID NO:8) is G; the nucleotide at the position corresponding to 3156 of SEQ ID NO: 1 (3226 of SEQ ID NO:8) is T and/or the nucleotide at the position corresponding to 3422 SEQ ID NO: 1 (3492 of SEQ ID NO:8) is G. More preferably, the antigen is in part encoded by a nucleic acid sequence wherein the nucleotide at the position
 15 corresponding to 2605 of SEQ ID NO:1 (2675 of SEQ ID NO:8) is G and/or the nucleotide at the position corresponding to 3156 of SEQ ID NO: 1 (3226 of SEQ ID NO:8) is T.

A further aspect of the disclosure provides a method for detecting the presence of the attenuated virus in a plant sample comprising reacting said sample with an antibody according to the
 20 disclosure. Suitable methods for performing immunoassays are well-known to a skilled person and include, e.g., radio-immunoassay (RIA), immunogold labeling, immunosorbent electron microscopy (ISEM), enzyme-linked immunosorbent assay (ELISA), Western blotting and immunoblotting.

25 A further aspect of the disclosure provides a method for identifying a pepino mosaic virus (PepMV)-resistant plant, comprising
 a) exposing a plant or plant part to an infective dosage of the attenuated viruses or nucleic acid molecules disclosed herein,
 b) exposing the plant or plant part to an infective dosage of PepMV, and
 30 c) identifying said plant as PepMV-resistant plant when, after exposure to PepMV, disease-symptoms in said plant or plant part are reduced or delayed and/or PepMV accumulation in said plant or plant parts is reduced in comparison to a control plant.

It is clear to a skilled person that step a) includes an incubation period of sufficient duration to
 35 allow establishment of the attenuated virus. Preferably, such incubation period is at least one week,

more preferably at least 5 weeks. In some embodiments, the presence of virus in the plant can be confirmed by one of the methods disclosed herein. It is also clear to a skilled person that step b) includes an incubation period of sufficient duration to allow establishment of the PepMV virus and detectable symptoms in control plants. Preferably, such incubation period is at least one week,
5 more preferably at least 5 weeks.

As used herein, “resistant” refers to a reduction in multiplication of PepMV, a reduction of movement/spread of the virus to other cells, and/or a reduction or delay in the development of disease symptoms after infection with PepMV. Resistance can be determined by comparing a
10 PepMV infected plant with a plant exposed to VCA and PepMV. Preferably, the PepMV referred to above is a CH2, US-1, EU, or LP strains, however, it also includes other disease causing PepMV strains.

Preferably, the accumulation of PepMV in a plant is determined using a quantitative detection
15 method (e.g. an ELISA method or PCR, such as a quantitative reverse transcriptase-polymerase chain reaction [RT-PCR]).

As used herein, an “infective dosage” refers to the dosage of viral particles or viral nucleic acid molecule capable of infecting a plant. As is clear to as skilled person, the dosage may vary between
20 plant species.

Methods of exposing a plant or a plant part to virus are well-known in the art and include dusting, coating, injecting, rubbing, rolling, dipping, spraying, or brushing. Exemplary methods include mechanical inoculation (e.g., rubbing plants or plant parts with infected plant material) and
25 spraying plants with a solution containing virus particles or viral nucleic acid (see Example 1). The attenuated virus may be isolated from infected plants or other sources by any method known to one of the art.

As is known to a skilled person, cross protection may not lead to resistance in 100% of plants of the
30 same species. Typically, cross protection protects more that 50% of the plants, preferably more than 80% of the plants.

A further aspect of the disclosure provides a method for producing a pepino mosaic virus (PepMV)-resistant plant using the attenuated viruses or nucleic acid molecules disclosed herein for
35 cross-protection. Also provided are methods for controlling or preventing plant disease, in

particular PepMV causing disease. Also provided are methods for controlling or preventing infection by PepMV. The methods comprise exposing a plant or plant part to an infective dosage of the attenuated virus, the nucleic acid molecules disclosed herein, or the compositions disclosed herein. In some embodiments, the methods further comprise detecting the attenuated virus in said
5 plants or plant parts, such as by a method disclosed herein.

The disclosure also provides for PepMV-resistant plants comprising the attenuated virus or the nucleic acid sequences disclosed herein. Such plants may have been infected by the attenuated virus or are the progeny of a plant infected by the virus. The plants may also have been transformed
10 by the nucleic acid molecules disclosed herein or a vector comprising the nucleic acid molecule. Progeny of said plants are also encompassed by the invention. Such plants are obtainable by the methods described herein.

PepMV is an RNA virus. As such it is preferred that the nucleic acid molecule that is comprised in
15 the virion is RNA. Sequences indicated herein contain a T and as such refer to DNA. Wherein herein reference is made to a virus comprising a nucleic acid molecule with a certain nucleic acid sequence and reference is made to a DNA sequence in the context of a virus, it is of course clear to the person skilled in the art that the corresponding RNA sequence is intended. In other words that the reference is to the SEQ ID wherein the T is replaced by a U. Vectors and other compositions
20 that do not refer to a virus or virus particle can have the referenced DNA, an RNA with the same sequence or a combination thereof.

Definitions

As used herein, "to comprise" and its conjugations is used in its non-limiting sense to mean that
25 items following the word are included, but items not specifically mentioned are not excluded. In addition the verb "to consist" may be replaced by "to consist essentially of" meaning that a compound or adjunct compound as defined herein may comprise additional component(s) than the ones specifically identified, said additional component(s) not altering the unique characteristic of the invention.

30

The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The word “approximately” or “about” when used in association with a numerical value (approximately 10, about 10) preferably means that the value may be the given value of 10 more or less 1% of the value.

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The invention is further explained in the following examples. These examples do not limit the scope of the invention, but merely serve to clarify the invention.

30 EXAMPLES

Example 1: Cross-protection experiments with new mild isolates of the CH2 strain of PepMV
 VC1 is a mild isolate of the CH2 strain of pepino mosaic virus (PepMV). During wintertime, VC1 infection can produce unwanted symptoms in inoculated plants, namely, nettle-heads and growth retardation. New variants of the CH2 strain were produced in order to identify viruses that would
 35 offer cross-protection but with reduced unwanted symptoms. In this trial, the new mild isolate

VCA is compared with VC1 for symptoms and their cross-protection effectivity. The RNA-dependent RNA-polymerase (RdRp) of VCA was sequenced and was found to comprise a mixture of closely related viruses having the sequence of SEQ ID NO:1. Additional sequencing was performed to determine the complete coding sequence of the RdRp which is depicted in SEQ ID

5 NO:8. The overlapping sequences of SEQ ID NO:1 and 8 are identical with the exception of position 6290 of SEQ ID NO:8. A “C” is present at this position in SEQ ID NO:8 instead of a “T” in the SEQ ID NO:1. This may reflect a mutation, but does not lead to an amino acid change.

A sequence alignment of VCA with known PepMV viruses is depicted in Figure 5. Three of the

10 nucleotides in SEQ ID NO:1 (corresponding to positions 2605, 3156 and 3422 of SEQ ID NO:1) are unique to VCA in comparison to not only the known PepMV viruses, but also to the attenuated strain VC1. While not wishing to be bound by theory, it is believed that these two nucleotide changes alter the amino acid sequence, which in turn results in milder symptoms.

Set-up:

15 Tomato plants of the cultivar Merlice (on rootstock) were used. Each row of 12 plants was a different treatment. The plants were grown in two greenhouse compartments. The set temperatures were 20°C at daytime and 18°C at nighttime. The trial lasted 3 months. Inoculations were carried out by the rubbing protocol (see below).

Plants were inoculated first with mild isolates (VC1 or VCA) and tested with ELISA to determine

20 infection. The results of the ELISA are shown below.

VC1	4/4 +
VCA	4/4 +
Negative control	0/4 +

Approximately six weeks (39 days) after the first inoculation the plants were inoculated with the virulent isolate (CHD).

Results

25 Infection with the mild isolates VCA and VC1 resulted in very mild symptoms, namely, light bubbling on the young leaves and minor nettle-heads (Fig. 2). Infection with the virulent CH2 isolate CHD alone showed strong necrosis of the leaves and stems, from 3 weeks after inoculation of CHD (Fig. 1A). Treatment with VCA or VC1 protected plants from necrosis (see, e.g., Fig 1B)

Conclusions

- 30
- VCA is as mild as VC1 and maybe even milder.
 - Both VCA and VC1 prevented symptoms of the virulent CH2 isolate CHD.

Example 2: Symptoms observed from treatment with PepMV variants

VC1 infection can produce unwanted symptoms in inoculated plants, namely, nettle-heads and growth retardation. In this trial, the new mild isolate VCA is compared with VC1 for the induction of symptoms in treated plants.

5

Tomato plants of the cultivar Komeett were used. Inoculations were carried out by the rubbing protocol (see below). Plants were inoculated with mild isolates (VC1 or VCA) and tested two weeks later with ELISA to determine infection. It was found on average 95% of the virus inoculated plants had been infected. The virus-free plants remained free until the end of the test.

10 Treatment with either VCA or VC1 resulted in the development of light symptoms, such as leaf misformation. However, plants treated with VCA (Fig. 3B) had more leaf volume and grew better than those treated with VC1 (Fig. 3C).

Example 3: Comparison of symptoms in plants grown under optimal conditions versus sub-optimal conditions

15 Figure 4 depicts plants grown under optimal conditions versus sub-optimal conditions. In optimal growing conditions, plants treated with VC1 and VCA show a comparable level of very mild symptoms. However, in sub-optimal growing conditions, VC1 treated plants show much more severe symptoms than VCA treated plants. While not wishing to be bound by theory, it is believed that the nucleotide differences at position 2605, and 3156 of SEQ ID NO:1 result in an amino acid
20 alteration as compared to VC1 and that one or both of these amino acid alterations is responsible for the milder symptoms.

Material and methods:

Rubbing protocol:

25 Knead frozen or fresh infected plant material. Take 7.5-10 ml of extracted plant sap or 7.5-10 ml virus suspension of virus product.

Put the 7.5-10 ml in a plastic tray

Dilute virus suspension 10-times with PBS

Add 1-2% (w/v) carborundum

30 Mix suspension well.

Put disposable gloves on your hands.

Stir with your fingers and thumb in the suspension.

Inoculate two leaves on each plant in upper half on a leaflet by rubbing 5-times leaflet between thumb and index finger. Leaves should be damaged a little bit.

35 (light discolouration, without holes).

Dip for each plant your finger and inoculate the plant

After inoculation, collect all residual material and put this in a garbage bin or waste container. The residual material should be disinfected by 100-200 ppm hypochlorite and after that it can be processed as regular waste.

- 5 Test after 14 (± 2) days the percentage of infected plants. This can be determined by the method ELISA.

High pressure spraying protocol:

Usage of spraying liquid: 0,5 L/ m.

- 10 Measure the needed amount of cold tap water and put this in the tank of the spraying cart.

Prepare virus solution

Add carborundum 800gram/100 L to spraying liquid.

Mix carborundum well in spray cart, by hand, cover your fore-arm in a

- 15 disposable overboot, circulate te contents of the tank

Pressure on nozzles in spraying arm: 12-15 bar

Spraying width: 1.20 m, 6 nozzles

Spraying height: 10-15 cm above the plants.

Check the nozzles for blockages and evenness of spray.

- 20 After inoculation, collect all residual material and put this in a garbage bin or waste container. The residual material should be disinfected by 100-200 ppm hypochlorite and after that it can be processed as regular waste.

Test after 14 (± 2) days the percentage of infected plants. This can be determined by the ELISA method.

25

ELISA for measuring PepMV in sample

Reagents for performing DAS-ELISA were obtained from PRIME Diagnostics, Wageningen, The Netherlands. The ELISAs were carried out according to the manufacturer's instructions.

Claims

1. An attenuated Pepino mosaic virus comprising a nucleic acid molecule with a nucleic acid sequence that encodes phenylalanine at the position corresponding to 1052 of SEQ ID NO:2.
5
2. The virus of claim 1, wherein the nucleic acid sequence further encodes arginine at the position corresponding to 868 of SEQ ID NO:2.
3. An attenuated Pepino mosaic virus comprising a nucleic acid molecule with a nucleic acid
10 sequence that encodes arginine at the position corresponding to 868 of SEQ ID NO:2.
4. The virus according to any one of claims 1-3, wherein the nucleic acid sequence is at least 80% identical to SEQ ID NO:1.
- 15 5. The virus according to any one of claims 1-4, wherein the nucleic acid sequence is at least 80% identical to SEQ ID NO:8.
6. An isolated nucleic acid molecule encoding an amino acid sequence having at least 95% identity to any one of the amino acid sequences depicted in Figure 6, wherein the nucleic acid sequence
20 encodes arginine at position 887 of Figure 6 and/or the nucleic acid sequence encodes phenylalanine at position 1071 of Figure 6.
7. An isolated nucleic acid molecule encoding an amino acid sequence having at least 95% identity to SEQ ID NO:8.
25
8. A vector, preferably an expression vector, comprising the nucleic acid molecule according to claims 6-7 or the virus according to any one of claims 1-5.
9. An isolated polypeptide encoded by a nucleic acid molecule of claim 6 or 7.
30
10. A composition for biological control of plant disease comprising the virus of any one of claims 1-5, the nucleic acid molecule of claim 6 or 7, or the vector of claim 8; and an agriculturally acceptable carrier.

11. A method for the detection of a pepino mosaic virus (PepMV) comprising providing a sample suspected of containing PepMV and detecting in said sample the virus of any one of claims 1-5, the nucleic acid molecule of claim 6 or 7, or the vector of claim 8.
- 5 12. A method for producing a pepino mosaic virus (PepMV)-resistant plant, comprising exposing a plant or plant part to the virus of any one of claims 1-5, the nucleic acid molecule of claim 6 or 7, the vector of claim 8, or the composition of claim 10.
- 10 13. A PepMV-resistant plant comprising a virus according to any one of claims 1-5 or the nucleic acid molecule of claim 6 or 7.

Figure 1B:



Figure 1A

Figure 2B



Figure 2A



Figure 3A



Figure 3C

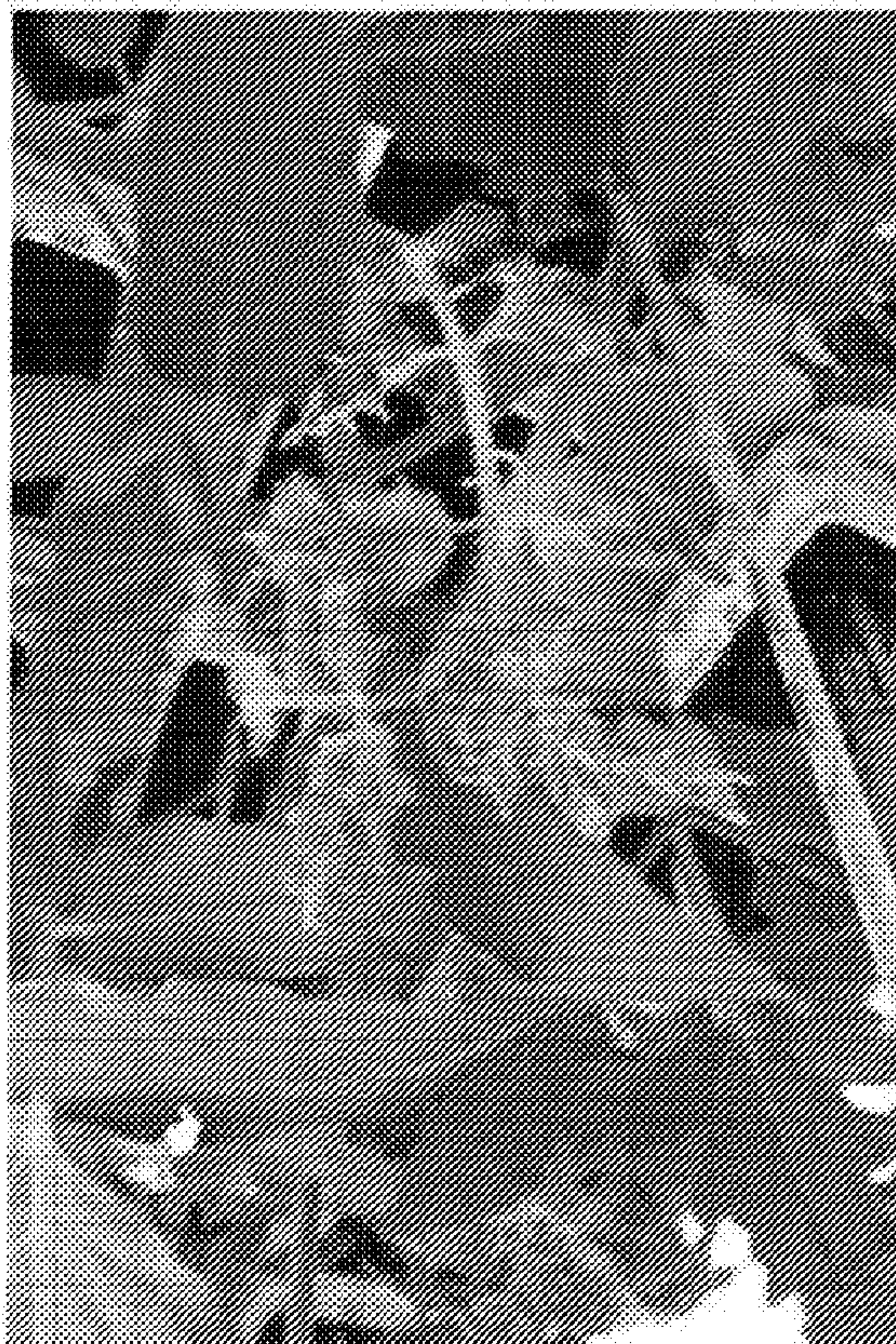
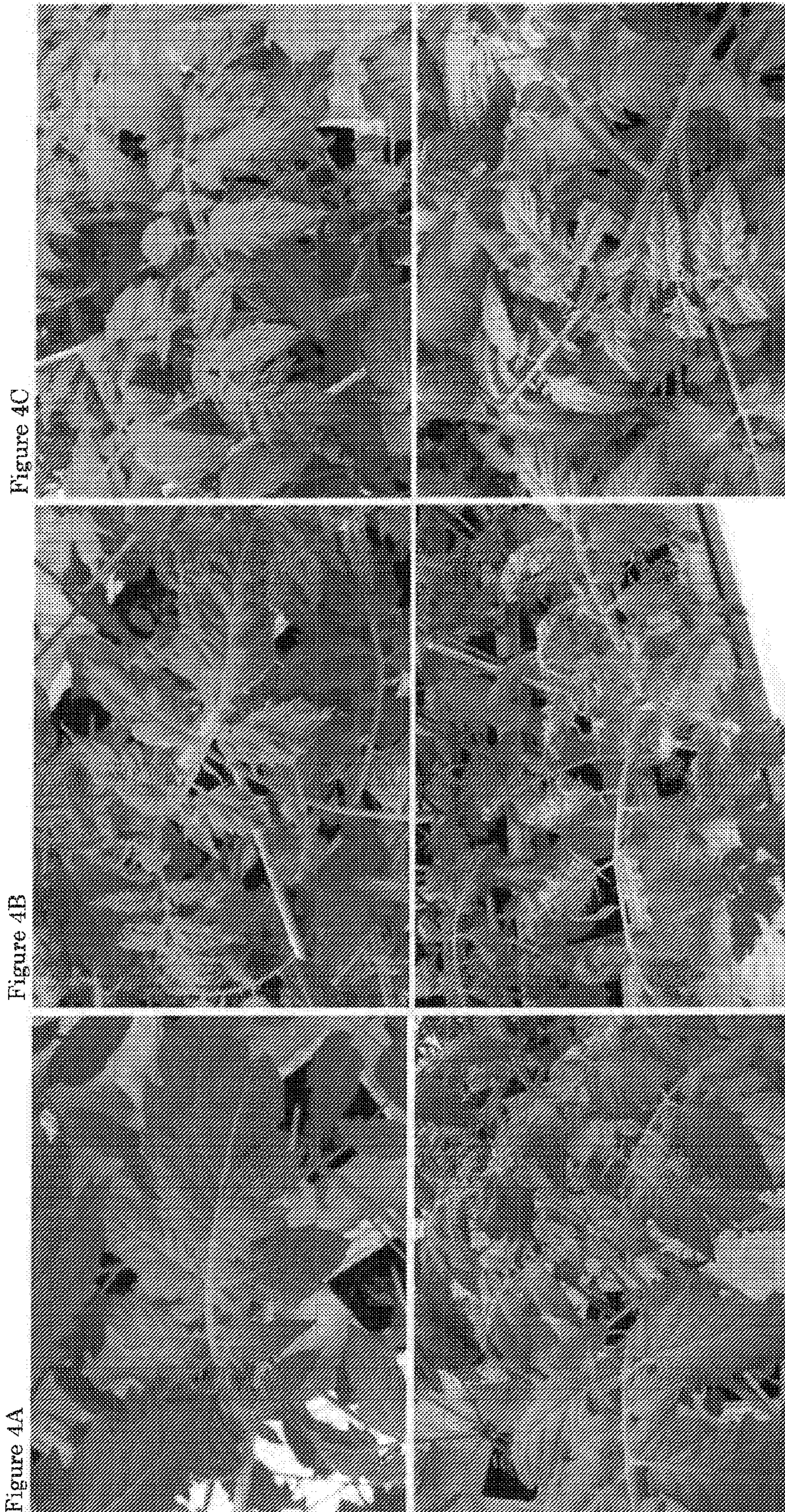


Figure 3B





Section 1

1906 (1) 10 20 30 40 50 60 70 80 90 100

Pa (1)

220606A1 (1)

VFBC12-04 (1)

VFBC12-08 (1)

PCH06/104 (1)

FJ212288 (1)

P5 (1)

DQ000985 (1)

PK (1)

VCA (1)

Section 2

1906 (101) 101 110 120 130 140 150 160 170 180 190 200

Pa (101)

220606A1 (1)

VFBC12-04 (101)

VFBC12-08 (101)

PCH06/104 (16)

FJ212288 (100)

P5 (101)

DQ000985 (101)

PK (101)

VCA (1)

Section 4

Alignment VCA - PepMV CH2 29sept2015.apr

[illegible]

Section 8

[illegible]

[illegible]

[illegible]

Alignment VCA - PepMV CH2 29sept2015.apr

	(1401)	1401	1410	1420	1430	1440	1450	1460	1470	1480	1490	1500	Section 15
1906 (1316)	TAGTC	AACAG	GGGCT	AGTAA	CAATTA	AGCTG	ATTAAG	CTGCA	GTTCAG	CTTAA	TCCACT	GTTC	
Pa (1401)	TAGTC	AACAG	GGGCT	AGTAA	CAATTA	AGCTG	ATTAAG	CTGCA	GTTCAG	CTTAA	TCCACT	GTTC	
220606A1 (1271)	TAGTC	AACAG	GGGCT	AGTAA	CAATTA	AGCTG	ATTAAG	CTGCA	GTTCAG	CTTAA	TCCACT	GTTC	
VFBC12-04 (1401)	TAGTC	AACAG	GGGCT	AGTAA	CAATTA	AGCTG	ATTAAG	CTGCA	GTTCAG	CTTAA	TCCACT	GTTC	
VFBC12-08 (1401)	TAGTC	AACAG	GGGCT	AGTAA	CAATTA	AGCTG	ATTAAG	CTGCA	GTTCAG	CTTAA	TCCACT	GTTC	
PCH06/104 (1316)	TAGTC	AACAG	GGGCT	AGTAA	CAATTA	AGCTG	ATTAAG	CTGCA	GTTCAG	CTTAA	TCCACT	GTTC	
FJ212288 (1400)	TAGTC	AACAG	GGGCT	AGTAA	CAATTA	AGCTG	ATTAAG	CTGCA	GTTCAG	CTTAA	TCCACT	GTTC	
P5 (1401)	TAGTC	AACAG	GGGCT	AGTAA	CAATTA	AGCTG	ATTAAG	CTGCA	GTTCAG	CTTAA	TCCACT	GTTC	
DQ000985 (1401)	TAGTC	AACAG	GGGCT	AGTAA	CAATTA	AGCTG	ATTAAG	CTGCA	GTTCAG	CTTAA	TCCACT	GTTC	
PK (1401)	TAGTC	AACAG	GGGCT	AGTAA	CAATTA	AGCTG	ATTAAG	CTGCA	GTTCAG	CTTAA	TCCACT	GTTC	
VCA (1264)	TAGTC	AACAG	GGGCT	AGTAA	CAATTA	AGCTG	ATTAAG	CTGCA	GTTCAG	CTTAA	TCCACT	GTTC	
	(1501)	1501	1510	1520	1530	1540	1550	1560	1570	1580	1590	1600	Section 16
1906 (1416)	CCACC	GAGCT	ATGAA	TGGCAT	CAACAA	CTTGG	CAATTC	CAACCA	CTTGG	CAATTC	CAACCA	CTTGG	
Pa (1501)	CCACC	GAGCT	ATGAA	TGGCAT	CAACAA	CTTGG	CAATTC	CAACCA	CTTGG	CAATTC	CAACCA	CTTGG	
220606A1 (1371)	CCACC	GAGCT	ATGAA	TGGCAT	CAACAA	CTTGG	CAATTC	CAACCA	CTTGG	CAATTC	CAACCA	CTTGG	
VFBC12-04 (1501)	CCACC	GAGCT	ATGAA	TGGCAT	CAACAA	CTTGG	CAATTC	CAACCA	CTTGG	CAATTC	CAACCA	CTTGG	
VFBC12-08 (1501)	CCACC	GAGCT	ATGAA	TGGCAT	CAACAA	CTTGG	CAATTC	CAACCA	CTTGG	CAATTC	CAACCA	CTTGG	
PCH06/104 (1416)	CCACC	GAGCT	ATGAA	TGGCAT	CAACAA	CTTGG	CAATTC	CAACCA	CTTGG	CAATTC	CAACCA	CTTGG	
FJ212288 (1500)	CCACC	GAGCT	ATGAA	TGGCAT	CAACAA	CTTGG	CAATTC	CAACCA	CTTGG	CAATTC	CAACCA	CTTGG	
P5 (1501)	CCACC	GAGCT	ATGAA	TGGCAT	CAACAA	CTTGG	CAATTC	CAACCA	CTTGG	CAATTC	CAACCA	CTTGG	
DQ000985 (1501)	CCACC	GAGCT	ATGAA	TGGCAT	CAACAA	CTTGG	CAATTC	CAACCA	CTTGG	CAATTC	CAACCA	CTTGG	
PK (1501)	CCACC	GAGCT	ATGAA	TGGCAT	CAACAA	CTTGG	CAATTC	CAACCA	CTTGG	CAATTC	CAACCA	CTTGG	
VCA (1364)	CCACC	GAGCT	ATGAA	TGGCAT	CAACAA	CTTGG	CAATTC	CAACCA	CTTGG	CAATTC	CAACCA	CTTGG	

[illegible]

[illegible]

Alignment VCA - PepMV CH2 29sept2015.apr

	(2001)	2001	2010	2020	2030	2040	2050	2060	2070	2080	2090	2100	Section 21
1906 (1916)	CTCTG	CCATG	TTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC
Pa (2001)	CTCTG	CCATG	TTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC
220606A1 (1871)	CTCTG	CCATG	TTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC
VFBC12-04 (2001)	CTCTG	CCATG	TTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC
VFBC12-08 (2001)	CTCTG	CCATG	TTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC
PCH06/104 (1916)	CTCTG	CCATG	TTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC
FJ212288 (2000)	CTCTG	CCATG	TTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC
P5 (2001)	CTCTG	CCATG	TTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC
DQ000985 (2001)	CTCTG	CCATG	TTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC
PK (2001)	CTCTG	CCATG	TTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC
VCA (1864)	CTCTG	CCATG	TTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC
1906 (2016)	CAGAA	ATATG	AGAA	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	Section 22
Pa (2101)	CAGAA	ATATG	AGAA	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	2100
220606A1 (1971)	CAGAA	ATATG	AGAA	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	2110
VFBC12-04 (2101)	CAGAA	ATATG	AGAA	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	2120
VFBC12-08 (2101)	CAGAA	ATATG	AGAA	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	2130
PCH06/104 (2016)	CAGAA	ATATG	AGAA	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	2140
FJ212288 (2100)	CAGAA	ATATG	AGAA	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	2150
P5 (2101)	CAGAA	ATATG	AGAA	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	2160
DQ000985 (2101)	CAGAA	ATATG	AGAA	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	2170
PK (2101)	CAGAA	ATATG	AGAA	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	2180
VCA (1964)	CAGAA	ATATG	AGAA	CTT	GTG	GAAC	CTT	GTG	GAAC	CTT	GTG	GAAC	2190

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Section 49												
	(4801)	4801	4810	4820	4830	4840	4850	4860	4870	4880	4890	4900
1906 (4716)	ATCCAC	TCGTC	CTAC	TAAT	AGTAA	TTGAT	CTAA	TCAT	CAAC	CTAG	AGCT	TTGAT
Pa (4801)	ATCCAC	TCGTC	CTAC	TAAT	AGTAA	TTGAT	CTAA	TCAT	CAAC	CTAG	AGCT	TTGAT
220606A1 (4671)	ATCCAC	TCGTC	CTAC	TAAT	AGTAA	TTGAT	CTAA	TCAT	CAAC	CTAG	AGCT	TTGAT
VFBC12-04 (4801)	ATCCAC	TCGTC	CTAC	TAAT	AGTAA	TTGAT	CTAA	TCAT	CAAC	CTAG	AGCT	TTGAT
VFBC12-08 (4801)	ATCCAC	TCGTC	CTAC	TAAT	AGTAA	TTGAT	CTAA	TCAT	CAAC	CTAG	AGCT	TTGAT
PCH06/104 (4716)	ATCCAC	TCGTC	CTAC	TAAT	AGTAA	TTGAT	CTAA	TCAT	CAAC	CTAG	AGCT	TTGAT
FJ212288 (4800)	ATCCAC	TCGTC	CTAC	TAAT	AGTAA	TTGAT	CTAA	TCAT	CAAC	CTAG	AGCT	TTGAT
P5 (4801)	ATCCAC	TCGTC	CTAC	TAAT	AGTAA	TTGAT	CTAA	TCAT	CAAC	CTAG	AGCT	TTGAT
DQ000985 (4801)	ATCCAC	TCGTC	CTAC	TAAT	AGTAA	TTGAT	CTAA	TCAT	CAAC	CTAG	AGCT	TTGAT
PK (4801)	ATCCAC	TCGTC	CTAC	TAAT	AGTAA	TTGAT	CTAA	TCAT	CAAC	CTAG	AGCT	TTGAT
VCA (4664)	ATCCAC	TCGTC	CTAC	TAAT	AGTAA	TTGAT	CTAA	TCAT	CAAC	CTAG	AGCT	TTGAT
Section 50												
	(4901)	4901	4910	4920	4930	4940	4950	4960	4970	4980	4990	5000
1906 (4816)	CCCTTC	CGAC	CAAT	TCGTC	TCAG	AAAG	CAAG	CTTT	CAAG	CTTT	CAAG	CTTT
Pa (4901)	CCCTTC	CGAC	CAAT	TCGTC	TCAG	AAAG	CAAG	CTTT	CAAG	CTTT	CAAG	CTTT
220606A1 (4771)	CCCTTC	CGAC	CAAT	TCGTC	TCAG	AAAG	CAAG	CTTT	CAAG	CTTT	CAAG	CTTT
VFBC12-04 (4901)	CCCTTC	CGAC	CAAT	TCGTC	TCAG	AAAG	CAAG	CTTT	CAAG	CTTT	CAAG	CTTT
VFBC12-08 (4901)	CCCTTC	CGAC	CAAT	TCGTC	TCAG	AAAG	CAAG	CTTT	CAAG	CTTT	CAAG	CTTT
PCH06/104 (4816)	CCCTTC	CGAC	CAAT	TCGTC	TCAG	AAAG	CAAG	CTTT	CAAG	CTTT	CAAG	CTTT
FJ212288 (4900)	CCCTTC	CGAC	CAAT	TCGTC	TCAG	AAAG	CAAG	CTTT	CAAG	CTTT	CAAG	CTTT
P5 (4901)	CCCTTC	CGAC	CAAT	TCGTC	TCAG	AAAG	CAAG	CTTT	CAAG	CTTT	CAAG	CTTT
DQ000985 (4901)	CCCTTC	CGAC	CAAT	TCGTC	TCAG	AAAG	CAAG	CTTT	CAAG	CTTT	CAAG	CTTT
PK (4901)	CCCTTC	CGAC	CAAT	TCGTC	TCAG	AAAG	CAAG	CTTT	CAAG	CTTT	CAAG	CTTT
VCA (4764)	CCCTTC	CGAC	CAAT	TCGTC	TCAG	AAAG	CAAG	CTTT	CAAG	CTTT	CAAG	CTTT

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Section 61

	6001	6010	6020	6030	6040	6050	6060	6070	6080	6090	6100	
1906 (5916)	ACAAATTCGCAATGTAATTCGCAAAATGTTTGGACCATATGTTAGACAGTGTGGACGCTGGCAATGGGAAATATGGGTAATCGAATACG											
Pa (6001)	ACAAATTCGCAATGTAATTCGCAAAATGTTTGGACCATATGTTAGACAGTGTGGACGCTGGCAATGGGAAATATGGGTAATCGAATACG											
220606A1 (5871)	ACAAATTCGCAATGTAATTCGCAAAATGTTTGGACCATATGTTAGACAGTGTGGACGCTGGCAATGGGAAATATGGGTAATCGAATACG											
VFBC12-04 (6001)	ACAAATTCGCAATGTAATTCGCAAAATGTTTGGACCATATGTTAGACAGTGTGGACGCTGGCAATGGGAAATATGGGTAATCGAATACG											
VFBC12-08 (6001)	ACAAATTCGCAATGTAATTCGCAAAATGTTTGGACCATATGTTAGACAGTGTGGACGCTGGCAATGGGAAATATGGGTAATCGAATACG											
PCH06/104 (5916)	ACAAATTCGCAATGTAATTCGCAAAATGTTTGGACCATATGTTAGACAGTGTGGACGCTGGCAATGGGAAATATGGGTAATCGAATACG											
FJ121288 (6000)	ACAAATTCGCAATGTAATTCGCAAAATGTTTGGACCATATGTTAGACAGTGTGGACGCTGGCAATGGGAAATATGGGTAATCGAATACG											
P5 (6001)	ACAAATTCGCAATGTAATTCGCAAAATGTTTGGACCATATGTTAGACAGTGTGGACGCTGGCAATGGGAAATATGGGTAATCGAATACG											
DQ000985 (6001)	ACAAATTCGCAATGTAATTCGCAAAATGTTTGGACCATATGTTAGACAGTGTGGACGCTGGCAATGGGAAATATGGGTAATCGAATACG											
PK (6001)	ACAAATTCGCAATGTAATTCGCAAAATGTTTGGACCATATGTTAGACAGTGTGGACGCTGGCAATGGGAAATATGGGTAATCGAATACG											
VCA (5864)	ACAAATTCGCAATGTAATTCGCAAAATGTTTGGACCATATGTTAGACAGTGTGGACGCTGGCAATGGGAAATATGGGTAATCGAATACG											

Section 62

	6101	6110	6120	6130	6140	6150	6160	6170	6180	6190	6200	
1906 (6016)	AAAGTTTGCTGCTGCTTGGACTTTTGAATGGAGTCAAGAAATGACGCTAGTCTACAGCCGCGGATGCGCTAAATAGGCAAGTCCCATGCAAAAGAGCTTCC											
Pa (6101)	AAAGTTTGCTGCTGCTTGGACTTTTGAATGGAGTCAAGAAATGACGCTAGTCTACAGCCGCGGATGCGCTAAATAGGCAAGTCCCATGCAAAAGAGCTTCC											
220606A1 (5971)	AAAGTTTGCTGCTGCTTGGACTTTTGAATGGAGTCAAGAAATGACGCTAGTCTACAGCCGCGGATGCGCTAAATAGGCAAGTCCCATGCAAAAGAGCTTCC											
VFBC12-04 (6101)	AAAGTTTGCTGCTGCTTGGACTTTTGAATGGAGTCAAGAAATGACGCTAGTCTACAGCCGCGGATGCGCTAAATAGGCAAGTCCCATGCAAAAGAGCTTCC											
VFBC12-08 (6101)	AAAGTTTGCTGCTGCTTGGACTTTTGAATGGAGTCAAGAAATGACGCTAGTCTACAGCCGCGGATGCGCTAAATAGGCAAGTCCCATGCAAAAGAGCTTCC											
PCH06/104 (6016)	AAAGTTTGCTGCTGCTTGGACTTTTGAATGGAGTCAAGAAATGACGCTAGTCTACAGCCGCGGATGCGCTAAATAGGCAAGTCCCATGCAAAAGAGCTTCC											
FJ121288 (6100)	AAAGTTTGCTGCTGCTTGGACTTTTGAATGGAGTCAAGAAATGACGCTAGTCTACAGCCGCGGATGCGCTAAATAGGCAAGTCCCATGCAAAAGAGCTTCC											
P5 (6101)	AAAGTTTGCTGCTGCTTGGACTTTTGAATGGAGTCAAGAAATGACGCTAGTCTACAGCCGCGGATGCGCTAAATAGGCAAGTCCCATGCAAAAGAGCTTCC											
DQ000985 (6101)	AAAGTTTGCTGCTGCTTGGACTTTTGAATGGAGTCAAGAAATGACGCTAGTCTACAGCCGCGGATGCGCTAAATAGGCAAGTCCCATGCAAAAGAGCTTCC											
PK (6101)	AAAGTTTGCTGCTGCTTGGACTTTTGAATGGAGTCAAGAAATGACGCTAGTCTACAGCCGCGGATGCGCTAAATAGGCAAGTCCCATGCAAAAGAGCTTCC											
VCA (5964)	AAAGTTTGCTGCTGCTTGGACTTTTGAATGGAGTCAAGAAATGACGCTAGTCTACAGCCGCGGATGCGCTAAATAGGCAAGTCCCATGCAAAAGAGCTTCC											

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Section 63									
(6201)	6201	6210	6220	6230	6240	6250	6260	6270	6280
1906 (6116)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
Pa (6201)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
220606A1 (6071)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
VFBC12-04 (6201)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
VFBC12-08 (6201)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
PCH06/104 (6116)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
FJ212288 (6200)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
P5 (6201)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
DQ000985 (6201)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
PK (6201)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
VCA (6064)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
Section 64									
(6301)	6301	6310	6320	6330	6340	6350	6360	6370	6380
1906 (6216)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
Pa (6301)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
220606A1 (6171)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
VFBC12-04 (6301)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
VFBC12-08 (6301)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
PCH06/104 (6216)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
FJ212288 (6300)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
P5 (6301)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
DQ000985 (6301)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
PK (6301)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								
VCA (6164)	CTCAGTCGGTTCGTAATAATATGGCGGCGTTCGCGCCGAGAAATATTCACCTGGG								

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	Section 65				
	6401	6410	6420	6430	6441
(6401)					
1906 (6292)					
Pa (6401)					
220606A1 (6246)					
VFBC12-04 (6400)					
VFBC12-08 (6401)					
PCH06/104 (6292)					
FJ212288 (6400)					
P5 (6401)					
DQ000985 (6401)					
PK (6401)					
VCA (6232)					

	(1)	1	10	20	30	40	50	60	70	80	97
LE-2002 RdRp	(1)	1	10	20	30	40	50	60	70	80	97
AJ438767 RdRp	(1)	1	10	20	30	40	50	60	70	80	97
Sp-13 RdRp	(1)	1	10	20	30	40	50	60	70	80	97
LP-2001 RdRp	(1)	1	10	20	30	40	50	60	70	80	97
US1 RdRp	(1)	1	10	20	30	40	50	60	70	80	97
DQ000985 RdRp	(1)	1	10	20	30	40	50	60	70	80	97
FJ212288 RdRp	(1)	1	10	20	30	40	50	60	70	80	97
220606A1 RdRp	(1)	1	10	20	30	40	50	60	70	80	97
1906 RdRp	(1)	1	10	20	30	40	50	60	70	80	97
VCA RdRp	(1)	1	10	20	30	40	50	60	70	80	97
LE-2002 RdRp	(98)	98	110	120	130	140	150	160	170	180	194
AJ438767 RdRp	(98)	98	110	120	130	140	150	160	170	180	194
Sp-13 RdRp	(98)	98	110	120	130	140	150	160	170	180	194
LP-2001 RdRp	(98)	98	110	120	130	140	150	160	170	180	194
US1 RdRp	(98)	98	110	120	130	140	150	160	170	180	194
DQ000985 RdRp	(98)	98	110	120	130	140	150	160	170	180	194
FJ212288 RdRp	(98)	98	110	120	130	140	150	160	170	180	194
220606A1 RdRp	(83)	83	110	120	130	140	150	160	170	180	194
1906 RdRp	(98)	98	110	120	130	140	150	160	170	180	194
VCA RdRp	(80)	80	110	120	130	140	150	160	170	180	194
LE-2002 RdRp	(195)	195	200	210	220	230	240	250	260	270	291
AJ438767 RdRp	(195)	195	200	210	220	230	240	250	260	270	291
Sp-13 RdRp	(195)	195	200	210	220	230	240	250	260	270	291
LP-2001 RdRp	(195)	195	200	210	220	230	240	250	260	270	291
US1 RdRp	(195)	195	200	210	220	230	240	250	260	270	291
DQ000985 RdRp	(195)	195	200	210	220	230	240	250	260	270	291
FJ212288 RdRp	(195)	195	200	210	220	230	240	250	260	270	291
220606A1 RdRp	(180)	180	200	210	220	230	240	250	260	270	291
1906 RdRp	(195)	195	200	210	220	230	240	250	260	270	291
VCA RdRp	(177)	177	200	210	220	230	240	250	260	270	291

Section 6

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Section 10									
(874)	874	880	890	900	910	920	930	940	950
LE-2002 RdRp	(874)	ECNVPIIVPS	ENKQDA	MDIIGRR	EMFYAGCGGSEDA	VOILDNHTQHCSDNYL	ITCISRAVDST	NTGPRASSTW	NTGPRASSTW
AJ438767 RdRp	(874)	KCEVPIIVPS	ENKQDA	MDIIGRR	EMFYAGCGGSEDA	VOILDNHTQHCSDNYL	ITCISRAVDST	NTGPRASSTW	NTGPRASSTW
Sp-13 RdRp	(874)	KCEVPIIVPS	ENKQDA	MDIIGRR	EMFYAGCGGSEDA	VOILDNHTQHCSDNYL	ITCISRAVDST	NTGPRASSTW	NTGPRASSTW
LP-2001 RdRp	(874)	KCEVPIIVPS	ENKQDA	MDIIGRR	EMFYAGCGGSEDA	VOILDNHTQHCSDNYL	ITCISRAVDST	NTGPRASSTW	NTGPRASSTW
US1 RdRp	(874)	KCEVPIIVPS	ENKQDA	MDIIGRR	EMFYAGCGGSEDA	VOILDNHTQHCSDNYL	ITCISRAVDST	NTGPRASSTW	NTGPRASSTW
DQ000985 RdRp	(873)	KCEVPIIVPS	ENKQDA	MDIIGRR	EMFYAGCGGSEDA	VOILDNHTQHCSDNYL	ITCISRAVDST	NTGPRASSTW	NTGPRASSTW
FJ212288 RdRp	(873)	KCEVPIIVPS	ENKQDA	MDIIGRR	EMFYAGCGGSEDA	VOILDNHTQHCSDNYL	ITCISRAVDST	NTGPRASSTW	NTGPRASSTW
220606A1 RdRp	(858)	KCEVPIIVPS	ENKQDA	MDIIGRR	EMFYAGCGGSEDA	VOILDNHTQHCSDNYL	ITCISRAVDST	NTGPRASSTW	NTGPRASSTW
1906 RdRp	(873)	KCEVPIIVPS	ENKQDA	MDIIGRR	EMFYAGCGGSEDA	VOILDNHTQHCSDNYL	ITCISRAVDST	NTGPRASSTW	NTGPRASSTW
VCA RdRp	(855)	KCEVPIIVPS	ENKQDA	MDIIGRR	EMFYAGCGGSEDA	VOILDNHTQHCSDNYL	ITCISRAVDST	NTGPRASSTW	NTGPRASSTW
Section 11									
(971)	971	980	990	1000	1010	1020	1030	1040	1050
LE-2002 RdRp	(971)	STEMF	NSKKAADDS	SPVHFA	ATNHE	NGNNLEKLA	SLSEKKAARE	YDKHHG	YDKHHG
AJ438767 RdRp	(971)	STEMF	NSKKAADDS	SPVHFA	ATNHE	NGNNLEKLA	SLSEKKAARE	YDKHHG	YDKHHG
Sp-13 RdRp	(971)	STEMF	NSKKAADDS	SPVHFA	ATNHE	NGNNLEKLA	SLSEKKAARE	YDKHHG	YDKHHG
LP-2001 RdRp	(971)	STEMF	NSKKAADDS	SPVHFA	ATNHE	NGNNLEKLA	SLSEKKAARE	YDKHHG	YDKHHG
US1 RdRp	(971)	STEMF	NSKKAADDS	SPVHFA	ATNHE	NGNNLEKLA	SLSEKKAARE	YDKHHG	YDKHHG
DQ000985 RdRp	(970)	STEMF	NSKKAADDS	SPVHFA	ATNHE	NGNNLEKLA	SLSEKKAARE	YDKHHG	YDKHHG
FJ212288 RdRp	(970)	STEMF	NSKKAADDS	SPVHFA	ATNHE	NGNNLEKLA	SLSEKKAARE	YDKHHG	YDKHHG
220606A1 RdRp	(955)	STEMF	NSKKAADDS	SPVHFA	ATNHE	NGNNLEKLA	SLSEKKAARE	YDKHHG	YDKHHG
1906 RdRp	(970)	STEMF	NSKKAADDS	SPVHFA	ATNHE	NGNNLEKLA	SLSEKKAARE	YDKHHG	YDKHHG
VCA RdRp	(952)	STEMF	NSKKAADDS	SPVHFA	ATNHE	NGNNLEKLA	SLSEKKAARE	YDKHHG	YDKHHG
Section 12									
(1068)	1068	1080	1090	1100	1110	1120	1130	1140	1150
LE-2002 RdRp	(1068)	ETVETKNDVGDII	EFNNYHNV	NCILPAP	DPVDTEE	ITWEICAAABV	ENTYLA	KPMANL	INAAAGQ
AJ438767 RdRp	(1068)	ETVETKNDVGDII	EFNNYHNV	NCILPAP	DPVDTEE	ITWEICAAABV	ENTYLA	KPMANL	INAAAGQ
Sp-13 RdRp	(1068)	ETVETKNDVGDII	EFNNYHNV	NCILPAP	DPVDTEE	ITWEICAAABV	ENTYLA	KPMANL	INAAAGQ
LP-2001 RdRp	(1068)	ETVETKNDVGDII	EFNNYHNV	NCILPAP	DPVDTEE	ITWEICAAABV	ENTYLA	KPMANL	INAAAGQ
US1 RdRp	(1068)	ETVETKNDVGDII	EFNNYHNV	NCILPAP	DPVDTEE	ITWEICAAABV	ENTYLA	KPMANL	INAAAGQ
DQ000985 RdRp	(1067)	ETVETKNDVGDII	EFNNYHNV	NCILPAP	DPVDTEE	ITWEICAAABV	ENTYLA	KPMANL	INAAAGQ
FJ212288 RdRp	(1067)	ETVETKNDVGDII	EFNNYHNV	NCILPAP	DPVDTEE	ITWEICAAABV	ENTYLA	KPMANL	INAAAGQ
220606A1 RdRp	(1052)	ETVETKNDVGDII	EFNNYHNV	NCILPAP	DPVDTEE	ITWEICAAABV	ENTYLA	KPMANL	INAAAGQ
1906 RdRp	(1067)	ETVETKNDVGDII	EFNNYHNV	NCILPAP	DPVDTEE	ITWEICAAABV	ENTYLA	KPMANL	INAAAGQ
VCA RdRp	(1049)	ETVETKNDVGDII	EFNNYHNV	NCILPAP	DPVDTEE	ITWEICAAABV	ENTYLA	KPMANL	INAAAGQ

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	1165	1170	1180	1190	1200	1210	1220	1230	1240	1250	Section 13	
(1165)	EMQQTVM	LGNNRR	YLRMROR	QEKH	FINCE	TTUNH	ICV	SGNN	NRRTA	CTND	TAED	1261
LE-2002 RdRp (1165)	EMQQTVM	LGNNRR	YLRMROR	QEKH	FINCE	TTUNH	ICV	SGNN	NRRTA	CTND	TAED	1261
AJ438767 RdRp (1165)	EMQQTVM	LGNNRR	YLRMROR	QEKH	FINCE	TTUNH	ICV	SGNN	NRRTA	CTND	TAED	1261
Sp-13 RdRp (1165)	SMQQTVM	LGNNRR	YLRMROR	QEKH	FINCE	TTUNH	ICV	SGNN	NRRTA	CTND	TAED	1261
LP-2001 RdRp (1165)	EMQQTVM	LGNNRR	YLRMROR	QEKH	FINCE	TTUNH	ICV	SGNN	NRRTA	CTND	TAED	1261
US1 RdRp (1165)	EMQQTVM	LGNNRR	YLRMROR	QEKH	FINCE	TTUNH	ICV	SGNN	NRRTA	CTND	TAED	1261
DQ000985 RdRp (1164)	EMQQTVM	LGNNRR	YLRMROR	QEKH	FINCE	TTUNH	ICV	SGNN	NRRTA	CTND	TAED	1261
FJ212288 RdRp (1164)	EMQQTVM	LGNNRR	YLRMROR	QEKH	FINCE	TTUNH	ICV	SGNN	NRRTA	CTND	TAED	1261
220606A1 RdRp (1149)	EMQQTVM	LGNNRR	YLRMROR	QEKH	FINCE	TTUNH	ICV	SGNN	NRRTA	CTND	TAED	1261
1906 RdRp (1164)	EMQQTVM	LGNNRR	YLRMROR	QEKH	FINCE	TTUNH	ICV	SGNN	NRRTA	CTND	TAED	1261
VCA RdRp (1146)	EMQQTVM	LGNNRR	YLRMROR	QEKH	FINCE	TTUNH	ICV	SGNN	NRRTA	CTND	TAED	1261
Section 14												
(1262)	1262	1270	1280	1290	1300	1310	1320	1330	1340	1358		
LE-2002 RdRp (1262)	KIPLEG	TSIMPL	SGEGPT	EDANT	EC	SIATAT	RA	AKV	YAG	DDMAL	DG	1358
AJ438767 RdRp (1262)	KIPLEG	TSIMPL	SGEGPT	EDANT	EC	SIATAT	RA	AKV	YAG	DDMAL	DG	1358
Sp-13 RdRp (1262)	KIPLEG	TSIMPL	SGEGPT	EDANT	EC	SIATAT	RA	AKV	YAG	DDMAL	DG	1358
LP-2001 RdRp (1262)	KIPLEG	TSIMPL	SGEGPT	EDANT	EC	SIATAT	RA	AKV	YAG	DDMAL	DG	1358
US1 RdRp (1262)	KIPLEG	TSIMPL	SGEGPT	EDANT	EC	SIATAT	RA	AKV	YAG	DDMAL	DG	1358
DQ000985 RdRp (1261)	KIPLEG	TSIMPL	SGEGPT	EDANT	EC	SIATAT	RA	AKV	YAG	DDMAL	DG	1358
FJ212288 RdRp (1261)	KIPLEG	TSIMPL	SGEGPT	EDANT	EC	SIATAT	RA	AKV	YAG	DDMAL	DG	1358
220606A1 RdRp (1246)	KIPLEG	TSIMPL	SGEGPT	EDANT	EC	SIATAT	RA	AKV	YAG	DDMAL	DG	1358
1906 RdRp (1261)	KIPLEG	TSIMPL	SGEGPT	EDANT	EC	SIATAT	RA	AKV	YAG	DDMAL	DG	1358
VCA RdRp (1243)	KIPLEG	TSIMPL	SGEGPT	EDANT	EC	SIATAT	RA	AKV	YAG	DDMAL	DG	1358
Section 15												
(1359)	1359	1370	1380	1390	1400	1410	1420	1439				
LE-2002 RdRp (1359)	TKNPIK	KNH	ASINL	QEA	IGN	HTA	AS	YAL	DM	KHS	YOM	1439
AJ438767 RdRp (1359)	TKNPIK	KNH	ASINL	QEA	IGN	HTA	AS	YAL	DM	KHS	YOM	1439
Sp-13 RdRp (1359)	TKNPIK	KNH	ASINL	QEA	IGN	HTA	AS	YAL	DM	KHS	YOM	1439
LP-2001 RdRp (1359)	TKNPIK	KNH	ASINL	QEA	IGN	HTA	AS	YAL	DM	KHS	YOM	1439
US1 RdRp (1359)	TKNPIK	KNH	ASINL	QEA	IGN	HTA	AS	YAL	DM	KHS	YOM	1439
DQ000985 RdRp (1358)	TKNPIK	KNH	ASINL	QEA	IGN	HTA	AS	YAL	DM	KHS	YOM	1439
FJ212288 RdRp (1358)	TKNPIK	KNH	ASINL	QEA	IGN	HTA	AS	YAL	DM	KHS	YOM	1439
220606A1 RdRp (1343)	TKNPIK	KNH	ASINL	QEA	IGN	HTA	AS	YAL	DM	KHS	YOM	1439
1906 RdRp (1358)	TKNPIK	KNH	ASINL	QEA	IGN	HTA	AS	YAL	DM	KHS	YOM	1439
VCA RdRp (1340)	TKNPIK	KNH	ASINL	QEA	IGN	HTA	AS	YAL	DM	KHS	YOM	1439

Figure 7**SEQ ID NO:1**

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SEQ ID NO: 4 EU Sp-13

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SEQ ID NO: 7 LP-2001

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Figure 8

SEQ ID NO: 8

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SEQ ID NO: 9

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