Streptococcus infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza. The methods provided herein also find use in inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof. The methods provided herein find further use in decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, neutrophils, natural killer (NK) cells, myeloid-derived suppressor cells, tumor-associated macrophages, neutrophils, NK cells, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cell in an individual in need thereof

[0023a] In one aspect, the present disclosure refers to an isolated humanized antibody that binds to a human TREM2 protein, wherein the antibody: a) induces one or more TREM2 activities when the antibody is in solution and not clustered, as determined by a luciferase-based reporter assay using a luciferase reporter gene under the control of a nuclear factor of activated T-cells (NFAT) promoter to measure TREM2-dependent gene expression in BW5147.G.1.4 cells expressing mouse TREM2 and DAP12 or a human TREM2-DAP12 fusion protein, using an increase in TREM-2 dependent gene transcription compared to the level of TREM-2 dependent gene transcription in the absence of stimulation to indicate inducement, and b) enhances one or more TREM2 activities induced by binding of phosphatidylserine to the TREM2 protein when the antibody is in solution and not clustered, as determined by a luciferase-based reporter assay using a luciferase reporter gene under the control of an NFAT promoter to measure TREM2-dependent gene expression in BW5147.G.1.4 cells expressing mouse TREM2 and DAP12 or a human TREM2-DAP12 fusion protein, wherein when the antibody is used at a concentration that ranges from 0.5 nM to 50 nM, an increase of at least 2-fold as compared to the level of TREM2-dependent gene transcription induced by binding of phosphatidylserine to the TREM2 protein in the absence of the antibody indicates enhancement, wherein phosphatidylserine is used at its EC50 concentration.

[0023b] In another aspect, the present disclosure refers to an isolated nucleic acid comprising a nucleic acid sequence encoding the antibody disclosed herein.

[0023c] In yet another aspect, the present disclosure refers to a vector comprising the nucleic acid disclosed herein.

[0023d] In yet another aspect, the present disclosure refers to an isolated host cell comprising the vector disclosed herein.

[0023e] In yet another aspect, the present disclosure refers to a method of producing an antibody that binds to TREM2, comprising culturing the host cell disclosed herein so that the antibody is produced.

[0023f] In yet another aspect, the present disclosure refers to an isolated antibody that binds to TREM2 produced by the method disclosed herein.

[0023g] In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody disclosed herein and a pharmaceutically acceptable carrier.

[0023h] In yet another aspect, the present disclosure refers to use of a therapeutically effective amount of the isolated antibody disclosed herein in the manufacture of a medicament for reducing risk or treating an individual having a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, ~~Nasu-Hakola disease,~~ cognitive deficit, memory loss, spinal cord injury, traumatic brain injury, ~~multiple sclerosis,~~ chronic colitis, and ulcerative colitis.

[0023i] Disclosed is use of a therapeutically effective amount of the isolated antibody disclosed herein in the manufacture of a medicament for inducing one or more TREM2 activities and enhancing one or more TREM2 activities

induced by binding of one or more TREM2 ligands to a TREM2 protein in an individual in need thereof.

[0023j] In yet another aspect, the present disclosure refers to an in vitro method for inducing or promoting innate immune cell survival, comprising contacting one or more cells with the isolated ~~anti-TREM2~~ antibody as described herien.

[0024] In some examples, tumor cells, such as acute myeloblastic leukemia (AML) cell, express TREM2. Accordingly, anti-TREM2 antibodies of the present disclosure also find use in treating cancers. In some examples, anti-TREM2 antibodies, including antibodies that display antibody-dependent cell-mediated cytotoxicity (ADCC) and/or TREM2 antibody drug conjugates, can be used to target and inhibit cancer, such as AML.

[0025] Certain examples of the present disclosure are based, at least in part, on the identification of two distinct classes of isolated antibodies that specifically bind to and modulate TREM2 proteins.

[0026] One class of antibodies relates to agonist antibodies that induce one or more TREM2 activities on, for example, human primary immune cells and TREM2-expressing cell lines, and when combined with one or more TREM2 ligands enhance one or more TREM2 activities induced by binding of the one or more TREM2 ligands to the TREM2 protein. Advantageously, such agonist anti-TREM2 antibodies can enhance ligand-induced TREM2 activity without competing with our otherwise blocking binding of the one or more TREM2 ligands to the TREM2 protein. In some examples, the agonist antibodies can activate and/or enhance the one or more TREM2 activities regardless of whether the antibodies are clustered or in solution. In some examples, the agonist antibodies can activate TREM2 in solution without the need to be clustered by secondary antibodies, by Fc receptors, or by binding to plates. In some examples, the agonist antibodies may activate TREM2 regardless of whether the mechanism for antibody clustering are present at the therapeutic site of action *in vivo*. In some examples, the agonist antibodies may have increased safety and efficacy. In some examples, the agonist antibodies can ensure that immune cells that express TREM2 will act primarily in the location where they are required for therapeutic efficacy and will be able to interact with their physiological targets. In some examples, the agonist antibodies do not block TREM2 activity that leads to increased disease risks similar to those observed with genetic mutations that reduce TREM2 activity.

[0027] The second class of antibodies relates to antagonist antibodies that specifically bind to and inhibit TREM2, and are incapable of activating TREM2 regardless of whether the antibodies are clustered or in solution. In some examples, the antagonist antibodies have increases safety and

CLAIMS

What is claimed is:

1. An isolated humanized antibody that binds to a human TREM2 protein, wherein the antibody: a) induces one or more TREM2 activities when the antibody is in solution and not clustered, as determined by a luciferase-based reporter assay using a luciferase reporter gene under the control of a nuclear factor of activated T-cells (NFAT) promoter to measure TREM2-dependent gene expression in BW5147.G.1.4 cells expressing mouse TREM2 and DAP12 or a human TREM2-DAP12 fusion protein, using an increase in TREM-2 dependent gene transcription compared to the level of TREM-2 dependent gene transcription in the absence of stimulation to indicate inducement, and

b) enhances one or more TREM2 activities induced by binding of phosphatidylserine to the TREM2 protein when the antibody is in solution and not clustered, as determined by a luciferase-based reporter assay using a luciferase reporter gene under the control of an NFAT promoter to measure TREM2-dependent gene expression in BW5147.G.1.4 cells expressing mouse TREM2 and DAP12 or a human TREM2-DAP12 fusion protein, wherein when the antibody is used at a concentration that ranges from 0.5 nM to 50 nM, an increase of at least 2-fold as compared to the level of TREM2-dependent gene transcription induced by binding of phosphatidylserine to the TREM2 protein in the absence of the antibody indicates enhancement, wherein phosphatidylserine is used at its EC50 concentration.

2. The isolated antibody of claim 1, wherein the antibody enhances the one or more TREM2 activities without blocking binding of phosphatidylserine to the TREM2 protein.

3. The isolated antibody of claim 1 or claim 2, wherein the antibody does not compete with phosphatidylserine for binding to the TREM2 protein.

4. The isolated antibody of any one of claims 1-3, wherein the antibody enhances binding of APOE3 to the TREM2 protein.

5. The isolated antibody of any one of claims 1-4, wherein the antibody is also capable of inducing one or more TREM2 activities and enhancing one or more TREM2 activities induced by binding of phosphatidylserine to the TREM2 protein when the antibody is clustered by secondary antibodies, by Fc receptors, or by binding to plates.

6. The isolated antibody of any one of claims 1-5, wherein the antibody further binds a non-human mammalian TREM2 protein.

7. The isolated antibody of any one of claims 1-6, wherein the one or more TREM2 activities are selected from the group consisting of:

(a) TREM2 binding to DAP12;

(b) DAP12 phosphorylation;

(c) activation of Syk kinase;

(d) modulation of one or more pro-inflammatory mediators selected from the group consisting of IFN-β, IL-1α, IL-1β, TNF-α, IL-6, IL-8, CRP, CD86, MCP-1/CCL2, CCL3, CCL4, CCL5, CCR2, CXCL-10, Gata3, IL-20 family members, IL-33, LIF, IFN-gamma, OSM, CNTF, CSF-1, OPN, CD11c, GM-CSF, IL-11, IL-12, IL-17, IL-18, and IL-23, optionally wherein the modulation occurs in one or more cells selected from the group consisting of macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, dendritic cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and microglial cells;

(e) recruitment of Syk to a DAP12/TREM2 complex;

(f) increasing activity of one or more TREM2-dependent genes, optionally wherein the one or more TREM2-dependent genes comprise nuclear factor of activated T-cells (NFAT) transcription factors;

(g) increased survival of dendritic cells, macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, microglia, M1 microglia, activated M1 microglia, ~~and~~ or M2 microglia, or any combination thereof;

(h) modulated expression of one or more stimulatory molecules selected from the group consisting of CD83, CD86 MHC class II, CD40, and any combination thereof, optionally wherein the CD40 is expressed on dendritic cells, monocytes, macrophages, or any combination thereof, and optionally wherein the dendritic cells comprise bone marrow-derived dendritic cells;

(i) increasing memory; and

(j) reducing cognitive deficit.

8. The isolated antibody of any one of claims 1-7, wherein the antibody is of the IgG class, the IgM class, or the IgA class.

9. The isolated antibody of claim 8, wherein the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype.

10. The isolated antibody of claim 9, wherein:

(a) the isolated antibody has a human or mouse IgG1 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: N297A, D265A, D270A, L234A, L235A, G237A, C226S, C229S, E233P, L234V, L234F, L235E, P331S, S267E, L328F, A330L, M252Y, S254T, T256E, ~~,~~L328E, P238D, S267E, L328F, E233D, G237D, H268D, P271G, A330R, and any combination thereof, wherein the numbering of the residues is according to EU numbering, or comprises an amino acid deletion in the Fc region at a position corresponding to glycine 236 according to EU numbering;

(b) the isolated antibody has an IgG1 isotype and comprises an IgG2 isotype heavy chain constant domain 1(CH1) and hinge region, optionally wherein the IgG2 isotype CH1 and hinge region comprises the amino acid sequence of ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVERKCCVECPPCP (SEQ ID NO: 886), and optionally wherein the antibody Fc region comprises a S267E amino acid substitution, a L328F amino acid substitution, or both, and/or a N297A or N297Q amino acid substitution, wherein the numbering of the residues is according to EU numbering;

(c) the isolated antibody has an IgG2 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: P238S, V234A, G237A, H268A, H268Q, V309L, A330S, P331S, C214S, C232S, C233S, S267E, L328F, M252Y, S254T, T256E, H268E, N297A, N297Q, A330L, and any combination thereof, wherein the numbering of the residues is according to EU numbering;

(d) the isolated antibody has a human or mouse IgG4 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: L235A, G237A, S228P, L236E, S267E, E318A, L328F, M252Y, S254T, T256E, E233P, F234V, L234A/F234A, S228P, S241P, L248E, T394D, N297A, N297Q, L235E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or

(e) the isolated antibody has a hybrid IgG2/4 isotype, and optionally wherein the antibody comprises an amino acid sequence comprising amino acids 118 to 260 of human IgG2 and amino acids 261 to 447 of human IgG4, wherein the numbering of the residues is according to EU numbering.

11. The isolated antibody of any one of claims 1-10, wherein the antibody binds to one or more amino acids within amino acid residues selected from the group consisting of:

i. amino acid residues 149-157 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 149-157 of SEQ ID NO: 1;

ii. amino acid residues 137-146 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 137-146 of SEQ ID NO: 1;

iii. amino acid residues 139-147 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 139-147 of SEQ ID NO: 1;

iv. amino acid residues 139-149 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 139-149 of SEQ ID NO: 1; and

v. amino acid residues 142-152 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 142-152 of SEQ ID NO: 1.

12. The isolated antibody of any one of claims 1-10, wherein the antibody binds to amino acid residues E151, D152, H154, and E156 of SEQ ID NO: 1, or amino acid residues on a mammalian TREM2 protein corresponding to amino acid residues E151, D152, H154, and E156 of SEQ ID NO: 1.

13. The isolated antibody of any one of claims1-12, wherein the antibody competes with one or more antibodies selected from the group consisting of:
i. an antibody comprising the HVR-L1 of SEQ ID NO: 19, the HVR-L2 of SEQ ID NO: 28, the HVR-L3 of SEQ ID NO: 43, the HVR-H1 of SEQ ID NO: 60, the HVR-H2 of SEQ ID NO: 78, and the HVR-H3 of SEQ ID NO: 97;
ii. an antibody comprising the HVR-L1 of SEQ ID NO: 16, the HVR-L2 of SEQ ID NO: 29, the HVR-L3 of SEQ ID NO: 35, the HVR-H1 of SEQ ID NO: 55, the HVR-H2 of SEQ ID NO: 73, and the HVR-H3 of SEQ ID NO: 92;
iii. an antibody comprising the HVR-L1 of SEQ ID NO: 16, the HVR-L2 of SEQ ID NO: 29, the HVR-L3 of SEQ ID NO: 35, the HVR-H1 of SEQ ID NO: 65, the HVR-H2 of SEQ ID NO: 84, and the HVR-H3 of SEQ ID NO: 102;
iv. an antibody comprising the HVR-L1 of SEQ ID NO: 11, the HVR-L2 of SEQ ID NO: 26, the HVR-L3 of SEQ ID NO: 36, the HVR-H1 of SEQ ID NO: 51, the HVR-H2 of SEQ ID NO: 69, and the HVR-H3 of SEQ ID NO: 88;
and any combination thereof for binding to TREM2.

14. The isolated antibody of any one of claims 1 - 12, wherein the antibody comprises an HVR-L1, an HVR-L2, an HVR-L3, an HVR-H1, an HVR-H2, and an HVR-H3, wherein:

(a) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19 or an amino acid sequence of SEQ ID NO: 19 having one or more conservative amino acid substitutions, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28 or an amino acid sequence of SEQ ID NO: 28 having one or more conservative amino acid substitutions, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 43 or an amino acid sequence of SEQ ID NO: 43 having one or more conservative amino acid substitutions, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence of SEQ ID NO: 60 having one or more conservative amino acid substitutions, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 78 or an amino acid sequence of SEQ ID NO: 78 having one or more conservative amino acid substitutions, and the HVR-H3 comprises the

amino acid sequence of SEQ ID NO: 97 or an amino acid sequence of SEQ ID NO: 97 having one or more conservative amino acid substitutions;

(b) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 11 or an amino acid sequence of SEQ ID NO: 11 having one or more conservative amino acid substitutions, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 26 or an amino acid sequence of SEQ ID NO: 26 having one or more conservative amino acid substitutions, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 36 or an amino acid sequence of SEQ ID NO: 36 having one or more conservative amino acid substitutions, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 51 or an amino acid sequence of SEQ ID NO: 51 having one or more conservative amino acid substitutions, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence of SEQ ID NO: 69 having one or more conservative amino acid substitutions, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 88 or an amino acid sequence of SEQ ID NO: 88 having one or more conservative amino acid substitutions**;**

(c) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16 or an amino acid sequence of SEQ ID NO: 16 having one or more conservative amino acid substitutions, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29 or an amino acid sequence of SEQ ID NO: 29 having one or more conservative amino acid substitutions, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 35 or an amino acid sequence of SEQ ID NO: 35 having one or more conservative amino acid substitutions, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 55 or an amino acid sequence of SEQ ID NO: 55 having one or more conservative amino acid substitutions, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence of SEQ ID NO: 73 having one or more conservative amino acid substitutions, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 92 or an amino acid sequence of SEQ ID NO: 92 having one or more conservative amino acid substitutions;

(d) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 19 or an amino acid sequence of SEQ ID NO: 19 having one or more conservative amino acid substitutions, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 28 or an amino acid sequence of SEQ ID NO: 28 having one or more conservative amino acid substitutions, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 43 or an amino acid sequence of SEQ ID NO: 43 having one or more conservative amino acid substitutions, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence of SEQ ID NO: 60 having one or more conservative amino acid substitutions, the HVR-H2 comprises the amino acid

sequence of SEQ ID NO: 888 or an amino acid sequence of SEQ ID NO: 888 having one or more conservative amino acid substitutions, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 97 or an amino acid sequence of SEQ ID NO: 97 having one or more conservative amino acid substitutions; or

(e) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 16 or an amino acid sequence of SEQ ID NO: 16 having one or more conservative amino acid substitutions, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 29 or an amino acid sequence of SEQ ID NO: 29 having one or more conservative amino acid substitutions, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 35 or an amino acid sequence of SEQ ID NO: 35 having one or more conservative amino acid substitutions, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 65 or an amino acid sequence of SEQ ID NO: 65 having one or more conservative amino acid substitutions, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 84 or an amino acid sequence of SEQ ID NO: 84 having one or more conservative amino acid substitutions, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 102 or an amino acid sequence of SEQ ID NO: 102 having one or more conservative amino acid substitutions.

15. The isolated antibody of any one of claims 1 - 14, wherein the antibody is an antibody fragment and the antibody fragment is an Fab, Fab', Fab'-SH, F(ab')2, Fv or scFv fragment.

16. The isolated antibody of any one of claims 1-15, wherein the antibody is a monoclonal antibody.

17. The isolated antibody of any one of the preceding claims, wherein the antibody binds specifically to both human TREM2 and mouse TREM2.

18. The isolated antibody of any one of the preceding claims, wherein the antibody:

(a) has a dissociation constant (K_D) for human TREM2 that ranges from 0.9 nM to 12.8 nM, wherein the K_D is determined at a temperature of approximately 4ºC; and/or

(b) has a dissociation constant (K_D) for mouse TREM2 that ranges from 1.2 nM to 10.4 nM, wherein the K_D is determined at a temperature of approximately 4ºC.

19. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of the preceding claims.

20. A vector comprising the nucleic acid of claim 19.

21. An isolated host cell comprising the vector of claim 20.

22. A method of producing an antibody that binds to TREM2, comprising culturing the host cell of claim 21 so that the antibody is produced.

23. An isolated antibody that binds to TREM2 produced by the method of claim 22.

24. A pharmaceutical composition comprising the antibody of any one of claims 1-18 and a pharmaceutically acceptable carrier.

25. Use of a therapeutically effective amount of the isolated antibody of any one of claims 1-18 in the manufacture of a medicament for reducing risk or treating an individual having a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, ~~Nasu-Hakola disease,~~ cognitive deficit, memory loss, spinal cord injury, traumatic brain injury, ~~multiple sclerosis,~~ chronic colitis, and ulcerative colitis.

26. The use of claim 25, wherein the disease, disorder, or injury is Alzheimer's disease.

27. An in vitro method for inducing or promoting innate immune cell survival, comprising contacting one or more cells with the isolated ~~anti-TREM2~~ antibody of any one of claims 1-18.

28. The use of claim 25 or 26, wherein the individual has a heterozygous variant of TREM2, wherein the variant comprises one or more substitutions selected from the group consisting of:

i. a glutamic acid to stop codon substitution in the nucleic acid sequence encoding amino acid residue Glu14 of SEQ ID NO: 1;
ii. a glutamine to stop codon substitution in the nucleic acid sequence encoding amino acid residue Gln33 of SEQ ID NO: 1;
iii. a tryptophan to stop codon substitution in the nucleic acid sequence encoding amino acid residue Trp44 of SEQ ID NO: 1;
iv. an arginine to histidine amino acid substitution at an amino acid corresponding to amino acid residue Arg47 of SEQ ID NO: 1;
v. a tryptophan to stop codon substitution in the nucleic acid sequence encoding amino acid residue Trp78 of SEQ ID NO: 1;
vi. a valine to glycine amino acid substitution at an amino acid corresponding to amino acid residue Val126 of SEQ ID NO: 1;
vii. an aspartic acid to glycine amino acid substitution at an amino acid corresponding to amino acid residue Asp134 of SEQ ID NO: 1; and
viii. a lysine to asparagine amino acid substitution at an amino acid corresponding to amino acid residue Lys186 of SEQ ID NO: 1.

29. The use of any one of claims 25, 26 and 28, wherein the individual has a heterozygous variant of TREM2, wherein the variant comprises a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G313 of the nucleic acid sequence encoding SEQ ID NO: 1; a guanine

nucleotide deletion at a nucleotide corresponding to nucleotide residue G267 of the nucleic acid sequence encoding SEQ ID NO: 1; or both.

30. The use of any one of claims 25, 26, 28 and 29, wherein the individual has a heterozygous variant of DAP12, wherein the variant comprises one or more variants selected from the group consisting of:

i. a methionine to threonine substitution at an amino acid corresponding to amino acid residue Met1 of SEQ ID NO: 8872;
ii. a glycine to arginine amino acid substitution at an amino acid corresponding to amino acid residue Gly49 of SEQ ID NO: 8872;
iii. a deletion within exons 1-4 of the nucleic acid sequence encoding SEQ ID NO: 8872;
iv. an insertion of 14 amino acid residues at exon 3 of the nucleic acid sequence encoding SEQ ID NO: 8872; and
v. a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G141 of the nucleic acid sequence encoding SEQ ID NO: 8872.