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Our Reference : 2161SG244/KJR/SEL(EVA)/hba
Your Reference : 201209289-6

Dear Colleagues,

Singapore Patent Application No. 201209289-6
Invention : Methods Of Treatment Using TLR7 And/Or TLR9 Inhibitors
Applicant : Dynavax Technologies Corporation

We refer to the Patents Form 13 filed today.

Claim Amendments

Pending Claims 1-30 are replaced with new claims 1-16.

New claims 1 – 16 find basis throughout the specification as filed, *inter alia*, at the following pages and parts of the specification set out in the following table:

New Claim	Basis
1	Original claim 25 on file
2	Original claim 26 on file
3	End of paragraph [0183]
4	End of paragraph [0190]
5	Original claim 27 on file
6	Original claim 28 on file
7	Original claim 29 on file
8	Original claim 30 on file
9	Original claim 1 on file
10	Original claim 3 on file and end of paragraph [0151]
11	Original claim 11 on file and paragraph [0193]

12	Original claim 12 on file
13	End of paragraphs [0019] and [0020]
14	Original claim 10 on file
15	Original claim 18 on file
16	Original claim 19 on file

We trust the above is in order.

Yours faithfully,

SAF

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CLAIMS

What is claimed is:

1. A method of treating an autoimmune disease in an individual comprising administering to the individual an effective amount of a TLR7 inhibitor and/or TLR9 inhibitor, wherein an elevated inflammatory gene expression pattern as compared to that of control sample(s) from healthy subject(s) is present in a sample from the individual at the onset of treatment, and wherein the TLR7 and/or TLR9 inhibitor is a polynucleotide comprising the nucleotide sequence of the formula: RγJGCKαGIGGLβ-3' (SEQ ID NO:146), wherein each R, K, and L is a nucleotide, J is U or T, γ is an integer from about 0 to 10, α is an integer from about 1 to about 20, and β is an integer from about 1 to about 20.

2. The method of Claim 1, further comprising selecting the individual having the elevated inflammatory gene expression pattern, prior to the administering step.

3. The method of Claim 1 or Claim 2, wherein the TLR7 inhibitor and/or TLR9 inhibitor is administered in an amount effective to achieve one or more of the following outcomes:

a. reduce the inflammatory gene expression pattern in a post-treatment sample from the individual;

b. reduce a clinical disease activity measure of the autoimmune disease;

c. reduce a serologic disease measure of the autoimmune disease; and

d. increase plasmacytoid dendritic cells in a post-treatment peripheral blood mononuclear cell sample from the individual.

4. The method of any one of Claims 1-3, further comprising administering a second therapeutic agent.

5. The method of Claim 4, wherein the second therapeutic agent is selected from the group consisting of a corticosteroid, a nonsteroidal anti-inflammatory drug (NSAID), an IFN-alpha inhibitor, and an anti-malarial.

6. A method of treating an autoimmune disease in an individual comprising - administering to the individual an amount of a TLR7 inhibitor and/or TLR9 inhibitor effective to reduce glucocorticoid use by the individual, wherein an elevated inflammatory gene expression pattern as compared to that of control sample(s) from healthy subject(s) is present in a sample from the individual at the onset of treatment, and wherein the TLR7 and/or TLR9 inhibitor is a

~~polynucleotide comprising the nucleotide sequence of the formula: RγJGCKαGIGGLβ-3' (SEQ~~ ID NO:146), wherein each R, K, and L is a nucleotide, J is U or T, γ is an integer from about 0 to 10, α is an integer from about 1 to about 20, and β is an integer from about 1 to about 20.

7. A method of assessing whether an individual having an autoimmune disease is likely to respond to a treatment comprising an effective amount of a TLR7 inhibitor and/or TLR9 inhibitor, the method comprising measuring an inflammatory gene expression pattern in a sample from the individual, wherein an elevated inflammatory gene expression pattern as compared to that of control sample(s) from healthy subject(s) indicates that the individual is likely to respond to the treatment and wherein the TLR7 and/or TLR9 inhibitor is a polynucleotide comprising the nucleotide sequence of the formula: RγJGCKαGIGGLβ-3' (SEQ ID NO:146), wherein each R, K, and L is a nucleotide, J is U or T, γ is an integer from about 0 to 10, α is an integer from about 1 to about 20, and β is an integer from about 1 to about 20.

8. A method of monitoring responsiveness of an individual having an autoimmune disease to a treatment comprising an effective amount of a TLR7 inhibitor and/or TLR9 inhibitor, the method comprising measuring an inflammatory gene expression pattern in a sample from the individual pre- and post-treatment, wherein when the inflammatory gene expression pattern is reduced in the post-treatment sample as compared to the pre-treatment sample, the individual is determined to be responsive to the treatment, and wherein the TLR7 and/or TLR9 inhibitor is a polynucleotide comprising the nucleotide sequence of the formula: RγJGCKαGIGGLβ-3' (SEQ ID NO:146), wherein each R, K, and L is a nucleotide, J is U or T, γ is an integer from about 0 to 10, α is an integer from about 1 to about 20, and β is an integer from about 1 to about 20.

9. The method of any one of Claims 1-8, wherein the individual is a human patient.

10. The method of any one of Claims 1-9, wherein the autoimmune disease is systemic lupus erythematosus (SLE) or cutaneous lupus erythematosus (CLE).

11. The method of any one of Claims 1-10, wherein the polynucleotide comprises or consists of a nucleotide sequence selected from the group consisting of SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:78, SEQ ID NO:143 and SEQ ID NO:144. [SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:78, SEQ ID NO:141, SEQ ID NO:143 and SEQ ID NO:144]

12. The method of any one of Claims 1-10, wherein the polynucleotide comprises or consists of a nucleotide sequence selected from the group consisting of SEQ ID NO:73, SEQ ID ~~NO:134, SEQ ID NO:143 and SEQ ID NO:144.~~

13. The method of any one of Claims 1-12, wherein one or more nucleotides comprise a modification.

14. The method of Claim 13, wherein the modification comprises at least one phosphorothioate backbone modification.

15. The method of Claim 13, wherein the modification comprises a 2'-sugar modification.

16. The method of Claim 15, wherein the 2'-sugar modification comprises a 2'-O-methyl sugar modification or a 2'-O-methoxyethyl sugar modification.

17. The method of any one of Claims 1-16, wherein the elevated inflammatory gene expression pattern comprises an interferon (IFN) signature comprising elevated levels in the sample of one or more biomarkers selected from the group consisting of BATF2, CMPK2, CXCL10, DDX60, EPSTI1, HERC5, HES4, IFI44, IFI44L, IFIT1, IFIT3, IFITM3, ISG15, LAMP3, LOC26010, LY6E, MX1, OAS1, OAS2, OAS3, OASL, OTOF, RSAD2, RTP4, SERPING1, TRIM6, XAF1, cl02h05 5, Agencourt-7914287 NIH-MCG_71, ISG20, IFI16, IRF7, and AIM2, as compared to the control sample(s).

18. The method of any one of Claims 1-16, wherein the elevated inflammatory gene expression pattern comprises an interferon (IFN) signature comprising elevated levels in the sample of one or more biomarkers selected from the group consisting of BATF2, CMPK2, DDX60, EPSTI1, HERC5, HES4, IFI44, IFI44L, IFIT1, IFIT3, IFITM3, ISG15, LAMP3, LOC26010, MX1, OAS1, OAS2, OAS3, OASL, OTOF, RSAD2, RTP4, SERPING1, TRIM6, XAF1, cl02h05 5, Agencourt-7914287 NIH-MCG_71, ISG20, IRF7, and AIM2, as compared to the control sample(s).

19. The method of any one of Claims 1-16, wherein the elevated inflammatory gene expression pattern comprises elevated levels in the sample of one or more cytokines selected from the group consisting of IL-1alpha, IL-1 beta, TNF-alpha, IL-6, IL-17, IFN-alpha, IFN-omega, IFN-lambda1, IFN-lambda2, and IP-10, as compared to the control sample(s).

20. The method of any one of Clams 1-19, wherein the sample comprises peripheral blood mononuclear cells (PBMC) or skin tissue.

21. The method of any one of Claims 9- 20, wherein the control sample(s) from healthy subject(s) comprises PBMC from at least 10 healthy human subjects.

22. The method of any one of Claims 1-21, wherein the elevated inflammatory gene expression pattern further comprises a SLE signature comprising elevated levels in the sample of

~~one or more biomarkers selected from the group consisting of GTPBP2, PCTAIRE2BP,~~ DNAPTP96, GPR84, B4GALT5, FRAT2, and PAFAH1B, as compared to the control sample(s).

23. The method of any one of Claims 1-22, wherein the elevated inflammatory gene expression pattern is determined by measuring mRNA expressed from a gene of the biomarker.

24. The method of any one of Claims 1-22, wherein the elevated inflammatory gene expression pattern is determined by measuring protein expression from a gene of the biomarker.

25. A polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NO:73, SEQ ID NO:134, SEQ ID NO:143 and SEQ ID NO:144.

26. A polynucleotide consisting of nucleotide sequence selected from the group consisting of SEQ ID NO:73, SEQ ID NO:134, SEQ ID NO:143 and SEQ ID NO:144.

27. The polynucleotide of Claim 25 or 26, wherein one or more nucleotides comprises a modification.

28. The polynucleotide of Claim 27, wherein the modification comprises at least one phosphorothioate backbone modification.

29. The polynucleotide of Claim 27, wherein the modification comprises a 2'-sugar modification.

30. The polynucleotide of Claim 29, wherein the 2'-sugar modification comprises a ~~2'-O-methyl sugar modification or a 2'-O-methoxyethyl sugar modification.~~

CLAIMS

1. A polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NO:73, SEQ ID NO:134, SEQ ID NO:143 and SEQ ID NO:144.

2. The polynucleotide of Claim 1, wherein the polynucleotide consists of the nucleotide sequence selected from the group consisting of SEQ ID NO:73, SEQ ID NO:134, SEQ ID NO:143 and SEQ ID NO:144.

3. The polynucleotide of Claim 1, wherein the polynucleotide does not comprise a CG.

4. The polynucleotide of Claim 1 or Claim 3, wherein the polynucleotide is less than 50 bases or base pairs in length.

5. The polynucleotide of any one of Claims 1-4, wherein one or more nucleotides comprises a modification.

6. The polynucleotide of Claim 5, wherein the modification comprises at least one phosphorothioate backbone modification.

7. The polynucleotide of Claim 5, wherein the modification comprises a 2'-sugar modification.

8. The polynucleotide of any one of Claims 1-7, for use in treating an autoimmune disease in an individual.

9. A polynucleotide for use in treating an autoimmune disease in an individual, wherein an elevated inflammatory gene expression pattern as compared to that of control sample(s) from healthy subject(s) is present in a sample from the individual at the onset of treatment, and wherein the polynucleotide comprises a nucleotide sequence of the formula: RγJGCKαGIGGLβ-3' (SEQ ID NO:146), wherein each R, K, and L is a nucleotide, J is U or T, γ is an integer from 0 to 10, α is an integer from 1 to 20, and β is an integer from 1 to 20.

10. The polynucleotide for use according to Claim 9, wherein treating the autoimmune disease achieves one or more of the following outcomes:

a.) reduces the inflammatory gene expression pattern in a post-treatment sample from the individual;

b.) reduces a clinical disease activity measure of the autoimmune disease;

c.) reduces a serologic disease measure of the autoimmune disease;

d.) increases plasmacytoid dendritic cells in a post-treatment peripheral blood mononuclear cell sample from the individual; and

e) reduces concurrent corticosteroid use by the individual.

11. The polynucleotide for use according to Claim 9 or Claim 10, wherein the polynucleotide comprises or consists of a nucleotide sequence selected from the group consisting of SEQ ID NOS:64, 65, 66, 70, 71, 72, 73, 74, 75, 77, 78, 79, 123, 124, 125, 126, 127, 128, 129, 130, 132, 133, 134, 135, 142, 143, 144 and 145.

12. The polynucleotide for use according to Claim 9 or Claim 10, wherein the polynucleotide comprises or consists of a nucleotide sequence selected from the group consisting of SEQ ID NO:73, SEQ ID NO:134, SEQ ID NO:143, and SEQ ID NO:144.

13. The polynucleotide for use according to any one of Claims 9-12, wherein the individual is a human patient.

14. The polynucleotide for use according to any one of Claims 9-13, wherein the autoimmune disease is systemic lupus erythematosus (SLE) or cutaneous lupus erythematosus (CLE).

15. The polynucleotide for use according to any one of Claims 9-14, wherein the elevated inflammatory gene expression pattern comprises an interferon (IFN) signature comprising elevated levels in the sample of one or more biomarkers selected from the group consisting of BATF2, CMPK2, DDX60, EPSTI1, HERC5, HES4, IFI44, IFI44L, IFIT1, IFIT3, IFITM3, ISG15, LAMP3, LOC26010, MX1, OAS1, OAS2, OAS3, OASL, OTOF, RSAD2, RTP4, SERPING1, TRIM6, XAF1, cl02h05 5, Agencourt-7914287 NIH-MCG_71, ISG20, IRF7, and AIM2, as compared to the control sample(s).

16. The polynucleotide for use according any one of Claims 9-14, wherein the elevated inflammatory gene expression pattern comprises elevated levels in the sample of one or more cytokines selected from the group consisting of IL-1alpha, IL-1 beta, TNF-alpha, IL-6, IL-17, IFN-alpha, IFN-omega, IFN-lambda1, IFN-lambda2, and IP-10, as compared to the control sample(s).