

CLAIMS

1. A method for predicting Natural Killer T-Cell Lymphoma (NKTCL) susceptibility and/or diagnosing NKTCL in a subject, comprising testing for the genotype of said subject for at least one *JAK* gene, wherein the presence of a mutant *JAK* gene indicates that a subject is at risk of developing and/or has NKTCL.
2. The method according to claim 1, comprising testing for the genotype of said subject for at least one of *JAK1*, *JAK2*, *JAK3* and/or *TYK2* genes.
3. The method according to claim 1 or 2, comprising testing for the genotype of said subject for at least one of *JAK3* and/or *JAK1* genes.
4. The method according to any one of the preceding claims, wherein wildtype *JAK3* gene comprises SEQ ID NO: 1 and the mutant *JAK3* gene comprises a substitution of C with T at nucleotide 15792 and/or a substitution of C with T at nucleotide 15795 of SEQ ID NO: 1.
5. The method according to any one of the preceding claims, wherein wildtype *JAK1* gene comprises SEQ ID NO: 3 and the mutant gene comprises a substitution of T with G at nucleotide 124823 of SEQ ID NO:3.
6. The method according to any one of the preceding claims, further comprising providing an isolated blood and/or cell sample from the subject for said testing.
7. The method according to claim any one of the preceding claims, further comprising isolating nucleic acid molecules from the subject, the isolated blood and/or cell sample from the subject for said testing.
8. The method according to claim 7, wherein the isolated nucleic acid molecules comprise genomic DNA or mRNA.
9. The method according to any one of the preceding claims, wherein said testing is performed on genomic DNA, mRNA and/or cDNA.
10. The method according to claim 8 or 9, wherein the testing comprises sequence analysis, restriction fragment length polymorphism analysis, hybridization, polymerase chain reaction (PCR) and/or reverse transcription PCR.

11. A method for predicting Natural Killer T-Cell Lymphoma (NKTCL) susceptibility and/or diagnosing NKTCL in a subject, comprising testing for whether said subject expresses a wildtype or mutant JAK protein, wherein expression of a mutant JAK protein indicates that the subject is at risk of developing and/or has NKTCL.
12. The method according to claim 11, comprising testing for whether said subject expresses wildtype and/or at least one mutant JAK1, JAK2, JAK3 and/or TYK2 proteins.
13. The method according to claim 11 or 12, comprising testing for whether said subject expresses wildtype or mutant JAK3 and/or JAK1 proteins.
14. The method according to any one of claims 11 to 13, wherein wildtype JAK3 protein comprises SEQ ID NO:2 and the mutant JAK3 protein comprises a substitution of A with V at amino acid 572 and/or a substitution of A with V at amino acid 573 of SEQ ID NO:2.
15. The method according any one of claims 11 to 14, where wildtype JAK1 protein comprises SEQ ID NO: 4 and the mutant JAK1 protein comprises a substitution of Y with D at amino acid 652 of SEQ ID NO:4.
16. The method according to any one of claims 11 to 15, further comprising providing an isolated blood and/or cell sample from the subject for said testing.
17. The method according to any one of claims 11 to 16, further comprising isolating at least one protein from the subject, the isolated blood and/or cell sample from the subject for said testing.
18. The method according to any one of claims 11 to 17, wherein the testing comprises protein sequencing and antibody detection methods.
19. A method for screening for an agent capable of treating NKTCL, comprising:
 - (i) providing a NKTCL cell line comprising at least one mutant JAK gene;
 - (ii) contacting the NKTCL cell line with the agent; and

(iii) determining the effect of the agent on the mammalian NKTCL cell line;

wherein the ability of the agent to reduce the viability, growth and/or multiplication and/or increase apoptosis of the NKTCL cell line is indicative of the ability of the agent to treat NKTCL.

5 20. A method for screening for an agent capable of reducing the activity of at least one JAK protein, comprising:

(i) providing a NKTCL cell line carrying at least one mutant *JAK* gene

(ii) contacting the NKTCL cell line with the agent; and

(iii) determining the effect of the agent on the NKTCL cell line;

10 wherein the ability of the agent to reduce the viability, growth and/or multiplication and/or increase apoptosis of cell line is indicative of the ability of the candidate agent to reduce the activity of at least one *JAK* protein.

21. The method according to claim 19 or 20, wherein the NKTCL cell line carries at least one of mutant *JAK1*, *JAK2*, *JAK3* and/or *TYK2* genes.

15 22. The method according to any one of claims 19 to 21, wherein the NKTCL cell line carries a mutant *JAK3* gene and/or a mutant *JAK1* gene.

23. The method according to any one of claims 19 to 22, wherein the NKTCL cell line carries at least one of the following *JAK* mutations:

(i) a substitution of C with T at nucleotide 15792 of SEQ ID NO: 1;

20 (ii) a substitution of C with T at nucleotide 15795 of SEQ ID NO: 1; and

(iii) a substitution of T with G at nucleotide 124823 of SEQ ID NO: 3.

24. An NKTCL animal model comprising at least one mutant *JAK* gene.

25. The NKTCL animal model according to claim 24, comprising at least one of mutant *JAK1*, *JAK2*, *JAK3* and/or *TYK2* genes.

25 26. The NKTCL animal model according to claim 24, comprising a mutant *JAK3* gene and/or a mutant *JAK1* gene.

27. The NKTCL animal model according to any one of claims 24 to 26, comprising at least one of the following mutations:
- (i) a substitution of C with T at nucleotide 15792 of SEQ ID NO: 1;
 - (ii) a substitution of C with T at nucleotide 15795 of SEQ ID NO: 1; or
 - (iii) a substitution of T with G at nucleotide 124823 of SEQ ID NO: 3.
28. A method of treating Natural Killer T-Cell Lymphoma (NKTCL) comprising administering at least one JAK inhibitor to a subject.
29. The method according to claim 28, wherein the JAK inhibitor inhibits at least one of JAK1, JAK2, JAK3 and/or TYK2 proteins.
30. The method according to claim 28 or 29, wherein the JAK inhibitor inhibits JAK3 and/or JAK1.
31. The method according to any one of claims 28 to 30, wherein the JAK inhibitor inhibits JAK3.
32. The method according to any one of claims 29 to 30, wherein the JAK inhibitor inhibits JAK1.
33. The method according to any one of claims 28 to 32, wherein the JAK inhibitor comprises 3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile (CP-690,550) and/or (E)-2-cyano-3-(4-nitrophenyl)-N-((R)-1-phenylethyl)acrylamide (WP-1034).
34. The method according to any one of claims 28 to 33, wherein the JAK inhibitor comprises 3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile (CP-690,550).
35. The method according to any one of claims 28 to 33, wherein the JAK inhibitor comprises (E)-2-cyano-3-(4-nitrophenyl)-N-((R)-1-phenylethyl)acrylamide (WP-1034).
36. The method according to any one of claims 28 to 35, wherein the subject comprises a mammal.

37. The method according to any one of claims 28 to 36, wherein the subject comprises a human.
38. The method according to claim 37, wherein the subject with at least one mutation selected from the group consisting of JAK3-A572V, JAK3-A573V and/or JAK1-Y652D.
39. Use of at least one JAK inhibitor for the preparation of a medicament for the treatment of Natural Killer T-Cell Lymphoma (NKTCL).
40. Use according to claim 39, wherein the JAK inhibitor inhibits at least one of JAK1, JAK2, JAK3 and/or TYK2 proteins.
41. Use according to claim 39 or 40, wherein the JAK inhibitor inhibits JAK1 and/or JAK3.
42. Use according to any one of claims 39 to 41, wherein the JAK inhibitor inhibits JAK3.
43. Use according to any one of claims 39 to 41, wherein the JAK inhibitor inhibits JAK1.
44. Use according to any one of claims 39 to 43, wherein the JAK inhibitor comprises 3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile (CP-690,550) and/or (E)-2-cyano-3-(4-nitrophenyl)-N-((R)-1-phenylethyl)acrylamide (WP-1034).
45. Use according to any one of claims 39 to 44, wherein the JAK inhibitor comprises 3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile (CP-690,550).
46. Use according to any one of claims 39 to 44, wherein the JAK inhibitor comprises (E)-2-cyano-3-(4-nitrophenyl)-N-((R)-1-phenylethyl)acrylamide (WP-1034).
47. Use according to any one of claims 39 to 46, wherein the medicament is for treatment of NKTCL in a subject comprising at least one mutation selected from the group consisting of JAK3-A572V, JAK3-A573V and JAK1-Y652D.
48. A JAK inhibitor for use in treating Natural Killer T-Cell Lymphoma (NKTCL).

49. The JAK inhibitor according to claim 48, wherein the JAK inhibitor inhibits at least one of JAK1, JAK2, JAK3 and/or TYK2 proteins.
50. The JAK inhibitor according to claim 48 or 49, wherein the JAK inhibitor inhibits JAK3 and/or JAK1.
- 5 51. The JAK inhibitor according any one of claims 48 to 50, wherein the JAK inhibitor inhibits JAK3.
52. The JAK inhibitor according to any one of claims 48 to 50, wherein the JAK inhibitor inhibits JAK1.
- 10 53. The JAK inhibitor according to any one of claims 48 to 52, wherein the JAK inhibitor comprises 3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile (CP-690,550) and/or (E)-2-cyano-3-(4-nitrophenyl)-N-((R)-1-phenylethyl)acrylamide (WP-1034).
- 15 54. The JAK inhibitor according to any one of claims 48 to 53, wherein the JAK inhibitor comprises 3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile (CP-690,550).
55. The JAK inhibitor according to any one of claims 48 to 53, wherein the JAK inhibitor comprises (E)-2-cyano-3-(4-nitrophenyl)-N-((R)-1-phenylethyl)acrylamide (WP-1034).
- 20 56. The JAK inhibitor according to any one of claims 48 to 55, wherein the NKTCL is in a subject comprising at least one mutation selected from the group consisting of JAK3-A572V, JAK3-A573V and JAK1-Y652D.

CLAIMS

1. A method for predicting Natural Killer T-Cell Lymphoma (NKTCL) susceptibility and/or diagnosing NKTCL in a subject, comprising analysing an isolated blood and/or cell sample from the subject by (i) testing for the genotype of said subject for the *JAK1* and/or *JAK3* gene or (ii) testing for whether said subject expresses a wildtype or mutant *JAK1* and/or *JAK3* protein, wherein the presence of a mutant *JAK1* and/or *JAK3* gene or a mutant *JAK1* and/or *JAK3* protein indicates that the subject is at risk of developing and/or has NKTCL.
2. The method according to claim 1, wherein:
 - a wildtype *JAK3* gene comprises a sequence with NCBI reference NG_007273.1 and the mutant *JAK3* gene comprises a substitution of C with T at nucleotide 15792 and/or a substitution of C with T at nucleotide 15795 of said sequence with NCBI reference NG_007273.1; and/or
 - a wildtype *JAK1* gene comprises a sequence with NCBI reference NG_023402.1 and the mutant gene comprises a substitution of T with G at nucleotide 124823 of said sequence with NCBI reference NG_023402.1.
3. The method according to claim 1 or 2, wherein:
 - the wildtype *JAK3* protein comprises a sequence with GenBank reference AAC50950.1 and the mutant *JAK3* protein comprises a substitution of A with V at amino acid 572 and/or a substitution of A with V at amino acid 573 of said sequence with GenBank reference AAC50950.1; and/or
 - the wildtype *JAK1* protein comprises a sequence with NCBI reference NP_002218.2 and the mutant *JAK1* protein comprises a substitution of Y with D at amino acid 652 of said sequence with NCBI reference NP_002218.2.
4. The method according to any one of the preceding claims, wherein when the method comprises testing for the genotype of said subject, the method comprises isolating nucleic acid molecules from an isolated blood and/or cell sample from the subject for said testing.

5. The method according to any claim 4, wherein said testing is performed on genomic DNA, mRNA and/or cDNA;
6. The method according to claim 4 or 5, wherein the testing comprises sequence analysis, restriction fragment length polymorphism analysis, hybridization,
5 polymerase chain reaction (PCR) and/or reverse transcription PCR.
7. The method according to any one of the preceding claims, wherein when the method comprises testing for whether said subject expresses a wildtype or mutant JAK1 and/or JAK3 protein, the method comprises isolating at least one protein from an isolated blood and/or cell sample from the subject for said testing.
- 10 8. The method according to claim 7; wherein the testing comprises protein sequencing and/or antibody detection methods.
9. A method for screening for an agent capable of treating NKTCL or for an agent capable of reducing the activity of at least one JAK protein,
the method comprising:
15 (i) providing a NKTCL cell line comprising a mutant *JAK1* and/or *JAK3* gene;
(ii) contacting the NKTCL cell line with the agent; and
(iii) determining the effect of the agent on the mammalian NKTCL cell line;
wherein the ability of the agent to reduce the viability, growth and/or multiplication and/or increase apoptosis of the NKTCL cell line is indicative of the ability of the
20 agent to treat NKTCL or to reduce the activity of a JAK1 and/or JAK3 protein.
10. The method according to claim 9, wherein the NKTCL cell line comprises at least one of the following mutations:
(i) a substitution of C with T at nucleotide 15792 of a sequence with NCBI reference NG_007273.1;
25 (ii) a substitution of C with T at nucleotide 15795 of a sequence with NCBI reference NG_007273.1; or

- (iii) a substitution of T with G at nucleotide 124823 of a sequence with NCBI reference NG_023402.1.

11. A non-human NKTCL animal model comprising at least one of the following mutations:

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- (i) a substitution of C with T at nucleotide 15795 of a sequence with NCBI reference NG_007273.1; or
 - (ii) a substitution of T with G at nucleotide 124823 of a sequence with NCBI reference NG_023402.1.