

SUMMARY

The present ~~invention~~disclosure provides novel peptides derived from Myelin Oligodendrocyte Glycoprotein (MOG) for the treatment of demyelinating disorders such as but not limited to Multiple Sclerosis and Neuromyelitis Optica (NMO). The peptides of the present ~~invention~~disclosure have the advantage that they bind to HLA-DRB1*03:01, HLA-DRB1*04:01 and HLA-DRB1*15:01 with much higher affinity than prior art peptides disclosed in WO2017182528. Stimulation of MS patients cells with the peptides of the ~~invention~~disclosure induced specific CD4+ T cells with lytic properties.

In one aspect, the disclosure provides an isolated immunogenic peptide with a length of between 12 and 50 amino acids, said immunogenic peptide comprising:

a1) an oxidoreductase motif with the sequence Z_m -[CST]- X_n -C- or Z_m -C- X_n -[CST], wherein n is an integer chosen from: 2, 0, 1 or 3, wherein m is an integer selected from 2, 1, 0, or 3, wherein X is any amino acid, wherein Z is any amino acid, in which C stands for cysteine, S for serine, T for threonine;

a2) a T-cell epitope with an amino acid sequence selected from the group consisting of: MHC class II T cell epitopes FLRVPSWKI (SEQ ID NO: 2) and FLRVPCWKI (SEQ ID NO: 1), or NKT cell epitopes FLRVPCW (SEQ ID NO: 63), and FLRVPSW (SEQ ID NO: 64), and

wherein said oxidoreductase motif and said epitope are separated by a linker sequence of between 3 to 7 amino acids comprising the sequence VRY, and wherein said peptide has a reducing activity for disulfide bonds on proteins.

In one aspect, the disclosure provides a polynucleotide encoding the peptide as disclosed herein, wherein said polynucleotide is selected from the group comprising DNA, pDNA, cDNA, RNA, and mRNA or modified versions thereof.

In one aspect, the disclosure provides a pharmaceutical composition comprising the peptide as disclosed herein, or the polynucleotide as disclosed herein.

In one aspect, the disclosure provides use of the peptide as disclosed herein, the polynucleotide as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating of, preventing and/or for reducing the symptoms of a demyelinating disorder, preferably wherein said demyelinating disorder is a disease or disorder caused by MOG auto-antigens or anti-MOG antibodies.

In one aspect, the disclosure provides an in vitro method for the generation of a population of cytolytic CD4+ T cells, against APC presenting MOG epitopes, comprising the steps of:

- providing peripheral blood cells;

- contacting said cells in vitro with the peptide as disclosed herein, or the polynucleotide as disclosed herein; and

- expanding said cells in the presence of IL-2.

In one aspect, the disclosure provides a population of cytolytic CD4+ T cells or NKT cells, against APC presenting MOG epitopes, obtainable by the method as disclosed herein.

In one aspect, the disclosure provides use of a population of cytolytic CD4+ T cells or NKT cells, against APC presenting MOG epitopes, obtainable by the method as disclosed herein, in the manufacture of a medicament for treating of, ameliorating the symptoms of, and/or preventing of a demyelinating disorder or reducing the symptoms of a demyelinating disorder.

In one aspect, the disclosure provides a pharmaceutical composition comprising the peptide as disclosed herein, the polynucleotide as disclosed herein, or the CD4+ T cells or NKT cells as disclosed herein, or any mixture thereof, and optionally further comprising a pharmaceutically acceptable carrier and optionally further comprising an additional active ingredient suitable for treatment of a demyelinating disorder, or reducing the symptoms of a demyelinating disorder or preventing a demyelinating disorder.

In one aspect, the disclosure provides use of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating of, ameliorating the symptoms of, and/or preventing of a demyelinating disorder, preferably caused or aggravated by MOG auto-antigens and/or anti-MOG antibodies, most preferably Multiple Sclerosis (MS) or Neuromyelitis Optica (NMO).

In another aspect, the disclosure provides use of an immunogenic peptide as disclosed herein, the polynucleotide as disclosed herein, or the CD4+ T cells or NKT cells as disclosed herein, or any mixture thereof, for the manufacture of a medicament for treating of, ameliorating the symptoms of, and/or preventing of a demyelinating disorder, preferably caused or aggravated by MOG auto-antigens and/or anti-MOG antibodies, most preferably Multiple Sclerosis (MS) or Neuromyelitis Optica (NMO).

In one aspect, the disclosure provides an *in vitro* method for detecting MHC class II restricted CD4+ T cells specific for a MOG antigen in a sample comprising the steps of:

- contacting a subject sample with a complex of an isolated MHC class II molecules and a peptide as disclosed herein, or the polynucleotide as disclosed herein;

- detecting CD4+ T cells by measuring the binding of said complex with cells in said sample, wherein the binding of the complex to a cell is indicative for the presence of CD4+ T cells in said sample.

The ~~invention~~disclosure therefore provides the following ~~aspect~~examples:

AspectExample 1. An isolated immunogenic peptide comprising:

a1) an oxidoreductase motif with the sequence Z_m -[CST]- X_n -C- (SEQ ID NO: 66 to 90) or Z_m -C- X_n -[CST]- (SEQ ID NO: 91 to 115), wherein n is an integer chosen from 0 to 6, preferably 0, 1, 2, or 3, wherein m is an integer selected from 0 to 3, wherein X is any amino acid, wherein Z is any amino acid, in which C stands for cysteine, S for serine, T for threonine;

a2) a T-cell epitope with an amino acid sequence selected from the group consisting of: MHC class II T cell epitopes FLRVPCWKI (SEQ ID NO: 1), and FLRVPSWKI (SEQ ID NO: 2), or NKT cell epitopes FLRVPCW (SEQ ID NO: 63), and FLRVPSW (SEQ ID NO: 64),

wherein said oxidoreductase motif and said epitope are separated by a linker sequence of between 3 to 7 amino acids and comprising the sequence VRY, leading to the following linker-epitope sequences: VRYFLRVPCWKI (SEQ ID NO: 241), VRYFLRVPSWKI (SEQ ID NO: 242), VRYFLRVPCW (SEQ ID NO: 243), and VRYFLRVPSW (SEQ ID NO: 244).

AspectExample 2. The peptide according to **aspectexample 1**, wherein said T-cell epitope is flanked at its C-terminus by the amino acid sequence TLF leading to the following T-cell epitope-flanker sequence: FLRVPCWKITLF (SEQ ID NO: 3), FLRVPSWKITLF (SEQ ID NO: 4), FLRVPCWTLF (SEQ ID NO: 245) or FLRVPSWTLF (SEQ ID NO: 246).

AspectExample 3. The peptide according to **aspectexample 1** or 2, wherein said immunogenic peptide additionally comprises one or more K amino acid residue(s) flanking the epitope at the C-terminus, leading for example to any one of the following sequences of linker-T-cell epitope-flanker:

FLRVPCWKITLFLK (SEQ ID NO: 5), FLRVPSWKITLFLK (SEQ ID NO: 6),
 FLRVPCWKITLFLKK (SEQ ID NO: 7), FLRVPSWKITLFLKK (SEQ ID NO: 8),
 FLRVPCWKITLFLKKK (SEQ ID NO: 9), or FLRVPSWKITLFLKKK (SEQ ID NO: 10),

Alternatively, said immunogenic peptide additionally comprises one or more H amino
 acid residue(s) flanking the epitope at the C-terminus, leading for example to any one
 of the following sequences of linker-T-cell epitope-flanker: FLRVPCWKITLFLH (SEQ ID
 NO: 11), FLRVPSWKITLFLH (SEQ ID NO: 12), FLRVPCWKITLFLHH (SEQ ID NO: 13),
 FLRVPSWKITLFLHH (SEQ ID NO: 14), FLRVPCWKITLFLHHH (SEQ ID NO: 15), or
 FLRVPSWKITLFLHHH (SEQ ID NO: 16),

Alternatively, said immunogenic peptide additionally comprises one or more R amino
 acid residue(s) flanking the epitope at the C-terminus, leading for example to any one
 of the following sequences of linker-T-cell epitope-flanker:

FLRVPCWKITLFR (SEQ ID NO: 17), FLRVPSWKITLFR (SEQ ID NO: 18),
 FLRVPCWKITLFRR (SEQ ID NO: 19), FLRVPSWKITLFRR (SEQ ID NO: 20), or
 FLRVPCWKITLFRRR (SEQ ID NO: 21), or FLRVPSWKITLFRRR (SEQ ID NO: 22).

AspectExample 4. The peptide according to any one of **aspectexamples** 1 to 3,
 wherein the oxidoreductase motif has a sequence of $Z_m\text{-C-X}_n\text{-C-}$ (SEQ ID NO: 116 to
 140).

AspectExample 5. The peptide according to any one of **aspectexamples** 1 to 3,
 wherein the oxidoreductase motif has a sequence of $Z_m\text{-[CST]-XX-C-}$ or $Z_m\text{-C-XX-}$
 [CST]- .

AspectExample 6. The peptide according to any one of **aspectexamples** 1 to 5,
 wherein said oxidoreductase motif is selected from the following amino acid motifs:

(a) $Z_m\text{-[CST]-X}_n\text{-C-}$ or $Z_m\text{-C-X}_n\text{[CST]-}$,

wherein n is 0, and wherein m is an integer selected from 0, 1, or 2,

wherein Z is any amino acid, preferably a basic amino acid preferably selected from:
 H, K, R, and a non-natural basic amino acid as defined herein, such as L-ornithine,
 more preferably K or H, most preferably K;

(b) $Z_m\text{-[CST]-X}_n\text{-C-}$ or $Z_m\text{-C-X}_n\text{[CST]-}$,

wherein n is 1, wherein X is any amino acid, preferably a basic amino acid selected
 from: H, K, R, and a non-natural basic amino acid such as L-ornithine, more preferably
 K or R,

wherein m is an integer selected from 0, 1, or 2,

wherein Z is any amino acid, preferably a basic amino acid preferably selected from:
 H, K, R, and a non-natural basic amino acid as defined herein, such as L-ornithine,
 more preferably K or H, most preferably K;

(c) Z_m -[CST]- X_n -C- or Z_m -C- X_n -[CST]- as defined in [aspectexample 1](#), wherein n is 2, thereby creating an internal X^1X^2 amino acid couple within the oxidoreductase motif, wherein X is any amino acid, preferably wherein at least one X is a basic amino acid selected from: H, K, R, and a non-natural basic amino acid such as L-ornithine, more preferably K or R,

wherein m is an integer selected from 0, 1, or 2,

wherein Z is any amino acid, preferably a basic amino acid preferably selected from: H, K, R, and a non-natural basic amino acid as defined herein, such as L-ornithine, more preferably K or H, most preferably K;

10 (d) Z_m -[CST]- X_n -C- or Z_m -C- X_n -[CST]- as defined in [aspectexample 1](#), wherein n is 3, thereby creating an internal $X^1X^2X^3$ amino acid stretch within the oxidoreductase motif, wherein X is any amino acid, preferably wherein at least one X is a basic amino acid selected from: H, K, R, and a non-natural basic amino acid such as L-ornithine, more preferably K or R,

15 wherein m is an integer selected from 0, 1, or 2,

wherein Z is any amino acid, preferably a basic amino acid preferably selected from: H, K, R, and a non-natural basic amino acid as defined herein, such as L-ornithine, more preferably K or H;

(e) Z_m -[CST]- X_n -C- or Z_m -C- X_n -[CST]- as defined in [aspectexample 1](#), wherein n is 4, 20 thereby creating an internal $X^1X^2X^3X^4$ (SEQ ID NO: 154) amino acid stretch within the oxidoreductase motif, wherein m is an integer selected from 0, 1, or 2, wherein Z is any amino acid, preferably a basic amino acid selected from: H, K, R, and a non-natural basic amino acid as defined herein, such as L-ornithine, preferably K or H, most preferably K ;

25 (f) Z_m -[CST]- X_n -C- or Z_m -C- X_n -[CST]- as defined in [aspectexample 1](#), wherein n is 5, thereby creating an internal $X^1X^2X^3X^4X^5$ (SEQ ID NO: 166) amino acid stretch within the oxidoreductase motif, wherein m is an integer selected from 0, 1, or 2, wherein Z is any amino acid, preferably a basic amino acid selected from: H, K, R, and a non-natural basic amino acid as defined herein, such as L-ornithine, preferably K or H, most preferably K;

30 (g) Z_m -[CST]- X_n -C- or Z_m -C- X_n -[CST]- as defined in [aspectexample 1](#), wherein n is 6, thereby creating an internal $X^1X^2X^3X^4X^5X^6$ (SEQ ID NO: 177) amino acid stretch within the oxidoreductase motif, wherein m is an integer selected from 0, 1, or 2, wherein Z is any amino acid, preferably a basic amino acid selected from: H, K, R, and a non-natural 35

basic amino acid as defined herein, such as L-ornithine, preferably K or H, most preferably K; or

(h) $Z_m\text{-[CST]}\text{-X}_n\text{-C-}$ or $Z_m\text{-C-X}_n\text{-[CST]-}$, wherein n is 0 to 6 and wherein m is 0, and wherein one of the C or [CST] residues has been modified so as to carry an acetyl, methyl, ethyl or propionyl group, either on the N-terminal amide of the amino acid residue of the motif or on the C-terminal carboxy group (SEQ ID NO: 184 to 203).

AspectExample 7. The peptide according to any one of aspectexamples 1 to 6, wherein at least one X is a Proline (P) or a Tyrosine (Y), preferably wherein each X is a Proline or a Tyrosine, more preferably wherein the X_n or the XX portion of said oxidoreductase motif comprises the sequence PY, preferably wherein the oxidoreductase motif comprises the sequence CPYC (SEQ ID NO: 23).

AspectExample 8. The peptide according to any one of aspectexamples 1 to 7, wherein amino acid Z of the oxidoreductase motif is a basic amino acid, preferably a basic amino acid selected from the group of amino acids consisting of: H, K, R, and any non-natural basic amino acid, more preferably a basic amino acid selected from: H, K, and R, most preferably wherein Z is H or K.

AspectExample 9. The peptide according to any one of aspectexamples 1 to 8, wherein the oxidoreductase motif b1) has a sequence of HCPYC (SEQ ID NO: 24).

AspectExample 10. The peptide according to any one of aspectexamples 1 to 9, wherein said peptide comprises or consists of: the amino sequence HCPYCVRYFLRVPSWKITLF (SEQ ID NO: 25), HCPYCVRYFLRVPCWKITLF (SEQ ID NO: 26), KHCPYCVRYFLRVPSWKITLFFK (SEQ ID NO: 27), KHCPYCVRYFLRVPCWKITLFFK (SEQ ID NO: 28), KHCPYCVRYFLRVPSWKITLF (SEQ ID NO: 247), or KHCPYCVRYFLRVPCWKITLF (SEQ ID NO: 248), preferably comprises or consists of the amino sequence KHCPYCVRYFLRVPSWKITLFFK (SEQ ID NO: 27).

AspectExample 11. The immunogenic peptide according to any one of aspectexamples 1 to 10, wherein said T cell epitope is an NKT cell epitope and the peptide has a length of between 12 and 50 amino acids, preferably of between 12 and 30 amino acids; or wherein said T-cell epitope is an MHC class II T cell epitope and the peptide has a length of between 12 and 50 amino acids, preferably of between 12 and 30 amino acids.

AspectExample 12. A polynucleotide (nucleic acid molecule) encoding the immunogenic peptide according to any one of aspectexamples 1 to 11, preferably selected from isolated

desoxyribonucleic acid (DNA), plasmid DNA (pDNA), coding DNA (cDNA), ribonucleic acid (RNA), messenger RNA (mRNA) or modified versions thereof. In some [embedimentexamples](#), said nucleic acid can be part of an expression cassette, optionally incorporated in a (viral) vector or plasmid that can be used for gene-therapy or can be present in the form of encapsulated or naked DNA or RNA to be administered according to techniques known in the pharmaceutical and gene therapeutic field.

[AspectExample](#) 13. The peptide according to any one of [aspectexamples](#) 1 to 11, or the polynucleotide according to [aspectexample](#) 12, for use as a medicament.

[AspectExample](#) 14. The peptide or polynucleotide according to [aspectexample](#) 13 for use in treating of, ameliorating the symptoms of, and/or preventing of a demyelinating disorder.

Demyelinating disorders include but are not limited to: Multiple Sclerosis (MS), Neuromyelitis Optica (NMO), Optic Neuritis, Acute Disseminated Encephalomyelitis, Balo's Disease, HTLV-I Associated Myelopathy, Schilder's Disease, Transverse Myelitis, Idiopathic inflammatory demyelinating diseases, vitamin B12-induced central nervous system neuropathies, Central pontine myelinolysis, Myelopathies including tabes dorsalis, Leukodystrophies such as Adrenoleukodystrophy, Leukoencephalopathies such as Progressive multifocal leukoencephalopathy (PML), Vanishing White Matter Disease, and Rubella induced mental retardation.

Preferred are demyelinating disorders caused or aggravated by MOG auto-antigens and/or anti-MOG antibodies such as Multiple Sclerosis (MS), Neuromyelitis Optica (NMO), Optic Neuritis, Acute Disseminated Encephalomyelitis, Transverse Myelitis, Adrenoleukodystrophy, Vanishing White Matter Disease, and Rubella induced mental retardation. More preferred demyelinating disorders are Multiple Sclerosis (MS) and Neuromyelitis Optica (NMO). In certain [embedimentexamples](#), said MS is selected from Clinically Isolated Syndrome (CIS), relapse-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), Acute Fulminant Multiple Sclerosis and MS-suspected radiology isolated syndrome (RIS).

[AspectExample](#) 15. An in vitro method for the generation of a population of cytolytic CD4+ T cells, against APC presenting MOG epitopes, comprising the steps of:

- providing peripheral blood cells;
- contacting said cells in vitro with the peptide of any one of [aspectexamples](#) 1 to 11, or the polynucleotide according to [aspectexample](#) 12; and
- expanding said cells in the presence of IL-2.

AspectExample 16. A method for the generation of a population of cytolytic CD4+ T cells, against APC presenting MOG epitopes, comprising the steps of:

- administering to a subject an effective amount of the peptide of any one of **aspectexamples** 1 to 11, or the polynucleotide according to **aspectexample** 12;
- obtaining said cytolytic CD4+ T cells from a peripheral blood cell population of said subject.

AspectExample 17. A method for the generation of a population of NKT cells, against APC presenting MOG epitopes, comprising the steps of:

- administering to a subject an effective amount of the peptide of any one of **aspectexamples** 1 to 11, or the polynucleotide according to **aspectexample** 12;
- obtaining said NKT cells from a peripheral blood cell population of said subject.

AspectExample 18. A population of cytolytic CD4+ T cells or NKT cells, against APC presenting MOG epitopes, obtainable by the method of **aspectexample** 15, 16 or 17.

AspectExample 19. A population of cytolytic CD4+ T cells or NKT cells, against APC presenting MOG epitopes, obtainable by the method of **aspectexample** 15, 16 or 17, for use as a medicament.

AspectExample 20. A population of cytolytic CD4+ T cells or NKT cells for use according to **aspectexample** 19, for use in the treatment of, ameliorating the symptoms of, and/or preventing of a demyelinating disorder or reducing the symptoms of a demyelinating disorder.

Demyelinating disorders include but are not limited to: Multiple Sclerosis (MS), Neuromyelitis Optica (NMO), Optic Neuritis, Acute Disseminated Encephalomyelitis, Balo's Disease, HTLV-I Associated Myelopathy, Schilder's Disease, Transverse Myelitis, Idiopathic inflammatory demyelinating diseases, vitamin B12-induced central nervous system neuropathies, Central pontine myelinolysis, Myelopathies including tabes dorsalis, Leukodystrophies such as Adrenoleukodystrophy, Leukoencephalopathies such as Progressive multifocal leukoencephalopathy (PML), Vanishing White Matter Disease, and Rubella induced mental retardation.

Preferred are demyelinating disorders caused or aggravated by MOG auto-antigens and/or anti-MOG antibodies such as Multiple Sclerosis (MS), Neuromyelitis Optica (NMO), Optic Neuritis, Acute Disseminated Encephalomyelitis, Transverse Myelitis, Adrenoleukodystrophy, Vanishing White Matter Disease, and Rubella induced mental retardation. More preferred demyelinating disorders are Multiple Sclerosis (MS) and Neuromyelitis Optica (NMO). In certain **embodimentexamples**, said MS is selected from Clinically Isolated Syndrome (CIS), relapse-remitting MS (RRMS), secondary

progressive MS (SPMS), primary progressive MS (PPMS), Acute Fulminant Multiple Sclerosis and MS-suspected radiology isolated syndrome (RIS).

AspectExample 21. A pharmaceutical composition comprising the peptide of any one of **aspectexamples** 1 to 11, the polynucleotide according to **aspectexample** 12, or the CD4+ T cells or NKT cells of any one of **aspectexamples** 18 to 20, or any mixture thereof.

AspectExample 22. The pharmaceutical composition of **aspectexample** 21, optionally further comprising a pharmaceutically acceptable carrier, and optionally further comprising an additional active ingredient suitable for treatment of a demyelinating disorder, or reducing the symptoms of a demyelinating disorder or preventing a demyelinating disorder.

Demyelinating disorders include but are not limited to: Multiple Sclerosis (MS), Neuromyelitis Optica (NMO), Optic Neuritis, Acute Disseminated Encephalomyelitis, Balo's Disease, HTLV-I Associated Myelopathy, Schilder's Disease, Transverse Myelitis, Idiopathic inflammatory demyelinating diseases, vitamin B12-induced central nervous system neuropathies, Central pontine myelinolysis, Myelopathies including tabes dorsalis, Leukodystrophies such as Adrenoleukodystrophy, Leukoencephalopathies such as Progressive multifocal leukoencephalopathy (PML), Vanishing White Matter Disease, and Rubella induced mental retardation.

Preferred are demyelinating disorders caused or aggravated by MOG auto-antigens and/or anti-MOG antibodies such as Multiple Sclerosis (MS), Neuromyelitis Optica (NMO), Optic Neuritis, Acute Disseminated Encephalomyelitis, Transverse Myelitis, Adrenoleukodystrophy, Vanishing White Matter Disease, and Rubella induced mental retardation. More preferred demyelinating disorders are Multiple Sclerosis (MS) and Neuromyelitis Optica (NMO). In certain **embodimentexamples**, said MS is selected from Clinically Isolated Syndrome (CIS), relapse-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), Acute Fulminant Multiple Sclerosis and MS-suspected radiology isolated syndrome (RIS).

AspectExample 23. The pharmaceutical composition of **aspectexample** 21 or 22, for use as a medicament.

AspectExample 24. The pharmaceutical composition for use according to **aspectexample** 23, for use in treating of, ameliorating the symptoms of, and/or preventing of a demyelinating disorder.

Demyelinating disorders include but are not limited to: Multiple Sclerosis (MS), Neuromyelitis Optica (NMO), Optic Neuritis, Acute Disseminated Encephalomyelitis,

Balo's Disease, HTLV-I Associated Myelopathy, Schilder's Disease, Transverse Myelitis, Idiopathic inflammatory demyelinating diseases, vitamin B12-induced central nervous system neuropathies, Central pontine myelinolysis, Myelopathies including tabes dorsalis, Leukodystrophies such as Adrenoleukodystrophy, Leukoencephalopathies such as Progressive multifocal leukoencephalopathy (PML), Vanishing White Matter Disease, and Rubella induced mental retardation.

Preferred are demyelinating disorders caused or aggravated by MOG auto-antigens and/or anti-MOG antibodies such as Multiple Sclerosis (MS), Neuromyelitis Optica (NMO), Optic Neuritis, Acute Disseminated Encephalomyelitis, Transverse Myelitis, Adrenoleukodystrophy, Vanishing White Matter Disease, and Rubella induced mental retardation. More preferred demyelinating disorders are Multiple Sclerosis (MS) and Neuromyelitis Optica (NMO). In certain [embodimentexamples](#), said MS is selected from Clinically Isolated Syndrome (CIS), relapse-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), Acute Fulminant Multiple Sclerosis and MS-suspected radiology isolated syndrome (RIS).

[AspectExample](#) 25. The peptide, polynucleotide, CD4+ T cells, NKT cells, or pharmaceutical composition for use in treating of, ameliorating the symptoms of, and/or preventing of MS according to any one of the previous [aspectexamples](#), wherein the subject is diagnosed with relapse-remitting MS (RRMS).

[AspectExample](#) 26. The peptide, polynucleotide, CD4+ T cells, NKT cells, or pharmaceutical composition for use in treating of, ameliorating the symptoms of, and/or preventing of MS according to any one of the previous [aspectexamples](#), wherein the subject has an HLA-DRB1* type selected from the group consisting of: HLA-DRB1*15:01, HLA-DRB1*03:01, HLA-DRB1*04:01, and HLA-DRB1*07:01, preferably wherein the subject has HLA-DRB1* 15:01.

[AspectExample](#) 27. The peptide, polynucleotide, CD4+ T cells, NKT cells, or pharmaceutical composition for use in treating of, ameliorating the symptoms of, and/or preventing NMO, according to any one of the previous [aspectexamples](#) wherein the subject has an HLA type selected from the group consisting of: HLA-DRB1*03:01 and HLA-DPB1*05:01.

[AspectExample](#) 28. Use of an immunogenic peptide according to any one of [aspectexamples](#) 1 to 11, the polynucleotide according to [aspectexample](#) 12, or the CD4+ T cells or NKT cells of any one of [aspectexamples](#) 18 to 20, or any mixture thereof, for the manufacture of a medicament for treating of, ameliorating the symptoms of, and/or preventing of a demyelinating disorder, preferably a demyelinating disorder caused or aggravated by MOG auto-

antigens and/or anti-MOG antibodies, most preferably Multiple Sclerosis (MS) or Neuromyelitis Optica (NMO).

AspectExample 29. A method for treating of, ameliorating the symptoms of, and/or preventing a demyelinating disorder in a subject, comprising the step of providing the peptide according to **aspectexamples** 1 to 11, the polynucleotide according to **aspectexample** 12, or the CD4+ T cells or NKT cells of any one of **aspectexamples** 18 to 20, or any mixture thereof, to a subject.

AspectExample 30. The method according to **aspectexample** 29, wherein said demyelinating disorder is selected from: Multiple Sclerosis (MS), Neuromyelitis Optica (NMO), Optic Neuritis, Acute Disseminated Encephalomyelitis, Balo's Disease, HTLV-I Associated Myelopathy, Schilder's Disease, Transverse Myelitis, Idiopathic inflammatory demyelinating diseases, vitamin B12-induced central nervous system neuropathies, Central pontine myelinolysis, Myelopathies including tabes dorsalis, Leukodystrophies such as Adrenoleukodystrophy, Leukoencephalopathies such as Progressive multifocal leukoencephalopathy (PML), Vanishing White Matter Disease, and Rubella induced mental retardation.

In preferred **embodimentexamples**, the demyelinating disorder is caused or aggravated by MOG auto-antigens and/or anti-MOG antibodies and hence selected from the group consisting of: Multiple Sclerosis (MS), Neuromyelitis Optica (NMO), Optic Neuritis, Acute Disseminated Encephalomyelitis, Transverse Myelitis, Adrenoleukodystrophy, Vanishing White Matter Disease, and Rubella induced mental retardation. In more preferred **embodimentexamples** the demyelinating disorder is Multiple Sclerosis (MS) or Neuromyelitis Optica (NMO). In certain **embodimentexamples**, said MS is selected from Clinically Isolated Syndrome (CIS), relapse-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), Acute Fulminant Multiple Sclerosis and MS-suspected radiology isolated syndrome (RIS).

AspectExample 31. The method according to **aspectexample** 29 or 30, further comprising a step of administering a fumarate compound to said subject. Examples of fumarate compounds are: monomethyl fumarate (MMF), dimethyl fumarate (DMF), compounds that can be metabolized into MMF *in vivo*, monomethyl fumarate prodrugs such as diroximel fumarate or tepilamide fumarate, or a combination of any one or more thereof, or a deuterated form, a clathrate, a solvate, a tautomer, a stereoisomer, or a pharmaceutically acceptable salt of any one or more thereof, or a combination of any one of the foregoing.

AspectExample 32. An *in vitro* method for detecting MHC class II restricted CD4+ T cells specific for a MOG antigen in a sample comprising the steps of;

- contacting a subject sample with a complex of an isolated MHC class II molecules and a peptide according to **aspectexample** 1 to 11, or the polynucleotide according to **aspectexample** 12;
- detecting CD4+ T cells by measuring the binding of said complex with cells in said sample, wherein the binding of the complex to a cell is indicative for the presence of CD4+ T cells in said sample.

The above and further **aspectexamples** ~~and preferred embodiments~~ of the **inventiondisclosure** are described in the following sections and in the appended claims. The subject matter of the appended claims is hereby specifically incorporated in this specification.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Kinetics of the redox activities of P1 to P5 immunogenic peptides. DTT is used as a positive control, while Blank represents the assay buffer. The results are expressed in Relative Fluorescent Units (RFU). The assay is described in detail in the Examples section.

Figure 2: Binding of the P1 to P5 peptides to HLA-DR3 (DRB1*03:01 MHC II) protein. The decreasing fluorescence signal (RFU) demonstrates the dose-dependent relationship produced following the competition with biotin-tagged high-affinity control peptide and revealed by Eu³⁺ streptavidin interaction.

Figure 3: Binding of the P1 to P5 peptides to HLA-DR4 (DRB1*04:01 MHC II) protein. The decreasing fluorescence signal (RFU) demonstrates the dose-dependent relationship produced following the competition with biotin-tagged high-affinity control peptide and revealed by Eu³⁺ streptavidin interaction.

Figure 4: Binding of the P1 to P5 peptides to HLA-DR15 (DRB1*15:01 MHC II) protein. The decreasing fluorescence signal (RFU) demonstrates the dose-dependent relationship produced following the competition with biotin-tagged high-affinity control peptide and revealed by Eu³⁺ streptavidin interaction.

Figure 5: Binding of the P1, P6 and P7 peptides to HLA-DR3 (DRB1*03:01 MHC II) protein. The decreasing fluorescence signal (RFU) demonstrates the dose-dependent relationship produced following the competition with biotin-tagged high-affinity control peptide and revealed by Eu³⁺ streptavidin interaction.