

CLAIMS (CLEAN COPY)

1. 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 $Z_m\text{-[CST]-X}_n\text{-C-}$ or $Z_m\text{-C-X}_n\text{-[CST]}$, 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.

2. The peptide according to claim 1, 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 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 such as L-ornithine, more preferably K or H, most preferably K;
 - (c) $Z_m\text{-[CST]-X}_n\text{-C-}$ or $Z_m\text{-C-X}_n\text{-[CST]-}$,
 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, such as L-ornithine, more preferably K or H, most preferably K;
 - (d) $Z_m\text{-[CST]-X}_n\text{-C-}$ or $Z_m\text{-C-X}_n\text{-[CST]-}$,
 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,
 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; or

(h) Z_m -[CST]- X_n -C- or Z_m -C- X_n -[CST]-,

wherein n is 0 to 3 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).

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3. The peptide according to claim 1 or 2, 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) or FLRVPSWKITLF (SEQ ID NO: 4), or

10 ~~4. The peptide according to any one of claims 1 to 3,~~ wherein said ~~immunogenic~~ peptide additionally comprises one or more K amino acid residue(s) flanking the epitope at the C-terminus, leading to the following sequences of linker-T-cell epitope-flanker: FLRVPCWKITLFK (SEQ ID NO: 5), FLRVPSWKITLFK (SEQ ID NO: 6), FLRVPCWKITLFFK (SEQ ID NO: 7), FLRVPSWKITLFFK (SEQ ID NO: 8), FLRVPCWKITLFFKK (SEQ ID NO: 9), or FLRVPSWKITLFFKK (SEQ ID NO: 10).

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~~54.~~ The peptide according to any one of claims 1 to ~~43~~, wherein the oxidoreductase motif has a sequence of Z_m -C-XX-C-, with Z being a basic amino acid, preferably selected from the group consisting of K and H, m being 0, 1, or 2, ~~preferably~~ wherein the oxidoreductase motif comprises the sequence CPYC (SEQ ID NO: 23), or CHGC (SEQ ID NO: 297), preferably -

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~~6.~~ The peptide according to claim ~~5~~, wherein the oxidoreductase motif has a sequence selected from the group consisting of: HCPYC (SEQ ID NO: 24), KCPYC (SEQ ID NO: 51), KHCPYC (SEQ ID NO: 50), KCRPYC (SEQ ID NO: 216), KHCRPYC (SEQ ID NO: 217), HCHGC (SEQ ID NO: 265), KCHGC (SEQ ID NO: 266), KHCHGC (SEQ ID NO: 267), KCRHGC (SEQ ID NO: 268), and KHCRHGC (SEQ ID NO: 269).

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~~75.~~ The peptide according to any one of claims 1 to ~~43~~, wherein the oxidoreductase motif has a sequence of Z_m -C-X-C-, with Z being a basic amino acid, preferably selected from the group consisting of K and H, m being 0, 1, or 2, and X preferably being R, preferably -

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~~8.~~ The peptide according to claim ~~7~~, wherein the oxidoreductase motif has a sequence selected from the group consisting of: CRC, KCRC (SEQ ID NO: 43), HCRC (SEQ ID NO: 270) and KHCR (SEQ ID NO: 271).

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~~96.~~ The peptide according to any one of claims 1 to ~~43~~, wherein said peptide comprises or consists of any one of the amino sequences selected from the group consisting of:

KCRCVRYFLRVPSWKITLFFK (SEQ ID NO: 272),

KCRCVRYFLRVPCWKITLFFK (SEQ ID NO: 273),

KCRCVRYFLRVPSWKITLFFK (SEQ ID NO: 274),

40 KCRCVRYFLRVPCWKITLFFK (SEQ ID NO: 275),

- KCRCVRYFLRVPSWKITLF (SEQ ID NO: 276),
 KCRCVRYFLRVPCWKITLF (SEQ ID NO: 277),
 KCRPYCVRYFLRVPSWKITLFFK (SEQ ID NO: 257),
 KCRPYCVRYFLRVPCWKITLFFK (SEQ ID NO: 278),
 5 KCRPYCVRYFLRVPSWKITLFFK (SEQ ID NO: 279),
 KCRPYCVRYFLRVPCWKITLFFK (SEQ ID NO: 280),
 KCRPYCVRYFLRVPSWKITLF (SEQ ID NO: 281),
 KCRPYCVRYFLRVPCWKITLF (SEQ ID NO: 282),
 KHCPYCVRYFLRVPSWKITLFFK (SEQ ID NO: 27),
 10 KHCPYCVRYFLRVPCWKITLFFK (SEQ ID NO: 28),
 KHCPYCVRYFLRVPSWKITLFFK (SEQ ID NO: 283),
 KHCPYCVRYFLRVPCWKITLFFK (SEQ ID NO: 284),
 KHCPYCVRYFLRVPSWKITLF (SEQ ID NO: 285),
 KHCPYCVRYFLRVPCWKITLF (SEQ ID NO: 286),
 15 HCPYCVRYFLRVPSWKITLFFK (SEQ ID NO: 287),
 HCPYCVRYFLRVPCWKITLFFK (SEQ ID NO: 288),
 HCPYCVRYFLRVPSWKITLFFK (SEQ ID NO: 289),
 HCPYCVRYFLRVPCWKITLFFK (SEQ ID NO: 290),
 HCPYCVRYFLRVPSWKITLF (SEQ ID NO: 25),
 20 HCPYCVRYFLRVPCWKITLF (SEQ ID NO: 26),
 CPYCVRYFLRVPSWKITLFFK (SEQ ID NO: 291),
 CPYCVRYFLRVPCWKITLFFK (SEQ ID NO: 292),
 CPYCVRYFLRVPSWKITLFFK (SEQ ID NO: 293),
 CPYCVRYFLRVPCWKITLFFK (SEQ ID NO: 294),
 25 CPYCVRYFLRVPSWKITLF (SEQ ID NO: 295), and
 CPYCVRYFLRVPCWKITLF (SEQ ID NO: 296).

30 ~~107.~~ A polynucleotide encoding the peptide according to any one of claims 1 to ~~96~~, wherein said polynucleotide is selected from the group comprising DNA, pDNA, cDNA, RNA, and mRNA or modified versions thereof.

~~118.~~ A pharmaceutical composition comprising the peptide according to any one of claims 1 to ~~96~~, or the polynucleotide according to claim ~~107~~.

35 ~~129.~~ Use of ~~The~~ peptide according to any one of claims 1 to ~~96~~, the polynucleotide according to claim ~~107~~, or the pharmaceutical composition according to claim ~~118~~, for use as in the manufacture of a medicament.

40 ~~13.~~ The peptide, polynucleotide, or pharmaceutical composition according to claim 12, for ~~use in~~ 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.

~~1410.~~ The ~~peptide, polynucleotide, or pharmaceutical composition for~~ use according to claim ~~129~~,
5 wherein said disorder is selected from: Multiple Sclerosis (MS) and Neuromyelitis Optica (NMO).

~~1511.~~ The ~~peptide, polynucleotide, or pharmaceutical composition~~ use according to ~~any one of~~
~~claims claim 12-9 to or 1410, wherein the use is for use in~~ treating of, preventing and/or for reducing the
10 symptoms of MS, 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*04:01 or HLA-DRB1* 15:01; ~~or~~.

~~16.~~ ~~The peptide, polynucleotide, or pharmaceutical composition according to any one of claims 12~~
15 ~~to 14, wherein the use is for use in~~ treating of, preventing and/or for reducing the symptoms of NMO or
reducing the symptoms of NMO, wherein the subject has an HLA type selected from the group consisting
of: HLA-DRB1*03:01 and HLA-DPB1*05:0114.

~~1712.~~ The ~~peptide, polynucleotide, or pharmaceutical composition for~~ use according to claim ~~12-9~~ or
20 ~~1410~~, wherein 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).

~~1813.~~ The ~~peptide, polynucleotide, or pharmaceutical composition for~~ use according to any one of
25 claims ~~12-9~~ to ~~1712~~, wherein said subject is being, has been, or is going to be treated with a fumarate
compound.

~~1914.~~ An in vitro method for the generation of a population of cytolytic CD4+ T cells, against APC
presenting MOG epitopes, comprising the steps of:

- 30 - providing peripheral blood cells;
- contacting said cells in vitro with the peptide of any one of claims 1 to ~~96~~, or the polynucleotide
according to claim ~~107~~; and
- expanding said cells in the presence of IL-2.

~~20.~~ ~~A method for the generation of a population of cytolytic CD4+ T cells, against APC presenting~~
35 ~~MOG epitopes, comprising the steps of:~~

- ~~- administering to a subject an effective amount of the peptide of any one of claims 1 to 9, or the~~
~~polynucleotide according to claim 10;~~
- ~~- obtaining said cytolytic CD4+ T cells from a peripheral blood cell population of said subject.~~

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~~21. 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 claims 1 to 9, or the polynucleotide according to claim 10;~~

~~-obtaining said NKT cells from a peripheral blood cell population of said subject.~~

~~2215. A population of cytolytic CD4+ T cells or NKT cells, against APC presenting MOG epitopes, obtainable by the method of claims 19, 20, or 2114.~~

~~2316. Use of a~~ population of cytolytic CD4+ T cells or NKT cells, against APC presenting MOG epitopes, obtainable by the method of claims ~~14-19, 20, or 21~~, ~~for use as in the manufacture of a~~ medicament-

~~24. A population of cytolytic CD4+ T cells or NKT cells for use according to claim 23,~~ ~~for use in the~~ ~~treatment~~ ~~treating~~ of, ameliorating the symptoms of, and/or preventing of a demyelinating disorder or reducing the symptoms of a demyelinating disorder.

~~2517. A pharmaceutical composition comprising the peptide of any one of claims 1 to 96, the polynucleotide according to claim 407, or the CD4+ T cells or NKT cells according to claim 2415, or any mixture thereof, and optionally further comprising a pharmaceutically acceptable carrier and optionally -~~

~~26. The pharmaceutical composition of claim 25,~~ 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.

~~2718. Use of T~~ the pharmaceutical composition of claim ~~25 or 2617~~, ~~for use as in the manufacture of a~~ medicament-

~~28. The pharmaceutical composition for use according to claim 27,~~ ~~for use in~~ 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).

~~2919. Use of an immunogenic peptide according to any one of claims 1 to 96, the polynucleotide according to claim 407, or the CD4+ T cells or NKT cells according to claim 2215, 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).~~

~~30. 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 claims 1 to 9, the polynucleotide according to claim 10, or the CD4+ T cells or NKT cells of claim 22, or any mixture thereof, to a subject.~~

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~~31. The method according to claim 29, wherein said demyelinating disorder is selected from: Multiple Sclerosis (MS), Neuromyelitis Optica (NMO), Optic Neuritis, Acute Disseminated Encephalomyelitis, Baló'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.~~

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~~32. The method according to claim 30 or 31, further comprising a step of administering a fumarate compound to said subject.~~

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~~33. The method according to claim 32, wherein said fumarate compound is selected from the group consisting of: 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.~~

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~~34~~20. 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;

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- contacting a subject sample with a complex of an isolated MHC class II molecules and a peptide according to claims 1 to 96, or the polynucleotide according to claim ~~107~~;
- 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.