COMPOSITIONS AND METHODS FOR BINDING MYELIN BINDING PROTEINS

BACKGROUND

The present invention relates generally to methods for studying, detecting, and treating multiple sclerosis by using peptide analogs of proteins structurally related to human myelin basic protein.

The present invention relates generally to the fields of chemistry and medicine and more particularly to compositions of matter and methods useable for detecting and inhibiting myelin binding proteins, related human and animal subject assessment, and treatments for multiple sclerosis.

Multiple sclerosis (MS) is a chronic, inflammatory disease primarily within the white matter of the central nervous system that is manifested by relapsing neurological deficits, in particular, paralysis, sensory deficits, and visual problems. The inflammatory process is mediated by T lymphocytes, B lymphocytes, and macrophages. The demyelination of axons in MS is accompanied by a macroscopic lesions called plaques. T cell reactivity to myelin basic protein may be a critical component in the development of MS as pathogenic T cells found in lesions have restricted heterogeneity of antigen receptors (TCR).

Jansen et al., in United States patents 7,208,270 and 6,489,299, described a method for diagnosing a person having MS or being at risk of developing MS, comprising the following steps: providing a sample of a body fluid or tissue from said person, said sample containing at least one of the wild type SCF-Apoptosis-Response Gene- (wt-SARG-1-*)* protein and nucleic acids encoding wt-SARG-1, if taken from a person not having MS or a risk of acquiring MS, detecting the presence of wt-SARG-1-protein or nucleic acids encoding wt-SARG-1 in said sample and diagnosing MS or a risk of acquiring MS, if wt-SARG-1-protein or nucleic acids encoding wt-SARG-1 are not present in said sample.

Steinman et al., in United States patents 6,740,638, 6,489,299, and 6,369,033, described peptide analogues of human myelin basic protein containing residues 87-99. Residue 91 of the peptide analogues is altered from the L-lysine residue found in the native protein to any other amino acid. Steinman claimed pharmaceutical compositions of the peptide analogues are provided with claims for the peptide analogues when administered to patients with multiple sclerosis.

Gaur et al., in United States patents 6,379,670 and 6,251,396, were directed toward peptide analogs of human myelin basic protein claiming peptide analogs that were at least seven amino acids long and derived from residues 83 to 99 of human

myelin basic protein. The analogs were altered from the native sequence at least at positions 91, 95, or 97. Additional alterations were claimed at other positions and pharmaceutical compositions containing these peptide analogs were claimed to be useful for treating multiple sclerosis.

Hashim, in United States patent 4,230,696, claimed synthetic compounds of the formula. Acid addition salts thereof are disclosed wherein R.sub.1 and R.sub.5 are each independently selected from the group consisting of hydrogen, hydroxy, the residue of an amino acid and the residue of a polypeptide and R.sub.4 is selected from the group consisting of lysine and arginine residues; provided that R.sub.1 and R.sub.5 are not both hydrogen or both hydroxyl at the same time. The disclosure of intermediate compounds for preparing the compounds of the above formula and derivative compounds having the same biological activity and pharmaceutical compositions wherein the essential active ingredient is a synthetic compound of the invention were made. The compounds and compositions of the invention were claimed to be useful for the prevention, suppression, treatment, and diagnosis of multiple sclerosis.

Nye et al., in United States patent 7,041,503, claimed compositions and methods for the clinical assessment, diagnosis, and treatment of multiple sclerosis. The compositions of the invention claimed were molecules related to the 21.5 kDa fetal isoform of human myelin basic protein, and include nucleic acids and polypeptides. The inventors claimed nucleic acid molecules were useful in the efficient production of modified and unmodified 21.5 kDa myelin basic protein polypeptides, such polypeptides being useful for assaying T cells for responsiveness to myelin basic protein epitopes. The inventors claimed polypeptides of the invention were also useful as therapeutic agents that act by inducing T cell responses, including apoptosis, as a means of treating multiple sclerosis.

For convenience, the amino acid groups are referred to by abbreviations, following accepted and common practice in peptide chemistry. For example, the following abbreviations for amino acids are used, at times, throughout the following specification and claims:

SER – serine
ASN – asparagine
PHE – phenylalanine
ASP – aspartic acid
GLU – glutamic acid
TYR – tyrosine
LEU – leucine
MET – methionine

ARG – arginine
LYS – lysine
ILE – isoleusine
VAL – valine
GLY – glycine
ALA – alanine

PRIOR ART

The following publications are cited in the specification and are incorporated by reference in their entirety in all jurisdictions where this is appropriate:

PATENT DOCUMENTS

United States Patent 4,230,696 Oct. 1980 Hahim
United States Patent 6,251,396 Jun. 2001 Gaur et al.
United States Patent 6,369,033 Apr. 2002 Steinman et al.
United States Patent 6,489,299 Dec. 2002 Steinman et al.
United States Patent 6,379,670 Apr. 2002 Gaur et al.
United States Patent 6,740,638 Jun. 2004 Steinman et al.
United States Patent 7,041,503 May 2006 Nye et al.
United States Patent 7,208,270 Apr. 2007 Jansen et al.

OTHER PUBLICATIONS

Protein Data Bank ID: 1CBS.
Kleywegt, G.J.; Bergfors, T.; Senn, H.; Le Motte, P; Gsell, B; Shudo, K.; Jones, T.A.; "Crystal structures of cellular retinoic acid binding proteins I and II in complex with all-trans-retinoic acid and a synthetic retinoid." *Structure* (1994) 2:1241

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Folli, C.; Calderone, V.; Ramazzina, I.; Zanotti, G.; Berni, R.; "Ligand binding and structural analysis of a human putative cellular retinol-binding protein." *J. Biol. Chem.* (2002) 277: 41970

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Majava, V.; Polverini, E.; Mazzini, A.; Nanekar, R.; Knoll, W.; Peters, J.; Natali, F.; Baumgartel, P.; Kursula, I.; Kursula, P.; "Structural and functional characterization of human peripheral nervous system myelin protein P2." *PLOS One (2010) 5: E300*

Protein Data Bank ID: 3NR3

Ugochukwu, E.; Pilka, E.; Phillips, C.; Yue, W.W.; Krojer, T.; Von Delft, F.; Bountra, C.; Arrowsmith, C.H.; Weigelt, J.; Edwards, A.; Kavanagh, K.L.; Crystal structure of human peripheral myelin protein 2., Structural Genomics Consortium (SGC)

BRIEF SUMMARY OF THE INVENTION

A first aspect of the invention is directed to a method for binding myelin binding proteins in any of: a human subject; an animal subject; a human derived substance and an animal-derived substance, said method comprising the step of: administering to the subject or applying to the animal-derived substance an effective amount of a MS-BLOCK Peptide or derivative thereof or combination thereof.

In some embodiments, the MS-BLOCK Peptide or derivative thereof or combination thereof is used to detect multiple sclerosis.

In some embodiments the MS-BLOCK Peptide or derivative thereof or combination thereof is labeled with a detectable compound.

In some embodiments, the method is carried out to bring about at least one therapeutic effect or diagnostic effect selected from the group consisting of: detecting myelin binding proteins; inhibiting multiple sclerosis; treating or preventing multiple sclerosis related disease.

In some embodiments. the method is for treating multiple sclerosis.

In some embodiments, the MS-BLOCK Peptide or derivative thereof has the following general formula: X-SBNFBBOUK-Z, where:

"S" is either the amino acid SER or ASN;

"B" is either the amino acid ASP or GLU;

"N" is the amino acid ASN;

"F" is the amino acid PHE;

"O" is either the amino acid TYR or the amino acid LEU;

"U" is either the amino acid LEU or amino acid MET;

"K" is the amino acid LYS;

"X" are N-terminal amino acids preceding the amino acids SBNFBBOUK-Z, and

"Z" are any C-terminal amino acids following X-SBNFBBOUK.

In some embodiments, the MS-BLOCK Peptide or derivative thereof has the following general formula: X-RKLGJK-Z, where:

"R" is the amino acid ARG;

"X" is the amino acid LYS;

"L" is an amino acid selected from the group of LEU, ILE and VAL;

"G" is the amino acid GLY or ALA

"J" is three, four or five amino acids,

"X" are any N-terminal amino acids preceding the amino acids RKLGJK-Z, and

"Z" are any C-terminal amino acids following X-RKLGJK.

In some embodiments, the J is selected from the group of peptides consisting of: ASN-LEU-ALA, ASN-LEU-LEU. VAL-ARG-LEU, LYS-LEU-LEU, GLY-MET-ALA, and

VAL-ALA-ALA-ALA-SER.

In some embodiments, the MS-BLOCK Peptide or derivative thereof or combination thereof comprises a multimeric MS-BLOCK Peptide.

In some embodiments, the multimeric MS-BLOCK Peptide is bound to an oligomerizing substance and the method is carried out for treating a multiple sclerosis.

In some embodiments, the oligomerizing substance is selected from the group consisting of: peptides, small molecules, and cross-linking reagents.

In some embodiments, the multimeric MS-BLOCK Peptides are covalently linked by residues in the X, Y, or J components.

In some embodiments, the covalent linkage is a disulfide bond.

In some embodiments, the method is for *in vivo* or *ex vivo* filtering of the blood of a human or animal subject.

A further aspect of the invention is directed to a composition of matter comprising an MS-BLOCK Peptide or a derivative thereof or a combination thereof.

Optionally, the composition according has a general formula X-SBNFBBOUK-Z, where:

"S" is either the amino acid SER or ASN;

"B" is either the amino acid ASP or GLU;

"N" is the amino acid ASN;

"F" is the amino acid PHE;

"O" is either the amino acid TYR or the amino acid LEU;

"U" is either the amino acid LEU or the amino acid MET;

"K" is the amino acid LYS;

"X" are N-terminal amino acids preceding the amino acids SBNFBBOUK-Z, and

"Z" are any C-terminal amino acids following X-SBNFBBOUK.

Optionally, the composition according has a general formula X-RKLGJK-Z, where:

"R" is the amino acid ARG;

"K" is the amino acid LYS;

"L" is the amino acid LEU, ILE, or VAL;

"G" is the amino acid GLY or ALA;

"J" is three, four or five amino acids;

"X" are any N-terminal amino acids preceding the amino acids RKLGJK-Z, and
"Z" are any C-terminal amino acids following X-RKLGJK.

Optionally, the composition is combined with or bound to a natural or synthetic material that is useable as a scaffold, a filter, a bioengineered material or a particle.

Optionally, the natural or synthetic material comprises at least one material selected from the group consisting of: hydrogels, collagens, hyaluronic acids, polymers, tissue bulking agents, and protein particles.

Optionally, the composition is expressed as the coding DNA or RNA for the MS-BLOCK Peptide.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of the specification, illustrate embodiments of the invention, and together with the general description given above and the detailed description of the preferred embodiments given below, serve to explain the principles of the invention.

FIG. 1 shows a ribbon diagram of the common myelin/retinoic acid binding protein structure and the placement of MS-BLOCK Peptide components of myelin and retinoic acid binding protein structures.

FIG. 2 shows a ribbon diagram of MS-BLOCK Peptide components in myelin and retinoic acid binding protein structures.

DETAILED DESCRIPTION OF THE INVENTION

Human myelin protein P2 (PDB: 2WUT), equine myelin protein P2 from spinal cord (PDB: 1YIV), human cellular retinol-binding protein IV (PDB: 1LPJ), and cellular retinoic-acid-binding proteins I and II (PDB: 1CAB) all have two sets of highly conserves sequences in the N-terminal region. These sequences present sets of highly charged residues to the surface of the protein. Table 1 shows the positions of the two sets of residues. Table 2 shows the consensus residues for two structures identified that present highly charged residues to the same surface. Figure 1 shows the spatial relationship between the residues in Table 1 in the crystal structures by showing the secondary structure ribbon positions in which these residues reside. Figure 1 also shows the relationship between the residues in the secondary structures containing MS-BLOCK Peptides and the rest of the protein. Figure 2 shows MS-BLOCK Peptides in the same spatial relationship as in myelins and retinoic acid binding proteins. Compounds based on this presentation of common residues that present to a surface are used to bind to proteins that bind to myelin in order to provide a means of detection and treatment of MS.

Aspects of the invention are directed to MS-BLOCK Peptides derivatives thereof and combinations therof, including pharmaceutically acceptable salts, hydrates, multimers, cyclic forms, linear forms, drug-conjugates, pro-drugs and their derivatives.

Selected sequences found in myelins and retinoic acid binding proteins present the same charged residues to form a common protein surface. Selected sequences of selected myelin and retinoic acid binding proteins are shown in Table I. The first and third column of residues in Table I for each protein form helices that are presented to the protein surface for each protein. Figure 1 shows a ribbon diagram **[1]** representing the common structure of the myelin and retinoic acid binding protein structures. Figure 1 also shows the position of two helices on the surfaces of the proteins **[2 and 3]**.

Helix one **[2]** represents the protein sequences found in Table I in the first column for each protein:

1CBS: SER-GLU-ASN-PHE-GLU-GLU-LEU-LEU-LYS
2WUT: SER-GLU-ASN-PHE-ASP-ASP-TYR-MET-LYS
3NR3: SER-GLU-ASN-PHE-ASP-ASP-TYR-MET-LYS
1LPJ: SER-ASP-ASN-PHE-GLU-GLY-TYR-MET-LEU

The structure of the presentation of the consensus sequence for residues in helix one **[2]** is shown in detail in Figure 2 and is:

SER [12A-12B] -
ASP/GLU [11A-11B] -
ASN [10] -
PHE [9] -
ASP/GLU [8A-8B] -
ASP/GLU/GLY [7] -
TYR/LEU [6A-6B] -
MET/LEU [5] -
LYS/LEU [4A-4B]

The second helix **[3]** represents the protein sequences found in Table I in the third column for each protein (where "( )" stands for a missing residue):

1CBS: ARG-LYS-ILE-ALA-VAL-ALA-ALA-ALA-SER-LYS
2WUT: ARG-LYS-LEU-GLY-ASN-LEU-ALA-( )-( )-LYS
3NR3: ARG-LYS-LEU-GLY-ASN-LEU-ALA-( )-( )-LYS
1LPJ: ARG-LYS-ILE-ALA-LYS-LEU-LEU-( )-( )-LYS

The structure of the presentation of the consensus sequence for residues in helix two **[3]** is shown in detail in Figure 2 and is:

ARG **[13]** -
LYS **[14]** -
ILE/LEU **[15]** -
ALA/GLY **[16A-16B]** -
VAL/ASN/LYS **[17]** -
ALA/LEU **[18A]** -
ALA/LEU **[18B]** -
ALA/( ) **[18C]** -
SER/( ) **[18C]** -
LYS **[19]**

The claimed MS-Block Peptides incorporate sequences found in helices one **[2,3A-12B]** and two **[3, 13-19]**:

MS-Block Peptide 1:

MS-BLOCK Peptide 1 or derivative thereof has the following general formula: X-SBNFBBOUK-Z, where: “S” is either the amino acid SER or ASN, “B” is either the amino acid ASP or GLU, “N” is the amino acid ASN, “F” is the amino acid PHE, “O” is either the amino acid TYR or LEU, “U” is either the amino acid LEU or MET, “K” is the amino acid LYS, “X” are N-terminal amino acids preceding the amino acids SBNFBBOUK-Z and “Z” are any C-terminal amino acids following X-SBNFBBOUK.

MS-Block Peptide 2:

MS-BLOCK Peptide 2 or derivative thereof has the following general formula: X-RKLGJK-Z, where: “R” is the amino acid ARG, “K” is the amino acid LYS, where “L” is the amino acid LEU, ILE, or VAL, “G” is the amino acid GLY or ALA, “J” is three, four or five amino acids, “X” are any N-terminal amino acids preceding the amino acids RKLGJK-Z, and “Z” are any C-terminal amino acids following X-RKLGJK.

MS-BLOCK Peptides can be made by conventional means including expression in bacteria and cell free synthesis. Nucleic acids, including DNA and RNA. encoding MS-BLOCK Peptides can be made by conventional means including synthesis in bacteria or on DNA and RNA automated chemical synthesizers.

An Embodiment

Any construct which presents helix one [2] and helix two [3] in a similar structural configuration to that of retinoic acid binding protein can be used as an embodiment of the invention. As an example, the following peptide presents both helices in the desirable configuration:

MET-CYS-LEU-VAL-SER- (X peptide of helix one with disulfide bridging CYS residue)
SER-GLU-ASN-PHE-ASP-ASP-TYR-MET-LYS-ALA- (helix one **[2]**)
LEU-GLY-VAL-GLY-LEU-ALA-THR- (Z peptide of helix one/X peptide of helix two)
ARG-LYS-LEU-GLY-ASN-LEU-ALA-LYS- (helix two **[3]**)
PRO-CYS-GLY-LYS (Z peptide of helix two with disulfide bridging CYS residue)

In this case the construct provides for a disulfide bridge stabilizing the helix one **[2]** and two **[3]** structures. Table 2 shows the coordinates for the structure of the protein incorporating MS-BLOCK Peptide One and MS-BLOCK Peptide Two as an example embodiment.

Additional advantages and modifications will readily occur to those skilled in the art. Therefore, the invention in its broader aspects is not limited to the specific details and representative embodiments shown and described herein. Accordingly, various modifications may be made without departing from the spirit or scope of the general inventive concept as defined by the appended claims and their equivalents.

The foregoing descriptions of specific embodiments of the present invention have been presented for purposes of illustration and description. They are not intended to be exhaustive or to limit the invention to the precise forms disclosed, and obviously many modifications and variations are possible in light of the above teaching. The embodiments were chosen and described in order to best explain the principles of the invention and its practical application, to thereby enable others skilled in the art to best use the invention and various embodiments with various modifications as are suited to the particular use contemplated. It is intended that the scope of the invention be defined by the claims appended hereto and their equivalents.

TABLE 1

Database Accession PDB 1CBS: Cellular Retinoic-Acid-Binding Protein I & II										
RES NUM	12	13	14	15	16	17	18	19	20	
RES NAM	SER	GLU	ASN	PHE	GLU	GLU	LEU	LEU	LYS	
RES NUM	21	22	23	24	25	26	27	28		
RES NAM	VAL	LEU	GLY	VAL	ASN	VAL	MET	LEU		
RES NUM	29	30	31	32	33	34	35	36	37	38
RES NAM	ARG	LYS	ILE	ALA	VAL	ALA	ALA	ALA	SER	LYS
Database Accession PDB 2WUT: Human Myelin Protein P2										
RES NUM	13	14	15	16	17	18	19	20	21	
RES NAM	SER	GLU	ASN	PHE	ASP	ASP	TYR	MET	LYS	
RES NUM	22	23	24	25	26	27	28	29		
RES NAM	ALA	LEU	GLY	VAL	GLY	LEU	ALA	THR		
RES NUM	30	31	32	33	34	35	36	37		
RES NAM	ARG	LYS	LEU	GLY	ASN	LEU	ALA	LYS		
Database Accession PDB 3NR3: Human Peripheral Myelin Protein P2										
RES NUM	14	15	16	17	18	19	20	21	22	
RES NAM	SER	GLU	ASN	PHE	ASP	ASP	TYR	MET	LYS	
RES NUM	23	24	25	26	27	28	29	30		
RES NAM	ALA	LEU	GLY	VAL	GLY	LEU	ALA	THR		
RES NUM	31	32	33	34	35	36	37	38		
RES NAM	ARG	LYS	LEU	GLY	ASN	LEU	ALA	LYS		
Database Accession PDB 1LPJ: Cellular Retinol-Binding Protein IV										
RES NUM	13	14	15	16	17	18	19	20	21	
PDB 1LPJ	SER	ASP	ASN	PHE	GLU	GLY	TYR	MET	LEU	
RES NUM	22	23	24	25	26	27	28	29		
PDB 1LPJ	ALA	LEU	GLY	ILE	ASP	PHE	ALA	THR		
RES NUM	30	31	32	33	34	35	36	37		
PDB 1LPJ	ARG	LYS	ILE	ALA	LYS	LEU	LEU	LYS		

Table 1: Shows the residues of helix one **[2,3A-12B]**, residues of helix two **[3, 13-19]**, and residues between helix one and two from myelin and retinoic acid binding protein structures.

CLAIMS

What is claimed is:

1. A method for binding myelin binding proteins in any of:
   a human subject,
   an animal subject ,
   a human derived substance;
   an animal-derived substance;
   said method comprising the step of: administering to the subject or applying to the animal-derived substance an effective amount of a MS-BLOCK Peptide or derivative thereof or combination thereof.
2. The method of claim 1 wherein the MS-BLOCK Peptide or derivative thereof or combination thereof is used to detect multiple sclerosis.
3. The method of claim 2 wherein the MS-BLOCK Peptide or derivative thereof or combination thereof is labeled with a detectable compound.
4. The method according to claim 1 wherein the method is carried out to bring about at least one therapeutic or diagnostic effect selected from the group consisting of: detecting myelin binding proteins; inhibiting multiple sclerosis; treating or preventing multiple sclerosis related disease; and binding myelin binding proteins; .
5. The method according to claim 1 for treating multiple sclerosis.
6. The method according to claim 1 wherein the MS-BLOCK Peptide or derivative thereof has the following general formula: X-SBNFBBOUK-Z, where:
   “S” is either the amino acid SER or ASN,
   “B” is either the amino acid ASP or GLU,
   “N” is the amino acid ASN,
   “F” is the amino acid PHE,
   “O” is either the amino acid TYR or LEU,
   “U” is either the amino acid LEU or MET,
   “K” is the amino acid LYS,
   “X” are N-terminal amino acids preceding the amino acids SBNFBBOUK-Z, and
   “Z” are any C-terminal amino acids following X-SBNFBBOUK.
7. The method according to claim 1 wherein the MS-BLOCK Peptide or derivative thereof has the following general formula: X-RKLGJK-Z, where:
   “R” is the amino acid ARG,
   “K” is the amino acid LYS,
   “L” is an amino acid selected from the group of LEU, ILE, or VAL;
   “G” is the amino acid GLY or ALA,

"J" is three, four or five amino acids

"X" are any N-terminal amino acids preceding the amino acids RKLGJK-Z, and

"Z" are any C-terminal amino acids following X-RKLGJK.

8. The method according to claim 7 wherein J is selected from the group of peptides consisting of: ASN-LEU-ALA, ASN-LEU-LEU, VAL-ARG-LEU, LYS-LEU-LEU, GLY-MET-ALA, and VAL-ALA-ALA-ALA-SER.

9. The method according to claim 1 wherein the MS-BLOCK Peptide or derivative thereof or combination thereof comprises a multimeric MS-BLOCK Peptide.

10. The method according to claim 9 wherein the multimeric MS-BLOCK Peptide is bound to an oligomerizing substance and wherein the method is carried out for treating a multiple sclerosis.

11. The method according to claim 10 wherein the oligomerizing substance is selected from the group consisting of: peptides, small molecule, and cross-linking reagents.

12. The method according to claim 1 wherein the multimeric MS-BLOCK Peptides are covalently linked by residues in the X, Y, or J components.

13. The method according to claim 12 wherein the covalent linkage is a disulfide bond.

14. The method for *in vivo* or *ex vivo* filtering of the blood of a human or animal subject.

15. A composition of matter comprising an MS-BLOCK Peptide or derivative thereof or combination thereof.

16. The composition according to claim 15 having the following general formula: X-SBNFBBOUK-Z, where:

"S" is either the amino acid SER or ASN,

"B" is either the amino acid ASP or GLU,

"N" is the amino acid ASN,

"F" is the amino acid PHE,

"O" is either the amino acid TYR or LEU,

"U" is either the amino acid LEU or MET,

"K" is the amino acid LYS,

"X" are N-terminal amino acids preceding the amino acids SBNFBBOUK-Z, and

"Z" are any C-terminal amino acids following X-SBNFBBOUK.

17. The composition according to claim 15 having the following general formula: X-RKLGJK-Z, where:

"R" is the amino acid ARG,

"K" is the amino acid LYS,

"L" is the amino acid LEU, ILE, or VAL,

"G" is the amino acid GLY or ALA,

"J" is three to five amino acids,

"X" are any N-terminal amino acids preceding the amino acids RKLGJK-Z, and

"Z" are any C-terminal amino acids following X-RKLGJK.

18. The composition according to claim 15 combined with, or bound to, a natural or synthetic material that is useable as a scaffold, filter, or bioengineered material or particle.

19. The composition according to claim 18 wherein the natural or synthetic material comprises at least one material selected from the group consisting of: hydrogels, collagens, hyaluronic acids, polymers, tissue bulking agents, and protein particles.

20. The composition according to claim 15 expressed as the coding DNA or RNA for the MS-BLOCK Peptide.

ABSTRACT

Compounds comprising peptides and derivatives thereof and combinations thereof, including pharmaceutically acceptable salts, hydrates, multimers, cyclic forms, linear forms, drug-conjugates, pro-drugs and their derivatives. Also disclosed are methods for making and using such compounds including methods for using such compounds in the diagnostic binding to, and therapeutic inhibiting of, myelin binding proteins in human and animal subjects.

1 / 2

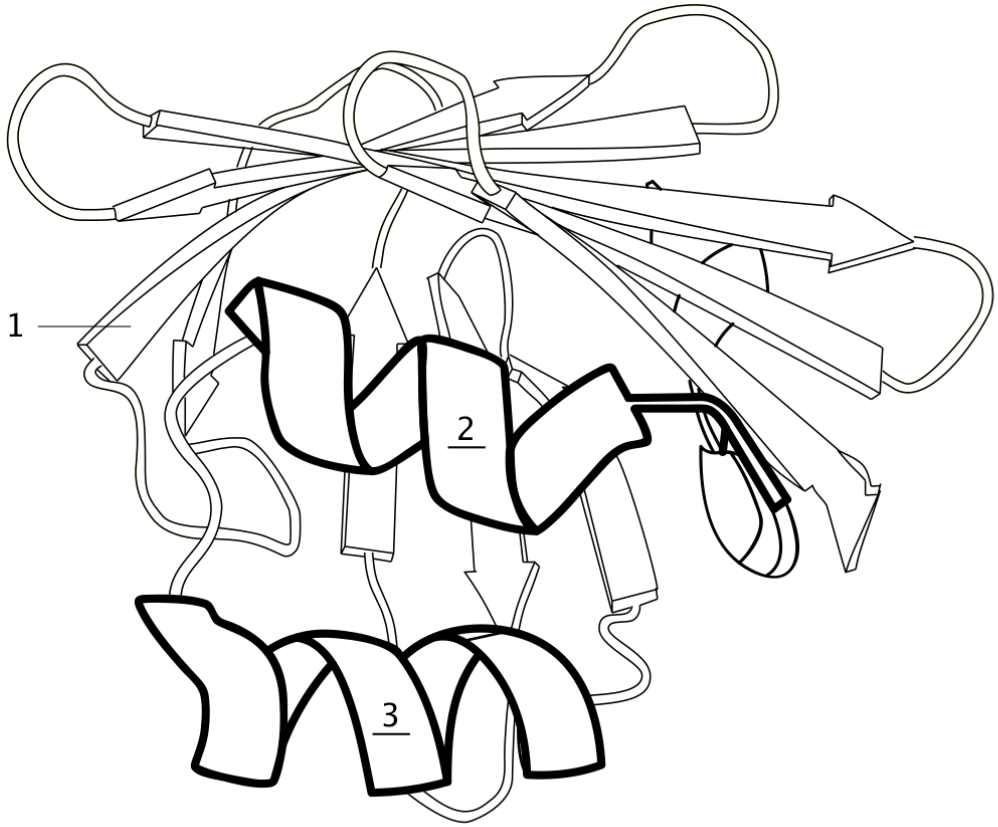

FIGURE 1

2 / 2

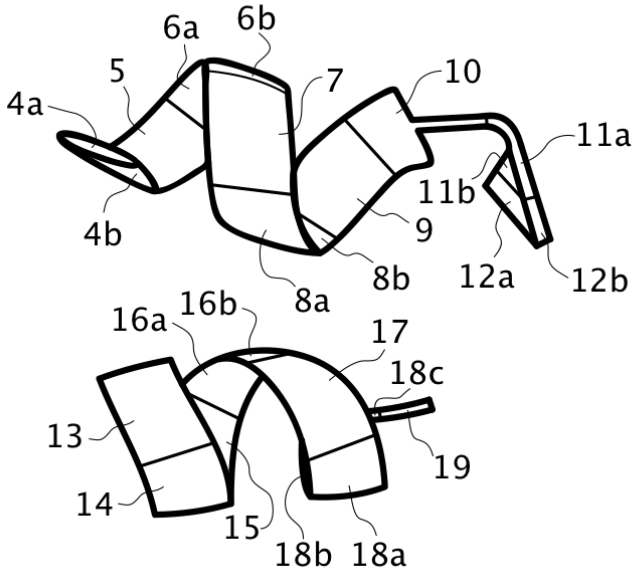
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FIGURE 2