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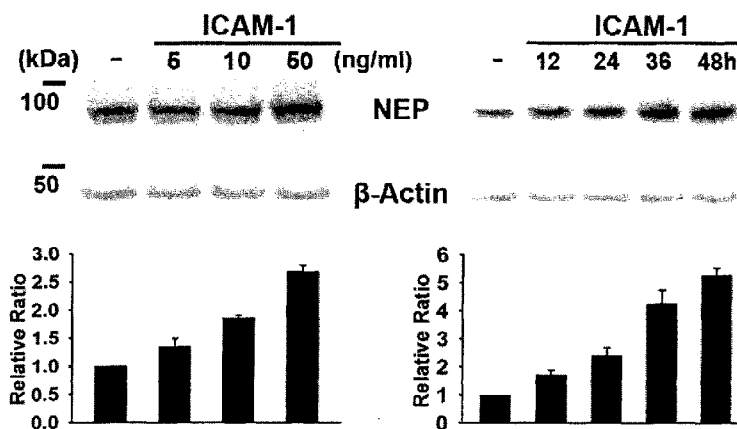
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(54) Title: USE OF ICAM-1 FOR PREVENTION OR TREATMENT OF NEUROLOGICAL DISEASES

FIG. 1



(57) Abstract: The present invention relates to a pharmaceutical composition for the prevention or treatment of neurological disorders, comprising an ICAM-1 (intercellular adhesion molecule-1) protein, or a fragment or a variant thereof as an active ingredient, which can increase the expression of neprilysin to remove amyloid-beta (A $\beta$ , a cause of dementia, and is thus useful in preventing or treating a neurological disease including Alzheimer's disease.



## USE OF ICAM-1 FOR PREVENTION OR TREATMENT OF NEUROLOGICAL DISEASES

### CROSS-REFERENCE

This application claims the benefits of U.S. Provisional Application No. 61/438,809 filed on February 2, 2011 and U.S. Provisional Application No. 61/541,487 filed on September 30, 2011, all of which are incorporated herein by reference.

### BACKGROUND OF THE INVENTION

Alzheimer's disease is manifested by the destruction of brain cells, partly due to accumulation of amyloid-beta ( $A\beta$ ) protein in the brain. Alzheimer's disease progresses in stages and gradually deteriorates the faculties of memory, reasoning, judgment and speech, as well as an ability to carry out simple tasks.

Parkinson's disease is manifested by the destruction of a specialized brain cells, known as the dopaminergic neurons. Loss of dopaminergic neurons lead to clinical symptoms including, but not limited to, the loss of motor control. The cause of onset of Parkinson's disease is not known.

Depression or major depressive disorder is also a disease of brain. The diagnosis is based on the patient's self-reporting experiences including low mood, low self-esteem, and loss of interest or pleasure in various activities.

Epilepsy is a neurological disorder of the brain. Patients with epilepsy suffer from frequent, unpredictable seizures. An epileptic episode is marked by an abnormally increased neuronal activity in the brain.

Multiple sclerosis is manifested by the inflammation of the myelin sheaths around the axons of the brain and the spinal cord. Demyelination leads to, over time, the loss of various physical and cognitive functions.

Mania is a state of abnormally elevated or irritable mood, often lasting for a week or more. Patients suffering from manic episode have been treated with drugs targeting on neurotransmission.

Lou Gehrig's disease, also known as amyotrophic lateral sclerosis is a form of motor neuron disease manifested by the degeneration of neurons in the spinal cord. Patients suffering from the disease experience muscle atrophy, weakness, and breathing difficulties.

Mild cognitive impairment (MCI, also known as incipient dementia, or isolated memory impairment) is a brain-function syndrome involving the onset and evolution of cognitive impairments beyond those expected based on the age and education of the individual, but which are not significant enough to interfere with their daily activities. It is often found to be a transitional stage between normal aging and dementia. Although MCI can present with a variety of symptoms, when memory loss is the predominant symptom it is termed "amnestic MCI" and is frequently seen as a prodromal stage of Alzheimer's disease. Studies suggest that these individuals tend to progress to probable Alzheimer's disease at a rate of approximately 10% to 15% per year.

Multi-infarct dementia is one type of vascular dementia. Vascular dementia is the second most common form of dementia after Alzheimer's disease (AD) in older adults. Multi-infarct dementia (MID) is thought to be an irreversible form of dementia, and its onset is caused by a number of small strokes or sometimes, one large stroke preceded or followed by other smaller strokes. The term refers to a group of syndromes caused by different mechanisms all resulting in vascular lesions in the brain. Early detection and accurate diagnosis are important, as vascular dementia is at least partially preventable.

Dementia with Lewy bodies (DLB), also known under a variety of other names including Lewy body dementia, diffuse Lewy body disease, cortical Lewy body disease, and senile dementia of Lewy type, is a type of dementia closely allied to both Alzheimer's and Parkinson's Diseases. It is characterized anatomically by the presence of Lewy bodies, clumps of alpha-synuclein and ubiquitin protein in neurons, detectable in post-mortem brain biopsies. Lewy Body dementia affects 1.3 million individuals in the United States alone.

Neprilysin is an enzyme that degrades amyloid beta peptide. Deficiency of neprilysin accelerates the extracellular accumulation of amyloid. An increase in neprilysin expression reduces A $\beta$  peptides.

Intracellular Adhesion Molecule-1 (ICAM-1) is a membrane glycoprotein encoded by the ICAM1 gene. Mice deficient of ICAM1 gene developed normally, were fertile, and had a moderate granulocytosis, but exhibited impaired neutrophil emigration to chemical stimulus and abnormalities in inflammatory responses.

### **SUMMARY OF THE INVENTION**

Described herein is a pharmaceutical composition for the prevention or treatment of a neurological disease, comprising an ICAM-1 (intercellular adhesion molecule-1) protein, or a fragment or a variant thereof as an active ingredient. In one embodiment, the ICAM-1 protein of said composition has the amino acid sequence of SEQ. ID. NO.: 1 or the amino acid sequence from which a signal peptide corresponding to the 1st to 27th amino acid residues is removed. In another embodiment, the fragment of the ICAM-1 protein has a biological activity equivalent to that of the ICAM-1 protein. In another embodiment, the variant of the ICAM-1 protein has the amino acid sequence of SEQ. ID. NO.: 1 in which one or more amino acids are substituted, deleted, inserted and/or added, and has a biological activity equivalent to that of the ICAM-1 protein. In another embodiment, the variant of the ICAM-1 protein has an amino acid sequence identical to at least about 90%, 93%, 95%, 96%, 97%, 98% or 99% of the ICAM-1 protein having the amino acid sequence of SEQ. ID. NO.: 1, and has a biological activity equivalent to that of the ICAM-1 protein. In another embodiment, the ICAM-1 protein, or the fragment or the variant thereof induces the expression of neprilysin (NEP) to promote degradation of amyloid-beta ( $A\beta$ ). In another embodiment, the neurological disease is a disease caused by at least one selected from the group consisting of formation of amyloid-beta plaque in neurons, hyperphosphorylation of tau protein in neurons, damage to neurites, reduction in expression of neprilysin in neurons, and a combination thereof. In another embodiment, the neurological disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, depression, epilepsy, multiple sclerosis, mania, Lou Gehrig's disease, mild cognitive impairment, multi-infarct dementia, and dementia with Lewy bodies.

Described herein is a method of preventing or treating a neurological disease in a subject, comprising administering to the subject in need thereof an ICAM-1 protein, or a fragment or a variant thereof.

Described herein is a method of increasing the expression of neprilysin in neurons, comprising co-culturing with neurons an ICAM-1 protein, or a fragment or a variant thereof.

Described herein is a method of increasing the expression of neprilysin in a subject, comprising administering to the subject an ICAM-1 (intercellular adhesion molecule-1) protein, or a fragment or a variant thereof.

Described herein is a composition comprising an ICAM-1 protein, or a fragment or a variant thereof, wherein said protein, fragment, or a variant thereof can increase the expression of neprilysin in neurons to remove amyloid-beta peptides, a cause of dementia, and is thus useful in preventing or treating a neurological disease including Alzheimer's disease.

### **INCORPORATION BY REFERENCE**

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

### **BRIEF DESCRIPTION OF DRAWINGS**

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

Figure 1 illustrates the effect of ICAM-1 on the expression of neprilysin in microglial cells.

Figure 2 illustrates the effect of ICAM-1 on the expression of neprilysin in hippocampus.

Figure 3 illustrates the effect of ICAM-1 on amyloid-beta<sub>42</sub>.

Figure 4A illustrates the structure of an ICAM-1 protein. Figure 4B illustrates four ICAM-1 fragments prepared in Example 4.

Figure 5 illustrates four ICAM-1 genes encoding ICAM-1 fragments prepared in Example 4.

Figure 6 illustrates nucleic acids obtained from an *E. coli* strain transformed with a plasmid containing ICAM-1 gene.

### **DETAILED DESCRIPTION OF THE INVENTION**

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Unless characterized differently, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

The term "about" in relation to a reference numerical value includes a range of values plus or minus 15% from that value. For example the amount "about 10" includes amounts from 8.5 to 11.5.

The term "amyloid-beta (A $\beta$ )" refers to a major element of amyloid plaque found in the brain of a patient having Alzheimer's disease. An A $\beta$  can be a peptide including an amino acid derived from the C-terminal of amyloid precursor protein (APP) that is a transmembrane glycoprotein. An A $\beta$  can be produced from APP by a continuous operation of  $\beta$ -secretase and  $\gamma$ -secretase. An A $\beta$  can be 39 to 43 amino acids, or 40 to 42 amino acids. An A $\beta$  can comprise 672-713 residues (A $\beta$ 42) or 672-711 residues (A $\beta$ 40) of the amino acid sequence of NCBI Accession No.: NP\_000475. An A $\beta$  can be a human amyloid-beta A4 protein isoform precursor. An A $\beta$  can be derived from a mammal. An A $\beta$  can be derived from a human or a mouse. An A $\beta$  can be recombinantly produced.

The term "tau protein" refers to a microtubule-associated protein found in neurons of the central nervous system. A tau protein interacts with tubulin to stabilize microtubule and

promotes tubulin assembly of the microtubule. A cerebral tissue can include six different tau isoforms. Hyperphosphorylation of a tau protein is related to the development of Alzheimer's disease. A tau protein can be highly soluble. In humans, a tau protein can be found in neurons rather than non-neuron cells. A protein can be involved in the stabilization of axonal microtubule. A tau protein can be microtubule-associated protein tau isoform 2 having the amino acid sequence of NCBI Accession No: NP\_005901. A tau protein can be derived from a mammal. A tau protein can be derived from a human or a mouse. A tau protein can be recombinantly produced.

The term "neprilysin" refers to a zinc-dependent metalloprotease enzyme decomposing a large number of small, secreted peptides. Neprilysin can decompose amyloid-beta that causes Alzheimer's disease if amyloid-beta is abnormally folded and aggregated in neural tissues. A neprilysin can be a peptide having the amino acid sequence of NCBI Accession No: NP\_000893. Neprilysin can be derived from a mammal. Neprilysin can be derived from a human or a mouse. Neprilysin can be recombinantly produced.

### ICAM-1

Described herein is a pharmaceutical composition comprising an ICAM-1 (intercellular adhesion molecule-1) protein, or a fragment or a variant thereof, as an active ingredient.

In one aspect, an ICAM-1 useful for compositions and methods described herein includes a naturally occurring ICAM-1. In one embodiment, a naturally occurring ICAM-1 includes, but is not limited to, an ICAM-1 having a wild-type amino acid sequence of an ICAM-1 normally associated with an animal. In another embodiment, a naturally occurring ICAM-1 includes, but is not limited to, a naturally occurring variant of an ICAM-1. In one embodiment, a naturally occurring variant is an allelic variant. In another embodiment, a naturally occurring variant is a polymorphic variant. In another aspect, an ICAM-1 useful for compositions and methods described herein includes a mutant of an ICAM-1. In one embodiment, a mutant can be an ICAM-1 having a mutation found in nature. In another embodiment, a mutation can be a mutation artificially introduced to an ICAM-1. In one embodiment, a mutation can be a mutation introduced to the nucleic acid sequence of an ICAM-1, either with or without having an

effect of replacing, deleting, or inserting one or more amino acid to a nucleic sequence encoding ICAM-1.

In one aspect, an ICAM-1 useful for compositions and methods described herein includes polypeptide sequences encoding an ICAM-1 of an animal. An animal encoding an ICAM-1 can include, but is not limited to, *Homo sapiens*, *Mus musculus*, *Rattus norvegicus*, *Bos taurus*, *Pan troglodytes*, *Canis lupus familiaris*, *Sus scrofa*, *Oryctolagus cuniculus*, *Macaca mulatta*, *Nomascus leucogenys*, *Cricetulus griseus*, *Gorilla gorilla*, *Pongo abelii*, *Callithrix jacchus*, and *Ailuropoda melanoleuca*. A variety of ICAM-1 peptide sequences discovered in these animals are available in public databases including National Center for Biotechnology Information (NCBI). In one embodiment, an ICAM-1 useful for compositions and methods described herein is an animal ICAM-1 with a sequence corresponding to a GenBank Accession Number. A GenBank Accession Number of an ICAM-1 useful for compositions and methods described herein includes, but is not limited to, P13597.1, Q00238.1, CAA41977.1, AAB19978.1, P05362.2, NP\_037099.1, NP\_000192.2, NP\_776773.1, NP\_001009946.1, P33729.2, Q5NKV4.1, Q28806.2, Q95132.1, NP\_001040600.1, DAA28002.1, Q5NKV9.1, Q5NKV6.1, AAA92551.1, NP\_034623.1, NP\_998981.1, AAA37875.1, AAF80287.1, NP\_001003291.1, AAD13617.1, NP\_001009731.1, ACJ49146.1, AAB51145.1, BAD04920.1, 1IAM\_A, 1MQ8\_C, 1MQ8\_A, 3TCX\_b, 3TCX\_a, 3TCX\_Z, 3TCX\_Y, 3TCX\_X, 3TCX\_W, 3TCX\_V, 3TCX\_U, 3TCX\_T, 3TCX\_S, 3TCX\_R, 3TCX\_Q, 3TCX\_P, 3TCX\_O, 3TCX\_N, 3TCX\_M, 3TCX\_L, 3TCX\_K, 3TCX\_J, 3TCX\_I, 3TCX\_H, 3TCX\_G, 3TCX\_F, 3TCX\_E, 3TCX\_D, 3TCX\_C, 3TCX\_B, 3TCX\_A, 2OZ4\_H, 2OZ4\_L, 2OZ4\_A, 1P53\_B, 1P53\_A, 1MQ8\_D, 1MQ8\_B, 1IC1\_B, 1IC1\_A, CAA30051.1, 1D3E\_I, 1D3E\_4, 1D3E\_3, 1D3E\_2, 1D3E\_1, 1D3L\_A, NP\_037021.1, 1DGI\_4, 1DGI\_3, 1DGI\_2, 1DGI\_1, 1DGI\_R, NP\_034624.1, NP\_001032869.2, NP\_001186763.1, NP\_542413.1, NP\_001069.1, P90489.1, NP\_579840.1, 3EO9\_H, 3EO9\_L, 3EOB\_J, 3EOB\_B, 3EOB\_A, 3EOB\_I, 3EOB\_H, 3EOB\_L, 3EOA\_J, 3EOA\_B, 3EOA\_A, 3EOA\_I, 3EOA\_H, 3EOA\_L, BAA00759.1, CAA36507.1, NP\_999056.1, NP\_036843.1, AAA84866.1, 3HI6\_Y, 3HI6\_X, 3HI6\_L, 3HI6\_H, 3HI6\_B, 3HI6\_A, 3HI5\_L, 3HI5\_H, AAA37876.1, 1MJN\_A, AAA35415.1, 1MQA\_A, 1MQ9\_A, NP\_001139280.1, NP\_000623.2, NP\_000425.1, EAW72950.1, EAW72949.1, NP\_938033.1, NP\_005408.1, NP\_002219.1, P29533.1, P19320.1, Q9UMF0.3, P13598.2, NP\_035823.3, NP\_937882.1, NP\_003871.1, NP\_001107852.1, NP\_002200.2, NP\_001093259.1, NP\_001093258.1,

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AAE20920.1, AAE20919.1, AAE10139.1, AAC89984.1, AAC89982.1, AAC87796.1, AAC87794.1, AAC19905.1, AAC19903.1, AAC19660.1, 225938, AAA55744.1, NP\_570116.2, Q5NKV2.1, Q5NKV1.1, NP\_570118.1, P41323.1, NP\_001029170.1, 2V7D\_S, 2V7D\_R, 2V7D\_Q, 2V7D\_P, 2V7D\_D, 2V7D\_C, 2V7D\_B, 2V7D\_A, 2JF1\_T, 2JF1\_A, AAE18933.1, AAE18932.1, AAE18931.1, AAE18930.1, AAE18929.1, AAE18928.1, AAE18927.1, AAE18926.1, AAE18925.1, AAE18924.1, AAE18923.1, AAE18922.1, AAE18921.1, AAE18920.1, AAE18919.1, AAE18918.1, AAE18917.1, AAE18916.1, AAE18915.1, 3M6F\_A, AAA60393.1, and AAA60392.1.

In one aspect, an ICAM-1 useful for compositions and methods described herein is glycosylated. In another aspect, an ICAM-1 useful for compositions and methods described herein is non-glycosylated. In one embodiment, a glycosylation can be naturally occurring. In another embodiment, a glycosylation can be artificially introduced to ICAM-1 through recombinant DNA technology generally known in the art.

In one aspect, an ICAM-1 useful for compositions and methods described herein is naturally modified. In one embodiment, a natural modification is a post-translational modification. In one embodiment, an ICAM-1 comprises a polypeptide containing the signal peptide portion of an ICAM-1. In another embodiment, an ICAM-1 comprises a polypeptide lacking the signal peptide portion of an ICAM-1.

In one aspect, an ICAM-1 useful for compositions and methods described herein has the amino acid sequence of SEQ. ID. NO.: 1 (Genbank Accession No. AAQ14901): MAPSSPRPALPALLVLLGALFPGPGNAQTSVSPSKVILPRGGSVLVTCSTSCDQPKLLGIETPLPKKELLPLGNNRK VYELSNVQEDSQPMCYSNCPDGQSTAKTFLT VYWT PERVELAPLPSWQPVGKNLTLRCQVEGGAPRANLTVVL LRGEKELKREPAVGEPAEVT TTVL VRRDHHGANFSCRTEL DLRPQGLEL FENTSAPYQLQTFVLPATPPQLVSPR VLEVDTQGT VVCSLDXLFPVSEAQVHLALGDQRLNPTV TYGNDSFSAKASVSVTAEDEGTQRLTCAVILGNQSQ ETLQTVTIYSFPAPNVILTKPEVSEGTEVTVKCEAHPRAKVT LNVGPAQPLGPRAQLLLKATPEDNGRSFSCSATL EVAGQLIHKNTRELRVLYGPR LDERDCPGNWTWPENSQQTPMCQAWGNPLPELKCLKDGT FPLPIGESVT VTR DLEGT YLCRARSTQGEVTREVT VNVLSPRYEIVITVVA AVIMGTAGLSTYLYNRQRKIKKYRLQQAQKGT PM KPNTQATPP (SEQ. ID. NO.: 1). In another embodiment, an ICAM-1 is a peptide corresponding to the amino acid sequence AAQ14901, but lacking a signal peptide, which corresponds to the 1<sup>st</sup> to 27<sup>th</sup> amino acid residues of SEQ. ID. NO.: 1. In another embodiment, an ICAM-1 is a

chimpanzee ICAM-1 protein. In another embodiment, an ICAM-1 has the amino acid sequence of SEQ. ID. NO.: 10 (Genbank Accession No. AAQ14896).

In one embodiment, an ICAM-1 useful for compositions and methods described herein is a fragment of an ICAM-1 protein. In one embodiment, a fragment of ICAM-1 protein has a biological activity equivalent to that of the ICAM-1 protein. In another embodiment, a fragment of ICAM-1 protein does not have a biological activity equivalent to that of the ICAM-1 protein. In another embodiment, a fragment of ICAM-1 protein is biological inactive.

In one aspect, an effect of an ICAM-1 on neprilysin expression is used to measure the biological activity of an ICAM-1. In one embodiment, an effect is a level of an increase in neprilysin expression. In another embodiment, an effect is a decrease in neprilysin expression. In one embodiment, a biological activity of an ICAM-1 fragment is measured as a percentage of the activity of another ICAM-1 serving as a standard for comparison. An ICAM-1 standard for comparison can be a full-length ICAM-1, truncated ICAM-1, mutated ICAM-1, post-translationally modified ICAM-1, or a fragment of an ICAM-1 different from the compared ICAM-1. Any ICAM-1 protein or polypeptide described herein can be used as a protein in comparison. A percentage of difference in biological activity can be about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 105%, 110%, 115%, 120%, 125%, 130%, 135%, 140%, 145%, 150%, 155%, 160%, 165%, 170%, 175%, 180%, 185%, 190%, 195%, or 200%. In one embodiment, a biological activity of an ICAM-1 fragment is measured as a fold-increase or decrease of the activity of another ICAM-1 serving as a standard for comparison. A fold-increase or decrease can be about 2-fold, 2.5-fold, 3-fold, 4-fold, 5-fold, 7-fold, -fold, 10-fold, 20-fold, 30-fold, 50-fold, 100-fold, 200-fold, 500-fold, 800-fold, or 1000-fold.

In one embodiment, an ICAM-1 fragment comprises 28<sup>th</sup> to 483<sup>rd</sup> amino acids of SEQ. ID. NO.: 1. In another embodiment, an ICAM-1 fragment comprises 28<sup>th</sup> to 380<sup>th</sup> amino acids of SEQ. ID. NO.: 1. In another embodiment, an ICAM-1 fragment comprises 28<sup>th</sup> to 300<sup>th</sup> amino acids of SEQ. ID. NO.: 1. In another embodiment, an ICAM-1 fragment comprises 28<sup>th</sup> to 200<sup>th</sup> amino acids of SEQ. ID. NO.: 1.

Described herein is an ICAM-1 variant of SEQ. ID. NO.: 1 useful for a treatment of a neurological disorder. In one embodiment, a variant of SEQ. ID. NO.: 1 is a polypeptide having one or more amino acids substituted, deleted, or inserted. In another embodiment, the sequence identity of a variant to SEQ. ID. NO.: 1 is at least 80%, 82%, 85%, 87%, 89%, 90%, 93%, 95%, 96%, 97%, 98% or 99%. In another embodiment, the sequence identity of the extracellular domain of a variant to that of SEQ. ID. NO.: 1 is at least 80%, 82%, 85%, 87%, 89%, 90%, 93%, 95%, 96%, 97%, 98% or 99%. In another embodiment, the sequence identity of the intracellular domain of a variant to that of SEQ. ID. NO.: 1 is at least 80%, 82%, 85%, 87%, 89%, 90%, 93%, 95%, 96%, 97%, 98% or 99%. In another embodiment, the sequence identity of the transmembrane domain of a variant to that of SEQ. ID. NO.: 1 is at least 80%, 82%, 85%, 87%, 89%, 90%, 93%, 95%, 96%, 97%, 98% or 99%.

In one aspect, compositions and methods described herein comprise one or more isolated polypeptides of ICAM-1. In one embodiment, one or more isolated polypeptides of ICAM-1 are ICAM-1s of different amino acid sequences. In another embodiment, one or more isolated polypeptides of ICAM-1 are ICAM-1s of differently processed by post-translational modification process.

In another aspect, compositions and methods described herein comprise one or more ICAM-1 polypeptides attached to a cell. In one embodiment, one or more ICAM-1 polypeptides are covalently attached to a cell. In another embodiment, the polypeptides are embedded in cell membrane. A cell includes, but is not limited to, mammalian cell, bacterial cell, fungal cell, or an insect cell. In one embodiment, a cell is a human cell. In another embodiment, a cell is a human stem cell. In another embodiment, a cell is a human mesenchymal stem cell. In another embodiment, a cell is a human stromal cell. In another embodiment, a cell is an umbilical cord blood cell. An umbilical cord blood cell useful for compositions and methods described herein includes, but is not limited to, cells normally found in, or cultured from the cells normally found in the umbilical cord, umbilical cord blood, amniotic sac, and the placenta.

In another aspect, compositions and methods described herein comprise one or more ICAM-1 polypeptides and a cell secreting ICAM-1 polypeptides.

In another aspect, compositions and methods described herein comprise one or more ICAM-1 polypeptides conjugated with another biological material. A biological material

includes, but is not limited to, various small peptides, another protein, a chemical means useful for isolating or identifying conjugated polypeptides (which are known as “tags” in the art).

In one aspect, ICAM-1 polypeptides described herein in are isolated from an organism, tissues or cells. In one embodiment, ICAM-1 is isolated from mesenchymal stem cells (MSCs) or a culture thereof. Examples of the source of mesenchymal stem cell include, but are not limited to, embryonic yolk sac, placenta, umbilical cord, umbilical cord blood, skin, peripheral blood, bone marrow, adipose tissue, muscle, liver, neural tissue, periosteum, fetal membrane, synovial membrane, synovial fluid, amniotic membrane, meniscus, anterior cruciate ligament, articular chondrocytes, deciduous teeth, pericyte, trabecular bone, infra patellar fat pad, spleen and thymus. In one embodiment, a source of MSCs is an umbilical cord blood-derived MSC or a bone marrow-derived MSC.

Described herein is a method of isolating MSCs from umbilical cord blood. In one embodiment, ICAM-1 is isolated by harvesting umbilical cord blood-derived MSCs. In one embodiment, umbilical cord blood-derived MSCs are isolated by centrifugation. In another embodiment, umbilical cord blood-derived MSCs are isolated by fluorescence-activated cell sorting. In another embodiment, umbilical cord blood-derived MSCs are isolated by using various tags including magnetic beads. In another embodiment, umbilical cord blood-derived MSCs are isolated by using MSC-specific antibodies. In some aspects, other methods of cell separation and isolation can be used. These methods, which are well known in the art, include, but are not limited to, separating by size, weight, or shape of a cell, differences on the types of cell surface molecules, resistance or attraction to chemicals, proteins, or other cells, and other physical or chemical properties useful for distinguishing MSCs from non-MSCs.

In one aspect, ICAM-1 is produced by a recombinant DNA technology. In one embodiment, nucleic acids encoding ICAM-1 or a fragment thereof are cloned into an appropriate recombinant expression system. In one embodiment, a recombinant expression system is ~~bacterial expression system.~~ In another embodiment, a recombinant expression system is an insect-cell expression system. In another embodiment, a recombinant expression system is a mammalian expression system. In one embodiment, a bacterial recombinant expression system is a pET vector expression system. In one embodiment, a pET vector useful for expressing ICAM-1 described herein is pET-28a plasmid DNA. In another embodiment, a bacterial recombinant expression system useful for compositions described herein is a pET vector

containing nucleic acids encoding an ICAM-1 having the nucleotide sequence of SEQ. ID. NO.:  
2 (GenBank Accession No. NM\_000201), or a fragment thereof:  
caagcttagcctggccgggaaacgggaggcgtggaggccgggagcagccccgggggtcatcgcctgccaccgcccccattgcttt  
agcttgaaattccggagctgaagcggccagcggaggatgacctctcggccgggcaccctgtcagtcggaaataactgcagca  
ttgttccggagggaaggcgcgaggttccgggaaagcagcaccgcccctggccccagggtggctagcgtataaaggatcacgcgc  
cccagtcgacgctgagctcctctgctactcagagttgcaacctcagcctcgtatggctcccagcagccccggccccgcgtgccgact  
cctggtcctgctcggggctctgttcccaggacctggcaatgccagacatctgtgtccccctcaaaagtcatcctgccccggggaggctcc  
gtgctggtgacatgcagcacctcctgtgaccagcccaagttgttggcatagagaccccgttgctctaaaaggagttgctcctgctgga  
acaaccggaagggtgatgaactgagcaatgtcaagaagatagccaaccaatgtgctattcaactgccctgatgggcagtaacagctaa  
aaccttctcaccgtgtactggactccagaacgggtggaactggcaccctcccccttggcagccagtgggcaagaaccttacctacgc  
tgccaggtggagggtggggcaccgggccaacctcaccgtggtgctcctgggggagaaggagctgaaacgggagccagctgtg  
ggggagcccgtgaggtcacgaccacggtgctggtgaggagagatcaccatggagccaatttctcgtgccgactgaactggacctgcg  
gccccagggtggagctgtttgagaacacctcggccccctaccagctccagaccttctcctgcccagcactccccacaactgtcagc  
ccccgggtcctagaggtggacacgcaggggaccgtggtctgttccctggacgggctgtcccagctcctggaggcccagggtccacctggc  
actgggggaccagaggtgaaccccacagtcacctatggcaacgactccttctcggccaaggcctcagtcagtgaccgcagaggacg  
agggcaccagcggctgacgtgtgcagtaactggggaaccagagccaggagacactgcagacagtgaccatctacagctttccggcg  
cccaacgtgattctgacgaagccagaggtctcagaaggaccgaggtgacagtgaaagtgtgaggcccaccctagagccaaggtgacgct  
gaaatgggggtccagcccagccactgggcccaggggccagctcctgctgaaaggccaccccagaggacaacggggcgcagcttctcctgc  
tctgcaacctggaggtggccggccagcttatacacaagaaccagaccgggagcttctgctctgtatggccccgactggacgagag  
ggattgtccgggaaactggacgtggccagaaaattcccagcagactccaatgtgccaggcttgggggaaccattgccgagctcaagt  
tctaaaggatggcactttcccactgccatcggggaatcagtgactgtcactcagatcttgagggcacctacctctgtcggccaggagca  
ctcaaggggaggtcaccgcaaggtgaccgtgaatgtgctctcccccggtatgagattgtcatcatcactgtggtagcagccgagtcata  
atgggcactgcaggcctcagcacgtacctctataaccgccagcggagatcaagaaatacagactacaacaggccccaaaaggacccc  
catgaaaccgaacacacaagccacgcctccctgaacctatcccgggacagggccttctcctggccttccatattggtggcagtggtgcc  
aactgaacagagtggaaagacatatgcatgacgtacacctaccggccctgggacgccggaggacagggcattgtcctcagtcagata  
caacagcatttggggccatggtacctgcacacctaaaactaggccacgcactctgactctgtagtcacatgactaagccaagaggaaggag  
caagactcaagacatgattgatggatgttaaagtctagcctgatgagaggggaagtgtgggggagacatagccccacctgaggacata  
caactgggaaataactgaaactgtgcctattgggtatgtgaggccccacagacttacagaagaagtggccctccatagacatgtgtagca  
tcaaaacacaaaggcccacacttctgacggatgccagcttgggcactgctgtctactgacccccacccttgatgatatttattcattgtt  
atttaccagctatttattgagtgcttttatgtaggctaaatgaacataggtctctggcctcacggagctcccagtcctaatcacattcaaggta  
ccaggtacagttgtacaggtgtactgcaggagagtgctggcaaaaagatcaaatggggctgggacttctcattggccaacctgccttt

ccccagaaggagtgatTTTTctatcggcacaaaagcactatatggactggtaatggttacagggtcagagattaccagtgaggccttattcctccctcccccaaaactgacacctttgtagccacctccccaccacatacatttctgccagtggtcacaatgacactcagcggcatgtctggacatgagtgcccagggaaatagccaagctatgccttgcctctgtcctgtttgcatttcactgggagcttgactatgcagctccagtttctgcagtgatcagggctctgcaagcagtggggaagggggccaaggattggaggactccctcccagcttggaaagcctcatccgcgtgtgtgtgtgtgtatgttagacaagctctcgtctgtcaccaggctggagtgagtggtgcaatcatggttcactgcagcttgacctttgggctcagtgatcctcccacctcagcctcctgagtagctgggacataggctcacaacaccacacctggcaaattgattttttttttccagagacgggtctcgcacaattgccagacttctttagttagtaataaagcttctcaactgcca (SEQ. ID. NO.: 2). In one embodiment, a bacterial cell useful for expressing ICAM-1 is *E. coli* BL21 variants. In one embodiment, a variant is *E. coli* BL21 (DE3). In one embodiment, the bacterial expression of recombinant ICAM-1 is induced by treating the transformed bacterial cells with IPTG.

Described herein is a pharmaceutical composition useful for the prevention or treatment of a neurological disorder. In one embodiment, a neurological disorder is a disease caused by any one selected from the group consisting of formation of amyloid-beta plaque in neurons, hyperphosphorylation of tau protein in neurons, damage to neurites, reduction in expression of neprilysin in neurons, and a combination thereof. In another embodiment, a neurological disorder is selected from the group consisting of Alzheimer's disease, Parkinson's disease, depression, epilepsy, multiple sclerosis, mania, Lou Gehrig's disease, mild cognitive impairment, multi-infarct dementia, and dementia with Lewy bodies.

In one aspect, ICAM-1 polypeptides described herein are administered to a subject to intervene with the progress of a neurological disorder. In one embodiment, ICAM-1 polypeptides described herein are administered to a subject suffering from Alzheimer's disease to slow or, stop, or reverse the progress of Alzheimer's disease. In one embodiment, a dose of ICAM-1 polypeptides is administered to a subject once. In another embodiment, a dose of ICAM-1 polypeptides is administered to a subject on a regular interval for an extended period of time. An interval can be a few days, weeks, months, or years. In another embodiment, an initial dose of ICAM-1 polypeptides is administered to a subject, and then the follow up dose is either reduced or increased depending on the clinical outcome of the subject. A clinical outcome is measured by neuropsychological tests including, but is not limited to, self-evaluation, clinical questionnaires, such as clinical dementia scoring, or a mental state examination.

Compositions described herein can be delivered via a topical administration or a systematic administration. In one embodiment, compositions described herein are administered in an amount effective for preventing or treating a neurological disorder. In one embodiment, an effective amount is determined by clinical trials. An effective dose can vary depending on various circumstances including, but is not limited to, types of neurological conditions, manufacturing processes, formulations, routes of administrations, and types of excipients.

A pre-dementia syndrome exhibiting mild cognitive impairment may be diagnosed using a neuropsychological test. It has been reported that about 12% of patients with mild cognitive impairment progress to Alzheimer's disease per year. Surprisingly, about 80% of patients with mild cognitive impairment progress to Alzheimer's disease after 6 years in the absence of any treatment. Thus, when the ICAM-1 protein, or the fragment or the variant thereof, according to the present invention is administered to patients with mild cognitive impairment, the progress to Alzheimer's disease may be prevented or delayed.

In one aspect, compositions described herein are administered in combination with other remedies or therapies effective on the prevention or treatment of Alzheimer's disease, Parkinson's disease, depression, epilepsy, multiple sclerosis, mania, Lou Gehrig's disease, mild cognitive impairment, multi-infarct dementia, or dementia with Lewy bodies. In one embodiment, compositions described herein are administered concomitantly with other remedial compositions or therapies. In another embodiment, compositions described herein are formulated to contain other remedial compositions known to be effective on Alzheimer's disease, Parkinson's disease, depression, epilepsy, multiple sclerosis, mania, Lou Gehrig's disease, mild cognitive impairment, multi-infarct dementia, or dementia with Lewy bodies.

Compositions described herein can contain pharmaceutically acceptable additives in addition to the effective ingredients. A formulation for parenteral administration such as an injection formulation or a topical administration formulation can be used. For example, a formulation for parenteral administration can be used in the form of an injection formulation of a sterile solution or suspension, if required, employing water or other pharmaceutically acceptable solvents. For example, a unit dosage formulation may be prepared using a pharmaceutically acceptable carrier or medium, e.g., sterile water, saline, vegetable oil, an emulsifier, a suspension, a surfactant, a stabilizer, an excipient, a vehicle, a preservative, and a binder. The parenteral

administration can include a topical administration and a systematic administration. The topical administration can be performed by directly administering the pharmaceutical formulation into an injury region or peripheral regions of the injury region, for example, brain or spinal cord, peripheral regions thereof, or opposite regions thereof. The topical administration can include intra-nasal administration and intra-arterial administration. The systematic administration can be performed by administering the pharmaceutical formulation into spinal fluid, vein or artery. The spinal fluid includes cerebrospinal fluid. The artery may be a region for supplying blood to the injury region. In one embodiment, the administration is performed according to a method disclosed in e.g., Douglas Kondziolka, Pittsburgh, *Neurology*, Vol. 55, pp. 565-569, 2000, which is incorporated herein in its entirety. In one embodiment, the skull of a subject is incised to make a hole having a diameter of about 1 cm, and a suspension of ICAM-1 in a Hank's balanced salt solution (HBSS) is injected through the hole with a long-needle syringe and a stereotactic frame used to inject the suspension into the target region. A dose of the ICAM-1 may range from 500 to 1000 ng/kg (body weight) per day, which can be administered in a single dose or in divided doses.

Described herein is a method of increasing the expression of neprilysin in neurons, comprising co-culturing with neurons an ICAM-1 (intercellular adhesion molecule-1) protein, or a fragment or a variant thereof. In one embodiment, neprilysin expression is increased by culturing ICAM-1 with neurons for less than a day, two days, three days, four days, five days, six days, seven days, nine days, or twelve days. In another embodiment, neprilysin expression is increased by culturing with neurons for more than twelve days. In one embodiment, ICAM-1 is added to a media containing neurons and co-cultured. In another embodiment, ICAM-1 expressing cells are added to a media containing neurons and co-cultured. In another embodiment, ICAM-1 or ICAM-1 expressing cells and the neurons are co-cultured in a separate compartment of a culture device that allows the flow of nutrients, but not proteins, ligands, or other cellular products, either secreted by the cells in the culture or added to each compartment of a culture device.

Described herein is a method of increasing the expression of neprilysin in a subject, comprising administering to the subject an ICAM-1 (intercellular adhesion molecule-1) protein,

or a fragment or a variant thereof. In one embodiment, the administration is a topical administration. In another embodiment, the administration is a systematic administration. In one embodiment, an effective amount for increasing the expression of neprilysin is administered. In one embodiment, a formulation comprising an effective amount of ICAM-1 further comprises additives selected from the group consisting of water, culture medium, buffer, and an excipient.

## **EXAMPLES**

Hereinafter, the present invention is described in more detail. The following Examples are given for the purpose of illustration only, and are not intended to limit the scope of the invention.

### **Example 1: *In vitro* efficacy of ICAM-1 protein on NEP expression**

A recombinant ICAM-1 protein having the amino acid sequence of SEQ. ID. NO.: 1 was obtained from R&D SYSTEMS (USA), and BV2 cells were obtained from Seoul National University (Korea). BV2 cells are immortalized cells prepared by infecting microglial cells of a mouse with v-raf/v-myc recombinant retrovirus, which express traits of activated microglial cells. BV2 cells were cultured in a serum-free DMEM medium and treated with the ICAM-1 recombinant protein at a concentration of 5, 10 and 50 ng/mL, respectively, followed by harvesting the cells after 24 hours. The harvested cells of each group were lysed using a sonicator (Branson Ultrasonics Corp.), and a protein extract was obtained therefrom by employing a buffer (9.8 M urea, 4% CHAPS, 130mM dithiothreitol, 40mM Tris-HCl, and 0.1% sodium dodecyl sulfate (SDS)). The extracted protein was quantified using the Bradford assay kit (Bio-Rad Laboratories, Hercules, CA), and 20 µg of the protein extract was resolved on SDS-PAGE and electrotransferred onto a nitrocellulose membrane. Each nitrocellulose membrane was incubated overnight with a primary antibody (anti-NEP antibody; R&D Systems, Minneapolis, MN), washed three times with PBS, and incubated with a secondary antibody (anti-goat IgG; Santa Cruz, USA). Then, the protein was visualized by an ECL kit (Amersham). Beta-actin was used as an internal control for quantification.

The results are shown on the left side of Figure 1. The top left hand picture of the Figure 1 is an immunoblot result and the bottom left hand graph of the Figure 1 presents the

strength of each band relative to the control (no treatment), measured by a densitometer (n=3, P < 0.05).

As shown in the results, NEP expression was increased in ICAM-1 treatment groups compared to the control (no treatment group). Further, NEP expression level was proportional to the concentration of ICAM-1 proteins.

Meanwhile, in order to evaluate the efficacy of ICAM-1 proteins in terms of treating time, BV2 cells were treated with ICAM-1 protein (20 ng/mL) for 12, 24 and 36 hrs, respectively, and then NEP expression was analyzed as above.

The results are shown on the right side of Figure 1. As shown in the results, NEP expression was increased in proportion to a treating time of ICAM- protein.

#### **Example 2: *In vivo* efficacy of ICAM-1 protein on NEP expression**

To evaluate the efficacy of ICAM-1 protein on NEP expression, 5  $\mu$ L of PBS (n=4), or 500 or 1000 ng/kg of ICAM-1 protein in PBS (5  $\mu$ L) (n=4/group) was administered into both hippocampi of each sacrificed anesthetized normal mice (B6C3F1/J, 13 weeks old, 30 g) by using a stereotaxic apparatus. After 7 days, the mice were sacrificed and brain tissue was collected. The brain tissue was lysed to obtain a protein extract and the extract was analyzed for NEP expression, as in Example 1.

The results are shown in Figure 2. As shown in Figure 2, NEP expression was increased in ICAM-1 treatment groups compared to the control (no treatment group). In particular, the NEP expression level of the treated group with 1000 ng/kg of ICAM-1 was more than double that of control (PBS) (P=0.005).

#### **Example 3: Effect of ICAM-1 on amyloid-beta42**

In order to investigate the effect of ICAM-1 on the degradation of amyloid-beta42, the following experiments were carried out. Specifically, BV2 cells cultured in a serum-free DMEM medium were pretreated with ICAM-1 protein (5 or 10 ng/mL) and amyloid-beta42 (10  $\mu$ M) at the same time and were further cultured for 24 hours. The level of amyloid-beta42 in the culture

medium was measured using an ELISA kit (Wako Pure Chemical Industries Ltd. Japan). The results are shown in Figure 3.

As shown in Figure 3, the levels of A $\beta$ 42 were significantly decreased in groups treated with ICAM-1 protein compared to the control. In particular, for ICAM-1-treated groups, the reduction of A $\beta$ 42 was proportional to the concentration of ICAM-1 protein. The results indicate that NEP induced by ICAM-1 protein degrades A $\beta$ 42.

#### Example 4: Preparation of ICAM-1 fragments and evaluation of their activities

In order to investigate an active domain responsible for ICAM-1 activity, four fragments were designed based on the location of ICAM-1 domains with a signal peptide removed (Figure 4). In a pre-PCR for inducing a precise amplification of ICAM-1 gene, synthesized were primers for amplifying a full-length ICAM-1 gene, and primers for amplifying each gene fragment in which the recognition sites for restriction enzymes *Nde*I (NEB, USA) and *Bam*HI (NEB, USA) were inserted.

The Pfu-PCR conditions were as follows: 40 cycles of 94°C for 30 sec; 58~60°C for 45 sec; 72°C for 40 sec. The ICAM-1 fragments thus obtained and pET-28a plasmid DNA (Novagen®, USA) were digested with *Nde*I and *Bam*HI. The primer sequences, annealing temperatures, and PCR product sizes are shown in Table 1.

<Table 1>

Target gene	Primer sequence	Annealing temperature (°C)	PCR product size (bp)
ICAM-1	5'-CCCCCAGGTGGCTAGCGCTA-3' (SEQ ID NO: 3) 5'-GTGCCCAAGCTGGCATCCGT-3' (SEQ ID NO: 4)	58	2153
A fragment	5'-CCGCCGCATATGCAGACATCTGTGTCCCC-3' (SEQ ID NO: 5) 5'-CCCCCCCCCGGGATCCTCATCAGATGACAATCTC-3' (SEQ ID NO: 6)	60	1404
B fragment	5'-CCGCCGCATATGCAGACATCTGTGTCCCC-3' (SEQ ID NO: 5) 5'-CATTCGGGATCCTCATCACTGGCCGGCCACCTC-3' (SEQ ID NO: 7)	60	1089
C fragment	5'-CCGCCGCATATGCAGACATCTGTGTCCCC-3' (SEQ ID NO: 5) 5'-CGGGGATCCTCATCACTCCTGGCTCTGGTTCCC-3' (SEQ ID NO: 8)	60	846
D fragment	5'-CCGCCGCATATGCAGACATCTGTGTCCCC-3' (SEQ ID NO: 5) 5'-CGGCGGGGATCCTCATCAAAACAGCTCCAGCCC-3' (SEQ ID NO: 9)	60	549

Fragment A thus prepared encodes the 28<sup>th</sup> to 483<sup>rd</sup> amino acids in the amino acid sequence of ICAM-1 protein; fragment B, the 28<sup>th</sup> to 380<sup>th</sup> amino acids; fragment C, the 28<sup>th</sup> to 300<sup>th</sup> amino acids; and fragment D, the 28<sup>th</sup> to 200<sup>th</sup> amino acids.

The sizes of the prepared ICAM-1 fragments were confirmed by an electrophoresis on 2% agarose gel (Invitrogen, USA). The electrophoresis results are shown in Figure 5. As shown in Figure 5, four fragments were confirmed to have the precise sizes.

The fragments were purified using a Gel Extraction Kit (QIAGEN, USA) and mixed with pET-28a plasmid DNA (Novagen<sup>®</sup>, USA) treated with *NdeI/BamHI*, followed by ligation with T4 DNA Ligase (NEB, USA). *E. coli* BL21 (DE3) (Sigma, USA) was transformed with the ligated plasmid, and the transformant was cultured in LB agar medium (BD, USA). The proliferated single colonies were picked, placed into each PCR tube, and then subjected to PCR reaction. The amplified inserts were confirmed by an electrophoresis as above (Figure 6), to select colonies. The chosen colonies were cultured in LB broth (BD, USA), and purified using QIAGEN<sup>®</sup> Plasmid Purification Kit (QIAGEN, USA) to obtain DNAs. The purified DNAs were digested with *NdeI* and *BamHI*, and then single colonies containing desired genes were confirmed again on 2% agarose gel with EtBr. The DNAs were purified using PCR Purification Kit (QIAGEN, USA) and the precise sequences of the inserted fragments were confirmed. The colonies of which DNA sequence was confirmed were cultured in LB broth in the presence of IPTG (Promega, USA). The resulting culture was centrifuged and the precipitated cells were treated with 8 M urea (pH 8.0) to lyse the cells. The recombinant protein was separated using Ni-NTA (nickel-nitrilotriacetic acid) agarose (QIAGEN, USA) based on the binding between 6X His attached to the N-terminal of the recombinant protein and Ni-NTA, and confirmed by SDS-PAGE and western blot.

### **Preparation Example 1: Formulation for injection**

To prepare a formulation for injection, 100 mg of ICAM-1 protein is dissolved in water and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for injection.

### **Preparation Example 2: Formulation for inhalation**

To prepare a formulation for inhalation delivery, 20 mg of ICAM-1 protein is mixed with 50 mg of anhydrous citric acid and 100 mL of 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

**Preparation Example 3: Formulation for nasal delivery**

To prepare a nasal spray solution, 10 g of ICAM-1 protein is mixed with 30 mL of a 0.05M phosphate buffer solution (pH 4.4). The solution is placed in a nasal administrator designed to deliver 100  $\mu$ l of spray for each application.

**What is claimed is:**

1. A pharmaceutical composition for the prevention or treatment of a neurological disease, comprising an ICAM-1 (intercellular adhesion molecule-1) protein, or a fragment or a variant thereof, as an active ingredient.

2. The pharmaceutical composition of claim 1, wherein the ICAM-1 protein has the amino acid sequence of SEQ. ID. NO.: 1 or the amino acid sequence from which a signal peptide corresponding to the 1<sup>st</sup> to 27<sup>th</sup> amino acid residues is removed.

3. The pharmaceutical composition of claim 1, wherein the fragment of the ICAM-1 protein has a biological activity equivalent to that of the ICAM-1 protein.

4. The pharmaceutical composition of claim 1, wherein the variant of the ICAM-1 protein has the amino acid sequence of SEQ. ID. NO.: 1 in which one or more amino acids are substituted, deleted, inserted and/or added, and has a biological activity equivalent to that of the ICAM-1 protein.

5. The pharmaceutical composition of claim 1, wherein the variant of the ICAM-1 protein has an amino acid sequence identical to at least about 90%, 93%, 95%, 96%, 97%, 98% or 99% of the ICAM-1 protein having the amino acid sequence of SEQ. ID. NO.: 1, and has a biological activity equivalent to that of the ICAM-1 protein.

6. The pharmaceutical composition of claim 1, wherein the ICAM-1 protein, or the fragment or the variant thereof induces the expression of neprilysin (NEP) to promote degradation of amyloid-beta (A $\beta$ ).

7. The pharmaceutical composition of claim 1, wherein the neurological disease is a disease caused by at least one selected from the group consisting of formation of amyloid-beta plaque in neurons, hyperphosphorylation of tau protein in neurons, damage to neurites, reduction in expression of neprilysin in neurons, and a combination thereof.

8. The pharmaceutical composition of claim 1, wherein the neurological disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, depression, epilepsy, multiple sclerosis, mania, Lou Gehrig's disease, mild cognitive impairment, multi-infarct dementia, and dementia with Lewy bodies.

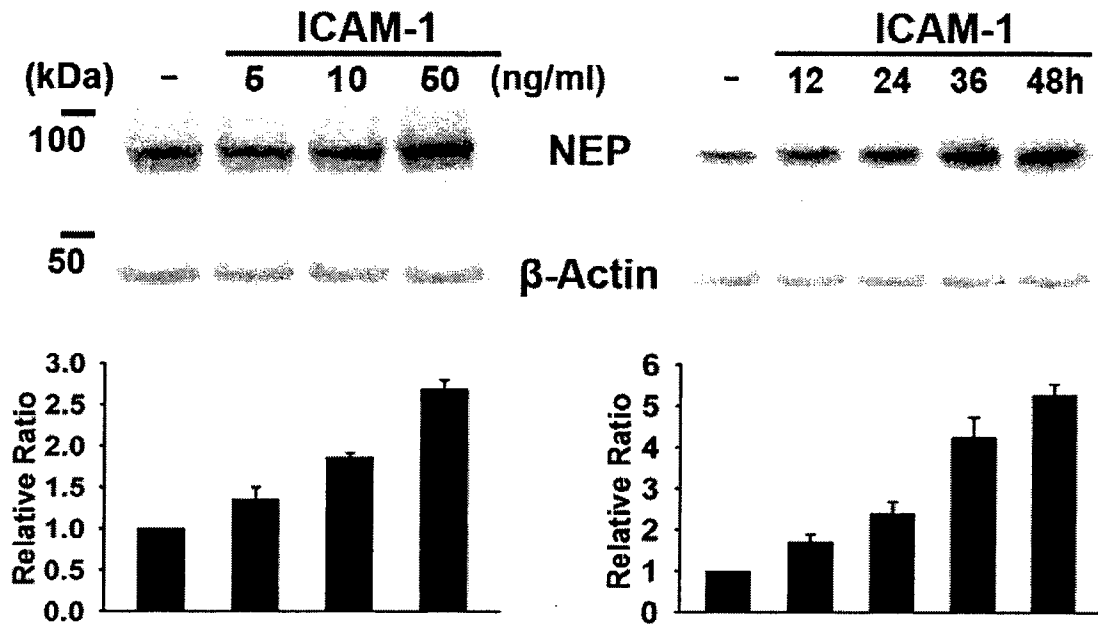
9. A method of preventing or treating a neurological disease in a subject, comprising administering to the subject in need thereof an ICAM-1 protein, or a fragment or a variant thereof.

10. A method of increasing expression of neprilysin in neurons, comprising co-culturing with the neurons an ICAM-1 protein, or a fragment or a variant thereof.

11. A method of increasing expression of neprilysin in a subject, comprising administering to the subject an ICAM-1 protein, or a fragment or a variant thereof.

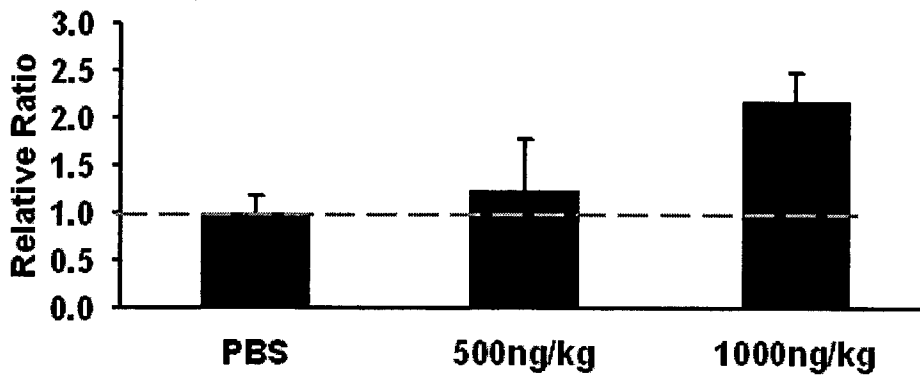
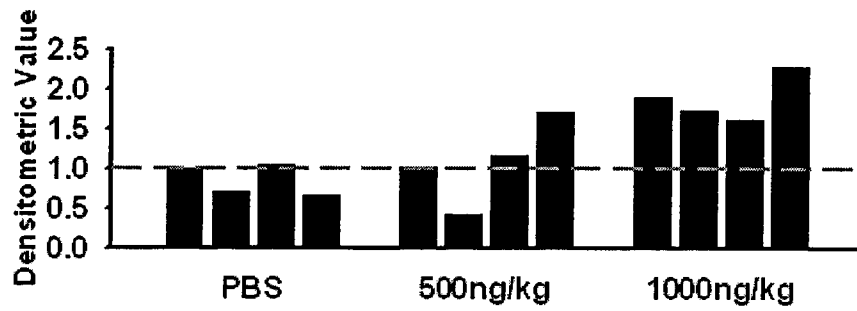
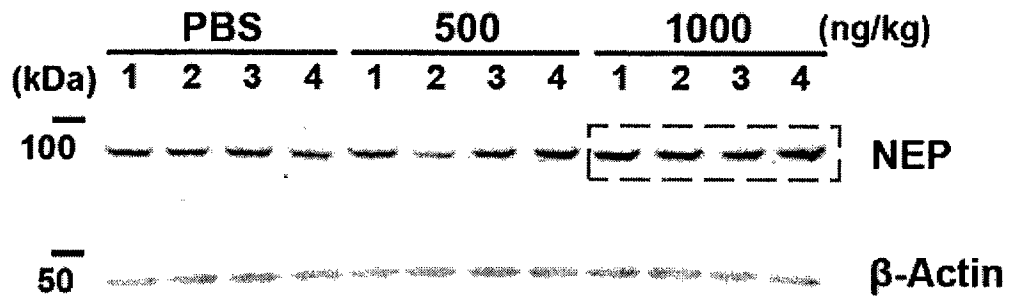
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FIG. 1



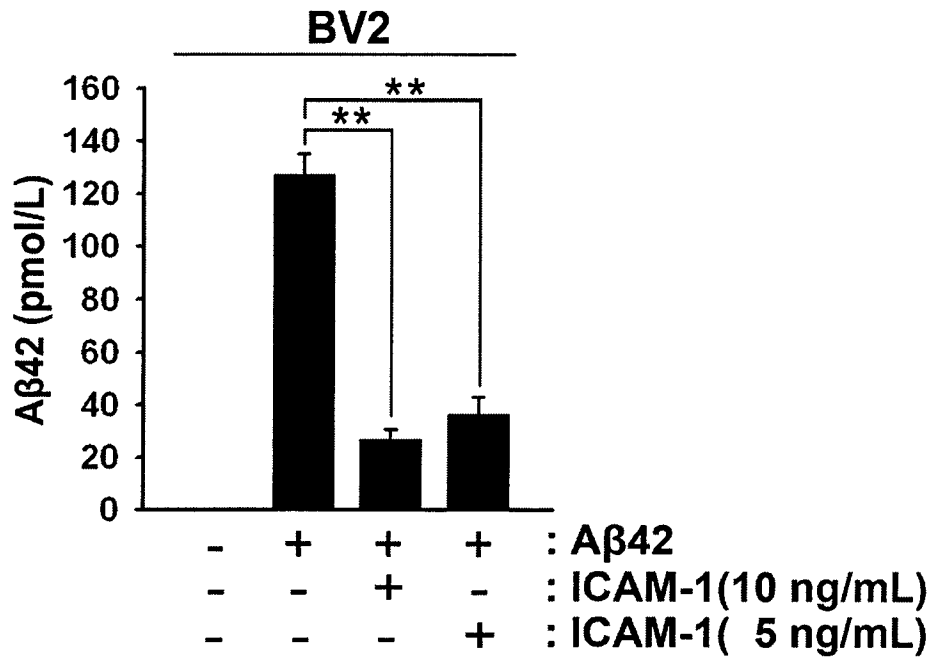
2/6

FIG. 2



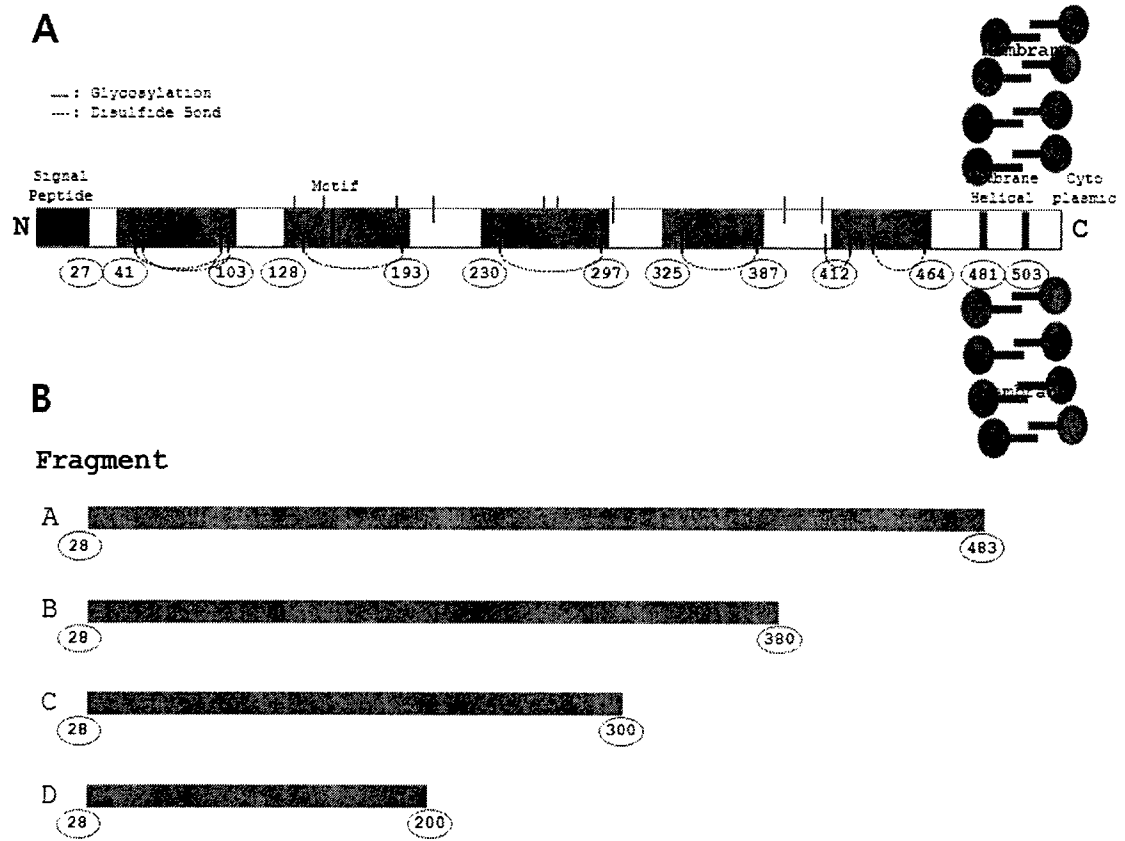
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FIG. 3



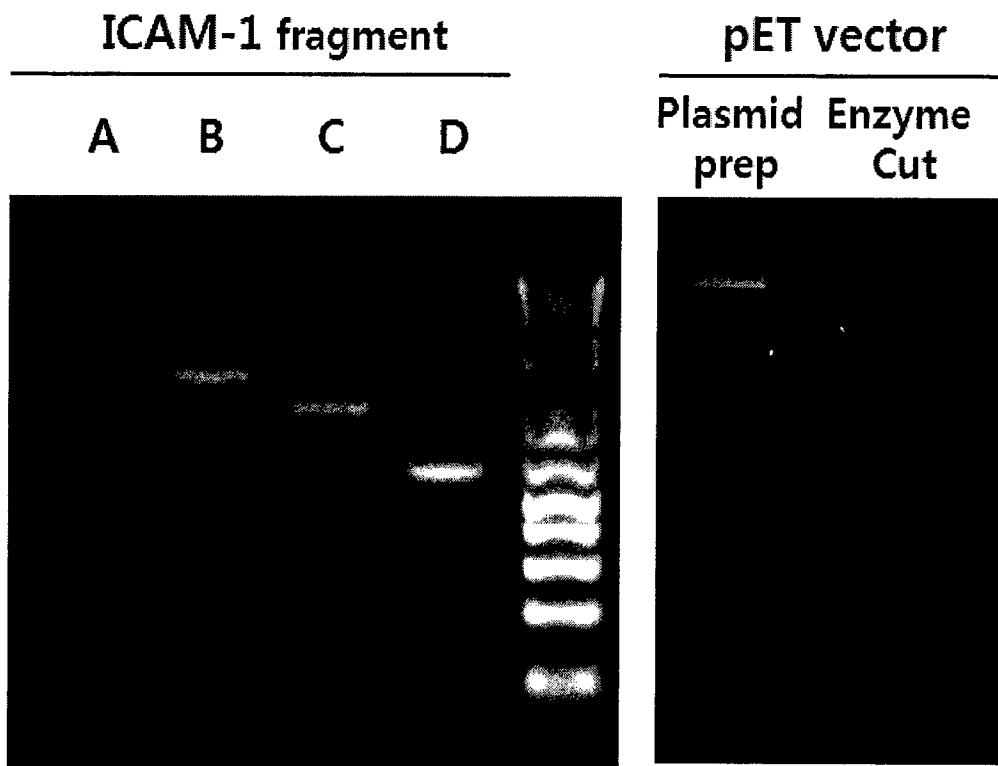
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FIG. 4



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FIG. 5



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FIG. 6

