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The present invention relates to a pharmaceutical composition wherein the active substance comprises or consists in: -a protein comprising the sequence SEQ ID NO: 1, representing the APRIL protein, -or any derived protein, which is derived from protein of sequence SEQ ID NO: by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte and/or CSPG, -or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 1, provided it allows the binding of the said homologous protein to an 1 astrocyte and/or CSPG, or any fragment of the protein of sequence SEQ ID NO: 1, provided it allows the binding of the said fragment to an astrocyte and/or CSPG, in association with an acceptable pharmaceutical vehicle. 20 (no figures)

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(54) Title: NEW PHARMACEUTICAL COMPOSITIONS AND THEIR USE FOR THE TREATMENT OF AUTOIMMUNE DISORDERS

(57) Abstract: The present invention relates to a pharmaceutical composition wherein the active substance comprises or consists in: -a protein comprising the sequence SEQ ID NO: 1, representing the APRIL protein, -or any derived protein, which is derived from protein of sequence SEQ ID NO: by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte and/or CSPG, -or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 1, provided it allows the binding of the said homologous protein to an 1 astrocyte and/or CSPG, or any fragment of the protein of sequence SEQ ID NO: 1, provided it allows the binding of the said fragment to an astrocyte and/or CSPG, in association with an acceptable pharmaceutical vehicle. 20 (no figures)

NEW PHARMACEUTICAL COMPOSITIONS AND THEIR USE FOR THE TREATMENT OF AUTOIMMUNE DISORDERS

The present invention relates to new pharmaceutical compositions and their use for the treatment of autoimmune disorders.

Multiple Sclerosis (MS) is one of the most common causes of neurologic disability in young adults with a huge impact on the quality of life and societal costs.

Multiple Sclerosis is an immune-mediated, demyelinating and neurodegenerative disease. The etiology is currently unknown and its pathogenesis is only partly understood. Complex genetic traits as well as environmental factors determine the susceptibility to develop the disease.

Remarkable progress has been made with regard to Multiple Sclerosis therapeutic treatment. Indeed, many disease-modifying therapies emerged that improve patient outcomes[1].

Nowadays, humoral immunity is thought to play an important role in the inflammatory response and development of demyelinated lesions.

Intrathecal antibody production is a hallmark of multiple sclerosis.

Indeed, histopathological studies have revealed prominent deposition of immunoglobulins and complement activation in some acute demyelinating lesions[2]. This group of patients (patients with MS and intrathecal antibody production) experienced a good response to therapeutic plasma exchange.

Moreover, the recent identification of lymphoid follicle-like structures in the cerebral meninges of some multiple sclerosis patients indicates that B-cell maturation can be sustained locally within the Central Nervous System (CNS), even if the detrimental or beneficial role of these structures is not yet fully discriminated.

Finally, depletion of B cells by therapeutic monoclonal antibody (Rituximab® commercialized by Hoffman-La Roche and Genentech) has an effect on inflammatory activity in patients with Multiple Sclerosis[3], and recently, antibodies directed against the potassium channel Kir 4.1 has been identified in a large subset of Multiple Sclerosis patients. It would therefore seem that, at least in a subgroup of patients with multiple sclerosis, B cells and antibodies contribute substantially to the disease.

Extensive tissue experimentation has also permit to characterize a key function for APRIL at the level of plasma-cell survival in the bone marrow[4] and the inflamed mucosa[5].

A proliferation inducing ligand (APRIL), also known as Tall-1 or TNFSF13, is the last cloned member of the tumor necrosis factor family[6]. APRIL has two canonical signalling receptors, the B-cell maturation antigen (BCMA) and the transmembrane activator and CAML interactor (TACI)[7], almost exclusively expressed by B cells, thus explaining the specific function of APRIL at the level of humoral immunity[8]. APRIL is produced by myeloid cells[9]. Quite unique among the TNF superfamily but common for growth factors, heparan sulphate proteoglycans (HSPG) constitute coreceptors for APRIL[10], rendering the trimeric soluble form of APRIL active for receptor signalling by oligomerization[11].

As a plasma-cell survival factor, extensive investigations have been carried out worldwide to study the role of APRIL in autoimmunity, including multiple sclerosis.

At the level of APRIL expression in Multiple Sclerosis, the cerebrospinal fluids and sera of a small cohort (n=30) of newly diagnosed and untreated patients revealed no APRIL upregulation compared to control non inflammatory neurodegenerative disorders[12].

In Multiple Sclerosis lesions, it was also reported that astrocytes produce APRIL[13]. In fact, APRIL is indeed present in Multiple Sclerosis lesions but the authors misconcluded their report.

More and more brain functions are devoted to the astrocyte, including structural and metabolic support, blood-brain barrier formation/function, regulation of cerebral blood flow, clearance of neurotransmitters at the synapses, ion balance maintenance and myelination support[14]. The role of astrocyte in neuroinflammatory diseases has been recently highlighted, notably in neuromyelitis optica (NMO)[14].

APRIL antagonism in preclinical Multiple Sclerosis has also been tested.

In early 2006, a soluble form of BCMA, antagonist of APRIL and the related B-cell activation factor from the TNF family (BAFF) was reported to inhibit murine experimental autoimmune encephalitis (EAE)[15].

Recently, an antibody to APRIL was reported to specifically delay induction of EAE in primates[16].

Both study concluded to a reduction of the immune responses raised against the priming peptide from myelin oligodendrocyte glycoprotein (MOG) (vaccination with the MOG peptide induces an autoimmune responses conducting to demyelination of nerves in the central nervous system).

A big surprise came when such approaches were translated to Multiple Sclerosis patients. The clinical trial ATAMS (ATACICEPT in Multiple Sclerosis) consisted in the treatment of relapsing MS patients with a soluble form of TACI (also an antagonist of BAFF

and APRIL). ATACICEPT is a recombinant fusion protein designed to inhibit B cells, thereby suppressing autoimmune disease. Indeed, B-cell depletion was well achieved with ATACICEPT in Multiple Sclerosis patients, but the trial was halted very rapidly due to an unexpected CNS inflammation exacerbation[17].

Thus, despite remarkable progress with regard to Multiple Sclerosis therapeutic treatment, none seems to be fully efficient. Indeed, continued relapses and eventual disability are still expected in the majority of patients on available therapies.

Thus, there is a need for a new treatment of autoimmune disorders, notably Multiple Sclerosis, which is more efficient than those of the prior art.

There is also a need for a new prevention of autoimmune disorders, notably Multiple Sclerosis.

There is also a need for a new treatment and/or prevention of autoimmune disorders, notably Multiple Sclerosis, which permits to avoid continued relapses and disability for patients with such autoimmune disorders, notably Multiple Sclerosis.

That is why, one of the aims of the invention is to provide new pharmaceutical compositions, useful for the prevention and/or treatment of autoimmune disorders, notably Multiple Sclerosis, more efficient than the pharmaceutical compositions used in the prior art.

Another aim of the invention is to provide new pharmaceutical compositions, useful for the prevention and/or treatment of autoimmune disorders, notably Multiple Sclerosis, which permits to avoid continued relapses and disability for patients with such autoimmune disorders, notably Multiple Sclerosis.

Another aim of the invention is to provide new chimeric proteins, and their use for the prevention and/or treatment of autoimmune disorders, notably Multiple Sclerosis.

Thus, the present invention concerns pharmaceutical compositions comprising as an active substance the APRIL protein or a nucleotidic sequence coding for an APRIL protein.

The present invention also concerns chimeric proteins comprising an APRIL protein.

The present invention also concerns compositions comprising as an active substance the APRIL protein or a nucleotidic sequence coding for an APRIL protein or a chimeric protein comprising an APRIL protein, for its use as a drug.

The present invention also concerns compositions comprising as an active substance the APRIL protein or a nucleotidic sequence coding for an APRIL protein or a chimeric

protein comprising an APRIL protein, for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder.

The present invention also concerns compositions comprising as an active substance the APRIL protein or a nucleotidic sequence coding for an APRIL protein or a chimeric protein comprising an APRIL protein, for its use for the prevention or the treatment of an autoimmune disorder.

The invention relies on the unexpected experimental results according to which APRIL may protect mice from experimental autoimmune encephalitis.

Moreover, the invention also relies on human studies demonstrating that APRIL is greatly upregulated in lesions from Multiple Sclerosis patients, and that the secreted form of APRIL specifically binds to reactive astrocytes in lesions.

The invention also relies on human studies demonstrating that the secreted form of APRIL binds to Chondroitin Sulfate ProteoGlycans (CSPG) in the surrounding astroglial scar rich in the said CSPG (in the extracellular matrice). In this structure, CSPG inhibit neural self-regeneration following trauma in the central nervous system[21].

In fact, the invention relies on the fact that APRIL may have some neuroprotective activities. More precisely, the invention relies on the fact that APRIL may have some neuroprotective activities by binding to astrocytes and/or by interfering with the anti-regenerative process mediated by CSPG (that is to say by binding to CSPG).

Thus, in a first embodiment, the present invention relates to a pharmaceutical composition wherein the active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 1, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 1 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 1, provided it allows the binding of the said homologous protein to an astrocyte,
- or any fragment of the protein of sequence SEQ ID NO: 1, provided it allows the binding of the said fragment to an astrocyte,

in association with an acceptable pharmaceutical vehicle.

In another embodiment, the present invention relates to a pharmaceutical composition wherein the active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 1, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 1 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to CSPG,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 1, provided it allows the binding of the said homologous protein to CSPG,
- or any fragment of the protein of sequence SEQ ID NO: 1, provided it allows the binding of the said fragment to CSPG,

in association with an acceptable pharmaceutical vehicle.

APRIL protein is a transmembrane protein undergoing cleavage by furin protase in order to be secreted[15]. Furin protease cleaves before the Alanine at position 88 (see the SEQ ID NO: 3 which is the complete sequence of APRIL protein).

Thus, secreted APRIL is from amino acid 88 (an alanine) to amino acid 233 (a leucine).

Thus, APRIL part remaining anchored at the membrane after furin processing is from amino acid 1 (a methionine) to amino acid 87 (an arginine).

Secreted APRIL and APRIL part remaining anchored at the membrane are shown in **Figure 1**.

SEQ ID NO: 1 is the following sequence in amino acids:

HSVLHLVPINATSKDDSDVTEVMWQPALRRGRGLQAQGYGVRIQDAGVYLLYSQV
LFQDVTFTMGQVVSREGQGRQETLFRCIRSMPSHPDRAYNSCYSAGVFHLHQGDILS
VIIPRARAKLNLSPHGTFLGFVKL

SEQ ID NO: 1 corresponds to the secreted APRIL protein, also named APRIL H_{98} because it is constituted by the sequence from amino acid 98 (a histidine) to amino acid 233 (a leucine) of the sequence of the full-length APRIL protein (see SEQ ID NO: 3). This secreted APRIL protein does not possess HSPG binding domains. HSPG (Heparan Sulphate ProteoGlycans) acts as coreceptor ensuring oligomerization of soluble APRIL to optimally signal via APRIL known receptors (TACI and BCMA).

APRIL is as all the TNF like molecules produced as a trimer and the active soluble APRIL is at least a dimer of this trimer.

According to the invention, the expression "the sequence of which has a percentage of identity of at least approximately 70 %" means that the percentage of identity can be 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%.

Astrocytes are characteristic star-shaped glial cells in the brain and spinal cord. They are the most abundant cells of the human brain and they perform many functions such as structural and metabolic support, blood-brain barrier formation/function, regulation of cerebral blood flow, clearance of neurotransmitters at the synapses, ion balance maintenance and myelination support.

Chondroitin sulfate proteoglycans (CSPG) are proteoglycans consisting of a protein core and a chondroitin sulfate side chain. They are structural components of a variety of human tissues, including cartilage. They also play key roles in neural development and glial scar formation. Notably, CSPG are known to inhibit axon regeneration after spinal cord injury, and they are known to contribute to glial scar formation post injury, acting as a barrier against new axons growing into the injury site.

CSPG are also ligands for the inhibitory receptors: NogoR1, NogoR3 and protein tyrosine phosphatase sigma.

APRIL can bind to one or several CSPG in central nervous system (CNS), including aggrecan, brevican, neurocan, phosphocan, keratane sulfate proteoglycan, neurone-glial antigen2. APRIL has the potential to bind to all these CSPG.

An acceptable pharmaceutical vehicle can be any kind of physiological solutions.

In another embodiment, the invention relates to a pharmaceutical composition wherein the active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 2, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 2 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 2, provided it allows the binding of the said homologous protein to an astrocyte,

- or any fragment of the protein of sequence SEQ ID NO: 2, provided it allows the binding of the said fragment to an astrocyte,

in association with an acceptable pharmaceutical vehicle.

In another embodiment, the invention relates to a pharmaceutical composition wherein the active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 2, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 2 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to CSPG,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 2, provided it allows the binding of the said homologous protein to CSPG,
- or any fragment of the protein of sequence SEQ ID NO: 2, provided it allows the binding of the said fragment to CSPG,

in association with an acceptable pharmaceutical vehicle.

SEQ ID NO: 2 is the following sequence in amino acids:

AVLTQKQKKQHSVLHLVPINATSKDDSDVTEVMWQPALRRGRGLQAQGYGVRIQD
AGVYLLYSQVLFQDVTFTMGQVVSREGQGRQETLFRCIRSMPSHPDRAYNSCYSA
GVFHLHQGDILSVIIPRARAKLNLSPHGTFLGFVKL

SEQ ID NO: 2 corresponds to the secreted APRIL protein which possess an HSPG binding domain which is KQKKQH.

Secreted APRIL protein which possesses an HSPG binding domain is also named APRIL A_{88} because it is constituted by the sequence from amino acid 88 (an alanine) to amino acid 233 (a leucine) of the sequence of the full-length APRIL protein (see SEQ ID NO: 3)

HSPG binding domain is situated among the first ten amino acids of the SEQ ID NO: 2. It is underlined in SEQ ID NO: 2. Thus, SEQ ID NO: 2 contains only the following supplementary amino acids in comparison with SEQ ID NO: 1 (AVLTQKQKKQ).

A test for checking the binding between the secreted APRIL protein and an astrocyte can be the following test:

- Immunostain CRT-MG astrocytes with Fc control and Fc-APRILA_{88} (1 µg/ml) or control Fas-Fc (1 µg/ml) for 30 minutes at 4 C in PBS 1% BSA ;

- Wash cells ;
- Incubate cells with Alexa488-conjugated human Ig antiserum for another 30 minutes at 4° C ;
- Wash cells ;
- Resuspend in PBS ;
- Analyse fluorescence with the LSRII Becton Dickinson flow cytometer.

CRT-MG is a human astrocyte cell line.

Fc-APRILA$_{88}$ is the fragment of secreted APRIL which begins at amino acid A88 (an alanine) of the sequence of the full-length APRIL protein (see SEQ ID NO: 3) linked with a Fc fragment from a human immunoglobulin. This link is carried out by genetic engineering. That is why this link it is a covalent bound.

Fas-Fc is used here as an irrelevant control for putative binding via Fc receptors. The extracellular domain of Fas was linked to the same Fc fragment.

A test for checking the binding between APRIL and CSPG can be the following test:

- Preincubate Fc-APRILA$_{88}$ (1 µg/ml) with or without CSPG for 30 minutes at 4 C in PBS 1% BSA ;
- Immunostain CRT-MG astrocytes for 30 minutes at 4°C ;
- Wash cells ;
- Incubate cells with Alexa488-conjugated human Ig antiserum for another 30 minutes at 4 C ;
- Wash cells ;
- Resuspend in PBS ;
- Analyse fluorescence with the LSRII Becton Dickinson flow cytometer.

In another embodiment, the invention relates to a pharmaceutical composition wherein the active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 3, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 3 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 3, provided it allows the binding of the said homologous protein to an astrocyte,

- or any fragment of the protein of sequence SEQ ID NO: 3, provided it allows the binding of the said fragment to an astrocyte,

in association with an acceptable pharmaceutical vehicle.

In another embodiment, the invention relates to a pharmaceutical composition wherein the active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 3, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 3 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to CSPG,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 3, provided it allows the binding of the said homologous protein to CSPG,
- or any fragment of the protein of sequence SEQ ID NO: 3, provided it allows the binding of the said fragment to CSPG,

in association with an acceptable pharmaceutical vehicle.

SEQ ID NO: 3 is the following sequence in amino acids:

MGGPVREPALSVALWLSWGAALGAVACAMALLTQQTELQSLRREVSRLQGTGGPS
QNGEGYPWQSLPEQSSDALEAWENGERSRKRRAVLTQKQKKQHSVLHLVPINATSK
DDSDVTEVMWQPALRRGRGLQAQGYGVRIQDAGVYLLYSQVLFQDVTFTMGQVVS
REGQGRQETLFRCIRSMPSHPDRAYNSCYSAGVFHLHQGDILSVIIPRARAKLNLSPH
GTFLGFVKL

SEQ ID NO: 3 corresponds to the sequence of the full-length human APRIL protein.

In another embodiment, the invention relates to a pharmaceutical composition wherein the active substance comprises or consists in:

- a nucleotidic sequence coding for a protein comprising SEQ ID NO: 1 or a nucleotidic sequence of SEQ ID NO: 4, coding for a protein having the sequence SEQ ID NO: 1,
- or any derived nucleotidic sequence, by degeneration of code genetic, of sequence SEQ ID NO: 4,
- or any derived nucleotidic sequence, by substitution, suppression or addition of one or more nucleotides, of sequence SEQ ID NO: 4,

- or any homologous nucleotidic sequence having a percentage of identity of at least approximately 70%, with sequence SEQ ID NO: 4,
- or any fragment of nucleotidic sequence SEQ ID NO: 4 or of the above defined nucleotidic sequences, the aforementioned fragment preferably making up of at least approximately 20 contiguous nucleotides in the aforementioned sequence.

The expression "a nucleotidic sequence coding for a protein comprising SEQ ID NO: 1" means for example a nucleotidic sequence coding for a fusion protein comprising the secreted APRIL protein corresponding to SEQ ID NO: 1.

The nucleotidic sequence of SEQ ID NO: 4, coding for a protein having the sequence SEQ ID NO: 1, is the following:

cactctgtcctgcacctggttcccattaacgccacctccaaggatgactccgatgtgacagaggtgatgtggcaaccagctcttaggcgt
gggagaggcctacaggcccaaggatatggtgtccgaatccaggatgctggagtttatctgctgtatagccaggtcctgtttcaagacgt
gactttcaccatgggtcaggtggtgtctcgagaaggccaaggaaggcaggagactctattccgatgtataagaagtatgccctcccacc
cggaccgggcctacaacagctgctatagcgcaggtgtcttccatttacaccaaggggatattctgagtgtcataattccccGggcaagg
gcgaaacttaacctctctccacatggaaccttcctggggtttgtgaaactgtga

SEQ ID NO: 4 is the coding sequence (CDS) of human soluble APRIL H_{98} of SEQ ID NO: 1.

In another embodiment, the invention relates to a pharmaceutical composition wherein the active substance comprises or consists in:

- a nucleotidic sequence coding for a protein comprising SEQ ID NO: 2 or a nucleotidic sequence of SEQ ID NO: 5, coding for a protein having the sequence SEQ ID NO: 2,
- or any derived nucleotidic sequence, by degeneration of code genetic, of sequence SEQ ID NO: 5,
- or any derived nucleotidic sequence, by substitution, suppression or addition of one or more nucleotides, of sequence SEQ ID NO: 5,
- or any homologous nucleotidic sequence having a percentage of identity of at least approximately 70%, with sequence SEQ ID NO: 5,
- or any fragment of nucleotidic sequence SEQ ID NO: 5 or of the above defined nucleotidic sequences, the aforementioned fragment preferably making up of at least approximately 20 contiguous nucleotides in the aforementioned sequence.

The expression "a nucleotidic sequence coding for a protein comprising SEQ ID NO: 2" means for example a nucleotidic sequence coding for a fusion protein comprising the secreted APRIL protein corresponding to SEQ ID NO: 2.

The nucleotidic sequence of SEQ ID NO: 5, coding for a protein having the sequence SEQ ID NO: 2, is the following:

gcagtgctcacccaaaaacagaagaagcagcactctgtcctgcacctggttcccattaacgccacctccaaggatgactccgatgtga
cagaggtgatgtggcaaccagctcttaggcgtgggagaggcctacaggcccaaggatatggtgtccgaatccaggatgctggagttt
atctgctgtatagccaggtcctgtttcaagacgtgactttcaccatgggtcaggtggtgtctcgagaaggccaaggaaggcaggagact
ctattccgatgtataagaagtatgccctcccacccggaccgggcctacaacagctgctatagcgcaggtgtcttccatttacaccaaggg
gatattctgagtgtcataattccccGggcaagggcgaaacttaacctctctccacatggaaccttcctggggtttgtgaaactgtga

SEQ ID NO: 5 is the coding sequence (CDS) of human soluble APRIL A_{88} of SEQ ID NO: 2.

In another embodiment, the invention relates to a pharmaceutical composition wherein the active substance comprises or consists in:

- a nucleotidic sequence coding for a protein comprising SEQ ID NO: 3 or a nucleotidic sequence of SEQ ID NO: 6, coding for a protein having the sequence SEQ ID NO: 3,
- or any derived nucleotidic sequence, by degeneration of code genetic, of sequence SEQ ID NO: 6,
- or any derived nucleotidic sequence, by substitution, suppression or addition of one or more nucleotides, of sequence SEQ ID NO: 6,
- or any homologous nucleotidic sequence having a percentage of identity of at least approximately 70%, with sequence SEQ ID NO: 6,
- or any fragment of nucleotidic sequence SEQ ID NO: 6 or of the above defined nucleotidic sequences, the aforementioned fragment preferably making up of at least approximately 20 contiguous nucleotides in the aforementioned sequence.

The expression "a nucleotidic sequence coding for a protein comprising SEQ ID NO: 3" means for example a nucleotidic sequence coding for a fusion protein comprising the secreted APRIL protein corresponding to SEQ ID NO: 3.

The nucleotidic sequence of SEQ ID NO: 6, coding for a protein having the sequence SEQ ID NO: 3, is the following:

atgggggcccagtcagagagccggcactctcagttgccctctggttgagttgggggcagctctgggggccgtggcttgtgccatg
gctctgctgacccaacaaacagagctgcagagcctcaggagagaggtgagccggctgcaggggacaggaggcccctcccagaat

ggggaagggtatccctggcagagtctcccggagcagagttccgatgccctggaagcctgggagaatggggagagatcccggaaaa
ggagagcagtgctcacccaaaaacagaagaagcagcactctgtcctgcacctggttcccattaacgccacctccaaggatgactccg
atgtgacagaggtgatgtggcaaccagctcttaggcgtgggagaggcctacaggcccaaggatatggtgtccgaatccaggatgctg
gagtttatctgctgtatagccaggtcctgtttcaagacgtgactttcaccatgggtcaggtggtgtctcgagaaggccaaggaaggcagg
agactctattccgatgtataagaagtatgccctcccacccggaccgggcctacaacagctgctatagcgcaggtgtcttccatttacacc
aaggggatattctgagtgtcataattccccgggcaagggcgaaacttaacctctctccacatggaaccttcctggggtttgtgaaactgtg
a

SEQ ID NO: 6 is the coding sequence (CDS) of full-length human APRIL of SEQ ID NO: 3.

In another embodiment, in the pharmaceutical composition according to the invention, the active substance comprises or consists in a vector in particular, plasmid, cosmid, phage or DNA of virus, containing a sequence as described in SEQ ID NO: 4 or SEQ ID NO: 5 or SEQ ID NO: 6.

In a particular embodiment, in the pharmaceutical composition of the invention, the protein has the sequence SEQ ID NO: 1.

In a particular embodiment, in the pharmaceutical composition of the invention, the protein has the sequence SEQ ID NO: 2.

In a particular embodiment, in the pharmaceutical composition of the invention, the protein has the sequence SEQ ID NO: 3.

In another embodiment, in the pharmaceutical composition of the invention, the protein is a chimeric protein constituted by an oligomer of the protein of sequence SEQ ID NO: 1, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 1, each protein or fragment being linked to the other by a constant region of an immunoglobulin.

An oligomer of the protein means at least two proteins or two fragments linked to the other by a constant region of an immunoglobulin.

An oligomer can be a dimer, a trimer, a multimer. As previously explained, in a particular embodiment the active protein is at least a dimer of trimer.

A chimeric protein can be produced by the methods known by the person having ordinary skill in the art, notably the methods of DNA subcloning.

A constant region of an immunoglobulin is the Fc fragment. In a preferred embodiment, a Fc fragment of a human immunoglobulin can be used. In another preferred embodiment, a Fc fragment of immunoglobulins IgG, IgA, or IgM can be used, in particular a Fc fragment of IgG1 which is represented by SEQ ID NO: 12.

SEQ ID NO: 12 is the following sequence:

PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

It corresponds to the Fc portion of a human immunoglobulin G, from amino acid 108 to 329 of accession number AAC82527.

In another embodiment, in the pharmaceutical composition of the invention, the protein is a chimeric protein constituted by an oligomer of the protein of sequence SEQ ID NO: 2, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 2, each protein or fragment being linked to the other by a constant region of an immunoglobulin.

In another embodiment, in the pharmaceutical composition of the invention, the protein is a chimeric protein constituted by an oligomer of the protein of sequence SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 3, each protein or fragment being linked to the other by a constant region of an immunoglobulin.

In another embodiment, in the pharmaceutical composition of the invention, the protein is a chimeric protein constituted by an oligomer of the protein of sequence SEQ ID NO: 1, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 1, each protein or fragment being linked to the headless region of a ACRP30 protein.

An oligomer of the protein means at least two proteins or two fragments linked to another by the headless region of a ACRP30 protein. An oligomer can also be a dimer, a trimer, a multimer.

ACRP30 protein is the Adipocyte Complement-Related Protein of 30kD. The headless region of ACRP30 protein is represented by SEQ ID NO: 11.

SEQ ID NO: 11 is the following sequence:

HDQETTTQGPGVLLPLPKGACTGWMAGIPGHPGHNGAPGRDGRDGTPGEKGEKGDP
GLIGPKGDIGETGVPGAEGPRGFPGIQGRKGEPGEGA

More information about the Fc fragment and headless region of ACRP30 protein which can be used according to the present invention can be found in Holler et al., Molecular and Cellular Biology, Feb 2003, p 1428-1440.

In another embodiment, in the pharmaceutical composition of the invention, the protein is a chimeric protein constituted by an oligomer of the protein of sequence SEQ ID

NO: 2, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 2, each protein or fragment being linked to the headless region of a ACRP30 protein.

In another embodiment, in the pharmaceutical composition of the invention, the protein is a chimeric protein constituted by an oligomer of the protein of sequence SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 3, each protein or fragment being linked to the headless region of a ACRP30 protein.

In another embodiment, in the pharmaceutical composition of the invention, the active substance forms a complex with an astrocyte and/or with CSPG.

The expression "a complex with an astrocyte and/or with CSPG" means that the active substance can form a complex with only an astrocyte. It also means that the active substance can form a complex with an astrocyte and one or several CSPG. It also means that the active substance can form a complex with one or several CSPG.

The complex can be formed by one active substance and one astrocyte and/or CSPG or several active substances and one astrocyte and/or CSPG.

For example, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins constituted by an oligomer of the protein of sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the other by a constant region of an immunoglobulin.

The complex can also be formed between one astrocyte and/or CSPG and one or several chimeric proteins constituted by an oligomer of the protein of sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the headless region of a ACRP30 protein.

The complex can also be formed between one astrocyte and/or CSPG and one or several chimeric proteins constituted by an oligomer of the protein of sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the other by a constant region of an immunoglobulin and one or several chimeric proteins constituted by an oligomer of the protein of sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the headless region of a ACRP30 protein.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL H_{98}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88} and one or several chimeric proteins MEGA-APRIL H_{98}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins Fc-APRIL A_{88}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins Fc-APRIL H_{98}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins Fc-APRIL A_{88} and one or several chimeric proteins Fc-APRIL H_{98}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88} and one or several chimeric proteins Fc-APRIL A_{88}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88} and one or several chimeric proteins Fc-APRIL H_{98}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL H_{98} and one or several chimeric proteins Fc-APRIL A_{88}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL H_{98} and one or several chimeric proteins Fc-APRIL H_{98}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins Fc-APRIL A_{88} and one or several chimeric proteins Fc-APRIL H_{98} and one or several MEGA-APRIL A_{88}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins Fc-APRIL A_{88} and one or several chimeric proteins Fc-APRIL H_{98} and one or several MEGA-APRIL H_{98}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88} and one or several chimeric proteins MEGA-APRIL H_{98} and one or several chimeric proteins Fc-APRIL A_{88}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88} and one or several chimeric proteins MEGA-APRIL H_{98} and one or several chimeric proteins Fc-APRIL H_{98}.

In a particular embodiment, the complex can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88} and one or several chimeric proteins MEGA-APRIL H_{98} and one or several chimeric proteins Fc-APRIL A_{88} and one or several chimeric proteins Fc-APRIL H_{98}.

In another particular embodiment, the complex can be formed by one active substance as defined above and one neuron or several active substances as defined above and one neuron.

In another particular embodiment, the complex can be formed by one active substance as defined above and one oligodendrocyte or several active substances as defined above and one oligodendrocyte.

In another embodiment, in the pharmaceutical composition of the invention, the protein of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3 is the active substance which forms a complex with an astrocyte and/or with CSPG.

In another embodiment, in the pharmaceutical composition of the invention, the chimeric protein constituted by an oligomer of the protein of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the other by a constant region of an immunoglobulin, is the active substance which forms a complex with an astrocyte and/or with CSPG.

In another embodiment, in the pharmaceutical composition of the invention, the chimeric protein constituted by an oligomer of the protein of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the headless region of a ACRP30 protein, is the active substance which forms a complex with an astrocyte and/or with CSPG.

In another embodiment, in the pharmaceutical composition of the invention, the chimeric protein comprising or consisting in SEQ ID NO: 7 or SEQ ID NO: 8 or SEQ ID NO:

9 or SEQ ID NO: 10 is the active substance which forms a complex with an astrocyte and/or with CSPG.

In another embodiment, the present invention relates to a pharmaceutical composition, wherein the active substance is formulated for administration in a range of doses from about 0.1 mg/kg to about 20 mg/kg.

The expression "doses from about 0.1 mg/kg to about 20 mg/kg" means for example 0,1 mg/kg ; 0,2 mg/kg ; 0,3 mg/kg ; 0,4 mg/kg ; 0,4 mg/kg ; 0,5 mg/kg ; 0,6 mg/kg; 0,7 mg/kg ; 0,8 mg/kg ; 0,9 mg/kg ; 1,0 mg/kg ; 2,0 mg/kg ; 3,0 mg/kg ; 4,0 mg/kg ; 5,0 mg/kg ; 6,0 mg/kg ; 7,0 mg/kg ; 8,0 mg/kg ; 9,0 mg/kg ; 10,0 mg/kg ; 11,0 mg/kg ; 12,0 mg/kg ; 13,0 mg/kg ; 14,0 mg/kg ; 15,0 mg/kg ; 16,0 mg/kg ; 17,0 mg/kg ; 18,0 mg/kg ; 19,0 mg/kg ; 20,0 mg/kg.

In another embodiment, the pharmaceutical composition according to the present invention is administered by an intravenous injection or an intrathecal injection.

The pharmaceutical composition according to the present invention can also be administered by intranasal injection and intracerebroventricular injection.

The pharmaceutical composition according to the present invention can also contain any other active substances which are considered appropriate by the one with ordinary skill in the art, for example any drug which can be used for the prevention and/or the treatment of neurodegenerative diseases or autoimmune diseases.

In another embodiment, the pharmaceutical composition of the present invention can also contain the following active substances: Teriflunomide ; Interferon Beta ; Fingolimod ; Alemtuzumab ; Glatiramer acetate ; Mitoxantrone ; Dimethyl Fumarate ; Natalizumab, notably if the said pharmaceutical composition is used for the prevention and/or the treatment of the multiple sclerosis or another autoimmune neurodegenerative disease (NDD).

In another embodiment, the pharmaceutical composition of the present invention can also contain the following active substance: Riluzole, notably if the said pharmaceutical composition is used for the prevention and/or the treatment of Amyotrophic Lateral Sclerosis.

In another embodiment, the pharmaceutical composition of the present invention can also contain cholinesterase inhibitors such as Donepezil ; Galantamine ; Rivastigmine, notably if the said pharmaceutical composition is used for the prevention and/or the treatment of Alzheimer disease

In another embodiment, the pharmaceutical composition of the present invention can also contain susbtances which act on the dopamine pathway such as Levodopa ; Pramipexole ;

Ropinirole, notably if the said pharmaceutical composition is used for the prevention and/or the treatment of Parkinson Disease.

In another embodiment, the pharmaceutical composition of the present invention can also contain the following active substances: Aripiprazole ; Asenapine ; Clozapine ; Iloperidone ; Lurasidone ; Olanzapine ; Paliperidone ; Quetiapine ; Risperidone ; Ziprasidone ; Chlorpromazine ; Fluphenazine ; Haloperido ; Perphenazine, notably if the said pharmaceutical composition is used for the prevention and/or the treatment of Schizophrenia.

In a second embodiment, the present invention relates to chimeric proteins comprising or consisting in SEQ ID NO: 7 or SEQ ID NO: 8 or SEQ ID NO: 9 or SEQ ID NO: 10.

SEQ ID NO: 7 corresponds to the sequence of "MEGA-APRIL A_{88} protein" and is constituted by:

- the sequence of the human ACRP30 headless which corresponds to SEQ ID NO : 11
- the sequence of the human APRIL A_{88} which corresponds to SEQ ID NO : 2

SEQ ID NO: 7 corresponds to the following sequence:

HDQETTTQGPGVLLPLPKGACTGWMAGIPGHPGHNGAPGRDGRDGTPGEKGEKGDP
GLIGPKGDIGETGVPGAEGPRGFPGIQGRKGEPGEGAAVLTQKQKKQHSVLHLVPINA
TSKDDSDVTEVMWQPALRRGRGLQAQGYGVRIQDAGVYLLYSQVLFQDVTFTMGQ
VVSREGQGRQETLFRCIRSMPSHPDRAYNSCYSAGVFHLHQGDILSVIIPRARAKLNL
SPHGTFLGFVKL

SEQ ID NO: 8 corresponds to the sequence of "MEGA-APRIL H_{98} protein" and is constituted by:

- the sequence of the human ACRP30 headless which corresponds to SEQ ID NO : 11
- the sequence of the human APRIL H_{98} which corresponds to SEQ ID NO : 1

SEQ ID NO: 8 corresponds to the following sequence:

HDQETTTQGPGVLLPLPKGACTGWMAGIPGHPGHNGAPGRDGRDGTPGEKGEKGDP
GLIGPKGDIGETGVPGAEGPRGFPGIQGRKGEPGEGAHSVLHLVPINATSKDDSDVTE
VMWQPALRRGRGLQAQGYGVRIQDAGVYLLYSQVLFQDVTFTMGQVVSREGQGRQ
ETLFRCIRSMPSHPDRAYNSCYSAGVFHLHQGDILSVIIPRARAKLNLSPHGTFLGFVK
L

SEQ ID NO: 9 corresponds to the sequence of "Fc-APRIL A_{88} protein" and is constituted by:

- the sequence of the Fc portion of human immunoglobulin G which corresponds to SEQ ID NO : 12
- a linker sequence which corresponds to SEQ ID NO : 13
- the sequence of the human APRIL A_{88} which corresponds to SEQ ID NO : 2

SEQ ID NO: 9 corresponds to the following sequence:

PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKRSPQPQPK
PQPKPEPEGSLQAVLTQKQKKQHSVLHLVPINATSKDDSDVTEVMWQPALRRGRGL
QAQGYGVRIQDAGVYLLYSQVLFQDVTFTMGQVVSREGQGRQETLFRCIRSMPSHP
DRAYNSCYSAGVFHLHQGDILSVIIPRARAKLNLSPHGTFLGFVKL

SEQ ID NO: 10 corresponds to the sequence of "Fc-APRIL H_{98} protein" and is constituted by:

- the sequence of the Fc portion of human immunoglobulin G which corresponds to SEQ ID NO : 12
- a linker sequence which corresponds to SEQ ID NO : 13
- the sequence of the human APRIL H_{98} which corresponds to SEQ ID NO : 1

SEQ ID NO: 10 corresponds to the following sequence:

PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKRSPQPQPKPQPKPEPEGSLQHSVLHLVPIN
ATSKDDSDVTEVMWQPALRRGRGLQAQGYGVRIQDAGVYLLYSQVLFQDVTFTMGQVVSR
EGQGRQETLFRCIRSMPSHPDRAYNSCYSAGVFHLHQGDILSVIIPRARAKLNLSPHGTFLGFV
KL

SEQ ID NO: 13 is a linker which corresponds to the following sequence: RSPQPQPKPQPKPEPEGSLQ.

SEQ ID NO: 7 is coded by the sequence in nucleotides SEQ ID NO: 14 which corresponds to the following sequence:

catgaccaggaaaccacgactcaagggcccggagtcctgcttcccctgcccaaggggcctgcacaggttggatggcgggcatccc
agggcatccgggccataatggggccccaggccgtgatggcagagatggcacccctggtgagaagggtgagaaaggagatccagg
tcttattggtcctaagggagacatcggtgaaaccggagtacccggggctgaaggtccccgaggctttccgggaatccaaggcaggaa
aggagaacctggagaaggtgccgcagtgctcacccaaaaacagaagaagcagcactctgtcctgcacctggttcccattaacgccac

ctccaaggatgactccgatgtgacagaggtgatgtggcaaccagctcttaggcgtgggagaggcctacaggcccaaggatatggtgt
ccgaatccaggatgctggagtttatctgctgtatagccaggtcctgtttcaagacgtgactttcaccatgggtcaggtggtgtctcgagaa
ggccaaggaaggcaggagactctattccgatgtataagaagtatgccctcccacccggaccgggcctacaacagctgctatagcgca
ggtgtcttccatttacaccaaggggatattctgagtgtcataattccccgggcaagggcgaaacttaacctctctccacatggaaccttcct
ggggtttgtgaaactgtga

SEQ ID NO: 8 is coded by the sequence in nucleotides SEQ ID NO: 15 which corresponds to the following sequence:

catgaccaggaaaccacgactcaagggcccggagtcctgcttcccctgcccaaggggcctgcacaggttggatggcgggcatccc
agggcatccgggccataatggggccccaggccgtgatggcagagatggcacccctggtgagaagggtgagaaaggagatccagg
tcttattggtcctaagggagacatcggtgaaaccggagtacccggggctgaaggtccccgaggctttccgggaatccaaggcaggaa
aggagaacctggagaaggtgcccactctgtcctgcacctggttcccattaacgccacctccaaggatgactccgatgtgacagaggtg
atgtggcaaccagctcttaggcgtgggagaggcctacaggcccaaggatatggtgtccgaatccaggatgctggagtttatctgctgta
tagccaggtcctgtttcaagacgtgactttcaccatgggtcaggtggtgtctcgagaaggccaaggaaggcaggagactctattccgat
gtataagaagtatgccctcccacccggaccgggcctacaacagctgctatagcgcaggtgtcttccatttacaccaaggggatattctg
agtgtcataattccccGggcaagggcgaAacttaacctctctccacatggaaccttcctggggtttgtgaaactgtga

SEQ ID NO: 9 is coded by the sequence in nucleotides SEQ ID NO: 16 which corresponds to the following sequence:

ATGGCTATCATCTACCTCATCCTCCTGTTCACCGCTGTGCGGGGCCTCGACAAAACTCACAC
ATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAA
AACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTG
AGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGC
CAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCG
TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTC
CCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTA
CACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCA
AAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAAC
TACAAGACCACGCCTCCCGTGTTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCAC
CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTC
TGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAAGATCTCCGCAGCCG
CAGCCGAAACCGCAGCCGAAACCGGAACCGGAAGGATCCCTGCAGGCAGTGCTCACCCAAAA
ACAGAAGAAGCAGCACTCTGTCCTGCACCTGGTTCCCATTAACGCCACCTCCAAGGATGACT
CCGATGTGACAGAGGTGATGTGGCAACCAGCTCTTAGGCGTGGGAGAGGCCTACAGGCCCAA
GGATATGGTGTCCGAATCCAGGATGCTGGAGTTTATCTGCTGTATAGCCAGGTCCTGTTTCA
AGACGTGACTTTCACCATGGGTCAGGTGGTGTCTCGAGAAGGCCAAGGAAGGCAGGAGACTC

TATTCCGATGTATAAGAAGTATGCCCTCCCACCCGGACCGGGCCTACAACAGCTGCTATAGC
GCAGGTGTCTTCCATTTACACCAAGGGGATATTCTGAGTGTCATAATTCCCCGGGCAAGGGC
GAAACTTAACCTCTCTCCACATGGAACCTTCCTGGGGTTTGTGAAACTG

SEQ ID NO: 10 is coded by the sequence in nucleotides SEQ ID NO: 17 which corresponds to the following sequence:

ATGGCTATCATCTACCTCATCCTCCTGTTCACCGCTGTGCGGGGCCTCGACAAAACTCACAC
ATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAA
AACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTG
AGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGC
CAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCG
TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTC
CCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTA
CACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCA
AAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAAC
TACAAGACCACGCCTCCCGTGTTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCAC
CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTC
TGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAAGATCTCCGCAGCCG
CAGCCGAAACCGCAGCCGAAACCGGAACCGGAAGGATCCCTGCAGCACTCTGTCCTGCACCT
GGTTCCCATTAACGCCACCTCCAAGGATGACTCCGATGTGACAGAGGTGATGTGGCAACCAG
CTCTTAGGCGTGGGAGAGGCCTACAGGCCCAAGGATATGGTGTCCGAATCCAGGATGCTGGA
GTTTATCTGCTGTATAGCCAGGTCCTGTTTCAAGACGTGACTTTCACCATGGGTCAGGTGGT
GTCTCGAGAAGGCCAAGGAAGGCAGGAGACTCTATTCCGATGTATAAGAAGTATGCCCTCCC
ACCCGGACCGGGCCTACAACAGCTGCTATAGCGCAGGTGTCTTCCATTTACACCAAGGGGAT
ATTCTGAGTGTCATAATTCCCCGGGCAAGGGCGAAACTTAACCTCTCTCCACATGGAACCTT
CCTGGGGTTTGTGAAACTG

In a third embodiment, the present invention also relates to a composition comprising an active substance which comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 1, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 1 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte and/or to CSPG,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 1, provided it allows the binding of the said homologous protein to an astrocyte and/or to CSPG,
- or any fragment of the protein of sequence SEQ ID NO: 1, provided it allows the binding of the said fragment to an astrocyte and/or to CSPG,

for its use as a drug.

In another embodiment, the present invention also relates to a composition comprising an active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 1, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 1 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 1, provided it allows the binding of the said homologous protein to an astrocyte,
- or any fragment of the protein of sequence SEQ ID NO: 1, provided it allows the binding of the said fragment to an astrocyte,

for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder.

In another embodiment, the present invention also relates to a composition comprising an active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 1, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 1 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to CSPG,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 1, provided it allows the binding of the said homologous protein to CSPG,
- or any fragment of the protein of sequence SEQ ID NO: 1, provided it allows the binding of the said fragment to CSPG,

for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder.

In another embodiment, the present invention relates to a composition comprising an active substance which comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 1, representing the APRIL protein,

- or any derived protein, which is derived from protein of sequence SEQ ID NO: 1 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte and/or to CSPG,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 1, provided it allows the binding of the said homologous protein to an astrocyte and/or to CSPG,
- or any fragment of the protein of sequence SEQ ID NO: 1, provided it allows the binding of the said fragment to an astrocyte and/or to CSPG,

for its use for the prevention or the treatment of a neurodegenerative disease.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 2, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 2 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte and/or to CSPG,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 2, provided it allows the binding of the said homologous protein to an astrocyte and/or to CSPG,
- or any fragment of the protein of sequence SEQ ID NO: 2, provided it allows the binding of the said fragment to an astrocyte and/or to CSPG,

for its use as a drug.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 2, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 2 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ

ID NO: 2, provided it allows the binding of the said homologous protein to an astrocyte,

- or any fragment of the protein of sequence SEQ ID NO: 2, provided it allows the binding of the said fragment to an astrocyte,

for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 2, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 2 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to CSPG,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 2, provided it allows the binding of the said homologous protein to CSPG,
- or any fragment of the protein of sequence SEQ ID NO: 2, provided it allows the binding of the said fragment to CSPG,

for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 2, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 2 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte and/or to CSPG,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 2, provided it allows the binding of the said homologous protein to an astrocyte and/or to CSPG,
- or any fragment of the protein of sequence SEQ ID NO: 2, provided it allows the binding of the said fragment to an astrocyte and/or to CSPG,

for its use for the prevention or the treatment of a neurodegenerative disease.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 3, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 3 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte and/or to CSPG,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 3, provided it allows the binding of the said homologous protein to an astrocyte and/or to CSPG,
- or any fragment of the protein of sequence SEQ ID NO: 3, provided it allows the binding of the said fragment to an astrocyte and/or to CSPG,

for its use as a drug.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 3, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 3 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 3, provided it allows the binding of the said homologous protein to an astrocyte,
- or any fragment of the protein of sequence SEQ ID NO: 3, provided it allows the binding of the said fragment to an astrocyte,

for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 3, representing the APRIL protein,

- or any derived protein, which is derived from protein of sequence SEQ ID NO: 3 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to CSPG,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 3, provided it allows the binding of the said homologous protein to CSPG,
- or any fragment of the protein of sequence SEQ ID NO: 3, provided it allows the binding of the said fragment to CSPG,

for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a protein comprising the sequence SEQ ID NO: 3, representing the APRIL protein,
- or any derived protein, which is derived from protein of sequence SEQ ID NO: 3 by substitution, removal or addition of one or more amino-acids, provided it allows the binding of the said derived protein to an astrocyte and/or to CSPG,
- or any homologous protein, the sequence of which has a percentage of identity of at least approximately 70 %, and in particular 85 % with said sequence SEQ ID NO: 3, provided it allows the binding of the said homologous protein to an astrocyte and/or to CSPG,
- or any fragment of the protein of sequence SEQ ID NO: 3, provided it allows the binding of the said fragment to an astrocyte and/or to CSPG,

for its use for the prevention or the treatment of a neurodegenerative disease.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a nucleotidic sequence coding for a protein comprising the SEQ ID NO: 1 or a nucleotidic sequence of SEQ ID NO: 4, coding for a protein having the sequence SEQ ID NO: 1,
- or any derived nucleotidic sequence, by degeneration of code genetic, of sequence SEQ ID NO: 4,
- or any derived nucleotidic sequence, by substitution, suppression or addition of one or more nucleotides, sequence SEQ ID NO: 4,

- or any homologous nucleotidic sequence having a percentage of identity of at least approximately 70%, with sequence SEQ ID NO: 4,
- or any fragment of nucleotidic sequence SEQ ID NO: 4 or of the above defined nucleotidic sequences, the aforementioned fragment preferably making up of at least approximately 20 contiguous nucleotides in the aforementioned sequence,

for its use as a drug.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a nucleotidic sequence coding for a protein comprising the SEQ ID NO: 1 or a nucleotidic sequence of SEQ ID NO: 4, coding for a protein having the sequence SEQ ID NO: 1,
- or any derived nucleotidic sequence, by degeneration of code genetic, of sequence SEQ ID NO: 4,
- or any derived nucleotidic sequence, by substitution, suppression or addition of one or more nucleotides, sequence SEQ ID NO: 4,
- or any homologous nucleotidic sequence having a percentage of identity of at least approximately 70%, with sequence SEQ ID NO: 4,
- or any fragment of nucleotidic sequence SEQ ID NO: 4 or of the above defined nucleotidic sequences, the aforementioned fragment preferably making up of at least approximately 20 contiguous nucleotides in the aforementioned sequence,

for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a nucleotidic sequence coding for a protein comprising the SEQ ID NO: 1 or a nucleotidic sequence of SEQ ID NO: 4, coding for a protein having the sequence SEQ ID NO: 1,
- or any derived nucleotidic sequence, by degeneration of code genetic, of sequence SEQ ID NO: 4,
- or any derived nucleotidic sequence, by substitution, suppression or addition of one or more nucleotides, sequence SEQ ID NO: 4,

- or any homologous nucleotidic sequence having a percentage of identity of at least approximately 70%, with sequence SEQ ID NO: 4,
- or any fragment of nucleotidic sequence SEQ ID NO: 4 or of the above defined nucleotidic sequences, the aforementioned fragment preferably making up of at least approximately 20 contiguous nucleotides in the aforementioned sequence,

for its use for the prevention or the treatment of a neurodegenerative disease.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a nucleotidic sequence coding for a protein comprising the SEQ ID NO: 2 or a nucleotidic sequence of SEQ ID NO: 5, coding for a protein having the sequence SEQ ID NO: 2,
- or any derived nucleotidic sequence, by degeneration of code genetic, of sequence SEQ ID NO: 5,
- or any derived nucleotidic sequence, by substitution, suppression or addition of one or more nucleotides, sequence SEQ ID NO: 5,
- or any homologous nucleotidic sequence having a percentage of identity of at least approximately 70%, with sequence SEQ ID NO: 5,
- or any fragment of nucleotidic sequence SEQ ID NO: 5 or of the above defined nucleotidic sequences, the aforementioned fragment preferably making up of at least approximately 20 contiguous nucleotides in the aforementioned sequence,

for its use as a drug.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a nucleotidic sequence coding for a protein comprising the SEQ ID NO: 2 or a nucleotidic sequence of SEQ ID NO: 5, coding for a protein having the sequence SEQ ID NO: 2,
- or any derived nucleotidic sequence, by degeneration of code genetic, of sequence SEQ ID NO: 5,
- or any derived nucleotidic sequence, by substitution, suppression or addition of one or more nucleotides, sequence SEQ ID NO: 5,
- or any homologous nucleotidic sequence having a percentage of identity of at least approximately 70%, with sequence SEQ ID NO: 5,

- or any fragment of nucleotidic sequence SEQ ID NO: 5 or of the above defined nucleotidic sequences, the aforementioned fragment preferably making up of at least approximately 20 contiguous nucleotides in the aforementioned sequence,

for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a nucleotidic sequence coding for a protein comprising the SEQ ID NO: 2 or a nucleotidic sequence of SEQ ID NO: 5, coding for a protein having the sequence SEQ ID NO: 2,
- or any derived nucleotidic sequence, by degeneration of code genetic, of sequence SEQ ID NO: 5,
- or any derived nucleotidic sequence, by substitution, suppression or addition of one or more nucleotides, sequence SEQ ID NO: 5,
- or any homologous nucleotidic sequence having a percentage of identity of at least approximately 70%, with sequence SEQ ID NO: 5,
- or any fragment of nucleotidic sequence SEQ ID NO: 5 or of the above defined nucleotidic sequences, the aforementioned fragment preferably making up of at least approximately 20 contiguous nucleotides in the aforementioned sequence,

for its use for the prevention or the treatment of a neurodegenerative disease.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a nucleotidic sequence coding for a protein comprising the SEQ ID NO: 3 or a nucleotidic sequence of SEQ ID NO: 6, coding for a protein having the sequence SEQ ID NO: 3,
- or any derived nucleotidic sequence, by degeneration of code genetic, of sequence SEQ ID NO: 6,
- or any derived nucleotidic sequence, by substitution, suppression or addition of one or more nucleotides, sequence SEQ ID NO: 6,
- or any homologous nucleotidic sequence having a percentage of identity of at least approximately 70%, with sequence SEQ ID NO: 6,

- or any fragment of nucleotidic sequence SEQ ID NO: 6 or of the above defined nucleotidic sequences, the aforementioned fragment preferably making up of at least approximately 20 contiguous nucleotides in the aforementioned sequence,

for its use as a drug.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a nucleotidic sequence coding for a protein comprising the SEQ ID NO: 3 or a nucleotidic sequence of SEQ ID NO: 6, coding for a protein having the sequence SEQ ID NO: 3,
- or any derived nucleotidic sequence, by degeneration of code genetic, of sequence SEQ ID NO: 6,
- or any derived nucleotidic sequence, by substitution, suppression or addition of one or more nucleotides, sequence SEQ ID NO: 6,
- or any homologous nucleotidic sequence having a percentage of identity of at least approximately 70%, with sequence SEQ ID NO: 6,
- or any fragment of nucleotidic sequence SEQ ID NO: 6 or of the above defined nucleotidic sequences, the aforementioned fragment preferably making up of at least approximately 20 contiguous nucleotides in the aforementioned sequence,

for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder.

In another embodiment, the invention relates to a composition comprising an active substance comprises or consists in:

- a nucleotidic sequence coding for a protein comprising the SEQ ID NO: 3 or a nucleotidic sequence of SEQ ID NO: 6, coding for a protein having the sequence SEQ ID NO: 3,
- or any derived nucleotidic sequence, by degeneration of code genetic, of sequence SEQ ID NO: 6,
- or any derived nucleotidic sequence, by substitution, suppression or addition of one or more nucleotides, sequence SEQ ID NO: 6,
- or any homologous nucleotidic sequence having a percentage of identity of at least approximately 70%, with sequence SEQ ID NO: 6,

- or any fragment of nucleotidic sequence SEQ ID NO: 6 or of the above defined nucleotidic sequences, the aforementioned fragment preferably making up of at least approximately 20 contiguous nucleotides in the aforementioned sequence,

for its use for the prevention or the treatment of a neurodegenerative disease.

In another embodiment, the invention relates to a composition wherein the active substance comprises or consists in a vector in particular, plasmid, cosmid, phage or DNA of virus, containing a sequence chosen among SEQ ID NO: 4 or SEQ ID NO: 5 or SEQ ID NO: 6, for its use as a drug, or for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease.

In another embodiment, the invention relates to a composition wherein the protein has one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, for its use as a drug, or for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease.

In another embodiment, the invention relates to a composition wherein the protein is a chimeric protein constituted by an oligomer of the protein of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the other by a constant region of an immunoglobulin, for its use as a drug, or for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease.

In another embodiment, the invention relates to a composition wherein the protein is a chimeric protein constituted by an oligomer of the protein of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the headless region of a ACRP30 protein, for its use as a drug, or for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease.

In another embodiment, the invention relates to a composition wherein the active substance forms a complex with an astrocyte and/or CSPG, for its use as a drug, or for its use

for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease.

The complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed by one active substance and one astrocyte and/or CSPG or several active substances and one astrocyte and/or CSPG.

For example, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins constituted by an oligomer of the protein of sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the other by a constant region of an immunoglobulin.

The complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can also be formed between one astrocyte and/or CSPG and one or several chimeric proteins constituted by an oligomer of the protein of sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the headless region of a ACRP30 protein.

The complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can also be formed between one astrocyte and/or CSPG and one or several chimeric proteins constituted by an oligomer of the protein of sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the other by a constant region of an immunoglobulin and one or several chimeric proteins constituted by an oligomer of the protein of sequence SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of the sequence SEQ ID NO: 1 or

SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the headless region of a ACRP30 protein.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL H_{98}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88} and one or several chimeric proteins MEGA-APRIL H_{98}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins Fc-APRIL A_{88}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins Fc-APRIL H_{98}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins Fc-APRIL A_{88} and one or several chimeric proteins Fc-APRIL H_{98}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88} and one or several chimeric proteins Fc-APRIL A_{88}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88} and one or several chimeric proteins Fc-APRIL H_{98}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL H_{98} and one or several chimeric proteins Fc-APRIL A_{88}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL H_{98} and one or several chimeric proteins Fc-APRIL H_{98}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins Fc-APRIL A_{88} and one or several chimeric proteins Fc-APRIL H_{98} and one or several MEGA-APRIL A_{88}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or

several chimeric proteins Fc-APRIL A_{88} and one or several chimeric proteins Fc-APRIL H_{98} and one or several MEGA-APRIL H_{98}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88} and one or several chimeric proteins MEGA-APRIL H_{98} and one or several chimeric proteins Fc-APRIL A_{88}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88} and one or several chimeric proteins MEGA-APRIL H_{98} and one or several chimeric proteins Fc-APRIL H_{98}.

In a particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed between one astrocyte and/or CSPG and one or several chimeric proteins MEGA-APRIL A_{88} and one or several chimeric proteins MEGA-APRIL H_{98} and one or several chimeric proteins Fc-APRIL A_{88} and one or several chimeric proteins Fc-APRIL H_{98}.

In another particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed by one active substance as defined above and one neuron or several active substances as defined above and one neuron.

In another particular embodiment, the complex used as a drug or the complex used for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder or the complex used for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease can be formed by one active substance as defined above and one oligodendrocyte or several active substances as defined above and one oligodendrocyte.

In another embodiment, the invention relates to a composition wherein the protein of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3 is the active substance which forms a complex with an astrocyte and/or CSPG, for its use as a drug, or for

its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease.

In another embodiment, the invention relates to a composition wherein the chimeric protein constituted by an oligomer of the protein of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the other by a constant region of an immunoglobulin, is the active substance which forms a complex with an astrocyte and/or CSPG, for its use as a drug, or for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease.

In another embodiment, the invention relates to a composition wherein the chimeric protein constituted by an oligomer of the protein of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, or a derived protein, or a homologous protein or a fragment of one of the sequences SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, each protein or fragment being linked to the headless region of a ACRP30 protein, is the active substance which forms a complex with an astrocyte and/or CSPG, for its use as a drug, or for the its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease.

In another embodiment, the invention relates to a composition wherein a chimeric protein comprising or consisting in SEQ ID NO: 7 or SEQ ID NO: 8 or SEQ ID NO: 9 or SEQ ID NO: 10 is the active substance which forms a complex with an astrocyte and/or CSPG, for its use as a drug, or for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease.

In another embodiment, the invention relates to a composition wherein the active substance is formulated for administration in a range of doses from about 0.1 mg/kg to about 20 mg/kg, for its use as a drug, or for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder or a neurodegenerative disease.

The expression “doses from about 0.1 mg/kg to about 20 mg/kg” means for example 0,1 mg/kg ; 0,2 mg/kg ; 0,3 mg/kg ; 0,4 mg/kg ; 0,4 mg/kg ; 0,5 mg/kg ; 0,6 mg/kg; 0,7 mg/kg

; 0,8 mg/kg ; 0,9 mg/kg ; 1,0 mg/kg ; 2,0 mg/kg ; 3,0 mg/kg ; 4,0 mg/kg ; 5,0 mg/kg ; 6,0 mg/kg ; 7,0 mg/kg ; 8,0 mg/kg ; 9,0 mg/kg ; 10,0 mg/kg ; 11,0 mg/kg ; 12,0 mg/kg ; 13,0 mg/kg ; 14,0 mg/kg ; 15,0 mg/kg ; 16,0 mg/kg ; 17,0 mg/kg ; 18,0 mg/kg ; 19,0 mg/kg ; 20,0 mg/kg.

In another embodiment, the invention relates to a composition wherein the autoimmune disorder is a neurodegenerative disease.

In another embodiment, the invention relates to a composition wherein the autoimmune disorder is selected from: multiple sclerosis, autoimmune encephalitis, neuromyelitis optica (NMO), neurolupus, neurobehcet, neurosjogren, neurosarcoidosis, acute disseminated encephalomyelitis (ADEM), clinically isolated syndrome, multifocal motor neuropathy (MMN), anti-MAG neuropathy, neuropathy associated with paraptoteinemia, chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain–Barré syndrome, for its use for the manufacture of a drug for the prevention or the treatment of an autoimmune disorder, or for its use for the prevention or the treatment of an autoimmune disorder.

In a particular embodiment, the multiple sclerosis is a relapsing remitting multiple sclerosis (RRMS) or a primary progressive multiple sclerosis (PPMS) or a secondary progressive multiple sclerosis (SPMS) or a progressive relapsing multiple sclerosis (PRMS).

In another embodiment, the invention relates to a composition for its use for the manufacture of a drug for the prevention or the treatment of the multiple sclerosis, or for its use for the prevention or the treatment of the multiple sclerosis.

In another embodiment, the invention relates to a composition wherein the neurodegenerative disease is selected from: Alzheimer disease, Parkinson Disease, Schizophrenia and Sclerosis Lateral Amyotrophic.

In another embodiment, the invention relates to a composition for its use for the prevention or the treatment of Alzheimer disease, Parkinson Disease, Schizophrenia and Sclerosis Lateral Amyotrophic.

The present invention is illustrated by the following Figures and Examples, which do not limit the scope of the invention.

DESCRIPTION OF THE FIGURES

Figure 1 represents a home-made tissue reactive anti-human APRIL. Furin cleavage site and reactivity of the tissue-reactive antibodies are indicated. One antibody, Aprily-8, reacts with the secreted product and another one, Stalk-1, reacts with the APRIL part remaining anchored at the membrane of producing cells after furin processing.

Figure 2 represents serial sections of Multiple Sclerosis (upper panel) and Parkinson disease (bottom panel) lesions immunostained with Stalk-1 and Aprily-8.

Figure 3 represents serial sections of one representative Multiple Sclerosis lesion immunostained for Stalk-1/ CD68 (upper panel) and GFAP/Aprily-8 (bottom panel).

Single and merge stainings are shown. Nuclear DAPI staining has been added to the merge stainings.

Figure 4 represents experimental autoimmune encephalitis (EAE) induced by MOG_{35-55} peptide immunization in wild-type mice (WT) or mice genetically deficient in APRIL (APRIL KO (knock-out) C57Bl/6 mice).

The clinical score (left panel) and death induced by EAE pathologies (right panel) are shown.

Abscissa represents the days after vaccination with the MOG peptide, and the ordinate axis represents the clinical score of the two mice goups.

Figure 5 represents the results of immunological responses between the two mice groups induced against the MOG_{35-55} peptide used for animal priming (splenic T-cell proliferation).

The two mice groups are wild-type mice (WT) and mice genetically deficient in APRIL (APRIL KO (knock-out) C57Bl/6 mice), in which experimental autoimmune encephalitis (EAE) is induced by MOG_{35-55} peptide immunization.

Abscissa represents the concentration of MOG peptide (ug/ml) (or µg/ml) and the ordinate axis shows incorporation of tritiated thymidine monitored by count per minute (CPM) for the two mice goups.

Figure 6 represents CRT astrocytes immunostained with Fc-control (thin lines) and Fc-APRIL (bold lines), and analyzed by flow cytometry. Overlayed histogram plots are shown.

Figure 7A represents a recombinant APRIL with indication of a furin site, a processed N-terminus and a HSPG binding domain.

Figure 7B represents a recombinant APRIL with and without the HSPG binding domain.

Soluble recombinant APRIL forms starting at alanine 88 (A_{88}) or histidine 98 (H_{98}) have been generated. APRIL A_{88} possesses the HSPG binding domain, APRIL H_{98} do not possess the HSPG binding domain.

The term valency means the maximal number of bonds that can be formed with an APRIL receptor.

Figure 8A represents a recombinant APRIL, with indication of a furin site, a processed N-terminus and a HSPG binding domain.

A schematic representation of an oligomer with the adipocyte complement-related protein of 30kDa (ACRP30) and a human Fc fragment is also represented.

Figure 8B represents soluble recombinant APRIL forms starting at alanine 88 (A_{88}) and histidine 98 (H_{98}), with and without the HSPG binding domain, respectively, oligomerized by fusion with the adipocyte complement-related protein of 30kDa (ACRP30) or a human Fc region.

Figure 9 represents a biopsy from a Multiple Sclerosis patient immunostained with Aprily-8. The binding to the astrocytes and the Extracellular Matrix is shown.

Figure 10 represents CRT astrocytes immunostained with medium and APRIL in the presence or absence of inhibitory CSPG and analyzed by flow cytometry.

Abcissa represents the fluorescence intensity and the ordinate axis shows the number of cells.

The black line corresponds to the results of APRIL in absence of inhibitory CSPG, the black dashed line corresponds to the results of APRIL pre-incubated with CSPG, and the grey line corresponds to the control.

Figure 11 represents the treatment by intravenous injection of APRIL of two mice with experimental autoimmune encephalitis.

Abcissa represents the day after the first APRIL injection and the ordinate axis represents the clinical score. Arrows indicate time of APRIL injections (0, 2, 4 and 6).

EXAMPLES

The following examples have been carried out according to the experimental procedures hereafter described.

Example 1: APRIL expression in multiple sclerosis (MS) patient lesions – Human Studies

The first tissue-reactive antibodies against human APRIL have been generated, as explained in Schwaller *et al., Blood*, vol 109, pp 331-337, 2007.

APRIL is a transmembrane protein undergoing cleavage by furin proteases in order to be secreted[18]. Antibodies which link to the two parts of the protein after cleavage are known. Indeed, one antibody, Aprily-8, reacts with the secreted product and another one, Stalk-1,

reacts with the APRIL part remaining anchored at the membrane of producing cells after furin processing (see **Figure 1**). Enzo Life Sciences distributes these antibodies.

There is no full-length product detected by this antibody pair in tissues[9], probably because of a fast processing after translation, so that Aprily-8 detects the localisation of secreted APRIL only and does not react with APRIL-producing cells.

1. Immunohistochemistry (Stalk-1/Aprily-8)

Material & Methods

Serial sections form biopsies of the indicated patients were fixed, paraffin-embedded and subjected to immunostaining with Stalk-1 (5 µg/ml, rabbit polyclonal antibody recognizing cells producing APRIL) and Aprily-8 (2 µg/ml, mouse monoclonal antibody recognizing the secreted form of APRIL).

Indicated patients are patients with Multiple Sclerosis (upper panel) and patients with Parkinson disease (bottom panel).

Tissues were washed, and incubated with a biotin-conjugated rabbit and mouse Ig antiserum, respectively.

Tissues were washed, and incubated with horse raddish peroxidase (HRP)-conjugated streptavidin.

Tissue were washed and incubated with the HRP substrate amino ethyl courmarin. Light microscopy was analyzed with an Axiocam microscope (Carl Zeiss).

Pictures from a relevant case of an inflammatory (multiple sclerosis, MS) and a non-inflammatory (Parkinson disease) neurodegenerative disease are shown.

Results

A perilesional production of APRIL and a lesional retention of the secreted product have been observed in multiple sclerosis (**Figure 2**, upper panel).

By contrast, APRIL expression has not been detected in non-inflammatory disorders such as Parkinson diseases (**Figure 2**, bottom panel).

This pattern of APRIL expression has been observed in a majority of multiple sclerosis patients (16/17) with a trend towards expression in progressive and/or acute forms of the disease (see below the Table 1).

cases	Stalk-1	Aprily-8	type
1	-	-	RRMS
2	-	-	RRMS
3	+	+	SPMS
4	+	+	SPMS
5	+	+	PPMS
6	+	+	SPMS
7	+	++	acute
8	+	++	PPMS
9	+	+++	PPMS
10	+	++	acute
11	+	++	PPMS
12	+	++	SPMS
13	+	++	PPMS
14	++	++	SPMS
15	++	++	acute
16	++	++	acute
17	+++	++	acute

"RR" means "relapsing remitting"

"PP" means "primary progressive"

"SP" means "secondary progressive"

"-" means that the antibodies Stalk-1 and Aprily-8 do not react with APRIL protein.

2. Two-color immunohistofluorescence (Stalk-1/anti-CD68 _ anti-GFAP/Aprily-8)

Material & Methods

Serial sections from biopsy of the same MS patient (as previously mentioned) was immunostained with Stalk-1 (rabbit polyclonal antibody) and an anti-CD68 (macrophage /microglial-specific mouse antibody) (upper panel).

The same biopsy was immunostained with an anti-GFAP (astrocyte-specific rabbit polyclonal antibody) and Aprily-8 (mouse antibody) (bottom panel).

Tissues were washed and binding was detected with an alexa488-conjugated anti-rabbit serum (green) and a phycoerythrin-conjugated anti-mouse serum (red).

Fluorescence was analyzed with an Axiocam microscope (Carl Zeiss).

Single and merged pictures are shown.

Nuclear (DAPI) staining is shown in the merge pictures.

Results

Unlike what has been reported (Reference[13] for example), in the lesions of multiple sclerosis, APRIL is produced by a subset of $CD68^+$ cells that could be either microglia or infiltrating macrophages, and the secreted product from these cells binds specifically onto surrounding reactive astrocytes (**Figure 3**).

The conclusion of the prior art claiming APRIL production by astrocytes in MS is misleading. In fact, it seems that the authors of reference[13] used the monoclonal antibody against secreted APRIL used in the present invention, obtained an identical staining on reactive astrocytes, but misconcluded on the cellular source of APRIL.

Thus, $CD68^+$ cells are cells which express the Cluster of Differentiation 68.

GFAP is a Glial Fibrilary Acidic Protein which is expressed by the astrocytes.

3. Immunohistochemistry (Aprily-8)

Material & Methods

A biopsy from a MS patient (as previously mentioned) was immunostained with Aprily-8 (2 µg/ml, mouse IgG1 recognizing the secreted form of human APRIL).

Tissues were washed, and incubated with a biotin-conjugated mouse Ig antiserum (available at Thermo Fisher Scientific, Inc.).

Tissues were washed, and incubated with horse raddish peroxidase (HRP)-conjugated streptavidin (available at Thermo Fisher Scientific, Inc.)

Tissue were washed and incubated with the HRP substrate amino ethyl courmarin. Light microscopy was analyzed with an Axiocam microscope (provided by Carl Zeiss).

Results

Secreted APRIL is retained by astrocytes present in lesions but also by the surrounding extracellular matrix rich in chondroitin sulfate proteoglycan (CSPG) (**Figure 9**).

This also confirms the results of **Figure 2** and **Figure 3**.

Example 2: Role of APRIL in Multiple Sclerosis (MS)

Plasmocytes have not been observed in the lesions used to stain for APRIL (CD138 staining, data not shown).

The Multiple Sclerosis lesions used were also devoid of ectopic germinal centers reported by others[19].

Altogether, this indicates that APRIL may play locally a new unpreviously described role in Multiple Sclerosis.

To elucidate the putative function of APRIL in Multiple Sclerosis, experimental autoimmune encephalitis (EAE) are performed in C57Bl/6 mice.

Material & Methods

EAE was induced by MOG_{35-55} peptide immunization in wild-type mice (WT) or mice genetically deficient in APRIL (APRIL KO (knock-out) C57Bl/6 mice.

Wild type and *APRIL*-deficient C57Bl/6 mice were vaccinated against the MOG $peptide_{35-55}$ to induce a MOG-specific $CD8^+$ T cell autoimmune responses. Clinical score and neuropathy-induced death were monitored. At the peak of the disease, spleens were harvested, dissociated, and total splenocytes were stimulated by increasing concentrations of the MOG peptide. Proliferation was assessed three days later by tritiated thymidine incorporation.

* $p<0.01$

Results

The clinical score (left panel) and death induced by EAE pathologies (right panel) are shown in **Figure 4**.

The results show that in mice genetically deficient in APRIL the clinical EAE score was increased: for example at 19 days, the clinical score is 2 with the wild-type mice (WT) and 3 with the APRIL KO C57BI/6 mice (APRIL KO).

The results also show that the percent death of mouse death induced by EAE associated pathologies is increased in mice genetically deficient in APRIL: for example at 20 days, the percentage is 11% for the wild-type mice (WT) and 40% for APRIL KO C57BI/6 mice (APRIL KO).

Moreover, in this experiment, no differences in proportion and number of immune cells (myeloid, B and T cells) present in the periphery (spleen and bone marrow) and the affected spinal cord have been detected.

There was also no difference in the immunological responses between the two mice groups induced against the MOG peptide used for animal priming (splenic T-cell proliferation, **Figure 5**). This absence of immunological differences is not a big surprise,

since a T-cell immune response is induced by MOG peptide immunization, and APRIL role focuses on B-cell responses[8].

This suggests that APRIL may be implicated in a neuroprotective pathway.

Example 3: Treatment of Multiple Sclerosis (MS) with APRIL

Experimental Autoimmune Encephalitis (EAE) is an accepted murine model for human MS[20].

Material & Methods

EAE was induced at day 0 in 8 weeks female C57Bl/6 mice by injecting subcutaneously in both flanks 0.1 ml of an emulsion composed of 1 volume of complete Freund's adjuvant (available at Sigma) supplemented with 4 mg/ml of a *Mycobacterium Tuberculosis* lysate (available at Difco Laboratories) and 1 volume of 2.5 mg/ml of peptide 35-55 from the rat myelin oligodendrocyte glycoprotein (available at PolyPeptide Group).

Immediately after, 500 ng of *Bordetella Pertussis* toxin in PBS was injected intraperitoneally. Toxin injection was repeated on day 1.

The clinical score was evaluated as followed:

- 0 : no sign
- 1 : limp tail
- 2 : limp tail associated to walking disability without any limb paralysis
- 3 : limp tail and partial hind limb paralysis
- 4 : limp tail and complete hind limb paralysis
- 5 : limp tail, complete hind limb paralysis and partial anterior limb paralysis
- 6 : moribund state conducting to animal sacrifice

Mice suffering from EAE with a clinical score of 2 were treated by intravenous injections of 50 µg of Fc-APRIL A_{88} in PBS every other day.

Results

APRIL treatment induces a decline in the clinical score of EAE Mice (**Figure 11**).

Consequently, APRIL treatment may inhibit the neurodegenerative process occurring during MS?

Example 4: Determination of APRIL receptor(s) on astrocytes

Material & Methods

CRT-MG astrocytes were immunostained with Fc-control and Fc-APRIL, then analysed by flow cytometry.

CRT-MG astrocytes were immunostained with Fc-APRIL A_{88} (1 µg/ml, bold lines) or control Fas-Fc (1 µg/ml, thin lines) for 30 minutes at 4 C in PBS 1% BSA.

Cells were washed, and incubated with Alexa488-conjugated human Ig antiserum for another 30 mn at 4 C.

Cells were washed again, resuspended in PBS and fluorescence was analyzed with the LSRII Becton Dickinson flow cytometer.

CRT-MG is a human astrocyte cell line.

Results

Overlayed histogram plots are shown.

The thin lines represent CRT-MG astrocytes immunostained with Fc-control.

The bold lines represent CRT-MG astrocytes immunostained with Fc-APRIL.

The results confirm *in vitro* binding of a soluble form of APRIL (April A_{88}) onto the human astrocyte cells CRT (**Figure 6**).

Example 5: APRIL bind to CSPG

Material & Methods

CRT-MG astrocytes were immunostained with 50 µl of supernatant conditonned by 293-T cells mock transfected (control supernatant) or transfected with Flag-tagged megaAPRIL A_{88} (APRIL).

APRIL was pre-incubated 15 minutes at 4°C in medium alone or with 200 µg/ml of CSPG type B (available at Sigma) before being added onto cells.

Cells were washed and incubated with an anti Flag (1 µg/ml, clone M2, avaialable at Sigma) conjugated to biotin for 30 minutes at 4°C.

Cells were washed and incubated with streptavidin conjugated to phycoerythrin (1/300, available at Becton Dickinson).

Cells were washed, resuspended in PBS and analyzed by flow cytometry.

Results

Overlayed histograms are shown.

Grey line corresponds to control.

Black line corresponds to APRIL.

Black dashed line corresponds to APRIL pre-incubated with CSPG.

The results confirm that the inhibition mediated by CSPG (Chondroitin Sulfate ProteoGlycan) revealed the capacity of APRIL to interact with CSPG (**Figure 10**).

Example 6: APRIL recombinant forms to be tested

Several forms of recombinant APRIL are planned to be tested.

Indeed, APRIL has a domain binding to HSPG. HSPG acts as coreceptor ensuring oligomerization of soluble APRIL to optimally signal via APRIL known receptors (TACI and BCMA). HSPG binding may trap the injected recombinant APRIL at undesired places, such as endothelial cells lining blood vessels. This has been already observed with other HSPG-binding recombinant proteins.

Hence, recombinant natural APRIL with or without the HSPG biding domain will be tested.

Recombinant natural APRIL with or without the HSPG biding domain are shown in **Figure 7**.

Sequence FLAG can be used for the purification step and does not belong to the active protein or the active fragment of the protein according to the present invention.

In the case a recombinant form without the HSPG binding domain is retained, an artificially oligomerize recombinant soluble APRIL with fusion partners may needed (see **Figure 8**).

As explained below, the sequence FLAG can be used for the purification step and does not belong to the active protein or the active fragment of the protein according to the present invention.

The two fusions partners retained for the study are a constant part of a human immunoglobulin (Fc) and the headless portion of the adipocyte complement related protein of 30 kDa (ACRP30). This latter chimeric APRIL is called Mega-APRIL.

Generation of Fc- and Mega-recombinant proteins have been described in Holler N., *et al.*, Molecular and Cellular Biology, Feb. 2003, p. 1428-1440.

Both chimeric molecules have been shown to signal via TACI and BCMA in the absence of the HSPG binding domain.

Example 7: Best injection route for recombinant APRIL

Pursuant to the results of Example 2 and Example 3, the best injection route for recombinant APRIL to distribute in brain lesions from EAE mice is tested.

After technetium labeling, 50 µg of the different recombinant forms of APRIL are injected in EAE mice. The recombinant forms of APRIL usedf are notably the forms described in example 6.

In vivo distribution of recombinant APRIL is monitored non-invasively by nuclear imaging, followed by invasive immunohistochemistry to localize the binding of recombinant APRIL in mouse brain lesions.

Three different routes are tested: intravenous, intranasal and intracerebroventricular.

Once the best route for APRIL brain biodistribution is determined, EAE mice are treated before disease induction (mice harboring a clinical score of 0), and once the disease is induced (mice harboring a clinical score of 1-2) 0.1mg/kg, 1 mg/kg, and 10 mg/kg of recombinant APRIL are injected every two, three and seven days.

Daily evolution of the clinical score in treated mice is monitored.

For treated mice having recovered from EAE and showing a stable low clinical score over a week, disease reinduction is performed (according to the same protocol as induction described in Example 2 and in Example 3. The subsequent increase in the clinical score is followed daily.

This test permits to determine whether APRIL treatment during the primary disease phase is able to diminish secondary phases, knowing that human MS is a chronic progressive disease.

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CLAIMS

1. Composition comprising (i) an active substance which comprises or consists in:

- a protein comprising a sequence set forth in SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO:3, representing the APRIL protein,
- or any derived protein, which is derived from a protein consisting of the sequence set forth in SEQ ID NO: 1,SEQ ID NO: 2 or SEQ ID NO:3, by substitution, removal or addition of one or more amino-acids, provided said derived protein is an APRIL protein which binds to an astrocyte and/or to Chondroitin Sulfate ProteoGlycans (CSPG),
- or any homologous protein, the sequence of which has a percentage of identity of at least 70 %, with said sequence set forth in SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO:3, provided said homologous protein is an APRIL protein which binds to an astrocyte and/or to CSPG,
- or any fragment of the protein consisting of the sequence set forth in SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO:3, provided said fragment is an APRIL protein which binds to an astrocyte and/or to CSPG, and wherein said fragment makes up of at least 60 contiguous amino acids of said SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO:3, and

(ii) a pharmaceutically acceptable vehicle,

for use in the prevention or the treatment of multiple sclerosis, autoimmune encephalitis, neuromyelitis optica (NMO), Alzheimer's disease or Parkinson Disease.

2. The composition for use according to claim 1, wherein the sequence of the homologous protein has a percentage of identity of at least 85% with said sequence set forth in SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO:3, provided said homologous protein is an APRIL protein which binds to an astrocyte and/or to CSPG.

3. The composition for use according to claim 1 or 2, wherein the active substance is a chimeric protein constituted by an oligomer of (i) the protein comprising the sequence set forth in SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, (ii) the derived protein, (iii) the homologous protein, or (iv) the fragment, each of said protein or fragment being linked to the other by a constant region of an immunoglobulin.

4. The composition for use according to claim 3, wherein the chimeric protein comprises or consists of a sequence set forth in SEQ ID NO: 9 or SEQ ID NO: 10.

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5. The composition for use according to claim 1 or 2, wherein the active substance is a chimeric protein constituted by an oligomer of (i) the protein comprising the sequence set forth in SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, (ii) the derived protein, (iii) the homologous protein, or (iv) the fragment, each protein or fragment being linked to the headless region of a ACRP30 protein.

6. The composition for use according to claim 5, wherein the chimeric protein comprises or consists of a sequence set forth in SEQ ID NO: 7 or SEQ ID NO: 8.

7. Composition comprising (i) an active substance which comprises or consists in:

- a nucleotide molecule coding for the protein comprising the sequence set forth in SEQ ID NO: 1 or a nucleotide molecule set forth in SEQ ID NO: 4, coding for the protein consisting in said sequence set forth in SEQ ID NO: 1,
- or a nucleotide molecule coding for a protein comprising the sequence set forth in SEQ ID NO: 2 or a nucleotide molecule set forth in SEQ ID NO: 5, coding for the protein consisting in said sequence set forth in SEQ ID NO: 2,
- or a nucleotide molecule coding for a protein comprising the sequence set forth in SEQ ID NO: 3 or a nucleotide molecule set forth in SEQ ID NO: 6, coding for the protein consisting in said sequence set forth in SEQ ID NO: 3,
- or any derived nucleotide molecule, by degeneration of the genetic code, of said sequence SEQ ID NO: 4, SEQ ID NO: 5 or SEQ ID NO:6, provided said derived nucleotide molecule encodes an APRIL protein which binds to an astrocyte and/or to Chondroitin Sulfate ProteoGlycans (CSPG),
- or any derived nucleotide molecule, by substitution, suppression or addition of one or more nucleotides of said sequence SEQ ID NO: 4, SEQ ID NO: 5 SEQ ID NO:6, provided said derived nucleotide molecule encodes an APRIL protein which binds to an astrocyte and/or to CSPG,
- or any homologous nucleotide molecule having a percentage of identity of at least 70%, with said sequence SEQ ID NO: 4, SEQ ID NO: 5 or SEQ ID NO:6, provided said homologous nucleotide molecule encodes an APRIL protein which binds to an astrocyte and/or to CSPG,
- or any fragment of said nucleotide molecule set forth in SEQ ID NO: 4, SEQ ID NO: 5 or SEQ ID NO:6 or of the above defined nucleotide molecules, provided

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said fragment encodes an APRIL protein which binds to an astrocyte and/or to CSPG, and wherein said fragment makes up of at least 20 contiguous nucleotides of said SEQ ID NO: 4, SEQ ID NO: 5 or SEQ ID NO:6, and

(ii) a pharmaceutically acceptable vehicle,

for use in the prevention or the treatment of multiple sclerosis, autoimmune encephalitis, neuromyelitis optica (NMO), Alzheimer's disease or Parkinson Disease.

8. The composition for use according to claim 7, wherein said active substance comprises or consists in a vector containing said nucleotide molecule.

9. The composition for use according to claim 7 or 8, wherein said active substance comprises or consists of a plasmid, cosmid, phage or virus DNA comprising said nucleotide molecule.

10. The composition for use according to any one of claims 1 to 5, wherein said active substance forms a complex with an astrocyte and/or CSPG.

11. The composition for use according to any one of claims 1 to 10, wherein the active substance is formulated for administration in a range of doses from about 0.1 mg/kg to about 20 mg/kg.

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Figure 1:

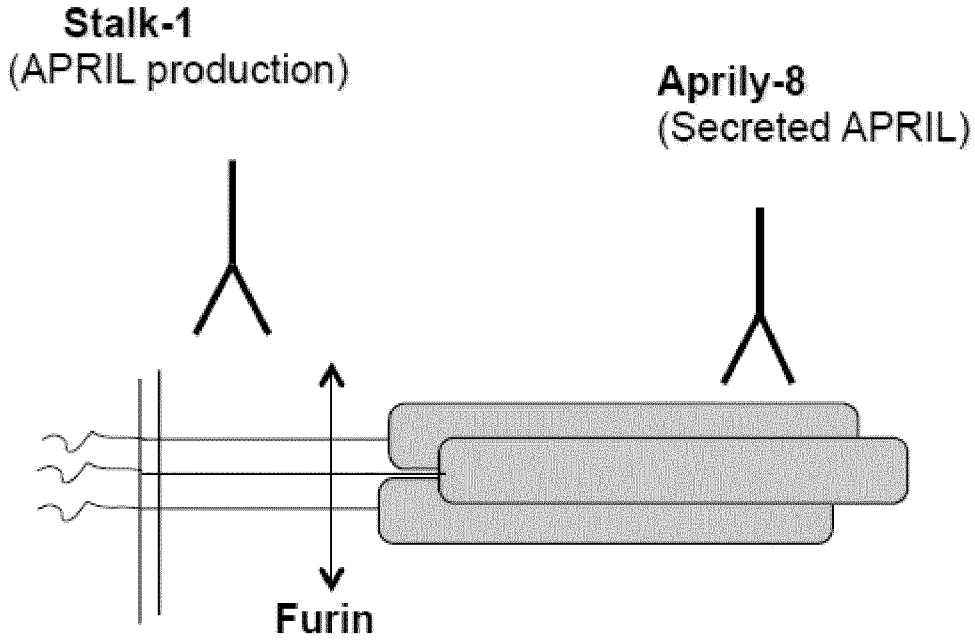

Figure 2:

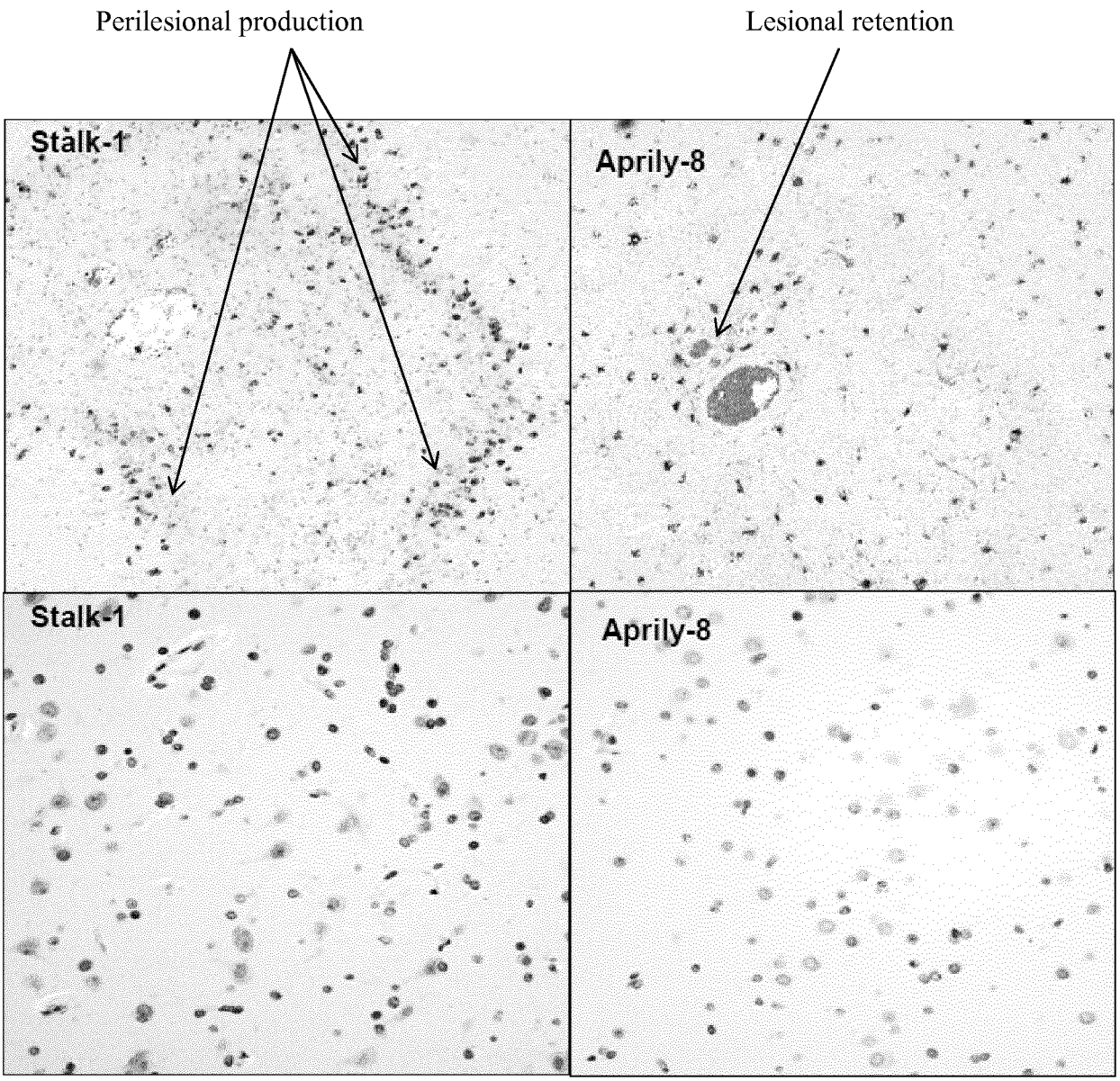
Perilesional production
Lesional retention
Stalk-1
Aprily-8
Stalk-1
Aprily-8

Figure 3:

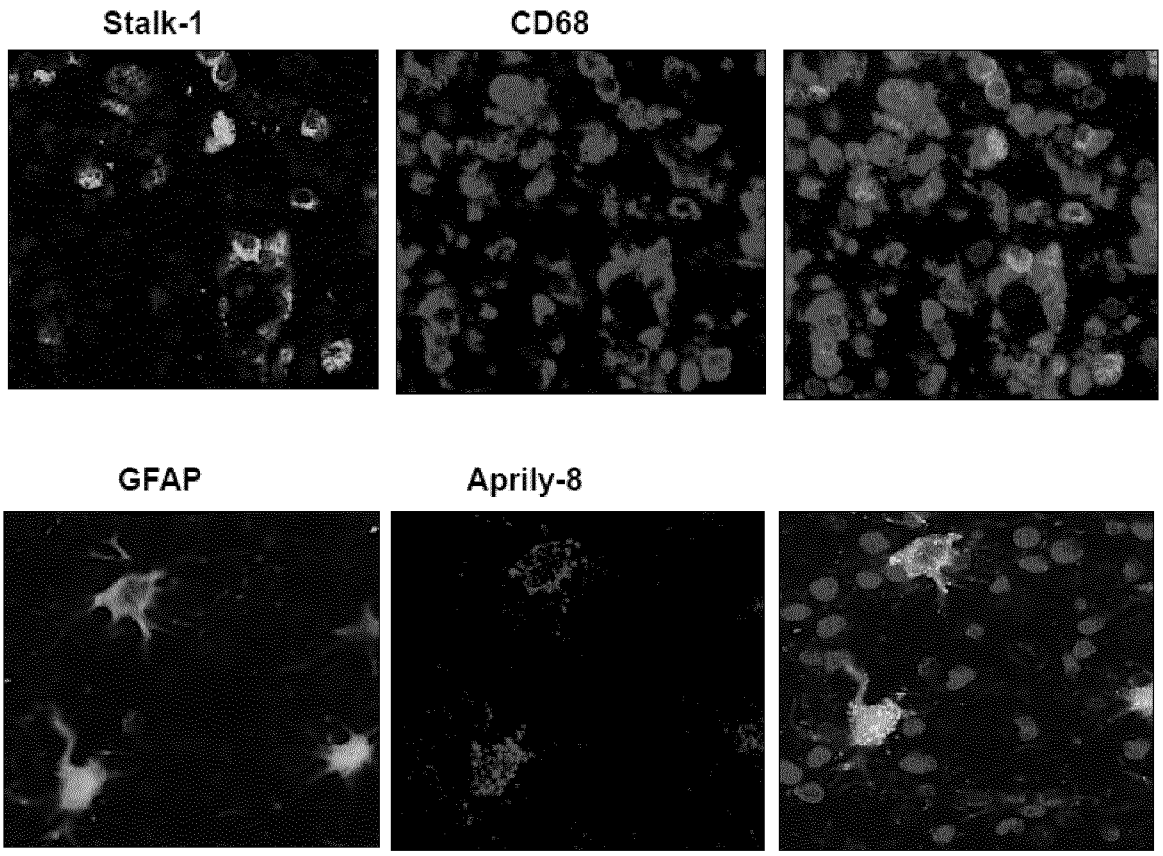

Figure 4:

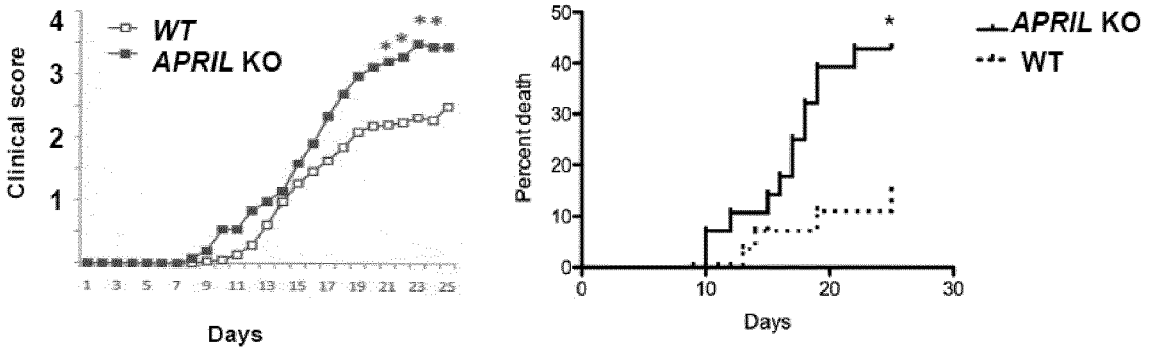
Clinical score
4
3
2
1
WT
APRIL KO
1 3 5 7 9 11 13 15 17 19 21 23 25
Days
Percent death
50
40
30
20
10
0
0 10 20 30
Days
APRIL KO
WT

Figure 5:

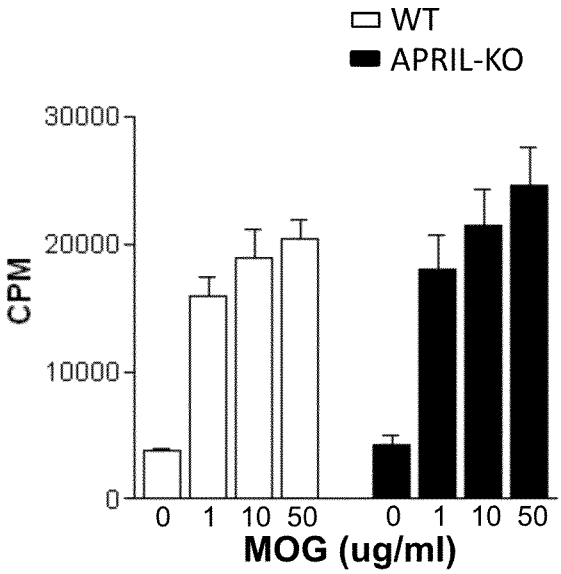

Figure 6:

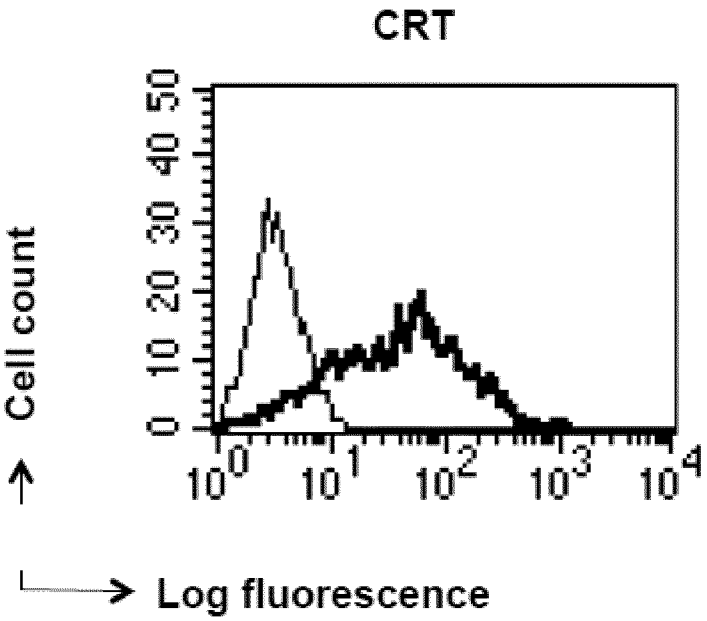
CRT
Cell count
0 10 20 30 40 50
10^0 10^1 10^2 10^3 10^4
Log fluorescence

Figure 7A:

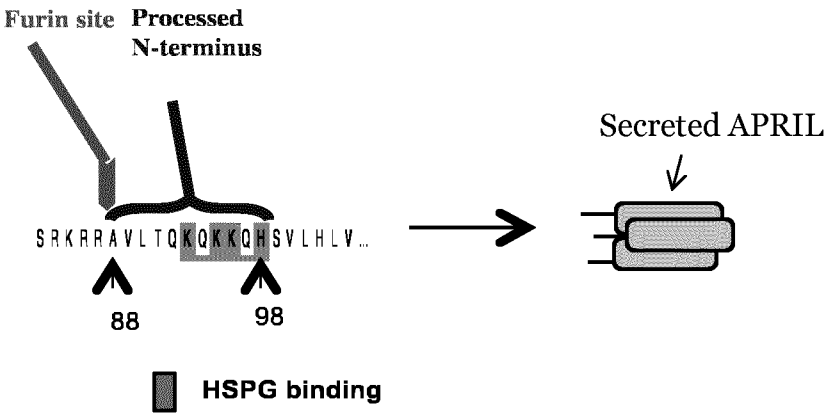
Furin site
Processed N-terminus
SRKRRAVLTQKQKKQHSVLHLV...
88
98
Secreted APRIL
HSPG binding

Figure 7B:

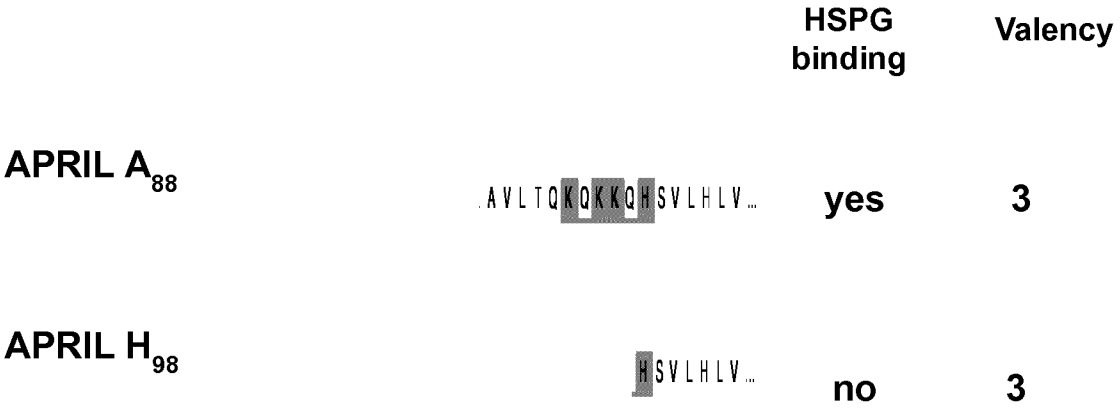
HSPG binding
Valency
APRIL A88
AVLTQKQKKQHSVLHLV...
yes
3
APRIL H98
HSVLHLV...
no
3

Figure 8A:

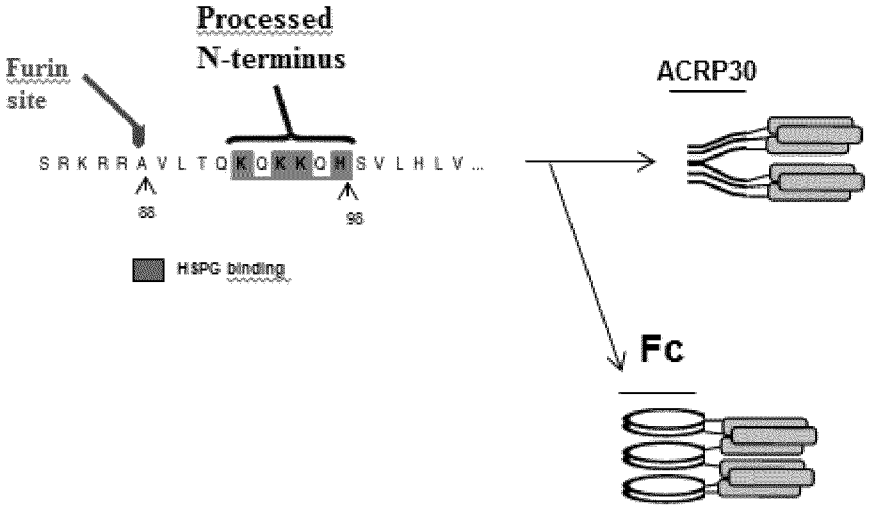
Processed
N-terminus
Furin
site
S R K R R A V L T Q K Q K K Q H S V L H L V ...
88
98
HSPG binding
ACRP30
Fc

Figure 8B:


HSPG binding
Valency
Mega-APRIL A88
ACRP30
— A V L T Q K Q K K Q H S V L H L V ...
yes
6
Mega-APRIL H98
ACRP30
— H S V L H L V ...
no
6
Fc-APRIL A88
Fcγ1
— A V L T Q K Q K K Q H S V L H L V ...
yes
6
Fc-APRIL H98
Fcγ1
— H S V L H L V ...
no
6

Figure 9:

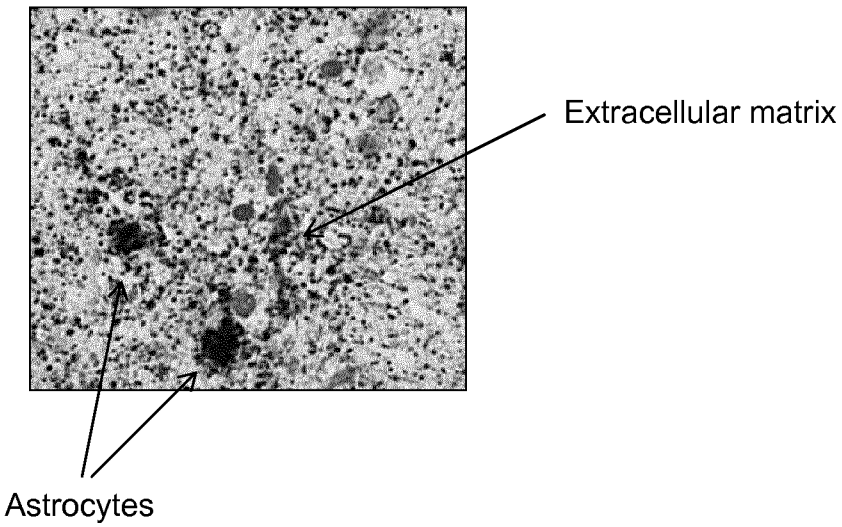

Figure 10:

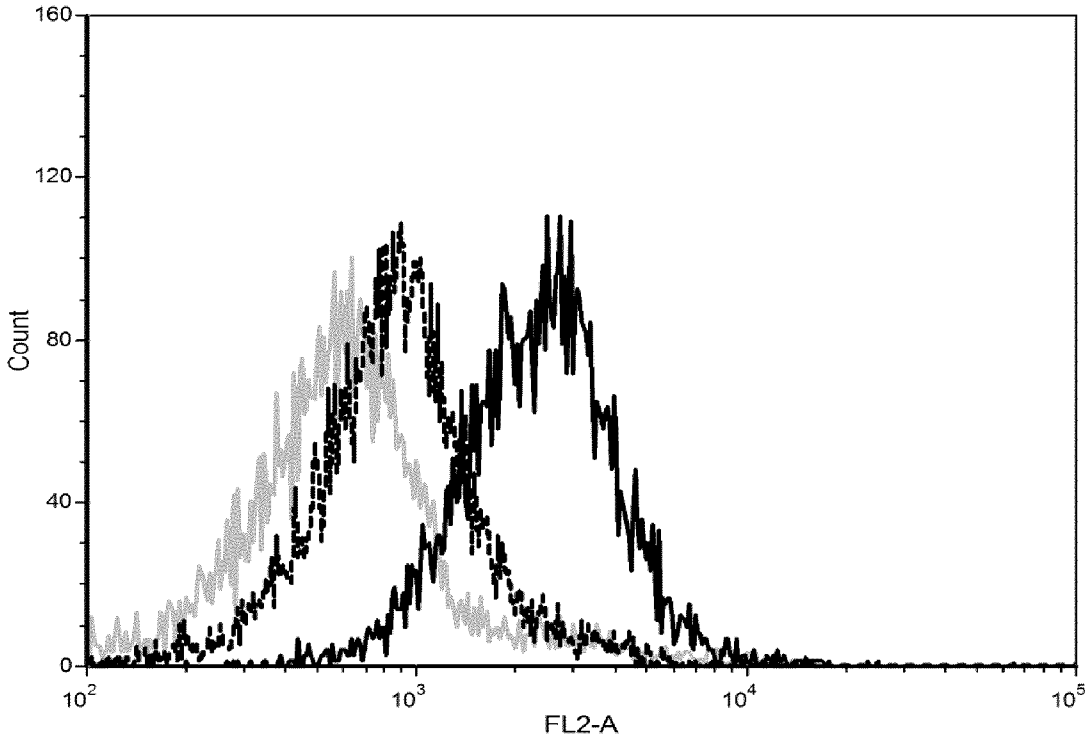

Figure 11: