(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 February 2004 (26.02.2004)

PCT

(10) International Publication Number
WO 2004/016261 A1

(51) International Patent Classification[7]: A61K 31/198, A61P 33/00

(21) International Application Number: PCT/JP2002/008209

(22) International Filing Date: 12 August 2002 (12.08.2002)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated State *(national)*: US.

(84) Designated States *(regional)*: European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).

Declarations under Rule 4.17:
— *as to the identity of the inventor (Rule 4.17(i)) for all designations*
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *with amended claims and statement*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR SUPPRESSING PROLIFERATION OF ABNORMAL PRION PROTEIN WITH LEUCINE, ISOLEUCINE OR VALINE

(57) Abstract: A method for suppressing proliferation of abnormal prion proteins is provided. Specifically, the method involves systemically, orally, intracerebrally or intraspinally administering an essential amino acid, in particular, one having a branched side chain, that is, one selected from leucine, isoleucine, and valine. Of these, leucine is most preferred.

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DESCRIPTION

METHOD FOR SUPPRESSING PROLIFERATION OF ABNORMAL PRION PROTEIN WITH LEUCINE, ISOLEUCINE OR VALINE

Technical Field

The present invention relates to a method for suppressing proliferation of abnormal prion proteins, and more particularly, to a method for suppressing proliferation of abnormal prion proteins through administration of essential amino acids having a branched side chain.

Background Art

Scrapie, the first to be discovered of a group of diseases caused by proliferation of abnormal prion protein, is found in sheep and impairs motor functions of the animal. Scrapie is characterized by porous, sponge-like appearance of affected brains. Other diseases similarly resulting from proliferation of abnormal prion protein were later identified, including bovine spongiform encephalopathy (BSE) in cows, commonly known as mad cow disease, Creutzfeldt-Jakob disease (CJD), and Gerstmann-Straussler-Scheinker syndrome (GSS) in humans.

These diseases were not caused by viral infection, nor had any known pathogen been identified to cause them. However, a specific type of protein commonly found in individuals suffering the disease was suspected to be a pathogenic agent involved in the transmission, or infection, of the disease. The protein was hypothetically named as a prion, or small proteinaceous infectious particle, and the group of diseases caused by the agent has come to be collectively referred to as prion diseases.

Of the known prion diseases, GSS is known to be a familial

disease and has proven to be triggered at 100% probability by a point mutation in a prion protein in which one amino acid of the protein is substituted for another type of amino acid (leucine).

The gene encoding prion protein, which consists of 235 amino acids, is located on chromosome 20. The infectious factor of the prion diseases is thought to mostly consist of this prion protein. The type of prion protein that acts as the infectious factor is termed as scrapie-type prion or abnormal prion (PrP^{SC}) while the normal prion is referred to as PrP.

As with the case of GSS, a point mutation in the prion protein can cause onset of other diseases. For example, substitution of proline (Pro) for leucine (Leu) in codon 102 of prion protein triggers cerebellar ataxia, substitution of proline (Pro) for leucine (Leu) in codon 102/219 (Lys) causes dementia or cerebellar ataxia, and substitution of proline (Pro) for leucine (Leu) in codon 105/129 (Val) causes spastic tetraplegia.

Also, in patients suffering fatal familial insomnia (FFI), a prion disease characterized by persistent insomnia and deaths within one year, aspartic acid (Asp) has been substituted for asparagine (Asn) in codon 178 of the prion protein.

Similar diseases caused by mutant prion proteins are also found in various animal species and are observed to transmit from one animal species to another via abnormal prion protein. For example, animal feed contaminated with materials prepared from scrapie-infected sheep has given rise to BSE in cows. Similarly, cat food containing materials prepared from BSE-infected cows has caused feline spongiform encephalopathy (FSE) in cats. Recent studies suggest that there is a significant chance that prion diseases, particularly BSE, are transmitted to human (Collinge J. et. al., *Nature* 383: 685-690, 1996).

While the manner by which the prion diseases are transmitted via abnormal prion proteins has yet to be clearly understood, it is known that an abnormal prion, despite its nature as protein, retains its infectivity after undergoing sterilizing processes under high pressure or by drying. Furthermore, abnormal prions are not denatured through treatment with formalin, alcohol or phenol. For these reasons, when a person is infected with abnormal prion protein, it is necessary to minimize proliferation of the abnormal prion in order to prevent onset of the disease. However, no effective approach has ever been developed that can suppress the proliferation of abnormal prion protein, nor has any attempt been made to this date to prevent onset of the disease based on such approaches.

Disclosure of Invention

In view of the present state of the art, it is a primary objective of the present invention to suppress proliferation of abnormal prion protein in animals, including humans, infected with the prion. Also, it is an ultimate goal of the present invention to prevent onset of prion diseases in animals, including humans, infected with the prion.

In an effort to find a way to achieve these objectives, the present inventors have made a finding that proliferation of abnormal prion protein is effectively suppressed by essential amino acids, in particular those having a branched side chain, and thus investigated the possibility of these essential amino acids as a viable suppressive agent for suppressing proliferation of abnormal prion protein. The finding ultimately led the present inventors to bring the present invention to completion.

Accordingly, one essential aspect of the present invention

is a method for suppressing proliferation of abnormal prion proteins. The method involves systemically, orally, intracerebrally or intraspinally administering an essential amino acid having a branched side chain at a high concentration.

Specifically, examples of the essential amino acid having a branched side chain for use in the present invention include leucine (Leu), isoleucine (Ile), and valine (Val) and a mixture thereof. The present inventors discovered that, of these amino acids, leucine is particularly effective in suppressing proliferation of abnormal prion protein.

Accordingly, a most preferred embodiment of the present invention is a method for suppressing proliferation of abnormal prion proteins, which involves systemically, orally, intracerebrally or intraspinally administering leucine at a high concentration.

A second essential aspect of the present invention is a method for administering an essential amino acid, involving systemically, orally, intracerebrally or intraspinally administering an essential amino acid having a branched side chain at a high concentration so as to suppress proliferation of abnormal prion proteins.

More specifically, the essential amino acid having a branched side chain to be administered systemically, orally, intracerebrally or intraspinally for the purpose of suppressing proliferation of abnormal prion protein is selected from the group consisting of leucine, isoleucine, valine and a mixture thereof, and most preferably, leucine.

A third essential aspect of the present invention is a suppressive agent for suppressing proliferation of abnormal prion proteins. The suppressive agent contains as an active ingredient

an essential amino acid having a branched side chain.

In one specific embodiment, the suppressive agent contains, as the essential amino acid having a branched side chain to serve as an active ingredient, one selected from the group consisting of leucine, isoleucine, valine, and a mixture thereof.

In the most preferred embodiment, the suppressive agent contains leucine as an active ingredient.

A fourth essential aspect of the present invention is a use of an essential amino acid having a branched side chain for being administered systemically, orally, intracerebrally or intraspinally so as to suppress proliferation of abnormal prion proteins.

Specifically, the fourth aspect of the present invention concerns the use of leucine, isoleucine, valine, or a mixture thereof, and most preferably, the use of leucine as the essential amino acid having a branched side chain to be administered systemically, orally, intracerebrally or intraspinally so as to prevent proliferation of abnormal prion protein.

Brief Description of Drawing

Figure 1 is a photograph showing the results of luminescence reactions obtained in Test Example 1 using ECL Western blotting technique.

Best Mode Carrying Out the Invention

One essential aspect of the present invention is a method for preventing proliferation of an abnormal prion protein through systemic, oral, intracerebral, or intraspinal administration of an essential amino acid having a branched side chain, specifically, one selected from the group consisting of leucine,

isoleucine, valine, and a mixture thereof at a high concentration.

The essential amino acid having a branched side chain, or specifically, one selected from the group consisting of leucine, isoleucine and valine, is a safe compound, and the fact that essential amino acids promote growth of human body and help us stay healthy makes the method of the present invention highly effective.

Of the different essential amino acids with a branched side chain, use of leucine has resulted in particularly favorable results. Considering the fact that the infectious, abnormal prion proteins result from a point mutation occurring in the normal prion protein, in particular, substitution of one amino acid for leucine, it is thought that administering leucine can somehow help prevent proliferation of abnormal prion protein.

Thus, in order to suppress proliferation of abnormal prion protein, the essential amino acid having a branched side chain, such as leucine, may be systemically administered through injection. Alternatively, it may be administered orally, intracerebrally or intraspinally. In the latter two cases, the essential amino acid is delivered to brain tissue or spinal cord.

The dosage of the essential amino acid is not limited to a particular range and can be any amount sufficient to suppress proliferation of abnormal prion protein. For example, it may be administered at a large dose of 5 to 15g/kg. The essential amino acid may be administered as a solution having a high concentration of 20 to 40mg/mL or, in the case of oral administration, as a solid preparation. In general, the essential amino acid can be administered in the form of a solution with a proper concentration, tablet, powder preparation or other suitable preparations.

Examples

The present invention will now be described in detail with reference to the results of a test in which an abnormal prion protein derived from scrapie-infected sheep was used and suppression of proliferation of the protein was observed.

Test Example 1:

Effects that the essential amino acids having a branched side chain have on the proliferation reaction of abnormal prion protein were examined in the following experiment.

1. Method:

Using the protein misfolding cyclic amplification technique (PMCA), abnormal prion protein was amplified *in vitro*. Brains of sheep collected from a healthy sheep and a scrapie-infected sheep were independently homogenized in 0.5% Triton X-0.05% SDS-PBS (containing a protease inhibitor) to form 10%(w/v) solutions. To each of 10μL aliquots of the brain homogenate derived from healthy sheep, one-hundredth as much of the brain homogenate derived from scrapie-infected sheep was added to perform PMCA amplification. Leucine was added to a group of the resulting mixtures to a final concentration of 15mg/mL.

Each mixture of the brain homogenates was incubated for 1 hour while being stirred at 37°C and was then sonicated using Digital Sonifier 450D available from Branson. Sonication was performed by setting power output to 100% and repeating 5 times a cycle of 0.2-second oscillation period followed by 0.1-second interval.

The mixtures with and without leucine were individually subjected to 0 time (control), 1 time and 10 times of the

incubation-sonication treatment to give samples. Proteinase K (PK) was added to each sample to a final concentration of 50μg/mL, and the samples were incubated for 1 hour at 37° C.

Abnormal prion protein was detected by Western blotting technique. Each sample was separated and electrophoresed by 10% SDS-PAGE and then transferred to a membrane. After blocking nonspecific binding sites on the membrane, each membrane was incubated with rabbit anti-PrP_{94-112} antibody for 1 hour at room temperature, washed, and then incubated with HRP-labeled anti-rabbit IgG antibody. The membranes were then washed and luminescence was detected by ECL + plus.

2. Results

After PMCA, bands of PK resistant fragments were significantly enhanced in the leucine-free group (*e.g.*, 5-fold in the sample subjected to 10 cycles of the treatment). The degree of enhancement was dependent on the number of cycles.

In contrast, no prominent bands were formed suggesting the presence of PK resistant fragments in the leucine-treated group, including the sample subjected to 10 cycles of PMCA.

Collectively, the results suggest that addition of leucine has effectively suppressed proliferation of abnormal prion protein *in vitro*.

Shown in the figure 1 are the results of luminescence reaction performed by ECL + plus. The results obtained for the leucine-treated group are shown on the left of the figure and the results for the leucine-free group on the right.

Industrial Applicability

As set forth, the method of the present invention to

administer essential amino acids having a branched side chain, in particular leucine, can suppress proliferation of abnormal prion proteins.

In view of the fact that no effective measure has been proposed to this date to suppress proliferation of abnormal prion proteins, the suppression of proliferation of abnormal prions, made possible by the present invention, will ultimately lead to prevention of the onset of prion diseases in animals, including humans, infected with an abnormal prion protein and thus proposes a possibility for the treatment of various prion diseases now attracting significant public attention, such as BSE in cows and CJD in humans.

CLAIMS

1. A method for suppressing proliferation of abnormal prion proteins, comprising the step of systemically, orally, intracerebrally or intraspinally administering an essential amino acid having a branched side chain.

2. The method according to claim 1, wherein the essential amino acid having a branched side chain is selected from the group consisting of leucine, isoleucine, valine, and a mixture thereof.

3. A method for suppressing proliferation of abnormal prion proteins, comprising the step of systemically, orally, intracerebrally or intraspinally administering leucine.

4. A method for administering an essential amino acid having a branched side chain, comprising the step of systemically, orally, intracerebrally or intraspinally administration so as to suppress proliferation of abnormal prion proteins.

5. The method according to claim 4, wherein the essential amino acid having a branched side chain is selected from the group consisting of leucine, isoleucine, valine, and a mixture thereof.

6. A method for administering leucine, comprising the step of systemically, orally, intracerebrally or intraspinally administering leucine so as to suppress proliferation of abnormal prion proteins.

7. A suppressive agent containing an essential amino acid having a branched side chain as an active ingredient for suppressing proliferation of abnormal prion proteins.

8. The suppressive agent according to claim 7, wherein the essential amino acid having a branched side chain is selected from the group consisting of leucine, isoleucine, valine, and a mixture thereof.

9. A suppressing agent for suppressing proliferation of abnormal prion proteins, the agent containing leucine as an active ingredient.

10. A use of an essential amino acid having a branched side chain for being administered systemically, orally, intracerebrally or intraspinally so as to suppress proliferation of abnormal prion proteins.

11. The use according to claim 10, wherein the essential amino acid having a branched side chain is selected from the group consisting of leucine, isoleucine, valine, and a mixture thereof.

12 A use of leucine for being administered systemically, orally, intracerebrally or intraspinally so as to suppress proliferation of abnormal prion proteins.

AMENDED CLAIMS
[received by the International Bureau on 06 June 2003 (06.06.03);
new claims 13 to 19 added;
remaining claims unchanged (2 pages)]

7. A suppressive agent containing an essential amino acid having a branched side chain as an active ingredient for suppressing proliferation of abnormal prion proteins.

8. The suppressive agent according to claim 7, wherein the essential amino acid having a branched side chain is selected from the group consisting of leucine, isoleucine, valine, and a mixture thereof.

9. A suppressing agent for suppressing proliferation of abnormal prion proteins, the agent containing leucine as an active ingredient.

10. A use of an essential amino acid having a branched side chain for being administered systemically, orally, intracerebrally or intraspinally so as to suppress proliferation of abnormal prion proteins.

11. The use according to claim 10, wherein the essential amino acid having a branched side chain is selected from the group consisting of leucine, isoleucine, valine, and a mixture thereof.

12 A use of leucine for being administered systemically, orally, intracerebrally or intraspinally so as to suppress proliferation of abnormal prion proteins.

(the claim is new)

13. A method for preventing prion diseases by suppressing proliferation of abnormal prion proteins which comprises the step of systemically, orally, intracerebrally or intraspinally administering an essential amino acid having a branched side chain as active ingredient.

(the claim is new)

14. The method according to claim 13, wherein the essential amino acid having a branched side chain is selected from the group consisting of leucine, isoleucine, valine, and a mixture thereof.

(the claim is new)

15. The method according to claim 13, wherein the essential amino acid having a branched side chain is leucine.

(the claim is new)

16. The method according to claim 13, wherein said prion diseases is scrapie.

(the claim is new)

17. The method according to claim 13, wherein said prion diseases is bovine spongiform encephalopathy (BSE).

(the claim is new)

18. The method according to claim 13, wherein said prion diseases is Creutzfeldt-Jakob disease (CJD).

(the claim is new)

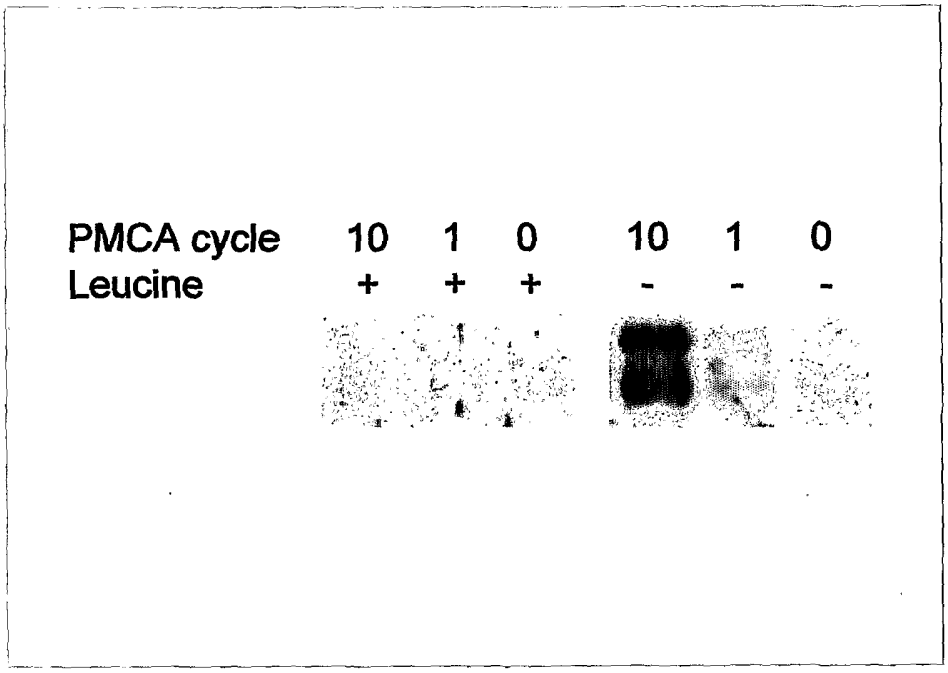
19. The method according to claim 13, wherein said prion diseases is Gerstmann-Straussler-Scheinker syndrome.

STATEMENT UNDER ARTICLE 19 (1)

The present claims 1 to 12 are retained unchanged.

The newly added claim 13 to 19 are divided from present claim 1 to specify the target disease. The target disease of the invention is stated at lines 15 to 21 on page 1 and lines 16 to 21 on page 3 of the description. This amendment, however, has no impact neither on the description nor drawings.

Figure 1



INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/08209

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/198 A61P33/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, PAJ, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 21437 A (NEW YORK STATE OFFICE OF MENTA) 18 July 1996 (1996-07-18) page 2, paragraph 4 - paragraph 5 claims 1,7 ---	1-12
X	US 5 919 823 A (RICHARDSON MARY ANN) 6 July 1999 (1999-07-06) claims 7,8 ---	1-12
Y	EP 0 764 442 A (HOLT JOHN ALFRED GORTON) 26 March 1997 (1997-03-26) claims 1,8 ---	1-12
Y	EP 0 824 919 A (HOLT JOHN ALFRED GORTON) 25 February 1998 (1998-02-25) claims 1,4 --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 March 2003	17/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bonzano, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/08209

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 64420 A (KONG XIANQI ;NEUROCHEM INC (CA); SZAREK WALTER (CA); UNIV KINGSTON) 2 November 2000 (2000-11-02) page 1, paragraph 3 page 9, paragraph 4 page 22, paragraph 3 - paragraph 1; figure 23 ---	1-12
A	WO 01 26623 A (LAXDALE LTD) 19 April 2001 (2001-04-19) claims 1-3 page 10, paragraph 1 ---	
A	CALLEBAUT, ISABELLE ET AL: "Common prevalence of alanine and glycine in mobile reactive center loops of serpins and viral fusion peptides: do prions possess a fusio peptide?" JOURNAL OF COMPUTER-AIDED MOLECULAR DESIGN (1994), 8(2), 175-91 , XP008015408 page 189, paragraph 4 ---	
X	DATABASE WPI Section Ch, Week 200264 Derwent Publications Ltd., London, GB; Class B05, AN 2002-599522 XP002236107 & WO 02 49638 A (AJINOMOTO KK), 27 June 2002 (2002-06-27) abstract -----	7-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/08209

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-6,10-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims 1-12 relate to the treatment of diseases which are actually not well defined. The use of the definition "proliferation of abnormal prion proteins" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is not fully possible to determine the diseases for which protection might legitimately be sought. The lack of clarity is such as to render a meaningful complete search not fully possible.
Consequently, the search has been restricted to the parts relating to the diseases described in the description at page 1, lines 13-21, with due regard to the general idea underlying the present invention.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 02/08209

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