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*With international search report.*

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9 November 2000 (09.11.00)

(54) Title: NEUROTROPHIC GROWTH FACTOR

(57) Abstract

There is disclosed an isolated nucleic acid molecule encoding a human neurotrophic growth factor designated enovin and having the amino acid sequence illustrated in Figure 1, 21, 23 or 24 or encoding a functional equivalent, derivative or bioprecursor of said growth factor. The growth factor preferably comprises the amino acid sequence from position 27 to 139 of the sequence illustrated in Figure 1, or a functional equivalent, derivative or bioprecursor thereof. The nucleic acid molecule encoding enovin can be used to transform a host cell, tissue or organism by including it in an appropriate vector. The host cell, tissue or organism and the vector also form part of the invention.

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# INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 99/05031

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/475 C12N15/11 C12N15/63 C12N5/16 A61K38/18
G01N33/53 G01N33/68 C12Q1/68

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 C07K C12N A61K G01N C12Q

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | LIN L F ET AL: "GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons [see comments]." SCIENCE, (1993 MAY 21) 260 (5111) 1130-2., XP002914283 the whole document --- | 1-6, 8-12, 14-26, 29-38, 40-45, 49-51 |
| A | CREEDON D J ET AL: "Neurturin shares receptors and signal transduction pathways with glial cell line-derived neurotrophic factor in sympathetic neurons." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 JUN 24) 94 (13) 7018-23., XP000882989 the whole document --- | 1-6, 8-12, 14-26, 29-38, 40-45, 49-51 |

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 23 May 2000 | 29. 08. 00 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Mennessier, T |

4

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

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | MILBRANDT J ET AL: "Persephin, a novel neurotrophic factor related to GDNF and neurturin." NEURON, (1998 FEB) 20 (2) 245-53., XP000886826 the whole document | 1-6, 8-12, 14-38, 40-45, 49-51 |
| E | WO 00 01815 A (BLOM NIKOLAJ ;HANSEN CLAUS (DK); JOHANSEN TEIT E (DK); NEUROSEARCH) 13 January 2000 (2000-01-13) page 1-4 page 6-29 | 1-6, 8-12, 14-38, 40-45, 49-51 |
| P,X | SAARMA M ET AL: "Other neurotrophic factors: glial cell line-derived neurotrophic factor (GDNF)." MICROSCOPY RESEARCH AND TECHNIQUE, (1999 MAY 15-JUN 1) 45 (4-5) 292-302. REF: 83, XP000885944 the whole document | 1-6, 8-12, 14-38, 40-45, 49-51 |
| P,X | BALOH R H ET AL: "Artemin, a novel member of the GDNF ligand family, supports peripheral and central neurons and signals through the GFRalpha3-RET receptor complex." NEURON, (1998 DEC) 21 (6) 1291-302., XP000857438 the whole document | 1-6, 8-12, 14-38, 40-45, 49-51 |
| T | MASURE S ET AL: "Enovin, a member of the glial cell-line-derived neurotrophic factor (GDNF) family with growth promoting activity on neuronal cells. Existence and tissue-specific expression of different splice variants." EUROPEAN JOURNAL OF BIOCHEMISTRY, (1999 DEC) 266 (3) 892-902., XP000882986 the whole document | 1-6, 8-12, 14-38, 40-45, 49-51 |

# INTERNATIONAL SEARCH REPORT

In ational application No.
PCT/EP 99/05031

**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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 7,13,39,46-48,52
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:

See additional sheet

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.:

1-32, 33-34 (partly), 35, 36-47 (partly), 48-51 and 52 (part)

**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 Nos.: 7,13,39,46-48,52

A functional equivalent of "enovin" as mentioned in claims 1, 9, 10, 19 and 20 appears to be defined only in terms of its growth properties and as its function(s) (see page 11, lines 21-24 of the description). Such a definition may encompass compounds which are not related to "enovin" in terms of their structure. As it is not possible to assess whether each and every known compound shares the growth properties and is functionally associated with "enovin", a meaningful search cannot be carried out with respect to that aspect of the invention. Therefore, claims 1-6, 8-12, 14-32, 40-45 and 49 have not been searched, insofar as their subject-matter is defined with a reference to such a functional equivalent of "enovin".

As it is not clear what is meant under the term "enovin" as used in claim 35, the search has been limited to those embodiments of the claimed method in which "enovin" is the factor having the amino acid sequence illustrated in Figure 1 acording to the definition given in claim 1.

Under the expression "a sequence capable of binding under conditions of high stringency" as referred to in claim 6 is meant an infinity of sequences which are more or less complementary to at least one part of the nucleic sequence encoding "enovin". As it not possible to practically assess whether each and every of the candidate sequences is comprised within the state of the art, a meaningful search cannot be carried out. Therefore, claim 6 as well as claims 21-22, 24-25, 40-45 and 49 have not been searched, insofar as their subject-matter is defined with a reference to such a sequence.

The same remark applies to "antisense molecules" as referred to in claim 7. There appears to be an infinity of candidate molecules. As it is not possible to practically assess whether each and every of them is comprised within the state of the art, a meaningful search cannot be carried out. Therefore, and as morever, no particular antisense molecule has been identified in the application, claims 7 and 13, both as a whole, as well as claims 14-16, each partly, i.e., insofar as their subject-matter is defined with reference to such an antisence molecule, have not been searched.

Claims 19 and 20 appear not to exclude a neurotrophic growth factor, derivatives or bioprecursors thereof intrinsically produced by the cell, tissue or organism and not encoded by a nucleic acid molecule encoding "enovin". The search has been limited to those embodiments of said claims which are directed to a neurotrophic growth factor actually encoded by a nucleic acid molecule encoding "enovin", derivatives and bioprecursors thereof.

As no particular agonist or antagonist has been identified in the application, a meaningful search cannot be carried out with respect to aspects of the invention dealing with such compounds or medical uses thereof. Therefore, claim 39, claims 40-45 (partly, insofar as they

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

relate to the use of an agonist or antagonist), claims 46-48 and claim 52 have not been searched.

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.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

1. Claims: 1-32, 33-34 (partly), 35, 36-47 (partly), 48-51 and 52 (part)

Claims taken into consideration:

- Claim 1 (-> an isolated nucleic molecule encoding "enovin") and claims 2-6 (dependent thereon)

- Claim 7 (-> an antisense molecule capable of hybridising to a nucleic acid molecule as defined in any of claims 1-6)

- Claims 8-11, 19 and 20 (-> "enovin")

- Claims 12 and 14 (-> expression vectors comprising a DNA molecule as defined in any of claims 2-7)

- Claim 13 (-> an expression vector comprising an antisense molecule as defined in claim 7)

- Claim 15 (-> a host cell transformed or infected with a vector as defined in any of claims 12-14) and claim 16 (dependent thereon)

- Claim 17 (-> a transgenic cell, tissue or organism comprising a transgene capable of expressing "enovin") and claim 18 (dependent thereon)

- Claim 21 (-> the use of a nucleic acid molecule as defined in claims 1-6 in the manufacture of a medicament) and claim 22 (dependent thereon)

- Claim 23 (-> the use of "enovin" in the manufacture of a medicament) and claim 24 (dependent thereon)

- Claim 25 (-> a pharmaceutical composition comprising a nucleic acid molecule as defined in claims 1-6)

- Claim 26 (-> a pharmaceutical composition comprising "enovin"

- Claim 27 (-> the use of an antisence molecule as defined in claim 7 in the manufacture of a medicament) and claim 28 (dependent thereon)

- Claim 29 (-> an antibody capable of binding to "enovin")

- Claim 30 (-> a diagnosis method involving the use of an antibody as defined in claim 29) and claim 31 (dependent thereon)

- Claim 32 (-> a diagnosis kit or device comprising an antibody as defined in claim 29)

- Claims 33, 34 and 36-38, insofar as they are directed to a

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

method of identifying an agonist or antagonist of "evonin", as well as claim 35 as a whole

- Claims 40-45, insofar as the compound first referred to therein is an agonist or antagonist of "evonin"

- Claims 39, 46, 47 and 52, insofar as the compound referred to therein is an agonist or antagonist of "enovin"

- Claim 48 (-> a method of making a pharmaceutical formulation comprising an agonist or antagonist of "enovin")

- Claim 49 (-> a pharmaceutical composition comprising an antibody of claim 29)

- Claim 50 (-> particular molecules related to "enovin")

- Claim 51 (-> particular plasmid containing a sequence encoding "enovin")

2. Claims: 33-34 (part), 36-47 (part) and 52 (part)

Claims taken into consideration:

- Each of independent claims 33 and 34, insofar as it is directed to a method of identifying an agonist or antagonist of a human neurotrophic growth factor other than "enovin"

- Claims 36-38, insofar as they are not dependent on claim 35

- Claim 39, insofar as it is directed to an agonist or an antagonist of a neurotrophic growth factor other than "evonin"

- Claims 40-45 and 52, insofar as they are directed to the use of such an agonist or antagonist of a neurotrophic growth factor other than "evonin" in the manufacture of a medicament

- Claim 46, insofar as it is directed to a pharmaceutical composition comprising an agonist or antagonist of a neurotrophic growth factor other than "evonin"

- Claim 47, insofar as it is directed to a method for making a pharmaceutical composition as defined above

# INTERNATIONAL SEARCH REPORT

Internat[illegible]al Application No
PCT/EP 99/05031

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 0001815 A | 13-01-2000 | AU 4769399 A | 24-01-2000 |