

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

To: Simmons & Simmons LLP Claude Debussylaan 247 1082 MC Amsterdam PAYS-BAS		Date of mailing (day/month/year) 18.09.2024	
Applicant's or agent's file reference AMS-202324PC		IMPORTANT NOTIFICATION	
International application No. PCT/NL2023/050374	International filing date (day/month/year) 12.07.2023	Priority date (day/month/year) 12.07.2022	
Applicant Resiliun B.V.			

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0	Authorized Officer Brell, Eva Tel. +49 89 2399-6724	
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference AMS-202324PC	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/NL2023/050374	International filing date (day/month/year) 12.07.2023	Priority date (day/month/year) 12.07.2022	
International Patent Classification (IPC) or national classification and IPC INV. A61P3/08			
Applicant Resiliun B.V.			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>10</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ a total of <u>6</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ a separate electronic file containing a sequence listing (<i>sent to the International Bureau only</i>)			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☒ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☒ Box No. VIII Certain observations on the international application			
Date of submission of the demand 13.05.2024		Date of completion of this report 18.09.2024	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0		Authorized officer Habedanck, Robert Telephone No. +49 89 2399-5879	



Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-70 as originally filed

Claims, Numbers

1-14 filed in electronic form on 13-05-2024

Drawings, Sheets

1/10-10/10 as originally filed

- ☒ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/NL2023/050374

6. ☒ With regard to top-up searches (Rules 66.1 *ter* and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 10.06.2024 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	<u>1-14</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-14</u>
Industrial applicability (IA)	Yes: Claims	<u>1-14</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)
and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed.
 - b. ☒ furnished subsequent to the international filing date for the purposes of international search and/or examination,
 - ☒ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
 - c. ☐ furnished to this Authority as an amendment* under PCT Article 34 on .
 2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established to the extent that a meaningful opinion referred to in Article 33(1) could be formed without a WIPO Standard ST.26 compliant sequence listing.
 3. Additional comments:
- * *If item 4 in Box No. I applies, the sequence listing, which forms part of the basis of the report, may be marked "superseded."*

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1 WO 2011/056447 A2 (CEBIX INC [US]; WAHREN JOHN [SE] ET AL.) 12 May 2011 (2011-05-12)
- D2 S. Blaise ET AL: "Elastin-Derived Peptides Are New Regulators of Insulin Resistance Development in Mice",
Diabetes,
vol. 62, no. 11, 6 August 2013 (2013-08-06), pages 3807-3816,
XP055461109,
US
ISSN: 0012-1797, DOI: 10.2337/db13-0508
- D3 WO 2017/024285 A2 (XOMA (US) LLC [US]) 9 February 2017 (2017-02-09)
- D4 US 2015/031633 A1 (HORNEBECK WILLIAM [FR] ET AL) 29 January 2015 (2015-01-29)
- D5 WO 2018/141969 A1 (BIOTEMPT BV [NL]) 9 August 2018 (2018-08-09)
- D6 WO 2023/059188 A1 (BIOTEMPT BV [NL]; RESILIUN B V [NL]) 13 April 2023 (2023-04-13)
- 1 The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.
- 2 Patentability, in particular novelty and inventive step, of claims 1-9 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Novelty - Article 33(2) PCT

- 3 Due to the unclear term 'hypoglycemia associated with hyperinsulinemia in congenital hyperinsulinemia' (see item VIII below), any disclosure in the prior art of the same peptides used for the treatment of any hypoglycemia will be considered prejudicial to the novelty of the claims.
- 4 D1 discloses C-peptides for use in treating hypoglycemia (claims 1 and 2), wherein the C-peptide comprises the LGGGPG motif (SEQ ID No. 1, paragraph 214).
- 5 The C-peptide is 'functionally equivalent' to any of the peptides defined in the claims.
- 6 D1 discloses the subject-matter of claims 1-14.
- 7 D2 discloses elastin derived peptides having the GXXPG motif as regulators of insulin resistance in mice (abstract, page 3809, right column, paragraph 1). The peptide used was VGVAPG (page 3807, right column, paragraph 4), which resulted in hyperglycemia when injected in mice, caused by reduced glucose uptake in skeletal muscle (fig. 1, abstract).
- 8 D2 discloses the subject-matter of claims 10-12.
- 9 However, D2 does not disclose the treatment of hypoglycemia.
- 10 D3 discloses inhibitory antibodies targeting the insulin receptor for use in treatment hypoglycemia caused by hyperinsulinemia (paragraph 2).
- 11 D3 does not appear to disclose an elastin receptor binding motif.
- 12 D4 discloses in general discloses peptides having the XGXXPG motif (claims 1, 2), such as the peptide comprising the sequence of SEQ ID NO. 13 (SEQ ID No. 9), or the bifunctional peptide (claim 8). Peptides are used to activate the synthesis of collagen, for the repair of dermal tissue, treating scars, sores or ulcers (claims 12-15).
- 13 D4 discloses the subject-matter of claims 10-12.
- 14 D4 does not disclose any treatment of hypoglycemia.

- 15 D5 discloses C-peptide (SEQ ID NO. 1) that comprises the LGGGPG sequence which falls under the elastic receptor binding motif xGxxPG (page 12, lines 14-25, page 15, lines 22-27), which is used for treating human disease such as type 1 or type 2 diabetes (claims 1-10). A peptide comprises the LGGGPG sequence (SEQ ID No. 47).
- 16 D5 discloses the subject-matter of claims 10-12.
- 17 D5 does not disclose any treatment of hypoglycemia.
- 18 Claims 1-14 thus lack novelty.

Inventive step - Article 33(3) PCT

- 19 The application does not meet the requirements of Article 33(3) PCT because claims 1-14 lack an inventive step.
- 20 D1 can be taken as the closest prior art.
- 21 No inventive step can be acknowledged for claims 1-14 lacking novelty as no technical difference can be identified over the cited prior art.
- 22 The examples show the following:
- 23 Example 1 relates to an in silico screen of plasmodial proteins for identifying the best-fitting amino acid motif of the human elastin receptor-complex. The GVAP motif of the VGVAP peptide was repeatedly found.
- 24 Example 2 concerns peptide synthesis of relevant peptides intended for the treatment of insulin secretion related disorders.
- 25 Example 3 provides background on the elastin receptor complex.
- 26 Example 4 shows the effects of three elastin fragment peptides on the sprouting ability of cultured human pulmonary microvascular endothelial cells in an angiogenesis assay in vitro. The peptides VGVAPGVGVAPGVGVAPG, QVGQVELGGGPGAGSLQP and GAYPGAPGAYPGAPAPGV were used. The three peptides resulted in increased tube length.
- 27 None of the examples show any effect that would plausibly give rise to a treatment of hypoglycemia. An angiogenesis assay is not an accepted model for hypoglycemia caused by hyperinsulinemia.
- 28 No effects are shown for the nearly limitless number of peptides falling under the scope of the claims.

- 29 Based on the features defined in the present claims, the objective technical problem to be solved in respect of the present invention may be regarded as the provision of peptides for the treatment of hypoglycemia. In the absence of any experimental data or results establishing any technical effects, it is considered however that this objective technical problem has not been shown to have been solved across reasonably the full scope of the present claims.
- 30 In the event that the objective technical problem is reformulated in a less ambitious way, i.e. involving the provision of alternative compounds vis a vis the peptides of document D1, the provision of arbitrary alternative peptides without any associated technical effects being established is considered to be within the capability of skilled addressee and is not considered to represent an inventive contribution to the present art. Hence, lack of inventive step arises.
- 31 Furthermore, the glucose increasing effects of peptides having the XGXXPG motif are already known from D2. The skilled person would therefore prepare alternative peptides harbouring the same motif with a reasonable expectation of success and without resorting to any inventive skill.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/ year)	Filing date (day/month/ year)	Priority date(<i>valid claim</i>) (day/month/year)
WO2023/059188	13.4.2023	5.10.2022	5.20.2021

Re Item VIII

Certain observations on the international application

- 32 Claim 1 lacks clarity and support by the description in the sense of Article 6 PCT, because the expression 'a modulator of insulin-insulin receptor signalling... wherein said modulator is provided with a molecule carrying an elastin receptor binding motif' is a functional definition that does not define the compound to be used in terms of a technical feature such as a structure or a peptide sequence, and thus could apply to an infinitely large number of possible

- compounds, thus leaving the skilled person in doubt as to which compounds fall under the scope of the claims. The description and the examples convey the impression that the claimed invention is carried out in a particular manner, namely by the use of particular peptides only only, with no alternative means envisaged. Thus, the scope of claims 1 is both unclear and broader than justified by the technical contents of the description. Claim 1 therefore does not meet the requirements of Article 6 PCT.
- 33 Moreover, the person skilled in the art would not be able to perform the invention over the whole area claimed. A skilled person cannot reduce to practice the claimed subject-matter, because the compounds employed in the claims are not generally known, have potentially limitless structural possibilities and are only functionally defined as 'a modulator of insulin-insulin receptor signalling' or 'elastin receptor binding motif' with no clear indication as to their structure, such that the skilled person would not be able to perform the invention over the whole area claimed without undue burden and without resorting to inventive skill. Consequently, claim 1 does not fulfil the requirements of Article 5 PCT.
- 34 The also applies to claims 2-14 because these claims do not further define the compound or peptide to be used in a manner that is clear, supported or sufficiently disclosed. In particular, the expression 'functionally equivalent' leaves the peptide wholly undefined. Claims 2-14 thus lack compliance with Articles 6 and 5 PCT.
- 35 The expression 'for use in the treatment of a mammalian subject deemed having episodes of hypoglycemia..' in claim 1 leaves the disease to be treated undefined, thus rendering the claim unclear. At present, the claim includes the treatment of any, undefined disease that coincidental to hypoglycemia. Moreover, the expression 'hypoglycemia *associated* with hyperinsulinemia' in claim 1 leaves the skilled reader in doubt as to which forms of hypoglycemia fall under the scope of the claims, thus rendering the claim unclear. The term 'associated' itself is unclear and is not equivalent to 'caused by'.
- 36 None of the peptides are defined by SEQ ID Nos., thus rendering the scope of claims 4-9 unclear in the sense of Article 6 PCT.
- 37 In so far as the claims define peptides in the context of the treatment of hypoglycemia and wherein these latter technical effects have not been substantiated in the present application at the effective date of filing of the application, it is considered that the subject matter of claims 1-9 and 13-14 contravenes the provisions of Article 5 PCT (sufficiency of disclosure). In this

regard, it has not been presently established that the technical effects which are defined in the claims are achievable in the context of the claimed invention. Whereas it is not absolutely necessary for a therapeutic effect to have been demonstrated clinically in order for a second medical use claim to be deemed sufficiently disclosed, the effect shown in the application must directly and unambiguously reflect the therapeutic applications which are the subject of the claims. This is not the case here; the examples of the present application merely show an angiogenic effect without establishing a link to the claimed disease.

European Patent Office
80298 Munich

13 May 2024

International Patent Application No : PCT/NL2023/050374 published as WO 2024/014953
Biotempt B.V.,
TREATING CONDITIONS WITH HYPOGLYCEMIA ASSOCIATED WITH HYPERINSULINEMIA
Our Ref: AMS-202324PC JRE/XHU/XHU

1. This letter accompanies a Demand for International Preliminary Examination on the above case under Chapter II PCT. As indicated on the enclosed Fee Sheet, it is requested that the fee for International Examination and the Handling fee be debited from deposit account number 28090458, held in the name of Simmons & Simmons Intellectual Property LLP. If incorrect amounts are specified on the Fee Sheet, please deduct the correct amounts.

Amendments under Article 34 PCT

2. In response to the Written Opinion accompanying the International Search Report mailed on 4 October 2023, the Examiner is requested to replace the set of claims currently on file with the attached amended set of claims. It is requested that International Preliminary Examination be carried out on the basis of amended claims filed herewith.

3. Basis for amendments filed herewith is explained in more detail below.

4. Former claim 1 has been amended to incorporate the feature of claim 4 of the PCT application as filed. It has also been amended to specify congenital hyperinsulinemia, based on the disclosure on page 1, lines 13-14 of the PCT application as filed.

5. Former claim 4 has been deleted. Former claims 5 to 15 have been renumbered as amended claims 4 to 14, and their dependencies have been updated accordingly.

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6. Former claims 7 and 8, now renumbered as amended claims 6 and 7, have also been amended to specify that the lowercase letters indicate D-amino acids and the uppercase letters indicate L-amino, with the notable exception of glycine, wherein both g and/or G indicate the amino acid glycine, for the purpose of enhanced clarity. Basis for this can be found, for example, on page 10, lines 15-17 of the PCT application as filed.

7. Former claim 14, now renumbered as amended claim 13, has been amended to be brought into consistency with amended claim 1.

8. For the avoidance of doubt, no subject matter deleted from the claims is hereby abandoned and the Applicant reserves the right to reintroduce that subject matter, for example, in national or regional phase applications derived from the present PCT application.

Response to Objections Raised in the Written Opinion

9. The following submissions are provided in response to the objections raised in the Written Opinion accompanying the International Search Report:

Item V – Novelty

10. The Applicant respectfully submits that none of the cited prior art documents discloses the present invention as claimed, namely a C-peptide for use in the treatment of hypoglycemia associated with hyperinsulinemia in congenital hyperinsulinemia.

11. In particular, D1 discloses the use of C-peptide to reduce the risk of hypoglycemia in a patient with insulin dependent diabetes having been provided with exogenous insulin. However, there is no disclosure in D1 of the use of a C-peptide to reduce the risk of hypoglycemia, or for that matter the use of a peptide functionally equivalent to C-peptide, in a non-diabetic subject having not been provided with exogenous insulin, such as a subject with congenital hyperinsulinism.

12. D3 discloses an antibody or fragment thereof to use in a method of treating hypoglycemia in congenital hyperinsulinism. However, there is no disclosure in D3 of any C-peptide or any peptide functionally equivalent to C-peptide or the use of it to reduce the risk of hypoglycemia in congenital hyperinsulinism.

13. As acknowledged by the Examiner in §8, §13 and §16 of Item V, none of D2, D4 and D5 discloses the treatment of hypoglycemia. D6 was published after the priority date of the current application, and therefore does not form part of the prior art.

14. It is therefore respectfully submitted that the present invention is novel over the prior art.

Item V - Inventive Step

15. It is suggested in §18 to §30 of the Written Opinion that the present invention lacks an inventive step over the prior art. In particular, the Examiner is of the view that “none of the examples show any effect that would plausibly give rise to a treatment of hypoglycemia” (see §26 of Item V of the Written Opinion). The Applicant respectfully disagrees.

16. It is disclosed in the current application that the mechanism of action of the modulator of the present invention is to create insulin resistance in hyperinsulinemic patients, thereby reducing (GLUT4-mediated) glucose uptake and promote increased blood glucose levels (see page 9, lines 1 to 4 of the description). The Examples of the current application demonstrate the angiogenic activities of the modulators of the present invention. For example, Example 4 (and Figure 4) shows the effects of three elastin fragment peptides and related GXXP-peptides on endothelial cell sprouting. Angiogenic activities are known to have an effect on insulin resistance, which in turn is used to treat hyperinsulinemic patients.

17. Claim 1 as amended now specifies congenital hyperinsulinemia, and therefore D3 may be considered the closest prior art for the assessment of inventive step because it is in the field of treatment of congenital hyperinsulinemia. As already discussed above in §12, there is no disclosure in D3 of any C-peptide or any peptide functionally equivalent to C-peptide or the use of it to reduce the risk of hypoglycemia in congenital hyperinsulinism. There is no such disclosure in any other cited documents either. The skilled person would not have found anything that would prompt him or her to modify the method and product of D3 in the direction of the present invention as claimed.

18. It is therefore respectfully submitted that the present invention as claimed is inventive over the prior art.

Item VIII

19. The Applicant wishes to delay any amendments and/or arguments in response to Item VIII of the Written Opinion until the national phases.

Concluding remarks

20. It is believed that all the patentability objections raised have been addressed and a positive International Preliminary Report on Patentability may now be issued.

21. For the sake of expediting prosecution, the Examiner is kindly requested to contact the undersigned by telephone in the event that any objections remain outstanding. In the event that the Examiner contemplates issuing a negative opinion concerning the patentability of the present International application, it is requested that a second written opinion be issued

under Rule 66.4 PCT setting out the nature of any objections in a reasoned statement in accordance with the procedure set out in the notice of 31 August 2011 (OJ EPO 10/2011, 532).

Yours faithfully,

A handwritten signature in black ink, appearing to read 'Xingye Huang', written in a cursive style.

Dr. Xingye Huang
European Patent Attorney

Enclosure: Amended Claims 1 to 14 (mark-up)
Amended Claims 1 to 14 (clean)

CLAIMS (clean)

- 1 A modulator of insulin-insulin receptor signaling for use in the treatment of a mammalian subject deemed having episodes of hypoglycemia associated with hyperinsulinemia in congenital hyperinsulinemia, wherein said modulator is provided with a molecule carrying an elastin receptor binding motif.
- 2 The modulator for use according to claim 1, wherein said subject is a primate or a rodent.
- 3 The modulator for use according to claim 1 or 2, wherein said modulator is capable of reducing insulin-induced translocation of glucose transporter 4 (GLUT4) to the plasma membrane of a fat- or muscle-cell of said subject.
- 4 The modulator for use according to any one of claims 1 to 3, wherein said modulator is provided with a molecule carrying an elastin receptor binding motif that is at least functionally equivalent to a peptide XGXXPG wherein G stands for the amino acid glycine, P for proline and X for any amino acid.
- 5 The modulator for use according to any one of claims 1 to 4, wherein said modulator comprises a peptide or peptidomimetic carrying an elastin receptor binding motif that is at least functionally equivalent to a peptide XGXXPG wherein G stands for the amino acid glycine, P for proline and X for any amino acid.
- 6 The modulator for use according to claim 5, wherein said peptide with said motif is selected from the group of peptides at least functionally equivalent to any of a peptide VGVAPG(n), vGVAPG(n), vGvAPG(n), vGVaPG(n), vGvaPG(n), gpavgv(n) PGAVPG(n), pGvAPG(n), pGVaPG(n), pGvaPG(n), gpvagp(n), LGGGPG(n), IGGGPG(n), gpgggI(n), PGAYPG(n), pGAYPG(n), pGaYPG(n), pGAyPG(n), pGayPG(n), or gpyagp(n), AQGVAPG(n), gpavgqa(n), LQGVAPG(n), gpavgql(n), wherein lowercase letters indicate D-amino acids, whereas uppercase letters indicate L-amino acids, with the notable exception of glycine, wherein both g and/or G indicate the amino acid glycine and wherein (n) indicates the number of occurrences of said motif and wherein (n) varies from 1 to 8, allowing targeting of the modulator to the elastin receptor.
- 7 The modulator for use according to claim 5, wherein said peptide with said motif is selected from the group of peptides at least functionally equivalent to any of a peptide VGVAPG(n), gpavgv(n) PGAVPG(n), gpvagp(n) wherein lowercase letters indicate D-amino acids, whereas uppercase letters indicate L-amino acids, with the notable exception of glycine, wherein both g and/or G indicate the amino acid glycine and wherein (n) indicates the number of repeat occurrences of said motif and wherein (n) varies from 1 to 8, allowing targeting of the modulator to the elastin receptor.

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- 8 The modulator for use according to claim 5, wherein said peptide with said motif is at least functionally equivalent to a peptide VGVAPGVGVAPGVGVAPG, QVGQVELGGGPGAGSLQP or GAYPGAPGAYPGAPAPGV.
- 9 The modulator for use according to claim 5, wherein said peptide with said motif is at least functionally equivalent to a peptide VGVAPGVGVAPGVGVAPG or AVPGAVPGAVPG.
- 10 A pharmaceutical composition comprising the modulator as defined in any one of claims 1 to 9.
- 11 The pharmaceutical composition according to claim 10, formulated for parenteral application.
- 12 The pharmaceutical composition according to claim 10, formulated for oral application.
- 13 A method for treatment of a mammalian subject deemed having episodes of hypoglycemia associated with hyperinsulinemia in congenital hyperinsulinemia, comprising administering to said subject the modulator as defined in any one of claims 1 to 9, or a pharmaceutical composition according to any one of claims 10 to 12.
- 14 The method according to claim 13, wherein said subject is a primate or a rodent.

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