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(54) Title: GLP-1 AND EXENDIN RELATED INVENTION

(54) Bezeichnung: ERFINDUNG BETREFFEND GLP-1 UND EXENDIN

(57) Abstract: The invention relates to peptides derived from GLP-1 (Glucagon-like Peptide 1) and exendin-3 and/or exendin-4, which bind to GLP-1 receptors and may be used either marked or unmarked for the production of a means for diagnosis and therapy of benign and pernicious diseases in which GLP-1 receptor expression plays a role.

(57) Zusammenfassung: In der vorliegenden Erfindung werden Peptide abgeleitet von GLP-1 (Glucagon-like Peptide-1) und Exendin-3 und/oder Exendin-4 bereitgestellt, die an den GLP-1-Rezeptor binden und unmarkiert oder markiert zur Herstellung eines Mittels zur Diagnostik und Therapie gut- und bösartiger Erkrankungen, bei denen die GLP-1 Rezeptorexpression eine Rolle spielt, eingesetzt werden.

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Invention concerning GLP-1 and exendin

The invention at hand concerns a method for the production of a pharmakon for the depiction and therapy of primarily gastroenteropancreatic tumors, but also
20 other benign and malignant diseases of different organ systems, based upon the incretin hormone GLP-1 and the analogs thereof.

Description and Introduction of the general field of the invention

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In the localization of gastroenteropancreatic neuroendocrine tumors, somatostatin receptor scintigraphy (SRS) is the most important diagnostic method next to
5 ultrasound. The principle here is the specific depiction of tumors with the help of radioactively labeled peptides, which are absorbed by the tumor cells. Then, with the help of gamma cameras, the accumulation of the radioactivity in the tumor tissue can be verified visually. When a type of tumor possesses one of the necessary receptors for SRS, e.g. for the somatostatin analog octreotide[®],
10 verification of these tumors is unproblematic. If corresponding receptors are not expressed, however, they evade scintigraphic verification. In addition to localization diagnosis, radioactive labeled peptides also allow for an approach to the treatment of tumors in which one can implement a specific receptor-directed radiopeptide therapy through labeling a somatostatin analog, e.g. octreotide[®], with
15 an appropriate radionuclide (α - or β - emitter). The fact that the corresponding radionuclides are bound chemically by the peptide (e.g. through complexation with a metal chelator which was previously bound to that peptide) in such a way that they will indeed be absorbed by the tumor cells but can no longer be discharged, results in a high specific accumulation in the tumor tissue.

20

However, a whole series of neuroendocrine tumors (NET), among them insulinomas and small cell bronchial carcinomas, do not express the necessary subtypes of the somatostatin receptor which are essential for SRS or radiopeptide therapy with the somatostatin analog octreotide[®]. A substantial percentage of
25 insulinomas in particular are not detectable by scintigraphic diagnosis. In small cell bronchial carcinomas SRS also does not constitute an appropriate method as, although primary tumors are often visible, metastases are not able to be shown due to loss of receptor expression. Consequently they are inaccessible for radiopeptide therapy, which presents an interesting additional or alternative
30 therapy method. Therefore the need exists for an appropriate peptide, which will be absorbed by the previously mentioned tumors.

The incretin hormone glucagon-like peptide-1 (GLP-1), as well as its analogs exendin-3 and exendin-4 (from the saliva of the gila monster *Heloderma horridum* and *Heloderma suspectum*), are peptides, for which insulinomas and small cell bronchial carcinomas - along with many other kinds of tumors -
5 express receptors. Insulinomas originate from the insulin producing β -cells in the islet of Langerhans in the pancreas, in which GLP-1 as well as exendin-3 and exendin-4 elicit a postprandial insulin secretion.

Throughout this specification the word "comprise", or variations such as
10 "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

15 Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

20

Technical state of the art

For the utilization of glucagon-like peptide-1 (GLP-1) in scintigraphy it is necessary to label the peptide. The method for that and for the labeling of
25 proteins with radionuclides is known to the expert and documented in numerous patent applications (e.g. DE 690 18 226 T2) and scientific publications. The peptides described there for application in diagnostic imaging and for the exchange of therapeutically effective molecules in pathological tissue are normally inserted on the N-terminal end through an amino in the
30 peptide. The peptides must be further modified concurrently regarding stabilization.

The GLP-1 used in the US 2003/0232761A1 and its derivative GLP-1(7-37) are, for example, modified on the N-terminal end by one amino. Hence, the N-terminal end of GLP-1 is no longer available to bond a GLP-1 receptor, therefore both receptor bonding and internalization is inadequate in these

5 peptides. The latter are thus inappropriate for utilization in radiopeptide therapy of insulinomas and small cell bronchial carcinomas. As experience shows, a mutation, such as a substitution of an amino acid within the sequence of peptides of GLP-1 and exendin 3 or exendin 4, and their possible modifications through a therapeutic or a signaling molecule most often causes damage to

10 the peptide structure, Obstructing any further bonding to the receptor.

A further method for the modification of GLP-1, without affecting the N-terminus, is not known at this time. Furthermore, no GLP-1 derivatives are known which are appropriate, either labeled or unlabeled, for use in the radiotherapy of insulinomas and small cell bronchial carcinomas.

Task

The task of the invention at hand, therefore, is to eliminate the deficiency of the technological state of the art and make peptides available which can be labeled and still bond the GLP-1 receptor with this labeling and be utilized in the
5 production of an agent for the diagnosis and therapy of diseases, in which the expression of the GLP-1 receptor plays a role.

Solution of the task

This task is solved, based on the present invention, by the claims, through peptide
10 derivatives of GLP-1, exendin-3 and exendin-4, which are modified by an amino at the C-terminus and bond via the N-terminus at the GLP-1 receptor as well as chimeric peptides of GLP-1 with exendin-3 or exendin-4. These peptide derivatives as well as the chimeric peptides are being unlabeled or labeled in order to be utilized in the production of an agent for diagnostic and therapy of
15 benign or malignant diseases in which GLP-1 receptor expression plays a role.

Through these peptide derivatives of GLP-1, exendin-3 and exendin-4 as well as chimeric peptides of GLP-1, exendin-3 or exendin-4 the production of a means for scintigraphic applications is carried out which will be utilized for diagnostic and
20 therapy of GLP-1 receptor expressing tumors, including NET (especially from insulinomas) and small cell bronchial carcinomas.

This is possible for the first time, as the peptide derivatives based on the current invention are modified by an amino at the C-terminus, making thus available the N-terminus for bonding to the GLP-1 receptor.
25

Through the bonding of the peptide derivatives based on the current invention, for instance radioactively labeled, and chimeric peptides of GLP-1, exendin-3 and extending-4 to the GLP-1 receptor, the representation of GLP-1 receptor expressing tumors is possible, enabling hereby a considerable improvement of the
30 patients' medical care. NET are, above all, gastroenteropancreatic NET, such as insulinomas, for which to date no non-invasive method with sufficient sensitivity is available or of small cell bronchial carcinomas localized in the area of the lung in which case the specific differentiation between inflammable processes and tumors or metastases is neither possible by means of a non-invasive method.

Furthermore, by means of the peptide derivatives and the chimeric peptides, both based in the current invention, the density of insulin producing cells within the pancreas as well as the expression of GLP-1 receptors *in vivo* and *in vitro* are visualized. This is for instance in the representation of GLP-1 receptor expressing
5 cells in the case of the diabetes mellitus a *in vivo* representation, as these are the cells which also secrete insulin. The representation of the GLP-1 receptor density within the pancreas is particularly important in the case of patients with diabetes mellitus during and after therapy with pharmaceuticals.

Additionally the distribution of GLP-1 receptors in malignant and benign tissues is
10 represented. The articulated questions are hereby both of clinical as well as of scientific nature, as there is to date no all inclusive data available concerning the arrangement of GLP-1 receptors in human beings.

Thus, the advantage of the current invention is that peptide derivatives of GLP-1
15 (glucagon-like peptide-1), exendin-3 and exendin-4 as well as chimeric peptides of GLP-1, exendin-3 or exendin-4 are utilized for the production of an agent, especially for the receptor-oriented specific representation and therapy, particularly of NET, in the case at hand especially of insulinomas and small cell bronchial carcinomas.

20 A GLP-1 receptor scintigraphy is particularly applicable in the diagnosis of small cell bronchial carcinomas, allowing for the first time the specific detection of metastases within lymph nodes (lymph nodes changed by inflammation versus lymph nodes attacked by metastases).

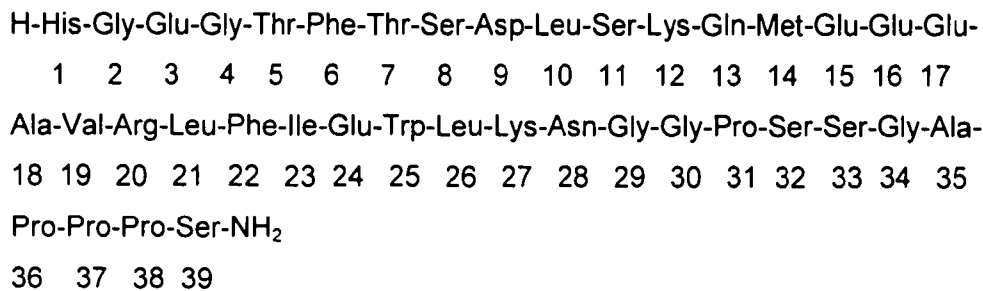
The application of peptide derivatives from (glucagon-like peptide-1), exendin-3
25 und exendin-4, as well as chimeric peptide from GLP-1, exendin-3 or exendin-4 according to the current invention remains an agent of diagnostic and therapy for all malignant and benign diseases in which GLP-1 receptor expression plays a role, in particular in the following: as a contrast agent in Magnetic Resonance Imaging (MRI); as a radioactive agent in scintigraphy (SPECT, Single Photon
30 Emission Computed Tomography) as well as in radiopeptide therapy; in PET (Positron Emissions Tomography); in receptor-mediated chemotherapy; and in optical diagnostic. Optical diagnostic here means the stimulation of a fluorescent molecule by a particular wave length, inducing a successive light emission of a different wave length. It is the emitted wave length which is detected.

An expert can easily choose the kind of labeling at the C-terminus of the peptide derivative from GLP-1 (glucagon-like peptide-1), exendin-3 and exendin-4 as well as the chimeric peptides from GLP-1, exendin-3 or exendin-4 depending on the desired application: for example, for scintigraphy or radiotherapy from radioactive nuclides; for contrast agent in Magnetic Resonance Imaging (MRI) from gadolinium; and for endoscopic or scientific examinations from fluorescent pigments.

According to the current invention malignant diseases are those in which the affected tissue shows changes in its level of differentiation as compared to healthy tissue, invasive growth or a spreading of its tissue into the blood stream or lymphatic system. All neuroendocrine tumors fall into this category, in particular those of the gastrointestinal tract; especially insulinomas, bronchial carcinomas, pancreatic carcinomas and all other malignant diseases which are connected to the over-expression of GLP-1 receptors.

According to the current invention benign diseases are those characterized by the fact the affected tissue does not significantly lose its level of differentiation, shows no invasive growth and does not have any tissue metastasis into the blood stream or lymphatic system. This includes, for example, diabetes mellitus, but also eating disorders of disorders of the psyche.

According to the invention there is also provided a peptide derivatives of exendin-4, wherein their C-terminus is modified by an amine and wherein their N-terminus binds to the GLP-1 receptor, with a sequence identity of over 90% to the amino acid sequence of exendin-4:



wherein the peptide derivatives are based on exendin-4 (1-39)A

with A being an attachment group comprising of one or more amino acids or its derivatives as a signal molecule, or to bond signal molecules or to stabilize them, which is located at the C-terminus and represents an amine, wherein a chelator is coupled with attachment group A for the labeling with radionuclides.

5

According to the invention there is also provided peptide derivatives of exendin-4, wherein their N-terminus binds to the GLP-1 receptor, with a sequence identity of over 90% to the amino acid sequence of exendin-4:

10 H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-
 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
 Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-
 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
 Pro-Pro-Pro-Ser-NH₂
 36 37 38 39

15 wherein the peptide derivatives are based on exendin-4 (1-39)A

with A being an attachment group comprising of one or more amino acids or its derivatives located at the C-terminus, wherein a chelator is coupled with attachment group A and labelled with a radionuclide.

20 According to the invention, there is also provided peptide derivatives of exendin-4, wherein their N-terminus binds to the GLP-1 receptor, with the amino acid sequence of exendin-4:

25 H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-
 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
 Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-
 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
 Pro-Pro-Pro-Ser-NH₂
 36 37 38 39

wherein the peptide derivatives are based on exendin-4 (1-39)A

30 with A being an attachment group comprising of one or more amino acids or its derivatives located at the C-terminus, wherein a chelator is coupled with attachment group A and labelled with a radionuclide.

35 According to the invention there is also provided use of peptide derivatives from exendin-4, according to the above mentioned claims for the production of an agent for diagnostic and therapy of benign and malignant diseases, in which the GLP-1 receptor expression plays a role.

According to the invention there is also provided an application of peptide derivatives from exendin-4 according to the invention in order to determine the density of insulin producing cells in a tissue.

- 5 According to the invention there is also provided an application of peptide derivatives from exendin-4 according to the invention in order to determine the expression of GLP-1 receptors or their density.

10 According to the invention there is also provided an agent for the diagnostic and therapy of benign and malignant diseases, in which GLP-1 receptor expression plays a role, wherein it contains labeled peptide derivatives of exendin-4 according to the invention.

15 According to the invention there is also provided an agent for the diagnostic and therapy of benign and malignant diseases, in which GLP-1 receptor expression plays a role, wherein it contains unlabeled peptide derivatives from exendin-4 according to the invention.

20 According to the invention there is also provided an agent according to the invention wherein the labeling contains a coupling of radionuclides, MRI contrast agents, fluorescent pigments and/or chemotherapeutic agent.

25 According to the invention there is also provided use of an agent according to the invention for diagnostic and therapy of benign and malignant diseases, in which GLP-1 receptor expression plays a role.

30 According to the invention there is also provided use of an agent according to the invention for diagnostic and therapy of neuroendocrine tumors (NET), particularly insulinomas and small cell bronchial carcinomas.

According to the invention there is also provided use of an agent according to the invention in scintigraphy, PET, SPECT, MRI, optical diagnostic, receptor-mediated chemotherapy, receptor-mediated, cytostatic or cytotoxic therapy and radiopeptide therapy.

Characterization of peptide derivatives and chimeric peptides

Surprisingly it was found that peptide derivatives from GLP-1, exendin-3 and exendin-4, as well as chimeric peptides from GLP-1, exendin-3 or exendin-4, which are modified via an amino at the C-terminus, bond at the N-terminus to the GLP-1 receptor. They even shown a high degree of affinity to the GLP-1 receptor, as do natural peptides. Experiments with tumor carrying hairless mice show a specific uptake in GLP-1 receptors of positive tumor tissue.

Peptide derivatives as well as chimeric peptides according to the current invention are unlabelled or, via a chelator at the C-terminus amino, labeled as an agent for application in the diagnostic and therapy of benign and malignant diseases in which GLP-1 receptor expression plays a role. The type of labeling here consists
 5 mainly of a radiometal, a MRI contrast agent, a fluorescent chromophore or a chemotherapeutic agent.

The process and method of labeling are well known to an expert (e.g. DE 690 18 226 T2), which take place, for example, through the coupling of radionuclides,
 10 non-magnetic metals and other MRI contrast agents or fluorescent pigments; this means that the bonding of the receptors or the internalization of the peptide derivatives, as well as the chimeric peptides according to the current invention, are not impaired and the GLP-1 receptor bonding N-terminus remains free (unlinked).

15

The sequences of amino acids of the original peptides:

GLP-1:

20 H-His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser- Asp-Val-Ser-Ser-
 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
 Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly-OH
 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37

25 **Exendin-3:**

H-His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-
 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
 Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-
 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37
 30 Pro-Ser-NH₂
 38 39

Exendin-4:

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-
 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
 Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-
 5 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37
 Pro-Ser-NH₂
 38 39

According to the current invention the following peptide derivatives of GLP-1 (1-
 10 37), exendin-3 and exendin-4 are produced:

GLP-1(x-y)A¹⁻³⁷

Exendin-3 (z-k)A¹⁻⁴⁰

15 **Exendin-4 (z-k)A¹⁻⁴⁰**

Whereby:

x= amino acids 1-36 of the GLP-1 amino acid sequence

20 y= amino acids 2-37 of the GLP-1 amino acid sequence

z= amino acids 1-38 of the exendin-3 or exendin-4 amino acid sequence

k= amino acids 2-39 of the exendin-3 or exendin-4 amino acid sequence

A = Attachment group consisting of one or more amino acid or its derivative as a
 25 signal molecule, or to bond signal molecules or to stabilize them. The preference
 is for A to be located at the C-terminus and the amino is preferably lysine or
 alternatively another amino acid with a free amino, e.g. ornithine or an organic
 group with a free amino onto which a chelator is coupled for the labeling with
 radionuclides or a MRI contrast agent, fluorescent pigments or a
 30 chemotherapeutic agent.

Chelators which can be used include DTPA (diethylenetriaminepentaacetic acid), alternatively N,N-Bis(2-[bis(carboxymethyl)amino]-ethyl)glycine), alternatively DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra-acetic acid), HYNIC (6-hydrazinopyridin-3-carbonic acid), MAG3 (mercaptoacetyl-glycylglycylglycine), N4
 5 (1,4,8,11-tetraazaundecane) and all known derivatives of the above named chelators.

The exponent indicates at which position the attachment group alternatively can be found within the amino acid sequence.

10 GLP-1(x-y)A¹⁻³⁷

Here GLP-1 derivatives of different lengths are included, whereby x can accept the numbers 1 to 36, which is smaller than y, which accepts the numbers 2 to 37. A is the attachment group which can be placed at any position, preferably however at the C-terminus and is one higher than y. Preferably, the attachment
 15 group is the amino lysine.

Exendin-3 (z-k)A¹⁻⁴⁰

Here exendin-3 derivatives of different lengths are included, whereby z can accept the numbers 1 to 38, which is smaller than k, which accepts the numbers 2 to 39.
 20 A is the attachment group which can be placed at any position, preferably, however, at the C-terminus and is one higher than y. Preferably, the attachment group is the amino lysine.

Exendin-4 (z-k)A¹⁻⁴⁰

25 Here exendin-4 derivatives of different lengths are included, whereby z can accept the numbers 1 to 38, which is smaller than k, which accepts the numbers 2 to 39. A is the attachment group which can be placed at any position, preferably, however, at the C-terminus and is one higher than y. Preferably, the attachment group is the amino lysine.

30 The following peptide derivatives are particularly preferred:

1. MC 10: (DTPA-Lys³⁷) GLP1 (7-36) amide
2. MC 13: (DTPA-Lys⁴⁰) exendin-3 amide
3. MC 11: (DTPA-Lys⁴⁰) exendin-4 amide

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The synthesis takes place, for example, in the company Peptide Specialty Laboratories GmbH according to the Merrifield method and purification via HPLC.

- 5 MC 10 (DTPA-Lys³⁷) GLP1 (7-36) amide consists of the amino acids 7-36 of GLP-1, carrying at the C-terminal end as an amino acid with a free amino, preferably lysine at position 37 as well as the chelator DTPA.

- 10 MC 13 (DTPA-Lys⁴⁰) exendin-3 amide consists of the complete amino acid sequence of exendin-3, carrying at the C-terminal end as an amino acid with a free amino, preferably lysine at position 40 as well as the chelator DTPA.

- 15 MC 11 (DTPA-Lys⁴⁰) exendin-4 amide consists of the complete amino acid sequence of exendin-3, carrying at the C-terminal end as an amino acid with a free amino, preferably lysine at position 39 as well as the chelator DTPA.

According to the current invention the following chimeric peptides from GLP-1 (1-37) and exendin-3 or exendin-4 are produced:

20 **GLP-1(x-y) exendin-3(z-k)A¹⁻⁷⁵**

GLP-1(x-y) exendin-4(z-k)A¹⁻⁷⁵

Exendin-3(z-k) GLP-1(x-y)A¹⁻⁷⁵

Exendin-4(z-k) GLP-1(x-y)A¹⁻⁷⁵

- 25 Here the following applies:

x= amino acids 1-36 of the GLP-1 amino acid sequence

y= amino acids 2-37 of the GLP-1 amino acid sequence

z= amino acids 1-38 of exendin-3 or exendin-4 amino acid sequence

k= amino acids 2-39 of exendin-3 or exendin-4 amino acid sequence

30

A = Attachment group consisting of one or more amino acid or its derivative as a signal molecule, or to bond signal molecules or to stabilize them. The preference is for A to be located at the C-terminus and the amino is preferably lysine or

alternatively another amino acid with a free amino, e.g. ornithine or an organic group with a free amino onto which a chelator is coupled for the labeling with radionuclides or a MRI contrast agent, fluorescent pigments or a chemotherapeutic agent.

- 5 Chelators which can be used include DTPA (diethylenetriaminepentaacetic acid), alternatively N,N-Bis(2-[bis(carboxymethyl)amino]-ethyl)glycine), alternatively DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra-acetic acid), HYNIC (6-hydrazinopyridin-3-carbonic acid), MAG3 (mercaptoacetyl-glycylglycylglycine), N4 (1,4,8,11-tetraazaundecane) and all known derivatives of the above named
10 chelators.

The exponent indicates at which position the attachment group alternatively can be found within the amino acid sequence.

15 **GLP-1(x-y) exendin-3(z-k)A¹⁻⁷⁵**

Here chimeric peptides from GLP-1 and exendin-3 are included, in which the amino acids 1 to 36 come from GLP-1 and then after that the amino acids 1 to 39 from exendin-3. A is the attachment group which can be placed at any position, preferably, however, at the C-terminus, and is one higher than the number of
20 amino acids from GLP-1 and exendin-3, preferably the amino lysine.

GLP-1(x-y) exendin-4(z-k)A¹⁻⁷⁶

Here chimeric peptides from GLP-1 and exendin-3 are included, in which the amino acids 1 to 36 come from GLP-1 and then after that the amino acids 1 to 39
25 from exendin-4. A is the attachment group which can be placed at any position, preferably, however, at the C-terminus, and is one higher than the number of amino acids from GLP-1 and exendin-4, preferably the amino lysine.

Exendin-3(z-k) GLP-1(x-y)A¹⁻⁷⁵

30 Here chimeric peptides from exendin-3 and GLP-1 are included, whereby z can accept the numbers 1 to 38, but is smaller than k, which can accept the numbers 2 to 39. A is the attachment group which can be placed at any position, preferably,

however, at C-terminus and is one higher than y. Preferably, the attachment group is the amino lysine.

Exendin-4(z-k) GLP-1(x-y)A¹⁻⁷⁵

- 5 Here chimeric peptides from exendin-4 and GLP-1 are included, whereby z can accept the numbers 1 to 38, but is smaller than k, which can accept the numbers 2 to 39. A is the attachment group which can be placed at any position, preferably, however, at C-terminus and is one higher than y. Preferably, the attachment group is the amino lysine.

10

Exemplary for a chimeric GLP-1(x-y) exendin-3(z-k)A¹⁻⁷⁵ or GLP-1(x-y) exendin-4(z-k)A¹⁻⁷⁵ peptide is MC12, consisting of GLP-1 (7-36) exendin (33-39) Lys amide (Synthesis takes place in the company Peptide Specialty Laboratories GmbH

- 15 according to the Merrifield method and purification via HPLC.).

MC 12: (Ser³⁷, Gly³⁸, Ala³⁹, Pro⁴⁰, Pro⁴¹, Pro⁴², Ser⁴³, DTPA-Lys⁴⁴ amide) GLP1 (7-36)

- 20 MC 12 consists of the complete amino acid sequence of GLP-1 (7-36), carrying at the C-terminal end an amino, preferably lysine at position 44 as well as the chelator DTPA, as well as a chain of 7 amino acids from exendin (33-39) Lys amide. Thus there is a chimeric peptide GLP-1 (7-36) exendin (33-39)Lys amide.

- 25 It is clear to the expert that hereby peptide derivatives of different lengths from GLP-1, exendin-3 and exendin-4, as well as chimeric peptides of different lengths from GLP-1, exendin-3 or exendin-4 exist, which contain various combinations of the amino acid sequences from GLP-1, exendin-3 and exendin-4 on which they are based.

- 30 The peptide derivatives from GLP-1, exendin-3 and exendin-4, as well as chimeric peptides from GLP-1, exendin-3 or exendin-4 based on the current invention, which are modified by an amino at the C-terminus and bond via the N-terminus at the GLP-1 receptor, also include molecules which are distinguishable at one or more positions from the peptide GLP-1, exendin-3 and exendin-4

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described above and have a high degree of homology to those sequences. Homology here means a sequence identity of at least 40 %, in particular an identity of 60 %, preferably over 80 % and especially preferably over 90 %. The deviation to the amino acid sequences described above could arise through
5 deletion, substitution and/or insertion

Furthermore, the chimeric peptides from GLP-1, exendin-3 or exendin-4 according to the current invention are also produced without any modifications to the C-terminus. They are particularly used in the production of an agent for the
10 therapy of diabetes.

GLP-1(x-y) exendin-3(z-k)

GLP-1(x-y) exendin-4(z-k)

Exendin-3(z-k) GLP-1(x-y)

15 **Exendin-4(z-k) GLP-1(x-y)**

MC 20: (Ser³³, Gly³⁴, Ala³⁵, Pro³⁶, Pro³⁷, Pro³⁸, Ser³⁹) exendin GLP1 (7-36)

MC 20 consists of the complete amino acid sequence of GLP-1 (7-36), carrying at the C-terminal end a chain of 7 amino acids from exendin (33-39). Thus there is
20 an unmodified chimeric peptide GLP-1 (7-36) exendin (33-39).

Labeling of the peptide derivatives and the chimeric peptides

Peptide derivatives as well as chimeric peptides according to the current invention are dissolved in a suitable stabilizing buffer, for example, in order to stabilize
25 metals, preferably in 0.5 M sodium acetate pH 5.4 with a concentration of approx. 10⁻³ M. Alternatively, for the stabilization of fluorescent pigments a buffer of ammonium acetate is preferable; for the stabilization of chemotherapeutic agent and contrast agents a physiological buffer is preferable.

The labeling occurs at the attachment group A through the coupling of
30 radionuclides, MRI contrast agents, fluorescent pigments or chemotherapeutic agent. Different methods are applied according to whether the application will be *in vitro* or *in vivo*.

The following are used as radionuclides for covalent or complex coupling:

Nuclide	Procedure in which applied	$t_{1/2}$ [h]	Emitted radiation	Energy [keV]	Type of coupling
F-18	PET	1,8	β^+	634	covalent
Cu-64	PET	12.7	β^+	1673	complex
Cu-67	therapy	61.8	β^- γ	391 184	complex
Ga-67	SPECT	79.2	γ	93/184/300	complex
Ga-68	PET	1.1	β^+	2921	complex
Y-86	PET	14.8	β^+ γ	1220 1076/1153	complex
Y-90	therapy	64.1	β^-	2280	complex
Tc-99m	SPECT	6	γ	140	complex
In-111	SPECT	67.2	γ	171/245	complex
I-123	SPECT	13.2	γ	158	covalent
I-124	PET	101	β^+ γ	2137/1534 602	covalent
I-131	therapy	192	γ β^-	364 606	covalent
Lu-177	therapy	158	γ β^-	208 112/208	complex
Re-186	therapy	88.8	γ β^-	137 1071	complex
Re-188	therapy	17	γ β^-	155/477/632 1965/2120	complex
Pt-193m	therapy	104	γ auger e^-	135	complex
Pt-195m	therapy	96	γ auger e^-	98	complex
Ac-225	therapy	240	γ α	99, 150	complex
At-211	therapy	7.2	γ auger e^-	687	complex covalent
Bi-213	therapy	0.76	γ α	440	complex
Sm-153	therapy	46	γ β^-	103	complex
Er-169	therapy	226	β^-	100	complex

PET (Positron Emissions Tomography), SPECT (Single Photon Emissions Computed Tomography)

Fluorescent pigments/ chromophores such as the following were used:

- 5 Fluorescein, Rhodamin, Coumarin, BODIPY, Pyrene (Cascade Blue), Lucifer Yellow, Phycobiliprotein, Cyanin, AlexaFluoro, Oregon Green, Texas Red and their derivatives.

- 10 Chelators which can be used include DTPA (diethylenetriaminepentaacetic acid), alternatively N,N-Bis(2-[bis(carboxymethyl)amino]-ethyl)glycine), alternatively DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra-acetic acid), HYNIC (6-hydrazinopyridin-3-carbonic acid), MAG3 (mercaptoacetyl-glycylglycylglycine), N4 (1,4,8,11-tetraazaundecane) and all known derivatives of the above named chelators.

15

MRI contrast agents which can be used include: gadolinium, manganese, iron, europium, copper, nickel, chrome, prasodymium, dysprosium or holmium or their compounds, but also the negative MRI contrast agents such as perfluorocarbone, as well as isotopes such as such as F-19, H-1, P-31, Na-19 for MRI spectroscopy.

- 20 Negative MRI contrast agents according to the current invention are those which obliterate the MRI signal or greatly weaken it, i.e. not amplifying it.

- 25 Chemotherapeutic agents which can be used include: alkylating agents, intercalators, antimetabolite, enzyme inhibitors and blockers and spindle poisons (for example alkylsulfonate, ethylimine, nitrosomonas (N. ureae), nitrogen mustard derivatives, folic acid analogs, purine analogs, pyrimidine analogs, podophyllin derivatives, taxane, vincaalcaloide, anthracycline, other cytostatic antibiotics, platinum compounds, camptothecin derivatives, different hormones,
- 30 growth factors, interferons or interleukins), otherwise the chemotherapeutic agents described in "Onkologie 2004/05", authors Preiss, Dornhoff, Hagmann, Schmiieder, published by Zuckschwerdtverlag, at pp. 230-287, but also all other cytostatic or cytotoxic substances.

Depending on the type of application in which the protein derivatives and chimeric proteins according to the current invention are used, and the agent produced with the above mentioned proteins for diagnostic and therapy of benign and malignant diseases, in which GLP-1 receptor expression plays a role, the labeling reaction will be carried out in two variations.

Labeling for *in vitro* application in radiotherapy

3 μL of the peptide derivative or the chimeric peptide according to the invention which has been dissolved in a suitable stabilizing buffer, preferably 0.5 M sodium acetate pH 5.4 with a concentration of approx. 10^{-3} M, are added to 500 μL 0.5 M sodium acetate pH 5.4 for the purpose of labeling. The pH-value is between 3 and 6. Then 185 MBq $^{111}\text{InCl}_3$ (Tyco, Petten, The Netherlands) in 0.1 M HCl 500 μL is added and incubated for 30 minutes at 37°C . Finally 3 μL 10^{-3} M solution $^{\text{nat}}\text{InCl}_3$ is added, followed by a further incubation for 30 min in order to saturate all bond sites.

Quality control is carried out via a HPLC column:

Column: CC 250/4.6 Nucleosil 120-5 C18 (Machery-Nagel, Oenisingen, Switzerland)

20 Gradient: 0 \rightarrow 5 min 100% 0.05 M $\text{NH}_4\text{OOCCH}_3$, pH 5.4 (buffer A); 5 \rightarrow 25 min 100% buffer A \rightarrow 50% buffer A/50% acetone nitrile.

Quality control for an *in vitro* application is fulfilled with a labeling yield of over 98 %.

Thus a radioactive labeled agent is available for diagnostic and therapy of benign and malignant diseases, in which GLP-1 receptor expression plays a role, which can, for example, which can be employed in cell and tissue cultures of pancreatic cells.

Labeling for *in vivo* application in radiotherapy

30 3 μL of the peptide derivative or the chimeric peptide according to the invention which has been dissolved in a suitable stabilizing buffer, preferably 0.5 M sodium acetate pH 5.4 with a concentration of approx. 10^{-3} M, are added to 500 μL 0.5 M sodium acetate pH 5.4 for the purpose of labeling. Finally 185 MBq $^{111}\text{InCl}_3$ (Tyco,

Petten, The Netherlands) in 0.1 M HCl 500 μ L is added and incubated for 30 minutes at 37°C. Quality control is carried out via a HPLC-Column:

Column: CC 250/4.6 Nucleosil 120-5 C18 (Machery-Nagel, Oenisingen, Switzerland)

- 5 Gradient: 0→5 min 100% 0.05 M $\text{NH}_4\text{OOCCH}_3$, pH 5.4 (buffer A); 5→25 min 100% buffer A →50% buffer A/50% acetone nitrile.

Quality control for an in vivo application is fulfilled with a labeling yield of over 98 %.

- 10 Thus a radioactive labeled agent is available for diagnostic and therapy of benign and malignant diseases, in which GLP-1 receptor expression plays a role, which can, for example, be employed to detect tumors in patients.

- The term "patient" refers to humans and vertebrates alike. Thus, the agent can be applied both in human and veterinary medicine. The therapeutically and diagnostically effective agent based on the current invention is given to patients as part of an acceptable pharmaceutical composition in one of the following forms: oral, rectal, parenteral, intravenous / intraarterial, intramuscular, subcutaneous, intrathecal, intracisternal, intracranial, intravaginal, intraperitoneal, intravascular, local (powder, ointment or drops) or spray form (aerosol).
- 15
20

The required dose is to be determined by a doctor in each individual case of diagnostic and therapy of benign and malignant diseases, in which GLP-1 receptor expression plays a role.

25

Internalization study

- The internalization study shows, in exemplary manner, the transport into the cell of the peptide derivatives and chimeric proteins, both in vitro radioactively labeled, according to the current invention.
- 30

In a 6 well plate 100,000 GLP-1 receptor transfected CHO cells are sown. The cells grow until they are confluent. Then 4 groups are formed:

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Group 1: complete bonding, washed with PBS

100,000 cpm ^{111}In (10^{-15} Mol) labeled peptide is added to 2 mL medium and incubated for 1 h at 37°C . Then it is washed 3x with PBS and the cells are
5 separated with 20 mM MOPS (3-Morpholinopropanesulfonic-acid) + 0.1% Triton-X-100 (pH 7.4). The uptake into the cells is measured with a γ -counter. The number of cells is measured by the protein content, using the protein assay kit from Bio-Rad (Munich, Germany), based on the Bradford method. The results are given in proteins cpm/ μg .

10

Group 2: non-specific bonding, washed with PBS

20 μL of a 10^{-3} M GLP-1 solution and 100,000 cpm ^{111}In labeled peptide are added to 2 mL medium and incubated for 1 h at 37°C . Then it is washed 3x with PBS and the cells are separated with 20 mM MOPS (3-
15 Morpholinopropanesulfonic-acid) + 0.1% Triton-X-100 (pH 7.4). The uptake into the cells is measured with a γ -counter. The number of cells is measured by the protein content, using the protein assay kit from Bio-Rad (Munich, Germany), based on the Bradford method. The results are given in proteins cpm/ μg .

20 Group 3: complete bonding, washed with acid

20 μL of a 10^{-3} M GLP-1 solution and 100,000 cpm ^{111}In labeled peptide are added to 2 mL medium and incubated for 1 h at 37°C . Then it is washed 1x with 0.1 M sodium acetate buffer pH 4 and 2x with PBS and the cells are separated
25 (pH 7.4). The uptake into the cells is measured with a γ -counter. The number of cells is measured by the protein content, using the protein assay kit from Bio-Rad (Munich, Germany), based on the Bradford method. The results are given in proteins cpm/ μg .

30 Group 4: non-specific bonding, washed with acid

20 μL of a 10^{-3} M GLP-1 solution and 100,000 cpm ^{111}In labeled peptide are added to 2 mL medium and incubated for 1 h at 37°C . Then it is washed 1x with 0.1 M sodium acetate buffer pH 4 and 2x with PBS and the cells are separated

with 20 mM MOPS (3-Morpholinopropanesulfonic-acid) + 0.1% Triton-X-100 (pH 7.4). The uptake into the cells is measured with a γ -counter. The number of cells is measured by the protein content, using the protein assay kit from Bio-Rad (Munich, Germany), based on the Bradford method. The results are given in

5 proteins cpm/ μ g.

$$\text{Evaluation: \%IDsB} = \frac{\text{Res3.} - \text{Res4.}}{\text{Res1.} - \text{Res2.}} * 100$$

10 %IDsB = % of internalization of the specific bonding

	%IDsB
MC10	75 \pm 5
MC11	70 \pm 7
MC12	73 \pm 9

The results show that a good transport has taken place into the cells.

15 **Bonding studies**

Bonding studies show the specific bonding which takes place via the vivo-labeling radioactive labeled peptide derivatives and chimeric proteins according to the current invention onto the GLP-1 receptor.

In a 6-well plate 100,000 GLP-1 receptor transfected CHO cells are sown. The

20 cells grow until they are confluent. Then 2 mL 100,000 cpm ^{111}In labeled peptide is added. In order to test the bonding it is then blocked with 20 μ L of a 10^{-3} M GLP-1 solution.

	% Blocking
MC10	80 \pm 3
MC11	85 \pm 3
MC12	77 \pm 6

The *in vivo* bio-distribution can, for example, be shown in rodents such as hairless mice. For this purpose GLP-1 transfected CHO cells are injected into hairless mice. After approx. 3 to 5 weeks tumors approx. 300 mg in size had grown. The mice are then injected in a tail vein with 37 MBq ^{111}In labeled peptide according to the invention and are measured after 4 h under a γ -camera.

In the course of this procedure there was quick clearance via the kidneys and an uptake in the kidneys. There was also a high uptake in the GLP-1 receptor positive tumor, whereas the GLP-1 receptor negative tumor barely showed any uptake. There was also a slight uptake in the pancreas; other organs showed no visible uptake.

Ex vivo bio-distribution studies are conducted in groups of 4 mice each, in which 555 kBq In-111 labeled MC10 is injected into the tail vein. 1, 4 und 24 h p.i. all the mice are killed and their organs removed.

The uptake of radioactivity is measured and the organs are weighed. The % of injected dose pro gram of organ weight is calculated.

The results are as follows:

Organ	1 h	Stadev	4 h	Stadev	24 h	Stadev
Blood	0.01	0.00	0.00	0.00	0.00	0.00
Liver	0.03	0.01	0.01	0.01	0.01	0.00
Stomach	0.14	0.10	0.13	0.07	0.07	0.06
Spleen	0.02	0.02	0.01	0.00	0.01	0.00
Pancreas	0.58	0.50	0.62	0.28	0.37	0.27
Kidneys	7.90	3.62	7.41	3.56	4.85	3.05
Intestine	0.12	0.06	0.07	0.06	0.04	0.03
Lungs	0.80	0.56	0.36	0.17	0.22	0.07
Heart	0.02	0.01	0.01	0.01	0.00	0.00
Bones	0.02	0.04	0.01	0.00	0.01	0.01
Muscle	0.01	0.00	0.00	0.00	0.00	0.00
Tumor -	0.03	0.03	0.02	0.01	0.01	0.00
Tumor +	0.42	0.19	0.31	0.30	0.20	0.16

Mean value from the bio-distribution with 4 mice pro group in % i.D./g Stadev: standard deviation.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Peptide derivatives of exendin-4, wherein their N-terminus binds to the GLP-1 receptor, with the amino acid sequence of exendin-4:
- 5 H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-
 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
 Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-
 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
 Pro-Pro-Pro-Ser-NH₂
 10 36 37 38 39
- wherein the peptide derivatives are based on exendin-4 (1-39)A
 with A being an attachment group comprising of one or more amino acids or its derivatives located at the C-terminus, wherein a chelator is coupled with attachment group A and labelled with a radionuclide.
- 15 2. Peptide derivatives from exendin-4 according to claim 1, wherein the attachment group A is lysine.
3. Peptide derivatives from exendin-4 according to claim 1, wherein the
 20 attachment group A is an amino acid or an organic group comprising free amine.
4. Peptide derivatives according to claim 3, wherein the attachment group A is ornithine.
- 25 5. Peptide derivatives from exendin-4 according to any one of the above mentioned claims, wherein the chelator is selected from N,N-Bis(2-[bis(carboxymethyl)amino]-ethyl)glycine), DOTA (1,4,7,10-Tetraazacyclodecane-1,4,7,10-tetra-acetic acid), HYNIC (6-Hydrazinopyridin-3-carbonic acid), MAG3 (mercaptoacetyl-glycylglycylglycine), N4 (1,4,8,11-tetraazaundecane) and all known
 30 derivatives.
6. The peptide derivatives according to claim 5, wherein the chelator is DTPA (Diethylenetriaminepentaacetic acid).
- 35 7. Peptide derivatives from exendin-4 according to any one of the above mentioned claims, wherein the chosen radionuclide is selected from F-18, Cu-64, Cu-

67, Ga-67, Ga-68, Y-86, Y-90, Tc-99m, In-111, I-123, I-124, I-131, Lu-177, Re-186, Re-188, Pt-193m, Pt-195m, Ac-225, At-211, Bi-213, Sm-153 or Er-169.

8. Peptide derivatives from exendin-4 according to any one of the above
5 mentioned claims, wherein the labeling via the coupling of radionuclides for in vitro applications takes place through the saturation of the bonding sites with $^{nat}\text{InCl}_3$.
9. Use of peptide derivatives from exendin-4, according to any one of the above
10 mentioned claims for the production of an agent for diagnostic and/or therapy of benign and malignant diseases, in which the GLP-1 receptor expression plays a role.
10. Application of peptide derivatives from exendin-4 according to any one of
claims 1 to 8 in order to determine the density of insulin producing cells in a tissue.
- 15 11. Application of peptide derivatives from exendin-4 according to any one of
claims 1 to 8 in order to determine the expression of GLP-1 receptors or their density.
12. Agent for the diagnostic and/or therapy of benign and malignant diseases, in
20 which GLP-1 receptor expression plays a role, wherein it contains labeled peptide derivatives of exendin-4 according to any one of claims 1 to 8.
13. Use of an agent according to claim 12 for diagnostic and/or therapy of benign
and malignant diseases, in which GLP-1 receptor expression plays a role.
- 25 14. Use of an agent according to claim 12 or claim 13 for diagnostic and/or therapy
of neuroendocrine tumors (NET), particularly insulinomas and small cell bronchial carcinomas.
15. Use according to claim 14, wherein the neuroendocrine tumors are selected from
30 insulinomas and small cell bronchial carcinomas.
16. Use of an agent according claim 12 in scintigraphy, PET, SPECT, MRI, optical
diagnostic, receptor-mediated chemotherapy, receptor-mediated, cytostatic or cytotoxic
therapy and/or radiopeptide therapy.

17. A peptide derivatives of exendin-4 according to any one of claims 1 to 8, substantially as described herein with reference to any one or more of the Examples.
- 5 18. Use of peptide derivatives from exendin-4 according to any one of claims 9 or 13 to 16 substantially as described herein with reference to any one or more of the Examples.
- 10 19. Application of peptide derivatives from exendin-4 according to claim 10 or 11, substantially as described herein with reference to any one or more of the Examples.
- 15 20. Agent for the diagnostic and therapy of benign and malignant diseases according to claim 12 substantially as described herein with reference to any one or more of the Examples.

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