Title: PEPTIDES HAVING TrkA-RECEPTOR-AGONISTIC ACTIVITY OR HAVING NGF-ANTAGONISTIC ACTIVITY

Abstract: The invention relates to novel peptides and peptide fragments and their use. In particular the present invention relates to peptides and peptide fragments having TrkA-receptor-agonistic activity useful in treating, preventing or managing diseases or disorders such as peripheral neuropathies, multiple sclerosis, Alzheimer's disease, Parkinson's disease, hypoxic brain injuries, ischemic heart disease, heart failure, diabetes and its comorbidities, optic nerve atrophy, ulcers, neurotropic keratitis and/or glaucoma. The invention further relates to peptides and peptide fragments having TrkA antagonistic activity useful in treating, preventing or managing diseases or disorders such as pain, hyperinnervation, cardiac arrhythmias and sudden cardiac death.
PEPTIDES HAVING TrkA-RECEPTOR-AGONISTIC ACTIVITY OR HAVING NGF-ANTAGONISTIC ACTIVITY

TECHNICAL FIELD

The present invention relates to peptides and peptide fragments and their use. In particular, the present invention relates to peptides and peptide fragments having TrkA-receptor-agonistic activity and their use for the treatment of conditions, diseases and disorders benefiting from an increased activation of the TrkA-receptor, in particular for the treatment of peripheral neuropathies, multiple sclerosis, Alzheimer's disease, Parkinson's disease, hypoxic brain injuries and optic nerve atrophy.

In particular, the present invention further relates to peptides and peptide fragments having NGF-antagonistic activity and their use for the treatment of conditions, diseases and disorders related to elevated levels of NGF, in particular for the treatment of pain and cardiac arrhythmias.

The invention further relates to the use of the peptides and peptide fragments of the invention for the treatment of diseases characterised or aggravated by a loss of innervation such as ischemic heart disease, heart failure and diabetes and its comorbidities, in particular diabetic neuropathies.

Furthermore, the present invention relates to the use of the peptides and peptide fragments of the invention for the treatment of conditions, diseases and disorders shown to benefit from a treatment with NGF such as ulcers, neurotropic keratitis and glaucoma.

The invention further relates to the use of the peptides and peptide fragments of the invention for the treatment of diseases characterised or aggravated by a loss of innervation such as ischemic heart disease, heart failure and diabetes and its comorbidities, in particular diabetic neuropathies.

Furthermore, the present invention relates to the use of the peptides and peptide fragments of the invention for the treatment of conditions, diseases and disorders shown to benefit from a treatment with NGF such as ulcers, neurotropic keratitis and glaucoma.
Nerve growth factor (NGF) is a protein that regulates the growth and survival of sympathetic and sensory nerve cells (neurons). NGF thereby belongs to a family of growth factors called neurotrophins. NGF binds to and activates its high affinity tyrosine kinase receptor TrkA. Upon activation the TrkA-receptor dimerises and autophosphorylates starting important signaling pathways for the growth and survival of sympathetic neurons.

The ability of NGF to activate the TrkA receptor and therewith stimulate the survival and growth of neurons has made it of great interest in the search for new treatment options of diseases and disorders of both the peripheral and the central nervous system.

In the light of this numerous studies on the use of NGF in the treatment of various diseases and disorders of the central and peripheral nervous system have already been reported. These diseases and disorders include diabetic polyneuropathy, HIV-associated peripheral neuropathy, Alzheimer’s disease, Parkinson’s disease, optic glioma and advance optic nerve atrophy and hypoxic-ischemic perinatal brain injury (for a review of studies on the clinical use of NGF see Aloe et al, J. Transl Med. (2012) 10: 239).

Furthermore other studies indicate that NGF might be suitable for the treatment of other diseases and disorders such as ulcer, neurotropic keratitis and glaucoma (y.s.).

A large multicenter trial under the name ADMIRE-HF has recently provided clinical evidence documenting the inverse relation between cardiac innervation and survival in heart failure. On the other hand, experimental data show that NGF administration induces nerve sprouting in the upper thoracic sympathetic ganglia. These data indicate that it might be possible to use NGF to restore innervation when it is in the process of being lost and such a loss has negative prognostic consequences. Diseases that benefit from such treatments include heart failure and diabetes.
In the light of the above, novel compounds having TrkA-receptor-agonistic activity (NGF-like activity) would be helpful to provide further therapeutic options.

While in most cases the growth of neurons is desirable the uncontrolled growth of neurons can be associated with medical issues. For example the hyperinnervation of cardiac tissue has been linked to cardiac arrhythmia and even sudden cardiac death (see e.g. Chen et al. Cardiovasc Res (2001) 50, 409-416).

In recent years NGF has also been identified as an important mediator of pain, in particular chronic pain and correspondingly has become a target in the search for new pain management strategies. One approach thereby employs NGF sequestration using anti-NGF antibodies such as Tanezumab (Pfizer), Fulranumab (Johnson and Johnson), REGN475/SAR164877 (Regeneron together with Sanofi Aventis) or medi578 (AstraZeneca). For a review of pain management via an intervention in the NGF-mediated regulation of pain see e.g. McKelvey et al. J. Neurochem. (2013) 124, 276-289.

Clinical trials performed on patients suffering from osteoarthritic hip pain (Brown et al., Arthritis & Rheumatism (2013) 65, Vol. 7, 1795-1803) and pain from osteoarthritis of the knee (Lane et al, N. Engl. J. Med. (2010), 363, 1521-1531) have demonstrated that Tanezumab is effective in reducing pain in both patient groups compared to placebo. The trials for the treatment of osteoarthritic knee pain using Tanezumab were suspended by the US Food and Drug Administration (FDA) in June 2010 though due to a number of patients involved in the trial needing joint replacements due to progressively worsening knee and hip osteoarthritis (Schnitzer et al, Osteoarthritis and Cartilage (2011) 19, 639-646).

While the above suspension on the clinical trials using Tanezumab was lifted by the FDA in March 2012 it is clear that further compounds with NGF-antagonistic activity and possibly
different modes of action would be desirable to add further options for the management of pain and in particular chronic pain as well as for the treatment and prevention of cardiac arrhythmias.

SUMMARY OF THE INVENTION

The invention relates to peptides and peptide fragments having an amino acid sequence selected from the group consisting of,

SER-SER-HIS-PRO-TRP-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-VAL-SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-ARG-PHE-SER-VAL-CYS-ASP-SER-VAL-SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-VAL-SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-ARG-VAL-CYS-ASP-SER-VAL-SER-VAL-TRP-VAL-GLY-ASP,
ASP-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-MET-LYS-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PPIE-LYS-VAL-CYS-ASP-SER-VAL-
HIS-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
SER-MET-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PRO-SER-VAL-CYS-ASP-SER-VAL-
SER-ILE-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-TRP-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-CYS-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-GLU-ASP,
LYS-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PRO-SER-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-VAL-ILE-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-HIS-ASP,
SER-SER-HIS-VAL-ILE-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-VAL-
SER-ILE-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-TRP-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-HIS-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-VAL-
GLU-VAL-PHE-VAL-GLY-ASP,

THR-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
HIS-VAL-TRP-VAL-GLY-ASP,

SER-SER-HIS-PRO-VAL-PHE-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
HIS-VAL-TRP-VAL-GLY-ASP,

SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-ASP-PHE-LYS-VAL-CYS-ASP-SER-VAL-
HIS-VAL-TRP-VAL-GLY-ASP, and

SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
HIS-VAL-ILE-VAL-GLY-ASP,

and the salts, solvates and the solvates of the salts thereof.

Peptides and peptide fragments of the invention are the peptides and peptide fragments having an amino acid sequence listed above and their salts, their solvates and the solvates of their salts as well as peptides and peptide fragments mentioned below as exemplary embodiments and the salts, solvates and solvates of the salts thereof, insofar as the peptide and peptide fragments mentioned below are not already salts, solvates or solvates of the salts.

 salts preferred for the purpose of the invention are physiologically acceptable salts of the peptides and peptide fragments of the invention. Also included however are salts which themselves are not suitable for pharmaceutical applications but can be used for example for the isolation or purification of the peptides and peptide fragments of the invention.

 solvates for the purpose of the invention refer to those forms of the peptides and peptide fragments of the invention which in the solid or liquid state form a complex by complexation
with one or more solvent molecules. Hydrates are a specific form of solvates in which the complexation takes place with water.

The term peptide fragment in the context of the invention refers to peptides in which the amino acid sequences of the invention are incorporated into a larger peptide molecule. This can happen via a chain-extension at the C-terminus, the N-terminus or both termini. Preferably the larger peptide molecule is not longer than 50 amino acids in total including the amino acid sequences of the invention. More preferably the larger peptide molecule is not longer than 35 amino acids including the amino acid sequences of the invention. In some embodiments it may be preferred if the amino acid sequences of the invention are extended by no more than 5 amino acids at either terminus. In some embodiments it may be preferred if the peptide or peptide fragments of the invention have an amino acid sequence that does not comprise further amino acids added to either terminus. In any case the amino acid sequences of the invention will always be present in the sequences listed above and not interrupted by other amino acids.

In the context of the invention the reference to an amino acid includes proteinogenic amino acids but also non-proteinogenic amino acids, such as D-amino acids or amino acids in which the amino group and the carbonyl group are not bonded to the same carbon but separated by at least one further carbon (e.g. β- or γ-amino acids). If an amino acid is mentioned only by name this includes both L- and D-amino acids as well as β-, γ- and higher order amino acids. In some embodiments α-amino acids may be preferred. In some embodiments L-amino acids may be preferred. In some embodiments α-L-amino acids may be preferred. In some embodiments the peptides or peptide fragments of the invention may consist exclusively of L-amino acids or exclusively of D-amino acids. In some embodiments the peptides and peptide fragments of the invention consist of a mixture of L- and D-amino acids. In some embodiments the peptides and
peptide fragments of the invention may contain at least one L-amino acid. In some embodiments
the peptides and peptide fragments of the invention may contain at least one D-amino acid.
In the context of the invention the names and abbreviations used have the usual meaning known
to a person skilled in the art.
The present invention also relates to peptides or peptide fragments having an amino acid
sequence selected from the group consisting of
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-ARG-PHE-SER-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-MET-LYS-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
HIS-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
SER-MET-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
SER-LEU-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-CYS-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-GLU-ASP,
LYS-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PRO-SER-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-VAL-Ile-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-HIS-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-VAL-
GLU-VAL-PHE-VAL-GLY-ASP,

Thr-Ser-His-Pro-Ile-Phe-His-Arg-Gly-GLu-Pro-Lys-Val-Cys-Asp-Ser-Val-
Ser-Val-Trp-Val-GLy-ASP, and

SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
HIS-VAL-TRP-VAL-GLY-ASP, and

and the salts thereof, the solvates thereof and the solvates of the salts thereof.

Preferably the peptides and peptide fragments of the invention have an amino acid sequence
selected from the group consisting of

SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
HIS-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
SER-MET-TRP-VAL-GLY-ASP,
LYS-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PRO-SER-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-VAL-Ile-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-HIS-ASP,
THR-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
HIS-VAL-TRP-VAL-GLY-ASP, and
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
HIS-VAL-ILE-VAL-GLY-ASP,
and the salts thereof, the solvates thereof and the solvates of the salts thereof.

In particular the peptides and peptide fragments of the invention have an amino acid sequence selected from
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-
HIS-VAL-TRP-VAL-GLY-ASP,
LYS-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PRO-SER-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-GLY-ASP, and
SER-SER-HIS-VAL-ILE-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-VAL-
SER-VAL-TRP-VAL-HIS-ASP,
and the salts thereof, the solvates thereof and the solvates of the salts thereof.

The peptides and peptide fragments of the invention show a valuable range of pharmaceutical properties that could not have been predicted.

They are therefore suitable for use as medicaments for the treatment of diseases and disorders in humans and animals.

The peptides and peptide fragments of the invention are in particular distinguished by their capability to bind to and activate the TrkA-receptor. They are therefore useful as in the treatment of diseases and disorders benefiting from an increased activation of the TrkA-receptor. In particular the peptides and peptide fragments of the invention are useful for the treatment of peripheral neuropathies, multiple sclerosis, Alzheimer's disease, Parkinson's disease, hypoxic
brain injuries and/or optic nerve atrophy. The peptides and peptide fragments of the invention are furthermore useful in the treatment of diseases and disorders characterised or aggravated by a loss of innervation such as ischemic heart disease, heart failure and diabetes and its comorbidities, in particular diabetic neuropathies. The peptides and peptide fragments of the invention are also useful in the treatment of other diseases and disorders that have been shown to benefit from a treatment with NGF such as ulcers, neurotropic keratitis and/or glaucoma.

In another aspect of the invention, the peptides and peptide fragments of the invention are in particular distinguished by their capability to bind to the TrkA receptor more strongly than NGF without activating this receptor. They are therefore useful as NGF-antagonists in the treatment of diseases and disorders associated with an increase in the NGF-level. In particular the peptides and peptide fragments are useful in the treatment and management of pain and in the treatment and prophylaxis of hyperinnervation and conditions associated therewith such as cardiac arrhythmia and sudden cardiac death.

The present invention therefore also relates to the peptides and peptide fragments of the invention for use as medicaments.

The present invention further relates to the peptides and peptide fragments of the invention for use in the treatment, prophylaxis and/or management of diseases or disorders, in particular diseases or disorders benefiting from an increased activation of the TrkA-receptor, in particular for use in the treatment, prophylaxis and/or management of peripheral neuropathies, multiple sclerosis, Alzheimer's disease, Parkinson's disease, hypoxic brain injuries and/or optic nerve atrophy.

The present invention further relates to the peptides and peptide fragments of the invention for use in the treatment, prophylaxis and/or management of diseases or disorders characterised or
aggravated by a loss of innervation, in particular for use in the treatment, prophylaxis and/or management of ischemic heart disease, heart failure and diabetes and its comorbidities, in particular diabetic neuropathies.

The present invention further relates to the peptides and peptide fragments of the invention for use in the treatment, prophylaxis and/or management of other diseases and disorders that have been shown to benefit from a treatment with NGF, in particular for use in the treatment, prophylaxis and/or management of ulcers, neurotropic keratitis and/or glaucoma.

The present invention further relates to the peptides and peptide fragments of the invention for use in the treatment, prophylaxis and/or management of diseases or disorders, in particular diseases or disorders related to NGF, more particularly diseases or disorders related to an elevated level of NGF.

The present invention further relates to the peptides and peptide fragments of the invention for use in the treatment and/or management of pain.

The present invention further relates to the peptides and peptide fragments of the invention for use in the treatment and/or prophylaxis of hyperinnervation.

The present invention further relates to the peptides and peptide fragments of the invention for use in the treatment and/or prophylaxis of cardiac arrhythmias and/or sudden cardiac death.

PEPDITES HAVING TrkA-RECEPTOR ACITIVITY.

The peptides and peptide fragments of the present invention bind to the TrkA receptor and activate it, therefore acting as TrkA-receptor-agonists. Correspondingly the peptides and peptide fragments of the invention are useful in the prophylaxis, treatment and management of diseases and disorders benefiting from an increased activation of the TrkA-receptor. In particular the peptides and peptide fragments of the invention are suitable to treat, prevent and/or manage
peripheral neuropathies, multiple sclerosis, Alzheimer's disease, Parkinson's disease, hypoxic brain injuries and/or optic nerve atrophy.

Furthermore the peptides and peptide fragments of the invention are useful for the treatment, prophylaxis and/or management of diseases or disorders characterised or aggravated by a loss of innervation such as ischemic heart disease, heart failure and diabetes and its comorbidities, in particular diabetic neuropathies.

Furthermore the peptides and peptide fragments of the invention are useful for the treatment, prophylaxis and/or management of other diseases and disorders that have been shown to benefit from a treatment with NGF, such as ulcers, neurotropic keratitis and/or glaucoma.

In addition to humans the peptides and peptide fragments of the invention can also be used in the treatment and prophylaxis of the above conditions in animals such as primates, pigs, ruminants (cows, sheep, goats), horses, cats, dogs, poultry (e.g. chickens, ducks, geese, quails, pigeons, turkeys or ornamental birds) as well as productive and ornamental fish, reptiles and amphibians.

The present invention therefore further relates to a method for the prophylaxis, treatment and/or management of diseases or disorders benefiting from an increased activation of the TrkA-receptor in humans and animals comprising administering a therapeutically effective amount of the peptides or peptide fragments of the invention.

The present invention further relates to a method for treating, preventing and/or managing peripheral neuropathies, multiple sclerosis, Alzheimer's disease, Parkinson's disease, hypoxic brain injuries and/or optic nerve atrophy in humans and animals comprising administering a therapeutically effective amount of the peptides or peptide fragments of the invention.

The present invention further relates to a method for treating, preventing and/or managing diseases or disorders characterised or aggravated by a loss of innervation in humans and animals
comprising administering a therapeutically effective amount of the peptides or peptide fragments of the invention.

The present invention further relates to a method for treating, preventing and/or managing ischemic heart disease, heart failure and diabetes and its comorbidities, in particular diabetic neuropathies in humans and animals comprising administering a therapeutically effective amount of the peptides or peptide fragments of the invention.

The present invention further relates to a method for treating, preventing and/or managing other diseases and disorders that have been shown to benefit from a treatment with NGF in humans and animals comprising administering a therapeutically effective amount of the peptides or peptide fragments of the invention.

The present invention further relates to a method for treating, preventing and/or managing ulcers, neurotropic keratitis and/or glaucoma in humans and animals comprising administering a therapeutically effective amount of the peptides or peptide fragments of the invention.

The peptides and peptide fragments of the invention may act systemically and/or locally. For this purpose they can be administered in a suitable way, such as, for example, orally, parenterally, pulmonarily, nasally, sublingually, lingually, bucally, rectally, dermally, transdermally, conjunctivally, otically or as an implant or stent.

For these routes of administration the peptides and peptide fragments of the invention can be administered in suitable administration forms.

Suitable for oral application are application forms which work according to the prior art and release the peptides and peptide fragments of the invention quickly or in a modified fashion, for example as a sustained release formulation. These application forms may contain the peptides and peptide fragments of the invention in crystalline and/or amorphised and/or dissolved form.
Examples for such application forms include tablets (uncoated tablets or tablets having coatings such as enteric coatings or coatings that modify the release of the peptides and peptide fragments of the invention such as slowly dissolving coatings or insoluble coatings), tablets or films/wafers that disintegrate rapidly in the oral cavity, capsules (for example hard or soft gelatin capsules), films/lyophilisates, granules, pellets powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can take place with avoidance of an absorption step (e.g. intravenous, intraarterial, intracardiac, intraspinal or intralumbar) or with the inclusion of an absorption step (e.g. intramuscular, subcutaneous, percutaneous or intraperitoneal). Administration forms for parenteral administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilisates or sterile powders.

Suitable for other administration routes are, for example, pharmaceutical forms for inhalation (inter alia powder inhalers or nebulisers) nasal drops, nasal solutions or nasal sprays; tablets, films/wafers or capsules for lingual, sublingual or buccal administration, suppositories, preparations for eyes and ears, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (such as for example patches), milks, pastes, foams, implants or stents.

The peptides and peptide fragments of the invention can be incorporated into the listed administration forms. This can take place in ways that are know per se by mixing with inert, non-toxic, pharmaceutically suitable excipients. Such pharmaceutically suitable excipients include for example carriers (e.g. microcrystalline cellulose, lactose or mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersants and wetting agents (e.g. sodium dodecyl sulfate, polyoxysobitane oleate), binders (e.g. polyvinylpyrrolidone), synthetic and natural
polymers (e.g. albumin), stabilisers (e.g. antioxidants such as ascorbic acid), colours (e.g. inorganic pigments such as iron oxides) and smell and/or taste masking agents.

In some aspects of the invention it can be useful to administer the peptides and peptide fragments of the invention in administration forms that modulate their pharmacokinetics and increase their transport through the blood brain barrier. Such administration forms can be provided by absorbing or incorporating the peptides and peptide fragments of the invention onto/into nanoparticulate carriers. Carriers that modulate the pharmacokinetics and increase the transport through the blood brain barrier include carriers made from biodegradable polymers such as biodegradable poly(alkyl cyanoacrylates), polyesters, polyanhydrides, polyethers or mixtures or copolymers thereof. Examples of potentially useful nano-scale carriers include carriers made from poly(butyl cyanoacrylate), polylactic acid, poly(lactic-co-glycolic acid), chitosan, polyethylene glycol or mixtures or copolymers thereof.

In some aspects it may be useful if the nanoparticulate carriers are surface treated, for example coated with further compounds to promote the transport through the blood brain barrier. Such further compounds for surface treating the nanoparticulate carriers include surfactants, polyethers, biological molecules and mixtures thereof. In some cases it may be preferable to treat the nanoparticulate carriers with one or more compounds selected from the group consisting of polysorbate 80, pluronic, poly(ethylene glycol), poly(vinyl alcohol), human serum albumin and mixtures thereof.

The invention further relates to medicaments comprising at least one peptide or peptide fragment of the invention usually together with at least one inert, non-toxic, pharmaceutically acceptable excipient and their use for the above mentioned purposes.
In some embodiments it may be preferred to combine the peptides and peptides fragments of the invention with other pharmaceutically active compounds, for example other neuroprotective compounds.

PEPTIDES HAVING NGF-ANTAGONISTIC ACTIVITY

The peptides and peptide fragments of the present invention bind to the TrkA receptor and block it, therefore acting as an NGF antagonist. Correspondingly the peptides and peptide fragments of the invention are useful in the prophylaxis, treatment and management of diseases and disorders related to an elevated level of NGF. In particular the peptides and peptide fragments of the invention are suitable to treat and/or manage pain, in particular chronic pain such as osteoarthritic pain, rheumatoid arthritis, chronic lower back pain, interstitial cystitis, prostatitis, chronic pelvic pain syndrome, fibromyalgia, endometriosis, degenerative intervertebral disc disease and cancer pain. Furthermore the peptides and peptide fragments of the invention are useful for the treatment and/or prophylaxis of hyperinnervation and conditions related thereto such as cardiac arrhythmias and sudden cardiac death.

In addition to humans the peptides and peptide fragments of the invention can also be used in the treatment and prophylaxis of NGF related conditions in animals such as primates, pigs, ruminants (cows, sheep, goats), horses, cats, dogs, poultry (e.g. chickens, ducks, geese, quails, pigeons, turkeys or ornamental birds) as well as productive and ornamental fish, reptiles and amphibians.

The present invention therefore further relates to a method for the prophylaxis, treatment and/or management of diseases or disorders related to NGF, in particular elevated levels of NGF in humans and animals comprising administering a therapeutically effective amount of the peptides or peptide fragments of the invention.
The present invention further relates to a method for treating and/or managing pain in humans and animals comprising administering a therapeutically effective amount of the peptides or peptide fragments of the invention.

The present invention further relates to a method for treating and/or preventing hyperinnervation in humans and animals comprising administering a therapeutically effective amount of the peptides or peptide fragments of the invention.

The present invention further relates to a method for treating and/or preventing cardiac arrhythmias and/or sudden cardiac death in humans and animals comprising administering a therapeutically effective amount of the peptides or peptide fragments of the invention.

The expression managing pain or management of pain relates to all treatment regimes that will not completely rid the patient of the pain but will reduce the pain to improve or significantly improve the patient's quality of life.

The peptides and peptide fragments of the invention may act systemically and/or locally. For this purpose they can be administered in a suitable way, such as, for example, orally, parenterally, pulmonarily, nasally, sublingually, lingually, bucally, rectally, dermally, transdermally, conjunctivally, otically or as an implant or stent.

For these routes of administration the peptides and peptide fragments of the invention can be administered in suitable administration forms.

Suitable for oral application are application forms which work according to the prior art and release the peptides and peptide fragments of the invention quickly or in a modified fashion, for example as a sustained release formulation. These application forms may contain the peptides and peptide fragments of the invention in crystalline and/or amorphised and/or dissolved form.

Examples for such application forms include tablets (uncoated tablets or tablets having coatings
such as enteric coatings or coatings that modify the release of the peptides and peptide fragments of the invention such as slowly dissolving coatings or insoluble coatings), tablets or films/wafers that disintegrate rapidly in the oral cavity, capsules (for example hard or soft gelatin capsules), films/lyophilisates, granules, pellets powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can take place with avoidance of an absorption step (e.g. intravenous, intraarterial, intracardiac, intraspinal or intralumbar) or with the inclusion of an absorption step (e.g. intramuscular, subcutaneous, percutaneous or intraperitoneal). Administration forms for parenteral administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilisates or sterile powders.

Suitable for other administration routes are, for example, pharmaceutical forms for inhalation (inter alia powder inhalers or nebulisers) nasal drops, nasal solutions or nasal sprays; tablets, films/wafers or capsules for lingual, sublingual or buccal administration, suppositories, preparations for eyes and ears, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (such as for example patches), milks, pastes, foams, implants or stents.

The peptides and peptide fragments of the invention can be incorporated into the listed administration forms. This can take place in ways that are know per se by mixing with inert, non-toxic, pharmaceutically suitable excipients. Such pharmaceutically suitable excipients include for example carriers (e.g. microcrystalline cellulose, lactose or mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersants and wetting agents (e.g. sodium dodecyl sulfate, polyoxysorbitane oleate), binders (e.g. polyvinylpyrrolidone), synthetic and natural polymers (e.g. albumin), stabilisers (e.g. antioxidants such as ascorbic acid), colours (e.g. inorganic pigments such as iron oxides) and smell and/or taste masking agents.
In some aspects of the invention it can be useful to administer the peptides and peptide fragments of the invention in administration forms that modulate their pharmacokinetics and increase their transport through the blood brain barrier. Such administration forms can be provided by absorbing or incorporating the peptides and peptide fragments of the invention onto/into nanoparticulate carriers. Carriers that modulate the pharmacokinetics and increase the transport through the blood brain barrier include carriers made from biodegradable polymers such as biodegradable poly(alkyl cyanoacrylates), polyesters, polyanhydrides, polyethers or mixtures or copolymers thereof. Examples of potentially useful nano-scale carriers include carriers made from poly(butyl cyanoacrylate), polylactic acid, poly(lactic-co-glycolic acid), chitosan, polyethylene glycol or mixtures or copolymers thereof.

In some aspects it may be useful if the nanoparticulate carriers are surface treated, for example coated with further compounds to promote the transport through the blood brain barrier. Such further compounds for surface treating the nanoparticulate carriers include surfactants, polyethers, biological molecules and mixtures thereof. In some cases it may be preferable to treat the nanoparticulate carriers with one or more compounds selected from the group consisting of polysorbate 80, pluronic, poly(ethylene glycol), poly(vinyl alcohol), human serum albumin and mixtures thereof.

The invention further relates to medicaments comprising at least one peptide or peptide fragment of the invention usually together with at least one inert, non-toxic, pharmaceutically acceptable excipient and their use for the above mentioned purposes.

In some embodiments it may be preferred to combine the peptides and peptides fragments of the invention with other pharmaceutically active compounds, for example other analgesics or
compounds useful in the treatment of cardiac arrhythmias and sudden cardiac death such as for example beta-blockers.

Analgesics suitable for use in combination with the peptides and peptides fragments of the invention include for example non-steroidal anti-inflammatories such as paracetamol, ibuprofen, aspirin, diclofenac or naproxen, COX-2 inhibitors such as rofexocib, celecoxib and etoricoxib and opioids such as codeine, oxycodone, hydrocodone, dihydromorphine or pethidine, as well as other known analgesics.

Beta-blockers suitable for use in combination with the peptides and peptides fragments of the invention include for example acebutolol, atenolol, betaproxol, bisoprolol, bucindolol, butaxamine, carteolol, carvedilol, celiprolol, esmolol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol and timolol.

The invention further relates to medicaments comprising at least one peptide or peptide fragment having TrkA agonistic activity or NGF-antagonistic activity according to the invention usually together with at least one further pharmaceutically active ingredient and their use for the above mentioned purposes.

The minimum amount of the peptides and peptide fragments of the invention to be administered is a therapeutic amount. The term "therapeutically effective amount" means an amount of compound which prevents the onset of, alleviates the symptoms of, manages, stops the progression and/or eliminates a disease, disorder or condition benefiting from an increased activation of the TrkA-receptor, a disease, disorder or condition characterized or aggravated by a loss of innervation or another disease, disorder or condition shown to benefit from a treatment with NGF.
Typically an effective dosing scheme of the peptides and peptide fragments of the invention in adults is about 1 to 1000 µg/kg of the peptides or peptide fragments of the invention, preferably 5 to 500 µg/kg. In some embodiments the effective dose is 5 to 100 µg/kg or 10 to 50 µg/kg. In other embodiments the effective dose is 1 to 20 µg/kg or 2 to 10 µg/kg. In some embodiments the peptides and peptide fragments of the invention are administered daily. In some embodiments the peptides or peptide fragments of the invention are administered every other day or every 3, 5, 7 or 10 days. In some cases it might be necessary to titrate the patient to find the optimal dose.

It may nevertheless be necessary to deviate for the above amounts where appropriate. These deviations might be due to body weight, administration route, individual response to the active ingredient, severity of the condition, disease or disorder, type of preparation and time or interval over which the administration takes place. Thus, in some cases it might be sufficient to make do with less than the aforementioned minimum amount, whereas in other cases the upper limit mentioned above must be exceeded. In the case of the administration of large amounts of the peptides and peptide fragments of the invention it may be advisable to distribute these in a plurality of single doses over the day.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS RELATED TO PEPTIDES HAVING TrkA- RECEPTOR AGONISTIC ACTIVITY

The present invention will now be illustrated in more detail based on selected but not limiting examples. In the following examples all mentioned amino acids are a-L-amino acids unless indicated otherwise.

A.) Binding considerations
In the following examples all calculations were performed using the dock module of the Molecular Operating Environment software available from the Chemical Computing Group. All values are based on the "London dG" scoring function.

The relevant term for the calculations was

$$
AG = c + E_{f_{\text{flex}}} + \frac{3}{4} \sum_{i} B_{i} + \sum_{i} \omega
$$

in which,

- $c$ represents the protein-ligand interaction energy;
- $E_{f_{\text{flex}}}$ accounts for the loss of flexibility of the ligand;
- $CHB$ and $f_{HB}$ are compensatory functions for the non-ideality of the specific bond and are expressed as a sum over all hydrogen-bond sites; and
- $\Delta D_{j}$ is a term for the atomic desolvation describing variations in the solvation field of ligand atoms.

It is known that during the action of NGF on the TrkA receptor, TrkA and NGF form a unique complex from two NGF and two TrkA molecules each, forming two homo-dimers. The present inventors have mapped the short contact distances between the two TrkA molecules and the two NGF molecules in order to find the smallest representative TrkA-NGF complex. This investigation has shown that the highest number of short range interactions occur between the first molecule of the NGF and second molecule of TrkA. Specific distances between the closest a-carbon atoms in the first NGF molecule and the second TrkA molecule are given below in Table 1.
Based on the calculations it becomes clear that all α-carbon atoms with a distance of less than 7 Å between the NGF molecule and the TrkA molecule are found in the first 24 amino acids of NGF, in particular they are found in amino acid residues 2 to 24 of NGF.

Based on this information the present inventors have defined a peptide based on amino acids 2 to 24 of NGF as the starting point for their investigation and performed investigations into peptides with an improved binding profile over the starting peptide. The amino acid sequence of the starting peptide is given below

The free binding energy of the starting peptide to TrkA was calculated as -13.02 Kcal/mol. Based on this the present inventors have investigated various mutated form of the starting peptide showing one, two or three mutations. They have then selected those peptides which showed an improvement of at least -4 kcal/mol in the free binding energy compared to the starting peptide for further investigation. This improvement in free binding energy shows an increased ability of the peptide to bind to TrkA and activate it. The improvements in free binding energy of the mutated peptides are given below in Table 2.

**Table 2** Improvement in free binding energy of mutated peptides over starting peptide

<table>
<thead>
<tr>
<th>Mutations compared to starting peptide</th>
<th>Improvement of free binding energy [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5ILE =&gt; TRP</td>
<td>-4.21</td>
</tr>
<tr>
<td>10Glu =&gt; Arg</td>
<td>-4.81</td>
</tr>
<tr>
<td>10GLU =&gt; HIS</td>
<td>-4.25</td>
</tr>
<tr>
<td>11PHE =&gt; PRO</td>
<td>-4.45</td>
</tr>
<tr>
<td>11PHE =&gt; VAL</td>
<td>-4.21</td>
</tr>
<tr>
<td>12SER =&gt; LYS</td>
<td>-5.30</td>
</tr>
<tr>
<td>12SER =&gt; ARG</td>
<td>-4.32</td>
</tr>
<tr>
<td>22GLY =&gt; HIS</td>
<td>-4.06</td>
</tr>
<tr>
<td>12SER =&gt; LYS, 1SER =&gt; ASP</td>
<td>-4.02</td>
</tr>
<tr>
<td>12SER =&gt; LYS</td>
<td>-4.58</td>
</tr>
<tr>
<td>11PHE =&gt; MET</td>
<td></td>
</tr>
<tr>
<td>Reaction</td>
<td>ΔG  (kcal/mol)</td>
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<tr>
<td>--------------</td>
<td>----------------</td>
</tr>
<tr>
<td>SER $\rightarrow$ LYS</td>
<td>-6.84</td>
</tr>
<tr>
<td>18SER $\rightarrow$ HIS</td>
<td>-5.47</td>
</tr>
<tr>
<td>12SER $\rightarrow$ LYS</td>
<td>-5.47</td>
</tr>
<tr>
<td>19VAL $\rightarrow$ MET</td>
<td>-5.47</td>
</tr>
<tr>
<td>12SER $\rightarrow$ LYS</td>
<td>-4.50</td>
</tr>
<tr>
<td>19VAL $\rightarrow$ LEU</td>
<td>-4.50</td>
</tr>
<tr>
<td>12SER $\rightarrow$ LYS</td>
<td>-4.70</td>
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<tr>
<td>22GLY $\rightarrow$ CYS</td>
<td>-4.70</td>
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<td>12SER $\rightarrow$ LYS</td>
<td>-4.55</td>
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<td>22GLY $\rightarrow$ GLU</td>
<td>-4.55</td>
</tr>
<tr>
<td>1SER $\rightarrow$ LYS</td>
<td>-6.93</td>
</tr>
<tr>
<td>11PHE $\rightarrow$ PR0</td>
<td>-6.93</td>
</tr>
<tr>
<td>4PRO $\rightarrow$ VAL</td>
<td>-6.72</td>
</tr>
<tr>
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<tr>
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<td>-4.10</td>
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<td>5ILE $\rightarrow$ TRP</td>
<td>-4.10</td>
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<td>22GLY $\rightarrow$ HIS</td>
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<td>-4.52</td>
</tr>
<tr>
<td>20TRP $\rightarrow$ PHE</td>
<td>-4.52</td>
</tr>
<tr>
<td>12SER $\rightarrow$ LYS</td>
<td>-5.29</td>
</tr>
<tr>
<td>18SER $\rightarrow$ HIS</td>
<td>-5.29</td>
</tr>
<tr>
<td>1SER $\rightarrow$ THR</td>
<td>-5.29</td>
</tr>
</tbody>
</table>
B.) Peptide synthesis

The above peptides can be prepared by conventional solid state synthesis.

The synthesis proceeds along the well known cycle of coupling step, washing step, removal of the protecting group and washing step after which another coupling step follows or if the peptide is complete the peptide is cleaved from the solid support.

In such a synthesis for example a polystyrene resin can be used as support.

The amino functionality of the amino acid can for example be protected using a tert.-butyloxy carbonyl (Boc) protecting group. Other suitable protecting groups can be used for any present reactive side-chain functionality. In case orthogonal protection is necessary the Boc protecting group can be replaced by a 9-fluorenylmethyloxycarbonyl (Fmoc) protecting group.

The coupling reaction proceeds using coupling agents usual in the art, such as a combination of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) or N,N'-dicyclohexylcarbodiimide (DCC) with 1-hydroxy-benzotriazole (HOBT) and 1-hydroxy-7-aza-benzotriazole (HOAt), where
appropriate in the presence of a base, in particular a hindered base such as diisoproplethylamine (DIEA) or tetramethypiperidine (TMP). Suitable solvents for the coupling reaction include dimethylformamide (DMF), N-methylpyrrolidone (NMP), trichloromethane (TCM) and dichloromethane (DCM) or mixtures thereof. Additionally further solvents such as trifluorethanol (TFE), hexafluoro-2-propanol (HFIP) or dimethylsulfoxide (DMSO) may be added to suppress peptide aggregation.

The washing steps in general use solvents similar to those of the coupling steps.

The removal of the protecting groups proceeds using suitable deprotecting agents. The Boc protecting group is usually removed under acidic conditions using for example hydrochloric acid (HCl) or trifluoroacetic acid (TFA), where appropriate in a suitable solvent such as for example methanol or ethanol for HCl and for example DCM or TCM for TFA.

The Fmoc protecting group is usually removed in the presence of a base, such as for example pyridine, where appropriate in a suitable solvent.

After the peptide is complete it can be cleaved from the solid support in a suitable manner and purified as necessary. The whole process can be performed on an automated synthesizer.

C.) Assessment of the physiological activity

In-vitro assays

ELISA

The ability of the peptides and peptide fragments of the invention to act as a TrkA-receptor-agonist can for example be measured using an enzyme-linked immunosorbertent assay (ELISA) for the phosphorylated TrkA-receptor. Such an ELISA kit is commercially available for example from Cell Signalling Technologies under the designation PathScan® Phospho-TrkA (Tyr674/675) Sandwich ELISA Kit (catalogue number 7212). The assay is used according to the
manufacturers instructions exposing PC12 or other cellular types expressing TrkA receptors to the peptides and peptide fragments of the invention. The measurements can be calibrated against various NGF concentrations.

Neurite Regeneration Bioassay

The ability of the peptides and peptide fragments of the invention to act as a TrkA-receptor-agonist can also be measured using a β-NGF-induced neurite regeneration bioassay. The assay used is based on the methodology described by Chandler et al. (J. Biol. Chem. (1984) 259, No. 11, 6882-6889).

PC12 cells are grown on tissue culture plates (e.g. 60-mm Falcon © cell culture dishes) at an initial cell density of 4-5 x 10^5 cells/plate. During the cultivation β-NGF is added every other day for 8 days. The cells are harvested mechanically using a pasteur pipet, washed once in serum-containing growth medium and twice in serum-free growth medium and collected by centrifugation (500 g for 3 min. each time). The cell are resuspended at 6 x 10^3 cells/ml in serum-free growth medium and 0.5 ml each were plated into each well of a 24-well tissue culture plate. The tissue culture plate was pre-treated with 50 µg/ml poly-L-lysine (Sigma Aldrich) and washed four times with sterile distilled water. The cells are incubated at 37° C for 30 min and 400 µl Dulbecco's modified Eagle's medium containing bovine serum albumin (BSA) are added to bring the final serum albumin concentration to 1 mg/ml. The cells are returned to the incubator for 15 min before 10 pm of β-NGF or various concentrations of the peptides of the invention (e.g. 0, 1, 2, 5, 10, 20 pm) are added. At least one set of cells is used as control without the addition of β-NGF. The cells are incubated for 24h at 37° C and read-out using a phase contrast microscope. Positives are cells which show a neurite growth of at least more than 25 µm. The TrkA-receptor-agonistic activity of the peptides of the invention is
evaluated based on their ability to stimulate neurite growth compared to NGF-induced positive cells.

In-vivo assay

The ability of the peptides and peptide fragments of the invention to treat, manage or prevent diseases or disorders benefiting from an increased activation of the TrkA-receptor or other diseases and disorders that have been shown to benefit from a treatment with NGF can be shown in suitable animal models.

The ability of the peptides of the invention to treat or prevent Alzheimer's disease can for example be demonstrated in a rat model using the Morris water maze. For a review of rat models for Alzheimer's disease see e.g. Do Carmo and Cuello, Molecular Neurodegeneration (2013) 8: 37. Furthermore the Morris water maze can generally provide information on the activity of the tested compounds on memory, a target of potential interest for aging and dementing diseases, further conditions that might benefit from an increased TrkA-receptor agonism.

The ability of the peptides of the invention to treat diabetic ulcers can for example be demonstrated in a mouse model. Diabetes can be induced in mice using streptozotocin. Diabetic mice are then wounded using e.g. a biopsy punch and treated topically with the peptides and peptide fragments in a suitable solvent, e.g. saline solution. The wound closure is then observed visually or using digital imaging and compared to control animals treated with placebo, e.g. just the suitable solvent without the addition of the peptides or peptide fragments of the invention.

D.) Example for a pharmaceutical composition

1% DMSO/99% Plasma
The peptide is completely dissolved in a calculated volume of DMSO. The DMSO solution is then suspended in plasma and the suspension is mixed until a clear solution is obtained. The solution is sterilized by filtration and dispensed into suitable containers.

**DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS RELATED TO NGF-ANTAGONISTIC ACTIVITY**

The present invention will now be illustrated in more detail based on selected but not limiting examples. In the following examples all mentioned amino acids are a-L-amino acids unless indicated otherwise.

A.) Binding considerations

In the following examples all calculations were performed using the dock module of the Molecular Operating Environment software available from the Chemical Computing Group. All values are based on the "London dG" scoring function. The relevant term for the calculations was

\[
AG = c + E_{flex} + \sum C_{HB} + \sum f_{HB} + \sum D
\]

in which,

- \( c \) represents the protein-ligand interaction energy;
- \( E_{flex} \) accounts for the loss of flexibility of the ligand;
- \( C_{HB} \) and \( f_{HB} \) are compensatory functions for the non-ideality of the specific bond and are expressed as a sum over all hydrogen-bond sites; and
- \( AD \) is a term for the atomic desolvation describing variations in the solvation field of ligand atoms.

It is known that during the action of NGF on the TrkA receptor, TrkA and NGF form a unique complex from two NGF and two TrkA molecules each, forming two homo-dimers. The present
inventors have mapped the short contact distances between the two TrkA molecules and the two NGF molecules in order to find the smallest representative TrkA-NGF complex. This investigation has shown that the highest number of short range interactions occur between the first molecule of the NGF and second molecule of TrkA. Specific distances between the closest a-carbon atoms in the first NGF molecule and the second TrkA molecule are given below in Table 1.

Table 1 Distances between the α-carbon atoms of NGF(1) and TrkA(2)

<table>
<thead>
<tr>
<th>Residue of TrkA</th>
<th>Atom No. of TrkA</th>
<th>Residue No. of NGF</th>
<th>Atom No. of NGF</th>
<th>Distances (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>84</td>
<td>297</td>
<td>114</td>
<td>4.20</td>
</tr>
<tr>
<td>13</td>
<td>95</td>
<td>297</td>
<td>114</td>
<td>4.59</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>291</td>
<td>68</td>
<td>5.65</td>
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<td>11</td>
<td>75</td>
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<td>5.79</td>
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<td>6.14</td>
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<td>141</td>
<td>379</td>
<td>753</td>
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<td>135</td>
<td>379</td>
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<td>5</td>
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<td>343</td>
<td>487</td>
<td>6.91</td>
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<td>6.93</td>
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<td>7.96</td>
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<tr>
<td>50</td>
<td>369</td>
<td>382</td>
<td>777</td>
<td>10.65</td>
</tr>
</tbody>
</table>

Based on the calculations it becomes clear that all α-carbon atoms with a distance of less than 7Å between the NGF molecule and the TrkA molecule are found in the first 24 amino acids of NGF, in particular they are found in amino acid residues 2 to 24 of NGF.
Based on this information the present inventors have defined a peptide based on amino acids 2 to 24 of NGF as the starting point for their investigation and performed investigations into peptides with an improved binding profile over the starting peptide. The amino acid sequence of the starting peptide is given below:


The free binding energy of the starting peptide to TrkA was calculated as -13.02 Kcal/mol. Based on this, the present inventors have investigated various mutated forms of the starting peptide showing one, two or three mutations. They have then selected those peptides which showed an improvement of at least -4 kcal/mol in the free binding energy compared to the starting peptide for further investigation. This improved in free binding energy shows an increased ability of the peptide to bind to TrkA and displace NGF. Due to the small size of the peptides they lack the ability to dimerise or to induce the dimerization in TrkA. Consequently, these peptides cannot activate TrkA. Due to their improved free binding energy these peptides will furthermore displace NGF and consequently act as an NGF antagonist. The improvements in free binding energy of the mutated peptides are given below in Table 2.

Table 2 Improvement in free binding energy of mutated peptides over starting peptide

<table>
<thead>
<tr>
<th>Mutations compared to starting peptide</th>
<th>Improvement of free binding energy [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5ILE =&gt; TRP</td>
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<tr>
<td>10Glu =&gt; Arg</td>
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</tr>
<tr>
<td>10GLU =&gt; HIS</td>
<td>-4.25</td>
</tr>
<tr>
<td></td>
<td>Value</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------</td>
</tr>
<tr>
<td>PHE -&gt; PRO</td>
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<td>PHE -&gt; VAL</td>
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<tr>
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</tr>
<tr>
<td>GLY -&gt; HIS</td>
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</table>
**B.) Peptide synthesis**

The above peptides can be prepared by conventional solid state synthesis.
The synthesis proceeds along the well known cycle of coupling step, washing step, removal of the protecting group and washing step after which another coupling step follows or if the peptide is complete the peptide is cleaved from the solid support.

In such a synthesis for example a polystyrene resin can be used as support.

The amino functionality of the amino acid can for example be protected using a tert.-butyloxy carbonyl (Boc) protecting group. Other suitable protecting groups can be used for any present reactive side-chain functionality. In case orthogonal protection is necessary the Boc protecting group can be replaced by a 9-fluorenylmethyloxycarbonyl (Fmoc) protecting group.

The coupling reaction proceeds using coupling agents usual in the art, such as a combination of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) or N,N'-dicyclohexylcarbodiimide (DCC) with 1-hydroxy-benzotriazole (HOBt) and 1-hydroxy-7-aza-benzotriazole (HOAt), where appropriate in the presence of a base, in particular a hindered base such as diisopropylethylamine (DIEA) or tetramethylpiperidine (TMP). Suitable solvents for the coupling reaction include dimethylformamide (DMF), N-methylpyrrolidone (NMP), trichloromethane (TCM) and dichloromethane (DCM) or mixtures thereof. Additionally further solvents such as trifluorethanol (TFE), hexafluoro-2-propanol (FIFIP) or dimethylsulfoxide (DMSO) might be added to suppress peptide aggregation.

The washing steps in general use solvents similar to those of the coupling steps.

The removal of the protecting groups proceeds using suitable deprotecting agents. The Boc protecting group is usually removed under acidic conditions using for example hydrochloric acid (HCl) or trifluoroacetic acid (TFA), where appropriate in a suitable solvent such as for example methanol or ethanol for HCl and for example DCM or TCM for TFA.
After the peptide is complete it can be cleaved from the solid support in a suitable manner and purified as necessary. The whole process can be performed on an automated synthesizer.

C.) Assessment of the physiological activity

ELISA

The ability of the peptides and peptide fragments of the invention to act as an NGF antagonist can for example be measured using an enzyme-linked immunosorbent assay (ELISA) for the phosphorylated TrKA-receptor. Such an ELISA kit is commercially available for example from Cell Signalling Technologies under the designation PathScan® Phospho-TrkA (Tyr674/675) Sandwich ELISA Kit (catalogue number 7212). The assay is used according to the manufacturers instructions exposing PC12 or other cellular types expressing TrkA receptors to a given amount of NGF added per well in combination with various quantities of the peptides and peptide fragments of the invention. The activity of the peptides and peptide fragments is evaluated based on their ability to suppress the NGF induced autophosphorylation of TrkA and consequently the appearance of phospho-TrkA.

Neurite Regeneration Bioassay

The ability of the peptides and peptide fragments of the invention to act as an NGF antagonist can also be measured using a β-NGF-induced neurite regeneration bioassay. The assay used is based on the methodology described by Chandler et al. (J. Biol. Chem. (1984) 259, No. 11, 6882-6889).

PC12 cells are grown on tissue culture plates (e.g. 60-mm Falcon © cell culture dishes) at an initial cell density of 4-5 x 10^5 cells/plate. During the cultivation β-NGF is added every other day for 8 days. The cells are harvested mechanically using a pasteur pipet, washed once in serum-containing growth medium and twice in serum-free growth medium and collected by
centrifugation (500 g for 3 min. each time). The cells are resuspended at $6 \times 10^3$ cells/ml in serum-free growth medium and 0.5 ml each were plated into each well of a 24-well tissue culture plate. The tissue culture plate was pre-treated with 50 µg/ml poly-L-lysine (Sigma Aldrich) and washed four times with sterile distilled water. The cells are incubated at 37°C for 30 min and 400 µl Dulbecco's modified Eagle's medium containing bovine serum albumin (BSA) are added to bring the final serum albumin concentration to 1 mg/ml. The cells are returned to the incubator for 15 min before 10 pm of β-NGF and various concentrations of the peptides of the invention (e.g. 0, 1, 2, 5, 10, 20 pm) are added. At least one set of cells is used as control without the addition of β-NGF. The cells are incubated for 24h at 37°C and read-out using a phase contrast microscope. Positives are cells which show a neurite growth of at least more than 25 µm. The NGF-antagonistic activity of the peptides of the invention is evaluated based on their ability to reduce the number of NGF-induced positive cells.

In-vivo assay

The ability of the peptides of the invention to treat or manage pain can be demonstrated in a mouse or rat model. Arthritis can be induced by the injection of bovine type II collagen into the joints of a test animal. After the arthritis has established the animals are treated once or several times with different doses of the peptides and peptide fragments of the invention. The ability of the peptides and peptide fragments of the invention to treat pain can be observed through the restoration of mobility in arthritic animals.

D.) Example for a pharmaceutical composition

1% DMSO/99% Plasma
The peptide is completely dissolved in a calculated volume of DMSO. The DMSO solution is then suspended in plasma and the suspension is mixed until a clear solution is obtained. The solution is sterilized by filtration and dispensed into suitable containers.

What is claimed is:
CLAIMS

1. A peptide or peptide fragment having an amino acid sequence selected from the group consisting of,

   SER-SER-HIS-PRO-TRP-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-
   VAL-SER-VAL-TRP-VAL-GLY-ASP,
   
   SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-ARG-PHE-SER-VAL-CYS-ASP-SER-
   VAL-SER-VAL-TRP-VAL-GLY-ASP,
   
   SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-HIS-PHE-SER-VAL-CYS-ASP-SER-
   VAL-SER-VAL-TRP-VAL-GLY-ASP,
   
   SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PRO-SER-VAL-CYS-ASP-SER-
   VAL-SER-VAL-TRP-VAL-GLY-ASP,
   
   SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-VAL-SER-VAL-CYS-ASP-SER-
   VAL-SER-VAL-TRP-VAL-GLY-ASP,
   
   SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
   VAL-SER-VAL-TRP-VAL-GLY-ASP,
   
   SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-ARG-VAL-CYS-ASP-SER-
   VAL-SER-VAL-TRP-VAL-GLY-ASP,
   
   SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-
   VAL-SER-VAL-TRP-VAL-HIS-ASP,
   
   ASP-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
   VAL-SER-VAL-TRP-VAL-GLY-ASP,
   
   SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-MET-LYS-VAL-CYS-ASP-SER-
   VAL-SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
VAL-HIS-VAL-TRP-VAL-GLY-ASP,
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VAL-SER-VAL-TRP-VAL-GLU-ASP,
LYS-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PRO-SER-VAL-CYS-ASP-SER-
VAL-SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-VAL-ILE-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-
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SER-SER-HIS-VAL-ILE-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-
VAL-SER-IIE-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-TRP-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-
VAL-SER-VAL-TRP-VAL-HIS-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-
VAL-GLU-VAL-PHE-VAL-GLY-ASP,
THR-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
VAL-HIS-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-VAL-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
VAL-HIS-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-ASP-PHE-LYS-VAL-CYS-ASP-SER-
VAL-HIS-VAL-TRP-VAL-GLY-ASP, and
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
VAL-HIS-VAL-ILE-VAL-GLY-ASP,
and its salts, solvates and the solvates of its salts.

2. The peptide or peptide fragment of claim 1 wherein the amino acid sequence is selected from the group consisting of

SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-ARG-PHE-SER-VAL-CYS-ASP-SER-
VAL-SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-ASP-PHE-LYS-VAL-CYS-ASP-SER-
VAL-SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-MET-LYS-VAL-CYS-ASP-SER-
VAL-SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
VAL-HIS-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
VAL-SER-MET-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
VAL-SER-LEU-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
VAL-SER-VAL-TRP-VAL-CYS-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-SER-VAL-TRP-VAL-GLU-ASP,
LYS-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PRO-SER-VAL-CYS-ASP-SER-VAL-SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-VAL-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-SER-VAL-TRP-VAL-HIS-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PRO-SER-VAL-CYS-ASP-SER-VAL-SER-VAL-TRP-VAL-HIS-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-GLU-VAL-PHE-VAL-GLY-ASP,
THR-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-HIS-VAL-TRP-VAL-GLY-ASP, and
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-HIS-VAL-ILE-VAL-GLY-ASP,
and its salts, its solvates and the solvates of its salts.

3. The peptide or peptide fragment of claim 1 or 2 wherein the amino acid sequence is
selected from the group consisting of
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-HIS-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-HIS-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-VAL-SER-MET-TRP-VAL-GLY-ASP,
LYS-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PRO-SER-VAL-CYS-ASP-SER-VAL-SER-VAL-TRP-VAL-GLY-ASP,
SER-SER-HIS-VAL-ILE-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-
VAL-VAL-TRP-VAL-HIS-ASP,

THR-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
VAL-HIS-VAL-TRP-VAL-GLY-ASP, and

SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
VAL-HIS-VAL-ILE-VAL-GLY-ASP,

and its salts, its solvates and the solvates of its salts.

4. The peptide or peptide fragment of any one of claims 1 to 3 wherein the amino acid
sequence is selected from the group consisting of

SER-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
VAL-HIS-VAL-TRP-VAL-GLY-ASP,

LYS-SER-HIS-PRO-ILE-PHE-HIS-ARG-GLY-GLU-PHE-LYS-VAL-CYS-ASP-SER-
VAL-SER-VAL-TRP-VAL-GLY-ASP, and

SER-SER-HIS-VAL-ILE-PHE-HIS-ARG-GLY-GLU-PHE-SER-VAL-CYS-ASP-SER-
VAL-SER-VAL-TRP-VAL-HIS-ASP,

and its salts, its solvates and the solvates of its salts.

5. The peptide or peptide fragment of any one of claims 1 to 4 for use as a medicament.

6. The peptide or peptide fragment of any one of claims 1 to 4 for use in the treatment,
prophylaxis and/or management of diseases or disorders, in particular diseases or
disorders benefiting from an increased activation of the TrkA-receptor, in particular for
use in the treatment, prophylaxis and/or management of peripheral neuropathies, multiple
sclerosis, Alzheimer's disease, Parkinson's disease, hypoxic brain injuries and/or optic
nerve atrophy.
7. The peptide or peptide fragment of any one of claims 1 to 4 for use in the treatment, prophylaxis and/or management of diseases or disorders characterised or aggravated by a loss of innervation, in particular for use in the treatment, prophylaxis and/or management of ischemic heart disease, heart failure and diabetes and its comorbidities, in particular diabetic neuropathies.

8. The peptide or peptide fragment of any one of claims 1 to 4 for use in the treatment, prophylaxis and/or management of diseases and disorders that have been shown to benefit from a treatment with NGF, in particular for use in the treatment, prophylaxis and/or management of ulcers, neurotropic keratitis and/or glaucoma.

9. The peptide or peptide fragment of any one of claims 1 to 4 for use in the treatment, prophylaxis and/or management of diseases or disorders, in particular diseases or disorders related to NGF, more particularly diseases or disorders related to an elevated level of NGF and especially for use in the treatment and/or management of pain and/or the treatment and/or prophylaxis of cardiac arrhythmia and/or sudden cardiac death.

10. A use of a peptide or peptide fragment of any one of claims 1 to 4 for the manufacture of a medicament for the treatment, prophylaxis and/or management of diseases or disorders, in particular diseases or disorders benefiting from an increased activation of the TrkA-receptor, in particular for the treatment, prophylaxis and/or management of peripheral neuropathies, multiple sclerosis, Alzheimer's disease, Parkinson's disease, hypoxic brain injuries, heart failure, ischemic heart disease and/or optic nerve atrophy.

11. A use of a peptide or peptide fragment of any one of claims 1 to 4 for the manufacture of a medicament for the treatment, prophylaxis and/or management of diseases or disorders characterised or aggravated by a loss of innervation, in particular for use in the treatment,
prophylaxis and/or management of ischemic heart disease, heart failure and diabetes and its comorbidities, in particular diabetic neuropathies.

12. A use of a peptide or peptide fragment of any one of claims 1 to 4 for the manufacture of a medicament for the treatment, prophylaxis and/or management of diseases or disorders that have been shown to benefit from a treatment with NGF, in particular for the treatment, prophylaxis and/or management of ulcers, neurotropic keratitis and/or glaucoma.

13. A use of a peptide or peptide fragment of any one of claims 1 to 4 for the manufacture of a medicament for the treatment, prophylaxis and/or management of diseases or disorders, in particular diseases or disorders related to NGF, more particularly diseases or disorders related to an elevated level of NGF and especially for use in the treatment and/or management of pain and/or the treatment and/or prophylaxis of cardiac arrhythmia and/or sudden cardiac death.

14. A medicament comprising a peptide or peptide fragment of any one of claims 1 to 4 in combination with at least one inert, non-toxic, pharmaceutically acceptable excipient.

15. A medicament comprising a peptide or peptide fragment of any one of claims 1 to 4 in combination with at least further active ingredient.

16. The medicament of claim 14 or 15 for use in the treatment, prophylaxis and/or management of diseases or disorders, in particular diseases or disorders benefiting from an increased activation of the TrkA-receptor, in particular for use in the treatment, prophylaxis and/or management of peripheral neuropathies, multiple sclerosis, Alzheimer's disease, Parkinson's disease, hypoxic brain injuries, heart failure, ischemic heart disease and/or optic nerve atrophy.
17. The medicament of claim 14 or 15 for use in the treatment, prophylaxis and/or management of diseases or disorders characterised or aggravated by a loss of innervation, in particular for use in the treatment, prophylaxis and/or management of ischemic heart disease, heart failure and diabetes and its comorbidities, in particular diabetic neuropathies.

18. The medicament of claim 14 or 15 for use in the treatment, prophylaxis and/or management of diseases or disorders that have been shown to benefit from a treatment with NGF, in particular for use in the treatment, prophylaxis and/or management of ulcers, neurotropic keratitis and/or glaucoma.

19. The medicament of claim 14 or 15 for use in the treatment, prophylaxis and/or management of diseases or disorders, in particular diseases or disorders related to NGF, more particularly diseases and disorders related to an elevated level of NGF and especially for use in the treatment and/or management of pain and/or the treatment and/or prophylaxis of cardiac arrhythmia and/or sudden cardiac death.

20. A method for the prophylaxis, treatment and/or management of diseases or disorders benefiting from an increased activation of the TrkA-receptor in humans and animals comprising administering a therapeutically effective amount of a peptide or peptide fragment of any one of claims 1 to 4.

21. A method for treating, preventing and/or managing peripheral neuropathies, multiple sclerosis, Alzheimer's disease, Parkinson's disease, hypoxic brain injuries, heart failure, ischemic heart disease and/or optic nerve atrophy in humans and animals comprising administering a therapeutically effective amount of a peptide or peptide fragment of any one of claims 1 to 4.
22. A method for treating, preventing and/or managing diseases or disorders characterized or aggravated by a loss of innervation in humans and animals comprising administering a therapeutically effective amount of the peptides or peptide fragments of any one of claims 1 to 4.

23. A method for treating, preventing and/or managing ischemic heart disease, heart failure and diabetes and its comorbidities, in particular diabetic neuropathies in humans and animals comprising administering a therapeutically effective amount of the peptides or peptide fragments of any one of claims 1 to 4.

24. A method for treating, preventing and/or managing other diseases and disorders that have been shown to benefit from a treatment with NGF in humans and animals comprising administering a therapeutically effective amount of a peptide or peptide fragment according to any one of claims 1 to 4.

25. A method for treating, preventing and/or managing ulcers, neurotrophic keratitis and/or glaucoma in humans and animals comprising administering a therapeutically effective amount of a peptide or peptide fragment according to any one of claims 1 to 4.

26. A method for the prophylaxis, treatment and/or management of diseases or disorders related to NGF, in particular elevated levels of NGF in humans and animals comprising administering a therapeutically effective amount of a peptide or peptide fragment of any one of claims 1 to 4.

27. A method for treating and/or managing pain in humans and animals comprising administering a therapeutically effective amount of a peptide or peptide fragment of any one of claims 1 to 4.
28. A method for treating and/or preventing hyperinnervation in humans and animals comprising administering a therapeutically effective amount of a peptide or peptide fragment of any one of claims 1 to 4.

29. A method for treating and/or preventing cardiac arrhythmias and/or sudden cardiac death in humans and animals comprising administering a therapeutically effective amount of a peptide or peptide fragment of any one of claims 1 to 4.
### Box No. 1  Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
   
   a. [✓] forming part of the international application as filed:
      
      - in the form of an Annex C/ST.25 text file.
      - on paper or in the form of an image file.
   
   b. [ ] furnished together with the international application under PCT Rule 13ter.1 (a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
   
   c. [✓] furnished subsequent to the international filing date for the purposes of international search only:
      
      - in the form of an Annex C/ST.25 text file (Rule 13ter.1 (a)).
      - on paper or in the form of an image file (Rule 13ter.1 (b) and Administrative Instructions, Section 713).

2. [✓] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:
# A. CLASSIFICATION OF SUBJECT MATTER

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<th>C07K14/48</th>
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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)
  - C07K 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 practicable, search terms used)

- EPO-Internal, EMBASE, FSTA, WPI Data

# C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of Box C. See patent family annex.

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent 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
- "A" document member of the same patent family

Date of the actual completion of the international search

17 June 2016

Date of mailing of the international search report

29/06/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HJ Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer

Bonello, Steve
<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>D Dawbarn ET AL: &quot;NGF receptor TrkAd5: therapeuti c agent and drug design target&quot;, Biomedicai Society Transactions, 1 August 2006 (2006-08-01), page 587, XP055281187, England DOI : 10.1042/BST0340587 Retri eved from the Internet: URL: <a href="https://www.researchgate.net/profi">https://www.researchgate.net/profi</a> le/Dawbarn_Shoemark/publi cations where the NGF receptor TrkAd5 Therapeuti c agent and drug design target is described in detail p. 588 col. 1 par. 4 -----</td>
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