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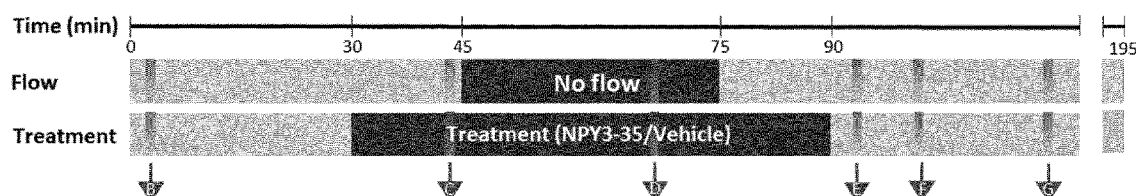


FIGURE 1

(57) Abstract: The present invention relates to neuropeptide Y (NPY)-derived peptide fragments that bind to Neural Cell Adhesion Molecule (NCAM), for use in the treatment of cardiovascular diseases, in particular cardiac disease, such as cardiac diseases associated with arrhythmias, such as cardiac arrhythmia.

Treatment of cardiovascular diseases

Technical field

The present invention relates to compounds that bind to Neural Cell Adhesion Molecule (NCAM), in particular neuropeptide Y (NPY)-derived peptide fragments, for use in the
5 treatment of cardiovascular diseases, such as a cardiac disease, such as cardiac diseases associated with arrhythmias, such as cardiac arrhythmia.

Background

Cardiovascular disease is a general term for conditions affecting the heart or blood vessels. According to the World Health Organization (WHO), more people die from
10 cardiovascular diseases than from any other cause. In 2016, approximately 17.9 million people died from cardiovascular diseases, representing 31% of all global deaths.

Cardiac arrest, which is a sudden loss of blood flow resulting from the failure of the heart to pump effectively, is the cause of about half of deaths due to cardiovascular disease. About 80% of sudden cardiac death is the result of ventricular arrhythmias.
15 There are several types of antiarrhythmic drugs on the market today, which mainly target ion channels and changes in action potential morphology. These antiarrhythmic drugs are often associated with pro-arrhythmias or severe side effects, and hence, there is a need for more safe anti-arrhythmic drugs, such as drugs that target cardiac conduction velocity rather than the action potential.

20 Neuropeptide Y (NPY) is a 36 amino acid-long polypeptide (NPY1-36; SEQ ID NO: 1) widely distributed in the central and peripheral nervous system of mammals. NPY is the most abundant neuropeptide in the brain and is known to induce vasoconstriction, to inhibit noradrenaline release at a pre-synaptic level, and to regulate diverse functions
25 including blood pressure, stress, pain, hormone secretion, reproduction, circadian rhythm and food intake. NPY has been implicated in feeding disorders, epilepsy, hypertension, pain disorders, depression and anxiety.

NPY is known to bind and stimulate receptors belonging to the GPCR family, also
30 known as seven-transmembrane receptors (7TM); including NPY receptors Y1, Y2, Y3, Y4, Y5 and Y6 (aka y6). In the central nervous system, NPY predominantly acts via Y1, Y2 and Y5. These 7TM receptors display different affinities for full-length NPY and N-terminally truncated fragments thereof such as NPY3-36; a physiological cleavage

product which loses affinity for the Y1 receptor to become an Y2/Y5 receptor agonist. NPY is known to exert neuroprotective and neurogenic effects reported to occur via activation of the GPCR NPY-receptors.

5 A number of NPY fragments have been disclosed that retain activity at the native NPY receptors, including some of 8 to 18 amino acids in length with a D-Thr amino acid substitution of the Thr32 position, such as NPY27-36, for inducing satiety and lowering blood pressure (Nyce et al. US 6,426,330); expression vectors comprising a nucleic acid encoding NPY or a functional fragment thereof, such as NPY2-36, NPY13-36,
10 NPY16-36 and NPY18-36, for treating neurological diseases (During et al. US2010/0168215); and NPY19-36 and NPY 17-36 for lowering blood pressure (Boublik et al. US 5,026,685 and US 5,328,899).

Native NPY is known to bind to and exert its various biological effects through NPY
15 receptors Y1-Y6. NPY as an Y1-Y6 ligand or agonist is dependent on amino acid residue 36 (Tyr36), which position is amidated. It has previously been shown that NPY not comprising Tyr36 lacks the classical NPY effects such as on food intake which is mediated through the classical or cognate NPY-receptors (Y1-Y6). Also, NPY3-35 is known in the art as a degradation product with no biological effects through the known
20 NPY-receptors (Abid et al. J Biol Chem Vol 284, No 37, pp. 24715-24724, 2009).

WO 2014/166497 discloses that NPY as well as fragments thereof lacking Tyr36 bind predominantly to the Ig1 module of NCAM, in the area where two NCAM molecules would otherwise interact. Without residue Tyr36, the NPY fragments do not bind to and
25 activate the cognate NPY-receptors and thus effectively avoids the risk of adverse effects through general activation of Y1-Y6 receptors. The NPY peptides have several neuronal effects and are known to be useful in treating disorders of the central nervous system and the eye.

30 Interaction with the NPY receptors has been coupled to cardiovascular effects. For example, NPY attenuates vagal bradycardia via a pre-synaptic decrease in acetylcholine release that appears to be mediated by a Y2 receptor pathway (Herring et al. J Mol Cell Cardiol. 2008 Mar;44(3):477-85). Furthermore, WO 2002/083137 discloses the use of non-peptide NPY Y2 receptor antagonists for the prevention of
35 sudden death due to cardiac arrhythmias, and US 2012/040885 discloses NPY peptide

variants having at least one unnatural amino acid substitution for treating diseases mediated by neuropeptide-Y-receptor binding such as arrhythmia.

5 Contradicting data exists regarding the correlation between NCAM modulation and cardio-protective effects, and no direct link between NCAM modulation and cardiac arrhythmias has been provided to date.

Summary

The invention is as defined in the claims.

10 The present inventors have surprisingly demonstrated that fragments of NPY that do not comprise the Tyr amino acid at position 36 of NPY (SEQ ID NO:1), Tyr36, increases cardiac conduction velocity (CV), and that this effect is attributed to its binding to NCAM located on cardiomyocytes; subsequently, the associated risk of arrhythmias in stressed tissue is reduced. This novel property makes the NPY
15 fragments lacking Tyr36 disclosed herein useful for treatment of a range cardiovascular diseases. Thus, in one aspect, the present disclosure concerns a compound that binds to NCAM for use in the treatment of cardiovascular diseases; such as a cardiac disease, such as cardiac diseases associated with arrhythmias, such as cardiac arrhythmia.

20 Said compound binding to NCAM are in preferred embodiments a peptide. Thus, in another aspect, the present disclosure concerns a peptide, said peptide consisting of from 15 to 35 contiguous amino acid residues derived from NPY (SEQ ID NO: 1), wherein said peptide comprises at least the sequence YSALRHYNLITRQR (NPY21-35; SEQ ID NO: 22), or a functional variant having at least 60% sequence identity to
25 SEQ ID NO: 22, wherein said peptide does not comprise the Tyr amino acid of position 36 of SEQ ID NO: 1, for use in a method of treating cardiovascular diseases; such as a cardiac disease, such as cardiac diseases associated with arrhythmias, such as cardiac arrhythmia.

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Description of the drawings

Figure 1. Treatment protocol for Langendorff perfused hearts, and representative electrical and mechanical traces. An overview of the protocol is depicted in Figure 1A.

Hearts were perfused for 30 min at baseline before treatment was initiated (NPY3-35 or vehicle) and maintained for 60 min. After 15 min of treatment, flow was stopped for 35 min to induce global no flow ischemia. The flow was subsequently reestablished, reperfusion the hearts for 15 min with treatment followed by 105 min without treatment. ECG (panel 1 and 3) and developed pressure (panel 2 and 4) was continuously recorded. The 6 images from each group represent **B**: baseline, **C**: 13 min. into treatment but before no flow, **D**: during no flow, **E**, **F** and **G**: after reperfusion. All hearts lost electrical and mechanical function during no flow ischemia. During reperfusion, all hearts regained sinus rhythm, but some hearts degenerated into ventricular tachycardia, fibrillation or asystole (failed recovery, panel 1 and 2), whereas others maintained sinus rhythm (successful recovery, panel 3 and 4).

Figure 2. Recovery after ischemia. Successful recovery of sinus rhythm was obtained in 3 of 10 vehicle treated hearts vs 7 of 8 NPY3-35 treated hearts (* $p < 0.05$, Fisher's exact test).

Figure 3. Relative infarct size after ischemia-reperfusion. At the end of the experiments, hearts were stained for infarct size (IS), and IS and area at risk (AAR, total area of left and right ventricle) was quantified. The relative IS pr. AAR was calculated and we found no significant difference between the hearts treated with either vehicle or NPY3-35 (Student's t-test). Data are presented as mean $\pm$ SEM.

Figure 4. Effect of NPY3-35 on conduction velocity (mouse model). In neurons, NPY3-35 exerts its effect by binding to and subsequent signaling via NCAM and NPY3-35 was therefore tested in wild-type (WT; A) mice and in NCAM knock-out (KO; B) mice. Conduction velocity (CV) measured in right ventricular tissue strips at baseline (10 min, buffer pH 7.4, glucose 5 mM, equilibrated with 100 % O₂) followed by treatment with either vehicle (black lines) or NPY3-35 (grey lines) for the remainder of the experiment. After 10 minutes of treatment, strips were subjected to 30 minutes of simulated ischemia (buffer pH 6.8, no glucose, equilibrated with atmospheric air) followed by reperfusion. In WT-mice, neither vehicle treatment, ischemia nor reperfusion significantly affected CV, although ischemia significantly reduced developed force by approximately 50% (data not shown). In contrast, CV significantly increased during reperfusion in the NPY3-35 treated WT mice (by 0.12 m/sec, $P < 0.05$), whereas no significant changes occurred during NPY3-35 treatment or subsequent ischemia. The ability of NPY3-35 to increase CV was lost in NCAM KO animals where CV remained

unaffected over time irrespective of treatment, which shows the dependence of NCAM as a receptor in the response. Average CV was determined during the last two minutes of each period and we used a linear mixed-effects model analysis (R, lme) to test for statistical significance. Data are presented as mean $\pm$ SEM.

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Figure 5. Relative conduction velocity (CV) change between time point 20 and 70 min. The CV recovery after ischemia is illustrated as relative CV change for WT and NCAM KO mice treated with either NPY3-35 or vehicle. In NCAM KO mice there were no difference in relative CV change between vehicle and NPY3-35 treated hearts. In contrast, CV increased significantly in WT mice treated with NPY3-35 (15.5 % vs 0.6 % in vehicle treated strips (* p < 0.05, Student t-test). Data are presented as mean $\pm$ SEM.

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Figure 6. Conduction velocity (CV) recovery during reperfusion. The CV recovery after ischemia is illustrated as CV development for every 4 min. (as an average over 2 min) from time point 50 to 70 min. in WT (A) and NCAM KO mice (B) treated with either NPY3-35 or vehicle. The CV recovery in WT mice was significantly influenced by treatment (P < 0.05, two-way repeated measures ANOVA). CV was significantly higher in the NPY3-35 treated group at time point 62, 66 and 70, compared to the vehicle treated group (Bonferroni post hoc test). In NCAM KO mice, the CV recovery was not influenced by the treatment indicating a role of NCAM for CV recovery. In the WT groups, the relative CV recovery from 50-70 min. was 8 ± 4 % in vehicle treated hearts, whereas the hearts treated with NPY3-35 showed a relative recovery of 30 ± 11 %. In the KO groups, the relative recovery was 14 ± 5 % and 5 ± 3 % in vehicle and NPY3-35 treated hearts respectively. Data are presented as mean $\pm$ SEM, * P < 0.05.

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Figure 7. Effect of NPY3-35 on conduction velocity in rat right ventricular myocardium. Conduction velocity (CV) was measured in right ventricular tissue strips at baseline (10 min, buffer pH 7.4, glucose 5 mM, equilibrated with 100 % O₂) followed by treatment with either vehicle (black line) or two different doses of NPY3-35 (0.1 μ M in dashed line and 1 μ M in dotted line) for the remainder of the experiment. After 10 min treatment, strips were subjected to 30 min simulated ischemia (buffer pH 6.8, no glucose, equilibrated with atmospheric air) followed by reperfusion (same buffer as baseline). CV decreased significantly in all groups during simulated ischemia with variable degree of recovery during reperfusion. Compared to vehicle, NPY3-35 did not significantly affect CV during treatment before or during simulated ischemia. However, as was observed in mice (Fig. 4), CV significantly increased during reperfusion in the NPY3-35

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treated groups. The inserted bar graph in the lower right corner shows that treatment with NPY3-35 significantly increased conduction velocity relative to baseline by 11% (0.1 μ M, light grey) and 9% (1 μ M, dark grey) during reperfusion compared to a 4% reduction in vehicle treated myocardium (black). Average CV was determined during the last two minutes of reperfusion and we used a linear mixed-effects model analysis (R, lme) to test for statistical significance. Lines represent the mean, whereas data are presented as mean $\pm$ SEM in the bar graph (insert). * indicates $P < 0.05$.

Figure 8. Effect of NPY10-35 and NPY21-35 on conduction velocity in rat right ventricular myocardium. Conduction velocity (CV) was measured in right ventricular tissue strips at baseline (10 min, buffer pH 7.4, glucose 5 mM, equilibrated with 100 % O₂) followed by treatment with either vehicle (black bar), NPY10-35 (1 μ M, n=3, white bar), or NPY21-35 (1 μ M or 0.1 μ M, n=6, grey bar) for the remainder of the experiment. After 10 min treatment, strips were subjected to 30 min simulated ischemia (buffer pH 6.8, no glucose, equilibrated with atmospheric air) followed by reperfusion (same buffer as baseline). Bars show average change in CV during reperfusion relative to baseline. Error bars show SEM.

Definitions and abbreviations

Affinity: the strength of binding between receptors and their ligands.

The term “agonist” in the present context refers to a compound as defined herein, capable of binding to and activating a receptor.

The term “antagonist” in the present context refers to a compound as defined herein, capable of binding to a receptor and blocking or damping a biological response of said receptor.

The term “individual” refers to vertebrates, particular members of the mammalian species, preferably primates including humans. As used herein, ‘subject’ and ‘individual’ may be used interchangeably.

A “polypeptide”, “peptide” or “protein” is a polymer of amino acid residues preferably joined exclusively by peptide bonds, whether produced naturally or synthetically. The term “polypeptide” as used herein covers proteins, peptides and polypeptides, wherein said proteins, peptides or polypeptides may or may not have been post-translationally modified. A peptide is usually shorter in length than a protein, and single-chained.

An "isolated polypeptide" is a polypeptide or protein separated and/or recovered from a component of their natural, typically cellular, environment, that is essentially free from contaminating cellular components, such as carbohydrate, lipid, or other proteinaceous impurities associated with the polypeptide in nature. However, the term "isolated" does not exclude the presence of the same polypeptide in alternative physical forms, such as dimers, tetramers or alternatively glycosylated or derived forms.

An "amino acid residue" can be a natural or non-natural amino acid residue linked peptide bonds or bonds different from peptide bonds. The amino acid residues can be in D-configuration or L-configuration. An amino acid residue comprises an amino terminal part (NH₂) and a carboxy terminal part (COOH) separated by a central part comprising a carbon atom, or a chain of carbon atoms, at least one of which comprises at least one side chain or functional group. NH₂ refers to the amino group present at the amino terminal end of an amino acid or peptide, and COOH refers to the carboxy group present at the carboxy terminal end of an amino acid or peptide. The generic term amino acid comprises both natural and non-natural amino acids. Natural amino acids of standard nomenclature as listed in J. Biol. Chem., 243:3552-59 (1969) and adopted in 37 C.F.R., section 1.822(b)(2) belong to the group of amino acids listed in Table 1 herein below. Non-natural amino acids are those not listed in Table 1. Also, non-natural amino acid residues include, but are not limited to, modified amino acid residues, L-amino acid residues, and stereoisomers of D-amino acid residues.

Symbols		Amino acid
1-Letter	3-Letter	
Y	Tyr	tyrosine
G	Gly	glycine
F	Phe	phenylalanine
M	Met	methionine
A	Ala	alanine
S	Ser	serine
I	Ile	isoleucine
L	Leu	leucine
T	Thr	threonine
V	Val	valine
P	Pro	proline
K	Lys	lysine
H	His	histidine
Q	Gln	glutamine
E	Glu	glutamic acid
W	Trp	tryptophan
R	Arg	arginine
D	Asp	aspartic acid

N	Asn	asparagine
C	Cys	cysteine

Table 1. Natural amino acids and their respective codes.

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An “equivalent amino acid residue” refers to an amino acid residue capable of replacing another amino acid residue in a polypeptide without substantially altering the structure and/or functionality of the polypeptide. Equivalent amino acids thus have similar properties such as bulkiness of the side-chain, side chain polarity (polar or non-polar), hydrophobicity (hydrophobic or hydrophilic), pH (acidic, neutral or basic) and side chain organization of carbon molecules (aromatic/aliphatic). As such, “equivalent amino acid residues” can be regarded as “conservative amino acid substitutions”.

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The classification of equivalent amino acids refers in one embodiment to the following classes: 1) HRK, 2) DENQ, 3) C, 4) STPAG, 5) MILV and 6) FYW.

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Within the meaning of the term “equivalent amino acid substitution” as applied herein, one amino acid may be substituted for another, in one embodiment, within the groups of amino acids indicated herein below:

- i) Amino acids having polar side chains (Asp, Glu, Lys, Arg, His, Asn, Gln, Ser, Thr, Tyr, and Cys,)
- 20 ii) Amino acids having non-polar side chains (Gly, Ala, Val, Leu, Ile, Phe, Trp, Pro, and Met)
- iii) Amino acids having aliphatic side chains (Gly, Ala, Val, Leu, Ile)
- iv) Amino acids having cyclic side chains (Phe, Tyr, Trp, His, Pro)
- v) Amino acids having aromatic side chains (Phe, Tyr, Trp)
- 25 vi) Amino acids having acidic side chains (Asp, Glu)
- vii) Amino acids having basic side chains (Lys, Arg, His)
- viii) Amino acids having amide side chains (Asn, Gln)
- ix) Amino acids having hydroxy side chains (Ser, Thr)
- x) Amino acids having sulphur-containing side chains (Cys, Met),
- 30 xi) Neutral, weakly hydrophobic amino acids (Pro, Ala, Gly, Ser, Thr)
- xii) Hydrophilic, acidic amino acids (Gln, Asn, Glu, Asp), and
- xiii) Hydrophobic amino acids (Leu, Ile, Val)

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In the present context the standard one-letter code for amino acid residues as well as the standard three-letter code is applied. Abbreviations for amino acids are in accordance with the recommendations in the IUPAC-IUB Joint Commission on

Biochemical Nomenclature Eur. J. Biochem, 1984, vol. 184, pp 9-37. Throughout the application either the three letter code or the one letter code for natural amino acids are used. Where the L or D form (optical isomers) has not been specified it is to be understood that the amino acid in question has the natural L form, cf. Pure & Appl. Chem. Vol. (56(5) pp 595-624 (1984) or the D form, so that the peptides formed may be constituted of amino acids of L form, D form, or a sequence of mixed L forms and D forms.

A "Bioactive agent" (i. e., biologically active substance/agent) is any agent, drug, compound, composition of matter or mixture which provides some pharmacologic, often beneficial, effect that can be demonstrated *in vivo* or *in vitro*. It may refer to the peptide sequences according to the present invention, compounds or compositions comprising these and nucleic acid constructs encoding said peptides. As used herein, this term further includes any physiologically or pharmacologically active substance that produces a localized or systemic effect in an individual. Further examples of bioactive agents include, but are not limited to, agents comprising or consisting of an oligosaccharide, agents comprising or consisting of a polysaccharide, agents comprising or consisting of an optionally glycosylated peptide, agents comprising or consisting of an optionally glycosylated polypeptide, agents comprising or consisting of a nucleic acid, agents comprising or consisting of an oligonucleotide, agents comprising or consisting of a polynucleotide, agents comprising or consisting of a lipid, agents comprising or consisting of a fatty acid, agents comprising or consisting of a fatty acid ester and agents comprising or consisting of secondary metabolites. It may be used either prophylactically, therapeutically, in connection with treatment of an individual, such as a human or any other animal.

The terms "drug", "medicament" as used herein include biologically, physiologically, or pharmacologically active substances that act locally or systemically in the human or animal body.

The terms "treatment" and "treating" as used herein refer to the management and care of a patient for the purpose of combating a condition, disease or disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, and refer equally to curative therapy, prophylactic or preventative therapy and ameliorating or palliative therapy, such as administration of the peptide or composition for the purpose of: alleviating or relieving symptoms or complications; delaying the progression of the condition, partially arresting the clinical manifestations,

disease or disorder; curing or eliminating the condition, disease or disorder; amelioration or palliation of the condition or symptoms, and remission (whether partial or total), whether detectable or undetectable; and/or preventing or reducing the risk of acquiring the condition, disease or disorder, wherein "preventing" or "prevention" is to be understood to refer to the management and care of a patient for the purpose of hindering the development of the condition, disease or disorder, and includes the administration of the active compounds to prevent or reduce the risk of the onset of symptoms or complications. The term "palliation", and variations thereof, as used herein, means that the extent and/or undesirable manifestations of a physiological condition or symptom are lessened and/or time course of the progression is slowed or lengthened, as compared to not administering compositions of the present invention.

The individual to be treated is preferably a mammal, in particular a human being. Treatment of animals, such as mice, rats, dogs, cats, cows, horses, sheep and pigs, is, however, also within the scope of the present disclosure.

An "individual in need thereof" refers to an individual who may benefit from the present disclosure. In one embodiment, said individual in need thereof is a diseased individual, wherein said disease may be a cardiovascular disease, such as a cardiac disease, such as cardiac diseases associated with arrhythmias, such as cardiac arrhythmia.

A "treatment effect" or "therapeutic effect" is manifested if there is a change in the condition being treated, as measured by the criteria constituting the definition of the terms "treating" and "treatment." There is a "change" in the condition being treated if there is at least 5% improvement, preferably 10% improvement, more preferably at least 25%, even more preferably at least 50%, such as at least 75%, and most preferably at least 100% improvement. The change can be based on improvements in the severity of the treated condition in an individual, or on a difference in the frequency of improved conditions in populations of individuals with and without treatment with the bioactive agent, or with the bioactive agent in combination with a pharmaceutical composition of the present invention.

A treatment according to the invention may be prophylactic, ameliorating or curative.

"Pharmacologically effective amount", "pharmaceutically effective amount" or "physiologically effective amount" of a "bioactive agent" is the amount of an active agent present in a pharmaceutical composition as described herein that is needed to provide a desired level of active agent in the bloodstream or at the site of action in an

individual (e.g. the heart, blood vessels, the lungs, the gastric system, the colorectal system, prostate, etc.) to be treated to give an anticipated physiological response when such composition is administered. The precise amount will depend upon numerous factors, e.g., the active agent, the activity of the composition, the delivery device
5 employed, the physical characteristics of the composition, intended patient use (i.e. the number of doses administered per day), patient considerations, and the like, and can readily be determined by one skilled in the art, based upon the information provided herein. An "effective amount" of a bioactive agent can be administered in one administration, or through multiple administrations of an amount that total an effective
10 amount, preferably within a 24-hour period. It can be determined using standard clinical procedures for determining appropriate amounts and timing of administration. It is understood that the "effective amount" can be the result of empirical and/or individualized (case-by-case) determination on the part of the treating health care professional and/or individual.

15 The terms "enhancing" and "improving" a beneficial effect, and variations thereof, as used herein, refers to the therapeutic effect of the bioactive agent against placebo, or an increase in the therapeutic effect of a state-of-the-art medical treatment above that normally obtained when a pharmaceutical composition is administered without the bioactive agent of this invention. "An increase in the therapeutic effects" is manifested
20 when there is an acceleration and/or increase in intensity and/or extent of the therapeutic effects obtained as a result of administering the bioactive agent(s). It also includes extension of the longevity of therapeutic benefits. It can also manifest where a lower amount of the pharmaceutical composition is required to obtain the same benefits and/or effects when it is co-administered with bioactive agent(s) provided by
25 the present invention as compared to the administration in a higher amount of the pharmaceutical composition in the absence of bioactive agent. The enhancing effect preferably, but not necessarily, results in treatment of acute symptoms for which the pharmaceutical composition alone is not effective or is less effective therapeutically. Enhancement is achieved when there is at least a 5% increase in the therapeutic
30 effects, such as at least 10% increase in the therapeutic effects when a bioactive agent of the present invention is co-administered with a pharmaceutical composition compared with administration of the pharmaceutical composition alone. Preferably the increase is at least 25%, more preferably at least 50%, even more preferably at least 75%, most preferably at least 100%.

- "Co-administering" or "co-administration" of bioactive agents / peptides of the invention and state-of-the-art medicaments, as used herein, refer to the administration of one or more bioactive agents of the present invention, or administration of one or more bioactive agents of the present invention and a state-of-the-art pharmaceutical composition within a certain time period. The time period is preferably less than 72 hours, such as 48 hours, for example less than 24 hours, such as less than 12 hours, for example less than 6 hours, such as less than 3 hours. However, these terms also mean that the bioactive agent and a therapeutic composition can be administered together.
- Due to the imprecision of standard analytical methods, molecular weights and lengths of polymers are understood to be approximate values. When such a value is expressed as "about" X or "approximately" X, the stated value of X will be understood to be accurate to +/- 20%, such as +/- 10%, for example +/- 5%.

Detailed description

15 *Neuropeptide Y*

Pro-neuropeptide Y is a 97-amino acid long peptide (SEQ ID NO: 35) which is cleaved into the following 2 chains: Neuropeptide Y (alternative name: neuropeptide tyrosine), and C-flanking peptide of NPY (Short name=CPON: SEQ ID NO: 36).

- Neuropeptide Y (NPY; NPY1-36; SEQ ID NO: 1) is a highly conserved 36-amino acid endogenous peptide neurotransmitter, the most abundant neuropeptide in the brain and the autonomic nervous system of humans. Classically, the effects of NPY1-36 are mediated through binding to cognate NPY-receptors with varying degree. At least six NPY receptors have been identified so far; Y1, Y2, Y3, Y4, Y5 and Y6; five NPY receptors in mammals: Y1, Y2, Y4, Y5 and Y6 (or y6; used interchangeably herein). They are G-protein coupled receptors belonging to the 7TM (7 transmembrane domains) family.

- These receptors display different affinities for different forms of NPY. The Y1 receptor has highest affinity for full-length NPY, while Y2 and Y5 bind and are stimulated by full-length NPY and N-terminally truncated NPY. The physiological effects associated with the Y1 and Y2 receptors are the best known; exposure to a Y1 agonist causes an increase in blood pressure and potentiates postsynaptically the action of other

vasoactive substances, whereas Y2 receptors are mainly located presynaptically, and upon stimulation mediate the inhibition of neurotransmitter release. Moreover, Y2 exerts a negative-feedback pathway in that its activation by NPY or NPY fragments in turn negatively regulates NPY release.

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NPY is a prototype of peptide whose function can be altered by proteases. Among peptidases displaying a high affinity for NPY, the primary role appears to be played by serine-type protease dipeptidyl peptidase IV (CD26) that releases an N-terminal dipeptide. By cleaving the N-terminal Tyr-Pro dipeptide off NPY CD26 generates NPY3–36, a truncated form that loses its affinity for the Y1 receptor and becomes a Y2/Y5 receptor agonist. NPY can also be degraded by aminopeptidase P (AmP) by removing the N-terminal tyrosine from NPY to generate NPY2–36, a selective Y2 agonist. It has been indicated that the 36th, 35th, and 33rd residues of NPY analogues may also be removed by carboxypeptidases.

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In addition to the brain, NPY and its receptors are expressed throughout the body, both in the central nervous system (CNS) and in the sympathetic nervous system. NPY regulates cardiovascular and other sympathetic functions together with norepinephrine. NPY displays vasoconstrictor activity exerted by inhibiting Ca^{2+} -activated K^{+} channels in vascular smooth muscle, and it has been implicated in the control of blood pressure, sexual behaviour, food intake, neurological disorders, alcoholism, bone physiology, regulation of energy, circadian rhythms, balance, memory and learning.

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Further, NPY plays an important role in mood disorders, anxiety, epilepsy and depression. Central NPY levels in the cerebrospinal fluid are low in subjects suffering from depression and correlate inversely with anxiety. Anti-depressant-like effects can be achieved in mice by administering a Y2 antagonist or a Y1 agonist. Y1 has also been implicated in the mediation of adult neuronal proliferation and hippocampal neurogenesis. Importantly, the effects of NPY are commonly accepted to be a result of its interactions with its 7TM receptors.

30

Because NPY and the 7TM receptors are thought to be involved in so many pathways, NPY-based treatments such as treatments involving receptor agonists are likely to cause severe pleiotropic effects, such as obesity, anxiety and hypertension.

35

NPY1-36 is characterised by C-terminal amidation of the amino acid at position 36 (Tyr36). The Tyr36 amino acid and its amidation is important for the classical binding of NPY1-36 to the cognate NPY-receptors (Y1-Y6/y6) (Berglund et al. 2003).

5 NPY is also known to interact with NCAM (WO 2014/166497). This interaction is shown not only for full-length NPY1-36 and certain N-terminally truncated fragments, but to a greater extent for specified NPY fragments not comprising Tyr36, including NPY3-35 (SEQ ID NO: 4). This interaction occurs predominantly through binding to the Ig1 module of NCAM (i.e. where two NCAM molecules usually interact – NCAM homophilic
10 *cis*-interaction). No binding is observed to the Ig3 module of NCAM.

NPY1-36 retains its binding capability to its cognate NPY-receptors (Y1-Y6) besides the interaction with NCAM. However, peptide fragments not comprising Tyr36 (SEQ ID NO:s 2-22), including NPY3-35 (SEQ ID NO: 4), interacts with NCAM *without* a
15 concomitant binding of the cognate NPY-receptors. This is due to the lack of Tyr36 of SEQ ID NO:s 2-22. Thus, the NCAM binding of SEQ ID NO:s 2 to 22 is highly specific. This holds great potential in reducing the risk of adverse effects associated with administering NPY1-36, by avoiding the general activation of the cognate NPY-receptors.

20

Neural Cell Adhesion Molecule (NCAM)

NCAM is a homophilic binding glycoprotein expressed on the surface of neurons, glia, striated muscle (skeletal and cardiac) and natural killer cells. NCAM has been implicated as having a role in cell–cell adhesion, neurite outgrowth, synaptic formation
25 and plasticity, path-finding of axons, early synaptogenesis, synaptic maturation and learning and memory. Many aspects of neuronal development involve cell-cell adhesion mechanisms; these include neuronal cell migration, axon-bundle and synapse formation, formation of glial networks surrounding axons and synapses.

30 NCAM is a member of the Ig superfamily Cell Adhesion Molecules (CAMs) and is found predominantly in the synapses. Evidence suggests that NCAM mediates neuritogenesis by signalling via the Fibroblast growth factor receptor (FGFR) and the p59Fyn signalling pathway. NCAM comprises five Ig-like domains (Ig1, Ig2, Ig3, Ig4 and Ig5) and two fibronectin type III (FNIII) repeats. In striated muscle, NCAM
35 additionally contains a muscle specific domain (MSD) inserted between the two

fibronectin repeats. NCAM is known to have heterophilic and homophilic interactions with various ligands at the synapses. The different domains of NCAM have different roles, with the Ig domains being involved in homophilic (NCAM-NCAM) binding, while the FNIII domains are involved in signalling leading to neurite outgrowth.

5

Alternative splicing of NCAM results in at least 27 isoforms, of which the main three vary only by their cytoplasmic domain: NCAM-120kDa (GPI anchored); NCAM-140kDa (short cytoplasmic domain); NCAM-180kDa (long cytoplasmic domain). NCAM can also be modified by the insertion of minor exons, which can modulate its activities. NCAM can further be modified by the addition to its fifth Ig domain of the negatively charged, polysialic acid (PSA) which appears to play an important role in the synapse formation mediated by NCAM. PSA has indeed been shown to be important for long-term potentiation (LTP). NCAM further interacts with brain derived neurotrophic factor (BDNF) and Glial cell-derived neurotrophic factor (GDNF).

10

15

Compounds

The present inventors have surprisingly found and demonstrated herein that NPY fragments not comprising the C-terminal amino acid of native NPY1-36; Tyr36 increase cardiac conduction velocity (CV), and that this effect occurs through a specific interaction with NCAM. It has previously been shown that NPY fragments not comprising the C-terminal amino acid of native NPY1-36; Tyr36 do not bind to the cognate NPY-receptors, and hence said NPY fragments not comprising Tyr36 provides for a more specific approach to targeting NCAM; in the present setting for targeting NCAM in the heart. Thus, in one aspect, the present disclosure concerns a compound that is capable of binding to NCAM for use in the treatment of a cardiovascular disease in particular cardiac disease, such as cardiac diseases associated with arrhythmias, such as cardiac arrhythmia.

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25

30

The compounds disclosed herein are capable of interacting (i.e. interacts) with NCAM and/or are capable of binding to (i.e. binds to) NCAM. Thus, in one embodiment, the binding of the compound to NCAM causes an increase in cardiac conduction velocity. In one embodiment the compounds disclosed herein are capable of interacting with and/or binding to NCAM via the Ig1 module, and/or the Ig2 module of NCAM, and/or not the Ig3 module of NCAM. In a particular embodiment, the present peptides bind to the NCAM Ig1 module. In a particular embodiment, the peptides bind to the NCAM Ig1

module and not the NCAM Ig3 module. In a particular embodiment, the peptides do not bind to the NCAM Ig3 module.

5 In one embodiment, binding of the compounds disclosed herein to NCAM results in a modulation of NCAM mediated cell-cell adhesion or cell-extracellular matrix interaction. In one embodiment, said NCAM mediated cell-cell adhesion is homophilic or heterophilic. In one embodiment, said NCAM mediated cell-cell adhesion or cell-extracellular matrix interaction is a cis-interaction or a trans-interaction.

10 In one embodiment, binding of the compounds disclosed herein to NCAM results in a modulation of NCAM-induced signalling. In one embodiment, binding of the compound of the present invention to NCAM results in an increase in NCAM-induced signalling.

Peptides

15 In one aspect, the present disclosure provides a compound that is capable of binding to NCAM for use in the treatment of a cardiovascular disease. In one embodiment, said compound binding to NCAM is a peptide, such as a peptide derived from NPY.

20 Provided herein is a peptide consisting of a peptide sequence of from 15 to 35 contiguous amino acid residues derived from NPY (SEQ ID NO: 1), wherein said peptide does not comprise the amino acid of position 36 of SEQ ID NO: 1, for use in a method of treating a cardiovascular disease, such as a cardiac disease, such as cardiac diseases associated with arrhythmias, such as cardiac arrhythmia.

25 In one embodiment, said peptide does not comprise the Tyr amino acid of position 36 of SEQ ID NO: 1. In one embodiment, said peptide does not comprise any amino acid corresponding to position 36 of SEQ ID NO: 1. In one embodiment, the amino acid at the C-terminal is not a Tyr amino acid.

30 Provided herein is a peptide consisting of from 15 to 35 contiguous amino acid residues derived from NPY (YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY; SEQ ID NO: 1), wherein said peptide does not comprise the Tyr amino acid of position 36 of SEQ ID NO: 1, for use in a method of treating a cardiovascular disease, such as a cardiac disease, such as cardiac diseases associated with arrhythmias, such as cardiac arrhythmia.

35

In one embodiment, said peptide is an isolated peptide. The terms 'peptide' and 'isolated peptide' may be used interchangeably herein. When reference is made to a 'peptide', this term will encompass both references to a peptide *per se*, and also to a peptide for use according to the present invention.

5

Preferably, said peptide comprises at least the sequence YSALRHYINLITRQR (NPY21-35; SEQ ID NO: 22) or a functional variant thereof having at least 60% sequence identity to SEQ ID NO: 22; such as at least 65% sequence identity, for example at least 70% sequence identity, such as at least 75% sequence identity, such as at least 80% sequence identity, such as at least 85% sequence identity, such as at least 90% sequence identity, such as at least 95% sequence identity, for example at least 99% sequence identity to SEQ ID NO: 22.

10

15

In one embodiment, the peptide comprises at least the sequence YSALRHYINLITRQR (NPY21-35; SEQ ID NO: 22), or a functional variant thereof with 6 amino acid substitutions, such as 5 amino acid substitutions, such as 4 amino acid substitutions, such as 3 amino acid substitutions, such as 2 amino acid substitutions, such as 1 amino acid substitutions.

20

In one embodiment, the peptide comprises at least the sequence YSALRHYINLITRQR (NPY21-35; SEQ ID NO: 22), or a functional variant thereof having one or more conservative amino acid substitutions, such as 6 conservative amino acid substitutions, such as 5 conservative amino acid substitutions, such as 4 conservative amino acid substitutions, such as 3 conservative amino acid substitutions, such as 2 conservative amino acid substitutions, such as 1 conservative amino acid substitutions.

25

In one embodiment, the peptide comprises at least the sequence YSALRHYINLITRQR (NPY21-35; SEQ ID NO: 22).

30

Provided herein is a peptide consisting of from 15 to 35 contiguous amino acid residues derived from NPY (YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY; SEQ ID NO: 1), wherein said peptide does not comprise the Tyr amino acid of position 36 of SEQ ID NO: 1, wherein the peptide comprises at least the sequence YSALRHYINLITRQR (NPY21-35; SEQ ID NO: 22), or a functional variant thereof having at least 60% sequence identity to said peptide,

35

for use in a method of treating a cardiovascular disease,
such as a cardiac disease, such as cardiac diseases associated with arrhythmias, such
as cardiac arrhythmia.

- 5 The terms 'variant' and 'functional variant' may be used interchangeably herein. A
functional variant is a variant that retains the same biological activity or capabilities as
the peptide from which it is derived. Variants of peptides as disclosed herein are meant
to be the functional equivalents of said sequences, i.e. retaining the functional
capabilities of the native or unmodified sequences, such as retaining their ability to bind
10 to NCAM and/or retaining their ability not to bind to cognate NPY receptors and/or
retaining their ability to increase cardiac conduction velocity.

- A peptide that 'comprises or consist of' a sequence means that the peptide may
comprise the sequence, consist of the sequence, or comprise at least the full
15 sequence. A peptide that 'comprises at least' a peptide sequence, such as 'comprising
at least the sequence YSALRHYNLITRQR' means that the peptide includes all of the
peptide sequence YSALRHYNLITRQR (NPY21-35; SEQ ID NO: 22). It does not,
however, exclude that additional components or amino acids may be present.

- 20 In one embodiment, the peptide for use according to the present disclosure is selected
from the group consisting of:

- YPSKPDNPGEDAPAEDMARYYSALRHYNLITRQR (NPY 1-35, SEQ ID NO: 2)
PSKPDNPGEDAPAEDMARYYSALRHYNLITRQR (NPY 2-35, SEQ ID NO: 3)
SKPDNPGEDAPAEDMARYYSALRHYNLITRQR (NPY 3-35, SEQ ID NO: 4)
25 KPDNPGEDAPAEDMARYYSALRHYNLITRQR (NPY4-35, SEQ ID NO: 5),
PDNPGEDAPAEDMARYYSALRHYNLITRQR (NPY5-35, SEQ ID NO: 6),
DNPGEEDAPAEDMARYYSALRHYNLITRQR (NPY6-35, SEQ ID NO: 7),
NPGEDAPAEDMARYYSALRHYNLITRQR (NPY7-35, SEQ ID NO: 8),
PGEDAPAEDMARYYSALRHYNLITRQR (NPY8-35, SEQ ID NO: 9),
30 GEDAPAEDMARYYSALRHYNLITRQR (NPY9-35, SEQ ID NO: 10),
EDAPAEDMARYYSALRHYNLITRQR (NPY10-35, SEQ ID NO: 11),
DAPAEDMARYYSALRHYNLITRQR (NPY11-35, SEQ ID NO: 12),
APAEDMARYYSALRHYNLITRQR (NPY12-35, SEQ ID NO: 13),
PAEDMARYYSALRHYNLITRQR (NPY13-35, SEQ ID NO: 14),
35 AEDMARYYSALRHYNLITRQR (NPY14-35, SEQ ID NO: 15),

EDMARYYSALRHYINLITRQR (NPY15-35, SEQ ID NO: 16),
DMARYYSALRHYINLITRQR (NPY16-35, SEQ ID NO: 17),
MARYYSALRHYINLITRQR (NPY17-35, SEQ ID NO: 18),
ARYYSALRHYINLITRQR (NPY18-35, SEQ ID NO: 19),
5 RYYSALRHYINLITRQR (NPY19-35, SEQ ID NO: 20),
YYALRHYINLITRQR (NPY20-35, SEQ ID NO: 21), and
YSALRHYINLITRQR (NPY21-35, SEQ ID NO: 22),
or a functional variant thereof.

10 In another embodiment, said peptide is a functional variant having at least 60%
sequence identity to a peptide selected from the group consisting of SEQ ID NO: 2,
SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID
NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO:
13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18,
15 SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22.

In another embodiment, said peptide variant has at least 60% sequence identity, such
as at least 65% sequence identity, for example at least 70% sequence identity, such as
at least 75% sequence identity, for example at least 80% sequence identity, such as at
20 least 85% sequence identity, for example at least 90% sequence identity, such as at
least 95% sequence identity, for example at least 99% sequence identity to a peptide
selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4,
SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID
NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID
25 NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID
NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22.

In one embodiment, said peptide variant comprises one or more amino acid
substitutions as compared to any one of SEQ ID NO:s 2 to 22.

30

In one embodiment, said peptide variant comprises one amino acid substitution, such
as two amino acid substitutions, such as three amino acid substitutions, such as four
amino acid substitutions, such as five amino acid substitutions, such as six amino acid
substitutions, such as seven amino acid substitutions to the peptide sequence selected
35 from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO:
5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ

ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22.

- 5 In one embodiment, said peptide variant comprises one or more conservative or equivalent amino acid substitutions as compared to any one of SEQ ID NO:s 2 to 22.

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 35 contiguous amino acid residues having the sequence
10 YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY1-35, SEQ ID NO: 2), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:2, or YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

15 In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 34 contiguous amino acid residues having the sequence
PSKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY2-35, SEQ ID NO: 3), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:3, or
20 PSKPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 33 contiguous amino acid residues having the sequence
SKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY3-35, SEQ ID NO: 4), or a
25 functional variant thereof having at least 60% sequence identity to SEQ ID NO:4, or SKPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

In one embodiment, the peptide for use according to the present disclosure is a peptide
30 consisting of 32 contiguous amino acid residues having the sequence
KPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY4-35, SEQ ID NO: 5), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:5, or KPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

35 In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 31 contiguous amino acid residues having the sequence

PDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY5-35, SEQ ID NO: 6), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:6, or PDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

5 In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 30 contiguous amino acid residues having the sequence DNPGE
DNPGE DAPAEDMARYYSALRHYINLITRQR (NPY6-35, SEQ ID NO: 7), or a functional
variant thereof having at least 60% sequence identity to SEQ ID NO:7, or
DNPGE DAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

10

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 29 contiguous amino acid residues having the sequence
NPGEDAPAEDMARYYSALRHYINLITRQR (NPY7-35, SEQ ID NO: 8), or a functional
variant thereof having at least 60% sequence identity to SEQ ID NO:8, or
15 NPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 28 contiguous amino acid residues having the sequence
PGEDAPAEDMARYYSALRHYINLITRQR (NPY8-35, SEQ ID NO: 9), or a functional
20 variant thereof having at least 60% sequence identity to SEQ ID NO:9, or
PGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 27 contiguous amino acid residues having the sequence
25 GEDAPAEDMARYYSALRHYINLITRQR (NPY9-35, SEQ ID NO: 10), or a functional
variant thereof having at least 60% sequence identity to SEQ ID NO:10, or
GEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 26 contiguous amino acid residues having the sequence
30 EDAPAEDMARYYSALRHYINLITRQR (NPY10-35, SEQ ID NO: 11), or a functional
variant thereof having at least 60% sequence identity to SEQ ID NO:11, or
EDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

35 In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 25 contiguous amino acid residues having the sequence

DAPAEDMARYYSALRHYINLITRQR (NPY11-35, SEQ ID NO: 12), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:12, or DAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

5 In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 24 contiguous amino acid residues having the sequence APAEDMARYYSALRHYINLITRQR (NPY12-35, SEQ ID NO: 13), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:13, or APAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

10

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 23 contiguous amino acid residues having the sequence PAEDMARYYSALRHYINLITRQR (NPY13-35, SEQ ID NO: 14), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:14, or
15 PAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 22 contiguous amino acid residues having the sequence AEDMARYYSALRHYINLITRQR (NPY14-35, SEQ ID NO: 15), or a functional variant
20 thereof having at least 60% sequence identity to SEQ ID NO:15, or AEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 21 contiguous amino acid residues having the sequence
25 EDMARYYSALRHYINLITRQR (NPY15-35, SEQ ID NO: 16); or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:16, or EDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 20 contiguous amino acid residues having the sequence
30 DMARYYSALRHYINLITRQR (NPY16-35, SEQ ID NO: 17), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:17, or DMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

35 In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 19 contiguous amino acid residues having the sequence

MARYYSALRHYINLITRQR (NPY17-35, SEQ ID NO: 18), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:18, or MARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

5 In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 18 contiguous amino acid residues having the sequence ARYYALSALRHYINLITRQR (NPY18-35, SEQ ID NO: 19), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:19, or ARYYALSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

10

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 17 contiguous amino acid residues having the sequence RYYALSALRHYINLITRQR (NPY19-35, SEQ ID NO: 20), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:20, or RYYALSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

15

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 16 contiguous amino acid residues having the sequence YYALSALRHYINLITRQR (NPY20-35, SEQ ID NO: 21), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:21, or YYALSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

20

In one embodiment, the peptide for use according to the present disclosure is a peptide consisting of 15 contiguous amino acid residues having the sequence YALSALRHYINLITRQR (NPY21-35, SEQ ID NO: 22), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO:22, or YALSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

25

In a particular embodiment, the peptide for use according to the present disclosure is selected from the group consisting of:

30

SKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY3-35; SEQ ID NO: 4), a functional variant thereof having at least 60% sequence identity to SEQ ID NO: 4, and SKPDNPGEDAPAEDMARYYSALRHYINLITRQR (SEQ ID NO: 4) with 1, 2 or 3 amino acid substitutions;

35

EDAPAEDMARYYSALRHYINLITRQR (NPY10-35, SEQ ID NO: 11), a functional variant thereof having at least 60% sequence identity to SEQ ID NO: 11, and

EDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions; and YSALRHYINLITRQR (NPY21-35, SEQ ID NO: 22), a functional variant thereof having at least 60% sequence identity to SEQ ID NO: 22, and YSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

5

The peptide variants according to the present disclosure may comprise one or more amino acid substitutions introduced independently of one another. In one embodiment, said one or more amino acid substitutions are each selected from conservative and non-conservative amino acid substitutions. In one embodiment, said one or more amino acid substitution is a conservative amino acid substitution (or synonymous or equivalent substitution), that is the substitution of amino acids whose side chains have similar biochemical properties and thus do not affect the function of the peptide.

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Among the common amino acids, for example, a "conservative amino acid substitution" can also be illustrated by a substitution among amino acids within each of the following groups: (1) glycine, alanine, valine, leucine, and isoleucine, (2) phenylalanine, tyrosine, and tryptophan, (3) serine and threonine, (4) aspartate and glutamate, (5) glutamine and asparagine, and (6) lysine, arginine and histidine.

20

Conservative substitutions may be introduced in any one or more positions of a peptide according to the invention or a fragment thereof, as long as the variant remains functional. It may however also be desirable to introduce non-conservative substitutions in one or more positions (non-synonymous substitutions).

25

A non-conservative substitution leading to the formation of a variant of the peptide according to the invention would for example differ substantially in polarity, for example a residue with a non-polar side chain (Ala, Leu, Pro, Trp, Val, Ile, Leu, Phe or Met) substituted for a residue with a polar side chain such as Gly, Ser, Thr, Cys, Tyr, Asn, or Gln or a charged amino acid such as Asp, Glu, Arg, or Lys, or substituting a charged or a polar residue for a non-polar one; and/or ii) differ substantially in its effect on peptide backbone orientation such as substitution of or for Pro or Gly by another residue; and/or iii) differ substantially in electric charge, for example substitution of a negatively charged residue such as Glu or Asp for a positively charged residue such as Lys, His or Arg (and vice versa); and/or iv) differ substantially in steric bulk, for example substitution of a bulky residue such as His, Trp, Phe or Tyr for one having a minor side chain, e.g. Ala, Gly or Ser (and vice versa).

30

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Substitution of amino acids may in one embodiment be made based upon their hydrophobicity and hydrophilicity values and the relative similarity of the amino acid side-chain substituents, including charge, size, and the like.

5

A peptide according to the disclosure in one embodiment may also comprise one or more non-naturally occurring amino acid residues (unnatural, non-proteinogenic or non-standard amino acids). Non-naturally occurring amino acids include e.g., without limitation, beta-2-naphthyl-alanine, trans-3-methylproline, 2,4-methanoproline, cis-4-hydroxyproline, trans-4-hydroxyproline, N-methylglycine, allo-threonine, methylthreonine, hydroxyethylcysteine, hydroxyethylhomocysteine, nitroglutamine, homoglutamine, pipecolic acid, thiazolidine carboxylic acid, dehydroproline, 3- and 4-methylproline, 3,3-dimethylproline, tert-leucine, norleucine, norvaline, 2-azaphenylalanine, 3-azaphenylalanine, 4-azaphenylalanine, and 4-fluorophenylalanine.

15

Any amino acids according to the present disclosure may be in the L- or D-configuration, apart from glycine, which does not comprise a stereocenter. If nothing is specified, reference to the L-isomeric form is preferably meant. In one embodiment, one or more of said amino acid residues of the peptide are L amino acid residues. In one embodiment, all amino acid residues of the peptide are L amino acid residues. In another embodiment, one or more of the amino acid residues of the peptide are D amino acid residues. In one embodiment, all amino acid residues of the peptide are D amino acid residues.

20

The standard and/or non-standard amino acids may be linked by peptide bonds (to form a linear peptide chain), or by non-peptide bonds (e.g. via the variable side-chains of the amino acids). Preferably, the amino acids of the present invention are linked by peptide bonds.

25

The term peptide also embraces post-translational modifications introduced by chemical or enzyme-catalyzed reactions, as are known in the art. These include acetylation, phosphorylation, methylation, glucosylation, glycation, amidation, hydroxylation, deimination, deamidation, carbamylation and sulfation of one or more amino acid residues, and also proteolytic modification by known proteinases including lysosomal cathepsins, and also calpains, secretases and matrix-metalloproteinases.

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Also, functional equivalents of the peptides may comprise chemical modifications such as ubiquitination, labeling (e.g., with radionuclides, various enzymes, etc.), pegylation (derivatization with polyethylene glycol), or by insertion (or substitution by chemical synthesis) of amino acids such as ornithine, which do not normally occur in human proteins (non-proteinogenic).

Sterically similar compounds may be formulated to mimic the key portions of the peptide structure. This may be achieved by techniques of modelling and chemical designing known to those of skill in the art. For example, esterification and other alkylations may be employed to modify the amino terminus of e.g a di-arginine peptide backbone, to mimic a tetra peptide structure. It will be understood that all such sterically similar constructs fall within the scope of the present invention. Peptides with N-terminal and C-terminal alkylations and esterifications are also encompassed within the present invention.

Where nothing is specified it is to be understood that the C-terminal amino acid of a peptide according to the present invention exists as the free carboxylic acid, this may also be specified as “-OH”. However, the C-terminal amino acid of a peptide for use according to the invention may in another embodiment be the amidated derivative, which is indicated as “-NH₂” (or CONH₂). In one embodiment, the C-terminal amino acid of the peptide exists as the free carboxylic acid (“-OH”). In one embodiment, the C-terminal amino acid of the peptide is amidated (-NH₂).

Where nothing else is stated, the N-terminal amino acid of the peptide comprises a free amino-group, this may also be specified as “H-” (or “NH₂”). However, the N-terminal amino acid of a peptide according to the invention may in another embodiment be the acetylated derivative, which is indicated as “Acetyl” or “COCH₃”.

In one embodiment the C-terminal amino acid of the peptide according to the present invention exists as the free carboxylic acid (“-OH”). In another embodiment the C-terminal amino acid of the peptide according to the present invention is an amidated derivative (“-NH₂”). In one embodiment the N-terminal amino acid of the peptide according to the present invention comprises a free amino-group (“H-”). In another embodiment the N-terminal amino acid of the peptide according to the present invention is the acetylated derivative (“-Acetyl” or “COCH₃”).

A contiguous or consecutive peptide sequence is a sequence of consecutive amino acids being linked linearly by peptide bonds. Contiguous and consecutive amino acid sequence is used interchangeably herein.

5 In one embodiment, the peptide according to the present disclosure comprises a contiguous amino acid sequence of 32 amino acids, such as 31 amino acids, for example 30 amino acids, for example 29 amino acids, such as 28 amino acids, for example 27 amino acids, such as 26 amino acids, for example 25 amino acids, such as 24 amino acids, for example 23 amino acids, such as 22 amino acids, for example 21
10 amino acids, such as 20 amino acids, for example 19 amino acids, such as 18 amino acids, for example 17 amino acids, such as 16 amino acids, for example 15 amino acids derived from NPY (SEQ ID NO: 1) which comprises at least NPY21-35 (SEQ ID NO: 22) or a variant thereof.

15 It follows that in one embodiment, a peptide variant of a sequence as defined herein is a functional variant, i.e. a variant retaining some biological function and/or activity associated with the native sequence. In one embodiment a peptide variant according to the present invention is capable of binding to NCAM. In one embodiment a variant is capable of binding to the NCAM Ig1 module. In one embodiment, said peptide does not
20 bind to and/or does not activate cognate NPY-receptors Y1, Y2 and/or Y5.

In one embodiment, the peptide does not bind to and/or does not stimulate or activate the cognate NPY-receptors. In one embodiment said cognate NPY-receptors comprise G-protein coupled receptors, in one embodiment receptors Y1, Y2 and/or Y5.

25 In one embodiment said peptide or functional variant thereof increases conduction velocity (CV). In one embodiment said peptide or functional variant thereof increases conduction velocity (CV) during reperfusion. In one embodiment said peptide or functional variant thereof increases conduction velocity (CV) after ischemic stress. In
30 one embodiment said peptide or functional variant thereof increases ischemia-reperfusion conduction velocity (CV). In one embodiment said peptide or functional variant thereof increases cardiac conduction velocity (CV).

In one embodiment said peptide or functional variant thereof suppresses reperfusion
35 arrhythmias. In one embodiment said peptide or functional variant thereof reduces or

suppresses cardiac arrhythmia. In one embodiment said peptide or functional variant thereof has antiarrhythmic effect.

Multimeric compounds

5 Provided herein are compounds for use in methods of treating a cardiovascular or cardiac disease, such as cardiac diseases associated with arrhythmias, such as cardiac arrhythmia, in particular NPY-derived peptides. In one embodiment said peptide is formulated as a monomer (i.e. comprising 1 copy of the peptide), whereas in another embodiment, said peptide is formulated as a multimer.

10

In one embodiment, the peptide according to the present disclosure is formulated as a multimer. A multimer is a protein comprising or consisting of multiple monomers. A multimer is an aggregate of multiple molecules (aka monomers, as mono = one) that is usually held together with non-covalent bonds. This definition distinguishes a multimer from a polymer, which is a series of monomers that are held together with covalent bonds.

15

A peptide sequence of the present invention may be connected to another (identical or non-identical) peptide sequence of the present invention by a chemical bond or through a linker group. In some embodiments a peptide of the invention may be formulated as an oligomer or multimer of monomers, wherein each monomer is as a peptide sequence as defined according to the present disclosure.

20

25

Thus, according to the invention a multimeric compound may be a polymer comprising two or more peptide sequences of the invention, said peptide sequences being identical or non-identical, wherein at least one of the two or more peptide sequences is a peptide according to the present invention. Preferably, both peptide sequences are a peptide according to the present disclosure.

30

It is an aspect to provide a multimeric peptide consisting of i) two or more peptides, such as consisting of two peptides, three peptides or four peptides; or wherein said peptide consist of a dendrimer, such as a dendrimer consisting of 4 peptides, 8 peptides, 16 peptides, or 32 peptides, and ii) optionally a linker group, wherein each of said two or more peptides are selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO:

35

13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22; or a functional variant thereof.

5 In one embodiment the multimeric compound is a dimer, comprising two peptides according to the present disclosure, said two peptides being identical or non-identical with respect to each other.

10 In another embodiment the multimeric compound is a trimer, comprising three peptides according to the present disclosure, said peptides being identical or non-identical with respect to each other.

15 In another embodiment the multimeric compound is a tetramer, comprising four peptides according to the present disclosure, said peptides being identical or non-identical with respect to each other.

20 In one embodiment, the multimeric compound is a dendrimer, such as a tetrameric or octameric dendrimer. Dendrimers are repeatedly branched, roughly spherical large molecules, typically symmetric around the core, and often adopts a spherical three-dimensional morphology.

25 Dendrimers according to the present disclosure may comprise 4 peptides, 8 peptides, 16 peptides, or 32 peptides. In one particular embodiment said dendrimer comprises four peptides (i.e. a tetrameric dendrimer) or eight peptides (octameric dendrimer).

30 In some particular embodiments, the multimeric compound may comprise two identical amino acid sequences of the present invention (dimer) or the compound may comprise four identical copies of an amino acid sequence of the present invention (tetrameric dendrimer).

35 The multimers according to the disclosure may be made by linking two or more peptide monomers via a peptide bond or a linker group. They may be linked to a lysine backbone, such as a lysine residue (each peptide chain is linked to a single lysine residue), or coupled to a polymer carrier, for example a protein carrier. Said linker group in one embodiment comprises a plurality of lysine residues, such as a core

moiety having a plurality of lysine residues, such as seen in a lysine-based dendromeric structure containing three, seven, fifteen and more lysine residues. However, any other linking of peptide monomers known to the skilled person may be envisioned.

5

The linking may in one embodiment occur at the N-terminal or C-terminal end of the peptide monomers.

Nucleic acid constructs encoding peptides

10 It is also an aspect to provide a nucleic acid construct encoding for and being capable of expressing a peptide according to the present disclosure. By nucleic acid construct is understood a genetically engineered nucleic acid. The nucleic acid construct may be a non-replicating and linear nucleic acid, a circular expression vector or an autonomously replicating plasmid. A nucleic acid construct may comprise several
15 elements such as, but not limited to genes or fragments of same, promoters, enhancers, terminators, poly-A tails, linkers, polylinkers, operative linkers, multiple cloning sites (MCS), markers, STOP codons, internal ribosomal entry sites (IRES) and host homologous sequences for integration or other defined elements. It is to be understood that the nucleic acid construct according to the present invention may
20 comprise all or a subset of any combination of the above-mentioned elements.

Methods for engineering nucleic acid constructs are well known in the art (see, e.g., Molecular Cloning: A Laboratory Manual, Sambrook et al., eds., Cold Spring Harbor Laboratory, 2nd Edition, Cold Spring Harbor, N.Y., 1989). Further, nucleic acid
25 constructs according to the present invention may be synthesized without template, and may be obtained from various commercial suppliers.

In one embodiment, the nucleic acid constructs are naked DNA constructs comprising sequences encoding the peptide of the disclosure.

30

Preferably said nucleic acid construct will be able to continuously express a peptide according to the present invention for a prolonged period of time, such as at least 1 month, for example at least 2 months, such as at least 3 months, for example at least 4 months, such as at least 5 months, for example at least 6 months, such as at least 7

months, for example at least 8 months, such as at least 9 months, for example at least 12 months.

5 In one embodiment, said nucleic acid construct encodes a peptide consisting of a peptide sequence of from 15 to 35 contiguous amino acid residues derived from neuropeptide Y (NPY) (SEQ ID NO: 1), wherein said peptide comprises at least, or consists of, the sequence YSALRHYINLITRQR (NPY21-35; SEQ ID NO: 22), or a functional variant having at least 60% sequence identity to SEQ ID NO: 22, wherein said peptide does not comprise the amino acid of position 36 of SEQ ID NO: 1. In one
10 embodiment, said peptide does not comprise an amino acid, such as the Tyr amino acid, of position 36 of SEQ ID NO: 1.

In one embodiment, said nucleic acid construct encodes a peptide selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ
15 ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22; or a functional variant thereof.

20 In one embodiment the encoded peptide of the a nucleic acid construct is a variant having at least 60% sequence identity to any one of SEQ ID NO:s 2 to 22, such as at least 65% sequence identity, for example at least 70% sequence identity, such as at least 75% sequence identity, for example at least 80% sequence identity, such as at least 85% sequence identity, for example at least 90% sequence identity, such as at
25 least 95% sequence identity, for example at least 99% sequence identity to any one of SEQ ID NO:s 2 to 22.

In one embodiment, said nucleic acid construct as described herein above is comprised within a delivery vehicle. A delivery vehicle is an entity whereby a nucleotide
30 sequence or polypeptide or both can be transported from at least one media to another. Delivery vehicles are generally used for expression of the sequences encoded within the nucleic acid construct and/or for the intracellular delivery of the construct or the polypeptide encoded therein.

35 In one embodiment, there is provided a delivery vehicle comprising the nucleic acid construct according to the present disclosure. A delivery vehicle may be selected from

the group consisting of: RNA based vehicles, DNA based vehicles/ vectors, lipid based vehicles (such as a liposome), polymer based vehicles (such as a cationic polymer DNA carrier), colloidal gold particles (coating) and virally derived DNA or RNA vehicles or vectors.

5

Methods of non-viral delivery include physical (carrier-free delivery) and chemical approaches (synthetic vector-based delivery).

10

Physical approaches, including needle injection, gene gun, jet injection, electroporation, ultrasound, and hydrodynamic delivery, employ a physical force that permeates the cell membrane and facilitates intracellular gene transfer. Said physical force may be electrical or mechanical.

15

Examples of chemical delivery vehicles include, but are not limited to: biodegradable polymer microspheres, lipid based formulations such as liposome carriers, cationically charged molecules such as liposomes, calcium salts or dendrimers, lipopolysaccharides, polypeptides and polysaccharides.

20

Another embodiment of the present invention comprises a vector which herein is denoted a viral vector (i.e. not a virus) as a delivery vehicle. Viral vectors according to the present invention are made from a modified viral genome, i.e. the actual DNA or RNA forming the viral genome, and introduced in naked form. Thus, any coat structures surrounding the viral genome made from viral or non-viral proteins are not part of the viral vector according to the present invention.

25

30

The virus from which the viral vector is derived may be selected from the non-exhaustive group of: adenoviruses, retroviruses, lentiviruses, adeno-associated viruses, herpesviruses, vaccinia viruses, foamy viruses, cytomegaloviruses, Semliki forest virus, poxviruses, RNA virus vector and DNA virus vector. Such viral vectors are well known in the art.

35

In one embodiment, said viral vectors may be selected from the group consisting of adenoviruses, lentiviruses, adeno-associated viruses (AAV) and recombinant adeno-associated viruses (rAAV). In one preferred embodiment, said viral vector is a therapeutic rAAV vector such as a therapeutic rAAV vector.

An adenovirus is a group of double-stranded DNA containing viruses. Adenoviruses can be genetically modified making them replication incompetent or conditionally replication incompetent. In this form, as adenoviral constructs or adenovectors, they can be used as gene delivery vehicles for vaccination or gene therapy.

5

Gene therapy vectors using AAV can infect both dividing and quiescent cells and persist in an extrachromosomal state without integrating into the genome of the host cell. These features make AAV a very attractive candidate for creating viral vectors for gene therapy. To date, AAV vectors have been used in over 80 clinical trials worldwide.

10

At least 11 serotypes of AAV exists, and all of these are encompassed by the present invention.

15

Viral expression vectors that have been utilized to target retinal cells include adenoviruses, lentiviruses, and recombinant adeno-associated viruses (rAAV).

20

Recombinant adeno-associated viral vectors (rAAV) are moving to the forefront of gene therapy experiments. Given the non-pathogenic nature, low immunogenicity, ease of delivery, persistence, and targeting possibilities of rAAV, it is poised to become a major player in retinal gene therapy.

Cardiovascular disease

In one aspect, the present disclosure provides compounds that binds to NCAM for use in the treatment of a cardiovascular disease.

25

The term "cardiovascular disease" as used herein relates to a range of conditions that affect the heart, its vessels, muscles, valves, or internal electric pathways responsible for muscular contraction, as well as diseases affecting vessels of the systemic or pulmonary circulation.

30

Cardiovascular diseases include:

Coronary artery diseases (CAD) - disease of the blood vessels supplying the heart muscle - such as angina and myocardial infarction;

cerebrovascular disease - disease of the blood vessels supplying the brain, such as stroke;

35

heart failure;

hypertensive heart disease;

rheumatic heart disease – damage to the heart muscle and heart valves from
rheumatic fever, caused by streptococcal bacteria;

cardiomyopathy;

5 cardiac arrhythmias;

congenital heart disease – electrophysiological disturbances and malformations of
heart structure existing at birth, including genetic cardiomyopathies;

valvular heart disease;

carditis,

10 aortic aneurysms;

peripheral artery disease – disease of blood vessels supplying the arms and legs as
well as internal organs;

thromboembolic disease; and

15 venous thrombosis – blood clots in the leg veins, which can dislodge and move to the
heart and lungs.

Thus, in one embodiment, the cardiovascular disease is selected from the group
consisting of Cardiac arrhythmias; Coronary artery disease; Acute Myocardial infarction
(AMI); Cardiomyopathy; Hypertensive heart disease; Heart failure; Pulmonary heart
20 disease (cor pulmonale); Inflammatory heart disease such as Endocarditis and carditis,
Inflammatory cardiomegaly, Myocarditis or Eosinophilic myocarditis; Valvular heart
disease; Congenital heart disease; Rheumatic heart disease; Aortic aneurysms; Long
or short QT syndrome; Brugada syndrome; Arrhythmogenic cardiomyopathy (ACM);
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT); Cerebrovascular
25 disease; Peripheral artery disease; Thromboembolic disease; and Venous thrombosis.

Cardiac disease

In one aspect, the present disclosure provides compounds that binds to NCAM for use
in the treatment of a cardiac disease or heart disease.

30

A cardiac disease as used herein describes a range of conditions that affect the heart.
These include cardiac blood vessel diseases, such as coronary artery disease; heart
rhythm problems (arrhythmias); and inborn heart defects (congenital heart defects),
among others.

35

Cardiac diseases include a subset of the cardiovascular diseases namely those directly affecting the heart and heart vessels. Cardiovascular diseases that are not considered cardiac diseases include for example Cerebrovascular disease; Peripheral artery disease; Thromboembolic disease; and Venous thrombosis.

5

Cardiac diseases include: Coronary artery diseases (CAD), such as angina and myocardial infarction; heart failure; hypertensive heart disease; rheumatic heart disease; cardiomyopathy; cardiac arrhythmias; congenital heart disease; valvular heart disease; carditis and aortic aneurysms.

10

Thus, in one embodiment, the cardiac disease is selected from the group consisting of Cardiac arrhythmias; Coronary artery disease; Acute Myocardial infarction (AMI); Cardiomyopathy; Hypertensive heart disease; Heart failure; Pulmonary heart disease (cor pulmonale); Inflammatory heart disease such as Endocarditis and carditis, Inflammatory cardiomegaly, Myocarditis or Eosinophilic myocarditis; Valvular heart disease; Congenital heart disease; Rheumatic heart disease; Aortic aneurysms; Long or short QT syndrome; Brugada syndrome; Arrhythmogenic cardiomyopathy (ACM); and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT).

15

20 In one embodiment, the cardiac disease is Coronary artery disease (CAD), also known as ischemic heart disease (IHD).

25

In one embodiment the cardiac disease is a cardiac disease associated with arrhythmia, such as a cardiac disease presenting with arrhythmia; such as a cardiac disease with arrhythmia; such as arrhythmic cardiac disease.

In a preferred embodiment, the cardiac disease of the present disclosure is cardiac arrhythmia.

30

Cardiac arrhythmias

Cardiac (or heart) arrhythmia, also known as arrhythmia, dysrhythmia, or irregular heartbeat, is a group of conditions in which the heartbeat is irregular. Ventricular arrhythmias occur in the lower chambers of the heart, called the ventricles.

35

Supraventricular arrhythmias (or atrial arrhythmias) occur in the area above the ventricles, usually in the upper chambers of the heart, called the atria. The irregular beats can either be too slow, such as below 60 beats per minute (called bradycardia),

or too fast, such as above 100 beats per minute in adults (tachycardia). In some embodiments, the cardiac arrhythmia is congenital.

5 In one embodiment, the cardiac arrhythmia is a bradycardia. Bradycardia (or bradyarrhythmia) happens when the electrical impulse that signals the heart to contract is not formed in the sinoatrial node (SA node), or is not sent to the heart's lower chambers (the ventricles) through the proper conduction pathway in the atrioventricular node (AV node).

10 In one embodiment, the cardiac arrhythmia is a tachycardia. There are many forms of tachycardia, classified depending on where the fast heart rate begins. If it begins in the ventricles, it is called ventricular tachycardia. If it begins above the ventricles, it is called supraventricular tachycardia.

15 Arrhythmia may be classified by rate (tachycardia, bradycardia), mechanism (automaticity, re-entry, triggered), duration or by site of origin.

In one embodiment, the cardiac disease is a cardiac arrhythmia selected from the group consisting of:

- 20
- Supraventricular tachycardias (including atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia);
 - Extra beats (including premature atrial activations, premature ventricular contractions, and premature junctional contractions);
 - Ventricular arrhythmias (including ventricular fibrillation and ventricular

25 tachycardia); and

 - Bradycardias.

30 In one embodiment, the cardiac arrhythmia is a junctional arrhythmia (or junctional rhythm). Junctional rhythm results from impulses coming from a locus of tissue in the area of the atrioventricular node, i.e. the "junction" between atria and ventricles.

In one embodiment, the cardiac disease is a bradycardia. In one embodiment, the cardiac disease is a tachycardia.

In one embodiment, the cardiac disease is Supraventricular tachycardia (SVT). SVT is an abnormally fast regular heart rate arising from improper electrical activity in the upper part of the heart, i.e. above the bundle of His.

5 In one embodiment, the cardiac disease is Atrial fibrillation (AF or A-fib). AF is one of the most common abnormal heart rhythms. In AF, the atria beat out of coordination with the ventricles, which leads to a rapid and irregular heart rhythm. AF is a main cause of stroke, especially among elderly people

10 AF may be classified as "First detected", "Paroxysmal", "Persistent" or "Permanent". Furthermore, AF may be "Secondary AF", i.e. when AF occurs in the setting of a primary condition which may be the cause of the AF.

15 In one embodiment, the cardiac disease is Atrial flutter (AFL), AFL is a type of SVT, which often degenerates into AF. In AFL, the atria are activated by a single re-entry loop with a stable but faster than normal rhythm, and the atria beat more frequently than the ventricles. There are two types of atrial flutter, the common type I and rarer type II.

20 AF and AFL with rapid ventricular response are classified as SVT:s, but without rapid ventricular response, fibrillation and flutter are usually not classified as SVT. AF and AFL may be classified under I48 in ICD-10.

25 In one embodiment, the cardiac disease is Atrioventricular nodal re-entrant tachycardia (AVNRT). AVNRT is a type of SVT, and may be classified under I47 in ICD-10. There are several types of AVNRT classified as the "common form" and the "uncommon form". In common AVNRT, the anterograde conduction is via the slow pathway and the retrograde conduction is via the fast pathway ("slow-fast" AVNRT). In uncommon AVNRT, the anterograde conduction is via the fast pathway and the retrograde
30 conduction is via the slow pathway ("fast-slow" AVNRT), or both anterograde and retrograde conduction are over slow pathways. ("slow-slow" AVNRT).

35 In one embodiment, the heart disease is Wolff-Parkinson-White (WPW) syndrome, which is a group of abnormalities caused by extra muscle pathways between the atria and the ventricles. The pathways cause the electrical signals to arrive at the ventricles too soon, and the signals are sent back to the atria. The result is a very fast heart rate.

In one embodiment, the cardiac disease is an arrhythmia selected from the group consisting of Atrial arrhythmias; Junctional arrhythmias; Ventricular arrhythmias and Heart blocks.

5

In one embodiment, the cardiac arrhythmia is an atrial arrhythmia. Atrial arrhythmias include Sinus bradycardia; Premature atrial contractions (PACs); Wandering atrial pacemaker; Atrial tachycardia; Multifocal atrial tachycardia; Supraventricular tachycardia (SVT); Atrial flutter; and Atrial fibrillation.

10

In one embodiment, the cardiac arrhythmia is a junctional arrhythmia (or junctional rhythm). Junctional rhythm results from impulses coming from a locus of tissue in the area of the atrioventricular node, i.e. the "junction" between atria and ventricles.

Junctional arrhythmias include AV nodal re-entrant tachycardia; Junctional rhythm;

15

Junctional tachycardia and Premature junctional contraction.

In one embodiment, the cardiac arrhythmia is a ventricular arrhythmia. Ventricular arrhythmias include Premature ventricular contractions (PVCs); Ventricular extra beats (VEBs); Accelerated idioventricular rhythm; Monomorphic ventricular tachycardia; Polymorphic ventricular tachycardia; Ventricular fibrillation; and Torsades de pointes.

20

In one embodiment, the cardiac arrhythmia is a heart block. Heart blocks, or AV blocks, are the most common causes of bradycardia and includes First degree heart block; Second degree heart block; and Third degree heart block. Heart block is a disorder in the heart's rhythm, caused by an obstruction - a block - in the electrical conduction system of the heart.

25

In one embodiment, the cardiac arrhythmia is selected from the group consisting of Sinoatrial nodal re-entrant tachycardia (SNRT); Ectopic (unifocal) atrial tachycardia (EAT); Multifocal atrial tachycardia (MAT); Atrial fibrillation (AF); Atrial flutter (AFL); Junctional tachycardia; Atrioventricular nodal re-entrant tachycardia (AVNRT) or junctional reciprocating tachycardia (JRT); Permanent (or persistent) junctional reciprocating tachycardia (PJRT); Atrioventricular reciprocating tachycardia (AVRT); Wolff-Parkinson-White syndrome and Junctional ectopic tachycardia (JET). The four main types of SVT are: atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardia, and Wolff-Parkinson-White syndrome. SVT:s may be classified under I47

30

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to I49 in the International Statistical Classification of Diseases and Related Health Problems - Tenth Revision (ICD-10).

5 Cardiac arrhythmias are generally produced by one of three mechanisms: enhanced automaticity, triggered activity, or re-entry.

10 Re-entry occurs when a propagating impulse fails to die out after normal activation of the heart and persists to re-excite the heart after the refractory period has ended. Re-entry is the electrophysiological mechanism responsible for the majority of clinically important arrhythmias, such as sustained ventricular fibrillation and sudden cardiac death. Included among the arrhythmias caused by re-entry are atrial fibrillation, atrial flutter, atrioventricular (AV) nodal re-entry, AV re-entry involving a bypass tract, ventricular tachycardia after myocardial infarction (MI) with the presence of left ventricular scar, and ventricular fibrillation. In one embodiment, the cardiac arrhythmia is selected from the group consisting of atrial fibrillation, atrial flutter, atrioventricular (AV) nodal re-entry, AV re-entry involving a bypass tract, ventricular tachycardia after myocardial infarction (MI) with the presence of left ventricular scar, and ventricular fibrillation.

20 Cardiac arrhythmia can be underlain or triggered by several causes, such as cardiac causes. Said cardiac causes include acute or chronic ischemic heart disease, vascular heart disease, valvular heart disease, or degenerative primary electrical disease. Ultimately, the causes act by three mechanisms: depressed automaticity of the heart, conduction slowing or block, or escape pacemakers and rhythms.

25 In one embodiment, the cardiac arrhythmia is a secondary disease, i.e. a cardiac arrhythmia that follows and results from an earlier disease, injury, or event. For example, said cardiac arrhythmia may be secondary to another cardiac disease.

30 Cardiac arrhythmias may also lead to (or cause) sudden cardiac arrest or stroke.

For example, the cardiac arrhythmia may be caused by Long or short QT syndrome. Said Long or short QT syndrome may be congenital or drug induced. In one embodiment, the cardiac arrhythmia is caused by a cardiomyopathy. Said cardiomyopathy may be classified as hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, diabetic cardiomyopathy, arrhythmogenic

right ventricular dysplasia, or takotsubo cardiomyopathy. In one embodiment, the cardiac arrhythmia is caused by Brugada syndrome. In another embodiment, the cardiac arrhythmia is caused by Arrhythmogenic cardiomyopathy (ACM); ACM is also known as Arrhythmogenic Right Ventricular cardiomyopathy (ARVC) and
5 Arrhythmogenic Right Ventricular dysplasia (ARVD). In another embodiment, the cardiac arrhythmia is caused by catecholaminergic polymorphic ventricular tachycardia (CPVT). In one embodiment, the cardiac arrhythmia occurs after cardiac surgery or other surgery (post-operative cardiac arrhythmia or post-operative atrial fibrillation).

10 In one embodiment, the cardiac arrhythmia is part of, or associated with, another cardiac disease.

Cardiac arrhythmias may be diagnosed by an electrocardiogram (ECG).

Administration

15 According to the present disclosure, a compound as defined herein is administered to individuals in need of treatment in pharmaceutically effective doses or a therapeutically effective amount. The dosage requirements will vary with the particular drug composition employed, the route of administration and the particular subject being treated, which depend on the severity and the sort of the disorder as well as on the
20 weight and general state of the subject. It will also be recognized by one skilled in the art that the optimal quantity and spacing of individual dosages of a compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optima can be determined by conventional techniques. It will also be appreciated by one of skill in
25 the art that the optimal course of treatment, i.e., the number of doses of a compound given per day for a defined number of days, can be ascertained using conventional course of treatment determination tests.

It will be appreciated that the preferred route of administration will depend on the
30 general condition and age of the subject to be treated, the nature of the condition to be treated, the location of the tissue to be treated in the body and the active ingredient chosen.

In one embodiment, the compound for use in the treatment of a cardiovascular
35 disease, such as a cardiac disease, such as cardiac diseases associated with

arrhythmias, such as cardiac arrhythmia, as described herein is administered by means of parental administration. Parenteral administration is any administration route not being the oral/enteral route whereby the medicament avoids first-pass degradation in the liver. Accordingly, parenteral administration includes any injections and infusions, for example bolus injection or continuous infusion, such as intravenous administration, intramuscular administration or subcutaneous administration. Furthermore, parenteral administration includes inhalations and topical administration. In one embodiment, the parental administration is intraperitoneal (IP), intravenous (IV) or subcutaneous (SC).

In one embodiment, the compound is to be administered in combination with one or more second bioactive agents.

Items

1. A compound that binds to Neural Cell Adhesion Molecule (NCAM) for use in the treatment of a cardiovascular disease.
2. The compound for use according to item 1, wherein the compound is a peptide that binds to NCAM.
3. The compound for use according to any one of the preceding items, wherein the peptide consists of from 15 to 35 contiguous amino acid residues derived from neuropeptide Y (NPY, SEQ ID NO:1), and said peptide does not comprise an amino acid at position 36 of SEQ ID NO:1.
4. The compound for use according to any one of the preceding items, wherein the peptide does not comprise the Tyr amino acid of position 36 of SEQ ID NO: 1.
5. The compound for use according to any one of the preceding items, wherein the peptide does not bind to and/or does not activate cognate NPY-receptors Y1, Y2 and/or Y5.
6. The compound for use according to any one of the preceding items, wherein the peptide comprises at least the sequence YSALRHYNLITRQR (NPY21-35; SEQ ID NO: 22), or a functional variant thereof having at least 60% sequence identity to SEQ ID NO: 22.
7. The compound for use according to any one of the preceding items, wherein the peptide comprises at least the sequence YSALRHYNLITRQR (NPY21-35;

SEQ ID NO: 22), or a functional variant thereof wherein no more than 6 amino acids have been substituted, such as no more than 5 amino acids, such as no more than 4 amino acids, such as no more than 3 amino acids, such as no more than 2 amino acids, such as no more than 1 amino acid has been substituted.

8. The compound for use according to any one of the preceding items, wherein the peptide is selected from the group consisting of:

YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY 1-35, SEQ ID NO: 2)
 PSKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY 2-35, SEQ ID NO: 3)
 SKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY 3-35, SEQ ID NO: 4)
 KPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY4-35, SEQ ID NO: 5),
 PDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY5-35, SEQ ID NO: 6),
 DNPGE DAPAEDMARYYSALRHYINLITRQR (NPY6-35, SEQ ID NO: 7),
 NPGEDAPAEDMARYYSALRHYINLITRQR (NPY7-35, SEQ ID NO: 8),
 PGEDAPAEDMARYYSALRHYINLITRQR (NPY8-35, SEQ ID NO: 9),
 GEDAPAEDMARYYSALRHYINLITRQR (NPY9-35, SEQ ID NO: 10),
 EDAPAEDMARYYSALRHYINLITRQR (NPY10-35, SEQ ID NO: 11),
 DAPAEDMARYYSALRHYINLITRQR (NPY11-35, SEQ ID NO: 12),
 APAEDMARYYSALRHYINLITRQR (NPY12-35, SEQ ID NO: 13),
 PAEDMARYYSALRHYINLITRQR (NPY13-35, SEQ ID NO: 14),
 AEDMARYYSALRHYINLITRQR (NPY14-35, SEQ ID NO: 15),
 EDMARYYSALRHYINLITRQR (NPY15-35, SEQ ID NO: 16),
 DMARYYSALRHYINLITRQR (NPY16-35, SEQ ID NO: 17),
 MARYYSALRHYINLITRQR (NPY17-35, SEQ ID NO: 18),
 ARYYSALRHYINLITRQR (NPY18-35, SEQ ID NO: 19),
 RYYSALRHYINLITRQR (NPY19-35, SEQ ID NO: 20),
 YYSALRHYINLITRQR (NPY20-35, SEQ ID NO: 21), and
 YSALRHYINLITRQR (NPY21-35, SEQ ID NO: 22),
 or a functional variant thereof.

9. The compound for use according to any one of the preceding items, wherein the peptide is a functional variant having at least 60% sequence identity to a peptide selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID

NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22.

10. The compound for use according to any one of the preceding items, wherein the peptide variant has at least 60% sequence identity, such as at least 65% sequence identity, for example at least 70% sequence identity, such as at least 75% sequence identity, for example at least 80% sequence identity, such as at least 85% sequence identity, for example at least 90% sequence identity, such as at least 95% sequence identity, for example at least 99% sequence identity to a peptide selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22.
11. The compound for use according to any of the preceding items, wherein the peptide variant comprises one or more amino acid substitution, such as one amino acid substitution, such as two amino acid substitutions, such as three amino acid substitutions, such as four amino acid substitutions, such as five amino acid substitutions, such as six amino acid substitutions, such as seven amino acid substitutions.
12. The compound for use according to any one of the preceding items, wherein the peptide is selected from the group consisting of:
- a peptide consisting of 35 contiguous amino acid residues having the sequence YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY1-35, SEQ ID NO: 2) or YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 34 contiguous amino acid residues having the sequence PSKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY2-35, SEQ ID NO: 3) or PSKPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 33 contiguous amino acid residues having the sequence SKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY3-35, SEQ ID NO: 4) or SKPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 32 contiguous amino acid residues having the sequence KPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY4-35, SEQ ID NO: 5)

- or KPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 5 a peptide consisting of 31 contiguous amino acid residues having the sequence PDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY5-35, SEQ ID NO: 6) or PDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 10 a peptide consisting of 30 contiguous amino acid residues having the sequence DNPGEDAPAEDMARYYSALRHYINLITRQR (NPY6-35, SEQ ID NO: 7) or DNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 15 a peptide consisting of 29 contiguous amino acid residues having the sequence NPGEDAPAEDMARYYSALRHYINLITRQR (NPY7-35, SEQ ID NO: 8) or NPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 20 a peptide consisting of 28 contiguous amino acid residues having the sequence PGEDAPAEDMARYYSALRHYINLITRQR (NPY8-35, SEQ ID NO: 9) or PGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 25 a peptide consisting of 27 contiguous amino acid residues having the sequence GEDAPAEDMARYYSALRHYINLITRQR (NPY9-35, SEQ ID NO: 10) or GEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 26 contiguous amino acid residues having the sequence EDAPAEDMARYYSALRHYINLITRQR (NPY10-35, SEQ ID NO: 11) or EDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 30 a peptide consisting of 25 contiguous amino acid residues having the sequence DAPAEDMARYYSALRHYINLITRQR (NPY11-35, SEQ ID NO: 12) or DAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 24 contiguous amino acid residues having the sequence APAEDMARYYSALRHYINLITRQR (NPY12-35, SEQ ID NO: 13) or APAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,

- a peptide consisting of 23 contiguous amino acid residues having the sequence PAEDMARYYSALRHYINLITRQR (NPY13-35, SEQ ID NO: 14)
or PAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 5 a peptide consisting of 22 contiguous amino acid residues having the sequence AEDMARYYSALRHYINLITRQR (NPY14-35, SEQ ID NO: 15)
or AEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 21 contiguous amino acid residues having the sequence EDMARYYSALRHYINLITRQR (NPY15-35, SEQ ID NO: 16)
or EDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 10 a peptide consisting of 20 contiguous amino acid residues having the sequence DMARYYSALRHYINLITRQR (NPY16-35, SEQ ID NO: 17)
or DMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 19 contiguous amino acid residues having the sequence MARYYSALRHYINLITRQR (NPY17-35, SEQ ID NO: 18)
15 or MARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 18 contiguous amino acid residues having the sequence ARYYSALRHYINLITRQR (NPY18-35, SEQ ID NO: 19)
or ARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 17 contiguous amino acid residues having the sequence RYYSALRHYINLITRQR (NPY19-35, SEQ ID NO: 20)
20 or RYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 16 contiguous amino acid residues having the sequence YYSALRHYINLITRQR (NPY20-35, SEQ ID NO: 21)
or YYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions, and
- 25 a peptide consisting of 15 contiguous amino acid residues having the sequence YSALRHYINLITRQR (NPY21-35, SEQ ID NO: 22)
or YSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.
13. The compound for use according to any of the preceding items, wherein the peptide consists of SKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY3-35; SEQ ID NO: 4),
30 or a functional variant thereof having at least 60% sequence identity to SEQ ID NO: 4,

or SKPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

- 5 14. The compound for use according to any one of the preceding items, wherein said one or more amino acid substitutions are each selected from conservative and non-conservative amino acid substitutions.
15. The compound for use according to any one of the preceding items, wherein said one or more amino acid substitutions are each a conservative amino acid substitution.
- 10 16. The compound for use according to any one of the preceding items, wherein the amino acid residues of the peptide are L amino acid residues.
17. The compound for use according to any one of the preceding items, wherein one or more of the amino acid residues of the peptide are D amino acid residues.
- 15 18. The compound for use according to any one of the preceding items, wherein all of the amino acid residues of the peptide are D amino acid residues.
19. The compound for use according to any of the preceding items, wherein the C-terminal amino acid of the peptide exists as the free carboxylic acid ("OH").
20. The compound for use according to any of the preceding items, wherein the C-terminal amino acid of the peptide is amidated (-NH₂).
- 20 21. The compound for use according to any of the preceding items, wherein the peptide is formulated as a monomer.
22. The compound for use according to any the preceding items, wherein the peptide is formulated as a multimer comprising two or more peptides.
- 25 23. The compound for use according to any the preceding items, wherein the peptide is formulated as a multimer consisting of two or more peptides, and optionally a linker group.
24. The compound for use according to any one of the preceding items, wherein the multimeric peptide is a dimer.
25. The compound for use according to any one of the preceding items, wherein 30 the multimeric peptide is a trimer.
26. The compound for use according to any one of the preceding items, wherein the multimeric peptide is a tetramer.
27. The compound for use according to any one of the preceding items, wherein 35 the multimeric peptide is a dendrimer, such as a dendrimer comprising 4, 8, 16 or 32 peptides.

28. The compound for use according to any one of the preceding items, wherein said two or more peptides are identical with respect to each other.
29. The compound for use according to any one of the preceding items, wherein the two or more peptides are not identical with respect to each other.
- 5 30. The compound for use according to any one of the preceding items, wherein the linker group comprises one or more lysine residues.
31. The compound for use according to any one of the preceding items, wherein the compound is a nucleic acid construct encoding said peptide.
32. The compound for use according to any one of the preceding items, wherein
10 the compound is a delivery vehicle comprising the nucleic acid construct according to item 31.
33. The compound for use according to any one of the preceding items, wherein the vehicle is selected from the group consisting of: RNA based vehicles, DNA based vehicles, lipid based vehicles, polymer based vehicles, colloidal gold
15 particles and virally derived DNA or RNA vehicles.
34. The compound for use according to any one of the preceding items, wherein the vehicle is a viral vector selected from the group consisting of adenoviruses, retroviruses, lentiviruses, adeno-associated viruses, herpesviruses, vaccinia viruses, foamy viruses, cytomegaloviruses, Semliki forest virus, poxviruses,
20 RNA virus vector and DNA virus vector.
35. The compound for use according to any one of the preceding items, wherein the cardiovascular disease is a cardiac arrhythmia.
36. The compound for use according to any one of the preceding items, wherein the cardiovascular disease is selected from the group consisting of Cardiac
25 arrhythmias; Coronary artery disease; Acute Myocardial infarction (AMI); Cardiomyopathy; Hypertensive heart disease; Heart failure; Pulmonary heart disease; Inflammatory heart disease such as Endocarditis, Inflammatory cardiomegaly, Myocarditis or Eosinophilic myocarditis; Valvular heart disease; Congenital heart disease; Rheumatic heart disease; Cerebrovascular disease;
30 Aortic aneurysms; Thromboembolic disease; Venous thrombosis; Peripheral artery disease; Long or short QT syndrome; Brugada syndrome; Arrhythmogenic cardiomyopathy (ACM); and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT).
37. The compound for use according to any one of the preceding items, wherein
35 the cardiovascular disease is selected from the group consisting of Cardiac dysrhythmias; Cardiomyopathy; Hypertensive heart disease; Heart failure;

Pulmonary heart disease; Inflammatory heart disease such as Endocarditis, Inflammatory cardiomegaly, Myocarditis or Eosinophilic myocarditis; Valvular heart disease; Congenital heart disease; Rheumatic heart disease; Long or short QT syndrome; Brugada syndrome; Arrhythmogenic cardiomyopathy (ACM); and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT).

38. The compound for use according to any one of the preceding items, wherein the cardiovascular disease is selected from the group consisting of cardiac arrhythmia; coronary artery disease; cerebrovascular disease; heart failure; hypertensive heart disease; rheumatic heart disease; cardiomyopathy; congenital heart disease; valvular heart disease; carditis, aortic aneurysms; peripheral artery disease; thromboembolic disease; and venous thrombosis.

39. The compound for use according to any one of the preceding items, wherein the cardiovascular disease is Coronary artery disease.

40. The compound for use according to any one of the preceding items, wherein the cardiovascular disease is Acute Myocardial infarction (AMI).

41. A compound that binds to Neural Cell Adhesion Molecule (NCAM) for use in the treatment of cardiac arrhythmia.

42. The compound for use according to any of the preceding items, wherein binding of the compound to NCAM causes an increase in cardiac conduction velocity (CV).

43. The compound for use according to any of the preceding items, wherein the compound binds to the Ig1 module of NCAM.

44. The compound for use according to any one of the preceding items, wherein binding of the compound to NCAM causes a modulation of NCAM mediated cell-cell or cell-matrix adhesion.

45. The compound for use according to any one of the preceding items, wherein the NCAM mediated cell-cell adhesion is homophilic or heterophilic.

46. The compound for use according to any one of the preceding items, wherein the NCAM mediated cell-cell adhesion is a cis-interaction or a trans-interaction.

47. The compound for use according to any one of the preceding items, wherein the binding to NCAM results in a modulation of NCAM-induced signalling.

48. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is secondary to another cardiovascular disease.

49. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is caused by or part of a disease selected from the group consisting of Long or short QT syndrome; cardiomyopathy; Brugada syndrome;

Arrhythmogenic cardiomyopathy (ACM); catecholaminergic polymorphic ventricular tachycardia (CPVT).

50. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia occurs after cardiac or other surgery.
- 5 51. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is a ventricular arrhythmia.
52. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is a supraventricular arrhythmia.
- 10 53. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is a bradycardia.
54. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is a tachycardia.
55. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is selected from the group consisting of Supraventricular tachycardia, Ventricular arrhythmia, Extra beats and Bradycardia.
- 15 56. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is an atrial arrhythmia.
57. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is a junctional arrhythmia.
- 20 58. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is a heart block.
59. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is caused by re-entry.
- 25 60. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is selected from the group consisting of Atrial fibrillation (AF); Atrial flutter (AFL); Sinoatrial nodal re-entrant tachycardia (SNRT); Ectopic (unifocal) atrial tachycardia (EAT); Multifocal atrial tachycardia (MAT); Junctional tachycardia; Atrioventricular nodal re-entrant tachycardia (AVNRT) or junctional reciprocating tachycardia (JRT); Permanent (or persistent) junctional reciprocating tachycardia (PJRT); Atrioventricular reciprocating tachycardia (AVRT); Wolff-Parkinson-White syndrome and Junctional ectopic tachycardia (JET).
- 30 61. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is selected from the group consisting of atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardia, and Wolff-Parkinson-White syndrome.
- 35

62. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is selected from the group consisting of atrial fibrillation, atrial flutter, and atrioventricular (AV) nodal re-entry.
- 5 63. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is ventricular fibrillation.
64. The compound for use according to any one of the preceding items, wherein the cardiac arrhythmia is congenital.
65. The compound for use according to any one of the preceding items, wherein the compound is to be administered by means of parental administration.
- 10 66. The compound for use according to any one of the preceding items, wherein the parental administration is intraperitoneal (IP), intravenous (IV) or subcutaneous (SC).
67. The compound for use according to any one of the preceding items, wherein the compound is to be administered in combination with one or more second
- 15 bioactive agents.
68. A composition comprising a compound that binds to Neural Cell Adhesion Molecule (NCAM) according to any one of the preceding items, for use in the treatment of a cardiovascular disease.
69. A method for treatment of a cardiac disease comprising administration of
- 20 compound as defined in any one of items 1 to 34 to an individual in need thereof.
70. Use of a compound as defined in any one of items 1 to 34 in the manufacture of a medicament for treatment of a cardiac disease.

Examples

Example 1: Antiarrhythmic effect of NPY3-35 in Langendorff perfused hearts subjected to ischemia-reperfusion

5 The effect of NPY3-35 (SEQ ID NO: 4) versus vehicle treatment on electrical and mechanical recovery was investigated, as well as infarct size after no flow ischemia in Langendorff perfused rat hearts. NPY3-35 (SEQ ID NO: 4) showed an antiarrhythmic effect by significantly increasing the recovery rate after ischemia, which was demonstrated in the following way:

10 Method

Male Wistar rats were anesthetized in a 5% isoflurane filled container, and transferred to an isoflurane inhalation mask (35% O₂ and 65% N₂, flow = 3 L min⁻¹).

When fully anaesthetized, hearts were quickly dissected, the aorta cannulated; and the
15 heart transferred to the Langendorff setup and perfused at 80 mmHg with a 37 °C Krebs-Henseleit (KH) buffer (in mM: 118 NaCl, 4.7 KCl, 1.2 KH₂PO₄, 1.2 MgSO₄, 1.75 CaCl₂, 25 NaHCO₃ and 11 glucose), equilibrated with carbogen (95% O₂ - 5% CO₂). To assess contractile function, a latex balloon connected to a pressure transducer was inserted into the left ventricle through an incision in the left auricle. The heart was then
20 immersed in KH buffer (37 °C). ECG recordings were obtained using a 6-lead Einthoven ECG recording. Coronary flow, left ventricular pressure and ECG were continuously recorded.

Hearts were perfused for 30 min at baseline before treatment was initiated (NPY3-35 (1 µM) or vehicle) and maintained for 60 min (see fig. 1 A for protocol timeline). After
25 15 min of treatment, flow was stopped for 30 min to induce global no flow ischemia. Hearts were subsequently reperused for 15 min with treatment followed by 105 min without treatment.

At the end of the protocol, hearts were wrapped in vita wrap and placed at - 80° for 10 min. Subsequently, the hearts were sliced transversely into 7 pieces of 2 mm
30 thickness and incubated in 2,3,5-triphenyltetrazoliumchloride (TTC) (10 mg/ml in 0.1 M phosphate buffer (pH 7.4)) for 10 min at 37 °C while shaken. The tissue slices were then washed 3 times in ELGA and stored in 4 % formalin overnight. The tissue slices were weighed and scanned on both sides at 1200 DPI to determine infarct size.

Images were analyzed using ImageJ software by two persons with the treatment blinded to the operator.

Relative infarct size was determined as the total volume of diseased myocardium (pale in images) divided by the area at risk (whole volume) and statistical significance evaluated by an unpaired two-sample Student's t-test ($p < 0.05$ considered significant).

Arrhythmogenesis was determined from the number of hearts in arrhythmia at the end of reperfusion (failed recovery) versus hearts in sinus rhythm (successful recovery). Statistical significance was evaluated using Fisher's exact test ($p < 0.05$ considered significant).

Data are presented as mean $\pm$ SEM.

Results

In rat hearts exposed to ischemia and reperfusion, NPY3-35 had a significant antiarrhythmic effect. Vehicle treated hearts failed to recover sinus rhythm in 7 of 10 cases, whereas NPY3-35 treated hearts only failed in 1 of 8 cases ($p < 0.05$, fig. 1 and 2). Infarct size not significantly different between vehicle and NPY3-35 treated hearts (fig. 3), showing that the antiarrhythmic effect is independent of infarct area.

Example 2: Improvement of cardiac conduction after ischemia in NPY3-35 treated tissue strips

As illustrated in example 1 (fig. 1-3), NPY3-35 suppresses reperfusion arrhythmias in isolated rat hearts. Next, we pursued the mechanism and target receptor for the protective effect. Hypothesizing that re-entry arrhythmias are involved in the observed arrhythmias, we investigated conduction velocity, which when slowed supports sustained re-entry. In neurons, NPY3-35 exerts its effect by binding to and subsequent signaling via NCAM and we therefore tested NPY3-35 in wild-type (WT) mice and in NCAM knock-out (KO) mice.

NPY3-35, NPY10-35 and NPY21-35 were demonstrated to increase conduction velocity after ischemic stress, which was demonstrated in the following way:

Method

Male mice (either WT or NCAM KO) were euthanized by cervical dislocation. A thoracotomy was performed and the hearts were quickly removed and immersed in oxygenated HEPES-Tyrodes buffer (HT-buffer), with a pH of 7.4. (in mM: 136 NaCl, 4 KCl, 5 HEPES, 5 MES, 0.8 MgCl₂, 1 CaCl₂ and 10 glucose).

Strips of right ventricular tissue were dissected in a Petri-dish with HT-buffer and a loop sutured to each end. The tissue was connected to a force-transducer and a stationary hook in a fluid filled chamber (1.7 mL) with the endocardium facing upward. The chamber was continuously perfused with oxygenated H-T-buffer (temp = 34-36 °C, flow = 2 mL min⁻¹) using a roller-pump.

The ventricular strip was paced with a unipolar stimulation electrode at 2 Hz, impulse duration 0.5 ms and double threshold voltage. The tissue was subsequently allowed to rest for 15-30 min.

By use of an isometric force-transducer built into the tissue chamber, developed force and diastolic force was determined.

To measure conduction velocity, two Platinum/Iridium electrodes were placed on the longitudinal axis of a muscle fiber bundle and the inter-electrode distance as well as tissue length measured. The signals were amplified and band-pass filtered at 300 – 10,000 Hz and sampled at 30 kHz.

The ventricular strip was perfused at baseline (10 min, buffer pH 7.4, glucose 5 mM, equilibrated with 100 % O₂) followed by treatment with either vehicle or NPY3-35 (1 µM) for the remainder of the experiment. After 10 minutes of pre-treatment, strips were subjected to 30 minutes of simulated ischemia (buffer pH 6.8, no glucose, equilibrated with atmospheric air) followed by 20 minutes of reperfusion.

The tissue strip was weighed after the experiment. Muscle volume (V) was determined by mass (m), divided by a density (δ) of 1,063 mg/mm³; $V = m / \delta$. Cross-sectional area (A) was calculated by dividing muscle volume by muscle length (L); $A = V / L$. Cross sectional area was used to normalize developed and diastolic force.

Time of local activation under the first and second microelectrode was determined as the time of minimum dU/dt by custom written MatLab script. Conduction velocity was calculated as the inter-electrode distance divided by the inter-electrode delay.

Average conduction velocity was determined during the last two minutes of each period and we used a linear mixed-effects model analysis (R, lme) to test for statistical significance (p<0.05 considered significant).

Data are presented as mean ± SEM.

Results

In vehicle treated WT-mice, neither vehicle treatment, ischemia nor reperfusion significantly affected conduction velocity, although ischemia significantly reduced developed force by approximately 50 % (data not shown). In contrast, conduction velocity significantly increased during reperfusion in the NPY3-35 treated WT mice, whereas no significant changes occurred during NPY3-35 treatment or subsequent ischemia (fig. 4). NPY3-35 did not increase conduction velocity in NCAM KO mice where conduction velocity remained unaffected over time at all time-points including reperfusion (fig. 4), which supports the involvement of NCAM as a receptor in the response. As depicted in figure 5, CV increased significantly in WT mice treated with NPY3-35 (15.5 % vs 0.6 % in vehicle treated strips (* $p < 0.05$, Student's t-test), whereas no such effect was observed in NCAM KO mice.

To further analyze the time-course of the increase in CV, we plotted CV after reperfusion with a 4 minute time resolution (figure 6). Figure 6A shows that CV was significantly higher in the NPY3-35 treated tissue from WT animals from 12 minutes after reperfusion (time points 62, 64 and 70 minutes) compared to vehicle treated tissue. As shown in figure 6B, NPY3-35 treatment did not affect tissue from NCAM KO animals.

As shown in figure 7, CV increased significantly in WT rats treated with NPY3-35 and hence similar results are obtained for NPY3-35 when the experiment is performed on rats instead of mice. The experiment in rats is further detailed in the figure legend herein above (Fig. 7).

As shown in figure 8, an increase in CV in WT rats is also observed when the rats are treated with NPY10-35 and NPY21-35. The experiment for NPY10-35 and NPY21-35 is further detailed in the figure legend herein above (Fig. 8).

Sequences

SEQ ID NO: 1	NPY1-36 (NPY, full-length NPY) (Tyr36 optionally amidated) YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY
SEQ ID NO: 2	NPY1-35 YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQR
SEQ ID NO: 3	NPY 2-35 PSKPDNPGEDAPAEDMARYYSALRHYINLITRQR
SEQ ID NO: 4	NPY3-35 SKPDNPGEDAPAEDMARYYSALRHYINLITRQR
SEQ ID NO: 5	NPY4-35 KPDNPGEDAPAEDMARYYSALRHYINLITRQR
SEQ ID NO: 6	NPY5-35 PDNPGEDAPAEDMARYYSALRHYINLITRQR
SEQ ID NO: 7	NPY6-35 DNPGE DAPAEDMARYYSALRHYINLITRQR
SEQ ID NO: 8	NPY7-35 NPGEDAPAEDMARYYSALRHYINLITRQR
SEQ ID NO: 9	NPY8-35 PGEDAPAEDMARYYSALRHYINLITRQR
SEQ ID NO: 10	NPY9-35 GEDAPAEDMARYYSALRHYINLITRQR
SEQ ID NO: 11	NPY10-35 EDAPAEDMARYYSALRHYINLITRQR
SEQ ID NO: 12	NPY11-35 DAPAEDMARYYSALRHYINLITRQR
SEQ ID NO: 13	NPY12-35 APAEDMARYYSALRHYINLITRQR
SEQ ID NO: 14	NPY13-35 PAEDMARYYSALRHYINLITRQR
SEQ ID NO: 15	NPY14-35

AEDMARYYSALRHYINLITRQR

SEQ ID NO: 16 NPY15-35
EDMARYYSALRHYINLITRQR

SEQ ID NO: 17 NPY16-35
DMARYYSALRHYINLITRQR

SEQ ID NO: 18 NPY17-35
MARYYSALRHYINLITRQR

SEQ ID NO: 19 NPY18-35
ARYYSALRHYINLITRQR

SEQ ID NO: 20 NPY19-35
RYYSALRHYINLITRQR

SEQ ID NO: 21 NPY20-35
YYSALRHYINLITRQR

SEQ ID NO: 22 NPY21-35
YSALRHYINLITRQR

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Claims

1. A peptide consisting of from 15 to 35 contiguous amino acid residues derived from neuropeptide Y (NPY),
5 YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQR (SEQ ID NO: 1),
wherein said peptide does not comprise the Tyr amino acid of position 36 of SEQ ID NO: 1,
wherein the peptide comprises at least the sequence YSALRHYINLITRQR (NPY21-35; SEQ ID NO: 22),
10 or a functional variant thereof having at least 60% sequence identity to said peptide,
for use in the treatment of a cardiovascular disease and/or a cardiac disease.
2. The peptide for use according to claim 1, wherein the peptide is selected from the group consisting of:
15 YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY 1-35, SEQ ID NO: 2)
PSKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY 2-35, SEQ ID NO: 3)
SKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY 3-35, SEQ ID NO: 4)
KPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY4-35, SEQ ID NO: 5),
20 PDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY5-35, SEQ ID NO: 6),
DNPGE DAPAEDMARYYSALRHYINLITRQR (NPY6-35, SEQ ID NO: 7),
NPGEDAPAEDMARYYSALRHYINLITRQR (NPY7-35, SEQ ID NO: 8),
PGEDAPAEDMARYYSALRHYINLITRQR (NPY8-35, SEQ ID NO: 9),
GEDAPAEDMARYYSALRHYINLITRQR (NPY9-35, SEQ ID NO: 10),
25 EDAPAEDMARYYSALRHYINLITRQR (NPY10-35, SEQ ID NO: 11),
DAPAEDMARYYSALRHYINLITRQR (NPY11-35, SEQ ID NO: 12),
APAEDMARYYSALRHYINLITRQR (NPY12-35, SEQ ID NO: 13),
PAEDMARYYSALRHYINLITRQR (NPY13-35, SEQ ID NO: 14),
AEDMARYYSALRHYINLITRQR (NPY14-35, SEQ ID NO: 15),
30 EDMARYYSALRHYINLITRQR (NPY15-35, SEQ ID NO: 16),
DMARYYSALRHYINLITRQR (NPY16-35, SEQ ID NO: 17),
MARYYSALRHYINLITRQR (NPY17-35, SEQ ID NO: 18),
ARYYSALRHYINLITRQR (NPY18-35, SEQ ID NO: 19),
RYYYSALRHYINLITRQR (NPY19-35, SEQ ID NO: 20),
35 YYSALRHYINLITRQR (NPY20-35, SEQ ID NO: 21), and

YSALRHYINLITRQR (NPY21-35, SEQ ID NO: 22),
or a functional variant thereof.

- 5 3. The peptide for use according to any one of the preceding claims, wherein said peptide variant has at least 60% sequence identity, such as at least 65% sequence identity, for example at least 70% sequence identity, such as at least 75% sequence identity, for example at least 80% sequence identity, such as at least 85% sequence identity, for example at least 90% sequence identity, such as at least 95% sequence identity, for example at least 99% sequence identity
- 10 to a peptide selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22.
- 15 4. The peptide for use according to according to any of the preceding claims, wherein said peptide variant comprises one or more amino acid substitution, such as one amino acid substitution, such as two amino acid substitutions, such as three amino acid substitutions, such as four amino acid substitutions, such as five amino acid substitutions, such as six amino acid substitutions, such as
- 20 seven amino acid substitutions.
5. The peptide for use according to any one of the preceding claims, wherein the peptide is selected from the group consisting of:
- 25 a peptide consisting of 35 contiguous amino acid residues having the sequence YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY1-35, SEQ ID NO: 2) or YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 34 contiguous amino acid residues having the sequence
- 30 PSKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY2-35, SEQ ID NO: 3) or PSKPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 33 contiguous amino acid residues having the sequence SKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY3-35, SEQ ID NO: 4)

- or SKPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 5 a peptide consisting of 32 contiguous amino acid residues having the sequence KPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY4-35, SEQ ID NO: 5) or KPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 10 a peptide consisting of 31 contiguous amino acid residues having the sequence PDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY5-35, SEQ ID NO: 6) or PDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 15 a peptide consisting of 30 contiguous amino acid residues having the sequence DNPGE DAPAEDMARYYSALRHYINLITRQR (NPY6-35, SEQ ID NO: 7) or DNPGE DAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 20 a peptide consisting of 29 contiguous amino acid residues having the sequence NPGEDAPAEDMARYYSALRHYINLITRQR (NPY7-35, SEQ ID NO: 8) or NPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 25 a peptide consisting of 28 contiguous amino acid residues having the sequence PGEDAPAEDMARYYSALRHYINLITRQR (NPY8-35, SEQ ID NO: 9) or PGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 30 a peptide consisting of 27 contiguous amino acid residues having the sequence GEDAPAEDMARYYSALRHYINLITRQR (NPY9-35, SEQ ID NO: 10) or GEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 26 contiguous amino acid residues having the sequence EDAPAEDMARYYSALRHYINLITRQR (NPY10-35, SEQ ID NO: 11) or EDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 25 contiguous amino acid residues having the sequence DAPAEDMARYYSALRHYINLITRQR (NPY11-35, SEQ ID NO: 12) or DAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,

- a peptide consisting of 24 contiguous amino acid residues having the sequence
APAEDMARYYSALRHYINLITRQR (NPY12-35, SEQ ID NO: 13)
or APAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 5 a peptide consisting of 23 contiguous amino acid residues having the
sequence PAEDMARYYSALRHYINLITRQR (NPY13-35, SEQ ID NO: 14)
or PAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 22 contiguous amino acid residues having the sequence
AEDMARYYSALRHYINLITRQR (NPY14-35, SEQ ID NO: 15)
or AEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 10 a peptide consisting of 21 contiguous amino acid residues having the sequence
EDMARYYSALRHYINLITRQR (NPY15-35, SEQ ID NO: 16)
or EDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 20 contiguous amino acid residues having the sequence
DMARYYSALRHYINLITRQR (NPY16-35, SEQ ID NO: 17)
15 or DMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 19 contiguous amino acid residues having the sequence
MARYYSALRHYINLITRQR (NPY17-35, SEQ ID NO: 18)
or MARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 18 contiguous amino acid residues having the sequence
20 ARYYSALRHYINLITRQR (NPY18-35, SEQ ID NO: 19)
or ARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- a peptide consisting of 17 contiguous amino acid residues having the sequence
RYYSALRHYINLITRQR (NPY19-35, SEQ ID NO: 20)
or RYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions,
- 25 a peptide consisting of 16 contiguous amino acid residues having the sequence
YYSALRHYINLITRQR (NPY20-35, SEQ ID NO: 21)
or YYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions, and
- a peptide consisting of 15 contiguous amino acid residues having the sequence
YSALRHYINLITRQR (NPY21-35, SEQ ID NO: 22)
30 or YSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.

6. The peptide for use according to any of the preceding claims, wherein the peptide is selected from the group consisting of:
SKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY3-35; SEQ ID NO: 4),
a functional variant thereof having at least 60% sequence identity to SEQ ID NO: 4, and
SKPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.
7. The peptide for use according to any of the preceding claims, wherein the peptide is selected from the group consisting of:
EDAPAEDMARYYSALRHYINLITRQR (NPY10-35, SEQ ID NO: 11),
a functional variant thereof having at least 60% sequence identity to SEQ ID NO: 11, and
EDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.
8. The peptide for use according to any of the preceding claims, wherein the peptide is selected from the group consisting of: YSALRHYINLITRQR (NPY21-35, SEQ ID NO: 22),
a functional variant thereof having at least 60% sequence identity to SEQ ID NO: 22, and
YSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions.
9. The peptide for use according to any one of the preceding claims, wherein said one or more amino acid substitutions are each a conservative amino acid substitution.
10. The peptide for use according to any one of the preceding claims, wherein said peptide or functional variant thereof:
does not bind to and/or does not activate cognate NPY receptors, such as cognate NPY-receptors Y1, Y2 and/or Y5;
binds to NCAM, such as the NCAM Ig1 module;
increases cardiac conduction velocity (CV); and/or
reduces or suppresses cardiac arrhythmia.
11. The peptide for use according to any one of the preceding claims, wherein the cardiac disease is selected from the group consisting of Cardiac arrhythmias;

5 Coronary artery disease; Acute Myocardial infarction (AMI); Cardiomyopathy; Hypertensive heart disease; Heart failure; Pulmonary heart disease; Inflammatory heart disease such as Endocarditis and carditis, Inflammatory cardiomegaly, Myocarditis or Eosinophilic myocarditis; Valvular heart disease; Congenital heart disease; Rheumatic heart disease; Aortic aneurysms; Long or short QT syndrome; Brugada syndrome; Arrhythmogenic cardiomyopathy (ACM); and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT).

10 12. The peptide for use according to any one of the preceding claims, wherein the cardiac disease is selected from the group consisting of Cardiac arrhythmia; Coronary artery disease and Acute Myocardial infarction (AMI).

15 13. The peptide for use according to any one of the preceding claims, wherein the cardiac disease is Cardiac arrhythmia.

14. The peptide for use according to any one of the preceding claims, wherein the peptide is selected from the group consisting of:

20 SKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY3-35; SEQ ID NO: 4), a functional variant thereof having at least 60% sequence identity to SEQ ID NO: 4, and

SKPDNPGEDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions;

25 EDAPAEDMARYYSALRHYINLITRQR (NPY10-35, SEQ ID NO: 11), a functional variant thereof having at least 60% sequence identity to SEQ ID NO: 11, and

EDAPAEDMARYYSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions; and

30 YSALRHYINLITRQR (NPY21-35, SEQ ID NO: 22), a functional variant thereof having at least 60% sequence identity to SEQ ID NO: 22, and YSALRHYINLITRQR with 1, 2 or 3 amino acid substitutions;

and the cardiac disease is Cardiac arrhythmia.

15. The peptide for use according to any one of the preceding claims, wherein the peptide is selected from the group consisting of
SKPDNPGEDAPAEDMARYYSALRHYINLITRQR (NPY3-35; SEQ ID NO: 4),
EDAPAEDMARYYSALRHYINLITRQR (NPY10-35, SEQ ID NO: 11) and
5 YSALRHYINLITRQR (NPY21-35, SEQ ID NO: 22),
and the cardiac disease is Cardiac arrhythmia.
16. The peptide for use according to any one of claims 11-15, wherein the cardiac
arrhythmia is secondary to another cardiac disease, such as secondary to a
10 cardiac disease selected from the group consisting of acute or chronic ischemic
heart disease, vascular heart disease, valvular heart disease, degenerative
primary electrical disease, Long or short QT syndrome; cardiomyopathy;
Brugada syndrome; Arrhythmogenic cardiomyopathy (ACM); catecholaminergic
polymorphic ventricular tachycardia (CPVT) and surgery, including general
15 surgery and cardiac surgery.
17. The peptide for use according to any one of claims 11-15, wherein the cardiac
arrhythmia is selected from the group consisting of ventricular arrhythmias,
supraventricular arrhythmias, bradycardias, tachycardias, Supraventricular
20 tachycardias, Ventricular arrhythmias, Extra beats, Bradycardia, atrial
arrhythmias, junctional arrhythmias and heart block.
18. The peptide for use according to any one of claims 11-15, wherein the cardiac
arrhythmia is selected from the group consisting of atrial fibrillation, atrial flutter,
25 paroxysmal supraventricular tachycardia, Wolff–Parkinson–White syndrome,
atrioventricular (AV) nodal re-entry, Ventricular fibrillation, ventricular
tachycardia, premature atrial activations, premature ventricular contractions,
and premature junctional contractions.
19. The peptide for use according to any one of claims 11-15, wherein the cardiac
30 arrhythmia is produced by enhanced automaticity, triggered activity, or re-entry.

A

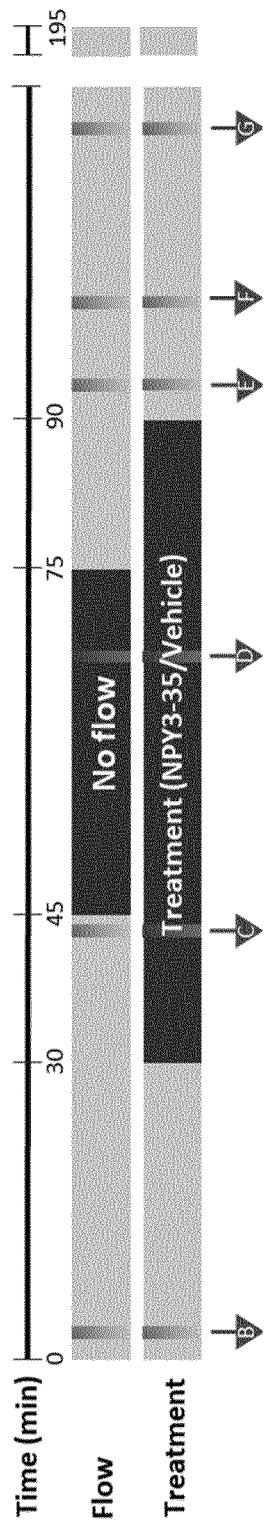
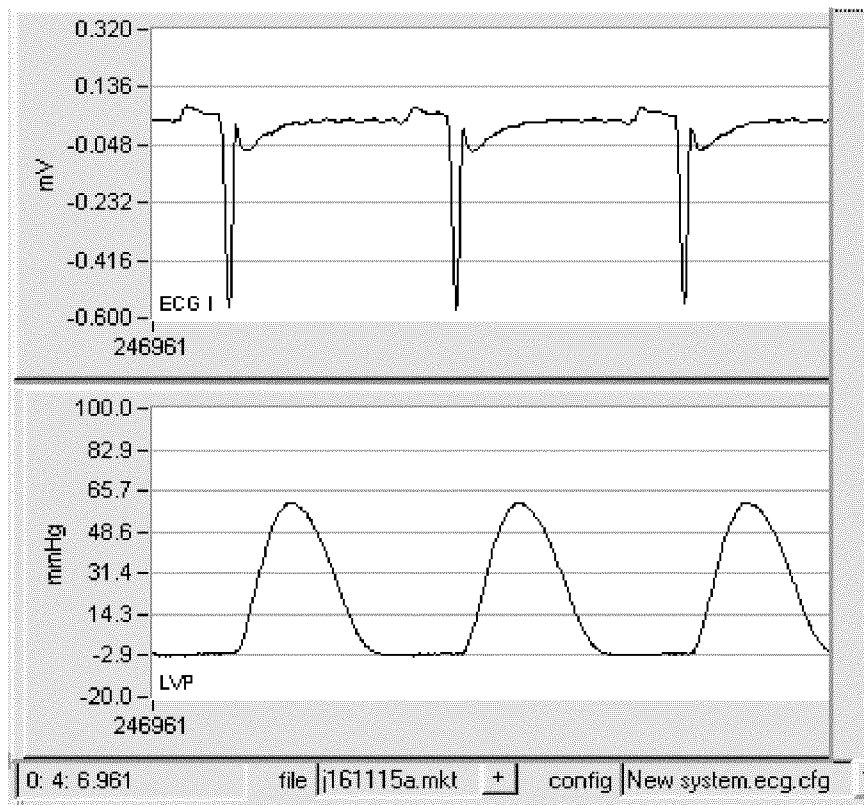


FIGURE 1

B

Failed
recovery
(Vehicle)



Panel 1

Panel 2

Panel 3

Panel 4

Successful
Recovery
(NPY3-35)

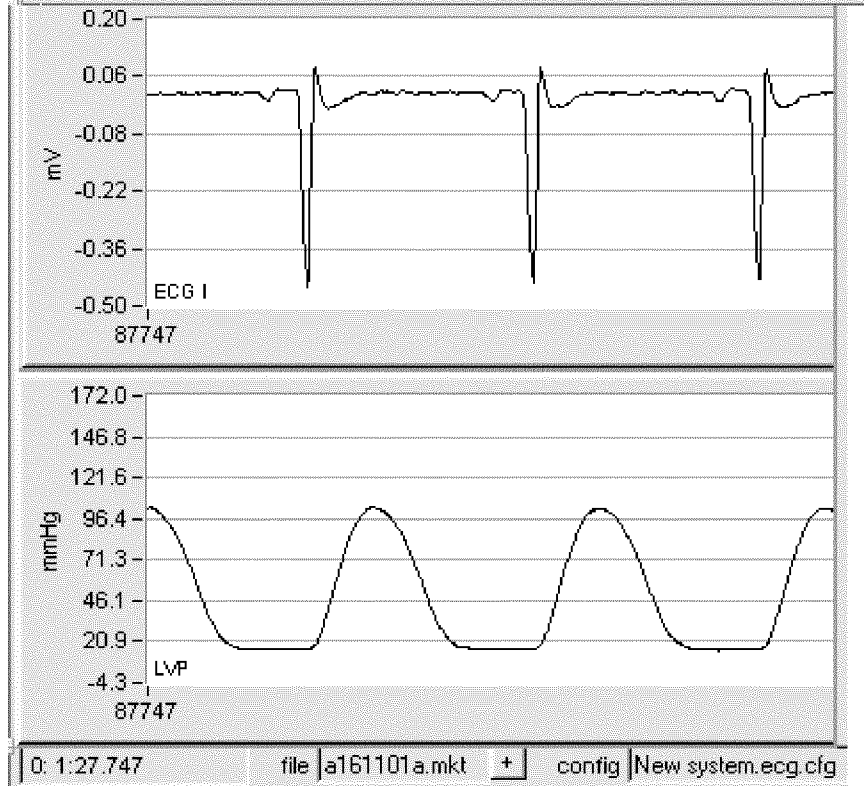
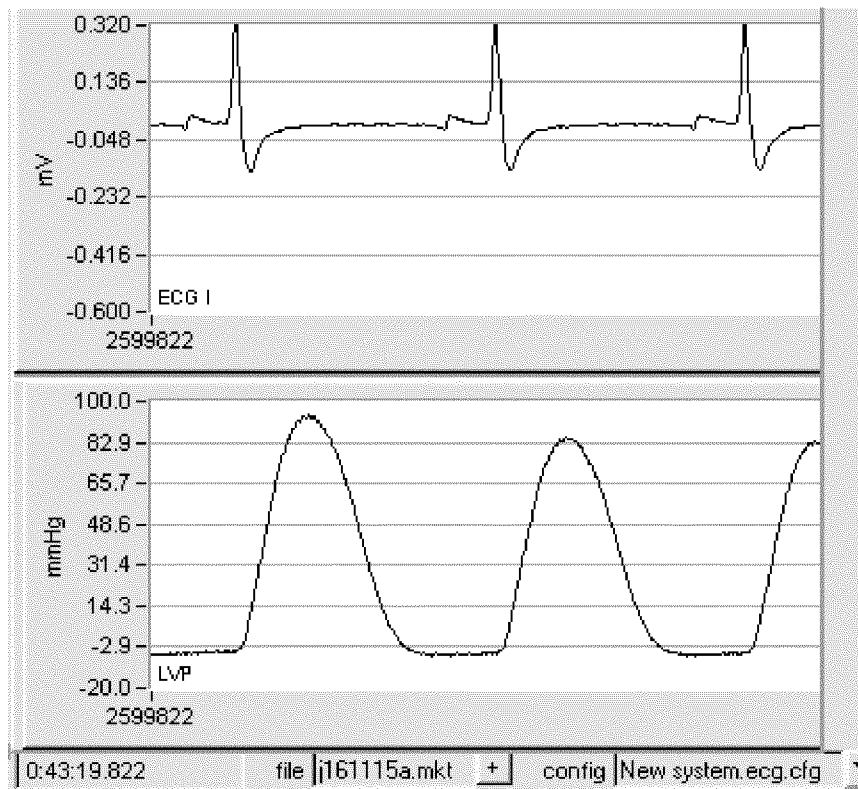


FIGURE 1 CONT.

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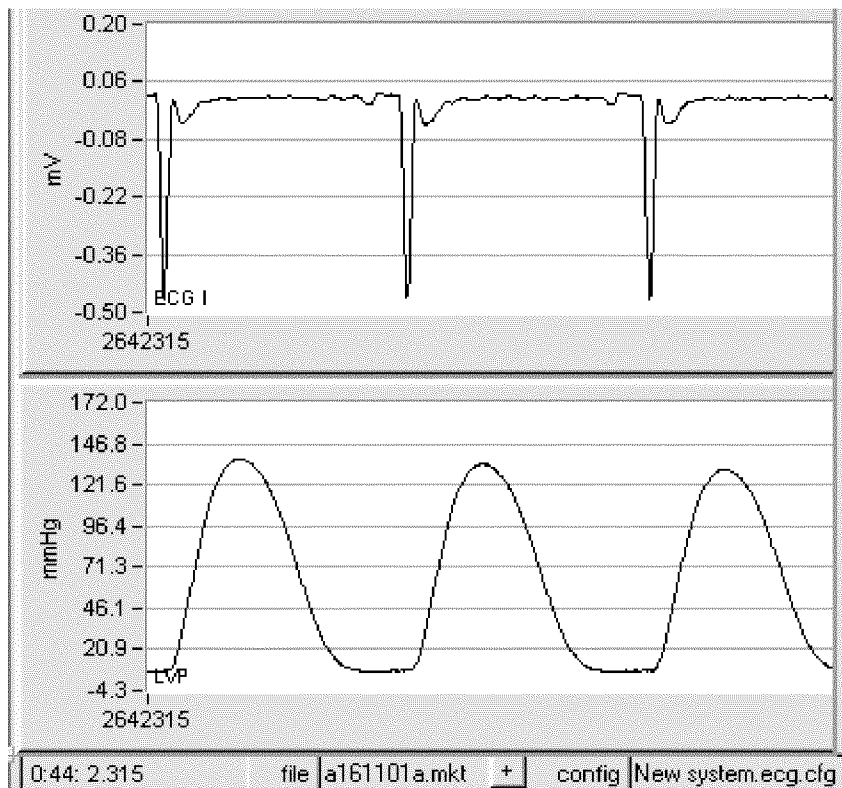
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(Vehicle)



Panel 1

Panel 2

Successful
Recovery
(NPY3-35)



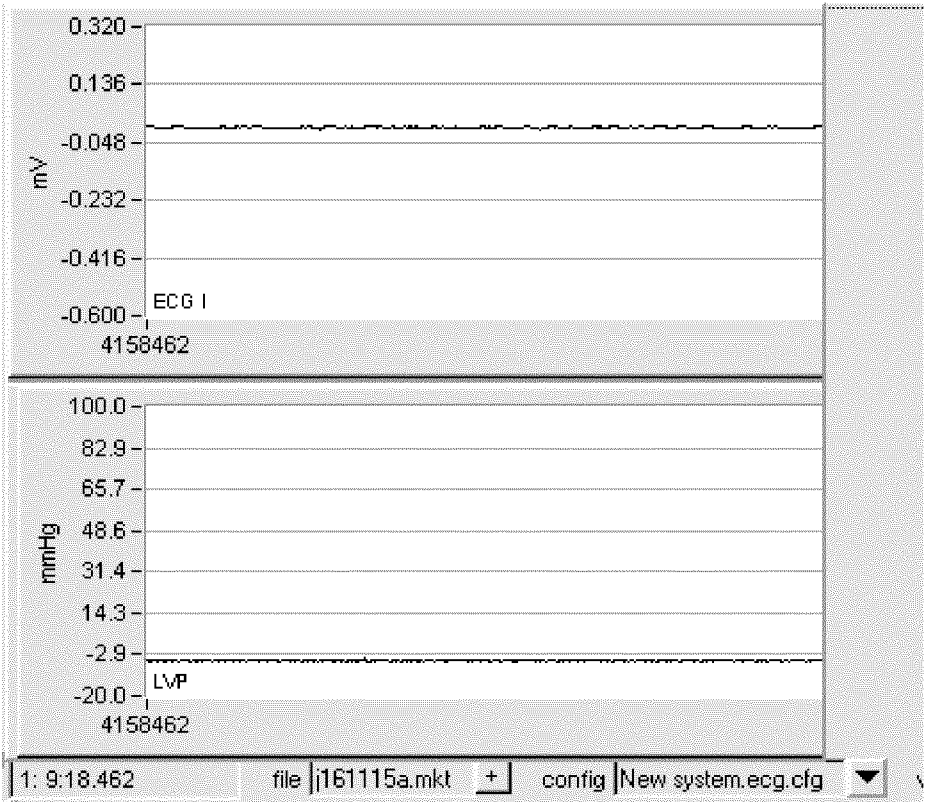
Panel 3

Panel 4

FIGURE 1 CONT.

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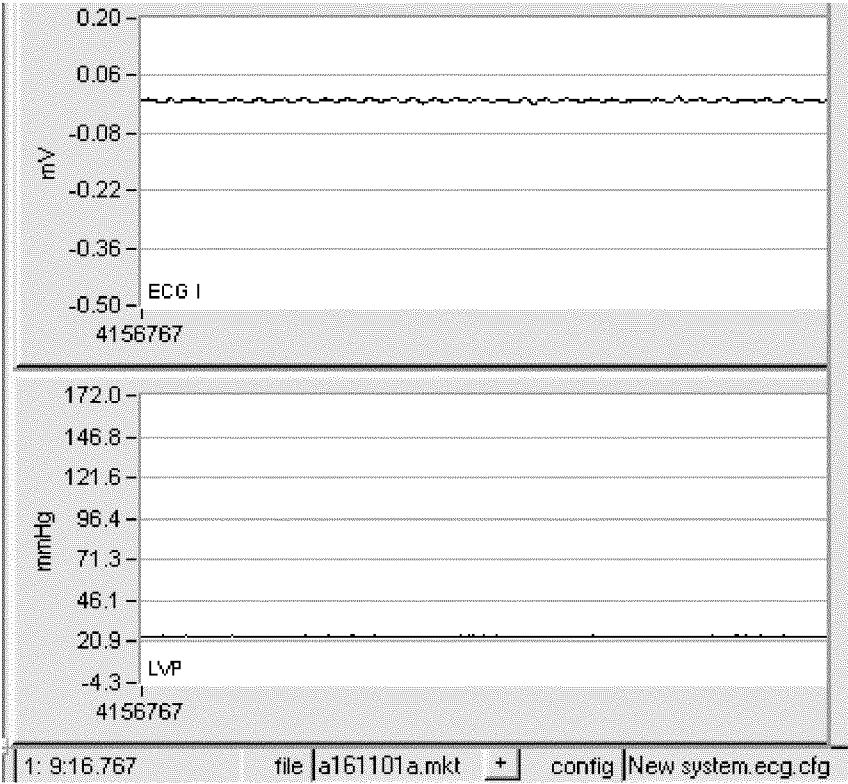
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recovery
(Vehicle)



Panel 1

Panel 2

Successful
Recovery
(NPY3-35)



Panel 3

Panel 4

FIGURE 1 CONT.

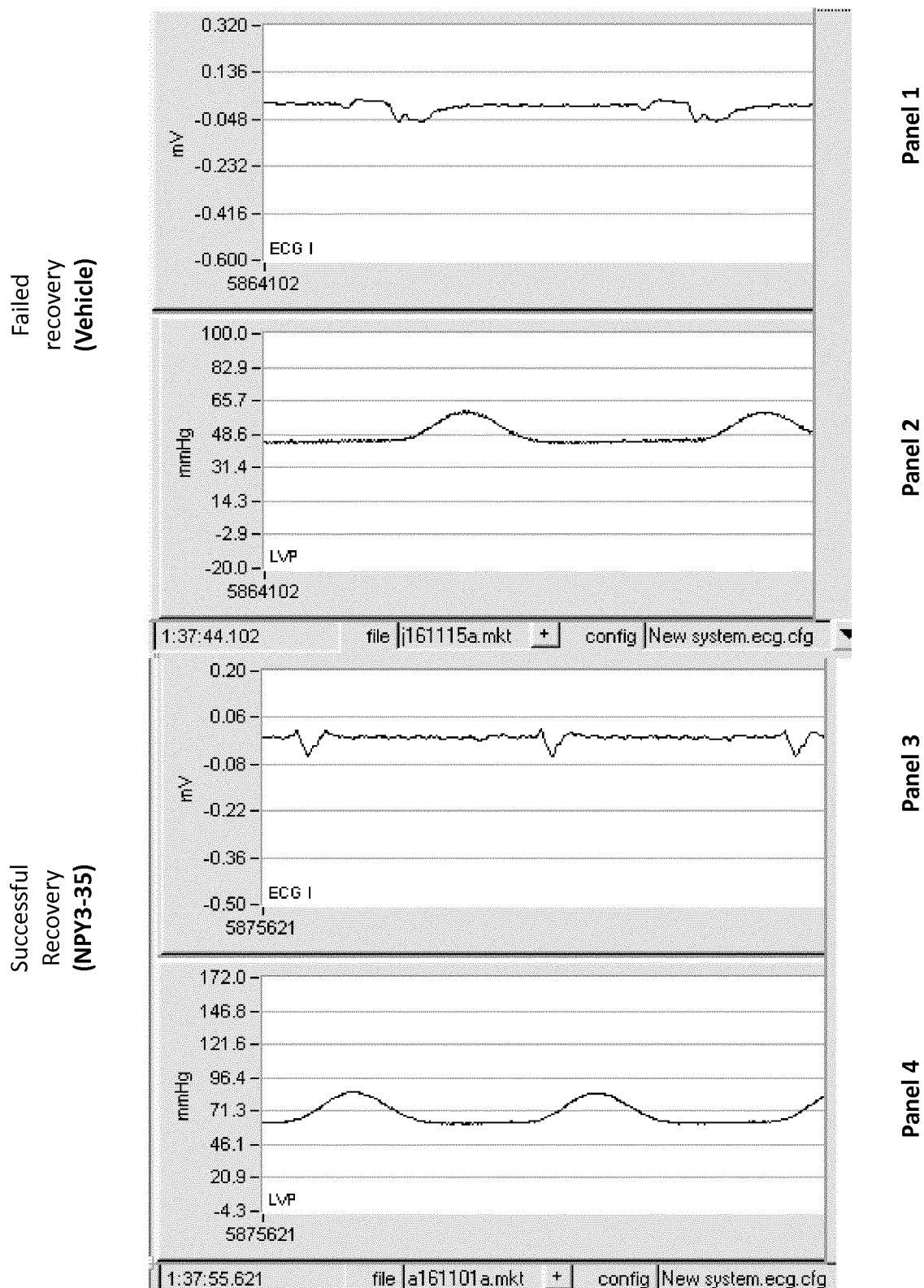
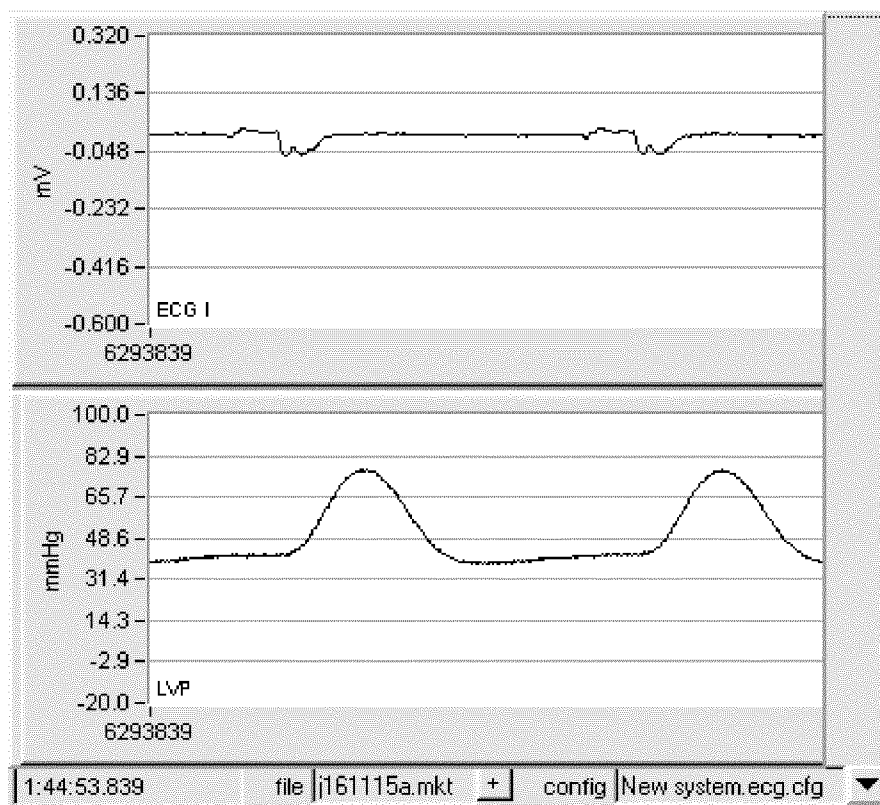
E

FIGURE 1 CONT.

F

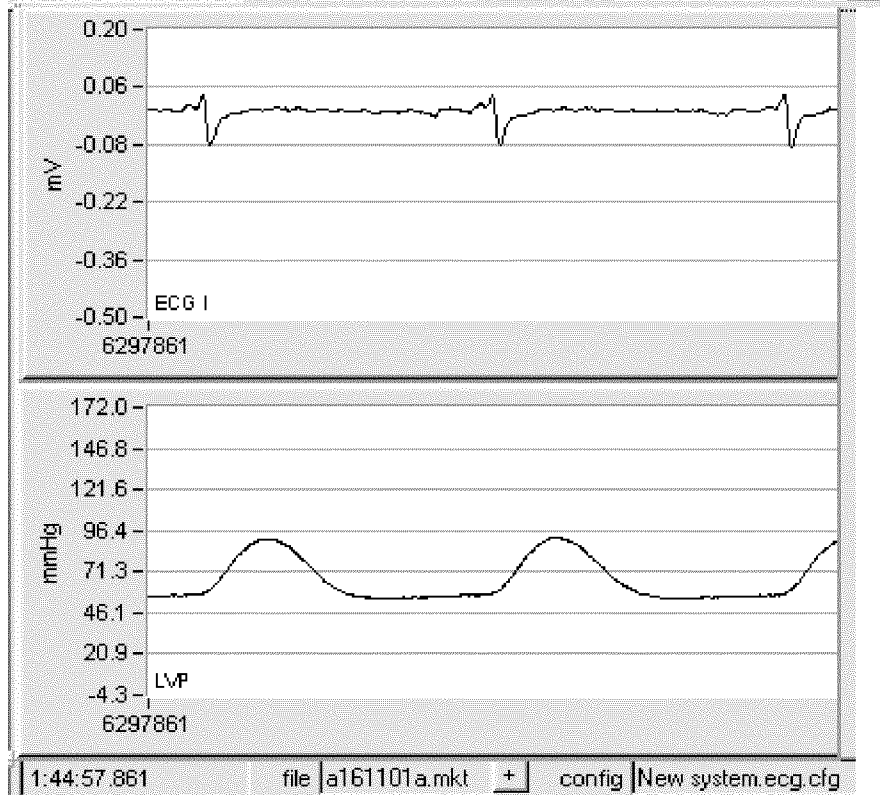
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recovery
(Vehicle)



Panel 1

Panel 2

Successful
Recovery
(NPY3-35)



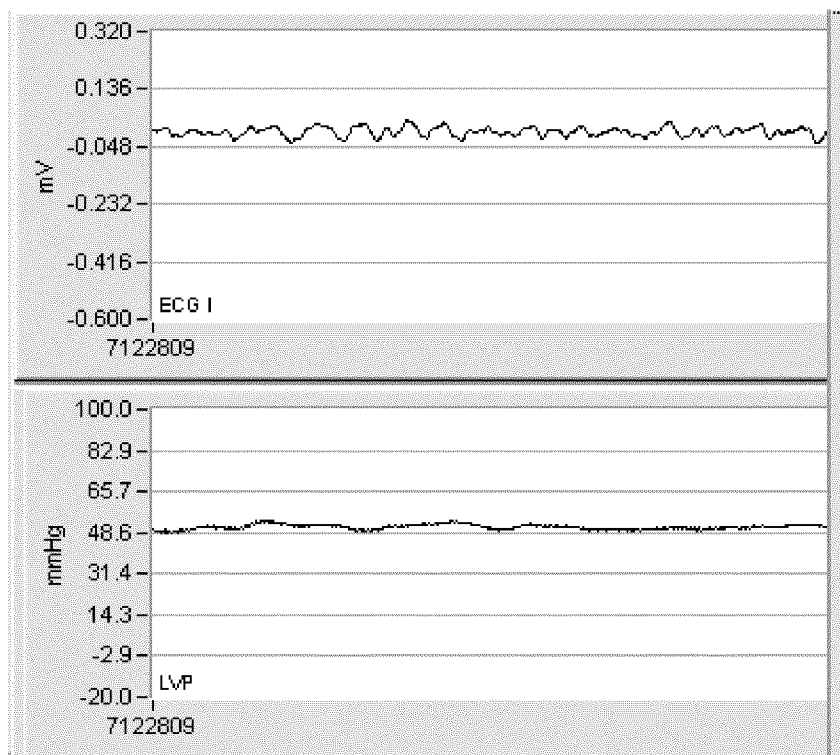
Panel 3

Panel 4

FIGURE 1 CONT.

G

Failed
recovery
(Vehicle)



Panel 1

Panel 2

Successful
Recovery
(NPY3-35)



Panel 3

Panel 4

FIGURE 1 CONT.

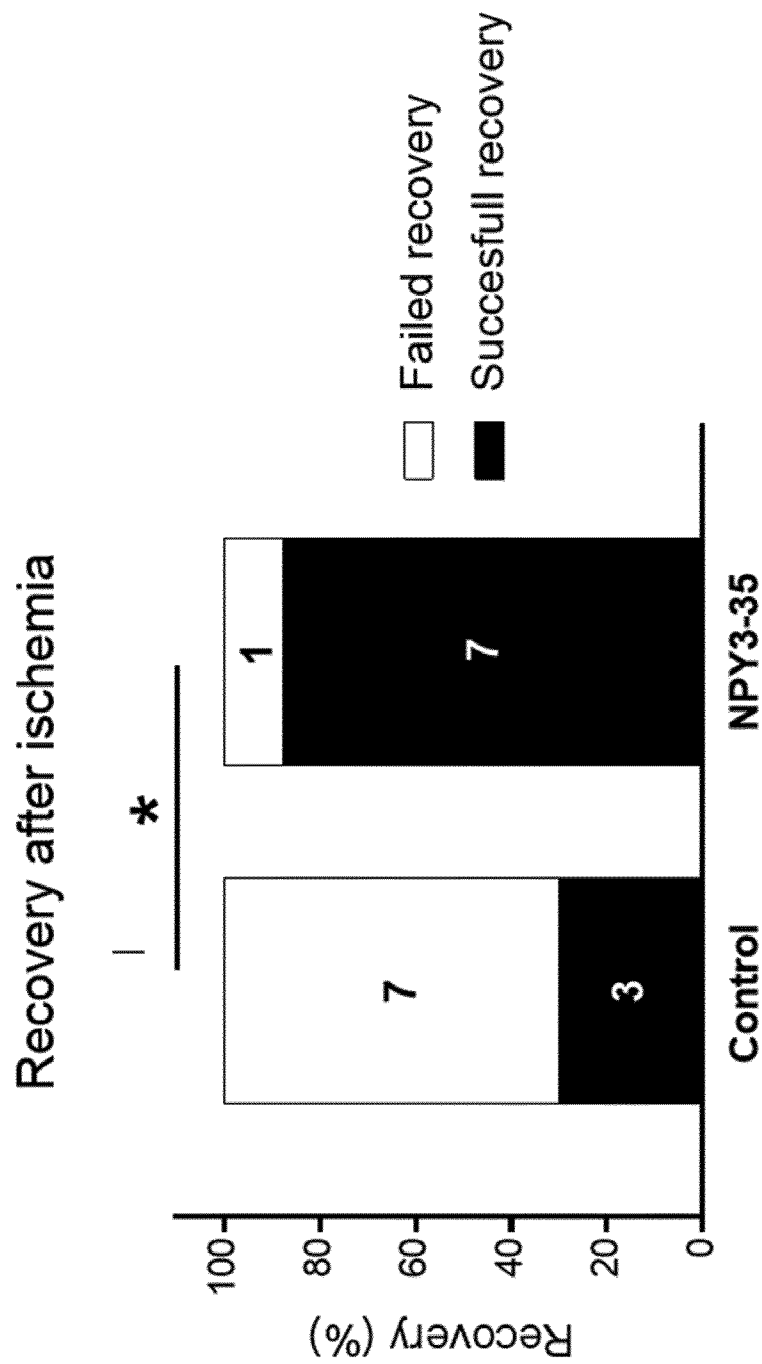
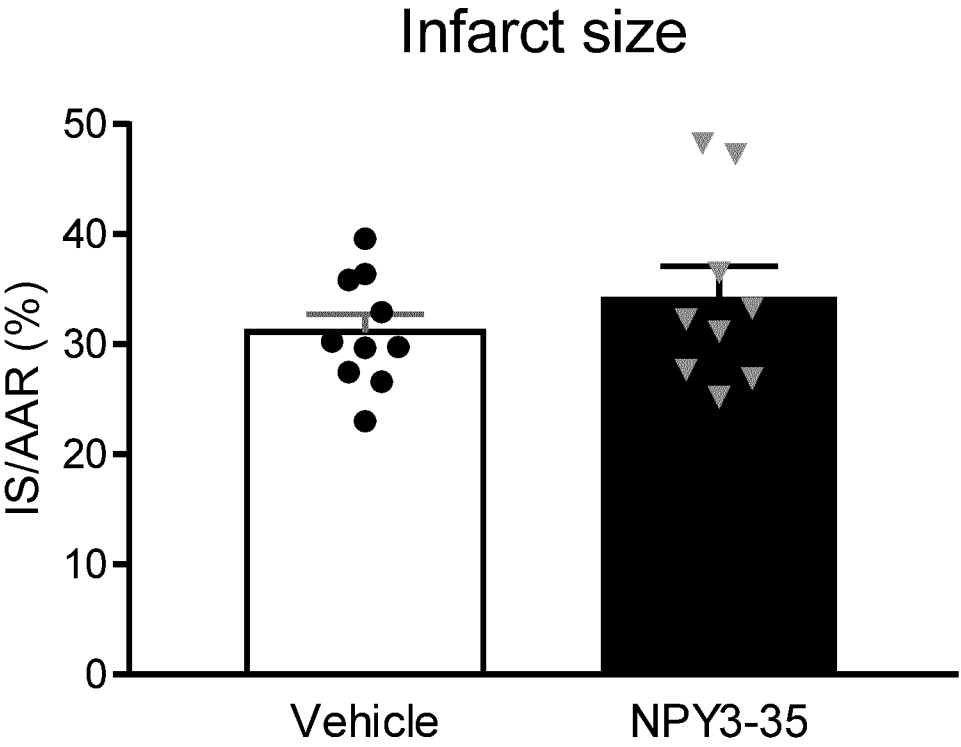
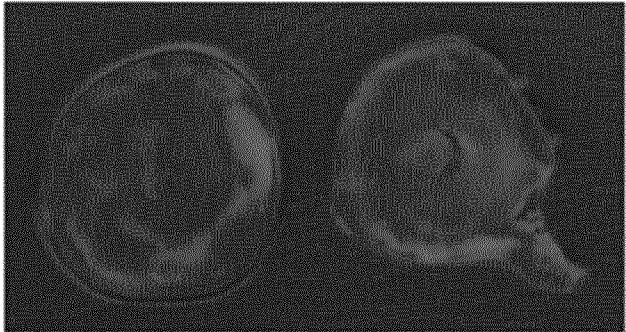


FIGURE 2



Vehicle



NPY3-35

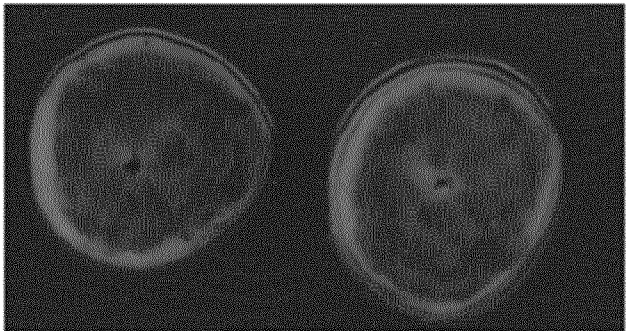


FIGURE 3

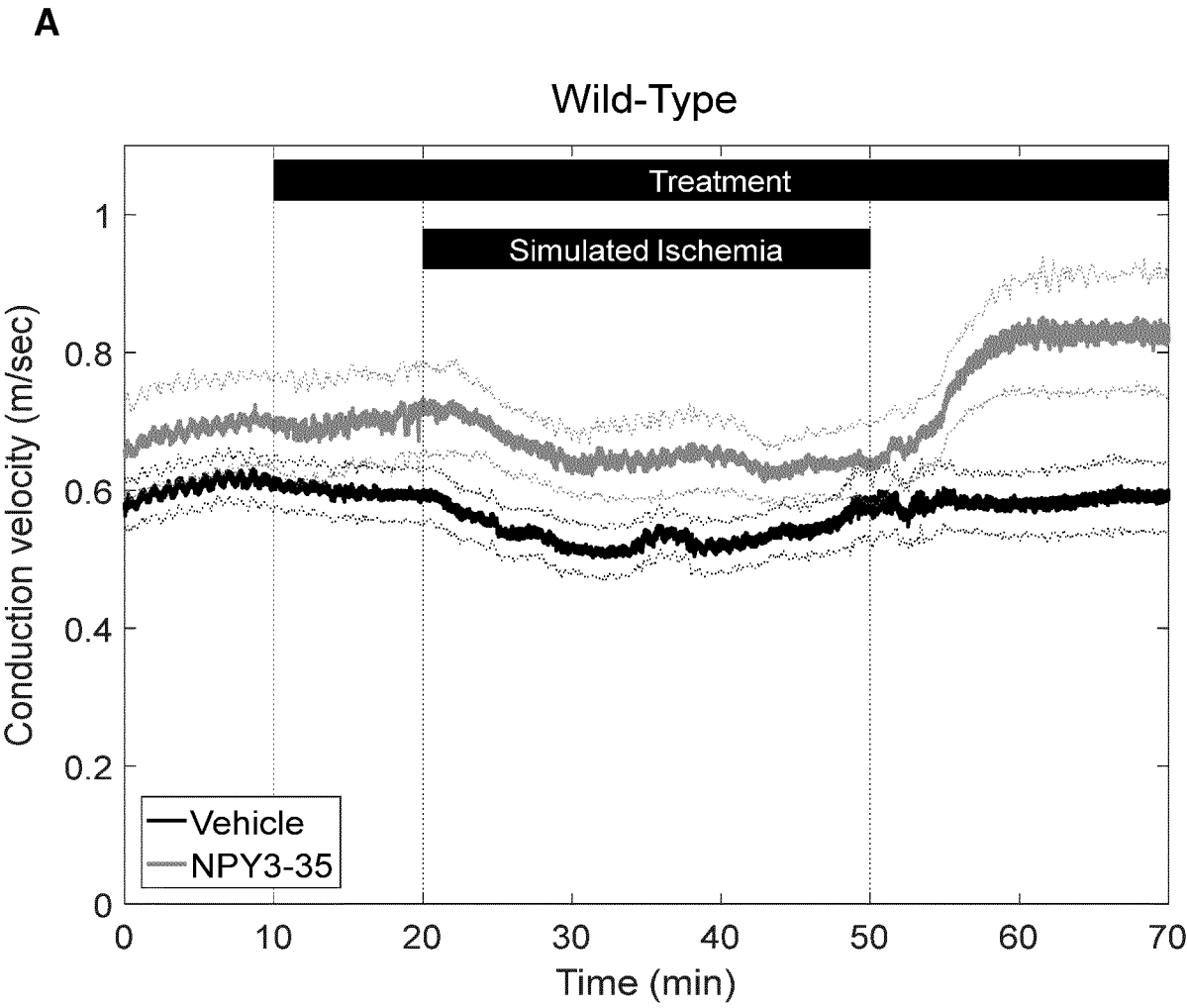


FIGURE 4

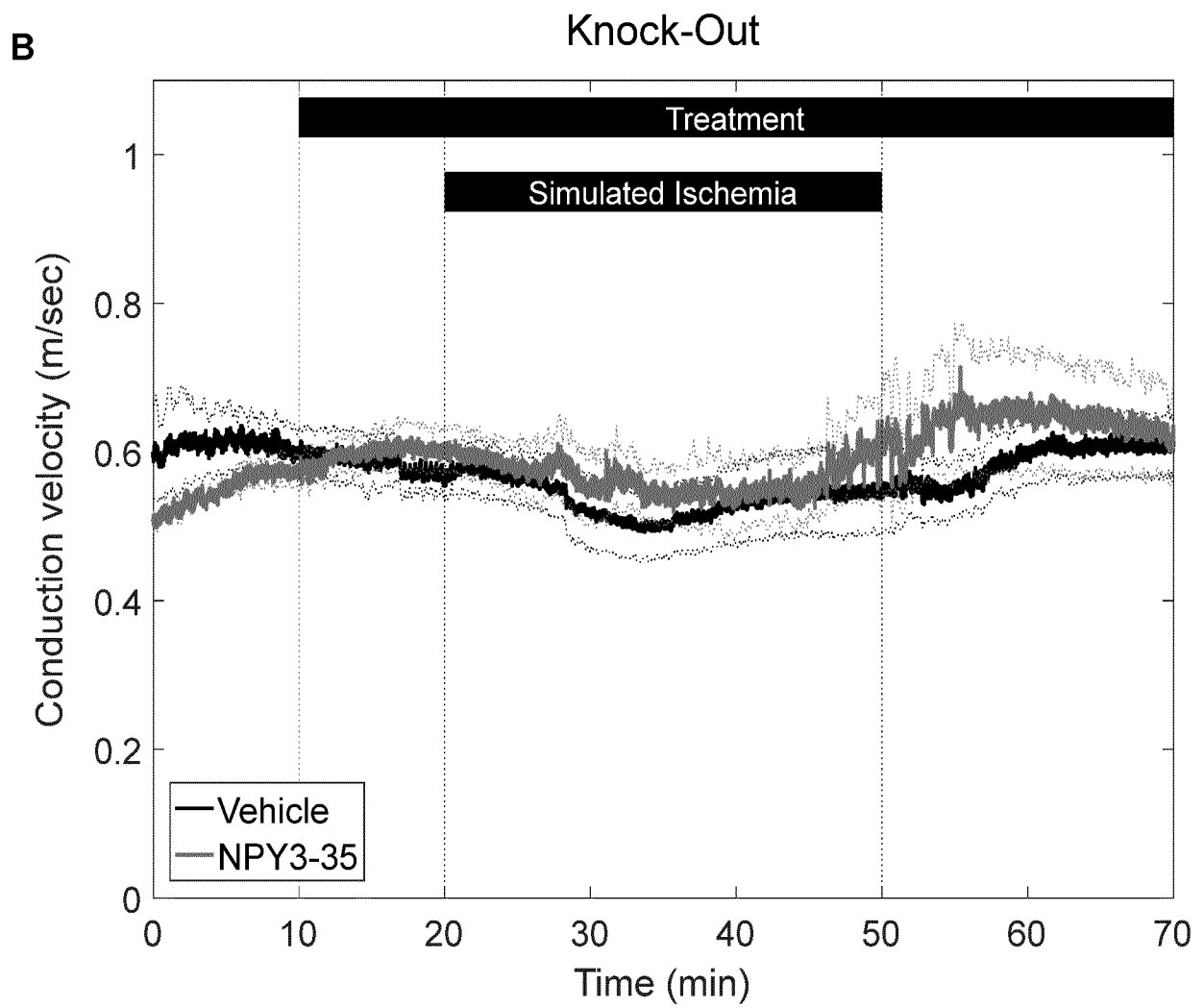


FIGURE 4 CONT.

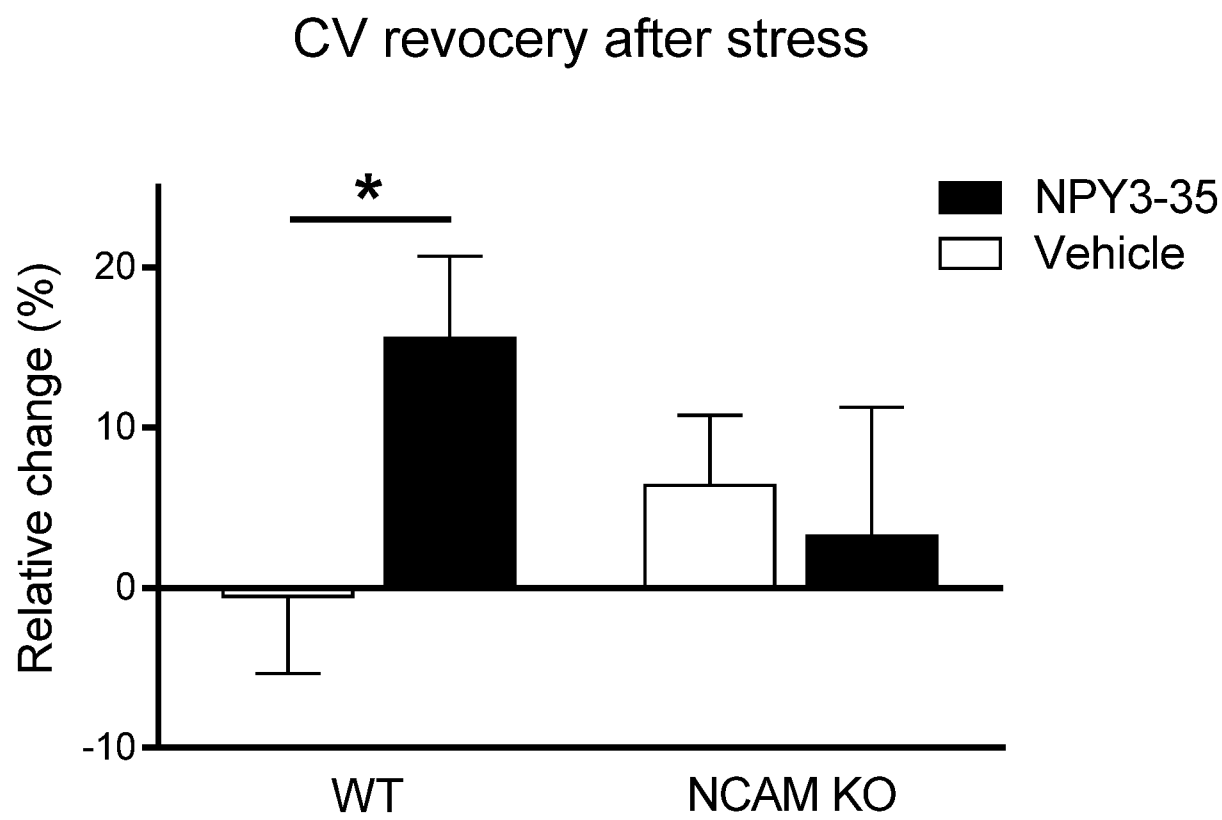
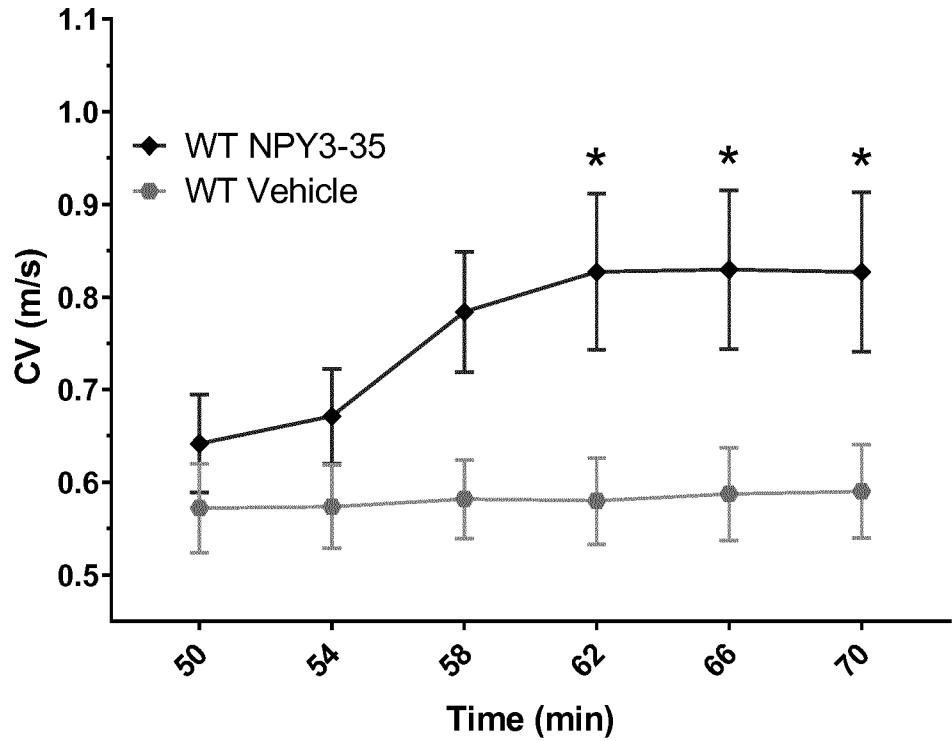


FIGURE 5

A **Conduction velocity recovery during reperfusion**



B **Conduction velocity recovery during reperfusion**

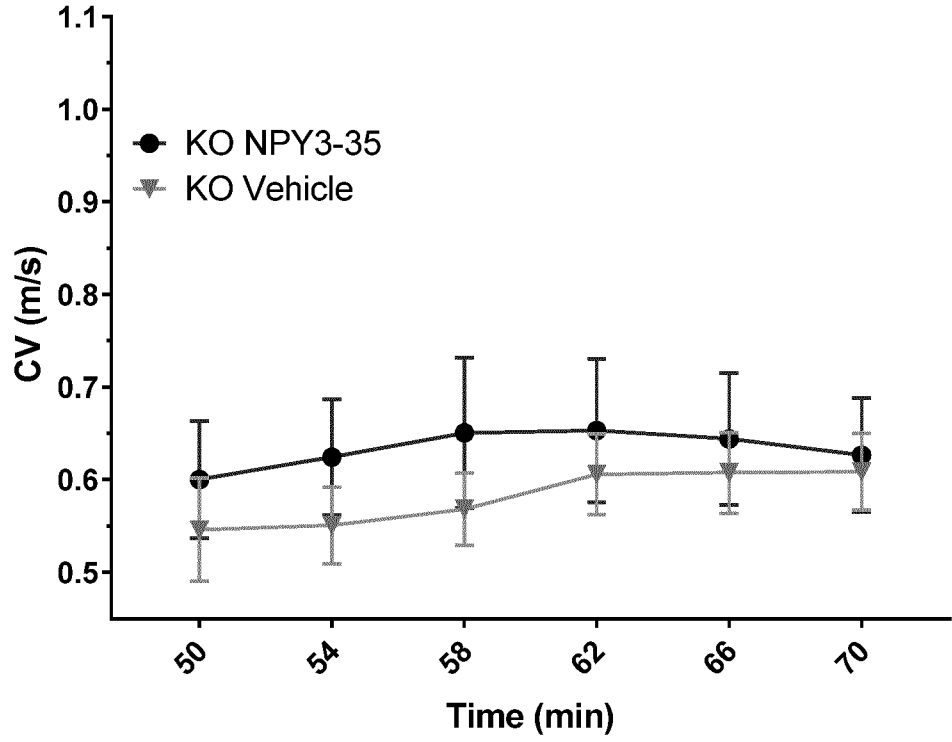


FIGURE 6

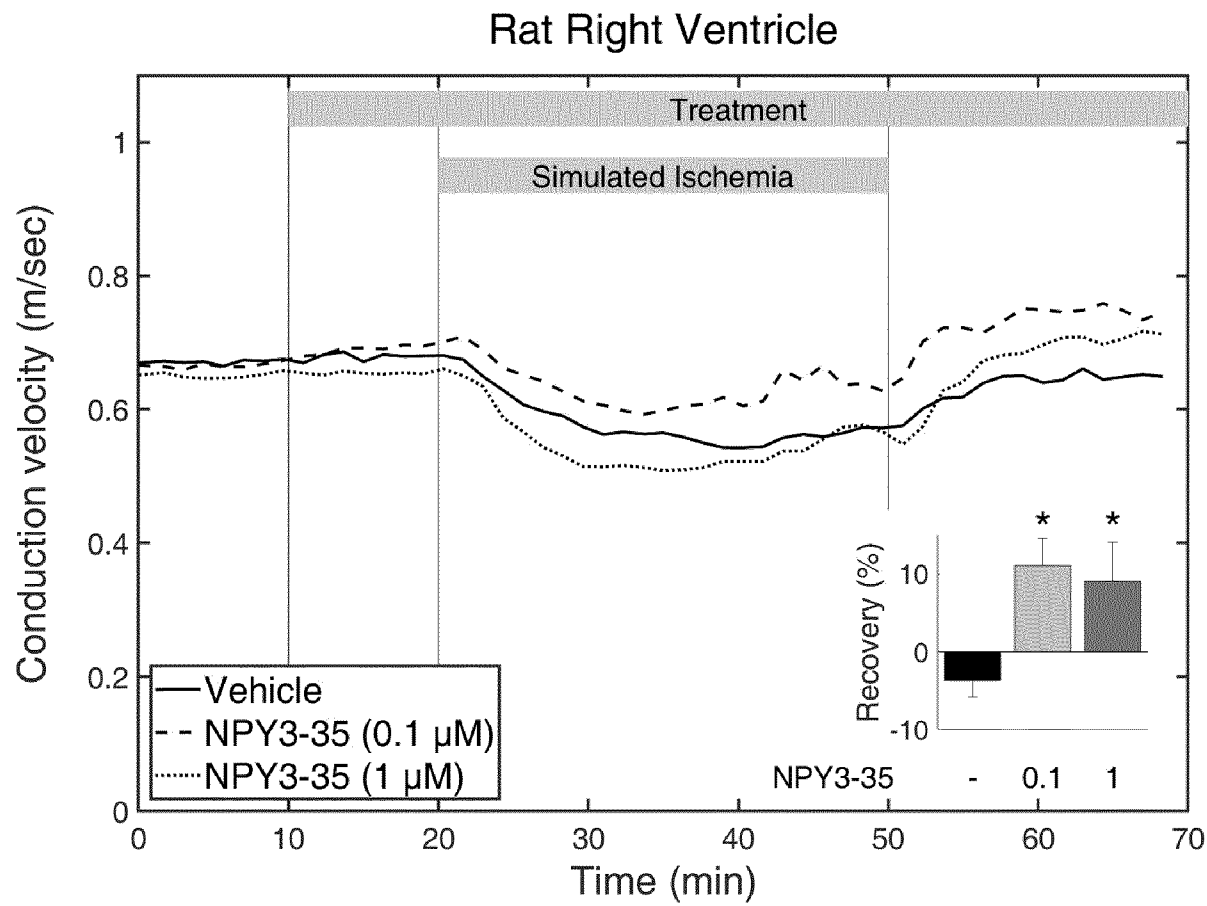
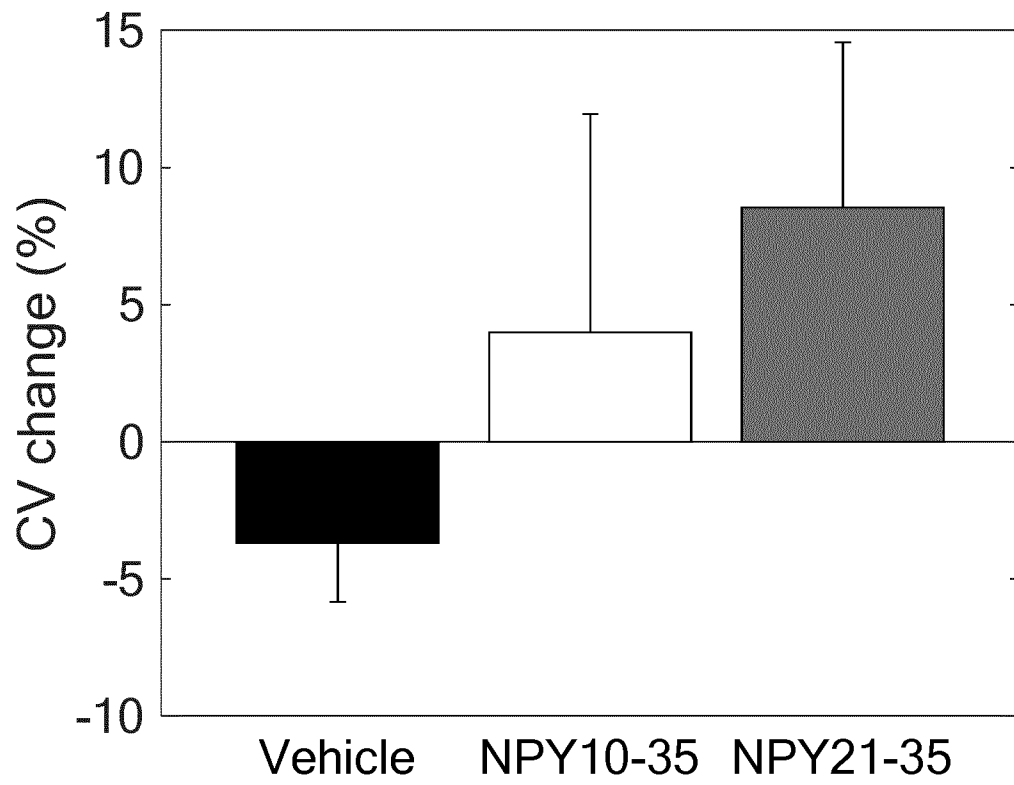


FIGURE 7

**FIGURE 8**

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/083077

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K38/10 A61K38/17 A61K38/22 A61P9/06 ADD.		
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) A61K A61P		
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, WPI Data, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/166497 A2 (UNIV COPENHAGEN [DK]; N STVED HOSPITAL [DK]) 16 October 2014 (2014-10-16) cited in the application	1-13
Y	page 2, line 31 - page 3, line 2 page 4, line 31 - page 5, line 4 page 19, line 9 - line 16 page 21, line 1 - line 9 page 22, line 25 - page 23, line 20 page 50, line 21 - page 51, line 29 page 57, line 11 - line 25 page 58, line 5 - line 15 page 65, line 23 - page 66, line 8 -----	9-13
X	WO 2013/181472 A1 (NEW YORK MEDICAL COLLEGE [US]) 5 December 2013 (2013-12-05) page 3, line 9 - line 19 page 5, line 27 - page 6, line 1 ----- -/--	1-19
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier 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 "&" document member of the same patent family		
Date of the actual completion of the international search 30 January 2020		Date of mailing of the international search report 10/02/2020
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Pilling, Stephen

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/083077

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HOU YUEMEI ET AL: "Neuromodulation for cardiac arrhythmia.", HEART RHYTHM FEB 2016, vol. 13, no. 2, February 2016 (2016-02), pages 584-592, XP009512936, ISSN: 1556-3871 abstract -----	9-13
A	WO 96/12489 A1 (LILLY CO ELI [US]) 2 May 1996 (1996-05-02) abstract -----	1-19
A	TAN CHERYL M J ET AL: "The Role of Neuropeptide Y in Cardiovascular Health and Disease.", FRONTIERS IN PHYSIOLOGY 2018, vol. 9, 19 September 2018 (2018-09-19), page 1281, XP002791018, ISSN: 1664-042X abstract -----	1-19
A	ABID K ET AL: "Kinetic Study of Neuropeptide Y (NPY) Proteolysis in Blood and Identification of NPY3-35 A NEW PEPTIDE GENERATED BY PLASMA KALLIKREIN", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, US, vol. 284, no. 37, 11 September 2009 (2009-09-11), pages 24715-24724, XP002697330, ISSN: 0021-9258, DOI: 10.1074/JBC.M109.035253 [retrieved on 2009-07-20] abstract -----	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2019/083077

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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