Title: PEPTIDES AS MODULATORS OF FPRL1 AND/OR FPRL2

Abstract: The present invention provides new peptides containing 11 or 12 amino acids which are modulators of human FPRL1 and/or FPRL2 receptor.
**Peptides as modulators of FPRL1 and/or FPRL2**

The present invention relates to novel peptides, their use as pharmaceuticals and their use in screening assays. The invention also concerns related aspects including processes for the preparation of the peptides, pharmaceutical compositions containing one or more of said peptides, and especially their use as FPRL1 and/or FPRL2 receptor modulators.

FPRL1 (alias Lipoxin A4 Receptor, ALXR, FPR2; disclosed in WO2003/082314 as nucleotide sequence SEQ ID NO:1 and amino acid sequence SEQ ID NO:2) is a member of the G-protein coupled receptor family. FPRL1 was found to mediate calcium mobilisation in response to high concentration of the formyl-methionine-leucyl-phenylalanine peptide. Furthermore, a lipid metabolite, lipoxin A4 (LXA4), and its analogues, were found to bind FPRL1 with high affinity and increase arachidonic acid production and G-protein activation in FPRL1 transfected cells (Chiang et al., Pharmacol. Rev., 2006, 58, 463-487). The effects of LXA4 have been evaluated in a variety of animal models of diseases; and LXA4 was demonstrated to have potent anti-inflammatory and pro-resolution activities. The disease models where LXA4, or derivatives, or stable analogs, demonstrated in vivo activities are for example dermal inflammation, dorsal air pouch, ischemia/reperfusion injury, peritonitis, colitis, mesangioproliferative nephritis, pleuritis, asthma, cystic fibrosis, sepsis, corneal injury, angiogenesis, periodontitis, carrageenan-induced hyperalgesia, and graft-vs-host disease (GvHD) (Schwab and Serhan, Current Opinion in Pharmacology., 2006, 414-420). FPRL1 was also identified as a functional receptor of a various number of peptides, including a fragment of the prion protein, a peptide derived from gp120 of the Human Immunodeficiency Virus (HIV)-I LAI strain, and amyloid-beta 1-42 (Ab42) (for review, Le et al., Protein Pept Lett., 2007, 14, 846-853), and has been suggested to participate in the pathogenesis of Alzheimer's Disease (AD) in several crucial ways (Yazawa et al., FASEB J., 2001, 15, 2454-2462). Activation of FPRL1 on macrophages and microglial cells initiates a G protein-mediated signaling cascade that increases directional cell migration, phagocytosis, and mediator release. These events may account for the recruitment of mononuclear cells to the vicinity of senile plaques in the diseased areas of AD brain where Ab42 is overproduced and accumulated. Although accumulation of leukocytes at the sites of tissue injury may be considered an innate host response aimed at the clearance of noxious agents, activated mononuclear phagocytes also release a variety of substances such as superoxide anions that may be toxic to neurons. Thus, FPRL1 may mediate pro-inflammatory responses
elicited by Ab42 in AD brain and exacerbate disease progression. It was also reported that humanin (HN), a peptide with neuroprotective capabilities, shares the human FPRL1 with Ab42 on mononuclear phagocytes and neuronal cell lines and it has been suggested that the neuroprotective activity of HN may be attributed to its competitive occupation of FPRL1 (Ying et al., J. Immunol., 2004, 172, 7078-7085). Bae et al. (J. Immunol., 2004, 173, 607-614 and WO2005075505) have screened hexapeptide libraries and found several novel peptides that could block FPRL1-induced cellular signaling and cellular response, including effects mediated by Ab42. Zhou et al. (Mol. Pharmacol., 2007, 72, 976-983) described the first small molecule antagonist of FPRL1. Even if the reported activities on the target were weak, the molecule demonstrated effects similar to the dexamethasone in an arachidonic acid-induced ear edema model.

FPRL2 (alias Formyl Peptide Receptor Like-2, FPR3; disclosed in US2006/0078559 as nucleotide sequence SEQ ID NO:1 and amino acid sequence SEQ ID NO: 2) is a member of the G-protein coupled receptor family. The mRNA of FPRL2 was detected in various tissues, including heart, aorta, vein, spleen, lung, trachea, liver, pancreas, adrenal gland, cervix, rectum, small intestine, ileum chronic inflammation, placenta, spinal cord, lymph node, dorsal rot ganglia, pons, cerebral meninges, postcentral gyrus, Alzheimer brain frontal lobe and breast tumor. FPRL2 is expressed in human monocytes, macrophages, myeloid dendritic cells, plasmacytoid dendritic cells, eosinophils, but not in neutrophils (Migeotte et al., J. Exp. Med., 2005, 201, 83-89; Devosee et al., J. Immunol., 2009, 4974-4984). Humanin, and its analogues, were found to bind FPRL2 with high affinity (Harada et al., Biochem. Biophys. Res. Commun., 2004, 324, 255-261). Humanin was found to protect neuronal cells from a number of toxic insults. This includes neurotoxicity mediated by three mutant genes that cause FAD as well as by Aβ (Hashimoto et al., Biochem. Biophys. Res. Commun., 2001, 283, 460-468). Humanin has also been reported to have protective activity for neurons against serum deprivation (Takahashi et al., Neuroreport, 2002, 13, 903-907) and against excitotoxic death (Caricasole et al., FASEB J., 2002, 1331-1333). Humanin has also been shown to rescue cortical neurons from prion-peptide-induced apoptosis. Humanin has been further shown to improve learning and memory impairment in mice, thereby evidencing utility as a beneficial agent for the prevention or treatment of learning or memory impairment (Mamiya et al., 2001, Br. J. Pharmacol., 134, 1597-1599). Humanin has also been shown to be protective for muscle cells and rescues human cerebrovascular smooth muscle cells from Aβ-induced toxicity. Furthermore, FPRL2 was found to recognize F2L, a Heme Binding Protein (HBP) polypeptide (Migeotte
et al., US2006/0078559). Migeotte et al. (J. Exp. Med., 2005, 201, 83-89) suggested that F2L could be released from HBP after cell suffering or cell death. This molecule would thereafter mediate the recruitment of monocytes and Dendritic cells via FPRL2. Immature and mature dendritic cells (iDC and mDC, respectively) migrate to different anatomical sites, e.g., sites of antigen (Ag) deposition and secondary lymphoid organs, respectively, to fulfill their roles in the induction of primary, Ag-specific immune responses. The trafficking pattern of iDC and mDC is based on their expression of functional chemotactic receptors and the in vivo sites expressing the corresponding ligands including chemokines and/or classical chemoattractants. FPRL2 expressed by DC must be functional and mediate the effect of some known ligands on DC, suggesting that the interaction of FPRL2 and its endogenous ligand(s) may be involved in regulating DC trafficking during Ag uptake and processing in the periphery as well as the T cell-stimulating phase of the immune responses. Kang et al. (J. Immunol, 2005, 175, 685-692) demonstrated that FPRL2 ligands, Helicobacter pylori-derived peptide Hp(2-20) and F2L, inhibited IL-12 production in Monocyte-derived DC (MoDC) induced by LPS, supporting the notion that FPRL2 participates in the inhibition of MoDC maturation by LPS. Therefore, FPRL2 might be involved in the initiation of a variety of inflammatory diseases based on cell death and could represent an attractive target for therapeutic approaches.

The biological properties of FPRL1 modulators include, but are not limited to, monocyte/macrophage/microglia/dendritic cell migration/activation, neutrophil migration/activation, regulation of lymphocyte activation, proliferation and differentiation, regulation of inflammation, regulation of cytokine production and/or release, regulation of proinflammatory mediator production and/or release, regulation of immune reaction.

The biological properties of FPRL2 modulators include, but are not limited to, monocyte/macrophage/microglia cell migration/activation, regulation of lymphocyte activation, proliferation and differentiation, maturation and migration of dendritic cells, regulation of inflammation, regulation of cytokine production and/or release, regulation of proinflammatory mediator production and/or release, regulation of immune reaction.

A FPRL1 modulating peptide containing 12 amino acids (WPLTHTLRHTIW) was described by Boxio et al. (Scand. J. Immunol, 2005, 62, 140-147).

The present invention provides new peptides containing 11 or 12 amino acids which are modulators of human FPRL1 and/or FPRL2 receptor. The peptides are useful for the
prevention or treatment of diseases, which respond to the modulation of FPRL1 and/or FPRL2 such as inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders (especially Alzheimer's disease); in addition they are useful for the prevention or treatment of autoimmune diseases and for the modulation of immune responses (especially those elicited by vaccination). Furthermore, the invention encompasses the use of the interaction of FPRL1 and/or FPRL2 polypeptides with the new peptides as the basis of screening assays for agents that modulate the activity of the FPRL1 and/or FPRL2 receptor.

Various embodiments of the invention are presented hereafter:

1) The present invention relates to a peptide containing 11 or 12 amino acids selected from the group consisting of:

- Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln (SEQ ID No: 1);
- Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr (SEQ ID No: 2);
- Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr (SEQ ID No: 3);
- Phe-Pro-Thr-Leu-Asn-Pro-Ile-Leu-Leu-Thr-Tyr-Ser (SEQ ID No: 4);
- Trp-Ser-Pro-Ser-Arg-Pro-Gly-Leu-Pro-Leu-Ile (SEQ ID No: 5);
- Trp-Pro-Leu-Pro-Lys-Leu-Ala-Thr-Ser-Gly-Ile-Leu (SEQ ID No: 6);
- Leu-Ala-Pro-Arg-Pro-Met-Leu-Glu-Leu-Leu-Thr (SEQ ID No: 7);
- Phe-Pro-Tyr-His-Val-Ala-Met-Arg-His-Thr-Leu (SEQ ID No: 8);
- Ser-Pro-Gln-Phe-Ser-His-Val-Leu-Arg-Leu-Gly-Leu (SEQ ID No: 9);
- Asn-His-Arg-Leu-Pro-Leu-Pro-Ala-Leu-Leu-Trp (SEQ ID No: 10);
- Trp-Ser-Phe-Gly-Asn-Pro-Gly-Leu-Leu-Phe-Ser-Ile (SEQ ID No: 11);
- Ile-Leu-Ala-Asn-Val-Leu-Thr-Ala-Pro-Gly-Pro-Arg (SEQ ID No: 12);
- His-Met-Trp-Asn-Pro-Gly-Ile-Tyr-Ser-Ile-Lys (SEQ ID No: 13); and
- Ile-Pro-Ile-Ser-Arg-Glu-Leu-Val-Thr-His-Asp-Pro (SEQ ID No: 14);

or a homologous peptide thereof in which one amino acid is replaced by another proteinogenic amino acid;

or a salt (especially a pharmaceutically acceptable salt) thereof.

The following paragraphs provide definitions of the various terms according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader or narrower definition.
The term "homologous peptide" means a peptide in which one amino acid is replaced by
another proteinogenic amino acid. Preferably the exchanged amino acids have similar
physical and chemical properties. Similar properties of the respective amino acids may
result from similar size, polarity and/or charge (at physiological pH) of the amino acid side-
chains.

The term "proteinogenic amino acid" means an amino acid in its L-form selected from the
group consisting of:
alanine (Ala, A); arginine (Arg, R); asparagine (Asn, N); aspartic acid (Asp, D); cysteine
(Cys, C); glutamic acid (Glu, E); glutamine (Gin, Q); glycine (Gly, G); histidine (His, H);
iso-leucine (Ile, I); leucine (Leu, L); lysine (Lys, K); methionine (Met, M); phenylalanine
(Phe, F); proline (Pro, P); serine (Ser, S); threonine (Thr, T); tryptophan (Trp, W); tyrosine
(Tyr, Y); and valine (Val, V).

For avoidance of any doubt, all amino acid sequences mentioned throughout the
specification and claims are written according to the usual convention with the N-terminal
amino acid on the left and the C-terminal amino acid on the right. The amino acids are
connected to each other by a peptide bond between the carboxy function of one amino
acid and the a-amino group of another amino acid; such connections are indicated in the
formulas by a hyphen. If not expressly indicated otherwise, all amino acids mentioned are
in their L-forms. For convenience, the conventional abbreviations as listed above are used
for describing amino acids and their sequences.

2) A further embodiment of the invention relates to a peptide according to embodiment 1),
wherein the peptide is selected from the group consisting of:
Phe-Pro-Thr-Leu-Asn-Pro-Ile-Leu-Leu-Thr-Tyr-Ser  (SEQ ID No: 4);
His-Met-Trp-Asn-Pro-Gly-Ile-Ile-Tyr-Ser-Ile-Lys  (SEQ ID No: 13);
Phe-His-Tyr-His-Val-Ala-Ala-Met-Arg-His-Thr-Leu  (SEQ ID No: 8);
Asn-His-Arg-Leu-Pro-Leu-Pro-Ala-Leu-Leu-Trp  (SEQ ID No: 10);
Ser-Pro-Gln-Phe-Ser-His-Val-Leu-Arg-Leu-Gly-Leu  (SEQ ID No: 9);
Trp-Pro-Leu-Pro-Lys-Leu-Ala-Thr-Ser-Gly-Ile-Leu  (SEQ ID No: 6);
Trp-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln  (SEQ ID No: 1);
Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr  (SEQ ID No: 3);
Trp-Ser-Phe-Gly-Asn-Pro-Gly-Leu-Leu-Phe-Ser-Ile  (SEQ ID No: 11);
Trp-Ser-Pro-Ser-Arg-Pro-Gly-Leu-Pro-Leu-Ile  (SEQ ID No: 5);
Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr  (SEQ ID No: 2);
Ile-Leu-Ala-Asn-Val-Leu-Thr-Ala-Pro-Gly-Pro-Arg (SEQ ID No: 12); and
Leu-Ala-Pro-Asn-Arg-Pro-Met-Leu-Glu-Leu-Leu-Thr (SEQ ID No: 7);
or a homologous peptide thereof in which one amino acid is replaced by another
proteinogenic amino acid;
or a salt (especially a pharmaceutically acceptable salt) thereof.

3) A further embodiment of the invention relates to a peptide according to embodiment 1),
wherein the peptide is selected from the group consisting of:
Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln (SEQ ID No: 1);
Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr (SEQ ID No: 2);
Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr (SEQ ID No: 3);
Phe-Pro-Thr-Leu-Asn-Pro-Ile-Leu-Thr-Tyr-Ser (SEQ ID No: 4);
Trp-Ser-Pro-Arg-Pro-Gly-Leu-Pro-Leu-Ile (SEQ ID No: 5);
Trp-Pro-Leu-Pro-Lys-Leu-Ala-Thr-Ser-Gly-Ile-Leu (SEQ ID No: 6);
Leu-Ala-Pro-Asn-Arg-Pro-Met-Leu-Glu-Leu-Leu-Thr (SEQ ID No: 7);
Phe-Pro-Tyr-His-Val-Ala-Met-Arg-His-Thr-Leu (SEQ ID No: 8);
Ile-Pro-Ile-Ser-Arg-Glu-Leu-Val-Thr-His-Asp-Pro (SEQ ID No: 14);
Ser-Pro-Gln-Phe-Ser-His-Val-Leu-Arg-Gly-Leu (SEQ ID No: 9);
Asn-His-Arg-Leu-Pro-Leu-Pro-Leu-Leu-Trp (SEQ ID No: 10); and
Trp-Ser-Phe-Gly-Asn-Pro-Gly-Leu-Leu-Phe-Ser-Ile (SEQ ID No: 11);
or a homologous peptide thereof in which one amino acid is replaced by another
proteinogenic amino acid;
or a salt (especially a pharmaceutically acceptable salt) thereof.

4) A further embodiment of the invention relates to a peptide according to embodiment 1),
wherein the peptide is selected from the group consisting of:
Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln (SEQ ID No: 1);
Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr (SEQ ID No: 2);
Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr (SEQ ID No: 3);
Phe-Pro-Thr-Leu-Asn-Pro-Ile-Leu-Thr-Tyr-Ser (SEQ ID No: 4);
Trp-Ser-Pro-Arg-Pro-Gly-Leu-Pro-Leu-Ile (SEQ ID No: 5);
Trp-Pro-Leu-Pro-Lys-Leu-Ala-Thr-Ser-Gly-Ile-Leu (SEQ ID No: 6);
Leu-Ala-Pro-Asn-Arg-Pro-Met-Leu-Glu-Leu-Leu-Thr (SEQ ID No: 7);
Phe-Pro-Tyr-His-Val-Ala-Met-Arg-His-Thr-Leu (SEQ ID No: 8);
Ile-Pro-Ile-Ser-Arg-Glu-Leu-Val-Thr-His-Asp-Pro (SEQ ID No: 14);
Ser-Pro-Gln-Phe-Ser-His-Val-Leu-Arg-Gly-Leu (SEQ ID No: 9);
Asn-His-Arg-Leu-Pro-Leu-Pro-Ala-Leu-Leu-Trp (SEQ ID No: 10);
Trp-Ser-Phe-Gly-Asn-Pro-Gly-Leu-Leu-Phe-Ser-Ile (SEQ ID No: 11);
Ile-Leu-Ala-Asn-Val-Leu-Thr-Ala-Pro-Gly-Pro-Arg (SEQ ID No: 12); and
His-Met-Trp-Asn-Gly-Ile-Ile-Tyr-Ser-Ile-Lys (SEQ ID No: 13);
or a salt (especially a pharmaceutically acceptable salt) thereof.

5) A further embodiment of the invention relates to a peptide according to embodiment 1),
wherein the peptide is
Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln (SEQ ID No: 1) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln);
or a salt (especially a pharmaceutically acceptable salt) thereof.

6) A further embodiment of the invention relates to a peptide according to embodiment 1),
wherein the peptide is
Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr (SEQ ID No: 2) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr);
or a salt (especially a pharmaceutically acceptable salt) thereof.

7) A further embodiment of the invention relates to a peptide according to embodiment 1),
wherein the peptide is
Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr (SEQ ID No: 3) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr);
or a salt (especially a pharmaceutically acceptable salt) thereof.

8) A further embodiment of the invention relates to a peptide according to embodiment 1),
wherein the peptide is
Phe-Pro-Thr-Leu-Asn-Pro-Ile-Leu-Leu-Thr-Tyr-Ser (SEQ ID No: 4) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably Phe-Pro-Thr-Leu-Asn-Pro-Ile-Leu-Leu-Thr-Tyr-Ser);
or a salt (especially a pharmaceutically acceptable salt) thereof.

9) A further embodiment of the invention relates to a peptide according to embodiment 1),
wherein the peptide is
Trp-Ser-Pro-Ser-Arg-Pro-Gly-Leu-Pro-Leu-Leu-lle (SEQ ID No: 5) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably Trp-Ser-Pro-Ser-Arg-Pro-Gly-Leu-Pro-Leu-Leu-lle); or a salt (especially a pharmaceutically acceptable salt) thereof.

10) A further embodiment of the invention relates to a peptide according to embodiment 1), wherein the peptide is
Trp-Pro-Leu-Pro-Lys-Leu-Ala-Thr-Ser-Gly-Ile-Leu (SEQ ID No: 6) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably Trp-Pro-Leu-Pro-Lys-Leu-Ala-Thr-Ser-Gly-Ile-Leu); or a salt (especially a pharmaceutically acceptable salt) thereof.

11) A further embodiment of the invention relates to a peptide according to embodiment 1), wherein the peptide is
Leu-Ala-Pro-Asn-Arg-Pro-Met-Leu-Glu-Leu-Thr (SEQ ID No: 7) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably Leu-Ala-Pro-Asn-Arg-Pro-Met-Leu-Glu-Leu-Thr); or a salt (especially a pharmaceutically acceptable salt) thereof.

12) A further embodiment of the invention relates to a peptide according to embodiment 1), wherein the peptide is
Phe-Pro-Tyr-His-Val-Ala-Ala-Met-Arg-His-Thr-Leu (SEQ ID No: 8) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably Phe-Pro-Tyr-His-Val-Ala-Ala-Met-Arg-His-Thr-Leu); or a salt (especially a pharmaceutically acceptable salt) thereof.

13) A further embodiment of the invention relates to a peptide according to embodiment 1), wherein the peptide is
Ser-Pro-Gln-Phe-Ser-His-Val-Leu-Arg-Leu-Gly-Leu (SEQ ID No: 9) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably Ser-Pro-Gln-Phe-Ser-His-Val-Leu-Arg-Leu-Gly-Leu); or a salt (especially a pharmaceutically acceptable salt) thereof.

14) A further embodiment of the invention relates to a peptide according to embodiment 1), wherein the peptide is
Asn-His-Arg-Leu-Pro-Leu-Pro-Ala-Leu-Leu-Trp (SEQ ID No: 10) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably Asn-His-Arg-Leu-Pro-Leu-Pro-Ala-Leu-Leu-Trp);
or a salt (especially a pharmaceutically acceptable salt) thereof.

15) A further embodiment of the invention relates to a peptide according to embodiment 1), wherein the peptide is
Trp-Ser-Phe-Gly-Asn-Pro-Gly-Leu-Leu-Phe-Ser-Ile (SEQ ID No: 11) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably Trp-Ser-Phe-Gly-Asn-Pro-Gly-Leu-Leu-Phe-Ser-Ile);
or a salt (especially a pharmaceutically acceptable salt) thereof.

16) A further embodiment of the invention relates to a peptide according to embodiment 1), wherein the peptide is
lle-Leu-Ala-Asn-Val-Thr-Ala-Pro-Gly-Pro-Arg (SEQ ID No: 12) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably lle-Leu-Ala-Asn-Val-Thr-Ala-Pro-Gly-Pro-Arg);
or a salt (especially a pharmaceutically acceptable salt) thereof.

17) A further embodiment of the invention relates to a peptide according to embodiment 1), wherein the peptide is
His-Met-Trp-Asn-Pro-Gly-Ile-Ile-Tyr-Ser-Ile-Lys (SEQ ID No: 13) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably His-Met-Trp-Asn-Pro-Gly-Ile-Ile-Tyr-Ser-Ile-Lys);
or a salt (especially a pharmaceutically acceptable salt) thereof.

18) A further embodiment of the invention relates to a peptide according to embodiment 1), wherein the peptide is
lle-Pro-Ile-Ser-Arg-Glu-Leu-Val-Thr-His-Asp-Pro (SEQ ID No: 14) or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid (and notably lle-Pro-Ile-Ser-Arg-Glu-Leu-Val-Thr-His-Asp-Pro);
or a salt (especially a pharmaceutically acceptable salt) thereof.

19) A further embodiment of the invention relates to a method of identifying an agent that modulates the function of FPRL1, the method comprising: a) contacting a FPRL1 polypeptide with a peptide according to any one of embodiments 1) to 18) in the presence and absence of a candidate modulator under conditions permitting the interaction of the
peptide to the FPRL1 polypeptide; and b) measuring the interaction of the FPRL1 polypeptide to the peptide, wherein an increase or a decrease in interaction in the presence of the candidate modulator, relative to the interaction in the absence of the candidate modulator, identifies the candidate modulator as an agent that modulates the function of FPRL1.

20) A further embodiment of the invention relates to a method of identifying an agent that modulates the function of FPRL2, the method comprising: a) contacting a FPRL2 polypeptide with a peptide according to any one of embodiments 1) to 18) in the presence and absence of a candidate modulator under conditions permitting the interaction of the peptide to the FPRL2 polypeptide; and b) measuring the interaction of the FPRL2 polypeptide to the peptide, wherein an increase or a decrease in interaction in the presence of the candidate modulator, relative to the interaction in the absence of the candidate modulator, identifies the candidate modulator as an agent that modulates the function of FPRL2.

21) A further embodiment of the invention relates to a method of identifying an agent that modulates the function of FPRL2, the method comprising: a) contacting a FPRL2 polypeptide with a peptide according to any one of embodiments 1) to 18) in the presence and absence of a candidate modulator under conditions permitting the interaction of the peptide to the FPRL2 polypeptide; and b) measuring a signaling activity of the FPRL2 polypeptide, wherein a change in the activity in the presence of the candidate modulator relative to the activity in the absence of the candidate modulator identifies the candidate modulator as an agent that modulates the function of FPRL2.

22) A further embodiment of the invention relates to a method according to any one of embodiments 19) to 21), wherein said agent is an antagonist.

23) A further embodiment of the invention relates to a method of identifying an agent that modulates the function of FPRL2, the method comprising: a) contacting a FPRL2 polypeptide with a candidate modulator; b) measuring a signaling activity of the FPRL2 polypeptide in the presence of the candidate modulator; and c) comparing the activity measured in the presence of the candidate modulator to the activity measured in a sample in which the FPRL2 polypeptide is contacted with a peptide according to any one of embodiments 1) to 18), wherein the candidate modulator is identified as an agent that modulates the function of FPRL2 when the amount of the activity measured in the
presence of the candidate modulator is at least 50% of the amount induced by the peptide present at its $\text{EC}_{50}$.

24) A further embodiment of the invention relates to a method according to embodiment 23), wherein said peptide according to any one of embodiments 1) to 18) is present at about its $\text{EC}_{50}$ (and preferably at its $\text{EC}_{25}$).

25) A further embodiment of the invention relates to a method according to embodiment 23) or 24), wherein said agent is an agonist.

26) In a preferred embodiment according to any one of embodiments 19) to 25), the measurement is performed using a method selected from label displacement, surface plasmon resonance, fluorescence resonance energy transfer, fluorescence quenching, and fluorescence polarization.

27) A further embodiment of the invention relates to a method according to any one of embodiments 19) to 26), wherein the candidate modulator is selected from the group consisting of a peptide, a polypeptide, an antibody or antigen-binding fragment thereof, a lipid, a carbohydrate, a nucleic acid, and a small organic molecule (and notably a small organic molecule).

28) A further embodiment of the invention relates to a method according to any one of embodiments 19) to 27), wherein the assay is selected from the group consisting of a FLIPR assay (intracellular calcium measurement), a radioligand binding assay, a $\Theta$TP-$\gamma$-S membrane binding assay, and a Beta-arrestin 2 recruitment assay.

As used herein, the term "FPRL1 polypeptide" refers to a polypeptide having two essential properties: 1) a FPRL1 polypeptide has at least 70% amino acid identity, and preferably at least 80%, more preferably at least 90%, most preferably at least 95% and notably 100% amino acid identity, to the sequence disclosed in WO2003/082314 as amino acid sequence SEQ ID NO:2; and 2) a FPRL1 polypeptide has FPRL1 activity, i.e., the polypeptide responds to Lipoxin A4, Humanin and/or WKYMVm. Optimally, a "FPRL1 polypeptide" also has FPRL1 signaling activity as defined herein.

As used herein, the term "FPRL2 polypeptide" refers to a polypeptide having two essential properties: 1) a FPRL2 polypeptide has at least 70% amino acid identity, and preferably at least 80%, more preferably at least 90%, most preferably at least 95% and notably 100% amino acid identity, to the sequence disclosed in US2006/0078559 as amino acid
sequence SEQ ID NO: 2; and 2) a FPRL2 polypeptide has FPRL2 activity, i.e., the polypeptide responds to the Heme Binding Protein F2L, to Humanin and/or to Gly14-Humanin. Optimally, a "FPRL2 polypeptide" also has FPRL2 signaling activity as defined herein.

As used herein, the term "FPRL1 signaling activity" (or "FPRL2 signaling activity" respectively) refers to the initiation or propagation of signaling by a FPRL1 polypeptide (or FPRL2 polypeptide respectively). FPRL1 signaling activity (or FPRL2 signaling activity) is monitored by measuring a detectable step in a signaling cascade by assaying one or more of the following: stimulation of GDP for GTP exchange on a G protein; recruitment of beta-arrestin1; recruitment of beta-arrestin 2; alteration of adenylate cyclase activity; protein kinase C modulation; phosphatidylinositol breakdown (generating second messengers diacylglycerol, and inositol trisphosphate); intracellular calcium flux; activation of MAP kinases; modulation of tyrosine kinases; or modulation of gene or reporter gene activity. The measurable activity can be measured directly, as in, for example, measurement of beta-arrestin recruitment. Alternatively, the measurable activity can be measured indirectly, as in, for example, a reporter gene assay.

As used herein, the term "detectable step" refers to a step that can be measured, either directly, e.g., by measurement of a second messenger or detection of a modified (e.g., phosphorylated) protein, or indirectly, e.g., by monitoring a downstream effect of that step. For example, adenylate cyclase activation results in the generation of cAMP. The activity of adenylate cyclase can be measured directly, e.g., by an assay that monitors the production of cAMP in the assay, or indirectly, by measurement of actual levels of cAMP.

As used herein, the term "candidate modulator" refers to a compound or a composition being evaluated for the ability to modulate ligand binding to a FPRL1 polypeptide (or a FPRL2 polypeptide respectively) or the ability to modulate an activity of a FPRL1 polypeptide (or a FPRL2 polypeptide respectively). Candidate modulators can be natural or synthetic compounds, including, for example, small molecules, compounds contained in extracts of animal, plant, bacterial or fungal cells, as well as conditioned medium from such cells. Preferably candidate modulators can be natural or synthetic compounds and especially small organic molecules.

As used herein, the term "small molecule" refers to a compound having molecular mass of less than 1500 Daltons, preferably less than 1000, still more preferably less than 600, and
most preferably less than 500 Daltons. A "small organic molecule" is a small molecule that comprises carbon.

As used herein, the term "change in activity" refers to an at least 10% increase or decrease in binding, or signaling activity in a given assay.

As used herein, the term "conditions permitting the interaction of the peptide to the FPRL1 polypeptide (or to the FPRL2 polypeptide respectively)" refers to conditions of, for example, temperature, salt concentration, pH and protein concentration under which a peptide according to any one of embodiments 1) to 18) binds FPRL1 (or FPRL2 respectively). Exact binding conditions will vary depending upon the nature of the assay, for example, whether the assay uses viable cells, only membrane fraction of cells, or only protein fraction of cells.

As used herein, the term "agent that modulates the function of a FPRL1 polypeptide (or FPRL2 polypeptide respectively)" is a molecule or compound that increases or decreases FPRL1 activity (or FPRL2 activity respectively), including a molecule or a compound that changes the binding of a peptide according to any one of embodiments 1) to 18) or other agonists, and/or a molecule or a compound that changes FPRL1 downstream signaling activities (or FPRL2 downstream signaling activities, respectively).

The term "pharmacetically acceptable salt" refers to non-toxic, inorganic or organic acid and/or base addition salts, Lit. e.g. "Salt selection for basic drugs", Int. J. Pharm. (1986), 33, 201-217.

The present invention also includes isotopically labelled, especially ²H (deuterium) labelled peptides, which peptides are identical to the peptides according to any one of embodiments 1) to 18) except that one or more atoms have each been replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Isotopically labelled, especially ²H (deuterium) labelled peptides and salts thereof are within the scope of the present invention. Substitution of hydrogen with the heavier isotope ²H (deuterium) may lead to greater metabolic stability, resulting e.g. in increased in-vivo half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the peptides are not isotopically labelled, or they are labelled only with one or more deuterium atoms. In a sub-embodiment, the peptides are not isotopically labelled at all. Isotopically labelled peptides may be prepared in analogy to the
methods described hereinafter, but using the appropriate isotopic variation of suitable reagents or starting materials.

Where the plural form is used for peptides, salts, pharmaceutical compositions, diseases and the like, this is intended to mean also a single peptide, salt, pharmaceutical composition, disease or the like.

The peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, may be used for the preparation of a medicament. In particular, peptides modulate FPRL1 (especially as FPRL1 antagonists) and/or FPRL2 (especially as FPRL2 agonists), and are useful for the prevention or treatment of diseases which respond to the modulation of FPRL1 and/or FPRL2 such as inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders (especially Alzheimer’s disease); in addition they are useful for the modulation of immune responses (especially those elicited by vaccination).

In particular, the peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of diseases selected from inflammatory diseases, obstructive airway diseases and allergic conditions.

Inflammatory diseases, obstructive airway diseases and allergic conditions include, but are not limited to, one, several or all of the following groups of diseases and disorders:

1) Acute lung injury (ALI); adult/acute respiratory distress syndrome (ARDS); chronic obstructive pulmonary, airway or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith; emphysema; as well as exacerbation of airway hyper reactivity consequent to other drug therapy, in particular other inhaled drug therapy. Especially, inflammatory diseases, obstructive airway diseases and allergic conditions include COPD, COAD and COLD.

2) Further inflammatory diseases, obstructive airway diseases and allergic conditions include bronchitis of whatever type or genesis.
3) Further inflammatory diseases, obstructive airway diseases and allergic conditions include bronchiectasis, and pneumoconiosis of whatever type or genesis.

4) Further inflammatory diseases, obstructive airway diseases and allergic conditions include asthma of whatever type or genesis, including intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and induced asthma following bacterial infection.

5) In a further embodiment the peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are particularly suitable for the prevention or treatment of inflammatory diseases. Inflammatory diseases include one, several or all of the following groups of diseases and disorders:

5a) In particular, inflammatory diseases refer to neutrophil related disorders, especially neutrophil related disorders of the airway including hyper-neutrophilia as it affects the airway and/or lungs. Further neutrophil related disorders also include periodontitis, glomerulonephritis, and cystic fibrosis.

5b) Further inflammatory diseases include skin diseases such as psoriasis, contact dermatitis, atopic dermatitis, dermatitis herpetiformis, scleroderma, hypersensitivity angiitis, urticaria, lupus erythematosus, and epidermolysis.

5c) Further inflammatory diseases also relate to diseases or conditions having an inflammatory component. Diseases or conditions having an inflammatory component include, but are not limited to, diseases and conditions affecting the eye such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis; diseases affecting the nose including allergic rhinitis; and inflammatory diseases in which autoimmune reactions are implicated or which have an autoimmune component or aetiology, such as systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Stevens-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine opthalmopathy, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis.

5d) Further inflammatory diseases in which autoimmune reactions are implicated or which have an autoimmune component or aetiology include rheumatoid arthritis, Hashimoto's thyroid and diabetes type I or II.
Further, the peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of organ or tissue transplant rejection, for example for the treatment of the recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants, and the prevention of graft-versus-host disease, such as sometimes occurs following bone marrow transplantation, particularly in the treatment of acute or chronic allo- and xenograft rejection or in the transplantation of insulin producing cells, e.g. pancreatic islet cells.

Further, the peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of HIV-mediated retroviral infections.

HIV-mediated retroviral infections include, but are not limited to, one, several or all of the groups of diseases and disorders caused by HIV-1 and HIV-2 strains such as GUN-4v, GUN-7wt, AG204, AG206, AG208, HCM305, HCM308, HCM342, mSTD104, and HCM309.

Further, the peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of cardiovascular disorders.

Cardiovascular disorders refer to one or more disease states of the cardiovascular tree (including the heart) and to diseases of dependent organs. Disease states of the cardiovascular tree and diseases of dependent organs include, but are not limited to, disorders of the heart muscle (cardiomyopathy or myocarditis) such as idiopathic cardiomyopathy, metabolic cardiomyopathy which includes diabetic cardiomyopathy, alcoholic cardiomyopathy, drug-induced cardiomyopathy, ischemic cardiomyopathy, and hypertensive cardiomyopathy; atheromatous disorders of the major blood vessels (macrovascular disease) such as the aorta, the coronary arteries, the carotid arteries, the cerebrovascular arteries, the renal arteries, the iliac arteries, the femoral arteries, and the popliteal arteries; toxic, drug-induced, and metabolic (including hypertensive and/or diabetic) disorders of small blood vessels (microvascular disease) such as the retinal arterioles, the glomerular arterioles, the vasa nervorum, cardiac arterioles, and associated capillary beds of the eye, the kidney, the heart, and the central and peripheral nervous systems; and, plaque rupture of atheromatous lesions of major blood vessels such as the
aorta, the coronary arteries, the carotid arteries, the cerebrovascular arteries, the renal arteries, the iliac arteries, the femoral arteries and the popliteal arteries.

Further, the peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of neuroinflammation. Neuroinflammation refers to cell signalling molecule production, activation of glia or glial activation pathways and responses, proinflammatory cytokines or chemokines, activation of astrocytes or astrocyte activation pathways and responses, activation of microglia or microglial activation pathways and responses, oxidative stress-related responses such as nitric oxide synthase production and nitric oxide accumulation, acute phase proteins, loss of synaptophysin and Post Synaptic Density-95 Protein (PSD-95), components of the complement cascade, loss or reduction of synaptic function, protein kinase activity (e.g., death associated protein kinase activity), behavioral deficits, cell damage (e.g., neuronal cell damage), cell death (e.g., neuronal cell death), and/or amyloid β deposition of amyloid plaques.

Further, the peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of neurological disorders.

In particular, neurological disorders include, but are not limited to, epilepsy, stroke, cerebral ischemia, cerebral palsy, relapsing remitting multiple sclerosis, progressive multiple sclerosis, Alpers' disease, amyotrophic lateral sclerosis (ALS), senile dementia, dementia with Lewy bodies, Rhett syndrome, spinal cord trauma, traumatic brain injury, trigeminal neuralgia, glossopharyngeal neuralgia, Bell's palsy, myasthenia gravis, muscular dystrophy, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured or prolapsed vertebral disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, mild cognitive decline, cognitive decline, Alzheimer's disease, Parkinson's disease, and Huntington's chorea.

Further, the peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of pain. Pain includes, but is not limited to, neuropathic pain exemplified by conditions such as diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, painful diabetic polyneuropathy,
post-stroke pain, post-amputation pain, myelopathic or radiculopathic pain, atypical facial pain and causalgia-like syndromes.

Further, the peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of prion-mediated diseases. Prion-mediated diseases, also known as transmissible spongiform encephalopathies (TSEs), include, but are not limited to, kuru, Gerstmann-Straussler-Scheinker syndrome (GSS), Fatal Familial Insomnia (FFI) and Creutzfeldt-Jakob Disease (CJD).

Further, the peptides of formula (I) according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are suitable for the treatment of amyloid-mediated disorders. Amyloid-mediated disorders are defined as diseases and disorders, that are caused by or associated with amyloid or amyloid-like proteins. Diseases and disorders caused by or associated with amyloid or amyloid-like proteins include, but are not limited to, Alzheimer's Disease (AD), including diseases or conditions characterized by a loss of cognitive memory capacity such as, for example, mild cognitive impairment (MCI); dementia with Lewy bodies; Down's syndrome; cerebral hemorrhage with amyloidosis. In another embodiment, diseases and disorders caused by or associated with amyloid or amyloid-like proteins include progressive supranuclear palsy, multiple sclerosis, Creutzfeld Jakob disease, Parkinson's disease, HIV-related dementia, Amyotrophic Lateral Sclerosis (ALS), inclusion-body myositis (IBM), Adult Onset Diabetes, and senile cardiac amyloidosis.

Further, the peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are suitable for the modulation of immune responses.

The modulation of immune responses includes, but is not limited to, methods based on the administration to a subject a composition of at least one antigen and at least one peptide according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof. In some cases, the antigen-containing composition is administrated first, followed by administration of a composition of at least one peptide according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof. In other cases, the antigen-containing composition is administrated last. The different compositions may be administrated simultaneously, closely in sequence, or separated in time. Those methods and compositions are provided for therapeutic and prophylactic immunisation (i.e., the
deliberate provocation, enhancement, intensification or modulation of an adaptative and/or innate immune response). Particular advantages may include one or more of the following:

1) An accelerated immune response following administration of at least one peptide according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, and the antigen, as compared to sole administration of the antigen;

2) A greater sensitivity to small amounts of antigen (e.g., toxin or pathogen) or antigens that do not habitually induce strong immune responses; and

3) More effective anti-tumor therapies.

Further, the peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of cystic fibrosis, pulmonary fibrosis, pulmonary hypertension, wound healing, diabetic nephropathy, reduction of inflammation in transplanted tissue, inflammatory diseases caused by pathogenic organisms.

Especially, peptides according to any one of embodiments 1) to 18), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of diseases selected from one, several or all of the following groups of diseases and disorders:

1) Inflammatory diseases, obstructive airway diseases and allergic conditions such as acute lung injury (ALI); adult/acute respiratory distress syndrome (ARDS); chronic obstructive pulmonary, airway or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith; and asthma of whatever type or genesis, including intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and induced asthma following bacterial infection;

2) Inflammatory diseases such as neutrophil related disorders, especially neutrophil related disorders of the airway including hyper-neutrophilia as it affects the airway and/or lungs; periodontitis; glomerulonephritis; cystic fibrosis; and skin diseases such as psoriasis, contact dermatitis, atopic dermatitis, dermatitis herpetiformis, scleroderma, hypersensitivity angiitis, urticaria, lupus erythematosus, and epidermolysis;

3) Diseases having an inflammatory component such as diseases and conditions affecting the eye such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis;
inflammatory disease in which autoimmune reactions are implicated or which have an autoimmune component or aetiology; and autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease);

4) HIV-mediated retroviral infections such as diseases and disorders caused by HIV-1 and HIV-2 strains such as GUN-4v, GUN-7wt, AG204, AG206, AG208, HCM305, HCM308, HCM342, mSTD104, and HCM309;

5) Neuroinflammation which refers to cell signalling molecule production, activation of glia or glial activation pathways and responses, proinflammatory cytokines or chemokines, activation of astrocytes or astrocyte activation pathways and responses, activation of microglia or microglial activation pathways and responses, oxidative stress-related responses such as amyloid β deposition of amyloid plaques;

6) Neurological disorders such as stroke, cerebral ischemia, Alzheimer's disease, and Parkinson's disease;

7) Prion-mediated diseases, also known as transmissible spongiform encephalopathies (TSEs), such as kuru, Gerstmann-Straussler-Scheinker syndrome (GSS), Fatal Familial Insomnia (FFI) and Creutzfeldt- Jakob Disease (CJD);

8) Amyloid-mediated disorders;

9) Cystic fibrosis, wound healing and inflammatory diseases caused by pathogenic organisms.

The invention also relates to the use of a peptide according to any one of embodiments 1) to 18) for the preparation of pharmaceutical compositions for the treatment and/or prophylaxis of the above-mentioned diseases. The present invention also relates to pharmaceutically acceptable salts and to pharmaceutical compositions and formulations of peptides according to any one of embodiments 1) to 18).

A pharmaceutical composition according to the present invention contains at least one peptide according to any one of embodiments 1) to 18) (or a pharmaceutically acceptable salt thereof) as the active agent and optionally carriers and/or diluents and/or adjuvants. The peptides according to any one of embodiments 1) to 18) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical
compositions for enteral (such especially oral) or parenteral administration (including topical application or inhalation).

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, “Pharmaceutical Manufacturing” [published by Lippincott Williams & Wilkins]) by bringing the described peptides or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

The present invention also relates to a method for the prevention or treatment of a disease or disorder mentioned herein comprising administering to a subject a pharmaceutically active amount of a peptide according to any one of embodiments 1) to 18), or a pharmaceutically acceptable salt thereof.

It is to be understood that in any embodiment disclosing specifically mentioned peptide(s) or homologous peptide(s) thereof, the specifically mentioned peptide(s) is/are preferred. A peptide is a "specifically mentioned peptide" if its sequence is specifically disclosed.

Any reference to a peptide according to embodiments 1) to 18) in this text is to be understood as referring also to the salts (and especially the pharmaceutically acceptable salts) of such a peptide, as appropriate and expedient. The preferences indicated for the peptides according to embodiments 1) to 18) of course apply mutatis mutandis to the salts and pharmaceutically acceptable salts of the peptides according to embodiments 1) to 18). The same applies to these peptides as medicaments, to pharmaceutical compositions containing these peptides as active principles or to the uses of these peptides for the manufacture of a medicament for the treatment of the diseases according to this invention.

Unless used regarding temperatures, the term "about" (or alternatively "around") placed before a numerical value "X" refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term "about" (or alternatively "around") placed before a temperature "Y" refers in the current application to an interval extending from the temperature Y minus 10 °C to Y plus 10 °C, and
preferably to an interval extending from Y minus 5 °C to Y plus 5 °C. Besides, the term "room temperature" (RT) as used herein refers to a temperature of about 25°C. The peptides according to embodiments 1) to 18) can be manufactured by the methods given in the Examples or by any known conventional procedure for the formation of a peptide linkage between amino acids.

Such conventional procedures include, for example, any solution phase procedure permitting a condensation between the free ε-amino group of an amino acid or a peptide having its carboxyl group and other reactive groups protected and the free primary carboxyl group of another ε-amino acid or peptide having its amino group and other reactive groups protected.

In a preferred alternative, such conventional procedures include, for example, any solid phase peptide synthesis method. In such a method the synthesis of the peptides can be carried out by sequentially incorporating the desired amino acid residues one at a time into the growing peptide chain according to the general principles of solid phase methods.

Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by a person skilled in the art by routine optimisation procedures.

Common to chemical synthesis of peptides is the protection of reactive side chain groups of the various amino acid moieties with suitable protecting groups, which will prevent a chemical reaction from occurring at that site until the protecting group is ultimately removed. Usually also common is the protection of the a-amino group of an amino acid or fragment while that entity reacts at the carboxyl group, followed by the selective removal of the a-amino protecting group allowing a subsequent reaction to take place at that site. While specific protecting groups have been disclosed in regard to the solid phase synthesis method, it should be noted that each amino acid can be protected by a protective group conventionally used for the respective amino acid in solution phase synthesis.

a-amino groups may be protected by a suitable protecting group selected from aromatic urethane-type protecting groups, such as benzylxycarbonyl (Z) and substituted benzylxycarbonyl, such as p-chiorobenzyloxycarbonyL p-nitrobenzyloxycarbonyl, p-
bromohenzylloxycarbonyl, p-biphenyl-isopropylloxycarbonyl, 9-fluorenylmethyloxycarbonyl (Fmoc) and p-methoxybenzylloxycarbonyl (Moz); aliphatic urethane-type protecting groups, such as t-butylloxycarbonyl (BOG), diisopropylmethyloxycarbonyl, isopropylloxycarbonyl and allyloxycarbonyl. Herein, Fmoc is most preferred for α-amino protection.

5 Experimental Part

Abbreviations

Aβ Amyloid beta peptide
Ac Acetyl
ACN Acetone
BSA Bovine Serum Albumin
cAMP cyclic Adenosine Monophosphate
cpm counts per minute
DAD Diode Array Detector
DC Dendritic Cell(s) (iDC: immature DC; mDC: mature DC)
DMEM Dulbecco’s Modified Eagle’s Medium
DMF DiMethylFormamide
DMSO DiMethylSulfoxide
ELSD Evaporative Light Scattering Detector
eq. Equivalent
FAD Familial Alzheimer Disease
FLIPR Fluorescent Imaging Plate Reader
Fmoc 9-Fluorenlymethyloxycarbonyl
GDP Guanosine Diphosphate
GTP Guanosine Triphosphate
h Hour(s)
Hank’s BSS Hank’s Balanced Salt Solution
HBTU 1-H-Benzotriazolilm
HEPES 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HPLC High Performance Liquid Chromatography
LPS Lipopolysaccharide(s)
MAP (kinase) Mitogen-Activated Protein (kinase)
min Minute(s)
MS Mass Spectrometry
General Procedure for the Synthesis of Peptides:

All peptides were prepared by automatic solid-phase synthesis using an Advanced ChemTech automatic synthetizer following the Fmoc methodology on a 40 µmol scale. Peptide coupling was performed by reacting the resin-bound amino acid or precursor peptide with a Fmoc protected amino acid (5 eq.) in the presence of HBTU (5 eq.) and NMM (10 eq.). The subsequent Fmoc deprotection was done with 20% piperidine in DMF. These steps were repeated until the final peptide was obtained. The peptides were cleaved within 3 h at RT using a 95:2.5:2.5 v/v/v TFA-water-Triisopropylsilane mixture (5 ml/100 mg resin), precipitated in cold ethyl ether, lyophilized from a 50% water/ACN solution and purified by prep. HPLC.

Peptide Purification: HPLC Waters prep LC 4000 system. Column: Kromasil C18, 250x20 mm. Eluents: A: H₂O + 0.1% TFA; B: ACN + 0.1% TFA; Gradient: 0% B → 60% B. Flow: 20 mL/min. Injection volume: 10 ml. Detection: UV 214 nm. Peptides are finally solubilised in H₂O/ACN 50%/50% (v/v).

Analytical LC-MS (method A): Dionex HPG-3200RS Pump, MS: Thermo MSQ Plus, DAD: Dionex 3000RS, ELSD: Sedere Sedex 85. Column: Waters Atlantis T3, 5 µm, 4.6x30 mm ID, thermostated in Dionex TCC-3200 compartment at 40°C. Eluents: A: H₂O + 0.04% TFA; B: ACN. Method: Gradient: 5% B → 95% B over 1 min. Flow: 4.5 mL/min. Detection: UV/Vis and/or ELSD, and MS.

The following peptides were synthesized according to the general procedure described above:
EXAMPLE 1:
Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln (SEQ ID No: 1);
LC-MS (method A): $t_R = 0.48$ min; $[M+2H]^{2+} = 747.8$.

EXAMPLE 2:
5 Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr (SEQ ID No: 2);
LC-MS (method A): $t_R = 0.51$ min; $[M+2H]^{2+} = 733.5$.

EXAMPLE 3:
Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr (SEQ ID No: 3);
LC-MS (method A): $t_R = 0.42$ min; $[M+2H]^{2+} = 725.2$.

EXAMPLE 4:
Phe-Pro-Thr-Leu-Asn-Pro-Ile-Leu-Leu-Thr-Tyr-Ser (SEQ ID No: 4);
LC-MS (method A): $t_R = 0.59$ min; $[M+2H]^{2+} = 689.6$.

EXAMPLE 5:
Trp-Ser-Pro-Ser-Arg-Pro-Gly-Leu-Pro-Leu-Leu-Ile (SEQ ID No: 5);
LC-MS (method A): $t_R = 0.56$ min; $[M+2H]^{2+} = 668.1$.

EXAMPLE 6:
Trp-Pro-Leu-Pro-Lys-Leu-Ala-Thr-Ser-Gly-Ile-Leu (SEQ ID No: 6);
LC-MS (method A): $t_R = 0.55$ min; $[M+2H]^{2+} = 648.2$.

EXAMPLE 7:
Leu-Ala-Pro-Asn-Arg-Pro-Met-Leu-Glu-Leu-Leu-Thr (SEQ ID No: 7);
LC-MS (method A): $t_R = 0.54$ min; $[M+2H]^{2+} = 684.1$.

EXAMPLE 8:
Phe-Pro-Tyr-His-Val-Ala-Ala-Met-Arg-His-Thr-Leu (SEQ ID No: 8);
LC-MS (method A): $t_R = 0.43$ min; $[M+2H]^{2+} = 721.5$.

EXAMPLE 9:
Ser-Pro-Gln-Phe-Ser-His-Val-Leu-Arg-Leu-Gly-Leu (SEQ ID No: 9);
LC-MS (method A): $t_R = 0.49$ min; $[M+2H]^{2+} = 677.1$.

EXAMPLE 10:
Asn-His-Arg-Leu-Pro-Leu-Pro-Ala-Leu-Leu-Trp (SEQ ID No: 10);
LC-MS (method A): $t_R = 0.56$ min; $[M+2H]^{2+} = 665.2$.

EXAMPLE 11:
Trp-Ser-Phe-Gly-Asn-Pro-Gly-Leu-Leu-Phe-Ser-Ile (SEQ ID No: 11);
LC-MS (method A): $t_R = 0.63$ min; $[M+2H]^{2+} = 669.1$.

**EXAMPLE 12:**
lle-Leu-Ala-Asn-Val-Leu-Thr-Ala-Pro-Gly-Pro-Arg  (SEQ ID No: 12);
LC-MS (method A): $t_R = 0.47$ min; $[M+2H]^{2+} = 611.1$.

**EXAMPLE 13:**
His-Met-Trp-Asn-Pro-Gly-lle-lle-Tyr-Ser-lle-Lys  (SEQ ID No: 13);
LC-MS (method B): $t_R = 2.61$ min; $[M+2H]^{2+} = 729.7$.

**EXAMPLE 14:**
lle-Pro-lle-Ser-Arg-Glu-Leu-Val-Thr-His-Asp-Pro  (SEQ ID No: 14);
LC-MS (method A): $t_R = 0.42$ min; $[M+2H]^{2+} = 688.7$.

**In vitro assays**

The activities on FPRL1 receptor and/or FPRL2 of the peptides of formula (I) are determined in accordance with the following experimental method.

**Experimental method:**

**Intracellular calcium measurements (FPRL1):**

Cells expressing recombinant human FPRL1 receptor and the G-protein Ga16 (HEK293-hFPRL1-Ga16) were grown to 80% confluency in Growing Medium (GM). Cells were detached from culture dishes with a cell dissociation buffer (Invitrogen, 13151-014), and collected by centrifugation at 1000 rpm at rt for 5 min in Assay Buffer (AB) (equal parts of Hank's BSS (Gibco, 14065-049) and DMEM without Phenol Red (Gibco, 11880-028)). After 60 min incubation at 37°C under 5% CO2 in AB supplemented with 1 µM Fluo-4 (AM) (Invitrogen, F14202), and 20 mM HEPES (Gibco, 15630-056), the cells were washed and resuspended in AB. They were then seeded onto 384-well FLIPR assay plates (Greiner, 781091) at 50000 cells in 70 µl per well and sedimented by centrifugation at 1000 rpm for 1 min. Stock solutions of test peptides were made up at a concentration of 10 mM in DMSO, and serially diluted in AB to concentrations required for activation dose response curves. WKYMVm (Phoenix Peptides) was used as a reference agonist. FLIPR384 or FLIPR Tetra instruments (Molecular Devices) were operated according to the manufacturer's standard instructions, adding 4 µl of test peptide dissolved at 10 mM in DMSO and diluted prior to the experiment in assay buffer to obtain the desired final
concentration. Changes in fluorescence were monitored before and after the addition of test peptide, and after the addition of a reference agonist, at \( \lambda_{ex}=488 \) nm and \( \lambda_{em}=540 \) nm. Emission peak values above base level after peptide addition were exported after base line subtraction. Values were normalized to high-level control (WKYMVM, 10 nM final concentration) after subtraction of the base line value (AB addition).

Antagonistic activities (IC50 values) of selected peptides are displayed in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Peptide</th>
<th>IC50 (FPRLI) [nM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXAMPLE 1: Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln (SEQ ID No: 1)</td>
<td>3</td>
</tr>
<tr>
<td>EXAMPLE 2: Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr (SEQ ID No: 2)</td>
<td>28</td>
</tr>
<tr>
<td>EXAMPLE 3: Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr (SEQ ID No: 3)</td>
<td>65</td>
</tr>
<tr>
<td>EXAMPLE 4: Phe-Pro-Thr-Leu-Asn-Pro-Ile-Leu-Leu-Thr-Tyr-Ser (SEQ ID No: 4)</td>
<td>159</td>
</tr>
<tr>
<td>EXAMPLE 5: Trp-Ser-Pro-Ser-Arg-Pro-Gly-Leu-Pro-Leu-Ile (SEQ ID No: 5)</td>
<td>113</td>
</tr>
<tr>
<td>EXAMPLE 6: Trp-Pro-Leu-Pro-Lys-Leu-Ala-Thr-Ser-Gly-Ile-Leu (SEQ ID No: 6)</td>
<td>77</td>
</tr>
<tr>
<td>EXAMPLE 7: Leu-Ala-Pro-Asn-Arg-Pro-Met-Leu-Glu-Leu-Leu-Thr (SEQ ID No: 7)</td>
<td>272</td>
</tr>
<tr>
<td>EXAMPLE 8: Phe-Pro-Tyr-His-Val-Ala-Ala-Met-Arg-His-Thr-Leu (SEQ ID No: 8)</td>
<td>578</td>
</tr>
<tr>
<td>EXAMPLE 9: Ser-Pro-Gln-Phe-Ser-His-Val-Leu-Arg-Leu-Gly-Leu (SEQ ID No: 9)</td>
<td>863</td>
</tr>
<tr>
<td>EXAMPLE 10: Asn-His-Arg-Leu-Pro-Leu-Pro-Ala-Leu-Leu-Trp (SEQ ID No: 10)</td>
<td>2830</td>
</tr>
<tr>
<td>EXAMPLE 14: Ile-Pro-Ile-Ser-Arg-Glu-Leu-Val-Thr-His-Asp-Pro (SEQ ID No: 14)</td>
<td>2980</td>
</tr>
</tbody>
</table>
Intracellular calcium measurements (FPRL2):

Cells expressing recombinant human FPRL2 and the G-protein Ga16 (HEK293-hFPRL2-Ga16) were grown to 80% confluency in Growing Medium (GM). Cells were detached from culture dishes with a cell dissociation buffer (Invitrogen, 13151-014), and collected by centrifugation at 1000 rpm at r for 5 min in Assay Buffer (AB) (equal parts of Hank’s BSS (Gibco, 14065-049) and DMEM without Phenol Red (Gibco, 11880-028)). After 60 min incubation at 37°C under 5% CO2 in AB supplemented with 1 µM Fluo-4 (AM) (Invitrogen, F14202), and 20 mM HEPES (Gibco, 15630-056), the cells were washed and resuspended in AB. They were then seeded onto 384-well FLIPR assay plates (Greiner, 781091) at 50000 cells in 70 µl per well and sedimented by centrifugation at 1000 rpm for 1 min. Stock solutions of test peptides were made up at a concentration of 10 mM in DMSO, and serially diluted in AB to concentrations required for activation dose response curves. Gly14-Humanin (Humanin peptide with replacement of Serine by Glycine at position 14, Phoenix Peptides) was used as a reference agonist. FLIPR384 or FLIPR Tetra instruments (Molecular Devices) were operated according to the manufacturer’s standard instructions, adding 4 µl of test peptide dissolved at 10 mM in DMSO and diluted prior to the experiment in assay buffer to obtain the desired final concentration. Changes in fluorescence were monitored before and after the addition of test peptides, and after the addition of a reference agonist, at lex=488 nm and lem=540 nm. Emission peak values above base level after peptide addition were exported after base line subtraction. Values were normalized to high-level control (GLY14-Humanin, 100 nM final concentration) after subtraction of the base line value (AB addition).

Agonistic activities (EC50 values) of exemplified peptides are displayed in Table 2.

Table 2

<table>
<thead>
<tr>
<th>Peptide</th>
<th>EC50 (FPRL2) [nM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXAMPLE 1: Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln (SEQ ID No: 1)</td>
<td>619</td>
</tr>
<tr>
<td>EXAMPLE 2: Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr (SEQ ID No: 2)</td>
<td>857</td>
</tr>
<tr>
<td>EXAMPLE 3: Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr (SEQ ID No: 3)</td>
<td>433</td>
</tr>
</tbody>
</table>
Preparation of hFPRL1 receptor membranes and radioligand binding assay:

Membranes were prepared from HEK293 cells expressing recombinant human FPRL1. Cells were detached from culture plates with a buffer based on 5 mM Tris, pH 7.4, 1 mM MgCl2 (Fluka, 63064), 0.1 mM PMSF using a police rubber and were transferred into centrifugation tubes and frozen at -80°C. After thawing, the cells were centrifuged at 500 g for 5 min and then resuspended in buffer based on 5 mM Tris, pH 7.4, 1 mM MgCl2 (Fluka, 63064), 0.1 mM PMSF. Cells were then fragmented by homogenization with a Polytron cell homogenizer for 30 s. The membrane fragments were collected by centrifugation at 3000 g for 40 min and resuspended in storage membrane buffer based
on 50 mM Tris, pH 7.4, 25 mM MgCl2 (Fluka, 63064), 250 mM saccharose. Aliquots were stored at -20°C.

0.5 µg of HEK293-hFPRL1 (HEK293 cells expressing recombinant human FPRL1) membranes were incubated in Binding Buffer (50 mM Tris-HCl pH 7.4, 5 mM MgCl2 (Fluka, 63064), 1 mM CaCl2, 0.5% (w/v) BSA (Calbiochem, 126609)). Binding assay was performed by co-incubation of HEK-293-hFPRL1 membranes with various concentrations of peptides and 10 pM of [125I]-WKYMVm (PerkinElmer, NEX386025UC). For unspecific binding, WKYMVm (Tocris, 1800) was added to the reaction mixture at 1 µM final concentration. This binding assay mix was incubated at RT for 120 min and then filtered through a GF/C filter plate. The plates were washed three times with ice cold Binding Buffer. After addition of 40 µl Microscint-40 (Packard Biosciences, 6013621), membrane-bound [125I]-WKYMVm was measured with a TopCount from Packard Biosciences.

Antagonistic activities (IC50 values) of selected peptides are displayed in Table 3.

Table 3

<table>
<thead>
<tr>
<th>Peptide</th>
<th>IC50 (FPRL1) [nM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXAMPLE 1: Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln (SEQ ID No: 1)</td>
<td>7</td>
</tr>
<tr>
<td>EXAMPLE 2: Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr (SEQ ID No: 2)</td>
<td>26</td>
</tr>
<tr>
<td>EXAMPLE 3: Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr (SEQ ID No: 3)</td>
<td>34</td>
</tr>
<tr>
<td>EXAMPLE 4: Phe-Pro-Thr-Leu-Asn-Pro-Ile-Leu-Leu-Thr-Tyr-Ser (SEQ ID No: 4)</td>
<td>97</td>
</tr>
<tr>
<td>EXAMPLE 5: Trp-Ser-Pro-Ser-Arg-Pro-Gly-Leu-Pro-Leu-Ile (SEQ ID No: 5)</td>
<td>157</td>
</tr>
<tr>
<td>EXAMPLE 6: Trp-Pro-Leu-Pro-Lys-Leu-Ala-Thr-Ser-Gly-Ile-Leu (SEQ ID No: 6)</td>
<td>172</td>
</tr>
<tr>
<td>EXAMPLE 7: Leu-Ala-Pro-Asn-Arg-Pro-Met-Leu-Glu-Leu-Leu-Thr (SEQ ID No: 7)</td>
<td>294</td>
</tr>
<tr>
<td>EXAMPLE 8: Phe-Pro-Tyr-His-Val-Ala-Ala-Met-Arg-His-Thr-Leu (SEQ ID No: 8)</td>
<td>325</td>
</tr>
</tbody>
</table>
EXAMPLE 9:  
Ser-Pro-Gln-Phe-Ser-His-Val-Leu-Arg-Leu-Gly-Leu  (SEQ ID No: 9)  

EXAMPLE 10:  
Asn-His-Arg-Leu-Pro-Leu-Pro-Ala-Leu-Leu-Trp  (SEQ ID No: 10)  

EXAMPLE 14:  
Ile-Pro-Ile-Ser-Arg-Glu-Leu-Val-Thr-Asp-Pro  (SEQ ID No: 14)  

GTP-y-S membrane binding assays:  

[^35]S-GTP-y-S exchange assays were performed in duplicate in 96 well microtiter plates (Nunc, 442587). 3 μg of HEK293-hFPRL1 (HEK293 cells expressing recombinant human FPRL1) membranes were pre-incubated with 10 μl saponin (1% (w/v)), 10 μl GDP (60 μM, (Sigma, G-7127)), 125 μl of Binding Buffer (20 mM HEPES (Fluka, 54461), 100 mM NaCl (Fluka, 71378), 5 mM MgCl2 (Fluka, 63064), 0.3% (w/v) BSA (Calbiochem, 126609), pH 7.4), and 5 μl of various concentrations of peptides in DMSO (Fluka, 41644). The reaction was allowed to equilibrate by incubation for 30 minutes at 20°C. 50 μl of[^35]S-GTP-y-S (200 pM, (Amersham Biosciences, SJ 1320)) was added and let to incubate for 60 min at RT. The assay was stopped by transfer of the reaction mixture to a Multiscreen plate (Millipore, MAHFC1 H60) using a cell harvester from Packard Biosciences pre-wetted with 50 μl of Wash Buffer (WB, Na2HP04/NaH2P04, 10 mM (70%/30%), pH 7.4). The plates were washed four times using a UniFilter-96 vacuum manifold (PerkinElmer) with ice-cold WB, dried for 60 min at 40-50°C, sealed at the bottom and on the top after addition of 25 μl MicroScint 20 (Packard Biosciences, order# 6013621). Membrane-bound[^35]S-GTP-y-S was measured with a TopCount from Packard Biosciences. IC50 is the concentration of antagonist blocking 50 % of the maximal specific[^35]S-GTP-y-S binding. Specific binding is determined by subtracting non-specific binding from maximal binding. Maximal binding is the amount of cpm bound to the Multiscreen plate in the presence of 10 nM of WKYMVM. Non-specific binding is the amount of binding in the absence of an agonist in the assay. 

Antagonistic activities (IC50 values) of selected peptides are displayed in Table 4.
Table 4

<table>
<thead>
<tr>
<th>Peptide</th>
<th>IC$_{50}$ (FPRL1) [nM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXAMPLE 1: Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln (SEQ ID No: 1)</td>
<td>80</td>
</tr>
<tr>
<td>EXAMPLE 2: Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr (SEQ ID No: 2)</td>
<td>143</td>
</tr>
<tr>
<td>EXAMPLE 3: Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Leu-Thr (SEQ ID No: 3)</td>
<td>740</td>
</tr>
<tr>
<td>EXAMPLE 9: Ser-Pro-Gln-Phe-Ser-His-Val-Leu-Arg-Leu-Gly-Leu (SEQ ID No: 9)</td>
<td>&gt;10000</td>
</tr>
</tbody>
</table>

**Beta-arrestin 2 recruitment assays:**

HEK293 expressing human FPRL1 and beta-arrestin 2 (Discoverx, 93-031 9C1) were seeded onto 384-well FLIPR assay plates (Greiner, 781091) in Growing Medium (GM) at 200 000 cells in 25 µl per well and microplates were placed into a 37°C, 5% CO$_2$ humidified incubator for 24 hours. Three-fold serial dilutions of peptides were prepared. The concentration of each dilution was prepared at seven fold of the final screening concentration. FLIPR Tetra instruments (Molecular Devices) was operated according to the manufacturer’s standard instructions, adding 5 µl of test peptide and diluted prior to the experiment in assay buffer to obtain the desired final concentration. Plates were incubated for 60 min at 37°C, 5% CO$_2$. WKYMVM, a reference FPRL1 agonist, was further added at a final concentration of 5 nM and plates were incubated at 37°C, 5% CO$_2$. Detection reagent was prepared according to the manufacturer and 25 µl was added per well. Changes in luminescence were monitored before and for 15 minutes after the addition of the detection reagent.

Antagonistic activities (IC50 values) of selected peptides are displayed in Table 5.
Table 5

<table>
<thead>
<tr>
<th>Peptide</th>
<th>IC_{50} (FPRLI) [nM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXAMPLE 1: Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln (SEQ ID No: 1)</td>
<td>418</td>
</tr>
<tr>
<td>EXAMPLE 2: Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr (SEQ ID No: 2)</td>
<td>595</td>
</tr>
<tr>
<td>EXAMPLE 3: Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr (SEQ ID No: 3)</td>
<td>841</td>
</tr>
<tr>
<td>EXAMPLE 4: Phe-Pro-Thr-Leu-Asn-Pro-Ile-Leu-Leu-Thr-Tyr-Ser (SEQ ID No: 4)</td>
<td>143</td>
</tr>
<tr>
<td>EXAMPLE 5: Trp-Ser-Pro-Ser-Arg-Pro-Gly-Leu-Pro-Leu-Ile (SEQ ID No: 5)</td>
<td>442</td>
</tr>
<tr>
<td>EXAMPLE 7: Leu-Ala-Pro-Asn-Arg-Pro-Met-Leu-Glu-Leu-Leu-Thr (SEQ ID No: 7)</td>
<td>1240</td>
</tr>
<tr>
<td>EXAMPLE 8: Phe-Pro-Tyr-His-Val-Ala-Ala-Met-Arg-His-Thr-Leu (SEQ ID No: 8)</td>
<td>3650</td>
</tr>
<tr>
<td>EXAMPLE 9: Ser-Pro-Gln-Phe-Ser-His-Val-Leu-Arg-Leu-Gly-Leu (SEQ ID No: 9)</td>
<td>13700</td>
</tr>
<tr>
<td>EXAMPLE 10: Asn-His-Arg-Leu-Pro-Leu-Pro-Ala-Leu-Leu-Trp (SEQ ID No: 10)</td>
<td>5030</td>
</tr>
<tr>
<td>EXAMPLE 11: Trp-Ser-Phe-Gly-Asn-Pro-Gly-Leu-Phe-Ser-Ile (SEQ ID No: 11)</td>
<td>3050</td>
</tr>
<tr>
<td>EXAMPLE 12: Ile-Leu-Ala-Asn-Val-Leu-Thr-Ala-Pro-Gly-Pro-Arg (SEQ ID No: 12)</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>EXAMPLE 14: Ile-Pro-Ile-Ser-Arg-Glu-Leu-Val-Thr-His-Asp-Pro (SEQ ID No: 14)</td>
<td>4970</td>
</tr>
</tbody>
</table>
**Claims**

1. A peptide containing 11 or 12 amino acids selected from the group consisting of:
   Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln;
   Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr;
   Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr;
   Phe-Pro-Thr-Leu-Asn-Pro-Ile-Leu-Thr-Tyr-Ser;
   Trp-Ser-Pro-Ser-Arg-Pro-Gly-Leu-Pro-Leu-Ile;
   Trp-Pro-Leu-Pro-Lys-Leu-Ala-Thr-Ser-Gly-Ile-Leu;
   Leu-Ala-Pro-Asn-Arg-Pro-Met-Leu-Glu-Leu-Leu-Thr;
   Phe-Pro-Tyr-His-Val-Ala-Met-Arg-His-Thr-Leu;
   Ser-Pro-Gln-Phe-Ser-His-Val-Leu-Arg-Leu-Gly-Leu;
   Asn-His-Arg-Leu-Pro-Leu-Pro-Ala-Leu-Leu-Arg;
   Ile-Leu-Ala-Asn-Val-Leu-Arg-Asp-Pro;
   His-Met-Trp-Asn-Pro-Gly-Ile-Ile-Tyr-Ser-Ile-Lys; and
   Ile-Pro-Ile-Ser-Arg-Glu-Leu-Val-Thr-His-Asp-Pro;
   or a homologous peptide thereof in which one amino acid is replaced by another proteinogenic amino acid;
   or a salt thereof.

2. A peptide according to claim 1, wherein the peptide is
   Trp-Pro-Pro-Leu-Arg-Ala-His-Leu-Leu-Thr-Tyr-Gln or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid;
   or a salt thereof.

3. A peptide according to claim 1, wherein the peptide is
   Leu-Pro-Ser-Arg-Tyr-Asn-Leu-Asn-Leu-Leu-Thr-Tyr or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid;
   or a salt thereof.

4. A peptide according to claim 1, wherein the peptide is
   Tyr-Leu-Lys-Pro-His-Lys-Ser-Leu-His-Leu-Leu-Thr or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid;
   or a salt thereof.
5. A peptide according to claim 1, wherein the peptide is Phe-Pro-Thr-Leu-Asn-Pro-Ile-Leu-Leu-Thr-Tyr-Ser or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid; or a salt thereof.

6. A peptide according to claim 1, wherein the peptide is Phe-Pro-Tyr-His-Val-Ala-Ala-Met-Arg-His-Thr-Leu or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid; or a salt thereof.

7. A peptide according to claim 1, wherein the peptide is His-Met-Trp-Asn-Pro-Gly-Ile-Ile-Tyr-Ser-Ile-Lys or a homologous peptide in which one amino acid is replaced by another proteinogenic amino acid; or a salt thereof.

8. A method of identifying an agent that modulates the function of FPRL2, the method comprising: a) contacting a FPRL2 polypeptide with a peptide according to any one of claims 1 to 7 in the presence and absence of a candidate modulator under conditions permitting the interaction of the peptide to the FPRL2 polypeptide; and b) measuring the interaction of the FPRL2 polypeptide to the peptide, wherein an increase or a decrease in interaction in the presence of the candidate modulator, relative to the interaction in the absence of the candidate modulator, identifies the candidate modulator as an agent that modulates the function of FPRL2.

9. A method of identifying an agent that modulates the function of FPRL2, the method comprising: a) contacting a FPRL2 polypeptide with a peptide according to any one of claims 1 to 7 in the presence and absence of a candidate modulator under conditions permitting the interaction of the peptide to the FPRL2 polypeptide; and b) measuring a signaling activity of the FPRL2 polypeptide, wherein a change in the activity in the presence of the candidate modulator relative to the activity in the absence of the candidate modulator identifies the candidate modulator as an agent that modulates the function of FPRL2.

10. A method of identifying an agent that modulates the function of FPRL2, the method comprising: a) contacting a FPRL2 polypeptide with a candidate modulator; b) measuring a signaling activity of the FPRL2 polypeptide in the presence of the candidate modulator; and c) comparing the activity measured in the presence of the candidate modulator to the
activity measured in a sample in which the FPRL2 polypeptide is contacted with a peptide according to any one of claims 1 to 7, wherein the candidate modulator is identified as an agent that modulates the function of FPRL2 when the amount of the activity measured in the presence of the candidate modulator is at least 50% of the amount induced by the peptide present at its EC\textsubscript{50}.

11. A peptide according to claim 1, or a pharmaceutically acceptable salt thereof, for use as medicament.

12. A pharmaceutical composition containing, as active principle, a peptide according to claim 1 or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

13. Use of a peptide according to claim 1, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or treatment of a disease selected from inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders; and for the modulation of immune responses.

14. A peptide according to claim 1, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of a disease selected from inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders; and for the modulation of immune responses.