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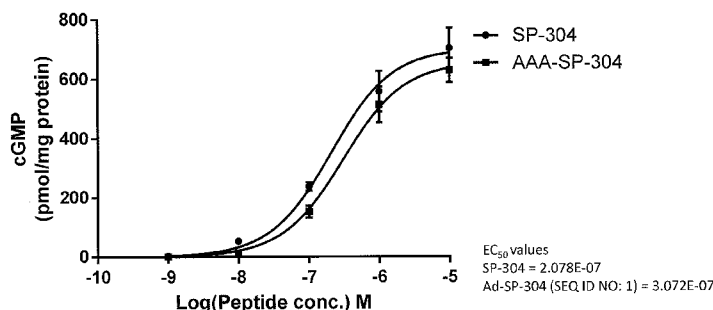


FIG. 1

(57) Abstract: This invention provides novel guanylate cyclase C (GC-C) agonists and their therapeutic use. The agonists may be used either alone or in combination with one or more additional agents.

AGONISTS OF GUANYLATE CYCLASE AND THEIR USES

5

RELATED APPLICATIONS

This application claims priority to, and benefit of, the U.S. Provisional Application No. 61/790,266, filed on March 15, 2013 and the U.S. Provisional Application No.

10 61/826,749, filed on May 23, 2013, the contents of each of which are incorporated herein by reference in their entireties.

INCORPORATION-BY-REFERENCE OF SEQUENCE LISTING

The contents of the text file named "40737-514001WO_ST25.txt", which was created
15 on March 4, 2014 and is 55 KB in size, are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to novel guanylate cyclase C (GC-C) agonists and their
20 therapeutic use. The agonists may be used either alone or in combination with one or more additional agents.

BACKGROUND OF THE INVENTION

Irritable bowel syndrome (IBS) is a common chronic disorder of the intestine that
25 affects 20 to 60 million individuals in the US alone (Lehman Brothers, Global Healthcare-Irritable Bowel Syndrome Industry Update, September 1999). IBS is the most common disorder diagnosed by gastroenterologists (28% of patients examined) and accounts for 12% of visits to primary care physicians (Camilleri 2001 Gastroenterology 120:652-668).

Diabetes mellitus (DM) is a group of metabolic diseases characterized by
30 hyperglycemia, resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Well-

known risk factors of type 2 DM are family history, obesity, age, race, prediabetes [impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)], gestational DM, and polycystic ovarian syndrome. An association between insulin resistance and inflammation has been reported. Data also indicated a correlation that prediabetes was common in patients with IBS, which suggested that the chronic inflammation process might be responsible for the progression to DM.

Hypercholesterolemia has been recognized as a major risk factor for coronary heart disease (CHD). In clinical trials, reducing serum LDL cholesterol has been demonstrated to decrease the incidence of CHD and to reverse atherosclerotic lesions. Two main classes of clinically useful hypocholesterolemic agents are the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (e.g., statins) and the bile acid sequestrants. Both induce hepatic LDL receptor activity by increasing hepatic cholesterol demand. Because the major determinant of serum cholesterol level is hepatic LDL receptor activity (38), these agents may share a common mechanism leading to reduction in serum cholesterol.

The guanylate cyclase-C (GC-C) receptor (reviewed by Lucas et al. 2000 Pharmacol. Rev 52:375-414 and Vaandrager et al. 2002 Molecular and Cellular Biochemistry 230:73-83) is a key regulator in mammals of intestinal function (although low levels of GC-C have been detected in other tissues). GC-C responds to the endogenous hormones, guanylin and uroguanylin, and to enteric bacterial polypeptides from the heat stable enterotoxin family (ST polypeptides). When an agonist binds to GC-C, there is an elevation of the second messenger, cyclic GMP, and an increase in chloride and bicarbonate secretion, resulting in an increase in intestinal fluid secretion.

Given the prevalence of diseases associated with GI inflammation, hypercholesterolemia, obesity and inflammatory conditions, there exists a need to develop compositions and methods for effective treatment.

SUMMARY OF THE INVENTION

The present invention provides novel peptides.

The present invention also provides a pharmaceutical composition that includes a peptide described herein in a therapeutically effective amount and a pharmaceutical carrier, excipient or diluent.

In some embodiments, the peptide increases cGMP production in a cell.

In some embodiments, the peptide is a bicyclic peptide.

The present invention also provides a composition that includes an inert carrier coated with peptides of the invention and an enteric coating that releases the peptide at pH5.0 or pH7.0. The inert carrier includes, for example, a selected from mannitol, lactose, a
5 microcrystalline cellulose or starch.

The present invention further provides a method for treating a condition that responds to enhanced cGMP levels in a subject by administering to the subject a therapeutically effective amount of a peptide of the invention, and the peptide is administered in an amount sufficient to increase water transport in the gastrointestinal tract and induce cGMP production
10 in a gastrointestinal epithelial cell.

The present invention further provides a method for preventing or treating a condition that includes, for example, ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, constipation, chronic constipation,
15 constipation associated with use of opiate pain killers, post-surgical constipation, constipation associated with neuropathic disorders, gastroesophageal reflux disease (GERD), Celiac disease, gastroparesis, heartburn, poor gastrointestinal motility, congestive heart failure, hypertension, benign prostatic hyperplasia (BPH), colon cancer, lung cancer, bladder cancer, liver cancer, salivary gland cancer or skin cancer, bronchitis, tissue inflammation, organ
20 inflammation, respiratory inflammation, asthma, COPD, lipid metabolism disorders, biliary disorders, cardiovascular disease, obesity or an endocrine disorder, by administering to a subject in need thereof a therapeutically effective amount of a peptide of the invention.

The present invention further provides a method of colonic cleansing by administering to a subject in need thereof an effective amount of a peptide of the invention.
25 The method may further include a step of administering to the subject an effective amount of L-glucose, lubiprostone (Amitiza), prucalopride, an agent for treating chronic constipation, or any combination thereof.

The present invention further provides a method of increasing cGMP production in a cell by contacting the cell with a peptide of the invention.

30 The present invention provides a use of a peptide described herein in the manufacture of a medicament for the treatment of a human disease.

Any methods and uses described herein may further include a step of administering a therapeutically effective amount of a cGMP-dependent phosphodiesterase inhibitor. The

cGMP-dependent phosphodiesterase inhibitor is administered either concurrently or sequentially with the peptide. The cGMP-dependent phosphodiesterase inhibitor includes, for example, sulindac sulfone, zaprinast, motapizone, vardenafil, and sildenafil.

Any methods and uses described herein may further include a step of administering a therapeutically effective amount of at least one anti-inflammatory agent. The anti-inflammatory agent is a steroid or nonsteroid anti-inflammatory drug (NSAID).

The peptide of the invention may have the sequence of any one of Table 1.

In some embodiments, the peptide is Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Leu¹⁶ (SEQ ID NO: 1), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Ser¹⁶ (SEQ ID NO: 32), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Thr¹⁶ (SEQ ID NO: 119), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Tyr¹⁶ (SEQ ID NO: 120), dAsn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-dLeu¹⁶ (SEQ ID NO: 17), or pyGlu¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Leu¹⁶ (SEQ ID NO: 56).

Other features and advantages of the invention will be apparent from and are encompassed by the following detailed description and claims.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the stimulation of cyclic GMP synthesis by SP-304 and SP-304 with α -aminoadipic acid in the 3rd position from the N-terminus.

DETAILED DESCRIPTION

The present invention is based upon the development of novel agonists of guanylate cyclase-C (GC-C). The agonists are plecanatide derivatives, analogs of uroguanylin, guanylin, lymphoguanylin and ST peptide and have superior properties such as higher activity or potency. Particularly, these analogs contain an α -aminoadipic acid (Aad), preferably at the 3rd position from the N-terminus of each peptide or at the position to the N-terminal side next to the first cysteine ("Cys") residue.

The guanylate cyclase-C agonists according to the invention include amino acid sequences represented by Formulae I-Aad, II-Aad, III-Aad, IV-Aad, V-Aad, VI-Aad, VII-a-

Aad, VII-b-Aad, VIII-Aad, IX-Aad, XVIII-Aad or XXI-Aad as well as those amino acid sequences summarized below in Table 1. The guanylate cyclase-C agonists according to the invention are collectively referred to herein as “Aad-GCRA peptides”.

Table 1. Alpha-amino adipic acid derivatives of GCRA Peptides

Corresponds to:	Position of Disulfide bond	Structure	SEQ ID NO
SP-304	C4:C12, C7:C15	Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	1
SP-326	C3:C11, C6:C14	Asp ¹ -Aad ² -Cys ³ -Glu ⁴ -Leu ⁵ -Cys ⁶ -Val ⁷ -Asn ⁸ -Val ⁹ -Ala ¹⁰ -Cys ¹¹ -Thr ¹² -Gly ¹³ -Cys ¹⁴ -Leu ¹⁵	2
SP-327	C3:C11, C6:C14	Asp ¹ -Aad ² -Cys ³ -Glu ⁴ -Leu ⁵ -Cys ⁶ -Val ⁷ -Asn ⁸ -Val ⁹ -Ala ¹⁰ -Cys ¹¹ -Thr ¹² -Gly ¹³ -Cys ¹⁴	3
SP-328	C2:C10, C5:C13	Aad ¹ -Cys ² -Glu ³ -Leu ⁴ -Cys ⁵ -Val ⁶ -Asn ⁷ -Val ⁸ -Ala ⁹ -Cys ¹⁰ -Thr ¹¹ -Gly ¹² -Cys ¹³ -Leu ¹⁴	4
SP-329	C2:C10, C5:C13	Aad ¹ -Cys ² -Glu ³ -Leu ⁴ -Cys ⁵ -Val ⁶ -Asn ⁷ -Val ⁸ -Ala ⁹ -Cys ¹⁰ -Thr ¹¹ -Gly ¹² -Cys ¹³	5
SP-332	C4:C12, C7:C15	Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶	6
SP-333	C4:C12, C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶	7
SP-334	C4:C12, C7:C15	dAsn ¹ -dAsp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶	8
SP-336	C4:C12, C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	9
SP-337	C4:C12, C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -dLeu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶	10
SP-338	C4:C12, C7:C15	Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵	11
SP-342	C4:C12, C7:C15	PEG3-Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶ -PEG3	12
SP-343	C4:C12, C7:C15	PEG3-dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶ -PEG3	13
SP-344	C4:C12, C7:C15	PEG3-dAsn ¹ -dAsp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶ -PEG3	14
SP-347	C4:C12, C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶ -PEG3	15
SP-348	C4:C12, C7:C15	PEG3-Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶	16
SP-350	C4:C12, C7:C15	PEG3-dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶	17
SP-352	C4:C12, C7:C15	Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶ -PEG3	18
SP-359	C4:C12, C7:C15	PEG3-dAsn ¹ -dAsp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶	19
SP-360	C4:C12, C7:C15	dAsn ¹ -dAsp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶ -PEG3	20
SP-368	C4:C12, C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dNal ¹⁶	21

SP-369	C4:C12, C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -AIB ⁸ -Asn ⁹ -AIB ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶	22
SP-370	C4:C12, 7:15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Asp[Lactam] ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Om ¹⁵ -dLeu ¹⁶	23
SP-371	C4:C12,C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Tyr ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶	24
SP-372	C4:C12,C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Ser ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶	25
N1	C4:C12,C7:C15	PEG3-dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Tyr ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶ -PEG3	26
N2	C4:C12,C7:C15	PEG3-dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Tyr ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶	27
N3	C4:C12,C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Tyr ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶ -PEG3	28
N4	C4:C12,C7:C15	PEG3-dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Ser ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶ -PEG3	29
N5	C4:C12,C7:C15	PEG3-dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Ser ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶	30
N6	C4:C12,C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Ser ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu ¹⁶ -PEG3	31
N7	C4:C12,C7:C15	Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	32
N8	C4:C12,C7:C15	PEG3-Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶ -PEG3	33
N9	C4:C12,C7:C15	PEG3-Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	34
N10	C4:C12,C7:C15	Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶ -PEG3	35
N11	C4:C12,C7:C15	PEG3-Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dSer ¹⁶ -PEG3	36
N12	C4:C12,C7:C15	PEG3-Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dSer ¹⁶	37
N13	C4:C12,C7:C15	Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dSer ¹⁶ -PEG3	38
Formula I (I-Aad)	C4:C12,C7:C15	Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Xaa ⁵ -Xaa ⁶ -Cys ⁷ -Xaa ⁸ -Xaa ⁹ -Xaa ¹⁰ -Xaa ¹¹ -Cys ¹² -Xaa ¹³ -Xaa ¹⁴ -Cys ¹⁵ -Xaa ¹⁶	39
Formula II (II-Aad)	C4:C12,C7:C15	Xaa _{n1} -Cys ⁴ -Xaa ⁵ -Xaa ⁶ -Cys ⁷ -Xaa ⁸ -Xaa ⁹ -Xaa ¹⁰ -Xaa ¹¹ -Cys ¹² -Xaa ¹³ -Xaa ¹⁴ -Cys ¹⁵ -Xaa _{n2} ¹⁶	40
Formula III (III-Aad)	4:12,7:15	Xaa _{n1} -Maa ⁴ -Glu ⁵ -Xaa ⁶ -Maa ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Maa ¹² -Thr ¹³ -Gly ¹⁴ -Maa ¹⁵ -Xaa _{n2}	41
Formula IV (IV-Aad)	4:12,7:15	Xaa _{n1} -Maa ⁴ -Xaa ⁵ -Xaa ⁶ -Maa ⁷ -Xaa ⁸ -Xaa ⁹ -Xaa ¹⁰ -Xaa ¹¹ -Maa ¹² -Xaa ¹³ -Xaa ¹⁴ -Maa ¹⁵ -Xaa _{n2}	42

Formula V (V-Aad)	C4:C12,C7:C15	Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Xaa ⁵ -Xaa ⁶ -Cys ⁷ -Xaa ⁸ -Asn ⁹ -Xaa ¹⁰ -Xaa ¹¹ -Cys ¹² -Xaa ¹³ -Xaa ¹⁴ -Cys ¹⁵ -Xaa ¹⁶	43
Formula VI (VI-Aad)	C4:C12,C7:C15	dAsn ¹ -Glu ² -Aad ³ -Cys ⁴ -Xaa ⁵ -Xaa ⁶ -Cys ⁷ -Xaa ⁸ -Asn ⁹ -Xaa ¹⁰ -Xaa ¹¹ -Cys ¹² -Xaa ¹³ -Xaa ¹⁴ -Cys ¹⁵ -d-Xaa ¹⁶	44
Formula VII-a (VI-a-Aad)	C4:C12,C7:C15	dAsn ¹ -dGlu ² -Aad ³ -Cys ⁴ -Xaa ⁵ -Xaa ⁶ -Cys ⁷ -Xaa ⁸ -Asn ⁹ -Xaa ¹⁰ -Xaa ¹¹ -Cys ¹² -Xaa ¹³ -Xaa ¹⁴ -Cys ¹⁵ -d-Xaa ¹⁶	45
Formula VII-b (VI-b-Aad)	C4:C12,C7:C15	dAsn ¹ -dAsp ² -Aad ³ -Cys ⁴ -Xaa ⁵ -Xaa ⁶ -Cys ⁷ -Xaa ⁸ -Asn ⁹ -Xaa ¹⁰ -Xaa ¹¹ -Cys ¹² -Xaa ¹³ -Xaa ¹⁴ -Cys ¹⁵ -d-Xaa ¹⁶	46
Formula VIII (VIII-Aad)	C4:C12,C7:C15	dAsn ¹ -dAsp ² -Aad ³ -Cys ⁴ -Xaa ⁵ -Xaa ⁶ -Cys ⁷ -Xaa ⁸ -Tyr ⁹ -Xaa ¹⁰ -Xaa ¹¹ -Cys ¹² -Xaa ¹³ -Xaa ¹⁴ -Cys ¹⁵ -d-Xaa ¹⁶	47
Formula IX (IX-Aad)	C4:C12,C7:C15	dAsn ¹ -dGlu ² -Aad ³ -Cys ⁴ -Xaa ⁵ -Xaa ⁶ -Cys ⁷ -Xaa ⁸ -Tyr ⁹ -Xaa ¹⁰ -Xaa ¹¹ -Cys ¹² -Xaa ¹³ -Xaa ¹⁴ -Cys ¹⁵ -d-Xaa ¹⁶	48
Formula XXI (XXI-Aad)	C4:C12,C7:C15	Xaa _{n1} ¹ -Cys ⁴ -Xaa ⁵ -Xaa ⁶ -Xaa ⁷ -Xaa ⁸ -Xaa ⁹ -Xaa ¹⁰ -Xaa ¹¹ -Cys ¹² -Xaa ¹³ -Xaa ¹⁴ -Xaa ¹⁵ -Xaa _{n2} ¹⁶	49
SP-363	C4:C12,C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu-AMIDE ¹⁶	50
SP-364	C4:C12,C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dSer ¹⁶	51
SP-365	C4:C12,C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dSer-AMIDE ¹⁶	52
SP-366	C4:C12,C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dTyr ¹⁶	53
SP-367	C4:C12,C7:C15	dAsn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dTyr-AMIDE ¹⁶	54
SP-373	C4:C12,C7:C15	Pyglu ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -dLeu-AMIDE ¹⁶	55
/	C4:C12,C7:C15	Pyglu ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	56
SP- 304diPEG	C4:C12,C7:C15	PEG3-Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶ -PEG3	57

SP-304N- PEG	C4:C12,C7:C15	PEG3-Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	58
SP-304C- PEG	C4:C12,C7:C15	Asn ¹ -Asp ² -Glu ³ -Cys ⁴ -Aad ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶ -PEG3	59
Formula XVIII (XVIII- Aad)	C4:C12,C7:C15	Xaa ¹ -Xaa ² -Aad ³ -Maa ⁴ -Xaa ⁵ -Xaa ⁶ -Maa ⁷ -Xaa ⁸ -Xaa ⁹ -Xaa ¹⁰ -Xaa ¹¹ -Maa ¹² -Xaa ¹³ -Xaa ¹⁴ -Maa ¹⁵ -Xaa ¹⁶	60
N32	C4:C12,C7:C15	Glu ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	61
N34	C4:C12,C7:C15	Glu ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	62
N36	C4:C12,C7:C15	Asp ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	63
N38	C4:C12,C7:C15	Asp ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	64
N40	C4:C12,C7:C15	Gln ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	65
N42	C4:C12,C7:C15	Gln ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	66
N44	C4:C12,C7:C15	Lys ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	67
N46	C4:C12,C7:C15	Lys ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	68
N48	C4:C12,C7:C15	Glu ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	69
N50	C4:C12,C7:C15	Glu ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	70
N52	C4:C12,C7:C15	Asp ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	71
N54	C4:C12,C7:C15	Asp ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	72
N56	C4:C12,C7:C15	Gln ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	73
N58	C4:C12,C7:C15	Gln ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	74
N60	C4:C12,C7:C15	Lys ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	75
N62	C4:C12,C7:C15	Lys ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	76
N65	C4:C12,C7:C15	Glu ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	77
N67	C4:C12,C7:C15	Glu ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	78
N69	C4:C12,C7:C15	Asp ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	79

N71	C4:C12,C7:C15	Asp ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	80
N73	C4:C12,C7:C15	Gln ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	81
N75	C4:C12,C7:C15	Gln ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	82
N77	C4:C12,C7:C15	Lys ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	83
N79	C4:C12,C7:C15	Lys ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Leu ¹⁶	84
N81	C4:C12,C7:C15	Glu ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	85
N83	C4:C12,C7:C15	Glu ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	86
N85	C4:C12,C7:C15	Asp ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	87
N87	C4:C12,C7:C15	Asp ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	88
N88	C4:C12,C7:C15	Asp ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	89
N89	C4:C12,C7:C15	Gln ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	90
N91	C4:C12,C7:C15	Gln ¹ -Glu ² -Asp ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	91
N92	C4:C12,C7:C15	Gln ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	92
N93	C4:C12,C7:C15	Lys ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	93
N95	C4:C12,C7:C15	Lys ¹ -Glu ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Ile ⁸ -Asn ⁹ -Met ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Ser ¹⁶	94
	C4:C12,C7:C15	Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Thr ¹⁶	119
	C4:C12,C7:C15	Asn ¹ -Asp ² -Aad ³ -Cys ⁴ -Glu ⁵ -Leu ⁶ -Cys ⁷ -Val ⁸ -Asn ⁹ -Val ¹⁰ -Ala ¹¹ -Cys ¹² -Thr ¹³ -Gly ¹⁴ -Cys ¹⁵ -Tyr ¹⁶	120

The Aad-GCRA peptides described herein bind the guanylate cyclase C (GC-C) and stimulate intracellular production of cyclic guanosine monophosphate (cGMP). Optionally, the Aad-GCRA peptides induce apoptosis. In some aspects, the Aad-GCRA peptides stimulate intracellular cGMP production at higher levels than naturally occurring GC-C agonists (*e.g.*, uroguanylin, guanylin, lymphoguanylin and ST peptides) and/or SP-304.

For example, the Aad-GCRA peptides of the invention stimulate 5, 10%, 20%, 30%, 40%, 50%, 75%, 90% or more intracellular cGMP compared to naturally occurring GC-C agonists and/or SP-304. The terms induced and stimulated are used interchangeably throughout the specification.

The Aad-GCRA peptides described herein have therapeutic value in the treatment of a wide variety of disorders and conditions including for example lipid metabolism disorders, biliary disorders, gastrointestinal disorders, inflammatory disorders, lung disorders, cancer, cardiac disorders including cardiovascular disorders, eye disorders, oral disorders, blood disorders, liver disorders, skin disorders, prostate disorders, endocrine disorders, increasing gastrointestinal motility and obesity. Lipid metabolism disorders include, but not limited to, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, sitosterolemia, familial hypercholesterolemia, xanthoma, combined hyperlipidemia, lecithin cholesterol acyltransferase deficiency, tangier disease, abetalipoproteinemia, erectile dysfunction, fatty liver disease, and hepatitis. Biliary disorders include gallbladder disorders such as for example, gallstones, gall bladder cancer cholangitis, or primary sclerosing cholangitis; or bile duct disorders such as for example, cholecystitis, bile duct cancer or fascioliasis. Gastrointestinal disorders include for example, irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastroesophageal reflux disease (GERD), ileus inflammation (*e.g.*, post-operative ileus), gastroparesis, heartburn (high acidity in the GI tract), constipation (*e.g.*, chronic constipation; constipation associated with use of medications such as opioids, osteoarthritis drugs, osteoporosis drugs; post surgical constipation, constipation associated with neuropathic disorders). Inflammatory disorders include tissue and organ inflammation such as kidney inflammation (*e.g.*, nephritis), gastrointestinal system inflammation (*e.g.*, Crohn's disease and ulcerative colitis); necrotizing enterocolitis (NEC); pancreatic inflammation (*e.g.*, pancreatitis), lung inflammation (*e.g.*, bronchitis or asthma) or skin inflammation (*e.g.*, psoriasis, eczema).

Lung Disorders include for example chronic obstructive pulmonary disease (COPD), and fibrosis. Cancer includes tissue and organ carcinogenesis including metastases such as for example gastrointestinal cancer, (*e.g.*, gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer; lung cancer; thyroid cancer; skin cancer (*e.g.*, melanoma); oral cancer; urinary tract cancer (*e.g.*, bladder cancer or kidney cancer); blood cancer (*e.g.* myeloma or leukemia) or prostate cancer. Cardiac disorders include for example, congestive heart failure, trachea cardia hypertension, high cholesterol, or high tryglycerides. Cardiovascular disorders include for example aneurysm, angina, atherosclerosis, cerebrovascular accident (stroke), cerebrovascular disease, congestive heart failure, coronary artery disease, myocardial infarction (heart attack), or peripheral vascular disease. Liver disorders include for example cirrhosis and fibrosis. In addition, Aa derivatives of GC-C agonist described herein may also be useful to facilitate liver regeneration in liver transplant patients. Eye disorders include for example increased intra-ocular pressure, glaucoma, dry eyes retinal degeneration, disorders of tear glands or eye inflammation. Skin disorders include for example xerosis. Oral disorders include for example dry mouth (xerostomia), Sjögren's syndrome, gum diseases (*e.g.*, periodontal disease), or salivary gland duct blockage or malfunction. Prostate disorders include for example benign prostatic hyperplasia (BPH). Endocrine disorders include for example diabetes mellitus, hyperthyroidism, hypothyroidism, and cystic fibrosis.

As used herein, the term “guanylate cyclase receptor (GCR)” refers to the class of guanylate cyclase C receptor on any cell type to which the inventive agonist peptides or natural agonists described herein bind. As used herein, “intestinal guanylate cyclase receptor” is found exclusively on epithelial cells lining the GI mucosa. Uroguanylin, guanylin, and ST peptides are expected to bind to these receptors and may induce apoptosis. The possibility that there may be different receptors for each agonist peptide is not excluded. Hence, the term refers to the class of guanylate cyclase receptors on epithelial cells.

As used herein, the term “GCR agonist” is meant to refer to peptides and/or other compounds that bind to an intestinal guanylate cyclase receptor and stimulate fluid and electrolyte transport. This term also covers fragments and pro-peptides that bind to GCR and stimulate fluid and water secretion.

As used herein, the term “substantially equivalent” is meant to refer to a peptide that has an amino acid sequence equivalent to that of the binding domain where certain residues may be deleted or replaced with other amino acids without impairing the peptide’s ability to bind to an intestinal guanylate cyclase receptor and stimulate fluid and electrolyte transport.

5 Addition of carriers (*e.g.*, phosphate-buffered saline or PBS) and other components to the composition of the present invention is well within the level of skill in this art. In addition to the compound, such compositions may contain pharmaceutically acceptable carriers and other ingredients known to facilitate administration and/or enhance uptake. Other formulations, such as microspheres, nanoparticles, liposomes, and immunologically-based systems may also be used
10 in accordance with the present invention. Other examples include formulations with polymers (*e.g.*, 20% w/v polyethylene glycol) or cellulose, or enteric formulations.

Without intending to be bound by any theory, it is envisioned that ion transport across the plasma membrane may prove to be an important regulator of the balance between cell proliferation and apoptosis that will be affected by agents altering cGMP concentrations.

15 Uroguanylin has been shown to stimulate K⁺ efflux, Ca⁺⁺ influx and water transport in the gastrointestinal tract (3). Moreover, atrial natriuretic peptide (ANP), a peptide that also binds to a specific guanylate cyclase receptor, has also been shown to induce apoptosis in rat mesangial cells, and to induce apoptosis in cardiac myocytes by a cGMP mechanism (21-24).

Binding of the present agonists to a guanylate cyclase receptor stimulates production of
20 cGMP. This ligand-receptor interaction, via activation of a cascade of cGMP-dependent protein kinases and CFTR, induces apoptosis in target cells. Therefore, administration of the novel peptides defined by Formulae I-Aad, II-Aad, III-Aad, IV-Aad, V-Aad, VI-Aad, VII-a-Aad, VII-b-Aad, VIII-Aad, IX-Aad, XVIII-Aad or XXI-Aad and those listed in Table 1 are useful in eliminating or, at least retarding, the onset of lipid metabolism disorders, biliary disorders,
25 gastrointestinal disorders, inflammatory disorders, lung disorders, cancer, cardiac disorders including cardiovascular disorders, eye disorders, oral disorders, blood disorders, liver disorders, skin disorders, prostate disorders, endocrine disorders, increasing gastrointestinal motility and obesity. Lipid metabolism disorders include, but not limited to, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, sitosterolemia, familial hypercholesterolemia,
30 xanthoma, combined hyperlipidemia, lecithin cholesterol acyltransferase deficiency, tangier disease, abetalipoproteinemia, erectile dysfunction, fatty liver disease, and hepatitis. Biliary

disorders include gallbladder disorders such as for example, gallstones, gall bladder cancer cholangitis, or primary sclerosing cholangitis; or bile duct disorders such as for example, cholecystitis, bile duct cancer or fascioliasis. Gastrointestinal disorders include for example, irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastroesophageal reflux disease (GERD), ileus inflammation (*e.g.*, post-operative ileus), gastroparesis, heartburn (high acidity in the GI tract), constipation (*e.g.*, chronic constipation, constipation associated with use of medications such as opioids, osteoarthritis drugs, osteoporosis drugs; post surgical constipation, constipation associated with neuropathic disorders). Inflammatory disorders include tissue and organ inflammation such as kidney inflammation (*e.g.*, nephritis), gastrointestinal system inflammation (*e.g.*, Crohn's disease and ulcerative colitis); necrotizing enterocolitis (NEC); pancreatic inflammation (*e.g.*, pancreatitis), lung inflammation (*e.g.*, bronchitis or asthma) or skin inflammation (*e.g.*, psoriasis, eczema). Lung Disorders include for example chronic obstructive pulmonary disease (COPD), and fibrosis. Cancer includes tissue and organ carcinogenesis including metastases such as for example gastrointestinal cancer, (*e.g.*, gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer; lung cancer; thyroid cancer; skin cancer (*e.g.*, melanoma); oral cancer; urinary tract cancer (*e.g.* bladder cancer or kidney cancer); blood cancer (*e.g.* myeloma or leukemia) or prostate cancer. Cardiac disorders include for example, congestive heart failure, trachea cardia hypertension, high cholesterol, or high tryglycerides. Cardiovascular disorders include for example aneurysm, angina, atherosclerosis, cerebrovascular accident (stroke), cerebrovasculardisease, congestive heart failure, coronary artery disease, myocardial infarction (heart attack), or peripheral vascular disease. Liver disorders include for example cirrhosis and fibrosis. In addition, Aa derivatives of GC-C agonist described herein may also be useful to facilitate liver regeneration in liver transplant patients. Eye disorders include for example increased intra-ocular pressure, glaucoma, dry eyes retinal degeneration, disorders of tear glands or eye inflammation. Skin disorders include for example xerosis. Oral disorders include for example dry mouth (xerostomia), Sjögren's syndrome, gum diseases (*e.g.*, periodontal disease), or salivary gland duct blockage or malfunction. Prostate disorders include for example benign prostatic hyperplasia (BPH).

Endocrine disorders include for example diabetes mellitus, hyperthyroidism, hypothyroidism, and cystic fibrosis.

AAD-GCRA PEPTIDES

In one aspect, the invention provides an Aad-GCRA peptide. The Aad-GCRA peptides are analogues uroguanylin, guanylin, lymphoguanylin and ST peptides. No particular length is implied by the term “peptide”. Particularly, these analogs contain an α -aminoadipic acid (Ad), preferably at the 3rd position from the N-terminus of each peptide or at the position to the N-terminal side next to the first cysteine (“Cys) residue. In some embodiments, the Aad-GCRA peptide is less than 25 amino acids in length, *e.g.*, less than or equal to 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, or 5 amino acid in length.

The Aad-GCRA peptides can be polymers of L-amino acids, D-amino acids, or a combination of both. For example, in various embodiments, the peptides are D retro-inverso peptides. The term “retro-inverso isomer” refers to an isomer of a linear peptide in which the direction of the sequence is reversed and the chirality of each amino acid residue is inverted. *See, e.g.*, Jameson *et al.*, *Nature*, 368, 744-746 (1994); Brady *et al.*, *Nature*, 368, 692-693 (1994). The net result of combining D-enantiomers and reverse synthesis is that the positions of carbonyl and amino groups in each amide bond are exchanged, while the position of the side-chain groups at each alpha carbon is preserved. Unless specifically stated otherwise, it is presumed that any given L-amino acid sequence of the invention may be made into a D retro-inverso peptide by synthesizing a reverse of the sequence for the corresponding native L-amino acid sequence. For example an Aad-GCRA peptide includes the sequence defined by Formulae I-Aad, II-Aad, III-Aad, IV-Aad, V-Aad, VI-Aad, VII-a-Aad, VII-b-Aad, VIII-Aad, IX-Aad, XVIII-Aad or XXI-Aad and those listed in Table 1.

By inducing cGMP production is meant that the Aad-GCRA peptide induces the production of intracellular cGMP. Intracellular cGMP is measured by methods known in the art. For example, the Aad-GCRA peptide of the invention stimulate 5%, 10%, 20%, 30%, 40%, 50%, 75%, 90% or more intracellular cGMP compared to naturally occurring GC-C agonists. Optionally, the Aad-GCRA peptides of the invention of the invention stimulate 5%, 10%, 20%, 30%, 40%, 50%, 75%, 90% or more intracellular cGMP compared SP-304. In further

embodiments, the Aad-GCRA peptide stimulates apoptosis, *e.g.*, programmed cell death or activates the cystic fibrosis transmembrane conductance regulator (CFTR).

As used herein PEG3, 3 PEG, is meant to denote polyethylene glycol such as include aminoethyloxy-ethyloxy-acetic acid (AeeA).

5 As used herein, the term “AMIDE” is meant to denote that the terminal carboxylic acid is replaced with an amide group, *i.e.*, the terminal COOH is replaced with CONH₂.

As used herein, the term “pyGlu” refers to pyroglutamic acid.

As used herein (*e.g.*, in Formulae I-Aad, II-Aad, III-Aad, IV-Aad, V-Aad, VI-Aad, VII-a-Aad, VII-b-Aad, VIII-Aad, IX-Aad, XVIII-Aad or XXI-Aad), X_{aa} is any natural, unnatural
10 amino acid or amino acid analogue; M_{aa} is a Cysteine (Cys), Penicillamine (Pen) homocysteine, or 3-mercaptoproline.

Xaa_{n1} is meant to denote an amino acid sequence of any any natural, unnatural amino acid or amino acid analogue that is one, two or three residues in length. In some embodiments, when Xaa_{n1} represents one amino acid, Xaa_{n1} is an α -aminoadipic acid (Aad). In some
15 embodiments, when Xaa_{n1} represents two amino acids, the second residue from the N-terminus is an α -aminoadipic acid (Aad). In some embodiments, when Xaa_{n1} represents three amino acids, the third residue from the N-terminus is an α -aminoadipic acid (Aad).

Xaa_{n2} is meant to denote an amino acid sequence of any any natural, unnatural amino acid or amino acid analogue that is zero or one residue in length; and Xaa_{n3} is meant to denote an
20 amino acid sequence of any any natural, unnatural amino acid or amino acid analogue that is zero, one, two, three, four, five or six residues in length. Additionally, any amino acid represented by Xaa, may be an L-amino acid, a D-amino acid, a methylated amino acid, a fluorinated amino acid or any combination of thereof. Preferably the amino acids at the N-terminus, C-terminus or both are D-amino acids. Optionally, any Aad-GCRA peptide
25 represented by Formulae I-Aad, II-Aad, III-Aad, IV-Aad, V-Aad, VI-Aad, VII-a-Aad, VII-b-Aad, VIII-Aad, IX-Aad, XVIII-Aad or XXI-Aad may contain on or more polyethylene glycol residues at the N-terminus, C-terminus or both. An exemplary polyethylene glycol includes aminoethyloxy-ethyloxy-acetic acid and polymers thereof. In some embodiments, any Aad-GCRA peptide represented by Formulae I-Aad, II-Aad, III-Aad, IV-Aad, V-Aad, VI-Aad, VII-a-
30 Aad, VII-b-Aad, VIII-Aad, IX-Aad, XVIII-Aad or XXI-Aad may contain AMIDE at the C-terminus.

Specific examples of Aad-GCRA peptides that can be used in the methods and formulations of the invention include a peptide selected from Table 1.

In some embodiments, Aad-GCRA peptides include peptides having the amino acid sequence of Formula I-Aad. In some embodiments, at least one amino acid of Formula I-Aad is a D-amino acid or a methylated amino acid and/or the amino acid at position 16 is a serine. Preferably, the amino acid at position 16 of Formula I-Aad is a D-amino acid or a methylated amino acid. For example, the amino acid at position 16 of Formula I-Aad is a d-leucine or a d-serine. Optionally, one or more of the amino acids at positions 1-2 of Formula I-Aad are D-amino acids or methylated amino acids or a combination of D-amino acids or methylated amino acids. For example, Asn¹ or Asp² (or a combination thereof) of Formula I-Aad is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position Xaa⁶ of Formula I-Aad is a leucine, serine or tyrosine.

In alternative embodiments, Aad-GCRA peptides include peptides having the amino acid sequence of Formula II-Aad. In some embodiments, at least one amino acid of Formula II-Aad is a D-amino acid or a methylated amino acid. Preferably, the amino acid denoted by Xaa_{n2} of Formula II-Aad is a D-amino acid or a methylated amino acid. In some embodiments, the amino acid denoted by Xaa_{n2} of Formula II-Aad is a leucine, a d-leucine, a serine, or a d-serine. Preferably, the one or more amino acids denoted by Xaa_{n1} of Formula II-Aad are D-amino acids or methylated amino acids. Preferably, the amino acid at position Xaa⁶ of Formula II-Aad is a leucine, a serine, or a tyrosine. In some embodiments, when Xaa_{n1} represents one amino acid, Xaa_{n1} is an α -amino adipic acid (Aad). In some embodiments, when Xaa_{n1} represents two amino acids, the second residue from the N-terminus is an α -amino adipic acid (Aad). In some embodiments, when Xaa_{n1} represents three amino acids, the third residue from the N-terminus is an α -amino adipic acid (Aad). In some embodiments, Xaa¹ is a pyroglutamic acid. In some embodiments, Xaa² is glutamic acid or d-glutamic acid. In some embodiments, Xaa⁸ and Xaa¹⁰ are AIB. In some embodiments, Xaa⁹ is tyrosine. In some embodiments, Xaa¹⁶ is dNal.

In some embodiments, Aad-GCRA peptides include peptides having the amino acid sequence of Formula III-Aad. In some embodiments, at least one amino acid of Formula III-Aad is a D-amino acid or a methylated amino acid and/or Maa is not a cysteine. Preferably, the amino acid denoted by Xaa_{n2} of Formula III-Aad is a D-amino acid or a methylated amino acid. In some embodiments the amino acid denoted by Xaa_{n2} of Formula III-Aad is a leucine, a d-

leucine, a serine, or a d-serine. Preferably, the one or more amino acids denoted by Xaa_{n1} of Formula III-Aad are D-amino acids or methylated amino acids. Preferably, the amino acid at position Xaa⁶ of Formula III-Aad is a leucine, a serine, or a tyrosine. In some embodiments, when Xaa_{n1} represents one amino acid, Xaa_{n1} is an α -aminoadipic acid (Aad). In some
5 embodiments, when Xaa_{n1} represents two amino acids, the second residue from the N-terminus is an α -aminoadipic acid (Aad). In some embodiments, when Xaa_{n1} represents three amino acids, the third residue from the N-terminus is an α -aminoadipic acid (Aad). In some embodiments, Xaa¹ is a pyroglutamic acid. In some embodiments, Xaa² is glutamic acid or d-glutamic acid. In some embodiments, Xaa¹⁶ is dNal.

10 In other embodiments, Aad-GCRA peptides include peptides having the amino acid sequence of Formula IV-Aad. In some embodiments, at least one amino acid of Formula IV-Aad is a D-amino acid or a methylated amino acid, and/or Maa is not a cysteine. Preferably, the Xaa_{n2} of Formula IV-Aad is a D-amino acid or a methylated amino acid. In some embodiments, the amino acid denoted by Xaa_{n2} of Formula IV-Aad is a leucine, a d-leucine, a serine, or a d-
15 serine. Preferably, the one or more of the amino acids denoted by Xaa_{n1} of Formula IV-Aad are D-amino acids or methylated amino acids. In some embodiments, when Xaa_{n1} represents one amino acid, Xaa_{n1} is an α -aminoadipic acid (Aad). In some embodiments, when Xaa_{n1} represents two amino acids, the second residue from the N-terminus is an α -aminoadipic acid (Aad). In some embodiments, when Xaa_{n1} represents three amino acids, the third residue from the N-
20 terminus is an α -aminoadipic acid (Aad). Preferably, the amino acid denoted Xaa⁶ of Formula IV is a leucine, a serine, or a tyrosine. In some embodiments, Xaa¹ is a pyroglutamic acid. In some embodiments, Xaa² is glutamic acid or d-glutamic acid. In some embodiments, Xaa⁸ and Xaa¹⁰ are AIB. In some embodiments, Xaa⁹ is tyrosine. In some embodiments, Xaa¹⁶ is dNal.

25 In further embodiments, Aad-GCRA peptides include peptides having the amino acid sequence of Formula V-Aad. In some embodiments, at least one amino acid of Formula V-Aad is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position 16 of Formula V-Aad is a D-amino acid or a methylated amino acid. For example, the amino acid at position 16 (i.e., Xaa¹⁶) of Formula V-Aad is a d-leucine or a d-serine. Optionally, one or more of the amino acids at positions 1 and 2 of Formula V-Aad are D-amino acids or methylated
30 amino acids or a combination of D-amino acids or methylated amino acids. For example, Asn¹ or Asp² (or a combination thereof) of Formula V-Aad is a D-amino acids or a methylated amino

acid. Preferably, the amino acid denoted at Xaa⁶ of Formula V-Aad is a leucine, a serine, or a tyrosine.

In additional embodiments, Aad-GCRA peptides include peptides having the amino acid sequence of Formula VI-Aad, VII-a-Aad, VII-b-Aad, VIII-Aad or IX-Aad. Preferably, the amino acid at position 6 of Formula VI-Aad, VII-a-Aad, VII-b-Aad, VIII-Aad or IX-Aad is a leucine, a serine, or a tyrosine. In some aspects the amino acid at position 16 of Formula VI-Aad, VII-a-Aad, VII-b-Aad, VIII-Aad or IX-Aad is a leucine or a serine. Preferably, the amino acid at position 16 of Formula VI-Aad, VII-a-Aad, VII-b-Aad, VIII-Aad or IX-Aad is a D-amino acid or a methylated amino acid.

In some embodiments, GCRA peptides include peptides containing the amino acid sequence of Formula XVIII-Aad. Preferably, the amino acid at position 1 of Formula XVIII-Aad is a glutamic acid, aspartic acid, glutamine or lysine. Preferably, the amino acid at position 2 and 3 of Formula XVIII-Aad is a glutamic acid, or an aspartic acid. Preferably, the amino acid at position 5 is a glutamic acid. Preferably, the amino acid at position 6 of Formula XVIII-Aad is an isoleucine, valine, serine, threonine or tyrosine. Preferably, the amino acid at position 8 of Formula XVIII-Aad is a valine or isoleucine. Preferably, the amino acid at position 9 of Formula XVIII-Aad is an asparagine. Preferably, the amino acid at position 10 of Formula XVIII-Aad is a valine or a methionine. Preferably, the amino acid at position 11 of Formula XVIII-Aad is an alanine. Preferably, the amino acid at position 13 of Formula XVIII-Aad is a threonine. Preferably, the amino acid at position 14 of Formula XVIII-Aad is a glycine. Preferably, the amino acid at position 16 of Formula XVIII-Aad is a leucine, serine, threonine or tyrosine.

In some embodiments, GCRA peptides include peptides having the amino acid sequence of Formula XXI-Aad. In some embodiments, at least one amino acid of Formula XXI-Aad is a D-amino acid or a methylated amino acid. Preferably, the amino acid denoted by Xaa_{n2} of Formula XXI-Aad is a D-amino acid or a methylated amino acid. In some embodiments, the amino acid denoted by Xaa_{n2} of Formula XXI-Aad is a leucine, a d-leucine, a serine, or a d-serine. Preferably, the one or more amino acids denoted by Xaa_{n1} of Formula XXI-Aad are D-amino acids or methylated amino acids. In some embodiments, when Xaa_{n1} represents one amino acid, Xaa_{n1} is an α -aminoadipic acid (Aad). In some embodiments, when Xaa_{n1} represents two amino acids, the second residue from the N-terminus is an α -aminoadipic acid (Aad). In some embodiments, when Xaa_{n1} represents three amino acids, the third residue from the N-

terminus is an α -aminoadipic acid (Aad). Preferably, the amino acid at position Xaa⁶ of Formula XXI-Aad is a leucine, a serine, or a tyrosine. In some embodiments, Xaa¹ is a pyroglutamic acid. In some embodiments, Xaa² is glutamic acid or d-glutamic acid. In some embodiments, Xaa⁷ is an aspartic acid and forms a lactam bridge with Xaa¹⁵. In some embodiments, Xaa⁸ and Xaa¹⁰ are AIB. In some embodiments, Xaa⁹ is tyrosine. In some embodiments, Xaa¹⁵ is an Orn. In some embodiments, Xaa¹⁶ is dNal.

In certain embodiments, one or more amino acids of the Aad-GCRA peptides can be replaced by a non-naturally occurring amino acid or a naturally or non-naturally occurring amino acid analog. There are many amino acids beyond the standard 20 (Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val). Some are naturally-occurring others are not. (See, for example, Hunt, The Non-Protein Amino Acids: In Chemistry and Biochemistry of the Amino Acids, Barrett, Chapman and Hall, 1985). For example, an aromatic amino acid can be replaced by 3,4-dihydroxy-L-phenylalanine, 3-iodo-L-tyrosine, triiodothyronine, L-thyroxine, phenylglycine (Phg) or nor-tyrosine (norTyr). Phg and norTyr and other amino acids including Phe and Tyr can be substituted by, e.g., a halogen, -CH₃, -OH, -CH₂NH₃, -C(O)H, -CH₂CH₃, -CN, -CH₂CH₂CH₃, -SH, or another group. Any amino acid can be substituted by the D-form of the amino acid.

With regard to non-naturally occurring amino acids or naturally and non-naturally occurring amino acid analogs, a number of substitutions in the polypeptide and agonists described herein are possible alone or in combination.

For example, glutamine residues can be substituted with gamma-Hydroxy-Glu or gamma- Carboxy-Glu. Tyrosine residues can be substituted with an alpha substituted amino acid such as L-alpha-methylphenylalanine or by analogues such as: 3-Amino-Tyr; Tyr(CH₃); Tyr(PO₃(CH₃)₂); Tyr(SO₃H); beta-Cyclohexyl-Ala; beta-(1-Cyclopentenyl)-Ala; beta-Cyclopentyl-Ala; beta-Cyclopropyl-Ala; beta-Quinolyl-Ala; beta-(2-Thiazolyl)-Ala; beta-(Triazole-1-yl)-Ala; beta-(2-Pyridyl)-Ala; beta-(3-Pyridyl)-Ala; Amino-Phe; Fluoro-Phe; Cyclohexyl-Gly; tBu-Gly; beta-(3-benzothienyl)-Ala; beta-(2-thienyl)-Ala; 5-Methyl-Trp; and A- Methyl-Trp. Proline residues can be substituted with homopro (L-pipecolic acid); hydroxy-Pro; 3,4-Dehydro-Pro; 4-fluoro-Pro; or alpha-methyl-Pro or an N(alpha)-C(alpha) cyclized amino acid analogues with the structure: n = 0, 1, 2, 3 Alanine residues can be substituted with alpha-substituted or N-methylated amino acid such as alpha-amino isobutyric acid (aib), L/D-

alpha-ethylalanine (L/D-isovaline), L/D-methylvaline, or L/D-alpha-methylleucine or a non-natural amino acid such as beta-fluoro-Ala. Alanine can also be substituted with: n = 0, 1, 2, 3
Glycine residues can be substituted with alpha-amino isobutyric acid (aib) or L/D-alpha-ethylalanine (L/D-isovaline).

5 Further examples of unnatural amino acids include: an unnatural analog of alanine (e.g., L-1-Nal or L-2-Nal); an unnatural analog of tyrosine; an unnatural analogue of glutamine; an unnatural analogue of phenylalanine; an unnatural analogue of serine; an unnatural analogue of threonine; an alkyl, aryl, acyl, azido, cyano, halo, hydrazine, hydrazide, hydroxyl, alkenyl, alkynyl, ether, thiol, sulfonyl, seleno, ester, thioacid, borate, boronate, phospho, phosphono, phosphine, heterocyclic, enone, imine, aldehyde, hydroxylamine, keto, or amino substituted
10 amino acid, or any combination thereof; an amino acid with a photoactivatable cross-linker; a spin-labeled amino acid; a fluorescent amino acid; an amino acid with a novel functional group; an amino acid that covalently or noncovalently interacts with another molecule; a metal binding amino acid; an amino acid that is amidated at a site that is not naturally amidated, a metal-
15 containing amino acid; a radioactive amino acid; a photocaged and/or photoisomerizable amino acid; a biotin or biotin-analogue containing amino acid; a glycosylated or carbohydrate modified amino acid; a keto containing amino acid; amino acids comprising polyethylene glycol or polyether; a heavy atom substituted amino acid (e.g., an amino acid containing deuterium, tritium, ¹³C, ¹⁵N, or ¹⁸O); a chemically cleavable or photocleavable amino acid; an amino acid
20 with an elongated side chain; an amino acid containing a toxic group; a sugar substituted amino acid, e.g., a sugar substituted serine or the like; a carbon-linked sugar-containing amino acid; a redox-active amino acid; an α -hydroxy containing acid; an amino thio acid containing amino acid; an α, α disubstituted amino acid; a β - amino acid; a cyclic amino acid other than proline; an O-methyl-L-tyrosine; an L-3-(2- naphthyl)alanine; a 3-methyl-phenylalanine; a p-acetyl-L-
25 phenylalanine; an O-4-allyl-L-tyrosine; a 4-propyl-L-tyrosine; a tri-O-acetyl-GlcNAc β -serine; an L-Dopa; a fluorinated phenylalanine; an isopropyl-L-phenylalanine; a p-azido-L-phenylalanine; a p-acyl-L-phenylalanine; a p- benzoyl-L-phenylalanine; an L-phosphoserine; a phosphoserine; a phosphonotyrosine; a p- iodo-phenylalanine; a 4-fluorophenylglycine; a p-bromophenylalanine; a p-amino-L- phenylalanine; an isopropyl-L-phenylalanine; L-3-(2-
30 naphthyl)alanine; D- 3-(2-naphthyl)alanine (dNal); an amino-, isopropyl-, or O-allyl-containing phenylalanine analogue; a dopa, 0-methyl-L-tyrosine; a glycosylated amino acid; a p-

(propargyloxy)phenylalanine; dimethyl-Lysine; hydroxy-proline; mercaptopropionic acid; methyl-lysine; 3-nitro-tyrosine; norleucine; pyro-glutamic acid; Z (Carbobenzoxyl); ϵ - Acetyl-Lysine; β -alanine; β -aspartic acid; β -cyclohexylalanine; aminobenzoyl derivative; aminobutyric acid (Abu); citrulline; aminohexanoic acid (Ahx); aminoisobutyric acid (AIB);

5 cyclohexylalanine; d-cyclohexylalanine; cyclohexylglycine; hydroxyproline; nitro-arginine; nitro-phenylalanine; nitro-tyrosine; norvaline; octahydroindole carboxylate; ornithine (Orn); penicillamine (PEN); tetrahydroisoquinoline; diaminobutyric acid; diaminopimelic acid; pyroglutamic acid; homocysteine; homoserine; N- ϵ -dinitrophenyl-lysine; N- ϵ -methyl-lysine; N- ϵ -dimethyl-lysine; N,N,N- ϵ -trimethyl-lysine; acetamidomethyl protected amino acids and

10 pegylated amino acids. Further examples of unnatural amino acids and amino acid analogs can be found in U.S. 20030108885, U.S. 20030082575, US20060019347 (paragraphs 410-418) and the references cited therein. The polypeptides of the invention can include further modifications including those described in US20060019347, paragraph 589.

“Nal” used herein refers to both L-1-naphthylalanine (L-1-Nal) and L-2-naphthylalanine (L-2-Nal).

15

In some embodiments, an amino acid can be replaced by a naturally-occurring, non-essential amino acid, *e.g.*, taurine.

Alternatively, the Aad-GCRA peptides are cyclic peptides. Aad-GCRA cyclic peptides are prepared by methods known in the art. For example, macrocyclization is often accomplished

20 by forming an amide bond between the peptide N- and C-termini, between a side chain and the N- or C-terminus [*e.g.*, with $K_3Fe(CN)_6$ at pH 8.5] (Samson *et al.*, *Endocrinology*, 137: 5182-5185 (1996)), or between two amino acid side chains, such as cysteine. See, *e.g.*, DeGrado, *Adv Protein Chem*, 39: 51-124 (1988). In various aspects the Aad-GCRA peptides are [4,12; 7,15] bicycles.

25 In some Aad-GCRA peptides one or both members of one or both pairs of Cys residues which normally form a disulfide bond can be replaced by homocysteine, penicillamine, 3-mercaptoproline (Kolodziej *et al.* 1996 *Int J Pept Protein Res* 48:274); β , β dimethylcysteine (Hunt *et al.* 1993 *Int JPept Protein Res* 42:249) or diaminopropionic acid (Smith *et al.* 1978 *J Med Chem* 21:117) to form alternative internal cross-links at the positions of the normal

30 disulfide bonds.

In addition, one or more disulfide bonds can be replaced by alternative covalent cross-links, *e.g.*, an amide linkage (-CH₂CH(O)NHCH₂- or -CH₂NHCH(O)CH₂-), an ester linkage, a thioester linkage, a lactam bridge (such as Asp[lactam]), a carbamoyl linkage, a urea linkage, a thiourea linkage, a phosphonate ester linkage, an alkyl linkage (-CH₂CH₂CH₂CH₂-), an alkenyl linkage(-CH₂CH=CHCH₂-), an ether linkage (-CH₂CH₂OCH₂- or -CH₂OCH₂CH₂-), a thioether linkage (-CH₂CH₂SCH₂- or -CH₂SCH₂CH₂-), an amine linkage (-CH₂CH₂NHCH₂- or -CH₂NHCH₂CH₂-) or a thioamide linkage (-CH₂CH(S)HNHCH₂- or -CH₂NHCH(S)CH₂-). For example, Ledu et al. (Proc Nat'l Acad. Sci. 100:11263-78, 2003) describe methods for preparing lactam and amide cross-links.

The Aad-GCRA peptides can have one or more conventional polypeptide bonds replaced by an alternative bond. Such replacements can increase the stability of the polypeptide. For example, replacement of the polypeptide bond between a residue amino terminal to an aromatic residue (*e.g.* Tyr, Phe, Trp) with an alternative bond can reduce cleavage by carboxy peptidases and may increase half-life in the digestive tract. Bonds that can replace polypeptide bonds include: a retro-inverso bond (C(O)-NH instead of NH-C(O)); a reduced amide bond (NH-CH₂); a thiomethylene bond (S-CH₂ or CH₂-S); an oxomethylene bond (O-CH₂ or CH₂-O); an ethylene bond (CH₂-CH₂); a thioamide bond (C(S)-NH); a trans-olefine bond (CH=CH); a fluoro substituted trans-olefine bond (CF=CH); a ketomethylene bond (C(O)-CHR or CHR-C(O) wherein R is H or CH₃); and a fluoro-ketomethylene bond (C(O)-CFR or CFR-C(O) wherein R is H or F or CH₃).

The Aad-GCRA peptides can be modified using standard modifications. Modifications may occur at the amino (N-), carboxy (C-) terminus, internally or a combination of any of the preceeding. In one aspect described herein, there may be more than one type of modification on the polypeptide. Modifications include but are not limited to: acetylation, amidation, biotinylation, cinnamoylation, farnesylation, formylation, myristoylation, palmitoylation, phosphorylation (Ser, Tyr or Thr), stearylation, succinylation, sulfurylation and cyclisation (via disulfide bridges or amide cyclisation), and modification by Cys3 or Cys5. The Aad-GCRA peptides described herein may also be modified by 2, 4-dinitrophenyl (DNP), DNP-lysine, modification by 7-Amino-4-methyl- coumarin (AMC), fluorescein, NBD (7-Nitrobenz-2-Oxa-1,3-Diazole), p-nitro-anilide, rhodamine B, EDANS (5-((2-aminoethyl)amino)naphthalene-1-sulfonic acid), dabcytl, dabsyl, dansyl, texas red, Fmoc, and Tamra (Tetramethylrhodamine).

The Aad-GCRA peptides described herein may also be conjugated to, for example, polyethylene glycol (PEG); alkyl groups (*e.g.*, C1-C20 straight or branched alkyl groups); fatty acid radicals; combinations of PEG, alkyl groups and fatty acid radicals (*See*, U.S. Patent 6,309,633; Soltero et al., 2001 Innovations in Pharmaceutical Technology 106-110); BSA and KLH (Keyhole Limpet Hemocyanin). The addition of PEG and other polymers which can be used to modify polypeptides of the invention is described in US2006019347 section IX.

Also included in the invention are peptides that biologically or functionally equivalent to the peptides described herein. The term "biologically equivalent" or functionally equivalent" is intended to mean that the compositions of the present invention are capable of demonstrating some or all of the cGMP production modulatory effects.

Aad-GCRA peptides can also include derivatives of Aad-GCRA peptides which are intended to include hybrid and modified forms of Aad-GCRA peptides in which certain amino acids have been deleted or replaced and modifications such as where one or more amino acids have been changed to a modified amino acid or unusual amino acid and modifications such as glycosylation so long the modified form retains the biological activity of Aad-GCRA peptides. By retaining the biological activity, it is meant that cGMP and or apoptosis is induced by the Aad-GCRA peptide, although not necessarily at the same level of potency as that of a naturally-occurring GCRA peptide identified.

Preferred variants are those that have conservative amino acid substitutions made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in an Aad-GCRA polypeptide is replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of

an Aad-GCRA coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened to identify mutants that retain activity.

Also included within the meaning of substantially homologous is any Aad-GCRA peptide which may be isolated by virtue of cross-reactivity with antibodies to the Aad-GCRA peptide.

5

PREPARATION OF AAD-GCRA PEPTIDES

Aad-GCRA peptides are easily prepared using modern cloning techniques, or may be synthesized by solid state methods or by site-directed mutagenesis. An Aad-GCRA peptide may include dominant negative forms of a polypeptide.

10 Chemical synthesis may generally be performed using standard solution phase or solid phase peptide synthesis techniques, in which a peptide linkage occurs through the direct condensation of the amino group of one amino acid with the carboxy group of the other amino acid with the elimination of a water molecule. Peptide bond synthesis by direct condensation, as formulated above, requires suppression of the reactive character of the amino group of the first
15 and of the carboxyl group of the second amino acid. The masking substituents must permit their ready removal, without inducing breakdown of the labile peptide molecule.

In solution phase synthesis, a wide variety of coupling methods and protecting groups may be used (*See*, Gross and Meienhofer, eds., "The Peptides: Analysis, Synthesis, Biology," Vol. 1-4 (Academic Press, 1979); Bodansky and Bodansky, "The Practice of Peptide Synthesis,"
20 2d ed. (Springer Verlag, 1994)). In addition, intermediate purification and linear scale up are possible. Those of ordinary skill in the art will appreciate that solution synthesis requires consideration of main chain and side chain protecting groups and activation method. In addition, careful segment selection is necessary to minimize racemization during segment condensation. Solubility considerations are also a factor. Solid phase peptide synthesis uses an insoluble
25 polymer for support during organic synthesis. The polymer-supported peptide chain permits the use of simple washing and filtration steps instead of laborious purifications at intermediate steps. Solid-phase peptide synthesis may generally be performed according to the method of Merrifield et al., J. Am. Chem. Soc., 1963, 85:2149, which involves assembling a linear peptide chain on a resin support using protected amino acids. Solid phase peptide synthesis typically utilizes either
30 the Boc or Fmoc strategy, which is well known in the art.

Those of ordinary skill in the art will recognize that, in solid phase synthesis, deprotection and coupling reactions must go to completion and the side-chain blocking groups must be stable throughout the synthesis. In addition, solid phase synthesis is generally most suitable when peptides are to be made on a small scale.

5 Acetylation of the N-terminal can be accomplished by reacting the final peptide with acetic anhydride before cleavage from the resin. C-amidation is accomplished using an appropriate resin such as methylbenzhydrylamine resin using the Boc technology.

Alternatively the Aad-GCRA peptides are produced by modern cloning techniques. For example, the Aad-GCRA peptides are produced either in bacteria including, without limitation,
10 *E. coli*, or in other existing systems for polypeptide or protein production (*e.g.*, *Bacillus subtilis*, baculovirus expression systems using *Drosophila* Sf9 cells, yeast or filamentous fungal expression systems, mammalian cell expression systems), or they can be chemically synthesized.

If the Aad-GCRA peptide or variant peptide is to be produced in bacteria, *e.g.*, *E. coli*, the nucleic acid molecule encoding the polypeptide may also encode a leader sequence that permits
15 the secretion of the mature polypeptide from the cell. Thus, the sequence encoding the polypeptide can include the pre sequence and the pro sequence of, for example, a naturally-occurring bacterial ST polypeptide. The secreted, mature polypeptide can be purified from the culture medium.

The sequence encoding an Aad-GCRA peptide described herein can be inserted into a
20 vector capable of delivering and maintaining the nucleic acid molecule in a bacterial cell. The DNA molecule may be inserted into an autonomously replicating vector (suitable vectors include, for example, pGEM3Z and pcDNA3, and derivatives thereof). The vector nucleic acid may be a bacterial or bacteriophage DNA such as bacteriophage lambda or M13 and derivatives thereof. Construction of a vector containing a nucleic acid described herein can be followed by
25 transformation of a host cell such as a bacterium. Suitable bacterial hosts include but are not limited to, *E. coli*, *B. subtilis*, *Pseudomonas*, *Salmonella*. The genetic construct also includes, in addition to the encoding nucleic acid molecule, elements that allow expression, such as a promoter and regulatory sequences. The expression vectors may contain transcriptional control sequences that control transcriptional initiation, such as promoter, enhancer, operator, and
30 repressor sequences.

A variety of transcriptional control sequences are well known to those in the art. The expression vector can also include a translation regulatory sequence (*e.g.*, an untranslated 5' sequence, an untranslated 3' sequence, or an internal ribosome entry site). The vector can be capable of autonomous replication or it can integrate into host DNA to ensure stability during polypeptide production.

The protein coding sequence that includes an Aad-GCRA peptide described herein can also be fused to a nucleic acid encoding a polypeptide affinity tag, *e.g.*, glutathione S-transferase (GST), maltose E binding protein, protein A, FLAG tag, hexa-histidine, myc tag or the influenza HA tag, in order to facilitate purification. The affinity tag or reporter fusion joins the reading frame of the polypeptide of interest to the reading frame of the gene encoding the affinity tag such that a translational fusion is generated. Expression of the fusion gene results in translation of a single polypeptide that includes both the polypeptide of interest and the affinity tag. In some instances where affinity tags are utilized, DNA sequence encoding a protease recognition site will be fused between the reading frames for the affinity tag and the polypeptide of interest.

Genetic constructs and methods suitable for production of immature and mature forms of the Aad-GCRA peptides and variants described herein in protein expression systems other than bacteria, and well known to those skilled in the art, can also be used to produce polypeptides in a biological system.

The peptides disclosed herein may be modified by attachment of a second molecule that confers a desired property upon the peptide, such as increased half-life in the body, for example, pegylation. Such modifications also fall within the scope of the term "variant" as used herein.

COMPOSITIONS

The present invention also provides compositions comprising at least one Aad-GCRA peptide, at least one enteric coating which releases the peptide at a specific pH (*e.g.*, about pH 4.0, pH 5.0, pH 6.0 or pH 7.0) and an inert carrier.

A composition may comprise an enteric coating which releases the peptide at pH5 and an inert carrier coated with Aad-GCRA peptides.

A composition may comprise an enteric coating which releases the peptide at pH6 and an inert carrier coated with Aad-GCRA peptides.

A composition may comprise an enteric coating which releases the peptide at pH7 and an inert carrier coated with Aad-GCRA peptides.

The present invention further provides a formulation comprising a mixture of compositions that contain different peptides and/or that release the peptides at different pH levels. The mixture may comprise at least 2, 3, 4 or more compositions that release the peptides at different pH levels. The mixture may comprise at least 2, 3, 4 or more compositions that contain different Aad-GCRA peptides. A skilled artisan can determine the ratio of these compositions within the mixture, for example, according to the activity of each peptide, solubility of each peptide, and/or the targeting region of the GI tract.

In some embodiments, a formulation comprises a mixture of (1) a composition having an inert carrier coated with Aad-GCRA peptides and an enteric coating that releases the peptides at pH5.0 ("pH5.0 composition") and (2) a composition having an inert carrier coated with Aad-GCRA peptides and an enteric coating that releases the peptides at pH6.0 ("pH6.0 composition").

The ratio of pH5.0 composition to pH6.0 composition can be any value between 100:1 (v/v) and 1: 100 (v/v) and can be determined, for example, by the activity of each peptide, solubility of each peptide, and/or the targeting region of the GI tract. In some embodiments, the ratio of pH5.0 composition to pH6.0 composition is 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2: 1, 1: 1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, or 1:10.

In some embodiments, a formulation comprises a mixture of (1) a composition having an inert carrier coated with Aad-GCRA peptides and an enteric coating that releases the peptides at pH5.0 ("pH5.0 composition") and (2) a composition having an inert carrier coated with Aad-GCRA peptides and an enteric coating that releases the peptides at pH7.0 ("pH7.0 composition").

The ratio of pH5.0 composition to pH7.0 composition can be any value between 100:1 (v/v) and 1: 100 (v/v) and can be determined, for example, by the activity of each peptide, solubility of each peptide, and/or the targeting region of the GI tract. In some embodiments, the ratio of pH5.0 composition to pH7.0 composition is 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2: 1, 1: 1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, or 1:10.

In some embodiments, a formulation comprises a mixture of (1) a composition having an inert carrier coated with Aad-GCRA peptides and an enteric coating that releases the peptides at

pH6.0 (“pH6.0 composition”) and (2) a composition having an inert carrier coated with Aad-GCRA peptides and an enteric coating that releases the peptides at pH7.0 (“pH7.0 composition”).

5 The ratio of pH6.0 composition to pH7.0 composition can be any value between 100:1 (v/v) and 1: 100 (v/v) and can be determined, for example, by the activity of each peptide, solubility of each peptide, and/or the targeting region of the GI tract. In some embodiments, the ratio of pH6.0 composition to pH7.0 composition is 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2: 1, 1: 1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, or 1:10.

10 In some embodiments, a formulation comprises a mixture of (1) a composition having an inert carrier coated with Aad-GCRA peptides and an enteric coating that releases the peptides at pH5.0 (“pH5.0 composition”); (2) a composition having an inert carrier coated with Aad-GCRA peptides and an enteric coating that releases the peptides at pH6.0 (“pH6.0 composition”) and (3) a composition having an inert carrier coated with Aad-GCRA and an enteric coating that releases the peptides at pH7.0 (“pH7.0 composition”).

15 The ratio of pH5.0 composition to pH6.0 composition to pH7.0 composition can be determined, for example, by the activity of each peptide, solubility of each peptide, and/or the targeting region of the GI tract.

In some embodiments, a formulation comprises a mixture of (1) a composition having an inert carrier coated with Aad-GCRA peptides and an enteric coating that releases the peptides at 20 duodenum or jejunum (“duodenum composition”) and (2) a composition having an inert carrier coated with Aad-GCRA peptides and an enteric coating that releases the peptides at ileum, terminal ileum, or ascending colon (“ileum composition”).

25 In some embodiments, a formulation comprises a mixture of (1) a composition having an inert carrier coated with Aad-GCRA peptides and an enteric coating that releases the peptides in a pH range of 4.5 to 5.5 or in a pH range of 5.5 to 6.5 at duodenum or jejunum (“duodenum composition”); and (2) a composition having an inert carrier coated with Aad-GCRA peptides and an enteric coating that releases the peptides in a pH range of 5.5 to 6.5 or in a pH range of 6.5 to 7.5 at ileum, terminal ileum, or ascending colon (“ileum composition”).

30 The ratio of duodenum composition to ileum composition can be any value between 100:1 (v/v) and 1: 100 (v/v) and can be determined, for example, by the activity of each peptide, solubility of each peptide, and/or the targeting region of the GI tract. In some embodiments, the

ratio of duodenum composition to ileum composition is 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, or 1:10.

The targeting region of the GI track includes, but is not limited to, duodenum, jejunum, ileum, terminal ileum, and ascending colon.

In some embodiments, the inert carrier is selected from the group consisting of sorbitol, mannitol, EMDEX, and starch. In some embodiments, the carrier is mannitol (*e.g.*, MANNOGEM) or microcrystalline cellulose (*e.g.*, PROSOLV, CELPHERE®, CELPHERE® beads). In a preferred embodiment, the carrier is microcrystalline cellulose spheres or spherical microcrystalline cellulose, such as Celphere® SCP-100.

The enteric coating material is chosen to target the release of the composition of the present invention to a specific region of the gastrointestinal tract. The enteric coating material preferably comprises one of the following: (1) a pH dependent polymer; (2) a swellable polymer; or (3) a degradable composition. More coating materials and formulations can be found in PCT publications WO 10/065751, WO 12/118972, and WO 12/037380 and US publication 20120237593, each of which is incorporated herein by reference in its entirety.

THERAPEUTIC METHODS

The present invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) developing a disorder or having a disorder that is mediated by guanylate cyclase receptor agonists by administering an Aad-GCRA peptide described herein.

The present invention also provides methods for treating a condition that responds to enhanced cGMP levels in a subject by administering an Aad-GCRA peptide described herein.

Disorders mediated by the guanylate cyclase receptor agonists and conditions that respond to enhanced cGMP levels include lipid metabolism disorders, biliary disorders, gastrointestinal disorders, inflammatory disorders, lung disorders, cancer, cardiac disorders including cardiovascular disorders, eye disorders, oral disorders, blood disorders, liver disorders, skin disorders, prostate disorders, endocrine disorders, increasing gastrointestinal motility and obesity. Lipid metabolism disorders include, but not limited to, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, sitosterolemia, familial hypercholesterolemia, xanthoma, combined hyperlipidemia, lecithin cholesterol acyltransferase deficiency, tangier disease, abetalipoproteinemia, erectile dysfunction, fatty liver disease, and hepatitis. Biliary

disorders include gallbladder disorders such as for example, gallstones, gall bladder cancer cholangitis, or primary sclerosing cholangitis; or bile duct disorders such as for example, cholecystitis, bile duct cancer or fascioliasis. Gastrointestinal disorders include for example, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), non-ulcer

5 dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastroesophageal reflux disease (GERD), ileus inflammation (*e.g.*, post-operative ileus), gastroparesis, heartburn (high acidity in the GI tract), constipation (*e.g.*, chronic constipation, constipation associated with IBS, constipation associated with use of medications such as opioids, osteoarthritis drugs, osteoporosis drugs; post surgical

10 constipation, constipation associated with neuropathic disorders). Inflammatory disorders include tissue and organ inflammation such as kidney inflammation (*e.g.*, nephritis), gastrointestinal system inflammation (*e.g.*, Crohn's disease and ulcerative colitis), IBD, necrotizing enterocolitis (NEC); pancreatic inflammation (*e.g.*, pancreatitis), lung inflammation (*e.g.*, bronchitis or asthma) or skin inflammation (*e.g.*, psoriasis, eczema). Lung Disorders include for example chronic

15 obstructive pulmonary disease (COPD), and fibrosis. Cancer includes tissue and organ carcinogenesis including metastases such as for example gastrointestinal cancer (*e.g.*, gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer); lung cancer; thyroid cancer; skin cancer (*e.g.*, melanoma); oral cancer; urinary tract cancer (*e.g.* bladder cancer or kidney cancer); blood cancer

20 (*e.g.* myeloma or leukemia) or prostate cancer. Cardiac disorders include for example, congestive heart failure, trachea cardia hypertension, high cholesterol, or high tryglycerides. Cardiovascular disorders include for example aneurysm, angina, atherosclerosis, cerebrovascular accident (stroke), cerebrovasculardisease, congestive heart failure, coronary artery disease, myocardial infarction (heart attack), or peripheral vascular disease. Liver disorders include for

25 example cirrhosis and fibrosis. In addition, Aa derivatives of GC-C agonist described herein may also be useful to facilitate liver regeneration in liver transplant patients. Eye disorders include for example increased intra-ocular pressure, glaucoma, dry eyes retinal degeneration, disorders of tear glands or eye inflammation. Skin disorders include for example xerosis. Oral disorders include for example dry mouth (xerostomia), Sjögren's syndrome, gum diseases (*e.g.*,

30 periodontal disease), or salivary gland duct blockage or malfunction. Prostate disorders include

for example benign prostatic hyperplasia (BPH). Endocrine disorders include for example diabetes mellitus, hyperthyroidism, hypothyroidism, and cystic fibrosis.

The term “treatment” refers to reducing or alleviating symptoms in a subject, preventing symptoms from worsening or progressing, and/or preventing disease in a subject who is free
5 therefrom. For a given subject, improvement in a symptom, its worsening, regression, or progression may be determined by any objective or subjective measure. Efficacy of the treatment may be measured as an improvement in morbidity or mortality (*e.g.*, lengthening of survival curve for a selected population). Thus, effective treatment would include therapy of
10 existing disease, control of disease by slowing or stopping its progression, prevention of disease occurrence, reduction in the number or severity of symptoms, or a combination thereof. The effect may be shown in a controlled study using one or more statistically significant criteria.

Intracellular cGMP is produced by exposing, *e.g.*, contacting a tissue (*e.g.*,
gastrointestinals tissue) or cell with Aad-GCRA peptides. By inducing is meant an increase in
cGMP production compared to a tissue or cell that has not been in contact with Aad-GCRA
15 peptide or variant. Tissues or cells are directly contacted with an Aad-GCRA peptide or variant. Alternatively, the Aad-GCRA peptide or variant is administered systemically. Aad-GCRA peptides or variants are administered in an amount sufficient to increase intracellular cGMP concentration. cGMP production is measured by a cell-based assay known in the art (25).

Disorders are treated, prevented or alleviated by administering to a subject, *e.g.*, a
20 mammal such as a human in need thereof, a therapeutically effective dose of any Aad-GCRA peptide described herein.

The Aad-GCRA peptides may be in a pharmaceutical composition in unit dose form, together with one or more pharmaceutically acceptable excipients. The term “unit dose form” refers to a single drug delivery entity, *e.g.*, a tablet, capsule, solution or inhalation formulation.
25 The amount of peptide present should be sufficient to have a positive therapeutic effect when administered to a patient (typically, between 10 µg and 3 g). What constitutes a “positive therapeutic effect” will depend upon the particular condition being treated and will include any significant improvement in a condition readily recognized by one of skill in the art.

The present invention also provides a method of colonic cleansing by administering to a
30 subject in need thereof an effective amount of any compositions of the present invention, for example an Aad-GCRA peptide described herein.

This method can be used in cleansing or purging the bowels or colon prior to carrying out a diagnostic, therapeutic or surgical procedure on the colon, rectum or anus or elsewhere in the abdomen. The diagnostic or surgical procedure may, for example, be sigmoidoscopy, colonoscopy, radiographic examination, preparation for patients undergoing bowel surgery, and other medical or diagnostic procedures. It has been believed that profuse, uncontrolled diarrhea was necessary to produce adequate cleansing of the colon. This present invention provides a safe and effective cleansing method for the bowels and colon, without the ingestion of large volumes of lavage solutions, without the unpleasant, bitter, and dangerous hypertonic salt solutions, thus providing an improved patients compliance.

"Subject", as used herein, means an individual. In one aspect, the subject is a mammal such as a primate, and, in another aspect, the subject is a human. The term "subject" also includes domesticated animals (e.g., cats, dogs, etc.), and livestock (e.g., cattle, horses, pigs, sheep, goats, etc.). The subject may be at risk of (or susceptible to) developing a disorder that is mediated by guanylate cyclase receptor agonists or may have a disorder that is mediated by guanylate cyclase receptor agonists. The subject may be a human over 50 years old.

Preferably, the Aad-GCRA peptide used for any methods described herein is Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Leu¹⁶ (SEQ ID NO: 1), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Ser¹⁶ (SEQ ID NO: 32), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Thr¹⁶ (SEQ ID NO: 119), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Tyr¹⁶ (SEQ ID NO: 120), dAsn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-dLeu¹⁶ (SEQ ID NO: 17), or pyGlu¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Leu¹⁶ (SEQ ID NO: 56).

The Aad-GCRA peptides can be administered alone or in combination with other agents. For example the Aad-GCRA peptides can be administered in combination with inhibitors of cGMP dependent phosphodiesterase, such as, for example, sulindac sulfone, zaprinast, motapizone, vardenafil, and sildenafil; one or more other chemotherapeutic agents; or anti-inflammatory drugs such as, for example, steroids or non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin.

The Aad-GCRA peptides described herein can be administered with one or more other agents, for example, L-glucose, cholera toxin, osmotic colonic evacuants, cathartic, laxatives and agents for treating chronic constipation, or any combination thereof, for cleansing or purging the bowels or colon prior to carrying out a diagnostic, therapeutic or surgical procedure on the colon, rectum or anus or elsewhere in the abdomen. In some embodiments, the compositions (*e.g.*, Aad-GCRA peptides) or the formulations described herein can be administered with L-glucose.

Combination therapy can be achieved by administering two or more agents, *e.g.*, an Aad-GCRA peptide described herein and another compound, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

The Aad-GCRA peptides described herein may be combined with cGMP-dependent phosphodiesterase inhibitors, *e.g.*, sulindac sulfone, zaprinast, motapizone, vardenafil, and sildenafil to further enhance levels of cGMP in the target tissues or organs.

Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, *e.g.*, in the order X-Y- X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

Combination therapy can also include the administration of one of the Aad-GCRA peptides with azothioprine and/or other immunomodulating agents. The immunomodulating agents may include small molecule drugs and biologics such as Remicade, Humaira, Cimzia etc.

Combination therapy can also include the administration of two or more agents via different routes or locations. For example, (a) one agent is administered orally and another agent is administered intravenously or (b) one agent is administered orally and another is administered locally. In each case, the agents can either simultaneously or sequentially. Approximate dosages for some of the combination therapy agents described herein are found in the "BNF Recommended Dose" column of tables on pages 11-17 of WO01/76632 (the data in the tables being attributed to the March 2000 British National Formulary) and can also be found in other standard formularies and other drug prescribing directories. For some drugs, the customary prescribed dose for an indication will vary somewhat from country to country.

The Aad-GCRA peptides, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, and one or more inert excipients (which include starches, polyols, granulating agents, microcrystalline cellulose (*e.g.* celphere, Celphere beads®), diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of

sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, an Aad-GCRA peptide) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization.

Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. Such as mannitol, fructooligosaccharides, polyethylene glycol and other excipients. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and

expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or
5 lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol
10 spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for
15 example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional
20 suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid,
25 collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to
30 those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811, incorporated fully herein by reference.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired
5 therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

10 Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, glidants, anti-adherents, anti-static agents, surfactants (wetting agents), anti-oxidants, film-coating agents, and the like. Any such optional ingredient must be compatible with the compound described herein to insure the stability of the formulation.

15 The composition may contain other additives as needed, including for example lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and betaine, and polypeptides and proteins, for example albumen.

20 Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, and coating agents such as: BINDERS: corn starch, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, xanthan, sodium alginate, alginic acid, other alginates, powdered
25 tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone (*e.g.*, povidone, crospovidone, copovidone, etc), methyl cellulose, Methocel, pre-gelatinized starch (*e.g.*, STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, microcrystalline cellulose (FMC Corporation, Marcus Hook, PA, USA), or
30 mixtures thereof, FILLERS: talc, calcium carbonate (*e.g.*, granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (*e.g.*, granules or powder),

microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, dextrose, fructose, honey, lactose anhydrate, lactose monohydrate, lactose and aspartame, lactose and cellulose, lactose and microcrystalline cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose & guar gum, molasses, sucrose, or mixtures thereof, DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other alginates, other celluloses, gums (like gellan), low-substituted hydroxypropyl cellulose, or mixtures thereof, LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, sodium stearyl fumarate, vegetable based fatty acids lubricant, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Deaussa Co., Plano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof, ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof, ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures thereof, and COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, gellan gum, maltodextrin, methacrylates, microcrystalline cellulose and carrageenan or mixtures thereof.

The formulation can also include other excipients and categories thereof including but not limited to L-histidine, Pluronic®, Poloxamers (such as Lutrol® and Poloxamer 188), ascorbic acid, glutathione, permeability enhancers (*e.g.* lipids, sodium cholate, acylcarnitine, salicylates, mixed bile salts, fatty acid micelles, chelators, fatty acid, surfactants, medium chain glycerides),

protease inhibitors (*e.g.* soybean trypsin inhibitor, organic acids), pH lowering agents and absorption enhancers effective to promote bioavailability (including but not limited to those described in US6086918 and US5912014), creams and lotions (like maltodextrin and carrageenans); materials for chewable tablets (like dextrose, fructose, lactose monohydrate, lactose and aspartame, lactose and cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose and guar gum, sorbitol crystalline); parenterals (like mannitol and povidone); plasticizers (like dibutyl sebacate, plasticizers for coatings, polyvinylacetate phthalate); powder lubricants (like glyceryl behenate); soft gelatin capsules (like sorbitol special solution); spheres for coating (like sugar spheres); spheronization agents (like glyceryl behenate and microcrystalline cellulose); suspending/gelling agents (like carrageenan, gellan gum, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, xanthan gum); sweeteners (like aspartame, aspartame and lactose, dextrose, fructose, honey, maltodextrin, maltose, mannitol, molasses, sorbitol crystalline, sorbitol special solution, sucrose); wet granulation agents (like calcium carbonate, lactose anhydrous, lactose monohydrate, maltodextrin, mannitol, microcrystalline cellulose, povidone, starch), caramel, carboxymethylcellulose sodium, cherry cream flavor and cherry flavor, citric acid anhydrous, citric acid, confectioner's sugar, D&C Red No. 33, D&C Yellow #10 Aluminum Lake, disodium edetate, ethyl alcohol 15%, FD&C Yellow No. 6 aluminum lake, FD&C Blue # 1 Aluminum Lake, FD&C Blue No. 1, FD&C blue no. 2 aluminum lake, FD&C Green No.3, FD&C Red No. 40, FD&C Yellow No. 6 Aluminum Lake, FD&C Yellow No. 6, FD&C Yellow No.10, glycerol palmitostearate, glyceryl monostearate, indigo carmine, lecithin, manitol, methyl and propyl parabens, mono ammonium glycyrrhizinate, natural and artificial orange flavor, pharmaceutical glaze, poloxamer 188, Polydextrose, polysorbate 20, polysorbate 80, polyvidone, pregelatinized corn starch, pregelatinized starch, red iron oxide, saccharin sodium, sodium carboxymethyl ether, sodium chloride, sodium citrate, sodium phosphate, strawberry flavor, synthetic black iron oxide, synthetic red iron oxide, titanium dioxide, and white wax.

Solid oral dosage forms may optionally be treated with coating systems (*e.g.* Opadry® fx film coating system, for example Opadry® blue (OY-LS-20921), Opadry® white (YS-2-7063), Opadry® white (YS- 1-7040), and black ink (S- 1-8 106).

The agents either in their free form or as a salt can be combined with a polymer such as polylactic-glycolic acid (PLGA), poly-(l)-lactic-glycolic-tartaric acid (P(l)LGT) (WO

01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628), poly(ϵ -caprolactone) and poly(alkylene oxide) (U.S. 20030068384) to create a sustained release formulation. Such formulations can be used to implants that release a polypeptide or another agent over a period of a few days, a few weeks or several months depending on the polymer, the particle size of the polymer, and the size of the implant (*See, e.g.*, U.S. 6,620,422). Other sustained release formulations and polymers for use in are described in EP 0 467 389 A2, WO 93/24150, U.S. 5,612,052, WO 97/40085, WO 03/075887, WO 01/01964A2, U.S. 5,922,356, WO 94/155587, WO 02/074247A2, WO 98/25642, U.S. 5,968,895, U.S. 6,180,608, U.S. 20030171296, U.S. 20020176841, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, U.S. 4,668,506, U.S. 4,713,244, U.S. 5,445,832 U.S. 4,931,279, U.S. 5,980,945, WO 02/058672, WO 97/26015, WO 97/04744, and US20020019446. In such sustained release formulations microparticles (Delie and Blanco-Prieto 2005 Molecule 10:65-80) of polypeptide are combined with microparticles of polymer. One or more sustained release implants can be placed in the large intestine, the small intestine or both. U.S. 6,011,011 and WO 94/06452 describe a sustained release formulation providing either polyethylene glycols (*i.e.* PEG 300 and PEG 400) or triacetin. WO 03/053401 describes a formulation which may both enhance bioavailability and provide controlled release of the agent within the GI tract. Additional controlled release formulations are described in WO 02/38129, EP 326151, U.S. 5,236,704, WO 02/30398, WO 98/13029; U.S. 20030064105, U.S. 20030138488A1, U.S. 20030216307A1, U.S. 6,667,060, WO 01/49249, WO 01/49311, WO 01/49249, WO 01/49311, and U.S. 5,877,224 materials which may include those described in WO04041195 (including the seal and enteric coating described therein) and pH-sensitive coatings that achieve delivery in the colon including those described in US4,910,021 and WO9001329. US4910021 describes using a pH-sensitive material to coat a capsule. WO9001329 describes using pH-sensitive coatings on beads containing acid, where the acid in the bead core prolongs dissolution of the pH-sensitive coating. U. S. Patent No. 5,175,003 discloses a dual mechanism polymer mixture composed of pH-sensitive enteric materials and film-forming plasticizers capable of conferring permeability to the enteric material, for use in drug-delivery systems; a matrix pellet composed of a dual mechanism polymer mixture permeated with a drug and sometimes covering a pharmaceutically neutral nucleus; a membrane- coated pellet comprising a matrix pellet coated with a dual mechanism polymer mixture envelope of the same or different composition; and a

pharmaceutical dosage form containing matrix pellets. The matrix pellet releases acid-soluble drugs by diffusion in acid pH and by disintegration at pH levels of nominally about 5.0 or higher.

The Aad-GCRA peptides described herein may be formulated in the pH triggered targeted control release systems described in WO04052339. The agents described herein may be formulated according to the methodology described in any of WO03105812 (extruded hydratable polymers); WO0243767 (enzyme cleavable membrane translocators); WO03007913 and WO03086297 (mucoadhesive systems); WO02072075 (bilayer laminated formulation comprising pH lowering agent and absorption enhancer); WO04064769 (amidated polypeptides); WO05063156 (solid lipid suspension with pseudotropic and/or thixotropic properties upon melting); WO03035029 and WO03035041 (erodible, gastric retentive dosage forms); US5007790 and US5972389 (sustained release dosage forms); WO041 1271 1 (oral extended release compositions); WO05027878, WO02072033, and WO02072034 (delayed release compositions with natural or synthetic gum); WO05030182 (controlled release formulations with an ascending rate of release); WO05048998 (microencapsulation system); US Patent 5,952,314 (biopolymer); US5,108,758 (glassy amylose matrix delivery); US 5,840,860 (modified starch based delivery). JP10324642 (delivery system comprising chitosan and gastric resistant material such as wheat gliadin or zein); US 5,866,619 and US 6,368,629 (saccharide containing polymer); US 6,531,152 (describes a drug delivery system containing a water soluble core (Ca pectinate or other water-insoluble polymers) and outer coat which bursts (*e.g.* hydrophobic polymer-Eudragit)); US 6,234,464; US 6,403,130 (coating with polymer containing casein and high methoxy pectin; WO0174 175 (Maillard reaction product); WO05063206 (solubility increasing formulation); WO040 19872 (transferring fusion proteins).

The Aad-GCRA peptides described herein may be formulated using gastrointestinal retention system technology (GIRES; Merrion Pharmaceuticals). GIRES comprises a controlled-release dosage form inside an inflatable pouch, which is placed in a drug capsule for oral administration. Upon dissolution of the capsule, a gas-generating system inflates the pouch in the stomach where it is retained for 16-24 hours, all the time releasing agents described herein.

The Aad-GCRA peptides described herein can be formulated in an osmotic device including the ones disclosed in US4,503,030, US5,609,590 and US5,358,502. US4,503,030 discloses an osmotic device for dispensing a drug to certain pH regions of the gastrointestinal tract. More particularly, the invention relates to an osmotic device comprising a wall formed of a

semi-permeable pH sensitive composition that surrounds a compartment containing a drug, with a passageway through the wall connecting the exterior of the device with the compartment. The device delivers the drug at a controlled rate in the region of the gastrointestinal tract having a pH of less than 3.5, and the device self- destructs and releases all its drug in the region of the gastrointestinal tract having a pH greater than 3.5, thereby providing total availability for drug absorption. U.S. Patent Nos. 5,609,590 and 5, 358,502 disclose an osmotic bursting device for dispensing a beneficial agent to an aqueous environment. The device comprises a beneficial agent and osmagent surrounded at least in part by a semi-permeable membrane. The beneficial agent may also function as the osmagent. The semi-permeable membrane is permeable to water and substantially impermeable to the beneficial agent and osmagent. A trigger means is attached to the semi-permeable membrane (*e.g.*, joins two capsule halves). The trigger means is activated by a pH of from 3 to 9 and triggers the eventual, but sudden, delivery of the beneficial agent. These devices enable the pH-triggered release of the beneficial agent core as a bolus by osmotic bursting.

EXEMPLARY AGENTS FOR COMBINATION THERAPY

Analgesic Agents

The Aad-GCRA peptides described herein can be used in combination therapy with an analgesic agent, *e.g.*, an analgesic compound or an analgesic polypeptide. These polypeptides and compounds can be administered with the Aad-GCRA peptides described herein (simultaneously or sequentially). They can also be optionally covalently linked or attached to an agent described herein to create therapeutic conjugates. Among the useful analgesic agents are: Calcium channel blockers, 5HT receptor antagonists (for example 5HT3, 5HT4 and 5HT1 receptor antagonists), opioid receptor agonists (loperamide, fedotozine, and fentanyl), NK1 receptor antagonists, CCK receptor agonists (*e.g.*, loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists, norepinephrine-serotonin reuptake inhibitors (NSRI), vanilloid and cannabinoid receptor agonists, and sialorphin. Analgesics agents in the various classes are described in the literature.

Among the useful analgesic polypeptides are sialorphin-related polypeptides, including those comprising the amino acid sequence QHNPR (SEQ ID NO: 95), including: VQHNPR (SEQ ID NO: 96); VRQHNPR (SEQ ID NO: 97); VRGQHNPR (SEQ ID NO: 98);

VRGPQHNPR (SEQ ID NO: 99); VRGPRQHNPR (SEQ ID NO: 100); VRGPRRQHNPR (SEQ ID NO: 101); and RQHNPR (SEQ ID NO: 102). Sialorphin-related polypeptides bind to neprilysin and inhibit neprilysin-mediated breakdown of substance P and Met-enkephalin. Thus, compounds or polypeptides that are inhibitors of neprilysin are useful analgesic agents which can be administered with the polypeptides described herein in a co-therapy or linked to the polypeptides described herein, *e.g.*, by a covalent bond. Sialorphin and related polypeptides are described in U.S. Patent 6,589,750; U.S. 20030078200 A1; and WO 02/051435 A2.

Opioid receptor antagonists and agonists can be administered with the GCRA peptides described herein in co-therapy or linked to the agent described herein, *e.g.*, by a covalent bond. For example, opioid receptor antagonists such as naloxone, naltrexone, methyl naloxone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine are thought to be useful in the treatment of IBS. It can be useful to formulate opioid antagonists of this type is a delayed and sustained release formulation such that initial release of the antagonist is in the mid to distal small intestine and/or ascending colon. Such antagonists are described in WO 01/32180 A2. Enkephalin pentapeptide (HOE825; Tyr-D-Lys-Gly-Phe-L-homoserine) (SEQ ID NO: 103) is an agonist of the mu and delta opioid receptors and is thought to be useful for increasing intestinal motility {Eur. J. Pharm. 219:445, 1992}, and this polypeptide can be used in conjunction with the polypeptides described herein. Also useful is trimebutine which is thought to bind to mu/delta/kappa opioid receptors and activate release of motilin and modulate the release of gastrin, vasoactive intestinal polypeptide, gastrin and glucagons. Kappa opioid receptor agonists such as fedotozine, asimadoline, and ketocyclazocine, and compounds described in WO03/097051 and WO05/007626 can be used with or linked to the polypeptides described herein. In addition, mu opioid receptor agonists such as morphine, diphenyloxyate, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH₂ (SEQ ID NO: 104); WO 01/019849 A1) and loperamide can be used.

Tyr-Arg (kyotorphin) is a dipeptide that acts by stimulating the release of met-enkephalins to elicit an analgesic effect (J. Biol. Chem 262:8165, 1987). Kyotorphin can be used with or linked to the Aad-GCRA peptides described herein.

Chromogranin-derived polypeptide (CgA 47-66; *See, e.g.*, Ghia et al. 2004 Regulatory polypeptides 119:199) can be used with or linked to the Aad-GCRA peptides described herein.

CCK receptor agonists such as caerulein from amphibians and other species are useful analgesic agents that can be used with or linked to the Aad-GCRA peptides described herein.

Conotoxin polypeptides represent a large class of analgesic polypeptides that act at voltage gated calcium channels, NMDA receptors or nicotinic receptors. These polypeptides can be used with or linked to the polypeptides described herein.

Peptide analogs of thymulin (FR Application 2830451) can have analgesic activity and can be used with or linked to the polypeptides described herein.

CCK (CCKa or CCKb) receptor antagonists, including loxiglumide and dexloxiglumide (the R- isomer of loxiglumide) (WO 88/05774) can have analgesic activity and can be used with or linked to the polypeptides described herein.

Other useful analgesic agents include 5-HT4 agonists such as tegaserod (Zelnorm®), mosapride, metoclopramide, zacopride, cisapride, renzapride, benzimidazolone derivatives such as BIMU 1 and BIMU 8, and lorexapride. Such agonists are described in: EP1321 142 A1, WO 03/053432A1, EP 505322 A1, EP 505322 B1, US 5,510,353, EP 507672 A1, EP 507672 B1, and US 5,273,983.

Calcium channel blockers such as ziconotide and related compounds described in, for example, EP625162B1, US 5,364,842, US 5,587,454, US 5,824,645, US 5,859,186, US 5,994,305, US 6,087,091, US 6,136,786, WO 93/13128 A1, EP 1336409 A1, EP 835126 A1, EP 835126 B1, US 5,795,864, US 5,891,849, US 6,054,429, WO 97/01351 A1, can be used with or linked to the polypeptides described herein.

Various antagonists of the NK-1, NK-2, and NK-3 receptors (for a review see Giardina et al. 2003. Drugs 6:758) can be used with or linked to the polypeptides described herein.

NK1 receptor antagonists such as: aprepitant (Merck & Co Inc), vofopitant, ezlopitant (Pfizer, Inc.), R-673 (Hoffmann-La Roche Ltd), SR-48968 (Sanofi Synthelabo), CP-122,721 (Pfizer, Inc.), GW679769 (Glaxo Smith Kline), TAK-637 (Takeda/Abbot), SR-14033, and related compounds described in, for example, EP 873753 A1, US 20010006972 A1, US 20030109417 A1, WO 01/52844 A1, can be used with or linked to the polypeptides described herein.

NK-2 receptor antagonists such as nepadutant (Menarini Ricerche SpA), saredutant (Sanofi- Synthelabo), GW597599 (Glaxo Smith Kline), SR-144190 (Sanofi-Synthelabo) and UK-290795 (Pfizer Inc) can be used with or linked to the polypeptides described herein.

NK3 receptor antagonists such as osanetant (SR-142801; Sanofi-Synthelabo), SSR-241586, talnetant and related compounds described in, for example, WO 02/094187 A2, EP 876347 A1, WO 97/21680 A1, US 6,277,862, WO 98/1 1090, WO 95/28418, WO 97/19927, and Boden et al. (J Med Chem. 39:1664-75, 1996) can be used with or linked to the polypeptides described herein.

Norepinephrine-serotonin reuptake inhibitors (NSRI) such as milnacipran and related compounds described in WO 03/077897 A1 can be used with or linked to the polypeptides described herein.

Vanilloid receptor antagonists such as arvanil and related compounds described in WO 01/64212 A1 can be used with or linked to the polypeptides described herein.

The analgesic polypeptides and compounds can be administered with the polypeptides and agonists described herein (simultaneously or sequentially). The analgesic agents can also be covalently linked to the polypeptides and agonists described herein to create therapeutic conjugates. Where the analgesic is a polypeptide and is covalently linked to an agent described herein the resulting polypeptide may also include at least one trypsin cleavage site. When present within the polypeptide, the analgesic polypeptide may be preceded by (if it is at the carboxy terminus) or followed by (if it is at the amino terminus) a trypsin cleavage site that allows release of the analgesic polypeptide.

In addition to sialorphin-related polypeptides, analgesic polypeptides include: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, ziconotide, and substance P.

Agents to Treat Gastrointestinal Disorders

Examples of additional therapeutic agents to treat gastrointestinal and other disorders include agents to treat constipation (e.g., a chloride channel activator such as the bicyclic fatty acid, Lubiprostone (formerly known as SPI-0211; Sucampo Pharmaceuticals, Inc.; Bethesda, MD), a laxative (e.g. a bulk-forming laxative (e.g. nonstarch polysaccharides, Colonel Tablet (polycarbophil calcium), Plantago Ovata®, Equalactin® (Calcium Polycarbophil)), fiber (e.g. FIBERCON® (Calcium Polycarbophil), an osmotic laxative, a stimulant laxative (such as diphenylmethanes (e.g. bisacodyl), anthraquinones (e.g. cascara, senna), and surfactant laxatives (e.g. castor oil, docusates), an emollient/lubricating agent (such as mineral oil, glycerine, and docusates), MiraLax (Braintree Laboratories, Braintree MA), dexloxiglumide (Forest Laboratories, also known as CR 2017 Rottapharm (Rotta Research Laboratorium SpA)), saline

laxatives, enemas, suppositories, and CR 3700 (Rottapharm (Rotta Research Laboratorium SpA); acid reducing agents such as proton pump inhibitors (*e.g.*, omeprazole (Prilosec®), esomeprazole (Nexium®), lansoprazole (Prevacid®), pantoprazole (Protonix®) and rabeprazole (Aciphex®)) and Histamine H₂ -receptor antagonist (also known as H₂ receptor blockers including

5 cimetidine, ranitidine, famotidine and nizatidine); prokinetic agents including itopride, octreotide, bethanechol, metoclopramide (Reglan®), domperidone (Motilium®), erythromycin (and derivatives thereof) or cisapride (propulsid®); Prokineticin polypeptides homologs, variants and chimeras thereof including those described in US 7,052,674 which can be used with or linked to the polypeptides described herein; pro-motility agents such as the vasostatin-derived

10 polypeptide, chromogranin A (4-16) (*See, e.g.*, Ghia et al. 2004 Regulatory polypeptides 121:31) or motilin agonists (*e.g.*, GM-611 or mitemincinal fumarate) or nociceptin/Orphanin FQ receptor modulators (US20050169917); other peptides which can bind to and/or activate GC-C including those described in US20050287067; complete or partial 5HT (*e.g.* 5HT₁, 5HT₂, 5HT₃, 5HT₄) receptor agonists or antagonists (including 5HT_{1A} antagonists (*e.g.* AGI-001 (AGI

15 therapeutics), 5HT_{2B} antagonists (*e.g.* PGN 1091 and PGN1 164 (Pharmagene Laboratories Limited), and 5HT₄ receptor agonists (such as tegaserod (ZELNORM®), prucalopride, mosapride, metoclopramide, zacopride, cisapride, renzapride, benzimidazolone derivatives such as BIMU 1 and BIMU 8, and lirenzapride). Such agonists/modulators are described in: EP1321142 A1, WO 03/053432A1, EP 505322 A1, EP 505322 B1, US 5,510,353, EP 507672 A1,

20 EP 507672 B1, US 5,273,983, and US 6,951,867); 5HT₃ receptor agonists such as MKC-733; and 5HT₃ receptor antagonists such as DDP-225 (MCI-225; Dynogen Pharmaceuticals, Inc.), cilansetron (Calmactin®), alosetron (Lotronex®), Ondansetron HCl (Zofran®), Dolasetron (ANZEMET®), palonosetron (Aloxi®), Granisetron (Kytril®), YM060(ramosetron; Astellas Pharma Inc.; ramosetron may be given as a daily dose of 0.002 to 0.02 mg as described in

25 EP01588707) and ATI-7000 (Aryx Therapeutics, Santa Clara CA); muscarinic receptor agonists; anti-inflammatory agents; antispasmodics including but not limited to anticholinergic drugs (like dicyclomine (*e.g.* Colimex®, Formulex®, Lomine®, Protylol®, Visceral®, Spasmoban®, Bentyl®, Bentytol®), hyoscyamine (*e.g.* IB-Stat®, Nulev®, Levsin®, Levbid®, Levsinex Timecaps®, Levsin/SL®, Anaspaz®, A-Spas S/L®, Cystospaz®, Cystospaz-M®, Donnamar®,

30 Colidrops Liquid Pediatric®, Gastrosed®, Hyco Elixir®, Hyosol®, Hyospaz®, Hyosyne®, Losamine®, Medispaz®, Neosol®, Spacol®, Spasdel®, Symax®, Symax SL®), Donnatal (*e.g.*

Donnatal Extentabs®), clidinium (*e.g.* Quarzan, in combination with Librium = Librax), methantheline (*e.g.* Banthine), Mepenzolate (*e.g.* Cantil), homatropine (*e.g.* hycodan, Homapin), Propantheline bromide (*e.g.* Pro-Banthine), Glycopyrrolate (*e.g.* Robinul®, Robinul Forte®), scopolamine (*e.g.* Transderm-Scop®, Transderm-V®), hyosine-N-butylbromide (*e.g.* Buscopan®), Pirenzepine (*e.g.* Gastrozepin®) Propantheline Bromide (*e.g.* Propanthel®), dicycloverine (*e.g.* Merbentyl®), glycopyrronium bromide (*e.g.* Glycopyrrolate®), hyoscine hydrobromide, hyoscine methobromide, methanthelinium, and octatropine); peppermint oil; and direct smooth muscle relaxants like cimetropium bromide, mebeverine (DUSPATAL®, DUSPATALIN®, COLOFAC MR®, COLOTAL®), otilonium bromide (octilonium), pinaverium (*e.g.* Dicitel® (pinaverium bromide; Solvay S. A.)), Spasfon® (hydrated phloroglucinol and trimethylphloroglucinol) and trimebutine (including trimebutine maleate (Modulon®); antidepressants, including but not limited to those listed herein, as well as tricyclic antidepressants like amitriptyline (Elavil®), desipramine (Norpramin®), imipramine (Tofranil®), amoxapine (Asendin®), nortriptyline; the selective serotonin reuptake inhibitors (SSRTs) like paroxetine (Paxil®), fluoxetine (Prozac®), sertraline (Zoloft®), and citalopram (Celexa®); and others like doxepin (Sinequan®) and trazodone (Desyrel®); centrally-acting analgesic agents such as opioid receptor agonists, opioid receptor antagonists (*e.g.*, naltrexone); agents for the treatment of Inflammatory bowel disease; agents for the treatment of Crohn's disease and/or ulcerative colitis (*e.g.*, alequel (Enzo Biochem, Inc.; Farmingsale, NY), the anti-inflammatory polypeptide RDP58 (Genzyme, Inc.; Cambridge, MA), and TRAFICET-EN™ (ChemoCentryx, Inc.; San Carlos, CA); agents that treat gastrointestinal or visceral pain; agents that increase cGMP levels (as described in US20040121994) like adrenergic receptor antagonists, dopamine receptor agonists and PDE (phosphodiesterase) inhibitors including but not limited to those disclosed herein; purgatives that draw fluids to the intestine (*e.g.*, VISICOL®, a combination of sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrate); Corticotropin Releasing Factor (CRF) receptor antagonists (including NBI-34041 (Neurocrine Biosciences, San Diego, CA), CRH9-41, astressin, R121919 (Janssen Pharmaceutica), CP154,526, NBI-27914, Antalarmin, DMP696 (Bristol-Myers Squibb) CP-316,311 (Pfizer, Inc.), SB723620 (GSK), GW876008 (Neurocrine/Glaxo Smith Kline), ONO-2333Ms (Ono Pharmaceuticals), TS-041 (Janssen), AAG561 (Novartis) and those disclosed in US 5,063,245, US 5,861,398, US20040224964, US20040198726, US20040176400,

US20040171607, US20040110815, US20040006066, and US20050209253); glucagon- like polypeptides (glp-1) and analogues thereof (including exendin-4 and GTP-010 (Gastrotech Pharma A)) and inhibitors of DPP-IV (DPP-IV mediates the inactivation of glp-1); tofisopam, enantiomerically-pure R-tofisopam, and pharmaceutically-acceptable salts thereof (US 20040229867); tricyclic anti-depressants of the dibenzothiazepine type including but not limited to Dextofisopam® (Vela Pharmaceuticals), tianeptine (Stablon®) and other agents described in US 6,683,072; (E)-4 (1,3bis(cyclohexylmethyl)-1,2,3,4,-tetrahydro-2,6-dione-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester and related compounds described in WO 02/067942; the probiotic PROBACTRIX® (The BioBalance Corporation; New York, NY) which contains microorganisms useful in the treatment of gastrointestinal disorders; antidiarrheal drugs including but not limited to loperamide (Imodium, Pepto Diarrhea), diphenoxylate with atropine (Lomotil, Lomocot), cholestyramine (Questran, Cholybar), atropine (Co-Phenotrope, Diarsed, Diphenoxylate, Lofene, Logen, Lonox, Vi-Atro, atropine sulfate injection) and Xifaxan® (rifaximin; Salix Pharmaceuticals Ltd), TZP-201(Tranzyme Pharma Inc.), the neuronal acetylcholine receptor (nAChR) blocker AGI-004 (AGI therapeutics), and bismuth subsalicylate (Pepto-bismol); anxiolytic drugs including but not limited to Ativan (lorazepam), alprazolam (Xanax®), chlordiazepoxide/clidinium (Librium®, Librax®), clonazepam (Klonopin®), clorazepate (Tranxene®), diazepam (Valium®), estazolam (ProSom®), flurazepam (Dalmane®), oxazepam (Serax®), prazepam (Centrax®), temazepam (Restoril®), triazolam (Halcion®; Bedelix® (Montmorillonite beidellitic; Ipsen Ltd), Solvay SLV332 (ArQuIe Inc), YKP (SK Pharma), Asimadoline (Tioga Pharmaceuticals/Merck), AGI-003 (AGI Therapeutics); neurokinin antagonists including those described in US20060040950; potassium channel modulators including those described in US7,002,015; the serotonin modulator AZD7371 (AstraZeneca Plc); M3 muscarinic receptor antagonists such as darifenacin (Enablex; Novartis AG and zamifenacin (Pfizer); herbal and natural therapies including but not limited to acidophilus, chamomile tea, evening primrose oil, fennel seeds, wormwood, comfrey, and compounds of Bao-Ji-Wan (magnolol, honokiol, imperatorin, and isoimperatorin) as in US6923992; and compositions comprising lysine and an anti-stress agent for the treatment of irritable bowel syndrome as described in EPO 1550443.

Insulin and Insulin Modulating Agents

The Aad-GCRA peptides described herein can be used in combination therapy with insulin and related compounds including primate, rodent, or rabbit insulin including biologically active variants thereof including allelic variants, more preferably human insulin available in recombinant form. Sources of human insulin include pharmaceutically acceptable and sterile
 5 formulations such as those available from Eli Lilly (Indianapolis, Ind. 46285) as Humulin™ (human insulin rDNA origin). See, the THE PHYSICIAN'S DESK REFERENCE, 55^{sup}.th Ed. (2001) Medical Economics, Thomson Healthcare (disclosing other suitable human insulins).

The Aad-GCRA peptides described herein can also be used in combination therapy with agents that can boost insulin effects or levels of a subject upon administration, e.g. glipizide
 10 and/or rosiglitazone. The polypeptides and agonists described herein can be used in combitherapy with SYMLIN® (pramlintide acetate) and Exenatide® (synthetic exendin-4; a 39 aa polypeptide).

Agents for the Treatment of Postoperative Ileus

The Aad-GCRA peptides described herein can also be used in combination therapy with
 15 agents (e.g., Entereg™ (alvimopan; formerly called ado lor/ ADL 8-2698), conivaptan and related agents describe in US 6,645,959) used for the treatment of postoperative ileus and other disorders.

Anti-Hypertensive Agents

The Aad-GCRA peptides described herein can be used in combination therapy with an
 20 anti-hypertensive agent including but not limited to: (1) diuretics, such as thiazides, including chlorthalidone, chlorthiazide, dichlorophenamide, hydroflumethiazide, indapamide, polythiazide, and hydrochlorothiazide; loop diuretics, such as bumetanide, ethacrynic acid, furosemide, and torsemide; potassium sparing agents, such as amiloride, and triamterene; carbonic anhydrase inhibitors, osmotics (such as glycerin) and aldosterone antagonists, such as spironolactone,
 25 epirenone, and the like; (2) beta-adrenergic blockers such as acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, indenolol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propanolol, sotalol, tertatolol, tilisolol, and timolol, and the like; (3) calcium channel blockers such as amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, diltiazem, efonidipine, felodipine,
 30 gallopamil, isradipine, lacidipine, lemdipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, manidipine, pranidipine, and verapamil, and the like; (4)

angiotensin converting enzyme (ACE) inhibitors such as benazepril; captopril; ceranapril; cilazapril; delapril; enalapril; enalapril; fosinopril; imidapril; lisinopril; losinopril; moexipril; quinapril; quinaprilat; ramipril; perindopril; perindopril; quanipril; spirapril; tenocapril; trandolapril, and zofenopril, and the like; (5) neutral endopeptidase inhibitors such as

5 omapatrilat, cadoxatril and ecadotril, fosidotril, sampatrilat, AVE7688, ER4030, and the like; (6) endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; (7) vasodilators such as hydralazine, clonidine, minoxidil, and nicotiny alcohol, and the like; (8) angiotensin II receptor antagonists such as aprosartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, prazosartan, tasosartan, telmisartan, valsartan, and EXP-3137, FI6828K,

10 and RNH6270, and the like; (9) α/β adrenergic blockers such as nipradilol, arotinolol and amosulalol, and the like; (10) alpha 1 blockers, such as terazosin, urapidil, prazosin, tamsulosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHP 164, and XENOIO, and the like; (11) alpha 2 agonists such as lofexidine, tiamenidine, moxonidine, rilmenidine and guanobenz, and the like; (12) aldosterone inhibitors, and the like; and (13) angiopoietin-2 -binding agents

15 such as those disclosed in WO03/030833. Specific anti-hypertensive agents that can be used in combination with polypeptides and agonists described herein include, but are not limited to: diuretics, such as thiazides (*e.g.*, chlorthalidone, cyclothiazide (CAS RN 2259-96-3), chlorothiazide (CAS RN 72956-09-3, which may be prepared as disclosed in US2809194), dichlorophenamide, hydroflumethiazide, indapamide, polythiazide, bendroflumethazide,

20 methyclothazide, polythiazide, trichlormethazide, chlorthalidone, indapamide, metolazone, quinethazone, althiazide (CAS RN 5588-16-9, which may be prepared as disclosed in British Patent No. 902,658), benzthiazide (CAS RN 91-33-8, which may be prepared as disclosed in US3108097), buthiazide (which may be prepared as disclosed in British Patent Nos. 861 ,367), and hydrochlorothiazide), loop diuretics (*e.g.* bumetanide, ethacrynic acid, furosemide, and

25 torasemide), potassium sparing agents (*e.g.* amiloride, and triamterene (CAS Number 396-01-O)), and aldosterone antagonists (*e.g.* spironolactone (CAS Number 52-01-7), epirenone, and the like); β -adrenergic blockers such as Amiodarone (Cordarone, Pacerone), bunolol hydrochloride (CAS RN 31969-05-8, Parke-Davis), acebutolol (\pm N-[3-Acetyl-4-[2-hydroxy-3-[(1

30 (isopropylamino) propoxy] phenyl]-butanamide, or (\pm)-3'-Acetyl-4'-[2-hydroxy -3-(methylethyl)amino]propoxy] phenyl]-butanamide, or (\pm)-3'-Acetyl-4'-[2-hydroxy -3-(isopropylamino) propoxy] butyranilide), acebutolol hydrochloride (*e.g.* Sectral®, Wyeth-Ayerst), alprenolol hydrochloride (CAS RN 13707-88-5 see Netherlands Patent Application No.

6,605,692), atenolol (*e.g.* Tenormin®, AstraZeneca), carteolol hydrochloride (*e.g.* Cartrol® Filmtab®, Abbott), Celiprolol hydrochloride (CAS RN 57470-78-7, also see in US4034009), cetamolol hydrochloride (CAS RN 77590-95-5, see also US4059622), labetalol hydrochloride (*e.g.* Normodyne®, Schering), esmolol hydrochloride (*e.g.* Brevibloc®, Baxter), levobetaxolol hydrochloride (*e.g.* Betaxon™ Ophthalmic Suspension, Alcon), levobunolol hydrochloride (*e.g.* Betagan® Liquifilm® with C CAP® Compliance Cap, Allergan), nadolol (*e.g.* Nadolol, Mylan), practolol (CAS RN 6673-35-4, see also US3408387), propranolol hydrochloride (CAS RN 318-98-9), sotalol hydrochloride (*e.g.* Betapace AF™, Berlex), timolol (2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-, hemihydrate, (S)-, CAS RN 91524-16-2), timolol maleate (S)-I-[(1,1-dimethylethyl) amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl] oxy]-2-propanol (Z)-2-butenedioate (1 :1) salt, CAS RN 26921-17-5), bisoprolol (2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]-methyl]phenoxy]-3-[(1-methylethyl)amino]-, (±), CAS RN 66722-44-9), bisoprolol fumarate (such as (±)-1-[4-[[2-(1-methylethoxy) ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol (E) -2-butenedioate (2:1) (salt), *e.g.*, Zebeta™, Lederle Consumer), nebivolol (2H-1-Benzopyran-2-methanol, $\alpha\alpha'$ -[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-, CAS RN 99200-09-6 see also U.S. Pat. No. 4,654,362), cicloprolol hydrochloride, such 2-Propanol, 1-[4-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-[1-methylethyl)amino]-, hydrochloride, A.A.S. RN 63686-79-3), dextropropranolol hydrochloride (2-Propanol, 1-[1-methylethyl)-amino]-3-(1-naphthalenyloxy)-hydrochloride (CAS RN 13071-11-9), diacetolol hydrochloride (Acetamide, N-[3-acetyl-4-[2-hydroxy-3-[(1-methyl-ethyl)amino]propoxy] [phenyl]-, monohydrochloride CAS RN 69796-04-9), dilevalol hydrochloride (Benzamide, 2-hydroxy-5-[1-hydroxy-2-[1-methyl-3-phenylpropyl)amino]ethyl]-, monohydrochloride, CAS RN 75659-08-4), exaprolool hydrochloride (2-Propanol, 1-(2-cyclohexylphenoxy)-3 - [(1-methylethyl)amino] -, hydrochloride CAS RN 59333-90-3), fleistolol sulfate (Benzoic acid, 2-fluoro-, 3-[[2-[aminocarbonyl)amino]- - dimethylethyl]amino]-2-hydroxypropyl ester, (+)- sulfate (1 :1) (salt), CAS RN 88844-73-9; metalol hydrochloride (Methanesulfonamide, N-[4-[1-hydroxy-2-(methylamino)propyl]phenyl]-, monohydrochloride CAS RN 7701-65-7), metoprolol 2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[1-methylethyl)amino]-; CAS RN 37350-58-6), metoprolol tartrate (such as 2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-, *e.g.*, Lopressor®, Novartis), pamatolol sulfate (Carbamic acid, [2-[4-[2-

hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]-ethyl)-, methyl ester, (\pm) sulfate (salt) (2:1), CAS RN 59954-01-7), penbutolol sulfate (2-Propanol, 1-(2-cyclopentylphenoxy)-3-[1,1-dimethylethyl)amino] 1, (S)-, sulfate (2:1) (salt), CAS RN 38363-32-5), practolol (Acetamide, N-[4-[2-hydroxy-3-[(1-methylethyl)amino]-propoxy]phenyl]-, CAS RN 6673-35-4;) tiprenolol

5 hydrochloride (Propanol, 1-[(1-methylethyl)amino]-3-[2-(methylthio)-phenoxy]-, hydrochloride, (\pm), CAS RN 39832-43-4), tolamolol (Benzamide, 4-[2-[[2-hydroxy-3-(2-methylphenoxy)-propyl] amino] ethoxy]-, CAS RN 38103-61-6), bopindolol, indenolol, pindolol, propanolol, tertatolol, and tilisolol, and the like; calcium channel blockers such as besylate salt of amlodipine (such as 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-

10 3,5-pyridinedicarboxylate benzenesulphonate, *e.g.*, Norvasc®, Pfizer), clentiazem maleate (1,5-Benzothiazepin-4(5H)-one, 3-(acetyloxy)-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-(2S-cis)-, (Z)-2-butenedioate (1 : 1), see also US4567195), isradipine (3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester, (\pm)-4(4-benzofurazanyl)- 1,4-dihydro-2,6-dimethyl-3,5-

15 pyridinedicarboxylate, see also US4466972); nimodipine (such as is isopropyl (2-methoxyethyl) 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine-dicarboxylate, *e.g.* Nimotop®, Bayer), felodipine (such as ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate-, *e.g.* Plendil® Extended-Release, AstraZeneca LP), nilvadipine (3,5-Pyridinedicarboxylic acid, 2-cyano-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-,3-methyl 5-(1-methylethyl) ester, also see US3799934), nifedipine (such as 3,5-pyridinedicarboxylic acid,1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, *e.g.*, Procardia XL® Extended Release

20 Tablets, Pfizer), diltiazem hydrochloride (such as 1,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,3-dihydro-2(4-methoxyphenyl)-, monohydrochloride, (+)-cis., *e.g.*, Tiazac®, Forest), verapamil hydrochloride (such as benzeneacetonitrile, (alpha)-[[3-[[2-(3,4-dimethoxyphenyl) ethyl]methylamino]propyl] -3,4-dimethoxy-(alpha)-(1-methylethyl) hydrochloride, *e.g.*, Isoptin® SR, Knoll Labs), teludipine hydrochloride (3,5-Pyridinedicarboxylic acid, 2-[(dimethylamino)methyl]4-[2-[(1E)-3-(1,1-dimethylethoxy)-3-oxo-1-propenyl]phenyl]-1,4-dihydro-6-methyl-, diethyl ester, monohydrochloride) CAS RN 108700-03-4), belfosdil (Phosphonic acid, [2-(2-phenoxy ethyl)- 1,3 -propane- diyl]bis-, tetrabutyl ester

30 CAS RN 103486-79-9), fostedil (Phosphonic acid, [[4-(2-benzothiazolyl)phenyl]methyl]-, diethyl ester CAS RN 75889-62-2), aranidipine, azelnidipine, barnidipine, benidipine, bepridil,

cinaldipine, clevidipine, efonidipine, gallopamil, lacidipine, lemildipine, lercanidipine, monatepil maleate (1-Piperazinebutanamide, N-(6, 11 -dihydrodibenzo(b,e)thiepin- 11 -yl)₄-(4-fluorophenyl)-, (+)-, (Z)-2-butenedioate (1 :1) (±)-N-(6,1 l-Dihydrodibenzo(b,e)thiep- in-1 l-yl)-4-(p- fluorophenyl)-l-piperazinebutyramide maleate (1 :1) CAS RN 132046-06-1), nicardipine, nisoldipine, nitrendipine, manidipine, pranidipine, and the like; T-channel calcium antagonists such as mibefradil; angiotensin converting enzyme (ACE) inhibitors such as benazepril, benazepril hydrochloride (such as 3-[[1-(ethoxycarbonyl)-3- phenyl-(1 S)-propyl]amino]-2,3 ,4,5-tetrahydro-2-oxo- 1 H - 1 -(3 S)-benzazepine- 1 -acetic acid monohydrochloride, *e.g.*, Lotrel®, Novartis), captopril (such as 1-[(2S)-3-mercapto-2- methylpropionyl]-L-proline, *e.g.*, Captopril, Mylan, CAS RN 62571-86-2 and others disclosed in US4046889), ceranapril (and others disclosed in US4452790), cetapril (alacepril, Dainippon disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986)), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987), indalapril (delapril hydrochloride (2H-1,2,4- Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-, 1,1- dioxide CAS RN 2259-96-3); disclosed in US4385051), enalapril (and others disclosed in US4374829), enalapril, enalaprilat, fosinopril, ((such as L-proline, 4-cyclohexyl-1-[[[2-methyl- 1-(1-oxopropoxy) propoxy](4-phenylbutyl) phosphinyl]acetyl]-, sodium salt, *e.g.*, Monopril, Bristol-Myers Squibb and others disclosed in US4168267), fosinopril sodium (L- Proline, 4-cyclohexyl-1-[(R)-[(1S)-2-methyl-1-(1-ox- opropoxy)propox], imidapril, indolapril (Schering, disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983)), lisinopril (Merck), losinopril, moexipril, moexipril hydrochloride (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[[(1S)- 1 -(ethoxycarbonyl)-3-phenylpropyl]amino]- 1 -oxopropyl]- 1 , - 2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, (3S)- CAS RN 82586-52-5), quinapril, quinaprilat, ramipril (Hoechst) disclosed in EP 79022 and Curr. Ther. Res. 40:74 (1986), perindopril erbumine (such as 2S,3aS,7aS- 1 -[(S)-N-[(S)- 1 -Carboxybutyl]alanyl]hexahydro[^]-indolinecarboxylic acid, 1 -ethyl ester, compound with tert-butylamine (1 :1), *e.g.*, Aceon®, Solvay), perindopril (Servier, disclosed in Eur. J. clin. Pharmacol. 31 :519 (1987)), quanipril (disclosed in US4344949), spirapril (Schering, disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5): 173 (1986)), tenocapril, trandolapril, zofenopril (and others disclosed in US4316906), rentiapril (fentiapril, disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983)), pivopril, YS980, teprotide (Bradykinin potentiator BPP9a CAS RN 35115-60-7), BRL 36,378 (Smith Kline Beecham, see EP80822 and EP60668), MC-838

(Chugai, see CA. 102:72588v and Jap. J. Pharmacol. 40:373 (1986), CGS 14824 (Ciba-Geigy, 3-
 ([l-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino)-2,3,4,5-tetrahydro-2-oxo-*o*-l-(3S)-benzazepine-l
 acetic acid HCl, see U.K. Patent No. 2103614), CGS 16,617 (Ciba-Geigy, 3(S)-[[l-(1S)-5-amino-l-
 carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-l-benzazepine-1-ethanoic acid, see
 5 US4473575), Ru 44570 (Hoechst, see *Arzneimittelforschung* 34:1254 (1985)), R 31-2201
 (Hoffman-LaRoche see *FEBS Lett.* 165:201 (1984)), CI925 (*Pharmacologist* 26:243, 266
 (1984)), WY-44221 (Wyeth, see *J. Med. Chem.* 26:394 (1983)), and those disclosed in
 US2003006922 (paragraph 28), US4337201, US4432971 (phosphoramidates); neutral
 endopeptidase inhibitors such as omapatrilat (Vanlev®), CGS 30440, cadoxatril and ecadotril,
 10 fasidotril (also known as aladotril or alatriopril), sampatrilat, mixanpril, and gemopatrilat,
 AVE7688, ER4030, and those disclosed in US5362727, US5366973, US5225401, US4722810,
 US5223516, US4749688, US5552397, US5504080, US5612359, US5525723, EP0599444,
 EP0481522, EP0599444, EP0595610, EP0534363, EP534396, EP534492, EP0629627;
 endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; vasodilators
 15 such as hydralazine (apresoline), clonidine (clonidine hydrochloride (1H-Imidazol-2-amine, N-
 (2,6-dichlorophenyl)4,5-dihydro-, monohydrochloride CAS RN 4205-91-8), catapres, minoxidil
 (loniten), nicotinyl alcohol (roniacol), diltiazem hydrochloride (such as 1,5-Benzothiazepin-
 4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,3-dihydro-2(4-methoxyphenyl)-,
 monohydrochloride, (+)-cis, *e.g.*, Tiazac®, Forest), isosorbide dinitrate (such as 1,4:3,6-
 20 dianhydro-D-glucitol 2,5-dinitrate *e.g.*, Isordil® Titradose®, Wyeth-Ayerst), sosorbide
 mononitrate (such as 1,4:3,6-dianhydro-D-glucitol-1,5-nitrate, an organic nitrate, *e.g.*, Ismo®,
 Wyeth-Ayerst), nitroglycerin (such as 2,3 propanetriol trinitrate, *e.g.*, Nitrostat® Parke-Davis),
 verapamil hydrochloride (such as benzeneacetonitrile, (±)-(α)[3-[[2-(3,4 dimethoxyphenyl)
 1)ethyl]methylamino]propyl]-3,4-dimethoxy-(α)-(1-methylethyl) hydrochloride, *e.g.*,
 25 Covera HS® Extended-Release, Searle), chromonar (which may be prepared as disclosed in
 US3282938), clonitate (*Annalen* 1870 155), droprenilamine (which may be prepared as disclosed
 in DE2521113), lidoflazine (which may be prepared as disclosed in US3267104); prenylamine
 (which may be prepared as disclosed in US3152173), propatyl nitrate (which may be prepared as
 disclosed in French Patent No. 1,103,113), mioflazine hydrochloride (1-Piperazineacetamide, 3-
 30 (aminocarbonyl)₄-[4,4-bis(4-fluorophenyl)butyl]-N-(2,6-dichlorophenyl)-, dihydrochloride CAS
 RN 83898-67-3), mixidine (Benzeneethanamine, 3,4-dimethoxy-N-(1-methyl-2-

pyrrolidinylidene)- Pyrrolidine, 2-[(3,4-dimethoxyphenethyl)imino]- 1 -methyl- 1-Methyl-2- [(3, 4-dimethoxyphenethyl)imino]pyrrolidine CAS RN 27737-38-8), molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0), isosorbide mononitrate (D-Glucitol, 1,4:3,6-dianhydro-, 5-nitrate CAS RN 16051-77-7),
 5 erythrityl tetranitrate (1,2,3,4-Butanetetrol, tetranitrate, (2R,3S)-rel-CAS RN 7297-25-8), clonitrate(1,2-Propanediol, 3-chloro-, dinitrate (7CI, 8CI, 9CI) CAS RN 2612-33-1), dipyridamole Ethanol, 2,2',2'',2'''-[(4,8-di-1-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetrakis- CAS RN 58-32-2), nicorandil (CAS RN 65141-46-0 3-), pyridinecarboxamide (N-[2-(nitrooxy)ethyl]-Nisoldipine3,5-Pyridinedicarboxylic acid, 1,4-
 10 dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester CAS RN 63675-72-9), nifedipine3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester CAS RN 21829-25-4), perhexiline maleate (Piperidine, 2-(2,2-dicyclohexylethyl)-, (2Z)-2-butenedioate (1 :1) CAS RN 6724-53-4), oxprenolol hydrochloride (2-Propanol, 1-[(1-methylethyl)amino]-3-[2-(2-propenyloxy)phenoxy]-, hydrochloride CAS RN 6452-73-9),
 15 pentrinitrol (1,3-Propanediol, 2,2-bis[(nitrooxy)methyl]-, mononitrate (ester) CAS RN 1607-17-6), verapamil (Benzeneacetonitrile, α -[3-[[2-(3,4-dimethoxyphenyl)ethyl]- methylamino]propyl]- 3, 4-dimethoxy- α -(1 -methylethyl)- CAS RN 52-53-9) and the like; angiotensin II receptor antagonists such as, aprosartan, zolasartan, olmesartan, prazosartan, FI6828K, RNH6270, candesartan (1 H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[l,l'-
 20 biphenyl]4-yl]methyl]- CAS RN 139481-59-7), candesartan cilexetil ((+/-)-1-(cyclohexylcarbonyloxy)ethyl-2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-1H-benzimidazole carboxylate, CAS RN 145040-37-5, US5703110 and US5196444), eprosartan (3-[l-4-carboxyphenylmethyl)-2-n-butyl-imidazol-5-yl]-(2-thienylmethyl) propenoic acid, US5185351 and US5650650), irbesartan (2-n-butyl-3- [[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl] 1,3-
 25 diazazspiro[4,4]non-1-en-4-one, US5270317 and US5352788), losartan (2-N-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazole, potassium salt, US5138069, US5153197 and US5128355), tasosartan (5,8-dihydro-2,4-dimethyl-8-[(2'-(1H-tetrazol-5-yl)[l,r-biphenyl]4-yl)methyl]-pyrido[2,3-d]pyrimidin-7(6H)-one, US5149699), telmisartan (4'-[(1,4-dimethyl-2'-propyl-(2,6'-bi-1H-benzimidazol-r-yl)]-[1,1'-biphenyl]-2-
 30 carboxylic acid, CAS RN 144701-48-4, US5591762), milfasartan, abitesartan, valsartan (Diovan® (Novartis), (S)-N-valeryl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]valine,

US5399578), EXP-3137 (2-N-butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazole-5-carboxylic acid, US5138069, US5153197 and US5128355), 3-(2'-(tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, 4-[2-ethyl-4-methyl-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl]-methyl-1,1'-biphenyl]-2-carboxylic acid, 2-butyl-6-(1-methoxy-1-methylethyl)-2-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl] guinazolin-4(3H)-one, 3-[2'-(2-carboxybiphenyl-4-yl)methyl]-2-cyclopropyl-7-methyl-3H-imidazo[4,5-b]pyridine, 2-butyl-4-chloro-1-[(2'-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-carboxylic acid, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylic acid-1-(ethoxycarbonyloxy)ethyl ester potassium salt, dipotassium 2-butyl-4-(methylthio)-1-[[2-[[[(propylamino)carbonyl]amino]sulfonyl](1,1'-biphenyl)-4-yl]methyl]-1H-imidazole-5-carboxylate, methyl-2-[[4-butyl-2-methyl-6-oxo-5-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl]-4-yl]methyl]-1-(6H)-pyrimidinyl]methyl]-3-thiophencarboxylate, 5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-[2-(1H-tetrazol-5-yl)phenyl]pyridine, 6-butyl-2-(2-phenylethyl)-5[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl]-4-methyl]pyrimidin-4(3H)-one D,L lysine salt, 5-methyl-7-n-propyl-8-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-c]pyrimidin-2(3H)-one, 2,7-diethyl-5-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-5H-pyrazolo[1,5-b][1,2,4]triazole potassium salt, 2-[2-butyl-4,5-dihydro-4-oxo-3-[2'-(1H-tetrazol-5-yl)-4-biphenylmethyl]-3H-imidazo[4,5-c]pyridine-5-ylmethyl]benzoic acid, ethyl ester, potassium salt, 3-methoxy-2,6-dimethyl-4-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methoxy]pyridine, 2-ethoxy-1-[[2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid, 1-[N-(2'-(1H-tetrazol-5-yl)biphenyl-4-yl-methyl)-N-valerolylaminomethyl]cyclopentane-1-carboxylic acid, 7-methyl-2n-propyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-3H-imidazo[4,5-b]pyridine, 2-[5-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine-3-yl)methyl]-2-quinolinyl]sodium benzoate, 2-butyl-6-chloro-4-hydroxymethyl-5-methyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]pyridine, 2-[[[2-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methyl]amino]benzoic acid tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-6-one, 4(S)-[4-(carboxymethyl)phenoxy]-N-[2(R)-[4-(2-sulfobenzamido)imidazol-1-yl]octanoyl]-L-proline, 1-(2,6-dimethylphenyl)-4-butyl-1,3-dihydro-3-[[6-[2-(1H-tetrazol-5-yl)phenyl]-3-pyridinyl]methyl]-2H-imidazol-2-one, 5,8-ethano-5,8-dimethyl-2-n-propyl-5,6,7,8-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H,4H-1,3,4a,8a-tetrazacyclopentanaphthalene-9-

one, 4-[1-[2'-(1,2,3,4-tetrazol-5-yl)biphen-4-yl)methylamino]-5,6,7,8-tetrahydro-2-trifylquinazoline, 2-(2-chlorobenzoyl)imino-5-ethyl-3-[2'-(1H-tetrazole-5-yl)biphenyl-4-yl)methyl-1,3,4-thiadiazoline, 2-[5-ethyl-3-[2-(1H-tetrazole-5-yl)biphenyl-4-yl)methyl-1,3,4-thiazoline-2-ylidene]aminocarbonyl-1-cyclopentencarboxylic acid dipotassium salt, and 2-butyl-4-[N-methyl-N-(3-methylcrotonoyl)amino] - 1 - [2'-(1 H-tetrazol-5 -yl)biphenyl-4-yl)methyl]- 1 H- imidazole-5 -carboxylic acid 1-ethoxycarbonyloxyethyl ester, those disclosed in patent publications EP475206, EP497150, EP539086, EP539713, EP535463, EP535465, EP542059, EP497121, EP535420, EP407342, EP415886, EP424317, EP435827, EP433983, EP475898, EP490820, EP528762, EP324377, EP323841, EP420237, EP500297, EP426021, EP480204, EP429257, EP430709, EP434249, EP446062, EP505954, EP524217, EP514197, EP514198, EP514193, EP514192, EP450566, EP468372, EP485929, EP503162, EP533058, EP467207 EP399731, EP399732, EP412848, EP453210, EP456442, EP470794, EP470795, EP495626, EP495627, EP499414, EP499416, EP499415, EP511791, EP516392, EP520723, EP520724, EP539066, EP438869, EP505893, EP530702, EP400835, EP400974, EP401030, EP407102, EP411766, EP409332, EP412594, EP419048, EP480659, EP481614, EP490587, EP467715, EP479479, EP502725, EP503838, EP505098, EP505111 EP513,979 EP507594, EP510812, EP511767, EP512675, EP512676, EP512870, EP517357, EP537937, EP534706, EP527534, EP540356, EP461040, EP540039, EP465368, EP498723, EP498722, EP498721, EP515265, EP503785, EP501892, EP519831, EP532410, EP498361, EP432737, EP504888, EP508393, EP508445, EP403159, EP403158, EP425211, EP427463, EP437103, EP481448, EP488532, EP501269, EP500409, EP540400, EP005528, EP028834, EP028833, EP411507, EP425921, EP430300, EP434038, EP442473, EP443568, EP445811, EP459136, EP483683, EP518033, EP520423, EP531876, EP531874, EP392317, EP468470, EP470543, EP502314, EP529253, EP543263, EP540209, EP449699, EP465323, EP521768, EP415594, WO92/14468, WO93/08171, WO93/08169, WO91/00277, WO91/00281, WO91/14367, WO92/00067, WO92/00977, WO92/20342, WO93/04045, WO93/04046, WO91/15206, WO92/14714, WO92/09600, WO92/16552, WO93/05025, WO93/03018, WO91/07404, WO92/02508, WO92/13853, WO91/19697, WO91/11909, WO91/12001, WO91/11999, WO91/15209, WO91/15479, WO92/20687, WO92/20662, WO92/20661, WO93/01177, WO91/14679, WO91/13063, WO92/13564, WO91/17148, WO91/18888, WO91/19715, WO92/02257, WO92/04335, WO92/05161, WO92/07852, WO92/15577, WO93/03033, WO91/16313,

WO92/00068, WO92/02510, WO92/09278, WO9210179, WO92/10180, WO92/10186, WO92/10181, WO92/10097, WO92/10183, WO92/10182, WO92/10187, WO92/10184, WO92/10188, WO92/10180, WO92/10185, WO92/20651, WO93/03722, WO93/06828, WO93/03040, WO92/19211, WO92/22533, WO92/06081, WO92/05784, WO93/00341, WO92/04343, WO92/04059, US5104877, US5187168, US5149699, US5185340, US4880804, US5138069, US4916129, US5153197, US5173494, US5137906, US5155126, US5140037, US5137902, US5157026, US5053329, US5132216, US5057522, US5066586, US5089626, US5049565, US5087702, US5124335, US5102880, US5128327, US5151435, US5202322, US5187159, US5198438, US5182288, US5036048, US5140036, US5087634, US5196537, US5153347, US5191086, US5190942, US5177097, US5212177, US5208234, US5208235, US5212195, US5130439, US5045540, US5041152, and US5210204, and pharmaceutically acceptable salts and esters thereof; α/β adrenergic blockers such as nipradilol, arotinolol, amosulalol, bretylium tosylate (CAS RN: 61-75-6), dihydroergtamine mesylate (such as ergotaman-3', 6', 18-trione, 9, -10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-, (5'(α))-monomethanesulfonate, *e.g.*, DHE 45® Injection, Novartis), carvedilol (such as (\pm)-1-(Carbazol-4-yloxy)-3-[[2-(*o*-methoxyphenoxy)ethyl] amino] -2-propanol, *e.g.*, Coreg®, SmithKline Beecham), labetalol (such as 5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl]salicylamide monohydrochloride, *e.g.*, Normodyne®, Schering), bretylium tosylate (Benzenemethanaminium, 2-bromo-N-ethyl-N,N-dimethyl-, salt with 4-methylbenzenesulfonic acid (1 :1) CAS RN 61-75-6), phentolamine mesylate (Phenol, 3-[[4,5-dihydro-1H-imidazol-2-yl)methyl](4-methylphenyl)amino]-, monomethanesulfonate (salt) CAS RN 65-28-1), solypertine tartrate (5H-1,3-Dioxolo[4,5-f]indole, 7-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1 :1) CAS RN 5591-43-5), zolertine hydrochloride (Piperazine, 1-phenyl4-[2-(1H-tetrazol-5-yl)ethyl]-, monohydrochloride (8Cl, 9Cl) CAS RN 7241-94-3) and the like; α adrenergic receptor blockers, such as alfuzosin (CAS RN: 81403-68-1), terazosin, urapidil, prazosin (Minipress®), tamsulosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHP 164, XENOIO, fenspiride hydrochloride (which may be prepared as disclosed in US3399192), proroxxan (CAS RN 33743-96-3), and labetalol hydrochloride and combinations thereof; α 2 agonists such as methyldopa, methyldopa HCL, lofexidine, tiamenidine, moxonidine, rilmenidine, guanobenz, and the like; aldosterone inhibitors, and the like; renin inhibitors including Aliskiren (SPPIOO; Novartis/Speedel);

angiotensin-2-binding agents such as those disclosed in WO03/030833; anti-angina agents such as ranolazine (hydrochloride 1-Piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, dihydrochloride CAS RN 95635-56-6), betaxolol hydrochloride (2-Propanol, 1-[4-[2 (cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]-, hydrochloride CAS RN 63659-19-8), butopropine hydrochloride (Methanone, [4-[3(dibutylamino)propoxy]phenyl](2-ethyl-3-indoliziny)-, monohydrochloride CAS RN 62134-34-3), cinepazet maleate-Piperazineacetic acid, 4-[1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-, ethyl ester, (2Z)-2-butenedioate (1:1) CAS RN 50679-07-7), tofisipin (Benzenesulfonamide, 4-methyl-N-[[[(1S)-1-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184), verapamilhydrochloride (Benzeneacetonitrile, α -[3-[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy- α -(1-methylethyl)-, monohydrochloride CAS RN 152-114), molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0), and ranolazine hydrochloride (1-Piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, dihydrochloride CAS RN 95635-56-6); tofisipin (Benzenesulfonamide, 4-methyl-N-[[[(1S)-1-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184); adrenergic stimulants such as guanfacine hydrochloride (such as N-amidino-2-(2,6-dichlorophenyl)acetamide hydrochloride, *e.g.*, Tenex® Tablets available from Robins); methyl dopa-hydrochlorothiazide (such as levo-3-(3,4-dihydroxyphenyl)-2-methylalanine) combined with Hydrochlorothiazide (such as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, *e.g.*, the combination as, *e.g.*, Aldoril® Tablets available from Merck), methyl dopa-chlorothiazide (such as 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and methyl dopa as described above, *e.g.*, Aldoclor®, Merck), clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride and chlorthalidone (such as 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzenesulfonamide), *e.g.*, Combipres®, Boehringer Ingelheim), clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride, *e.g.*, Catapres®, Boehringer Ingelheim), clonidine (1H-Imidazol-2-amine, N-(2,6-dichlorophenyl)-4,5-dihydro-CAS RN 4205-90-7), Hyzaar (Merck; a combination of losartan and hydrochlorothiazide), Co-Diovan (Novartis; a combination of valsartan and hydrochlorothiazide), Lotrel (Novartis; a combination of benazepril and amlodipine) and Caduet (Pfizer; a combination of amlodipine and atorvastatin), and those agents disclosed in US20030069221.

Agents for the Treatment of Respiratory Disorders

The Aad-GCRA peptides described herein can be used in combination therapy with one or more of the following agents useful in the treatment of respiratory and other disorders including but not limited to: (1) β -agonists including but not limited to: albuterol (PRO VENTIL® , S ALBUT AMOI® , VENTOLIN®), bambuterol, bitoterol, clenbuterol, fenoterol, formoterol, isoetharine (BRONKOSOL®, BRONKOMETER®), metaproterenol (ALUPENT®, METAPREL®), pirbuterol (MAXAIR®), reproterol, rimiterol, salmeterol, terbutaline (BRETHAIRE®, BRETHINE®, BRICANYL®), adrenalin, isoproterenol (ISUPREL®), epinephrine bitartrate (PRIMATENE®), ephedrine, orciprenline, fenoterol and isoetharine; (2) steroids, including but not limited to beclomethasone, beclomethasone dipropionate, betamethasone, budesonide, bunedoside, butixocort, dexamethasone, flunisolide, fluocortin, fluticasone, hydrocortisone, methyl prednisone, mometasone, predonisolone, predonisone, tipredane, tixocortal, triamcinolone, and triamcinolone acetonide; (3) β 2-agonist-corticosteroid combinations [*e.g.*, salmeterol-fluticasone (AD V AIR®), formoterol-budesonid (S YMBICORT®)] ; (4) leukotriene D4 receptor antagonists/leukotriene antagonists/LTD4 antagonists (*i.e.*, any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between leukotrienes and the Cys LTI receptor) including but not limited to: zafhiukast, montelukast, montelukast sodium (SINGULAIR®), pranlukast, iralukast, pobilukast, SKB-106,203 and compounds described as having LTD4 antagonizing activity described in U.S. Patent No. 5,565,473; (5) 5 -lipoxygenase inhibitors and/or leukotriene biosynthesis inhibitors [*e.g.*, zileuton and BAY1005 (CA registry 128253-31-6)]; (6) histamine H1 receptor antagonists/antihistamines (*i.e.*, any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between histamine and its receptor) including but not limited to: astemizole, acrivastine, antazoline, azatadine, azelastine, astemizole, bromopheniramine, bromopheniramine maleate, carbinoxamine, carebastine, cetirizine, chlorpheniramine, chlorpheniramine maleate, cimetidine clemastine, cyclizine, cyproheptadine, descarboethoxyloratadine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine succinate, doxylamine, ebastine, efletirizine, epinastine, famotidine, fexofenadine, hydroxyzine, hydroxyzine, ketotifen, levocabastine, levocetirizine, levocetirizine, loratadine, meclizine, mepyramine, mequitazine, methdilazine, mianserin, mizolastine, noberastine, norastemizole, noraztemizole, phenindamine, pheniramine, picumast,

promethazine, pynlamine, pyrilamine, ranitidine, temelastine, terfenadine, trimeprazine, tripelenamine, and triprolidine; (7) an anticholinergic including but not limited to: atropine, benztropine, biperiden, flutropium, hyoscyamine (*e.g.* Levsin®; Levbid®; Levsin/SL®, Anaspaz®, Levsinex timecaps®, NuLev®), ilutropium, ipratropium, ipratropium bromide, methscopolamine, oxybutinin, rispenzepine, scopolamine, and tiotropium; (8) an anti-tussive including but not limited to: dextromethorphan, codeine, and hydromorphone; (9) a decongestant including but not limited to: pseudoephedrine and phenylpropanolamine; (10) an expectorant including but not limited to: guaifenesin, guaicol sulfate, terpin, ammonium chloride, glycerol guaicolate, and iodinated glycerol; (11) a bronchodilator including but not limited to: theophylline and aminophylline; (12) an anti-inflammatory including but not limited to: flurbiprofen, diclophenac, indomethacin, ketoprofen, S-ketoprophen, tenoxicam; (13) a PDE (phosphodiesterase) inhibitor including but not limited to those disclosed herein; (14) a recombinant humanized monoclonal antibody [*e.g.* xolair (also called omalizumab), rhuMab, and talizumab]; (15) a humanized lung surfactant including recombinant forms of surfactant proteins SP-B, SP-C or SP-D [*e.g.* SURFAXIN®, formerly known as dsc-104 (Discovery Laboratories)], (16) agents that inhibit epithelial sodium channels (ENaC) such as amiloride and related compounds; (17) antimicrobial agents used to treat pulmonary infections such as acyclovir, amikacin, amoxicillin, doxycycline, trimethoprim sulfamethoxazole, amphotericin B, azithromycin, clarithromycin, roxithromycin, clarithromycin, cephalosporins(ceffoxitin, cefmetazole etc), ciprofloxacin, ethambutol, gentimycin, ganciclovir, imipenem, isoniazid, itraconazole, penicillin, ribavirin, rifampin, rifabutin, amantadine, rimantidine, streptomycin, tobramycin, and vancomycin; (18) agents that activate chloride secretion through Ca⁺⁺ dependent chloride channels (such as purinergic receptor (P2Y(2) agonists); (19) agents that decrease sputum viscosity, such as human recombinant DNase 1, (Pulmozyme®); (20) nonsteroidal anti-inflammatory agents (acemetacin, acetaminophen, acetyl salicylic acid, alclofenac, alminoprofen, apazone, aspirin, benoxaprofen, bezpiperylon, bucloxic acid, carprofen, clidanac, diclofenac, diclofenac, diflunisal, diflusinal, etodolac, fenbufen, fenbufen, fenclofenac, fenclozic acid, fenoprofen, fentiazac, feprazone, flufenamic acid, flufenisal, flufenisal, fluprofen, flurbiprofen, flurbiprofen, furofenac, ibufenac, ibuprofen, indomethacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketoprofen, ketorolac, meclofenamic acid, meclofenamic acid, mefenamic acid, mefenamic acid, miroprofen, mofebutazone,

nabumetone oxaprozin, naproxen, naproxen, niflumic acid, oxaprozin, oxpinac, oxyphenbutazone, phenacetin, phenylbutazone, phenylbutazone, piroxicam, piroxicam, pirprofen, pranoprofen, sudoxicam, tenoxicam, sulfasalazine, sulindac, sulindac, suprofen, tiaprofenic acid, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, tolmetin, zidometacin, zomepirac, and zomepirac); and (21) aerosolized antioxidant therapeutics such as S-Nitrosoglutathione.

Anti-obesity agents

The Aad-GCRA peptides described herein can be used in combination therapy with an anti-obesity agent. Suitable such agents include, but are not limited to: 1 β HSD-I (11-beta hydroxy steroid dehydrogenase type 1) inhibitors, such as BVT 3498, BVT 2733, 3-(1-adamantyl)-4-ethyl-5-(ethylthio)-4H-1,2,4-triazole, 3-(1-adamantyl)-5-(3,4,5-trimethoxyphenyl)-4-methyl-4H-1,2,4-triazole, 3-adamantany-4,5,6,7,8,9,10,11,12,3a-decahydro-1,2,4-triazolo[4,3-a][1,1]annulene, and those compounds disclosed in WO01/90091, WO01/90090, WO01/90092 and WO02/072084; 5HT antagonists such as those in WO03/037871, WO03/037887, and the like; 5HT1a modulators such as carbidopa, benserazide and those disclosed in US6207699, WO03/031439, and the like; 5HT2c (serotonin receptor 2c) agonists, such as BVT933, DPCA37215, IK264, PNU 22394, WAY161503, R-1065, SB 243213 (Glaxo Smith Kline) and YM 348 and those disclosed in US3914250, WO00/77010, WO02/36596, WO02/48124, WO02/10169, WO01/66548, WO02/44152, WO02/51844, WO02/40456, and WO02/40457; 5HT6 receptor modulators, such as those in WO03/030901, WO03/035061, WO03/039547, and the like; acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al, Obesity Research, 9:202-9 (2001) and Japanese Patent Application No. JP 2000256190; anorectic bicyclic compounds such as 1426 (Aventis) and 1954 (Aventis), and the compounds disclosed in WO00/18749, WO01/32638, WO01/62746, WO01/62747, and WO03/015769; CB 1 (cannabinoid-1 receptor) antagonist/inverse agonists such as rimonabant (Acomplia; Sanofi), SR-147778 (Sanofi), SR-141716 (Sanofi), BAY 65-2520 (Bayer), and SLV 319 (Solvay), and those disclosed in patent publications US4973587, US5013837, US5081122, US5112820, US5292736, US5532237, US5624941, US6028084, US6509367, US6509367, WO96/33159, WO97/29079, WO98/31227, WO98/33765, WO98/37061, WO98/41519, WO98/43635, WO98/43636, WO99/02499, WO00/10967, WO00/10968, WO01/09120, WO01/58869, WO01/64632, WO01/64633, WO01/64634, WO01/70700, WO01/96330, WO02/076949, WO03/006007,

WO03/007887, WO03/020217, WO03/026647, WO03/026648, WO03/027069, WO03/027076, WO03/027114, WO03/037332, WO03/040107, WO03/086940, WO03/084943 and EP658546; CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771 (GSK), JMV-180, A-71378, A-71623 and SR146131 (Sanofi), and those described in US5739106; CNTF (Ciliary neurotrophic factors), such as GI- 181771 (Glaxo-SmithKline), SRI 46131 (Sanofi Synthelabo), butabindide, PD 170,292, and PD 149164 (Pfizer); CNTF derivatives, such as Axokine® (Regeneron), and those disclosed in WO94/09134, WO98/22128, and WO99/43813; dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, P93/01, P 3298, TSL 225 (tryptophyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540), TMC-2A/2B/2C, CD26 inhibitors, FE 999011, P9310/K364, VIP 0177, SDZ 274-444, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) and the compounds disclosed patent publications. WO99/38501, WO99/46272, WO99/67279 (Probiodrug), WO99/67278 (Probiodrug), WO99/61431 (Probiodrug), WO02/083128, WO02/062764, WO03/000180, WO03/000181, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/004498, WO03/004496, WO03/017936, WO03/024942, WO03/024965, WO03/033524, WO03/037327 and EP1258476; growth hormone secretagogue receptor agonists/antagonists, such as NN703, hexarelin, MK- 0677 (Merck), SM-130686, CP-424391 (Pfizer), LY 444,711 (Eli Lilly), L-692,429 and L- 163,255, and such as those disclosed in USSN 09/662448, US provisional application 60/203335, US6358951, US2002049196, US2002/022637, WO01/56592 and WO02/32888; H3 (histamine H3) antagonist/inverse agonists, such as thioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and A331440, O-[3-(1H-imidazol-4-yl)propanol]carbamates (Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000)), piperidine-containing histamine H3-receptor antagonists (Lazewska, D. et al., Pharmazie, 56:927-32 (2001), benzophenone derivatives and related compounds (Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)), substituted N- phenylcarbamates (Reidemeister, S. et al., Pharmazie, 55:83-6 (2000)), and proxifan derivatives (Sasse, A. et al., J. Med. Chem.. 43:3335-43 (2000)) and histamine H3 receptor modulators such as those disclosed in WO02/15905, WO03/024928 and WO03/024929; leptin derivatives, such as those disclosed in US5552524, US5552523, US5552522, US5521283,

WO96/23513, WO96/23514, WO96/23515, WO96/23516, WO96/23517, WO96/23518, WO96/23519, and WO96/23520; leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); lipase inhibitors, such as tetrahydrolipstatin (orlistat/Xenical®), Triton WRI 339, RHC80267, lipstatin, teasaponin, diethylumbelliferyl phosphate, FL-386, WAY-121898, Bay-N-3176, valilactone, esteracin, ebelactone A, ebelactone B, and RHC 80267, and those disclosed in patent publications WO01/77094, US4598089, US4452813, USUS5512565, US5391571, US5602151, US4405644, US4189438, and US4242453; lipid metabolism modulators such as maslinic acid, erythrodiol, ursolic acid uvaol, betulinic acid, betulin, and the like and compounds disclosed in WO03/011267; Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME-10142, ME-10145, and HS-131 (Melacure), and those disclosed in PCT publication Nos. WO99/64002, WO00/74679, WO01/991752, WO01/25192, WO01/52880, WO01/74844, WO01/70708, WO01/70337, WO01/91752, WO02/059095, WO02/059107, WO02/059108, WO02/059117, WO02/06276, WO02/12166, WO02/11715, WO02/12178, WO02/15909, WO02/38544, WO02/068387, WO02/068388, WO02/067869, WO02/081430, WO03/06604, WO03/007949, WO03/009847, WO03/009850, WO03/013509, and WO03/031410; Mc5r (melanocortin 5 receptor) modulators, such as those disclosed in WO97/19952, WO00/15826, WO00/15790, US20030092041; melanin-concentrating hormone 1 receptor (MCHR) antagonists, such as T-226296 (Takeda), SB 568849, SNP-7941 (Synaptic), and those disclosed in patent publications WO01/21169, WO01/82925, WO01/87834, WO02/051809, WO02/06245, WO02/076929, WO02/076947, WO02/04433, WO02/51809, WO02/083134, WO02/094799, WO03/004027, WO03/13574, WO03/15769, WO03/028641, WO03/035624, WO03/033476, WO03/033480, JP13226269, and JP1437059; mGluR5 modulators such as those disclosed in WO03/029210, WO03/047581, WO03/048137, WO03/051315, WO03/051833, WO03/053922, WO03/059904, and the like; serotonergic agents, such as fenfluramine (such as Pondimin® (Benzeneethanamine, N-ethyl- alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Robbins), dexfenfluramine (such as Redux® (Benzeneethanamine, N-ethyl-alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Interneuron) and sibutramine ((Meridia®, Knoll/Reductil™) including racemic mixtures, as optically pure isomers (+) and (-), and pharmaceutically acceptable salts, solvents, hydrates, clathrates and prodrugs thereof including sibutramine hydrochloride monohydrate salts thereof, and those compounds disclosed in US4746680,

US4806570, and US5436272, US20020006964, WO01/27068, and WO01/62341; NE (norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; NPY 1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI- 264879A, and those disclosed in US6001836, WO96/14307, WO01/23387, 5 WO99/51600, WO01/85690, WO01/85098, WO01/85173, and WO01/89528; NPY5 (neuropeptide Y Y5) antagonists, such as 152,804, GW-569180A, GW-594884A, GW-587081X, GW-548118X, FR235208, FR226928, FR240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, LY-366377, PD-160170, SR- 120562A, SR-120819A, JCF-104, and H409/22 and those compounds disclosed in patent publications US6140354, US6191160, 10 US6218408, US6258837, US6313298, US6326375, US6329395, US6335345, US6337332, US6329395, US6340683, EP01010691, EP-01044970, WO97/19682, WO97/20820, WO97/20821, WO97/20822, WO97/20823, WO98/27063, WO00/107409, WO00/185714, WO00/185730, WO00/64880, WO00/68197, WO00/69849, WO/0113917, WO01/09120, WO01/14376, WO01/85714, WO01/85730, WO01/07409, WO01/02379, WO01/23388, 15 WO01/23389, WO01/44201, WO01/62737, WO01/62738, WO01/09120, WO02/20488, WO02/22592, WO02/48152, WO02/49648, WO02/051806, WO02/094789, WO03/009845, WO03/014083, WO03/022849, WO03/028726 and Norman et al, J. Med. Chem. 43:4288-4312 (2000); opioid antagonists, such as nalmefene (REVEX ®), 3-methoxynaltrexone, methylnaltrexone, naloxone, and naltrexone (*e.g.* PT901; Pain Therapeutics, Inc.) and those 20 disclosed in US20050004155 and WO00/21509; orexin antagonists, such as SB-334867-A and those disclosed in patent publications WO01/96302, WO01/68609, WO02/44172, WO02/51232, WO02/51838, WO02/089800, WO02/090355, WO03/023561, WO03/032991, and WO03/037847; PDE inhibitors (*e.g.* compounds which slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibition of the phosphodiesterases, which can lead to a 25 relative increase in the intracellular concentration of cAMP and cGMP; possible PDE inhibitors are primarily those substances which are to be numbered among the class consisting of the PDE3 inhibitors, the class consisting of the PDE4 inhibitors and/or the class consisting of the PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors) such as those disclosed in patent 30 publications DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801, DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048,

DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EPOI 12987, EPOI 16948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, 5 EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, US4963561, US5141931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024, WO9319068, WO9319720, WO9319747, WO9319749, 10 WO9319751, WO9325517, WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836, WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926, 15 WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DE1 116676, DE2162096, EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6331543, US20050004222 (including those disclosed in formulas I- XIII and paragraphs 37-39, 85-0545 and 557-577), WO9307124, EP0163965, EP0393500, EP0510562, EP0553174, WO9501338 and WO9603399, as well as PDE5 inhibitors (such as RX-RA-69, 20 SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (ViagraTM)), PDE4 inhibitors (such as etazolate, ICI63197, RP73401, imazolidinone (RO-20-1724), MEM 1414 (R1533/R1500; Pharmacia Roche), denbufylline, rolipram, oxagrelate, nitraquazone, Y-590, DH-6471, SKF-94120, motapizone, lixazinone, indolidan, olprinone, atizoram, KS-506-G, dipamfylline, BMY-43351, atizoram, arofylline, filaminast, 25 PDB-093, UCB-29646, CDP-840, SKF-107806, piclamilast, RS-17597, RS-25344- 000, SB-207499, TIBENELAST, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, mopidamol, anagrelide, ibudilast, amrinone, pimobendan, cilostazol, quazinone and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, PDE3 inhibitors (such as ICI153, 100, bemorandane (RWJ 22867), MCI-154, UD-CG 212, sulmazole, 30 ampizone, cilostamide, carbazeran, piroximone, imazodan, CI-930, siguazodan, adibendan, saterinone, SKF-95654, SDZ-MKS-492, 349-U-85, emoradan, EMD-53998, EMD- 57033, NSP-

306, NSP-307, revizinone, NM-702, WIN-62582 and WIN-63291, enoximone and milrinone, PDE3/4 inhibitors (such as benafentrine, trequinsin, ORG-30029, zardaverine, L- 686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and tolafentrine) and other PDE inhibitors (such as vinpocetin, papaverine, enprofylline, cilomilast, fenoximone, pentoxifylline, roflumilast, 5 tadalafil(Cialis®), theophylline, and vardenafil(Levitra®); Neuropeptide Y2 (NPY2) agonists include but are not limited to: polypeptide YY and fragments and variants thereof (*e.g.* YY3-36 (PYY3-36)(N. Engl. J. Med. 349:941, 2003; IKPEAPGE DASPEELNRY YASLRHYLNL VTRQRY (SEQ ID NO: 105)) and PYY agonists such as those disclosed in WO02/47712, WO03/026591, WO03/057235, and WO03/027637; serotonin reuptake inhibitors, such as, 10 paroxetine, fluoxetine (Prozac™), fluvoxamine, sertraline, citalopram, and imipramine, and those disclosed in US6162805, US6365633, WO03/00663, WO01/27060, and WO01/162341; thyroid hormone β agonists, such as KB-2611 (KaroBioBMS), and those disclosed in WO02/15845, WO97/21993, WO99/00353, GB98/284425, U.S. Provisional Application No. 60/183,223, and Japanese Patent Application No. JP 2000256190; UCP-I (uncoupling protein-1), 15 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5, 6,7,8- tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-l-propenyl]benzoic acid (TTNPB), retinoic acid, and those disclosed in WO99/00123; β_3 (beta adrenergic receptor 3) agonists, such as AJ9677/TAK677 (Dainippon/Takeda), L750355 (Merck), CP331648 (Pfizer), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, GW 427353, 20 Trecadrine, Zeneca D7114, N-5984 (Nisshin Kyorin), LY-377604 (Lilly), SR 59119A, and those disclosed in US5541204, US5770615, US5491134, US5776983, US488064, US5705515, US5451677, WO94/18161, WO95/29159, WO97/46556, WO98/04526 and WO98/32753, WO01/74782, WO02/32897, WO03/014113, WO03/016276, WO03/016307, WO03/024948, WO03/024953 and WO03/037881; noradrenergic agents including, but not limited to, 25 diethylpropion (such as Tenuate® (1- propanone, 2-(diethylamino)-l -phenyl-, hydrochloride), Merrell), dextroamphetamine (also known as dextroamphetamine sulfate, dexamphetamine, dexedrine, Dexampex, Ferndex, Oxydess II, Robese, Spancap #1), mazindol ((or 5-(p-chlorophenyl)-2,5-dihydro-3H- imidazo[2,l-a]isoindol-5-ol) such as Sanorex®, Novartis or Mazanor®, Wyeth Ayerst), phenylpropanolamine (or Benzenemethanol, alpha-(l-aminoethyl)-, 30 hydrochloride), phentermine ((or Phenol, 3-[[4,5-duhydro-1H-imidazol-2-yl)ethyl](4-methylphenyl-l)amino], monohydrochloride) such as Adipex-P®, Lemmon, FASTIN®, Smith-

Kline Beecham and Ionamin®, Medeva), phendimetrazine ((or (2S,3S)-3,4-Dimethyl-
 2-phenylmorpholine L-(+)- tartrate (1 :1)) such as Metra® (Forest) , Plegine® (Wyeth- Ay erst),
 Prelu-2® (Boehringer Ingelheim), and Statobex® (Lemmon), phendamine tartrate (such as
 Thephorin® (2,3,4,9- Tetrahydro-2-methyl-9-phenyl-1H-indenol[2,1-c]pyridine L-(+)-tartrate (1
 5 :1)), Hoffmann- LaRoche), methamphetamine (such as Desoxyn®, Abbot ((S)-N, (alpha)-
 dimethylbenzeneethanamine hydrochloride)), and phendimetrazine tartrate (such as Bontril®
 Slow-Release Capsules, Amarin (-3,4-Dimethyl-2-phenylmorpholine Tartrate); fatty acid
 oxidation upregulator/inducers such as Famoxin® (Genset); monamine oxidase inhibitors
 including but not limited to befloxatone, moclobemide, brofaromine, phenoxathine, esuprone,
 10 befol, toloxatone, pirlindol, amiflamine, sercloremine, bazinaprine, lazabemide, milacemide,
 caroxazone and other certain compounds as disclosed by WO01/12176; and other anti-obesity
 agents such as 5HT-2 agonists, ACC (acetyl-CoA carboxylase) inhibitors such as those described
 in WO03/072197, alpha-lipoic acid (alpha-LA), AOD9604, appetite suppressants such as those
 in WO03/40107, ATL-962 (Alizyme PLC), benzocaine, benzphetamine hydrochloride (Didrex),
 15 bladderwrack (focus vesiculosus), BRS3 (bombesin receptor subtype 3) agonists, bupropion,
 caffeine, CCK agonists, chitosan, chromium, conjugated linoleic acid, corticotropin-releasing
 hormone agonists, dehydroepiandrosterone, DGAT1 (diacylglycerol acyltransferase 1) inhibitors,
 DGAT2 (diacylglycerol acyltransferase 2) inhibitors, dicarboxylate transporter inhibitors,
 ephedra, exendin-4 (an inhibitor of glp-1) FAS (fatty acid synthase) inhibitors (such as Cerulenin
 20 and C75), fat resorption inhibitors (such as those in WO03/053451, and the like), fatty acid
 transporter inhibitors, natural water soluble fibers (such as psyllium, plantago, guar, oat, pectin),
 galanin antagonists, galega (Goat's Rue, French Lilac), garcinia cambogia, germander (teucrium
 chamaedrys), ghrelin antibodies and ghrelin antagonists (such as those disclosed in
 WO01/87335, and WO02/08250), polypeptide hormones and variants thereof which affect the
 25 islet cell secretion, such as the hormones of the secretin/gastric inhibitory polypeptide
 (GIP)/vasoactive intestinal polypeptide (VIP)/pituitary adenylate cyclase activating polypeptide
 (PACAP)/glucagon-like polypeptide II (GLP- II)/glicentin/glucagon gene family and/or those of
 the adrenomedullin/amylin/calcitonin gene related polypeptide (CGRP) gene family
 including GLP-1 (glucagon- like polypeptide 1) agonists (e.g. (1) exendin-4, (2) those GLP-I
 30 molecules described in US20050130891 including GLP- 1(7-34), GLP-I(7-35), GLP-I(7-36) or
 GLP-I(7-37) in its C-terminally carboxylated or amidated form or as modified GLP-I

polypeptides and modifications thereof including those described in paragraphs 17-44 of US20050130891, and derivatives derived from GLP-1-(7-34)COOH and the corresponding acid amide are employed which have the following general formula: R-NH-

HAEGTFTSDVSYLEGQAAKEFIWLVK-CONH₂ wherein R=H or an organic compound

5 having from 1 to 10 carbon atoms (SEQ ID NO: 106). Preferably, R is the residue of a carboxylic acid. Particularly preferred are the following carboxylic acid residues: formyl, acetyl, propionyl, isopropionyl, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl.) and glp-1 (glucagon-like polypeptide-1), glucocorticoid antagonists, glucose transporter inhibitors, growth hormone secretagogues (such as those disclosed and specifically described in
10 US5536716), interleukin-6 (IL-6) and modulators thereof (as in WO03/057237, and the like), L-carnitine, Mc3r (melanocortin 3 receptor) agonists, MCH2R (melanin concentrating hormone 2R) agonist/antagonists, melanin concentrating hormone antagonists, melanocortin agonists (such as Melanotan II or those described in WO 99/64002 and WO 00/74679), nomame herba, phosphate transporter inhibitors, phytopharm compound 57 (CP 644,673), pyruvate, SCD-I
15 (stearoyl-CoA desaturase-1) inhibitors, T71 (Tularik, Inc., Boulder CO), Topiramate (Topimax®, indicated as an anti-convulsant which has been shown to increase weight loss), transcription factor modulators (such as those disclosed in WO03/026576), β -hydroxy steroid dehydrogenase-1 inhibitors (β -HSD-I), β -hydroxy- β -methylbutyrate, p57 (Pfizer), Zonisamide (Zonegran™, indicated as an anti-epileptic which has been shown to lead to weight loss), and the
20 agents disclosed in US20030119428 paragraphs 20-26.

Anti-Diabetic Agents

The Aad-GCRA peptides described herein can be used in therapeutic combination with one or more anti-diabetic agents, including but not limited to: PPAR γ agonists such as glitazones (e.g., WAY-120,744, AD 5075, balaglitazone, ciglitazone, darglitazone (CP-86325, Pfizer),
25 englitazone (CP-68722, Pfizer), isaglitazone (MIT/J&J), MCC-555 (Mitsubishi disclosed in US5594016), pioglitazone (such as such as Actos™ pioglitazone; Takeda), rosiglitazone (Avandia™; Smith Kline Beecham), rosiglitazone maleate, troglitazone (Rezulin®, disclosed in US4572912), rivoglitazone (CS-Ol 1, Sankyo), GL-262570 (Glaxo Welcome), BRL49653 (disclosed in WO98/05331), CLX-0921, 5-BTSD, GW-0207, LG-100641, JJT-501
30 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/Pfizer), NN-2344 (Dr. Reddy/NN), YM-440 (Yamanouchi), LY-300512, LY-519818, R483 (Roche), T131 (Tularik), and the like and

compounds disclosed in US4687777, US5002953, US5741803, US5965584, US6150383, US6150384, US6166042, US6166043, US6172090, US6211205, US6271243, US6288095, US6303640, US6329404, US5994554, W097/10813, W097/27857, W097/28115, W097/28137, W097/27847, W000/76488, W003/000685, W003/027112, W003/035602, W003/048130, W003/055867, and pharmaceutically acceptable salts thereof; biguanides such as metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride, such as Glucophage™, Bristol-Myers Squibb); metformin hydrochloride with glyburide, such as Glucovance™, Bristol-Myers Squibb); buformin (Imidodicarbonimidic diamide, N-butyl-); etoformine (l-Butyl-2-ethylbiguanide, Schering A. G.); other metformin salt forms (including where the salt is chosen from the group of, acetate, benzoate, citrate, ftimarate, embonate, chlorophenoxyacetate, glycolate, palmoate, aspartate, methanesulphonate, maleate, parachlorophenoxyisobutyrate, formate, lactate, succinate, sulphate, tartrate, cyclohexanecarboxylate, hexanoate, octanoate, decanoate, hexadecanoate, octodecanoate, benzenesulphonate, trimethoxybenzoate, paratoluenesulphonate, adamantanecarboxylate, glycoxylate, glutarnate, pyrrolidonecarboxylate, naphthalenesulphonate, 1-glucosephosphate, nitrate, sulphite, dithionate and phosphate), and phenformin; protein tyrosine phosphatase- IB (PTP-IB) inhibitors, such as A-401,674, KR 61639, OC- 060062, OC-83839, OC-297962, MC52445, MC52453, ISIS 113715, and those disclosed in WO99/585521, WO99/58518, WO99/58522, WO99/61435, WO03/032916, WO03/032982, WO03/041729, WO03/055883, WO02/26707, WO02/26743, JP2002114768, and pharmaceutically acceptable salts and esters thereof; sulfonylureas such as acetohexamide (*e.g.* Dymelor, Eli Lilly), carbutamide, chlorpropamide (*e.g.* Diabinese®, Pfizer), gliamilide (Pfizer), gliclazide (*e.g.* Diamcron, Servier Canada Inc), glimepiride (*e.g.* disclosed in US4379785, such as Amaryl , Aventis), glipentide, glipizide (*e.g.* Glucotrol or Glucotrol XL Extended Release, Pfizer), gliquidone, glisolamide, glyburide/glibenclamide (*e.g.* Micronase or Glynase Prestab, Pharmacia & Upjohn and Diabeta, Aventis), tolazamide (*e.g.* Tolinase), and tolbutamide (*e.g.* Orinase), and pharmaceutically acceptable salts and esters thereof; meglitinides such as repaglinide (*e.g.* Prandin®, Novo Nordisk), KAD1229 (PF/Kissei), and nateglinide (*e.g.* Starlix®, Novartis), and pharmaceutically acceptable salts and esters thereof; α glucoside hydrolase inhibitors (or glucoside inhibitors) such as acarbose (*e.g.* Precose™, Bayer disclosed in US4904769), miglitol (such as GLYSET™, Pharmacia & Upjohn disclosed in US4639436), camiglibose (Methyl 6-deoxy-6-[(2R,3R,4R,5S)-

3,4,5-trihydroxy-2- (hydroxymethyl)piperidino]-alpha-D-glucopyranoside, Marion Merrell Dow), voglibose (Takeda), adiposine, emiglitate, pradimicin-Q, salbostatin, CKD-711, MDL-25,637, MDL- 73,945, and MOR 14, and the compounds disclosed in US4062950, US4174439, US4254256, US4701559, US4639436, US5192772, US4634765, US5157116, US5504078, 5 US5091418, US5217877, and WO01/47528 (polyamines); α -amylase inhibitors such as tendamistat, trestatin, and AI -3688, and the compounds disclosed in US4451455, US4623714, and US4273765; SGLT2 inhibitors including those disclosed in US6414126 and US6515117; an aP2 inhibitor such as disclosed in US6548529; insulin secretagogues such as linogiride, A-4166, forskilin, dibutyl cAMP, isobutylmethylxanthine (IBMX), and pharmaceutically acceptable salts and esters thereof; fatty acid oxidation inhibitors, such as clomoxir, and 10 etomoxir, and pharmaceutically acceptable salts and esters thereof; A2 antagonists, such as midaglizole, isaglidole, deriglidole, idazoxan, ecaroxan, and fluparoxan, and pharmaceutically acceptable salts and esters thereof; insulin and related compounds (*e.g.* insulin mimetics) such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension 15 (lente and ultralente), Lys-Pro insulin, GLP-I (1-36) amide, GLP-I (73-7) (insulintropin, disclosed in US5614492), LY-315902 (Lilly), GLP-I (7-36)-NH₂), AL-401 (Autoimmune), certain compositions as disclosed in US4579730, US4849405, US4963526, US5642868, US5763396, US5824638, US5843866, US6153632, US6191105, and WO 85/05029, and primate, rodent, or rabbit insulin including biologically active variants thereof including allelic 20 variants, more preferably human insulin available in recombinant form (sources of human insulin include pharmaceutically acceptable and sterile formulations such as those available from Eli Lilly (Indianapolis, Ind. 46285) as Humulin[™] (human insulin rDNA origin), also see the THE PHYSICIAN'S DESK REFERENCE, 55^{sup}.th Ed. (2001) Medical Economics, Thomson Healthcare (disclosing other suitable human insulins); non-thiazolidinediones such as JT-501 and 25 farglitazar (GW-2570/GI- 262579), and pharmaceutically acceptable salts and esters thereof; PPAR α / γ dual agonists such as AR-HO39242 (Astrazeneca), GW-409544 (Glaxo-Wellcome), BVT-142, CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297 (Kyorin Merck; 5-[(2,4-Dioxo thiazolidinyl)methyl] methoxy-N-[[4-(trifluoromethyl)phenyl] methyl]benzamide), L-796449, LR-90, MK-0767 (Merck/Kyorin/Banyu), SB 219994, muraglitazar (BMS), tesaglitazar 30 (Astrazeneca), reglitazar (JTT-501) and those disclosed in WO99/16758, WO99/19313, WO99/20614, WO99/38850, WO00/23415, WO00/23417, WO00/23445, WO00/50414,

WO01/00579, WO01/79150, WO02/062799, WO03/004458, WO03/016265, WO03/018010, WO03/033481, WO03/033450, WO03/033453, WO03/043985, WO 031053976, U.S. application Ser. No. 09/664,598, filed Sep. 18, 2000, Murakami et al. Diabetes 47, 1841-1847 (1998), and pharmaceutically acceptable salts and esters thereof; other insulin sensitizing drugs; 5 VPAC2 receptor agonists; GLK modulators, such as those disclosed in WO03/015774; retinoid modulators such as those disclosed in WO03/000249; GSK 3 β /GSK 3 inhibitors such as 4-[2-(2-bromophenyl)-4-(4-fluorophenyl)-1H-imidazol-5-yl]pyridine and those compounds disclosed in WO03/024447, WO03/037869, WO03/037877, WO03/037891, WO03/068773, EP1295884, EP1295885, and the like; glycogen phosphorylase (HGLPa) inhibitors such as CP-368,296, CP- 10 316,819, BAYR3401, and compounds disclosed in WO01/94300, WO02/20530, WO03/037864, and pharmaceutically acceptable salts or esters thereof; ATP consumption promoters such as those disclosed in WO03/007990; TRB3 inhibitors; vanilloid receptor ligands such as those disclosed in WO03/049702; hypoglycemic agents such as those disclosed in WO03/015781 and WO03/040114; glycogen synthase kinase 3 inhibitors such as those disclosed in WO03/035663 15 agents such as those disclosed in WO99/51225, US20030134890, WO01/24786, and WO03/059870; insulin-responsive DNA binding protein-1 (IRDBP-I) as disclosed in WO03/057827, and the like; adenosine A2 antagonists such as those disclosed in WO03/035639, WO03/035640, and the like; PPAR δ agonists such as GW 501516, GW 590735, and compounds disclosed in JP10237049 and WO02/14291; dipeptidyl peptidase IV (DP-IV) inhibitors, such as 20 isoleucine thiazolidide, NVP-DPP728A (1- [[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999), P32/98, NVP-LAF-237, P3298, TSL225 (tryptophyl-L,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540), valine pyrrolidide, TMC-2A/2B/2C, CD- 26 inhibitors, FE999011, 25 P9310/K364, VIP 0177, DPP4, SDZ 274-444, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996), and the compounds disclosed in US6395767, US6573287, US6395767 (compounds disclosed include BMS-477118, BMS-471211 and BMS 538,305), WO99/38501, WO99/46272, WO99/67279, WO99/67278, WO99/61431 WO03/004498, WO03/004496, 30 EP1258476, WO02/083128, WO02/062764, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/000180, and WO03/000181; GLP-I agonists such as

exendin-3 and exendin-4 (including the 39 aa polypeptide synthetic exendin-4 called Exenatide®), and compounds disclosed in US2003087821 and NZ 504256, and pharmaceutically acceptable salts and esters thereof; peptides including amlintide and Symlin® (pramlintide acetate); and glyckinase activators such as those disclosed in US2002103199 (fused heteroaromatic compounds) and WO02/48106 (isoindolin-1-one-substituted propionamide compounds).

Phosphodiesterase inhibitors

The Aad-GCRA peptides described herein can be used in combination therapy with a phosphodiesterase inhibitor. PDE inhibitors are those compounds which slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibition of the phosphodiesterases, which can lead to a relative increase in the intracellular concentration of cAMP and/or cGMP.

Possible PDE inhibitors are primarily those substances which are to be numbered among the class consisting of the PDE3 inhibitors, the class consisting of the PDE4 inhibitors and/or the class consisting of the PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors. By way of example, those PDE inhibitors may be mentioned such as are described and/or claimed in the following

patent applications and patents: DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801, DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048, DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EPO1 12987, EPO1 16948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, U.S. Pat. Nos. 4,963,561, 5,141,931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024, WO9319068, WO9319720, WO9319747, WO9319749, WO9319751, WO9325517, WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836,

WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926, WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DE1 116676, DE2162096, EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6,331,543, US20050004222
 5 (including those disclosed in formulas I-XIII and paragraphs 37-39, 85-0545 and 557-577) and WO9307124, EP0163965, EP0393500, EP0510562, EP0553174, WO9501338 and WO9603399. PDE5 inhibitors which may be mentioned by way of example are RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (Viagra®). PDE4 inhibitors which may be mentioned by way of example are RO-20-1724,
 10 MEM 1414 (R1533/R1500; Pharmacia Roche), DENBUFYLLINE, ROLIPRAM, OXAGRELATE, NITRAQUAZONE, Y-590, DH-6471, SKF-94120, MOTAPIZONE, LIXAZINONE, INDOLIDAN, OLPRINONE, ATIZORAM, KS-506-G, DIPAMFYLLINE, BMY-43351, ATIZORAM, AROFYLLINE, FILAMINAST, PDB-093, UCB-29646, CDP-840, SKF- 107806, PICLAMILAST, RS- 17597, RS-25344-000, SB-207499, TIBENELAST, SB-
 15 210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, MOPIDAMOL, ANAGRELIDE, IBUDILAST, AMRINONE, PIMOBENDAN, CILOSTAZOL, QUAZINONE and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide. PDE3 inhibitors which may be mentioned by way of example are SULMAZOLE, AMPIZONE, CILOSTAMIDE, CARBAZERAN, PIROXIMONE, IMAZODAN, CI-930, SIGUAZODAN,
 20 ADIBENDAN, SATERINONE, SKF-95654, SDZ-MKS-492, 349-U-85, EMORADAN, EMD-53998, EMD-57033, NSP-306, NSP-307, REVIZINONE, NM-702, WIN-62582 and WIN-63291, ENOXIMONE and MILRINONE. PDE3/4 inhibitors which may be mentioned by way of example are BENAFENTRINE, TREQUINSIN, ORG-30029, ZARDAVERINE, L-686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and TOLAFENTRINE. Other PDE inhibitors include:
 25 **cilomilast, pentoxifylline, roflumilast, tadalafil(Cialis®), theophylline, and vardenafil(Levitra®),** zaprinast (PDE5 specific).

Anti- Uterine Contractions Agents

The Aad-GCRA peptides described herein can be used in combination therapy (for example, in order to decrease or inhibit uterine contractions) with a tocolytic agent including but
 30 not limited to beta-adrenergic agents, magnesium sulfate, prostaglandin inhibitors, and calcium channel blockers.

Anti- Neoplastic Agents

The Aad-GCRA peptides described herein can be used in combination therapy with an antineoplastic agents including but not limited to alkylating agents, epipodophyllotoxins, nitrosoureas, antimetabolites, vinca alkaloids, anthracycline antibiotics, nitrogen mustard agents, and the like. Particular anti-neoplastic agents may include tamoxifen, taxol, etoposide and 5-fluorouracil.

The Aad-GCRA peptides described herein can be used in combination therapy (for example as in a chemotherapeutic composition) with an antiviral and monoclonal antibody therapies.

Agents to treat Congestive Heart Failure

The Aad-GCRA peptides described herein can be used in combination therapy (for example, in prevention/treatment of congestive heart failure or another method described herein) with the partial agonist of the nociceptin receptor ORL1 described by Dooley et al. (The Journal of Pharmacology and Experimental Therapeutics, 283 (2): 735-741, 1997). The agonist is a hexapeptide having the amino acid sequence Ac- RYY (RK) (WI) (RK)-NH₂ ("the Dooley polypeptide"), where the brackets show allowable variation of amino acid residue. Thus Dooley polypeptide can include but are not limited to KYRWR (SEQ ID NO: 107), RYYRWR (SEQ ID NO: 108), KWRYR (SEQ ID NO: 109), RYYRWK (SEQ ID NO: 110), RYYRWK (all-D amin acids) (SEQ ID NO: 111), RYYRIK (SEQ ID NO: 112), RYYRIR (SEQ ID NO: 113), RYYKIK (SEQ ID NO: 114), RYYKIR (SEQ ID NO: 115), RYYKWR (SEQ ID NO: 116), RYYKWK (SEQ ID NO: 117), and KYRWK (SEQ ID NO: 118), wherein the amino acid residues are in the L-form unless otherwise specified. The Aad-GCRA peptides described herein can also be used in combination therapy with polypeptide conjugate modifications of the Dooley polypeptide described in WO0198324.

Fibrate

The Aad-GCRA peptides described herein can be used in combination therapy with a fibrate. The term "fibrate" is also interchangeably used herein and in the art with the term "fibric acid derivative," and means any of the fibric acid derivatives useful in the methods described herein, e.g., fenofibrate. Fenofibrate is a fibrate compound, other examples of which include, for example, bezafibrate, beclofibrate, benzaefibrate, binifibrate, ciprofibrate, clinofibrate, clofibrate,

etofibrate, gemcabene, gemfibrozil, lifibrol, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, etc.

Lipid Altering Agents

The Aad-GCRA peptides described herein can be used in combination therapy with a lipid altering agent. As used herein the term "lipid altering agent" or "dyslipidemia agent" refers to compounds including, but not limited to, bile acid sequestrants such as cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT® cholestyramine which are available from Bristol-Myers Squibb), colestevlam hydrochloride (such as WELCHOL® Tablets (polyallylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) which are available from Sankyo), colestipol (a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, such as COLESTID® tablets which are available from Pharmacia), dialkylaminoalkyl derivatives of a cross-linked dextran, LOCHOLEST®, DEAE-Sephadex (SECHOLEX®, POLICEXIDE®), water soluble derivatives such as 3,3-ioene, N- (cycloalkyl)alkylamines and poliglusam, insoluble quaternized polystyrenes, saponins and mixtures thereof and those bile acid sequestrants disclosed in WO97/11345, WO98/57652, US3692895, and US5703 188. Suitable inorganic cholesterol sequestrants include bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

HMG-CoA reductase inhibitors

The Aad-GCRA peptides described herein can be used in combination therapy with a HMG-CoA reductase inhibitor. HMG-CoA reductase inhibitors are dyslipidemic agents that can be used in therapeutic combinations with compounds described herein. Suitable HMG-CoA reductase inhibitors for use in therapeutic combination with a compounds described herein include: atorvastatin (LIPITOR®; disclosed in US4681893, US5385929 and US5686104), atorvastatin calcium (disclosed in US5273995), dihydrocompactin, (disclosed in US4450171), bervastatin (disclosed in US5082859), carvastatin, cerivastatin (BAYCOL®; disclosed in US5006530, US5502199, and US5 177080), crilvastatin, dalvastatin (disclosed in EP738510A2), fluvastatin (LESCOL®; disclosed in US4739073 and US534772), glenvastatin, fluindostatin (disclosed in EP363934A1), velostatin (visinolin; disclosed in US4448784 and US4450171), lovastatin (mevinolin; MEVACOR® (Merck and Co.) and related compounds disclosed in

US4231938), mevastatin (and related compound disclosed in US3983140), compactin (and related compounds disclosed in US4804770), pravastatin (also known as NK-104, itavastatin, nisvastatin, nisbastatin disclosed in US5 102888), pravastatin (PRAVACHOL® (Bristol Myers Squibb) and related compounds disclosed in US4346227), rivastatin (sodium 7-(4-fluorophenyl)-
5 2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate), rosuvastatin (CRESTOR®; also known as ZD-4522 disclosed in US5260440), atorvastatin, visastatin, simvastatin (ZOCOR® (Merck and Co.) and related compounds as disclosed in US4448784 and US4450171), simvastatin, CI-981, compounds disclosed in WO03/033481, US4231938, US4444784, US4647576, US4686237, US4499289, US4346227, US5753675, US4613610,
10 EP0221025, and EP491226, and optical or geometric isomers thereof; and nontoxic pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof. In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Pharmaceutically
15 acceptable salts with respect to the HMG-CoA reductase inhibitor includes non-toxic salts of the compounds which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine
20 (Orn), choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, pantothenate, phosphate/diphosphate,
25 polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.
30

Other dyslipidemic agents which can be used in therapeutic combination with a compound described herein include: HMG-CoA synthase inhibitors such as L-659,699 ((E E)-I 1-[3'R-(hydroxy- methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid) and those disclosed in US5 120729, US5064856, and US4847271; cholesterol absorption inhibitors

5 such as plant sterols, plant stanols and/or fatty acid esters of plant stanols such as sitostanol ester used in BENECOL® margarine, stanol esters, beta-sitosterol, and sterol glycosides such as tiqueside. Other cholesterol absorption inhibitors include 1,4-Diphenylazetidin-2-ones; 4-biaryl-1-phenylazetidin-2-ones; 4-(hydroxyphenyl)azetidin-2-ones; 1,4-diphenyl-3-hydroxyalkyl-2-azetidinones; 4-biphenyl-1-phenylazetidin-2-ones; 4-biaryl-1-phenylazetidin-2-ones; and 4-biphenylazetidinones. acyl coenzyme A -cholesterol acyl

10 transferase (ACAT) inhibitors such as avasimibe (Current Opinion in Investigational Drugs. 3(9):291-297 (2003)), eflucimibe, HL-004, lecimibe, DuP-128, KY505, SMP 797, CL-277,082 (Clin Pharmacol Ther. 48(2): 189-94 (1990)) and the like; and those disclosed in US55 10379, WO96/26948 and WO96/10559; CETP inhibitors such as JTT 705 identified as in Nature 406,

15 (6792):203-7 (2000), torcetrapib (CP-529,414 described in US20030186952 and WO00/017164), CP 532,632, BAY63-2149, SC 591, SC 795, and the like including those described in Current Opinion in Investigational Drugs. 4(3):291-297 (2003) and those disclosed in J. Antibiot, 49(8): 815-816 (1996), and Bioorg. Med. Chem. Lett, 6:1951-1954 (1996) and patent publications US55 12548, US6147090, WO99/20302, WO99/14204, WO99/41237,

20 WO95/04755, WO96/15141, WO96/05227, WO038721, EP796846, EP818197, EP818448, DE19704244, DE19741051, DE19741399, DE197042437, DE19709125, DE19627430, DE19832159, DE19741400, JP 11049743, and JP 09059155; squalene synthetase inhibitors such as squalenstatin- 1, TAK-475, and those disclosed in US4871721, US4924024, US57 12396 (α -phosphono-sulfonates), Biller et al (1988) J. Med. Chem., 31:1869 (e.g. isoprenoid (phosphinyl-methyl)phosphonates), Biller et al (1996) Current Pharmaceutical Design, 2:1, P. Ortiz de

25 Montellano et al (1977) J. Med. Chem. 20:243 (terpenoid pyrophosphates), Corey and Volante (1976) J. Am. Chem. Soc, 98:1291 (farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs), McClard et al (1987) J.A.C.S., 109:5544 (phosphinylphosphonates), Capson, T. L., PhD dissertation, June, 1987, Dept. Med. Chem. U of

30 Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary, (cyclopropanes), Curr. Op. Ther. Patents (1993) 861, and patent publications EP0567026A1, EP0645378A1,

EP0645377A1, EP0611749A1, EP0705607A2, EP0701725A1, and WO96/09827; antioxidants such as probucol (and related compounds disclosed in US3674836), probucol derivatives such as AGI-1067 (and other derivatives disclosed in US6121319 and US6147250), tocopherol, ascorbic acid, β -carotene, selenium and vitamins such as vitamin B6 or vitamin B12 and pharmaceutically acceptable salts and esters thereof; PPAR α agonists such as those disclosed in US6028109 (fluorophenyl compounds), WO00/75103 (substituted phenylpropionic compounds), WO98/43081 and fibric acid derivatives (fibrates) such as beclofibrate, benzafibrate, bezafibrate (C.A.S. Registry No. 41859-67-0, see US3781328), binifibrate (C.A.S. Registry No. 69047-39-8, see BE884722), ciprofibrate (C.A.S. Registry No. 52214-84-3, see US3948973), clinofibrate (C.A.S. Registry No. 30299-08-2, see US3716583), clofibrate (such as ethyl 2-(p-chlorophenoxy)-2-methyl-propionate, e.g. Atromid-S[®] capsules (Wyeth-Ayerst), etofibrate, fenofibrate (such as Tricor[®] micronized fenofibrate ((2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid, 1-methylethyl ester; Abbott Laboratories) or Lipanthyl[®] micronized fenofibrate (Laboratoire Fournier, France)), gemcabene, gemfibrozil (such as 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid, e.g. Lopid[®] tablets (Parke Davis)), lifibrol, GW 7647, BM 170744, LY5 18674 and those fibrate and fibrate acid derivatives disclosed in WO03/033456, WO03/033481, WO03/043997, WO03/048116, WO03/053974, WO03/059864, and WO03/05875; FXR receptor modulators such as GW 4064, SR 103912, and the like; LXR receptor modulators such as GW 3965, T9013137, and XTC0179628, and those disclosed in US20030125357, WO03/045382, WO03/053352, WO03/059874, and the like; HM74 and HM74A (human HM74A is Genbank Accession No. AY148884 and rat HM74A is EMM_patAR09 8624) receptor agonists such as nicotinic acid (niacin) and derivatives thereof (e.g. compounds comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions and tautomers, where available) including but not limited to those disclosed in Wise et al (2003) J. Biol. Chem. 278: 9869 (e.g. 5-methylpyrazole-3-carboxylic acid and acifran (4,5-dihydro-5-methyl-4-oxo-5-phenyl-2-furan carboxylic acid pyridine-3-acetic acid)), as well as 5-methyl nicotinic acid, nicotinuric acid, niceritrol, nicofuranose, acipimox (5-methylpyrazine-2-carboxylic acid 4-oxide), Niaspan[®] (niacin extended-release tablets; Kos) and those which can be easily identified by one skilled in the art which bind to and agonize the HM74A or HM74 receptor (for example using the assays disclosed in Wise et al (2003) J. Biol. Chem 278:9869 (nicotine binding and [³⁵S]-GTPyS

binding assays), Soga et al (2003) Biochem. Biophys. Res. Comm. 303:364 (radiolabel binding assay using the HM74 receptor which could be adapted to the HM74A receptor), Tunaru et al (2003) Nature Medicine 9:352 (calcium mobilization assay using the HM74 receptor which could be adapted to the HM74A receptor) and US6420183 (FLIPR assays are described generally in and may be adapted to the HM74A or HM74 receptor); renin angiotensin system inhibitors; bile acid reabsorption inhibitors (bile acid reuptake inhibitors), such as BARI 1453, SC435, PHA384640, S8921, AZD7706, and the like; PPAR δ agonists (including partial agonists) such as GW 501516, and GW 590735, and those disclosed in US5859051 (acetophenols), WO03/024395, W097/28149, WO01/79197, WO02/14291, WO02/46154, WO02/46176, WO02/076957, WO03/016291, WO03/033493, WO99/20275 (quinoline phenyl compounds), WO99/38845 (aryl compounds), WO00/63161 (1,4-disubstituted phenyl compounds), WO01/00579 (aryl compounds), WO01/12612 & WO01/12187 (benzoic acid compounds), and WO97/31907 (substituted 4-hydroxy-phenylallic acid compound); sterol biosynthesis inhibitors such as DMP-565; triglyceride synthesis inhibitors; microsomal triglyceride transport (MTTP) inhibitors, such as inplitapide, LAB687, and CP346086, AEGR 733, inplitapide and the like; HMG-CoA reductase gene expression inhibitors (e.g. compounds that decrease HMG-CoA reductase expression by affecting (e.g. blocking) transcription or translation of HMG-CoA reductase into protein or compounds that maybe biotransformed into compounds that have the aforementioned attributes by one or more enzymes in the cholesterol biosynthetic cascade or may lead to the accumulation of an isoprene metabolite that has the aforementioned activities (such regulation is readily determined by those skilled in the art according to standard assays (Methods of Enzymology, 110:9-19 1985))) such as those disclosed in US5041432 (certain 15- substituted lanosterol derivatives) and E. I. Mercer (1993) Prog. Lip. Res. 32:357 (oxygenated sterols that suppress the biosynthesis of HMG-CoA reductase); squalene epoxidase inhibitors such as NB-598 ((E)-N-ethyl-N-(6,6- dimethyl-2-hepten-4-y- nyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride); low density lipoprotein (LDL) receptor inducers such as HOE-402 (an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity, see Huettinger et al (1993) Arterioscler. Thromb. 13:1005); platelet aggregation inhibitors; 5-LO or FLAP inhibitors; PPAR modulators (including compounds that may have multiple functionality for activating various combinations of PPAR α , PPAR γ , and PPAR δ) such as those disclosed in US6008237, US6248781, US6166049,

WO00/12491, WO00/218355, WO00/23415, WO00/23416, WO00/23425, WO00/23442, WO00/23445, WO00/23451, WO00/236331, WO00/236332, WO00/238553, WO00/50392, WO00/53563, WO00/63153, WO00/63190, WO00/63196, WO00/63209, WO00/78312, WO00/78313, WO01/04351, WO01/14349, WO01/14350, WO01/16120, WO01/17994, 5 WO01/21181, WO01/21578, WO01/25 181, WO01/25225, WO01/25226, WO01/40192, WO01/79150, WO02/081428, WO02/100403, WO02/102780, WO02/79162, WO03/016265, WO03/033453, WO03/042194, WO03/043997, WO03/066581, WO97/25042, WO99/07357, WO99/11255, WO99/12534, WO99/15520, WO99/46232, and WO98/05331 (including GW233 1 or (2-(4-[difluorophenyl]-1 heptylureido)ethyl]phenoxy)-2-methylbutyric)); niacin-bound 10 chromium, as disclosed in WO03/039535; substituted acid derivatives disclosed in WO03/040114; apolipoprotein B inhibitors such as those disclosed in WO02/090347, WO02/28835, WO03/045921, WO03/047575; Factor Xa modulators such as those disclosed in WO03/047517, WO03/047520, WO03/048081; ileal bile acid transport ("IBAT") inhibitors (or apical sodium co-dependent bile acid transport ("ASBT") inhibitors) such as benzothiepinines 15 (including 1,2- benzothiazepines; 1,4- benzodiazepines; 1,5-benzothiazepines; 1,2, 5-benzothiadiapazines); PPAR δ activators such as disclosed in WO01/00603 (thiazole and oxazole derivates (e.g. C.A.S. Registry No. 317318-32-4), WO97/28149 (fluoro, chloro and thio phenoxy phenylacetic), US5093365 (non-1-oxidizable fatty acid analogues), and WO99/04815. Tests showing the efficacy of the therapy and the rationale for the combination therapy with a 20 dyslipidemic agent are presented in US2003 0069221 (where the dyslipidemic agents are called 'cardiovascular agents').

DOSAGE

25 Dosage levels of active ingredients in a pharmaceutical composition can also be varied so as to achieve a transient or sustained concentration of the compound in a subject, especially in and around the site of inflammation or disease area, and to result in the desired response. It is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired effect and to gradually increase the dosage until the desired effect is achieved. It will be understood that the specific dose level for any particular subject will depend on a variety of 30 factors, including body weight, general health, diet, natural history of disease, route and scheduling of administration, combination with one or more other drugs, and severity of disease.

An effective dosage of the composition will typically be between about 1 µg and about 10 mg per kilogram body weight, preferably between about 10 µg to 5 mg of the compound per kilogram body weight. Adjustments in dosage will be made using methods that are routine in the art and will be based upon the particular composition being used and clinical considerations.

5 The guanylate cyclase receptor agonists used in the methods described above may be administered orally, systemically or locally. Dosage forms include preparations for inhalation or injection, solutions, suspensions, emulsions, tablets, capsules, topical salves and lotions, transdermal compositions, other known peptide formulations and pegylated peptide analogs. Agonists may be administered as either the sole active agent or in combination with other drugs, 10 *e.g.*, an inhibitor of cGMP-dependent phosphodiesterase and anti-inflammatory agent. In all cases, additional drugs should be administered at a dosage that is therapeutically effective using the existing art as a guide. Drugs may be administered in a single composition or sequentially.

Dosage levels of the Aad-GCRA peptides for use in methods of this invention typically are from about 0.001 mg to about 10,000 mg daily, preferably from about 0.005 mg to about 15 1,000 mg daily. For example, an effective dosage of the Aad-GCRA peptides for use in methods of this invention is 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg per day or optionally twice a day. Preferably the Aad-GCRA peptide is given after a meal (*i.e.*, 30 minutes). In some embodiments a second agent described above is administered. In some aspects the 20 second agent is administered at less than the standard does for treating the particular disorder because the Aad-GCRA peptide acts synergistically with the second agent. For example, 2.5, 5, 7.5 or 10 mg of Liptor is given twice a day after a meal (*i.e.*, 30 minutes). On the basis of mg/kg daily dose, either given in single or divided doses, dosages typically range from about 0.001/75 mg/kg to about 10,000/75 mg/kg, preferably from about 0.005/75 mg/kg to about 1,000/75 25 mg/kg.

The total daily dose of each inhibitor can be administered to the patient in a single dose, or in multiple subdoses. Typically, subdoses can be administered two to six times per day, preferably two to four times per day, and even more preferably two to three times per day. Doses can be in immediate release form or sustained release form sufficiently effective to obtain 30 the desired control over the medical condition.

The dosage regimen to prevent, treat, give relief from, or ameliorate a medical condition or disorder, or to otherwise protect against or treat a medical condition with the combinations and compositions of the present invention is selected in accordance with a variety of factors.

These factors include, but are not limited to, the type, age, weight, sex, diet, and medical

5 condition of the subject, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular inhibitors employed, whether a drug delivery system is utilized, and whether the inhibitors are administered with other active ingredients. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth
10 above.

CLAIMS

We claim:

- 5 1. A peptide consisting essentially of the sequence of any one of Table 1.
2. The peptide of claim 1, wherein said peptide is Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Leu¹⁶ (SEQ ID NO: 1), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Ser¹⁶ (SEQ ID NO: 32), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Thr¹⁶ (SEQ ID NO: 119), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Tyr¹⁶ (SEQ ID NO: 120), dAsn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-dLeu¹⁶ (SEQ ID NO: 17), or pyGlu¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Leu¹⁶ (SEQ ID NO: 56).
- 15 3. A pharmaceutical composition comprising the peptide of claim 1 or claim 2 in a therapeutically effective amount and a pharmaceutical carrier, excipient or diluent.
4. The peptide of claim 1, wherein said peptide increases cGMP production in a cell.
5. The peptide of claim 1, wherein said peptide is a bicyclic peptide.
6. A composition comprising an inert carrier coated with peptides of claim 1 and an enteric coating that releases the peptide at pH5.0 or pH7.0.
- 20 7. The composition of claim 6, wherein said inert carrier is selected from mannitol, lactose, a microcrystalline cellulose, or starch.
8. A method for treating a condition that responds to enhanced cGMP levels in a patient comprising administering to said patient a therapeutically effective amount of a peptide of claim 1, wherein said peptide is administered in an amount sufficient to increase water transport in the gastrointestinal tract and induce cGMP production in a gastrointestinal epithelial cell.
- 25 9. A method for preventing or treating a condition selected from the group consisting of ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, constipation, chronic constipation, constipation associated with use of opiate pain killers, post-surgical constipation, constipation associated with neuropathic
- 30

disorders, gastroesophageal reflux disease (GERD), Celiac disease, gastroparesis, heartburn, poor gastrointestinal motility, congestive heart failure, hypertension, benign prostatic hyperplasia (BPH), colon cancer, lung cancer, bladder cancer, liver cancer, salivary gland cancer or skin cancer, bronchitis, tissue inflammation, organ inflammation, respiratory inflammation, asthma, COPD, lipid metabolism disorders, biliary disorders, cardiovascular disease, obesity and an endocrine disorder comprising administering to a patient in need thereof a therapeutically effective amount of a peptide of claim 1.

10. A method of colonic cleansing, comprising administering to a subject in need thereof an effective amount of a peptide of claim 1.

11. A method of increasing cGMP production in a cell comprising contacting said cell with a peptide of claim 1.

12. The method of claims 8, 9, 10 or 11, wherein said peptide is Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Leu¹⁶ (SEQ ID NO: 1), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Ser¹⁶ (SEQ ID NO: 32), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Thr¹⁶ (SEQ ID NO: 119), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Tyr¹⁶ (SEQ ID NO: 120), dAsn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-dLeu¹⁶ (SEQ ID NO: 17), or pyGlu¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Leu¹⁶ (SEQ ID NO: 56).

13. The method of claims 8, 9, 10 or 11, further comprising administering a therapeutically effective amount of a cGMP-dependent phosphodiesterase inhibitor.

14. The method of claim 13, wherein said cGMP-dependent phosphodiesterase inhibitor is administered either concurrently or sequentially with said guanylate cyclase receptor agonist.

15. The method of claim 13, wherein said cGMP-dependent phosphodiesterase inhibitor is selected from the group consisting of sulindac sulfone, zaprinast, motapizone, vardenafil, and sildenafil.

16. The method of claims 8 or 9, further comprising administering a therapeutically effective amount of at least one anti-inflammatory agent.

17. The method of 16, wherein said anti-inflammatory agent is a steroid or nonsteroid anti-inflammatory drug (NSAID).

18. The method of claim 10, further comprising administering to said subject an effective amount of L-glucose, lubiprostone (Amitiza), prucalopride, an agent for treating chronic constipation, or any combination thereof.

19. Use of a peptide of claim 1 in the manufacture of a medicament for the treatment of a human disease.

20. The use of claim 19, wherein said peptide is Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Leu¹⁶ (SEQ ID NO: 1), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Ser¹⁶ (SEQ ID NO: 32), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Thr¹⁶ (SEQ ID NO: 119), Asn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Tyr¹⁶ (SEQ ID NO: 120), dAsn¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-dLeu¹⁶ (SEQ ID NO: 17), or pyGlu¹-Asp²-Aad³-Cys⁴-Glu⁵-Leu⁶-Cys⁷-Val⁸-Asn⁹-Val¹⁰-Ala¹¹-Cys¹²-Thr¹³-Gly¹⁴-Cys¹⁵-Leu¹⁶ (SEQ ID NO: 56).

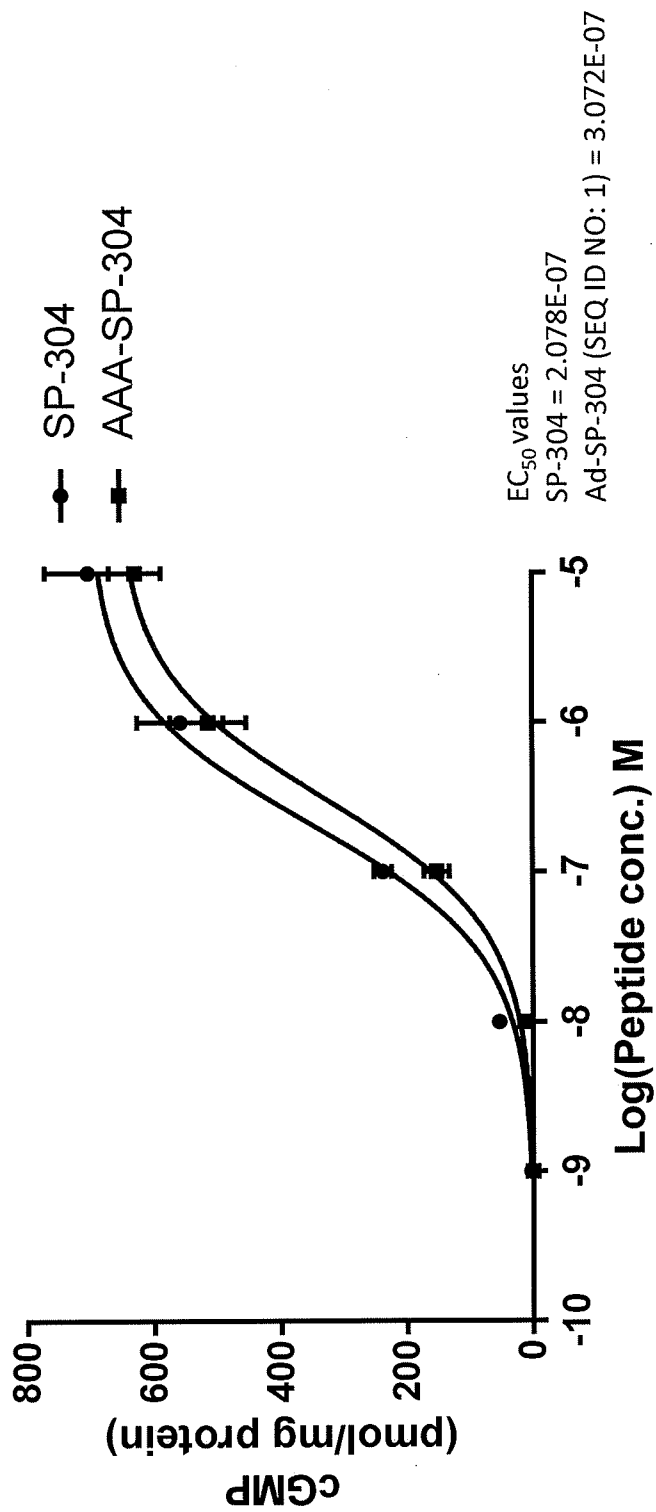


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/025207

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K7/08 A61K38/10 A61P1/00 A61P29/00
 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)

C07K

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/237593 A1 (COMISKEY STEPHEN [US] ET AL) 20 September 2012 (2012-09-20) cited in the application paragraph [0022]; claims; table 1 -----	1-20



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 June 2014

Date of mailing of the international search report

07/07/2014

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/025207

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2012237593 A1	20-09-2012	US 2012237593 A1	20-09-2012
		WO 2013138352 A1	19-09-2013
