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[54] Title: ANALOGS OF PITUARY ADENYLADE CYCLASE-ACTIVATING POLYPEPTIDE (PACAP) AND METHODS FOR THEIR USE

[57] Abstract: This invention relates to novel analogs of pituitary adenylate cyclase-activating polypeptide (PACAP), which are agonists for the PACAP/vasoactive intestinal peptide (VIP) receptors: PAC1, VPAC1 and VPAC2 receptors. These PACAP analogs can be used as prophylactic/therapeutic agents for a wide range of medical disorders, including (but not limited to) cancer and autoimmune disease. These PACAP analogs can be coupled to suitable radionuclides and used in the localization, diagnosis and treatment of disseminated cancers and metastatic tumors, or coupled to small molecule therapeutics and used as vectors for targeted drug delivery. This invention also provides pharmaceutical compositions of one or more PACAP-like compounds of the invention either alone or in combination with one or more other prophylactic/therapeutic agents.
ANALOGS OF PITUITARY ADENYlate CYCLASE-ACTIVATING
POLYPEPTIDE (PACAP) AND METHODS FOR THEIR USE

FIELD OF THE INVENTION

This invention relates to novel analogs of pituitary adenylate cyclase-activating polypeptide (PACAP), which are agonists for the PACAP/vasoactive intestinal peptide (VIP) receptors: PAC$_1$, VPAC$_1$ and VPAC$_2$ receptors. These PACAP analogs can be used as prophylactic/therapeutic agents for a wide range of medical disorders, including (but not limited to) age-related neurodegenerative diseases (such as Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis), injuries to the central nervous system caused by stroke, heart attack and blunt force trauma (such as concussions and spinal cord trauma), Huntington’s disease and other CAG codon repeat expansion diseases, retinal diseases (such as diabetic retinopathy, macular degeneration and glaucoma), autoimmune diseases (such as rheumatoid arthritis, Crohn’s disease, ulcerative colitis, scleroderma, Sjögren’s disease, idiopathic membranous nephropathy, Goodpasture’s disease, autoimmune hepatitis, myasthenia gravis, multiple sclerosis, Guillain-Barré syndrome, type I diabetes, Hashimoto’s thyroiditis, Graves’ disease, pemphigus vulgaris, and lupus erythematosus), keratoconjunctivitis sicca caused by autoimmune diseases or LASIK surgery, type II diabetes, sepsis caused by bacteria and/or viruses (including bacterial and viral toxins), acute and chronic cardiovascular diseases (such as myocardial infarction, atherosclerosis and restenosis), acute and chronic renal diseases (such as ischemia/reperfusion injury, nephritis and drug-induced nephrotoxicity), acute and chronic pulmonary diseases (such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, and pulmonary arterial hypertension), systemic hypertension, hematological cancers (such as leukemias, lymphomas and plasma cell dyscrasias), eating disorders, acute and chronic liver diseases (such as ischemia/reperfusion injury, hepatitis and fatty liver), osteoporosis, pre-eclampsia, cell and solid organ transplantation, cognitive disorders, AIDS dementia complex, and aging of the central nervous system.

These PACAP analogs coupled to suitable radionuclides can be used in the
localization, diagnosis and treatment of disseminated cancers and metastatic tumors, and coupled to small molecule therapeutics can be used as vectors for targeted drug delivery. This invention also provides pharmaceutical compositions of one or more PACAP-like compounds of the invention either alone or in combination with one or more other prophylactic/therapeutic agents.

BACKGROUND OF THE INVENTION

Pituitary adenylate cyclase-activating polypeptide (PACAP) was isolated from ovine (sheep) hypothalami based on its ability to stimulate adenylate cyclase activity in rat anterior pituitary cell cultures (Miyata et al., *Biochem Biophys Res Commun* **164**:567-574, 1989). PACAP exists as two α-amidated peptides with 38 (PACAP38; SEQ ID NO:1) or 27 (PACAP27; SEQ ID NO:2) amino acids. Both peptides have the same N-terminal 27 amino acids and are synthesized from the same prohormone. The sequence of PACAP38 is identical in all mammals and differs from the avian and amphibian orthologs by only one amino acid (Vaudry et al., *Pharmacol Rev* **52**:269-324, 2000). PACAP is a member of the secretin/vasoactive intestinal peptide (VIP)/growth hormone-releasing hormone (GHRH) family, and PACAP27 has 68% sequence identity with VIP (SEQ ID NO:3). PACAP is most abundant in the brain and testis, but there are significant levels in other organs, including the pancreas, adrenals, thymus, spleen, lymph nodes, and duodenal mucosa (Vaudry et al., *Pharmacol Rev* **52**:269-324, 2000). PACAP is synthesized as a preprohormone and is processed mainly by prohormone convertase 1, prohormone convertase 2 and prohormone convertase 4 (Li et al., *Neuroendocrinology* **69**:217-226, 1999; Li et al., *Endocrinology* **141**:3723-3730, 2000). The half-life of $[^{125}]$-PACAP38 in the bloodstream of rats following intravenous injection is 5-6 minutes (Banks et al., *J Pharmacol Exp Ther* **267**:690-696, 1993). Members of the secretin/VIP/GHRH family are degraded in plasma mainly by aminopeptidases, especially dipeptidyl peptidase IV (Zhu et al., *J Biol Chem* **278**:22418-2223, 2003).
A PACAP-specific receptor, designated as the PAC$_1$ receptor, has been cloned from several vertebrate species (Arimura, Jpn J Physiol 48:301-331, 1998; Vaudry et al., Pharmacol Rev 52:269-324, 2000). It is a G-protein-coupled receptor with seven putative membrane-spanning domains and belongs to a family of glycoprotein receptors that are coupled to multiple signal transduction pathways (Segre and Goldring, Trends Endocrinol Metab 4:309-314, 1993). PACAP binds not only to the PAC$_1$ receptor with a high affinity, but it also binds to the VIP$_1$ (VPAC$_1$) and VIP$_2$ (VPAC$_2$) receptors with an affinity comparable to or greater than VIP. On the other hand, VIP binds to the PAC$_1$ receptor with an affinity 1,000 times less than PACAP (Arimura, Jpn J Physiol 48:301-331, 1998). At least 10 splice variants of the rat PAC$_1$ receptor have been cloned and each variant is coupled to distinct combinations of signal transduction pathways (Vaudry et al., Pharmacol Rev 52:269-324, 2000). The "second" messengers include adenylate cyclase, phospholipase C, mitogen-activated protein (MAP) kinases, and calcium.

PACAP/VIP receptor can be coupled to G$_{as}$ and/or G$_{ai}$ in different types of cells. PACAP/VIP receptors are expressed in many different types of normal and cancer cells, including the catecholamine-containing cells in the adrenal medulla and the sympathetic ganglia; microglia, astrocytes and some types of neurons in the central nervous system; and T- and B-lymphocytes, macrophages, neutrophils, and dendritic cells in the immune system (Vaudry et al., Pharmacol Rev 52:269-324, 2000). PACAP is a potent stimulator of catecholamine secretion from the adrenal medulla (Watanabe et al., Am J Physiol 269:E903-E909, 1995), but a potent inhibitor of the secretion of tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-12 from activated macrophages (Ganea and Delgado, Crit Rev Oral Biol Med 13:229-237, 2002). More pertinent to the present invention, PACAP stimulates the proliferation of C6 glioblastoma cells (Dufes et al., J Mol Neurosci 21:91-102, 2003), AR4-2J pancreatic carcinoma cells (Buscai et al., Gastroenterology 103:1002-1008, 1992) and MCF-7 breast cancer cells (Leyton et al., Breast Cancer Res Treat 56:177-186, 1999), but inhibits the proliferation of HEL myeloid leukemia cells (Hayez et al., J Neuroimmunol 149:167-181, 2004), SW403 colonic adenocarcinoma cells (Lelièvre et al., Cell Signal 10:13-26,
1998) and multiple myeloma cells (Li et al., Regul Pept 145:24-32, 2008; see Figures 3 and 4).

Although PACAP was isolated during a screen for novel hypophysiotropic factors, it soon became apparent that it is a pleiotropic peptide (Arimura, Jpn J Physiol 48:301-331, 1998; Vaudry et al., Pharmacol Rev 52:269-324, 2000). The extraordinarily potent neuroprotective/neurotrophic properties of PACAP were investigated by several laboratories shortly after its isolation. The cytoprotective effects of PACAP and VIP have been studied much more extensively in the nervous system than in any other major organ of the body. The cell types that were protected by PACAP in various in vitro models include cerebellar granule cells, dorsal root ganglion cells, sympathetic ganglion cells, mesencephalic dopaminergic neurons, and basal forebrain cholinergic neurons (Arimura, Jpn J Physiol 48:301-331, 1998; Vaudry et al., Pharmacol Rev 52:269-324, 2000).

PACAP also prevented the neuronal death induced by gp120, the envelope glycoprotein of the human immunodeficiency virus (HIV), in rat hippocampal neuron/glia co-cultures. The dose-response curve was bimodal, with peaks at $10^{-13}$ M and $10^{-10}$ M (Arimura et al., Ann NY Acad Sci 739:228-243, 1994). The critical findings in this study have been confirmed by Kong et al. (Neuroscience 91:493-500, 1999), who used lipopolysaccharide as the neurotoxin in primary murine cortical neuron/glia co-cultures. The neuroprotective effect at $10^{-12}$ M was correlated with a significant reduction in the accumulation of nitrite in the culture medium. The neuroprotective effect of "low" (femtomolar) doses of PACAP in neuron/glia co-cultures was abolished by PD98059, a MAP kinase inhibitor, but the neuroprotective effect of "high" (nanomolar) doses of PACAP was not affected by PD98059 (Li et al., J Mol Neurosci 27:91-106, 2005). However, the neuroprotective effect of nanomolar doses of PACAP was abolished by Rp-cAMP, a protein kinase A inhibitor.

The drawbacks of using peptides for neuroprotection in the brain include their poor transport across the blood-brain barrier and their short half-life in the circulation after systematic administration. However, PACAP has been shown to be transported from the blood to the brain via a saturable
mechanism (Banks et al., *J Pharmacol Exp Ther* **267**:690-696, 1993). Therefore, PACAP38 was tested as a neuroprotectant in common in vivo preclinical models of heart attack and stroke. Four-vessel occlusion in the rat was used to model the consequences of a heart attack for the brain (transient global forebrain ischemia). Blood flow to the forebrain was interrupted for 15 minutes. Following the 15-minute occlusion, there was a significant reduction in the number of pyramidal cells in the CA1 field of the hippocampus after 7 days in vehicle-infused rats. The reduction in the number of pyramidal cells at day 7 post-occlusion was significantly reversed in the rats continuously infused intravenously with PACAP38 (Uchida et al., *Brain Res* **736**:280-286, 1996). Middle cerebral artery occlusion (MCAO) in the rat was used to model a stroke (transient focal cerebral ischemia). The middle cerebral artery was occluded for 2 hours using the intraluminal filament technique. The continuous intravenous infusion of PACAP38 beginning at 4, 8 or 12 hours after the start of the transient MCAO resulted in a reduction of the infarct volume of approximately 51%, 22% or 12%, respectively, 48 hours after the start of the MCAO (Reglodi et al., *Stroke* **31**:1411-1417, 2000). These observations suggest that small changes in the concentration of PACAP in the brain can alter the vulnerability of nerve cells to injury.

The neuroprotective effects of low concentrations of PACAP in the nervous system are indirect and are probably mediated by at least four distinct mechanisms. (1) PACAP is a potent anti-inflammatory peptide. It has been shown to inhibit the induction of inducible nitric oxide synthase (iNOS) in activated macrophages, to inhibit the production of the pro-inflammatory cytokines TNF-α, IL-6 and IL-12 in activated macrophages, and to stimulate the production of the anti-inflammatory cytokine IL-10 in activated macrophages (Ganea and Delgado, *Crit Rev Oral Biol Med* **13**:229-237, 2002). PACAP probably inhibits inflammation at multiple steps in the inflammatory cascade because it is an endogenous counter-regulator of the inflammatory process. PACAP is also an extraordinarily potent "deactivator" of activated microglial cells (Kong et al., *Neuroscience* **91**:493-500, 1999; Delgado et al., *Glia* **39**:148-161, 2002), which are the resident macrophage-like cells in the nervous system. (2) Femtomolar ($10^{-15}$ M) concentrations of...
PACAP increase the levels of the mRNA for activity-dependent neurotrophic factor in murine neuron/glia co-cultures (David et al., Society for Neuroscience [33rd Annual Meeting], New Orleans, Louisiana, # 38.1 [Abstract], 2003). Furthermore, the number of PAC1 receptors on "reactive" glial cells is increased following injury (Uchida et al., Brain Res 736:280-286, 1996). Brenneman et al. (Neuropeptides 36:271-280, 2002) had previously shown that femtomolar concentrations of PACAP stimulate the release of RANTES in astrocyte cultures and that immunoneutralization of RANTES reduces the neuroprotective effect of PACAP in neuron/glia co-cultures. (3) Yang et al. (J Pharmacol Exp Ther 319:595-603, 2006) have shown that femtomolar concentrations of PACAP inhibit microglial NADPH oxidase activity and extracellular superoxide levels in mesencephalic neuron/glia co-cultures. (4) Figiel and Engele (J Neurosci 20:3596-3605, 2000) have reported that PACAP increased the expression of the glutamate transporters GLT-1 and GLAST and increased the activity of the glutamate metabolizing enzyme glutamine synthetase in astrocytes. These effects of PACAP would be expected to decrease glutamatergic neurotransmission. The extensive studies about the cytoprotective properties of PACAP in the nervous system have provided a solid framework for studying the cytoprotective properties of PACAP in other organs.

Native PACAP has already been administered to normal human volunteers by investigators in at least four different laboratories (Chiodera et al., Neuroendocrinology 64:242-246, 1996; Filipsson et al., J Clin Endocrinol Metab 82:3093-3098, 1997; Doberer et al., Eur J Clin Invest 37:665-672, 2007; Murck et al., Am J Physiol 292:E853-E857, 2007) and to a patient with multiple myeloma under a U.S. Food and Drug Administration (FDA)-approved protocol (Li et al., Peptides 28:1891-1895, 2007). The only untoward effect reported was a transient flushing.

PACAP is an extraordinarily potent peptide in vitro. However, the usefulness of PACAP as a drug is limited by its very short half-life in the circulation following systemic administration due to both rapid proteolysis and rapid filtration by the kidney. Therefore, there is a need for PACAP analogs
that are resistant to proteolysis and/or have reduced rates of filtration by the kidney.

Citation or discussion of a reference herein shall not be construed as an admission that such reference is prior art to the present invention.

SUMMARY OF THE INVENTION

The inventors have made novel peptide analogs of native human PACAP38 and native human PACAP27 that are agonists at one or more PACAP/VIP receptors, and that have significant biological activity in preclinical in vitro and in vivo models for several major medical disorders. The novel PACAP analogs of this invention can be synthesized by the methods of peptide chemistry.

In a first aspect, the invention features novel PACAP analogs that can be used for the prophylactic/therapeutic and diagnostic purposes described in more detail below can be defined by a general formula (I),

\[ R^1 \cdot A^1 \cdot A^2 \cdot A^3 \cdot A^4 \cdot A^6 \cdot A^7 \cdot A^8 \cdot A^9 \cdot A^{10} \cdot A^{11} \cdot A^{12} \cdot A^{13} \cdot A^{14} \cdot A^{15} \cdot A^{16} \cdot A^{17} \cdot A^{18} \cdot A^{19} \cdot A^{20} \cdot A^{21} \cdot A^{22} \cdot A^{23} \cdot A^{24} \cdot A^{25} \cdot A^{26} \cdot A^{27} \cdot A^{28} \cdot A^{30} \cdot A^{31} \cdot A^{32} \cdot A^{33} \cdot A^{34} \cdot A^{35} \cdot A^{36} \cdot A^{37} \cdot A^{38} \cdot R^2 \]

or a pharmaceutically acceptable salt thereof, wherein

\[ A^1 \] is His, ω-His, Tyr, D-Tyr, Trp, D-Trp, Pal, or D-Pal;
\[ A^2 \] is Ser, ω-Ser, hSer, N-Me-Ser, Thr, D-Thr, Ala, D-Ala, Ile, D-Ile, Pro, D-Pro,
\[ A^3 \] is Abu, Aib, Acb, Ach, Acpe, or Acpr;
\[ A^4 \] is Pip;
\[ A^5 \] is Gly, Ala, ω-Ala, β-Ala, Gaba, Abu, Aib, Acb, Ach, Acpe, or Acpr;
\[ A^6 \] is Ile, Leu, Nle, Val, Nva, Aib, Acb, Ach, Acpe, or Acpr;
\[ A^7 \] is Phe, Tyr, Trp, Cha, Bip, or Nal;
\[ A^8 \] is Thr, Ser, hSer, or Val;
\[ A^9 \] is Thr, Ser, hSer, Thr, Asn, Asp, Ala, Abu, Aib, Acb, Ach, Acpe, or Acpr;
\[ A^{10} \] is Tyr, Phe, Cha, Nal, or Trp;
\[ A^{11} \] is Ser, hSer, Thr, Ala, Abu, Aib, Acb, Ach, Acpe, or Acpr;
\[ A^{12} \] is Arg, Lys, Dab, Dap, or Orn;
A<sup>13</sup> is Tyr, Phe, Cha, Nal, or Trp;
A<sup>14</sup> is Arg, Lys, Dab, Dap, or Orn;
A<sup>15</sup> is Lys, Ala, Dab, Dap, Orn, Abu, Aib, Acb, Ach, Acpe, or Acpr;
A<sup>16</sup> is Gln, Glu, Asn, Asp; Aib, Acb, Ach, Acpe, or Acpr;
A<sup>17</sup> is Met, Nle, Leu, Ile, Ala, Abu, Aib, Acb, Ach, Acpe, or Acpr;
A<sup>18</sup> is Ala, Abu, Aib, Acb, Ach, Acpe, or Acpr;
A<sup>19</sup> is Val, Nva, Ser, Leu, Thr, Aib, Acb, Ach, Acpe, or Acpr;
A<sup>20</sup> is Lys, Ala, Dab, Dap, Orn, Abu, Aib, Acb, Ach, Acpe, or Acpr;
A<sup>21</sup> is Lys, Ala, Dab, Dap, Orn, Abu, Aib, Acb, Ach, Acpe, or Acpr;
A<sup>22</sup> is Tyr, Phe, Cha, Nal, Trp, Ala, Abu, Aib, Acb, Ach, Acpe, or Acpr;
A<sup>23</sup> is Leu, Nle, Ile, Val, Nva, Aib, Acb, Ach, Acpe, or Acpr;
A<sup>24</sup> is Ala, Asn, Abu, Aib, Acb, Ach, Acpe, or Acpr;
A<sup>25</sup> is Ala, Val, Leu, Met, Nle, Ile, Ser, hSer, Thr, Abu, Aib, Acb, Ach, Acpe,
Acpr, or is deleted;
A<sup>26</sup> is Val, Nva, Leu, Met, Nle, Ile, Ala, Abu, Aib, Acb, Ach, Acpe, Acpr, or is
deleted;
A<sup>27</sup> is Leu, d-Leu, Met, d-Met, Nle, Ile, d-Ile, Val, d-Val, Gaba, Ala, d-Ala, Abu,
Aib, Acb, Ach, Acpe, Acpr, or is deleted;
A<sup>28</sup> is Gly, Ala, d-Ala, β-Ala, Gaba, Asn, d-Asn, Gln, d-Gln, Asp, d-Asp, Abu,
Aib, Acb, Ach, Acpe, Acpr, or is deleted;
A<sup>29</sup> is Lys, d-Lys, Arg, d-Arg, Dab, d-Dab, Dap, d-Dap, Orn, d-Orn, or is
deleted;
A<sup>30</sup> is Arg, d-Arg, Lys, d-Lys, Dab, d-Dab, Dap, d-Dap, Orn, d-Orn, or is
deleted;
A<sup>31</sup> is Tyr, d-Tyr, Phe, d-Phe, Trp, d-Trp, Cha, Nal, or is deleted;
A<sup>32</sup> is Lys, d-Lys, Arg, d-Arg, Dab, d-Dab, Dap, d-Dap, Orn, d-Orn, or is
deleted;
A<sup>33</sup> is Gln, d-Gln, Glu, d-Glu, Asn, d-Asn, Asp; d-Asp, Abu, Aib, Acb, Ach,
Acpe, Acpr, or is deleted;
A<sup>34</sup> is Arg, d-Arg, Lys, d-Lys, Dab, d-Dab, Dap, d-Dap, Orn, d-Orn, or is
deleted;
A<sup>35</sup> is Val, d-Val, Nva, Ser, d-Ser, Thr; d-Thr, Abu, Aib, Acb, Ach, Acpe, Acpr,
or is deleted;
$A^{30}$ is Lys, D-Lys, Arg, D-Arg, Dab, D-Dab, Dap, D-Dap, Orn, D-Orn, or is deleted;

$A^{37}$ is Asn, D-Asn, Gln, D-Gln, Asp, D-Asp, Ala, D-Ala, Aib, Acb, Ach, Acpe, Acpr, or is deleted;

$A^{38}$ is Lys, D-Lys, Arg, D-Arg, Dab, D-Dab, Dap, D-Dap, Orn, D-Orn, or is deleted;

$R^1$ is independently selected from a group of H, (C$_1$-C$_{18}$)alkyl and CO(C$_1$-C$_{18}$)alkyl

$R^2$ is independently selected from a group of OH, NH$_2$, (C$_1$-C$_{18}$)alkoxyl, and NH(C$_1$-C$_{18}$)alkyl.

In other embodiments, the PACAP-like compound is a polypeptide having a sequence with at least 80%, 85%, 90%, 95%, 97%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 4-13, or an analog or peptidomimetic thereof, and pharmaceutically acceptable salts thereof. In yet other embodiments, the compound is present in a composition having a pharmaceutically acceptable carrier. In still other embodiments, the polypeptide is conjugated one or more radionuclides (e.g., $^{11}$C, $^{13}$N, $^{15}$O, $^{18}$F, $^{52}$Fe, $^{55}$Co, $^{61}$Cu, $^{62}$Cu, $^{64}$Cu, $^{67}$Cu, $^{67}$Ga, $^{68}$Ga, $^{62}$Zn, $^{62}$Zn, $^{70}$As, $^{71}$As, $^{74}$As, $^{76}$Br, $^{79}$Br, $^{82}$Rb, $^{86}$Y, $^{89}$Zr, $^{110}$In, $^{111}$In, $^{120}$I, $^{123}$I, $^{124}$I, $^{125}$I, $^{131}$I, $^{122}$Xe, $^{175}$Lu, $^{154}$Gd, $^{155}$Gd, $^{156}$Gd, $^{157}$Gd, $^{158}$Gd, $^{94m}$Tc, $^{94}$Tc, and $^{99m}$Tc) or small molecules (e.g., a therapeutic or anticancer agent, such as cisplatin, carboplatin, oxaliplatin, bleomycin, mitomycin C, calicheamicins, maytansinoids, geldanamycin, doxorubicin, idarubicin, daunorubicin, epirubicin, busulfan, carmustine (BCNU), lomustine (CCNU), semustine, thalidomide, lenalidomide, methotrexate, azathioprine, 6-mercaptopurine, fludarabine, 5-azacytidine, pentostatin (2’-deoxycoformycin), cytarabine (cytosine arabinoside), gemcitabine, 5-fluorouracil, hydroxyurea, elesclomol, etoposide, teniposide, amsacrine, camptothecin, topotecan, irinotecan, chlorambucil, cyclophosphamide, ifosfamide, melphalan, bortezomib, vincristine, vinblastine, vincorelbine, paclitaxel, docetaxel, cyclosporine A, tacrolimus (FK506), sirolimus (rapamycin), everolimus, temsirolimus, zotarolimus, or biolimus).
In a second aspect, the invention features a method for treating, managing, or preventing a disease selected from age-related neurodegenerative disease, a central nervous system disorder, Huntington's disease or other CAG codon repeat expansion disease, a retinal disease, an autoimmune disease, keratoconjunctivitis sicca caused by autoimmune diseases or LASIK surgery, type II diabetes, sepsis caused by a bacteria and/or a virus, an acute or chronic cardiovascular disease, an acute or chronic renal diseases, an acute or chronic pulmonary disease, systemic hypertension, a hematological cancer, an eating disorder, an acute or chronic liver disease, osteoporosis, pre-eclampsia, cell and solid organ transplantation, a cognitive disorder, acquired immunodeficiency syndrome (AIDS) dementia complex, aging of the central nervous system, and a disease caused in part by premature in-frame stop codons that result in the synthesis of truncated nonfunctional proteins, said method comprising administering to a subject (e.g., a mammal, such as a human) in need thereof an effective amount of one or more PACAP-like compounds or a pharmaceutically acceptable salt thereof. In several embodiments of the method, the age-related neurodegenerative disease is selected from Alzheimer's disease, Parkinson’s disease and amyotrophic lateral sclerosis; the central nervous system disorder is caused by stroke, heart attack or blunt force trauma, in which, preferably, the blunt force trauma is a concussion or spinal cord trauma; the retinal disease is diabetic retinopathy, macular degeneration or glaucoma; the autoimmune disease is rheumatoid arthritis, Crohn's disease, ulcerative colitis, scleroderma, Sjögren's disease, idiopathic membranous nephropathy, Goodpasture's disease, autoimmune hepatitis, myasthenia gravis, multiple sclerosis, Guillain-Barré syndrome, type I diabetes, Hashimoto's thyroiditis, Graves' disease, pemphigus vulgaris, or lupus erythematosus; the sepsis is caused by a bacterial or viral toxin; the acute or chronic cardiovascular disease is myocardial infarction, atherosclerosis, or restenosis; the acute or chronic renal disease is ischemia/reperfusion injury, nephritis, or drug-induced nephrotoxicity; the acute or chronic pulmonary disease is asthma, chronic obstructive pulmonary disease, cystic fibrosis, or pulmonary arterial hypertension; the hematological cancer is a lymphoid or
myeloid hematopoietic cancer, wherein preferably said lymphoid or myeloid hematopoietic cancer is a leukemia, a lymphoma, a plasma cell dyscrasia, multiple myeloma, or an adenocarcinoma; the acute or chronic liver disease is ischemia/reperfusion injury, hepatitis, and fatty liver; or the disease caused in part by premature in-frame stop codons that result in the synthesis of truncated nonfunctional proteins is selected from cystic fibrosis, Duchenne muscular dystrophy, Hurler's syndrome, nephropathic cystinosis, polycystic kidney disease, retinitis pigmentosa, and ataxia telangiectasia.

In other embodiments of the second aspect of the invention, the subject has an injury to one or more major organs of the body due to treatment with a prophylactic or therapeutic agent other than the PACAP-like compound, trauma, or acute or chronic disease. In other embodiments, the subject is being treated with a primary therapeutic selected from one or more of cisplatin, carboplatin, oxaliplatin, bleomycin, mitomycin C, calicheamicins, maytansinoids, geldanamycin, doxorubicin, idarubicin, daunorubicin, epirubicin, busulfan, carmustine (BCNU), lomustine (CCNU), semustine, thalidomide, lenalidomide, methotrexate, azathioprine, 6-mercaptopurine, fludarabine, 5-azacytidine, pentostatin (2'-deoxycoformycin), cytarabine (cytosine arabinoside), gemcitabine, 5-fluorouracil, hydroxyurea, elesclomol, etoposide, teniposide, amsacrine, camptothecin, topotecan, irinotecan, chlorambucil, cyclophosphamide, ifosfamide, melphalan, bortezomib, vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, cyclosporine A, G418, gentamicin, streptomycin, kanamycin, tobramycin, amikacin, arbekacin, neomycin, netilmicin, paromomycin, rhodostreptomycin, neomycin, framycetin, ribostamycin, bekanamycin, dibekacin, spectinomycin, hygromycin B, paraomomycin sulfate, sisomicin, isepamicin, verdmicin, astromicin, apramycin, amphotericin B, rifampicin, pentamidine, cyclosporine A, tacrolimus (FK506), sirolimus (rapamycin), everolimus, temsirolimus, zotarolimus, or biolimus (e.g., the subject is being treated with a primary therapy that includes treatment with carmustine, vincristine, paclitaxel, or thalidomide). In another embodiment, the subject has a lymphoid or myeloid cancer.
In still other embodiments of the second aspect of the invention, the PACAP-like compounds, or pharmaceutically acceptable salts thereof, bind to one or more of the PACAP/MIP receptors and/or reduce one or more injuries to one or more major organs of the body of the subject due to treatment with a prophylactic or therapeutic agent other than the PACAP-like compound, trauma, or acute or chronic disease. In other embodiments, the PACAP-like compound is a compound of the first aspect of the invention, or a pharmaceutically acceptable salt thereof. In an embodiment, the subject is resistant to treatment with a glucocorticoid (e.g., dexamethasone, prednisolone, methylprednisolone, or prednisone). In another embodiment, administration of the PACAP-like compound in the subject replaces administration of a corticosteroid selected from prednisone or dexamethasone when the subject is treated using the COP (cyclophosphamide, vincristine and prednisone) or VAD (vincristine, doxorubicin and dexamethasone) regimen.

In other embodiments of the second aspect of the invention, the PACAP-like compound is linked to a polyethylene glycol polymer with a molecular weight from about 4 kilodaltons to about 40 kilodaltons. In still other embodiments, the PACAP-like compound is the unamidated (free acid) form of one or more of the compounds of the first aspect of the invention, and the compound may be flanked by amino-acid consensus sequences for one or more proteolytic enzymes. The method may also involve administration of a PACAP-like compound of the first aspect of the invention that is a peptidomimetic analog.

In still other embodiments of the first aspect of the invention, the PACAP-like compound is administered at a dosage that produces a concentration of $10^{-14}$ M to $10^{-6}$ M in the blood of the subject. In another embodiment, the PACAP-like compound is administered by intravenous infusion at a rate of about 1 pmol/kg body weight/hour to about 20 pmol/kg body weight/hour. In other embodiments, the compound is administered for about 1-12 hours. In still other embodiments, the PACAP-like compound is injected intraperitoneally, subcutaneously, intramuscularly, intranasally, or as an aerosol one or more times (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 times) per day, week, month, or year. In other embodiments, the PACAP-like compound is
administered orally in a time-dependent or pH-dependent formulation one or more times per day, week, month, or year; the PACAP-like compound is administered as a controlled release or a sustained release formulation; the PACAP-like compound is administered after encapsulation in liposomes or microparticles; the PACAP-like compound is administered transcutaneously after encapsulation in dendrimers; the PACAP-like compound is used to coat a metallic or a biodegradable stent; or the PACAP-like compound is administered in combination with one or more other cytoprotective adjuvants, such as amifostine, dexrazoxane, mesna, palifermin, or N-acetylcysteine.

In other embodiments of the second aspect of the invention, the injuries to one or more major organs of the body (e.g., the nervous system, heart, lung, kidneys, liver, ear, or gastrointestinal tract) are caused by a prophylactic or therapeutic agent other than a PACAP-like compound (e.g., an anticancer agent, a steroid, or an aminoglycoside). The prophylactic or therapeutic agent may be one or more of cisplatin, carboplatin, oxaliplatin, bleomycin, mitomycin C, calicheamicins, maytansinoids, geldanamycin, doxorubicin, idarubicin, daunorubicin, epirubicin, busulfan, carmustine (BCNU), lomustine (CCNU), semustine, thalidomide, lenalidomide, methotrexate, azathioprine, 6-mercaptopurine, fludarabine, 5-azacytidine, pentostatin (2'-deoxycoformycin), cytarabine (cytosine arabinoside), gemcitabine, 5-fluorouracil, hydroxyurea, elesclomol, etoposide, teniposide, amsacrine, camptothecin, topotecan, irinotecan, chlorambucil, cyclophosphamide, ifosfamide, melphalan, bortezomib, vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, cyclosporine A, G418 (GENETICIN™), gentamicin, streptomycin, kanamycin, tobramycin, amikacin, arbekacin, neomycin, netilmicin, paromomycin, rhodostreptomycin, neomycin, framycetin, ribostamycin, bekanamycin, dibekacin, spectinomycin, hygromycin B, paraomomycin sulfate, sisomicin, isepamicin, verdmicin, astromicin, apramycin, amphotericin B, rifampicin, pentamidine, cyclosporine A, tacrolimus (FK506), sirolimus (rapamycin), everolimus, temsirolimus, zotarolimus, or biolimus. In yet other embodiments, the injuries to one or more major organs of the body are due to treatment with an unconjugated therapeutic or anticancer agent, a therapeutic or anticancer agent conjugated
to a monoclonal antibody or a bioactive peptide, or an unconjugated bioactive peptide. In other embodiments, the PACAP-like compound is conjugated to a therapeutic or anticancer agent or the PACAP-like compound has an additive anticancer effect when administered with one or more other anticancer agents (e.g., those described herein). In an embodiment, the subject is being treated with one or more therapeutic or anticancer agents for a hematopoietic cancer, a myeloproliferative disorder, or multiple myeloma. In other embodiments, the subject is being treated with an aminoglycoside and the PACAP-like compound is administered to inhibit or reduce side-effects resulting from administration of said aminoglycoside (e.g., amikacin, arbekacin, G418, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, rhodostreptomycin, streptomycin, neomycin, framycetin, ribostamycin, bekanamycin, dibekacin, spectinomycin, hygromycin B, paraomomycin sulfate, sisomicin, isepamicin, verdamicin, tobramycin, astromicin, and apramycin). In other embodiments, the PACAP-like compound inhibits or reduces nephotoxicity or ototoxicity caused by the aminoglycoside (e.g., amikacin, arbekacin, G418, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, rhodostreptomycin, streptomycin, neomycin, framycetin, ribostamycin, bekanamycin, dibekacin, spectinomycin, hygromycin B, paraomomycin sulfate, sisomicin, isepamicin, verdamicin, tobramycin, astromicin, and apramycin), in particular gentamicin.

A third aspect of the invention features a method for the localization, diagnosis, or treatment of a disseminated cancer or a metastatic tumor (e.g., a hematological cancer, such as leukemia, lymphoma, or myeloma) in a subject (e.g., a mammal, such as a human) by administering an effective amount of a conjugate that includes one or more PACAP-like compounds or a pharmaceutically acceptable salt thereof coupled to one or more radionuclides (e.g., $^{11}$C, $^{13}$N, $^{15}$O, $^{18}$F, $^{52}$Fe, $^{55}$Co, $^{61}$Cu, $^{62}$Cu, $^{64}$Cu, $^{67}$Cu, $^{67}$Ga, $^{68}$Ga, $^{62}$Zn, $^{63}$Zn, $^{70}$As, $^{71}$As, $^{74}$As, $^{76}$Br, $^{79}$Br, $^{82}$Rb, $^{86}$Y, $^{90}$Zr, $^{110}$In, $^{111}$In, $^{120}$I, $^{123}$I, $^{124}$I, $^{125}$I, $^{131}$I, $^{125}$I, $^{127}$I, $^{154}$Gd, $^{155}$Gd, $^{156}$Gd, $^{157}$Gd, $^{158}$Gd, $^{94m}$Tc, $^{94}$Tc, and $^{99m}$Tc). In an embodiment, the PACAP-like compounds bind to one or more of PACAP/VIP receptor on the surface of one or more cells of the disseminated cancer or metastatic tumor; the PACAP-like compound includes one or more
of those compounds of the first aspect of the invention or a pharmaceutically acceptable salt thereof (e.g., a polypeptide with a sequence having a sequence identity of 85%-100% to a sequence selected from SEQ ID NOs: 4-13). In other embodiments, the conjugate targets a cell that is a component of a granuloma caused by one or more infectious agents or an autoimmune disease; the subject is being treated with one or more of the conjugates for lymphoid, myeloid hematopoietic cancer, or multiple myeloma.

A fourth aspect of the invention features a method of producing a conjugate by coupling one or more radionuclides (¹¹C, ¹³N, ¹⁸O, ³²P, ⁵²Fe, ⁵⁵Co, ⁶¹Cu, ⁶²Cu, ⁶⁴Cu, ⁶⁷Cu, ⁶⁷Ga, ⁶⁸Ga, ⁶²Zn, ⁶³Zn, ⁷⁰As, ⁷¹As, ⁷⁴As, ⁷⁶Br, ⁷⁸Br, ⁸²Rb, ⁸⁶Y, ⁹⁰Zr, ¹⁰⁰In, ¹¹¹In, ¹²⁰I, ¹²³I, ¹²⁴I, ¹²⁵I, ¹³¹I, ¹²²Xe, ¹⁷⁵Lu, ¹⁵⁴Gd, ¹⁵⁵Gd, ¹⁵⁶Gd, ¹⁵⁷Gd, ¹⁵⁸Gd, ¹⁹⁴mTc, ¹⁹⁴Tc, and ⁹⁹mTc) or small molecules (e.g., a therapeutic or anticancer agent, such as cisplatin, carboplatin, oxaliplatin, bleomycin, mitomycin C, calicheamicins, maytansinoids, geldanamycin, doxorubicin, idarubicin, daunorubicin, epirubicin, busulfan, carmustine (BCNU), lomustine (CCNU), semustine, thalidomide, lenalidomide, methotrexate, azathioprine, 6-mercaptopurine, fludarabine, 5-azacytidine, pentostatin (2'-deoxycoformycin), cytarabine (cytosine arabinoside), gemcitabine, 5-fluorouracil, hydroxyurea, elesclomol, etoposide, teniposide, amsacrine, camptothecin, topotecan, irinotecan, chlorambucil, cyclophosphamide, ifosfamide, melphalan, bortezomib, vincristine, vinblastine, vincristine, paclitaxel, docetaxel, cyclosporin A, G418, gentamicin, streptomycin, kanamycin, tobramycin, amikacin, arbekacin, neomycin, netilmicin, paromomycin, rhodostreptomycin, neomycin, framycetin, ribostamycin, bekanamycin, dibekacin, spectinomycin, hygromycin B, paraomomycin sulfate, sisomicin, isepamicin, vermicicin, astromicin, apramycin, amphotericin B, rifampicin, pentamidine, cyclosporine A, tacrolimus (FK506), sirolimus (rapamycin), everolimus, temsirolimus, zotarolimus, or biolimus) to one or more PACAP-like compounds. In other embodiments, the PACAP-like compound includes one or more of those compounds of the first aspect of the invention or a pharmaceutically
acceptable salt thereof (e.g., a polypeptide with a sequence having a sequence identity of 85%-100% to a sequence selected from SEQ ID NOs: 4-13).

A fifth aspect of the invention features a method for targeting delivery of a therapeutic or anticancer agent to a specific cell or tissue of a subject (e.g., a mammal, such as a human) by administering to the subject an effective amount of a conjugate that includes one or more PACAP-like compounds (e.g., one or more of those compounds of the first aspect of the invention (e.g., a polypeptide with a sequence having a sequence identity of 85%-100% to a sequence selected from SEQ ID NOs: 4-13)), or a pharmaceutically acceptable salt thereof, coupled to one or more small molecules (e.g., a therapeutic agent or anticancer agent, such as cisplatin, carboplatin, oxaliplatin, bleomycin, mitomycin C, calicheamicins, maytansinoids, geldanamycin, doxorubicin, idarubicin, daunorubicin, epirubicin, busulfan, carmustine (BCNU), lomustine (CCNU), semustine, thalidomide, lenalidomide, methotrexate, azathioprine, 6-mercaptopurine, fludarabine, 5-azacytidine, pentostatin (2'-deoxycoformycin), cytarabine (cytosine arabinoside), gemcitabine, 5-fluorouracil, hydroxyurea, elesclomol, etoposide, teniposide, amsacrine, camptothecin, topotecan, irinotecan, chlorambucil, cyclophosphamide, ifosfamide, melphalan, bortezomib, vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, cyclosporine A, G418, gentamicin, streptomycin, kanamycin, tobramycin, amikacin, arbekacin, neomycin, netilmicin, paromomycin, rhodostreptomycin, neomycin, framycetin, ribostamycin, bekamycin, dibekacin, spectinomycin, hygromycin B, paraomomycin sulfate, sisomicin, isepamicin, verdimicin, astromicin, apramycin, amphotericin B, rifampicin, pentamidine, cyclosporine A, tacrolimus (FK506), sirolimus (rapamycin), everolimus, temsirolimus, zotarolimus, or biolimus, or an anti-inflammatory agent). In other embodiments, the one or more PACAP-like compounds bind to one or more PACAP/VIP receptors on the surface of the cell or tissue and the conjugate enters the interior of the cell or tissue by receptor-mediated endocytosis.

In other embodiments of the fifth aspect of the invention, the subject has a disease (e.g., age-related neurodegenerative disease, a central
nervous system disorder, Huntington's disease or other CAG codon repeat expansion disease, a retinal disease, an autoimmune disease, keratoconjunctivitis sicca caused by autoimmune diseases or LASIK surgery, type II diabetes, sepsis caused by a bacteria and/or a virus, an acute or chronic cardiovascular disease, an acute or chronic renal diseases, an acute or chronic pulmonary disease, systemic hypertension, a hematological cancer, an eating disorder, an acute or chronic liver disease, osteoporosis, pre-eclampsia, cell and solid organ transplantation, a cognitive disorder, acquired immunodeficiency syndrome (AIDS) dementia complex, aging of the central nervous system, or a disease caused in part by premature in-frame stop codons that result in the synthesis of truncated nonfunctional proteins). In several embodiments of the method of the fifth aspect of the invention, the age-related neurodegenerative disease is selected from Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis; the central nervous system disorder is caused by stroke, heart attack or blunt force trauma, in which, preferably, the blunt force trauma is a concussion or spinal cord trauma; the retinal disease is diabetic retinopathy, macular degeneration or glaucoma; the autoimmune disease is rheumatoid arthritis, Crohn's disease, ulcerative colitis, scleroderma, Sjögren's disease, idiopathic membranous nephropathy, Goodpasture's disease, autoimmune hepatitis, myasthenia gravis, multiple sclerosis, Guillain-Barré syndrome, type I diabetes, Hashimoto's thyroiditis, Graves' disease, pemphigus vulgaris, or lupus erythematosus; the sepsis is caused by a bacterial or viral toxin; the acute or chronic cardiovascular disease is myocardial infarction, atherosclerosis, or restenosis; the acute or chronic renal disease is ischemia/reperfusion injury, nephritis, or drug-induced nephrotoxicity; the acute or chronic pulmonary disease is asthma, chronic obstructive pulmonary disease, cystic fibrosis, or pulmonary arterial hypertension; the hematological cancer is a lymphoid or myeloid hematopoietic cancer, wherein preferably said lymphoid or myeloid hematopoietic cancer is a leukemia, a lymphoma, a plasma cell dyscrasia, multiple myeloma, or an adenocarcinoma; the acute or chronic liver disease is ischemia/reperfusion injury, hepatitis, and fatty liver; or the disease caused in part by premature in-frame stop codons that result in the synthesis of
truncated nonfunctional proteins is selected from cystic fibrosis, Duchenne muscular dystrophy, Hurler's syndrome, nephropathic cystinosis, polycystic kidney disease, retinitis pigmentosa, and ataxia telangiectasia.

In other embodiments, the subject has an injury to one or more major organs of the body due to treatment with a prophylactic or therapeutic agent other than the PACAP-like compound, trauma, or acute or chronic disease. In still other embodiments, the PACAP-like compounds, or pharmaceutically acceptable salts thereof, bind to one or more of the PACAP/VIP receptors and/or reduce one or more injuries to one or more major organs of the body of the subject due to treatment with a prophylactic or therapeutic agent other than the PACAP-like compound, trauma, or acute or chronic disease.

In still other embodiments, the small molecule is anti-inflammatory agent and the subject is being treated for rheumatoid arthritis; the small molecule is an anticancer agent and the subject is being treated for multiple myeloma; the prophylactic or therapeutic agent is an anticancer agent, a steroid, an anti-inflammatory, or an aminoglycoside.

A sixth aspect of the invention features a method for detecting a granuloma in subject by administering to the subject (e.g., a mammal, such as a human) an effective amount of the polypeptide of the first aspect of the invention, or a pharmaceutically acceptable salt thereof, conjugated to a radionuclide (e.g., $^{11}$C, $^{13}$N, $^{15}$O, $^{16}$F, $^{52}$Fe, $^{55}$Co, $^{61}$Cu, $^{62}$Cu, $^{64}$Cu, $^{67}$Cu, $^{67}$Ga, $^{68}$Ga, $^{62}$Zn, $^{63}$Zn, $^{70}$As, $^{71}$As, $^{74}$As, $^{76}$Br, $^{79}$Br, $^{82}$Rb, $^{86}$Y, $^{89}$Zr, $^{110}$In, $^{111}$In, $^{120}$I, $^{123}$I, $^{124}$I, $^{125}$I, $^{131}$I, $^{122}$Xe, $^{175}$Lu, $^{154}$Gd, $^{155}$Gd, $^{156}$Gd, $^{157}$Gd, $^{158}$Gd, $^{94m}$Tc, $^{94}$Tc, or $^{99m}$Tc). In other embodiments, the subject has an infectious or autoimmune disease (e.g., tuberculosis or Crohn's disease); the polypeptide is a PACAP-like compound that is capable of binding to one or more of the PACAP/VIP receptors on the surface of target cells; the subject is being treated for tuberculosis; the subject is being treated with one or more of the conjugates of the invention that include an imaging agent for tuberculosis; the subject is being treated with $^{99m}$Tc-isonicotinylhydrazine (INH); the subject is being treated for Crohn's disease; the subject is being treated with one or more of the conjugates of the invention that include an imaging agent for Crohn's disease.
These novel PACAP analogs can be used as prophylactic/therapeutic agents for a wide range of medical disorders in humans or other mammals, including (but not limited to) age-related neurodegenerative diseases (such as Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis), injuries to the central nervous system caused by stroke, heart attack and blunt force trauma (such as concussions and spinal cord trauma), Huntington’s disease and other CAG codon repeat expansion diseases, retinal diseases (such as diabetic retinopathy, macular degeneration and glaucoma), autoimmune diseases (such as rheumatoid arthritis, Crohn’s disease, ulcerative colitis, scleroderma, Sjögren’s disease, idiopathic membranous nephropathy, Goodpasture’s disease, autoimmune hepatitis, myasthenia gravis, multiple sclerosis, Guillain-Barré syndrome, type I diabetes, Hashimoto’s thyroiditis, Graves’ disease, pemphigus vulgaris, and lupus erythematosus), keratoconjunctivitis sicca caused by autoimmune diseases or LASIK surgery, type II diabetes, sepsis caused by bacteria and/or viruses (including bacterial and viral toxins), acute and chronic cardiovascular diseases (such as myocardial infarction, atherosclerosis and restenosis), acute and chronic renal diseases (such as ischemia/reperfusion injury, nephritis and drug-induced nephrotoxicity), acute and chronic pulmonary diseases (such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, and pulmonary arterial hypertension), systemic hypertension, hematological cancers (such as leukemias, lymphomas and plasma cell dyscrasias), eating disorders, acute and chronic liver diseases (such as ischemia/reperfusion injury, hepatitis and fatty liver), osteoporosis, pre-eclampsia, cell and solid organ transplantation, cognitive disorders, AIDS dementia complex, and aging of the central nervous system. The rationale and documentation for these diverse medical indications are described and documented below.

As life expectancy has increased, age-related neurodegenerative disorders, such as Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis, have become more prevalent and placed a greater burden on society. The published literature indicates that PACAP-like peptides can protect neurons (neuroepithelial cells) in vitro against a very broad range of

Published experiments using common *in vivo* preclinical models indicate that PACAP-like peptides should be efficacious for the treatment of acute neurological diseases, including (but not limited to) stroke (Reglodi et al., *Stroke* 31:1411-1417, 2000; Chen et al., *Regul Pept* 137:4-19, 2006), the central nervous system sequelae of heart attack (Uchida et al., *Brain Res* 736:280-286, 1996; Lenti et al., *Brain Res* 1283:50-57, 2009) and blunt force trauma to the brain and spinal cord (Farkas et al., *Regul Pept* 123:69-75, 2004; Chen and Tzeng, *Neurosci Lett* 384:117-121, 2005; Kövesdi et al., *Neurotox Res* 13:71-78, 2008).

Huntington's disease is a fatal autosomal dominant disorder that is characterized by progressive cognitive and motor dysfunction. It is caused by expansion of the CAG codon (glutamine) repeat in the gene that codes for huntingtin. The neuropathological hallmark is the degeneration of neurons in the striatum. There are no effective treatments for Huntington's disease or the other CAG codon repeat diseases (such as spinobulbar muscular atrophy and the spinocerebellar ataxias). Published clinical experiments and experiments using common *in vivo* preclinical models indicate that PACAP-like peptides should be efficacious for the treatment of Huntington's disease or other CAG codon repeat diseases (Emson et al., *Brain Res* 173:174-178, 1979; Tamás et al., *Ann N Y Acad Sci* 1070:570-574, 2006; Fahrenkrug et al., *J Mol Neurosci* 31:139-148, 2007).


Keratoconjunctivitis sicca (dry eye) is an eye disorder that is caused by decreased tear production or increased tear evaporation, with decreased tear production being far more common. The most common cause of decreased tear production is aging. There are numerous other causes for decreased tear production, including hyposecretion of the lacrimal gland due to destruction, therapeutic agents (such as atropine, tricyclic antidepressants
and morphine) or post-radiation fibrosis, and hyposcretion of the lacrimal gland associated with systemic autoimmune diseases (such as Wegener's granulomatosis, lupus erythematosus and, especially, Sjögren's disease). Dry eye is also a common side-effect of LASIK surgery. Published experiments using common *in vitro* and *in vivo* preclinical models indicate that PACAP-like peptides should also be efficacious for the treatment of keratoconjunctivitis sicca (dry eye) caused by autoimmune diseases or LASIK surgery (Lodde et al., *Ann Rheum Dis* **65**:195-200, 2006; Fukiage et al., *Am J Ophthalmol* **143**:255-262, 2007; Gaal et al., *J Mol Neurosci* **36**:321-329, 2008; Nakamachi et al., *VIP, PACAP and Related Peptides* (Ninth International Symposium), Kagoshima, 2009).

The β-cells of the pancreas express both the PAC₁ receptor and the VPAC₂ receptor (Ahrén, *Ann NY Acad Sci* **1144**:28-35, 2008). PAC₁ receptor-deficient mice had reduced glucose-stimulated insulin secretion and reduced glucose tolerance compared to wild-type mice (Jamen et al., *J Clin Invest* **105**:1307-1315, 2000), while mice chronically treated with the PAC₁ receptor-specific agonist maxadilan had increased basal plasma levels of insulin and increased glucose tolerance compared to saline-treated mice (Yu et al., *Peptides* **29**:1347-1353, 2008). Mice continuously infused with the VPAC₂ receptor-selective agonist BAY 55-9837 had increased basal plasma levels of insulin and increased glucose tolerance compared to saline-treated mice (Tsutsumi et al., *Diabetes* **51**:1453-1460, 2002). These published articles indicate that PACAP-like peptides should be efficacious for the treatment of type II diabetes.


Published experiments using common *in vitro* and *in vivo* preclinical models indicate that PACAP-like peptides should also be efficacious for the

Published experiments using common in vitro and in vivo preclinical models indicate that PACAP-like peptides should be efficacious for the treatment of a wide range of acute renal injuries, including (but not limited to) injuries caused by ischemia/reperfusion (Riera et al., Transplantation 72:1217-1223, 2001; Szakaly et al., J Mol Neurosci 36:89-96, 2008; see Figures 6 and 7), light-chain immunoglobulin overload (Li et al., Regul Pept 145:24-32, 2008), and many commonly used therapeutic agents such as gentamicin (Li et al., Regul Pept 145:24-32, 2008), streptozotocin (Li et al., Regul Pept 145:24-32, 2008), cisplatin (Li et al., Peptides 31:592-602, 2010; see Figure 5), and doxorubicin (Racz et al., J Mol Neurosci 42:419-427, 2010; Moru et al., Circ J 74:1183-1190).

Published experiments using common in vivo preclinical models indicate that PACAP-like peptides should be efficacious for the treatment of a wide range of acute and chronic pulmonary diseases, including (but not limited to) asthma (Lindén et al., Thorax 58:217-221, 2003; Onoue et al., Peptides 28:1640-1650, 2007), chronic obstructive pulmonary disease (Kinhult et al., Peptides 22:2151-2154, 2001; Onoue et al., Eur J Biochem 271:1757-1767, 2004; Onoue et al., Peptides 28:1640-1650, 2007), cystic fibrosis (Ameen et al., J Cell Sci 112:887-894, 1999; Dérand et al., Br J Pharmacol 141:698-708, 2004; Sergejeva et al., Regul Pept 117:149-154, 2004; Chappe et al., J Pharmacol Exp Ther 327:226-238, 2008; Rafferty et al., J Pharmacol Exp Ther 331:2-13, 2009), and pulmonary arterial

Systemic hypertension is a polygenic disease. Polymorphisms in the PACAP gene appear to represent predispositions for the development of systemic hypertension (Rutherford et al., Am J Med Genet A 126:241-247, 2004). Thus, the invention also features a method of determining whether a subject (e.g., a mammal, such as a human) has an increased risk of systemic hypertension. In particular, the method involves detecting one or more polymorphisms in the PACAP gene of the subject, wherein the presence of the polymorphisms indicates an increased risk of systemic hypertension in the subject.

Cancer is the leading cause of death in industrialized countries.

Chemotherapy is the preferred treatment for disseminated cancers and metastatic tumors. Chemotherapy is also frequently used when surgery or radiation therapy have not completely eradicated a localized tumor, or as an adjunctive treatment with surgery or radiation therapy. Published experiments using common in vitro and in vivo preclinical models indicate that PACAP-like peptides should also be efficacious for the treatment of hematological cancers, including (but not limited to) blood cancers such as lymphoid and myeloid leukemias, lymphomas and plasma cell disorders (Waldenström's macroglobulinemia, multiple myeloma, etc.). The published literature suggests that PACAP-like peptides inhibit the proliferation of most normal hematopoietic cells (e.g., Ottaway and Greenberg, J Immunol 132:417-423, 1984; Boudard and Bastide, J Neurosci Res 29:29-41, 1991; Tatsuno et al., Endocrinology 128:728-734, 1991; Trejter et al., Histol Histopathol 16:155-158, 2001). PACAP-like peptides have been shown to inhibit the proliferation of HEL myeloid leukemia cells (Hayez et al., J Neuroimmunol 149:167-181, 2004). Two of the inventors of the present invention have shown that PACAP-like peptides potently inhibit the proliferation of multiple myeloma cells (Li et al., Regul Pept 145:24-32, 2008; see Figures 3 and 4). Two of the inventors of the present invention have also shown that PACAP-like peptides
are efficacious in a patient with multiple myeloma (Li et al., *Peptides* **28**:1891-1895, 2007). The inventors of the present invention have recently shown that PACAP-like peptides enhance the killing of both lymphoid and myeloid hematopoietic cancer cells by the commonly used anticancer agents carmustine, vincristine and thalidomide (Li et al., PCT/US2009/058445, 2009). Therefore, PACAP-like peptides should be efficacious for the treatment of lymphoid and myeloid hematopoietic cancers both as monotherapeutics and as adjunctive therapeutics with commonly used anticancer agents.

In contrast, the published literature suggests that PACAP-like peptides promote the proliferation and survival of most (though not all) epithelial cancer cells. Oka et al. (*Amer J Pathol* **155**:1893-1900, 1999) reported that PACAP protects HP75 human pituitary adenoma cells against apoptotic cell death caused by treatment with transforming growth factor-β1, and PACAP has been shown more recently to protect PC-3 androgen-independent human prostate cancer cells (Gutiérrez-Cañas et al., *Br J Pharmacol* **139**:1050-1058, 2003) and CRL-2768 rat schwannoma cells (Castorina et al., *Brain Res* **1241**:29-35, 2008) against apoptotic cell death caused by serum withdrawal. Onoue et al. (*FEBS J* **275**:5542-5551, 2008) have shown that PACAP protects RIN-m5F insulinoma cells against apoptotic cell death caused by the anticancer agent streptozotocin. In addition, PACAP(6-38), a PACAP/VIP receptor antagonist, inhibited the growth in nude mice of xenografts of PC-3 human prostate cancer cells (Leyton et al., *Cancer Lett* **125**:131-139, 1998), NCI-H838 human non-small cell lung cancer cells (Zia et al., *Cancer Res* **55**:4886-4891, 1995) and MCF-7 human breast cancer cells (Leyton et al., *Breast Cancer Res Treat* **56**:177-186, 1999). Therefore, parenteral administration of PACAP-like peptides cannot be used to treat patients with most (though perhaps not all) solid epithelial tumors. However, parenteral administration of PACAP/VIP receptor antagonists could be used to treat patients with solid epithelial tumors in combination with anticancer agents whose dose-limiting toxicity was myelosuppression.

Glucocorticoids are frequently used for the treatment of patients with blood cancers and autoimmune diseases in order to inhibit the activity of B- and T-lymphocytes. However, a significant portion of the patients treated with
glucocorticoids eventually become resistant to the steroid (Barnes & Adcock, *Lancet* 373:1905-1917, 2009). The inventors of the present invention have shown that PACAP-like peptides can still inhibit the proliferation of B-lymphocytes from a patient with multiple myeloma who was being treated with a dexamethasome-containing regimen (Greenstein et al., *Exp Hematol* 31:271-282, 2003) even after the B-lymphocytes have become resistant to dexamethasone (compare Figures 8 and 9). These experiments indicate that PACAP-like peptides should be efficacious in patients with blood cancers and autoimmune diseases even after the patients have become resistant to glucocorticoids.


Osteoporosis is characterized by a reduction in the mineral density of bone and, consequently, an increased risk of bone fractures. It is more common in women than men, especially in postmenopausal women. Osteoporosis is also a common side-effect of many glucocorticoid-containing anticancer therapeutic regimens. Published experiments using common in vitro preclinical models indicate that PACAP-like peptides should be efficacious for the treatment of osteoporosis (Winding et al., *Exp Physiol* 82:871-886, 1997; Mukohyama et al., *Biochem Biophys Res Commun* 271:158-163, 2000).
Pre-eclampsia is a life-threatening disorder that occurs during 5-10% of pregnancies, usually during the second and third trimester. Pre-eclampsia involves damage to the placental endothelium, kidneys and liver. The principal symptoms are systemic hypertension, inflammation and elevated levels of protein in the urine. Published clinical experiments and experiments using common in vitro and in vivo preclinical models indicate that PACAP-like peptides should be efficacious for the treatment of pre-eclampsia (Holst et al., Br J Obstet Gynaecol 98:803-806, 1991; Steenstrup et al., Regul Pept 61:197-204, 1996; Kinhult et al., Peptides 22:2151-2154, 2001; Lee et al., J Hypertens 21:395-402, 2003; Rácz et al., Gen Comp Endocrinol 153:115-123, 2007; Li et al., Regul Pept 145:24-32, 2008; Reglodi et al., J Endocrinol Invest 33:443-445, 2010).

Published experiments using common in vivo preclinical models also indicate that PACAP-like peptides should be efficacious for the treatment of cell (Scharf et al., J Mol Neurosci 36:79-88, 2008; Kim et al., Diabetes 58:641-651, 2009; Sakuma et al., Transplant Proc 41:343-345, 2009) and solid organ transplantation (Alessandri, Acta Biomed Ateneo Parmense 65:59-73, 1994; Riera et al., 2001; Ferencz et al., J Mol Neurosci 37:168-176, 2008; Jungraithmayr et al., Transplantation 88:478-485, 2009; Zhai et al., Transplantation 87:1140-1146, 2009; see Figure 6).


The AIDS dementia complex (HIV encephalopathy) a severe cognitive and motor disorder caused by infection of microglial cells in the brain by the human immunodeficiency virus. The pathological features include microglial activation, neuronal apoptosis and demyelination. Stimulation of the VPAC₂ receptor has been shown to inhibit integration of the human immunodeficiency
virus into genomic DNA (Bokaei et al., *Virology* **362**:38-49, 2007). In addition, PACAP has been shown to protect cortical neurons against the toxic effects of the envelope glycoprotein of the human immunodeficiency virus gp120 (Arinmura et al., *Ann NY Acad Sci* **739**:228-243, 1994; Brenneman et al., *Neuropeptides* **36**:271-280, 2002) and to "deactivate" activated microglial cells (Kong et al., *Neuroscience* **91**:493-500, 1999; Delgado et al., *Glia* **39**:148-161, 2002).

Normal aging of the central nervous system is accompanied by an increase in the levels of proinflammatory cytokines and superoxide, and a decrease in both the number of basal forebrain cholinergic neurons and the rate of proliferation of neural progenitor cells in the subependymal zone of the dentate gyrus (Ye and Johnson, *Neuroimmunomodulation* **9**:183-192, 2001; Godbout et al., *FASEB J* **19**:1329-1331, 2005; Baskerville et al., *Neuroreport* **17**:1819-1823, 2006). Reduction of extracellular superoxide levels and stimulation of neural progenitor cell proliferation in the subependymal zone of the dentate gyrus improves cognitive performance during aging (Sun et al., *Endocrinology* **146**:1138-1144, 2005; Hu et al., *J Neurosci* **26**:3933-3941, 2006). PACAP has been shown to protect basal forebrain cholinergic neurons against apoptosis, inhibit inflammation, reduce extracellular superoxide levels, stimulate the proliferation of neural progenitor cells in the subependymal zone of the dentate gyrus, and enhance learning and memory (Takei et al., *Eur J Neurosci* **12**:2273-2280, 2000; Otto et al., *J Neurosci* **21**:5520-5527, 2001; Sacchetti et al., *Neurobiol Learn Mem* **76**:1–6; 2001; Mercer et al., *J Neurosci Res* **76**:205-215, 2004). Therefore, PACAP-like compounds of the invention should be efficacious for reversing the cognitive and motor decline during normal aging.

The PACAP analogs and compounds of the invention can be coupled to suitable radionuclides and used in the localization, diagnosis and treatment of disseminated cancers and metastatic tumors in humans or other mammals (Raderer et al., *J Nucl Med* **39**:1570-1575, 1998; Reubi, *Endocr Rev* **24**:389–427, 2003; Zhang et al., *Regul Pept* **144**:91-100, 2007; Bodei et al., *J Endocrinol Invest* **32**:360-369, 2009), and/or coupled to small molecule therapeutics and used as vectors for targeted drug delivery to humans or
other mammals (Reubi, 2003; Moody et al., Peptides, 28:1883-1890, 2007). Examples of suitable radionuclides that can be coupled to the PACAP-like compounds of the invention (e.g., one or more of the PACAP-like compounds having the sequence of Formula (I) (e.g., the sequence of SEQ ID NOs: 4-13)) include, e.g., a γ-emitting radionuclide, Auger-emitting radionuclide, β-emitting radionuclide, an α-emitting radionuclide, or a positron-emitting radionuclide (e.g., 11C, 15N, 18O, 18F, 52Fe, 55Co, 61Cu, 62Cu, 64Cu, 67Cu, 67Ga, 68Ga, 62Zn, 63Zn, 70As, 71As, 74As, 76Br, 79Br, 82Rb, 86Y, 89Zr, 110In, 111In, 120I, 123I, 124I, 125I, 131I, 122Xe, 175Lu, 154Gd, 155Gd, 156Gd, 157Gd, 158Gd, 94mTc, 94Tc, and 99mTc). The PACAP analogs and compounds of the invention can also be coupled to suitable imaging agents and used in the localization of granulomas in humans or other mammals with various infectious or autoimmune diseases (e.g., Metwali et al., J Immunol 157:265-270, 1996). Examples of suitable imaging agents include, e.g., 99mTc, 51Cr, 67Ga, 68Ga, 111In, 168Yb, 140La, 90Y, 88Y, 153Sm, 156Ho, 165Dy, 64Cu, 97Ru, 103Ru, 186Re, 188Re, 203Pb, 211Bi, 212Bi, 213Bi, and 214Bi. Metal components that are useful as detectable labels may be a metal ion from heavy elements or rare earth ions, such as Gd³⁺, Fe³⁺, Mn³⁺, or Cr²⁺. Conjugates that include paramagnetic or superparamagnetic metals are useful as diagnostic agents in MRI imaging applications.

Paramagnetic metals that may be used in conjunction with the PACAP-like compounds of the invention include, but are not limited to, chromium (III), manganese (II), iron (II), iron (III), cobalt (II), nickel (II), copper (II), praseodymium (III), neodymium (III), samarium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III), erbium (III), and ytterbium (III). Examples of small molecules include compounds having a molecular weight of less than 4,000 g/mol, more preferably having a molecular weight in the range of 200 to 2,000 g/mol, e.g., less than 2,000 g/mol, less than 1,000 g/mol, or even less than 900 g/mol. Examples of small molecules include, but are not limited to camptothecin, homocamptothecin, colchicine, thiocolchicine, combretastatin, dolastatin, doxorubicin, methotrexate, podophyllotoxin, rhizoxin, rhizoxin D, a taxol, paclitaxel, CC1065, and a maytansinoid, as well as those therapeutic and anticancer agents described below.
The maximal tolerable dose of the most commonly used cancer therapeutics is limited by their toxic effects on one or more major organs of the body of humans or other mammals. For example, the dose-limiting toxicity for cancer chemotherapy with cisplatin is nephrotoxicity (Kintzel, *Drug Saf* 24:19-38, 2001), the dose-limiting toxicity for cancer chemotherapy with bleomycin is pulmonary toxicity (Chandler, *Clin Chest Med* 11:21-30, 1990), and the dose-limiting toxicity for cancer chemotherapy with doxorubicin is cardiotoxicity (Takemura & Fujiwara, *Prog Cardiovasc Dis* 49:330-352, 2007). Several strategies have been used to increase the maximal tolerable dose of cancer therapeutics and, thus, increase their therapeutic effectiveness. For example, cancer therapeutics have been conjugated to monoclonal antibodies directed against tumor-associated antigens (Wu & Senter, *Nat Biotechnol* 23:1137-1146, 2005) or to bioactive peptides whose receptors are highly expressed in selected types of tumors (Reubi, 2003) in order to preferentially deliver the anticancer agent to the interior of tumor cells (e.g., somatostatin, bombesin, gastrin-releasing peptide, cholecystokinin/gastrin, neurotensin, substance P, and neuropeptide Y). An alternate strategy to increase the efficacy of cancer therapeutics is to preferentially protect normal tissues against the cytotoxic effects of the anticancer agents (Hogle, *Semin Oncol Nurs* 23:213-224, 2007).

The U.S. FDA has approved several cytoprotective agents for use with anticancer agents, including amifostine (Ethyol), dexrazoxane (Zinecard) and mesna (Mesenex). None of these cytoprotective agents acts via G-protein-coupled receptors.

Accordingly, the present invention also relates to methods and compositions for the treatment, management, and prevention of injuries to the major organs of the body, such as the brain, heart, lung, kidneys, liver, and gastrointestinal tract, of humans or other mammals caused by trauma, acute or chronic diseases, or one or more prophylactic/therapeutic agents. The method comprises administering an effective amount of one or more of the novel PACAP analogs and compounds of the invention having activities at one or more PACAP/VIP receptors, for the inhibition of the pathology caused by trauma, chronic diseases, or one or more prophylactic/therapeutic agents.
PACAP-like compounds are extremely effective in protecting neurons, cardiomyocytes, hepatocytes, and lung, kidney and gastrointestinal epithelial cells in a concentration-dependent manner. Thus, the present invention relates to a method of treatment of these cells at a concentration of about $10^{-13}$ M to $10^{-6}$ M of the PACAP-like compound. When these cells are in culture, the concentration of the PACAP-like compound is preferably between $10^{-13}$ M and $10^{-6}$ M in the culture medium. When these cells are in the organs of a subject, the concentration of the PACAP-like compound is preferably between about $10^{-13}$ M to $10^{-6}$ M in the interstitial space or blood. Within the generally effective concentration range of the compositions of this invention, there is a peak effectiveness, below which the effectiveness of the composition falls off to a significant degree. In a preferred embodiment, the concentration of the PACAP composition of the present invention is between about $10^{-13}$ M and about $10^{-6}$ M, which permits treatment of the subject with minimal risk of adverse side effects from the treatment (Reglodi et al., 2000; Li et al., 2007). In a preferred embodiment, the concentration of the PACAP-like compound is about $10^{-9}$ M. The present discovery makes possible the use of the compositions of this invention in low concentrations to provide substantial protection of neurons, cardiomyocytes, hepatocytes, and lung, kidney and gastrointestinal epithelial cells. In a specific embodiment, the composition of the present invention protects these cells from injury or death. The injury or death of these cells may be due to trauma, chronic diseases, or one or more prophylactic/therapeutic agents.

The compositions of the present invention may be administered intravenously, intraperitoneally, subcutaneously, intramuscularly, or otherwise into the bloodstream in order to achieve the optimal concentration for the treatment, management or prevention of injuries to one or more of the major organs of the body of humans or other mammals caused by treatment with one or more anticancer agents. The intravenous administration of the composition of the present invention may be as a bolus injection, as a constant infusion or as a bolus injection followed immediately by a constant infusion. In a preferred embodiment, the subject is being treated with one or more chemotherapeutics for a hematological malignancy and the PACAP-like
adjuvant is administered as a bolus injection (in order to saturate any serum binding proteins) followed immediately by a constant infusion.

The compositions of the present invention may be administered by inhalation or intranasally in order to have preferential access to the lung (Doberer et al., *Eur J Clin Invest* 37:665-672, 2007) or the brain (Nonaka et al., *J Pharmacol Exp Ther* 325:513-519, 2008), respectively. In a preferred embodiment, a subject is treated by inhalation with one or more novel PACAP analogs for pulmonary arterial hypertension. In another preferred embodiment, a subject is treated intranasally with one or more novel PACAP analogs for a concussion.

The compositions of the present invention may be administered orally in a time-dependent (Gazzaniga et al., *Expert Opin Drug Deliv* 3:583-597, 2006) or a pH-dependent (Gallardo et al., *Pharm Dev Technol* 13:413-4232008) formulation in order to have preferential access to different levels of the gastrointestinal tract or an injured region of the gastrointestinal tract, respectively. In a preferred embodiment, a subject is treated with one or more novel PACAP analogs for Crohn’s disease or ulcerative colitis.


The compositions of the present invention may be administered transcutaneously after encapsulation in dendrimers (Grayson and Fréchet, *Chem Rev* 101:3819-3868, 2001). In a preferred embodiment, a subject is treated with one or more chemotherapeutics for a hematological malignancy.

The compositions of the present invention may be administered in combination with other cytoprotective adjunctive agents that have different mechanisms of action, such as amifostine, dexrazoxane, mesna, palifermin.
(human keratinocyte growth factor), and N-acetylcysteine, in order to have an additive or a synergistic effect.

The compositions of the present invention may be used to treat, manage or prevent injuries to one or more major organs of the body of humans or other mammals caused by both unconjugated anticancer agents and anticancer agents reversibly conjugated to a monoclonal antibody (Wu & Senter, Nat Biotechnol 23:1137-1146, 2005) or to one or more bioactive peptides, e.g., somatostatin, bombesin, gastrin-releasing peptide, cholecystokinin/gastrin, neurotensin, substance P, and neuropeptide Y (Reubi, Endocr Rev 24:389-427, 2003).

The compositions of the present invention may be used to directly enhance the efficacy of some anticancer agents on some cancer cells, especially the anticancer activity of some chemotherapeutics on lymphoid and myeloid hematopoietic cancers.

The compositions of the present invention may be coupled to radionuclides to localize, diagnose and treat disseminated cancers and metastatic tumors.

The compositions of the present invention may be coupled to small molecule therapeutics to target the delivery of the therapeutics preferentially to specific tissues or cell types.

The compositions of the present invention may be coupled to suitable imaging agents to localize granulomas in humans or other mammals with various infectious or autoimmune diseases.

The compositions of the present invention may be used to coat metallic or biodegradable stents to prevent restenosis of coronary arteries or other large arteries (Hwang et al., Circulation 104:600-605, 2001; Butt et al., Future Cardiol 5:141-157, 2009).

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 is a table showing the primary amino acid sequences of PACAP38 (SEQ ID NO:1), PACAP27 (SEQ ID NO:2), VIP (SEQ ID NO:3), [Pip<sup>3</sup>,Aib<sup>18,28</sup>,Ala<sup>17</sup>,Lys<sup>34</sup>,<i>d</i>-Lys<sup>36</sup>]PACAP38 (SEQ ID NO:4), [Pip<sup>3</sup>,Ala<sup>15,17</sup>,Aib<sup>16,26</sup>,Lys<sup>34</sup>,<i>d</i>-Lys<sup>36</sup>]PACAP38 (SEQ ID NO:5).
[Pip\textsuperscript{3}, Ala\textsuperscript{14,17}, Aib\textsuperscript{16,28}, Lys\textsuperscript{34}, D-Lys\textsuperscript{38}]PACAP38 (SEQ ID NO:6),
[Pip\textsuperscript{3}, Aib\textsuperscript{16,28}, Ala\textsuperscript{17,21}, Lys\textsuperscript{34}, D-Lys\textsuperscript{38}]PACAP38 (SEQ ID NO:7),
[Pip\textsuperscript{3}, Aib\textsuperscript{16,28}, Ala\textsuperscript{17,20}, Lys\textsuperscript{34}, D-Lys\textsuperscript{38}]PACAP38 (SEQ ID NO:8),
[Pip\textsuperscript{3}, Aib\textsuperscript{16}, Ala\textsuperscript{17}]PACAP27 (SEQ ID NO:9), N-acetyl[Pip\textsuperscript{3}, Aib\textsuperscript{16}, Ala\textsuperscript{17}]PACAP27 (SEQ ID NO:10),
[Ala\textsuperscript{2,17}, Pip\textsuperscript{3}, Aib\textsuperscript{16}]PACAP27 (SEQ ID NO:11), and [Pip\textsuperscript{3}]PACAP27 (SEQ ID NO:12). All of these compounds have been used in the experiments described in either Figure 3 or Figure 10 listed below.

Figure 2 is a table comparing the molecular weights of the ten novel PACAP analogs (SEQ ID NOs 4-13) as determined by matrix-assisted laser desorption/ionization (MALDI) mass spectroscopy (MS) using an Applied Biosystems Voyager DE machine with the calculated molecular weight based on the amino acid composition.

Figure 3 is a table listing the EC\textsubscript{50} for the inhibitory effects of PACAP38, PACAP27, VIP, and eight novel PACAP analogs on the proliferation of light-chain immunoglobulin-secreting myeloma cells. The light-chain immunoglobulin-secreting human multiple myeloma cells were cultured in RPMI 1640 medium supplemented with 10% non-inactivated fetal bovine serum and 0.05 mM 2-mercaptoethanol. The effects of PACAP38, PACAP27, VIP, and the eight novel PACAP analogs on myeloma cell proliferation were assessed by determining incorporation of bromodeoxyuridine into DNA during cell division. The number of myeloma cells approximately doubled during the 24-hour incubation period in the absence of treatment with PACAP-like peptides. Five different concentrations, ranging from 10\textsuperscript{-13} M to 10\textsuperscript{-5} M, were tested for PACAP38, PACAP27, VIP, and each of the eight novel PACAP analogs. The EC\textsubscript{50} was calculated from the concentration response curve using the software package Prism (GraphPad, San Diego, CA). Each value represents the mean of four-six determinations per experiment. The EC\textsubscript{50} for PACAP38 is based on the average of four separate experiments, while the EC\textsubscript{50} for PACAP27 and [Pip\textsuperscript{3}, Aib\textsuperscript{16,28}, Ala\textsuperscript{17}, Lys\textsuperscript{34}, D-Lys\textsuperscript{38}]PACAP38 is based on the average of two separate experiments.

Figure 4 is a graph showing a representative concentration response curve from a single experiment on the inhibitory effects PACAP38 and six
PACAP38 analogs on the proliferation of light-chain immunoglobulin-secreting human myeloma cells. Each value represents the mean plus/minus the standard error of four-six determinations. Note that replacing piperolic acid in position 3 of the novel analogs with either nipecotic acid or isonipecotic acid results in an analog with more than four orders of magnitude lower inhibitory potency.

Figure 5 is a graph showing the reduction in cisplatin-induced apoptotic cell death of rat renal proximal tubule epithelial cells caused by comparable concentrations of PACAP38, VIP and three novel PACAP38 analogs. Primary cultures of renal proximal tubule epithelial cells were made from the kidneys of 6- to 8-weeks-old mice. Kidney cortices were dissected from the medulla, minced and filtered. The tubule cells were purified by repeated centrifugation and washing. The final pellet was resuspended in medium, and the tubule cells were placed in a collagen-coated dish and incubated at 37°C. The medium was then changed every 2 to 3 days until the cells were confluent. Cells were checked for the expression of 

\[ \gamma \text{-glutamyltranspeptidase} \] and alkaline phosphatase, markers for renal proximal tubule epithelial cells. All three PACAP38 analogs appeared to be at least as potent as PACAP38 in the \textit{in vitro} bioassay. VIP was significantly (# \( p < 0.05 \)) less potent than PACAP38. The inhibitory effects of PACAP38, VIP and the three PACAP38 analogs on apoptotic cell death was assessed by the quantitative determination of cytoplasmic histone-associated DNA-fragmentation (mono- and oligonucleosomes) after exposure to cisplatin for 24 hours. Each value represents the mean plus/minus the standard deviation of eight determinations. **\( p < 0.01 \) and *\( p < 0.05 \) compared to the group treated only with cisplatin. # \( p < 0.05 \) compared to the group treated with cisplatin and 10\(^{-6}\) M VIP.

Figure 6 is a graph showing the effects of PACAP38 and two novel PACAP analogs on serum creatinine levels in mice following ischemia/reperfusion injury to the kidney. The renal artery in male C57BL/6 mice was clamped bilaterally for 45 minutes in all mice except for the sham-operated mice. Twenty micrograms of PACAP38 or one of the PACAP analogs were given intraperitoneally 1 hour after the start of reperfusion and
additional doses were given at 24 and 48 hours after the initial dose. The sham-operated group of mice was injected intraperitoneally with PACAP38 on the same schedule as the mice subjected to ischemia/reperfusion. The control group of mice was injected intraperitoneally with the same volume of saline as for the injections of PACAP38 on the same schedule. All of the mice were euthanized 24 hours after the final injection of saline, PACAP38 or one of the novel PACAP analogs. Each value represents the mean plus/minus the standard error of four determinations. **p < 0.01 and *p < 0.05 compared to the ischemia/reperfusion group treated with saline. I/R, ischemia/reperfusion; sham, sham-operated.

Figure 7 is a graph showing the effects of PACAP38 and two novel PACAP analogs on the production of TNF-α in the kidneys of mice following ischemia/reperfusion injury to the kidney. The renal artery in male C57BL/6 mice was clamped for 45 minutes in all mice except for the sham-operated mice. Twenty micrograms of PACAP38 or one of the PACAP analogs were given intraperitoneally 1 hour after the start of reperfusion and additional doses were given at 24 and 48 hours after the initial dose. The sham-operated group of mice was injected intraperitoneally with PACAP38 on the same schedule as the mice subjected to ischemia/reperfusion. The control group of mice was injected intraperitoneally with the same volume of saline as for the injections of PACAP38 on the same schedule. All of the mice were euthanized 24 hours after the final injection of saline, PACAP38 or one of the PACAP analogs. Each value represents the mean plus/minus the standard error of four determinations. **p < 0.01 compared to the ischemia/reperfusion group treated with saline. I/R, ischemia/reperfusion; sham, sham-operated.

Figure 8 is a graph showing the effects PACAP38, [Pip³,Ala¹⁴,¹⁷,Alb¹⁶,²⁸,Lys³⁴,D-Lys³⁸]PACAP38 and dexamethasone on the proliferation of light-chain immunoglobulin-secreting human myeloma cell line (MM·1S) that was derived from a patient who was being treated for multiple myeloma with a dexamethasome-containing regimen. The light-chain immunoglobulin-secreting multiple myeloma cells were cultured in RPMI 1640 medium supplemented with 10% non-inactivated fetal bovine serum and 0.05 mM 2-mercaptoethanol. The effects of dexamethasone, PACAP38 and the
novel PACAP38 analog on cell proliferation were assessed by determining the incorporation of bromodeoxyuridine into DNA during cell division. Each value represents the mean plus/minus the standard error of four-six determinations. The cell lines in Figures 8 and 9 were obtained from the same patient at different stages of the treatment (Greenstein et al., Exp Hematol 31:271-282, 2003).

Figure 9 is a graph showing the effects PACAP38, [Pip$^3$,Ala$^{14,17}$,Aib$^{16,28}$,Lys$^{34}$,D-Lys$^{38}$]PACAP38 and dexamethasone on the proliferation of light-chain immunoglobulin-secreting human myeloma cell line (MM.1R) that was derived from a patient who was being treated for multiple myeloma with a dexamethasone-containing regimen. The light-chain immunoglobulin-secreting multiple myeloma cells were cultured in RPMI 1640 medium supplemented with 10% non-inactivated fetal bovine serum and 0.05 mM 2-mercaptoethanol. The effects of dexamethasone, PACAP38 and the novel PACAP38 analog on cell proliferation were assessed by determining the incorporation of bromodeoxyuridine into DNA during cell division. Each value represents the mean plus/minus the standard error of four-six determination. The cell lines in Figures 8 and 9 were obtained from the same patient at different stages of the treatment (Greenstein et al., Exp Hematol 31:271-282, 2003).

Figure 10 shows the reduction in gentamicin-induced apoptotic cell death of human renal proximal tubule epithelial cells caused by various concentrations of PACAP38 and [Pip$^3$]PACAP38. The inhibitory effects of PACAP38 and the novel PACAP analog on apoptotic cell death was assessed by the quantitative determination of cytoplasmic histone-associated DNA-fragmentation (mono- and oligonucleosomes) after exposure to gentamicin for 24 hours. Both PACAP38 and [Pip$^3$]PACAP38 produced a dose-dependent inhibition of apoptosis, but the novel analog appeared to be less potent than PACAP38 in this in vitro model of aminoglycoside-induced renal proximal tubule epithelial cell injury. Each value represents the mean plus/minus the standard deviation of four determinations. ** $p < 0.01$ and * $p < 0.05$ compared to the group treated only with gentamicin.
SEQUENCES

SEQ ID NOs: 1-3 are human sequences. SEQ ID NOs: 4-13 are modifications of the corresponding human sequences. Below is a brief summary of the sequences presented in the accompanying sequence listing, which is incorporated by reference herein in its entirety:

SEQ ID NO: 1 is the amino-acid sequence of PACAP38.
SEQ ID NO: 2 is the amino-acid sequence of PACAP27.
SEQ ID NO: 3 is the amino-acid sequence of VIP.

SEQ ID NO: 4 is the amino-acid sequence of [Pip\(^3\), Aib\(^{15,28}\), Ala\(^{17}\), Lys\(^{34}\), D-Lys\(^{38}\)]PACAP38, which can be used for the purposes described in the present invention.

SEQ ID NO: 5 is the amino-acid sequence of [Pip\(^3\), Ala\(^{15,17}\), Aib\(^{16,28}\), Lys\(^{34}\), D-Lys\(^{38}\)]PACAP38, which can be used for the purposes described in the present invention.

SEQ ID NO: 6 is the amino-acid sequence of [Pip\(^3\), Ala\(^{14,17}\), Aib\(^{16,28}\), Lys\(^{34}\), D-Lys\(^{38}\)]PACAP38, which can be used for the purposes described in the present invention.

SEQ ID NO: 7 is the amino-acid sequence of [Pip\(^3\), Aib\(^{16,28}\), Ala\(^{17,21}\), Lys\(^{34}\), D-Lys\(^{38}\)]PACAP38, which can be used for the purposes described in the present invention.

SEQ ID NO: 8 is the amino-acid sequence of [Pip\(^3\), Aib\(^{16,28}\), Ala\(^{17,20}\), Lys\(^{34}\), D-Lys\(^{38}\)]PACAP38, which can be used for the purposes described in the present invention.

SEQ ID NO: 9 is the amino-acid sequence of [Pip\(^3\), Aib\(^{16}\), Ala\(^{17}\)]PACAP27, which can be used for the purposes described in the present invention.

SEQ ID NO: 10 is the amino-acid sequence of N-acetyl[Pip\(^3\), Aib\(^{16}\), Ala\(^{17}\)]PACAP27, which can be used for the purposes described in the present invention.

SEQ ID NO: 11 is the amino-acid sequence of [Ala\(^{2,17}\), Pip\(^3\), Aib\(^{16}\)]PACAP27, which can be used for the purposes described in the present invention.
SEQ ID NO:12 is the amino-acid sequence of [Pip³]PACAP38, which can be used for the purposes described in the present invention.

SEQ ID NO:13 is the amino-acid sequence of N-acetyl[Pip³]PACAP38, which can be used for the purposes described in the present invention.

DEFINITIONS

The following standard three-letter abbreviations are used herein to identify amino acid residues.

Abu, α-amino butyric acid

Acb, 1-aminoo-1-cyclobutanecarboxylic acid

Ach, 1-amino-1-cyclohexanecarboxylic acid

Acpe, 1-amino-1-cyclopentanecarboxylic acid

Acpr, 1-amino-1-cyclopropanecarboxylic acid

Aib, α-aminoisobutyric acid

Ala, alanine

Arg, arginine

Asn, asparagine

Asp, aspartic acid

Bip, 4-biphenylalanine

Cha, cyclohexylalanine
Cys, cysteine

Dab, diaminobutyric acid

Dap, diaminopropionic acid

Gaba, γ-amino-N-butyric acid

Gln, glutamine

Glu, glutamic acid

Gly, glycine

His, histidine

hSer, homoserine

Hyp, hydroxyproline

Ile, isoleucine

Ini, isonipecotic acid

Leu, leucine

Lys, lysine

N-Me-Asp, N-methylaspartic acid

N-Me-Ser, N-methylserine

Met, methionine
Nal, 2-naphthylalanine

Nip, nipecotic acid

Nle, norleucine

Nva, norvaline

Orn, ornithine

Pal, 3-pyridylalanine

Phe, phenylalanine

Pip, pipecolic acid

Pro, proline

Sar, sarcosine (N-methylglycine)

Ser, serine

Thr, threonine

Trp, tryptophan

Tyr, tyrosine

Val, valine

As used herein, the term "PACAP" refers to human PACAP27 (SEQ ID NO:2) and/or human PACAP38 (SEQ ID NO:1).

As used herein, the term "PACAP/VIP agonist" refers to any molecule, including a protein, naturally or synthetically post-translationally modified
protein, polypeptide, naturally or synthetically modified polypeptide, peptide, naturally or synthetically modified peptide, and large or small nonpeptide molecule that binds to and stimulates one or more of the PACAP/VIP receptors.

As used herein, the term "analog" refers to both conformational and linear sequence analogs. Maxadilan, a 61-amino-acid peptide with two disulfide bridges that is synthesized naturally in the salivary glands of the hematophagous sand fly Lutzomyia longipalpis, is one example of a conformational analog of PACAP. It has no obvious linear amino-acid sequence identities with PACAP but binds preferentially to the PAC₁ receptors with high affinity (Tatsuno et al., Brain Res 889:138-148, 2001; Lerner et al., Peptides 28:1651-1654, 2007). The amino-acid sequences of maxadilan made by sand flies from different regions of Central and South America can differ by more than 20%. However, the relative positions of the cysteine residues in these bioactive orthologs are invariant and all of these bioactive orthologs have a similar predicted secondary structure. The amino-acid sequences of some naturally occurring maxadilans are described by Lanzaro et al. (Insect Mol Biol 8:267-275, 1999). Therefore, linear analogs of conformational analogs of PACAP, such as linear analogs of maxadilan (Reddy et al., J Biol Chem 281:16197-16201, 2006), would be expected to bind to and stimulate PACAP/VIP receptors. Those skilled in the art will recognize that additional conformational analogs of PACAP could be created by synthetic combinatorial chemistry or phage display technologies. A peptide analog may contain one or more amino acids that occur naturally in mammalian cells but do not occur naturally in mammalian peptides. For example (but not by way of limitation), a peptide analog may contain γ-amino-N-butyric acid (GABA), β-alanine, ornithine, and citrulline. An analog of a peptide may also contain one or more nonnatural amino acids that do not occur naturally in mammalian cells. For example (but not by way of limitation), an analog of a peptide may also contain D-alanine, naphthylalanine, pyridylalanine, and norleucine. An analog may have an extension of one or more naturally occurring and/or nonnatural amino acids at its amino terminus and/or its carboxyl terminus. The extension at the amino
terminus and/or the carboxyl terminus may include one or more additional copies of the same peptide and/or other bioactive peptides (e.g., gastrin-releasing peptide, cholecystokinin/gastrin, neurotensin, substance P, and neuropeptide Y). The extension at the amino terminus and/or the carboxyl terminus may include one or more sites for proteolytic processing in order to make the extended peptide function as a precursor (prodrug) for the bioactive peptide. For example, the PACAP-like compounds may include cleavage sites at the amino terminus and/or the carboxyl terminus for one or more of the following proteolytic enzymes: trypsin, chymotrypsin, a prohormone convertase (e.g., prohormone convertase 1, 2, 4, 5, or 7), furin, chymase, thrombin, calpain, a cathepsin (e.g., cathepsin A, B, D, G, H, or L), papain, Factor Xa, Factor IXa, Factor XIa, renin, chymosin (rennin), thermolysin, a kallikrein, an elastase, and a matrix metalloproteinase.

As used herein, the term "PACAP-like compound" refers to human PACAP27 (SEQ ID NO:2), human PACAP38 (SEQ ID NO:1), human VIP (SEQ ID NO:3), lizard PACAP38 (Valiante et al., Brain Res 1127:66-75, 2007), frog PACAP38 (Chartrel et al., Endocrinology 129:3367-3371, 1991), and sand fly maxadilan (Lanzaro et al., Insect Mol Biol 8:267-275, 1999), and peptides or peptidomimetic compounds that are orthologs, paralogs, analogs, fragments, or derivatives of these naturally occurring peptides and that have agonist activity at one or more PACAP/VIP receptors. PACAP-like compounds of the invention include those having the sequence set forth in SEQ ID NOs: 4-13 and polypeptides having at least 75, 80, 85, 90, 95, 97, 95, or 99% or more sequence identity to the sequence of SEQ ID NOs: 4-13.

As used herein, the term "peptidomimetic" refers to both hybrid peptide/organic molecules and nonpeptide organic molecules that have critical functional groups in a three-dimensional orientation that is functionally equivalent to the corresponding peptide (Marshall, Tetrahedron 49:3547-3558, 1993). Peptidomimetic compounds that are functionally equivalents to the PACAP-like compounds of the present invention can be rationally designed by those skilled in the art based on published structure-activity studies (e.g., Igarashi et al., J Pharmacol Exp Ther 301:37-50, 2002; Igarashi

The terms "percent identity" and "percent similarity" can be used to compare the amino-acid sequences of two peptides. To determine the percent identity of two amino acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino-acid sequence for optimal alignment with a second amino-acid sequence). The amino-acid residues at the corresponding amino-acid positions are then compared. When a position in the first sequence is occupied by the same amino-acid residue at the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = the number of identical overlapping positions/total number of positions x 100%). In the most common embodiment, the two amino-acid sequences are the same length.

To determine the percent similarity of two amino acid sequences, the sequences are also aligned for optimal comparison purposes. When a position in the first sequence is occupied by either the same amino-acid residue or a "conserved" amino acid at the corresponding position in the second sequence, then the molecules are similar at that position. The percent similarity between the two sequences is a function of the number of corresponding positions in the amino acid sequences at which the amino acids are either identical or the different amino acids are conserved substituents (i.e., % similarity = the number of identical or conserved overlapping positions/total number of positions x 100%). A conservative substitution is a substitution of one amino acid by another amino acid with a similar side-chain. A conservative substitution frequently results in an analog with similar physical and biological properties. The following is a list of commonly defined classes of "similar" amino acids that occur naturally in mammalian peptides.

Aromatic side-chain: phenylalanine ≡ tyrosine ≡ tryptophan ≡ histidine
Acidic side-chain: aspartic acid ≡ glutamic acid
Basic side-chain: arginine ≡ lysine ≡ histidine
β-Branched side-chain: threonine ≡ valine ≡ isoleucine

Nonpolar side-chain: alanine ≡ valine ≡ leucine ≡ proline ≡ methionine ≡ phenylalanine ≡ tryptophan

Uncharged polar side-chain: glycine ≡ asparagine ≡ glutamine ≡ serine ≡ threonine ≡ cysteine ≡ tyrosine

Those skilled in the art will recognize that many amino acids that occur naturally in mammalian cells but do not occur naturally in mammalian peptides and many nonnatural amino acids that do not occur naturally in mammalian cells can be substituted conservatively for one or more of the amino acids that occur naturally in mammalian peptides. For example (but not by way of limitation), hydroxyproline, dehydroproline and N-alkylamino acids could be substituted conservatively for proline, sarcosine, dialkylglycine and α-aminoacycloalkane carboxylic acid could be substituted conservatively for glycine, and α-aminoisobutyric acid, naphthylalanine and pyridylalanine could be substituted conservatively for alanine. "Percent identity" and "percent similarity" are determined after optimal alignment of the two sequences without or without the introduction of one or more gaps in one or both amino-acid sequences. There are many algorithms that are well known to those skilled in the art that can be used to determine the optimal alignment.

In the most common embodiment, the two amino-acid sequences are the same length.

As used herein, the term "fragment" in the context of PACAP-like or VIP-like peptides refers to a peptide that has fewer amino acids than the PACAP-like or VIP-like peptide and has at least five amino acids with sequence similarity to the PACAP-like or VIP-like peptide, respectively.

As used herein, the term "derivative" refers to a peptide that has been modified by the covalent attachment of another molecule and/or a functional group to the peptide chain. For example (but not by way of limitation), a derivative of a peptide may be produced by glycosylation, acetylation, pegylation, acylation, alkylaion, oxidation, phosphorylation, sulfation, formylation, methylation, demethylation, amidation, \textit{gamma}-carboxylation, cyclization, lactamization, prenylation, myristoylation, iodination, selenoylation, ribosylation, ubiquitination, or hydroxylation. The derivatized
peptide can be a peptide analog. A derivative of a peptide can easily be made by standard techniques known to those of skilled in the art. A derivative of a peptide may possess an identical function(s) to the parent peptide. A derivative of a peptide may also have one or more other functions in addition to the function(s) of the parent peptide. For example (but not by way of limitation), a derivative of a peptide may have a longer half-life than the parent peptide and/or have cytoprotective or cytotoxic properties that are not possessed by the parent peptide.

As used herein, the term "subject" refers to either a non-primate (e.g., a cow, pig, horse, cat, dog, rat, etc.) or a primate (e.g., a monkey or a human being), most preferably a human being. In a specific embodiment, the subject is a farm animal (e.g., a horse, pig, lamb or cow) or a pet (e.g., a dog, cat, rabbit, or monkey). In another embodiment, the subject is an animal other than a farm animal or a pet (e.g., a mouse, rat or guinea pig). In a preferred embodiment, the subject is a normal human being. In another preferred embodiment, the subject is a human that has an untreated or treated cancer.

As used herein, the term "in combination with" refers to the use of more than one therapeutic or cytoprotective agent. The use of the term "in combination with" does not restrict the order in which the therapeutic or cytoprotective agent is administered to a subject. One therapeutic or cytoprotective agent can be administered prior to, concomitantly with, or subsequent to the administration of the other therapeutic or cytoprotective agent. The therapies are administered to a subject in a sequence and within a time interval such that the PACAP-like compound(s) of the present invention can act together with the other agent to provide a different response from the subject, preferably a greater therapeutic or cytoprotective benefit, than if they were administered otherwise.

As used herein, the term "nervous system" refers to the central nervous system (the brain and spinal cord), the sympathetic nervous system, the parasympathetic nervous system, and the enteric nervous system.

As used herein, the term "gastrointestinal tract" refers to the pharynx, esophagus, stomach, small intestine, pancreas, and large intestine.
As used herein, the term "hematological malignancies" refers to cancers of blood cells, bone marrow cells or cells of the lymph nodes, including (but not limited to) leukemias, lymphomas and plasma cell dyscrasias.

As used herein, the phrase "plasma cell dyscrasias" refers to monoclonal neoplasms of the B-lymphocyte lineage, including (but not limited to) multiple myeloma, Waldenström's macroglobulinemia, POEMS syndrome, Seligman's disease, and Franklin's disease.

As used herein, the adjective "hematopoietic" refers to cells (including cancer cells) that are derived from hematopoietic stem cells. The normal cells of the body that are derived from hematopoietic stem cells include (but are not limited to) erythrocytes, granulocytes (basophils, eosinophils and neutrophils), lymphocytes, monocytes (macrophages, microglia, splenocytes, and dendritic cells), and thrombocytes.

As used herein, the term "about" refers to a value that is ±10% of the recited value.

**DETAILED DESCRIPTION OF THE INVENTION**

The inventors of the present patent application have discovered that replacing aspartic acid in position 3 of native human PACAP27 or PACAP38 with pipecolic acid results in a series of novel PACAP analogs (SEQ ID NOs: 4-13, Figure 1 and Figure 2) with unique pharmacological properties. In addition, amino-acid substitutions in other positions of the PACAP analogs besides position 3 can be made in order to block proteolysis and/or renal clearance, reduce the cost of synthesis, and alter tissue distribution and/or receptor specificity.

The inventors of the present patent application have discovered that one or more of these novel PACAP analogs are extremely potent inhibitors of the proliferation of human multiple myeloma cells *in vitro* (Figures 3 and 4).
The inventors of the present patent application have discovered that the nephrotoxicity caused by cisplatin in primary cultures rat renal tubule epithelial cells can be dramatically reduced by these novel PACAP analogs (Figure 5).

The inventors of the present patent application have discovered that the increase in serum creatinine caused by ischemia/reperfusion injury to the kidney can be dramatically reduced by these novel PACAP analogs (Figure 6).

The inventors of the present patent application have discovered that the increase in the levels of tumor necrosis factor-α in the kidney caused by ischemia/reperfusion injury to the kidney can be dramatically reduced by these novel PACAP analogs (Figure 7).

The inventors of the present patent application have discovered that these novel PACAP analogs are still highly effective in lymphocytes that have become resistant to corticosteroids (Figures 8 and 9).

The inventors of the present patent application have discovered that the nephrotoxicity caused by gentamicin in cultured human renal proximal tubule epithelial cells can be dramatically reduced by PACAP38 and a novel PACAP analog (Figure 10).

The inventors of the present patent application have discovered that these novel PACAP analogs can be used as prophylactic/therapeutic agents for a wide range of medical disorders, including (but not limited to) age-related neurodegenerative diseases (such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis), injuries to the central nervous system caused by stroke, heart attack and blunt force trauma (such as concussions and spinal cord trauma), Huntington's disease and other CAG codon repeat expansion diseases, retinal diseases (such as diabetic retinopathy, macular degeneration and glaucoma), autoimmune diseases (such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, scleroderma, Sjögren's disease, idiopathic membranous nephropathy, Goodpasture's disease, autoimmune hepatitis, myasthenia gravis, multiple sclerosis, Guillain-Barré syndrome, type I diabetes, Hashimoto's thyroiditis, Graves' disease, pemphigus vulgaris, and lupus erythematosus), keratoconjunctivitis sicca
caused by autoimmune diseases or LASIK surgery, type II diabetes, sepsis caused by bacteria and/or viruses (including bacterial and viral toxins), acute and chronic cardiovascular diseases (such as myocardial infarction, atherosclerosis and restenosis), acute and chronic renal diseases (such as ischemia/reperfusion injury, nephritis and drug-induced nephrotoxicity), acute and chronic pulmonary diseases (such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, and pulmonary arterial hypertension), systemic hypertension, hematological cancers (such as leukemias, lymphomas and plasma cell dyscrasias), eating disorders, acute and chronic liver diseases (such as ischemia/reperfusion injury, hepatitis and fatty liver), osteoporosis, pre-eclampsia, cell and solid organ transplantation, cognitive disorders, AIDS dementia complex, and aging of the central nervous system.

The inventors of the present patent application have discovered that these PACAP analogs coupled to suitable radionuclides can be used in the localization, diagnosis and treatment of disseminated cancers and metastatic tumors, and coupled to small molecule therapeutics can be used as vectors for targeted drug delivery. The inventors of the present patent application have discovered that these novel PACAP analogs coupled to suitable imaging agents can also be used in the localization of granulomas in humans or other mammals with various infectious or autoimmune diseases.

IDENTIFICATION OF PACAP-LIKE COMPOUNDS

The present invention provides methods for assaying and screening for PACAP-like activity by incubating the compounds with epithelial cells containing one or more PACAP/VIP receptors, e.g., kidney, lung or liver epithelial cells, and multiple myeloma cells, and then assaying for a reduction in a pathology-causing cell phenotype and inhibition of multiple myeloma cell proliferation, respectively (Li et al., Regul Pept 145:24-32, 2008). For example, a PACAP-like peptide or peptidomimetic should increase the viability of cisplatin-treated kidney epithelial cells and decrease the rate of proliferation of multiple myeloma cells. In addition, the intrinsic activity of any PACAP-like compound at each of the three PACAP/VIP receptors can be
determined in stably transfected cell lines that express only one of these receptors by measuring the intracellular accumulation of cyclic AMP (Tatsuno et al., Brain Res 889:138-148, 2001). Radioligand receptor binding assays can be used to determine the affinity of a compound for each of the PACAP/VIP receptors. However, radioligand receptor binding assays do not differentiate between receptor agonists and receptor antagonists. Therefore, other types of assays well known to those skilled in the art must be used to discriminate between PACAP/VIP receptor agonists and PACAP/VIP receptor antagonists.

The viability of renal, pulmonary, hepatic, and neuronal epithelial cells can be determined by a variety of techniques well known to those skilled in the art, including (but not limited to) quantification of the fragmentation of nuclear DNA or caspase 3 activity, quantification of annexin V binding, counting of apoptotic (pyknotic) cells and counting of Trypan blue-positive cells. In the preferred embodiment, the fragmentation of nuclear DNA or caspase 3 activity is determined.

The cell proliferation of hematopoietic and epithelial cells can be determined by a variety of techniques well known to those skilled in the art, including (but not limited to) quantification of the incorporation of bromodeoxyuridine or [3H]thymidine into nuclear DNA, counting of the number of cells expressing proliferating cell nuclear antigen and counting of mitotic figures. In the preferred embodiment, the incorporation of bromodeoxyuridine or [3H]thymidine into nuclear DNA is determined.

The intracellular accumulation of cyclic AMP in stably transfected cell lines that express only one of these receptors can be determined following stimulation with PACAP-like compounds by a variety of techniques well known to those skilled in the art, including (but not limited to) a radioimmunoassay or an enzyme-linked immunosorbent assay. The stimulation is stopped by the addition of ice-cold 20% trifluoroacetic acid. The cAMP is extracted from the cells, the extracts are centrifuged, the supernatants are placed into small plastic vials, and the supernatants are lyophilized for assay of the levels of cAMP. In the preferred embodiment, the intracellular levels of cAMP are quantified with an enzyme-linked immunosorbent assay.
PATIENT POPULATIONS

The present invention provides methods for treating, preventing and managing damage caused by trauma, acute or chronic diseases, or one or more prophylactic/therapeutic agents to one or more major organs of the body, especially, nervous system, heart, lung, kidneys, liver, and gastrointestinal tract, of humans or other mammals by the therapeutic or prophylactic administration of effective amounts of one or more compositions of the present invention. In another embodiment, the composition of the present invention can be administered in combination with one or more other cytoprotective agents.

The methods and compositions of the present invention consists of the administration of one or more compositions of the invention to subjects with injuries caused by trauma, acute or chronic diseases, or one or more prophylactic/therapeutic agents who have suffered from, are suffering from or are expected to suffer from the side-effects of one or more prophylactic/therapeutic agents (e.g., an anticancer agent, a steroid (e.g., a corticosteroid or a glucocorticoid), an anti-inflammatory agent, or an aminoglycoside). In a preferred embodiment, the subject has been, is being or is expected to be administered one or more cancer chemotherapeutics for a hematological malignancy. In the most preferred embodiment, the hematological malignancy is multiple myeloma.

The subjects may or may not have previously been treated on one or more occasions for trauma injuries, acute or chronic diseases, or the side-effects of one or more prophylactic/therapeutic agents. The subjects may or may not have previously been refractory to one or more prophylactic/therapeutic agents (e.g., a cancer chemotherapeutic). The methods and compositions of the present invention may be used as an adjuvant for a first line, second line or nonstandard treatment regimen for trauma, acute or chronic diseases, or the side-effects of one or more prophylactic/therapeutic agents. The methods and compositions of the present invention can be used before any trauma, acute or chronic diseases, or the side-effects of one or more prophylactic/therapeutic agents are
observed or after the first or later observations of any trauma, acute or chronic
diseases, or the side-effects of one or more prophylactic/therapeutic agents.

OTHER THERAPEUTIC/PROPHYLACTIC AGENTS

In some embodiments, the present invention provides methods for
treating, managing or preventing of injuries to one or more of the major
organs of the body of humans or other mammals caused by trauma, acute or
chronic diseases, or one or more prophylactic/therapeutic agents by
administering one or more compositions of the present invention in
combination with one or more other cytoprotective agents. These other
cytoprotective agents include (but are not limited to) amifostine, dexrazoxane,
mesna, palifermin, and N-acetylcysteine. None of the listed cytoprotective
agents stimulate G-protein-coupled receptors and all of these cytoprotective
agents have mechanisms of action that are distinct from the presumed
cytoprotective mechanisms of action of PACAP-like peptides. Therefore, one
or more of these cytoprotective agents can have additive or even synergistic
effects when administered in combination with PACAP-like peptides.

SYNTHESIS OF THE NOVEL PACAP ANALOGS

Peptides were prepared by modified solid-phase procedures using
Fmoc chemistries on a CEM microwave-assisted automatic peptide
synthesizer (Matthews, NC) followed by trifluoroacetic acid (TFA) resin
cleavage. Briefly, a standard Rink amide resin (Advanced CheTech,
Louisville, KY) was used to yield peptide amides directly after TFA cleavage.
Treatment with 20% piperidine in a dimethylformamide solution containing 0.2
M 1-hydroxybenzotriazole (HOBr) acid (2 minutes at 70°C) was used for Fmoc
group removal and amino acid couplings were achieved using a 4 M excess
of each protected amino acid and 1 equivalent of the PyClocK reagent
(Peptides International, Louisville, KY) and 2 equivalents of 0.2 M
diisopropylpropylythymine in a dimethylformamide solution at 70°C accompanied
by microwave irradiation except for Fmoc-His(Trt), which was coupled at 50°C
for 15 minutes. Fmoc amino acid side-chain protection groups commonly used were: Asp, Glu, Ser, Thr, and Tyr: tBu; Arg: Pbf; Lys, Orn, Dab, and Dap: Boc; and His: Trt.

Peptides are simultaneously deprotected and cleaved from the resin support by shaking at room temperature for 4 hours with a mixture of TFA containing 1% water and 1% triisopropylsilane. The resin and solution were then poured into a large excess of cold diethylether and the precipitate and resin filtered through a fine glass frit. After washing with ether and allowing the precipitate and resin to dry, the cleaved peptide was extracted from the resin using dilute acetic acid/ water mixtures. The resulting solutions were applied directly to preparative chromatography systems (either 1.5 or 2.5 x 25 cm columns) containing Vydac C-18 silica of 300-angstrom pore size (particle size 10 µm). Two fully volatile solvent elution systems have been used successfully for all of these peptides: linear gradients of acetonitrile in 0.1%

TFA or acetonitrile in 20% acetic acid (which was excellent for insoluble peptides) at flow rates of about 8-20 ml/min. Fractions containing the desired peptide in acceptable purity (>95%) were identified using analytical high-performance liquid chromatography (HPLC) and MALDI MS and then lyophilized.

A long-chain saturated fatty acid could be covalently linked to the free epsilon-amino group of one of the four Lys residues near the C-terminus of PACAP38, to one of the four Lys residues near the C-terminus of $[^{Pip^3}]$PACAP38 (SEQ ID NO:12) or N-acetyll$[^{Pip^3}]$PACAP38 (SEQ ID NO:13), to one of the five Lys residues near the C-terminus of one of the other five novel PACAP38 analogs (SEQ ID NOs:4-NO:8), or to PACAP38 analogs containing similar free amino group-containing amino acids such as Orn, Dab and Dap near the C-terminus. PACAP27 and PACAP38 have similar affinities for the PAC$_1$, VPAC$_1$ and VPAC$_2$ receptors suggesting that the additional 11 amino acids are not essential for high-affinity receptor binding. The fatty acid attachment will promote high-affinity binding of the conjugate to serum albumin (Kurtzhals et al., J Pharm Sci 85:304-308, 1996), which is by far the most abundant protein in serum, and dramatically reduce the rate of filtration by the kidney. This strategy has been used to make long-acting analogs of
GLP-1 (Knudsen et al., J Med Chem 43:1664-1669, 2000), which is a member of the secretin/VIP/PACAP family.

The purity of each purified compound was confirmed by analytical HPLC and MALDI MS.

THERAPEUTIC OR ANTICANCER AGENTS ADMINISTERED WITH OR COUPLED TO PACAP COMPOUNDS OF THE INVENTION

The PACAP analogs of the invention (e.g., PACAP-like compounds having the structure of Formula I); e.g., PACAP-like compounds having the sequence of SEQ ID NOs: 4-13) can be administered or formulated with, or coupled to, a therapeutic or anticancer agent. Examples of therapeutic and anticancer agents include, e.g., antineoplastic agents such as: Aciclovir; Aclarubicin; Acodazole Hydrochloride; Acronine; Adozelesin; Adriamycin; Aldesleukin; Altretamine; Ambomycin; A. metantrone Acetate; Aminoglutethimide; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrene Hydrochloride; Bisnafide Dimesylate; Bizelesin; Bleomycin Sulfate; Brequinar Sodium; Bropririme; Busulfan; Cactinomycin; Calsterone; Camptothecin; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin; Cisplatin; Cidribine; Combretestatin A-4; Crisnatol Mesylate; Cyclophosphamide; Cytarabine; Dacarbazine; DACA (N- [2- (Dimethyl-amino) ethyl] acridine-4-carboxamide); Dactinomycin; Daonorubicin Hydrochloride; Daunomycin; Decitabine; Dexormaplatin; Dezaguanine; Dezaguianine Mesylate; Diaziquone; Docetaxel; Dolasatins; Doxorubicin; Doxorubicin Hydrochloride; Droloxifene; Droluxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexate; Efornithine Hydrochloride; Ellipticine; Elsamitracin; Enloplatin; Enpromate; Epipodiphiline; Epirubicin Hydrochloride; Erbulazole; Esorubicin Hydrochloride; Estramustine; Estramustine Phosphate Sodium; Etaenidazole; Ethidized Oil I 131; Etoposide; Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabine; Fenretinide; Flouxuridine; Fludarabine Phosphate; Fluorouracil; 5-FdUMP; Flurocitabine; Fosquidone; Fostriecin
Sodium; Gemcitabine; Gemcitabine Hydrochloride; Gold Au 198;
Homocamptothecin; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide;
Ilmofosine; Interferon Alfa-2a; Interferon Alfa-2b; Interferon Alfa-n1; Interferon
Alfa-n3; Interferon Beta-1 a; Interferon Gamma-1 b; Iproplatin; Irinotecan
5 Hydrochloride; Lanreotide Acetate; Letrozole; Leuprolide Acetate; Liarozole
Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride;
Masoprocol; Maytansine; Mechlorethamine Hydrochloride; Megestrol Acetate;
Melengestrol Acetate; Melphalan; Menogaril; Mercaptopurine; Methotrexate;
Methotrexate Sodium; Metoprine; Meturedepa; Mitindomide; Mitocarcin;
10 Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane;
Mitoxantrone Hydrochloride; Mycophenolic Acid; Nocodazole;
Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegasparagase; Peliomycin;
Pentamustine; PeploycinSulfate; Perfosfamide; Pipobroman; Piposulfan;
Piroxantrone Hydrochloride; Plicamycin; Plomestane; Porfimer Sodium;
Porfiromycin; Prednimustine; Procarbazine Hydrochloride; Puromycin;
25 Puromycin Hydrochloride; Pyrazofurin; Rhizoxin; Rhizoxin D; Riboprine;
Rogletimide; Safingol; Safingol Hydrochloride; Semustine; Simtrazene;
Sparfosate Sodium; Sparsumycin; Spirogermanium Hydrochloride;
Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Strontium Chloride Sr
30 89; Sulofenur; Talisomycin; Taxane; Taxoid; Tecogalan Sodium; Tegafur;
Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone;
Testolactone; Thiamiprine; Thioguanine; Thiopeta; Thymitaq; Tiazofurin;
Tirapazamine; Tomudex; TOP53; Topotecan Hydrochloride; Toremifene
Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate
Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa;
Vapreotide; Verteporfin; Vinblastine; Vinblastine Sulfate; Vincristine;
Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate;
Vinglyciniate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate; Vinrosidine
Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; Zorubicin
35 Hydrochloride; 2-Chlorodeoxyadenosine; 2'-Deoxyformycin; 9-
aminocamptothecin; raltitrexed; N-propargyl-5,8-dideazaflonic acid; 2chloro-2'-
arabino-fluoro-2'-deoxyadenosine; 2-chloro-2'-deoxyadenosine; anisomycin;
trichostatin A; hPRL-G129R; CEP-751; linomide; sulfur mustard; nitrogen
mustard (mechlor ethamine); cyclophosphamide; melphalan; chlorambucil; ifosfamide; busulfan; N-methyl-Nitrosourea (MNU); N, N'-Bis (2-chloroethyl)-N-nitrosourea (BCNU); N- (2-chloroethyl)-N' cyclohexyl-N-nitrosourea (CCNU); N- (2-chloroethyl)-N' - (trans-4-methylcyclohexyl-N-nitrosourea (MeCCNU); N- (2-chloroethyl)-N' - (diethyl) ethylphosphonate-N-nitrosourea (fotemustine); streptozotocin; diacarbazine (DTIC); mitozomilide; temozolomide; thiotepa; mitomycin C; AZQ; adozelesin; Cisplatin; Carboplatin; Ormaplatin; Oxaliplatin; C1-973; DWA 2114R; JM216; JM335; Bis (platinum); tomudex; azacitidine; cytarabine; gemcitabine; 6-Mercaptopurine; 6-Thioguanine; Hypoxanthine; teniposide 9-amino camptothecin; Topotecan; CPT-11; Doxorubicin; Daunomycin; Epirubicin; darubicin; mitoxantrone; Iosoxantrone; Dactinomycin (Actinomycin D); amsacrine; pyrazoloacridine; all-trans retinol; 14-hydroxy-retro-retinol; all-trans retinoic acid; N- (4-Hydroxyphenyl) retinamide; 13-cis retinoic acid; 3-Methyl TTNEB; 9-cis retinoic acid; fludarabine (2-F-ara-AMP); or 2-chlorodeoxyadenosine (2-Cda).

Preferred anticancer agents for administration or formulation with, or coupling to, e.g., PACAP-like compounds having the structure of Formula (I) (e.g., PACAP-like compounds having the sequence of SEQ ID NOs: 4-13) include cisplatin, carboplatin, oxaliplatin, bleomycin, mitomycin C, calicheamicins, maytansinoids, geldanamycin, doxorubicin, idarubicin, daunorubicin, epirubicin, busulfan, carmustine (BCNU), lomustine (CCNU), semustine, thalidomide, lenalidomide, methotrexate, azathioprine, 6-mercaptopurine, fludarabine, 5-azacytidine, pentostatin (2'-deoxycoformycin), cytarabine (cytosine arabinoside), gemcitabine, 5-fluorouracil, hydroxyurea, elesclomol (STA-4783), etoposide, teniposide, amsacrine, camptothecin, topotecan, irinotecan, chlorambucil, cyclophosphamide, ifosfamide, melphalan, bortezomib, vincristine, vinblastine, vinorelbine, paclitaxel, and docetaxel.

Other anti-neoplastic compounds that can be administered or formulated with, or coupled to, PACAP-like compounds of the invention (e.g., PACAP-like compounds having the structure of Formula (I); e.g., PACAP-like compounds having the sequence of SEQ ID NOs: 4-13) can be administered or formulated with, or coupled to, include, but are not limited to, 20-pi-1,25 dihydroxyvitamin D3; 5-ethyluracil; abiraterone; aclacinomycin; acylfulvene;
adecymefenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubcin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen; prostatic carcinoma; antiestrogen; antineoplas ton; antisense oligonucleotides; aphidicolin glycin ate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; argininedeaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyr osine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylestaurosporine; beta lactam derivatives; beta-alethine; betacalamin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylsperrmine; bisnafide; bistratene A; bizelesin; breflata; bleomycin A2; bleomycin B2; bropirimine; budotitane; buthionine sulfoximine; calcipiotril; calphostin C; camptothecin derivatives (e.g., 10-hydroxy- camptothecin); canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatam; cyprémicos; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodideimin B; 2'deoxycoformycin (DCF); deslorelin; dexifosfamid; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylorspermine; dihydro-5- azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; discodermolide; docosanol; dolasetron; doxisiluridine; drol oxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflingtonin; elemene; emitefur; eprirubicin; epothilones (A, R = H; B, R = Me); epipthere; epiristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; elesclomol; etoposide; etoposide 4'-phosphate (etopofos); exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopi ridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin

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hydrochloride; forfenimex; formestane; foscarnet; fotemustine; gadolinium
texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors;
gemcitabine; glutathione inhibitors; hepsulfam; herengulin; hexamethylene
bisacetamide; homoharringtonine (HHT); hypericin; ibandronic acid;
idarubicin; idoxifene; idramantone; ilmosofosine; ilomastat; imidazoacridones;
imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor
inhibitor; interferon agonists; interferons; interleukins; iobenguane;
iododoxorubicin; ipomeanol, 4- ; irinotecan; iropolact; irso-gludine;
isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F;
lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate;
leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon;
leuprolide + estrogen + progesterone; leuprolelin; levamisole; liarozole; linear
polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum
compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine;
losoxantrone; lovastatin;loxoribine; lurmetocan; lutetium texaphyrin; lysofoline;
lytic peptides; maytansine; mannostatin A; marimastat; masoprostol; maspin;
matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril;
merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor;
ifepristone; miltefosine; mirimostim; mismatched double stranded RNA;
mithracin; mitoguazone; mitolactol; mitomycin analogues; mitonafide;
mitoxatin fibroblast growth factor-saporin; mitoxantrone; mofarotene;
molgramostim; monoclonal antibody, human chorionic gonadotrophin;
monophosphoryl lipid A + myobacterium cell wall sk; mopidamol; multiple drug
resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard
anticancer agent; mcyperoxide B; mycobacterial cell wall extract;
myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin;
nagrestip; naloxone + pentazocine; napavin; naphterin; nartograstim;
nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide;
nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; 06-
benzylguanaine; octreotide; okicenone; oligonucleotides; onapristone;
ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin;
osaterone; oxaliplatin; oxauonycin; paclitaxel analogues; paclitaxel
derivatives; palauamine; palmitoyl-rlhizoxin; pamidronic acid; panaxytriol;
panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; podophyllotoxin; porfimer sodium; porfiromycin; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors; microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramoteron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogeletimide; rohitukine; romurtide; roquinimex; rubiginone B 1; ruboxyt; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topotecan; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrhostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor;
urokinase receptor antagonists; vaptorectide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

PACAP-like compounds of the invention can also be administered or formulated with, or coupled to, an antiproliferative agent, for example piritrexim isothionate, an antiprostastic hypertrophy agent, such as, for example, sitogluside, a benign prostatic hyperplasia therapy agent, such as, for example, tamsulosin hydrochloride, or a prostate growth inhibitor such as, for example, pentomone.

PACAP-like compounds of the invention can also be administered or formulated with, or coupled to, a radioactive agent, including, but not limited to: Fibrinogen $^{125}$I; Fluodeoxyglucose $^{18}$F; Fluorodopa $^{18}$F; Insulin $^{125}$I; Insulin $^{131}$I; lobenguane $^{123}$I; iodipamide Sodium $^{131}$I; iodocantpyrine $^{131}$I; Iodocholesterol $^{131}$I; iodohippurate Sodium $^{123}$I; iodohippurate Sodium $^{125}$I; iodohippurate Sodium $^{131}$I; iodopyracet $^{125}$I; iodopyracet $^{131}$I; lofetamine Hydrochloride $^{123}$I; lomethin $^{125}$I; lomethin $^{131}$I; lothalamate Sodium $^{125}$I; lothalamate Sodium $^{131}$I; tyrosine $^{131}$I; Liothyronine $^{125}$I; Liothyronine $^{131}$I; Merisoprol Acetate $^{197}$Hg; Merisoprol Acetate $^{203}$Hg; Merisoprol $^{197}$Hg; Selenomethionine $^{75}$Se; Technetium $^{99m}$Tc Antimony Trisulfide Colloid; Technetium $^{99m}$Tc Bicisate; Technetium $^{99m}$Tc Disofenin; Technetium $^{99m}$Tc Etidronate; Technetium $^{99m}$Tc Exemtazime; Technetium $^{99m}$Tc Furifosmin; Technetium $^{99m}$Tc Gluceptate; Technetium $^{99m}$Tc Lidofenin; Technetium $^{99m}$Tc Mebrofenin; Technetium $^{99m}$Tc Medronate; Technetium $^{99m}$Tc Medronate Disodium; Technetium $^{99m}$Tc Mertiatide; Technetium $^{99m}$Tc Oxidronate; Technetium $^{99m}$Tc Pentetate; Technetium $^{99m}$Tc Pentetate Calcium Trisodium; Technetium $^{99m}$Tc Sestamibi; Technetium $^{99m}$Tc Siboroxime; Technetium $^{99m}$Tc; Succimer; Technetium $^{99m}$Tc Sulfur Colloid; Technetium $^{99m}$Tc Teboroxime; Technetium $^{99m}$Tc Tetrofosmin; Technetium $^{99m}$Tc Tiatide; Thyroxine $^{125}$I; Thyroxine $^{131}$I; Tolpovidone $^{131}$I; Triolein $^{125}$I; or Triolein $^{131}$I.

PACAP-like compounds of the invention can also be administered or formulated with, or coupled to, anti-cancer Supplementary Potentiating Agents, including, but not limited to: Tricyclic anti-depressant drugs (e.g.,
imipramine, desipramine, amitriptyline, clomipramine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine, and maprotiline); non-tricyclic anti-depressant drugs (e.g., sertraline, trazodone, and citalopram); Ca++ antagonists (e.g., verapamil, nifedipine, nitrendipine, and caroverine); Calmodulin inhibitors (e.g., prenylamine, trifluoroperazine, and clomipramine); Amphoterin B; Triparanol analogues (e.g., tamoxifen); antiarrhythmic drugs (e.g., quinidine); antihypertensive drugs (e.g., reserpine); Thiol depleters (e.g., buthionine and sulfoximine) and Multiple Drug Resistance reducing agents such as Cremaphor EL.

PACAP-like compounds of the invention that are coupled to a therapeutic or cytotoxic agent can also be administered or formulated with anticancer cocktails. Preferred anticancer agents used in anti-cancer cocktails include (some with their MTDs shown in parentheses): gemcitabine (1000 mg/m²); methotrexate (15 gm/m² i.v. + leuco. < 500 mg/m² i.v. w/o leuco); 5-FU (500 mg/m²/day x 5days); FUDR (100 mg/kg x 5 in mice, 0.6 mg/kg/day in human i.a.); FdUMP; Hydroxyurea (35 mg/kg/d in man); Docetaxel (60-100 mg/m²); discodermolide; epothilones; vincristine (1.4 mg/m²); vinblastine (escalating: 3.3-11.1mg/m², or rarely to 18.5 mg/m²); vinorelbine (30 mg/m²/wk); meta-pac; irinotecan (50-150 mg/m², 1 x/wk depending on patient response); SN-38 (~100 times more potent than Irinotecan); 10-OH campto; topotecan (1.5 mg/m²/day in humans, 1 x iv LDIOmice=75 mg/m²); etoposide (100 mg/m² in man); adriamycin; flavopiridol; Cis-Pt (100mg/m² in man); carbo-Pt (360 mg/m² in man); bleomycin (20 mg/m2); mitomycin C (20 mg/m²); mithramycin (30 ug/kg); capecitabine (2.5 g/m² orally); cytarabine (100 mg/m²/day); 2-CI-2’dexoyadenosine; Fludarabine-P04 (25 mg/m²/day, x 5days); mitoxantrone (12-14 mg/m²); mitozolomide (> 400 mg/m²); Pentostatin; or Tomudex.

PACAP-like compounds of the invention can also be administered or formulated with, or coupled to, a cytokine (e.g., granulocyte colony stimulating factor). Alternatively, PACAP-like compounds of the invention can be administered or formulated with, or coupled to, one or more immunomodulatory molecules, such as a molecule selected from the group consisting of antibodies, cytokines (e.g., interleukins, interferons, tumor
necrosis factor (TNF), granulocyte macrophage colony stimulating factor (GM-CSF), macrophage colony stimulating factor (M-CSF), and granulocyte colony stimulating factor (G-CSF)), chemokines, complement components, complement component receptors, immune system accessory molecules, adhesion molecules, and adhesion molecule receptors.

PACAP-like compounds of the invention can also be administered or formulated with, or coupled to, an antimetabolic agent or a member of the anthracycline family of neoplastic agents. Antimetabolic agents include, but are not limited to, the following compounds and their derivatives:

- azathioprine, cladribine, cytarabine, dacarbazine, fludarabine phosphate, fluorouracil, gencitabine chlorhydrate, mercaptopurine, methotrexate, mitobronitol, mitotane, proguanil chlorhydrate, pyrimethamine, raltitrexed, trimetrexate glucuronate, urethane, vinblastine sulfate, vincristine sulfate, etc.

More preferably, the antimetabolic agent is a folic acid-type antimetabolite, e.g., a class of agents that includes, for example, methotrexate, proguanil chlorhydrate, pyrimethamine, trimethoprim, or trimetrexate glucuronate, or derivatives of these compounds. Agents within the anthracycline family of neoplastic agents include, but are not limited to, aclacinomycin A, daunorubicin chlorhydrate, doxorubicin chlorhydrate, epirubicin chlorhydrate, idarubicin chlorhydrate, pirarubicin, or zorubicin chloride; a camptothecin, or its derivatives or related compounds, such as 10, 11 methylenedioxycamptothecin; or a member of the maytansinoid family of compounds, which includes a variety of structurally related compounds, e.g., ansamitocin P3, maytansine, 2'-N-demethylmaytansine, and maytansibicyclinol.

The PACAP-like compounds of the invention can be coupled directly to a therapeutic or anticancer agent using known chemical methods. Alternatively the PACAP-like compounds can be coupled to an anticancer or therapeutic agent via an indirect linkage. For example, the PACAP-like compounds may be attached to a chelating group that is attached to the anticancer or therapeutic agent. Chelating groups include, but are not limited to, iminocarboxylic and polyaminopolycarboxylic reactive groups,
diethylenetriaminepentaacetic acid (DTPA), and 1,4,7,10-
tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). For general
methods, see, e.g., Liu et al., *Bioconjugate Chem.* 12(4):653, 2001; Cheng et
al., WO 89/12631; Kieffer et al., WO 93/12112; Albert et al., U.S.P.N.
5 5,753,627; and WO 91/01144 (each of which are hereby incorporated by
reference). When coupled to a therapeutic or anticancer agent, the specific
targeting by the PACAP-like compounds of the invention allows selective
destruction of cells expressing a PACAP/VIP receptor, including, e.g., the
catecholamine-containing cells in the adrenal medulla and the sympathetic
ganglia; microglia, astrocytes and some types of neurons in the central
nervous system; and T- and B-lymphocytes, macrophages, neutrophils,
dendritic cells in the immune system, and cancer cells (e.g., leukemia,
lymphoma, and myeloid cancer cells; in particular granuloma cells). PACAP-
like compounds of the invention may be administered to a mammalian
subject, such as a human, directly or in combination with any
pharmaceutically acceptable carrier, excipient, or salt known in the art, as is
discussed in more detail herein.

**DIAGNOSTIC AGENTS COUPLED TO PACAP-LIKE
COMPOUNDS OF THE INVENTION**

PACAP-like compounds of the invention can be modified or labeled
to facilitate diagnostic or therapeutic uses. Detectable labels, such as a
radioactive, fluorescent, heavy metal, or other agent may be bound (ionically
or covalently) to the PACAP-like compounds of the invention. Single, dual, or
multiple labeling of a PACAP-like compound of the invention may be
advantageous. For example, dual labeling with radioactive iodination of one
or more residues combined with the additional coupling of, for example, \(^{90}\)Y
via a chelating group to amine-containing side or reactive groups, would allow
combination labeling. This may be useful for specialized diagnostic needs,
such as identification of widely dispersed small neoplastic cell masses.
PACAP-like compounds of the invention may also be modified, for example,
by halogenation. Halogens include fluorine, chlorine, bromine, iodine, and
astatine. Such halogenated compounds may be detectably labeled, e.g., if
the halogen is a radioisotope, such as, for example, $^{18}$F, $^{76}$Br, $^{77}$Br, $^{122}$I, $^{123}$I, $^{124}$I, $^{125}$I, $^{129}$I, $^{131}$I, or $^{211}$At. Other suitable detectable modifications include binding of other compounds (e.g., a fluorochrome, such as fluorescein) to the PACAP-like compounds of the invention.

Radioisotopes for radiolabeling the PACAP-like compounds of the invention can be selected from radioisotopes that emit either beta or gamma radiation. Alternatively, PACAP-like compounds of the invention can be modified to contain a chelating group. The chelating group can then be modified to contain any of a variety of radioisotopes, such as gallium, indium, technetium, ytterbium, rhenium, or thallium (e.g., $^{125}$I, $^{67}$Ga, $^{111}$In, $^{99m}$Tc, $^{168}$Yb, $^{186}$Re). PACAP-like compounds of the invention that include radioactive metals are useful in radiographic imaging or radiotherapy.

Preferred radioisotopes also include $^{99m}$Tc, $^{51}$Cr, $^{67}$Ga, $^{68}$Ga, $^{111}$In, $^{188}$Yb, $^{140}$La, $^{90}$Y, $^{153}$Sm, $^{156}$Ho, $^{165}$Dy, $^{64}$Cu, $^{97}$Ru, $^{103}$Ru, $^{186}$Re, $^{188}$Re, $^{203}$Pb, $^{211}$Bi, $^{212}$Bi, $^{213}$Bi, and $^{214}$Bi. The choice of metal is determined based on the desired therapeutic or diagnostic application. PACAP-like compounds of the invention that include a metal component are useful as diagnostic and/or therapeutic agents. A detectable label may be a metal ion from heavy elements or rare earth ions, such as Gd$^{3+}$, Fe$^{3+}$, Mn$^{3+}$, or Cr$^{2+}$. Conjugates that include paramagnetic or superparamagnetic metals are useful as diagnostic agents in MRI imaging applications. Paramagnetic metals that may be used in conjunction with PACAP-like compounds of the invention include, but are not limited to, chromium (III), manganese (II), iron (II), iron (III), cobalt (II), nickel (II), copper (II), praseodymium (III), neodymium (III), samarium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III), erbium (III), and ytterbium (III). Preferably, the PACAP-like compounds have a relativity of at least 10, 12, 15, or 20 mM$^{-1}$ sec$^{-1}$ Z$^{-1}$, wherein Z is the concentration of paramagnetic metal.

PACAP-like compounds of the invention can be coupled to a chelating agent to form diagnostic conjugate of the invention. Chelating groups may be used to indirectly couple detectable labels or other molecules to PACAP-like compounds of the invention. Chelating groups may be used to link radiolabels to the PACAP-like compounds of the invention. Examples of
chelators known in the art include, for example, the iminocarboxylic and polyaminopolycarboxylic reactive groups, ininocarboxylic and polyaminopolycarboxylic reactive groups, diethylenetriaminepentaacetic acid (DTPA), and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). Diagnostic conjugates may be prepared by various methods depending upon the chelator chosen. The PACAP-like compound portion of the conjugate can be prepared by techniques known in the art, and by techniques described herein.

DEMONSTRATION OF THE THERAPEUTIC USEFULNESS

The protocols and compositions of the present invention are preferably tested in vitro, and then in preclinical models in vivo, for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays that can be used to determine whether administration of a specific therapeutic protocol is indicated include in vitro cell culture assays in which an appropriate cell line or a patient's tissue sample is grown in culture, and exposed to or otherwise administered a protocol, and the effect of such protocol upon the tissue sample is observed. For example (but not by way of limitation), rescuing of sensory neurons, renal or pulmonary epithelial cells, hepatocytes, or cardiomyocytes; decreased NFκB activation; decreased survival or proliferation of B- or T-lymphocytes; or decreased production of TNF-α and IL-6. A demonstration of one or more of the aforementioned properties of the exposed cells indicates that the therapeutic agent is effective for treating the condition in the patient. Many assays standard in the art can be used to assess such survival and/or growth of neurons, epithelial cells, hepatocytes, and/or B- or T-lymphocytes. Furthermore, any of the assays known to those skilled in the art can be used to evaluate the prophylactic and/or therapeutic utility of the therapies disclosed herein for treatment, management or prevention of injuries to one or more major organs of the body caused by trauma, diseases or other prophylactic or therapeutic agents.

The injuries to one or more major organs of the body of humans or other mammals caused by trauma, acute or chronic diseases, or one or more
prophylactic/therapeutic agents (e.g., one or more anticancer agents) can be monitored in the subjects with commonly used biomarkers. For example (but not by way of limitation), injury to the kidney can be monitored by determining the concentration of protein in the urine, or the concentration of creatinine or urea nitrogen in the bloodstream. Injury to the liver can be monitored by determining the enzyme activity or concentration of alanine aminotransferase in the bloodstream, or the concentration of conjugated bilirubin in the urine. Injury to the heart can be monitored by determining the concentration of troponin I or the MB isoenzyme of creatinine kinase in the bloodstream. Injury to the β-cells of the pancreas can be monitored by determining the activity or concentration of glutamic acid decarboxylase in the bloodstream, and injury to the nervous system can be monitored by determining the activity or concentration of neuron-specific enolase in the bloodstream.

The injuries to one or more major organs of the body of humans or other mammals caused by trauma, acute or chronic diseases, or one or more prophylactic/therapeutic agents (e.g., one or more anticancer agents) can also be monitored in the subjects with commonly used imaging techniques. For example (but not by way of limitation), injury to the heart can be monitored by electrocardiography or serial echocardiography.

The injuries to one or more major organs of the body of humans or other mammals caused by trauma, acute or chronic diseases, or one or more prophylactic/therapeutic agents (e.g., one or more anticancer agents) can also be monitored in the subjects with commonly used functional tests. For example (but not by way of limitation), injury to the kidney can be monitored by determining the glomerular filtration rate with cystatin C or with sodium ¹²⁵I-iothalamate clearance. Injury to the peripheral nerves can be monitored by determining nerve conduction velocities or somatosensory perception. Injury to the heart can be monitored with a variety of exercise tests.

Based on the currently available data, there is a correlation between the reduction in the rate of proliferation of some cancer cells by PACAP-like compounds and the enhancement of the therapeutic efficacy of anticancer agents by PACAP-like compounds. Cancer cells can be obtained from biopsy samples from humans and other mammals, cultured in multi-well plates, and
the effect of PACAP-like peptides on their rate of proliferation can be quantified in order to determine whether the PACAP-like compounds will protect the cancer cells against cancer chemotherapeutics or enhance the efficacy of cancer chemotherapeutics.

The definitive diagnosis of multiple myeloma can be made in about 95% of the patients after a bone marrow aspiration or bone marrow biopsy. In the other patients, the bone marrow involvement is probably focal rather than diffuse. The efficacy of the adjunctive treatment with PACAP-like peptides can be determined subjectively by the patient reporting an improvement in symptoms, such as bone pain, fatigue, and overall well-being. The efficacy of the adjunctive treatment with PACAP-like peptides can be determined objectively by a physical examination that shows an improvement in overall appearance and muscle strength, by laboratory tests that show a reduction in anemia (a rise in hemoglobin and hematocrit), serum and urinary levels of the monoclonal paraprotein (Bence-Jones protein), and serum and urinary β-2 microglobulin, and by laboratory tests that show an improvement in kidney function (blood creatinine, urea nitrogen and cystatin C). In a preferred embodiment, serum and urinary levels of the monoclonal free light-chain immunoglobulin (Bence-Jones protein) are monitored with a highly sensitive nephelometric assay during the course of the treatment with the PACAP-like cytoprotective adjunctive agents.

Those skilled in the art will recognize, or be able to ascertain using no more than routine searches of the medical literature that there are similar standard methods for selecting appropriate patient populations to study of the effects of the compositions of the present invention on age-related neurodegenerative diseases; injuries to the central nervous system caused by stroke, heart attack and blunt force trauma; Huntington's disease and other CAG codon repeat expansion diseases; retinal diseases; autoimmune diseases; keratoconjunctivitis sicca; type II diabetes; sepsis; acute and chronic cardiovascular diseases; acute and chronic renal diseases; acute and chronic pulmonary diseases; systemic hypertension; hematological cancers; eating disorders; acute and chronic liver diseases; osteoporosis;
pre-eclampsia; cell and solid organ transplantation; cognitive disorders; AIDS dementia complex; and aging of the central nervous system.

PHARMACEUTICAL COMPOSITIONS

The compositions of the present invention include bulk drug compositions useful in the manufacture of pharmaceutical compositions (e.g., impure or non-sterile compositions) and parenteral pharmaceutical compositions (i.e., compositions that are suitable for administration to a subject or patient) which can be used in the preparation of unit dosage forms. Such compositions comprise a prophylactically or therapeutically effective amount of a prophylactic and/or therapeutic agent disclosed herein or a combination of those agents and a pharmaceutically acceptable carrier. Preferably, compositions of the present invention comprise a prophylactically or therapeutically effective amount of one or more PACAP-like compounds useful in the method of the invention and a pharmaceutically acceptable carrier. In a further embodiment, the composition of the present invention further comprises an additional therapeutic as discussed above.

In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and particularly for use in humans. The term "carrier" refers to a diluent, adjuvant (e.g., Freund's adjuvant or, more preferably, MF59C.I adjuvant), excipient, or vehicle with which the therapeutic is administered. The pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include (but are not limited to) starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene,
glycol, water, and ethanol. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take many forms, including (but not limited to) suspensions, emulsions, tablets, pills, capsules, powders, and sustained-release formulations.

Generally, the ingredients of the compositions of the present invention are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compositions of the present invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include (but are not limited to) those formed with anions such as those derived from hydrochloric acid, phosphoric acid, acetic acid, oxalic acid, and tartaric acid, and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, and procaine.

As desired, additives such as a dissolution aid (e.g., sodium salicylate or sodium acetate), a buffer (e.g., sodium citrate or glycerin), an isotonicizing agent (e.g., glucose or invert sugar), a stabilizer (e.g., human serum albumin or polyethylene glycol), a preservative (e.g., benzyl alcohol or phenol), or an analgesic (e.g., benzalkonium chloride or procaine hydrochloride) may be added.

There are many delivery methods known to those skilled in the art that can be used to administer the PACAP-like compound(s), or the PACAP-like compound(s) in combination with other cytoprotective agents, in order to treat, manage or prevent injuries to one or more of the major organs of the body of humans or other mammals caused by one or more anticancer agents. For example (but not by way of limitation), encapsulation in liposomes,
microparticles or microcapsules, secretion from mammalian cells genetically engineered to synthesize one or more PACAP-like peptides, or synthesis by various recombinant viral vectors. The routes of administration of the PACAP-like compounds of the present invention include (but are not limited to), parenteral (e.g., intradermal, intramuscular, intraperitoneal, intravenous, and subcutaneous), vaginal, rectal, epidural, and mucosal (e.g., intranasal, inhaled, and oral routes). In a specific embodiment, prophylactic or therapeutic agents of the present invention are administered intramuscularly, intravenously, intraosseously, or subcutaneously. The prophylactic or therapeutic agents may be administered by any convenient route or regimen, for example by infusion or a bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal, topical, including buccal and sublingual, and intestinal mucosa, etc.) and may be administered in combination with other biologically active agents. Administration can be systemic or local.

In a specific embodiment, it may be desirable to administer the prophylactic or therapeutic agents of the present invention locally to the area in need of treatment; this may be achieved by, for example, but not by way of limitation, local infusion, by injection, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as Silastic membranes, or fibers.

In another embodiment, the compositions of this invention can be delivered in a controlled release or sustained release manner. In one embodiment, a pump can be used to achieve controlled or sustained release. In another embodiment, polymeric materials can be used to achieve controlled release or sustained release. Suitable polymers for controlled release or sustained release formulations include (but are not limited to) poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In a preferred embodiment, the polymer used in a controlled release or a sustained release formulation is
inert, free of leachable impurities, stable on storage, sterile, and biodegradable. In a specific embodiment, a controlled release, or a sustained release device or formulation can be placed in proximity of the prophylactic or therapeutic target, thus reducing the required amount of the PACAP-like compound to only a fraction of the systemic dose. Many other techniques known to one skilled in the art can be used to produce controlled release or sustained release formulations comprising one or more therapeutic agents of the present invention.

The compositions for administration of the PACAP-like compounds include (but are not limited to) those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal, or parenteral (including subcutaneous, transcutaneous, intramuscular, intravenous, and intradermal) administration. The formulations may conveniently be presented in unit dosage forms and may be prepared by any methods well known in the art of pharmacy. Thus, the PACAP-like compounds of the present invention and their physiologically acceptable salts and solvates may be formulated for administration by inhalation or insufflation (either through the mouth or the nose), or by oral, parenteral or mucosal (such as buccal, vaginal, rectal, and sublingual) routes. In a preferred embodiment, parenteral administration is used.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium dodecyl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents
(e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol, or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavoring, coloring, and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release or sustained release of the active compound.

For buccal administration, the compositions of the present invention may be conventionally formulated as tablets or lozenges.

For administration by inhalation, the prophylactic or therapeutic agents for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The prophylactic or therapeutic agents may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative.

The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in a powder form for reconstitution before use with a suitable vehicle, e.g., sterile pyrogen-free water.

In addition to the formulations described previously, the prophylactic or therapeutic agents may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation (e.g., subcutaneously or intramuscularly) or by intramuscular injection. Thus, for
example, the prophylactic or therapeutic agents may be formulated with suitable polymeric or hydrophobic materials (e.g., as an emulsion in an acceptable oil) or ion-exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Compositions suitable for topical administration to the skin may be presented as ointments, creams, gels, and pastes comprising the compound and a pharmaceutically acceptable carrier. For example (but not by way of limitation), a suitable topical delivery system is a transdermal patch containing the PACAP-like compound to be administered.

Sublingual tablets can be prepared by using binders (e.g., hydroxypropylcellulose, hydroxypropylmethylcellulose, or polyethylene glycol), disintegrating agents (e.g., starch or carboxymethylcellulose calcium), and/or lubricants (e.g., magnesium stearate or talc).

Suitable formulations for nasal administration wherein the carrier is a solid include a coarse powder having a particle size, for example, in the range 20 to 500 microns (µm). Suitable formulations for nasal administration wherein the carrier is a liquid (e.g., a nasal spray or nasal drops) include aqueous or oily solutions of the active ingredient.

Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostatic agents, and solutes that make the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions that may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. It should be understood that in addition to the ingredients specifically mentioned above, the formulations of this invention may include other agents commonly used in the art for the type of formulation in question. For example (but not by way of limitation), those suitable for oral administration may include flavoring agents.
EXAMPLES

In order to make the uses of the present invention clearer, the following examples are presented. These examples are only for illustrative purposes and should not be interpreted in any way as limitations in the uses of this invention.

Example 1. Novel PACAP Analogs

Peptides can have extraordinarily high affinities for their cognate receptors. The major drawback of using native peptides as therapeutics is their short half-life in the circulation after parenteral administration due mainly to rapid proteolysis and rapid filtration by the kidney. Therefore, analogs of PACAP have been made in order to reduce the rates of proteolysis and/or renal clearance. In addition, other changes have been made in the native amino-acid sequences of PACAP27 and PACAP38 in order to reduce the cost of synthesis, and alter tissue distribution and/or receptor specificity.

Ten novel peptide analogs of PACAP27 or PACAP38 have been made by solid-phase synthesis (SEQ ID NOs: 4-13; Figure1 and Figure 2) using the procedures briefly described above.

Some of the biological properties of nine of these ten PACAP analogs are illustrated below (Figures 3-10) and the potential medical applications of these novel PACAP analogs suggested by these illustrations are briefly outlined.

Example 2. Inhibition of the Proliferation of Multiple Myeloma Cells by PACAP38, PACAP27, VIP, and Novel PACAP Analogs

Multiple myeloma, a malignant cancer of plasma cells, is the sixth most common cancer in the USA. It accounts for about 10% of the hematological malignancies diagnosed in the USA. Multiple myeloma is slightly more prevalent in men than in women. The disease can cause serious medical complications, including bone resorption (osteolysis), hypercalcemia, anemia,
thrombocytopenia, and kidney failure. Inflammation of the kidney is the second most frequent complication and occurs in about half of the patients with multiple myeloma. The cause of this inflammation is the overproduction by plasma cells of light-chain immunoglobulins (Bence-Jones proteins), which aggregate to form casts in the distal convoluted tubules and collecting ducts of the kidneys. Plasma cells are derived from activated B lymphocytes by clonal expansion. The normal restraints on the expansion of a single plasma cell clone is lost in patients with multiple myeloma, which results in the excessive production of a single type of light-chain immunoglobulin.

The effects of PACAP38, PACAP27, VIP, and PACAP analogs on myeloma cell proliferation were assessed by determining incorporation bromodeoxyuridine into DNA during cell division. The number of myeloma cells approximately doubled during the 24-hour incubation period in the absence of treatment with PACAP-like peptides. The addition of PACAP38 to the medium resulted in 50% inhibition of the rate of proliferation of the light-chain immunoglobulin-secreting human myeloma cells at a concentration of about 250 picomolar (Figure 3). Four of the five novel PACAP38 analogs caused 50% inhibition of the rate of proliferation of the light-chain immunoglobulin-secreting human myeloma cells at concentrations substantially below 1 nanomolar (Figure 3). PACAP27, VIP and the novel PACAP27 analogs were significantly less potent than either PACAP38 or the novel PACAP38 analogs in this in vitro model of hematopoietic cancer cell proliferation. These results suggest that inhibition of the proliferation of this human multiple myeloma cell line is mediated primarily by stimulation of the PAC1 receptor and the phospholipase C-mediated signal transduction pathway (Spengler et al., Nature 365:170-175, 1993). PACAP38 analogs with either nipecotic acid or isonipecotic acid in position 3 were more than 10,000 times less potent as inhibitors of multiple myeloma cell proliferation than the corresponding analog with pipecolic acid in position 3 (Figure 4).

PACAP and PACAP analogs have also been shown to inhibit the proliferation of myeloid hematopoietic cancer cells (Hayez et al., J Neuroimmunol 149:167-181, 2004) and to enhance the killing of both lymphoid and myeloid hematopoietic cancer cells by commonly used
anticancer agents such as carmustine, vincristine and thalidomide (PCT/US2009/058445). PACAP38 can also directly protect the kidney against light-chain immunoglobulin overload and would be expected to inhibit bone resorption in patients with multiple myeloma (Li et al., Regul Pept 145:24-32, 2008). PACAP protects kidney, lung, pancreatic and neuronal epithelial cells against commonly used anticancer agents such as cisplatin, doxorubicin, bleomycin, and streptozotocin (Aubert et al., Neurobiol Dis 32:66-80, 2008; Onoue et al., FEBS J 275:5542-5551, 2008; PCT/US2009/058445; Figure 5). These results indicate that these novel PACAP38 analogs could be used as either monotherapeutics or adjunctive therapeutics for both lymphoid and myeloid hematopoietic cancers, especially multiple myeloma.

**Example 3. Reduction of Cisplatin-Induced Cytotoxicity by PACAP38, PACAP27 and Novel PACAP Analogs**

Cisplatin (cis-diamminedichloroplatinum(II), Platinol) is the first-in-class platinum-based DNA-crosslinking anticancer therapeutic. It was approved for clinical use by the U.S. FDA in 1978. The other members of this class of "alkylating-like" platinum-based anticancer agents now include (but are not limited to) carboplatin, oxaliplatin and satraplatin. Cisplatin is one of the most widely used cancer chemotherapeutics and is the cornerstone of many multi-drug anticancer regimens. Nephrotoxicity is usually the "dose-limiting" toxicity for the use of cisplatin in cancer chemotherapy, but sensory neuropathies can sometimes limit the doses that can be used to treat some patients.

Treatment of rat renal proximal tubule epithelial cells with cisplatin resulted in a large significant increase in apoptotic cell death (Figure 5). The addition of PACAP38 to the medium at a concentration of 10^{-6} M resulted in a significant reduction in cisplatin-induced apoptotic cell death of these proximal tubule epithelial cells. VIP also reduced the cisplatin-induced apoptotic cell death of the human renal proximal tubule epithelial cells, but VIP was significantly less potent than PACAP38. The three novel PACAP38 analogs (SEQ IN NOs 4, 5 and 6) were either as effective or more effective than...
PACAP38 as cytoprotectants in this \textit{in vitro} model of acute renal proximal tubule cell injury (Figure 5).

These experiments show that PACAP38 and the three novel PACAP38 analogs are potent cytoprotectants against cisplatin-induced damage to the kidney, which is the "dose-limiting" toxicity for cancer chemotherapy with cisplatin. Therefore, pre- and/or post-treatment of subjects undergoing cisplatin-based cancer chemotherapy with therapeutic doses of these novel PACAP38 analogs should result in a higher maximal tolerable dose of cisplatin, and an increased frequency of partial clinical responses and/or an increased number of complete remissions. We have previously shown that PACAP38 protects the kidney against acute injury due to light-chain immunoglobulin overload, gentamicin, streptozotocin, and doxorubicin (Li et al., \textit{Regul Pept} \textbf{145}:24-32, 2008; Maderdrut et al., \textit{VIP, PACAP and Related Peptides} [Ninth International Symposium], Kagoshima, 2009). Therefore, these novel PACAP38 analogs should also protect the kidney against a similarly broad range of potential nephrotoxins.

\textbf{Example 4. Reduction of Ischemia/Reperfusion Injury by PACAP38 and Novel PACAP Analogs}

Ischemia/reperfusion injury to one or more major organs of the body can be caused by blunt force trauma, transient arterial stenosis, hemorrhagic shock, severe sepsis, solid organ transplantation, and deliberately during some common surgical procedures.

Transient clamping of the renal artery for 45 minutes resulted in a large significant increase in serum creatinine after 72 hours. The administration of PACAP38, [Pip\(^3\),Ala\(^{15,17}\),Aib\(^{16,28}\),Lys\(^{34}\),D-Lys\(^{38}\)]PACAP38 (SEQ ID NO 5) or [Pip\(^3\),Ala\(^{14,17}\),Aib\(^{16,28}\),Lys\(^{34}\),D-Lys\(^{38}\)]PACAP38 (SEQ ID NO 6) almost completely reversed the rise in serum creatinine caused by ischemia/reperfusion (Figure 6). Both novel PACAP38 analogs appear to be slightly more potent than native PACAP38 in this \textit{in vivo} model.
These experiments show that PACAP38 and the two novel PACAP38 analogs are potent cytoprotectants against injury to the kidney caused by ischemia/reperfusion. PACAP-like peptides have already been shown to protect the brain, heart, lung, pancreas, and intestine against injury caused by ischemia/reperfusion. Therefore, these novel PACAP38 analogs should also protect a similarly broad range of major organs of the body of humans and other mammals against injuries caused by ischemia/reperfusion. These novel PACAP analogs should be useful therapeutics for injuries caused by blunt force trauma, transient arterial stenosis, hemorrhagic shock, severe sepsis, solid organ transplantation, and the side-effects of some common surgical procedures. These novel PACAP analogs could be used at one or more stages of the organ transplantation process: for perfusion of the brain-dead organ donor, as an additive in the organ storage solution or for treatment of the organ recipient after transplantation.

Example 5. Inhibition of Dexamethasone-Sensitive and Dexamethasone-Resistant B-Lymphocytes by PACAP38 and A Novel PACAP Analogs

Glucocorticoids are frequently used for the treatment of patients with blood cancers and autoimmune diseases in order to inhibit the activity of B- and T-lymphocytes. However, a significant portion of the patients treated with glucocorticoids eventually become resistant to the steroid (Barnes & Adcock, Lancet 373:1905-1917, 2009).

Figures 8 and 9 shows the effects PACAP38, [Pip₃,Ala₁⁴,₁⁷,Aib₁⁶,₂₈,Lys₃⁴,D-Lys₃⁶]PACAP38 (SEQ ID NO: 6) and dexamethasone on the proliferation of two different light-chain immunoglobulin-secreting human myeloma cell lines that were derived from the same patient who was being treated for multiple myeloma with a dexamethasone-containing regimen (Greenstein et al., Exp Hematol 31:271-282, 2003). The cell line in Figure 8 (MM.1S) appears to be as sensitive to dexamethasone as it is to PACAP38, while the cell line in Figure 9 (MM.1R) is almost completely insensitive to dexamethasone but is still sensitive to both PACAP38 and the novel PACAP38 analog.
These observations indicate that PACAP-like peptides should be
efficacious in patients with blood cancers and autoimmune diseases even
after the patients have become resistant to glucocorticoids. Therefore, these
novel PACAP analogs could be used to replace the glucocorticoid in common
multiple drug regimens, such as COP (cyclophosphamide, ONCOVIN™
(vincristine) and prednisone) and VAD (vincristine, ADRIAMYCIN™
doxorubicin) and dexamethasone), as soon as the patient becomes
insensitive to the steroid. These observations also indicate that these novel
PACAP analogs could be used as monotherapy to replace the commonly
used glucocorticoid for diseases such as systemic lupus erythematosus and
rheumatoid arthritis. In addition, these observations indicate that PACAP-like
peptides could be efficacious in patients with inflammatory diseases that are
usually insensitive to treatment with glucocorticoids such as cystic fibrosis and
interstitial pulmonary fibrosis.

The above examples show that these novel PACAP analogs (SEQ ID
NOs: 4-13) should be efficacious monotherapeutics and/or adjunctive
therapeutics for an extraordinarily wide range of major medical disorders. The
above examples show that these novel PACAP38 analogs could be used as
either monotherapeutics and/or adjunctive therapeutics for both lymphoid and
myeloid hematopoietic cancers, for acute and chronic drug-induced
nephropathies, and for injuries caused by blunt force trauma, transient arterial
stenosis, hemorrhagic shock, severe sepsis, solid organ transplantation, and
the side-effects of some common surgical procedures. In addition, these
novel PACAP analogs should be efficacious monotherapeutics and/or
adjunctive therapeutics for the extraordinarily wide range of other major
medical disorders already shown for native PACAP27, native PACAP38 and
native VIP (see SUMMARY OF THE INVENTION).

Example 6. Reduction of Gentamicin-Induced Cytotoxicity by PACAP38
and a Novel PACAP Analog

Aminoglycosides are commonly used as antibiotics for the treatment of
Gram-negative bacterial infections. The use of aminoglycosides as

Treatment of human renal proximal tubule epithelial cells with gentamicin (Figure 10) resulted in a large significant increase in apoptotic cell death. The addition of PACAP38 or [Pip$^3$]PACAP38 (SEQ ID NO 12) to the medium resulted in a significant dose-dependent reduction in gentamicin-induced apoptotic cell death of these proximal tubule epithelial cells. PACAP38 was more effective as a cytoprotectant in this *in vitro* model of aminoglycoside-induced renal proximal tubule epithelial cell injury than the novel PACAP38 analog (Figures 10).

These observations indicate that PACAP-like peptides should be useful as adjunctive agents in combination with aminoglycosides for the treatment of bacterial infections, especially Gram-negative bacterial infections.

There are more than 1,000 human genetic diseases that are caused in part by premature in-frame stop codons that result in the synthesis of truncated nonfunctional proteins. Burke & Mogg (*Nucleic Acids Res* 13:6265-6272, 1985) discovered that aminoglycosides could impair the recognition of premature stop codons in mammalian cells. Aminoglycosides have now been shown to impair the recognition of premature stop codons *in vitro* and/or in animal models *in vivo* for numerous genetic diseases, including cystic fibrosis, Duchenne muscular dystrophy, Hurler's syndrome, nephropathic cystinosis, polycystic kidney disease, retinitis pigmentosa, and ataxia telangiectasia. Gentamicin has been shown to promote the synthesis of small quantities of full-length functional proteins in human clinical trials for cystic fibrosis (Wilschanski et al., *N Engl J Med* 349:1433-1441, 2003) and Duchenne muscular dystrophy (Politano et al., *Acta Myol* 22:15-21, 2003). However, the use of aminoglycosides to impair recognition of premature stop codons and promote the synthesis of full-length functional proteins is limited by their nephrotoxic (Mingeot-Leclercq & Tulkens, *Antimicrob Agents Chemother* 43:1003-1012, 1999) and ototoxic (Selimoglu, *Curr Pharm Des* 13:119-126).
side-effects. These side-effects should be extremely serious limitations for the treatment of life-long diseases. PACAP-like peptides should be useful as adjunctive agents in combination with aminoglycosides for the treatment of genetic diseases caused by in-frame premature stop codons because of their cytoprotective effects against aminoglycoside-induced renal proximal tubule epithelial cell injury. Cystic fibrosis is one of the most common genetic diseases among Caucasians. It is an autosomal recessive disease that is caused by mutations in both alleles of the gene for the cystic fibrosis transmembrane conductance regulator. Over 1,000 different mutations have been described in the cystic fibrosis transmembrane conductance regulator gene. About 10% of these mutations are in-frame premature stop codons. The combination of an aminoglycoside and a PACAP-like peptide should be especially efficacious in a significant portion of patients with cystic fibrosis because published articles indicate that PACAP should be modestly efficacious in some patients with cystic fibrosis even as a monotherapeutic. PACAP stimulates the activity of the cystic fibrosis transmembrane conductance regulator (Dérand et al., Br J Pharmaco 141:698-708, 2004) and would facilitate the insertion of the cystic fibrosis transmembrane conductance regulator into membranes (Ameen et al., J Cell Sci 112:887-894, 1999; Chappe et al., J Pharmaco Exp Ther 327:226-238, 2008). In addition, PACAP inhibits neutrophil infiltration into the lung (Kinhult et al., Peptides 22:2151-2154, 2001; Sergejeva et al., Regul Pept 117:149-154, 2004). Furthermore, lung inflammation in persons with cystic fibrosis is usually insensitive to corticosteroids (see above). The combination of an aminoglycoside and a PACAP-like peptide should also be especially efficacious in a significant portion of other recessive diseases where PACAP-like peptides would be expected to have modest efficacy as monotherapeutics, including (but not limited to) Duchenne muscular dystrophy, nephtopathic cystinosis and polycystic kidney disease.
EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the present invention described herein. Such equivalents are intended to be encompassed by the following claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically indicated to be incorporated herein by reference.

What is claimed is:
CLAIMS

1. An isolated compound having formula (I), or a pharmaceutically acceptable salt thereof:

$$R^1-A^1-A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-R^2,$$

wherein:

10 $A^1$ is His, d-His, Tyr, d-Tyr, Trp, d-Trp, Pal, or d-Pal;
$A^2$ is Ser, d-Ser, hSer, N-Me-Ser, Thr, d-Thr, Ala, d-Ala, Ile, d-Ile, Pro, d-Pro,
   Abu, Aib, Acb, Ach, Acpe, or Acpr;
$A^3$ is Pip;
$A^4$ is Gly, Ala, d-Ala, β-Ala, Gaba, Abu, Aib, Acb, Ach, Acpe, or Acpr;
15 $A^5$ is Ile, Leu, Nle, Val, Nva, Aib, Acb, Ach, Acpe, or Acpr;
$A^6$ is Phe, Tyr, Trp, Cha, Bip, or Nal;
$A^7$ is Thr, Ser, hSer, or Val;
$A^8$ is Asp, Asn, or Glu;
$A^9$ is Ser, hSer, Thr, Asn, Asp, Ala, Abu, Aib, Acb, Ach, Acpe, or Acpr;
20 $A^{10}$ is Tyr, Phe, Cha, Nal, or Trp;
$A^{11}$ is Ser, hSer, Thr, Ala, Abu, Aib, Acb, Ach, Acpe, or Acpr;
$A^{12}$ is Arg, Lys, Dab, Dap, or Orn;
$A^{13}$ is Tyr, Phe, Cha, Nal, or Trp;
$A^{14}$ is Arg, Lys, Dab, Dap, or Orn;
25 $A^{15}$ is Lys, Ala, Dab, Dap, Orn, Abu, Aib, Acb, Ach, Acpe, or Acpr;
$A^{16}$ is Gin, Glu, Asn, Asp; Aib, Acb, Ach, Acpe, or Acpr;
$A^{17}$ is Met, Nle, Leu, Ile, Ala, Abu, Aib, Acb, Ach, Acpe, or Acpr;
$A^{18}$ is Ala, Abu, Aib, Acb, Ach, Acpe, or Acpr;
$A^{19}$ is Val, Nva, Ser, Leu, Thr, Aib, Acb, Ach, Acpe, or Acpr;
30 $A^{20}$ is Lys, Ala, Dab, Dap, Orn, Abu, Aib, Acb, Ach, Acpe, or Acpr;
$A^{21}$ is Lys, Ala, Dab, Dap, Orn, Abu, Aib, Acb, Ach, Acpe, or Acpr;
$A^{22}$ is Tyr, Phe, Cha, Nal, Trp, Ala, Abu, Aib, Acb, Ach, Acpe, or Acpr;
$A^{23}$ is Leu, Nle, Ile, Val, Nva, Aib, Acb, Ach, Acpe, or Acpr;
A^{24} is Ala, Asn, Abu, Aib, Acb, Ach, Acpe, or Acpr;  
A^{25} is Ala, Val, Leu, Met, Nle, Ile, Ser, hSer, Thr, Abu, Aib, Acb, Ach, Acpe, Acpr, or is omitted;  
A^{26} is Val, Nva, Leu, Met, Nle, Ile, Ala, Abu, Aib, Acb, Ach, Acpe, Acpr, or is omitted;  
A^{27} is Leu, D-Leu, Met, D-Met, Nle, Ile, D-Ile, Val, D-Val, Gaba, Ala, D-Ala, Abu,  
Aib, Acb, Ach, Acpe, Acpr, or is omitted;  
A^{28} is Gly, Ala, D-Ala, β-Ala, Gaba, Asn, D-Asn, Gln, D-Gln, Asp, D-Asp, Abu,  
Aib, Acb, Ach, Acpe, Acpr, or is omitted;  
A^{29} is Lys, D-Lys, Arg, D-Arg, Dab, D-Dab, Dap, D-Dap, Orn, D-Orn, or is omitted;  
A^{30} is Arg, D-Arg, Lys, D-Lys, Dab, D-Dab, Dap, D-Dap, Orn, D-Orn, or is omitted;  
A^{31} is Tyr, D-Tyr, Phe, D-Phe, Trp, D-Trp, Cha, Nal, or is omitted;  
A^{32} is Lys, D-Lys, Arg, D-Arg, Dab, D-Dab, Dap, D-Dap, Orn, D-Orn, or is omitted;  
A^{33} is Gln, D-Gln, Glu, D-Glu, Asn, D-Asn, Asp, D-Asp, Abu, Aib, Acb, Ach,  
Acpe, Acpr, or is omitted;  
A^{34} is Arg, D-Arg, Lys, D-Lys, Dab, D-Dab, Dap, D-Dap, Orn, D-Orn, or is  
omitted;  
A^{35} is Val, D-Val, Nva, Ser, D-Ser, Thr, D-Thr, Abu, Aib, Acb, Ach, Acpe, Acpr,  
or is omitted;  
A^{36} is Lys, D-Lys, Arg, D-Arg, Dab, D-Dab, Dap, D-Dap, Orn, D-Orn, or is  
omitted;  
A^{37} is Asn, D-Asn, Gln, D-Gln, Asp, D-Asp, Ala, D-Ala, Aib, Acb, Ach, Acpe,  
Acpr, or is omitted;  
A^{38} is Lys, D-Lys, Arg, D-Arg, Dab, D-Dab, Dap, D-Dap, Orn, D-Orn, or is  
omitted;  
R^1 is independently selected from H, (C_1-C_{18})alkyl, and CO(C_1-C_{18})alkyl, or is  
omitted; and  
R^2 is independently selected from OH, NH_2, (C_1-C_{18})alkoxy, and NH(C_1-C_{18})alkyl, or is omitted.
2. The compound of claim 1, wherein the compound is selected from
the following, or pharmaceutically acceptable salts thereof:

His-Ser-Pip-Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-
Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-
Lys-NH₂ (SEQ ID NO:4),

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Ala Aib Ala Ala Val-
Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-
Lys-NH₂ (SEQ ID NO:5),

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Ala Lys Aib Ala Ala Val-
Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-
Lys-NH₂ (SEQ ID NO:6),

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-
Lys Ala Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-
Lys-NH₂ (SEQ ID NO:7),

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-
Ala Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-
Lys-NH₂ (SEQ ID NO:8),

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val
Lys Lys Tyr Leu Ala Ala Val Leu-NH₂ (SEQ ID NO:9),

N-acetyl-His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala
Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu-NH₂ (SEQ ID NO:10),

His Ala Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val
Lys Lys Tyr Leu Ala Ala Val Leu-NH₂ (SEQ ID NO:11),
His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Gln Met Ala Val Lys Tyr Leu Ala Ala Val Leu Gly Lys Tyr Lys Gln Arg Val Lys Asn Lys-NH₂ (SEQ ID NO:12), and

5 N-acetyl-His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Gln Met Ala Val Lys Tyr Leu Ala Ala Val Leu Gly Lys Tyr Lys Gln Arg Val Lys Asn Lys-NH₂ (SEQ ID NO:13).

3. A polypeptide having at least 90% sequence identity to a sequence selected from SEQ ID NOs: 4-13.

4. The polypeptide of claim 3, wherein said polypeptide has at least 95% sequence identity to a sequence selected from SEQ ID NOs: 4-13.

5. The polypeptide of claim 3, wherein said polypeptide has at least 99% sequence identity to a sequence selected from SEQ ID NOs: 4-13.

6. The polypeptide of claim 3 further comprising a pharmaceutically acceptable carrier.

7. The polypeptide of any one of claims 1 to 6, wherein said polypeptide is conjugated one or more radionuclides or small molecules.

8. The polypeptide of claim 7, wherein said radionuclide is \(^{11}\text{C}, ^{13}\text{N}, ^{15}\text{O}, ^{18}\text{F}, ^{52}\text{Fe}, ^{55}\text{Co}, ^{61}\text{Cu}, ^{62}\text{Cu}, ^{64}\text{Cu}, ^{67}\text{Cu}, ^{67}\text{Ga}, ^{68}\text{Ga}, ^{62}\text{Zn}, ^{63}\text{Zn}, ^{70}\text{As}, ^{71}\text{As}, ^{74}\text{As}, ^{76}\text{Br}, ^{79}\text{Br}, ^{82}\text{Rb}, ^{86}\text{Y}, ^{89}\text{Zr}, ^{110}\text{In}, ^{111}\text{In}, ^{120}\text{I}, ^{123}\text{I}, ^{124}\text{I}, ^{125}\text{I}, ^{131}\text{I}, ^{122}\text{Xe}, ^{175}\text{Lu}, ^{154}\text{Gd}, ^{155}\text{Gd}, ^{156}\text{Gd}, ^{157}\text{Gd}, ^{158}\text{Gd}, ^{94m}\text{Tc}, ^{94}\text{Tc}, \text{or} ^{99m}\text{Tc}.

9. The polypeptide of claim 7, wherein said small molecule is a therapeutic or anticancer agent.

10. The polypeptide of claim 9, wherein said therapeutic or anticancer agent is cisplatin, carboplatin, oxaliplatin, bleomycin, mitomycin C,
calicheamicins, maytansinoids, geldanamycin, doxorubicin, idarubicin, daunorubicin, epirubicin, busulfan, carmustine (BCNU), lomustine (CCNU), semustine, thalidomide, lenalidomide, methotrexate, azathioprine, 6-mercaptopurine, fludarabine, 5-azacytidine, pentostatin (2'-deoxycoformycin), cytarabine (cytosine arabinoside), gemcitabine, 5-fluorouracil, hydroxyurea, elesclomol, etoposide, teniposide, amsacrine, camptothecin, topotecan, irinotecan, chlorambucil, cyclophosphamide, ifosfamide, melphanal, bortezomib, vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, cyclosporine A, tacrolimus, sirolimus (rapamycin), everolimus, temsirolimus, zotarolimus, or biolimus.

11. A method for treating, managing, or preventing a disease selected from age-related neurodegenerative disease, a central nervous system disorder, Huntington's disease or other CAG codon repeat expansion disease, a retinal disease, an autoimmune disease, keratoconjunctivitis sicca caused by autoimmune diseases or LASIK surgery, type II diabetes, sepsis caused by a bacteria and/or a virus, an acute or chronic cardiovascular disease, an acute or chronic renal diseases, an acute or chronic pulmonary disease, systemic hypertension, a hematological cancer, an eating disorder, an acute or chronic liver disease, osteoporosis, pre-eclampsia, cell and solid organ transplantation, a cognitive disorder, acquired immunodeficiency syndrome (AIDS) dementia complex, aging of the central nervous system, and a disease caused in part by premature in-frame stop codons that result in the synthesis of truncated nonfunctional proteins, said method comprising administering to a subject in need thereof an effective amount of one or more PACAP-like compounds or a pharmaceutically acceptable salt thereof.

12. The method of claim 10, wherein:
   i) said age-related neurodegenerative disease is selected from Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis;
   ii) said central nervous system disorder is caused by stroke, heart attack or blunt force trauma, wherein preferably said blunt force trauma is a concussion or spinal cord trauma;
iii) said retinal disease is diabetic retinopathy, macular degeneration or glaucoma;
iv) said autoimmune disease is rheumatoid arthritis, Crohn's disease, ulcerative colitis, scleroderma, Sjögren's disease, idiopathic membranous nephropathy, Goodpasture's disease, autoimmune hepatitis, myasthenia gravis, multiple sclerosis, Guillain-Barré syndrome, type I diabetes, Hashimoto's thyroiditis, Graves' disease, pemphigus vulgaris, or lupus erythematosus;
v) said sepsis is caused by a bacterial or viral toxin;
vi) said acute or chronic cardiovascular disease is myocardial infarction, atherosclerosis, or restenosis;
vii) said acute or chronic renal disease is ischemia/reperfusion injury, nephritis, or drug-induced nephrotoxicity;
viii) said acute or chronic pulmonary disease is asthma, chronic obstructive pulmonary disease, cystic fibrosis, or pulmonary arterial hypertension;
ix) said hematological cancer is a lymphoid or myeloid hematopoietic cancer, wherein preferably said lymphoid or myeloid hematopoietic cancer is a leukemia, a lymphoma, a plasma cell dyscrasia, or an adenocarcinoma;
x) said acute or chronic liver disease is ischemia/reperfusion injury, hepatitis, and fatty liver; or
xi) said disease caused in part by premature in-frame stop codons that result in the synthesis of truncated nonfunctional proteins is selected from cystic fibrosis, Duchenne muscular dystrophy, Hurler's syndrome, nephropathic cystinosis, polycystic kidney disease, retinitis pigmentosa, and ataxia telangiectasia.

13. The method of claim 11 or 12, wherein said subject has an injury to one or more major organs of the body due to treatment with a prophylactic or therapeutic agent other than said PACAP-like compound, trauma, or acute or chronic disease.
14. The method of any one of claims 11 to 13, wherein the PACAP-like compounds, or pharmaceutically acceptable salts thereof, bind to one or more of the PACAP/VIP receptors and/or reduce one or more injuries to one or more major organs of the body of said subject due to treatment with a prophylactic or therapeutic agent other than said PACAP-like compound, trauma, or acute or chronic disease.

15. The method of any one of claims 11 to 14, wherein the PACAP-like compound comprises the compound of any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof.

16. The method of claim 15, wherein said PACAP-like compound is selected from one or more of the following:

His-Ser-Pip-Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-Lys-NH₂ (SEQ ID NO:4);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Ala Aib Ala Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-Lys-NH₂ (SEQ ID NO:5);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Ala Lys Aib Ala Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-Lys-NH₂ (SEQ ID NO:6);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-Lys Ala Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-Lys-NH₂ (SEQ ID NO:7);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-Ala Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-Lys-NH₂ (SEQ ID NO:8);
His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val Lys Lys Tyr Leu Ala Ala Val Leu-NH$_2$ (SEQ ID NO:9);

N-acetyl-His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu-NH$_2$ (SEQ ID NO:10);

His Ala Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val Lys Lys Tyr Leu Ala Ala Val Leu-NH$_2$ (SEQ ID NO:11);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Gln Met Ala Val Lys Lys Tyr Leu Ala Ala Val Leu Gly Lys Arg Tyr Lys Gln Arg Val Lys Asn Lys-NH$_2$ (SEQ ID NO:12); and

N-acetyl-His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Gln Met Ala Val Lys Lys Tyr Leu Ala Ala Val Leu Gly Lys Arg Tyr Lys Gln Arg Val Lys Asn Lys-NH$_2$ (SEQ ID NO:13).

17. The method of claim 15, wherein the PACAP-like compound is one or more of the compounds of claim 1 or a pharmaceutically acceptable salt thereof.

18. The method of claim 11, wherein said disease is a hematological cancer.

19. The method of claim 11, wherein said disease is an autoimmune disease.

20. The method of claim 18 or 19, wherein said subject is resistant to treatment with a glucocorticoid.

21. The method of claim 20, wherein said glucocorticoid is dexamethasone, prednisolone, methylprednisolone, or prednisone.
22. The method of claim 18, 20, or 21, wherein said hematological cancer is multiple myeloma.

23. The method of claim 18 to 22, wherein said PACAP-like compound has the sequence of SEQ ID NOs: 4-13.

24. The method of any one of claims 18 and 20-22, wherein said PACAP-like compound has the sequence of SEQ ID NO: 12.

25. The method of claim 18 or 19, wherein said administration of said PACAP-like compound in said subject replaces the corticosteroid selected from prednisone or dexamethasone using the COP (cyclophosphamide, vincristine and prednisone) or VAD (vincristine, doxorubicin and dexamethasone) regimen.

26. The method of claim 11, wherein the PACAP-like compound is one or more of the compounds of any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, linked to a polyethylene glycol polymer with a molecular weight from about 4 kilodaltons to about 40 kilodaltons.

27. The method of claim 11, wherein the PACAP-like compound is the unamidated (free acid) form of one or more of the compounds of any one of claims 1 to 9 flanked by amino-acid consensus sequences for one or more proteolytic enzymes.

28. The method of claim 11, wherein the PACAP-like compound is one or more peptidomimetic analogs of one or more of the compounds of any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof.

29. The method of claim 11, wherein the PACAP-like compound is administered at a dosage that produces a concentration of $10^{-14}$ M to $10^{-6}$ M in the blood of the subject.
30. The method of claim 11, wherein the PACAP-like compound is administered by intravenous infusion at a rate of about 1 pmol/kg body weight/hour to about 20 pmol/kg body weight/hour.

31. The method of claim 30, wherein the administration by intravenous infusion is for about 1-12 hours.

32. The method of claim 13, wherein the injuries to one or more major organs of the body are due to treatment with one or more of cisplatin, carboplatin, oxaliplatin, bleomycin, mitomycin C, calicheamicins, maytansinoids, geldanamycin, doxorubicin, idarubicin, daunorubicin, epirubicin, busulfan, carmustine (BCNU), lomustine (CCNU), semustine, thalidomide, lenalidomide, methotrexate, azathioprine, 6-mercaptopurine, fludarabine, 5-azacytidine, pentostatin (2′-deoxycoformycin), cytarabine (cytosine arabinoside), gemcitabine, 5-fluorouracil, hydroxyurea, elesclomol, etoposide, teniposide, amsacrine, camptothecin, topotecan, irinotecan, chlorambucil, cyclophosphamide, ifosfamide, melphalan, bortezomib, vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, cyclosporine A, G418, gentamicin, streptomycin, kanamycin, tobramycin, amikacin, arbekacin, neomycin, netilmicin, paromomycin, rhodostreptomycin, neomycin, framycetin, ribostamycin, bekamycin, dibekacin, spectinomycin, hygromycin B, paraomomycin sulfate, sisomicin, isepamicin, verdamicin, astromicin, apramycin, amphotericin B, rifampicin, pentamidine, cyclosporine A, tacrolimus (FK506), sirolimus (rapamycin), everolimus, temsirolimus, zotarolimus, or biolimus.

33. The method of claim 32, wherein the injury is to the nervous system, heart, lung, kidneys, liver, ear, or gastrointestinal tract.

34. The method of any one of claims 11 to 33, wherein the PACAP-like compound is injected intraperitoneally one or more times per day.
35. The method of any one of claims 11 to 33, wherein the PACAP-like compound is injected subcutaneously one or more times per week.

36. The method of any one of claims 11 to 33, wherein the PACAP-like compound is injected intramuscularly one or more times per week.

37. The method of any one of claims 11 to 33, wherein the PACAP-like compound is administered intranasally one or more times per day.

38. The method of any one of claims 11 to 33, wherein the PACAP-like compound is administered as an aerosol one or more times per day.

39. The method of any one of claims 11 to 33, wherein the PACAP-like compound is administered orally in a time-dependent or pH-dependent formulation one or more times per day.

40. The method of any one of claims 11 to 33, wherein the PACAP-like compound is administered as a controlled release or a sustained release formulation.

41. The method of any one of claims 11 to 33, wherein the PACAP-like compound is administered after encapsulation in liposomes or microparticles.

42. The method of any one of claims 11 to 33, wherein the PACAP-like compound is administered transcutaneously after encapsulation in dendrimers.

43. The method of any one of claims 11 to 33, wherein the PACAP-like compound is used to coat a metallic or a biodegradable stent.

44. The method of any one of claims 11 to 33, wherein the PACAP-like compound is administered in combination with one or more other cytoprotective adjuvants.
45. The method of claim 44, wherein said cytoprotective adjuvant is amifostine, dexrazoxane, mesna, palifermin, or N-acetylcysteine.

46. The method of claim 13, wherein the injuries to one or more major organs of the body are due to treatment with an unconjugated therapeutic or anticancer agent, a therapeutic or anticancer agent conjugated to a monoclonal antibody or a bioactive peptide, or an unconjugated bioactive peptide.

47. The method of claim 11, wherein the PACAP-like compound is one or more of the compounds of any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, conjugated to a therapeutic or anticancer agent.

48. The method of claim 11, wherein the PACAP-like compound has an additive anticancer effect with one or more other anticancer agents.

49. The method of claim 11, wherein the subject is being treated with one or more anticancer agents for a hematopoietic cancer.

50. The method of claim 11, wherein the subject is being treated with one or more therapeutic or anticancer agents for a myeloproliferative disorder.

51. The method of claim 11, wherein the subject is being treated with one or more therapeutic or anticancer agents for multiple myeloma.

52. The method of claim 13, wherein the subject is being treated with an aminoglycoside and wherein the PACAP-like compound is administered to inhibit or reduce side-effects resulting from administration of said aminoglycoside.

53. The method of claim 52, wherein said aminoglycoside is amikacin, arbekacin, G418, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, rhodostreptomycin, streptomycin, neomycin, framycetin, ribostamycin,
bekanamycin, dibekacin, spectinomycin, hygromycin B, paraomomycin sulfate, sisomicin, isepamicin, verdmicin, tobramycin, astromicin, and apramycin.

54. The method of claim 53, wherein said PACAP-like compound inhibits or reduces nephotoxicity or ototoxicity caused by said aminoglycoside.

55. The method of claim 13 or 14, wherein said prophylactic or therapeutic agent is an anticancer agent, a steroid, an anti-inflammatory agent, or an aminoglycoside.

56. The method of any one of claims 11 to 55, wherein said subject is a mammal.

57. The method of claim 56, wherein said mammal is a human.

58. The method of claim 49, wherein said subject is being treated with a primary therapeutic selected from one or more of cisplatin, carboplatin, oxaliplatin, bleomycin, mitomycin C, calicheamicins, maytansinoids, geldanamycin, doxorubicin, idarubicin, daunorubicin, epirubicin, busulfan, carmustine (BCNU), lomustine (CCNU), semustine, thalidomide, lenalidomide, methotrexate, azathioprine, 6-mercaptopurine, fludarabine, 5-azacytidine, pentostatin (2'-deoxycoformycin), cytarabine (cytosine arabinoside), gemcitabine, 5-fluorouracil, hydroxyurea, elesclomol, etoposide, teniposide, amsacrine, camptothecin, topotecan, irinotecan, chlorambucil, cyclophosphamide, ifosfamide, melphalan, bortezomib, vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, cyclosporine A, G418, gentamicin, streptomycin, kanamycin, tobramycin, amikacin, arbekacin, neomycin, netilmicin, paromomycin, rhodostreptomycin, neomycin, framycetin, ribostamycin, bekanamycin, dibekacin, spectinomycin, hygromycin B, paraomomycin sulfate, sisomicin, isepamicin, verdmicin, astromicin, apramycin, amphotericin B, rifampicin, pentamidine, cyclosporine A,
tacrolimus (FK506), sirolimus (rapamycin), everolimus, temsirolimus, zotarolimus, or biolimus.

59. The method of claim 49, wherein said subject is being treated with a primary therapy that comprises treatment with carmustine, vincristine, paclitaxel, or thalidomide.

60. The method of claim 58, wherein said subject has a lymphoid or myeloid cancer.

61. A method for the localization, diagnosis, or treatment of a disseminated cancer or a metastatic tumor in a subject comprising administering an effective amount of a conjugate comprising one or more PACAP-like compounds or a pharmaceutically acceptable salt thereof coupled to one or more radionuclides.

62. The method of claim 61, wherein said one or more PACAP-like compounds bind to one or more of PACAP/MIP receptor on the surface of one or more cells of the disseminated cancer or metastatic tumor.

63. The method of claim 61 or 62, wherein said PACAP-like compound comprises the compound of any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof.

64. The method of claim 63, wherein said PACAP-like compound is selected from one or more of the following:

His-Ser-Pip-Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn d-Lys-NH₂ (SEQ ID NO:4);
His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Ala Aib Ala Ala Val-
Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-
Lys-NH₂ (SEQ ID NO:5);

5  His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Ala Lys Aib Ala Ala Val-
    Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-
    Lys-NH₂ (SEQ ID NO:6);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-
Lys Ala Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-
Lys-NH₂ (SEQ ID NO:7);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-
Ala Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-
Lys-NH₂ (SEQ ID NO:8);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val
Lys Tyr Leu Ala Ala Val Leu-NH₂ (SEQ ID NO:9);

20  N-acetyl-His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala
    Ala Val-Lys Tyr Leu Ala Ala Val Leu-NH₂ (SEQ ID NO:10);

His Ala Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val
Lys Tyr Leu Ala Ala Val Leu-NH₂ (SEQ ID NO:11);

25  His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Gln Met Ala Val
    Lys Tyr Leu Ala Ala Val Leu Gly Lys Arg Tyr Lys Gln Arg Val Lys Asn Lys-
    NH₂ (SEQ ID NO:12); and

N-acetyl-His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Gln Met
Ala Val Lys Tyr Leu Ala Ala Val Leu Gly Lys Arg Tyr Lys Gln Arg Val Lys
Asn Lys-NH₂ (SEQ ID NO:13).
65. The method of any one of claims 61 to 64, wherein said disseminated cancer or metastatic tumor is a hematological cancer.

66. The method of claim 65, wherein said hematological cancer is leukemia, lymphoma, or myeloma.

67. The method of any one of claims 61 to 64, wherein said conjugate targets a cell that is a component of a granuloma caused by one or more infectious agents or an autoimmune disease.

68. The method of claim 61, wherein the subject is being treated with one or more of said conjugates for lymphoid or myeloid hematopoietic cancer.

69. The method of claim 61, wherein the subject is being treated with one or more of said conjugates for multiple myeloma.

70. The method of any one of claims 61 to 69, wherein said subject is a mammal.

71. The method of claim 70, wherein said mammal is a human.

72. A method of producing a conjugate comprising coupling one or more radionuclides or small molecules to one or more PACAP-like compounds.

73. The method of claim 72, wherein said PACAP-like compound comprises the compound of any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof.

74. The method of claim 73, wherein said PACAP-like compound is selected from one or more of the following, or a pharmaceutically acceptable salt thereof:
His-Ser-Pip-Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn d-Lys-NH$_2$ (SEQ ID NO:4);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Ala Aib Ala Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn d-Lys-NH$_2$ (SEQ ID NO:5);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Ala Lys Aib Ala Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn d-Lys-NH$_2$ (SEQ ID NO:6);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-Ala Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn d-Lys-NH$_2$ (SEQ ID NO:7);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-Ala Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn d-Lys-NH$_2$ (SEQ ID NO:8);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val Lys Lys Tyr Leu Ala Ala Val Leu-NH$_2$ (SEQ ID NO:9);

N-acetyl-His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-Lys Tyr Leu Ala Ala Val Leu-NH$_2$ (SEQ ID NO:10);

His Ala Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val Lys Lys Tyr Leu Ala Ala Val Leu-NH$_2$ (SEQ ID NO:11);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Gln Met Ala Val Lys Lys Tyr Leu Ala Ala Val Leu Gly Lys Arg Tyr Lys Gln Arg Val Lys Asn Lys-NH$_2$ (SEQ ID NO:12); and
N-acetyl-His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Gln Met Ala Val Lys Tyr Leu Ala Ala Val Leu Gly Lys Arg Tyr Lys Gln Arg Val Lys Asn Lys-NH₂ (SEQ ID NO:13).

75. The method of claim 73 or 74, wherein said radionuclide is selected from \(^{11}\)C, \(^{13}\)N, \(^{15}\)O, \(^{18}\)F, \(^{52}\)Fe, \(^{61}\)Co, \(^{65}\)Cu, \(^{65}\)Cu, \(^{67}\)Cu, \(^{67}\)Ga, \(^{68}\)Ga, \(^{62}\)Zn, \(^{62}\)As, \(^{71}\)As, \(^{74}\)As, \(^{76}\)Br, \(^{79}\)Br, \(^{82}\)Rb, \(^{86}\)Y, \(^{89}\)Zr, \(^{110}\)In, \(^{111}\)In, \(^{124}\)I, \(^{123}\)I, \(^{124}\)I, \(^{125}\)I, \(^{131}\)I, \(^{122}\)Xe, \(^{175}\)Lu, \(^{154}\)Gd, \(^{155}\)Gd, \(^{156}\)Gd, \(^{157}\)Gd, \(^{158}\)Gd, \(^{94}\)mTc, \(^{94}\)Tc, and \(^{99}\)mTc.

76. The method of claim 73 or 74, wherein said small molecule is a therapeutic or anticancer agent.

77. The method of claim 76, wherein said therapeutic or anticancer agent is cisplatin, carboplatin, oxaliplatin, bleomycin, mitomycin C, calicheamicins, maytansinoids, geldanamycin, doxorubicin, idarubicin, daunorubicin, epirubicin, busulfan, carmustine (BCNU), lomustine (CCNU), semustine, thalidomide, lenalidomide, methotrexate, azathioprine, 6-mercaptopurine, fludarabine, 5-azacytidine, pentostatin (2'-deoxycoformycin), cytarabine (cytosine arabinoside), gemcitabine, 5-fluorouracil, hydroxyurea, elesclomol, etoposide, teniposide, amsacrine, camptothecin, topotecan, irinotecan, chlorambucil, cyclophosphamide, ifosfamide, melphalan, bortezomib, vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, cyclosporine A, G418, gentamicin, streptomycin, kanamycin, tobramycin, amikacin, arbekacin, neomycin, netilmicin, paromomycin, rhodostreptomycin, neomycin, framycetin, ribostamycin, bekanamycin, dibekacin, spectinomycin, hygromycin B, paraomomycin sulfate, sisomicin, isepamicin, verdamicin, astromicin, apramycin, amphotericin B, rifampicin, pentamidine, cyclosporine A, tacrolimus (FK506), sirolimus (rapamycin), everolimus, temsirolimus, zotarolimus, or biolimus.

78. A method for targeting delivery of a therapeutic or anticancer agent to a specific cell or tissue of a subject comprising administering to said subject
an effective amount of a conjugate comprising one or more PACAP-like compounds, or a pharmaceutically acceptable salt thereof, coupled to one or more small molecules.

79. The method of claim 78, wherein said one or more PACAP-like compounds bind to one or more PACAP/VIP receptors on the surface of said cell or tissue and the conjugate enters the interior of the cell or tissue by receptor-mediated endocytosis.

80. The method of claim 78 or 79, wherein said PACAP-like compound comprises the compound of any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof.

81. The method of claim 80, wherein said PACAP-like compound is selected from one or more of the following, or a pharmaceutically acceptable salt thereof:

His-Ser-Pip-Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-Lys-NH₂ (SEQ ID NO:4);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Ala Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-Lys-NH₂ (SEQ ID NO:5);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Ala Lys Aib Ala Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-Lys-NH₂ (SEQ ID NO:6);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-Lys Ala Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Lys Val Lys Asn D-Lys-NH₂ (SEQ ID NO:7);
His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val-
Ala Lys Tyr Leu Ala Ala Val Leu Aib Lys Arg Tyr Lys Gln Val Lys Asn D-
Lys-NH₂ (SEQ ID NO:8);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val
Lys Lys Tyr Leu Ala Ala Val Leu-NH₂ (SEQ ID NO:9);

N-acetyl-His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala
Ala Val-Lys Lys Tyr Leu Ala Ala Val Leu-NH₂ (SEQ ID NO:10);

His Ala Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Aib Ala Ala Val
Lys Lys Tyr Leu Ala Ala Val Leu-NH₂ (SEQ ID NO:11);

His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Gln Met Ala Val
Lys Lys Tyr Leu Ala Ala Val Leu Gly Lys Arg Tyr Lys Gln Arg Val Lys Asn Lys-
NH₂ (SEQ ID NO:12); and

N-acetyl-His Ser Pip Gly Ile Phe Thr Asp Ser Tyr Ser Arg Tyr Arg Lys Gln Met
Ala Val Lys Tyr Leu Ala Ala Val Leu Gly Lys Arg Tyr Lys Gln Arg Val Lys
Asn Lys-NH₂ (SEQ ID NO:13).

82. The method of any one of claims 78 to 81, wherein said subject
has a disease.

83. The method of claim 82, wherein said disease is selected from
age-related neurodegenerative disease, a central nervous system disorder,
Huntington's disease or other CAG codon repeat expansion disease, a retinal
disease, an autoimmune disease, keratoconjunctivitis sicca caused by
autoimmune diseases or LASIK surgery, type II diabetes, sepsis caused by a
bacteria and/or a virus, an acute or chronic cardiovascular disease, an acute
or chronic renal diseases, an acute or chronic pulmonary disease, systemic
hypertension, a hematological cancer, an eating disorder, an acute or chronic
liver disease, osteoporosis, pre-eclampsia, cell and solid organ
transplantation, a cognitive disorder, acquired immunodeficiency syndrome (AIDS) dementia complex, aging of the central nervous system, and a disease caused in part by premature in-frame stop codons that result in the synthesis of truncated nonfunctional proteins.

84. The method of claim 83, wherein:
   i) said age-related neurodegenerative disease is selected from Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis;
   ii) said central nervous system disorder is caused by stroke, heart attack or blunt force trauma, wherein preferably said blunt force trauma is a concussion or spinal cord trauma;
   iii) said retinal disease is diabetic retinopathy, macular degeneration or glaucoma,
   iv) said autoimmune disease is rheumatoid arthritis, Crohn's disease, ulcerative colitis, scleroderma, Sjögren's disease, idiopathic membranous nephropathy, Goodpasture's disease, autoimmune hepatitis, myasthenia gravis, multiple sclerosis, Guillain-Barré syndrome, type I diabetes, Hashimoto's thyroiditis, Graves' disease, pemphigus vulgaris, or lupus erythematosus;
   v) said sepsis is caused by a bacterial or viral toxin;
   vi) said acute or chronic cardiovascular disease is myocardial infarction, atherosclerosis, or restenosis;
   vii) said acute or chronic renal disease is ischemia/reperfusion injury, nephritis, or drug-induced nephrotoxicity;
   viii) said acute or chronic pulmonary disease is asthma, chronic obstructive pulmonary disease, cystic fibrosis, or pulmonary arterial hypertension;
   ix) said hematological cancer is a lymphoid or myeloid hematopoietic cancer, wherein preferably said lymphoid or myeloid hematopoietic cancer is a leukemia, a lymphoma, a plasma cell dyscrasia, or an adenocarcinoma;
   x) said acute or chronic liver disease is ischemia/reperfusion injury, hepatitis, and fatty liver; or
xi) said disease caused in part by premature in-frame stop codons that result in the synthesis of truncated nonfunctional proteins is selected from cystic fibrosis, Duchenne muscular dystrophy, Hurler's syndrome, nephropathic cystinosis, polycystic kidney disease, retinitis pigmentosa, and ataxia telangiectasia.

85. The method of claim 83 or 84, wherein said disease causes injury to one or more major organs of the body of said subject due to treatment with a therapeutic or anticancer agent other than said PACAP-like compound, trauma, or acute or chronic disease.

86. The method of any one of claims 78 to 85, wherein the conjugate, or a pharmaceutically acceptable salt thereof, binds to one or more of the PACAP/VIP receptors and/or reduce one or more injuries to one or more major organs of the body of said subject due to treatment with a prophylactic or therapeutic other than said PACAP-like compound, trauma, or acute or chronic disease.

87. The method of claim 83, wherein said disease is cancer or an autoimmune disease.

88. The method of any one of claims 78 to 87, wherein said small molecule is therapeutic agent or anticancer agent.

89. The method of claim 88, wherein said therapeutic or anticancer agent is cisplatin, carboplatin, oxaliplatin, bleomycin, mitomycin C, calicheamicins, maytansinoids, geldanamycin, doxorubicin, idarubicin, daunorubicin, epirubicin, busulfan, carmustine (BCNU), lomustine (CCNU), semustine, thalidomide, lenalidomide, methotrexate, azathioprine, 6-mercaptopurine, fludarabine, 5-azacytidine, pentostatin (2'-deoxycoformycin), cytarabine (cytosine arabinoside), gemcitabine, 5-fluorouracil, hydroxyurea, elesclomol, etoposide, teniposide, amsacrine, camptothecin, topotecan, irinotecan, chlorambucil, cyclophosphamide, ifosfamide, melphalan,
bortezomib, vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, cyclosporine A, G418, gentamicin, streptomycin, kanamycin, tobramycin, amikacin, arbekacin, neomycin, netilmicin, paromomycin, rhodostreptomycin, neomycin, framycetin, ribostamycin, bekanamycin, dibekacin, spectinomycin, hygromycin B, paraomomycin sulfate, sisomicin, isepamicin, verdamicin, astromicin, apramycin, amphotericin B, rifampicin, pentamidine, cyclosporine A, tacrolimus (FK506), sirolimus (rapamycin), everolimus, temsirolimus, zotarolimus, or biolimus.

90. The method of any one of claims 78 to 88, wherein said small molecule is anti-inflammatory agent and said subject is being treated for rheumatoid arthritis.

91. The method of any one of claims 78 to 88, wherein said small molecule is an anticancer agent and said subject is being treated for multiple myeloma.

92. The method of claim 86, wherein said prophylactic or therapeutic agent is an anticancer agent, a steroid, anti-inflammatory agent, or an aminoglycoside.

93. The method of any one of claims 82 or 92, wherein said subject is a mammal.

94. The method of claim 93, wherein said mammal is a human.

95. A method for detecting a granuloma in subject comprising administering to said subject an effective amount of the polypeptide of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, conjugated to a radionuclide.

96. The method of claim 95, wherein said radionuclide is $^{11}$C, $^{15}$N, $^{15}$O, $^{18}$F, $^{52}$Fe, $^{55}$Co, $^{61}$Cu, $^{62}$Cu, $^{64}$Cu, $^{67}$Cu, $^{67}$Ga, $^{68}$Ga, $^{62}$Zn, $^{63}$Zn, $^{70}$As, $^{71}$As, $^{74}$As,
$^{76}$Br, $^{79}$Br, $^{82}$Rb, $^{86}$Y, $^{89}$Zr, $^{110}$In, $^{111}$In, $^{120}$I, $^{123}$I, $^{124}$I, $^{125}$I, $^{131}$I, $^{122}$Xe, $^{175}$Lu, $^{154}$Gd, $^{155}$Gd, $^{156}$Gd, $^{157}$Gd, $^{158}$Gd, $^{94m}$Tc, $^{94}$Tc, or $^{99m}$Tc.

97. The method of claim 95 or 96, wherein said subject has an infectious or autoimmune disease.

98. The method of any one of claims 95 to 97, wherein the polypeptide is a PACAP-like compound that is capable of binding to one or more of the PACAP/VIP receptors on the surface of target cells.

99. The method of claim 95 or 96, wherein said subject is being treated for tuberculosis.

100. The method of any one of claims 95 to 99, wherein said subject is being treated with one or more of said conjugates comprising an imaging agent for tuberculosis.

101. The method of claim 99, wherein said subject is being treated with $^{99m}$Tc-isonicotinylhydrazine (INH).

102. The method of claim 95 or 98, wherein the subject is being treated for Crohn's disease.

103. The method of claim 102, wherein said subject is being treated with one or more of said conjugates comprising an imaging agent for Crohn's disease.

104. The method of any one of claims 95 to 103, wherein said subject is a mammal.

105. The method of claim 104, wherein said subject is a human.
Figure 1


His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Tyr-Leu-Ala-Ala-Val-Leu-NH₂ (SEQ ID NO:2)

His-Ser-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn-NH₂ (SEQ ID NO:3)


N-acetyl-His-Ser-Pip-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Aib-Ala-Ala-Val-Lys-Tyr-Leu-Ala-Ala-Val-Leu-NH₂ (SEQ ID NO:10)

His-Ala-Pip-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Aib-Ala-Ala-Val-Lys-Tyr-Leu-Ala-Ala-Val-Leu-NH₂ (SEQ ID NO:11)

## Figure 2

**MALDI/MS-Determined and Calculated Molecular Weights**

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<th>Peptide</th>
<th>MALDI/MS</th>
<th>Calculated</th>
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<td>[Pip³, Aib¹⁶,²⁸, Ala¹⁷, Lys³⁴, D-Lys³⁸]PACAP38</td>
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<td>4371</td>
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<td>4343</td>
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<td>4371</td>
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<td>Inhibition of Myeloma Cell Proliferation</td>
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<tr>
<td>VIP</td>
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</table>
Figure 5

ID NO 5: [Pip\(^3\), Ala\(^{15,17}\), Aib\(^{16,28}\), Lys\(^{34}\), D-Lys\(^{38}\)] PACAP38
ID NO 6: [Pip\(^3\), Ala\(^{14,17}\), Aib\(^{16,28}\), Lys\(^{34}\), D-Lys\(^{38}\)] PACAP38
ID NO 4: [Pip\(^3\), Aib\(^{16,28}\), Ala\(^{17}\), Lys\(^{34}\), D-Lys\(^{38}\)] PACAP38
Figure 6

ID NO 5: [Pip³, Ala¹⁵,¹⁷, Aib¹⁶,²⁸, Lys³⁴, D-Lys³⁸]PACAP38
ID NO 6: [Pip³, Ala¹⁴,¹⁷, Aib¹⁶,²⁸, Lys³⁴, D-Lys³⁸]PACAP38

Serum Creatinine (mg/dL)

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<th>ID NO 6</th>
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<tbody>
<tr>
<td>I/R + PEPTIDE</td>
<td></td>
<td>*</td>
<td></td>
<td>**</td>
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</tbody>
</table>
Figure 7

ID NO 5: [Pip\(^3\), Ala\(^{15,17}\), Aib\(^{16,28}\), Lys\(^{34}\), D-Lys\(^{38}\)]PACAP38
ID NO 6: [Pip\(^3\), Ala\(^{14,17}\), Aib\(^{16,28}\), Lys\(^{34}\), D-Lys\(^{38}\)]PACAP38
Figure 8

MM.1S (Steroid-Sensitive)

Myeloma Cell Proliferation (% Control)

[Pep^3, Ala_{14,17}, Aib_{16,28}, Lys_{34}, d-Lys_{38}]PACAP38

Dexamethasone
Figure 10

![Graph showing absorbance (A405nm/460nm) with different treatments. The treatments include None, Gentamicin (2 mg/ml), PACAP38 (10^-10 M), PACAP38 (10^-9 M), PACAP38 (10^-8 M), PACAP38 (10^-7 M), ID NO 12 (10^-10 M), ID NO 12 (10^-9 M), ID NO 12 (10^-8 M), and ID NO 12 (10^-7 M). The bars are labeled with statistical symbols.](image-url)