Suppression of neuroendocrine diseases

The present invention relates to therapeutics and corresponding therapies for the treatment of neuroendocrine diseases and conditions.

The neuroendocrine system is formed from cells derived from the embryonic neural crest, neuroectoderm and endoderm. It can be divided into cell types that form glands and others that are diffusely distributed, i.e. the disseminated or diffuse neuroendocrine system. The first group include those cells forming the pituitary, the parathyroid glands and the adrenal medulla. The second group include cells in the skin, lung, thymus thyroid, pancreas, and the GI, biliary and urogenital tracts. Neuroendocrine tumours can arise in all these locations and can cause pathophysiology by either their physical size causing localised pressure or constrictions on surrounding organs, or by abnormal secretions of a variety of hormones and other bioactive molecules. These molecules are normally secreted by non-tumour cells in physiologically appropriate amounts and under tight physiological control. When these cells form tumours, however, the secretions can be excessive leading to disease.

Current therapies for these hypersecretion diseases can include surgical removal of the tumour(s), generic anti-tumour chemotherapy, interferon therapy, radiotherapy and more specific treatment with, for example, somatostatin analogues. The preference for initial treatment mode varies according to the consultant physician and, while each of these approaches can be successful, they are not always appropriate. Depending on the size and location of the tumour surgical intervention may be considered too risky and the tumour may not be completely removed. Anti-tumour chemotherapy, interferon therapy and radiotherapy are sometimes poorly tolerated by the patient or may be contra-indicated for other reasons.

Furthermore, therapies resulting in tumour cell death also introduce the prospect of tumour lysis syndrome (TLS) occurring. TLS is a very serious and sometimes life-threatening complication of tumour therapy. It can be defined as a constellation of metabolic abnormalities resulting from spontaneous or treatment-related tumour necrosis or fulminant apoptosis. The metabolic

abnormalities observed in patients with TLS include: hyperkalaemia, hyperuricaemia, and hyperphosphataemia with secondary hypocalcaemia. TLS can also lead to acute renal failure (ARF).

In the majority of patients with metastatic carcinoids and pancreatic endocrine tumours, treatment with current medicaments such as octreotide may induce a rapid improvement in clinical symptoms, such as diarrhoea, dehydration, flushing attacks, hypokalaemia, peptic ulceration, hypoglycaemic attacks and necrotic skin lesions *(Kvols et al. 1986, 1987, Ruszniewski et al.1996, Caplin et al. 1998, Kulke & Mayer 1999, Wymenga et al. 1999)*. However, the majority of patients show desensitisation of the inhibition of hormone secretion by octreotide and lanreotide within weeks to months. These limitations on current therapies represent a major problem.

Neuroendocrine tumours, including gastroenteropancreatic endocrine tumours and pituitary adenomas are rare and heterogeneous diseases (table 1). As a result their prognosis and long-term survival are not well known. Regardless of survival prospects, the excessive secretions from such tumours can markedly affect quality of life for the affected individuals and so effective treatment of this aberrant function is a requirement to maintain quality of life in sufferers.

Table 1 Incidence/prevalence of major neuroendocrine tumours (U.S. unless otherwise stated)

Tumour type	Incidence
carcinoid tumours	Approximately 5,000 carcinoid tumours per annum are diagnosed. According to the National Cancer Institute (NCI), approximately 74% of these tumours originate in the GI tract and 25% occur in the respiratory tract. Carcinoids are rare in children and are more common in patients older than the age of 50. They are twice as common in men. Carcinoid tumours of the appendix usually are benign and often occur between the ages of 20 and 40.

Insulinomas	The incidence is approximately 4 cases per million per year and the prevalence is approximately 4 per million population per year
Gastrinomas	The incidence of gastrinomas occurring sporadically or in association with multiple endocrine neoplasia type 1 (MEN-1) is 0.1-3 per million. The prevalence of MEN-1 is 0.2-2 per 100,000. MEN-1 is diagnosed in 30-38% of patients with gastrinomas, whereas 20-61% of patients diagnosed with MEN-1 are found to have gastrinomas associated with ZES (Zollinger-Ellison Syndrome)
VIPomas	Prevalence = 1.12 per million of the population
Glucagonomas	Glucagonoma is listed as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH). Prevalence = approx 1 in 2,720,000 people in USA
Prolactinoma	Incidence: 6-10 per million per year. Prevalence 60-100 per million
somatotrophinoma	Prevalance of Acromegaly: 40-60 per million affected people at any time; Incidence (annual) of Acromegaly: 3 per million annual cases
corticotrophinoma	Incidence: 2-3 per million per year. Prevalence 20-30 per million
phaeochromocytoma	In Western countries the prevalence of phaeochromocytoma can be estimated to lie between 1:6,500 to 1:2,500 with an annual incidence in the United States of 500 to 1,100 cases per year
Thyrotrophinoma	Very rare

Generally the symptoms of these tumours vary depending on the tumour type as they each secrete different hormones causing different symptoms (table 2).

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Table 2 Symptoms or diseases caused by hypersecretion from neuroendocrine tumours

Tumour type	Pathophysiology and symptoms (caused by hypersecretion rather than tumour mass)
carcinoid tumours	A combination of symptoms that result from secretion of hormone or hormone-like substances (e.g. serotonin, gastrin, ACTH, histamine) that are produced by some carcinoid tumours. These symptoms include flushing, diarrhoea, cramp-like abdominal pain, swelling of skin or face and neck, wheezing, weight gain, increased body and facial hair, diabetes, headaches, oedema, lacrimation, weakness, pulmonary hypertension, symptoms of heart failure including shortness of breath
Insulinomas	Blurred vision, diplopia, weakness, palpitations, confusion and bizarre behaviour. Hypoglycaemia tends to occur 5 hours or so after a meal and the associated symptoms may be affected by diet, ingestion of ethanol and exercise
Gastrinomas	Diarrhoea, gastritis, recurrent gastric ulcers
VIPomas	Watery diarrhoea (3-20 litres per day), hypokalaemia, hypomagnesaemia, hypercalcaemia, acidosis, flushing, flaccid distended bladder, ileus/subileus. Diabetes or glucose intolerance are also common.
Glucagonomas	Necrolytic erythematous rash (often on the face, extremities and intertrigenous areas), anaemia, weight loss, impaired glucose tolerance, thrombosis and diarrhoea.
corticotrophinoma	Cushing's disease resulting from ACTH inducing excess circulating cortisol
somatotrophinoma	Acromegaly
prolactinoma	oligomenorrhea/amenorrhea, galactorrhea, vaginal dryness, loss of libido in females; sexual dysfunction (impotence), galactorrhea and gynaecomastia in

	males
phaeochromocytoma	A wide range of symptoms resulting from metabolic and hemodynamic actions of circulating catecholamines. Sustained or paroxysmal hypertension is the most common clinical sign found in more than 90% of patients; with decreasing frequency:- headache, palpitations, pallor, nausea, flushing, weight loss, tiredness. Anxiety/panic, orthostatic hypotension, hyperglycaemia
Thyrotrophinoma	Thyrotoxicosis (overactivity of the thyroid gland), symptoms of which include weight loss in spite of increased appetite, rapid heart rate, a fine tremor, increased nervousness and emotional instability, intolerance of heat, and excessive sweating staring, bulging eyes, enlargement of the thyroid gland; in about a third of cases, the tumour also produces excess growth hormone resulting in mild acromegaly

Current therapies are highly individualised as the symptoms experienced by each patient are often different and may also be changing over time. The three potential aims of treating a patient are (1) to remove the tumour, (2) to slow down or stop the growth of the tumour or (3) to ameliorate the symptoms caused by hypersecretion from the tumour – all three may be sought in combination. The most common current therapies are described below.

Carcinoid tumours/carcinoid syndrome

A 2-pronged approach is often used in the treatment of carcinoid syndrome, beginning with surgery to remove the tumour or reduce its size, followed by treatment with chemotherapy or interferons. A procedure known as hepatic embolisation may be used to control cancer that has spread from a carcinoid tumour into the liver; it helps reduce symptoms by decreasing blood supply to the liver and starving tumour cells.

A second approach involves treating symptoms with different medications: diuretics for heart disease, bronchodilators for wheezing, somatostatin analogues for wheezing, diarrhoea and flushing.

Insulinomas

The symptoms from insulinomas can sometimes be treated through diet regulation (e.g. by frequent, slow-release complex carbohydrate intake; guar gum). With malignant insulinoma, metastases may be found in the surrounding lymph nodes and liver. If the tumour cannot be localised before or during surgery (intra-operatively), it may be removed through distal pancreatectomy.

Gastrinomas

In patients with gastrinomas, antisecretory medication such as a proton pump inhibitor is used to control gastric acid hypersecretion. If a patient cannot take this medication, a total gastrectomy is recommended. Surgery has been shown to yield a 30% 5-year cure rate, and is recommended in patients without liver metastases, MEN 1, or complicating medical conditions that may limit life expectancy. (Ninety-five percent of patients with gastrinomas have tumours). Patients with metastatic disease may benefit from chemotherapy or octreotide, if chemotherapy fails.

VIPomas

First-line therapy for VIPomas aims to correct the profound hypokalaemia, dehydration and metabolic acidosis by replenishing fluids and electrolytes. Patients are typically given up to 5 L of fluid and 350 mEq of potassium daily. The optimal treatment for VIPomas is surgical removal of the primary tumour.

Glucagonomas

Surgery is used to relieve the effects of glucagonomas or to reduce the size of the tumours, though about two-third of patients are not cured by surgery even after successful tumour localisation and assessment of metastatic disease. Currently, active drugs used to treat glucagonoma do not exist

Prolactinomas

Medical treatment is usually with the dopamine agonists bromocriptine or cabergoline. These drugs shrink the tumour and return prolactin levels to normal in approximately 80 percent of patients. However, use of these agonists is associated with side effects such as nausea and dizziness. Surgery is an option where medical therapy cannot be tolerated or if it fails to reduce prolactin levels, restore normal reproduction and pituitary function, and reduce tumour size. However, the results of surgery depend a great deal on tumour size and prolactin level as well as the skill and experience of the neurosurgeon. Depending on the size of the tumour and how much of it is removed, studies show that 20 to 50 percent will recur, usually within five years

Somatotrophinomas (e.g. causing acromegaly)

Current treatment for patients with acromegaly include surgical, radiation, and medical therapies. Treatment depends on the size and extent of the tumour and the need for rapid cessation of hormone function that results in serious clinical sequelae. The standard treatments include surgery (usually a transsphenoidal approach) with or without postoperative radiation therapy, bromocriptine treatment, octreotide treatment and, more recently, pegvisomant treatment. The above-described therapies have variable success.

Corticotrophinomas

For patients with corticotroph adenomas, transsphenoidal microsurgery is the treatment of choice. However, remission rates reported in most series are approximately 70% to 90%. Drug therapy is considered to be an adjunct to transsphenoidal microsurgery in cases with a residual tumour and in cases in which one is awaiting the effects of the radiation therapy. Steroidogenesis inhibitors, including mitotane, metyrapone, ketoconazole, and aminoglutethimide are used. Ketoconazole is the best tolerated of these agents, though only in about 70% of patients. Radiation therapy has been used in patients who are deemed to be poor surgical candidates and has also been used as adjunctive therapy in patients with residual or recurrent active tumour.

Phaeochromocytoma

Laparoscopic tumour removal is the preferred procedure. However, complications during surgery need to be kept to a minimum by appropriate preoperative medical treatment to prevent catecholamine-induced, serious, and potentially life-threatening complications during surgery, including hypertensive crises, cardiac arrhythmias, pulmonary oedema, and cardiac ischaemia. Traditional regimens include α-adrenoceptor blockers, combined α/β-adrenoceptor blockers and, calcium-channel blockers, all of which can have undesired effects both before and after surgery.

Thyrotrophinomas

Transsphenoidal surgery is the treatment of choice for patients with thyrotrophic adenomas. Adjuvant radiation therapy may be employed when surgery is known to be non-curative even if the patient is still euthyroid because relapse is inevitable, and the full effect of radiation therapy requires months or years. Medical therapy may be required for patients who still have hyperthyroid symptoms despite surgery and external radiation.

As well as representing rare, but life-affecting, human conditions neuroendocrine tumours continue to pose a major problem for animal healthcare on a global scale. Accordingly, there is a need in the art for alternative and/ or improved therapeutics and therapies that address one or more of the above problems.

In all cases, surgery can be of limited success as well as carrying inherent risks to the patient. In addition, current drug treatments also are no guarantee of success in alleviating the symptoms in al patients.

The present invention solves one or more of the above problems or risks associated with surgery or existing medical therapies, by providing a new category of non-cytotoxic agent designed to suppress undesirable (e.g. abnormally elevated) tumour secretions and thus minimising or reversing the resultant disease.

Summary of Invention

In one aspect, there is provided the use of a polypeptide in the manufacture of a medicament for treating acromegaly, said polypeptide comprising:

a a non-cytotoxic protease, which protease is capable of cleaving a protein of the exocytic fusion apparatus in a pituitary tumour cell, wherein said non-cytotoxic protease comprises a clostridial neurotoxin endopeptidase or an IgA protease,

b. a peptide Targeting Moiety (TM) that binds to a Binding Site on a pituitary tumour cell, which Binding Site is capable of undergoing endocytosis to be incorporated into an endosome within the pituitary tumour cell; and

c a bacterial or viral translocation domain that translocates the protease from within the endosome, across the endosomal membrane and into the cytosol of said pituitary tumour cell;

wherein the polypeptide lacks the native H_{CC} binding domain of a clostridial neurotoxin.

In another aspect, there is provided a polypeptide for use as defined above, wherein the translocation domain comprises a clostridial neurotoxin translocation domain.

In another aspect, there is provided a polypeptide comprising:

a a non-cytotoxic protease, which protease is capable of cleaving a protein of the exocytic fusion apparatus in a pituitary tumour cell, wherein said non-cytotoxic protease comprises a clostridial neurotoxin endopeptidase or an IgA protease;

b. a peptide Targeting Moiety (TM) that binds to a Binding Site on a pituitary tumour cell, which Binding Site is capable of undergoing endocytosis to be incorporated into an endosome within the pituitary tumour cell; and

c a bacterial or viral translocation domain that translocates the protease from within the endosome, across the endosomal membrane and into the cytosol of said pituitary tumour cell;

wherein the polypeptide lacks the native H_{CC} binding domain of a clostridial neurotoxin, and wherein said polypeptide comprises an amino acid sequence having at least 90-92%, or at least 95-97%, or at least 98-99% sequence identity to any one of SEQ ID NOs: 34, 42, 43, 44, 45, 46, 47, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91 or 92.

In another aspect, there is provided a nucleic acid encoding a polypeptide as defined above.

In another aspect, there is provided the use of a polypeptide as defined above or a nucleic acid as defined above in the manufacture of a medicament for treating acromegaly in a patient.

Detailed Description of the Invention

In more detail, disclosed is a polypeptide for use in suppressing secretion(s) from a neuroendocrine tumour, said polypeptide comprising:

a. a non-cytotoxic protease, which protease is capable of cleaving a protein of the exocytic fusion apparatus in a neuroendocrine tumour cell;

b. a Targeting Moiety (TM) that is capable of binding to a Binding Site on a neuroendocrine tumour cell, which Binding Site is capable of undergoing endocytosis to be incorporated into an endosome within the neuroendocrine tumour cell; and

c. a translocation domain that is capable of translocating the protease from within an endosome, across the endosomal membrane and into the cytosol of the neuroendocrine tumour cell.

In use, a polypeptide of the invention binds to a neuroendocrine tumour cell. Thereafter, the translocation component effects transport of the protease component into the cytosol of the tumour cell. Finally, once inside, the protease inhibits the exocytic fusion process of the neuroendocrine tumour cell. Thus, by inactivating the exocytic fusion apparatus of the neuroendocrine tumour cell, the polypeptide of the invention inhibits secretion therefrom. Accordingly, the polypeptides of the present invention suppress/ treat one or more of the various pathophysiological conditions or symptoms listed in Table 2 above.

The principal target cells of the present invention are tumour cells of neuroendocrine origin that secrete one or more hormones (or other bioactive molecules) leading to the development of a pathophysiological condition.

The present invention provides polypeptides that are capable of (and for use in) suppression of the secretion of hormones and/or other bioactive molecules from neuroendocrine tumours.

In a related aspect of the present invention, there is provided a method for treating a neuroendocrine tumour in a patient, said method comprising administering to the patient a therapeutically effective amount of a polypeptide of the present invention.

Without wishing to be bound by any theory, the present inventors believe that undesirable (e.g. unusual levels of) secretion of physiologically active molecules from neuroendocrine tumours cause and maintain pathological conditions in a patient. Thus, by inhibiting said secretions, the progression of the disease state can be halted and the symptoms reversed.

The polypeptides of the present invention are particularly suited for use in treating a range of neuroendocrine tumours, including their hormone-secreting metastases, precancerous conditions and symptoms thereof. In this regard, 'treating' includes reducing or eliminating excessive secretions from such cells.

By way of example, important neuroendocrine tumour target cells of the present invention include: pituitary adenomas and/ or gastroenteropancreatic neuroendocrine tumours (GEP-NETs). GEP-NETs are located mainly in the stomach, intestine or pancreas and secrete excessive amounts of hormones and other bioactive molecules that are normally secreted at lower levels under physiological regulation. These secretions contribute to the symptoms experienced by the patients. GEP-NETs can be divided into carcinoid and non-carcinoid subtypes.

Carcinoid GEP-NETs (55% of all GEP-NETs) tend to be classified according to their tissue location and include, in order of prevalence, those arising from cells in the appendix (38%), ileum (23%), rectum (13%) and bronchus (11.5%).

Non-carcinoid GEP-NETs include insulinomas of the pancreatic islets secreting excess insulin (17%), tumours of unknown type (15%), gastrinomas of the pancreas or duodenum secreting excess gastrin (9%), VIPomas of the pancreas, lung or ganglioneuromas, secreting excess vasoactive intestinal

polypeptide, and glucagonomas, tumours of the pancreatic islets secreting excess glucagon.

The pituitary tumours, which tend to be classified according to their secretion type or cellular identity, include: prolactinomas secreting prolactin (the most common), somatotrophinomas (growth hormone, corticotrophinomas (adrenocorticotrophic hormone), thyrotrophinomas (thyroid stimulating hormone), gonadotrophinomas (FSH, LH), and non-functioning pituitary adenomas.

Other secretory tumours include thyroid medullary tumours, small and non-small cell lung tumours, Merkel cell tumours, and phaeochromocytomas. The latter can be deadly if excessive secreted adrenaline leads to severe hypertension. Such hypersecretion can make the individual unsuitable for surgery to remove tumour mass and so a reinforcing deleterious cycle can emerge and treatment of the tumour to minimise secretion is desirable.

A particularly preferred sub-set of neuroendocrine tumour cells addressed by the present invention is: insulinomas, gastrinomas, VIPomas, glucagonomas, prolactinomas, somatotrophinomas, corticotrophinomas, thyrotrophinomas and phaeochromocytomas.

By suppressing the secretory functions of neuroendocrine tumour cells (such as the above sub-set of tumour cells), the present invention provides a therapy for the treatment of, amongst others, conditions such as Cushing's disease, acromegaly, carcinoid syndrome, hypoglycaemic syndrome, necrolytic migratory erythema, Zollinger-Ellison syndrome and Verner-Morrison syndrome. Also provided are therapies for treatment of the symptoms ensuing from undesirable neuroendocrine tumour secretions (see Table 2).

The 'bioactive' component of the polypeptides of the present invention is provided by a non-cytotoxic protease. This distinct group of proteases act by proteolytically-cleaving intracellular transport proteins known as SNARE proteins (e.g. SNAP-25, VAMP, or Syntaxin) – see Gerald K (2002) "Cell and Molecular Biology" (4th edition) *John Wiley & Sons, Inc.* The acronym SNARE

derives from the term Soluble NSF Attachment Receptor, where NSF means N-ethylmaleimide-Sensitive Factor. SNARE proteins are integral to intracellular vesicle formation, and thus to secretion of molecules via vesicle transport from a cell. Accordingly, once delivered to a desired target cell, the non-cytotoxic protease is capable of inhibiting cellular secretion from the target cell.

Non-cytotoxic proteases are a discrete class of molecules that do not kill cells; instead, they act by inhibiting cellular processes other than protein synthesis. Non-cytotoxic proteases are produced as part of a larger toxin molecule by a variety of plants, and by a variety of microorganisms such as Clostridium sp. and Neisseria sp.

Clostridial neurotoxins represent a major group of non-cytotoxic toxin molecules, and comprise two polypeptide chains joined together by a disulphide bond. The two chains are termed the heavy chain (H-chain), which has a molecular mass of approximately 100 kDa, and the light chain (L-chain), which has a molecular mass of approximately 50 kDa. It is the L-chain, which possesses a protease function and exhibits a high substrate specificity for vesicle and/or plasma membrane associated (SNARE) proteins involved in the exocytic process (eg. synaptobrevin, syntaxin or SNAP-25). These substrates are important components of the neurosecretory machinery.

Neisseria sp., most importantly from the species *N. gonorrhoeae*, and Streptococcus sp., most importantly from the species *S. pneumoniae*, produce functionally similar non-cytotoxic toxin molecules. An example of such a non-cytotoxic protease is IgA protease (see WO99/58571, which is hereby incorporated in its entirety by reference thereto). Thus, the non-cytotoxic protease of the present invention is preferably a clostridial neurotoxin protease or an IgA protease.

Turning now to the Targeting Moiety (TM) component of the present invention, it is this component that binds the polypeptide of the present invention to a neuroendocrine tumour cell.

Thus, a TM of the present invention binds to a receptor on a neuroendocrine tumour cell. By way of example, a TM of the present invention may bind to a receptor selected from the group comprising: a somatostatin (sst) receptor, including splice variants thereof (e.g. sst_1, sst_2, sst_3, sst_4 and sst_5); a growth hormone-releasing hormone (GHRH) receptor – also known a GRF receptor; a ghrelin receptor; a bombesin receptor (eg. BRS-1, BRS-2, or BRS-3); a urotensin receptor (eg. a urotensin II receptor); a melanin-concentrating hormone receptor 1; a prolactin releasing hormone receptor; a gonadotropin-releasing hormone receptor (GnRHR) such as a Type 1 GnRHR and/ or a Type 2 GnRHR receptor; and/ or a KiSS-1 receptor.

In one embodiment, a TM of the present invention binds to a somatostatin (SST) receptor. Examples of suitable SST peptide TMs include full-length SST and cortistatin (CST), as well as truncations and peptide analogues thereof such as: SANSNPAMAPRERKAGCKNFFWKTFTSC (SST-28); AGCKNFFWKTFTSC (SST-14); QEGAPPQQSARRDRMPCRNFFWKTFSSCK (CST-29); QERPPLQQPPHRDKKPCKNFFWKTFSSCK (CST-29); QERPPPQQPPHLDKKPCKNFFWKTFSSCK (CST-29); DRMPCRNFFWKTFSSCK (CST-17); PCRNFFWKTFSSCK (CST-14); and PCKNFFWKTFSSCK (CST-14); D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH2 (BIM 23052), D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH2 (BIM 23056) or c[Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys]-NH_2 (BIM23268); octreotide peptides, lanreotide peptides, BIM23027, CYN154806, BIM23027, vapreotide peptides, seglitide peptides, and SOM230. These TMs bind to sst receptors, such as sst_1, sst_2, sst_3, sst_4 and sst_5 receptors, which are present on neuroendocrine tumour cells relevant to the present invention – see Table 3. SST and CST have high structural homology, and bind to all known sst receptors.

Table 3

Expression of somatostatin receptor subtypes in gastroenteropancreatic neuroendocrine tumours (%)

	sst1	sst2	sst3	sst4	sst5
All tumours	68	86	46	93	57

Insulinoma	33	100	33	100	67
Gastrinoma	33	50	17	83	50
Glucagonoma	67	100	67	67	67
VIPoma	100	100	100	100	100
Non-functioning	80	100	40	100	60
mid-gut NETs	80	95	65	35	75

In another embodiment, a TM of the present invention binds to a growth hormone releasing hormone (GHRH) receptor. GHRH is also known as growth-hormone-releasing factor (GRF or GHRF) or somatocrinin. Suitable GHRH peptides include full-length GHRH (1-44) peptide, and truncations thereof such as GHRH(1-27, 1-28, 1-29), GHRH(1-37), and GHRH(1-40, 1-43)-OH, as well as peptide analogues such as: BIM 28011 or NC-9-96; [MeTyr1,Ala15,22,Nle27]-hGHRH(1-29)-NH2; MeTyr1,Ala8,9,15,22,28,Nle27]-hGHRH(1-29)-NH2; cyclo(25-29)[MeTyr1,Ala15,DAsp25,Nle27,Orn29+ ++]-hGHRH(1-29)-NH2; (D-Tyr1)-GHRH (1-29)-NH2; (D-Ala2)-GHRH (1-29)-NH2; (D-Asp3)-GHRH (1-29)-NH2; (D-Ala4)-GHRH (1-29)-NH2; (D-Thr7)-GHRH (1-29)-NH2; (D-Asn8)-GHRH (1-29)-NH2; (D-Ser9)-GHRH (1-29)-NH2; (D-Tyr10)-GHRH (1-29)-NH2; (Phe4)-GHRH (1-29)-NH2; (pCl-Phe6)-GHRH (1-29)-NH2; (N-Ac-Tyr1)-GHRH (1-29)-NH2; (N-Ac-Tyr1, D-Ala2)-GHRH (1-29)-NH2; (N-Ac-D-Tyr1, D-Ala2)-GHRH (1-29)-NH2; (N-Ac-D-Tyr1, D-Ala 2, D-Asp3)-GHRH (1-29)-NH2; (D-Ala2, NLeu27)-GHRH (1-29)-NH2; (His1, D-Ala2, NLeu27)-GHRH (1-29)-NH2; (N-Ac-His1, D-Ala2, N-Leu27)-GHRH (1-29)-NH2; (His1, D-Ala 2, D-Ala 4, Nleu27)-GHRH (1-29)-NH2; (D-Ala2, D-Asp3, D-Asn8, NLeu27)-GHRH (1-29)-NH2; (D-Asp3, D-Asn8, NLeu27)-GHRH (1-29)-NH2; [His1, NLeu27]-hGHRH(1-29)-NH2; [NLeu27]-hGHRH(1-29)-NH2; H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH2; H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH2; H-Tyr-D-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH2; H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Ile-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Asn-Arg-Gln-Gln-Gly-Glu-Arg-Asn-Gln-Glu-Gln-Gly-Ala-Lys-Val-Arg-Leu-NH2; H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-

Gln-Asp-Ile-Met-Asn-Arg-Gln-Gln-Gly-Glu-Arg-Asn-Gln-Glu-Gln-Gly-Ala-Lys-Val-Arg-Leu-NH2; His-Val-Asp-Ala-Ile-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Leu-Asn-Arg; His-Val-Asp-Ala-Ile-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Leu-Asn-Arg-Gln-Gln-Gly-Glu-Arg-Asn-Gln-Glu-Gln-Gly-Ala.

In another embodiment, a TM of the present invention binds to a ghrelin receptor. Examples of suitable TMs in this regard include: ghrelin peptides such as full-length ghrelin (eg. ghrelin$_{117}$) and truncations and peptide analogues thereof such as ghrelin$_{24-117}$, ghrelin$_{52-117}$, [Trp3, Arg5]-ghrelin (1-5), des-Gln-Ghrelin, cortistatin-8, His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2, growth hormone releasing peptide (e.g. GHRP-6), or hexarelin.

In a further embodiment, the TM binds to a bombesin receptor (eg. BRS-1, BRS-2, or BRS-3). Examples of suitable bombesin peptides include full-length: bombesin - a 14 amino acid peptide originally isolated from the skin of a frog (pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2); and the two known homologs in mammals, namely neuromedin B, and gastrin releasing peptide (GRP) such as: porcine GRP - Ala-Pro-Val-Ser-Val-Gly-Gly-Gly-Thr-Val-Leu-Ala-Lys-Met-Tyr-Pro-Arg-Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met-NH_2, and human GRP - Val-Pro-Leu-Pro-Ala-Gly-Gly-Gly-Thr-Val-Leu-Thr-Lys-Met-Tyr-Pro-Arg-Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met-NH_2. Reference to bombesin peptides embraces homologs thereof such as neuromedin B and GRP, and includes truncations and peptide analogues thereof.

In another embodiment, a TM of the present invention binds to a urotensin receptor. Suitable TMs in this regard include urotensin peptides such as Urotensin-II (U-II), which is a cyclic neuropeptide. The C-terminal cyclic region of U-II is strongly conserved across different species, and includes the six amino acid residues (-Cys Phe-Trp-Lys-Tyr-Cys-), which is structurally similar to the central region of somatostatin-14 (-Phe-Trp-Lys-Thr-). Urotensin peptides of the present invention include the U-II precursor peptides, such as prepro-urotensin-II (including the two human 124 and 139 isoforms thereof) as

well as other truncations such as the eleven residue mature peptide form and peptide analogues thereof.

In a further embodiment, a TM of the present invention binds to a melanin-concentrating hormone receptor 1. Examples of suitable TMs in this regard include: melanin-concentrating hormone (MCH) peptides such as full-length MCH, truncations and analogues thereof.

In another embodiment, a TM of the present invention binds to a prolactin releasing hormone receptor. An example of a suitable TM in this regard includes prolactin releasing peptide, truncations and analogues thereof.

In another embodiment, a TM of the present invention binds to a gonadotropin-releasing hormone (GnRH) receptor. GnRH is also known as Luteinizing-Hormone Releasing Hormone (LHRH). Examples of suitable GnRH receptor TMs include: GnRHI peptides, GnRHII peptides and GnRHIII peptides, for example the full-length 92 amino acid GnRH precursor polypeptide and truncations thereof such as the decapeptide: pyroGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly CONH2.

In a further embodiment, a TM of the present invention binds to a KiSS-1 receptor. Examples of suitable TMs in this regard include Kisspeptin-10, Kisspeptin-54 peptides, truncations and analogues thereof.

According to a second aspect of the present invention, there is provided a composition of matter, namely a polypeptide comprising:

a a non-cytotoxic protease, which protease is capable of cleaving a protein of the exocytic fusion apparatus in a neuroendocrine tumour cell;

b. a Targeting Moiety (TM) that is capable of binding to a Binding Site on a neuroendocrine tumour cell, which Binding Site is capable of undergoing endocytosis to be

incorporated into an endosome within the neuroendocrine tumour cell; and

d. a translocation domain that is capable of translocating the protease from within an endosome, across the endosomal membrane and into the cytosol of the neuroendocrine tumour cell.

All of the features of the first aspect of the present invention apply equally to the above-described second aspect.

In a preferred embodiment of the first and/ or second aspects of the present invention, the TM has a human peptide amino acid sequence. Thus, a highly preferred TM is a human SST peptide, a human CST peptide or a human GHRH peptide.

Polypeptide preparation

The polypeptides of the present invention comprise 3 principal components: a 'bioactive' (ie. a non-cytotoxic protease); a TM; and a translocation domain. The general technology associated with the preparation of such fusion proteins is often referred to as re-targeted toxin technology. By way of exemplification, we refer to: WO94/21300; WO96/33273; WO98/07864; WO00/10598; WO01/21213; WO06/059093; WO00/62814; WO00/04926; WO93/15766; WO00/61192; and WO99/58571. All of these publications are herein incorporated by reference thereto.

In more detail, the TM component of the present invention may be fused to either the protease component or the translocation component of the present invention. Said fusion is preferably by way of a covalent bond, for example either a direct covalent bond or via a spacer/ linker molecule. The protease component and the translocation component are preferably linked together via a covalent bond, for example either a direct covalent bond or via a spacer/ linker molecule. Suitable spacer/ linked molecules are well known in the art, and typically comprise an amino acid-based sequence of between 5 and 40, preferably between 10 and 30 amino acid residues in length.

In use, the polypeptides have a di-chain conformation, wherein the protease component and the translocation component are linked together, preferably via a disulphide bond.

The polypeptides of the present invention may be prepared by conventional chemical conjugation techniques, which are well known to a skilled person. By way of example, reference is made to Hermanson, G.T. (1996), Bioconjugate techniques, Academic Press, and to Wong, S.S. (1991), Chemistry of protein conjugation and cross-linking, CRC Press, Nagy *et al.*, PNAS 95 p1794-99 (1998). Further detailed methodologies for attaching synthetic TMs to a polypeptide of the present invention are provided in, for example, EP0257742. The above-mentioned conjugation publications are herein incorporated by reference thereto.

Alternatively, the polypeptides may be prepared by recombinant preparation of a single polypeptide fusion protein (see, for example, WO98/07864). This technique is based on the *in vivo* bacterial mechanism by which native clostridial neurotoxin (i.e. holotoxin) is prepared, and results in a fusion protein having the following 'simplified' structural arrangement:

NH_2 - [protease component] – [translocation component] – [TM] - COOH

According to WO98/07864, the TM is placed towards the C-terminal end of the fusion protein. The fusion protein is then activated by treatment with a protease, which cleaves at a site between the protease component and the translocation component. A di-chain protein is thus produced, comprising the protease component as a single polypeptide chain covalently attached (via a disulphide bridge) to another single polypeptide chain containing the translocation component plus TM.

Alternatively, according to WO06/059093, the TM component of the fusion protein is located towards the middle of the linear fusion protein sequence, between the protease cleavage site and the translocation component. This ensures that the TM is attached to the translocation domain (ie. as occurs with

native clostridial holotoxin), though in this case the two components are reversed in order *vis-à-vis* native holotoxin. Subsequent cleavage at the protease cleavage site exposes the N-terminal portion of the TM, and provides the di-chain polypeptide fusion protein.

The above-mentioned protease cleavage sequence(s) may be introduced (and/ or any inherent cleavage sequence removed) at the DNA level by conventional means, such as by site-directed mutagenesis. Screening to confirm the presence of cleavage sequences may be performed manually or with the assistance of computer software (e.g. the MapDraw program by DNASTAR, Inc.). Whilst any protease cleavage site may be employed (ie. clostridial, or non-clostridial), the following are preferred:

Enterokinase	(DDDDK↓)
Factor Xa	(IEGR↓ / IDGR↓)
TEV(Tobacco Etch virus)	(ENLYFQ↓G)
Thrombin	(LVPR↓GS)
PreScission	(LEVLFQ↓GP).

Additional protease cleavage sites include recognition sequences that are cleaved by a non-cytotoxic protease, for example by a clostridial neurotoxin. These include the SNARE (eg. SNAP-25, syntaxin, VAMP) protein recognition sequences that are cleaved by non-cytotoxic proteases such as clostridial neurotoxins. Particular examples are provided in US2007/0166332, which is hereby incorporated in its entirety by reference thereto.

Also embraced by the term protease cleavage site is an intein, which is a self-cleaving sequence. The self-splicing reaction is controllable, for example by varying the concentration of reducing agent present. The above-mentioned 'activation' cleavage sites may also be employed as a 'destructive' cleavage site (discussed below) should one be incorporated into a polypeptide of the present invention.

In a preferred embodiment, the fusion protein of the present invention may comprise one or more N-terminal and/ or C-terminal located purification tags. Whilst any purification tag may be employed, the following are preferred:

His-tag (e.g. 6 × histidine), preferably as a C-terminal and/ or N-terminal tag
MBP-tag (maltose binding protein), preferably as an N-terminal tag
GST-tag (glutathione-S-transferase), preferably as an N-terminal tag
His-MBP-tag, preferably as an N-terminal tag
GST-MBP-tag, preferably as an N-terminal tag
Thioredoxin-tag, preferably as an N-terminal tag
CBD-tag (Chitin Binding Domain), preferably as an N-terminal tag.

One or more peptide spacer/ linker molecules may be included in the fusion protein. For example, a peptide spacer may be employed between a purification tag and the rest of the fusion protein molecule.

Thus, a third aspect of the present invention provides a nucleic acid (e.g. DNA) sequence encoding a polypeptide as described above (i.e. the second aspect of the present invention).

Said nucleic acid may be included in the form of a vector, such as a plasmid, which may optionally include one or more of an origin of replication, a nucleic acid integration site, a promoter, a terminator, and a ribosome binding site.

The present invention also includes a method for expressing the above-described nucleic acid sequence (i.e. the third aspect of the present invention) in a host cell, in particular in *E. coli* or via a baculovirus expression system.

The present invention also includes a method for activating a polypeptide of the present invention, said method comprising contacting the polypeptide with a protease that cleaves the polypeptide at a recognition site (cleavage site) located between the non-cytotoxic protease component and the translocation component, thereby converting the polypeptide into a di-chain polypeptide wherein the non-cytotoxic protease and translocation components are joined together by a disulphide bond. In a preferred embodiment, the recognition site is

not native to a naturally-occurring clostridial neurotoxin and/ or to a naturally-occurring igA protease.

The polypeptides of the present invention may be further modified to reduce or prevent unwanted side-effects associated with dispersal into non-targeted areas. According to this embodiment, the polypeptide comprises a destructive cleavage site. The destructive cleavage site is distinct from the 'activation' site (i.e. di-chain formation), and is cleavable by a second protease and not by the non-cytotoxic protease. Moreover, when so cleaved at the destructive cleavage site by the second protease, the polypeptide has reduced potency (e.g. reduced binding ability to the intended target cell, reduced translocation activity and/ or reduced non-cytotoxic protease activity). For completeness, any of the 'destructive' cleavage sites of the present invention may be separately employed as an 'activation' site in a polypeptide of the present invention.

Thus, according to this embodiment, the present invention provides a polypeptide that can be controllably inactivated and/ or destroyed at an off-site location.

In a preferred embodiment, the destructive cleavage site is recognised and cleaved by a second protease (i.e. a destructive protease) selected from a circulating protease (e.g. an extracellular protease, such as a serum protease or a protease of the blood clotting cascade), a tissue-associated protease (e.g. a matrix metalloprotease (MMP), such as an MMP of muscle), and an intracellular protease (preferably a protease that is absent from the target cell).

Thus, in use, should a polypeptide of the present invention become dispersed away from its intended target cell and/ or be taken up by a non-target cell, the polypeptide will become inactivated by cleavage of the destructive cleavage site (by the second protease).

In one embodiment, the destructive cleavage site is recognised and cleaved by a second protease that is present within an off-site cell-type. In this embodiment, the off-site cell and the target cell are preferably different cell types. Alternatively (or in addition), the destructive cleavage site is recognised and cleaved by a

second protease that is present at an off-site location (e.g. distal to the target cell). Accordingly, when destructive cleavage occurs extracellularly, the target cell and the off-site cell may be either the same or different cell-types. In this regard, the target cell and the off-site cell may each possess a receptor to which the same polypeptide of the invention binds.

The destructive cleavage site of the present invention provides for inactivation/ destruction of the polypeptide when the polypeptide is in or at an off-site location. In this regard, cleavage at the destructive cleavage site minimises the potency of the polypeptide (when compared with an identical polypeptide lacking the same destructive cleavage site, or possessing the same destructive site but in an uncleaved form). By way of example, reduced potency includes: reduced binding (to a mammalian cell receptor) and/ or reduced translocation (across the endosomal membrane of a mammalian cell in the direction of the cytosol), and/ or reduced SNARE protein cleavage.

When selecting destructive cleavage site(s) in the context of the present invention, it is preferred that the destructive cleavage site(s) are not substrates for any proteases that may be separately used for post-translational modification of the polypeptide of the present invention as part of its manufacturing process. In this regard, the non-cytotoxic proteases of the present invention typically employ a protease activation event (via a separate 'activation' protease cleavage site, which is structurally distinct from the destructive cleavage site of the present invention). The purpose of the activation cleavage site is to cleave a peptide bond between the non-cytotoxic protease and the translocation or the binding components of the polypeptide of the present invention, thereby providing an 'activated' di-chain polypeptide wherein said two components are linked together via a di-sulfide bond.

Thus, to help ensure that the destructive cleavage site(s) of the polypeptides of the present invention do not adversely affect the 'activation' cleavage site and subsequent di-sulfide bond formation, the former are preferably introduced into polypeptide of the present invention at a position of at least 20, at least 30, at least 40, at least 50, and more preferably at least 60, at least

70, at least 80 (contiguous) amino acid residues away from the 'activation' cleavage site.

The destructive cleavage site(s) and the activation cleavage site are preferably exogenous (i.e. engineered/ artificial) with regard to the native components of the polypeptide. In other words, said cleavage sites are preferably not inherent to the corresponding native components of the polypeptide. By way of example, a protease or translocation component based on BoNT/A L-chain or H-chain (respectively) may be engineered according to the present invention to include a cleavage site. Said cleavage site would not, however, be present in the corresponding BoNT native L-chain or H-chain. Similarly, when the Targeting Moiety component of the polypeptide is engineered to include a protease cleavage site, said cleavage site would not be present in the corresponding native sequence of the corresponding Targeting Moiety.

In a preferred embodiment of the present invention, the destructive cleavage site(s) and the 'activation' cleavage site are not cleaved by the same protease. In one embodiment, the two cleavage sites differ from one another in that at least one, more preferably at least two, particularly preferably at least three, and most preferably at least four of the tolerated amino acids within the respective recognition sequences is/ are different.

By way of example, in the case of a polypeptide chimera containing a Factor Xa 'activation' site between clostridial L-chain and H_N components, it is preferred to employ a destructive cleavage site that is a site other than a Factor Xa site, which may be inserted elsewhere in the L-chain and/ or H_N and/ or TM component(s). In this scenario, the polypeptide may be modified to accommodate an alternative 'activation' site between the L-chain and H_N components (for example, an enterokinase cleavage site), in which case a separate Factor Xa cleavage site may be incorporated elsewhere into the polypeptide as the destructive cleavage site. Alternatively, the existing Factor Xa 'activation' site between the L-chain and H_N components may be retained, and an alternative cleavage site such as a thrombin cleavage site incorporated as the destructive cleavage site.

When identifying suitable sites within the primary sequence of any of the components of the present invention for inclusion of cleavage site(s), it is preferable to select a primary sequence that closely matches with the proposed cleavage site that is to be inserted. By doing so, minimal structural changes are introduced into the polypeptide. By way of example, cleavage sites typically comprise at least 3 contiguous amino acid residues. Thus, in a preferred embodiment, a cleavage site is selected that already possesses (in the correct position(s)) at least one, preferably at least two of the amino acid residues that are required in order to introduce the new cleavage site. By way of example, in one embodiment, the Caspase 3 cleavage site (DMQD) may be introduced. In this regard, a preferred insertion position is identified that already includes a primary sequence selected from, for example, Dxxx, xMxx, xxQx, xxxD, DMxx, DxQx, DxxD, xMQx, xMxD, xxQD, DMQx, xMQD, DxQD, and DMxD.

Similarly, it is preferred to introduce the cleavage sites into surface exposed regions. Within surface exposed regions, existing loop regions are preferred.

In a preferred embodiment of the present invention, the destructive cleavage site(s) are introduced at one or more of the following position(s), which are based on the primary amino acid sequence of BoNT/A. Whilst the insertion positions are identified (for convenience) by reference to BoNT/A, the primary amino acid sequences of alternative protease domains and/ or translocation domains may be readily aligned with said BoNT/A positions.

For the protease component, one or more of the following positions is preferred: 27-31, 56-63, 73-75, 78-81, 99-105, 120-124, 137-144, 161-165, 169-173, 187-194, 202-214, 237-241, 243-250, 300-304, 323-335, 375-382, 391-400, and 413-423. The above numbering preferably starts from the N-terminus of the protease component of the present invention.

In a preferred embodiment, the destructive cleavage site(s) are located at a position greater than 8 amino acid residues, preferably greater than 10 amino acid residues, more preferably greater than 25 amino acid residues,

particularly preferably greater than 50 amino acid residues from the N-terminus of the protease component. Similarly, in a preferred embodiment, the destructive cleavage site(s) are located at a position greater than 20 amino acid residues, preferably greater than 30 amino acid residues, more preferably greater than 40 amino acid residues, particularly preferably greater than 50 amino acid residues from the C-terminus of the protease component.

For the translocation component, one or more of the following positions is preferred: 474-479, 483-495, 507-543, 557-567, 576-580, 618-631, 643-650, 669-677, 751-767, 823-834, 845-859. The above numbering preferably acknowledges a starting position of 449 for the N-terminus of the translocation domain component of the present invention, and an ending position of 871 for the C-terminus of the translocation domain component.

In a preferred embodiment, the destructive cleavage site(s) are located at a position greater than 10 amino acid residues, preferably greater than 25 amino acid residues, more preferably greater than 40 amino acid residues, particularly preferably greater than 50 amino acid residues from the N-terminus of the translocation component. Similarly, in a preferred embodiment, the destructive cleavage site(s) are located at a position greater than 10 amino acid residues, preferably greater than 25 amino acid residues, more preferably greater than 40 amino acid residues, particularly preferably greater than 50 amino acid residues from the C-terminus of the translocation component.

In a preferred embodiment, the destructive cleavage site(s) are located at a position greater than 10 amino acid residues, preferably greater than 25 amino acid residues, more preferably greater than 40 amino acid residues, particularly preferably greater than 50 amino acid residues from the N-terminus of the TM component. Similarly, in a preferred embodiment, the destructive cleavage site(s) are located at a position greater than 10 amino acid residues, preferably greater than 25 amino acid residues, more preferably greater than 40 amino acid residues, particularly preferably greater than 50 amino acid residues from the C-terminus of the TM component.

The polypeptide of the present invention may include one or more (e.g. two, three, four, five or more) destructive protease cleavage sites. Where more than one destructive cleavage site is included, each cleavage site may be the same or different. In this regard, use of more than one destructive cleavage site provides improved off-site inactivation. Similarly, use of two or more different destructive cleavage sites provides additional design flexibility.

The destructive cleavage site(s) may be engineered into any of the following component(s) of the polypeptide: the non-cytotoxic protease component; the translocation component; the Targeting Moiety; or the spacer peptide (if present). In this regard, the destructive cleavage site(s) are chosen to ensure minimal adverse effect on the potency of the polypeptide (for example by having minimal effect on the targeting/ binding regions and/ or translocation domain, and/ or on the non-cytotoxic protease domain) whilst ensuring that the polypeptide is labile away from its target site/ target cell.

Preferred destructive cleavage sites (plus the corresponding second proteases) are listed in the Table immediately below. The listed cleavage sites are purely illustrative and are not intended to be limiting to the present invention.

Second protease	**Destructive cleavage site recognition sequence**	**Tolerated recognition sequence variance P4-P3-P2-P1-▼-P1'-P2'-P3'**						
		P4	**P3**	**P2**	**P1**	**P1'**	**P2'**	**P 3'**
Thrombin	LVPR▼GS	A,F,G,I, L,T,V or M	A,F,G ,I,L,T, V,W or A	P	R	Not D or E	Not D or E	---
Thrombin	GR▼G			G	R	G		
Factor Xa	IEGR▼	A,F,G,I, L,T,V or M	D or E	G	R	---	---	---
ADAM17	PLAQA▼VRSSS							
Human airway trypsin-like protease (HAT)	SKGR▼SLIGRV							

ACE (peptidyl-dipeptidase A)		---	---	---	---	Not P	Not D or E	N /A
Elastase (leukocyte)	MEA▼VTY	M, R	E	A, H	V, T	V, T, H	Y	---
Furin	RXR/KR▼	R	X	R or K	R			
Granzyme	IEPD▼	I	E	P	D	---	---	---
Caspase 1		F,W,Y, L	---	H, A,T	D	Not P,E.D. Q.K or R	---	---
Caspase 2	DVAD▼	D	V	A	D	Not P,E.D. Q.K or R	---	---
Caspase 3	DMQD▼	D	M	Q	D	Not P,E.D. Q.K or R	---	---
Caspase 4	LEVD▼	L	E	V	D	Not P,E.D. Q.K or R	---	---
Caspase 5		L or W	E	H	D	---	---	---
Caspase 6		V	E	H or I	D	Not P,E.D. Q.K or R	---	---
Caspase 7	DEVD▼	D	E	V	D	Not P,E.D. Q.K or R	---	---
Caspase 8		I or L	E	T	D	Not P,E.D. Q.K or R	---	---
Caspase 9	LEHD▼	L	E	H	D	---	---	---
Caspase	IEHD▼	I	E	H	D	---	---	--

10								-

Matrix metalloproteases (MMPs) are a preferred group of destructive proteases in the context of the present invention. Within this group, ADAM17 (EC 3.4.24.86, also known as TACE), is preferred and cleaves a variety of membrane-anchored, cell-surface proteins to "shed" the extracellular domains. Additional, preferred MMPs include adamalysins, serralysins, and astacins.

Another group of preferred destructive proteases is a mammalian blood protease, such as Thrombin, Coagulation Factor VIIa, Coagulation Factor IXa, Coagulation Factor Xa, Coagulation Factor XIa, Coagulation Factor XIIa, Kallikrein, Protein C, and MBP-associated serine protease.

In one embodiment of the present invention, said destructive cleavage site comprises a recognition sequence having at least 3 or 4, preferably 5 or 6, more preferably 6 or 7, and particularly preferably at least 8 contiguous amino acid residues. In this regard, the longer (in terms of contiguous amino acid residues) the recognition sequence, the less likely non-specific cleavage of the destructive site will occur via an unintended second protease.

It is preferred that the destructive cleavage site of the present invention is introduced into the protease component and/ or the Targeting Moiety and/ or into the translocation component and/ or into the spacer peptide. Of these four components, the protease component is preferred. Accordingly, the polypeptide may be rapidly inactivated by direct destruction of the non-cytotoxic protease and/ or binding and/ or translocation components.

Polypeptide delivery

In use, the present invention employs a pharmaceutical composition, comprising a polypeptide, together with at least one component selected from a pharmaceutically acceptable carrier, excipient, adjuvant, propellant and/ or salt.

The polypeptides of the present invention may be formulated for oral, parenteral, continuous infusion, implant, inhalation or topical application. Compositions suitable for injection may be in the form of solutions, suspensions or emulsions, or dry powders which are dissolved or suspended in a suitable vehicle prior to use.

Local delivery means may include an aerosol, or other spray (eg. a nebuliser). In this regard, an aerosol formulation of a polypeptide enables delivery to the lungs and/or other nasal and/or bronchial or airway passages.

The preferred route of administration is selected from: systemic (eg. iv), laparoscopic and/ or localised injection (for example, transsphenoidal injection directly into the tumour).

In the case of formulations for injection, it is optional to include a pharmaceutically active substance to assist retention at or reduce removal of the polypeptide from the site of administration. One example of such a pharmaceutically active substance is a vasoconstrictor such as adrenaline. Such a formulation confers the advantage of increasing the residence time of polypeptide following administration and thus increasing and/or enhancing its effect.

The dosage ranges for administration of the polypeptides of the present invention are those to produce the desired therapeutic effect. It will be appreciated that the dosage range required depends on the precise nature of the polypeptide or composition, the route of administration, the nature of the formulation, the age of the patient, the nature, extent or severity of the patient's condition, contraindications, if any, and the judgement of the attending physician. Variations in these dosage levels can be adjusted using standard empirical routines for optimisation.

Suitable daily dosages (per kg weight of patient) are in the range 0.0001-1 mg/kg, preferably 0.0001-0.5 mg/kg, more preferably 0.002-0.5 mg/kg, and particularly preferably 0.004-0.5 mg/kg. The unit dosage can vary from less that 1 microgram to 30mg, but typically will be in the region of 0.01 to 1 mg

per dose, which may be administered daily or preferably less frequently, such as weekly or six monthly.

A particularly preferred dosing regimen is based on 2.5 ng of polypeptide as the 1X dose. In this regard, preferred dosages are in the range 1X–100X (i.e. 2.5-250 ng).

Fluid dosage forms are typically prepared utilising the polypeptide and a pyrogen-free sterile vehicle. The polypeptide, depending on the vehicle and concentration used, can be either dissolved or suspended in the vehicle. In preparing solutions the polypeptide can be dissolved in the vehicle, the solution being made isotonic if necessary by addition of sodium chloride and sterilised by filtration through a sterile filter using aseptic techniques before filling into suitable sterile vials or ampoules and sealing. Alternatively, if solution stability is adequate, the solution in its sealed containers may be sterilised by autoclaving. Advantageously additives such as buffering, solubilising, stabilising, preservative or bactericidal, suspending or emulsifying agents and or local anaesthetic agents may be dissolved in the vehicle.

Dry powders, which are dissolved or suspended in a suitable vehicle prior to use, may be prepared by filling pre-sterilised ingredients into a sterile container using aseptic technique in a sterile area. Alternatively the ingredients may be dissolved into suitable containers using aseptic technique in a sterile area. The product is then freeze dried and the containers are sealed aseptically.

Parenteral suspensions, suitable for intramuscular, subcutaneous or intradermal injection, are prepared in substantially the same manner, except that the sterile components are suspended in the sterile vehicle, instead of being dissolved and sterilisation cannot be accomplished by filtration. The components may be isolated in a sterile state or alternatively it may be sterilised after isolation, e.g. by gamma irradiation.

Advantageously, a suspending agent for example polyvinylpyrrolidone is included in the composition/s to facilitate uniform distribution of the components.

Definitions Section

Targeting Moiety (TM) means any chemical structure that functionally interacts with a Binding Site to cause a physical association between the polypeptide of the invention and the surface of a target cell (typically a mammalian cell, especially a human cell). The term TM embraces any molecule (ie. a naturally occurring molecule, or a chemically/physically modified variant thereof) that is capable of binding to a Binding Site on the target cell, which Binding Site is capable of internalisation (eg. endosome formation) - also referred to as receptor-mediated endocytosis. The TM may possess an endosomal membrane translocation function, in which case separate TM and Translocation Domain components need not be present in an agent of the present invention. Throughout the preceding description, specific TMs have been described. Reference to said TMs is merely exemplary, and the present invention embraces all variants and derivatives thereof, which possess a basic binding (i.e. targeting) ability to a Binding Site on the neuroendocrine tumour cell, wherein the Binding Site is capable of internalisation.

The TM of the present invention binds (preferably specifically binds) to the target cell in question. The term "specifically binds" preferably means that a given TM binds to the target cell (e.g. to an SST receptor) with a binding affinity (Ka) of 10^6 M^{-1} or greater, preferably 10^7 M^{-1} or greater, or 10^8 M^{-1} or greater, or 10^9 M^{-1} or greater. The TMs of the present invention (when in a free form, namely when separate from any protease and/ or translocation component), preferably demonstrate a binding affinity (IC_{50}) for the target receptor in question (eg. an SST receptor) in the region of 0.05-18nM.

The TM of the present invention is preferably not wheat germ agglutinin (WGA).

Reference to TM in the present specification embraces fragments and

variants thereof, which retain the ability to bind to the target cell in question. By way of example, a variant may have at least 80%, preferably at least 90%, more preferably at least 95%, and most preferably at least 97 or at least 99% amino acid sequence homology with the reference TM – the latter is any TM sequence recited in the present application. Thus, a variant may include one or more analogues of an amino acid (e.g. an unnatural amino acid), or a substituted linkage. Also, by way of example, the term fragment, when used in relation to a TM, means a peptide having at least five, preferably at least ten, more preferably at least twenty, and most preferably at least twenty five amino acid residues of the reference TM. The term fragment also relates to the above-mentioned variants. Thus, by way of example, a fragment of the present invention may comprise a peptide sequence having at least 7, 10, 14, 17, 20, 25, 28, 29, or 30 amino acids, wherein the peptide sequence has at least 80% sequence homology over a corresponding peptide sequence (of contiguous) amino acids of the reference peptide.

By way of example, somatostatin (SST) and cortistatin (CST) have high structural homology, and bind to all known SST receptors. Full-length SST has the amino acid sequence:

MLSCRLQCALAALSIVLALGCVTGAPSDPRLRQFLQKSLAAAAGKQELAKYF LAELLSEPNQTENDALEPEDLSQAAEQDEMRLELQRSANSNPAMAPRERKA GCKNFFWKTFTSC

Full-length CST has the amino acid sequence:

MYRHKNSWRLGLKYPPSSKEETQVPKTLISGLPGRKSSSRVGEKLQSAHKM PLSPGLLLLLLSGATATAALPLEGGPTGRDSEHMQEAAGIRKSSLLTFLAWW FEWTSQASAGPLIGEEAREVARRQEGAPPQQSARRDRMPCRNFFWKTFSS CK

Reference to these TMs includes the following fragments (and corresponding variants) thereof:

NFFWKTF;

(R or K)NFFWKTF;

C(R or K)NFFWKTF;

(P or G)C(R or K)NFFWKTF;

NFFWKTF(S or T);
NFFWKTF(S or T)S;
NFFWKTF(S or T)SC;
(R or K)NFFWKTF(S or T);
(R or K)NFFWKTF(S or T)S;
(R or K)NFFWKTF(S or T)SC;
C(R or K)NFFWKTF(S or T);
C(R or K)NFFWKTF(S or T)S;
C(R or K)NFFWKTF(S or T)SC;
(P or G)C(R or K)NFFWKTF(S or T);
(P or G)C(R or K)NFFWKTF(S or T)S; or
(P or G)C(R or K)NFFWKTF(S or T)C.

With regard to the above sequences, where a (P or G) alternative is given, a P is preferred in the case of a CST TM, whereas a G is preferred in the case of an SST TM. Where an (R or K) alternative is given, an R is preferred in the case of a CST TM, whereas a K is preferred in the case of an SST TM. Where an (S or T) alternative is given, an S is preferred in the case of a CST TM, whereas a T is preferred in the case of an SST TM.

Preferred fragments comprise at least 7 or at least 10 amino acid residues, preferably at least 14 or at least 17 amino acid residues, and more preferably at least 28 or 29 amino acid residues. By way of example, preferred sequences include: SANSNPAMAPRERKAGCKNFFWKTFTSC (SST-28); AGCKNFFWKTFTSC (SST-14); QEGAPPQQSARRDRMPCRNFFWKTFSSCK (CST-29); QERPPLQQPPHRDKKPCKNFFWKTFSSCK (CST-29); QERPPPQQPPHLDKKPCKNFFWKTFSSCK (CST-29); DRMPCRNFFWKTFSSCK (CST-17); PCRNFFWKTFSSCK (CST-14); and PCKNFFWKTFSSCK (CST-14).

The TM may comprise a longer amino acid sequence, for example, at least 30 or 35 amino acid residues, or at least 40 or 45 amino acid residues, so long as the TM is able to bind to a neuroendocrine tumour cell, preferably to an SST or to a CST receptor on a neuroendocrine tumour cell. In this regard, the TM is

preferably a fragment of full-length SST or CST, though including at least the core sequence "NFFWKTF" or one of the above-defined primary amino acid sequences.

By way of further example, GHRH peptides of the present invention include: YADAIFTASYRKVLGQLSARKLLQDILSR; YADAIFTASYRNVLGQLSARKLLQDILSR; YADAIFTNSYRKVLGQLSARKLLQDIM; YADAIFTNSYRKVLGQLSARKLLQDIMS; ADAIFTNSYRKVLGQLSARKLLQDIMSR; YADAIFTNSYRKVLGQLSARKLLQDIMSRQQGESNQERGARARL; YADAIFTNSYRKVLGQLSARKLLQDIMSRQQGESNQERGA; YADAIFTNAYRKVLGQLSARKLLQDIMSR; YADAIFTNSYRKVLGQLSARKALQDIMSR; YADAIFTASYKKVLGQLSARKLLQDIMSR; YADAIFTASYKRVLGQLSARKLLQDIMSR; YADAIFTASYNKVLGQLSARKLLQDIMSR; YADAIFTASYRKVLGQLSAKKLLQDIMSR; YADAIFTASYKKVLGQLSAKKLLQDIMSR; YADAIFTASYRKVLGQLSANKLLQDIMSR; YADAIFTASYRNVLGQLSARKLLQDIMSR; YADAIFTASYRKVLGQLSARNLLQDIMSR; YADAIFEASYRKVLGQLSARKLLQDIMSR; YADAIFTASERKVLGQLSARKLLQDIMSR; YADAIFTASYRKELGQLSARKLLQDIMSR; YADAIFTASYRKVLGQLSARKLLQDIMSR; YADAIFTESYRKVLGQLSARKLLQDIMSR; YADAIFTNSYRKVLAQLSARKLLQDIM; YADAIFTNSYRKVLAQLSARKLLQDIMSR; YADAIFTASYRKVLAQLSARKLLQDIMSR; YADAIFTAAYRKVLAQLSARKALQDIASR; YADAIFTAAYRKVLAQLSARKALQDIMSR; HVDAIFTQSYRKVLAQLSARKLLQDILNRQQGERNQEQGA; HVDAIFTQSYRKVLAQLSARKALQDILSRQQG; HVDAIFTSSYRKVLAQLSARKLLQDILSR; HVDAIFTTSYRKVLAQLSARKLLQDILSR; YADAIFTQSYRKVLAQLSARKALQDILNR; YADAIFTQSYRKVLAQLSARKALQDILSR.

It is routine to confirm that a TM binds to the selected target cell. For example, a simple radioactive displacement experiment may be employed in which tissue or cells representative of a neuroendocrine tumour cell are exposed to labelled (eg. tritiated) TM in the presence of an excess of unlabelled TM. In such an experiment, the relative proportions of non-specific and specific binding may be assessed, thereby allowing confirmation that the TM binds to the target cell. Optionally, the assay may include one or more binding antagonists, and the assay may further comprise observing a loss of TM binding. Examples of this type of experiment can be found in Hulme, E.C. (1990), Receptor-binding studies, a brief outline, pp. 303-311, In Receptor biochemistry, A Practical Approach, Ed. E.C. Hulme, Oxford University Press.

In the context of the present invention, reference to a peptide TM (e.g. SST peptide, CST peptide, or GHRH peptide, etc) embraces peptide analogues thereof, so long as the analogue TM binds to the same receptor as the corresponding 'reference' TM. Said analogues may include synthetic residues such as: ß-Nal = ß-naphthylalanine; ß-Pal = ß –pyridylalanine; hArg(Bu) = N-guanidino-(butyl)-homoarginine; $hArg(Et)_2$ = N, N'-guanidino-(dimethyl)-homoarginine; $hArg(CH_2CF_3)_2$ = N, N'-guanidino-bis-(2,2,2,-trifluoroethyl)-homoarginine; hArg(CH_3, hexyl) = N, N'-guanidino-(methyl, hexyl)-homoarginine; Lys(Me) = N^e-methyllysine; Lys(iPr) = N^e-isopropyllysine; AmPhe = aminomethylphenylalanine; AChxAla = aminocyclohexylalanine; Abu = α-aminobutyric acid; Tpo = 4-thiaproline; MeLeu = N-methylleucine; Orn = ornithine; Nle = norleucine; Nva = norvaline; Trp(Br) = 5-bromo-tryptophan; Trp(F) = 5-fluoro-tryptophan; $Trp(NO_2)$ = 5-nitro-tryptophan; Gaba = γ-aminobutyric acid; Bmp = J-mercaptopropionyl; Ac = acetyl; and Pen = penicillamine

By way of example, the above peptide analogue aspect is described in more detail with reference to specific peptide TMs, such as SST peptides, GHRH peptides, bombesin peptides, ghrelin peptides, GnRH (aka LHRH peptides), and urotensin peptides, though the same principle applies to all TMs of the present invention.

Somatostatin analogues, which can be used to practice the present invention include, but are not limited to, those described in the following publications, which are hereby incorporated by reference: Van Binst, G. et al. Peptide Research 5: 8 (1992); Horvath, A. et al. Abstract, "Conformations of Somatostatin Analogs Having Antitumor Activity", 22nd European peptide Symposium, September 13-19,1992, Interlaken, Switzerland; US5,506,339; EP0363589; US4,904,642; US4,871,717; US4,725,577; US4,684,620; US4,650,787; US4,585,755; US4,725,577; US4,522,813; US4,369,179; US4,360,516; US4,328,214; US4,316,890; US4,310,518; US4,291,022; US4,238,481; US4,235,886; US4,211,693; US4,190,648; US4,146,612; US4,133,782; US5,506,339; US4,261,885; US4,282,143; US4,190,575; US5,552,520; EP0389180; EP0505680; US4,603,120; EP0030920; US4,853,371; WO90/12811; WO97/01579; WO91/18016; WO98/08529 and

WO98/08528; WO/0075186 and WO00/06185; WO99/56769; and FR 2,522,655.

Preferred analogues include: cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe) or H-D-ß-Nal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH2; H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH2; H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH2; H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH2; H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH2; H-Cys-Phe-Phe-D-Trp-Lys-Thr-NH2; H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH2; H-Phe-Phe-Phe-D-Trp-Lys-Thr-NH2; H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-THr-NH2; H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH2; H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH2, H-D-Phe-p-NO2-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2, H-D-ß-Nal-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2, H-D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2, H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2, H-D-Phe-Ala-Tyr-D-Trp-Lys-Val-Ala-D-ß-Nal-NH2; H-D-ß-Nal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH2; H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-ß-Nal-NH2; H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-ß-Nal-NH2; H-D-ß-Nal-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH2; H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-NH2; H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-OH; H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-OH; H-Gly-Pen-Phe-D-Trp-Lys-Thr-Cys-Thr-OH; H-Phe-Pen-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH; H-Phe-Pen-Phe-D-Trp-Lys-Thr-Pen-Thr-OH; H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol; H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; H-D-Trp-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; H-D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH2; H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; Ac-D-Phe-Lys*-Tyr-D-Trp-Lys-Val-Asp*-Thr-NH2 (an amide bridge formed between Lys* and Asp*); Ac-hArg (Et) 2-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; Ac-D-hArg (Et) 2-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; Ac-D-hArg (Bu)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; Ac-D-hArg (Et) 2-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; Ac-L-hArg (Et) 2-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; Ac-D-hArg (CH2CF3) 2-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; Ac-D-hArg (CH2CF3) 2-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; Ac-D-hArg (CH2CF3) 2-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH2; Ac-D-hArg (CH2CF3) 2-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHEt; Ac-L-hArg (CH2-CF3) 2-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; Ac-D-hArg (CH2CF3)

2-Gly-Cys-Phe-D-Trp-Lys (Me)-Thr-Cys-Thr-NH2; Ac-D-hArg (CH2CF3) 2-Gly-Cys-Phe-D-Trp-Lys (Me)-Thr-Cys-Thr-NHEt; Ac-hArg (CH3, hexyl)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; H-hArg (hexyl2)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; Ac-D-hArg (Et) 2-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHEt; Ac-D-hArg (Et) 2-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH2; Propionyl-D-hArg (Et) 2-Gly-Cys-Phe-D-Trp-Lys (iPr)-Thr-Cys-Thr-NH2; Ac-D-ß-Nal-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Gly-hArg (Et) 2-NH2; Ac-D-Lys (iPr)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; Ac-D-hArg (CH2CF3) 2-D-hArg (CH2CF3) 2-Gly-Cys-Phe-D-Trp-Lys-Thr- Cys- Thr-NH2; Ac-D-hArg (CH2CF3) 2-D-hArg (CH2CF3) 2-Gly-Cys-Phe-D-Trp-Lys-Thr- Cys- Phe-NH2; Ac-D-hArg (Et) 2-D-hArg (Et) 2-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH2; c-Cys-Lys-Asn-4-Cl-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Ser-D-Cys-NH2; H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Phe-NH2; H-Bmp-Tyr-D-Trp-Lys-Val-Cys-p-Cl-Phe-NH2; H-Bmp-Tyr-D-Trp-Lys-Val-Cys-p-Nal-NH2; H-D-ß-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH2; H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-beta-Nal-NH2; H-pentafluoro-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; Ac-D-ß-Nal-Cys-pentafluoro-Phe-D-Trp-Lys-Val-Cys-Thr-NH2; H-D-i-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-p-Nal-NH2; H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-ß-Nal-NH2; H-D-, SNal-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH2; H-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH2; Ac-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH2; H-D-Phe-Cys-p-Nal-D-Trp-Lys-Val-Cys-Thr-NH2; H-D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH2; cyclo (Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe); cyclo (Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe); cyclo (Pro-Phe-D-Trp-Lys-Thr-N-Me-Phe); cyclo (N-Me-Ala-Tyr-D-Trp-Lys-Thr-Phe); cyclo (Pro-Tyr-D-Trp-Lys-Thr-Phe); cyclo (Pro-Phe-D-Trp-Lys-Thr-Phe); cyclo (Pro-Phe-L-Trp-Lys-Thr-Phe); cyclo (Pro-Phe-D-Trp (F)-Lys-Thr-Phe); cyclo (Pro-Phe-Trp (F)-Lys-Thr-Phe); cyclo (Pro-Phe-D-Trp-Lys-Ser-Phe); cyclo (Pro-Phe-D-Trp-Lys-Thr-p-Cl-Phe); cyclo (D-Ala-N-Me-D-Phe-D-Thr-D-Lys-Trp-D-Phe); cyclo (D-Ala-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Phe); cyclo (D-Ala-N-Me-D-Phe-D-Thr-Lys-D-Trp-D-Phe); cyclo (D-Abu-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Tyr); cyclo (Pro-Tyr-D-Trp-t-4-AchxAla-Thr-Phe); cyclo (Pro-Phe-D-Trp-t-4-AchxAla-Thr-Phe); cyclo (N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe); cyclo (N-Me-Ala-Tyr-D-Trp-t-4-AchxAla-Thr-Phe); cyclo (Pro-Tyr-D-Trp-4-Amphe-Thr-Phe); cyclo (Pro-Phe-D-Trp-4-Amphe-Thr-Phe); cyclo (N-Me-Ala-Tyr-D-Trp-4-Amphe-Thr-Phe); cyclo (Asn-Phe-Phe-D-

Trp-Lys-Thr-Phe-Gaba); cyclo (Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba-Gaba); cyclo (Asn-Phe-D-Trp-Lys-Thr-Phe); cyclo (Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-NH (CH2) 4CO); cyclo (Asn-Phe-Phe-D-Trp-Lys-Thr-Phe->Ala); cyclo (Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-D-Glu)-OH; cyclo (Phe-Phe-D-Trp-Lys-Thr-Phe); cyclo (Phe-Phe-D-Trp-Lys-Thr-Phe-Gly); cyclo (Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba); cyclo (Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gly); cyclo (Asn-Phe-Phe-D-Trp (F)-Lys-Thr-Phe-Gaba); cyclo (Asn-Phe-Phe-D-Trp (NO2)-Lys-Thr-Phe-Gaba); cyclo (Asn-Phe-Phe-Trp (Br)-Lys-Thr-Phe-Gaba); cyclo (Asn-Phe-Phe-D-Trp-Lys-Thr-Phe (I)-Gaba); cyclo (Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr (But)-Gaba); cyclo (Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-Cys)-OH; cyclo (Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-Cys)-OH; cyclo (Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Tpo-Cys)-OH; cyclo (Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-MeLeu-Cys)-OH; cyclo (Phe-Phe-D-Trp-Lys-Thr-Phe-Phe-Gaba); cyclo (Phe-Phe-D-Trp-Lys-Thr-Phe-D-Phe-Gaba); cyclo (Phe-Phe-D-Trp (5F)-Lys-Thr-Phe-Phe-Gaba); cyclo (Asn-Phe-Phe-D-Trp-Lys (Ac)-Thr-Phe-NH- (CH2) 3-CO); cyclo (Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba); cyclo (Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba); cyclo (Orn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba); H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH2; H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH2; H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH2; H-Cys-Phe-Tyr (I)-D-Trp-Lys-Thr-Phe-Cys-NH2.

Methods for synthesizing analogues are well documented, as illustrated, for example, by the patents cited above. For example, synthesis of H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH2, can be achieved by following the protocol set forth in Example 1 of EP0395417A1. Similarly, synthesis analogues with a substituted N-terminus can be achieved, for example, by following the protocol set forth in WO88/02756, EP0329295, and US5,240,561.

Preferred examples of linear analogues include: H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH2; H-D-Phe-p-N02-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; H-D-*Nal-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH2; H-D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; and H-D-Phe-Ala-Tyr-D-Trp-Lys-Val-Ala-D-beta-Nal-NH2.

One or more chemical moieties, eg. a sugar derivative, mono or poly-hydroxy (C2-12) alkyl, mono or poly-hydroxy (C2-12) acyl groups, or a piperazine derivative, can be attached to a SST analogue, e g. to the N-terminus amino acid - see WO88/02756, EP0329295, and US5,240,561.

Further examples of SST analogues that can be used as a TM in the present invention include the following: D-Cpa-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2; D-Phe-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2; D-Phe-cyclo[Cys-p-NH2-Phe-D-Trp-Lys-Val-Cys]-Thr-NH2; N-Me-D-Phe-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2; D-Phe-cyclo[Cys-Tyr-D-Pal-Lys-Val-Cys]-Thr-NH2; Ac-D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2; D-Phe-cyclo [Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH2; D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH2; D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-OH; ED-Phe-cyclo[Cys-Nal-D-Trp-Lys-Val-Cys]-Thr-NH2; D-Nal-cyclo[Cys-Tyr-D-Nal-Lys-Val-Cys]-Nal-NH2; D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-D-Cys]-Nal-NH2; D-Trp-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH2; D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-D-Nal-NH2; Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-D-Nal-NH2; (AcO-CH2)3-C-NH-CO-(CH2)2-CO-D-Nal-cyclo(Cys-Tyr-D-Trp-Lys-Val-Cys]Thr-NH2; [3-O-(2,5,6-triacetyl ascorbic)acetyl-D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2; D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Trp-NH2; Phe-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Trp-NH2; 3-O-(ascorbic)-butryrl-D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2; 3-O-(ascorbic acid)Ac-D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2; D-Bpa-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH2; D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Bpa-NH2; Tris-Suc-D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2; D-Dpa-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH2; D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Dpa-NH2; Ac-D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2; cyclo-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2; NmeCpa-cyclo (DCys-3-Pal-DTrp-Lys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo(NMeDCys-3-Pal-DTrp-Lys-Thr-Cys)-2-Nal-NHMe; Cpa-cyclo (DCys-NMe3-Pal-DTrp-Lys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo(DCys-3-Pal-NMeDTrp-Lys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo(DCys-3-Pal-DTrp-NMeLys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo(DCys-3-Pal-DTrp-Lys-NMeThr-Cys)-2-Nal-NH2; Cpa-cyclo (DCys-3-Pal-DTrp-Lys-Thr-NMeCys)-2-Nal-NH2; Cpa-cyclo (DCys-3-Pal-DTrp-Lys-Thr-Cys)-Nme2-Nal-NH2; Cpa-cyclo(NMeDCys-3-Pal-

DTrp-Lys-Thr-Cys)-Dip-NHMe; Cpa-cyclo (DCys-3-Pal-NMeDTrp-NMeLys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo(DCys-Tyr-DTrp-NMeLys-Thr-Cys)-2-Nal-NH2; Tfm-cyclo (DCys-3-Pal-DTrp-NMeLys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo(DCys-3-Pal-DTrp-NMeLys-Thr-Cys)-DTrp-NH2; Nal-cyclo (DCys-3-Pal-DTrp-NMeLys-Thr-Cys)-DTrp-NH2; 3-Pal-cyclo (DCys-3-Pal-DTrp-NMeLys-Thr-Cys)-DTrp-NH2; NmeCpa-cyclo (DCys-3-Pal-DTrp-Lys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo(DCys-3-Pal-DTrp-NMeLys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo(DCys-3-Pal-NMeDTrp-NMeLys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo (DCys-Tyr-DTrp-NMeLys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo(DCys-3-Pal-DTrp-NMeLys-Thr-Cys)-DTrp-NH2; Nal-cyclo (DCys-Pal-DTrp-NMeLys-Thr-Cys)-DTrp-NH2; or 3-Pal-cyclo(DCys-3-Pal-DTrp-NMeLys-Thr-Cys)-DTrp-NH2; NmeCpa-cyclo (DCys-3-Pal-DTrp-Lys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo(DCys-3-Pal-DTrp-NMeLys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo (DCys-3-Pal-NMeDTrp-NMeLys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo (DCys-Tyr-DTrp-NMeLys-Thr-Cys)-2-Nal-NH2; or Cpa-cyclo(DCys-3-Pal-DTrp-NMeLys-Thr-Cys)-DTrp-NH2; Cpa-cyclo (DCys-3-Pal-DTrp-NMeLys-Thr-Cys)-2-Nal-NH2; Cpa-cyclo(DCys-Tyr-DTrp-NMeLys-Thr-Cys)-2-Nal-NH2; methylpropionic acid-Tyr-D-Trp- ys-Val-Cys-Thr-NH_2; methylpropionic acid-Tyr-D-Trp- ys-Val-Cys-Phe-NH_2; methylpropionic acid-Tyr-D-Trp-Lys-Val-Cys-p-Cl-Phe-NH2; methylpropionic acid-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2; D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH2; D-Phe-Phe-Tyr-D-Trp-Lys-val-Phe-Thr-NH2; D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2; or D-Phe-Ala-Tyr-D-Trp-Lys-Val-Ala-β-D-Nal-NH_2; H_2-c[Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c[D-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c[Cys-Phe-Trp-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c[Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys]-NH_2, or H_2-c[Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c[Cys-Phe-Trp-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c[D-Cys-Phe-Trp-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c[Cys-Phe-His-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c[D-Cys-Phe-His-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c[D-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c[D-Cys-Phe-Trp-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c[Cys-Phe-His-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c[D-Cys-Phe-His-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c[D-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c[Cys-Phe-Tyr(I)-D-Trp-Lys-Ser-Phe-Cys]-NH_2, or H_2-c[D-Cys-Phe-Tyr(I)-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c[D-Cys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c[Cys-Asn-Phe-Trp-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c [D-Cys-Asn-Phe-Trp-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c [Cys-Asn-

Phe-His-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c[D-Cys-Asn-Phe-His-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c[Cys-Asn-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c[D-Cys-Asn-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c[Cys-Asn-Phe-Trp-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c[D-Cys-Asn-Phe-Trp-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c [Cys-Asn-Phe-His-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c [D-Cys-Asn-Phe-His-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c [Cys-Asn-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c [D-Cys-Asn-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys]-NH_2, H_2-c [Cys-Asn-Phe-Tyr(I)-D-rp-Lys-Ser-Phe-Cys]-NH_2, H_2-c [D-Cys-Asn-Phe-Tyr(I)-D-Trp-Lys-Ser-Phe-Cys]-NH_2, H_2-c[Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys]-NH_2; Ac-D-Phe-Tyr-cyclo (D-Cys-D-Trp-Lys-Cys)-Abu-Thr-NH2; Nal-Tyr-cyclo(Cys-D-Trp-Lys-D-Cys)-Val-Nal-NH2; Nal-Tyr-cyclo(Cys-D-Trp-Lys-D-Cys)-Abu-Nal-NH2; D-Dip-Tyr-cyclo(Cys-D-Trp-Lys-D-Cys)-Abu-Nal-NH2; Dip-Tyr-cyclo (D-Cys-D-Trp-Lys-D-Cys)-Abu-Nal-NH2; Nal-Tyr-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Abu-Nal-NH2; Dip-Tyr-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Val-Nal-NH2; Nal-Tyr-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Val-Nal-NH2; cyclo(D-Phe-Tyr-cyclo(D-Cys-D-Trp-Lys-Cys)-Abu-Thr); Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-A3c-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-A5c-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-A6c-Nal-NH2; (G(z))aeg-cyclo(D-Cys-D-Trp-Lys-D-Cys)-A5c-Nal-NH2; Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-A5c-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-ß-Ala-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Sar-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Gaba-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Pro-Nal-NH2; Pro-Phe-c(D-Cys-D-Trp-Lys-D-Cys)-Nle-Phe-NH2; Pro-Phe-c(D-Cys-D-Trp-Lys-D-Cys)-Thr-Nle-NH2; Pro-Phe-c (D-Cys-D-Trp-Lys-D-Cys)-Thr-Phe-NH2; Cpa-Phe-c (D-Cys-D-Trp-Lys-D-Cys)-Gaba-NH2 ; Cpa-Phe-c(D-Cys-D-Trp-Lys-D-Cys)-Gaba-Tyr-NH2; Pip-Phe-c (D-Cys-D-Trp-Lys-D-Cys)-NH2; Pip-Phe-c (Cys-D-Trp-Lys-Cys)-Gaba-NH2; or Pro-Phe-c(D-Cys-D-Trp-Lys-D-Cys)-Thr-NH2; Phe-cyclo(Cys-D-Trp-Lys-Cys)-Thr-NH2; Phe-Tyr-cyclo(D-Cys-D-Trp-Lys-Cys)-Abu-Thr-NH2; Ac-D-Phe-Tyr-cyclo(D-Cys-D-Trp-Lys-Cys)-Abu-Thr-NH2; Nal-Tyr-cyclo(Cys-D-Trp-Lys-D-Cys)-Val-Nal-NH2; Nal-Tyr-cyclo(Cys-D-Trp-Lys-D-Cys)-Abu-Nal-NH2; Dip-Tyr-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Abu-Nal-NH2; Nal-Tyr-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Abu-Nal-NH2; Dip-Tyr-cyclo (D-Cys-D-Trp-Lys-D-Cys)-Val-Nal-NH2; Nal-Tyr-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Val-Nal-NH2, Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-A3c-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-A5c-

Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-A6c-Nal-NH2; (G(z))aeg-cyclo(D-Cys-D-Trp-Lys-D-Cys)-A5c-Nal-NH2; D-Cpa-cyclo(Cys-D-Trp-Lys-D-Cys)-A5c-Nal-NH2; Pal-cyclo (D-Cys-D-Trp-Lys-D-Cys)-A5c-Nal-NH2; Cpa-cyclo(D-Cys-D-Trp-Lys-D-Cys)-A5c-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-ß-Ala-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Sar-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Aic-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Gaba-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Pro-Nal-NH2; (T)aeg-cyclo(D-Cys-D-Trp-Lys-D-Cys)-(A)aeg-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-A4c-Nal-NH2; Cpa-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Nal-NH2; Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Nal-NH2; Pro-Phe-cyclo(Cys-D-Trp-Lys-D-Cys)-Val-NH2; Pro-Phe-cyclo(D-Cys-D-Trp-Lys-Cys)-Val-NH2; Pip-4-NO2-Phe-cyclo(D-cys-D-Trp-Lys-D-Cys)-Nle-NH2; (G)aeg-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Thr(Bzl)-(C)aeg-NH2; or (C)aeg-Pal-cyclo(D-Cys-D-Trp-Lys-D-Cys)-Thr (Bzl)-(G)aeg-NH2; Nal-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; D-Nal-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; D-Phe-cyclo(Cys-Tyr-D-Trp-Lys-Cys)-Thr-NH2, D-4-NO2-Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; Ac-D-4-NO2-Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; D-4-NO2-Phe-Pal-cyclo(D-Cys-Phe (4-O-Bzl)-D-Trp-Lys-Cys)-Tyr-NH2; Cpa-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; D-4-NO2-Phe-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr-Tyr-NH2; D-4-NO2-Phe-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-NH2; D-4-NO2-Phe-cyclo (D-Cys-Pal-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; D-4-NO2-Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; 4-NO2-Phe-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; D-Nal-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; Pro-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; Cpa-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Nal-NH2; Ser(Bzl)-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; (A)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (G)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-4-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Phe-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-(T)aeg-D-Trp-Lys-Cys)-Thr (Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Ser(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Phe(4-O-Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-A5c-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Abu-Tyr-NH2; D-Cpa-

cyclo(D-Cys-(T)aeg-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (C)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; D-Cpa-c(D-Cys-Pal-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(Pen-Pal-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Trp-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Phe-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Pal-D-Trp-Orn-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Pal-D-Trp-hLys-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Pal-D-Trp-Iamp-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Pal-D-Trp-Cha(4-am)-D-Cys) Thr (Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Pal-D-Trp-Lys-D-Cys)-Ser(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Pal-D-Trp-Lys-D-Cys)Thr(Bzl)-D-Tyr-NH2; (T)aeg-c(D-Cys-Pal-D-Trp-Lys-D-Cys) Thr (Bzl)-Trp-NH2; (T) aeg-c (D-Cys-Pal-D-Trp-Lys-D-Pen)Thr(Bzl)-Tyr-NH2; (C)aeg-c(D-Cys-Phe-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; Ina-c(D-Cys-Phe-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; Mnf-c(D-Cys-Phe-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; Inp-c(D-Cys-Phe-D-Trp-Lys-D-Cys)-thr(Bzl)-Tyr-NH2; Nua-c(D-Cys-Phe-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-Pal-c(D-Cys-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-Pal-c(D-Cys-D-Trp-Lys-D-Cys)Tyr(Bzl)-Thr-NH2; (C)aeg-Phe-c(D-Cys-D-Trp-Lys-D-Cys) Thr(Bzl)-Tyr-NH2; or (T)aeg-D-Trp-c(D-Cys-Pal-Lys-D-Cys)Thr(Bzl)-Leu-NH2; Hca-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; Ac-Nal-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; Ac-D-Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; Ac-D-Nal-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; D-Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; Nal-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; D-Nal-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; D-Phe-cyclo(Cys-Tyr-D-Trp-Lys-Cys)-Thr-NH2; D-4-NO2-Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; Ac-D-4-NO2-Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Nal-NH2; D-4-NO2-Phe-Pal-cyclo(D-Cys-Phe(4-O-Bzl)-D-Trp-Lys-Cys)-Tyr-NH2; D-4-NO2-Phe-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; Cpa-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; D-4-NO2-Phe-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-NH2; D-4-NO2-Phe-cyclo(D-Cys-Pal-D-Trp-Lys-D-Cys)-Thr (Bzl)-Tyr-NH2; D-4-NO2-Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; 4-NO2-Phe-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; D-Nal-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr (Bzl)-Tyr-NH2; Pro-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; Cpa-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Nal-NH2; Ser(Bzl)-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (C)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; Aic-cyclo(D-

Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (C(z))aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (A(z))aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; (A)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (G)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-4-Pal-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Tyr-D-Trp-Lys-Cys)-Thr (Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Phe-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-(T)aeg-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Ser(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Phe(4-O-Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-A5c-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-Cys)-Abu-Tyr-NH2; D-Cpa-cyclo(D-Cys-(T)aeg-D-Trp-Lys-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-D-Cys)-Thr(Bzl)-p-Me-Phe-NH2; Ac-(T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-D-Cys)-Nal-NH2; D-Cpa-cyclo(D-Cys-Pal-D-Trp-Lys-D-Cys)-Nal-NH2; (A)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; (C)aeg-cyclo(D-Cys-Pal-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; (C)aeg-c(D-Cys-Pal-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; D-Cpa-c(D-Cys-Pal-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(Pen-Pal-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Trp-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Phe-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Pal-D-Trp-Orn-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Pal-D-Trp-hLys-D-Cys)Thr(Bzl)-Tyr-NH2, (T)aeg-c(D-Cys-Pal-D-Trp-Iamp-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Pal-D-Trp-Cha(4-am)-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-c(D-Cys-Pal-D-Trp-Lys-D-Cys)-Ser(Bzl)-Tyr-NH2; (T)aeg-c (D-Cys-Pal-D-Trp-Lys-D-Cys)Thr (Bzl)-D-Tyr-NH2; (T)aeg-c (D-Cys-Pal-D-Trp-Lys-D-Cys)Thr(Bzl)-Trp-NH2; (T)aeg-c(D-Cys-Pal-D-Trp-Lys-D-Pen)Thr(Bzl)-Tyr-NH2; (C)aeg-c(D-Cys-Phe-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; Ina-c(D-Cys-Phe-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; Mnf-c(D-Cys-Phe-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; Inp-c(D-Cys-Phe-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; Nua-c(D-Cys-Phe-D-Trp-Lys-D-Cys)-Thr(Bzl)-Tyr-NH2; (T)aeg-Pal-c(D-Cys-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; (T)aeg-Pal-c(D-Cys-D-Trp-Lys-D-Cys)Tyr(Bzl)-Thr-NH2; (C)aeg-Phe-c(D-Cys-D-Trp-Lys-D-Cys)Thr(Bzl)-Tyr-NH2; or (T)aeg-D-Trp-c(D-Cys-Pal-Lys-D-Cys)Thr(Bzl)-Leu-NH2; cyclo(Trp-D-Trp-Lys-Phe(4-O-Bzl)-Phe-(T)aeg);

cyclo(Trp-D-Trp-Lys-Pal-Phe-(T)aeg); cyclo(Phe-Phe-D-Trp-Lys-Thr-(T)aeg); or H-ß-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2 (also known as lanreotide) cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe), cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val- Phe); D-beta-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2; D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cysbeta-Nal-NH_2; D-Phe-Cys-Tyr-D-Trp-Lys-α-Aminobutyric acid-Cys-Thr-NH_2; pentafluoro-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2; N-Ac-D-beta-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;D-beta-Nal~Cys-pentafluoro-Phe-D-Trp-Lys-Val-Cys-Thr-NH_2 ; D-/3-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH_2; D-Phe-Cys-/3-Nal-D-Trp-Lys-Val-Cys-Thr-NH_2; D-beta-Nal-Cys-Tyr-D-Trp-Lys-α-aminobutyric acid-Cys-Thr-NH_2; D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-α-aminobutyric acid-Cys-Thr-NH_2; acetyl-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-α-aminobutyric acid-Cys-Thr-NH_2; cyclo(Pro-Phe-D-Trp- Lys-Thr-Phe); cyclo(N-Me-Ala-Tyr-D-Trp- Lys-Val-Phe); D-beta-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2; D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH_2; D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr(ol); D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2; D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(CH3CO)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)-(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)-(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(CH3CO)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)-(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)-(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(CH3CO)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(CH3CO)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-0-Nal-D-Cys-Pal-D-Trp-Lys-Val-Lys-Thr-NH2; H2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(CH3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-

piperazinylacetyl)-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyi)-1-piperizineethanesuifonyl)-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(CH3CO)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesuifonyi)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(CH3CO)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH2; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(CH3CO)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(CH3CO)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH2; H(CH3CO)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(CH3CO)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta- Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH2; H2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(CH3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; H2-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(CH3CO)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyi)-1-piperizineethanesulfonyl)Phe-D-Cys-

Pal-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; H2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(CH3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH2; H2-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(CH3CO)-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH2; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-beta-Nal-NH2; H2-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Abu-Cys-beta-Nal-NH2; H2-Phe-D-Cys-Pal-D-Trp-Lys-Abu-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH2; H2-Phe-D-Pen-Tyr-D-Trp-Lys-Val-Pen-beta-Nal-NH2; H2-Phe-D-Pen-Pal-D-Trp-Lys-Thr-Pen-Thr-NH2; H2-Dip-D-Cys-Pal-D-Trp-Lys-Val-Cys-Dip-NH2; H2-F5-Phe-D-Cys-His-D-Trp-Lys-Val-Cys-F5-Phe-NH2; H2-Dip-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-m-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-m-F-Phe-NH2 H2-o-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-o-F-Phe-NH2; H2-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-p-F-Phe-NH2; H2-F5-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-F5-Phe-NH2; H2-F5-Phe-D-Cys-2-Pal-D-Trp-Lys-Val-Cys-F5-Phe-NH2; H2-beta-Nal-D-Cys-His-D-Trp-Lys-Val-Cys-D-Dip-NH2; H2-Dip-D-Cys-His-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-Dip-D-Cys-His-D-Trp-Lys-Val-Cys-Dip-NH2; H2-beta-Nal-D-Cys-His-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-Trp-D-Cys-Tyr-D-Trp-Lys-Val-Cys-D-beta-Nal-NH2; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-D-beta-Nal-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-D-p-F-Phe-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Tle-Cys-beta-Nal-NH2; H2-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Nle-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Ile-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Gly-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Ala-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Leu-Cys-beta-Nal-NH2; H2-Bip-D-Cys-Tyr-D-Trp-Lys-Ile-Cys-Bip-NH2; H2-p-F-Phe-D-Cys-His-D-Trp Lys-Val-Cys-p-F-Phe-NH2; H2-Npa-D-Cys-Pal-D-Trp-Lys-Val-Cys-Tyr-NH2; H2-m-F-Phe-D-Cys-His-D-Trp-Lys-Val-Cys-m-F-Phe-NH2; H2-o-F-Phe-D-Cys-His-D-Trp-Lys-Val-Cys-o-F-Phe-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-Dip-NH2; H2-Cpa-D-Cys-Pal-D-Trp-Lys-Val-Cys-Cpa-NH2; H2-Igl-D-Cys-Pal-D-Trp-Lys-

Val-Cys-Igl-NH2; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-D-Dip-NH2; H2-beta-Nal-D-Cys-3-I-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-p-CN-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-p-CN-Phe-NH2; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-D-Dip-NH2; H2-beta-Nal-D-Cys-Bta-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-beta-Nal-NH2; H2-Bpa-D-Cys-Pal-D-Trp-Lys-Val-Cys-Bpa-NH2; H2-Iph-D-Cys-Pal-D-Trp-Lys-Val-Cys-Iph-NH2; H2-Trp-D-Cys-Pal-D-Trp-Lys-Tle-Cys-beta-Nal-NH2; H2-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-beta-Nal-NH2; H2-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-p-Cl-Phe-NH2; H2-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Cha-Cys-p-Cl-Phe-NH2; H2-p-Cl-Phe-D-Cys-Tr(I)-D-Trp-Lys-Val-Cys-p-Cl-Phe-NH2; H2-p-Cl-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-p-Cl-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Tle-Cys-beta-Nal-NH2; H2-p-F-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-p-F-Phe-D-Cys-Tyr(I)-D-Trp-Lys-Tle-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-beta-Nal-NH2; (H)(CH3CO)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-beta-Nal-NH2; H2-p-N02-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-beta-Nal-NH2; (H)(CH3CO)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-beta-Nal-NH2; H2-p-N02-Phe-D-Cys-Tyr(Bzl)-D-Trp-Lys-Thr(Bzl)-Cys-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO2-Phe-D-Cys-Tyr(Bzl)-D-Trp-Lys-Thr(Bzl)-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Tyr-NH2; H2-p-NO2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-P-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-beta-Nal-D-Cys-Tyr(Bzl)-D-Trp-Lys-Thr(Bzl)-Cys-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Tyr(Bzl)-D-Trp-Lys-Thr(Bzl)-Cys-Tyr(Bzl)-NH2; H2-D-Phe-D-Pen-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; H2-D-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; H2-D-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-D-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; H2-D-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH2; H2-D-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH2; H2-D-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH2; H2-D-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-D-beta-Nal-NH2; H2-D-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-D-p-F-Phe-NH2; H2-D-Bip-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; H2-D-Dip-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-

NH2; H2-D-p-F-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-beta-Nal-NH2; H2-D-p-Cl-Phe-D-Cys-Pal-D-Trp-Lys-Tle-Cys-p-Cl-Phe-NH2; p-N02-D-Phe-D-Cys-Pal-D-Trp-Lys-Thr(Bzl)-Cys-Tyr(Bzl)-NH2; p-N02-D-Phe-D-Cys-Tyr(Bzl)-D-Trp-Lys-Val-Cys-Tyr(Bzl)-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO2-P-Phe-D-Cys-Pal-D-Trp-Lys-Thr(Bzl)-Cys-Tyr(Bzl)-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-p-NO2-P-Phe-D-Cys-Tyr(Bzl)-D-Trp-Lys-Val-Cys-Tyr(Bzl)-NH2; (H) (5-phenylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(3-phenylpropionyl)-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(3-phenylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(3-phenylpropionyl)-D-Cys-Pal-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(3-phenylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(3-phenylpropionyl)-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(3-phenylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(3-phenylpropionyl)-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(3-[2-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(3-[2-naphthyl]propionyl)-D-Cys-Pal-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(3-[2-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(3-[2-naphthyl]propionyl)-D-Cys-Pal-D-Trp-Lys-Thr-Cys-beta-Nal-NH2; (H)(3-[2-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(3-[2-naphthyl]propionyl)-D-Cys-Pal-D-Trp-Lys-Val-Cys-Thr-NH2; (H)(3-[2-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(3-[2-naphthyl]propionyl)-D-Cys-Pal-D-Trp-Lys-Thr-Cys-Thr-NH2; (H)(3-[p-hydroxyphenyl])-D-Cys-Tyr-D-Trp-Lys-Val-Cys-beta-Nal-NH2; (H)(3-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-beta-Nal-NH2; (H)(3-naphthyl]propionyl)-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH2; (H)(3-phenylylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-beta-Nal-NH2; or (H)(3-phenylylpropionyl)-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH2; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(CH3CO)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesuifonyi)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(CH3CO)-beta-

Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(CH3CO)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(CH3CO)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; H2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(CH3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl) Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; H2-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; H(CH3CO)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl) Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; H2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(CH3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R, 3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide;

(H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; H2-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(CH3CO)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; H2-beta-Nal-D-ys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; (H)(CH3CO)-beta-Nal-D-Cys-Tyr-P-Trp-Lys-Vai-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-D-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; (H)(CH,CO)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; (H)(CH,CO)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; H2-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; (H)(CH3CO)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; H2-Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; (H)(CH3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-P-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; H2-Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; (H)(CH3CO)Phe-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-

piperazinylacetyl)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1l-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Val-Cys-2R-(2-naphthyl)ethylamide; H2-Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; (H)(CH3CO)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-P-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; H2-Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; (H)(CH3CO)Phe-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)Phe-P-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)Phe-D-Cys-Pal-D-Trp-Lys-Thr-Cys-2R-(2-naphthyl)ethylamide; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-2R-(2-naphthyl)ethylamide; H2-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-2R-(2-naphthyl)ethylamide; H2-beta-Nal-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; or H2-Phe-D-Cys-Tyr-D-Trp-Lys-Abu-Cys-2R,3R-(2-hydroxymethyl)-3-hydroxy)propylamide; H2-Phe-D-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH2; H2-Phe-D-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; H2-Phe-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; H2-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; (H)(CH3CO)-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl) -beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; H2-beta-Nal-D-Cpa-Pal-D-Trp-Lys-Val-Phe-Thr-NH2; (H)(CH3CO)-beta-Nal-D-Cpa-Pal-D-Trp-Lys-Val-Phe-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cpa-Pal-D-Trp-Lys-Val-Phe-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cpa-Pal-D-Trp-Lys-Val-Phe-Thr-NH2; H2-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH2; (H)(CH3CO)-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH2; H2-beta-Nal-D-Cpa-Pal-D-Trp-Lys-Thr-Phe-Thr-NH2; (H)(CH3CO)-beta-Nal-D-Cpa-Pal-D-Trp-Lys-Thr-Phe-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cpa-Pal-D-Trp-Lys-Thr-Phe-Thr-NH2; (H)(4-(2-hydroxyethyl)-1-

piperizineethanesulfonyl) -beta-Nal-D-Cpa-Pal-D-Trp-Lys-Thr-Phe-Thr-NH2; H2-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-beta-Nal-NH2; (H)(CH3CO)-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperazinylacetyl)-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-beta-Nal-NH2; (H)(4-(2-hydroxyethyl)-1-piperizineethanesulfonyl)-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-beta-Nal-NH2; H2-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-beta-Nal-NH2-; or H2-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; H2-D-beta-Nal-D-Cpa-Phe-D-Trp-Lys-Val-Phe-Thr-NH2; H2-D-beta-Nal-D-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH2; H2-D-Phe-D-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; H2-D-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH2; or H2-D-beta-Nal-D-Cpa-Tyr-D-Trp-Lys-Val-Phe-beta-Nal-NH2.

GHRH peptide analogues date back to the 1990s, and include the 'standard antogonist' [Ac-Tyr', D-Arg2jhGH-RH (1-29) Nha. US Patent 4, 659,693 (hereby incorporated in its entirety by reference thereto) discloses GH-RH antagonistic analogs which contain certain N, N'- dialkyl-omega-guanidino alpha-amino acyl residues in position 2 of the GH-RH (1-29) sequence. The following publications are of note, all of which are hereby incorporated by reference thereto. WO91/16923 describes hGH-RH modifications including: replacing Tyr1, Ala2, Asp3 or Asn8 with their D-isomers; replacing Asn8 with L-or D-Ser, D-Arg, Asn, Thr, Gln or D-Lys; replacing Ser9 with Ala to enhance amphiphilicity of the region; and replacing Goy'S with Ala or Aib. US5,084,555 describes an analogue [Se-psi [CH2-NH]-Tyrl°lhGH-RH (1- 29) that includes a pseudopeptide bond (ie. a peptide bond reduced to a [CH2-NH] linkage) between the R9 and R10 residues. US 5,550,212, US5,942,489, and US6,057,422 disclose analogs of hGH-RH (1-29) NH2 produced by replacement of various amino acids and acylation with aromatic or nonpotar acids at the N-terminus of GH-RH (1-29) NH2. The tumor inhibitory properties of antagonists featured in US Patent 5, 942,489 and US Patent 6,057, 422 have been demonstrated by using nude mice bearing xenografts of experimental human cancer models. Specific examples include: [PhAc-Tyr', D-Arg2, Phe (pCl) 6, Amp9, Tyr (Me010, Abu15, Nle27, D-Arg28, Har29]hGH-RH (1-29) NH2; [PhAc-Tyr', D-Arg2, Phe (pCl)6, Amp9, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [PhAc-Tyr', D-Arg2, Phe (pCl) 6, His9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [CH3 (CH2)

6CO-Tyr1, D-Arg2, Phe (pCl)6, Amp9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1- 29) NH2; [HOOC (CH2) 8CO-Tyr1, D-Arg2, Phe (pCl) 6, Amp9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29]hGH-RH (1-29) NH2; [HOOC (CH2) 2CO-Tyr1, D-Arg2, Phe (pCi) 6, Amp9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29]hGH-RH (1-29) NH2; [PhAc-Tyr', D-Arg2, Phe (pCl)6, Amp9, Tyr (Me)10, His11, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1- 29) NH2; [PhAc-Tyr', D-Arg2, Phe (pCl) 6, Cit8, Amp9, Tyr (Me)10, His", Abu'5, Nle27, D-Arg28, Har29] hGH-RH (1- 29) NH2; [1-nac-Tyr1, D-Arg2, Phe (pCl) 6, Cit8, Amp9, Tyr (Me)10, His11, Abu15, Nle27, D-Arg28, Har29]hGH- RH (1-29) NH2; [CH3 (CH2) 6CO-Tyr', D-Arg2, Phe (pCl) 6, Cit8, Amp9, Tyr (Me)10, His", Abu15, Nle27, D-Arg28 Har'] hGH-RH (1-29) NH2; [HOOC (CH2) 12CO-Tyr', D-Arg2, Phe (pCl) 6, Cit8, Amp9, Tyr (Me)10, His", Abu'5, Nle27, D-Arg28, Har29] hGH-RH (1-29)NH2; [CH3 (CH2) 6CO -Tyr1, D-Arg2, Phe (pCl)6, Cit8, Amp9, Tyr (Et)'°, His", Abu'5, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [CH3 (CH2) 6CO-Tyr', D-Arg2, Phe (pCl) 6, Cit8, His9, Tyr (Et010, His11, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [CH3 (CH2) 6CO -Tyr1, D-Arg2, Phe (pCl) 6, Alpe, His9, Tyr (Et)10, His11, Abu15, Nle27, D-Arg28, i Har29] hGH-RH (1-29) NH2; [HOOC (CH2) 8CO -Tyr1, D-Arg2, Phe(pCl)6, Ala8, His9, Tyr(Et)10, His11, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [HOOC(CH2)12CO -Tyr1, D-Arg2, Phe(pCl)6, Ala8, His9, Tyr(Et)10, His11, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [CH3 (CH2) 6CO-Tyr', D-Arg2, Phe (pCl)6, Ala8, His9, Tyr (Et)10, His11, Abu15, His20, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [CH3 (CH2) 6CO-Tyr1, D-Arg2, Phe (pCl)6, Ala8, Amp9, Tyr (Et)10, His11, Abu15, His20, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [HOOC (CH2)1 2CO-Tyr1, D-Arg2, Phe (pCl) 6, Ala8, His9, Tyr (Et)10, His11, Abu15, His20, Nle27, D-Arg28, Har2lhGH-RH' (1-29) NH2; [HOOC(CH2)12CO-Tyr1, D-Arg2, Phe(pCl)6, Ala8, Amp9, Tyr(Et)10, His11, Abu15, His20, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [1-Nac-Tyr1, D-Arg2, Phe (pCl) 6, Ala8, His9, Tyr (Et)10, His11, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29) NH2; [CH3 (CH2) 6CO -Tyr1, D-Arg2, Phe (pCl) 6, His9, Tyr (Et)'°, His", Abu'5, Nle27, D-Arg28, Har29]hGH- RH (1-29) NH2; [CH3 (CH2) 6CO-Tyr', D-Arg2, Phe (pCl)6, Ala8, His9, Cit15, Nle27, D-Arg28, har29]hGH-RH (1-29) NH2; [CH3 (CH2) 6CO-Tyr1, D-Arg2, Phe(pCl)6, Ala8, His9, tyr(Et)10, His11, His15, His20, Nle27, D-Arg28 Har29]hGH-RH (1-29) NH2; [CH3 (CH2) 6CO-Tyr', D-

Arg2, Phe (pCl) 6, Ala8, His9, Tyr (Et)10, His11, Orn12, Abu15, Orn21, Nle27, D- Arg28, Har29] hGH-RH (1-29) NH2; [CH3 (CH2) 6CO-Tyr', D-Arg2, Phe (pCl) 6, Alas, His9, Tyr (Et)10, His11, Orn12, Abu15, His20, Orn21, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [CH3 (CH2) 6CO -Tyr1, D-Arg2, Phe (pCl)6, Ala8, His9, Tyr (Et)", His", Abu", Nie 2', D-Arg2, Har29]hGH-RH (1-29) NHEt; [CH3 (CH2) 8CO -Tyr1, D-Arg2, Phe (pCl) 6, Ala8, His9, Tyr (Et)10, His11, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NHEt; [CH3 (CH2) 10CO -Tyr1, D-Arg2 Phe (pCl) 6 Ala8, His9, Tyr(Et)10, His11, Abu15, Nle27, D-Arg28 Har29] hGH-RH (1-29) NHEt; [Hca -Tyr1, D-Arg2, Phe(pCl)6, Ala8, His9, Tyr(Et)10, His11, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1- 29) NHEt; [CH3 (CH2) 6CO-Tyr', D-Arg2, Phe (pCl) 6, Ala8, His9, Tyr (Et)10, His11, Abu15, nie27, D-Arg28, Har29] hGH-RH (1-29)NHMe; [HOOC (CH2) 12CO-Tyr', D-Arg2, Phe (pCl) 6, Alas, His9, Tyr (Et)10, His11, Orn12, Abu15, His20, Orn21, Nle27 D-Arg28, Har29] hGH-RH (1-29) NH2; [CH3 (CH2) 6CO-Tyr', D-Arg2, Phe Cl)6, Ala8, Amp9, Tyr(Et)10, His11, Orn12, Abu15, His20, Orn21 Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [CH3(CH2)6CO -Tyr1, D-Arg2, Phe (pCl) 6, Ala8, His9, Dip10, His11, Orn12, Abu15, His20, Orn21, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [CH3 (CH2) 6CO-Tyr', D-Arg2, Phe (pCl) 6, Ala8, His9, Phe (pNO2)10, His11, Orn12, Abu15, His20, Orn21, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [CH3(CH2)6CO -Tyr1, D-Arg2, Phe(pCl)6, Ala8, His9, Tyr(Et)10, His11, Orn12, Abu15, His20, Orn21, Nle27, D-Arg28, Har29] hGH-RH (1-29) NHEt; [HOOC 9CH2)12CO -Tyr1, D-Arg2, Phe (pCl) 6, Alas, Amp9, Tyr (Et)10, His", Orn, Abu15, His20, Orn21, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [HOOC (CH2) 2CO -Tyr1, D-Arg2 Phe (pCl) 6, Ala8, His9, Dip°, His", Orn12, Abu'5, His, Orn21, Nie D-Arg28, Har29]hGH-RH (1-29) NH2; [HOOC(CH2)12CO -Tyr1, D-Arg2, Phe (pCl) 6, Ala8, His9, Phe (pNO2)10, His11, Orn12, Abu15, His20, Orn21, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [HOOC (CH2) 12CO-Tyr', D-Arg2, Phe (pCl) 6, Alas, His9, Tyr (Et)10, His11, Orn12, Abu15, His20, Orn21, Nle27, D-Arg28, Har29] hGH-RH (1-29) NHEt; [CH3(CH2)6CO -Tyr1, D-Arg2, Phe (pCl) 6, Ala8, Amp9, Dip10, His11, Orn12, Abu15, His20, Orn21, Nle27, d-Arg28, Har29]hGH-RH (1-29) NH2; [CH3(CH2)6CO -Tyr1, D-Arg2, Phe(pCl)6, Ala8, Amp9, Phe(pNO2)10, His11, Orn12, Abu15, His20, Orn21, Nle27, D-Arg28, har29]hGH-RH(1-29)NH2; [CH3 (CH2) 6CO -Tyr1, D-Arg2, Phe(pCl)6, Ala8, Amp9, Tyr(Et)10, His11, Orn12, Abu15, His20, Orn21, Nle27, D-Arg28,

Har29]hGH-RH(1-29) NHEt; [CH3 (CH2) 6CO -Tyr1, D-Arg2, Phe (pCl) 6, Ala8, His9, Dip10, His11, Orn12, Abu15, His20, Orn21, Nle27, D- Arg28, Har29]hGH-RH (1-29) NHEt; [CH3 (CH2) 6CO -Tyr1, D-Arg2, Phe (pCl) 6, Aia8, His9, Phe (pN02)'°, His", Orn'2, Abu'5, His20, Orn21, Nle27, D-Arg28, Har29] hGH-RH (1-29) NHEt; [HOOC (CH2) 12CO-Tyr', D-Arg2, Phe (pCl)6, Ala8, Amp9, Dip10, His", Orn12, Abu15, His20, Orn21, Nie27 D-Arg Har29] hGH-RH (1-29) NH2; [HOOC(CH2)12CO -Tyr1, D-Arg2, Phe (pCl) 6, Ala8, Amp9, Phe (pN02) 10, His11, Orn12, Abu15, His20, Orn21, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [CH3 (CH2) 6CO-Tyr1, D-Arg2, Phe (pCi) 6, Ala', Amp9 Dip'°, His", Orn12, Abu15, His20, Orn21, Nle27, D-Arg28, Har29]hGH-RH (1-29) NHEt; [CH3 (CH2) 6CO-Tyr', D-Arg2, Phe (pCl) 6, Ala8, Amp9, Phe (pNO2)10, His11, orn12, Abu15, His20, Orn21, Nle27, D-Arg28, Har29] hGH-RH (1-29) NHEt; [HOOC (CH2) 12CO -Tyr1, D-Arg2, Phe (pCl) 6, Ala8, Amp9, Dip10, His11, Orn12, Abu15, his20, Orn21, Nle27, D-Arg28, Har29] hGH-RH (1-29) NHEt; [HOOC (CH2)1 2CO -Tyr1, D-Arg2, Phe (pCl) 6, Alas, Amp9, Phe (pNO2)10, His", Orn12, Abu15, His20 Orn21, Nle27, D-Arg28, Har29] hGH-RH (1-29) NHEt; [CH3 (CH2) 4CO-Tyr1, D-Arg2, Phe (pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [HOOC (CH2) 4CO-Tyr', D-Arg2, Phe (pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [CH3 (CH2) 6CO-Tyr1, D-Arg2, Phe (pCl) 6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH (1-29) NH2; [HOOC(CH2)6CO-Tyr1, D-Arg2, Phe(pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [CH3(CH2)8CO-Tyr1, D-Arg2, Phe (pCl) 6, Arg9, Abu'5, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [HOOC(CH2)8CO-Tyr1, D-Arg2, Phe(pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [CH3 (CH2)1 0CO-Tyr1, D-Arg2 Phe Cl)6, Arg9, Abu15, Nle27, D-Arg26, Har29]hGH-RH(1-29)NH2; [HOOC (CH2) 0CO-Tyr1, D-Arg2, Phe (pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [CH3 (CH2) 12CO-Tyr', D-Arg2, Phe (pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH (1-29) NH2; [HOOC (CH2) l2CO-Tyr\ D-Arg2, Phe (pCl)6, Arg9, Abu15, Nie27, D-Arg28, Har29]hGH-RH (1-29) NH2; [CH3 (CH2) 4CO-Tyr1 D-Arg2, Phe (pCl) 6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH (1-29) NH2; [HOOC (CH2) 4CO-Tyr1, D-Arg2, Phe (pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH (1-29) NH2; [CH3 (CH2) CO-Tyr1, D-Arg2, Phe(pCl)6, Arg9, Abu15, Nle27, Har28, D-Arg29]hGH-RH(1-29)NH2; [PhAc-Tyr', D-Arg2, Phe (pCl) 6, Arg9,

Abu'5, Nle27, Har28, D-Arg29] hGH-RH (1-29) NH2; [CH3 (CH2) 4CO-Phe0, D-Arg2, Phe (pCl) 6, Arg9, Abu15, Nle27, D-Arg28, har29] hGH-RH (1-29) NH2; [CH3 (CH2) 14CO-D-Phe0, D-Arg2, Phe (pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH (1-29) NH2; [PhAc-Arg°, D-Arg2, Phe (pCi) 6, Arg9, Abu'5, NLe27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc-D-Arg°, D-Arg2, Phe (pCl) 6, Arg9, Abu'5, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc-Tyrl, D-Arg2, Phe (pCl) 6, Cite, Arg9 Abut5 Nie27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc-Tyr', D-Arg2, Phe (pCl) 6, Cite, Cit9, Abu15, Nle27, D-Arg28, har29]hGH-RH(1-29)NH2; [PhAc-Tyr', D-Arg2, Phe (pCl) 6, Cit8, Arg9, Abu'5, Nle27, Har28, D-Arg29]hGH-RH (1-29) NH2; [PhAc-Tyr1, D-Arg2, Phe (pCl)6, Cit8, Cit9, Abu15, Nle27, Har28, D-Arg29]hGH-RH (1-29) NH2; [HOOC (CH2) i2CO-Tyr\ D-Arg2, Phe (pCl)6, Cit8, Cit9, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1- 29) NH2; [PhAc-Tyr1, D-Arg2, Phe (pCl) 6, D-Ala8, Arg9, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc-Tyr1, D-Arg2, Phe (pCl) r3, Abu3, Arg9, Abu'5, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc-Tyr', D-Arg2, Phe (pCl)6, Cit9, Abu15, Nle27, Har28, D-Arg29]hGH-RH (1-29) NH2; [PhAc-Tyr', D-Arg2, Phe (pCl) 6, Arg9, Amp'°, Abu'5, Nle27, D-Arg28, Har29]hGH-RH (1-29) NH2; [PhAc-Tyr1, D-Arg2, Phe (pCl) 6, Har9, Amp10 Abu5, Nle27, D-Arg28, Har29 hGH-RH (1-29) NH2; PhAc-Tyr1, D-Arg2, Phe (pCl) 6 Arg9, His'o, Abu'5, Nle 27, D-Arg28, Ha) hGH-RH (1-29) NH2; [PhAc-Tyr', D-Arg2, Phe (pCl) 6, Arg9, Cha10, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [PhAc-Tyr', D-Arg2, Phe (pCl)6, Har9, Tpi10, Abu15, Nle27, D-Arg28, har29]hGH-RH (1-29) NH2; PhAc-Tyr1, D-Arg2, Phe(pCl)6, Har9, 2-Nal10, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [PhAc-Tyr1, D-Arg2, Phe (pCl) 6, Har9, Dip10, Abu15, Nle27, D-Arg28, Har29]hGH-RH (1-29) NH2; [PhAc-Tyr1, D-Arg2, Phe(pCl)6, Har9, Phe (pNH2)10, Abu15, Nle27, D-Arg28, Har29]hGH-RH (1-29) NH2; [PhAc-Tyr1, D-Arg2 Phe (pCl) zu Har9, Trpt°, Abu15 Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [PhAc-Tyr1, D-Arg2, Phe(pCl)6, Har9, Phe(pNO2)10, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [PhAc-Tyr1, D-Arg2, Phe (pCl)6, Har9, 3-Pal10, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc-Tyrl, D-Arg2, Phe (pCl) 6, Har9, Tyr (Et)'°, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc-His', D-Arg2, Tyr6, Har9, Bpa10, Abu'5, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc-Tyr', D-Arg2, Phe (pCl) 6, Arg9, Har12, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [Hca-Tyr', D-

Arg2, Phe (pCl) 6, Har9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29]hGH-RH (1-29) NHEt; [PhAc-Tyr'D-Arg2, Phe (pCl) 6 Har9, Tyr(Me)10, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NHEt; [Hca-Tyr1, D-Arg2, Phe (pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29[hGH-RH(1-29) NHEt; PhAc-Tyr1, D-Arg2 Phe Cl)6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29 NHEt; [PhAc-Tyr1, D-Arg2, Phe (pCl) 6, Har9, Tyr (Me)10, Aib15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NHEt; [PhAc-Tyr', D-Arg2, Phe (pCl) 6, Har9, Tyr (Me)10, Orn12, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1- 29) NHEt; [Hca-Tyr1, D-Arg2, Phe (pCl) 6, Har9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Agm29]hGH-RH (1-29); [PhAc-Tyr1, D-Arg2, Phe (pCl) 6, Har9, Tyr (Me)'°, Abu15, Nle27, D-Arg28, Agm29]hGH-RH(1-29); [Hca-Tyr1, D-Arg2, Phe (pCl) 6, Har9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29, Har30]hGH-RH(1- 30) NH2; [Dat-Tyr1, D-Arg2, Phe (pCl)6, Har9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29, Har30]hGH-RH (1-30) NH2; [Ipa-Tyr1, D-Arg2, Phe (pCl) 6, Har9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29, Har30]hGH-RH(1-30)NH2; [Hca-Tyr', D-Arg2, Phe (pCl) 6, Har9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29, Har30] hGH-RH (1-30) NHEt; [Hca-Tyr', D-Arg2, Phe (pCl) 6, Har9, Tyr (Me10), Abu15, Nle27, D-Arg28, D-Arg29, Har30]hGH-RH(1- 30) NH2; [Hca-Tyr', D-Arg2, Phe (pCl) 6, Har9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29, D-Arg30]hGH-RH(1- 30) NH2; [Hca-Tyr', D-Arg2, Phe (pCl) 6, Har9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29, Agm30] hGH-RH (1-30); [PhAc-Tyr', D-Arg2, Phe (pCl) 6, Har9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29, Agm30] hGH-RH (1-30); [PhAc-Tyr', D-Arg2, Phe (pCl) 6, Har9, Tyr (Me)10, His11, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [PhAc-Tyr1, D-Arg2, Phe(pCl)6, Har9, Tyr(Me)10, Har11, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29) NH2 [PhAc-Tyr1, D-Arg2, Phe(pCl)6, Har9, Tyr (Me)10, Amp11, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc-Tyr1, D-Arg2, Phe (pCl)6, Har9, Tyr (Me)10, Cit", Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29) NH2; [PhAc-Tyr1, D-Arg2, Phe (pCl)6, Har9, Tyr (Me)'°, Abu15, His20, Nle, D-Arg28, Har29]hGH-RH(1-29) NH2; [PhAc-Tyr', D-Arg2, Phe(pCl)6, Har9, Tyr (Me)10, His", Abu15, His20, Nle27, D-Arg28, Har29]hGH- RH (1-29) NH2; [PhAc-Tyr1, D-Arg2, Phe (pCl) 6, Arg9, Cit15, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [PhAc°, D-Arg2, Phe (pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [IndAc0, D-Arg2, Phe(pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1- 29) NH2; [PhAc°, D-Arg2, Phe pCl) r, Har9, Tyr(Me)10,

Abu15, Nle27, D-Arg28, Har29]hGH- RH (1-29) NH2; [PhAc°, D-Arg2, Phe(pCl)6, Arg9, Tyr(Me)10, Abu15, Nle27, D-Arg28, Har29] hGH- RH (1-29) NH2; [PhAc°, His', D-Arg2, Phe (pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1- 29) NH2; [Nac°, His', D-Arg2, Phe (pCl) 6, Arg9, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc°, D-Arg2, Phe (pCl) 6 Arg9, Abu'5, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [IndAc°, D-Arg2, Phe (pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc°, D-Arg2, Phe (pCl) 6, Har9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc°, D-Arg2, Phe (pCl) 6, Arg9, Tyr (Me)10, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2 ; [PhAc°, His', D- Arg2, Phe (pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29]hGH-RH(1-29)NH2; [Nac°, His', D-Arg2, Phe(pCl)6, Arg9, Abu15, Nle27, D-Arg28, Har29] hGH-RH (1-29) NH2; [PhAc^{0}, D-Arg^{2}, Phe(pCl)^{6}, Ala^{15}, Nle^{27}, Asp^{28}]hGH-RH(1-28)Agm; [Ibu°,D-Arg^{2}, Phe(pCl)$^{8\ 10}$, Abu^{15}, Nle^{27}]hGH-RH(1-28)Agm; [PhAc°,D-Arg^{2}, Phe(pCl)^{6}, Abu^{15}, Nle ^{7}]hGH-RH(1-28)Agm; [PhAc°,D-Arg^{2}, Phe(pCl)^{6}, Ala^{15}, Nle^{27}]hGH-RH(1-29)-NH_2; [PhAc°, D-Arg^{2},Phe(pCl)^{6},Abu^{8},Ala^{15},Nle^{27}]hGH-RH(1-29)NH_2; [PhAc^{0}, D-Arg^{2}, Phe(pCl)^{6}, Abu^{8,28}, Ala^{15}, Nle^{27}]hGH-RH(1-29)-NH_2; cyclo^{8,12}[PhAc°,D-Arg^{2},Phe(pCl)^{6},Glu^{8},Ala^{15},Nle^{27}]hGH-RH(1-29)-NH_2; cyclo^{17,21} [PhAc°,D-Arg^{2},Phe(pCl)^{6},Ser^{8},Ala^{15},Glu^{17},Nle^{27}]hGH-RH(1-29)-NH_2; cyclo$^{8,12;21,25}$[PhAc°,D-Arg^{2},Phe(pCl)^{8},Glu^{8,25} ,Abu^{15},Nle^{27}]hGH-RH(1-28)Agm; cyclo$^{8,12;21,25}$[PhAc°,D-Arg^{2},D-Asp^{3},Phe(pCl)^{8},Glu^{8,25},D-Lys^{12},Ala^{16},Nle^{27}]hGH-RH(1-29)-NH_2; cyclo$^{8,12;21,25}$[[PhAc°,D-Arg^{2}, Phe(pCl)^{6}, Glu^{8,25}, D-Lys^{12}, Ala^{15}, Nle^{27}] hGH-RH(1-29)-NH_2. Additional GHRH analogue examples are provided in WO96/032126, WO96/022782, WO96/016707, WO94/011397, WO94/011396, each of which is herein incorporated by reference thereto.

Examples of bombesin analogues suitable for use in the present invention include TMs comprising: D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2 (code named BIM-26218), D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-Leu-NH_2 (code named BIM-26187); D-Cpa-Gln-Trp-Ala-Val-Gly-His-Leu-φ [CH_2NH]-Phe-NH_2 (code named BIM-26159), and D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-φ [CH_2NH]-Cpa-NH_2 (code named BIM-26189); D-Phe-Gln-Trp-Ala-Val-N-methyl-D-Ala-His-Leu- methylester, and D-F_8-Phe-Gln-Trp-Ala-Val-D-Ala-His-Leu- methylester.

Bombesin analogues include peptides derived from the naturally-occurring, structurally-related peptides, namely, bombesin, neuromedin B, neuromedin C, litorin, and GRP. The relevant amino acid sequences of these naturally occurring peptides are: Bombesin (last 10 amino acids): Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2; Neuromedin B: Gly-Asn-Leu-Trp-Ala-Thr-Gly-His-Phe-Met-NH_2; Neuromedin C: Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met-NH_2; Litorin: pGlu-Gln-Trp-Ala-Val-Gly-His-Phe-Met-NH_2; Human GRP (last 10 amino acids): Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met-NH_2.

Analogs suitable for use in the present invention include those described in U.S. Serial Number 502,438, filed March 30, 1990, U.S. Serial No. 397,169, filed August 21, 1989, U.S. Serial No. 376,555, filed July 7, 1989, U.S. Serial Number 394,727, filed August 16, 1989, U.S. Serial No. 317,941, filed March 2, 1989, U.S. Serial Number 282,328, filed December 9, 1988, U.S. Serial No. 257,998, filed October 14, 1988, U.S. Serial No. 248,771, filed September 23, 1988, U.S. Serial No. 207,759, filed June 16, 1988, U.S. Serial No. 204,171, filed June 8, 1988, U.S. Serial No. 173,311, filed March 25, 1988, U.S. Serial No. 100,571, filed September 24, 1987; and U.S. Serial No. 520,225, filed May 9, 1990, U.S. Serial No. 440,039, filed November 21, 1989. All these applications are hereby incorporated by reference. Bombesin analogs are also described in Zachary et al., Proc. Nat. Aca. Sci. 82:7616 (1985); Heimbrook et al., "Synthetic Peptides: Approaches to Biological Problems", UCLA Symposium on Mol. and Cell. Biol. New Series, Vol. 86, ed. Tarn and Kaiser; Heinz-Erian et al. , Am. J. Physiol. G439 (1986); Martinez et al., J. Med. Chem. 28:1874 (1985); Gargosky et al., Biochem. J. 247:427 (1987); Dubreuil et al. , Drug Design and Delivery, Vol 2:49, Harwood Academic Publishers, GB (1987); Heikkila et al., J. Biol. Chem. 262:16456 (1987); Caranikas et al. , J. Med. Chem. 25:1313 (1982); Saeed et al., Peptides 10:597 (1989); Rosell et al., Trends in Pharmacological Sciences 3:211 (1982); Lundberg et al., Proc. Nat. Aca. Sci. 80:1120, (1983); Engberg et al., Nature 293:222 (1984); Mizrahi et al., Euro. J. Pharma. 82:101 (1982); Leander et al., Nature 294:467 (1981); Woll et al., Biochem. Biophys. Res. Comm. 155:359 (1988); Rivier et al., Biochem. 17:1766 (1978); Cuttitta et al., Cancer Surveys 4:707 (1985); Aumelas et al., Int. J. Peptide Res. 30:596 (1987); all of which are also hereby incorporated by reference.

The analogs can be prepared by conventional techniques, such as those described in WO92/20363 and EP0737691.

Additional bombesin analogues suitable for use in the present invention comprise: D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-jjsi-Tac-NH2; D-Tpi-Gln-Trp-Ala-Val-Gly-His-Leu-£si-Tac-NH_2; D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-£si-DMTac-NH_2; Hca-Gln-Trp-Ala-Val-Gly-His-Leu-jβsi-Tac-NH_2; D-Trp-Gln-Trp-Ala-Val-Gly-His-Leu-psi-Leu-NH_2; D-Trp-Gln-Trp-Ala-Val-Gly-His-Leu-psi-Phe-NH_2; D-Trp-Glu(MeNH)-Trp-Ala-Val-Gly-His-Leu-psi-Phe-NH_2; D-Trp-Gln-Trp-Ala-Val-Gly-His-Leu-psi-Trp-NH_2; D-Tpi-Gln-Trp-Ala-Val-Gly- His-Leu-psi-Leu-NH_2; D-Tpi-Gln-Trp-Ala-Val-Gly- His-Leu-psi-Phe-NH_2; D-Tpi-Gln-Trp-Ala-Val-Gly- His-Leu-psi-Trp-NH_2; D-pGlu-Gln-Trp-Ala-Val- Gly-His-Leu-psi-Tpi-NH_2.; D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-psi-Tpi-NH_2; D-Trp-Gln-Trp-Ala-Val-Gly-His-Leu-psi-Tpi-NH_2; Tpi-Gln-Trp-Ala-Val-Gly-His-Leu-psi-Tpi-NH2; NH_2CO-Tpi-Gln-Trp-Ala-Val-Gly-His-Leu-psi-Tpi-NH_2 and ACY-Tpi-Gln-Trp-Ala-Val-Gly-His-Leu-psi-Tpi-NH_2 wherein ACY is acetyl, octanoyl or 3-hydroxy-2-naphthoyl; D-Tpi-Gln-Trp-Ala-Val-Gly His-Leu-psi-Tpi-NH_2; D-Trp-Glu(MeO)-Trp-Ala-Val-Gly-His-Leu-psi-Tpi-NH_2; D-Trp-Glu(MeNH)-Trp-Ala-Val-Gly-His-Leu-psi-Tpi-NH_2; D-Trp-His(Bz)-Trp-Ala-Val Gly-His-Leu-psi-Tpi-NH_2; Phe-Glu-Trp-Ala-Val-Gly His-Leu-psi-Tpi-NH_2; H_2-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH_2; H_2-D-Nal-Cys-Tyr-D-Trp-Lys-Nal-Cys-Thr-NH_2; H_2-D-Nal-Cys-Tyr-D-Trp-Lys-Nal-Cys-Nal-NH_2; H_2-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH_2; H_2-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-D-Nal-NH_2; H_2-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-D-Nal-NH_2; H_2-D-Nal-D-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH_2; H_2-D-Nal-Cys-Tyr-D-Trp-Lys-Val-D-Cys-Nal-NH_2; H_2-D-Trp-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH_2; H_2-D-Nal-Cys-Tyr-D-Trp-Lys-Phe-Cys-Nal-NH_2; H_2-D-Nal-Cys-Tyr-D-Nal-Lys-Val-Cys-Nal-NH_2; H_2-D-Phe-Cys-Tyr-D-Trp-Lys-Nal-Cys-Thr-NH_2; H_2-D-Nal-Cys-Tyr-D-Trp-Orn-Val-Cys-Nal-NH_2; H_2-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Nal-NH_2; H_2-D-Phe-Cys-Tyr-D-Trp-Lys(iPr)-Thr-Cys-Nal-NH_2; H_2-D-Phe-Cys-Tyr-D-Trp-Lys(diEt)-Thr-Cys-Nal-NH_2 H_2-D-Phe-Cys-Tyr-D-Trp-Lys-Ser-Cys-Thr-NH_2; H_2-D-Nal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Nal-NH_2; H_2-D-Nal-D-Cys-Tyr-D-Trp-Lys-Thr-Cys-Nal-NH_2; or H_2-D-Nal-Cys-Phe-D-Trp-Lys-Thr-Cys-Nal-NH_2; H_2-D-Nal-Cys-Tyr-D-Trp-Dab-Val-Cys-Nal-NH_2, H_2-D-Nal-Cys-Tyr-D-Trp-Orn-Val-Cys-Nal-NH_2, H_2-D-Nal-Cys-Tyr-D-Trp-

Arg-Val-Cys-Nal-NH_2; pGlu-Gln-Trp-Ala-Val-Gly-His-Leu-Leu-NH_2, D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-Leu-NH_2, D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2, D-Cpa-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2, D-Cpa-Gln-Trp-Ala-Val-Gly-His-Leu-Leu-NH_2, D-Phe-Gln-Trp-Ala-Val-D-Ala-His-Leu-Leu-NH_2, D-Phe-Gln-Trp-Ala-Val-D-Ala-His-Leu-Met-NH_2, D-Cpa-Gln-Trp-Ala-Val-D-Ala-His-Leu-Met-NH_2, pGlu-Gln-Trp-Ala-Val-Gly-His-Phe-Leu-NH_2, D-Phe-Gln-Trp-Ala-Val-Gly-His-Phe-Leu-NH_2, D-Phe-Gln-Trp-Ala-Val-D-Ala-His-Phe-Met-NH_2, D-Phe-Gln-Trp-Ala-Val-D-Ala-His-Phe-Leu-NH_2, D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-Nle-NH_2, D-Phe-Gln-Trp-Ala-Val-D-Ala-His-Leu-Nle-NH_2, D-Phe-Gln-Trp-Ala-Val-Gly-His-Phe-Nle-NH_2, D-Phe-Gln-Trp-Ala-Val-D-Ala-His-Phe-Nle-NH_2, D-p-Cl-Phe-Gln-Trp-Ala-Val-Gly-His-Leuc[CH_2NH]Phe-NH_2, D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-proplyamide, Ac-His-Trp-Ala-Val-D-Ala-His-Leu-Leu-NH_2, D-Phe-Gln-Trp-Ala-Val-Gly-His-CHx-Ala-Leu-NH_2, cyclo-D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-Leu, D-Cys-Asn-Trp-Ala-Val-Gly-His-Leu-Cys-NH_2, cyclo-His-Trp-Ala-Val-Gly-His-Leu-Met, Cys-Trp-Ala-Val-Gly-His-Leu-Cys-NH_2, cyclo-D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-Met, cyclo-D-Phe-His-Trp-Ala-Val-Gly-His-Leu-Met, cyclo-Trp-Ala-Val-Gly-His-Leu-Met.

Additional bombesin analogues are described in, for example, WO89/02897, WO91/17181, WO90/03980 and WO91/02746, all of which are herein incorporated by reference thereto.

Examples of ghrelin analogues suitable for use as a TM of the present invention comprise: Tyr-DTrp-DLys-Trp-DPhe-NH_2, Tyr-DTrp-Lys-Trp-DPhe-NH_2, His-DTrp-DLys-Trp-DPhe-NH_2, His-DTrp-DLys-Phe-DTrp-NH_2, His-DTrp-DArg-Trp-DPhe-NH_2, His-DTrp-DLys-Trp-DPhe-Lys-NH_2, DesaminoTyr-DTrp-Ala-Trp-DPhe-NH_2, DesaminoTyr-DTrp-DLys-Trp-DPhe-NH_2, DeaminoTyr-DTrp-Ser-Trp-DPhe-Lys-NH_2, DesaminoTyr-DTrp-Ser-Trp-DPhe-NH_2, His-DTrp-DTrp-Phe-Met-NH_2, Tyr-DTrp-DTrp-Phe-Phe-NH_2, Glyψ[CH_2NH]-DβNal-Ala-Trp-DPhe-Lys-NH_2, Glyψ[CH2NH]-DbetaNal-DLyS-TrP-DPhe-Lys-NH_2, DAla-DbetaNal-DLys-DTrp-Phe-Lys-NH_2, His-DbetaNal-DLys-Trp-DPhe-Lys-NH_2, Ala-His-DTrp-DLys-Trp-DPhe-Lys-NH_2, Alaφ[CH_2NH]-DbetaNal-Ala-Trp-DPhe-Lys-NH_2, DbetaNal-Ala-Trp-DPhe-Ala-NH_2, DAla-DcyclohexylAla-Ala-Phe-DPhe-Nle-NH_2, DcyclohexylAla-Ala-Phe-DTrp-Lys-NH_2, DAla-DbetaAla-Thr-DThr-Lys-NH_2, DcyclohexylAla-Ala-Trp-

DPhe-NH2, DAla-DbetaNal-Ala-Ala-DAla-Lys-NH_2, DbetaNal-Ala-Trp-DPhe-Leu-NH_2, His-DTrp-Phe-Trp-DPhe-Lys-NH_2, DAla-DbetaNal-DAla-DTrp-Phe-Lys-NH_2, pAla-Trp-DAla-DTrp-Phe-NH_2, His-Trp-DAla-DTrp-Phe-LysNH_2, DLys-DβNal-Ala-Trp-DPhe-Lys-NH_2, DAla-DbetaNal-DLys-DTrp-Phe-Lys-NH_2, Tyr-DAla-Phe-Aib-NH_2, Tyr-DAla-Sar-NMePhe-NH_2, αγAbu-DTrp-DTrp-Ser-NH_2, αγAbu-DTrp-DTrp-Lys-NH_2, αγAbu-DTrp-DTrp-Orn-NH_2, αAbu-DTrp-DTrp-Orn-NH_2, DThr-DαNal-DTrp-DPro-Arg-NH_2, DAla-Ala-DAla-DTrp-Phe-Lys-NH_2, Alaψ[CH_2NH]His-DTrp-Ala-Trp-DPhe-Lys-NH_2, Lys-DHis-DTrp-Phe-NH_2, γAbu-DTrp-DTrp-Orn-NH_2, inip-Trp-Trp-Phe-NH_2, Ac-DTrp-Phe-DTrp-Leu-NH_2, Ac-DTrp-Phe-DTrp-Lys-NH_2, Ac-DTrp-DTrp-Lys-NH_2, DLys-Tyr-DTrp-DTrp-Phe-Lys-NH_2, Ac-DbetaNal-Leu-Pro-NH_2, pAla-Trp-DTrp-DTrp-Orn-NH_2, DVal-DαNal-DTrp-Phe-Arg-NH_2, DLeu-DαNal-DTrp-Phe-Arg-NH_2, CyclohexylAla-DαNal-DTrp- Phe-Arg-NH_2, DTp-DαNal-DTrp-Phe-Arg-NH_2, DAla-DβNal-DPro-Phe-Arg-NH_2, Ac-DαNal-DTrp-Phe-Arg-NH_2, DαNal-DTrp-Phe-Arg-NH_2, His-DTrp-DTrp-Lys-NH_2, Ac-DpNal-DTrp-NH_2, αAib-DTrp-DcyclohexylAla-NH_2, αAib-DTrp-DAla-cyclohexylAla-NH_2, DAla-DcyclohexylAla-Ala-Ala-Phe-DPhe-Nle-NH_2, DPhe-Ala-Phe-DPal-NH_2, DPhe-Ala-Phe-DPhe-Lys-NH_2, DLys-Tyr-DTrp-DTrp-Phe-NH_2, Ac-DLys-Tyr-DTrp-DTrp-Phe-NH_2, Arg-DTrp-Leu-Tyr-Trp-Pro(cyclic Arg-Pro), Ac-DβNal-PicLys-lLys-DPhe-NH2, DPal-Phe-DTrp-Phe-Met-NH_2, DPhe-Trp-DPhe-Phe-Met-NH_2, DPal-Trp-DPhe-Phe-Met-NH_2, pAla-Pal-DTrp-DTrp-Orn-NH_2, αγAbu-Trp-DTrp-DTrp-Orn-NH_2, βAla-Trp-DTrp-DTrp-Lys-NH_2, γAbu-Trp-DTrp-DTrp-Orn-NH_2, Ava-Trp-DTrp-DTrp-Orn-NH_2, DLys-Tyr-DTrp-Ala-Trp-DPhe-NH_2, His-DTrp-DArg-Trp-DPhe-NH_2, <Glu-His-Trp-DSer-DArg-NH_2, DPhe-DPhe-DTrp-Met-DLys-NH_2, 0-(2-methylallyl) benzophonone oxime, (R)-2-amino-3-(IH-indol-3-yl)-l-(4-phenylpiperidin-1-yl)propan-1-one, N-((R)-1-((R)-1-((S)-3-(IH-indol-3-yl)-1-oxo-1-(4-pheny lpiperidin-1-yl)propan-2-ylamino)-6-amino-1-oxohexan-2-yiamino)-3-hydroxy-1-oxopropan-2-yl)benzamide, (S)-N-((S)-3-(1H-indol-3-yl)-1-oxo-1-(4- phenylpiperidin-1-yl)propan-2-yl)-6-acetamido-2-((S)-2-amino-3-(benzyloxy)propanamido)hexanamide, (S)-N-((R)-3-(1H-indol-3-yl)-1-oxo-1-(4- phenylpiperidin-1-yl)propan-2-yl)-2-((S)-2-acetamido-3-(benzyloxy)propanamido)-6-aminohexanamide, (R)-N-(3-(1H-indol-3-yl)-1-(4-(2-methoxyphenyl)piperidin-1-yl)-1-oxopropan-2-yl)-4-aminobutanamide, (R)-N-(3-(1H-indol-3-yl)-1-(4-(2-methoxyphenyl)piperidin-1-yi)-1-oxopropan-2-yl)-2-amino-2-methylpropanamide, methyl 3-(p-tolylcarbamoyl)-2-naphthoate,

ethyl 3-(4-(2-methoxyphenyl)piperidine-1-carbonyl)-2-naphthoate, 3-(2-methoxyphenylcarbamoyl)-2-naphthoate, (S)-2,4-diamino-N-((R)-3-(naphthalen-2-ylmethoxy)-1-oxo-1-(4-phenylpiperidin-1-yl)propan-2-yl)butanamide, naphthalene-2,3-diylbis((4-(2-methoxyphenyl)piperazin-1-yl)methanone), (R)-2-amino-N-(3-(benzyloxy)-1-oxo-1-(4-phenylpiperazin-1-yl)propan-2-yl)-2-methylpropanamide, or (R)-2-amino-3-(benzyloxy)-1-(4-phenylpiperazin-1-yl)propan-1-one.

Examples of GnRH analogues suitable for use as a TM in the present invention include those known from, for example, EP171477, WO96/033729, WO92/022322, WO92/013883, and WO91/05563, each of which is herein incorporated by reference thereto. Specific examples comprise: (NAcDQal^1,DPtf^2,DPAl^3,cjsPzACAla^5,DPicLys^6,DAla^{10})LHRH; NAcDNal^1,DpClPhe^2,DPal^3,cjsPzACAla^5,DNicLys^6,ILys^8,DAla^{10})LHRH; (NAcDNal^1,DpClPhe^2,DPal^3,Thr^4,PicLys^5,DPicLys^6,ILys^8,DAla^{10})LHRH; (NAcDNal^1,DpClPhe^2,DPal^3,PicLys^5,DPicLys^6,Thr^7,ILys^8,DAla^{10})LHRH; (NapDThr^1, DpClPhe^2, DPal^3, PicLys^5,DPicLys^6,ILys^8,DAla^{10})LHRH; (NAcDNal^1 , DpClPhe^2,DPal^3,NicLys^5,DNicLys^6,Thr^7,ILys^8,DAla^{10})LHRH; (NAcDNal^1 , DpClPhe^2,DPal^3,Thr^{4}NicLys^5,DNicLys^6,Thr^7,ILys^8,DAla^{10})LHRH; (NAcDNal^1,DpClPhe^2,DPal^3,PicLys^5,D(PicSar)Lys^6,ILys^8,DAla^{10})LHRH' (NAcDNal^1,DpClPhe^2,DPal^3,D(PicSar)Lys^6,ILys^8,DAla^{10})LHRH; (NAcDNal^1,DpClPhe^2,DPal^3,PicLys^5,D(6ANic)Lys^6,ILys^8,DAla^{10})LHRH; (NAcDNal^1,DpClPhe^2,DPal^3,PicLys^5,D(6ANic)0rn^6,ILys^8,DAla^{10})LHRH; (NAcDQal^1,DCpa^2,DPal^3,cisPzACAla^5,DPicLys^6,NLeu^7,ILys^8,DAla^{10})LHRH; (NAcDNal^1,DCpa^2,DPal^3,DPicLys^5,DAPhe(PicSar)$^\beta$,ILys^8,DAla^{10})LHRH; NAcDQal^1,DCpa^2,DPal^3,PicLys^5,DPal^6,ILys^8,DAla^{10})LHRH; (NAcDNal^1,DCpa^2,DPal^3,PicLys^5,DOrn(ACyp)^6,ILys^8,DAla^{10})LHRH; N-acetyl-D-beta-Nal-D-Phe-D-Phe-Ser-Tyr-D-Lys(cyclo-pentyl)-Phe-Arg-Pro-D-Ala-NH_2; N-acetyl-D-ø-Nal-D-Phe-D-Phe-Ser-Tyr-D-Lys(cyclopentyl)-Phe-Lys(cyclopentyl)-Pro-D-Ala-NH_2; N-acetyl-D-beta-Nal-D-Phe-D-Phe-Ser-Tyr-D-Arg-Phe-(isopropyl)D-Lys-Pro-D-Ala-NH_2; N-acety1-D-beta-Nal-D-Phe-D-Phe-Ser-Tyr-D-Lys(benzyl)-Phe-Arg-Pro-D-Ala-NH_2; N-acetyl-D-beta-Nal-D-Phe-D-Phe-Ser-Tyr-D-Lys(Cl-benzyl)-Phe-Arg-Pro-D-Ala-NH_2; N-acetyl-D-beta-Nal-D-Phe-D-Phe-Ser-Tyr-D-Lys(heptyl)-Phe-Arg-Pro-D-Ala-NH_2; N-acetyl-D-beta-Nal-D-Phe-D-Phe-Ser-Tyr-D-Arg-Phe-Lys-(t-butylmethyl)-Pro-

D-Ala-NH_2; N-acetyl-D-beta-Nal-D-Phe-D-Phe-Ser-Tyr-D-Arg-Phe-Lys-(4-methyl-benzyl)-Pro-D-Ala-NH_2; N-acetyl-D-beta-Nal-D-Phe-D-Phe-Ser-Tyr-D-Arg-Phe-Lys-(benzyl)-Pro-D-Ala-NH_2; N-acetyl-D-beta-Nal-D-p-Cl-Phe-D-Trp-Ser-Tyr-D-p-NH_2-Phe-Phe-(isopropyl)Lys-Pro-D-Ala-NH_2; N-acetyl-D-beta-Nal-D-Phe-D-Phe-Ser-Tyr-D-Lys(heptyl)-Phe-Lys-(heptyl)-Pro-D-Ala-NH_2; N-acetyl-D-3-Nal-D-Phe-D-Phe-Ser-Tyr-D-Lys(1-butylpentyl)-Phe-Lys(1-butylpentyl)-Arg-Pro-D-Ala-NH_2.

Examples of urotensin analogues suitable for use as a TM of the present invention comprise: Cpa-c [D-Cys-Phe-Trp-Lys-Thr-Cys]-Val-NH2; and Asp-c[Cys-Phe-Trp-Lys-Tyr-Cys]-Val-OH.

The polypeptides of the present invention lack a functional H_C domain of a clostridial neurotoxin. Accordingly, said polypeptides are not able to bind rat synaptosomal membranes (via a clostridial H_C component) in binding assays as described in Shone *et al.* (1985) Eur. J. Biochem. 151, 75-82. In a preferred embodiment, the polypeptides preferably lack the last 50 C-terminal amino acids of a clostridial neurotoxin holotoxin. In another embodiment, the polypeptides preferably lack the last 100, preferably the last 150, more preferably the last 200, particularly preferably the last 250, and most preferably the last 300 C-terminal amino acid residues of a clostridial neurotoxin holotoxin. Alternatively, the Hc binding activity may be negated/ reduced by mutagenesis – by way of example, referring to BoNT/ A for convenience, modification of one or two amino acid residue mutations (W1266 to L and Y1267 to F) in the ganglioside binding pocket causes the H_C region to lose its receptor binding function. Analogous mutations may be made to non-serotype A clostridial peptide components, e.g. a construct based on botulinum B with mutations (W1262 to L and Y1263 to F) or botulinum E (W1224 to L and Y1225 to F). Other mutations to the active site achieve the same ablation of H_C receptor binding activity, e.g. Y1267S in botulinum type A toxin and the corresponding highly conserved residue in the other clostridial neurotoxins. Details of this and other mutations are described in Rummel et al (2004) (Molecular Microbiol. 51:631-634), which is hereby incorporated by reference thereto.

In another embodiment, the polypeptides of the present invention lack a functional H_C domain of a clostridial neurotoxin and also lack any functionally equivalent TM. Accordingly, said polypeptides lack the natural binding function of a clostridial neurotoxin and are not able to bind rat synaptosomal membranes (via a clostridial H_C component, or via any functionally equivalent TM) in binding assays as described in Shone *et al.* (1985) Eur. J. Biochem. 151, 75-82.

The H_C peptide of a native clostridial neurotoxin comprises approximately 400-440 amino acid residues, and consists of two functionally distinct domains of approximately 25kDa each, namely the N-terminal region (commonly referred to as the H_{CN} peptide or domain) and the C-terminal region (commonly referred to as the H_{CC} peptide or domain). This fact is confirmed by the following publications, each of which is herein incorporated in its entirety by reference thereto: Umland TC (1997) Nat. Struct. Biol. 4: 788-792; Herreros J (2000) Biochem. J. 347: 199-204; Halpern J (1993) J. Biol. Chem. 268: 15, pp. 11188-11192; Rummel A (2007) PNAS 104: 359-364; Lacey DB (1998) Nat. Struct. Biol. 5: 898-902; Knapp (1998) Am. Cryst. Assoc. Abstract Papers 25: 90; Swaminathan and Eswaramoorthy (2000) Nat. Struct. Biol. 7: 1751-1759; and Rummel A (2004) Mol. Microbiol. 51(3), 631-643. Moreover, it has been well documented that the C-terminal region (H_{CC}), which constitutes the C-terminal 160-200 amino acid residues, is responsible for binding of a clostridial neurotoxin to its natural cell receptors, namely to nerve terminals at the neuromuscular junction - this fact is also confirmed by the above publications. Thus, reference throughout this specification to a clostridial heavy-chain lacking a functional heavy chain H_C peptide (or domain) such that the heavy-chain is incapable of binding to cell surface receptors to which a native clostridial neurotoxin binds means that the clostridial heavy-chain simply lacks a functional H_{CC} peptide. In other words, the H_{CC} peptide region is either partially or wholly deleted, or otherwise modified (e.g. through conventional chemical or proteolytic treatment) to inactivate its native binding ability for nerve terminals at the neuromuscular junction.

Thus, in one embodiment, a clostridial H_N peptide of the present invention lacks part of a C-terminal peptide portion (H_{CC}) of a clostridial neurotoxin and

thus lacks the H_C binding function of native clostridial neurotoxin. By way of example, in one embodiment, the C-terminally extended clostridial H_N peptide lacks the C-terminal 40 amino acid residues, or the C-terminal 60 amino acid residues, or the C-terminal 80 amino acid residues, or the C-terminal 100 amino acid residues, or the C-terminal 120 amino acid residues, or the C-terminal 140 amino acid residues, or the C-terminal 150 amino acid residues, or the C-terminal 160 amino acid residues of a clostridial neurotoxin heavy-chain. In another embodiment, the clostridial H_N peptide of the present invention lacks the entire C-terminal peptide portion (H_{CC}) of a clostridial neurotoxin and thus lacks the H_C binding function of native clostridial neurotoxin. By way of example, in one embodiment, the clostridial H_N peptide lacks the C-terminal 165 amino acid residues, or the C-terminal 170 amino acid residues, or the C-terminal 175 amino acid residues, or the C-terminal 180 amino acid residues, or the C-terminal 185 amino acid residues, or the C-terminal 190 amino acid residues, or the C-terminal 195 amino acid residues of a clostridial neurotoxin heavy-chain. By way of further example, the clostridial H_N peptide of the present invention lacks a clostridial H_{CC} reference sequence selected from the group consisting of:

Botulinum type A neurotoxin - amino acid residues (Y1111-L1296)
Botulinum type B neurotoxin - amino acid residues (Y1098-E1291)
Botulinum type C neurotoxin - amino acid residues (Y1112-E1291)
Botulinum type D neurotoxin - amino acid residues (Y1099-E1276)
Botulinum type E neurotoxin - amino acid residues (Y1086-K1252)
Botulinum type F neurotoxin - amino acid residues (Y1106-E1274)
Botulinum type G neurotoxin - amino acid residues (Y1106-E1297)
Tetanus neurotoxin - amino acid residues (Y1128-D1315).

The above-identified reference sequences should be considered a guide as slight variations may occur according to sub-serotypes.

The protease of the present invention embraces all non-cytotoxic proteases that are capable of cleaving one or more proteins of the exocytic fusion apparatus in eukaryotic cells.

The protease of the present invention is preferably a bacterial protease (or fragment thereof). More preferably the bacterial protease is selected from the genera *Clostridium* or *Neisseria/ Streptococcus* (e.g. a clostridial L-chain, or a neisserial IgA protease preferably from *N. gonorrhoeae or S. pneumoniae*).

The present invention also embraces variant non-cytotoxic proteases (ie. variants of naturally-occurring protease molecules), so long as the variant proteases still demonstrate the requisite protease activity. By way of example, a variant may have at least 70%, preferably at least 80%, more preferably at least 90%, and most preferably at least 95 or at least 98% amino acid sequence homology with a reference protease sequence. Thus, the term variant includes non-cytotic proteases having enhanced (or decreased) endopeptidase activity – particular mention here is made to the increased K_{cat}/K_m of BoNT/A mutants Q161A, E54A, and K165L see Ahmed, S.A. (2008) Protein J. DOI 10.1007/s10930-007-9118-8, which is incorporated by reference thereto. The term fragment, when used in relation to a protease, typically means a peptide having at least 150, preferably at least 200, more preferably at least 250, and most preferably at least 300 amino acid residues of the reference protease. As with the TM 'fragment' component (discussed above), protease 'fragments' of the present invention embrace fragments of variant proteases based on a reference sequence.

The protease of the present invention preferably demonstrates a serine or metalloprotease activity (e.g. endopeptidase activity). The protease is preferably specific for a SNARE protein (e.g. SNAP-25, synaptobrevin/VAMP, or syntaxin).

Particular mention is made to the protease domains of neurotoxins, for example the protease domains of bacterial neurotoxins. Thus, the present invention embraces the use of neurotoxin domains, which occur in nature, as well as recombinantly prepared versions of said naturally-occurring neurotoxins.

Exemplary neurotoxins are produced by clostridia, and the term clostridial neurotoxin embraces neurotoxins produced by *C. tetani* (TeNT), and by *C.*

botulinum (BoNT) serotypes A-G, as well as the closely related BoNT-like neurotoxins produced by *C. baratii* and *C. butyricum*. The above-mentioned abbreviations are used throughout the present specification. For example, the nomenclature BoNT/A denotes the source of neurotoxin as BoNT (serotype A). Corresponding nomenclature applies to other BoNT serotypes.

BoNTs are the most potent toxins known, with median lethal dose (LD50) values for mice ranging from 0.5 to 5 ng/kg depending on the serotype. BoNTs are adsorbed in the gastrointestinal tract, and, after entering the general circulation, bind to the presynaptic membrane of cholinergic nerve terminals and prevent the release of their neurotransmitter acetylcholine. BoNT/B, BoNT/D, BoNT/F and BoNT/G cleave synaptobrevin/vesicle-associated membrane protein (VAMP); BoNT/C, BoNT/A and BoNT/E cleave the synaptosomal-associated protein of 25 kDa (SNAP-25); and BoNT/C cleaves syntaxin.

BoNTs share a common structure, being di-chain proteins of ~150 kDa, consisting of a heavy chain (H-chain) of ~100 kDa covalently joined by a single disulfide bond to a light chain (L-chain) of ~50 kDa. The H-chain consists of two domains, each of ~50 kDa. The C-terminal domain (H_C) is required for the high-affinity neuronal binding, whereas the N-terminal domain (H_N) is proposed to be involved in membrane translocation. The L-chain is a zinc-dependent metalloprotease responsible for the cleavage of the substrate SNARE protein.

The term L-chain fragment means a component of the L-chain of a neurotoxin, which fragment demonstrates a metalloprotease activity and is capable of proteolytically cleaving a vesicle and/or plasma membrane associated protein involved in cellular exocytosis.

Examples of suitable protease (reference) sequences include:

Botulinum type A neurotoxin	- amino acid residues (1-448)
Botulinum type B neurotoxin	- amino acid residues (1-440)
Botulinum type C neurotoxin	- amino acid residues (1-441)

Botulinum type D neurotoxin	- amino acid residues (1-445)
Botulinum type E neurotoxin	- amino acid residues (1-422)
Botulinum type F neurotoxin	- amino acid residues (1-439)
Botulinum type G neurotoxin	- amino acid residues (1-441)
Tetanus neurotoxin	- amino acid residues (1-457)
IgA protease	- amino acid residues (1-959)*

* Pohlner, J. et al. (1987). Nature 325, pp. 458-462, which is hereby incorporated by reference thereto.

The above-identified reference sequence should be considered a guide as slight variations may occur according to sub-serotypes. By way of example, US 2007/0166332 (hereby incorporated by reference thereto) cites slightly different clostridial sequences:

Botulinum type A neurotoxin	- amino acid residues (M1-K448)
Botulinum type B neurotoxin	- amino acid residues (M1-K441)
Botulinum type C neurotoxin	- amino acid residues (M1-K449)
Botulinum type D neurotoxin	- amino acid residues (M1-R445)
Botulinum type E neurotoxin	- amino acid residues (M1-R422)
Botulinum type F neurotoxin	- amino acid residues (M1-K439)
Botulinum type G neurotoxin	- amino acid residues (M1-K446)
Tetanus neurotoxin	- amino acid residues (M1-A457)

A variety of clostridial toxin fragments comprising the light chain can be useful in aspects of the present invention with the proviso that these light chain fragments can specifically target the core components of the neurotransmitter release apparatus and thus participate in executing the overall cellular mechanism whereby a clostridial toxin proteolytically cleaves a substrate. The light chains of clostridial toxins are approximately 420-460 amino acids in length and comprise an enzymatic domain. Research has shown that the entire length of a clostridial toxin light chain is not necessary for the enzymatic activity of the enzymatic domain. As a non-limiting example, the first eight amino acids of the BoNT/A light chain are not required for enzymatic activity. As another non-limiting example, the first eight amino acids of the TeNT light

chain are not required for enzymatic activity. Likewise, the carboxyl-terminus of the light chain is not necessary for activity. As a non-limiting example, the last 32 amino acids of the BoNT/A light chain (residues 417-448) are not required for enzymatic activity. As another non-limiting example, the last 31 amino acids of the TeNT light chain (residues 427-457) are not required for enzymatic activity. Thus, aspects of this embodiment can include clostridial toxin light chains comprising an enzymatic domain having a length of, for example, at least 350 amino acids, at least 375 amino acids, at least 400 amino acids, at least 425 amino acids and at least 450 amino acids. Other aspects of this embodiment can include clostridial toxin light chains comprising an enzymatic domain having a length of, for example, at most 350 amino acids, at most 375 amino acids, at most 400 amino acids, at most 425 amino acids and at most 450 amino acids.

The non-cytotoxic protease component of the present invention preferably comprises a BoNT/A, BoNT/B or BoNT/D serotype L-chain (or fragment or variant thereof).

The polypeptides of the present invention, especially the protease component thereof, may be PEGylated – this may help to increase stability, for example duration of action of the protease component. PEGylation is particularly preferred when the protease comprises a BoNT/A, B or C_1 protease. PEGylation preferably includes the addition of PEG to the N-terminus of the protease component. By way of example, the N-terminus of a protease may be extended with one or more amino acid (e.g. cysteine) residues, which may be the same or different. One or more of said amino acid residues may have its own PEG molecule attached (e.g. covalently attached) thereto. An example of this technology is described in WO2007/104567, which is incorporated in its entirety by reference thereto.

A Translocation Domain is a molecule that enables translocation of a protease into a target cell such that a functional expression of protease activity occurs within the cytosol of the target cell. Whether any molecule (e.g. a protein or peptide) possesses the requisite translocation function of the present invention may be confirmed by any one of a number of conventional assays.

For example, Shone C. (1987) describes an *in vitro* assay employing liposomes, which are challenged with a test molecule. Presence of the requisite translocation function is confirmed by release from the liposomes of K^+ and/ or labelled NAD, which may be readily monitored [see Shone C. (1987) Eur. J. Biochem; vol. 167(1): pp. 175-180].

A further example is provided by Blaustein R. (1987), which describes a simple *in vitro* assay employing planar phospholipid bilayer membranes. The membranes are challenged with a test molecule and the requisite translocation function is confirmed by an increase in conductance across said membranes [see Blaustein (1987) FEBS Letts; vol. 226, no. 1: pp. 115-120].

Additional methodology to enable assessment of membrane fusion and thus identification of Translocation Domains suitable for use in the present invention are provided by Methods in Enzymology Vol 220 and 221, Membrane Fusion Techniques, Parts A and B, Academic Press 1993.

The present invention also embraces variant translocation domains, so long as the variant domains still demonstrate the requisite translocation activity. By way of example, a variant may have at least 70%, preferably at least 80%, more preferably at least 90%, and most preferably at least 95% or at least 98% amino acid sequence homology with a reference translocation domain. The term fragment, when used in relation to a translocation domain, means a peptide having at least 20, preferably at least 40, more preferably at least 80, and most preferably at least 100 amino acid residues of the reference translocation domain. In the case of a clostridial translocation domain, the fragment preferably has at least 100, preferably at least 150, more preferably at least 200, and most preferably at least 250 amino acid residues of the reference translocation domain (eg. H_N domain). As with the TM 'fragment' component (discussed above), translocation 'fragments' of the present invention embrace fragments of variant translocation domains based on the reference sequences.

The Translocation Domain is preferably capable of formation of ion-permeable pores in lipid membranes under conditions of low pH. Preferably it has been found to use only those portions of the protein molecule capable of pore-formation within the endosomal membrane.

The Translocation Domain may be obtained from a microbial protein source, in particular from a bacterial or viral protein source. Hence, in one embodiment, the Translocation Domain is a translocating domain of an enzyme, such as a bacterial toxin or viral protein.

It is well documented that certain domains of bacterial toxin molecules are capable of forming such pores. It is also known that certain translocation domains of virally expressed membrane fusion proteins are capable of forming such pores. Such domains may be employed in the present invention.

The Translocation Domain may be of a clostridial origin, such as the H_N domain (or a functional component thereof). H_N means a portion or fragment of the H-chain of a clostridial neurotoxin approximately equivalent to the amino-terminal half of the H-chain, or the domain corresponding to that fragment in the intact H-chain. The H-chain lacks the natural binding function of the H_C component of the H-chain. In this regard, the H_C function may be removed by deletion of the H_C amino acid sequence (either at the DNA synthesis level, or at the post-synthesis level by nuclease or protease treatment). Alternatively, the H_C function may be inactivated by chemical or biological treatment. Thus, the H-chain is incapable of binding to the Binding Site on a target cell to which native clostridial neurotoxin (i.e. holotoxin) binds.

Examples of suitable (reference) Translocation Domains include:

Botulinum type A neurotoxin	- amino acid residues (449-871)
Botulinum type B neurotoxin	- amino acid residues (441-858)
Botulinum type C neurotoxin	- amino acid residues (442-866)
Botulinum type D neurotoxin	- amino acid residues (446-862)
Botulinum type E neurotoxin	- amino acid residues (423-845)

Botulinum type F neurotoxin	- amino acid residues (440-864)
Botulinum type G neurotoxin	- amino acid residues (442-863)
Tetanus neurotoxin	- amino acid residues (458-879)

The above-identified reference sequence should be considered a guide as slight variations may occur according to sub-serotypes. By way of example, US 2007/0166332 (hereby incorporated by reference thereto) cites slightly different clostridial sequences:

Botulinum type A neurotoxin	- amino acid residues (A449-K871)
Botulinum type B neurotoxin	- amino acid residues (A442-S858)
Botulinum type C neurotoxin	- amino acid residues (T450-N866)
Botulinum type D neurotoxin	- amino acid residues (D446-N862)
Botulinum type E neurotoxin	- amino acid residues (K423-K845)
Botulinum type F neurotoxin	- amino acid residues (A440-K864)
Botulinum type G neurotoxin	- amino acid residues (S447-S863)
Tetanus neurotoxin	- amino acid residues (S458-V879)

In the context of the present invention, a variety of Clostridial toxin H_N regions comprising a translocation domain can be useful in aspects of the present invention with the proviso that these active fragments can facilitate the release of a non-cytotoxic protease (e.g. a clostridial L-chain) from intracellular vesicles into the cytoplasm of the target cell and thus participate in executing the overall cellular mechanism whereby a clostridial toxin proteolytically cleaves a substrate. The H_N regions from the heavy chains of Clostridial toxins are approximately 410-430 amino acids in length and comprise a translocation domain. Research has shown that the entire length of a H_N region from a Clostridial toxin heavy chain is not necessary for the translocating activity of the translocation domain. Thus, aspects of this embodiment can include clostridial toxin H_N regions comprising a translocation domain having a length of, for example, at least 350 amino acids, at least 375 amino acids, at least 400 amino acids and at least 425 amino acids. Other aspects of this embodiment can include clostridial toxin H_N regions comprising translocation domain having a length of, for example, at most 350 amino

acids, at most 375 amino acids, at most 400 amino acids and at most 425 amino acids.

For further details on the genetic basis of toxin production in *Clostridium botulinum* and *C. tetani*, we refer to Henderson *et al* (1997) in *The Clostridia: Molecular Biology and Pathogenesis, Academic press.*

The term H_N embraces naturally-occurring neurotoxin H_N portions, and modified H_N portions having amino acid sequences that do not occur in nature and/ or synthetic amino acid residues, so long as the modified H_N portions still demonstrate the above-mentioned translocation function.

Alternatively, the Translocation Domain may be of a non-clostridial origin. Examples of non-clostridial (reference) Translocation Domain origins include, but not be restricted to, the translocation domain of diphtheria toxin [O'Keefe *et al.*, Proc. Natl. Acad. Sci. USA (1992) 89, 6202-6206; Silverman *et al.*, J. Biol. Chem. (1993) 269, 22524-22532; and London, E. (1992) *Biochem. Biophys. Acta., 1112, pp.25-51*], the translocation domain of *Pseudomonas* exotoxin type A [Prior *et al.* Biochemistry (1992) 31, 3555-3559], the translocation domains of anthrax toxin [Blanke *et al.* Proc. Natl. Acad. Sci. USA (1996) 93, 8437-8442], a variety of fusogenic or hydrophobic peptides of translocating function [Plank *et al.* J. Biol. Chem. (1994) 269, 12918-12924; and Wagner *et al* (1992) *PNAS, 89, pp.7934-7938*], and amphiphilic peptides [Murata *et al* (1992) *Biochem., 31, pp.1986-1992*]. The Translocation Domain may mirror the Translocation Domain present in a naturally-occurring protein, or may include amino acid variations so long as the variations do not destroy the translocating ability of the Translocation Domain.

Particular examples of viral (reference) Translocation Domains suitable for use in the present invention include certain translocating domains of virally expressed membrane fusion proteins. For example, Wagner *et al.* (1992) and Murata *et al.* (1992) describe the translocation (i.e. membrane fusion and vesiculation) function of a number of fusogenic and amphiphilic peptides derived from the N-terminal region of influenza virus haemagglutinin. Other virally expressed membrane fusion proteins known to have the desired

translocating activity are a translocating domain of a fusogenic peptide of Semliki Forest Virus (SFV), a translocating domain of vesicular stomatitis virus (VSV) glycoprotein G, a translocating domain of SER virus F protein and a translocating domain of Foamy virus envelope glycoprotein. Virally encoded Aspike proteins have particular application in the context of the present invention, for example, the E1 protein of SFV and the G protein of the G protein of VSV.

Use of the (reference) Translocation Domains listed in Table (below) includes use of sequence variants thereof. A variant may comprise one or more conservative nucleic acid substitutions and/ or nucleic acid deletions or insertions, with the proviso that the variant possesses the requisite translocating function. A variant may also comprise one or more amino acid substitutions and/ or amino acid deletions or insertions, so long as the variant possesses the requisite translocating function.

Translocation Domain source	**Amino acid residues**	**References**
Diphtheria toxin	194-380	**Silverman *et al.***, 1994, J. Biol. Chem. 269, 22524-22532 **London E.**, 1992, Biochem. Biophys. Acta., 1113, 25-51
Domain II of pseudomonas exotoxin	405-613	**Prior *et al.***, 1992, Biochemistry 31, 3555-3559 **Kihara & Pastan**, 1994, Bioconj Chem. 5, 532-538
Influenza virus haemagglutinin	GLFGAIAGFIENGWE GMIDGWYG, and Variants thereof	**Plank *et al.***, 1994, J. Biol. Chem. 269, 12918-12924 **Wagner *et al.***, 1992, PNAS, 89, 7934-7938 **Murata *et al.***, 1992, Biochemistry 31, 1986-1992
Semliki Forest virus fusogenic protein	**Translocation domain**	**Kielian *et al.***, 1996, J Cell Biol. 134(4), 863-872

Translocation Domain source	Amino acid residues	References
Vesicular Stomatitis virus glycoprotein G	118-139	**Yao *et al.***, 2003, Virology 310(2), 319-332
SER virus F protein	Translocation domain	**Seth *et al.***, 2003, J Virol 77(11) 6520-6527
Foamy virus envelope glycoprotein	Translocation domain	**Picard-Maureau *et al.***, 2003, J Virol. 77(8), 4722-4730

The polypeptides of the present invention may further comprise a translocation facilitating domain. Said domain facilitates delivery of the non-cytotoxic protease into the cytosol of the target cell and are described, for example, in WO 08/008803 and WO 08/008805, each of which is herein incorporated by reference thereto.

By way of example, suitable translocation facilitating domains include an enveloped virus fusogenic peptide domain, for example, suitable fusogenic peptide domains include influenzavirus fusogenic peptide domain (eg. influenza A virus fusogenic peptide domain of 23 amino acids), alphavirus fusogenic peptide domain (eg. Semliki Forest virus fusogenic peptide domain of 26 amino acids), vesiculovirus fusogenic peptide domain (eg. vesicular stomatitis virus fusogenic peptide domain of 21 amino acids), respirovirus fusogenic peptide domain (eg. Sendai virus fusogenic peptide domain of 25 amino acids), morbiliivirus fusogenic peptide domain (eg. Canine distemper virus fusogenic peptide domain of 25 amino acids), avulavirus fusogenic peptide domain (eg. Newcastle disease virus fusogenic peptide domain of 25 amino acids), henipavirus fusogenic peptide domain (eg. Hendra virus fusogenic peptide domain of 25 amino acids), metapneumovirus fusogenic peptide domain (eg. Human metapneumovirus fusogenic peptide domain of 25 amino acids) or spumavirus fusogenic peptide domain such as simian foamy virus fusogenic peptide domain; or fragments or variants thereof.

By way of further example, a translocation facilitating domain may comprise a Clostridial toxin H_{CN} domain or a fragment or variant thereof. In more detail, a

Clostridial toxin H_{CN} translocation facilitating domain may have a length of at least 200 amino acids, at least 225 amino acids, at least 250 amino acids, at least 275 amino acids. In this regard, a Clostridial toxin H_{CN} translocation facilitating domain preferably has a length of at most 200 amino acids, at most 225 amino acids, at most 250 amino acids, or at most 275 amino acids. Specific (reference) examples include:

Botulinum type A neurotoxin	- amino acid residues (872-1110)
Botulinum type B neurotoxin	- amino acid residues (859-1097)
Botulinum type C neurotoxin	- amino acid residues (867-1111)
Botulinum type D neurotoxin	- amino acid residues (863-1098)
Botulinum type E neurotoxin	- amino acid residues (846-1085)
Botulinum type F neurotoxin	- amino acid residues (865-1105)
Botulinum type G neurotoxin	- amino acid residues (864-1105)
Tetanus neurotoxin	- amino acid residues (880-1127)

The above sequence positions may vary a little according to serotype/ sub-type, and further examples of suitable (reference) Clostridial toxin H_{CN} domains include:

Botulinum type A neurotoxin	- amino acid residues (874-1110)
Botulinum type B neurotoxin	- amino acid residues (861-1097)
Botulinum type C neurotoxin	- amino acid residues (869-1111)
Botulinum type D neurotoxin	- amino acid residues (865-1098)
Botulinum type E neurotoxin	- amino acid residues (848-1085)
Botulinum type F neurotoxin	- amino acid residues (867-1105)
Botulinum type G neurotoxin	- amino acid residues (866-1105)
Tetanus neurotoxin	- amino acid residues (882-1127)

Any of the above-described facilitating domains may be combined with any of the previously described translocation domain peptides that are suitable for use in the present invention. Thus, by way of example, a non-clostridial facilitating domain may be combined with non-clostridial translocation domain peptide or with clostridial translocation domain peptide. Alternatively, a Clostridial toxin H_{CN} translocation facilitating domain may be combined with a non-clostridal translocation domain peptide. Alternatively, a Clostridial toxin

H_{CN} facilitating domain may be combined or with a clostridial translocation domain peptide, examples of which include:

Botulinum type A neurotoxin	- amino acid residues (449-1110)
Botulinum type B neurotoxin	- amino acid residues (442-1097)
Botulinum type C neurotoxin	- amino acid residues (450-1111)
Botulinum type D neurotoxin	- amino acid residues (446-1098)
Botulinum type E neurotoxin	- amino acid residues (423-1085)
Botulinum type F neurotoxin	- amino acid residues (440-1105)
Botulinum type G neurotoxin	- amino acid residues (447-1105)
Tetanus neurotoxin	- amino acid residues (458-1127)

Sequence homology:

Any of a variety of sequence alignment methods can be used to determine percent identity, including, without limitation, global methods, local methods and hybrid methods, such as, e.g., segment approach methods. Protocols to determine percent identity are routine procedures within the scope of one skilled in the. Global methods align sequences from the beginning to the end of the molecule and determine the best alignment by adding up scores of individual residue pairs and by imposing gap penalties. Non-limiting methods include, e.g., CLUSTAL W, see, e.g., Julie D. Thompson et al., CLUSTAL W: Improving the Sensitivity of Progressive Multiple Sequence Alignment Through Sequence Weighting, Position- Specific Gap Penalties and Weight Matrix Choice, 22(22) Nucleic Acids Research 4673-4680 (1994); and iterative refinement, see, e.g., Osamu Gotoh, Significant Improvement in Accuracy of Multiple Protein. Sequence Alignments by Iterative Refinement as Assessed by Reference to Structural Alignments, 264(4) J. Mol. Biol. 823-838 (1996). Local methods align sequences by identifying one or more conserved motifs shared by all of the input sequences. Non-limiting methods include, e.g., Match-box, see, e.g., Eric Depiereux and Ernest Feytmans, Match-Box: A Fundamentally New Algorithm for the Simultaneous Alignment of Several Protein Sequences, 8(5) CABIOS 501 -509 (1992); Gibbs sampling, see, e.g., C. E. Lawrence et al., Detecting Subtle Sequence Signals: A Gibbs Sampling Strategy for Multiple Alignment, 262(5131) Science 208-214 (1993); Align-M, see, e.g., Ivo Van Walle et al., Align-M - A New Algorithm for Multiple

Alignment of Highly Divergent Sequences, 20(9) Bioinformatics:1428-1435 (2004).

Thus, percent sequence identity is determined by conventional methods. See, for example, Altschul et al., Bull. Math. Bio. 48: 603-16, 1986 and Henikoff and Henikoff, Proc. Natl. Acad. Sci. USA 89:10915-19, 1992. Briefly, two amino acid sequences are aligned to optimize the alignment scores using a gap opening penalty of 10, a gap extension penalty of 1, and the "blosum 62" scoring matrix of Henikoff and Henikoff (ibid.) as shown below (amino acids are indicated by the standard one-letter codes).

Alignment scores for determining sequence identity

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	4																			
R	-1	5																		
N	-2	0	6																	
D	-2	-2	1	6																
C	0	-3	-3	-3	9															
Q	-1	1	0	0	-3	5														
E	-1	0	0	2	-4	2	5													
G	0	-2	0	-1	-3	-2	-2	6												
H	-2	0	1	-1	-3	0	0	-2	8											
I	-1	-3	-3	-3	-1	-3	-3	-4	-3	4										
L	-1	-2	-3	-4	-1	-2	-3	-4	-3	2	4									
K	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5								
M	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5							
F	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6						
P	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	7					
S	1	-1	1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	4				
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	1	5			
W	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	-2	11		
Y	-2	-2	-2	-3	-2	-1	-2	-3	2	-1	-1	-2	-1	3	-3	-2	-2	2	7	
V	0	-3	-3	-3	-1	-2	-2	-3	-3	3	1	-2	1	-1	-2	-2	0	-3	-1	4

The percent identity is then calculated as:

$$\frac{\text{Total number of identical matches}}{\text{[length of the longer sequence plus the number of gaps introduced into the longer sequence in order to align the two sequences]}} \times 100$$

Substantially homologous polypeptides are characterized as having one or more amino acid substitutions, deletions or additions. These changes are preferably of a minor nature, that is conservative amino acid substitutions (see below) and other substitutions that do not significantly affect the folding or activity of the polypeptide; small deletions, typically of one to about 30 amino acids; and small amino- or carboxyl-terminal extensions, such as an amino-terminal methionine residue, a small linker peptide of up to about 20-25 residues, or an affinity tag.

Conservative amino acid substitutions

Basic:	arginine
	lysine
	histidine
Acidic:	glutamic acid
	aspartic acid
Polar:	glutamine
	asparagine
Hydrophobic:	leucine
	isoleucine
	valine
Aromatic:	phenylalanine
	tryptophan
	tyrosine
Small:	glycine
	alanine
	serine

threonine
methionine

In addition to the 20 standard amino acids, non-standard amino acids (such as 4-hydroxyproline, 6-*N*-methyl lysine, 2-aminoisobutyric acid, isovaline and α -methyl serine) may be substituted for amino acid residues of the polypeptides of the present invention. A limited number of non-conservative amino acids, amino acids that are not encoded by the genetic code, and unnatural amino acids may be substituted for clostridial polypeptide amino acid residues. The polypeptides of the present invention can also comprise non-naturally occurring amino acid residues.

Non-naturally occurring amino acids include, without limitation, trans-3-methylproline, 2,4-methano-proline, cis-4-hydroxyproline, trans-4-hydroxy-proline, N-methylglycine, allo-threonine, methyl-threonine, hydroxy-ethylcysteine, hydroxyethylhomo-cysteine, nitro-glutamine, homoglutamine, pipecolic acid, tert-leucine, norvaline, 2-azaphenylalanine, 3-azaphenyl-alanine, 4-azaphenyl-alanine, and 4-fluorophenylalanine. Several methods are known in the art for incorporating non-naturally occurring amino acid residues into proteins. For example, an *in vitro* system can be employed wherein nonsense mutations are suppressed using chemically aminoacylated suppressor tRNAs. Methods for synthesizing amino acids and aminoacylating tRNA are known in the art. Transcription and translation of plasmids containing nonsense mutations is carried out in a cell free system comprising an *E. coli* S30 extract and commercially available enzymes and other reagents. Proteins are purified by chromatography. See, for example, Robertson et al., J. Am. Chem. Soc. 113:2722, 1991; Ellman et al., Methods Enzymol. 202:301, 1991; Chung et al., Science 259:806-9, 1993; and Chung et al., Proc. Natl. Acad. Sci. USA 90:10145-9, 1993). In a second method, translation is carried out in Xenopus oocytes by microinjection of mutated mRNA and chemically aminoacylated suppressor tRNAs (Turcatti et al., J. Biol. Chem. 271:19991-8, 1996). Within a third method, *E. coli* cells are cultured in the absence of a natural amino acid that is to be replaced (e.g., phenylalanine) and in the presence of the desired non-naturally occurring amino acid(s) (e.g., 2-azaphenylalanine, 3-azaphenylalanine, 4-

azaphenylalanine, or 4-fluorophenylalanine). The non-naturally occurring amino acid is incorporated into the polypeptdie in place of its natural counterpart. See, Koide et al., Biochem. 33:7470-6, 1994. Naturally occurring amino acid residues can be converted to non-naturally occurring species by *in vitro* chemical modification. Chemical modification can be combined with site-directed mutagenesis to further expand the range of substitutions (Wynn and Richards, Protein Sci. 2:395-403, 1993).

A limited number of non-conservative amino acids, amino acids that are not encoded by the genetic code, non-naturally occurring amino acids, and unnatural amino acids may be substituted for amino acid residues of polypeptides of the present invention.

Essential amino acids in the polypeptides of the present invention can be identified according to procedures known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, Science 244: 1081-5, 1989). Sites of biological interaction can also be determined by physical analysis of structure, as determined by such techniques as nuclear magnetic resonance, crystallography, electron diffraction or photoaffinity labeling, in conjunction with mutation of putative contact site amino acids. See, for example, de Vos et al., Science 255:306-12, 1992; Smith et al., J. Mol. Biol. 224:899-904, 1992; Wlodaver et al., FEBS Lett. 309:59-64, 1992. The identities of essential amino acids can also be inferred from analysis of homologies with related components (e.g. the translocation or protease components) of the polypeptides of the present invention.

Multiple amino acid substitutions can be made and tested using known methods of mutagenesis and screening, such as those disclosed by Reidhaar-Olson and Sauer (Science 241:53-7, 1988) or Bowie and Sauer (Proc. Natl. Acad. Sci. USA 86:2152-6, 1989). Briefly, these authors disclose methods for simultaneously randomizing two or more positions in a polypeptide, selecting for functional polypeptide, and then sequencing the mutagenised polypeptides to determine the spectrum of allowable substitutions at each position. Other methods that can be used include phage display (e.g., Lowman et al.,

Biochem. 30:10832-7, 1991; Ladner et al., U.S. Patent No. 5,223,409; Huse, WIPO Publication WO 92/06204) and region-directed mutagenesis (Derbyshire et al., Gene 46:145, 1986; Ner et al., DNA 7:127, 1988).

Multiple amino acid substitutions can be made and tested using known methods of mutagenesis and screening, such as those disclosed by Reidhaar-Olson and Sauer (Science 241:53-7, 1988) or Bowie and Sauer (Proc. Natl. Acad. Sci. USA 86:2152-6, 1989). Briefly, these authors disclose methods for simultaneously randomizing two or more positions in a polypeptide, selecting for functional polypeptide, and then sequencing the mutagenized polypeptides to determine the spectrum of allowable substitutions at each position. Other methods that can be used include phage display (e.g., Lowman et al., Biochem. 30:10832-7, 1991; Ladner et al., U.S. Patent No. 5,223,409; Huse, WIPO Publication WO 92/06204) and region-directed mutagenesis (Derbyshire et al., Gene 46:145, 1986; Ner et al., DNA 7:127, 1988).

There now follows a brief description of the Figures, which illustrate aspects and/ or embodiments of the present invention.

Figure 1 - Purification of LH_N/D-CT-CST28 fusion protein

Using the methodology outlined in Example 5, a LH_N/D-CT-CST28 fusion protein was purified from *E. coli* BL21 (DE3) cells. Briefly, the soluble products obtained following cell disruption were applied to a nickel-charged affinity capture column. Bound proteins were eluted with 200 mM imidazole, treated with enterokinase to activate the fusion protein and then re-applied to a second nickel-charged affinity capture column. Samples from the purification procedure were assessed by SDS-PAGE. *Lane 1*: First nickel chelating Sepharose column eluant, *Lane 2*: Second nickel chelating Sepharose column eluant under non-reducing conditions, *Lane 3*: Second nickel chelating Sepharose column eluant under reducing conditions, *lane 4*: Molecular mass markers (kDa).

Figure 2 - Purification of LH_N/A-CT-SST14 fusion protein

Using the methodology outlined in Example 6, an LH_N/A-CT-SST14 fusion protein was purified from *E. coli* BL21 (DE3) cells. Briefly, the soluble

products obtained following cell disruption were applied to a nickel-charged affinity capture column. Bound proteins were eluted with 200 mM imidazole, treated with Factor Xa to activate the fusion protein and then re-applied to a second nickel-charged affinity capture column. Samples from the purification procedure were assessed by SDS-PAGE. *Lane 1*: First nickel chelating Sepharose column eluant, *Lane 2*: Molecular mass markers (kDa), *Lanes 3-4*: Second nickel chelating Sepharose column eluant under non-reducing conditions, *Lanes* 5-6: Second nickel chelating Sepharose column eluant under reducing conditions.

Figure 3 - Activity of SST-LH$_N$/A in cultured endocrine cells (AtT20)

Figure 3a shows Inhibition of secretion of ACTH by SST-LH$_N$/A, and Figure 3b shows corresponding cleavage of SNAP-25 by SST-LH$_N$/A.

Figure 4 - Activity of SST-LH$_N$/D in cultured endocrine cells (GH3)

Figure 4 shows the effect of growth hormone release from GH3 cells. Higher administration dosages of SST-LH$_N$/D result in a greater inhibition of growth hormone release.

Figure 5 - Activity of CP-GHRH-LHD on rat IGF-1 levels *in vivo*

Figure 5 shows the effects of i.v. administration of CP-GHRH-LHD (SXN101000) on rat IGF-1 levels 5 days after treatment compared to a vehical only control.

Figure 6 - Activity of CP-GHRH-LHD on rat IGF-1 levels *in vivo*

Figure 6 shows the effects of i.v. administration of CP-GHRH-LHD (SXN101000) on rat IGF-1 levels on day 1 to 8 days after treatment compared to a vehical only control. Due to the blocking of the cannula on days 9 and 10 have too few an n number to be considered.

Figure 7 - Activity of CP-GHRH-LHD on rat growth hormone levels *in vivo*

Figure 7b shows the effects of i.v. administration of CP-GHRH-LHD (SXN101000) on rat growth hormone levels on day 5 days after treatment compared to a vehical only control (figure 7a) and octreotide infusion (figure 7c).

SEQ ID NOs

1. DNA sequence of LH_N/A
2. DNA sequence of LH_N/B
3. DNA sequence of LH_N/C
4. DNA sequence of LH_N/D
5. DNA sequence of the human CP-EN-GS15-SST28 linker
6. DNA sequence of the human CT-GS20-CST28 linker
7. Protein sequence of the CP-CST14-GS20-LHD fusion
8. Protein sequence of the CP-CST14-GS30-LHD fusion
9. Protein sequence of the CP-CST28-GS20-LHD fusion
10. Protein sequence of the CP-CST28-GS30-LHD fusion
11. Protein sequence of the CP-SST14-GS20-LHD fusion
12. Protein sequence of the CP-SST14-GS30-LHD fusion
13. Protein sequence of the CP-SST28-GS20-LHD fusion
14. Protein sequence of the CP-SST28-GS30-LHD fusion
15. Protein sequence of the CT-CST14-GS20-LHD fusion
16. Protein sequence of the CT-CST14-GS30-LHD fusion
17. DNA sequence of the CT-CST28-GS20-LHD fusion
18. Protein sequence of the CT-CST28-GS20-LHD fusion
19. Protein sequence of the CT-CST28-GS30-LHD fusion
20. Protein sequence of the CT-SST14-GS15-L(#Fxa)HD fusion
21. Protein sequence of the CT-SST14-GS30-LHD fusion
22. Protein sequence of the CT-SST28-GS20-LHD fusion
23. Protein sequence of the CT-SST28-GS30-LHD fusion
24. Protein sequence of the CT-SST14-GS35-LHC fusion
25. DNA sequence of the CP-GS15-SST28-LHA fusion
26. Protein sequence of the CP-GS15-SST28-LHA fusion
27. Protein sequence of the CT-SST28-GS15-LHB fusion
28. Protein sequence of the CT-CST14-GS20-LHC fusion
29. Protein sequence of the CT-CST17-GS25-LHC fusion
30. Protein sequence of the CT-CST29-GS15-LHA fusion
31. Protein sequence of the CT-CST29-GS30-LHB fusion
32. DNA sequence of IgA-$H_N$tet
33. Protein sequence of the CT-GHRP-LHC fusion

34. Protein sequence of the CT-GHRH-LHD fusion
35. Protein sequence of the CT-GHRP-LHD fusion
36. Protein sequence of the CT-ghrelin-LHA fusion
37. Protein sequence of the IgA-$H_N$tet-CT-SST14 Fusion
38. Protein sequence of the IgA-$H_N$tet-CT-GHRP Fusion
39. Protein sequence of the CT-ghrelin S3W-LHA fusion
40. Protein sequence of the CT-GRP-LHD fusion
41. Protein sequence of the CT-GRP-LHB fusion
42. Protein sequence of the CP-qGHRH29-LHD fusion
43. Protein sequence of the CP-qGHRH-LHA fusion
44. Protein sequence of the CP-qGHRH-LHC fusion
45. Protein sequence of the CP-qGHRH-LHD fusion
46. Protein sequence of the CP-qGHRH-LHD N10-PL5 fusion
47. Protein sequence of the CP-qGHRH-LHD N10-HX12 fusion
48. Protein sequence of the CP-UTS-LHA fusion
49. Protein sequence of LH_N/A
50. Protein sequence of LH_N/B
51. Protein sequence of LH_N/C
52. Protein sequence of LH_N/D
53. Protein sequence of IgA-$H_N$tet
54. Synthesised Octreotide peptide
55. Synthesised GHRH agonist peptide
56. Synthesised GHRH antagonist peptide
57. Protein sequence of the CP-MCH-LHD fusion
58. Protein sequence of the CT-KISS-LHD fusion
59. Protein sequence of the CT-PrRP-LHA fusion
60. Protein sequence of the CP-HS_GHRH_1-27-LHD fusion
61. Protein sequence of the CP-HS_GHRH_1-28-LHD fusion
62. Protein sequence of the CP-HS_GHRH_1-29-LHD fusion
63. Protein sequence of the CP-HS_GHRH_1-44-LHD fusion
64. Protein sequence of the CP-HS_GHRH_1-40-LHD fusion
65. Protein sequence of the CP-HS_GHRH_Ala9-LHD fusion
66. Protein sequence of the CP-HS_GHRH_Ala22-LHD fusion
67. Protein sequence of the CP-HS_GHRH_Ala8_Lys11_1-29-LHD fusion
68. Protein sequence of the CP-HS_GHRH_Ala8_Lys11_Arg12_1-29-LHD

fusion

69. Protein sequence of the CP-HS_GHRH_Ala8_Asn11_1-29-LHD fusion
70. Protein sequence of the CP-HS_GHRH_Ala8_Lys20_1-29-LHD fusion
71. Protein sequence of the CP-HS_GHRH_Ala8_Lys11_Lys20_1-29-LHD fusion
72. Protein sequence of the CP-HS_GHRH_Ala8_Asn20_1-29-LHD fusion
73. Protein sequence of the CP-HS_GHRH_Ala8_Asn12_1-29-LHD fusion
74. Protein sequence of the CP-HS_GHRH_Ala8_Asn21_1-29-LHD fusion
75. Protein sequence of the CP-HS_GHRH_Ala8_Glu_7_1-29-LHD fusion
76. Protein sequence of the CP-HS_GHRH_Ala8_Glu_10_1-29LHD fusion
77. Protein sequence of the CP-HS_GHRH_Ala8_Glu_13_1-29-LHD fusion
78. Protein sequence of the CP-HS_GHRH_Ala8-LHD fusion
79. Protein sequence of the CP-HS_GHRH_Glu8_1-29-LHD fusion
80. Protein sequence of the CP-HS_GHRH_Ala15_1-27-LHD fusion
81. Protein sequence of the CP-HS_GHRH_Ala15-LHD fusion
82. Protein sequence of the CP- HS_GHRH_Ala8_Ala15_1-29-LHD fusion
83. Protein sequence of the CP-HS_GHRH_Ala8_9_15_22_27-LHD fusion
84. Protein sequence of the CP-HS_GHRH_Ala8_9_15_22-LHD fusion
85. Protein sequence of the CP-HS_GHRH_HVQAL_1-32-LHD fusion
86. Protein sequence of the CP-HS_GHRH_HVSAL_1-29-LHD fusion
87. Protein sequence of the CP-HS_GHRH_HVTAL_1-29-LHD fusion
88. Protein sequence of the CP-HS_GHRH_QALN-LHD fusion
89. Protein sequence of the CP-HS_GHRH_QAL-LHD fusion
90. Protein sequence of the CP-hGHRH29 N8A M27L-LHD fusion
91. Protein sequence of the CP-hGHRH29 N8A K12N M27L-LHD fusion
92. Protein sequence of the N-terminal-hGHRH29 N8A M27L-LHD fusion
93. Protein sequence of the human GnRH-C fusion
94. Protein sequence of the human GnRH -D GS 20 fusion

SUMMARY OF EXAMPLES

Example 1 Preparation of a LHA backbone construct

Example 2 Construction of LHA-CP-SST28

Example 3 Expression and purification of a LHA-CP-SST28 fusion protein

Example 4 Construction of LHD-CT-CST28

Example 5 Expression and purification of a LHD-CT-CST28 fusion protein

Example 6 Chemical conjugation of LH_N/A to SST TM

Example 7 Activity of SST-LHA in cultured endocrine cells (AtT20)

Example 8 Activity of SST-LHD in cultured neuroendocrine cells (GH3)

Example 9 Method for alleviating acromegalic symptoms by reducing elevated GH and IGF-1 levels resulting from pituitary adenoma

Example 10 Method for normalising swollen hirsute fingers by reducing elevated GH and IGF-1 levels resulting from pituitary adenoma

Example 11 Method for ameliorating the consequences of re-emerging growth-hormone-secreting pituitary adenoma

Example 12 Method for treating acromegalic patients resistant to somatostatin analogues

Example 13 Method for treating Cushing's disease in patients intolerant of somatostatin analogues

Example 14 Method for reversing female sexual impotence by treating prolactinoma

Example 15 Method for bringing about weight loss by treating insulinoma

Example 16 Method for treating glucagonoma

Example 17 Method for treating diarrhoea and flushing caused by VIPoma

Example 18 Method for treating gastrinoma

Example 19 Method for treating thyrotoxicosis caused by thyrotrophinoma

Example 20 Method for treating recurrent soft tissue swelling caused by acromegaly

Example 21 Method for treating excessive facial hirsutism caused by Cushing's disease

Example 22 Method for treating male galactorrhoea caused by prolactinoma

Example 23 Method for treating multiple symptoms caused by insulinoma

Example 24 Method for treating acromegalic patients resistant to somatostatin analogues

Example 25 Method for treating Cushing's disease in patients intolerant of somatostatin analogues

Example 26 Method for reversing female sexual impotence by treating prolactinoma

Example 27 Method for treating Cushing's disease

Example 28 Method for treating gastrinoma

Example 29 Method for alleviating acromegalic symptoms by reducing elevated GH and IGF-1 levels resulting from pituitary adenoma

Example 30 Method for treating acromegalic patients resistant to somatostatin analogues

Example 31 Method for treating acromegaly

Example 32 Activity of CP-GHRH-LHD on rat IGF-1 levels *in vivo*

Example 33 Activity of CP-GHRH-LHD on rat IGF-1 levels *in vivo*

Example 34 Activity of CP-GHRH-LHD on rat growth hormone levels *in vivo*

SEQ IDs

1. DNA sequence of LH_N/A

ggatccATGGAGTTCGTTAACAAACAGTTCAACTATAAAGACCCAGTTAACGGTGTTGACATTGCTTAC
ATCAAAATCCCGAACGCTGGCCAGATGCAGCCGGTAAAGGCATTCAAAATCCACAACAAAATCTGGGTT
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GTTACTAAACTGTTCGAGCGTATTTACTCCACCGACCTGGGCCGTATGCTGCTGACTAGCATCGTTCGC
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CGTGGCACTCTGATCGGTCAGGTTGATCGTCTGAAGGACAAAGTGAACAATACCTTATCGACCGACATC
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2. DNA sequence of LH_N/B

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CAGGCTATCGACAACATCAACAACTTCATCAACGGTTGCAGTGTTAGCTACCTGATGAAGAAGATGATC
CCGCTGGCTGTTGAAAAACTGCTGGACTTCGACAACACCCTGAAAAAGAACCTGCTGAACTACATCGAC
GAAAACAAGCTGTACCTGATCGGTAGTGCTGAATACGAAAAAAGTAAAGTGAACAAATACCTGAAGACC
ATCATGCCGTTCGACCTGAGTATCTACACCAACGACACCATCCTGATCGAAATGTTCAACAAATACAAC
TCTtaataagctt

3. DNA sequence of LH_N/C

ggatccATGCCGATCACCATCAACAACTTCAACTACAGCGATCCGGTGGATAACAAAAACATCCTGTAC
CTGGATACCCATCTGAATACCCTGGCGAACGAACCGGAAAAAGCGTTTCGTATCACCGGCAACATTTGG
GTTATTCCGGATCGTTTTAGCCGTAACAGCAACCCGAATCTGAATAAACCGCCGCGTGTTACCAGCCCG
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ATCAAACTGTTCAAACGCATCAACAGCCGTGAAATTGGCGAAGAACTGATCTATCGCCTGAGCACCGAT
ATTCCGTTTCCGGGCAACAACAACACCCCGATCAACACCTTTGATTTCGATGTGGATTTCAACAGCGTT
GATGTTAAAACCCGCCAGGGTAACAATTGGGTGAAAACCGGCAGCATTAACCCGAGCGTGATTATTACC
GGTCCGCGCGAAAACATTATTGATCCGGAAACCAGCACCTTTAAACTGACCAACAACACCTTTGCGGCG
CAGGAAGGTTTTGGCGCGCTGAGCATTATTAGCATTAGCCCGCGCTTTATGCTGACCTATAGCAACGCG
ACCAACGATGTTGGTGAAGGCCGTTTCAGCAAAAGCGAATTTTGCATGGACCCGATCCTGATCCTGATG
CATGAACTGAACCATGCGATGCATAACCTGTATGGCATCGCGATTCCGAACGATCAGACCATTAGCAGC
GTGACCAGCAACATCTTTTACAGCCAGTACAACGTGAAACTGGAATATGCGGAAATCTATGCGTTTGGC
GGTCCGACCATTGATCTGATTCCGAAAAGCGCGCGCAAATACTTCGAAGAAAAAGCGCTGGATTACTAT
CGCAGCATTGCGAAACGTCTGAACAGCATTACCACCGCGAATCCGAGCAGCTTCAACAAATATATCGGC
GAATATAAACAGAAACTGATCCGCAAATATCGCTTTGTGGTGGAAAGCAGCGGCGAAGTTACCGTTAAC
CGCAATAAATTCGTGGAACTGTACAACGAACTGACCCAGATCTTCACCGAATTTAACTATGCGAAAATC
TATAACGTGCAGAACCGTAAAATCTACCTGAGCAACGTGTATACCCCGGTGACCGCGAATATTCTGGAT
GATAACGTGTACGATATCCAGAACGGCTTTAACATCCCGAAAAGCAACCTGAACGTTCTGTTTATGGGC
CAGAACCTGAGCCGTAATCCGGCGCTGCGTAAAGTGAACCCGGAAAACATGCTGTACCTGTTCACCAAA
TTTTGCGTCGACGCGATTGATGGTCGTAGCCTGTACAACAAAACCCTGCAGTGTCGTGAACTGCTGGTG
AAAAACACCGATCTGCCGTTTATTGGCGATATCAGCGATGTGAAAACCGATATCTTCCTGCGCAAAGAT
ATCAACGAAGAAACCGAAGTGATCTACTACCCGGATAACGTGAGCGTTGATCAGGTGATCCTGAGCAAA
AACACCAGCGAACATGGTCAGCTGGATCTGCTGTATCCGAGCATTGATAGCGAAAGCGAAATTCTGCCG
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AACAGCGCGAAAGTTTACACCTATTTTCCGACCCTGGCGAACAAAGTTAATGCGGGTGTTCAGGGCGGT
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GATAAAATCAGCGATGTTAGCGCGATTATTCCGTATATTGGTCCGGCGCTGAACATTAGCAATAGCGTG
CGTCGTGGCAATTTTACCGAAGCGTTTGCGGTTACCGGTGTGACCATTCTGCTGGAAGCGTTTCCGGAA
TTTACCATTCCGGCGCTGGGTGCGTTTGTGATCTATAGCAAAGTGCAGGAACGCAACGAAATCATCAAA
ACCATCGATAACTGCCTGGAACAGCGTATTAAACGCTGGAAAGATAGCTATGAATGGATGATGGGCACC
TGGCTGAGCCGTATTATCACCCAGTTCAACAACATCAGCTACCAGATGTACGATAGCCTGAACTATCAG
GCGGGTGCGATTAAAGCGAAAATCGATCTGGAATACAAAAAATACAGCGGCAGCGATAAAGAAAACATC
AAAAGCCAGGTTGAAAACCTGAAAAACAGCCTGGATGTGAAAATTAGCGAAGCGATGAATAACATCAAC
AAATTCATCCGCGAATGCAGCGTGACCTACCTGTTCAAAAACATGCTGCCGAAAGTGATCGATGAACTG
AACGAATTTGATCGCAACACCAAAGCGAAACTGATCAACCTGATCGATAGCCACAACATTATTCTGGTG
GGCGAAGTGGATAAACTGAAAGCGAAAGTTAACAACAGCTTCCAGAACACCATCCCGTTTAACATCTTC
AGCTATACCAACAACAGCCTGCTGAAAGATATCATCAACGAATACTTCAATtaataagctt

4. DNA sequence of LH_N/D

ggatccATGACGTGGCCAGTTAAGGATTTCAACTACTCAGATCCTGTAAATGACAACGATATTCTGTAC
CTTCGCATTCCACAAAATAAACTGATCACCACACCAGTCAAAGCATTCATGATTACTCAAAACATTTGG
GTCATTCCAGAACGCTTTTCTAGTGACACAAATCCGAGTTTATCTAAACCTCCGCGTCCGACGTCCAAA
TATCAGAGCTATTACGATCCCTCATATCTCAGTACGGACGAACAAAAAGATACTTTCCTTAAAGGTATC
ATTAAACTGTTTAAGCGTATTAATGAGCGCGATATCGGGAAAAAGTTGATTAATTATCTTGTTGTGGGT
TCCCCGTTCATGGGCGATAGCTCTACCCCCGAAGACACTTTTGATTTTACCCGTCATACGACAAACATC
GCGGTAGAGAAGTTTGAGAACGGATCGTGGAAAGTCACAAACATCATTACACCTAGCGTCTTAATTTTT
GGTCCGCTGCCAAACATCTTAGATTATACAGCCAGCCTGACTTTGCAGGGGCAACAGTCGAATCCGAGT
TTCGAAGGTTTTGGTACCCTGAGCATTCTGAAAGTTGCCCCGGAATTTCTGCTCACTTTTTCAGATGTC
ACCAGCAACCAGAGCTCAGCAGTATTAGGAAAGTCAATTTTTTGCATGGACCCGGTTATTGCACTGATG
CACGAACTGACGCACTCTCTGCATCAACTGTATGGGATCAACATCCCCAGTGACAAACGTATTCGTCCC
CAGGTGTCTGAAGGATTTTTCTCACAGGATGGGCCGAACGTCCAGTTCGAAGAGTTGTATACTTTCGGA
GGCCTGGACGTAGAGATCATTCCCCAGATTGAGCGCAGTCAGCTGCGTGAGAAGGCATTGGGCCATTAT
AAGGATATTGCAAAACGCCTGAATAACATTAACAAAACGATTCCATCTTCGTGGATCTCGAATATTGAT
AAATATAAGAAAATTTTTAGCGAGAAATATAATTTTGATAAAGATAATACAGGTAACTTTGTGGTTAAC
ATTGACAAATTCAACTCCCTTTACAGTGATTTGACGAATGTAATGAGCGAAGTTGTGTATAGTTCCCAA
TACAACGTTAAGAATCGTACCCATTACTTCTCTCGTCACTACCTGCCGGTTTTCGCGAACATCCTTGAC
GATAATATTTACACTATTCGTGACGGCTTTAACTTGACCAACAAGGGCTTCAATATTGAAAATTCAGGC
CAGAACATTGAACGCAACCCGGCCTTGCAGAAACTGTCGAGTGAATCCGTGGTTGACCTGTTTACCAAA
GTCTGCGTCGACAAAAGCGAAGAGAAGCTGTACGATGACGATGACAAAGATCGTTGGGGATCGTCCCTG
CAGTGTATTAAAGTGAAAAACAATCGGCTGCCTTATGTAGCAGATAAAGATAGCATTAGTCAGGAGATT
TTCGAAAATAAAATTATCACTGACGAAACCAATGTTCAGAATTATTCAGATAAATTTTCACTGGACGAA
AGCATCTTAGATGGCCAAGTTCCGATTAACCCGGAAATTGTTGATCCGTTACTGCCGAACGTGAATATG
GAACCGTTAAACCTCCCTGGCGAAGAGATCGTATTTTATGATGACATTACGAAATATGTGGACTACCTT
AATTCTTATTACTATTTGGAAAGCCAGAAACTGTCCAATAACGTGGAAAACATTACTCTGACCACAAGC
GTGGAAGAGGCTTTAGGCTACTCAAATAAGATTTATACCTTCCTCCCGTCGCTGGCGGAAAAAGTAAAT
AAAGGTGTGCAGGCTGGTCTGTTCCTCAACTGGGCGAATGAAGTTGTCGAAGACTTTACCACGAATATT
ATGAAAAAGGATACCCTGGATAAAATCTCCGACGTCTCGGTTATTATCCCATATATTGGCCCTGCGTTA
AATATCGGTAATAGTGCGCTGCGGGGGAATTTTAACCAGGCCTTTGCTACCGCGGGCGTCGCGTTCCTC
CTGGAGGGCTTTCCTGAATTTACTATCCCGGCGCTCGGTGTTTTTACATTTTACTCTTCCATCCAGGAG
CGTGAGAAAATTATCAAAACCATCGAAAACTGCCTGGAGCAGCGGGTGAAACGCTGGAAAGATTCTTAT
CAATGGATGGTGTCAAACTGGTTATCTCGCATCACGACCCAATTCAACCATATTAATTACCAGATGTAT
GATAGTCTGTCGTACCAAGCTGACGCCATTAAAGCCAAAATTGATCTGGAATATAAAAAGTACTCTGGT
AGCGATAAGGAGAACATCAAAAGCCAGGTGGAGAACCTTAAGAATAGTCTGGATGTGAAAATCTCTGAA
GCTATGAATAACATTAACAAATTCATTCGTGAATGTTCGGTGACGTACCTGTTCAAGAATATGCTGCCA
AAAGTTATTGATGAACTGAATAAATTTGATCTGCGTACCAAAACCGAACTTATCAACCTCATCGACTCC
CACAACATTATCCTTGTGGGCGAAGTGGATCGTCTGAAGGCCAAAGTAAACGAGAGCTTTGAAAATACG
ATGCCGTTTAATATTTTTTCATATACCAATAACTCCTTGCTGAAAGATATCATCAATGAATATTTCAAT
taataagctt

5. DNA sequence of the human CP-EN-GS15-SST28 linker

CATATGGGATCCGGTTTAAACGTCGACGGCATCATTACCTCCAAAACTAAATCTGACGATGACGATAAA
AGCGCCAATTCAAATCCTGCAATGGCGCCACGCGAACGCAAAGCTGGTTGCAAAAACTTCTTCTGGAAA
ACCTTCACCTCTTGCGCGCTAGCGGGCGGTGGCGGTAGCGGCGGTGGCGGTAGCGGCGGTGGCGGTAGC
GCACTAGTGCTGCAGCTAGAATAATGAAAGCTT

6. DNA sequence of the Human CT-GS20-CST28 linker

GGATCCGTCGACCTGCAGGGTCTAGAAGGCGGTGGCGGTAGCGGCGGTGGCGGTAGCGGCGGTGGCGGT
AGCGGCGGTGGCGGTAGCGCACTAGTGCAGGAAAGACCTCCATTACAACAACCTCCACATCGCGATAAG
AAACCATGTAAGAATTTCTTTTGGAAAACATTTAGCAGTTGCAAATGATAAAAGCTT

7. Protein sequence of the CP-CST14-GS20-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKPCKNFFWKTFSSCKALAGGGGSGGGGSGGGG
SALVLQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLL

PNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSL
AEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATA
GVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHI
NYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLF
KNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDII
NEYFN

8. Protein sequence of the CP-CST14-GS30-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKPCKNFFWKTFSSCKALAGGGGSGGGGSGGGG
SGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILDGQVP
INPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEALGYS
NKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGNSALR
GNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMVSNWL
SRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNNINKF
IRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFNIFSY
TNNSLLKDIINEYFN

9. Protein sequence of the CP-CST28-GS20-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKQERPPLQQPPHRDKKPCKNFFWKTFSSCKAL
AGGGGSGGGGSGGGGSALVLQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

10. Protein sequence of the CP-CST28-GS30-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKQERPPLQQPPHRDKKPCKNFFWKTFSSCKAL
AGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSALVLQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYS
DKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVE
NITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVII
PYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRV
KRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNS
LDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKV
NESFENTMPFNIFSYTNNSLLKDIINEYFN

11. Protein sequence of the CP-SST14-GS20-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD

VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKAGCKNFFWKTFTSCALAGGGGSGGGGSGGGG
SALVLQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLL
PNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSL
AEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATA
GVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHI
NYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLF
KNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDII
NEYFN

12. Protein sequence of the CP-SST14-GS30-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKAGCKNFFWKTFTSCALAGGGGSGGGGSGGGG
SGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILDGQVP
INPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEALGYS
NKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGNSALR
GNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMVSNWL
SRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNNINKF
IRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFNIFSY
TNNSLLKDIINEYFN

13. Protein sequence of the CP-SST28-GS20-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKSANSNPAMAPRERKAGCKNFFWKTFTSCALA
GGGGSGGGGSGGGGSALVLQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILD
GQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEA
LGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGN
SALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMV
SNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNN
INKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFN
IFSYTNNSLLKDIINEYFN

14. Protein sequence of the CP-SST28-GS30-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKSANSNPAMAPRERKAGCKNFFWKTFTSCALA
GGGGSGGGGSGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSD
KFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVEN
ITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIP
YIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVK
RWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSL
DVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVN
ESFENTMPFNIFSYTNNSLLKDIINEYFN

15. Protein sequence of the CT-CST14-GS20-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFEN
KIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSY
YYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKK
DTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREK
IIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDK
ENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNI
ILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSALVPCKNFF
WKTFSSCK

16. Protein sequence of the CT-CST14-GS30-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFEN
KIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSY
YYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKK
DTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREK
IIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDK
ENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNI
ILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSGGGGSGGGG
SALVPCKNFFWKTFSSCK

17. DNA sequence of the CT-CST28-GS20-LHD fusion

GGATCCATGACGTGGCCAGTTAAGGATTTCAACTACTCAGATCCTGTAAATGACAACGATATTCTGTAC
CTTCGCATTCCACAAAATAAACTGATCACCACACCAGTCAAAGCATTCATGATTACTCAAAACATTTGG
GTCATTCCAGAACGCTTTTCTAGTGACACAAATCCGAGTTTATCTAAACCTCCGCGTCCGACGTCCAAA
TATCAGAGCTATTACGATCCCTCATATCTCAGTACGGACGAACAAAAAGATACTTTCCTTAAAGGTATC
ATTAAACTGTTTAAGCGTATTAATGAGCGCGATATCGGGAAAAAGTTGATTAATTATCTTGTTGTGGGT
TCCCCGTTCATGGGCGATAGCTCTACCCCCGAAGACACTTTTGATTTTACCCGTCATACGACAAACATC
GCGGTAGAGAAGTTTGAGAACGGATCGTGGAAAGTCACAAACATCATTACACCTAGCGTCTTAATTTTT
GGTCCGCTGCCAAACATCTTAGATTATACAGCCAGCCTGACTTTGCAGGGGCAACAGTCGAATCCGAGT
TTCGAAGGTTTTGGTACCCTGAGCATTCTGAAAGTTGCCCCGGAATTTCTGCTCACTTTTTCAGATGTC
ACCAGCAACCAGAGCTCAGCAGTATTAGGAAAGTCAATTTTTTGCATGGACCCGGTTATTGCACTGATG
CACGAACTGACGCACTCTCTGCATCAACTGTATGGGATCAACATCCCCAGTGACAAACGTATTCGTCCC
CAGGTGTCTGAAGGATTTTTCTCACAGGATGGGCCGAACGTCCAGTTCGAAGAGTTGTATACTTTCGGA
GGCCTGGACGTAGAGATCATTCCCCAGATTGAGCGCAGTCAGCTGCGTGAGAAGGCATTGGGCCATTAT
AAGGATATTGCAAAACGCCTGAATAACATTAACAAAACGATTCCATCTTCGTGGATCTCGAATATTGAT
AAATATAAGAAAATTTTTAGCGAGAAATATAATTTTGATAAAGATAATACAGGTAACTTTGTGGTTAAC
ATTGACAAATTCAACTCCCTTTACAGTGATTTGACGAATGTAATGAGCGAAGTTGTGTATAGTTCCCAA
TACAACGTTAAGAATCGTACCCATTACTTCTCTCGTCACTACCTGCCGGTTTTCGCGAACATCCTTGAC
GATAATATTTACACTATTCGTGACGGCTTTAACTTGACCAACAAGGGCTTCAATATTGAAAATTCAGGC
CAGAACATTGAACGCAACCCGGCCTTGCAGAAACTGTCGAGTGAATCCGTGGTTGACCTGTTTACCAAA
GTCTGCGTCGACAAAAGCGAAGAGAAGCTGTACGATGACGATGACAAAGATCGTTGGGGATCGTCCCTG
CAGTGTATTAAAGTGAAAAACAATCGGCTGCCTTATGTAGCAGATAAAGATAGCATTAGTCAGGAGATT
TTCGAAAATAAAATTATCACTGACGAAACCAATGTTCAGAATTATTCAGATAAATTTTCACTGGACGAA
AGCATCTTAGATGGCCAAGTTCCGATTAACCCGGAAATTGTTGATCCGTTACTGCCGAACGTGAATATG
GAACCGTTAAACCTCCCTGGCGAAGAGATCGTATTTTATGATGACATTACGAAATATGTGGACTACCTT
AATTCTTATTACTATTTGGAAAGCCAGAAACTGTCCAATAACGTGGAAAACATTACTCTGACCACAAGC
GTGGAAGAGGCTTTAGGCTACTCAAATAAGATTTATACCTTCCTCCCGTCGCTGGCGGAAAAAGTAAAT
AAAGGTGTGCAGGCTGGTCTGTTCCTCAACTGGGCGAATGAAGTTGTCGAAGACTTTACCACGAATATT
ATGAAAAAGGATACCCTGGATAAAATCTCCGACGTCTCGGTTATTATCCCATATATTGGCCCTGCGTTA
AATATCGGTAATAGTGCGCTGCGGGGGAATTTTAACCAGGCCTTTGCTACCGCGGGCGTCGCGTTCCTC
CTGGAGGGCTTTCCTGAATTTACTATCCCGGCGCTCGGTGTTTTTACATTTTACTCTTCCATCCAGGAG

CGTGAGAAAATTATCAAAACCATCGAAAACTGCCTGGAGCAGCGGGTGAAACGCTGGAAAGATTCTTAT
CAATGGATGGTGTCAAACTGGTTATCTCGCATCACGACCCAATTCAACCATATTAATTACCAGATGTAT
GATAGTCTGTCGTACCAAGCTGACGCCATTAAAGCCAAAATTGATCTGGAATATAAAAAGTACTCTGGT
AGCGATAAGGAGAACATCAAAAGCCAGGTGGAGAACCTTAAGAATAGTCTGGATGTGAAAATCTCTGAA
GCTATGAATAACATTAACAAATTCATTCGTGAATGTTCGGTGACGTACCTGTTCAAGAATATGCTGCCA
AAAGTTATTGATGAACTGAATAAATTTGATCTGCGTACCAAAACCGAACTTATCAACCTCATCGACTCC
CACAACATTATCCTTGTGGGCGAAGTGGATCGTCTGAAGGCCAAAGTAAACGAGAGCTTTGAAAATACG
ATGCCGTTTAATATTTTTTCATATACCAATAACTCCTTGCTGAAAGATATCATCAATGAATATTTCAAT
CTAGAAGGCGGTGGCGGTAGCGGCGGTGGCGGTAGCGGCGGTGGCGGTAGCGCACTAGTGCAGGAAAGA
CCTCCATTACAACAACCTCCACATCGCGATAAGAAACCATGTAAGAATTTCTTTTGGAAAACATTTAGC
AGTTGCAAAtaataagctt

18. Protein sequence of the CT-CST28-GS20-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFEN
KIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSY
YYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKK
DTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREK
IIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDK
ENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNI
ILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSALVQERPPL
QQPPHRDKKPCKNFFWKTFSSCK

19. Protein sequence of the CT-CST28-GS30-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFEN
KIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSY
YYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKK
DTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREK
IIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDK
ENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNI
ILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSGGGGSGGGG
SALVQERPPLQQPPHRDKKPCKNFFWKTFSSCK

20. Protein sequence of the CT-SST14-GS15-L(#Fxa)HD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSIDGRNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYIDGRWGSSLQCIKVKNNRLPYVADKDSISQEIFENKII
TDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYL
ESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTL
DKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIK
TIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENI
KSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILV
GEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSALVAGCKNFFWK
TFTSC

21. Protein sequence of the CT-SST14-GS30-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFEN
KIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSY
YYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKK
DTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREK
IIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDK
ENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNI
ILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSGGGGSGGGG
SALVAGCKNFFWKTFTSC

22. Protein sequence of the CT-SST28-GS20-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFEN
KIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSY
YYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKK
DTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREK
IIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDK
ENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNI
ILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSALVSANSNP
AMAPRERKAGCKNFFWKTFTSC

23. Protein sequence of the CT-SST28-GS30-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFEN
KIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSY
YYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKK
DTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREK
IIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDK
ENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNI
ILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSGGGGSGGGG
SALVSANSNPAMAPRERKAGCKNFFWKTFTSC

24. Protein sequence of the CT-SST14-GS35-LHC fusion

PITINNFNYSDPVDNKNILYLDTHLNTLANEPEKAFRITGNIWVIPDRFSRNSNPNLNKPPRVTSPKSG
YYDPNYLSTDSDKDTFLKEIIKLFKRINSREIGEELIYRLSTDIPFPGNNNTPINTFDFDVDFNSVDVK
TRQGNNWVKTGSINPSVIITGPRENIIDPETSTFKLTNNTFAAQEGFGALSIISISPRFMLTYSNATND
VGEGRFSKSEFCMDPILILMHELNHAMHNLYGIAIPNDQTISSVTSNIFYSQYNVKLEYAEIYAFGGPT
IDLIPKSARKYFEEKALDYYRSIAKRLNSITTANPSSFNKYIGEYKQKLIRKYRFVVESSGEVTVNRNK
FVELYNELTQIFTEFNYAKIYNVQNRKIYLSNVYTPVTANILDDNVYDIQNGFNIPKSNLNVLFMGQNL
SRNPALRKVNPENMLYLFTKFCVDAIDGRSLYNKTLQCRELLVKNTDLPFIGDISDVKTDIFLRKDINE
ETEVIYYPDNVSVDQVILSKNTSEHGQLDLLYPSIDSESEILPGENQVFYDNRTQNVDYLNSYYYLESQ
KLSDNVEDFTFTRSIEEALDNSAKVYTYFPTLANKVNAGVQGGLFLMWANDVVEDFTTNILRKDTLDKI
SDVSAIIPYIGPALNISNSVRRGNFTEAFAVTGVTILLEAFPEFTIPALGAFVIYSKVQERNEIIKTID
NCLEQRIKRWKDSYEWMMGTWLSRIITQFNNISYQMYDSLNYQAGAIKAKIDLEYKKYSGSDKENIKSQ
VENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNEFDRNTKAKLINLIDSHNIILVGEV

DKLKAKVNNSFQNTIPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS
GGGGSALVAGCKNFFWKTFTSC

25. DNA sequence of the CP-SST28-GS15-LHA fusion

ggatccATGGAGTTCGTTAACAAACAGTTCAACTATAAAGACCCAGTTAACGGTGTTGACATTGCTTAC
ATCAAAATCCCGAACGCTGGCCAGATGCAGCCGGTAAAGGCATTCAAAATCCACAACAAAATCTGGGTT
ATCCCGGAACGTGATACCTTTACTAACCCGGAAGAAGGTGACCTGAACCCGCCACCGGAAGCGAAACAG
GTGCCGGTATCTTACTATGACTCCACCTACCTGTCTACCGATAACGAAAAGGACAACTACCTGAAAGGT
GTTACTAAACTGTTCGAGCGTATTTACTCCACCGACCTGGGCCGTATGCTGCTGACTAGCATCGTTCGC
GGTATCCCGTTCTGGGGCGGTTCTACCATCGATACCGAACTGAAAGTAATCGACACTAACTGCATCAAC
GTTATTCAGCCGGACGGTTCCTATCGTTCCGAAGAACTGAACCTGGTGATCATCGGCCCGTCTGCTGAT
ATCATCCAGTTCGAGTGTCTGAGCTTTGGTCACGAAGTTCTGAACCTCACCCGTAACGGCTACGGTTCC
ACTCAGTACATCCGTTTCTCTCCGGACTTCACCTTCGGTTTTGAAGAATCCCTGGAAGTAGACACGAAC
CCACTGCTGGGCGCTGGTAAATTCGCAACTGATCCTGCGGTTACCCTGGCTCACGAACTGATTCATGCA
GGCCACCGCCTGTACGGTATCGCCATCAATCCGAACCGTGTCTTCAAAGTTAACACCAACGCGTATTAC
GAGATGTCCGGTCTGGAAGTTAGCTTCGAAGAACTGCGTACTTTTGGCGGTCACGACGCTAAATTCATC
GACTCTCTGCAAGAAAACGAGTTCCGTCTGTACTACTATAACAAGTTCAAAGATATCGCATCCACCCTG
AACAAAGCGAAATCCATCGTGGGTACCACTGCTTCTCTCCAGTACATGAAGAACGTTTTTAAAGAAAAA
TACCTGCTCAGCGAAGACACCTCCGGCAAATTCTCTGTAGACAAGTTGAAATTCGATAAACTTTACAAA
ATGCTGACTGAAATTTACACCGAAGACAACTTCGTTAAGTTCTTTAAAGTTCTGAACCGCAAAACCTAT
CTGAACTTCGACAAGGCAGTATTCAAAATCAACATCGTGCCGAAAGTTAACTACACTATCTACGATGGT
TTCAACCTGCGTAACACCAACCTGGCTGCTAATTTTAACGGCCAGAACACGGAAATCAACAACATGAAC
TTCACAAAACTGAAAAACTTCACTGGTCTGTTCGAGTTTTACAAGCTGCTGTGCGTCGACGGCATCATT
ACCTCCAAAACTAAATCTGACGATGACGATAAAAGCGCCAATTCAAATCCTGCAATGGCGCCACGCGAA
CGCAAAGCTGGATGCAAAAACTTCTTTTGGAAGACATTTACTAGTTGTGCGCTAGCGGGCGGTGGCGGT
AGCGGCGGTGGCGGTAGCGGCGGTGGCGGTAGCGCACTAGTGCTGCAGTGTATCAAGGTTAACAACTGG
GATTTATTCTTCAGCCCGAGTGAAGACAACTTCACCAACGACCTGAACAAAGGTGAAGAAATCACCTCA
GATACTAACATCGAAGCAGCCGAAGAAAACATCTCGCTGGACCTGATCCAGCAGTACTACCTGACCTTT
AATTTCGACAACGAGCCGGAAAACATTTCTATCGAAAACCTGAGCTCTGATATCATCGGCCAGCTGGAA
CTGATGCCGAACATCGAACGTTTCCCAAACGGTAAAAAGTACGAGCTGGACAAATATACCATGTTCCAC
TACCTGCGCGCGCAGGAATTTGAACACGGCAAATCCCGTATCGCACTGACTAACTCCGTTAACGAAGCT
CTGCTCAACCCGTCCCGTGTATACACCTTCTTCTCTAGCGACTACGTGAAAAAGGTCAACAAAGCGACT
GAAGCTGCAATGTTCTTGGGTTGGGTTGAACAGCTTGTTTATGATTTTACCGACGAGACGTCCGAAGTA
TCTACTACCGACAAAATTGCGGATATCACTATCATCATCCCGTACATCGGTCCGGCTCTGAACATTGGC
AACATGCTGTACAAAGACGACTTCGTTGGCGCACTGATCTTCTCCGGTGCGGTGATCCTGCTGGAGTTC
ATCCCGGAAATCGCCATCCCGGTACTGGGCACCTTTGCTCTGGTTTCTTACATTGCAAACAAGGTTCTG
ACTGTACAAACCATCGACAACGCGCTGAGCAAACGTAACGAAAAATGGGATGAAGTTTACAAATATATC
GTGACCAACTGGCTGGCTAAGGTTAATACTCAGATCGACCTCATCCGCAAAAAAATGAAAGAAGCACTG
GAAAACCAGGCGGAAGCTACCAAGGCAATCATTAACTACCAGTACAACCAGTACACCGAGGAAGAAAAA
AACAACATCAACTTCAACATCGACGATCTGTCCTCTAAACTGAACGAATCCATCAACAAAGCTATGATC
AACATCAACAAGTTCCTGAACCAGTGCTCTGTAAGCTATCTGATGAACTCCATGATCCCGTACGGTGTT
AAACGTCTGGAGGACTTCGATGCGTCTCTGAAAGACGCCCTGCTGAAATACATTTACGACAACCGTGGC
ACTCTGATCGGTCAGGTTGATCGTCTGAAGGACAAAGTGAACAATACCTTATCGACCGACATCCCTTTT
CAGCTCAGTAAATATGTCGATAACCAACGCCTTTTGTCCACTtaataagctt

26. Protein sequence of the CP-SST28-GS15-LHA fusion

EFVNKQFNYKDPVNGVDIAYIKIPNAGQMQPVKAFKIHNKIWVIPERDTFTNPEEGDLNPPPEAKQVPV
SYYDSTYLSTDNEKDNYLKGVTKLFERIYSTDLGRMLLTSIVRGIPFWGGSTIDTELKVIDTNCINVIQ
PDGSYRSEELNLVIIGPSADIIQFECLSFGHEVLNLTRNGYGSTQYIRFSPDFTFGFEESLEVDTNPLL
GAGKFATDPAVTLAHELIHAGHRLYGIAINPNRVFKVNTNAYYEMSGLEVSFEELRTFGGHDAKFIDSL
QENEFRLYYYNKFKDIASTLNKAKSIVGTTASLQYMKNVFKEKYLLSEDTSGKFSVDKLKFDKLYKMLT
EIYTEDNFVKFFKVLNRKTYLNFDKAVFKINIVPKVNYTIYDGFNLRNTNLAANFNGQNTEINNMNFTK
LKNFTGLFEFYKLLCVDGIITSKTKSDDDDKSANSNPAMAPRERKAGCKNFFWKTFTSCALAGGGGSGG
GGSGGGGSALVLQCIKVNNWDLFFSPSEDNFTNDLNKGEEITSDTNIEAAEENISLDLIQQYYLTFNFD
NEPENISIENLSSDIIGQLELMPNIERFPNGKKYELDKYTMFHYLRAQEFEHGKSRIALTNSVNEALLN
PSRVYTFFSSDYVKKVNKATEAAMFLGWVEQLVYDFTDETSEVSTTDKIADITIIIPYIGPALNIGNML
YKDDFVGALIFSGAVILLEFIPEIAIPVLGTFALVSYIANKVLTVQTIDNALSKRNEKWDEVYKYIVTN
WLAKVNTQIDLIRKKMKEALENQAEATKAIINYQYNQYTEEEKNNINFNIDDLSSKLNESINKAMININ
KFLNQCSVSYLMNSMIPYGVKRLEDFDASLKDALLKYIYDNRGTLIGQVDRLKDKVNNTLSTDIPFQLS
KYVDNQRLLST

27. Protein sequence of the CT-SST28-GS15-LHB fusion

PVTINNFNYNDPIDNNNIIMMEPPFARGTGRYYKAFKITDRIWIIPERYTFGYKPEDFNKSSGIFNRDV
CEYYDPDYLNTNDKKNIFLQTMIKLFNRIKSKPLGEKLLEMIINGIPYLGDRRVPLEEFNTNIASVTVN
KLISNPGEVERKKGIFANLIIFGPGPVLNENETIDIGIQNHFASREGFGGIMQMKFCPEYVSVFNNVQE
NKGASIFNRRGYFSDPALILMHELIHVLHGLYGIKVDDLPIVPNEKKFFMQSTDAIQAEELYTFGGQDP
SIITPSTDKSIYDKVLQNFRGIVDRLNKVLVCISDPNININIYKNKFKDKYKFVEDSEGKYSIDVESFD
KLYKSLMFGFTETNIAENYKIKTRASYFSDSLPPVKIKNLLDNEIYTIEEGFNISDKDMEKEYRGQNKA
INKQAYEEISKEHLAVYKIQMCVDGIITSKTKSDDDDKNKALNLQCIDVDNEDLFFIADKNSFSDDLSK
NERIEYNTQSNYIENDFPINELILDTDLISKIELPSENTESLTDFNVDVPVYEKQPAIKKIFTDENTIF
QYLYSQTFPLDIRDISLTSSFDDALLFSNKVYSFFSMDYIKTANKVVEAGLFAGWVKQIVNDFVIEANK
SNTMDKIADISLIVPYIGLALNVGNETAKGNFENAFEIAGASILLEFIPELLIPVVGAFLLESYIDNKN
KIIKTIDNALTKRNEKWSDMYGLIVAQWLSTVNTQFYTIKEGMYKALNYQAQALEEIIKYRYNIYSEKE
KSNINIDFNDINSKLNEGINQAIDNINNFINGCSVSYLMKKMIPLAVEKLLDFDNTLKKNLLNYIDENK
LYLIGSAEYEKSKVNKYLKTIMPFDLSIYTNDTILIEMFNKYNSLEGGGGSGGGGSGGGGSALDSANSN
PAMAPRERKAGCKNFFWKTFTSC

28. Protein sequence of the CT-CST14-GS20-LHC fusion

PITINNFNYSDPVDNKNILYLDTHLNTLANEPEKAFRITGNIWVIPDRFSRNSNPNLNKPPRVTSPKSG
YYDPNYLSTDSDKDTFLKEIIKLFKRINSREIGEELIYRLSTDIPFPGNNNTPINTFDFDVDFNSVDVK
TRQGNNWVKTGSINPSVIITGPRENIIDPETSTFKLTNNTFAAQEGFGALSIISISPRFMLTYSNATND
VGEGRFSKSEFCMDPILILMHELNHAMHNLYGIAIPNDQTISSVTSNIFYSQYNVKLEYAEIYAFGGPT
IDLIPKSARKYFEEKALDYYRSIAKRLNSITTANPSSFNKYIGEYKQKLIRKYRFVVESSGEVTVNRNK
FVELYNELTQIFTEFNYAKIYNVQNRKIYLSNVYTPVTANILDDNVYDIQNGFNIPKSNLNVLFMGQNL
SRNPALRKVNPENMLYLFTKFCVDAIDGRSLYNKTLQCRELLVKNTDLPFIGDISDVKTDIFLRKDINE
ETEVIYYPDNVSVDQVILSKNTSEHGQLDLLYPSIDSESEILPGENQVFYDNRTQNVDYLNSYYYLESQ
KLSDNVEDFTFTRSIEEALDNSAKVYTYFPTLANKVNAGVQGGLFLMWANDVVEDFTTNILRKDTLDKI
SDVSAIIPYIGPALNISNSVRRGNFTEAFAVTGVTILLEAFPEFTIPALGAFVIYSKVQERNEIIKTID
NCLEQRIKRWKDSYEWMMGTWLSRIITQFNNISYQMYDSLNYQAGAIKAKIDLEYKKYSGSDKENIKSQ
VENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNEFDRNTKAKLINLIDSHNIILVGEV
DKLKAKVNNSFQNTIPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSGGGGSALVAGCKNFF
WKTFTSC

29. Protein sequence of the CT-CST17-GS25-LHC fusion

PITINNFNYSDPVDNKNILYLDTHLNTLANEPEKAFRITGNIWVIPDRFSRNSNPNLNKPPRVTSPKSG
YYDPNYLSTDSDKDTFLKEIIKLFKRINSREIGEELIYRLSTDIPFPGNNNTPINTFDFDVDFNSVDVK
TRQGNNWVKTGSINPSVIITGPRENIIDPETSTFKLTNNTFAAQEGFGALSIISISPRFMLTYSNATND
VGEGRFSKSEFCMDPILILMHELNHAMHNLYGIAIPNDQTISSVTSNIFYSQYNVKLEYAEIYAFGGPT
IDLIPKSARKYFEEKALDYYRSIAKRLNSITTANPSSFNKYIGEYKQKLIRKYRFVVESSGEVTVNRNK
FVELYNELTQIFTEFNYAKIYNVQNRKIYLSNVYTPVTANILDDNVYDIQNGFNIPKSNLNVLFMGQNL
SRNPALRKVNPENMLYLFTKFCVDAIDGRSLYNKTLQCRELLVKNTDLPFIGDISDVKTDIFLRKDINE
ETEVIYYPDNVSVDQVILSKNTSEHGQLDLLYPSIDSESEILPGENQVFYDNRTQNVDYLNSYYYLESQ
KLSDNVEDFTFTRSIEEALDNSAKVYTYFPTLANKVNAGVQGGLFLMWANDVVEDFTTNILRKDTLDKI
SDVSAIIPYIGPALNISNSVRRGNFTEAFAVTGVTILLEAFPEFTIPALGAFVIYSKVQERNEIIKTID
NCLEQRIKRWKDSYEWMMGTWLSRIITQFNNISYQMYDSLNYQAGAIKAKIDLEYKKYSGSDKENIKSQ
VENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNEFDRNTKAKLINLIDSHNIILVGEV
DKLKAKVNNSFQNTIPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSGGGGSGGGGSALVDR
MPCRNFFWKTFSSCK

30. Protein sequence of the CT-CST29-GS15-LHA fusion

EFVNKQFNYKDPVNGVDIAYIKIPNAGQMQPVKAFKIHNKIWVIPERDTFTNPEEGDLNPPPEAKQVPV
SYYDSTYLSTDNEKDNYLKGVTKLFERIYSTDLGRMLLTSIVRGIPFWGGSTIDTELKVIDTNCINVIQ
PDGSYRSEELNLVIIGPSADIIQFECLSFGHEVLNLTRNGYGSTQYIRFSPDFTFGFEESLEVDTNPLL
GAGKFATDPAVTLAHELIHAGHRLYGIAINPNRVFKVNTNAYYEMSGLEVSFEELRTFGGHDAKFIDSL
QENEFRLYYYNKFKDIASTLNKAKSIVGTTASLQYMKNVFKEKYLLSEDTSGKFSVDKLKFDKLYKMLT
EIYTEDNFVKFFKVLNRKTYLNFDKAVFKINIVPKVNYTIYDGFNLRNTNLAANFNGQNTEINNMNFTK
LKNFTGLFEFYKLLCVDGIITSKTKSDDDDKNKALNLQCIKVNNWDLFFSPSEDNFTNDLNKGEEITSD
TNIEAAEENISLDLIQQYYLTFNFDNEPENISIENLSSDIIGQLELMPNIERFPNGKKYELDKYTMFHY
LRAQEFEHGKSRIALTNSVNEALLNPSRVYTFFSSDYVKKVNKATEAAMFLGWVEQLVYDFTDETSEVS
TTDKIADITIIIPYIGPALNIGNMLYKDDFVGALIFSGAVILLEFIPEIAIPVLGTFALVSYIANKVLT
VQTIDNALSKRNEKWDEVYKYIVTNWLAKVNTQIDLIRKKMKEALENQAEATKAIINYQYNQYTEEEKN
NINFNIDDLSSKLNESINKAMININKFLNQCSVSYLMNSMIPYGVKRLEDFDASLKDALLKYIYDNRGT

LIGQVDRLKDKVNNTLSTDIPFQLSKYVDNQRLLSTLEGGGGSGGGGSGGGGSALVQEGAPPQQSARRD
RMPCRNFFWKTFSSCK

31. Protein sequence of the CT-CST29-GS30-LHB fusion

PVTINNFNYNDPIDNNNIIMMEPPFARGTGRYYKAFKITDRIWIIPERYTFGYKPEDFNKSSGIFNRDV
CEYYDPDYLNTNDKKNIFLQTMIKLFNRIKSKPLGEKLLEMIINGIPYLGDRRVPLEEFNTNIASVTVN
KLISNPGEVERKKGIFANLIIFGPGPVLNENETIDIGIQNHFASREGFGGIMQMKFCPEYVSVFNNVQE
NKGASIFNRRGYFSDPALILMHELIHVLHGLYGIKVDDLPIVPNEKKFFMQSTDAIQAEELYTFGGQDP
SIITPSTDKSIYDKVLQNFRGIVDRLNKVLVCISDPNININIYKNKFKDKYKFVEDSEGKYSIDVESFD
KLYKSLMFGFTETNIAENYKIKTRASYFSDSLPPVKIKNLLDNEIYTIEEGFNISDKDMEKEYRGQNKA
INKQAYEEISKEHLAVYKIQMCVDGIITSKTKSDDDDKNKALNLQCIDVDNEDLFFIADKNSFSDDLSK
NERIEYNTQSNYIENDFPINELILDTDLISKIELPSENTESLTDFNVDVPVYEKQPAIKKIFTDENTIF
QYLYSQTFPLDIRDISLTSSFDDALLFSNKVYSFFSMDYIKTANKVVEAGLFAGWVKQIVNDFVIEANK
SNTMDKIADISLIVPYIGLALNVGNETAKGNFENAFEIAGASILLEFIPELLIPVVGAFLLESYIDNKN
KIIKTIDNALTKRNEKWSDMYGLIVAQWLSTVNTQFYTIKEGMYKALNYQAQALEEIIKYRYNIYSEKE
KSNINIDFNDINSKLNEGINQAIDNINNFINGCSVSYLMKKMIPLAVEKLLDFDNTLKKNLLNYIDENK
LYLIGSAEYEKSKVNKYLKTIMPFDLSIYTNDTILIEMFNKYNSLEGGGGSGGGGSGGGGSGGGGSGGG
GSGGGGSALDQEGAPPQQSARRDRMPCRNFFWKTFSSCK

32. DNA sequence of IgA-$H_N$tet

ggatccATGGAGTCCAATCAGCCGGAAAAAAATGGAACCGCGACTAAACCCGAGAATTCGGGGAACACT
ACGTCGGAAAACGGCCAGACGGAACCTGAGAAGAAACTGGAACTACGAAATGTGTCCGATATCGAGCTA
TACTCTCAAACCAATGGAACCTATAGGCAGCATGTTTCATTGGACGGAATCCCAGAAAATACGGATACA
TATTTCGTCAAAGTGAAGTCTAGCGCATTCAAGGATGTATATATCCCCGTTGCGAGTATTACAGAAGAG
AAGCGGAACGGTCAAAGCGTTTATAAGATTACAGCAAAGGCCGAAAAGTTACAACAGGAGTTAGAAAAC
AAATACGTTGACAATTTCACTTTTTATCTCGATAAAAAGGCTAAAGAGGAAAACACGAACTTCACGTCA
TTTAGTAATCTGGTCAAAGCCATAAATCAAAATCCATCTGGTACATACCATCTCGCGGCAAGTCTAAAC
GCGAATGAAGTAGAACTTGGCCCGGACGAGCGTTCATACATTAAGGATACCTTTACTGGCAGACTCATA
GGGGAAAAAGACGGTAAGAACTATGCTATATACAATTTGAAAAAGCCTTTATTTGAGAACCTGTCGGGC
GCCACCGTCGAGAAATTGTCCCTTAAAAACGTAGCTATAAGCGGAAAGAATGACATCGGTAGTCTTGCA
AACGAGGCTACTAACGGGACAAAGATTAAACAAGTGCACGTAGATGGGtgtgtcgacggcatcattacc
tccaaaactaaatctgacgatgacgataaaaacaaagcgctgaacctgcagtgcattaaaataaagaat
gaggatttgacattcatcgcagaaaaaaatagcttcagcgaagagccgttccaagatgagatagtaagc
tacaacaccaagaacaagccgcttaattttaattactcgttagataaaatcatagttgactacaacctt
caatcgaagatcacgttaccgaatgacagaacaactcctgtcacaaaaggaattccctatgcacctgag
tataagtcaaatgccgcgtcaacaatagagattcataatatagatgacaacaccatctatcaatatctg
tacgctcagaaaagtccaacaactcttcagcgtataacaatgaccaatagtgtcgatgacgcattgata
aattctaccaagatatactcttatttcccgagcgtcatctccaaagttaatcaaggtgctcaaggcatt
ctatttttgcaatgggtccgagacatcatagatgacttcactaatgagtcgtctcagaaaaccacgatt
gataaaatatcagatgtttccaccatcgtcccctacatcggacctgcgcttaacattgtgaagcagggg
tatgaggggaattttatcggagcgttagaaactacgggggttgtgctattacttgaatacataccagag
ataacattgcccgttatagcggccctcagtatcgcagaatcaagtacacaaaaagaaaagataatcaaa
acaatcgacaacttcctagaaaagaggtacgaaaaatggatagaggtttataaactcgtgaaagcgaaa
tggttaggcactgttaatacgcagttccaaaagagatcctatcaaatgtatagatcactggagtaccag
gtggatgccataaagaaaattatcgactatgaatataaaatatattcaggtccagataaggagcagata
gctgatgaaataaacaatttaaaaaacaaacttgaagagaaggcgaataaggccatgatcaatatcaat
atttttatgcgagaatcttcacgatctttttggtaaatcagatgattaacgaagccaaaaagcagctg
cttgagttcgacacacagtccaaaaacatactaatgcaatatatcaaagcaaactcaaaattcattgga
attactgagctgaagaaactggaatccaaaataaataaagtattctctaccccgatcccgttctcttac
tctaaaaaccttgactgctgggtagataacgaagaagatattgacgttctagagtaataagctt

33. Protein sequence of the CT-GHRP-LHC fusion

PITINNFNYSDPVDNKNILYLDTHLNTLANEPEKAFRITGNIWVIPDRFSRNSNPNLNKPPRVTSPKSG
YYDPNYLSTDSDKDTFLKEIIKLFKRINSREIGEELIYRLSTDIPFPGNNNTPINTFDFDVDFNSVDVK
TRQGNNWVKTGSINPSVIITGPRENIIDPETSTFKLTNNTFAAQEGFGALSIISISPRFMLTYSNATND
VGEGRFSKSEFCMDPILILMHELNHAMHNLYGIAIPNDQTISSVTSNIFYSQYNVKLEYAEIYAFGGPT
IDLIPKSARKYFEEKALDYYRSIAKRLNSITTANPSSFNKYIGEYKQKLIRKYRFVVESSGEVTVNRNK
FVELYNELTQIFTEFNYAKIYNVQNRKIYLSNVYTPVTANILDDNVYDIQNGFNIPKSNLNVLFMGQNL
SRNPALRKVNPENMLYLFTKFCVDAIDGRSLYNKTLQCRELLVKNTDLPFIGDISDVKTDIFLRKDINE
ETEVIYYPDNVSVDQVILSKNTSEHGQLDLLYPSIDSESEILPGENQVFYDNRTQNVDYLNSYYYLESQ
KLSDNVEDFTFTRSIEEALDNSAKVYTYFPTLANKVNAGVQGGLFLMWANDVVEDFTTNILRKDTLDKI

SDVSAIIPYIGPALNISNSVRRGNFTEAFAVTGVTILLEAFPEFTIPALGAFVIYSKVQERNEIIKTID
NCLEQRIKRWKDSYEWMMGTWLSRIITQFNNISYQMYDSLNYQAGAIKAKIDLEYKKYSGSDKENIKSQ
VENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNEFDRNTKAKLINLIDSHNIILVGEV
DKLKAKVNNSFQNTIPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSALVGSSFLSPEHQRV
QQRKESKKPPAKLQPR

34. Protein sequence of the CT-GHRH-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFEN
KIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSY
YYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKK
DTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREK
IIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDK
ENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNI
ILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSALVYADAIF
TNSYRKVLGQLSARKLLQDIMSRQQGESNQERGA

35. Protein sequence of the CT-GHRP-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFEN
KIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSY
YYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKK
DTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREK
IIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDK
ENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNI
ILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSALVGSSFLS
PEHQRVQQRKESKKPPAKLQPR

36. Protein sequence of the CT-ghrelin-LHA fusion

EFVNKQFNYKDPVNGVDIAYIKIPNAGQMQPVKAFKIHNKIWVIPERDTFTNPEEGDLNPPPEAKQVPV
SYYDSTYLSTDNEKDNYLKGVTKLFERIYSTDLGRMLLTSIVRGIPFWGGSTIDTELKVIDTNCINVIQ
PDGSYRSEELNLVIIGPSADIIQFECKSFGHEVLNLTRNGYGSTQYIRFSPDFTFGFEESLEVDTNPLL
GAGKFATDPAVTLAHELIHAGHRLYGIAINPNRVFKVNTNAYYEMSGLEVSFEELRTFGGHDAKFIDSL
QENEFRLYYYNKFKDIASTLNKAKSIVGTTASLQYMKNVFKEKYLLSEDTSGKFSVDKLKFDKLYKMLT
EIYTEDNFVKFFKVLNRKTYLNFDKAVFKINIVPKVNYTIYDGFNLRNTNLAANFNGQNTEINNMNFTK
LKNFTGLFEFYKLLCVDGIITSKTKSDDDDKNKALNLQCIKVNNWDLFFSPSEDNFTNDLNKGEEITSD
TNIEAAEENISLDLIQQYYLTFNFDNEPENISIENLSSDIIGQLELMPNIERFPNGKKYELDKYTMFHY
LRAQEFEHGKSRIALTNSVNEALLNPSRVYTFFSSDYVKKVNKATEAAMFLGWVEQLVYDFTDETSEVS
TTDKIADITIIIPYIGPALNIGNMLYKDDFVGALIFSGAVILLEFIPEIAIPVLGTFALVSYIANKVLT
VQTIDNALSKRNEKWDEVYKYIVTNWLAKVNTQIDLIRKKMKEALENQAEATKAIINYQYNQYTEEEKN
NINFNIDDLSSKLNESINKAMININKFLNQCSVSYLMNSMIPYGVKRLEDFDASLKDALLKYIYDNRGT
LIGQVDRLKDKVNNTLSTDIPFQLSKYVDNQRLLSTLEGGGGSGGGGSGGGGSALVGSSFLSPEHQRVQ
QRKESKKPPAKLQPR

37. Protein sequence of the IgA-$H_F$tet-CT-SST14 Fusion

ESNQPEKNGTATKPENSGNTTSENGQTEPEKKLELRNVSDIELYSQTNGTYRQHVSLDGIPENTDTYFVKV
KSSAFKDVYIPVASITEEKRNGQSVYKITAKAEKLQQELENKYVDNFTFYLDKKAKEENTNFTSFSNLVKA
INQNPSGTYHLAASLNANEVELGPDERSYIKDTFTGRLIGEKDGKNYAIYNLKKPLFENLSGATVEKLSLK
NVAISGKNDIGSLANEATNGTKIKQVHVDGCVDGIITSKTKSDDDDKNKALNLQCIKIKNEDLTFIAEKNS
FSEEPFQDEIVSYNTKNKPLNFNYSLDKIIVDYNLQSKITLPNDRTTPVTKGIPYAPEYKSNAASTIEIHN

IDDNTIYQYLYAQKSPTTLQRITMTNSVDDALINSTKIYSYFPSVISKVNQGAQGILFLQWVRDIIDDFTN
ESSQKTTIDKISDVSTIVPYIGPALNIVKQGYEGNFIGALETTGVVLLLEYIPEITLPVIAALSIAESSTQ
KEKIIKTIDNFLEKRYEKWIEVYKLVKAKWLGTVNTQFQKRSYQMYRSLEYQVDAIKKIIDYEYKIYSGPD
KEQIADEINNLKNKLEEKANKAMININIFMRESSRSFLVNQMINEAKKQLLEFDTQSKNILMQYIKANSKF
IGITELKKLESKINKVFSTPIPFSYSKNLDCWVDNEEDIDVLEGGGGSGGGGSGGGGSALVAGCKNFFWKT
FTSC

38. Protein sequence of the IgA-$H_N$tet-CT-GHRP Fusion

ESNQPEKNGTATKPENSGNTTSENGQTEPEKKLELRNVSDIELYSQTNGTYRQHVSLDGIPENTDTYFVKV
KSSAFKDVYIPVASITEEKRNGQSVYKITAKAEKLQQELENKYVDNFTFYLDKKAKEENTNFTSFSNLVKA
INQNPSGTYHLAASLNANEVELGPDERSYIKDTFTGRLIGEKDGKNYAIYNLKKPLFENLSGATVEKLSLK
NVAISGKNDIGSLANEATNGTKIKQVHVDGCVDGIITSKTKSDDDDKNKALNLQCIKIKNEDLTFIAEKNS
FSEEPFQDEIVSYNTKNKPLNFNYSLDKIIVDYNLQSKITLPNDRTTPVTKGIPYAPEYKSNAASTIEIHN
IDDNTIYQYLYAQKSPTTLQRITMTNSVDDALINSTKIYSYFPSVISKVNQGAQGILFLQWVRDIIDDFTN
ESSQKTTIDKISDVSTIVPYIGPALNIVKQGYEGNFIGALETTGVVLLLEYIPEITLPVIAALSIAESSTQ
KEKIIKTIDNFLEKRYEKWIEVYKLVKAKWLGTVNTQFQKRSYQMYRSLEYQVDAIKKIIDYEYKIYSGPD
KEQIADEINNLKNKLEEKANKAMININIFMRESSRSFLVNQMINEAKKQLLEFDTQSKNILMQYIKANSKF
IGITELKKLESKINKVFSTPIPFSYSKNLDCWVDNEEDIDVLEGGGGSGGGGSGGGGSALVGSSFLSPEHQ
RVQQRKESKKPPAKLQPR

39. Protein sequence of the CT-ghrelin S3W-LHA fusion

EFVNKQFNYKDPVNGVDIAYIKIPNAGQMQPVKAFKIHNKIWVIPERDTFTNPEEGDLNPPPEAKQVPVSY
YDSTYLSTDNEKDNYLKGVTKLFERIYSTDLGRMLLTSIVRGIPFWGGSTIDTELKVIDTNCINVIQPDGS
YRSEELNLVIIGPSADIIQFECKSFGHEVLNLTRNGYGSTQYIRFSPDFTFGFEESLEVDTNPLLGAGKFA
TDPAVTLAHELIHAGHRLYGIAINPNRVFKVNTNAYYEMSGLEVSFEELRTFGGHDAKFIDSLQENEFRLY
YYNKFKDIASTLNKAKSIVGTTASLQYMKNVFKEKYLLSEDTSGKFSVDKLKFDKLYKMLTEIYTEDNFVK
FFKVLNRKTYLNFDKAVFKINIVPKVNYTIYDGFNLRNTNLAANFNGQNTEINNMNFTKLKNFTGLFEFYK
LLCVDGIITSKTKSDDDDKNKALNLQCIKVNNWDLFFSPSEDNFTNDLNKGEEITSDTNIEAAEENISLDL
IQQYYLTFNFDNEPENISIENLSSDIIGQLELMPNIERFPNGKKYELDKYTMFHYLRAQEFEHGKSRIALT
NSVNEALLNPSRVYTFFSSDYVKKVNKATEAAMFLGWVEQLVYDFTDETSEVSTTDKIADITIIIPYIGPA
LNIGNMLYKDDFVGALIFSGAVILLEFIPEIAIPVLGTFALVSYIANKVLTVQTIDNALSKRNEKWDEVYK
YIVTNWLAKVNTQIDLIRKKMKEALENQAEATKAIINYQYNQYTEEEKNNINFNIDDLSSKLNESINKAMI
NINKFLNQCSVSYLMNSMIPYGVKRLEDFDASLKDALLKYIYDNRGTLIGQVDRLKDKVNNTLSTDIPFQL
SKYVDNQRLLSTLEIYALVGSWFLSPEHQRVQQRKESKKPPAKLQPR

40. Protein sequence of the CT-GRP-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFEN
KIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSY
YYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKK
DTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREK
IIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDK
ENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNI
ILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSALVGNHWAV
GHLM

41. Protein sequence of the CT-GRP-LHB fusion

PVTINNFNYNDPIDNNNIIMMEPPFARGTGRYYKAFKITDRIWIIPERYTFGYKPEDFNKSSGIFNRDV
CEYYDPDYLNTNDKKNIFLQTMIKLFNRIKSKPLGEKLLEMIINGIPYLGDRRVPLEEFNTNIASVTVN
KLISNPGEVERKKGIFANLIIFGPGPVLNENETIDIGIQNHFASREGFGGIMQMKFCPEYVSVFNNVQE
NKGASIFNRRGYFSDPALILMHELIHVLHGLYGIKVDDLPIVPNEKKFFMQSTDAIQAEELYTFGGQDP
SIITPSTDKSIYDKVLQNFRGIVDRLNKVLVCISDPNININIYKNKFKDKYKFVEDSEGKYSIDVESFD
KLYKSLMFGFTETNIAENYKIKTRASYFSDSLPPVKIKNLLDNEIYTIEEGFNISDKDMEKEYRGQNKA
INKQAYEEISKEHLAVYKIQMCVDEEKLYDDDDKDRWGSSLQCIDVDNEDLFFIADKNSFSDDLSKNER
IEYNTQSNYIENDFPINELILDTDLISKIELPSENTESLTDFNVDVPVYEKQPAIKKIFTDENTIFQYL

YSQTFPLDIRDISLTSSFDDALLFSNKVYSFFSMDYIKTANKVVEAGLFAGWVKQIVNDFVIEANKSNT
MDAIADISLIVPYIGLALNVGNETAKGNFENAFEIAGASILLEFIPELLIPVVGAFLLESYIDNKNKII
KTIDNALTKRNEKWSDMYGLIVAQWLSTVNTQFYTIKEGMYKALNYQAQALEEIIKYRYNIYSEKEKSN
INIDFNDINSKLNEGINQAIDNINNFINGCSVSYLMKKMIPLAVEKLLDFDNTLKKNLLNYIDENKLYL
IGSAEYEKSKVNKYLKTIMPFDLSIYTNDTILIEMFNKYNSLEGGGGSGGGGSGGGGSALVGNHWAVGH
LM

42. Protein sequence of the CP-qGHRH29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDNNNNNNNNNNDDDDKHVDAIFTQSYRKVLAQLSARKLLQDILNRA
EAAAKEAAAKALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILDGQVPINP
EIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEALGYSNKI
YTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGNSALRGNF
NQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMVSNWLSRI
TTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNNINKFIRE
CSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFNIFSYTNN
SLLKDIINEYFN

43. Protein sequence of the CP-qGHRH-LHA fusion

EFVNKQFNYKDPVNGVDIAYIKIPNAGQMQPVKAFKIHNKIWVIPERDTFTNPEEGDLNPPPEAKQVPV
SYYDSTYLSTDNEKDNYLKGVTKLFERIYSTDLGRMLLTSIVRGIPFWGGSTIDTELKVIDTNCINVIQ
PDGSYRSEELNLVIIGPSADIIQFECKSFGHEVLNLTRNGYGSTQYIRFSPDFTFGFEESLEVDTNPLL
GAGKFATDPAVTLAHELIHAGHRLYGIAINPNRVFKVNTNAYYEMSGLEVSFEELRTFGGHDAKFIDSL
QENEFRLYYYNKFKDIASTLNKAKSIVGTTASLQYMKNVFKEKYLLSEDTSGKFSVDKLKFDKLYKMLT
EIYTEDNFVKFFKVLNRKTYLNFDKAVFKINIVPKVNYTIYDGFNLRNTNLAANFNGQNTEINNMNFTK
LKNFTGLFEFYKLLCVDGIITSKTKSLIEGRHVDAIFTQSYRKVLAQLSARKLLQDILNRQQGERNQEQ
GALAGGGGSGGGGSGGGGSALVLQCIKVNNWDLFFSPSEDNFTNDLNKGEEITSDTNIEAAEENISLDL
IQQYYLTFNFDNEPENISIENLSSDIIGQLELMPNIERFPNGKKYELDKYTMFHYLRAQEFEHGKSRIA
LTNSVNEALLNPSRVYTFFSSDYVKKVNKATEAAMFLGWVEQLVYDFTDETSEVSTTDKIADITIIIPY
IGPALNIGNMLYKDDFVGALIFSGAVILLEFIPEIAIPVLGTFALVSYIANKVLTVQTIDNALSKRNEK
WDEVYKYIVTNWLAKVNTQIDLIRKKMKEALENQAEATKAIINYQYNQYTEEEKNNINFNIDDLSSKLN
ESINKAMININKFLNQCSVSYLMNSMIPYGVKRLEDFDASLKDALLKYIYDNRGTLIGQVDRLKDKVNN
TLSTDIPFQLSKYVDNQRLLST

44. Protein sequence of the CP-qGHRH-LHC fusion

PITINNFNYSDPVDNKNILYLDTHLNTLANEPEKAFRITGNIWVIPDRFSRNSNPNLNKPPRVTSPKSG
YYDPNYLSTDSDKDTFLKEIIKLFKRINSREIGEELIYRLSTDIPFPGNNNTPINTFDFDVDFNSVDVK
TRQGNNWVKTGSINPSVIITGPRENIIDPETSTFKLTNNTFAAQEGFGALSIISISPRFMLTYSNATND
VGEGRFSKSEFCMDPILILMHELNHAMHNLYGIAIPNDQTISSVTSNIFYSQYNVKLEYAEIYAFGGPT
IDLIPKSARKYFEEKALDYYRSIAKRLNSITTANPSSFNKYIGEYKQKLIRKYRFVVESSGEVTVNRNK
FVELYNELTQIFTEFNYAKIYNVQNRKIYLSNVYTPVTANILDDNVYDIQNGFNIPKSNLNVLFMGQNL
SRNPALRKVNPENMLYLFTKFCVDAIDGRHVDAIFTQSYRKVLAQLSARKLLQDILNRQQGERNQEQGA
LAGGGGSGGGGSGGGGSALVLQCRELLVKNTDLPFIGDISDVKTDIFLRKDINEETEVIYYPDNVSVDQ
VILSKNTSEHGQLDLLYPSIDSESEILPGENQVFYDNRTQNVDYLNSYYYLESQKLSDNVEDFTFTRSI
EEALDNSAKVYTYFPTLANKVNAGVQGGLFLMWANDVVEDFTTNILRKDTLDKISDVSAIIPYIGPALN
ISNSVRRGNFTEAFAVTGVTILLEAFPEFTIPALGAFVIYSKVQERNEIIKTIDNCLEQRIKRWKDSYE
WMMGTWLSRIITQFNNISYQMYDSLNYQAGAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEA
MNNINKFIRECSVTYLFKNMLPKVIDELNEFDRNTKAKLINLIDSHNIILVGEVDKLKAKVNNSFQNTI
PFNIFSYTNNSLLKDIINEYFN

45. Protein sequence of the CP-qGHRH-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD

VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKHVDAIFTQSYRKVLAQLSARKLLQDILNRQQ
GERNQEQGAALAGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNY
SDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNV
ENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVI
IPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQR
VKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKN
SLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAK
VNESFENTMPFNIFSYTNNSLLKDIINEYFN

46. Protein sequence of the CP-qGHRH-LHD N10-PL5 fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDNNNNNNNNNNDDDDKHVDAIFTQSYRKVLAQLSARKLLQDILNRQ
QGERNQEQGAPAPAPLQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILDGQV
PINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEALGY
SNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGNSAL
RGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMVSNW
LSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNNINK
FIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFNIFS
YTNNSLLKDIINEYFN

47. Protein sequence of the CP-qGHRH-LHD N10-HX12 fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQSYY
DPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVEKFEN
GSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSNQSSAVL
GKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLDVEIIPQIE
RSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDKFNSLYSDLTN
VMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNIERNPALQKLSSE
SVVDLFTKVCVDNNNNNNNNNNNDDDDKHVDAIFTQSYRKVLAQLSARKLLQDILNRQQGERNQEQGAEAAA
KEAAAKALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPL
LPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLA
EKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVA
FLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMY
DSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKV
IDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFN

48. Protein sequence of the CP-UTS-LHA fusion

EFVNKQFNYKDPVNGVDIAYIKIPNAGQMQPVKAFKIHNKIWVIPERDTFTNPEEGDLNPPPEAKQVPV
SYYDSTYLSTDNEKDNYLKGVTKLFERIYSTDLGRMLLTSIVRGIPFWGGSTIDTELKVIDTNCINVIQ
PDGSYRSEELNLVIIGPSADIIQFECKSFGHEVLNLTRNGYGSTQYIRFSPDFTFGFEESLEVDTNPLL
GAGKFATDPAVTLAHELIHAGHRLYGIAINPNRVFKVNTNAYYEMSGLEVSFEELRTFGGHDAKFIDSL
QENEFRLYYYNKFKDIASTLNKAKSIVGTTASLQYMKNVFKEKYLLSEDTSGKFSVDKLKFDKLYKMLT
EIYTEDNFVKFFKVLNRKTYLNFDKAVFKINIVPKVNYTIYDGFNLRNTNLAANFNGQNTEINNMNFTK
LKNFTGLFEFYKLLCVDGGGGSADDDDKNDDPPISIDLTFHLLRNMIEMARIENEREQAGLNRKYLDEV
ALAGGGGSGGGGSGGGGSALVLQCIKVNNWDLFFSPSEDNFTNDLNKGEEITSDTNIEAAEENISLDLI
QQYYLTFNFDNEPENISIENLSSDIIGQLELMPNIERFPNGKKYELDKYTMFHYLRAQEFEHGKSRIAL
TNSVNEALLNPSRVYTFFSSDYVKKVNKATEAAMFLGWVEQLVYDFTDETSEVSTTDKIADITIIIPYI
GPALNIGNMLYKDDFVGALIFSGAVILLEFIPEIAIPVLGTFALVSYIANKVLTVQTIDNALSKRNEKW
DEVYKYIVTNWLAKVNTQIDLIRKKMKEALENQAEATKAIINYQYNQYTEEEKNNINFNIDDLSSKLNE
SINKAMININKFLNQCSVSYLMNSMIPYGVKRLEDFDASLKDALLKYIYDNRGTLIGQVDRLKDKVNNT
LSTDIPFQLSKYVDNQRLLST

49. Protein sequence of LH_N/A

EFVNKQFNYKDPVNGVDIAYIKIPNAGQMQPVKAFKIHNKIWVIPERDTFTNPEEGDLNPPPEAKQVPV
SYYDSTYLSTDNEKDNYLKGVTKLFERIYSTDLGRMLLTSIVRGIPFWGGSTIDTELKVIDTNCINVIQ
PDGSYRSEELNLVIIGPSADIIQFECKSFGHEVLNLTRNGYGSTQYIRFSPDFTFGFEESLEVDTNPLL
GAGKFATDPAVTLAHELIHAGHRLYGIAINPNRVFKVNTNAYYEMSGLEVSFEELRTFGGHDAKFIDSL
QENEFRLYYYNKFKDIASTLNKAKSIVGTTASLQYMKNVFKEKYLLSEDTSGKFSVDKLKFDKLYKMLT
EIYTEDNFVKFFKVLNRKTYLNFDKAVFKINIVPKVNYTIYDGFNLRNTNLAANFNGQNTEINNMNFTK
LKNFTGLFEFYKLLCVDGIITSKTKSDDDDKNKALNLQCIKVNNWDLFFSPSEDNFTNDLNKGEEITSD
TNIEAAEENISLDLIQQYYLTFNFDNEPENISIENLSSDIIGQLELMPNIERFPNGKKYELDKYTMFHY
LRAQEFEHGKSRIALTNSVNEALLNPSRVYTFFSSDYVKKVNKATEAAMFLGWVEQLVYDFTDETSEVS
TTDKIADITIIIPYIGPALNIGNMLYKDDFVGALIFSGAVILLEFIPEIAIPVLGTFALVSYIANKVLT
VQTIDNALSKRNEKWDEVYKYIVTNWLAKVNTQIDLIRKKMKEALENQAEATKAIINYQYNQYTEEEKN
NINFNIDDLSSKLNESINKAMININKFLNQCSVSYLMNSMIPYGVKRLEDFDASLKDALLKYIYDNRGT
LIGQVDRLKDKVNNTLSTDIPFQLSKYVDNQRLLST

50. Protein sequence of LH_N/B

PVTINNFNYNDPIDNNNIIMMEPPFARGTGRYYKAFKITDRIWIIPERYTFGYKPEDFNKSSGIFNRDV
CEYYDPDYLNTNDKKNIFLQTMIKLFNRIKSKPLGEKLLEMIINGIPYLGDRRVPLEEFNTNIASVTVN
KLISNPGEVERKKGIFANLIIFGPGPVLNENETIDIGIQNHFASREGFGGIMQMKFCPEYVSVFNNVQE
NKGASIFNRRGYFSDPALILMHELIHVLHGLYGIKVDDLPIVPNEKKFFMQSTDAIQAEELYTFGGQDP
SIITPSTDKSIYDKVLQNFRGIVDRLNKVLVCISDPNININIYKNKFKDKYKFVEDSEGKYSIDVESFD
KLYKSLMFGFTETNIAENYKIKTRASYFSDSLPPVKIKNLLDNEIYTIEEGFNISDKDMEKEYRGQNKA
INKQAYEEISKEHLAVYKIQMCVDEEKLYDDDDKDRWGSSLQCIDVDNEDLFFIADKNSFSDDLSKNER
IEYNTQSNYIENDFPINELILDTDLISKIELPSENTESLTDFNVDVPVYEKQPAIKKIFTDENTIFQYL
YSQTFPLDIRDISLTSSFDDALLFSNKVYSFFSMDYIKTANKVVEAGLFAGWVKQIVNDFVIEANKSNT
MDAIADISLIVPYIGLALNVGNETAKGNFENAFEIAGASILLEFIPELLIPVVGAFLLESYIDNKNKII
KTIDNALTKRNEKWSDMYGLIVAQWLSTVNTQFYTIKEGMYKALNYQAQALEEIIKYRYNIYSEKEKSN
INIDFNDINSKLNEGINQAIDNINNFINGCSVSYLMKKMIPLAVEKLLDFDNTLKKNLLNYIDENKLYL
IGSAEYEKSKVNKYLKTIMPFDLSIYTNDTILIEMFNKYNS

51. Protein sequence of LH_N/C

PITINNFNYSDPVDNKNILYLDTHLNTLANEPEKAFRITGNIWVIPDRFSRNSNPNLNKPPRVTSPKSG
YYDPNYLSTDSDKDTFLKEIIKLFKRINSREIGEELIYRLSTDIPFPGNNNTPINTFDFDVDFNSVDVK
TRQGNNWVKTGSINPSVIITGPRENIIDPETSTFKLTNNTFAAQEGFGALSIISISPRFMLTYSNATND
VGEGRFSKSEFCMDPILILMHELNHAMHNLYGIAIPNDQTISSVTSNIFYSQYNVKLEYAEIYAFGGPT
IDLIPKSARKYFEEKALDYYRSIAKRLNSITTANPSSFNKYIGEYKQKLIRKYRFVVESSGEVTVNRNK
FVELYNELTQIFTEFNYAKIYNVQNRKIYLSNVYTPVTANILDDNVYDIQNGFNIPKSNLNVLFMGQNL
SRNPALRKVNPENMLYLFTKFCVDAIDGRSLYNKTLQCRELLVKNTDLPFIGDISDVKTDIFLRKDINE
ETEVIYYPDNVSVDQVILSKNTSEHGQLDLLYPSIDSESEILPGENQVFYDNRTQNVDYLNSYYYLESQ
KLSDNVEDFTFTRSIEEALDNSAKVYTYFPTLANKVNAGVQGGLFLMWANDVVEDFTTNILRKDTLDKI
SDVSAIIPYIGPALNISNSVRRGNFTEAFAVTGVTILLEAFPEFTIPALGAFVIYSKVQERNEIIKTID
NCLEQRIKRWKDSYEWMMGTWLSRIITQFNNISYQMYDSLNYQAGAIKAKIDLEYKKYSGSDKENIKSQ
VENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNEFDRNTKAKLINLIDSHNIILVGEV
DKLKAKVNNSFQNTIPFNIFSYTNNSLLKDIINEYFN

52. Protein sequence of LH_N/D

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFEN
KIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSY
YYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKK
DTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREK
IIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDK
ENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNI
ILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFN

53. Protein sequence of IgA-$H_N$tet

ESNQPEKNGTATKPENSGNTTSENGQTEPEKKLELRNVSDIELYSQTNGTYRQHVSLDGIPENTDTYFV
KVKSSAFKDVYIPVASITEEKRNGQSVYKITAKAEKLQQELENKYVDNFTFYLDKKAKEENTNFTSFSN
LVKAINQNPSGTYHLAASLNANEVELGPDERSYIKDTFTGRLIGEKDGKNYAIYNLKKPLFENLSGATV
EKLSLKNVAISGKNDIGSLANEATNGTKIKQVHVDGCVDGIITSKTKSDDDDKNKALNLQCIKIKNEDL
TFIAEKNSFSEEPFQDEIVSYNTKNKPLNFNYSLDKIIVDYNLQSKITLPNDRTTPVTKGIPYAPEYKS
NAASTIEIHNIDDNTIYQYLYAQKSPTTLQRITMTNSVDDALINSTKIYSYFPSVISKVNQGAQGILFL
QWVRDIIDDFTNESSQKTTIDKISDVSTIVPYIGPALNIVKQGYEGNFIGALETTGVVLLLEYIPEITL
PVIAALSIAESSTQKEKIIKTIDNFLEKRYEKWIEVYKLVKAKWLGTVNTQFQKRSYQMYRSLEYQVDA
IKKIIDYEYKIYSGPDKEQIADEINNLKNKLEEKANKAMININIFMRESSRSFLVNQMINEAKKQLLEF
DTQSKNILMQYIKANSKFIGITELKKLESKINKVFSTPIPFSYSKNLDCWVDNEEDIDV

54. Synthesised Octreotide peptide

Cys-Dphe-Cys-Phe-Dtrp-Lys-Thr-Cys-Thr-ol

55. Synthesised GHRH agonist peptide

HIS-ALA-ASP-ALA-ILE-PHE-THR-ASN-SER-TYR-ARG-LYS-VAL-LEU-GLY-GLN-LEU-
SER-ALA-ARG-LYS-LEU-LEU-GLN-ASP-ILE-NLE-SER-ARG-CYS

56. Synthesised GHRH antagonist peptide

PhAc-Tyr-D-Arg-Asp-Ala-Ile-Phe(4-Cl)-Thr-Ala-Har-Tyr(Me)-His-Lys-Val-
Leu-Abu-Gln-Leu-Ser-Ala-His-Lys-Leu-Leu-Gln-Asp-Ile-Nle-D-Arg-Har-CYS

57. Protein sequence of CP-MCH-LHD

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKDFDMLRCMLGRVYRPCWQVALAKRLVLQCIK
VKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLN
LPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQ
AGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGF
PEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLS
YQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVID
ELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFN

58. Protein sequence of CT-KISS-LHD

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFEN
KIITDETNVQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSY
YYLESQKLSNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKK
DTLDKISDVSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREK
IIKTIENCLEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDK
ENIKSQVENLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNI
ILVGEVDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSALVYNWNSF
GLRFG

59. Protein sequence of CT-PrRP-LHA

EFVNKQFNYKDPVNGVDIAYIKIPNAGQMQPVKAFKIHNKIWVIPERDTFTNPEEGDLNPPPEAKQVPV
SYYDSTYLSTDNEKDNYLKGVTKLFERIYSTDLGRMLLTSIVRGIPFWGGSTIDTELKVIDTNCINVIQ
PDGSYRSEELNLVIIGPSADIIQFECKSFGHEVLNLTRNGYGSTQYIRFSPDFTFGFEESLEVDTNPLL
GAGKFATDPAVTLAHELIHAGHRLYGIAINPNRVFKVNTNAYYEMSGLEVSFEELRTFGGHDAKFIDSL

QENEFRLYYYNKFKDIASTLNKAKSIVGTTASLQYMKNVFKEKYLLSEDTSGKFSVDKLKFDKLYKMLT
EIYTEDNFVKFFKVLNRKTYLNFDKAVFKINIVPKVNYTIYDGFNLRNTNLAANFNGQNTEINNMNFTK
LKNFTGLFEFYKLLCVDGIITSKTKSDDDDKNKALNLQCIKVNNWDLFFSPSEDNFTNDLNKGEEITSD
TNIEAAEENISLDLIQQYYLTFNFDNEPENISIENLSSDIIGQLELMPNIERFPNGKKYELDKYTMFHY
LRAQEFEHGKSRIALTNSVNEALLNPSRVYTFFSSDYVKKVNKATEAAMFLGWVEQLVYDFTDETSEVS
TTDKIADITIIIPYIGPALNIGNMLYKDDFVGALIFSGAVILLEFIPEIAIPVLGTFALVSYIANKVLT
VQTIDNALSKRNEKWDEVYKYIVTNWLAKVNTQIDLIRKKMKEALENQAEATKAIINYQYNQYTEEEKN
NINFNIDDLSSKLNESINKAMININKFLNQCSVSYLMNSMIPYGVKRLEDFDASLKDALLKYIYDNRGT
LIGQVDRLKDKVNNTLSTDIPFQLSKYVDNQRLLSTLEGGGGSGGGGSGGGGSALVTPDINPAWYASRG
IRPVGRFG

60. Protein sequence of CP-HS_GHRH_1-27-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTNSYRKVLGQLSARKLLQDIMALAG
GGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILDG
QVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEAL
GYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGNS
ALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMVS
NWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNNI
NKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFNI
FSYTNNSLLKDIINEYFN

61. Protein sequence of the CP-HS_GHRH_1-28-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTNSYRKVLGQLSARKLLQDIMSALA
GGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILD
GQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEA
LGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGN
SALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMV
SNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNN
INKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFN
IFSYTNNSLLKDIINEYFN

62. Protein sequence of the CP-HS_GHRH_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTNSYRKVLGQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

63. Protein sequence of the CP-HS_GHRH_1-44-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTNSYRKVLGQLSARKLLQDIMSRQQ
GESNQERGARARLALAGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETN
VQNYSDKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKL
SNNVENITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISD
VSVIIPYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENC
LEQRVKRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVE
NLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDR
LKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFN

64. Protein sequence of the CP-HS_GHRH_1-40-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTNSYRKVLGQLSARKLLQDIMSRQQ
GESNQERGALAGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYS

DKFSLDESILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVE
NITLTTSVEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVII
PYIGPALNIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRV
KRWKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNS
LDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKV
NESFENTMPFNIFSYTNNSLLKDIINEYFN

65. Protein sequence of the CP-HS_GHRH_Ala9-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTNAYRKVLGQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

66. Protein sequence of the CP-HS_GHRH_Ala22-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTNSYRKVLGQLSARKALQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

67. Protein sequence of the CP-HS_GHRH_Ala8_Lys11_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTASYKKVLGQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

68. Protein sequence of the CP-HS_GHRH_Ala8_Lys11_Arg12_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTASYKRVLGQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

69. Protein sequence of the CP-HS_GHRH_Ala8_Asn11_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI

ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTASYNKVLGQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

70. Protein sequence of the CP-HS_GHRH_Ala8_Lys20_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTASYRKVLGQLSAKKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

71. Protein sequence of the CP-HS_GHRH_Ala8_Lys11_Lys20_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTASYKKVLGQLSAKKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF

NIFSYTNNSLLKDIINEYFN

72. Protein sequence of the CP-HS_GHRH_Ala8_Asn20_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTASYRKVLGQLSANKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

73. Protein sequence of the CP-HS_GHRH_Ala8_Asn12_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTASYRNVLGQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

74. Protein sequence of the CP-HS_GHRH_Ala8_Asn21_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE

KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTASYRKVLGQLSARNLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

75. Protein sequence of the CP-HS_GHRH_Ala8_Glu_7_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFEASYRKVLGQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

76. Protein sequence of the CP-HS_GHRH_Ala8_Glu_10_1-29LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTASERKVLGQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE

ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

77. Protein sequence of the CP-HS_GHRH_Ala8_Glu_13_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTASYRKELGQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

78. Protein sequence of the CP-HS_GHRH_Ala8-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTASYRKVLGQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

79. Protein sequence of the CP-HS_GHRH_Glu8_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTESYRKVLGQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

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80. Protein sequence of the CP-HS_GHRH_Ala15_1-27-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTNSYRKVLAQLSARKLLQDIMALAG
GGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILDG
QVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEAL
GYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGNS
ALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMVS
NWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNNI
NKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFNI
FSYTNNSLLKDIINEYFN

81. Protein sequence of the CP-HS_GHRH_Ala15-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTNSYRKVLAQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE

ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

82. Protein sequence of the CP- HS_GHRH_Ala8_Ala15_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTASYRKVLAQLSARKLLQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

83. Protein sequence of the CP-HS_GHRH_Ala8_9_15_22_27-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTAAYRKVLAQLSARKALQDIASRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

84. Protein sequence of the CP-HS_GHRH_Ala8_9_15_22-LHD

fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTAAYRKVLAQLSARKALQDIMSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

85. Protein sequence of the CP-HS_GHRH_HVQAL_1-32-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKHVDAIFTQSYRKVLAQLSARKALQDILSRQQ
GALAGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDE
SILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTS
VEEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPAL
NIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSY
QWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISE
AMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENT
MPFNIFSYTNNSLLKDIINEYFN

86. Protein sequence of the CP-HS_GHRH_HVSAL_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKHVDAIFTSSYRKVLAQLSARKLLQDILSRAL

AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

87. Protein sequence of the CP-HS_GHRH_HVTAL_1-29-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKHVDAIFTTSYRKVLAQLSARKLLQDILSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

88. Protein sequence of the CP-HS_GHRH_QALN-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTQSYRKVLAQLSARKALQDILNRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

89. Protein sequence of the CP-HS_GHRH_QAL-LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSDDDDKYADAIFTQSYRKVLAQLSARKALQDILSRAL
AGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESIL
DGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEE
ALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIG
NSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWM
VSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMN
NINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPF
NIFSYTNNSLLKDIINEYFN

90. Protein sequence of the CP-hGHRH29 N8A M27L -LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSIEGRYADAIFTASYRKVLGQLSARKLLQDILSR
ALAGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDES
ILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSV
EEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALN
IGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQ
WMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEA
MNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTM
PFNIFSYTNNSLLKDIINEYFN

91. Protein sequence of the CP-hGHRH29 N8A K12N M27L -LHD fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQS
YYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVE
KFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSN
QSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLD
VEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDK
FNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNI
ERNPALQKLSSESVVDLFTKVCVDGIITSKTKSIEGR YADAIFTASYRNVLGQLSARKLLQDILSR

ALAGGGGSGGGGSGGGGSALALQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDES
ILDGQVPINPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSV
EEALGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALN
IGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQ
WMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEA
MNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTM
PFNIFSYTNNSLLKDIINEYFN

92. Protein sequence of the N-termianal-hGHRH29 N8A M27L -LHD fusion

HVDAIFTQSYRKVLAQLSARKLLQDILNRNNNNNNNNNNTWPVKDFNYSDPVNDNDILYLRIPQNKLIT
TPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPTSKYQSYYDPSYLSTDEQKDTFLKGIIKLFKRINER
DIGKKLINYLVVGSPFMGDSSTPEDTFDFTRHTTNIAVEKFENGSWKVTNIITPSVLIFGPLPNILDYT
ASLTLQGQQSNPSFEGFGTLSILKVAPEFLLTFSDVTSNQSSAVLGKSIFCMDPVIALMHELTHSLHQL
YGINIPSDKRIRPQVSEGFFSQDGPNVQFEELYTFGGLDVEIIPQIERSQLREKALGHYKDIAKRLNNI
NKTIPSSWISNIDKYKKIFSEKYNFDKDNTGNFVVNIDKFNSLYSDLTNVMSEVVYSSQYNVKNRTHYF
SRHYLPVFANILDDNIYTIRDGFNLTNKGFNIENSGQNIERNPALQKLSSESVVDLFTKVCVDKSEEKL
YDDDDKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILDGQVPIN
PEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEALGYSNK
IYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPALNIGNSALRGN
FNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKRWKDSYQWMVSNWLSR
ITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKISEAMNNINKFIR
ECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGEVDRLKAKVNESFENTMPFNIFSYTN
NSLLKDIINEYFN

SEQ ID93 GnRH-C fusion protein

PITINNFNYSDPVDNKNILYLDTHLNTLANEPEKAFRITGNIWVIPDRFSRNSNPNLNKPPRVT
SPKSGYYDPNYLSTDSDKDTFLKEIIKLFKRINSREIGEELIYRLSTDIPFPGNNNTPINTFDFDV
DFNSVDVKTRQGNNWVKTGSINPSVIITGPRENIIDPETSTFKLTNNTFAAQEGFGALSIISISP
RFMLTYSNATNDVGEGRFSKSEFCMDPILILMHELNHAMHNLYGIAIPNDQTISSVTSNIFYSQ
YNVKLEYAEIYAFGGPTIDLIPKSARKYFEEKALDYYRSIAKRLNSITTANPSSFNKYIGEYKQK
LIRKYRFVVESSGEVTVNRNKFVELYNELTQIFTEFNYAKIYNVQNRKIYLSNVYTPVTANILDD
NVYDIQNGFNIPKSNLNVLFMGQNLSRNPALRKVNPENMLYLFTKFCVDAIDGRSLYNKTLQ
CRELLVKNTDLPFIGDISDVKTDIFLRKDINEETEVIYYPDNVSVDQVILSKNTSEHGQLDLLYP
SIDSESEILPGENQVFYDNRTQNVDYLNSYYYLESQKLSDNVEDFTFTRSIEEALDNSAKVYT
YFPTLANKVNAGVQGGLFLMWANDVVEDFTTNILRKDTLDKISDVSAIIPYIGPALNISNSVRR
GNFTEAFAVTGVTILLEAFPEFTIPALGAFVIYSKVQERNEIIKTIDNCLEQRIKRWKDSYEWM
MGTWLSRIITQFNNISYQMYDSLNYQAGAIKAKIDLEYKKYSGSDKENIKSQVENLKNSLDVKI
SEAMNNINKFIRECSVTYLFKNMLPKVIDELNEFDRNTKAKLINLIDSHNIILVGEVDKLKAKVN
NSFQNTIPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSALVMKPIQKLLAGLILLT
WCVEGCSSQHWSYGLRPGGKRDAENLIDSFQEIVKEVGQLAETQRFECTTHQPRSPLRDLK
GALESLIEEETGQKKI

SEQ ID94 GnRH-D fusion

TWPVKDFNYSDPVNDNDILYLRIPQNKLITTPVKAFMITQNIWVIPERFSSDTNPSLSKPPRPT
SKYQSYYDPSYLSTDEQKDTFLKGIIKLFKRINERDIGKKLINYLVVGSPFMGDSSTPEDTFDF
TRHTTNIAVEKFENGSWKVTNIITPSVLIFGPLPNILDYTASLTLQGQQSNPSFEGFGTLSILKV
APEFLLTFSDVTSNQSSAVLGKSIFCMDPVIALMHELTHSLHQLYGINIPSDKRIRPQVSEGFF
SQDGPNVQFEELYTFGGLDVEIIPQIERSQLREKALGHYKDIAKRLNNINKTIPSSWISNIDKYK
KIFSEKYNFDKDNTGNFVVNIDKFNSLYSDLTNVMSEVVYSSQYNVKNRTHYFSRHYLPVFA
NILDDNIYTIRDGFNLTNKGFNIENSGQNIERNPALQKLSSESVVDLFTKVCVDKSEEKLYDDD
DKDRWGSSLQCIKVKNNRLPYVADKDSISQEIFENKIITDETNVQNYSDKFSLDESILDGQVPI
NPEIVDPLLPNVNMEPLNLPGEEIVFYDDITKYVDYLNSYYYLESQKLSNNVENITLTTSVEEA
LGYSNKIYTFLPSLAEKVNKGVQAGLFLNWANEVVEDFTTNIMKKDTLDKISDVSVIIPYIGPAL
NIGNSALRGNFNQAFATAGVAFLLEGFPEFTIPALGVFTFYSSIQEREKIIKTIENCLEQRVKR
WKDSYQWMVSNWLSRITTQFNHINYQMYDSLSYQADAIKAKIDLEYKKYSGSDKENIKSQVE
NLKNSLDVKISEAMNNINKFIRECSVTYLFKNMLPKVIDELNKFDLRTKTELINLIDSHNIILVGE
VDRLKAKVNESFENTMPFNIFSYTNNSLLKDIINEYFNLEGGGGSGGGGSGGGGSGGGGSA
LVMKPIQKLLAGLILLTWCVEGCSSQHWSYGLRPGGKRDAENLIDSFQEIVKEVGQLAETQR
FECTTHQPRSPLRDLKGALESLIEEETGQKKI

Example 1 Preparation of a LH_N/A backbone construct

The following procedure creates a clone for use as an expression backbone for multidomain protein expression. This example is based on preparation of a serotype A based clone (SEQ ID1), though the procedures and methods are equally applicable to all LH_N serotypes such as serotype B (SEQ ID2), serotype C (SEQ ID3) and serotype D (SEQ ID4) and other protease or translocation domains such as IgA and Tetanus H_N by using the appropriate published sequence for synthesis (SEQ ID32).

Preparation of cloning and expression vectors

pCR 4 (Invitrogen) is the chosen standard cloning vector chosen due to the lack of restriction sequences within the vector and adjacent sequencing primer sites for easy construct confirmation. The expression vector is based on the pET (Novagen) expression vector which has been modified to contain the multiple cloning site *Nde*I-*Bam*HI-*Sal*I-*Pst*I-*Xba*I-*Hind*III for construct insertion, a fragment of the expression vector has been removed to create a non-mobilisable plasmid, a variety of different fusion tags have been inserted to increase purification options and an existing *Xba*I site in the vector backbone has been removed to simplify sub-cloning.

Preparation of LC/A

The DNA sequence is designed by back translation of the LC/A amino acid sequence (obtained from freely available database sources such as GenBank (accession number P10845) using one of a variety of reverse translation software tools (for example Backtranslation tool v2.0 (Entelechon)). *Bam*HI/*Sal*I recognition sequences are incorporated at the 5' and 3' ends respectively of the sequence maintaining the correct reading frame. The DNA sequence is screened (using software such as SeqBuilder, DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any cleavage sequences that are found to be common to those required by the cloning system are removed by the Backtranslation tool from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon

usage tables (for example GenBank Release 143, September 13 2004). This optimised DNA sequence containing the LC/A open reading frame (ORF) is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.

Preparation of H_N/A insert

The DNA sequence is designed by back translation of the H_N/A amino acid sequence (obtained from freely available database sources such as GenBank (accession number P10845) using one of a variety of reverse translation software tools (for example Back translation tool v2.0 (Entelechon)). A *Pst*I restriction sequence added to the N-terminus and *Xba*I-stop codon-*Hin*dIII to the C-terminus ensuring the correct reading frame in maintained. The DNA sequence is screened (using software such as SeqBuilder, DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any sequences that are found to be common to those required by the cloning system are removed by the Backtranslation tool from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, September 13 2004). This optimised DNA sequence is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.

Preparation of the interdomain (LC-H_N linker)

The LC-H_N linker can be designed from first principle, using the existing sequence information for the linker as the template. For example, the serotype A linker (in this case defined as the inter-domain polypeptide region that exists between the cysteines of the disulphide bridge between LC and H_N) has the sequence VRGIIPFKTKSLDEGYNKALNDL. This sequence information is freely available from available database sources such as GenBank (accession number P10845). For generation of a specific protease cleavage site, the native recognition sequence for Factor Xa can be used in the modified sequence VDGIITSKTKSLIEGR or an enterokinase recognition sequence is inserted into the activation loop to generate the sequence

VDGIITSKTKSDDDDKNKALNLQ. Using one of a variety of reverse translation software tools (for example Backtranslation tool v2.0 (Entelechon), the DNA sequence encoding the linker region is determined. *Bam*HI/*Sal*I and *Pst*I/*Xba*I/stop codon/*Hin*dIII restriction enzyme sequences are incorporated at either end, in the correct reading frames. The DNA sequence is screened (using software such as Seqbuilder, DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any sequences that are found to be common to those required by the cloning system are removed by the Backtranslation tool from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, September 13 2004). This optimised DNA sequence is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.

Assembly and confirmation of the backbone clone

Due to the small size, the activation linker must be transferred using a two step process. The pCR-4 linker vector is cleaved with *Bam*HI + *Sal*I combination restriction enzymes and the cleaved linker vector then serves as the recipient for *Bam*HI + *Sal*I restriction enzyme cleaved LC DNA. Once the LC encoding DNA is inserted upstream of the linker DNA, the entire LC-linker DNA fragment can then be isolated and transferred to the pET expression vector MCS. The LC-linker is cut out from the pCR 4 cloning vector using *Bam*HI/*Pst*I restriction enzymes digests. The pET expression vector is digested with the same enzymes but is also treated with antarctic phosphatase as an extra precaution to prevent re-circularisation. The LC-linker and the pET vector backbone are gel purified and the purified insert and vector backbone are ligated together using T4 DNA ligase. The product is transformed with TOP10 cells which are then screened for LC-linker using *Bam*HI/*Pst*I restriction digestion. The process is then repeated for the H_N insertion into the *Pst*I/*Hin*dIII restriction sites of the pET-LC-linker construct.

Screening with restriction enzymes is sufficient to ensure the final backbone is correct as all components are already sequenced confirmed during synthesis. However, during the sub-cloning of some components into the backbone, where similar size fragments are being removed and inserted, sequencing of a small region to confirm correct insertion is required.

Example 2 Construction of LH_N/AA-CP-GS15-SST28

The following procedure creates a clone for use as an expression construct for multidomain fusion expression where the targeting moiety (TM) is presented centrally between the protease and translocation domain. This example is based on preparation of the LH_N/A-CP-GS15-SST28 fusion (SEQ ID25), though the procedures and methods are equally applicable to create other protease, translocation and TM fusions, where the TM is N-terminal to the translocation domain. In this example, a flanking 15 amino acid glycine-serine spacer $(G_4S)3$ is engineered into the interdomain sequence ensure accessibility of the ligand to its receptor, but other spacers are applicable.

Preparation of spacer-human SST28 insert

The LC-H_N inter-domain polypeptide linker region exists between the cysteines of the disulphide bridge between LC and H_N. For insertion of a protease cleavage site, spacer and a targeting moiety (TM) region into the activation loop, one of a variety of reverse translation software tools (for example Backtranslation tool v2.0 (Entelechon) are used to determine the DNA sequence encoding the linker region. For central presentation of an SST28 sequence at the N-terminus of the H_N domain, a DNA sequence is designed for the GS spacer and targeting moiety (TM) regions allowing incorporation into the backbone clone (SEQ ID1). The DNA sequence can be arranged as *Bam*HI-*Sal*I-spacer-protease activation site-*SST28-spacer-Pst*I-*Xba*I-stop codon-*Hin*dIII (SEQ ID5). Once the TM DNA is designed, the additional DNA required to encode the preferred spacer is created *in silico*. It is important to ensure the correct reading frame is maintained for the spacer, SST28 and restriction sequences and that the *Xba*I sequence is not preceded by the bases TC, which would result in DAM methylation. The DNA sequence is screened for restriction sequence incorporated and any additional sites are removed manually from the remaining sequence ensuring common *E. coli*

codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, September 13 2004). This optimised DNA sequence is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.

Assembly and confirmation of the backbone clone

In order to create a LC-spacer-activation site-SST28-spacer-H_N construct (SEQ ID25) using the backbone construct (SEQ ID1) and the newly synthesised pCR 4-spacer-activation site-TM-spacer vector encoding the SST28 TM (SEQ ID5), a one or two step method can be used; typically the two step method is used when the TM DNA is less than 100 base pairs. Using the one step method the SST28 linker region can be inserted directly into the backbone construct buy cutting the pCR 4- spacer-activation site-TM-spacer vector with *Sal*I and *Pst*I restriction enzymes and inserting the TM encoding DNA fragment into a similarly cut pET backbone construct. Using the two-step method the LC domain is excised from the backbone clone using restriction enzymes *Bam*HI and *Sal*I and ligated into similarly digested pCR 4-spacer-activation site-TM-spacer vector. This creates a LC-spacer-activation site-SST28-spacer ORF in pCR 4 that can be excised from the vector using restriction enzymes *Bam*HI and *Pst*I for subsequent ligation into similarly pET expression construct. The final construct contains the LC-spacer-activation site-SST28-spacer-H_N DNA (SEQ ID25) which will result in a fusion protein containing the sequence illustrated in SEQ ID26.

Example 3 Expression and purification of a LH_N/A-CP-SST28 fusion protein

This example is based on preparation of an LH_N/A protein that incorporates a SST28 TM polypeptide into the interdomain linker region (SEQ ID26), where the pET expression vector ORF also encodes a histidine purification tag. These procedures and methods are equally applicable to the other fusion protein such as those shown in SEQ ID7-14, 42-48, 57, 60-91. Where appropriate, the activation enzyme should be selected to be compatible with

the protease activation site within each sequence

Expression of LH_N/A-CP-SST28

Expression of the LH_N/A-CP-SST28 protein is achieved using the following protocol. Inoculate 100 ml of modified TB containing 0.2 % glucosamine and 30 µg/ml kanamycin in a 250 ml flask with a single colony from the LHA-CP-SST28 expression strain. Grow the culture at 37°C, 225 rpm for 16 hours. Inoculate 1 L of modified TB containing 0.2 % glucosamine and 30 µg/ml kanamycin in a 2 L flask with 10 ml of overnight culture. Grow cultures at 37°C until an approximate OD_{600} nm of 0.5 is reached at which point reduce the temperature to 16°C. After 1 hour induce the cultures with 1 mM IPTG and grow at 16°C for a further 16 hours.

Purification of LH_N/A-CP-SST28 protein

Defrost falcon tube containing 35 ml 50 mM HEPES pH 7.2 200 mM NaCl and approximately 10 g of E. coli BL21 (DE3) cell paste. Homogenise the cell paste (20 psi) ensuring the sample remains cool. Spin the lysed cells at 18 000 rpm, 4°C for 30 minutes. Load the supernatant onto a 0.1 M NiSO4 charged Chelating column (20-30 ml column is sufficient) equilibrated with 50 mM HEPES pH 7.2 200 mM NaCl. Using a step gradient of 10, 40 and 100 mM imidazole, wash away the non-specific bound protein and elute the fusion protein with 200 mM imidazole. The eluted fusion protein is dialysed against 5 L of 50 mM HEPES pH 7.2 200 mM NaCl at 4°C overnight and the OD_{280} nm measured to establish the protein concentration. Add 3.2 µl enterokinase (New England Biolabs) per mg fusion protein and incubate static overnight at 25°C. Load onto a 0.1 M NiSO4 charged Chelating column (20-30 ml column is sufficient) equilibrated with 50 mM HEPES pH 7.2 200 mM NaCl. Wash column to baseline with 50 mM HEPES pH 7.2 200 mM NaCl. Using a step gradient of 10, 40 and 100 mM imidazole, wash away the non-specific bound protein and elute the fusion protein with 200 mM imidazole. Dialyse the eluted fusion protein against 5L of 50 mM HEPES pH 7.2 150 mM NaCl at 4°C overnight and concentrate the fusion to about 2 mg/ml, aliquot sample and freeze at -20°C. Test purified protein using OD_{280}, BCA and purity analysis.

Example 4 Construction of LH_N/D-CT-GS20-CST28

The following procedure creates a clone for use as an expression construct for multidomain fusion expression where the targeting moiety (TM) is presented C-terminally to the translocation domain. This example is based on preparation of the LH_N/D-CT-GS20-CST28 fusion (SEQ ID17), though the procedures and methods are equally applicable to create other protease, translocation and TM fusions, where the TM of C-terminal to the translocation domain. In this example, a flanking 20 amino acid glycine-serine spacer is engineered into the interdomain sequence ensure accessibility of the ligand to its receptor, but other spacers are applicable.

Preparation of spacer-human CST28 insert

For presentation of a CST28 sequence at the C-terminus of the H_N domain, a DNA sequence is designed to flank the spacer and targeting moiety (TM) regions allowing incorporation into the backbone clone (SEQ ID4). The DNA sequence can be arranged as *Bam*HI-*Sal*I-*Pst*I-*Xba*I-spacer-*CST28*-stop codon-*Hin*dIII (SEQ ID6). The DNA sequence can be designed using one of a variety of reverse translation software tools (for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)). Once the TM DNA is designed, the additional DNA required to encode the preferred spacer is created *in silico*. It is important to ensure the correct reading frame is maintained for the spacer, CST28 and restriction sequences and that the *Xba*I sequence is not preceded by the bases TC, which would result on DAM methylation. The DNA sequence is screened for restriction sequences incorporated and any additional sequences are removed manually from the remaining sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, September 13 2004). This optimised DNA sequence is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.

Assembly and confirmation of the backbone clone

In order to create a LH_N/D-GS20-CST28 construct (SEQ ID17) using the backbone construct (SEQ ID4) and the newly synthesised pCR 4-spacer-TM vector encoding the CST28 TM (SEQ ID6), a one or two step method can be used; typically the two step method is used when the TM DNA is less than 100 base pairs. Using the one step method the CST28 can be inserted directly into the backbone construct buy cutting the pCR 4-spacer-TM vector with *Xba*I and *Hind*III restriction enzymes and inserting the TM encoding DNA fragment into a similarly cut pET backbone construct. Using the two-step method the LH_N domain is excised from the backbone clone using restriction enzymes *Bam*HI and *Xba*I and ligated into similarly digested pCR 4-spacer-CST28 vector. This creates an LH_N-spacer-CST28 ORF in pCR 4 that can be excised from the vector using restriction enzymes *Bam*HI and *Hind*III for subsequent ligation into the similarly cleaved pET expression construct. The final construct contains the LC-linker-H_N-spacer-CST28 DNA (SEQ ID17) which will result in a fusion protein containing the sequence illustrated in SEQ ID18.

Example 5 Expression and purification of a LH_N/D-CT-CST28 fusion protein

This example is based on preparation of an LH_N/D protein that incorporates a CST28 TM polypeptide at the carboxyl terminus of the H_N domain (SEQ ID 18), where the pET expression vector ORF also encodes a histidine purification tag. These procedures and methods are equally applicable to fusion protein sequences such as those shown in SEQ ID15, 16, 18-24, 27-31, 33-41, 58-59, and 93-94. Where appropriate, the activation enzyme should be selected to be compatible with the protease activation site within each sequence.

Expression of LH_N/D-CT-CST28

Expression of the LH_N/D-CT-CST28 protein is achieved using the following protocol. Inoculate 100 ml of modified TB containing 0.2 % glucosamine and 30 µg/ml kanamycin in a 250 ml flask with a single colony from the LH_N/D-CT-CST28 expression strain. Grow the culture at 37°C, 225 rpm for 16 hours. Inoculate 1 L of modified TB containing 0.2 % glucosamine and 30 µg/ml kanamycin in a 2 L flask with 10 ml of overnight culture. Grow cultures at 37°C

until an approximate OD_{600} nm of 0.5 is reached at which point reduce the temperature to 16°C. After 1 hour induce the cultures with 1 mM IPTG and grow at 16°C for a further 16 hours.

Purification of LH_N/D-CT-CST28 protein

Defrost falcon tube containing 35 ml 50 mM HEPES pH 7.2 200 mM NaCl and approximately 10 g of *E. coli* BL21 (DE3) cell paste. Homogenise the cell paste (20psi) ensuring the sample remains cool. Spin the lysed cells at 18 000 rpm, 4°C for 30 minutes. Load the supernatant onto a 0.1 M $NiSO_4$ charged Chelating column (20-30 ml column is sufficient) equilibrated with 50 mM HEPES pH 7.2 200 mM NaCl. Using a step gradient of 10, 40 and 100 mM imidazole, wash away the non-specific bound protein and elute the fusion protein with 200 mM imidazole. The eluted fusion protein is dialysed against 5 L of 50 mM HEPES pH 7.2 200 mM NaCl at 4°C overnight and the OD_{280} nm measured to establish the protein concentration. Add 3.2 µl enterokinase (New England Biolabs) per mg fusion protein and incubate static overnight at 25°C. Load onto a 0.1 M $NiSO_4$ charged Chelating column (20-30 ml column is sufficient) equilibrated with 50 mM HEPES pH 7.2 200 mM NaCl. Wash column to baseline with 50 mM HEPES pH 7.2 200 mM NaCl. Using a step gradient of 10, 40 and 100 mM imidazole, wash away the non-specific bound protein and elute the fusion protein with 200 mM imidazole. Dialyse the eluted fusion protein against 5 L of 50 mM HEPES pH 7.2 150 mM NaCl at 4°C overnight and concentrate the fusion to about 2 mg/ml, aliquot sample and freeze at -20°C. Test purified protein using OD_{280}, BCA and purity analysis. Figures 1 and 2 demonstrate purification of fusion proteins as analysed by SDS-PAGE.

Example 6 Chemical conjugation of LH_N/A to SST TM

The following procedure creates a chemically conjugated molecule containing the LH_N/A amino acid sequence (SEQ ID49), prepared from SEQ ID1 using the production method outlined in example 3, and a SST Octreotide peptide which has been chemically synthesised (SEQ ID54). However, the procedures and methods are equally applicable for the conjugation of other peptides such as SEQ ID55 and SEQ ID56 to other protease/translocation

domain proteins such as those containing the amino acid sequences SEQ ID50, 51, 52 and 53.

The LH_N/A protein was buffer exchanged from 50 mM Hepes 150 mM salt into PBSE (100mM 14.2g NA2HPO4, 100mM 5.85g NaCl, 1mM $EDTANa_2$ pH 7.5 with 1M HCl) using the Bio-rad PD10 column. This was done by washing one column volume of PBSE through the PD10 column, the protein was then added to the column until no more drops exit the end of the PD10 column. 8 mls of PBSE was then added and 0.5ml fractions are collected. The collected fractions are the measured using the A_{280} reading and fractions containing protein are pooled. A concentration of 1.55 mg/ml of LH_N/A was obtained from the buffer exchange step and this was used to set up the following reactions:

LH_N/A 1.55 mg/ml	20 mM SPDP or Sulfo-LC-SPDP
A 200 µl	0
B 200 µl	4 fold increase 0.62 µl
C 200 µl	8 fold increase 1.24 µl

Sample were left to tumble at RT for 3 hours before being passed down another PD10 column to buffer exchange into PBSE and the protein containing fractions pooled. A final concentration of 25 mM DTT was then added to derivatised protein and then the samples left at room temperature for 10 minutes. A_{280} and A_{343} readings were then taken to work out the ratio of SPDP:LH_N/A interaction and the reaction which resulted in a derivatisation ration of between 1 and 3 was used for the peptide conjugation. The SPDP reagent binds to the primary amines of the LH_N/A via an N-hydroxysuccinimide (NHS) ester, leaving the sulphydryl-reactive portion to form a disulphide bond to the free SH group on the free cysteine on the synthesised peptide. In this case the peptide sequence is Octreotide which has been synthesised with a free cysteine on the N-terminus (SEQ ID91). The SPDP-derivatised LH_N/A was mixed with a 4-fold excess of the Octreotide ligand and the reaction was then left at RT for 90 minutes whilst tumbling. The excess octreotide was then removed using either a PD10 column leaving LH_N/A-Octreotide conjugated molecule.

Example 7 Activity of SST-LH$_N$/A in cultured endocrine cells (AtT20)

The rat pituitary tumour cell line AtT20 is an example of a cell line of endocrine origin. It thus represents a model cell line for the investigation of inhibition-of-release effects of the agents.

AtT20 cells possess surface receptors that allow for the binding, and internalisation, of SST-LH$_N$/A. In contrast, AtT20 cells lack suitable receptors for clostridial neurotoxins and are therefore not susceptible to botulinum neurotoxins (BoNTs).

Figure 3 (a) illustrates the inhibition of release of ACTH from AtT20 cells after prior incubation with SST-LH$_N$/A. It is clear that dose-dependent inhibition is observed, indicating that SST-LH$_N$/A can inhibit the release of ACTH from an endocrine cell model. Inhibition of ACTH release was demonstrated to correlate with cleavage of the SNARE protein SNAP25 (Fig 3 (a) and (b)) Thus, inhibition of release of chemical messenger is due to a clostridial endopeptidase-mediated effect of SNARE-protein cleavage.

Materials and Methods

ACTH enzyme immunoassay kits were obtained from Bachem Research Inc., CA, USA. Western blotting reagents were obtained from Invitrogen and Sigma. AtT20 cells were seeded onto 12 well plates and cultured in DMEM containing 10% foetal bovine serum, 4 mM Glutamax. After 1 day SST-LH$_N$/A was applied for 72 hours then the cells washed to remove unbound SST-LH$_N$/A. Secretion of ACTH was stimulated by elevating the concentration of extracellular potassium (60 mM KCl) and calcium (5 mM $CaCl_2$) for 30 min. The medium was harvested from the cells and stored at -20°C until assayed for ACTH content using the immunoassay kit and following the manufacturer's instructions. Cells were solubilised in 1x LDS electrophoresis reducing sample buffer, heated for 10 minutes at 90°C then stored at -20°c until used for Western blotting. Stimulated secretion was calculated by subtracting basal release from total release under stimulating conditions. Solubilised cell samples were separated by SDS-PAGE and transferred to nitrocellulose membrane. Proteolysis of SNAP-25, a crucial component of the

neurosecretory process and the substrate for the zinc-dependent endopeptidase activity of BoNT/A, was then detected by probing with an antibody that recognises both the intact and cleaved forms of SNAP-25. Quantitation of proteolysis was achieved by image analysis using a Synoptics Syngene GeneGnome imaging system and GeneTools software.

Example 8 Activity of SST-LH_N/D in cultured neuroendocrine cells (GH3)

The rat pituitary cell line GH3 is an example of a cell line of neuroendocrine origin. It thus represents a model cell line for the investigation of inhibition-of-release effects of the agents.

GH3 cells possess surface receptors that allow for the binding, and internalisation of SST-LH_N/D. In contrast, GH3 cells lack suitable receptors for clostridial neurotoxins and are therefore not susceptible to botulinum neurotoxins (BoNTs).

Figure 4 illustrates the inhibition of release of growth hormone (GH) from GH3 cells after prior incubation with SST-LH_N/D It is clear that dose-dependent inhibition is observed, indicating that SST-LH_N/D can inhibit the release of GH from a neuroendocrine cell model.

Comparison of the inhibition effects observed with conjugate and the untargeted LH_N/D demonstrate the contribution of the targeting moiety (TM) to efficient inhibition of transmitter release.

Materials and Methods

GH enzyme immunoassay kits were obtained from Millipore, MA, USA. GH3 cells were cultured on 24 well plates in F-10 nutrient mixture (Ham) supplemented with 15 % Horse Serum, 2.5 % FBS, 2 mM L-Glutamine. Cells were treated with SST-LH_N/D or LH_N/D for 72 hours then the cells washed to remove unbound SST-LH_N/D. Secretion was stimulated by exposing the cells to 10 μM tetradecanoyl phorbol acetate (TPA, PMA) over 30 min. The medium was harvested from the cells and stored at -20°C until assayed for GH content using the immunoassay kit and following the manufacturer's instructions.

Stimulated secretion was calculated by subtracting basal release from total release under stimulating conditions.

Example 9 Method for alleviating acromegalic symptoms by reducing elevated GH and IGF-1 levels resulting from pituitary adenoma

A 35 year old male member of a regional badminton team undergoes a spinal X-ray for lower back pain. The consultant notices abnormal bone growth and, on questioning, the man reports increasing incidents of sleep apnoea and also increasingly oily skin.

The physician recommends measurement of circulating IGF-1 and these are found to be elevated. Subsequent tests also show above-normal circulating GH levels so a cranial MRI scan is carried out. This shows a pituitary tumour of 9mm diameter. The patient is treated with a cortistatin or somatostatin peptide TM fusion protein (eg. SEQ ID 7-16, 18-24, 26-31) by i.v. injection.

At intervals of 1 week circulating IGF-1 levels are measured and are seen to be lower at the first measurement and to reduce steadily to 15% above normal over the following six weeks. The level of circulating GH is found to be normal at this time. A further dose of the medication with two-weekly IGF-1 measurements shows this hormone to have stabilised at the upper end of normal. At six weeks after the second treatment a cranial MRI scan reveals shrinkage of the tumour to 6 mm. The therapy is continued at a reduced dosage at two-monthly intervals with IGF-1 and GH levels measured on the seventh week. These are both stable in the normal range and the sleep apnoea and oily skin are now absent. A spinal X-ray at one year following the first treatment shows no increased bone size from the original observation.

Example 10 Method for normalising swollen hirsute fingers by reducing elevated GH and IGF-1 levels resulting from pituitary adenoma

A 50 year old female confectionery worker has increasing difficulty removing her wedding ring and eventually visits her medical practitioner. The physician also notices the patient's fingers are hairier than expected and, on

questioning, the patient admits that both these conditions have arisen gradually. Subsequent clinical tests reveal a higher-than-average level of circulating GH that does not change following a high-glucose drink. An acromegalic condition is suspected and a cranial CT scan confirms the presence of a small pituitary tumour.

Surgery is considered inappropriate so the patient is treated with an i.v. injection of a somatostatin or cortistatin peptide TM fusion protein (eg. SEQ ID 7-16, 18-24, 26-31). Within four weeks the glucose tolerance test shows a response in GH levels and IGF-1 levels are near normal. Treatment continues at six-weekly intervals and by the end of the eighteenth week the patient is able to remove her ring easily and the hirsutism has disappeared.

Example 11 Method for ameliorating the consequences of re-emerging growth-hormone-secreting pituitary adenoma

A 52 year-old male scuba diver presents with increasingly noticeable acromegalic symptoms, including soft tissue swelling and enlargement of the extremities. Thorough tests confirm the presence of a 12mm pituitary adenoma. Somatostatin analogues are poorly tolerated by the patient so the tumour is resected and regular tests over 2 years show circulating GH and IGF-1 levels to be in the upper range of normal and no further medication is given. Eighteen months later, upon presenting with hyperhydrosis and moderate hypertension, GH and IGF-1 levels are found to be above normal and a CT scan reveals regrowth of the pituitary adenoma. Repeat resection is considered undesirable.

The man is treated by i.v. administration of a somatostatin or cortistatin peptide TM fusion protein (eg. SEQ ID 7-16, 18-24, 26-31). A course of radiotherapy is also given and after four weeks the hyperhydrosis and hypertension are near normal as are the GH and IGF-1 levels. Over the next three years symptoms do not recur and there is no tumour regrowth at five years post-treatment.

Example 12 Method for treating acromegalic patients resistant to somatostatin analogues

After six years' successful control of circulating GH and IGF-1 by somatostatin analogues, a 60-year-old acromegalic fairground tarot reader reports increasingly obvious oily skin and also prominent body odour as a result of hyperhydrosis. She is found to be glucose-intolerant and to have elevated circulating IGF-1 levels and raising the SSA dosage does not control these.

She is treated by localised injection of a somatostatin or cortistatin peptide TM fusion protein (eg. SEQ ID 7-16, 18-24, 26-31). Within 14 days the patient reports a significant reduction in sweating. Over the following month her oily skin returns to normal and at this time her GH and IGF-1 levels are both within the normal range. This situation remains over the next five years.

Example 13 Method for treating Cushing's disease in patients intolerant of somatostatin analogues

A 30 year old female mature student visits her GP to request treatment for anxiety and depression. The physician observes the woman has a rounded face with increased fat around the neck and also thinner than normal arms and legs. Upon questioning she confirms an irregular menstrual cycle. A 24-hour urinary free cortisol level of 150µg is measured suggesting Cushing's syndrome. Abdominal MRI scan shows no adrenal tumours to be present but cranial MRI scan reveals a small pituitary tumour.

The patient is considered unsuitable for surgical intervention so is treated with a somatostatin or cortistatin peptide TM fusion protein (eg. SEQ ID 7-16, 18-24, 26-31).

Example 14 Method for reversing female sexual impotence by treating prolactinoma

A 36 year old woman visits her doctor, worried about her recent expression of breast milk, despite her negative pregnancy test. Examination also indicates vaginal dryness and she confirms that she has lost her libido. Clinical test results are largely normal with the notable exception of moderate hyperprolactinaemia. A cranial MRI scan indicates a pituitary adenoma, consistent with the elevated prolactin levels.

She is treated by oral administration with a preparation of a somatostatin or cortistatin peptide TM fusion protein (eg. SEQ ID 7-16, 18-24, 26-31). After eight days she no longer expresses breast milk and her vaginal moisture levels have significantly improved. After seven weeks the dryness begins to return but is almost immediately reversed by a second treatment. Treatments continue at six-weekly visits to the sexual health clinic where the woman reports a return to normal sexual activity.

Example 15 Method for bringing about weight loss by treating insulinoma

A 64 year old female with a BMI of 39 has been diagnosed with inoperable insulinoma. She wishes to achieve a sustained reduction in appetite and weight to enable her to maintain an active interest in aerobics so is treated by a systemic injection of a fusion protein comprising a somatostatin or cortistatin peptide TM (eg. SEQ ID 7-16, 18-24, 26-31). Within 10 to 14 days following treatment her weight gain has stabilised and by 30 days weight loss has occurred. The patient maintains a significant weight loss provided medication continues as a series of 24-weekly injections

Example 16 Method for treating glucagonoma

A 63-year-old woman visits her doctor in a distressed state, having had rashes develop on her buttocks, around her groin and on her lower legs. Blood tests show her to be anaemic and diabetic. She also has frequent diarrhoeal episodes. The physician suspects the presence of glucagonoma and a CT scan confirms the existence of a tumour in the tail of the pancreas.

The patient is treated with a fusion protein comprising a somatostatin or cortistatin peptide TM (eg. SEQ ID 7-16, 18-24, 26-31). After 4 weeks the diarrhoeal episodes have subsided and the rashes have cleared significantly. Her red-cell count has also returned to near normal. The treatment is repeated at six-weekly intervals and the symptoms remain largely under control.

Example 17 Method for treating diarrhoea and flushing caused by VIPoma

A 49 year old man suffers from secretory diarrhoea associated with chronic flushing. Clinical tests indicate metabolic acidosis, and an abdominal CT scan reveals a tumour – almost certainly a VIPoma – near the pancreas.

Surgery is not available to the patient so he is treated with a fusion protein comprising a somatostatin or cortistatin peptide TM (eg. SEQ ID 7-16, 18-24, 26-31). Within 3 weeks the flushing has stopped and the diarrhoea has become less frequent. By seven weeks after treatment all symptoms have disappeared and remain absent providing therapy is repeated at approximately 8-week intervals.

Example 18 Method for treating gastrinoma

A 47-year-old man suffers from severe peptic ulceration that causes debilitating abdominal pain. He also experiences unexplained diarrhoeal episodes and eventually is diagnosed with intrapancreatic gastrinoma by blood tests and abdominal ultrasound study.

He is treated by intra-tumoural injection of a medication consisting of a fusion protein comprising a somatostatin or cortistatin peptide TM (eg. SEQ ID 7-16, 18-24, 26-31), or fusion comprising a GnRH peptide TM (eg. SEQ ID 93-94). Within a week painful gastric symptoms start to improve. The hypergastrinaemia has subsided and the diarrhoeal episodes have reduced in severity and frequency. This status pertains for 7 weeks but blood gastrin levels start to rise thereafter. The therapy is repeated at 7 week intervals and this maintains blood gastrin at normal levels and no other symptoms recur.

Example 19 Method for treating thyrotoxicosis caused by thyrotrophinoma

A 39-year-old female airline cabin crew member visits her physician complaining of excessive sweating, coupled with previously unknown nervousness, that have started to affect her ability to perform her job. During the consultation a fine tremor is evident and the doctor suspects thyrotoxicosis. The woman is referred to an endocrinologist who carries out a number of blood tests. The major abnormalities detected are elevated thyroxine levels but also elevated TSH (thyrotrophin) levels, indicative of a

thyrotrophinoma. An MRI scan of the head confirms the presence of a pituitary tumour.

The woman is treated with a medication consisting of a fusion protein comprising somatostatin or cortistatin peptide TM (eg. SEQ ID 7-16, 18-24, 26-31). Both the sweating and nervousness decline over the following two weeks. Two-weekly follow-up blood tests show both thyroxine and thyrotrophin levels falling and they reach normal levels by six weeks. The patient is able to resume full employment activity.

Example 20 Method for treating recurrent soft tissue swelling caused by acromegaly

A 72-year-old woman, having already had transsphenoidal surgery to remove a pituitary macroadenoma, shows recurrence of acromegalic symptoms (primarily swelling of fingers and tongue and increasing tiredness and lethargy). Cranial MRI scanning reveals the presence of a putative pituitary microadenoma and subsequent blood tests confirm elevated circulating GH and IGF-1 levels.

Surgery is deemed incompatible with pre-existing medical conditions so she is treated with a medication consisting of a fusion protein comprising a somatostatin or cortistatin peptide TM (eg. SEQ ID 7-16, 18-24, 26-31). After a week she reports feeling generally more active and that the swelling of her fingers and tongue has reduced noticeably. By three weeks the recurrent symptoms have reverted completely and endocrinological examination confirms a normalisation of GH and IGF-1 levels. She is monitored on a monthly basis and given repeat treatments at 10-weekly intervals. This dosage regimen keeps the hormone levels within the normal range and prevents recurrence of symptoms.

Example 21 Method for treating excessive facial hirsutism caused by Cushing's Disease

A 27-rear-old beauty consultant starts to develop noticeable facial hair growth. This is not adequately treated by standard hair-removal methods and is causing her severe psychological problems (anxiety, depression) in relation to

both her employment and her personal life. Her physician suspects Cushing's syndrome so she is referred to an endocrinologist. Blood and urine tests show elevated levels of cortisol and ACTH levels, and a CRH stimulation test proves positive, confirming the likelihood of an ACTH-secreting pituitary tumour. Adrenal and pituitary CT-scans confirm the presence of a pituitary tumour but no adrenal abnormality.

Following discussions with consultants the patient opts for medical intervention and is treated with a medication consisting of a fusion protein comprising a somatostatin or cortistatin peptide TM (eg. SEQ ID 7-16, 18-24, 26-31), or fusion comprising a GnRH peptide TM (eg. SEQ ID 93-94). Within ten days the woman is starting to feel more positive and by the two week time point she has to use hair bleaching or depilatory creams with much lower frequency. The symptoms start to reappear at around ten to twelve weeks so a second treatment is given. A similar pattern of symptom remission, gradual reappearance and treatment occurs. During the third treatment, the patient elects for surgical removal of the pituitary tumour. Follow-up monitoring for the next two years shows no recurrence of symptoms or tumour.

Example 22 Method for treating male galactorrhea caused by prolactinoma

A 40-year-old male rugby player has been worried for some time about increasing breast size beyond that expected from training. He becomes highly stressed when a trickle of milk appears at the left breast. His physician immediately suspects the existence of a pituitary prolactinoma and refers him to a radiologist and endocrinologist. Blood tests show hyperprolactinaemia but normal thyroid function. A cranial MRI scan shows a pituitary tumour to be present.

In the absence of any tumour-mass effect the man is treated with a medication consisting of a fusion protein comprising a somatostatin or cortistatin peptide TM (eg. SEQ ID 7-16, 18-24, 26-31). After only four days the milk expression has ceased and after six weeks there has been a measurable reduction in non-muscle breast tissue. During this period the blood prolactin levels were measured fortnightly and had returned to normal

by the four-week measurement. The treatment is repeated at 12-week intervals during which time there is no recurrence of symptoms and no indication of tumour growth. Surgery or other tumour-reduction treatment is considered unnecessary while these conditions pertain.

Example 23 Method for treating multiple symptoms caused by insulinoma

A 51-year-old man is diagnosed with insulinoma after presenting to the doctor with a variety of recently occurring conditions including blurred vision, palpitations, weakness, amnesia and, on two occasions in three months has passed out. The diagnosis is confirmed by endocrinological and radiographic tests.

He is treated with a medication consisting of a fusion protein comprising a somatostatin or cortistatin peptide TM (eg. SEQ ID 7-16, 18-24, 26-31), or fusion comprising a GnRH peptide TM (eg. SEQ ID 93-94). Within a week his vision and energy levels have returned to near normal and continue to improve over the following fortnight. At four weeks he is no longer hypoglycaemic and at that point laparoscopic enucleation of a pancreatic head tumour is performed. Subsequent patient monitoring records no return of symptoms or tumour mass and the patient remains healthy after three years.

Example 24 Method for treating acromegalic patients resistant to somatostatin analogues

After 3 years' successful control of circulating GH and IGF-1 by somatostatin analogues, a 54-year-old acromegalic office worker reports increasingly obvious oily skin and also prominent body odour as a result of hyperhydrosis. She is found to be glucose-intolerant and to have elevated circulating IGF-1 levels and raising the SSA dosage does not control these.

She is treated by intravenous injection of a fusion protein comprising a growth hormone releasing hormone peptide TM (eg. SEQ ID 34, 42-47, 60-92). Within 14 days the patient reports a significant reduction in sweating. Over the following month her oily skin returns to normal and at this time her GH and

IGF-1 levels are both within the normal range. This situation remains over the next five years.

Example 25 Method for treating Cushing's disease in patients intolerant of somatostatin analogues

A 37 year old female receptionist visits her GP to request treatment for anxiety and depression. The physician observes the woman has a rounded face with increased fat around the neck and also thinner than normal arms and legs. Upon questioning she confirms an irregular menstrual cycle. A 24-hour urinary free cortisol level of 150 µg is measured suggesting Cushing's syndrome. Abdominal MRI scan shows no adrenal tumours to be present but cranial MRI scan reveals a small pituitary tumour.

The patient is considered unsuitable for surgical intervention so is treated with an intravenous injection of fusion protein comprising a urotensin peptide TM (eg. SEQ ID 48).

Example 26 Method for reversing female sexual impotence by treating prolactinoma

A 28 year old woman visits her doctor, worried about her recent expression of breast milk, despite her negative pregnancy test. Examination also indicates vaginal dryness and she confirms that she has lost her libido. Clinical test results are largely normal with the notable exception of moderate hyperprolactinaemia. A cranial MRI scan indicates a pituitary adenoma, consistent with the elevated prolactin levels.

She is treated by an intravenous injection of a fusion protein comprising a ghrelin peptide (GHRP) TM (eg. SEQ ID 33, 35, 38), or fusion comprising a GnRH peptide TM (eg. SEQ ID 93-94). After four days she no longer expresses breast milk and her vaginal moisture levels have significantly improved. After thirteen weeks the dryness begins to return but is almost immediately reversed by a second treatment. Treatments continue at twelve-weekly visits to the sexual health clinic where the woman reports a return to normal sexual activity.

Example 27 Method for treating Cushing's disease

A 30 year old female typist visits her GP to request treatment for anxiety and depression. The physician observes the woman has a rounded face with increased fat around the neck and also thinner than normal arms and legs. Upon questioning she confirms an irregular menstrual cycle. A 24-hour urinary free cortisol level of 200 µg is measured suggesting Cushing's syndrome. Abdominal MRI scan shows no adrenal tumours to be present but cranial MRI scan reveals a small pituitary tumour.

The patient is considered unsuitable for surgical intervention so is treated with a fusion protein comprising a bombesin peptide (GRP) TM (eg. SEQ ID 40-41), or fusion comprising a GnRH peptide TM (eg. SEQ ID 93-94).

Example 28 Method for treating gastrinoma

A 63-year-old man suffers from severe peptic ulceration that causes debilitating abdominal pain. He also experiences unexplained diarrhoeal episodes and eventually is diagnosed with intrapancreatic gastrinoma by blood tests and abdominal ultrasound study.

He is treated by intra-tumoural injection of a medication consisting of a fusion protein comprising a somatostatin or cortistatin peptide TM analogue (octreotide – SEQ ID 54), which has been chemically conjugated to the protease-translocation protein (eg. SEQ ID 49-53). Within a week painful gastric symptoms start to improve. The hypergastrinaemia has subsided and the diarrhoeal episodes have reduced in severity and frequency. This status pertains for 8 weeks but blood gastrin levels start to rise thereafter. The therapy is repeated at 8 week intervals and this maintains blood gastrin at normal levels and no other symptoms recur.

Example 29 Method for alleviating acromegalic symptoms by reducing elevated GH and IGF-1 levels resulting from pituitary adenoma

A 50 year old female reports to her GP increasing incidents of sleep apnoea and also increasingly oily skin and the GP observes abnormal bone growth.

The GP recommends measurement of circulating IGF-1 and these are found to be elevated. Subsequent tests also show above-normal circulating GH levels so a cranial MRI scan is carried out. This shows a pituitary tumour of 5mm diameter. The patient is treated with a MCH fusion protein (eg. SEQ ID 57) by i.v. injection.

At intervals of 1 week circulating IGF-1 levels are measured and are seen to be lower at the first measurement and to reduce steadily to 5% above normal over the following eight weeks. The level of circulating GH is found to be normal at this time. A further dose of the medication with two-weekly IGF-1 measurements shows this hormone to have stabilised at the upper end of normal. At six weeks after the second treatment a cranial MRI scan reveals shrinkage of the tumour to 3 mm. The therapy is continued at a reduced dosage at two-monthly intervals with IGF-1 and GH levels measured on the seventh week. These are both stable in the normal range and the sleep apnoea and oily skin are now absent.

Example 30 Method for treating acromegalic patients resistant to somatostatin analogues

After 1 years' successful control of circulating GH and IGF-1 by somatostatin analogues, a 40-year-old acromegalic digger driver reports increasingly obvious oily skin and also prominent body odour as a result of hyperhydrosis. He is found to be glucose-intolerant and to have elevated circulating IGF-1 levels and raising the SSA dosage does not control these.

He is treated by intravenous injection of a fusion protein comprising a KISS1R binding peptide TM (eg. SEQ ID 58), or fusion comprising a GnRH peptide TM (eg. SEQ ID 93-94). Within 14 days the patient reports a significant reduction in sweating. Over the following month his oily skin returns to normal and at this time her GH and IGF-1 levels are both within the normal range. This situation remains over the next five years.

Example 31 Method for treating acromegaly

A patient reports to her GP that she can no longer fit into her size 8 shoes, a size she have worn for the past 25 years, and that her wedding ring will no

longer fit. After ruling out obesity, the GP suspects this could be the result of a pituitary disorder the GP refers the patient for tests which confirm significantly elevated IGF-1 and GH levels. A cranial MRI confirms the presence of a pituitary adenoma.

She is treated by intravenous injection of a fusion protein comprising a prolactin releasing hormone receptor binding peptide TM (eg. SEQ ID 59). Over the following months GH and IGF-1 levels return to normal and this is maintained by a quarterly injection on the fusion protein.

Example 32 Activity of CP-GHRH-LHD on rat IGF-1 levels *in vivo*

Aims

To assess the impact of *i.v.* adminisation of CP-GHRH-LHD fusion on IGF-1 levels in rats five days after treatment compared with vehicle only treated control.

Materials and Methods

Animals: Adult male Sprague-Dawley rats maintained under standard housing conditions with lights on at 05.00h (14L:10D), food and water available ad libitum and habituated to housing conditions for at least 1 week prior to surgery.

Surgery: On day 1 of the study rats (200-250g) will be anaesthetised with a combination of Hypnorm (0.32 mg/kg fentanyl citrate and 10 mg/kg fluanisone, i.m.) and diazepam (2.6 mg/kg i.p.). The right jugular vein is exposed and a silastic tipped (i.d. 0.50 mm, o.d. 0.93 mm) polythene cannula (Portex, UK) inserted into the vessel until it lies close to the entrance of the right atrium. Cannulae will be prefilled with heparinised (10IU/ml) isotonic saline. The free end of the cannulae will be exteriorised through a scalp incision and then tunnelled through a protective spring anchored to the skull using two stainless steel screws and self-curing dental acrylic. Following recovery animals are housed in individual cages in the automated blood sampling room. The end of the protective spring is attached to a mechanical swivel that allows the animal maximum freedom of movement. Cannulae are flushed daily with heparinised saline to maintain patency.

Treatment: At 09:00 on day 2 of the study rats will receive in i.v. injection of CP-GHRH-LHD or vehicle only control.

Sampling: The automated blood-sampling system (ABS) has been previously described (Clark et al., 1986; Windle et al., 1997). Three to four days after surgery the jugular vein cannula of each animal will be connected to the automated blood-sampling system. At 07:00 on day 6 sampling will begin. Blood samples will be collected at 10 minute intervals using the automated system for a 24 hour period. A total of 144 blood samples will be collected for each will contain no more than 38µl of whole blood.

Results

The IGF-1 levels were measure using an IGF-1 ELISA kit. Figure 5 illistrates a statistically significant reduction in the IGF-1 levels in the fusion treated rats compared to the vehicle only control with a t-test P value = 0.0416 after only five days.

Example 33 Activity of CP-GHRH-LHD on rat IGF-1 levels *in vivo*

Aims:

This study is designed to investigate the activity timecourse for CP-GHRH-LHD fusion identifying the time delay between administration and initall effect of the compound in IGF-1 levels.

Materials and Methods:

Animals: Adult male Sprague-Dawley rats maintained under standard housing conditions with lights on at 05.00h (14L:10D), food and water available ad libitum and habituated to housing conditions for at least 1 week prior to surgery.

Surgery: On day 1 of the study rats (260-280g) will be anaesthetised with a combination of Hypnorm and diazepam. The right jugular vein is then exposed and a silastic tipped (i.d. 0.50 mm, o.d. 0.93 mm) polythene cannula (Portex, UK) inserted into the vessel until it lies close to the entrance of the right. Cannulae will be prefilled with heparinised (10 IU/ml) isotonic saline. The free

end of the cannulae will be exteriorised through a scalp incision and passed through a spring anchored to the skull using stainless steel screws and dental cement. Following recovery animals will be housed in individual cages in the ABS room. The spring will be attached to a swivel that allows the animal maximum freedom of movement. Cannulae will be flushed daily with heparinised saline to maintain patency.

Treatment: At 10:00h on day 5 of the study rats will receive in i.v. injection of the CP-GHRH-LHD or vehicle (sterile saline).

Blood sampling: After flushing the cannulae a single manual blood sample (100µl) will be taken from each rat at 09.30h. Samples will be taken from day 5 to day 18 of the experiment (or until the cannulae block). Plasma from blood samples will be stored at -20C for later analysis of IGF-1 content by ELISA kit.

Results

Figure 6 illistrates a statistically significant reduction in the IGF-1 levels in the fusion treated rats compared to the vehicle only control from day four after treatment.

Example 34 Activity of CP-GHRH-LHD on rat growth hormone levels *in vivo*

Aims

To assess the impact of *i.v.* adminisation of CP-GHRH-LHD fusion on growth hormone levels in rats five days after treatment compared with vehicle only treated and Octreotide infusion controls.

Materials and Methods

Animals: Adult male Sprague-Dawley rats maintained under standard housing conditions with lights on at 05.00h (14L:10D), food and water available ad libitum and habituated to housing conditions for at least 1 week prior to surgery.

Surgery: On day 1 of the study rats (200-250g) will be anaesthetised with a combination of Hypnorm (0.32 mg/kg fentanyl citrate and 10 mg/kg fluanisone,

i.m.) and diazepam (2.6 mg/kg i.p.). The right jugular vein is exposed and a silastic tipped (i.d. 0.50 mm, o.d. 0.93 mm) polythene cannula (Portex, UK) inserted into the vessel until it lies close to the entrance of the right atrium. Cannulae will be prefilled with heparinised (10IU/ml) isotonic saline. The free end of the cannulae will be exteriorised through a scalp incision and then tunnelled through a protective spring anchored to the skull using two stainless steel screws and self-curing dental acrylic. Following recovery animals are housed in individual cages in the automated blood sampling room. The end of the protective spring is attached to a mechanical swivel that allows the animal maximum freedom of movement. Cannulae are flushed daily with heparinised saline to maintain patency.

Treatment: At 09:00 on day 2 of the study rats will receive in i.v. injection of the Syntaxin active compound or vehicle. A 12 hour infusion of somatostatin (or an analogue) will begin 6 hours after the start of sampling (administered via one of the dual cannulae lines) and will continue for 12 hours only. [This infusion timing should be an excellent GH assay control as we should see baseline secretion then complete inhibition and then rapid recovery/rebound]

Sampling: The automated blood-sampling system (ABS) has been previously described (Clark et al., 1986; Windle et al., 1997). Three to four days after surgery the jugular vein cannula of each animal will be connected to the automated blood-sampling system. At 07:00 on day 6 sampling will begin. Blood samples will be collected at 10 minute intervals using the automated system for a 24 hour period. A total of 144 blood samples will be collected for each will contain no more than 38µl of whole blood.

Results

The growth hormone levels were measure using an RIA assay. Figure 7a illistrates the vehical treated animals which show typical pulsatile release of growth hormone, figure 7b illustrates the complete ablation of the pulsatile growth hormone release after treatment with GHRH-LHD chimera and figure 7c shows the blocking of the pulsatile growth hormone release and subsequent recovery when the Octreotide infusion is stopped.

CLAIMS

1. Use of a polypeptide in the manufacture of a medicament for treating acromegaly, said polypeptide comprising:

a a non-cytotoxic protease, which protease is capable of cleaving a protein of the exocytic fusion apparatus in a pituitary tumour cell, wherein said non-cytotoxic protease comprises a clostridial neurotoxin endopeptidase or an IgA protease,

b. a peptide Targeting Moiety (TM) that binds to a Binding Site on a pituitary tumour cell, which Binding Site is capable of undergoing endocytosis to be incorporated into an endosome within the pituitary tumour cell; and

c a bacterial or viral translocation domain that translocates the protease from within the endosome, across the endosomal membrane and into the cytosol of said pituitary tumour cell;

wherein the polypeptide lacks the native H_{CC} binding domain of a clostridial neurotoxin.

2. Use according to Claim 1, wherein the pituitary tumour cell is derived from or contributes to somatotrophinomas.

3. Use according to any preceding claim, wherein the TM binds to a receptor selected from the group comprising: a growth hormone-releasing hormone (GHRH) receptor; a somatostatin (SST) receptor, a cortistatin (CST) receptor; a ghrelin receptor; a bombesin receptor; a urotensin receptor; a melanin-concentrating hormone receptor 1; a KiSS-1 receptor; a gonadotropin-releasing hormone (GnRH) receptor; and/or a prolactin-releasing peptide receptor.

4. Use according to any preceding claim, wherein the TM comprises a growth hormone releasing hormone (GHRH) peptide, a somatostatin peptide, a cortistatin peptide, a ghrelin peptide, a bombesin peptide, a urotensin peptide, melanin-concentrating hormone peptide, a KISS-1 peptide, a gonadotropin-releasing hormone (GnRH) peptide, or a prolactin-releasing peptide.

5. A polypeptide for use according to any preceding claim, wherein the translocation domain comprises a clostridial neurotoxin translocation domain.

6. A polypeptide comprising:

a a non-cytotoxic protease, which protease is capable of cleaving a protein of the exocytic fusion apparatus in a pituitary tumour cell, wherein said non-cytotoxic protease comprises a clostridial neurotoxin endopeptidase or an IgA protease;

b. a peptide Targeting Moiety (TM) that binds to a Binding Site on a pituitary tumour cell, which Binding Site is capable of undergoing endocytosis to be incorporated into an endosome within the pituitary tumour cell; and

c a bacterial or viral translocation domain that translocates the protease from within the endosome, across the endosomal membrane and into the cytosol of said pituitary tumour cell;

wherein the polypeptide lacks the native H_{CC} binding domain of a clostridial neurotoxin, and wherein said polypeptide comprises an amino acid sequence having at least 90-92%, or at least 95-97%, or at least 98-99% sequence identity to any one of SEQ ID NOs: 34, 42, 43, 44, 45, 46, 47, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91 or 92.

7. A polypeptide according to Claim 6, wherein the TM binds to a growth hormone-releasing hormone (GHRH) receptor; and wherein the TM comprises a growth hormone releasing hormone (GHRH) peptide.

8. A nucleic acid encoding a polypeptide according to any of Claims 6-7.

9. Use of a polypeptide according to any of Claims 6-7 or a nucleic acid according to Claim 8 in the manufacture of a medicament for treating acromegaly in a patient.