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A fluorescence microscopy image of tissue, likely showing a cross-section of a vessel or duct. The tissue is stained with a bright green fluorescent marker, highlighting various cellular and structural components. The image shows a complex, layered structure with many small, dark spots and larger, more organized regions. The overall appearance is that of a highly detailed biological specimen.

**PEPTIDES IN  
CANCER  
RESEARCH**

# PEPTIDE-BASED CANCER THERAPEUTICS

This brochure discusses the potential use of peptides as anti-cancer drugs highlighting current scenario and future prospects. Some peptides are also used as diagnostic tools for cancer detection.

G-protein-coupled receptors are most important targets in drug development. Many of them are overexpressed in tumor cells. Amongst them, the GnRH receptor is the target of a considerable number of GnRH agonists and antagonists used in cancer management. GnRH (gonadotropin-releasing hormone) or LHRH (luteinizing hormone-releasing hormone) is a decapeptide produced in the hypothalamus and released in a pulsatile fashion into the pituitary portal circulation. Prolonged non-pulsatile administration of LHRH leads to down-regulation of LH and FSH secretion, followed by a suppression of gonadal steroid synthesis. For this reason, longer-acting GnRH agonists as well as antagonists are used for the treatment of hormone-dependent breast and prostate cancers.

Most neuroendocrine tumors show a marked overexpression of somatostatin receptors, especially of sst2, which instigated the development of somatostatin agonists as octreotide. These compounds also play an important role in diagnosis.

Bombesin/gastrin-releasing peptide receptors can be overexpressed in malignant cells. Antagonists of these peptides inhibit tumor growth.

Active immunization by peptide vaccines is another promising strategy to fight cancer.

## Introduction

Cancer is characterized by uncontrolled division of cells and the ability of these cells to invade other tissues leading to the formation of tumor mass, to vascularization and, finally, to metastasis (spread of cancer to other parts of the body). Though angiogenesis (growth of new blood vessels from existing vessels) is a normal and vital process during growth and development, it is also a fundamental step in the transition of tumors from a dormant state to a malignant one. So, angiogenesis inhibitors have been used to suppress tumor cell growth. Chemotherapy is one of the classical approaches to treat cancer, a cytotoxic agent is delivered to the cancer cells. The main problem with conventional chemotherapy is its inability to administer the correct amount of drug directly to cancer cells without affecting normal cells. Drug resistance, altered biodistribution, biotransformation and premature clearance are also common problems. Targeted chemotherapy and drug delivery techniques are emerging as a powerful method to circumvent such problems. This will allow the selective and effective localization of drugs at pre-defined targets (e.g. overexpressed receptors) while restricting its access to normal cell thus maximizing therapeutic index and reducing toxicity. The discovery of further receptors abnormally expressed in cancer cells and tumor-related peptides and proteins is expected to lead to a 'new wave' of more effective and selective anti-cancer drugs in the future.

The "biologics" approach to cancer therapy includes application of proteins, monoclonal antibodies and peptides. Monoclonal antibodies (mAb) and large protein ligands have two major limitations compared to peptides: poor delivery to tumors due to their large size and a dose-limiting toxicity in liver and bone marrow due to nonspecific uptake into the reticuloendothelial system. The use of such macromolecules has therefore been restricted to vascular targets present on the luminal side of the tumor vessel endothelium and to hematological malignancies.

Peptides possess many advantages such as small size, ease of synthesis and modification, they are biocompatible and can

penetrate tumor tissue. Their proteolytic degradation can be conveniently prevented by chemical modifications such as incorporation of D-amino acids or cyclization. Properties of bicyclic peptides are even better and comparable to those of antibody drugs.

The peptide drugs currently available on the market can be classified as analogs and antagonists of peptide hormones or tumor targeting agents carrying radionuclides.

## LHRH (GnRH) Agonists and Antagonists

The first example for the introduction of peptide drugs into cancer therapy is the use of LHRH (luteinizing hormone-releasing hormone) analogs. Schally et al. developed the first GnRH agonists which later were applied in the treatment of prostate and breast cancer. Since then, peptides such as

# MODIFICATION AT POSITION 6 WITH A D-AMINO ACID YIELDS POTENT LONG-ACTING LHRH AGONISTS

buserelin, leuprolide, goserelin, histrelin, and triptorelin have been developed and approved in cancer therapy. Depot formulations of these peptides allow for a more efficacious and convenient treatment of patients with prostate cancer. Administration of these peptides effects a down-regulation of GnRH receptors in the pituitary, leading to an inhibition of follicle-stimulating hormone (FSH) and LH release, and a concomitant decrease in testosterone production. The introduction of LHRH antagonists as cetorelix resulted in therapeutic improvement over agonists as they cause an immediate and dose-related inhibition of LH and

PEPTIDE	SEQUENCE	INDICATION
<b>GnRH</b>		
GONADORELIN	Pyr-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH <sub>2</sub>	none in cancer therapy
<b>GnRH Agonists</b>		
BUSERELIN	Pyr-His-Trp-Ser-Tyr-D-Ser(tBu)-Leu-Arg-Pro-NH <sub>2</sub>	Prostate cancer
GOSERELIN	Pyr-His-Trp-Ser-Tyr-D-Ser(tBu)-Leu-Arg-Pro-Azagly-NH <sub>2</sub>	Prostate and breast cancer
HISTRELIN	Pyr-His-Trp-Ser-Tyr-D-His(Bzl)-Leu-Arg-Pro-NH <sub>2</sub>	Prostate and breast cancer
LEUPROLIDE	Pyr-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NH <sub>2</sub>	Prostate and breast cancer
TRIPTORELIN	Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH <sub>2</sub>	Prostate and breast cancer
<b>GnRH Antagonists</b>		
ABARELIX	Ac-D-2-Nal-D-4-Cpa-D-3-Pal-Ser-N-Me-Tyr-D-Asn-Leu-Lys(isopropyl)-Pro-D-Ala-NH <sub>2</sub>	Prostate cancer
CETRORELIX	Ac-D-2-Nal-4-chloro-D-Phe-β-(3-pyridyl)-D-Ala-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH <sub>2</sub>	Prostate and breast cancer
DEGARELX	Ac-D-2-Nal-D-4-Cpa-D-3-Pal-Ser-4-amino-Phe(L-4,5-dihydroorotyl)-4-ureido-D-Phe-Leu-Lys(isopropyl)-Pro-D-Ala-NH <sub>2</sub>	Prostate cancer
OZARELIX	Ac-D-2-Nal-D-4-Cpa-D-3-Pal-Ser-N-Me-Tyr-D-Hci-Nle-Arg-Pro-D-Ala-NH <sub>2</sub>	Prostate cancer
TEVERELIX	Ac-D-2-Nal-D-4-Cpa-D-3-Pal-Ser-Tyr-D-Hci-Leu-Lys(isopropyl)-Pro-D-Ala-NH <sub>2</sub>	Prostate cancer

**Table 1. LHRH agonists and new generation antagonists available in the market.**

FSH by competitive blockade of the LHRH receptors. To date, many potent GnRH antagonists are available for therapeutic use in patients suffering from prostate cancer. A list of such agonists and antagonists available in the market can be found in Table 1

#### **Somatostatin Analogs in Cancer Therapy**

Apart from the use of peptidic LHRH agonists and antagonists for treating cancer, somatostatin analogs are the only approved cancer therapeutic peptides in the market. Potent agonists of somatostatin (SRIF) including octreotide (sandostatin) have been developed for the treatment of acromegaly, gigantism and thyrotropinoma associated with carcinoid syndrome, and diarrhea in patients with vasoactive intestinal peptide-secreting tumors (VIPomas). Lanreotide, another long-acting analog of somatostatin, is used in the management of acromegaly and symptoms caused by neuroendocrine tumors.

Most neuroendocrine tumors (NETs) feature a strong overexpression of somatostatin receptors, mainly of subtype 2 (sst2). Currently, five somatostatin receptor subtypes (sst) are known (sst1-5). The density of these receptors on tumor tissue is vastly higher than on healthy tissue. Therefore, sst are attractive targets for delivery of radionuclides employing appropriately modified somatostatin analogs. Introduced in the late 1980s by Sandoz, [<sup>111</sup>In-DTPA]-octreotide (pentetreotide, Octreoscan®), rapidly became the gold standard for diagnosis of sst-positive NETs. Numerous peptide-based tumor-imaging agents targeting sst have been developed over the past decades. Octreoscan® and NeoTect® (technetium-99m-labeled depreotide, cyclo(MePhe-Tyr-D-Trp-Lys-Val-Hcy(CH<sub>2</sub>CO-β-Dap-Lys-Cys-Lys-NH<sub>2</sub>)) are the only radiopeptide tracers on the market approved by the FDA. An octreotide scan or octreoscan is a scintigraphic method used

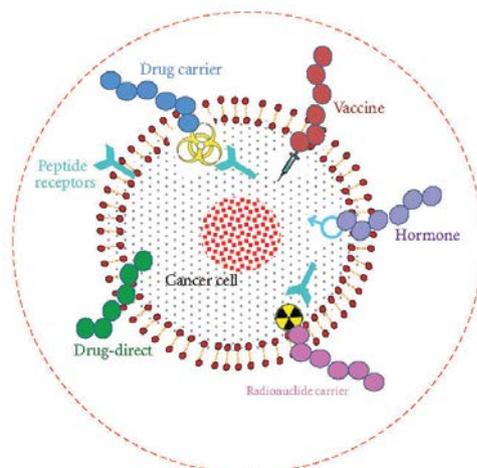
## THE FIVE KNOWN SOMATOSTATIN RECEPTORS ARE ATTRACTIVE TARGETS FOR TUMOR DIAGNOSIS AND THERAPY

to find carcinoids and other types of tumors and to localize sarcoidosis. DTPA-Octreotide, after radiolabeling with indium-111, is injected into a vein and travels through the bloodstream. The radioactive octreotide attaches to tumor cells that have receptors for somatostatin. A radiation-measuring device detects the radioactive octreotide, and generates images showing the precise location of the tumor in the body. The principle also works in cancer therapy. Peptide receptor radionuclide therapy (PRRT) combines appropriately modified octreotide with a radionuclide, which will bind to carcinoid tumor cells with overexpressed somatostatin receptors. Once bound, the targeted radiation will kill the malignant cells the peptide is bound to. The complex between radionuclide and peptide has to be stable, especially if the radiopeptide is used in therapy. Cyclic chelators as DOTA bind (radio)nuclides as  $^{68}\text{Ga}$ ,  $^{90}\text{Y}$ , or  $^{177}\text{Lu}$  more tightly, so (Tyr<sup>3</sup>)-DOTA-octreotide (DOTATOC, edotreotide) can be used in diagnosis and therapy of NETs. This also holds true for the C-terminal acid, DOTA-octreotate (DOTATATE). Somatostatin agonists vary in receptor selectivity: Lanreotide shows high affinity for sst2 and somewhat less to sst5. Pasireotide, another SRIF agonist, binds less selectively and thus mimics the natural ligand more closely.

### Peptide Vaccines

Active immunization seems to be the most promising strategy to treat cancer though many approaches based on the employment of immune cells or immune molecules have been followed. This method of treating

cancerous cells relies on vaccines consisting of peptides derived from the amino acid sequence of candidate tumor-associated or specific antigens. Tumor cells express antigens known as tumor-associated antigens (TAAs) that can be recognized by the T-cells of the host's immune system. A considerable number of TAAs could be identified and characterized. TAAs can be injected into cancer patients in an attempt to induce a systemic immune response that may result in the destruction of the cancer cells. Any protein/peptide produced in a tumor cell that has mal structure due to mutation can act as a tumor antigen. Such abnormal proteins are produced due to mutations in the corresponding gene. Hence, clinical



**Figure 1. Different treatment options of cancer using peptides. Peptides can be used as: anti-cancer drug, cytotoxic drug carrier, vaccine, hormone, radionuclide carrier and drug target (cancer drugs can be targeted towards tumor associated peptides or peptide receptors. (J. Thundimadathil, J. Amino Acids 2012, 13 (2012))**

studies have been initiated to assess the therapeutic potential of active immunization or vaccination with TAA peptides in patients with metastatic cancer. So far, only a limited number of TAA peptides, mostly those recognized by CD8 (+) T-cells in melanoma patients, have been clinically tested. Several melanoma TAAs have been identified and are being evaluated as peptide-based cancer vaccines in clinical trials around the world.

Recent advances in the field of molecular biology have enabled the rapid identification of dozens of candidate TAAs for several important human cancers

### **Current Status and Future of Peptide Based Anti-Cancer Agents**

The application of peptides as direct therapeutic agents, in targeted drug delivery and as diagnostic tools in cancer biology is growing. Among many improvements in targeted and controlled delivery of therapeutics, specifically binding peptides have emerged as the most valuable non-immunogenic approach to target cancer cells. Various cancer treatment options using peptides are summarized in Figure 1.

The RGD peptide iRGD (CRGDKGPDG) is able to specifically recognize and penetrate cancerous tumors but not normal tissues. The development of similar peptides with extraordinary tumor-penetrating properties will definitely make substantial improvements in cancer treatment in future. Chlorotoxin (Bachem product 4044876, a 36 amino acid peptide isolated from scorpion venom) has a higher affinity for glioma cells than for non-neoplastic and normal brain cells. This preferential binding has allowed the development of new methods for the treatment and diagnosis of brain cancer. Anti-angiogenesis as a therapeutic approach led to renewed interest in cilengitide. This integrin inhibitor, a cyclic RGD peptide, is being evaluated as non-small-cell lung cancer therapeutic in clinical trials.

Bombesin/gastrin-releasing peptide (BN/GRP) peptides were shown to bind selectively to the G-protein-coupled receptors on the cell surface, stimulating the growth of various malignancies in murine and human cancer models. Thus, it has been proposed that the secretion of BN/GRP by

neuroendocrine cells might be responsible for the development and progression of prostate cancer to androgen independence. GRP is widely distributed in lung and gastrointestinal tracts. It is produced in small cell lung cancer (SCLC), breast, prostatic, and pancreatic cancer, and functions as a growth factor. The involvement of bombesin-like peptides in the pathogenesis of a wide range of human tumors, their function as autocrine/paracrine tumoral growth factors, and the high incidence of BN/GRP receptors in various human cancers prompted the design and synthesis of BN/GRP receptor (GRPR) antagonists such as RC-3095, RC-3940-II, and RC-3950.

Currently, many researchers are focusing on the development of GHRH (growth hormone releasing hormone - a hypothalamic polypeptide) antagonists as potential anti-cancer therapeutics since GHRH is produced by various human tumors, including prostate cancer, and seems to exert an autocrine/paracrine stimulatory effect on them. Another promising approach for the therapy of prostate cancer consists of the use of cytotoxic analogues of GnRH, bombesin, and somatostatin, which can be targeted to receptors for these peptides in prostate cancers and their metastases. For example, a potential drug candidate, AEZS-108 consists of a peptide LHRH, coupled to the chemotherapeutic agent doxorubicin to directly target cells that express GnRH receptors, specifically, prostate cancer cells.

There is a tremendous effort to discover angiogenesis inhibitors, based on polypeptides as the safest and least toxic therapy for diseases associated with abnormal angiogenesis. A number of ongoing clinical trials in this area focus on peptides derived from: extracellular matrix proteins, growth factors and growth factor receptors, coagulation cascade proteins, chemokines, Type I Thrombospondin domain containing proteins and serpins.

**Peptides will make a huge impact in the area of cancer diagnosis and therapy in the near future.**

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# PEPTIDES FOR CANCER RESEARCH OFFERED BY BACHEM

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## BUSERELIN AND IMPURITIES

**(Des-Gly<sup>10</sup>,D-Ser(tBu)<sup>6</sup>,Pro-NHEt<sup>9</sup>)-LHRH (Buserelin)**

**4028150**

<EHWSYs(tBu)-LRP-NHEt

**(Des-Gly<sup>10</sup>,D-His<sup>2</sup>,D-Ser(tBu)<sup>6</sup>,Pro-NHEt<sup>9</sup>)-LHRH ((D-His<sup>2</sup>)-Buserelin)**

**4018942**

<EhWSYs(tBu)-LRP-NHEt

## GOSERELIN AND IMPURITIES

**(D-Ser(tBu)<sup>6</sup>,Azagly<sup>10</sup>)-LHRH (Goserelin)**

**4038252**

<EHWSYs(tBu)-LRP-Azagly-NH<sub>2</sub>

**(D-Ser<sup>4</sup>,D-Ser(tBu)<sup>6</sup>,Azagly<sup>10</sup>)-LHRH ((D-Ser<sup>4</sup>)-Goserelin)**

**4035304**

<EHWSYs(tBu)-LRP-Azagly-NH<sub>2</sub>

**(D-Ser(tBu)<sup>6</sup>,Azagly<sup>10</sup>)-LHRH (Goserelin (free base))**

**4073798**

<EHWSYs(tBu)-LRP-Azagly-NH<sub>2</sub>

**(D-Ser<sup>6</sup>,Azagly<sup>10</sup>)-LHRH ((D-Ser<sup>6</sup>)-Goserelin)**

**4047922**

<EHWSYsLRP-Azagly-NH<sub>2</sub>

**(D-His<sup>2</sup>,D-Ser(tBu)<sup>6</sup>,Azagly<sup>10</sup>)-LHRH ((D-His<sup>2</sup>)-Goserelin)**

**4035303**

<EhWSYs(tBu)-LRP-Azagly-NH<sub>2</sub>

**(D-Tyr<sup>5</sup>,D-Ser(tBu)<sup>6</sup>,Azagly<sup>10</sup>)-LHRH ((D-Tyr<sup>5</sup>)-Goserelin)**

**4035302**

<EHWSYs(tBu)-LRP-Azagly-NH<sub>2</sub>

**(D-Ser(tBu)<sup>6</sup>,D-Leu<sup>7</sup>,Azagly<sup>10</sup>)-LHRH ((D-Leu<sup>7</sup>)-Goserelin)**

**4037082**

<EHWSYs(tBu)-LRP-Azagly-NH<sub>2</sub>

**(Des-Gly<sup>10</sup>,D-Ser(tBu)<sup>6</sup>,Pro-NHNNH<sub>2</sub><sup>9</sup>)-LHRH ((Des-carboxamide)-Goserelin)**

**4039400**

<EHWSYs(tBu)-LRP-NHNNH<sub>2</sub>

**(Ser(Ac)<sup>4</sup>,D-Ser(tBu)<sup>6</sup>,Azagly<sup>10</sup>)-LHRH ((Ser(Ac)<sup>4</sup>)-Goserelin)**

**4054732**

<EHWS(Ac)-Ys(tBu)-LRP-Azagly-NH<sub>2</sub>

**(Ser(tBu)<sup>6</sup>,Azagly<sup>10</sup>)-LHRH ((Ser(tBu)<sup>6</sup>)-Goserelin)**

**4035307**

<EHWSYS(tBu)-LRP-Azagly-NH<sub>2</sub>

## HISTRELIN, ANALOGS AND FRAGMENTS

**(Des-Gly<sup>10</sup>,D-His(Bzl)<sup>6</sup>,Pro-NHET<sup>9</sup>)-LHRH (Histrelin)**

**4035442**

<EHWSYh(Bzl)-LRP-NHET

**(Des-Gly<sup>10</sup>,D-His<sup>2</sup>,D-His(Bzl)<sup>6</sup>,Pro-NHET<sup>9</sup>)-LHRH ((D-His<sup>2</sup>)-Histrelin)**

**4028762**

<EhWSYh(Bzl)-LRP-NHET

**(Des-Gly<sup>10</sup>,D-Ser<sup>4</sup>,D-His(Bzl)<sup>6</sup>,Pro-NHET<sup>9</sup>)-LHRH ((D-Ser<sup>4</sup>)-Histrelin)**

**4025431**

<EHWsYh(Bzl)-LRP-NHET

**(Des-Gly<sup>10</sup>,D-Tyr<sup>5</sup>,D-His(Bzl)<sup>6</sup>,Pro-NHET<sup>9</sup>)-LHRH ((D-Tyr<sup>5</sup>)-Histrelin)**

**4028763**

<EHWSYh(Bzl)-LRP-NHET

**(D-His(Bzl)<sup>6</sup>)-LHRH (1-7) (free acid) (Histrelin (1-7))**

**4029428**

<EHWSYh(Bzl)-L

## LEUPROLIDE AND IMPURITIES

**(Des-Gly<sup>10</sup>,D-Leu<sup>6</sup>,Pro-NHET<sup>9</sup>)-LHRH (Leuprolide)**

**4033014**

<EHWSYLRLP-NHET

**(Des-Gly<sup>10</sup>,D-Leu<sup>6</sup>,[<sup>13</sup>C<sub>6</sub>]Leu<sup>7</sup>,Pro-NHET<sup>9</sup>)-LHRH**

**(([<sup>13</sup>C<sub>6</sub>]Leu<sup>7</sup>)-Leuprolide)**

**4048762**

<EHWSY[<sup>13</sup>C<sub>6</sub>]LRP-NHET

**((D-Leu<sup>6</sup>)-LHRH (1-8) (free acid) ((Des-Pro-NHET<sup>9</sup>)-Leuprolide)**

**4037360**

<EHWSYLRL

**(D-Leu<sup>6</sup>,Pro-NHET<sup>9</sup>)-LHRH (4-9) (Leuprolide (4-9))**

**4027694**

SYLRLP-NHET

**(Des-Gly<sup>10</sup>,D-His<sup>2</sup>,D-Leu<sup>6</sup>,Pro-NHET<sup>9</sup>)-LHRH ((D-His<sup>2</sup>)-Leuprolide)**

**4028311**

<EhWSYLRLP-NHET

**(Des-Gly<sup>10</sup>,D-His<sup>2</sup>,D-Ser<sup>4</sup>,D-Leu<sup>6</sup>,Pro-NHET<sup>9</sup>)-LHRH ((D-His<sup>2</sup>,D-Ser<sup>4</sup>)-Leuprolide)**

**4048380**

<EhWsYLRLP-NHET

**(Des-Gly<sup>10</sup>,D-Leu<sup>6</sup>,D-Leu<sup>7</sup>,Pro-NHET<sup>9</sup>)-LHRH ((D-Leu<sup>7</sup>)-Leuprolide)**

**4028310**

<EHWSYLRLP-NHET

**(Des-Gly<sup>10</sup>,D-Leu<sup>6</sup>,Orn<sup>8</sup>,Pro-NHET<sup>9</sup>)-LHRH ((Orn<sup>8</sup>)-Leuprolide)**

**4065128**

<EHWSYL-Orn-P-NHET

## LEUPROLIDE AND IMPURITIES (CONTINUED)

(Des-Gly<sup>10</sup>,D-Pyr<sup>1</sup>,D-Leu<sup>6</sup>,Pro-NHt<sup>9</sup>)-LHRH ((D-Pyr<sup>1</sup>)-Leuprolide)

4046113

<eHWSYLRLP-NHt

(Des-Gly<sup>10</sup>,D-Ser<sup>4</sup>,D-Leu<sup>6</sup>,Pro-NHt<sup>9</sup>)-LHRH ((D-Ser<sup>4</sup>)-Leuprolide)

4033803

<EHWSYLRLP-NHt

(Des-Gly<sup>10</sup>,D-Trp<sup>3</sup>,D-Leu<sup>6</sup>,Pro-NHt<sup>9</sup>)-LHRH ((D-Trp<sup>3</sup>)-Leuprolide)

4058815

<EHwSYLRLP-NHt

(Des-Gly<sup>10</sup>,D-Tyr<sup>5</sup>,D-Leu<sup>6</sup>,Pro-NHt<sup>9</sup>)-LHRH ((D-Tyr<sup>5</sup>)-Leuprolide)

4028312

<EHWSyLRLP-NHt

(Des-Gly<sup>10</sup>,Des-Ser<sup>4</sup>,D-Leu<sup>6</sup>,Pro-NHt<sup>9</sup>)-LHRH ((Des-Ser<sup>4</sup>)-Leuprolide)

4065127

<EHWYLRLP-NHt

(Des-Gly<sup>10</sup>,Leu<sup>6</sup>,Pro-NHt<sup>9</sup>)-LHRH ((Leu<sup>6</sup>)-Leuprolide)

4033802

<EHWSYLLRP-NHt

(Des-Gly<sup>10</sup>,Ser(Ac)<sup>4</sup>,D-Leu<sup>6</sup>,Pro-NHt<sup>9</sup>)-LHRH ((Ser(Ac)<sup>4</sup>)-Leuprolide)

4034724

<EHWS(Ac)-YLRLP-NHt

(Des-Pyr<sup>1</sup>,Des-Gly<sup>10</sup>,D-Leu<sup>6</sup>,Pro-NHt<sup>9</sup>)-LHRH ((Des-Pyr<sup>1</sup>)-Leuprolide)

4034726

HWSYLRLP-NHt

## TRIPTORELIN, ANALOGS AND FRAGMENTS

(D-Trp<sup>6</sup>)-LHRH (Triptorelin Acetate salt)

4033016

<EHWSYwLRPG-NH<sub>2</sub> (Acetate salt)

(D-Trp<sup>6</sup>)-LHRH (Triptorelin Pamoate salt)

4039648

<EHWSYwLRPG-NH<sub>2</sub> (Pamoate salt)

(D-Trp<sup>6</sup>)-LHRH (Triptorelin (free acid))

4026526

<EHWSYwLRPG

(D-His<sup>2</sup>,D-Trp<sup>6</sup>)-LHRH ((D-His<sup>2</sup>)-Triptorelin)

4025364

<EhWSYwLRPG-NH<sub>2</sub>

(D-Trp<sup>6</sup>,D-Leu<sup>7</sup>)-LHRH ((D-Leu<sup>7</sup>)-Triptorelin)

4025366

<EHWSYwLRPG-NH<sub>2</sub>

(D-Ser<sup>4</sup>,D-Trp<sup>6</sup>)-LHRH ((D-Ser<sup>4</sup>)-Triptorelin)

4025363

<EHWSYwLRPG-NH<sub>2</sub>

(Trp<sup>6</sup>)-LHRH ((Trp<sup>6</sup>)-Triptorelin)

4029115

<EHWSYwLRPG-NH<sub>2</sub>

(D-Trp<sup>6</sup>)-LHRH-Leu-Arg-Pro-Gly amide

4029116

<EHWSYwLRPGLRPG-NH<sub>2</sub>

(D-Tyr<sup>5</sup>,D-Trp<sup>6</sup>)-LHRH ((D-Tyr<sup>5</sup>)-Triptorelin)

4025365

<EHWSYwLRPG-NH<sub>2</sub>

(D-Trp<sup>6</sup>)-LHRH (1-6) amide (Triptorelin (1-6) amide)

4029113

<EHWSYw-NH<sub>2</sub>

Formyl-(D-Trp<sup>6</sup>)-LHRH (2-10) (Formyl-Triptorelin (2-10))

4029114

For-HWSYwLRPG-NH<sub>2</sub>

(D-Trp<sup>6</sup>)-LHRH (2-10) ((Des-Pyr<sup>1</sup>)-Triptorelin)

4042497

HWSYwLRPG-NH<sub>2</sub>

## LHRH ANTAGONISTS

### Cetrorelix

4039760

Ac-D-2Nal-D-4Cpa-D-3Pal-SY-D-Cit-LRPa-NH<sub>2</sub>

### Degarelix\*

4047459

Ac-D-2Nal-D-4Cpa-D-3Pal-S-4-amino-Phe(L-4,5-dihydroorotyl)-4-ureido-D-Phe-LK(isopropyl)-Pa-NH<sub>2</sub>

### Ozarelix\*

4040823

Ac-D-2Nal-D-4-Cpa-D-3Pal-S-N-Me-Y-D-Hci-Nle-RPa-NH<sub>2</sub>

## SOMATOSTATIN, AGONISTS AND ANTAGONISTS

### Somatostatin-14

4033009

AGCKNFFWKFTTSC

### [[ring-D<sub>5</sub>]Phe<sup>6</sup>]-Somatostatin-14

4072026

AGCKNF(<sup>2</sup>H<sub>5</sub>)FWKFTTSC

### BIM-23627

4041642

F(4Cl)c-2Pal-WKVC-2Nal-NH<sub>2</sub>

### Cyclo-Somatostatin

(Somatostatin Antagonist)

4007608

c(7Aha-FwKT(Bzl))

### Lanreotide

(BIM-23014)

4067760

D-2Nal-CYwKVCT-NH<sub>2</sub>

### Octreotide acetate salt

(SMS 201-995)

4042822

fCFwKTC-ThrOl

### Octreotide pamoate salt

4076740

fCFwKTC-ThrOl

### [[ring-D<sub>5</sub>]Phe<sup>3</sup>]-Octreotide

4069671

fC(<sup>2</sup>H<sub>5</sub>)FwKTC-ThrO

### Octreotide trifluoroacetate salt (Dimer, Antiparallel)

4080984

(fCFwKTC-ThrO)<sub>2</sub>

### Octreotide trifluoroacetate salt (Dimer, Parallel)

4080983

(fCFwKTC-ThrO)<sub>2</sub>

### DOTA-(Tyr<sup>3</sup>)-Octreotate (DOTATATE)

4046724

DOTA-fCYwKTCT

### Pasireotide\* **NEW** (SOM230)

4060221

c(-Hyp(2-aminoethylcarbamoyl)-Phg-wKY(Bzl)F)

### Tyr-(D-Dab<sup>4</sup>,Arg<sup>5</sup>,D-Trp<sup>8</sup>)-cyclo-Somatostatin-14 (4-11)

(KE 108)

4041674

Y-c(D-Dab-RFFwKTF)

### (D-Phe<sup>5</sup>,Cys<sup>6</sup>,<sup>11</sup>,N-Me-D-Trp<sup>8</sup>)-Somatostatin-14 (5-12) amide (N-Me-D-Trp<sup>4</sup>)-Octreotate amide)

4039201

fCY(NMe-w)KTCT

### Vapreotide (RC-160)

4062833

fCYwKVCW-NH<sub>2</sub>

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## BOMBESIN AND BOMBESIN/GRP ANTAGONISTS

### Bombesin

4010579

pEQRLGNQWAVGHLM-NH<sub>2</sub>

### (Lys<sup>3</sup>)-Bombesin

4011270

pEQKLGNGWAVGHLM-NH<sub>2</sub>

### (D-Phe<sup>12</sup>)-Bombesin

4030216

pEQRLGNQWAVGfLM-NH<sub>2</sub>

### (D-Phe<sup>6</sup>,Leu-NHEt<sup>13</sup>,des-Met<sup>14</sup>)-Bombesin (6-14)

(DPDMB)

4030433

fQWAVGHL-NHEt

### (D-Phe<sup>6</sup>,Leu<sup>13</sup>-psi(CH<sub>2</sub>NH)p-chloro-Phe<sup>14</sup>)-Bombesin (6-14)

4030432

fQWAVGHL(Ψ[CH<sub>2</sub>NH])F(4-Cl)-NH<sub>2</sub>

### (Tyr<sup>4</sup>)-Bombesin

4011655

pEQRYGNQWAVGHLM-NH<sub>2</sub>

### (Tyr<sup>4</sup>,D-Phe<sup>12</sup>)-Bombesin

4016626

pEQRYGNQWAVGfLM-NH<sub>2</sub>

### (D-2-Nal<sup>5</sup>,Cys<sup>6,11</sup>,Tyr<sup>7</sup>,D-Trp<sup>8</sup>,Val<sup>10</sup>,2-Nal<sup>12</sup>)-Somatostatin-14 (5-12) amide (BIM 23042)

4025467

D-2Nal-CYwKVC-Nal-NH

### (Deamino-Phe<sup>19</sup>,D-Ala<sup>24</sup>,D-Pro<sup>26</sup>-psi(CH<sub>2</sub>NH)Phe<sup>27</sup>)-GRP (19-27) (human, porcine, canine)

(BW-10, BW2258U89)

4030653

Deamino-FHWAVaHpo(Ψ[CH<sub>2</sub>NH])F-NH<sub>2</sub>

## GHRH/NEUROTENSIN/SUBSTANCE P

### Phenylacetyl-(D-Arg<sup>2,28</sup>,p-chloro-Phe<sup>6</sup>,Homoarg<sup>9,29</sup>,Tyr(Me)<sup>10</sup>,Abu<sup>15</sup>,Nle<sup>27</sup>)-GRF (1-29) amide (human)

(JV-1-38)

4034002

Phac-YrDAIF(4Cl)TN-Har-Y(Me)RKVL-

Abu-QLSARKLLQDI-Nle-r-Har-NH<sub>2</sub>

### (D-Arg<sup>1</sup>,D-Pro<sup>2</sup>,D-Trp<sup>7,9</sup>,Leu<sup>11</sup>)-Substance P

((D-Pro<sup>2</sup>)-Spantide)

4004685

rpKPQQwFwLL-NH<sub>2</sub>

### (D-Arg<sup>1</sup>,D-Trp<sup>5,7,9</sup>,Leu<sup>11</sup>)-Substance P

4031292

rPKPwQwFwLL-NH<sub>2</sub>

### (Arg<sup>6</sup>,D-Trp<sup>7,9</sup>,N-Me-Phe<sup>8</sup>)-Substance P (6-11)

(Antagonist G)

4031294

Rw(MeF)wLM-NH<sub>22</sub>

### Ac-Trp-3,5-bis(trifluoromethyl)benzyl ester

(L-732,138, Substance P Antagonist)

4025344

### PACAP-38 (6-38) (human, chicken, mouse, ovine, porcine, rat)

4031158

FTDSYSRYRKQMAVKKYLAAVLG-

KRYKQRVKKNK-NH<sub>2</sub>

### Acetyl-(D-Phe<sup>2</sup>,Lys<sup>15</sup>,Arg<sup>16</sup>,Leu<sup>27</sup>)-VIP (1-7)-GRF (8-27)

(PG 97-269)

4048647

D-2Nal-CYw-Orn-VC-2Nal-NH<sub>2</sub>

## VIP/PACAP

**Myristoyl-(Lys<sup>12,27,28</sup>)-VIP-Gly-Gly-Thr (free acid)**

**4037992**

Myr-HSDAVFTDNYTKLRKQMAVK-KYLNSIKKGGT

**VIP Antagonist**

**4031352**

KPRRPYTDNYTRLRKQMAVKKYLN-SILN-NH<sub>2</sub>

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## EPITOPES

**Ovalbumin (257-264) (chicken)**

**4033142**

SIINFEKL

**Ovalbumin (323-339) (chicken, japanese quail)**

**4034255**

ISQAVHAAHAEINEAGR

**Cytochrome C (88-104) (domestic pigeon)**

**4044055**

KAERADLIAYLKQATAK

**Collagen Type IV α3 Chain (185-203)**

**4028340**

CNYYSNSYSFWLASLNP

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## VARIOUS

**Chlorotoxin**

**4044876**

MCMPCFITTDHQMARKCDDCCGGK-GRGKCYGPQCLCR-NH<sub>2</sub>

**Human CMV pp65 (495-503)**

**4039108**

NLVPMVATV

**Z-Val-Ala-DL-Asp-fluoromethylketone**

**4026865**

Z-VAD-FMK



## OESOPHAGEAL CANCER

Oesophageal cancer. Light micrograph of an oesophageal cancer biopsy. This is an epidermoid cancer, a type of cancer that arises from the epithelial cells that line the oesophagus (gullet). Left is a large vacuole filled with a whorl of the protein keratin. Symptoms of oesophageal cancer may include difficulty swallowing, weight loss and vomiting. Risk factors include smoking and alcohol consumption. Treatment is surgical removal of the tumor, often combined with chemotherapy or radiotherapy.

(KEYSTONE/SCIENCE PHOTO  
LIBRARY)

# API PRODUCTS

Bachem is the world's leading independent manufacturer of peptide active pharmaceutical ingredients (APIs) and a well established manufacturer of small molecules APIs. Each year, Bachem manufactures hundreds of batches of drug substance for projects in clinical trials and for products on the market.

Bachem is currently involved in more than 150 cGMP development projects targeting NCEs and Bachem offers a range of more than 30 generic drug substances. We have the capacity to produce peptide APIs from gram scale up to annual quantities of hundreds of kilograms and small molecules APIs from gram scale up to annual quantities of tens of tons. Our GMP manufacturing facilities are located in Switzerland and the United States and are regularly inspected by the FDA and local authorities.

In addition to close to 50 years of experience in the manufacture of drug substance, Bachem also has a strong regulatory background and we are well prepared to fully support you with the required regulatory documentation such as drug master files (DMFs). For complex development projects we support you with dedicated project teams comprising of our experts from R&D, production, quality control, quality assurance and regulatory affairs. A team of experienced Business Development Managers and Generics Managers look forward to working with you for your future requirements.

## GENERIC APIs

**Buserelin**  
**4028150-GMP**  
<EHWSYs(tBu)-LRP-NHEt

**Gonadorelin Acetate**  
**4033013-GMP**  
<EHWSYGLRPG-NH<sub>2</sub> (Acetate salt)

**Goserelin Acetate**  
**4038252-GMP**  
<EHWSYs(tBu)-LRP-Azagly-NH<sub>2</sub>

**Leuprolide Acetate**  
**4033014-GMP**  
<EHWSYLRLP-NHEt

**Triptorelin Acetate**  
**4033016-GMP**  
<EHWSYwLRPG-NH<sub>2</sub> (Acetate salt)

**Triptorelin Pamoate**  
**4039648-GMP**  
<EHWSYwLRPG-NH<sub>2</sub> (Pamoate salt)

## IMPURITIES OF THE LEUPRORELIN PH. EUR. MONOGRAPH

**Impurity A**  
**(D-Ser<sup>4</sup>)-Leuprolide**  
**4033803**  
<EHWSyILRP-NHEt

**Impurity B**  
**(D-His<sup>2</sup>)-Leuprolide**  
**4028311**  
<EhWSYILRP-NHEt

**Impurity C**  
**(Leu<sup>6</sup>)-Leuprolide**  
**4033802**  
<EHWSYLLRP-NHEt

**Impurity D**  
**(Ser(Ac)<sup>4</sup>)-Leuprolide**  
**4034724**  
<EHWS(Ac)YILRP-NHEt

**Impurity E**  
**(D-Trp<sup>3</sup>)-Leuprolide**  
**4058815**  
<EHwSYILRP-NHEt

**Impurity F**  
**(D-His<sup>2</sup>,D-Ser<sup>4</sup>)-Leuprolide**  
**4048380**  
<EhWsYILRP-NHEt

**Impurity G**  
**(D-Tyr<sup>5</sup>)-Leuprolide**  
**4028312**  
<EHWSyILRP-NHEt

**Impurity H**  
**(D-Leu<sup>7</sup>)-Leuprolide**  
**4028310**  
<EHWSYILRP-NHEt

**Impurity I**  
**(D-Pyr<sup>1</sup>)-Leuprolide**  
**4046113**  
<eHWSYILRP-NHEt

## IMPURITIES OF THE GOSERELIN PH. EUR. MONOGRAPH

**Impurity A**  
**(D-Ser<sup>4</sup>)-Goserelin**  
**4035304**  
<EHWSYs(tBu)-LRP-Azagly-NH<sub>2</sub>

**Impurity B**  
**(Ser(tBu)<sup>6</sup>)-Goserelin**  
**4035307**  
<EHWSYS(tBu)-LRP-Azagly-NH<sub>2</sub>

**Impurity E**  
**(Pro-NHNH<sub>2</sub><sup>9</sup>)-Buserelin**  
**4039400**  
<EHWSYs(tBu)-LRP-NHNH<sub>2</sub>

**Impurity F**  
**(D-Tyr<sup>5</sup>)-Goserelin**  
**4035302**  
<EHWSys(tBu)-LRP-Azagly-NH<sub>2</sub>

**Impurity G**  
**(D-His<sup>2</sup>)-Goserelin**  
**4035303**  
<EhWSYs(tBu)-LRP-Azagly-NH<sub>2</sub>

**Impurity K**  
**(Ser(Ac)<sup>4</sup>)-Goserelin**  
**4054732**  
<EHWS(Ac)-Ys(tBu)-LRP-Azagly-NH<sub>2</sub>

**Impurity L**  
**(D-Leu<sup>7</sup>)-Goserelin**  
**4037082**  
<EHWSYs(tBu)-LRP-Azagly-NH<sub>2</sub>

## IMPURITIES OF THE BUSERELIN PH. EUR. MONOGRAPH

**Impurity A**  
**(D-His<sup>2</sup>)-Buserelin**  
**4018942**  
<EhWSYs(tBu)-LRP-NHEt

## SOMATOSTATIN AND AGONISTS

**Somatostatin**  
**4033009-GMP**  
<EhWSYs(tBu)-LRP-NHEt

**Lanreotide**  
**4067760-GMP**  
<EHWSYs(tBu)-LRP-NHEt

**Octreotide Acetate**  
**4042822-GMP**  
<EHWSys(tBu)-LRP-NHEt

**Pasireotide Acetate\***  
**4067875**  
<eHWSYs(tBu)-LRP-NHEt

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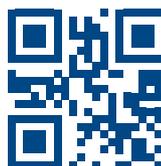
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