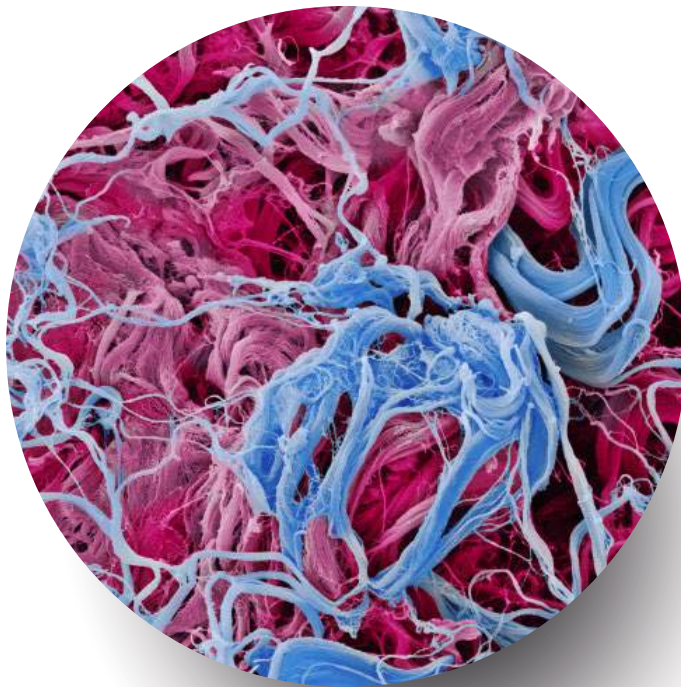


# COSMETIC PEPTIDES BACHEM

LEADING PARTNER IN TIDES



# PIONEERING PARTNER FOR COSMETIC PEPTIDES

Peptides are involved in many physiological processes. Their broad acceptance as natural molecules, relatively high stability and well-defined actions make them attractive for many skin-related indications, most notably in anti-aging therapy. We have considerable expertise and long-standing experience in peptide synthesis. With our capacity to upscale the production of simple and modified peptides, we are the partner of choice for the pharmaceutical and cosmetic industries. Our portfolio reaches from catalog products, which can be purchased in small amounts for research, to the production of commercial batch sizes used by our customers for formulation. In addition, we offer several services such as the assurance of the compatibility with CMR requirements and microbiological limits.

Step in project	Performed by
Catalog products (small amounts, mostly from stock) for early research	Bachem
R&D, discovery of new peptide cosmetic ingredients	Our customers
Handling of intellectual properties on the active ingredients	Our customers
Synthesis of the first proof of concept batch for early development	Bachem
Formulation development	Our customers
Early tests on mode of action and dosage	Our customers
Process development for scale-up till the commercial batch size	Bachem
Compatibility with CMR requirements (residual solvent, heavy metal traces)	Bachem
Compatibility with microbiological limits	Bachem
Toxicological studies	Our customers
INCI registration	Our customers
Production of commercial peptide batches	Bachem

## Introduction

The cosmetic industry requires a variety of different ingredients for skin care products. These include peptides, growth factors, antioxidants, anti-inflammatory botanicals, and polysaccharides. As these products show drug-like effects they are commonly referred to as cosmeceuticals. In contrast to drugs these ingredients are not regulated by the U.S. Food and Drug Administration (FDA).

Originally, peptides became of interest in cosmetics as a result of the discovery of their beneficial effects in wound healing. As peptides are involved in an immense number of physiological processes, it was logical to further exploit them for cosmetic applications. Most of the peptides used in cosmetics are designed to counteract the aging process of the skin. The need for such products is driven by the increasing desire in modern society to maintain a young appearance even at an older age, and the breadth of possible treatments to achieve this goal. The increasing knowledge about the molecular details of the skin-related aging processes has significantly contributed to the exploration of novel anti-aging agents.

## Skin Aging

Skin aging is a process influenced by extrinsic and intrinsic factors and is manifested by a progressive loss of skin tissue, the gradual loss of skin elasticity, and the appearance of fine lines and wrinkles. Extrinsic factors include exposure to UV-light, environmental pollution, cigarette smoke, and extreme weather conditions.

The continuous generation of reactive oxygen species (ROS) during cellular metabolism and genetic predispositions are considered as intrinsic factors. Extrinsic factors, most notably UV irradiation and smoking, seem to be the major contributors to premature skin aging. Exposure of skin to UV-light increases ROS levels leading to changes in gene and protein structure and function and subsequent skin damage. Obvious effects of UV exposure are the disruption of ongoing collagen synthesis, induction of collagenase and other extracellular matrix protein-degrading enzymes, and the damage of cellular

DNA. The premature skin-aging effects of tobacco smoking are caused by induction of collagenase activity and the reduced blood flow to the skin due to nicotine-induced vasoconstriction. Intrinsic factors such as the generation of ROS contribute to the loss of extracellular matrix proteins, a decrease in cutaneous blood flow, and a loss of cells and cell function.

## Peptides in Cosmetics

Peptides have become very important ingredients in cosmetic products, especially in anti-aging preparations, and many of them are already available as research-grade catalog products (Table 1). According to their mode of action, they have been divided into three main groups: signal peptides, neurotransmitter-affecting peptides, and carrier peptides. The first group mainly consists of peptides which are able to increase collagen synthesis, or alternatively, inhibit the breakdown of collagen by collagenase. The second group includes peptides mimicking the effects of botulinum neurotoxins whereas the third group, the carrier peptides, acts by delivering trace elements required for enzymatic processes.

## Signal peptides

Aged skin is, amongst others, characterized by reduced levels of collagen and elastin. Increasing the number of fibroblasts or their collagen production and/or inhibiting further collagen hydrolysis are therefore considered effective means to halt or slow the aging process of the skin. Many of the peptides used in cosmetic preparations are compounds which act on fibroblasts. One of the peptides described to act in this way is H-Val- Gly-Val-Ala-Pro-Gly-OH (VGVPAG) (Product: 4010536 Chemotactic Domain of Elastin). 4010536 is an elastin-derived peptide sequence repeated several times in tropoelastin. It was found to stimulate the proliferation of human skin fibroblasts presumably via the elastin receptor. The N-terminally palmitoylated peptide is marketed under the name of palmitoyl-oligo peptide and is supposed to penetrate more efficiently through the epidermis than the parent compound.

H-Lys-Thr-Thr-Lys-Ser-OH (KTTKS) (Product: 4025012 Procollagen Type I (212-216))

**Table 1: Cosmeceutical-related research quantities offered from our catalog**

Prod. No.	Product	Activity
4012417	Ac-Hyp-OH	Anti-inflammatory, wound healing
4003668	Ac-Met-OH	Anti-wrinkle
4016348	Ac-Ser-Asp-Lys-Pro-OH	Stimulation of keratinocyte, fibroblast and follicle dermal papilla cell growth
4001968	Ac-Tyr-NH <sub>2</sub>	Anti-wrinkle
4012005	H-Ala-His-Lys-OH	Enhancement of collagen synthesis
4027810	L-Anserine · nitrate	Antioxidant
4026204	Carcinine	Antioxidant
4030364	L-Carnosine	Antioxidant
4010536	Chemotactic Domain of Elastin (VGAPG)	Stimulation of skin fibroblast proliferation
4038287	rec $\beta$ -Defensin 2 (human)	Elevated expression in psoriasis and in the inflamed skin of mastitis
4061590	Dermcidin-1L (human)	Activation of keratinocytes
4030547	H- $\alpha$ -Difluoro-Me-DL-Orn-OH · HCl · H <sub>2</sub> O	Reduction of excessive hair growth (hirsutism)
4003792	(D-Ala <sup>2</sup> )-Leu-Enkephalin	Anti-wrinkle peptide
4008512	H-Gly-Pro-Hyp-OH	Anti-wrinkle and anti-aging
4009573	Z-Gly-Pro-Phe-Pro-Leu-OH	Inhibitor of desquamation of human skin
4030783	rec IL-1 $\alpha$ (human)	Role in skin renewal
4026408	Z-Ile-Glu(OtBu)-Ala-Leu-aldehyde	Inhibitor of accumulation of ubiquitinated proteins in neuronal cells
4003049	Kyotorphin	Reducing the sensitivity of the skin
4000308	Liver Cell Growth Factor (GHK)	Enhancement of collagen synthesis
4000074	H-Lys-Phe-Lys-OH (KFK)	Activation of LAP-TGF- $\beta$
4003800	(Nle <sup>4</sup> ,D-Phe <sup>7</sup> )- $\alpha$ -MSH	Anti-inflammatory
4026419	(Met <sup>5</sup> ,Pro <sup>6</sup> ,D-Phe <sup>7</sup> ,D-Trp <sup>9</sup> ,Phe <sup>10</sup> )- $\alpha$ -MSH (5-13)	Anti-inflammatory
4006104	$\alpha$ -MSH (11-13) (free acid)	Anti-inflammatory
4011677	(D-Pro <sup>12</sup> )- $\alpha$ -MSH (11-13) (free acid)	Anti-inflammatory
4001965	H-Phe- $\beta$ -Ala-OH	Inhibitor of hair growth. Eventually promoting effect on wound healing
4025012	Procollagen Type I (212-216) (KTTKS)	Enhancement of collagen synthesis
4001630	H-Pro-Hyp-OH	Stimulation of fibroblast proliferation, chondroprotective
4030572	rec EGF (human)	Aiding wound healing
4011277	Rigin (GQPR)	Immunomodulation
4026105	SPARC (119-122) (mouse)	Stimulation of endothelial cell proliferation and angiogenesis
4043020	Thymosin $\beta_4$ (human, bovine, horse, rat)	Potentially contributing to angiogenesis, wound healing, regulation of inflammation and other processes
4008196	H-Val-Trp-OH	Compound in various formulations, e.g. for anti-wrinkle and anti-aging cosmetics
4001260	H-Val-Tyr-Val-OH	Peptidic compound in various cosmetic formulations

is a subfragment of the carboxy-terminal propeptide of type I collagen (residues 197-241) and represents the minimal sequence shown to stimulate extracellular matrix biosynthesis in fibroblasts. It augments type I and II collagen and fibronectin production in a dose- and time-dependent manner with no effect on total protein synthesis or on the ratio of secreted proteins to cell-associated proteins. The N-terminally palmitoylated peptide is marketed as a cosmetic ingredient under the designation palmitoyl pentapeptide-3.

Another peptide shown to enhance collagen production when added to cultured fibroblasts is H-Gly-His-Lys-OH, also known as GHK (Product: 4000308 Liver Cell Growth Factor). Since similar enhancement of collagen synthesis was shown for the tripeptide in complex with copper (see below) it was not clear whether the activity was intrinsic to GHK or whether it was resulting from the formation of active copper complexes due to the presence of copper ions in the tissue culture medium.

As various matrix metalloproteinases are involved in the degradation of collagen and elastin, inhibition of these enzymes represents another strategy to prevent extracellular matrix breakdown and its influence on skin aging. Several peptides have been shown to act in this way: H-Tyr-Tyr-Arg-Ala-Asp-Asp-Ala-OH (YYRADD) corresponds to a sequence in  $\alpha$ -1 type I procollagen which is cleaved during the conversion of procollagen to collagen. The peptide was shown to attenuate collagen breakdown by inhibiting procollagen-C proteinase, which cleaves the C-propeptide from type I procollagen. Another compound, the tripeptide H-Lys-Phe-Lys-OH (Product: 4000074) linked to elaidic acid, was demonstrated to activate TGF- $\beta$ , a factor showing the capacity to increase collagen, elastin and TIMP-1 (tissue inhibitor of metalloproteinase 1) expression, and to inhibit MMPs via its lipophilic moiety, elaidic acid. The sequence of H-Lys-Phe-Lys-OH corresponds to the consensus BFB (B: basic amino acid, F: phenylalanine) shown to activate LAP-TGF- $\beta$  in several *in vitro* and *ex vivo* studies. Elaidic acid was chosen due to its inhibitory effect on gelatinase A (MMP-2) and B (MMP-9). Similar effects on TGF- $\beta$  were shown for the palmitoylated

peptide Palmitoyl-Lys-Val-Lys-OH and Palmitoyl-Val-Gly-Val-Val-Ala-Pro-Gly-OH, an elastin-derived peptide.

### Neurotransmitter-affecting peptides

Many of the peptides used in cosmetic preparations belong to the group of neurotransmitter-affecting peptides. These peptides act in a similar way as botulinum toxin (Botox). By inhibiting signal transduction pathways at neuromuscular junctions (Figure 1) they attenuate the formation of wrinkles and fine lines which appear over time due to the repetitive contraction of the intrinsic muscles of facial expression. Botulinum toxin, synthesized by the bacterium *Clostridium botulinum*, is the most potent toxin known. It is a disulfide-linked heterodimer consisting of a heavy and a light chain. Upon binding to the peripheral neuronal presynaptic membrane mediated by the heavy chain the toxin is internalized by receptor-mediated endocytosis. After translocation from the endocytotic vesicle into the cytoplasm, the light chain proteolytically cleaves either SNAP-25 or synaptobrevin depending on the serological subtype of the neurotoxin. Cleavage of these proteins which are essential for docking to and fusion of acetylcholine vesicles with the inner side of the nerve terminal membrane results in the inhibition of neurotransmitter release at neuromuscular junctions. A well-known mimic of botulinum toxin used in cosmetic preparations is Acetyl-Glu-Glu-Met-Gln-Arg-Arg-NH<sub>2</sub>. It is a synthetic peptide corresponding to a sequence within the N-terminal region of SNAP-25 (amino acids 12-17) and competes with SNAP-25 for a position in the SNARE complex, thereby modulating its formation. The resulting destabilization of the SNARE complex leads to an inhibition of neurotransmitter release and a subsequent attenuation of muscle contraction.

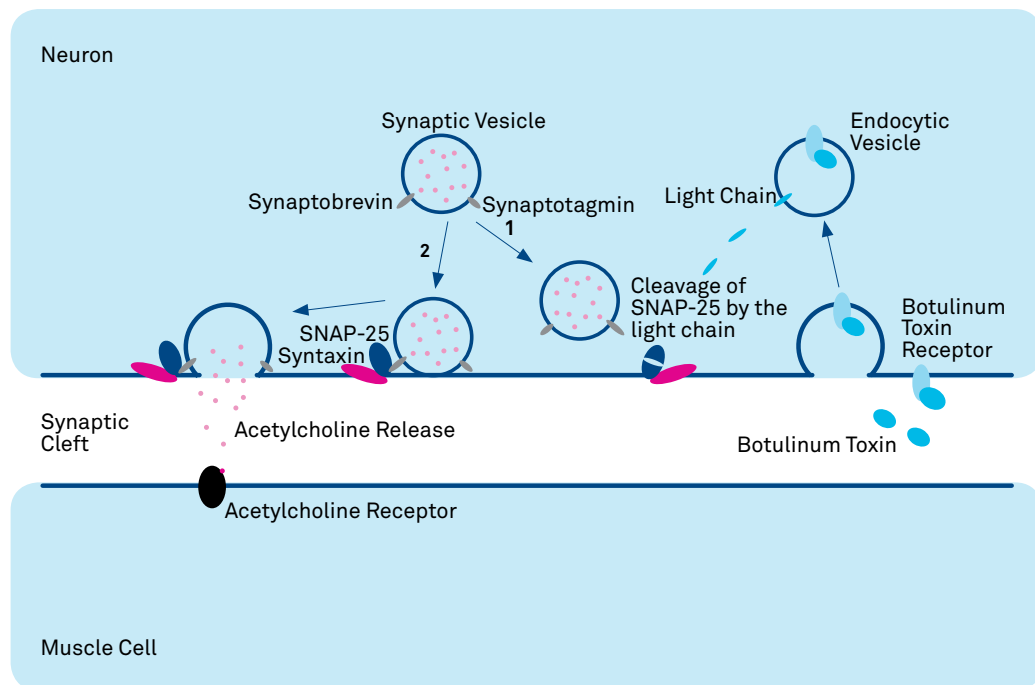
Another class of potentially interesting substances in the cosmetic industry includes peptides derived from snake venoms. Waglerin-1 (H-Gly-Gly-Lys-Pro-Asp-Leu-Arg-Pro-Cys-His-Pro-Pro-Cys-His-Tyr-Ile-Pro-Arg-Pro-Lys-Pro-Arg-OH), for example, is a peptide isolated from the venom of the temple viper, *Tropidolaemus wagleri*. It consists of 22 amino acids and selectively

blocks the epsilon form of the muscular nicotinic acetylcholine receptor (mnAChR) thereby keeping the affected muscles in a relaxed state. Another compound, the tripeptide H- $\beta$ -Ala-Pro-Dab-NHBzl mimicking the activity of waglerin-1 is now marketed in anti-wrinkle creams. Many other peptides acting similarly by affecting neurotransmitter release are pro-

to disrupt acetylcholine receptor clustering, a requirement for acetylcholine to trigger the signal for muscle contraction.

#### Carrier peptides

The tripeptide H-Gly-His-Lys-OH (GHK) (Product: 4000308 Liver Cell Growth Factor) was originally identified in human plasma and has a high affinity for copper<sup>2+</sup> (Cu<sup>2+</sup>).



**Figure1: Mode of Action of Botulinum Neurotoxin Type A**

Botulinum Neurotoxin Type A consists of a heavy and a light chain. Upon binding to the botulinum toxin receptor the toxin is internalized. Acidification of the vesicles leads to the translocation of the light chain to the cytosol. There it acts as a protease and cleaves the SNARE protein SNAP-25. Cleavage results in inhibition of exocytosis and acetylcholine neurotransmitter release (1) as intact SNAP-25 together with several other proteins is required for synaptic vesicle fusion with the presynaptic membrane (2).

moted by the cosmetic industry. Compounds include: a) a pentapeptide, which binds to the enkephalin receptors on the outside of neurons and thereby initiates a cascade leading to a decrease in acetylcholine release and subsequent muscle contraction; b) SNAP-8, an octapeptide related to and acting in the same way as Acetyl-Glu-Glu-Met-Gln-Arg-Arg-NH<sub>2</sub>; and c) a hexapeptide that reduces the activation of muscle-specific kinase (MuSK) by blocking the agrin binding site. The peptide was demonstrated

It acts as a signaling peptide and a carrier molecule for copper which is a co-factor for several enzymes involved in collagen and elastin formation. The copper peptide was shown to stimulate wound healing but also to reduce fine lines and wrinkles and to improve elasticity and firmness of aged skin. A wide variety of effects have been ascribed to GHK-Cu. The peptide exhibits anti-inflammatory actions by suppressing the expression of pro-inflammatory cytokines. It also chemoattracts capillary cells,

macrophages and mast cells, increases the synthesis of collagen and elastin, and stimulates the proliferation of fibroblasts and keratinocytes.

#### Other mechanisms

Many peptides used in cosmetic preparations act by other mechanisms to improve skin appearance or delay skin aging. These include ROS scavengers, collagen fiber organizing compounds, and anti-inflammatory peptides: Peptides such as carnosine (Product: 4030364 ), anserine (Product: 4027810 L-Anserine · nitrate) and carbinine (Product: 4026204) are histidine dipeptides with antioxidant activity. Carnosine has been shown to scavenge ROS and chelate prooxidative metals. It also inactivates reactive mono- and dialdehydes released during the oxidative breakdown of unsaturated lipids thereby protecting hydrophilic and lipophilic biological molecules from oxidative damage. However, in contrast to carbinine it is sensitive to enzymatic

hydrolysis by carnosinase. A tetrapeptide of unpublished sequence is a mimic of decorin which interacts with collagen and influences collagen fibrillogenesis. As functional decorin in the skin diminishes with age, the tetrapeptide is proposed to serve as a substitute. By controlling collagen aggregation and homogenization of fibril diameters and dimensions, it increases skin suppleness and thus improving its appearance. Rigin (Product: 4011277 H-Gly-Gln-Pro-Arg-OH (GQPR)) corresponds to amino acid sequence 341- 344 of the human IgG H-chain and has been shown to possess immunomodulatory activity. By suppressing inflammation the palmitoylated form is supposed to accelerate tissue repair thereby leading to increased skin firmness, smoothness, and elasticity.

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##### ✓ Support

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- Confidentiality



A scanning electron micrograph (SEM) of collagen fibers from the dermis of the skin. The image shows a dense, intricate network of fibers. Some fibers are thick and appear as large, blue, rope-like structures, while others are thin and delicate, appearing as fine, pinkish-red lines. The fibers are arranged in a complex, interwoven pattern, creating a mesh-like appearance. The background is dark, making the fibers stand out.

## COLLAGEN FIBRES

Collagen fibers. Colored scanning electron micrograph (SEM) of collagen from the dermis of the skin. Collagen is a protein with a high tensile strength, providing structure and elasticity to skin, tendons, ligaments and bones. It is the most abundant protein in the body. In the dermis, collagen forms rope-like fibers that are arranged irregularly.

(KEystone/SCIENCE PHOTO LIBRARY)



### Conclusions

Synthetic peptides have become important for the cosmetic industry. Due to demographic changes and the aging population wishing to maintain a young lifestyle and appearance, cosmetic industry research has focused on anti-aging skin therapy. Today, more than 30 peptides are used in anti-aging skin care products and there are many more in development.

Bachem is the market leader in the production of synthetic peptides and has long standing partnerships with major firms in

the pharmaceutical and cosmetic industry. We are well-equipped for small to industrial scale synthesis of peptides of any complexity. Bachem is therefore the ideal partner in the development and production of cosmetic peptides. Together with our customers, we accomplish each of the demanding steps in a development project, finally leading to the successful cosmetic product.



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