

# Alzheimer

## 1. Bioactive Peptides

Genaxxon offers customer defined peptides and peptidomimetics. Additionally, Genaxxon offers ex stock biologically active peptides and respective control peptides.

All peptides are provided as lyophilised powders. They are characterised by RP-HPLC and ESI mass spectrometry (analytical data sheet included). If not otherwise specified, the counter-ion of positively charged peptides is trifluoroacetic acid.

### 1.1 Amyloid- $\beta$ -peptides

Characteristic of Alzheimer disease is the accumulation of amyloid plaques in the brain. The major components of these plaques are 39-42 residue-long amyloid- $\beta$ -peptides, which form insoluble fibrils via self-assembly.

The amyloid- $\beta$ -peptides are fragments of the broadly distributed, membrane-bound amyloid precursor protein APP, encoded on chromosome 21. They are formed from the proteolytic cleavage of APP by  $\beta$ - and  $\gamma$ -secretases.

Cleavage occurs after residue 40 or after residue 42. Even slightly increased amounts of amyloid- $\beta$ 1-42 are described to be sufficient to cause Alzheimer's disease.

#### References:

M. Ahmed, J. Davis, D. Aucoin, T. Sato, S. Ahuja, S. Aimoto, J. I. Elliott, W. E. Van Nostrand, S. O. Smith (2010) Nat. Struct. Mol. Biol. 17, 561-567.  
T. Hartmann, S. C. Bieger, B. Brühl, P. J. Tienari, N. Ida, D. Allsop, G. W. Roberts, C. L. Masters, C. G. Dotti, K. Unsicker, K. Beyreuther (1997) Nat. Med. 3, 1016-1020.

#### Amyloid- $\beta$ -peptides and innate immunity

In Alzheimer's disease, deposition of amyloid- $\beta$  triggers a protracted sterile inflammatory response. Chronic stimulation of the innate immune system is believed to underlie the pathology of this disease. It was shown, that amyloid- $\beta$  triggers inflammatory signalling through a heterodimer of Toll-like receptors 4 and 6. Assembly of this recently identified heterodimer is regulated by signals from the scavenger receptor CD36, CD36-TLR4-TLR6 activation was

identified as a common molecular mechanism by which atherogenic lipids and amyloid- $\beta$  stimulate sterile inflammation (Stewart et al. 2010, Nature Immunology 11, 155-161 doi:10.1038/ni.1836).).

Amyloid- $\beta$ (1-42) human		P2247	
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA			
Purity	$\geq 95\%$	1mg	5mg

Amyloid- $\beta$ (1-42) human HCl salt		P2248	
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA			
Purity	$\geq 95\%$	1mg	5mg

Amyloid- $\beta$ (1-40) human		P2249	
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV			
Purity	$\geq 95\%$	1mg	5mg

Amyloid- $\beta$ (1-40) human HCl salt		P2250	
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV			
Purity	$\geq 95\%$	1mg	5mg

### Reverse control peptides of amyloid- $\alpha$ -peptides

The negative control peptides represent the reverse amino acid sequences of the corresponding amyloid- $\alpha$ -peptides.

Control peptide amyloid-B (40-1) rat		P2251	
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGV V			
Purity	≥95 %	1mg	5mg

Control peptide amyloid-B (40-1) human		P2252	
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGV V			
Purity	≥95 %	1mg	5mg

### Biotinylated amyloid- $\beta$ -peptides

Biotinylated peptides are a useful tool in many important applications. Biotin has a strong affinity for avidin or streptavidin. This interaction can be used for qualitative and quantitative detection, labelling or immobilisation.

The biotinylated amyloid- $\beta$  peptides are N-terminally labelled. Two 6-aminohexanoic acid residues are inserted as spacer between the amyloid- $\beta$  peptide itself and biotin. The enlarged distance minimise steric hindrance and improve the availability of biotin for avidin or streptavidin binding.

Biotinylated amyloid-B (1-40) rat		P2253	
DAEFGHDSGFVVRHQKLVFFAEDVGSNKGAIIGLMVGGV V			
Purity	≥95 %	1mg	5mg

Biotinylated amyloid-B (1-40) human		P2254	
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGV V			
Purity	≥95 %	1mg	5mg

### Peptides as inhibitors of amyloid- $\beta$

Several inhibitors of amyloid- $\beta$  aggregation have been published. Many of them are fragments and modified peptides derived from the native amyloid- $\beta$  sequence. Others were identified by phage display approaches.

An overview about peptides that target amyloid- $\beta$  is described by Stains et al. (2007) ChemMedChem 2, 1674-1692.

KLVFF			
	Purity		
P2255	≥70 %		5mg
P2300	≥95 %	1mg	5mg

Ac-KLVFF-NH <sub>2</sub>			
	Purity		
P2256	≥70 %		5mg
P2301	≥95 %	1mg	5mg

RIIGL			
	Purity		
P2257	≥70 %		5mg
P2302	≥95 %	1mg	5mg

DWGKGGWRLWPGASGKTEA			
	Purity		
P2258	≥70 %		5mg
P2303	≥95 %	1mg	5mg

PGRSPFTGKFLNQEFSQDQ			
	Purity		
P2259	≥70 %		5mg
P2304	≥95 %	1mg	5mg

qshyrhispaqv (D-amino acids)		P2260	
	Purity		
P2260	≥95 %	1mg	5mg

FYLKVPSSLHHHHGRDKLVFFHHH H			
	Purity		
P2261	≥70 %		5mg
P2305	≥95 %	1mg	5mg

<b>NYSKMIFSHHHH</b>			
	Purity		
P2262	≥70 %		5mg
P2306	≥95 %	1mg	5mg

<b>HNHKL VFFHHQH</b>			
	Purity		
P2263	≥70 %		5mg
P2307	≥95 %	1mg	5mg

Structure-activity studies with synthetic lipopeptide analogues revealed the structural features of their interaction with TLR1, TLR2 and TLR6 (Buwitt-Beckmann et al. 2005, 2006; Farhat et al. 2007). Recently, the interaction of lipopeptides with TLR10 has been described (Guan et al. 2010).



## General terms and conditions

The following terms and conditions shall exclusively apply to all sales and shall be an integral part of each single agreement concluded between the parties. Verbal agreements are only valid if confirmed in writing. By placing an order the Buyer acknowledges our terms and conditions. Other conditions require our previous consent in writing.

### Offers and orders

Our offers are subject to change without prior notice with respect to price, quantity, delivery time and availability. The Buyer's orders shall become binding for Genaxxon upon receipt by the Buyers of Genaxxon's written order acknowledgment (or invoice or delivery note).

Statements and any details in advertising materials shall not constitute any kind of warranty.

Any information, statements or representations, written or oral, by Genaxxon's employees, agents or representatives are not binding unless confirmed in writing on our business paper signed by a duly authorized officer. Genaxxon reserves the right to insist on a written order and/or references from the Buyer before proceeding the order. There is no minimum order value.

### Prices

All prices of this price list are net prices in Euro (EUR / €) except if otherwise indicated. Our prices are exclusive of VAT. Goods are charged with the prices valid on the date of delivery. Payment in other currency requires a written quotation in the foreign currency.

Any tax, duty or charge imposed by governmental authority or otherwise and any other applicable taxes, duties or charges shall be charged to the Buyer's account.

Freight and packing charges will be added, they can be invoiced as a lump-sum charge.

### Delivery / transfer of perils

Unless otherwise agreed by the Buyer and GENAXXON, the price shall be for delivery ex factory, packing excluded.

From the time of delivery the goods shall be at the risk of the Buyer. We are not liable for damage or loss during transportation. Except when explicitly specified by the Buyer we will decide on the appropriate type of transportation. If the type of transportation is specified, the Buyer has to bear any additional costs. The same shall apply in the case of raised transportation costs, additional expenses incurred by deviation, storage, etc. unless freight free delivery was explicitly agreed upon, after signing the agreement but before delivery.

### Date of delivery / force majeure

GENAXXON intends to ship the goods within 7 working days from receipt of order, if possible otherwise within 28 days. There shall be no fixed period of delivery. Notwithstanding the preceding paragraph, if a fixed period for delivery has been agreed upon, and should GENAXXON default with the supply, the Buyer shall grant GENAXXON a reasonable respite, normally four weeks. If GENAXXON is unable to meet Buyers written delivery conditions, or a 28 day delivery, GENAXXON will inform the Buyer at the earliest opportunity. Delivery shall be subject to punctual delivery of the appropriate goods by GENAXXON's own suppliers. The day of delivery shall be the day on which the goods leave GENAXXON's plant or, if that day cannot be ascertained, the day on which the goods are put at the Buyer's disposal.

Force Majeure and unforeseeable hindrances of any kind beyond the control of GENAXXON (e.g. shortage of raw materials and supplies, Force Majeure) shall relieve the party from its obligation to supply as long as and to the extent that the hindrance prevails.

If unforeseeable hindrances of any kind beyond the control of GENAXXON occur (e.g. shortage of raw materials, force majeure) delivery period shall be extended as long as and to the extent that the hindrance prevails.

If delivery is delayed due to the above reasons the Buyer cannot claim any rights.

### Terms of payment

Terms for customers with an open account are 14 days from invoice date unless otherwise agreed in writing. Other terms of payment require our previous written consent. For unpaid invoices 20 days beyond maturity we will charge interest on arrears amounting to the usual bank rate, at least 7% per annum exceeding the base rate of the European Central Bank. Delayed payment or irregular payments entitle us to discontinue delivery to the Buyer without any compensation. Instead of the agreed terms of payment we can ask for advance payment or security deposit, should doubts as to the solvency of a Buyer arise. In case of liquidation of the Buyer's company, or if GENAXXON learns about an oath of manifestation or a change of ownership due to financial difficulties we reserve the right to withdraw from the contract. We reserve the right to use incoming payments for liquidation of the oldest debts, in sequence as follows: costs, interests and then debt claims. Prepayments and advance payments must be paid plus VAT.

Government/Corporate Visa, MasterCard and JCB credit card may be accepted on approved accounts for payment of the Products. Payment by credit card will only be taken when ordered by fax or mail.

### Intellectual property rights / patents

No warranty or representation is given by GENAXXON that the Products do not infringe any letters patent, trademarks, registered designs or other industrial rights. The Buyer is liable for his infringements of copyrights and industrial or intellectual properties, especially patents and trademarks.

If products are custom-made to specification, the Buyer assumes the responsibility that the manufacture of these products does not infringe any patents or rights of a third party. The Buyer is liable for all damages and claims resulting from such infringement and hold the seller free and harmless from all claims.

The Buyer further warrants to GENAXXON that any use of the Products in the United States of America shall not result in the Products becoming adulterated or misbranded within the meaning of the Federal Food, Drug and Cosmetic Act (or such equivalent legislation in force in the Buyer's jurisdiction) and shall not be materials which may not, under sections 404, 505 or 512 of the Act, be introduced into interstate commerce.

## Retention of title

Title of the goods shall not pass to the Buyer until he has fulfilled all liabilities arising from his business connection with GENAXXON, which shall include settling accessory claims and claims for damages and honouring cheques and bills. In the event of non-payment, we shall have the right to re-sell the goods to a third party. GENAXXON shall have the absolute authority to retake, sell or otherwise deal with or dispose of all or any part of the goods in which title remains vested in the seller. Until such time as the property in the goods passes to the Buyer, the Buyer shall hold the goods as the seller's fiduciary agent, and shall keep the goods properly stored, protected, and insured on his own costs.

## Damages

No claims for compensation may be lodged by the Buyer including those of a non-contractual nature – for any minor negligent breach of duty by GENAXXON, his executive staff or other agents, unless such breach concerns damages resulting from death, injury or damage to health. However, this shall not affect the applicability of compelling statutory liability regulations.

## Notifications of defects

All goods have to be checked immediately on receipt. Damage claims are only acceptable in writing within 8 working days of receipt of all the goods. In case of legitimate claims the Buyer can only require replacement of the goods. If replacement is not possible, the Buyer has the right to choose between alternative products with same value or refund. The Buyer cannot claim further compensation. All returns must first be authorized by us in writing.

## Technical support, use and processing, properties of goods

Technical advice provided by GENAXXON verbally, in writing or by way of trials is given in good faith but without warranty, and this shall also apply where proprietary rights of third parties are involved. GENAXXON's technical advice shall not release the Buyer from the obligation to test the products supplied by GENAXXON as to their suitability for the intended processes and uses. The application, use and processing of the products are beyond GENAXXON's control and therefore entirely in the Buyer's responsibility.

Attention should be paid to the enclosed product descriptions, warnings and instruction leaflets.

Any arbitrary modification of the documents (e.g. instruction leaflets) and/or modification of the product is at your own risk.

## Safety

At the Buyer's firm, all chemicals must be handled only by competent, suitably trained persons, familiar with laboratory procedures and potential chemical hazards. The burden of safe use of the Products of GENAXXON vests in the Buyer. The Buyer assumes all responsibility for warning his employees, and any person who might reasonably be expected to come into contact with the Products, of all risks to person and property in any way connected with the Products and for instructing them in their safe handling and use. The Buyer also assumes the responsibility for the safe disposal of all products in accordance with all applicable laws.

## Product quality, specifications and technical information

Products are analysed in the laboratories of GENAXXON by methods and procedures which GENAXXON considers appropriate. In the event of any dispute concerning reported discrepancies arising from the Buyer's analytical results, determined by the Buyer's own analytical procedures, GENAXXON reserves the right to rely on the results of own analytical methods of GENAXXON. Certificates of Analysis or Certificates of Conformity are available at the discretion of GENAXXON for bulk orders but not normally for pre-pack orders. GENAXXON reserves the right to make a charge for such Certification.

Specifications may change and reasonable variation from any value listed should not form the basis of a dispute. Any supply by GENAXXON of bespoke or custom Product for a Buyer shall be to a specification agreed by both parties in writing.

Technical information provided orally, in writing, or by electronic means by or on behalf of GENAXXON, including any descriptions, references, illustrations or diagrams in any Catalogue or brochure, is provided for guidance purposes only and is subject to change.

## Uses, warranties and liabilities

All products of GENAXXON bioscience GmbH are not for any commercial use or resale. They are intended solely for laboratory research and development purposes and are not to be used for any other purpose. GENAXXON bioscience GmbH offers no warranty regarding the fitness of any Product for a particular purpose and shall not be responsible for any loss or damage whatsoever arising there from.

The Buyer acknowledges that, since the products of GENAXXON are intended for research purposes, they may not be on the Toxic Substances Control Act 1976 ("TSCA") inventory. The Buyer warrants that it shall ensure that the Products are approved for use under the TSCA (or such other equivalent legislation in force in the Buyer's jurisdiction), if applicable. The Buyer shall be responsible for complying with any legislation or regulations governing the use of the Products and their import into the country of destination (for the avoidance of doubt to include, without limitation, the TSCA and all its amendments, all EINECS, ELINCS and NONS regulations).

If any licence or consent of any government or other authority shall be required for the acquisition, carriage or use of the products by the Buyer the Buyer shall obtain the same at its own expense and if necessary produce evidence of the same to GENAXXON on demand. Failure to do so shall not entitle the Buyer to withhold or delay payment. Any additional expenses or charges incurred by GENAXXON resulting from such failure shall be for the Buyer's account.

Workings and syntheses are undertaken with all due care and attention. In case(s) of claims involving negligence, liability for such claims shall be limited to the total amount paid in respect of the invoice. In particular, liability cannot be accepted for results obtained with the product(s) or for loss of profits.

## Applicable law and jurisdiction / miscellaneous clauses

All contracts are subject to the laws of the Federal Republic of Germany. In the case of a legal dispute the jurisdiction of the court in Ulm (Germany) will be decisive and have exclusive jurisdiction. GENAXXON shall have the right to bring a claim before a court at the Buyer's principal place of business or at his discretion before any other court being competent according to any national or international law.



Application of the Uniform Law on the International Sale of Goods and the Uniform Law on the Formation of Contracts for the International Sale of Goods and of the UN agreement on the sale of goods shall be excluded. Customary clauses shall be interpreted in accordance with the applicable Incoterms.

Even if it has been agreed that GENAXXON pays the customs and import duties of the destination country, any increase in such duties which becomes effective between the date of the order acknowledgement and delivery of the goods shall be borne by the Buyer. All other charges, taxes and costs connected with the purchase contract shall also be borne by the Buyer.

In the event that any provision of these Terms and Conditions is invalid or becomes invalid, the remainder of the Terms and Conditions shall remain unaffected thereby. The invalid provision shall then be replaced by such provision as comes as close as possible to the economic purpose of such invalid provision, taking reasonable account of the interests of both Parties.