(19) DANMARK

(10) DK/EP 2834643 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *G 01 N 33/68 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2020-02-03**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2019-10-23**

(86) Europæisk ansøgning nr.: **13718522.9**

(86) Europæisk indleveringsdag: **2013-04-05**

(87) Den europæiske ansøgnings publiceringsdag: **2015-02-11**

(86) International ansøgning nr.: **EP2013057160**

(87) Internationalt publikationsnr.: **WO2013150126**

(30) Prioritet: **2012-04-05 DE 102012102999**
2012-09-14 DE 102012108598
2012-09-14 DE 102012108599

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **Forschungszentrum Jülich GmbH, , 52425 Jülich, Tyskland**

(72) Opfinder: **WILLBOLD, Dieter, Theodor-Heuss-Str. 179, 52428 Jülich, Tyskland**

(74) Fuldmægtig i Danmark: **Plougmann Vingtoft A/S, Strandvejen 70, 2900 Hellerup, Danmark**

(54) Benævnelse: **FREMGANGSMÅDE TIL BEHANDLING AF BLOD, BLODPRODUKTER OG ORGANER**

(56) Fremdragne publikationer:
WO-A2-02/081505
WO-A2-2004/056318
WO-A2-2006/005706
WO-A2-2007/047967
WO-A2-2010/062570
WO-A2-2011/147797
US-A1- 2005 158 306
ZHANG G ET AL: "Multiple-Peptide Conjugates for Binding ss-Amyloid Plaques of Alzheimer's Disease", BIOCONJUGATE CHEMISTRY, ACS, WASHINGTON, DC, US, Bd. 14, 1. Januar 2003 (2003-01-01), Seiten 86-92, XP002458160, ISSN: 1043-1802, DOI: 10.1021/BC025526I
SIDHARTHA M. CHAFEKAR ET AL: "Branched KLVFF Tetramers Strongly Potentiate Inhibition of [beta]-Amyloid Aggregation", CHEMBIOCHEM, Bd. 8, Nr. 15, 15. Oktober 2007 (2007-10-15), Seiten 1857-1864, XP055052606, ISSN: 1439-4227, DOI: 10.1002/cbic.200700338
STAINS CLIFF I ET AL: "Molecules that target beta-amyloid", CHEMMEDCHEM, WILEY - VCH VERLAG., WEINHEIM, DE, Bd. 2, Nr. 12, 1. Dezember 2007 (2007-12-01), Seiten 1675-1692, XP009107501, ISSN: 1860-7179, DOI: 10.1002/CMDC.200700140
SUSANNE AILEEN FUNKE ET AL: "Mirror image phage display-a method to generate d-peptide ligands for use in diagnostic or therapeutical applications", MOLECULAR BIOSYSTEMS, Bd. 5, Nr. 8, 1. Januar 2009 (2009-01-

Fortsættes ...

01), Seite 783, XP055069250, ISSN: 1742-206X, DOI: 10.1039/b904138a
THOMAS VAN GROEN ET AL: "Reduction of Alzheimer's Disease Amyloid Plaque Load in Transgenic Mice by D3, a D-Enantiomeric Peptide Identified by Mirror Image Phage Display", CHEMMEDCHEM, Bd. 3, Nr. 12, 15. Dezember 2008 (2008-12-15), Seiten 1848-1852, XP055239322, DE ISSN: 1860-7179, DOI: 10.1002/cmdc.200800273
SUSANNE AILEEN FUNKE ET AL: "-Enantiomeric Peptide D3 Improves the Pathology and Behavior of Alzheimer's Disease Transgenic Mice", ACS CHEMICAL NEUROSCIENCE, Bd. 1, Nr. 9, 15. September 2010 (2010-09-15), Seiten 639-648, XP055239332, US ISSN: 1948-7193, DOI: 10.1021/cn100057j
Hongmei Liu ET AL: "Transport of Alzheimer Disease Amyloid-b-Binding d-Amino Acid Peptides across an In Vitro Blood-Brain Barrier Model", , 2. Dezember 2009 (2009-12-02), XP055239347, Gefunden im Internet: URL:http://online.liebertpub.com/doi/pdf/1 0.1089/rej.2009.0926 [gefunden am 2016-01-07]
RANJINI K. SUNDARAM ET AL: "Novel Detox Gel Depot Sequesters [beta]-Amyloid Peptides in a Mouse Model of Alzheimer's Disease", INTERNATIONAL JOURNAL OF PEPTIDE RESEARCH AND THERAPEUTICS, Bd. 18, Nr. 2, 23. November 2011 (2011-11-23), Seiten 99-106, XP055070073, ISSN: 1573-3149, DOI: 10.1007/s10989-011-9283-7
FUNKE SUSANNE AILEEN ET AL: "Peptides for Therapy and Diagnosis of Alzheimer's Disease", CURRENT PHARMACEUTICAL DESIGN, BENTHAM SCIENCE PUBLISHERS, NL, Bd. 18, Nr. 6, 1. Februar 2012 (2012-02-01), Seiten 755-767, XP009170739, ISSN: 1381-6128
ANDREAS MÜLLER-SCHIFFMANN ET AL: "Combining Independent Drug Classes into Superior, Synergistically Acting Hybrid Molecules", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, Bd. 49, Nr. 46, 8. November 2010 (2010-11-08), Seiten 8743-8746, XP055083717, ISSN: 1433-7851, DOI: 10.1002/anie.201004437
DIRK BARTNIK ET AL: "Differently selected D-enantiomeric peptides act on different A.beta. species", REJUVENATION RESEARCH, MARY ANN LIEBERT, NEW ROCHELLE, NY, US, Bd. 13, Nr. 2-3, 12. Mai 2010 (2010-05-12) , Seiten 202-205, XP002654152, ISSN: 1549-1684, DOI: 10.1089/REJ.2009.0924 [gefunden am 2009-12-02]
ZHANG G ET AL: "Multiple-Peptide Conjugates for Binding ss-Amyloid Plaques of Alzheimer's Disease", BIOCONJUGATE CHEMISTRY, ACS, WASHINGTON, DC, US, vol. 14, 1 January 2003 (2003-01-01), pages 86-92, XP002458160, ISSN: 1043-1802, DOI: 10.1021/BC025526I
SIDHARTHA M. CHAFEKAR ET AL: "Branched KLVFF Tetramers Strongly Potentiate Inhibition of [beta]-Amyloid Aggregation", CHEMBIOCHEM, vol. 8, no. 15, 15 October 2007 (2007-10-15), pages 1857-1864, XP055052606, ISSN: 1439-4227, DOI: 10.1002/cbic.200700338
STAINS CLIFF I ET AL: "Molecules that target beta-amyloid", CHEMMEDCHEM, WILEY - VCH VERLAG., WEINHEIM, DE, vol. 2, no. 12, 1 December 2007 (2007-12-01), pages 1675-1692, XP009107501, ISSN: 1860-7179, DOI: 10.1002/CMDC.200700140
SUSANNE AILEEN FUNKE ET AL: "Mirror image phage display-a method to generate d-peptide ligands for use in diagnostic or therapeutical applications", MOLECULAR BIOSYSTEMS, vol. 5, no. 8, 1 January 2009 (2009-01-01) , page 783, XP055069250, ISSN: 1742-206X, DOI: 10.1039/b904138a
THOMAS VAN GROEN ET AL: "Reduction of Alzheimer's Disease Amyloid Plaque Load in Transgenic Mice by D3, a D-Enantiomeric Peptide Identified by Mirror Image Phage Display", CHEMMEDCHEM, vol. 3, no. 12, 15 December 2008 (2008-12-15), pages 1848-1852, XP055239322, DE ISSN: 1860-7179, DOI: 10.1002/cmdc.200800273
SUSANNE AILEEN FUNKE ET AL: "-Enantiomeric Peptide D3 Improves the Pathology and Behavior of Alzheimer's Disease Transgenic Mice", ACS CHEMICAL NEUROSCIENCE, vol. 1, no. 9, 15 September 2010 (2010-09-15), pages 639-648, XP055239332, US ISSN: 1948-7193, DOI: 10.1021/cn100057j
Hongmei Liu ET AL: "Transport of Alzheimer Disease Amyloid-b-Binding d-Amino Acid Peptides across an In Vitro Blood-Brain Barrier Model", , 2 December 2009 (2009-12-02), XP055239347, Retrieved from the Internet: URL:http://online.liebertpub.com/doi/pdf/1 0.1089/rej.2009.0926 [retrieved on 2016-01-07]
Katja Wiesehan ET AL: "Selection of D-Amino-Acid Peptides That Bind to Alzheimer's Disease Amyloid Peptide A[beta]142 by Mirror Image Phage Display", ChemBioChem, vol. 4, no. 8, 4 August 2003 (2003-08-04), pages 748-753, XP055069247, ISSN: 1439-4227, DOI: 10.1002/cbic.200300631

DESCRIPTION

Method for treating blood, blood products and organs

The present invention relates to a method for the treatment (ex vivo) of blood, blood products and organs for preventing the transmission of Alzheimer's disease and other amyloid-based diseases.

Due to the demographic development in the coming decades, the number of people suffering from age-related diseases will increase. The so-called Alzheimer's disease (AD, Alzheimer's dementia, Latin = Morbus Alzheimer) is particularly relevant here.

A feature of Alzheimer's disease is extracellular deposits of the amyloid beta peptide (A-beta peptide, Aß, or Aß peptide). This deposition of the A-beta peptide in plaques is typically found post-mortem in the brains of AD patients. Therefore, various forms of the A-beta peptide, such as fibrils, are deemed responsible for the development and progression of the illnesses. In addition, the small, freely diffusible A-beta oligomers have been seen as the main cause of the development and progress of AD for several years.

A-beta monomers as building blocks of the A-beta oligomers are formed constantly in the human body and are presumably not toxic per se. A-beta monomers can randomly accumulate depending on their concentration. The concentration depends on their rate of formation and breakdown in the body. If the concentration of A-beta monomers in the body increases with age, spontaneous accumulation of the monomers into A-beta oligomers is increasingly likely. The resulting A-beta oligomers could replicate analogously to the prions and ultimately lead to the Alzheimer's disease.

An important difference between prevention and treatment or even cure of AD lies in the fact that prevention can be achieved simply by preventing the formation of the first A-beta oligomers. For this, some small number of A-beta ligands are sufficient which have lower affinity and are less selective with regard to the A-beta oligomers.

The formation of the A-beta oligomers from many monomers is a reaction of high order and therefore highly dependent on the A-beta monomer concentration. Thus, even a small reduction in the active A-beta monomer concentration prevents the formation of the first A-beta oligomers. This mechanism has hitherto been the basis of prevention.

However, a completely altered situation is assumed in the treatment of AD. This is because there are A-beta oligomers or possibly even larger polymers or fibrils, which have arisen from the

prion-like replication of the oligomers. However, this is a low-order reaction and is hardly dependent on the A-beta monomer concentration.

So far, there is no approved drug for a causal treatment of Alzheimer's dementia (AD). Typically, post-mortem deposits of the so-called beta-amyloid peptide (Aß or A-beta) are found in plaques in the brains of AD patients. For this reason, various forms of the Aß oligomer, such as fibrils, have long been held responsible for the development and progression of AD. For some years now, the small, freely diffusible Aß oligomers, in particular, have been held responsible for the development and progress of AD. Aß monomers are constantly produced in the human body and are presumably not toxic in themselves. There is speculation as to whether Aß monomers accumulate randomly depending on their concentration and therefore are increasingly likely to accumulate spontaneously into Aß oligomers with increasing age. Aß oligomers, once formed, could replicate through a prion-like mechanism and ultimately lead to disease. For some time, it has been discussed whether AD, like prion diseases, can in principle be transmitted from person to person. The same applies to all amyloid-associated illnesses (e.g. Parkinson's disease). In particular, a possible transmission through blood transfusion, administration of blood products and organ transplants could lead to a massive risk to the health of recipients without suitable tests and prevention methods. In this context, the non-scientific literature has reported the premature onset of AD in a transgenic mouse after its entire blood was exchanged for that of a diseased mouse.

Based on these considerations, there should be a way to free blood, blood products and organs of infectious particles by (prophylactic or preventive) treatment, or to inactivate them. The aim should be to completely remove or destroy toxic Aß oligomers, i.e. to detoxify them and thus prevent their prion-like replication.

Various methods for eliminating bio-harmful substances, bioparticles, molecules and pathological protein deposits are known from the prior art. There is research according to which nanomagnets are used to purify blood of a toxin in a matter of minutes. The removal of LDL cholesterol from the blood by direct absorption of lipoproteins (DALI) has also been described.

The immobilisation of antibodies or peptides is described in DE 600 26 983 T2 or US 5,968,820.

Furthermore, DE 102009037015 A1 discloses a device and a method for eliminating bio-harmful substances from body fluids. The isolation of cells, bioparticles or molecules from liquids is described in DE 102005063175 A1. A method for the selective determination of pathological protein deposits is also known from DE 102005031429 A1. Finally, DE 102005009909 A1 describes compounds for the treatment of diseases in connection with misfolded proteins.

The substances known from the prior art reduce the concentration of A-beta monomers and/or oligomers in a wide variety of ways. For example, gamma secretase modulators are known which have been used in animal experiments for prevention.

Various sequences of D-amino acids which bind to A-beta peptides are known from WO 02/081505 and DE 101 17 281 A1. These sequences from WO 02/081505 of D-amino acids bind to amyloid beta peptides with a dissociation constant K_D value of 4 µM.

Hybrid compounds consisting of aminopyrazoles and peptides which prevent A-beta oligomerisation are known from WO 2011/147797.

However, the use of these compounds for the purification of blood, blood products and/or organs is not disclosed.

For many substances that have shown positive results in animal experiments, this effect could not be confirmed in human clinical studies. In phase II and III clinical studies, only people who are clearly diagnosed with AD may be treated. Here, a slight reduction in the A-beta monomer concentration is no longer sufficient to prevent larger amounts of A-beta oligomers and/or to influence the course of the disease.

So far, Alzheimer's dementia has mainly been diagnosed by neuro-psychological tests, by experiments on people in whom the symptoms have already been recognised. However, it is known that A-beta oligomers and the subsequent fibrils and plaques develop up to 20 years before the symptoms appear in the patient's brain and may have already caused irreversible damage. However, there is still no way to diagnose AD before the onset of symptoms.

Furthermore, WO 2010/062570 A2 discloses a composition for the treatment and/or prevention of Alzheimer's disease.

Sundaram et al. INTERNATIONAL JOURNAL OF PEPTIDE RESEARCH, 18(2) 2012 concerns the retro-inverso peptide, ffvlk, which binds artificial fibrils from Aß with moderate affinity.

WO 2004/056318 A2 discloses methods for treating amyloid disease in humans by removing amyloid peptides from one or more body fluids.

WO 2006/005706 A2 discloses a method for the prevention or treatment of Alzheimer's disease.

US 2005/158306 A1 discloses a method for the treatment of Alzheimer's disease.

WO 2011/147797 A2 relates to a hybrid compound based on aminopyrazole derivatives and peptides for use as a therapeutic agent in the treatment of diseases.

Funke et al. CURRENT PHARMACEUTICAL DESIGN, 18(6) 2012 describes peptides developed for the diagnosis and treatment of AD and the advantages and disadvantages of peptide drugs.

WO 02/081505 A2 discloses peptides that bind to the peptide beta-amyloid with high binding affinity.

Müller-Schiffmann et al. ANGEWANDTE CHEMIE INTERNATIONAL EDITION, 49(46), 2010 describes hybrid compounds consisting of an organic D-enantiomeric ß-sheet-resolving part and a peptide part that recognises D-enantiomeric Aß.

Bartinek et al. REJUVENANT RESEARCH, 13(2-3), 2010 discloses D-enantiomeric Aß-binding peptides.

Zhang G. et al. Bioconjugate Chemistry, 14(1), 2003 discloses that the formation of β-amyloid plaques in Alzheimer's is triggered by the intermolecular contact of the 5-amino acid sequence KLVFF in β-amyloid peptides with a size of 40 to 43 residues.

Sidhartha et al. ChemBioChem, 8(15), 2007 discloses a dendrimer of four peptides with the pattern KLVFF.

Stains et al, CHEMMEDCHEM, 2(12) 2007 relates to the current knowledge regarding molecules that have been shown to interact with oligomeric or fibrillar forms of the beta-amyloid peptide.

WO 2007/047967 A2 relates to a device which is placed inside a patient with Alzheimer's disease (AD) to extract neurotoxic beta-amyloid peptides (nt-bAP) from body fluids.

Funke et al. MOLECULAR BIOSYSTEMS, 5(8), 2009 describes a phage display assay for the identification of new potentially therapeutically active D-enantiomeric peptides

Van Groen et al, CHEMMEDCHEM, 3(12), 2008, Funke et al. ACS Chemical Neuroscience, 1(9), 2010, and Hongmei et al. 2009 disclosed that the D3 peptide binds to and removes A-beta oligomers.

The object of the present invention is now to free blood, blood products and/or organs of toxic and/or infectious particles by treatment, or to inactivate them. The aim is to completely remove the Aß oligomers present in blood, blood products or organs, or to convert them into harmless forms.

The invention accordingly relates to methods for treatment outside the human or animal body (in vitro, ex vivo) of blood, blood products and/or organs by removing and/or detoxifying amyloid-beta oligomers, said methods being characterised in that the D-enantiomeric compound rprtrlhthrnrrprtrlhthrnr (D3D3, SEQ ID NO:13) is used, which binds to amyloid-beta oligomers.

The treated blood can come from a blood bank and/or can be stored in a blood bank after treatment.

It is also possible to use the method according to the invention preventively in healthy people. The blood of those people who do not have AD symptoms is freed of any amyloid-beta oligomers present, without reference to method steps for the therapeutic treatment of the human or animal body.

The Aß oligomers can be removed, for example, by adding beads to the blood which bind or retain the Aß oligomers. For the treatment of blood samples, the substances which bind Aß oligomers can be bound to magnetic beads. Dynabeads® M-280 Streptavidin (Dynal AS, Oslo) are supramagnetic microspheres covalently linked with purified streptavidin, which binds biotin with high affinity ($K_D = 10^{-15}$). These beads with the Aß oligomers bound to them can subsequently be removed again, for example by affinity chromatography, filtration, size exclusion, sedimentation or centrifugation.

In one variant of the invention, the Aß oligomers can be removed by passing the blood and/or the blood sample over a surface that binds or retains Aß oligomers. According to the invention, the molecules which bind or detoxify Aß oligomer (so-called capture molecules) can be arranged on a support via which the liquid sample is passed. In one variant, immobilisation using nanomagnets is also possible for the capture molecules. It is also possible to arrange the capture molecules in a dialysis system. In a further variant, the capture molecules can consist of a biocompatible material. Carriers can also be membranes, filters, filter sponges, beads, rods, cords, columns and hollow fibres.

In a further variant relating to organs, the Aß oligomers can be removed by passing the capture molecule over and/or through an organ (in vitro/ex vivo).

In a further variant of the invention, Aß oligomers can be inactivated by adding a substance which converts Aß oligomers into non-toxic, non-amyloidogenic, non-infectious forms.

All Aß-oligomer-modifying ligands can be used as Aß-oligomer-inactivating substances or as Aß-oligomer-binding substances, for example Aß-antibodies or Aß-binding peptides. The substances to be used should have the highest possible affinity to Aß oligomers. The corresponding dissociation constant should be in the µM range, preferably nM range, in particular pM range or even lower. Since the target molecule of the therapeutic treatment is an Aß oligomer and thus naturally a multivalent target, in one variant of the invention for the treatment, the substance to be used can be produced from several copies of an already efficiently Aß oligomer-binding unit. In the absence of interfering influences (e.g. due to steric hindrance), an n-mer of an Aβ oligomer-binding unit which binds to Aß-oligomers with a dissociation constant (K_D) of at least x, an apparent K of x^n can be achieved. There are various ways of achieving this: the Aß oligomer-binding units

(monomer units) can be linked covalently or non-covalently (for example a biotin group or a streptavdin tetramer). In a variant of the invention, any number of copies can be immobilised on the surface of beads.

In the context of the present invention, the term A-beta oligomers denotes both A-beta aggregates and A-beta oligomers and also small, freely diffusing A-beta oligomers. In the context, oligomer means a polymer formed from 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 monomers or multiples thereof.

The present method is carried out outside the human or animal body. The terms used for this are in vitro or ex vivo.

In one embodiment, the polymers are peptides. These consist of D-amino acids.

In the context of the present invention, the term “substantially of D-amino acids” means that the monomers to be used are composed at least 60%, preferably 75%, 80%, most preferably 85%, 90%, 95%, in particular 96%, 97%, 98%, 99%, 100%, of D-amino acids.

In one variant, monomers are used which bind to an A-beta monomer and/or A-beta oligomers and/or fibrils of the A-beta peptide with a dissociation constant (K_D value) of at most 500 µM, preferably 250, 100, 50 µM, most preferably 25, 10, 6 µM, in particular 4 µM.

The polymer contains 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of the monomers described above.

In a further embodiment not according to the invention, the monomers are selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64. SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:79 and homologues thereof.

In a further variant, the polymers bind to the multimerisation domain of the amyloid beta peptide.

The term "multimerisation domain" defines those domains of the amyloid beta peptide that are involved in the interaction of the amyloid beta peptides with one another. In one variant, amino acids 10-42 of the amyloid beta peptide fulfil this function.

In a further variant not according to the invention, the monomers have sequences which differ from the specified sequences by up to three amino acids.

Furthermore, sequences which contain the above-mentioned sequences can also be used as monomers not according to the invention.

In a further variant not according to the invention, the monomers have fragments of the above-mentioned sequences or have homologous sequences to the above-mentioned sequences.

In the context of the invention, "homologous sequences" or "homologues" mean that an amino acid sequence has an identity with one of the above-mentioned amino acid sequences of the monomers of at least 50, 55, 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100%. Instead of the term "identity", the terms "homologous" or "homology" are used synonymously in the present description. The identity between two nucleic acid sequences or polypeptide sequences is calculated by comparison using the BESTFIT program based on the algorithm from Smith, TF and Waterman, MS (Adv. Appl. Math. 2: 482-489 (1981)) with adjustment of the following parameters for amino acids: Gap creation penalty: 8 and Gap extension penalty: 2; and the following parameters for nucleic acids: Gap creation penalty: 50 and Gap extension penalty: 3. The identity between two nucleic acid sequences or polypeptide sequences is preferably defined by the identity of the nucleic acid sequence/polypeptide sequence over the respective total sequence length, as is calculated by comparison using the GAP program based on the algorithm from Needleman, SB and Wunsch, CD (J. Mol. Biol. 48: 443-453) using the following parameters for amino acids: Gap creation penalty: 8 and Gap extension penalty: 2; and the following parameters for nucleic acids: Gap creation penalty: 50 and Gap extension penalty: 3. In the context of the present invention, two amino acid sequences are identical if they have the same amino acid sequence.

In one variant, homologues are understood to mean the corresponding retro-inverso sequences of the above-mentioned monomers. According to the invention, the term "retro-inverso sequence" designates an amino acid sequence which is composed of amino acids in the enantiomeric form (inverse: chirality of the alpha-C atom is inverted) and in which the sequence order has also been reversed for the original amino acid sequence (retro = backwards).

The polymer is composed of identical monomers or contains different monomers.

In an alternative not according to the invention, the polymer is composed of any desired combination of 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of the monomers described above.

The polymer is a dimer of two D3 monomers (SEQ ID NO:13). In an embodiment not according to the invention, the polymer is a dimer of two RD2 monomers (RD 2- RD 2: ptlhthnrrrrrptlhthnrrrrrr (SEQ ID NO:76).

Dimers can be produced, for example, by chemical synthesis or peptide synthesis.

In one embodiment of the invention, the monomers are covalently linked to one another. In a further embodiment not according to the invention, the monomers are not covalently linked to one another.

In the context of the invention, a covalent bond or link of the monomer units is present if the peptides are linearly linked to one another head to tail without the use of linkers or linker groups in between.

A non-covalent linkage exists if the monomers are linked to one another via biotin and streptavidin, in particular streptavidin tetramer.

A covalent linkage can be achieved by linearly coupling the monomer units head to head, tail to tail or head to tail, in each case without a linker or with a linker group. In an alternative, a link in a tree-like scaffold (dendrimers) on a platform molecule or a combination of these options is also possible. Non-identical monomer units can also be combined here.

The polymer is characterised in that it binds amyloid-beta oligomers with a dissociation constant of at most 1 mM, preferably 800, 600, 400, 200, 100, 10 µM, particularly preferably 1000, 900, 800, 700, 600, 500, 400, 300, 200, 100, 50 nM, most preferably, 1000, 900, 800, 700, 600, 500, 400, 300, 200, 100, 50 pM, most preferably at most 20 pM.

The polymer is suitable for use in medicine.

In one embodiment, it is a polymer which can be used to treat Alzheimer's disease. In a further embodiment, it is a polymer which can be used to treat Parkinson's disease, Creutzfeldt Jakob Disease (CJD), scrapie, bovine spongiform encephalopathy (BSE), or diabetes.

The polymers built up from monomers, which in turn bind to A-beta oligomers, show clear, synergistic effects with regard to their selectivity and affinity for the A-beta oligomers in comparison to the monomers. In other words, the polymers according to the present invention are superior to the monomers. Synergistic effects in the context of the present invention are effects which show a higher selectivity and affinity with regard to the A-beta oligomers, in particular the

K_D value with respect to the binding to A-beta oligomers, than the monomers individually or in their addition.

A linker is understood to mean one or more molecules which are bonded to the monomers via covalent bonds, it also being possible for these linkers to be linked with one another by covalent bonds.

In one alternative, the linkers do not change the properties of the polymer which are predetermined by the monomers, namely the binding to A-beta oligomers.

In a further alternative, the linkers bring about a change in the properties of the polymer which are predetermined by the monomers. In such an embodiment, the selectivity and/or affinity of the polymers with respect to the A-beta oligomers is increased and/or the dissociation constant is reduced. In a further embodiment, the linkers are selected or can be arranged such that they change the steric effect of the polymers in such a way that they selectively only bind to A-beta oligomers of a certain size.

Such a change in the steric effect of the polymers can also be achieved by the structure of branched polymers, by dendrimers of a special structure or the corresponding structure of the polymer by means of monomers and a platform molecule or combination of these options.

A further subject matter of the disclosure is a composition and use thereof for determining Alzheimer's disease, in which the D-peptide

a) contains a retro-inverso sequence of the amyloid beta peptide or amyloid beta peptide partial fragments and consists entirely of D-amino acids and/or

b) binds to the multimerisation domain of the amyloid beta peptide and/or

c) contains or has the sequence SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64. SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID

NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:79 and consists entirely of D-amino acids and/or

d) contains or has D-peptides with the sequence SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64. SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:79, wherein the D-peptides partially contain L-amino acids and/or

e) contains or has sequences homologous to SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64. SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:79.

In one variant, “D-peptides” consist of a retro-inverso sequence to the amyloid beta peptide or amyloid beta peptide partial fragments and entirely of D-amino acids.

A “partial fragment” consists of 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or more amino acids homologous to the amino acid sequence of the amyloid beta peptide.

In a further variant, the D-peptides bind to the multimerisation domain of the amyloid beta peptide. In a further variant, the D-peptides have the sequence SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NQ: 20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64. SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:79 and consist entirely of D-amino acids. In a further variant, the D-peptides have one of the above-mentioned sequences and in some cases contain L-amino acids. In a further variant, the D-peptides have sequences homologous to the above-mentioned sequences. “D-peptide” is understood to mean a peptide which is composed of amino acids in the D-form.

In one variant, the D-peptides also partially have L-amino acids. “Partially" L-amino acids means that 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acids homologous to the amino acid sequence of the D-peptide consisting of D-amino acids are replaced by respectively the same amino acid in the L-conformation.

In one variant, “D-peptides” consist of a retro-inverso sequence to the amyloid beta peptide or amyloid beta peptide partial fragments and entirely of D-amino acids.

A “partial fragment” consists of 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or more amino acids homologous to the amino acid sequence of the amyloid beta peptide.

In a further variant, the D-peptides according to the invention bind to the multimerisation domain of the amyloid beta peptide. In a further variant not according to the invention, the D-peptides have the above-mentioned sequences SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30,

SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64. SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:79 and consist entirely of D-amino acids.

In another embodiment, the peptide comprises the sequence pattern DB 4: RPRTRLRTHQNR (SEQ ID NO:1) or active fragments thereof.

In another embodiment, the peptide comprises the sequence pattern SHYRHISP (SEQ ID NO:3) or active fragments thereof.

In a further embodiment, the peptide comprises the sequence pattern GISWQQSHHLVA (SEQ ID NO:4) or active fragments thereof.

In a further embodiment, the peptide comprises the sequence pattern PRTRLHTH (SEQ ID NO:5) or active fragments thereof.

In a further variant not according to the invention, the peptide is selected from the group consisting of peptides with the D-amino acid sequences: a) QSHYRHISPAQV (SEQ ID NO:6); b) QSHYRHISPDQV (SEQ ID NO:7); c) QSHYRHISPAR (SEQ ID NO:8); d) KSHYRHISPAKV (SEQ ID NO:9); e) RPRTRLHTHRNR (SEQ ID NO:10); i) RPRTRLHTHRTE (SEQ ID NO:11); and g) KPRTRLHTHRNR (SEQ ID NO:12). Sequences which differ from the sequences a) to g) by up to three amino acids are also preferred, as well as sequences which comprise the sequences a) to g) and sequences which differ from the sequences a) to g) by up to three amino acids.

In a further variant, the peptide is selected from the group consisting of peptides with the D-amino acid sequences: D3D3: rprtrlhthrnrrprtrlhthrnr (SEQ ID NO:13), aD3nwnD3: rprtrlhthrnrnwnrprtrlhthrnr (SEQ ID NO:14), double-D3-free Ntermini: (rprtrlhthrnr)2-PEG3 (SEQ ID NO:15), double-D3-free Ctermini: PEG5-(rprtrlhthrnr)2 (SEQ ID NO:16), or double-D3-free-Ntermini: (rprtrlhthrnr)2- (SEQ ID NO:63), double-D3-free-Ctermini: (rprtrlhthrnr)2 (SEQ ID NO:64), DB 3: rpitrlrthqnr (SEQ ID NO:65), RD 2: ptlhthnrrrrr (SEQ ID NO:66), RD 1: pnhhrrrrrrtl (SEQ ID NO:67), RD 3: rrptlrhthnrr (SEQ ID NO:68), D3-delta-hth: rprtrlrnr (SEQ ID NO:69), NT-D3: rprtrl (SEQ ID NO:70), DB 1: rpitrlhtnrnr (SEQ ID NO:71), DB 2: rpittlqthqnr (SEQ ID NO:72), DB 5: rpitrlqtheqr (SEQ ID NO. 74), D3-delta-hth D3-delta-hth: rprtrlrnrrprtrlrnr (SEQ ID NO:75), RD 2- RD 2: ptlhthnrrrrrptlhthnrrrrrr (SEQ ID NO:76), DO 3: sgwhynwqywwk (SEQ ID NO:77),

rprtrsgwhynwqywwkrnr (SEQ ID NO:78) and ptlsgwhynwqywwkrrrrr (SEQ ID NO:79). Preference is furthermore given to sequences which differ from the above-mentioned sequences by up to three amino acids; as well as sequences which comprise each individual or each desired combination of the above-mentioned sequences.

In a further variant, the D-peptides have fragments of the above-mentioned sequences or have sequences homologous to the above-mentioned sequences.

Also disclosed are defined, homogeneous and stable preparations of standards for the quantification of pathogenic aggregates or oligomers of endogenous proteins, which can be used in particular for the treatment of blood, blood products and/or organs. Standards can be used here for the quantification of oligomers or pathogenic aggregates which characterise a protein aggregation disease or an amyloid degeneration or protein misfolding disease. Here, a polymer is built up from polypeptide sequences which, as regards their sequence, are identical in the corresponding subregion to the endogenous proteins or have a homology of at least 50% over the corresponding subregion with the endogenous proteins which characterise a protein aggregation disease or an amyloid degeneration or protein misfolding disease, wherein the polymers do not aggregate.

A standard in the context of the present disclosure is a generally valid and accepted, fixed reference variable which is used to compare and determine properties and/or quantity, in particular to determine the size and quantity of pathogenic aggregates from endogenous proteins. The standard in the context of the present invention can be used for calibrating devices and/or measurements.

In the context of the present invention, amyloid degenerations and protein misfolding diseases can also be included under the term “protein aggregation disease”. Examples of such diseases and the associated endogenous proteins are: A-beta and tau protein for AD, alpha-synuclein for Parkinson’s disease, amylin for diabetes or prion protein for prion diseases, such as the human Creutzfeldt-Jakob disease (CJD), the sheep disease scrapie and bovine spongiform encephalopathy (BSE).

The term “corresponding subregion” of endogenous proteins is to be understood as meaning the peptide sequence which, according to the definitions according to the invention, has an identical peptide sequence, or a peptide sequence homologous with the stated percentage, of a monomer from which the standards according to the invention are constructed.

It is essential for the standards that the standards do not aggregate, preferably as a result of the use of monomeric sequences that do not aggregate, since the “corresponding subregion” of

endogenous proteins is not responsible for the aggregation, or do not aggregate a result of blocking the groups responsible for the aggregation.

Aggregates in the context of the present disclosure are

- particles which consist of several, preferably identical, building blocks which are not covalently bonded to one another and/or

- non-covalent accumulations of several monomers.

In one embodiment, the standards have a precisely defined number of epitopes which are covalently linked to one another (directly or via amino acids, spacers and/or functional groups) for the binding of the corresponding probes.

Probes in the context of the disclosure are selected from the group consisting of: antibody, nanobody and affibody.

The number of epitopes is determined by using a polypeptide sequence which is identical in terms of sequence to the subregion of the endogenous proteins which forms an epitope or has at least 50% homology with this subregion, and thereby has the biological activity of the epitope.

In a further embodiment, the epitopes are epitopes of the A-beta peptide selected from the subregions A-Beta 1-11, A-Beta 3-11 or pyroGluA-Beta 3-11, for example the human N-terminal epitope (with the following sequence: DAEFRHDSGYE (1-11) (SEQ ID NO:17)).

The standard molecule is a polymer from the polypeptide sequences defined above. An oligomer in the context of the invention is a polymer formed of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 monomers (monomer is understood to mean the above-mentioned polypeptide sequence), or multiples thereof, preferably 2-16, 4-16, 8-16, most preferably 8 or 16, or multiples thereof.

In one alternative, the standards are water-soluble.

In one alternative, the standards are constructed from identical polypeptide sequences.

In a further alternative, the standards are constructed from different polypeptide sequences.

In one alternative, such polypeptide sequences defined above are arranged in series in a linear conformation.

In one alternative, such polypeptide sequences as defined above are arranged in series to form a branched oligomer according to the invention.

In one alternative, such polypeptide sequences as defined above are arranged in series to form a crosslinked oligomer.

Branched or cross-linked oligomers can be produced by linking individual building blocks using lysine or using click chemistry.

In an alternative, the disclosure relates to a standard molecule containing or built up from copies of the amino-terminal part of the A-beta peptide, selected from the subregions A-Beta 1-11, A-Beta 3-11, or pyroGluA-Beta 3-11, for example the human N-terminal epitope (with the following sequence: DAEFRHDSGYE (1-11) (SEQ ID NO:17)).

The replication of the epitopes by functional groups can be carried out before or after the synthesis of the individual building blocks. The covalent linkage of the polypeptide sequences is characteristic of the standards.

The polypeptide sequences to be used can be identical to the sequence of the A-beta full-length peptide or exhibit a homology of 50, 55, 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100% with the sequence of the A-beta full-length peptide.

Alternatively, for building the standard molecules, polypeptide sequences are used that are identical to a partial region of the A-beta full-length peptide or exhibit a homology of 50, 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100% with a subregion of A-beta full-length peptide.

Essential for the sequences used is their property of not aggregating (or only aggregating in a controlled manner according to the conditions) and/or their activity as an epitope.

In a further embodiment, the standards are constructed as dendrimers. The dendrimers are constructed from the polypeptide sequences to be used which are described above and can contain a central scaffold molecule.

In one variant, the dendrimers contain polypeptide sequences which have a sequence which is identical to a subregion of the A-beta peptide or which exhibits at least a 50% homology to the corresponding partial region.

The term “at least 50% homology” also means a higher homology, selected from the group consisting of 50, 55, 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100%.

In one embodiment, standards, advantageously with higher aqueous solubility than pathogenic aggregates or oligomers of endogenous proteins, are formed from polypeptide sequences which are identical to the N-terminal region of the A-beta peptide or have at least 50% homology thereto. According to the disclosure, the N-terminal region of an A-beta polypeptide is understood to mean the amino acid sequence A-Beta 1-8, A-Beta 1-11, A-Beta 1-16, A-Beta 3-11 or pyroGluA-Beta 3-11.

A usable standard molecule can contain epitopes for at least 2, 3, 4, 5, 6, 7, 8, 9, 10 or more different probes.

Epitopes characteristic of different probes can be incorporated into the standards by using polypeptide sequences which are identical to different regions of the A-beta peptide or have at least 50% homology thereto, but have the activity of the corresponding epitope.

In one embodiment, polypeptide sequences are used for this purpose that are identical to or have a 50% homology with the N-terminal region of the A-beta polypeptide, and polypeptide sequences that are identical or have at least a 50% homology with the C-terminus of the A-beta polypeptide.

In one embodiment, the standard molecules contain so-called spacers.

A spacer is to be understood as meaning a molecule which is incorporated into the standard molecule via covalent bonds and which has certain physical and/or chemical properties by means of which the properties of the standard molecule are changed. In one embodiment of the standards, hydrophilic or hydrophobic, preferably hydrophilic, spacers are used. Hydrophilic spacers are selected from the group of molecules formed from polyethylene glycol, sugar, glycerol, poly-L-lysine or beta-alanine.

In an alternative, the applicable standards contain (further) functional groups.

Functional groups are understood to be molecules that are covalently bonded to the standard molecules. In one variant, the functional groups contain biotin groups. This enables a strong covalent bond to streptavidin. Standard molecules containing biotin groups can thus be bonded to molecules containing streptavidin groups. If the standard molecules that can be used contain biotin and/or streptavidin groups, larger standards can be assembled in this way or several, possibly different, standard molecules can be bound to a scaffold.

In a further alternative, the standard molecules contain dyes for spectrophotometric determination and/or aromatic amino acids. Aromatic amino acids are, for example, tryptophan, tyrosine, phenylalanine or histidine, or are selected from this group. The incorporation of tryptophan enables a spectrophotometric determination of the concentration of standards in solution.

A further subject matter is the use of polypeptides which contain dendrimers and, as regards their sequence, are identical in the corresponding subregion to the endogenous proteins or have a homology of at least 50% over the corresponding subregion with the endogenous proteins which characterise a protein aggregation disease.

The dendrimers can contain any of the features of the standards described above, or any desired combination thereof.

In one alternative, they are dendrimers containing a precisely defined number of epitopes for the covalent bonding of probes has, dendrimer-containing epitopes of the A-beta peptide.

To examine blood, blood products and/or organs for amyloid-beta oligomers, a standard can be used for the quantification of pathogenic aggregates or oligomers of endogenous proteins which characterise a protein aggregation disease or an amyloid degeneration or protein misfolding disease, characterised in that a polymer is constructed from polypeptide sequences which as regards their sequence, are identical in the corresponding subregion to the endogenous proteins or have a homology of at least 50% over the corresponding subregion with the endogenous proteins which characterise a protein aggregation disease or an amyloid degeneration or protein misfolding disease, wherein the polymers do not aggregate.

For the binding of probes, the standard can have a precisely defined number of epitopes which are covalently linked to one another.

The standard can also contain epitopes of the A-beta peptide and/or the sequences according to the invention.

To test blood, blood products and/or organs for amyloid-beta oligomers, the following method can also be used for the selective quantification of A-beta aggregates:

Method comprising immobilisation of A-beta capture molecules on a substrate, application of the sample to be examined onto the substrate, addition of probes characterised for detection, which, as a result of specific binding to A-beta aggregates, mark these, and detection of the marked aggregates.

This method for the selective quantification and/or characterisation of A-beta aggregates comprises the following steps:

a) application of the sample to be examined to the substrate,

b) addition of probes characterised for detection, which, as a result of specific binding to A-beta aggregates, mark these and

detection of the marked aggregates, wherein step b) can be carried out before step a).

Standards are also made available which enable an exact and quantitative determination of pathogenic aggregates or oligomers of endogenous proteins. The standards should be usable as internal or external standards.

Furthermore, precisely defined, homogeneous and stable preparations of standards can be used for the quantification of pathogenic aggregates or oligomers of endogenous proteins.

Standards for the quantification of oligomers or pathogenic aggregates which characterise a protein aggregation disease or an amyloid degeneration or protein misfolding disease are characterised in that a polymer is constructed from polypeptide sequences which, as regards their sequence, are identical in the corresponding subregion to the endogenous proteins or have a homology of at least 50% over the corresponding subregion with the endogenous proteins which characterise a protein aggregation disease or an amyloid degeneration or protein misfolding disease, wherein the polymers do not aggregate.

The standard can be characterised in that it has a precisely defined number of epitopes which are covalently linked to one another for the binding of probes.

The standard can also be characterised in that it contains epitopes of the A-beta peptide and/or the sequences according to the invention.

The standards are used as capture molecules. In one alternative, the standards are used for removing and/or detoxifying amyloid-beta oligomers in blood, blood products and/or organs.

Also disclosed is a kit which comprises standards and/or sequences. The compounds and/or components of the kit can be packed in containers, optionally with/in buffers and/or solution. Alternatively, some components can be packaged in the same container. Additionally or alternatively, one or more of the components could be absorbed on a solid support such as a glass plate, a chip or a nylon membrane or on the well of a microtiter plate. The kit may also include instructions for using the kit for any of the embodiments.

The present invention also relates to a kit for the selective quantification of A-beta aggregates according to the method described above. Such a kit can contain one or more of the following components:

- substrate made of glass which is coated with a hydrophobic material;
- standard;
- capture molecule;
- probe;
- substrate with capture molecule;
- solutions;
- buffer.

The compounds and/or components of the kit of the present invention can be packaged in containers, optionally with/in buffers and/or solution. Alternatively, some components can be packaged in the same container. Additionally or alternatively, one or more of the components could

be absorbed on a solid support such as a glass plate, a chip or a nylon membrane or on the well of a microtiter plate. The kit may also include instructions for using the kit for any of the embodiments.

In a further variant of the kit, the capture molecules described above are immobilised on the substrate. The KIT can also contain solutions and/or buffers. To protect the dextran surface and/or the capture molecules immobilised thereon, these can be covered with a solution or a buffer.

The kit can also contain at least one standard or at least one dendrimer for the quantification of pathogenic aggregates or oligomers of endogenous proteins which contain a protein aggregation disease.

Polymers, D-peptides, antibodies and/or compounds which can be used according to the invention in a method for the treatment (in vitro) of blood, blood products and/or organs for the removal and/or detoxification of amyloid-beta oligomers are shown below.

D3D3: rprtrlhthrnrrprtrlhthrnr (SEQ ID NO:13)

Further polymers, D-peptides, antibodies and/or compounds which can be used in a method according to the invention for the treatment (in vitro) of blood, blood products and/or organs for the removal and/or detoxification of amyloid-beta oligomers are as follows:

DB 4: rprtrlrthqnr (SEQ ID NO:1)

D3nwnD3: rprtrlhthrnrnwnrprtrlhthrnr (SEQ ID NO:14)

double-D3-free-Ntermini: $(rprtrlhthrnr)_2$-PEG3 (SEQ ID NO:15)

double-D3-free-Ctermini: PEG5-$(rprtrlhthrnr)_2$ (SEQ ID NO:16)

kqhhveygsdhrfead (SEQ ID NO:2)

shyrhisp (SEQ ID NO:3)

giswqqshhlva (SEQ ID NO:4)

prtrlhth (SEQ ID NO:5)

qshyrhispaqv (SEQ ID NO:6)

qshyrhispdqv (SEQ ID NO:7)

qshyrhispar (SEQ ID NO:8)

kshyrhispakv (SEQ ID NO:9)

rprtrlhthrnr (SEQ ID NO:10)

rprtrlhthrte (SEQ ID NO:11)

kprtrlhthrnr (SEQ ID NO:12)

daefrhdsgye (SEQ ID NO:17)

hhghspnvsqvr (SEQ ID NO:18)

gsfstqvgslhr (SEQ ID NO:19)

htgtqsyvprl (SEQ ID NQ:20)

tlayaraymvap (SEQ ID NO:21)

tlayaraymvap (SEQ ID NO:22)

atpqndlktfph (SEQ ID NO:23)

tqpetdllrvqf (SEQ ID NO:24)

citwpptglty (SEQ ID NO:25)

tfletgpiyadg (SEQ ID NO:26)

lvppthrhwpvt (SEQ ID NO:27)

appgnwrnylmp (SEQ ID NO:28)

dnysnyvpgtkp (SEQ ID NO:29)

svsvgmkpsprp (SEQ ID NO:30)

slpnpfsvssfg (SEQ ID NO:31)

yvhnpyhlpnpp (SEQ ID NO:32)

crrlhtyigpvt (SEQ ID NO:33)

gatmkkmddhtv (SEQ ID NO:34)

lgktqklsdahs (SEQ ID NO:35)

ddqarpymaygp (SEQ ID NO:36)

gdtwvnmvsmvh (SEQ ID NO:37)

gytwvnmvsmvh (SEQ ID NO:38)

wtntvarlatpy (SEQ ID NO:39)

qtqalyhsrqvh (SEQ ID NO:40)

nsqtqtlhlfph (SEQ ID NO:41)

hntsanilhssh (SEQ ID NO:42)

shinptsfwpap (SEQ ID NO:43)

tfsnplymwprp (SEQ ID NO:44)

gpspfnpqptpv (SEQ ID NO:45)

fsdhksptpppr (SEQ ID NO:46)

stsvyppppsaw (SEQ ID NO:47)

yglptqansmql (SEQ ID NO:48)

hnrtdntyirpt (SEQ ID NO:49)

lqqplgnnrpns (SEQ ID NO:50)

kpedsaaypqnr (SEQ ID NO:51)

rpedsvitktqnt (SEQ ID NO:52)

raadsgctptkh (SEQ ID NO:53)

rprtrlhthrnt (SEQ ID NO:54)

rprtrlhthtnv (SEQ ID NO:55)

rprtrlhthtnr (SEQ ID NO:56)

rprtrlhthrkq (SEQ ID NO:57)

rprtrlhtlrnr (SEQ ID NO:58)

rrrsplhthrnr (SEQ ID NO:59)

lrsprqrripri (SEQ ID NO:60)

rkrqlrmttprp (SEQ ID NO:61)

shyrhispaqk (SEQ ID NO:62)

double-D3-free-Ntermini: (rprtrlhthrnr)2- (SEQ ID NO:63)

double-D3-free-Ctermini: (rprtrlhthrnr)2 (SEQ ID NO:64)

DB 3: rpitrlrthqnr (SEQ ID NO:65),

RD 2: ptlhthnrrrrr (SEQ ID NO:66)

RD 1: pnhhrrrrrrtl (SEQ ID NO:67)

RD 3: rrptlrhthnrr (SEQ ID NO:68)

D3-delta-hth: rprtrlrnr (SEQ ID NO:69)

NT-D3: rprtrl (SEQ ID NO:70)

DB 1: rpitrlhtnrnr (SEQ ID NO:71),

DB 2: rpittlqthqnr (SEQ ID NO:72),

D3: rprtrlhthrnr (SEQ ID NO:73 ()

DB 5: rpitrlqtheqr (SEQ ID NO. 74)

D3-delta-hth: rprtrlrnrrprtrlrnr (SEQ ID NO:75)

RD 2- RD 2: ptlhthnrrrrrptlhthnrrrrr (SEQ ID NO:76)

DO 3: sgwhynwqywwk (SEQ ID NO:77)

rprtrsgwhynwqywwkrnr (SEQ ID NO:78)

ptlsgwhynwqywwkrrrrr (SEQ ID NO:79)

Antibodies that can be used in a method for the treatment (in vitro) of blood, blood products and/or organs for the removal and/or detoxification of amyloid-beta oligomers are defined below:

Antibodies that

a) bind to a retro-inverso sequence of the amyloid beta-peptide or amyloid beta peptide partial fragments and/or

b) bind to the multimerisation domain of the amyloid beta-peptide and also to the amyloid beta peptide and/or

c) bind to one of the above-mentioned sequences selected from the group:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64. SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:79 or homologous sequences thereof.

Hybrid compounds that can be used in a method for the treatment (in vitro) of blood, blood products and/or organs for the removal and/or detoxification of amyloid-beta oligomers are defined below.

Hybrid compound of the formula A-B wherein A is an aminopyrazole or a derivative thereof and B is a peptide and A and B are covalently linked to one another directly or by means of a linker.

Hybrid compound, characterised in that B is a D-peptide, characterised in that the D-peptide is selected from the above-mentioned sequences.

Hybrid compound of the formula A-B, characterised in that

A is selected from the group of compounds consisting of:

3-aminopyrazole-5-carboxylic acid, derivatives thereof with heterocyclic CH group substituted for -CR- or -N-, -O-, -S-, 3-aminopyrazole-5-carboxylic acid dimer and -trimer or tetramer.

B is selected from the group of compounds consisting of:

D3-peptide, SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64. SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78 and SEQ ID NO:79;

the linker is selected from the group of compounds consisting of:

no linker, GABA, TEG, TEG dimer, PEG, alpha-amino acids, alpha-amino-omega- carboxylic acid.

The method according to the invention removes and/or detoxifies pathogenic particles, amyloid-beta oligomers, i.e. converts them into an innocuous form or destroys them. A further infection due to retention and replication of the pathogenic (amyloidogenic) particles is thus avoided. Synergistic effects occur here, triggered by the compounds to be used according to the invention. Thus, in particular, the co-aggregates of amyloid beta peptides (oligomers) and the compounds to be used according to the invention, as an innocuous form, later prevent or reduce further or new formation of A-beta aggregates.

The method according to the invention is therefore safer than the methods known from the prior art, since no absolutely complete removal of the pathogenic, toxic and/or infectious particles has to be carried out. There is detoxification by conversion into harmless forms, which can even prevent or reduce a later infection, i.e. the formation of A-beta aggregates.

Examples:

1. ThT Seeding assay: Foundations

Amyloidogenic peptides have the ability to form amyloid fibrils. This can happen spontaneously with a certain probability. If there are no amyloid “seeds”, it may take some time before the first amyloid fibrils are formed, the formation and replication of which can be monitored quantitatively using the fluorescence of thioflavin T (ThT). ThT interacts with A-Beta fibrils and the fibril-dye complex exhibits an increased fluorescence (λem: 450 nm, λex: 490 nm). The time until the ThT signal begins to rise is called the "lag phase". This "lag phase" can be avoided or greatly shortened if amyloid "seeds" are added to the aggregation batch. A well-known example is the addition of prion-containing brain material to a solution of monomeric recombinant prion protein, which then forms ThT-positive fibrils with a significantly shortened "lag phase". A further example is to add a small amount of abeta-amyloid fibrils to a solution of non-aggregated A-Beta peptide (Abeta). The "lag phase" for the formation of ThT-positive Abeta fibrils is also significantly reduced. As a result, this test (called “ThT seeding assay”) allows any substance or mixture of substances to be examined for their content of amyloids capable of forming seeds. If the substance mixture added to the aggregation batch contains amyloids capable of forming “seeds”, this leads to the absence or shortening of the "lag phase". This in vitro property is often considered analogous to prion-like infectivity or transferability in vivo.

In the first control experiment, it was examined whether preformed Abeta aggregates as aggregation seeds actually shorten the “lag phase” of the aggregation of freshly dissolved Abeta. To this end, the ThT fluorescence of freshly dissolved Abeta was monitored in the absence and presence of preformed Abeta aggregates. Subsequently, Abeta aggregates were prepared which were formed from a mixture of Abeta (1-42) and an inhibitor substance (in this example one of the D-peptides D3, DB1, DB2, DB3, DB4, DB5 in each case), which are intended to disrupt the formation of amyloid fibrils. The abeta inhibitor co-aggregates thus formed were added to a ThT seeding assay,

just like the amyloid Abeta aggregates, in order to determine the remaining amyloid potential of these co-aggregates.

2. ThT Seeding assay: Experimental details

20 µM A-beta peptide (1-42) was preincubated together with one of the inhibitor substances (20 µM) for 7 days at 37°C in 10 mM NaPi pH 7.4. The sample was then centrifuged (20 min, 16.100 × g), the aggregate pellet washed 3× and resuspended in 10 mM NaPi pH 7.4. Analogously, Aß fibrils were produced without an inhibitor as a positive control. Directly before the actual ThT seeding assay, fresh Aß (20 µM in 10 mM NaPi pH 7.4) was mixed (80:20 parts by volume) with the resuspended aggregation seeds which had formed in the presence or absence of the inhibitor substances, and 10 µM ThT was added. Fresh Aß solution served as the reference, which was mixed with buffer solution without aggregation seeds (80:20 parts by volume) and contained 10 µM ThT. 50 µl of the respective reaction solution was pipetted into a well of a black 384-well microtiter plate. The ThT fluorescence was measured every 30 min for 20 h at an excitation wavelength of 440 nm and an emission wavelength of 490 nm. For the evaluation, the fluorescence intensity was corrected by subtracting the 20% added aggregation seeds and the mean value was calculated. An eightfold determination was carried out.

3. Execution:

Fig. 1 shows the course over time of the ThT fluorescence in the absence (solid line) and presence of preformed Abeta aggregates which were formed without the addition of inhibitor substances.

It can clearly be seen that these aggregates significantly accelerate the aggregation of fresh Abeta (Δt of about 4 h), i.e. clearly exhibit a seeding effect.

Fig. 2 shows the course over time of the ThT fluorescence in the absence (solid line) and presence of preformed Abeta aggregates which were formed before the start of the experiment with the addition of the inhibitor substance D3.

It can be clearly seen that these aggregates cannot accelerate the aggregation of fresh Abeta, i.e. clearly do not exhibit a seeding effect.

Fig. 3 shows the course over time of the ThT fluorescence in the absence (solid line) and presence of preformed Abeta aggregates which were formed before the start of the experiment with the addition of the inhibitor substance DB1.

It can be clearly seen that these aggregates cannot accelerate the aggregation of fresh Abeta, i.e. clearly do not exhibit a seeding effect.

Fig. 4 shows the course over time of the ThT fluorescence in the absence (solid line) and presence of preformed Abeta aggregates which were formed before the start of the experiment with the addition of the inhibitor substance DB2.

It can be clearly seen that these aggregates cannot accelerate the aggregation of fresh Abeta, i.e. clearly do not exhibit a seeding effect.

Fig. 5 shows the course over time of the ThT fluorescence in the absence (solid line) and presence of preformed Abeta aggregates which were formed before the start of the experiment with the addition of the inhibitor substance DB3.

It can be clearly seen that these aggregates cannot accelerate the aggregation of fresh Abeta, i.e. clearly do not exhibit a seeding effect.

Fig. 6 shows the course over time of the ThT fluorescence in the absence (solid line) and presence of preformed Abeta aggregates which were formed before the start of the experiment with the addition of the inhibitor substance DB4.

It can be clearly seen that these aggregates cannot accelerate the aggregation of fresh Abeta, i.e. clearly do not exhibit a seeding effect. In addition, the DB4-Abeta co-aggregates even seem to reduce the formation of ThT-positive Abeta aggregates in the later phase.

Fig. 7 shows the course over time of the ThT fluorescence in the absence (solid line) and presence of preformed Abeta aggregates which were formed before the start of the experiment with the addition of the inhibitor substance DB5.

It can be seen that these aggregates cannot accelerate the aggregation of fresh Abeta, i.e. clearly do not exhibit a seeding effect.

4. Summary of results:

All D-peptides tested formed aggregates with Abeta that were no longer able to shorten the "lag phase" of the aggregation of freshly dissolved Abeta. These co-aggregates are therefore not amyloidogenic.

Sequence Listing

<110> Forschungszentrum Juelich GmbH

<120> Method for treating blood, blood products and organs

<130> FZJ1205PCT

<160> 79

<170> patentin version 3.5

<210> 1
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> D-Peptide

<400> 1

Arg Pro Arg Thr Arg Leu Arg Thr His Gln Asn Arg
1 5 10

<210> 2
<211> 16
<212> PRT
<213> artificial sequence

<220>
<223> D-Peptide

<400> 2

Lys Gln His His Val Glu Tyr Gly Ser Asp His Arg Phe Glu Ala Asp

1 5 10 15

<210> 3
<211> 8
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 3

Ser His Tyr Arg His Ile Ser Pro
1 5

<210> 4
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 4

Gly Ile Ser Trp Gln Gln Ser His His Leu Val Ala
1 5 10

<210> 5
<211> 8
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 5

Pro Arg Thr Arg Leu His Thr His

1 5

<210> 6
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 6

Gln Ser His Tyr Arg His Ile Ser Pro Ala Gln Val
1 5 10

<210> 7
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 7

Gln Ser His Tyr Arg His Ile Ser Pro Asp Gln Val
1 5 10

<210> 8
<211> 11
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 8

Gln Ser His Tyr Arg His Ile Ser Pro Ala Arg
1 5 10

<210> 9
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 9

Lys Ser His Tyr Arg His Ile Ser Pro Ala Lys Val
1 5 10

<210> 10
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 10

Arg Pro Arg Thr Arg Leu His Thr His Arg Asn Arg
1 5 10

<210> 11
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 11

Arg Pro Arg Thr Arg Leu His Thr His Arg Thr Glu
1 5 10

<210> 12
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 12

Lys Pro Arg Thr Arg Leu His Thr His Arg Asn Arg
1 5 10

<210> 13
<211> 24
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 13

Arg Pro Arg Thr Arg Leu His Thr His Arg Asn Arg Arg Pro Arg Thr
1 5 10 15

Arg Leu His Thr His Arg Asn Arg
20

<210> 14
<211> 27
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 14

Arg Pro Arg Thr Arg Leu His Thr His Arg Asn Arg Asn Trp Asn Arg
1 5 10 15

Pro Arg Thr Arg Leu His Thr His Arg Asn Arg
20 25

<210> 15
<211> 24
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<220>
<223> double-D3-free-Nterminii (rprtrlhthrnr)2-PEG3

<400> 15

Arg Pro Arg Thr Arg Leu His Thr His Arg Asn Arg Arg Pro Arg Thr
1 5 10 15

Arg Leu His Thr His Arg Asn Arg
20

<210> 16
<211> 24
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<220>
<223> double-D3-free-Ctermini: PEG5-(rprtrlhthrnr)2

<400> 16

Arg Pro Arg Thr Arg Leu His Thr His Arg Asn Arg Arg Pro Arg Thr
1 5 10 15

Arg Leu His Thr His Arg Asn Arg
20

<210> 17
<211> 11
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 17

Asp Ala Glu Phe Arg His Asp Ser Gly Tyr Glu
1 5 10

<210> 18
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 18

His His Gly His Ser Pro Asn Val Ser Gln Val Arg
1 5 10

<210> 19
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 19

Gly Ser Phe Ser Thr Gln Val Gly Ser Leu His Arg
1 5 10

<210> 20
<211> 11
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 20

His Thr Gly Thr Gln Ser Tyr Val Pro Arg Leu
1 5 10

<210> 21
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 21

Thr Leu Ala Tyr Ala Arg Ala Tyr Met Val Ala Pro
1 5 10

<210> 22
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 22

Thr Leu Ala Tyr Ala Arg Ala Tyr Met Val Ala Pro
1 5 10

<210> 23
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 23

Ala Thr Pro Gln Asn Asp Leu Lys Thr Phe Pro His
1 5 10

<210> 24
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 24

Thr Gln Pro Glu Thr Asp Leu Leu Arg Val Gln Phe
1 5 10

<210> 25
<211> 11
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 25

cys Ile Thr Trp Pro Pro Thr Gly Leu Thr Tyr
1 5 10

<210> 26
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 26

Thr Phe Leu Glu Thr Gly Pro Ile Tyr Ala Asp Gly
1 5 10

<210> 27
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 27

Leu Val Pro Pro Thr His Arg His Trp Pro Val Thr
1 5 10

<210> 28
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 28

Ala Pro Pro Gly Asn Trp Arg Asn Tyr Leu Met Pro
1 5 10

<210> 29
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 29

Asp Asn Tyr Ser Asn Tyr Val Pro Gly Thr Lys Pro
1 5 10

<210> 30
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 30

Ser Val Ser Val Gly Met Lys Pro Ser Pro Arg Pro
1 5 10

<210> 31
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 31

Ser Leu Pro Asn Pro Phe Ser Val Ser Ser Phe Gly
1 5 10

<210> 32
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 32

Tyr Val His Asn Pro Tyr His Leu Pro Asn Pro Pro
1 5 10

<210> 33
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 33

cys Arg Arg Leu His Thr Tyr Ile Gly Pro Val Thr
1 5 10

<210> 34
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 34

Gly Ala Thr Met Lys Lys Met Asp Asp His Thr Val
1 5 10

<210> 35
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 35

Leu Gly Lys Thr Gln Lys Leu Ser Asp Ala His Ser
1 5 10

<210> 36
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 36

Asp Asp Gln Ala Arg Pro Tyr Met Ala Tyr Gly Pro
1 5 10

<210> 37
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 37

Gly Asp Thr Trp Val Asn Met Val Ser Met Val His
1 5 10

<210> 38
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 38

Gly Tyr Thr Trp Val Asn Met Val Ser Met Val His
1 5 10

<210> 39
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 39

Trp Thr Asn Thr Val Ala Arg Leu Ala Thr Pro Tyr
1 5 10

<210> 40
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 40

Gln Thr Gln Ala Leu Tyr His Ser Arg Gln Val His
1 5 10

<210> 41
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 41

Asn Ser Gln Thr Gln Thr Leu His Leu Phe Pro His
1 5 10

<210> 42
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 42

His Asn Thr Ser Ala Asn Ile Leu His Ser Ser His
1 5 10

<210> 43
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 43

Ser His Ile Asn Pro Thr Ser Phe Trp Pro Ala Pro
1 5 10

<210> 44
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 44

Thr Phe Ser Asn Pro Leu Tyr Met Trp Pro Arg Pro
1 5 10

<210> 45
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 45

Gly Pro Ser Pro Phe Asn Pro Gln Pro Thr Pro Val

1 5 10

<210> 46
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 46

Phe Ser Asp His Lys Ser Pro Thr Pro Pro Pro Arg
1 5 10

<210> 47
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 47

Ser Thr Ser Val Tyr Pro Pro Pro Pro Ser Ala Trp
1 5 10

<210> 48
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 48

Tyr Gly Leu Pro Thr Gln Ala Asn Ser Met Gln Leu
1 5 10

<210> 49
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 49

His Asn Arg Thr Asp Asn Thr Tyr Ile Arg Pro Thr
1 5 10

<210> 50
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 50

Leu Gln Gln Pro Leu Gly Asn Asn Arg Pro Asn Ser
1 5 10

<210> 51
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 51

Lys Pro Glu Asp Ser Ala Ala Tyr Pro Gln Asn Arg
1 5 10

<210> 52
<211> 13
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 52

Arg Pro Glu Asp Ser Val Ile Thr Lys Thr Gln Asn Thr
1 5 10

<210> 53
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 53

Arg Ala Ala Asp Ser Gly cys Thr Pro Thr Lys His
1 5 10

<210> 54
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 54

Arg Pro Arg Thr Arg Leu His Thr His Arg Asn Thr
1 5 10

<210> 55
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 55

Arg Pro Arg Thr Arg Leu His Thr His Thr Asn Val
1 5 10

<210> 56
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 56

Arg Pro Arg Thr Arg Leu His Thr His Thr Asn Arg
1 5 10

<210> 57
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 57

Arg Pro Arg Thr Arg Leu His Thr His Arg Lys Gln

1 5 10

<210> 58
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 58

Arg Pro Arg Thr Arg Leu His Thr Leu Arg Asn Arg
1 5 10

<210> 59
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 59

Arg Arg Arg Ser Pro Leu His Thr His Arg Asn Arg
1 5 10

<210> 60
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 60

Leu Arg Ser Pro Arg Gln Arg Arg Ile Pro Arg Ile

1 5 10

<210> 61
<211> 12
<212> PRT
<213> artificial sequence

<220><223> D-Peptide

<400> 61

Arg Lys Arg Gln Leu Arg Met Thr Thr Pro Arg Pro
1 5 10

<210> 62
<211> 11
<212> PRT

<213> artificial sequence

<220><223> D-Peptide

<400> 62

Ser His Tyr Arg His Ile Ser Pro Ala Gln Lys
1 5 10

<210> 63
<211> 24
<212> PRT
<213> artificial sequence

<220>
<223> D-Peptide

<220>

<223> double-D3-free-Ntermini (rprtrlhthrnr)2

<400> 63

Arg Pro Arg Thr Arg Leu His Thr His Arg Asn Arg Arg Pro Arg Thr
1 5 10 15

Arg Leu His Thr His Arg Asn Arg
20

<210> 64
<211> 24
<212> PRT
<213> artificial sequence

<220>
<223> D-Peptide

<220>
<223> double-D3-free-Ctermini: (rprtrlhthrnr)2

<400> 64

Arg Pro Arg Thr Arg Leu His Thr His Arg Asn Arg Arg Pro Arg Thr
1 5 10 15

Arg Leu His Thr His Arg Asn Arg
20

<210> 65
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<223> D-Peptide

<400> 65

Arg Pro Ile Thr Arg Leu Arg Thr His Gln Asn Arg
1 5 10

<210> 66

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> D-Peptide

<400> 66

Pro Thr Leu His Thr His Asn Arg Arg Arg Arg Arg
1 5 10

<210> 67

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> D-Peptide

<400> 67

Pro Asn His His Arg Arg Arg Arg Arg Thr Thr Leu
1 5 10

<210> 68

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> D-Peptide

<400> 68

Arg Arg Pro Thr Leu Arg His Thr His Asn Arg Arg
1 5 10

<210> 69

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> D-Peptide

<400> 69

Arg Pro Arg Thr Arg Leu Arg Asn Arg
1 5

<210> 70

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> D-Peptide

<400> 70

Arg Pro Arg Thr Arg Leu
1 5

<210> 71
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> D-Peptide

<400> 71

Arg Pro Ile Thr Arg Leu His Thr Asp Arg Asn Arg
1 5 10

<210> 72
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> D-Peptide

<400> 72

Arg Pro Ile Thr Thr Leu Gln Thr His Gln Asn Arg
1 5 10

<210> 73
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> D-Peptide

<400> 73

Arg Pro Arg Thr Arg Leu His Thr His Arg Asn Arg
1 5 10

<210> 740
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> D-Peptide

<400> 74

Arg Pro Ile Thr Arg Leu Gln Thr His Glu Gln Arg
1 5 10

<210> 75
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> D-Peptide

<400> 75

Arg Pro Arg Thr Arg Leu Arg Asn Arg Arg Pro Arg Thr Arg Leu Arg Asn Arg
1 5 10 15

<210> 76
<211> 24
<212> PRT
<213> Artificial Sequence

<220>

<223> D-Peptide

<400> 76

Pro Thr Leu His Thr His Asn Arg Arg Arg Arg Arg Pro Thr Leu His Thr His Asn Arg
1 5 10 15
20

Arg Arg Arg Arg
1 5

<210> 77
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> D-Peptide

<400> 77

Ser Gly Trp His Tyr Asn Trp Gln Tyr Trp Trp Lys
1 5 10

<210> 78
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> D-Peptide

<400> 78

Arg Pro Arg Thr Arg Ser Gly Trp His Tyr Asn Trp Gln Tyr Trp Trp
1 5 10 15

Lys Arg Asn Arg
20

<210> 79
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> D-Peptide

<400> 79

Pro Thr Leu Ser Gly Trp His Tyr Asn Trp Gln Tyr Trp Trp Lys Arg
1 5 10 15

Arg Arg Arg Arg
20

Patentkrav

1. Fremgangsmåde til behandling uden for menneske- eller dyrekroppen (in vitro, ex vivo) af blod, blodprodukter og/eller organer, hvor amyloid-beta-oligomerer fjernes og/eller afgiftes **kendetegnet ved, at** D-enantiomerforbindelsen rprtrlhthmrrprtrlhthrnr (D3D3, SEQ ID NO:13) anvendes, hvilken binder til amyloid-beta-oligomerer.

2. Fremgangsmåde ifølge krav 1, **kendetegnet ved, at** at blodet, blodprodukterne eller organerne undersøges for amyloid-beta-oligomerer forud for behandlingen.

3. Fremgangsmåde ifølge et af de foregående krav, **kendetegnet ved, at** forbindelserne ifølge krav 1 er anbragt som indfangningsmolekyler på en bærer, via hvilken en prøve indeholdende blodet, blodprodukterne og/eller organet ledes.

4. Fremgangsmåde ifølge krav 3, **kendetegnet ved, at** indfangningsmolekylerne er fastgjort på beads.

5. Fremgangsmåde ifølge krav 3, **kendetegnet ved, at** indfangningsmolekylerne er immobiliseret på nanomagneter.

6. Fremgangsmåde ifølge krav 3, **kendetegnet ved, at** indfangningsmolekylerne er anbragt i et dialysesystem.

7. Fremgangsmåde ifølge krav 3, **kendetegnet ved, at** bæreren for indfangningsmolekylerne er fremstillet af et biokompatibelt materiale.

8. Fremgangsmåde ifølge krav 3, **kendetegnet ved, at** bærerne er membraner, filtre, filtersvampe, beads, stænger, reb, søjler, hule fibre.

9. Fremgangsmåde ifølge et af de foregående krav, **kendetegnet ved, at** der anvendes et kit til den selektive kvantificering af A-beta-aggregater og/eller til

behandling (in vitro) af blod, blodprodukter og/eller organer indeholdende en eller flere af følgende komponenter:

- substrat fremstillet af glas som er belagt med et hydrofobt materiale;
- standard;

Indfangningsmolekyle;

- sonde;
- substrat med indfangningsmolekyle;
- opløsninger;
- buffer.

10. Fremgangsmåde ifølge et af de foregående krav, **kendetegnet ved, at** forbindelsen fra krav 1 som indfangningsmolekyle ex vivo ledes over og/eller gennem et organ.

11. Fremgangsmåde ifølge et af de foregående krav, **kendetegnet ved, at** amyloid-beta-oligomerer afgiftes.

12. Anvendelse ex vivo af D3D3-peptidet (SEQ ID NO:13) ifølge krav 1 som indfangningsmolekyle for amyloid-beta-oligomerer.

13. Anvendelse af D3D3-peptidet, (SEQ ID NO:13) ifølge krav 1 til ex vivo behandling af blod, blodprodukter og/eller organer til frigørelse og/eller deaktivering af Aß-oligomerer til forebyggelse af overførsel af Alzheimers sygdom.

14. Anvendelse af D3D3-peptidet (SEQ ID NO:13) ifølge krav 1 til ex vivo behandling af Alzheimers sygdom, Parkinsons sygdom, Creutzfeldt Jakob sygdom (CJD), scrapie, kogalskab (BSE) eller diabetes.

DRAWINGS

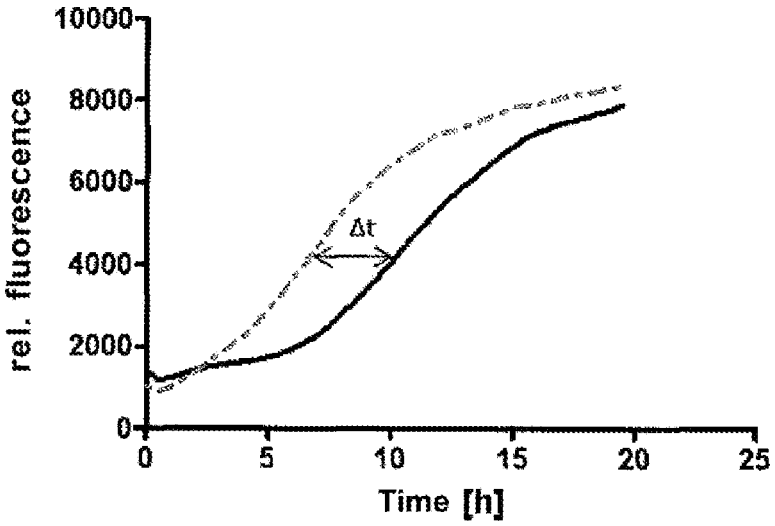

Fig. 1

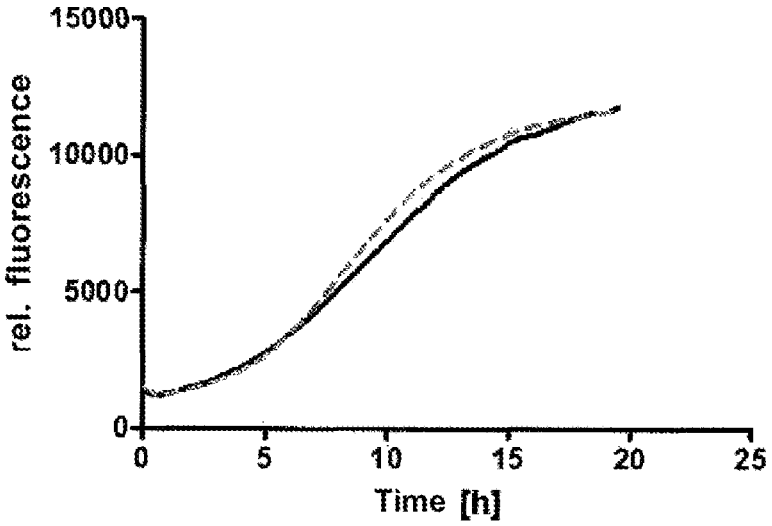

Fig. 2

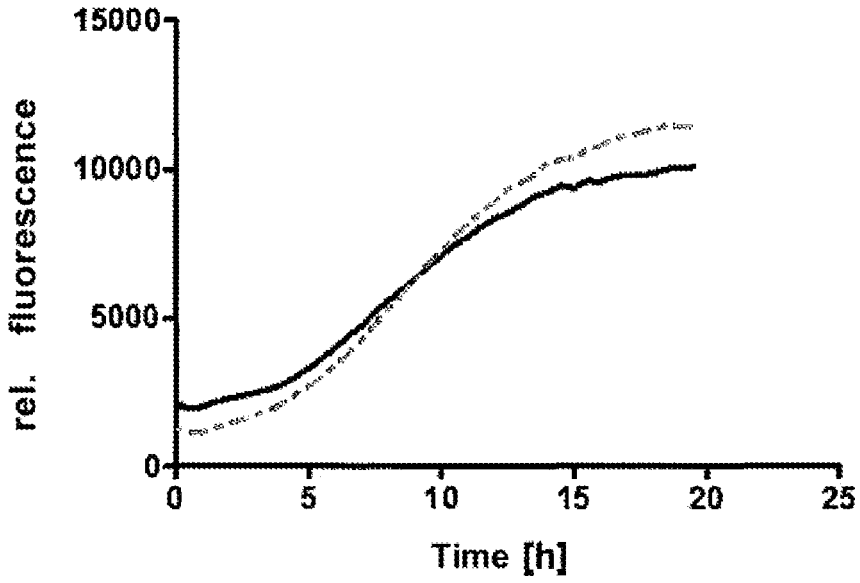
15000
10000
5000
0
rel. fluorescence
0
5
10
15
20
25
Time [h]

Fig. 3

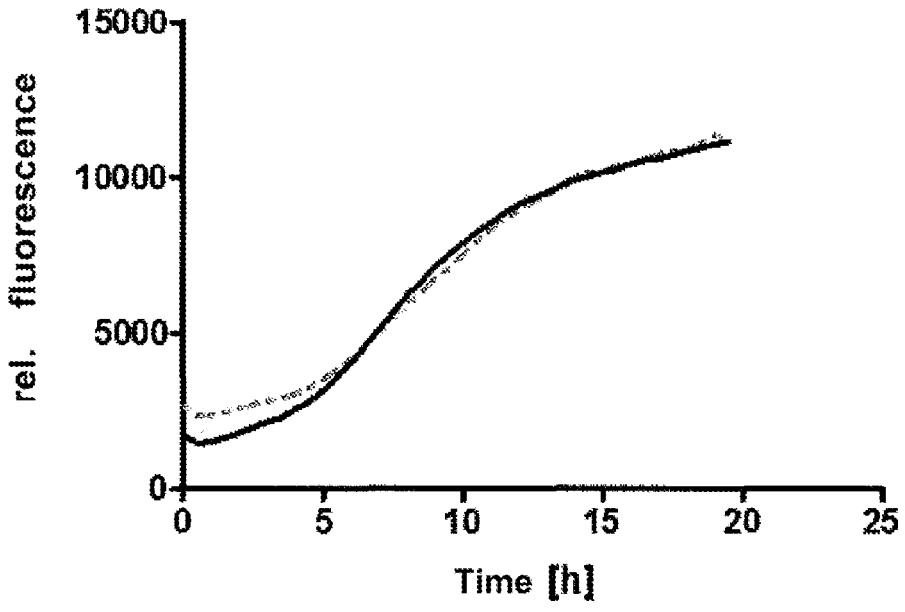
15000
10000
5000
0
rel. fluorescence
0
5
10
15
20
25
Time [h]

Fig. 4

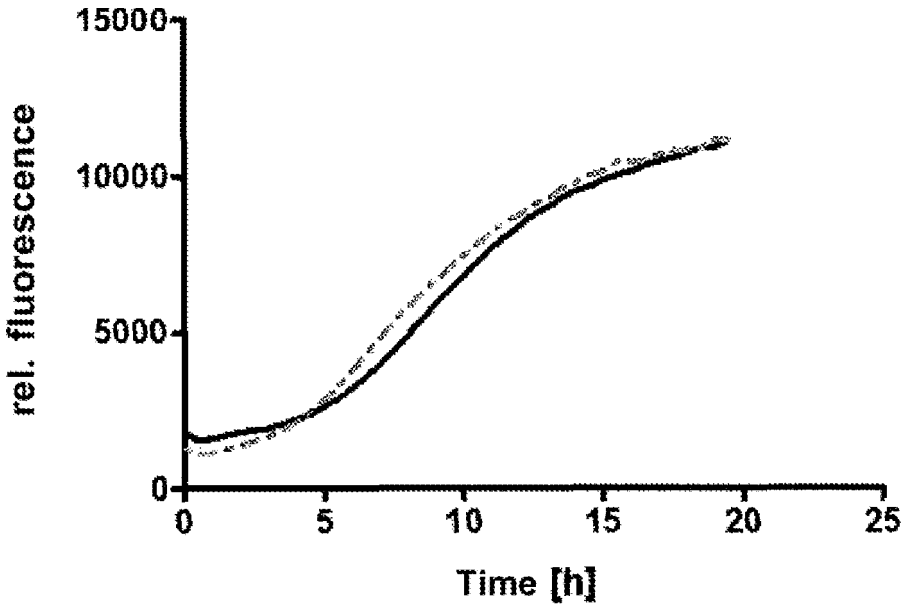
15000
10000
5000
0
rel. fluorescence
0
5
10
15
20
25
Time [h]

Fig. 5

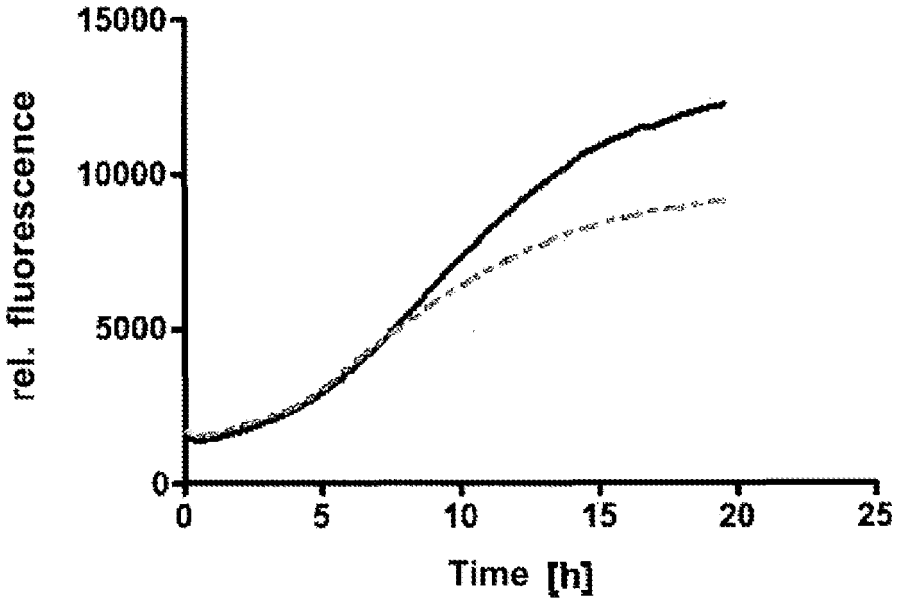
15000
10000
5000
0
rel. fluorescence
0
5
10
15
20
25
Time [h]

Fig. 6

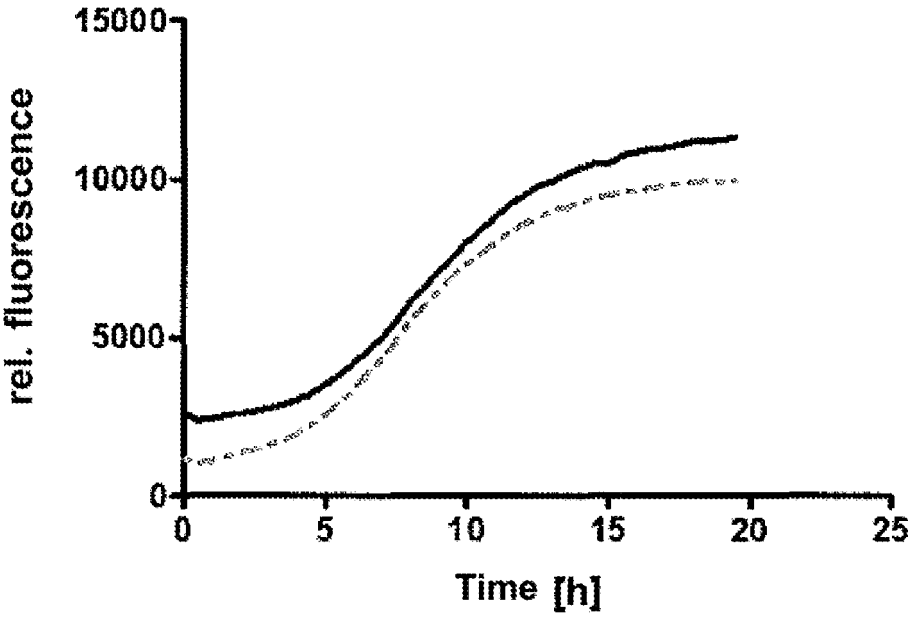

Fig. 7