on Alzheimer patients, for example, resulted in considerable side effects (meningoencephalitis, hemorrhages) in some of the patients since the antibodies formed also recognized the Aβ(1-42) forms presumably required for cell lining, resulting in inflammatory reactions (D. Schenk.; Nat. Rev. Neurosci. 3, 824-828 (2002)).

An Aβ oligomer vaccine should of course not only avoid eliciting autoantibodies binding to other than the pathogenic Aβ forms but in general should not induce the formation of autoantibodies that are capable of pathogenic cross-reactions. In certain cases it has, however, been found that monoclonal antibodies identified using preparations of wild type Aβ oligomers may exhibit cross-reactivity to platelet factor 4 (PF-4). PF-4 binds to heparin, thus forming neo-epitopes. This may elicit an immune response resulting in a required thrombotic disorder known as heparin-induced thrombocytopenia (HIT). HIT is known to be trigged by heparin treatment. Nevertheless, the symptoms of HIT, thrombocytopenia and thrombosis, as well as anti-PF-4 autoantibodies have also been observed in patients without prior administration of heparin (Warkentin et al., Am J Med 121(7): 632–6, 2008).

There exists a tremendous, unmet therapeutic need for the development of an Aβ oligomer vaccine that is effective against Alzheimer's disease and related disorders, while not inducing negative and potentially lethal side effects such as pathologic autoimmune responses on the patient's body. Such a need is particularly evident in view of the increasing longevity of the general population and, with this increase, an associated rise in the number of patients annually diagnosed with Alzheimer's disease or related disorders.

Summary

The present invention meets said need by providing a novel immunogenic product that is capable of eliciting an antiserum which specifically binds to Aβ globulomer epitopes, but has no or low cross-reactivity to platelet factor 4 (PF-4). Accordingly the novel immunogenic product comprises one or more epitopes which are recognized by globulomer-specific antibodies. Monoclonal antibodies binding such epitopes include 7C6, 4D10 and 5F7 which have been described in WO 2007/062852 and are obtainable from the hybridomas designated by American Type Culture Collection deposit numbers PTA-7240, PTA-7405, and PTA-7241, respectively.

In one aspect, the invention provides an immunogenic product comprising an amyloid β (Aβ) amino acid sequence having 62.5% or higher, 68.75% or higher, 75% or higher, 81.25% or higher, 87.5% or higher, or 93.75 or higher identity to the amino acid sequence $V_{18}F_{19}F_{20}A_{21}E_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}G_{29}A_{30}I_{31}I_{32}G_{33}$ (SEQ ID NO: 2), wherein the product i) is reactive with a monoclonal antibody selected from the group consisting of monoclonal antibody 7C6 obtainable from a hybridoma designated by American Type Culture Collection deposit number PTA-7240; monoclonal antibody 4D10 obtainable from a hybridoma designated by American Type Culture Collection deposit number PTA-7405, or monoclonal antibody 5F7 obtainable from a hybridoma designated by American Type Culture Collection deposit number PTA-7241, wherein the monoclonal antibody preferably binds the product with a K_D of $1x10^{-6}$ M or greater affinity; and ii) is capable of eliciting a polyclonal antiserum which has at least 100 times smaller cross-reactivity to platelet factor 4 (PF-4) than a reference anti-PF-4 antibody; wherein the amyloid β (Aβ) amino acid sequence comprises one, two, three, four, five or six amino acids that are substituted by different amino acids. In another aspect, the present invention also refers to a product as defined of the present inventio for use in therapy. In still another aspect, the present invention refers to the use of a product of the present invention in the manufacture of a medicament for treating or preventing an amyloidosis in a subject in need thereof.

Thus, the disclosure provides an immunogenic product comprising an amyloid β (Aβ) amino acid sequence having 62.5% or higher identity to the amino acid sequence $V_{18}F_{19}F_{20}A_{21}E_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}G_{29}A_{30}I_{31}I_{32}G_{33}$ [SEQ ID NO:2; Aβ(18-33)], wherein the product

i) is reactive with a monoclonal antibody selected from the group consisting of monoclonal antibody 7C6 obtainable from a hybridoma designated by American Type Culture Collection deposit number PTA-7240; monoclonal antibody 4D10 obtainable from a hybridoma designated by American Type Culture Collection deposit number PTA-7405, or monoclonal antibody 5F7 obtainable from a hybridoma designated by American Type Culture Collection deposit number PTA-7241; and

ii) is capable of eliciting a polyclonal antiserum which has no or low cross-reactivity to platelet factor 4 (PF-4)

The present invention also relates to a composition comprising an immunogenic product as disclosed herein.

The present disclosure further relates to a method of treating or preventing an amyloidosis in a subject in need thereof, which comprises administering an immunogenic product as disclosed herein to the subject. In a related example, the present disclosure relates to an immunogenic product as disclosed herein for use in treating or preventing an amyloidosis.

The present invention also relates to a method of diagnosing an amyloidosis which comprises providing a sample from the subject suspected of having the amyloidosis, contacting the sample with an immunogenic product as disclosed herein for a time and under conditions sufficient for the formation of a complex comprising the product and an antibody, the presence of the complex indicating the subject has the amyloidosis. In a related aspect, the present invention relates to an immunogenic product as disclosed herein for use in diagnosing an amyloidosis.

The present invention also relates to a method of identifying an agent capable of binding to an immunogenic product as disclosed herein, which method comprises the steps

CLAIMS

1. An immunogenic product comprising an amyloid β (Aβ) amino acid sequence having 62.5% or higher, 68.75% or higher, 75% or higher, 81.25% or higher, 87.5% or higher, or 93.75 or higher identity to the amino acid sequence $V_{18}F_{19}F_{20}A_{21}E_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}G_{29}A_{30}I_{31}I_{32}G_{33}$ (SEQ ID NO: 2), wherein the product

   i) is reactive with a monoclonal antibody selected from the group consisting of monoclonal antibody 7C6 obtainable from a hybridoma designated by American Type Culture Collection deposit number PTA-7240; monoclonal antibody 4D10 obtainable from a hybridoma designated by American Type Culture Collection deposit number PTA-7405, or monoclonal antibody 5F7 obtainable from a hybridoma designated by American Type Culture Collection deposit number PTA-7241, wherein the monoclonal antibody preferably binds the product with a K_D of $1x10^{-6}$ M or greater affinity; and

   ii) is capable of eliciting a polyclonal antiserum which has at least 100 times smaller cross-reactivity to platelet factor 4 (PF-4) than a reference anti-PF-4 antibody;

   wherein the amyloid β (Aβ) amino acid sequence comprises one, two, three, four, five or six amino acids that are substituted by different amino acids.

2. The product of claim 1 that is further characterized by one or more of the following features:
   (a) the polyclonal antiserum is a polyclonal antiserum from a mouse or a rabbit;
   (b) the polyclonal antiserum is affinity purified antiserum enriched in antibodies binding to the product;
   (c) the cross-reactivity of the polyclonal antiserum to PF-4 is at least 10 times, e. g. at least 20 times, at least 30 times or at least 50 times, more preferably at least 100 times, e. g. at least 200 times, at least 300 times or at least 500 times, and even more preferably at least 1000 times, e. g. at least 2000 times, at least 3000 times or at least 5000 times, even more preferably at least 10000 times, e. g. at least 20000 times, at least 30000 or at least 50000 times, and most preferably at least 100000 times smaller than the cross-reactivity of a reference anti-PF-4 antibody to PF-4;
   (d) platelet factor 4 is PF-4 in cynomolgus plasma or PF-4 in human plasma;

(e) cross-reactivity is binding of the polyclonal antiserum to plasma PF-4, with the polyclonal antiserum being immobilized.

3. The product of claim 1 or 2, wherein the polyclonal antiserum has an affinity to an Aβ globulomer which is at least 2 times, e. g. at least 3 times or at least 5 times, preferably at least 10 times, e. g. at least 20 times, at least 30 times or at least 50 times, more preferably at least 100 times, e. g. at least 200 times, at least 300 times or at least 500 times, and even more preferably at least 1000 times, e. g. at least 2000 times, at least 3000 times or at least 5000 times, even more preferably at least 10000 times, e. g. at least 20000 times, at least 30000 or at least 50000 times, and most preferably at least 100000 times greater than the affinity of the antiserum to at least one Aβ form selected from the group consisting of monomeric Aβ(1-42), monomeric Aβ(1-40), fibrillomeric Aβ(1-42), and fibrillomeric Aβ(1-40);
wherein the Aβ globulomer is preferably selected from Aβ(1-42) globulomers, Aβ(12-42) globulomers and Aβ(20-42) globulomers.

4. The product of any one of claims 1 to 3, wherein the polyclonal antiserum has an affinity to an Aβ(20-42) globulomer which is at least 2 times, e. g. at least 3 times or at least 5 times, preferably at least 10 times, e. g. at least 20 times, at least 30 times or at least 50 times, more preferably at least 100 times, e. g. at least 200 times, at least 300 times or at least 500 times, and even more preferably at least 1000 times, e. g. at least 2000 times, at least 3000 times or at least 5000 times, even more preferably at least 10000 times, e. g. at least 20000 times, at least 30000 or at least 50000 times, and most preferably at least 100000 times greater than the affinity of the antiserum to at least one Aβ globulomer selected from the group consisting of Aβ(1-42) globulomer and Aβ(12-42) globulomer.

5. The product of any one of claims 1 to 4 that is further characterized by one or more of the following features:
(a) at least part of said amino acid sequence forms a loop, preferably a ß-hairpin loop;
(b) the amino acid sequence portions of the product corresponding to $F_{19}F_{20}A_{21}$ (SEQ ID NO: 8) and $A_{30}I_{31}I_{32}$ (SEQ ID NO: 9) are in anti-parallel orientation;
(c) part of the amino acid sequence forms a loop comprising a sequence selected from $V_{24}G_{25}S_{26}N_{27}$ (SEQ ID NO: 10) and $D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$ (SEQ ID NO: 11)

6. The product of any one of claims 1 to 5, which is an oligomer comprising a plurality, preferably 2 to 48, of said Aβ amino acid sequences.

7. The product of any one of claims 1 to 6, which is obtainable by a process comprising the following steps:
(a) dissolving Aβ peptide comprising said Aβ amino acid sequence in a solvent;
(b) adding an amphipatic agent to the solution of the Aβ peptide; and
(c) incubating the resulting mixture to form the oligomer; and
(d) optionally, proteolytically cleaving the oligomer.

8. The product of any one of claims 1 to 7, wherein the Aβ amino acid sequence has 72% or higher, 77% or higher, 81% or higher, 86% or higher, 90% or higher, or 95% or higher identity to the amino acid sequence $V_{18}F_{19}F_{20}A_{21}E_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}$ (SEQ ID NO: 3).

9. The product of claim 8 that is further characterized by one or more of the following features:
(a) a first amino acid sequence $L^{A}{}_{34}M^{A}{}_{35}V^{A}{}_{36}G^{A}{}_{37}G^{A}{}_{38}$ (SEQ ID NO: 5) is in parallel orientation to a second amino acid sequence $L^{B}{}_{34}M^{B}{}_{35}V^{B}{}_{36}G^{B}{}_{37}G^{B}{}_{38}$ (SEQ ID NO: 5), wherein the interproton distance for at least one atom pair selected from the group consisting of $M^{A}{}_{35}$(NH)-$V^{B}{}_{36}$(NH), $G^{A}{}_{37}$(NH)-$G^{B}{}_{38}$(NH), $L^{A}{}_{34}$(NH)-$L^{B}{}_{34}(C_{\delta}H_3)$, $M^{A}{}_{35}$(NH)-$V^{B}{}_{36}(C\gamma H_3)$ is preferably 1.8 to 6.5 Angstroms;
(b) a first amino acid sequence $G^{A}{}_{33}L^{A}{}_{34}M^{A}{}_{35}V^{A}{}_{36}G^{A}{}_{37}G^{A}{}_{38}V^{A}{}_{39}$ (SEQ ID NO: 6) is in parallel orientation to a second amino acid sequence $G^{B}{}_{33}L^{B}{}_{34}M^{B}{}_{35}V^{B}{}_{36}G^{B}{}_{37}G^{B}{}_{38}V^{B}{}_{39}$ (SEQ ID NO: 6), wherein the interproton distance for at least one atom pair selected from the group consisting of $G^{A}{}_{33}$(NH)-$G^{B}{}_{34}$(NH), $M^{A}{}_{35}$(NH)-$V^{B}{}_{36}$(NH), $G^{A}{}_{37}$(NH)-$G^{B}{}_{38}$(NH), $L^{A}{}_{34}$(NH)-$L^{B}{}_{34}(C_{\delta}H_3)$, $M^{A}{}_{35}$(NH)-$V^{B}{}_{36}(C\gamma H_3)$, $G^{A}{}_{38}$(NH)-$V^{B}{}_{39}(C\gamma H_3)$ and $V^{A}{}_{39}$(NH)-$V^{B}{}_{39}(C\gamma H_3)$ is preferably 1.8 to 6.5 Angstroms;
(c) the product comprises an inter-molecular parallel β-sheet between two Aß amino acid sequences, wherein the inter-molecular parallel β-sheet preferably comprises a first amino acid sequence $G^{A}{}_{33}L^{A}{}_{34}M^{A}{}_{35}V^{A}{}_{36}G^{A}{}_{37}G^{A}{}_{38}V^{A}{}_{39}$ (SEQ ID NO: 7) and a second amino acid sequence $G^{B}{}_{33}L^{B}{}_{34}M^{B}{}_{35}V^{B}{}_{36}G^{B}{}_{37}G^{B}{}_{38}V^{B}{}_{39}$ (SEQ ID NO: 7), and wherein preferably the atom pairs $G^{A}{}_{33}$(CO)-$L^{B}{}_{34}$(N), $L^{B}{}_{34}$(CO)-$M^{A}{}_{35}$(N), $M^{A}{}_{35}$(CO)-$V^{B}{}_{36}$(N), $V^{B}{}_{36}$(CO)-$G^{A}{}_{37}$(N), and $G^{B}{}_{37}$(CO)-$G^{A}{}_{38}$(N) are at a distance of 3.3 ± 0.5 Å, CO indicates the backbone oxygen atom, the phi (φ) angles of the residues range from –180 to –30 and psi (ψ) angles of the residues range from approximately 60 to 180 or from approximately –180 to –150.

10. The product of any one of claims 1 to 9, wherein the Aβ amino acid sequence has 62.5% or higher, 64% or higher, 67% or higher, 71% or higher, 75% or higher, 78% or higher, 82% or higher, 85% or higher, 89% or higher, 92% or higher, or 96% or higher identity to a portion (X-Y) of amino acid sequence $V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}E_{22}D_{23}V_{24}$ $G_{25}S_{26}N_{27}K_{28}G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}$ (SEQ ID NO: 4), X being selected from the group consisting of the numbers 12..18 and Y being selected from the group consisting of the numbers 33..39.

11. The product of claim 10, wherein at least one of the amino acid residues corresponding to V_{12}, H_{13}, H_{14}, Q_{15}, K_{16}, L_{17}, V_{18}, F_{19}, F_{20}, A_{21} E_{22} or D_{23} of and at least one of the amino acid residues corresponding to K_{28}, G_{29}, A_{30}, I_{31}, I_{32}, G_{33}, L_{34}, M_{35}, V_{36}, G_{37}, G_{38}, V_{39} of are covalently linked with each other.

12. The product of any one of claims 1 to 11 that is further characterized by one or more of the following features:
(a) the amino acid corresponding to V_{18} is selected from the group consisting of histidine, arginine, lysine, aspartic acid, glutamic acid, cysteine, asparagine, serine, threonine, glutamine, proline, phenylalanine, tyrosine, and tryptophan;
(b) the amino acid corresponding to F_{19} is selected from the group consisting of histidine, arginine, lysine, aspartic acid, glutamic acid, cysteine, asparagine, serine, threonine, glutamine, alanine, glycine, proline, valine, leucine, methionine, and isoleucine;
(c) the amino acid corresponding to F_{20} is selected from the group consisting of histidine, arginine, lysine, aspartic acid, glutamic acid, cysteine, asparagine, serine, threonine, glutamine, proline, alanine, glycine, valine, leucine, methionine, and isoleucine;
(d) the amino acid corresponding to A_{21} is selected from the group consisting of histidine, arginine, lysine, glycine, proline, aspartic acid, glutamic acid, phenylalanine, tyrosine, and tryptophan;
(e) the amino acid corresponding to E_{22} is selected from the group consisting of valine, leucine, methionine, isoleucine, phenylalanine, tyrosine, tryptophan, alanine, cysteine, asparagine, serine, threonine, proline, and glutamine;
(f) the amino acid corresponding to D_{23} is selected from the group consisting of histidine, arginine, lysine, valine, leucine, methionine, isoleucine, phenylalanine, tyrosine, tryptophan, proline, cysteine, asparagine, serine, threonine, and glutamine;
(g) the amino acid corresponding to V_{24} is selected from the group consisting of

histidine, arginine, lysine, aspartic acid, glutamic acid, cysteine, asparagine, serine, threonine, glutamine, proline, phenylalanine, tyrosine, and tryptophan;
(h) the amino acid corresponding to G_{25} is selected from the group consisting of histidine, arginine, lysine, valine, leucine, methionine, isoleucine, phenylalanine, tyrosine, tryptophan, proline, aspartic acid, and glutamic acid;
(i) the amino acid corresponding to S_{26} is selected from the group consisting of histidine, arginine, lysine, proline, aspartic acid, glutamic acid, phenylalanine, tyrosine, tryptophan;
(j) the amino acid corresponding to N_{27} is selected from the group consisting of histidine, arginine, lysine, valine, leucine, methionine, isoleucine, phenylalanine, tyrosine, tryptophan, proline, aspartic acid, and glutamic acid;
(k) the amino acid corresponding to K_{28} is selected from the group consisting of aspartic acid, glutamic acid, alanine, glycine, valine, leucine, methionine, isoleucine, phenylalanine, tyrosine, tryptophan, proline, cysteine, asparagine, serine, threonine, and glutamine;
(l) the amino acid corresponding to G_{29} is selected from the group consisting of histidine, arginine, lysine, aspartic acid, glutamic acid, cysteine, asparagine, serine, threonine, glutamine, valine, leucine, methionine, isoleucine, phenylalanine, tyrosine, tryptophan, and proline;
(m) the amino acid corresponding to A_{30} is selected from the group consisting of histidine, arginine, lysine, aspartic acid, glutamic acid, cysteine, asparagine, serine, threonine, glutamine, glycine, valine, leucine, methionine, isoleucine, phenylalanine, tyrosine, tryptophan, and proline;
(n) the amino acid corresponding to I_{31} is selected from the group consisting of histidine, arginine, lysine, aspartic acid, glutamic acid, cysteine, asparagine, serine, threonine, glutamine, proline, phenylalanine, tyrosine, and tryptophan;
(o) the amino acid corresponding to I_{32} is selected from the group consisting of histidine, arginine, lysine, aspartic acid, glutamic acid, cysteine, asparagine, serine, threonine, glutamine, proline, phenylalanine, tyrosine, and tryptophan;
(p) the amino acid corresponding to G_{33} is selected from the group consisting of histidine, arginine, lysine, aspartic acid, glutamic acid, cysteine, asparagine, serine, threonine, glutamine, valine, leucine, methionine, isoleucine, phenylalanine, tyrosine, tryptophan, and proline;
(q) the amino acid corresponding to F_{20} is selected from the group consisting of histidine, arginine, lysine, aspartic acid, glutamic acid, cysteine, asparagine, serine, threonine, glutamine, proline, alanine, glycine, valine, leucine, methionine,

and isoleucine; and the amino acid corresponding to E_{22} is selected from the group consisting of alanine, valine, proline, phenylalanine, methionine, isoleucine, tryptophan, cysteine, asparagine, serine, threonine, tyrosine, and leucine;

(r) the amino acid corresponding to F_{20} is glycine, and the amino acid corresponding to E_{22} is alanine;

(s) the amino acid corresponding to F_{20} is selected from the group consisting of histidine, arginine, lysine, aspartic acid, glutamic acid, cysteine, asparagine, serine, threonine, glutamine, proline, alanine, glycine, valine, leucine, methionine, and isoleucine; and the amino acid corresponding to I_{31} is selected from the group consisting of histidine, arginine, lysine, aspartic acid, glutamic acid, cysteine, asparagine, serine, threonine, glutamine, proline, phenylalanine, tyrosine, and tryptophan;

(t) the amino acid corresponding to A_{21} is selected from the group consisting of histidine, arginine, lysine, glycine, proline, aspartic acid, glutamic acid, phenylalanine, tyrosine, and tryptophan; and the amino acid corresponding to E_{22} is selected from the group consisting of alanine, valine, proline, phenylalanine, methionine, isoleucine, tryptophan, cysteine, asparagine, serine, threonine, tyrosine, and leucine;

(u) the amino acid corresponding to A_{21} is selected from the group consisting of histidine, arginine, lysine, glycine, proline, aspartic acid, glutamic acid, phenylalanine, tyrosine, and tryptophan; and the amino acid corresponding to D_{23} is selected from the group consisting of histidine, arginine, lysine, valine, leucine, methionine, isoleucine, phenylalanine, tyrosine, tryptophan, proline, cysteine, asparagine, serine, threonine, and glutamine;

(v) the amino acid corresponding to E_{22} is selected from the group consisting of valine, leucine, methionine, isoleucine, phenylalanine, tyrosine, tryptophan, alanine, cysteine, asparagine, serine, threonine, proline, and glutamine; and the amino acid corresponding to G_{25} is selected from the group consisting of histidine, arginine, lysine, valine, leucine, methionine, isoleucine, phenylalanine, tyrosine, tryptophan, proline, aspartic acid, and glutamic acid;

(w) the amino acid corresponding to E_{22} is selected from the group consisting of valine, leucine, methionine, isoleucine, phenylalanine, tyrosine, tryptophan, alanine, cysteine, asparagine, serine, threonine, proline, and glutamine; and the amino acid corresponding to S_{26} is selected from the group consisting of histidine, arginine, lysine, proline, aspartic acid, glutamic acid, phenylalanine, tyrosine, tryptophan.

13. The product of any one of claims 1 to 12, wherein the Aβ amino acid sequence comprises an amino acid sequence identical to a portion (X-Y) of an amino acid sequence selected from the group consisting of

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}A_{19}F_{20}A_{21}E_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 13),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}A_{20}A_{21}E_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 14),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}A_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 15),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}F_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 16),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}V_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 17),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}L_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 18),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}E_{22}K_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 19),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}E_{22}L_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 20),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}E_{22}D_{23}V_{24}V_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 21),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}E_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}G_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 22),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}G_{20}A_{21}A_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 23),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}A_{20}A_{21}E_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}A_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 24),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}C_{20}A_{21}E_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}C_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 25),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}Q_{21}L_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 26),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}L_{21}Q_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 27),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}Q_{21}E_{22}N_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 28),

$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}A_{22}D_{23}V_{24}A_{25}S_{26}N_{27}K_{28}$

$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 29) and
$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}A_{22}D_{23}V_{24}G_{25}A_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 30)
with X being selected from the group consisting of the numbers 1..18, 4..18, or 12..18, or is 18; and with Y being selected from the group consisting of the numbers 33..43, 33..42, 33..41, or 33..40; or a crosslinked derivative thereof, wherein at least 2 non-contiguous residues of the amino acid sequence are covalently linked with each other;
wherein (X-Y) is preferably selected from the group consisting of (1-42), (4-42), (12-42), or (18-42).

14. A composition comprising a product as defined in any one of claims 1 to 13.

15. A product as defined in any one of claims 1 to 13 for use in therapy.

16. Use of a product as defined in any one of claims 1 to 13 in the manufacture of a medicament for treating or preventing an amyloidosis in a subject in need thereof.

17. The use according to claim 16, wherein the product is for active immunization.

18. A product as defined in any one of claims 1 to 13 for use in diagnosing an amyloidosis.

19. Method of diagnosing an amyloidosis which comprises providing a sample obtained from the subject suspected of having the amyloidosis, contacting the sample with a product as defined in any one of claims 1 to 13 for a time and under conditions sufficient for the formation of a complex comprising the product and an antibody, the presence of the complex indicating the subject has the amyloidosis.

20. The product for use according to claim 18, or the use of claim 16 or 17, or the method of claim 19, wherein the amyloidosis is Alzheimer's disease or Down's syndrome.

21. A method of identifying an agent capable of binding to a product as defined in any one of claims 1 to 13, which method comprises the steps of: a) exposing one or more agents of interest to the product for a time and under conditions sufficient for the one or more agents to bind to the product; and b) identifying those agents which bind to the product;
wherein the agent is preferably selected from antibodies, non-antibody binding molecules, aptamers and small molecular weight compounds.