In one example, the present disclosure provides an immunogenic product which: i) comprises 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 one, two, three, four, five or six amino acids are substituted by different amino acids and said one, two, three, four, five or six amino acid substitutions are selected from the group consisting of:

Amino acid	substituted by
V18	H, R, K, D, E, C, N, S, T, Q, P, F, Y, W
F19	H, R, K, D, E, C, N, S, T, Q, A, G, P, V, L, M, I
F20	H, R, K, D, E, C, N, S, T, Q, P, A, G, V, L, M, I
A21	H, R, K, G, P, D, E, F, Y, W
E22	V, L, M, I, F, Y, W, A, C, N, S, T, P, Q
D23	H, R, K, V, L, M, I, F, Y, W, P, C, N, S, T, Q
V24	H, R, K, D, E, C, N, S, T, Q, P, F, Y, W
G25	H, R, K, V, L, M, I, F, Y, W, P, D, E
S26	H, R, K, P, D, E, F, Y, W
N27	H, R, K, V, L, M, I, F, Y, W, P, D, E
K28	D, E, A, G, V, L, M, I, F, Y, W, P, C, N, S, T, Q
G29	H, R, K, D, E, C, N, S, T, Q, V, L, M, I, F, Y, W, P
A30	H, R, K, D, E, C, N, S, T, Q, G, V, L, M, I, F, Y, W, P
I31	H, R, K, D, E, C, N, S, T, Q, P, F, Y, W
I32	H, R, K, D, E, C, N, S, T, Q, P, F, Y, W
G33	H, R, K, D, E, C, N, S, T, Q, V, L, M, I, F, Y, W, P

and ii) 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.

In one aspect, the present disclosure refers to an immunogenic product which comprises an N-terminally truncated form of an Aβ-mutein oligomer, which is obtainable by limited proteolytic digestion of a non-truncated Aβ mutein oligomer, which non-truncated Aβ mutein oligomer comprises a plurality of amino acid sequences, derived from the Aβ sequence according SEQ ID NO:1 by one or two amino acid substitutions: i) wherein said one or two amino acid substitutions are performed in any one of the amino acid sequence positions F20, A21, E22, D23, V24, G25 and S26, in particular F20, E22, D23, G25 and S26, and ii) is reactive with monoclonal antibody 4D10 obtainable from a hybridoma designated by American Type Culture Collection deposit number PTA-7405, wherein the monoclonal antibody preferably binds the product with a K_D of $1x10^{-6}$ M or greater affinity.

In another aspect, the present disclosure refers to a composition comprising a product as defined herein, wherein the composition is preferably a vaccine and optionally comprises a pharmaceutically acceptable excipient, for example an adjuvant such as Complete Freund's Adjuvant (CFA) or an adjuvant comprising an aluminium salt.

In another example, the present disclosure refers to a product as defined herein for use in therapy.

In yet another aspect, the present disclosure refers to use of a product as defined herein in the manufacture of a medicament for treating or preventing an amyloidosis, wherein the product is for active immunization.

In yet another aspect, the present disclosure refers to a product as defined herein for use in diagnosing an amyloidosis.

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

CLAIMS

1. An immunogenic product which comprises an N-terminally truncated form of an Aβ-mutein oligomer, which is obtainable by limited proteolytic digestion of a non-truncated Aβ mutein oligomer, which non-truncated Aβ mutein oligomer comprises a plurality of amino acid sequences, derived from the Aβ sequence according SEQ ID NO:1 by one or two amino acid substitutions:

   i) wherein said one or two amino acid substitutions are performed in any one of the amino acid sequence positions F20, A21, E22, D23, V24, G25 and S26, in particular F20, E22, D23, G25 and S26,

   and

   ii) is reactive with monoclonal antibody 4D10 obtainable from a hybridoma designated by American Type Culture Collection deposit number PTA-7405, wherein the monoclonal antibody preferably binds the product with a K_D of $1x10^{-6}$ M or greater affinity.

2. The product of claim 1, wherein the newly introduced amino acid residues are selected from the following:

Amino acid	substituted by
F20	H, R, K, D, E, C, N, S, T, Q, P, A, G, V, L, M, I
A21	H, R, K, G, P, D, E, F, Y, W, L, Q
E22	V, L, M, I, F, Y, W, A, C, N, S, T, P, Q, G, K, D
D23	H, R, K, V, L, M, I, F, Y, W, P, C, N, S, T, Q, A
V24	H, R, K, D, E, C, N, S, T, Q, P, F, Y, W, A
G25	H, R, K, V, L, M, I, F, Y, W, P, D, E, T, A
S26	H, R, K, P, D, E, F, Y, W, A. L

3. The product of claim 1 or 2, which comprises amino acid substitutions selected from:

   - the single mutant E22A, E22F, E22V, D23A, D23K, G25A, G25V, G25T, S26A and S26L, and
   - the double mutant is selected from (F20G,E22A), (E22A,G25A), (E22A,S26A), and (G25A,S26A).

4. The product of any one of the claims 1 to 3, capable of eliciting an polyclonal antiserum, 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.

5. The product of any one of claims 1 to 4, capable of eliciting an polyclonal antiserum, 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.

6. The product of any one of claims 1 to 5 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)

7. The product of any one of claims 1 to 6, which is an oligomer comprising 2 to 28 of said Aβ amino acid sequences.

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

9. The product of any one of the claims 1 to 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 mutated Aβ amino acid sequence is identical to a portion (X-Y) of a mutated amino acid sequence selected from the group consisting of
$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}A_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (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),
$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}G_{20}A_{21}A_{22}D_{23}V_{24}G_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (SEQ ID NO: 23),
$D_1A_2E_3F_4R_5H_6D_7S_8G_9Y_{10}E_{11}V_{12}H_{13}H_{14}Q_{15}K_{16}L_{17}V_{18}F_{19}F_{20}A_{21}A_{22}D_{23}V_{24}A_{25}S_{26}N_{27}K_{28}$
$G_{29}A_{30}I_{31}I_{32}G_{33}L_{34}M_{35}V_{36}G_{37}G_{38}V_{39}V_{40}I_{41}A_{42}T_{43}$ (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, 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.
11. The product of claim 10, wherein (X-Y) is preferably selected from the group consisting of (1-42), (4-42), (12-42), or (18-42).

12. A composition comprising a product as defined in any one of claims 1 to 11, wherein the composition is preferably a vaccine and optionally comprises a pharmaceutically acceptable excipient, for example an adjuvant such as Complete Freund's Adjuvant (CFA) or an adjuvant comprising an aluminium salt.

13. Use of a product as defined in any one of claims 1 to 11 in the manufacture of a medicament for treating or preventing an amyloidosis, wherein the product is for active immunization.

14. A product as defined in any one of claims 1 to 11 for use in diagnosing an amyloidosis.

15. The product of claim 14 or the use of claim 13, wherein the amyloidosis is Alzheimer’s disease or Down’s syndrome.