Supporting Information

Innovative IgG Biomarkers Based on Phage Display
Microbial Amyloid Mimotope for State and Stage Diagnosis in Alzheimer’s Disease

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## Supplemental Data

**Table S1**

| ENTRY   | Protein names                                                                 | Organism                                                                 |
|---------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| P49278  | Mite group 2 allergen Der p 2 (Allergen Der p II) (DPX) (allergen Der p 2)    | *Dermatophagoidespteronyssinus* (European house dust mite)               |
| P38713  | Oxysterol-binding protein homolog 3                                            | *Saccharomyces cerevisiae* (strain ATCC 204508 / S288c) (Baker's yeast)  |
| P43603  | LAS seventeen-binding protein 3 (LAS17-binding protein 3)                      | *Saccharomyces cerevisiae* (strain ATCC 204508 / S288c) (Baker's yeast)  |
| P0A7L8  | 50S ribosomal protein L27 (Large ribosomal subunit protein bL27)              | *Escherichia coli* (strain K12)                                          |
| Q9QYE9  | Pleckstrin homology domain-containing family B member 1                        | *Mus musculus* (Mouse)                                                   |
| O04567  | Probable inactive receptor kinase At1g27190                                   | *Arabidopsis thaliana* (Mouse-ear cress)                                 |
| P0A7N4  | 50S ribosomal protein L32 (Large ribosomal subunit protein bL32)              | *Escherichia coli* (strain K12)                                          |
| P0A7M2  | 50S ribosomal protein L28 (Large ribosomal subunit protein bL28)              | *Escherichia coli* (strain K12)                                          |
| Q9KWN0  | Actinohvin                                                                    | *Actinomycete sp.* (strain K97-0003)                                      |
| P25638  | TPR repeat-containing protein associated with Hsp90                           | *Saccharomyces cerevisiae* (strain ATCC 204508 / S288c) (Baker's yeast)  |
| O14368  | Heat shock protein 16 (16 kDa heat shock protein)                             | *Schizosaccharomyces pombe* (strain 972 / ATCC 24843) (Fission yeast)     |
| Q12334  | Protein SCM3 (Suppressor of chromosome missegregation protein 3)              | *Saccharomyces cerevisiae* (strain ATCC 204508 / S288c) (Baker's yeast)  |
| O13985  | Uncharacterized WD repeat-containing protein C26H5.03                         | *Schizosaccharomyces pombe* (strain 972 / ATCC 24843) (Fission yeast)     |
| P43672  | ABC transporter ATP-binding protein uup                                        | *Escherichia coli* (strain K12)                                          |
| Q12335  | Protoplast secreted protein 2                                                 | *Saccharomyces cerevisiae* (strain ATCC 204508 / S288c) (Baker's yeast)  |
| P19243  | 18.1 kDa class I heat shock protein (HSP 18.1)                                | *Pisum sativum* (Garden pea)                                             |
| P79085  | Major allergen Alt a 1 (allergen Alt a 1)                                     | *Alternaria alternata* (Alternaria rotfungus) (Torula alternata)          |
| P9WG5  | Single-stranded DNA-binding protein (SSB)                                     | *Mycobacterium tuberculosis* (strain ATCC 25618 / H37Rv)                  |
| P0AG4K  | RNA-binding protein YhbY                                                      | *Escherichia coli* (strain K12)                                          |
| P9WLZ7  | Uncharacterized protein Rv1364c                                                | *Mycobacterium tuberculosis* (strain ATCC 25618 / H37Rv)                  |
| P77667  | Protein SufA                                                                   | *Escherichia coli* (strain K12)                                          |
| P04122  | Lactin beta-1 and beta-2 chains                                               | *Lathyrus ochrus* (Yellow-flowered pea) *(Pisum ochrus)*                  |
| P0A1J5  | Flagellar hook-associated protein 1 (HAP1)                                    | *Salmonella typhimurium* (strain LT2 / SGSC1412 / ATCC 700720)            |
| P46973  | Protein HIT1                                                                  | *Saccharomyces cerevisiae* (strain ATCC 204508 / S288c) (Baker's yeast)   |
| P0A917  | Outer membrane protein X                                                       | *Escherichia coli* (strain K12)                                          |
| P18481  | Trypsin-resistant surface T6 protein (T6 antigen)                             | *Streptococcus pyogenes* serotype M6 (strain ATCC BAA-946 / MGAS10394)   |
| Q36030  | Uncharacterized WD repeat-containing protein C4F10.18                         | *Schizosaccharomyces pombe* (strain 972 / ATCC 24843) (Fission yeast)     |
| P9WFN1  | UPF0098 protein Rv2140c                                                        | *Mycobacterium tuberculosis* (strain ATCC 25618 / H37Rv)                  |
| Accession | Description | Organism / Strain Details |
|-----------|-------------|--------------------------|
| Q9WYC4    | Uncharacterized ABC transporter ATP-binding protein TM_0288 | *Thermotoga maritima* (strain ATCC 43589 / MSB8 / DSM 3109 / JCM 10099) |
| P27862    | IMPACT family member YigZ | *Escherichia coli* (strain K12) |
| P0A1J1    | Flagellar hook protein FlgE | *Salmonella typhimurium* (strain LT2 / SGSC1412 / ATCC 700720) |
| O59188    | Uncharacterized HTH-type transcriptional regulator PH1519 | *Pyrococcus horikoshii* (strain ATCC 700680 / DSM 12428 / JCM 9974 / NBRC 100139 / OT-3) |
| P26948    | F1 capsule antigen | *Yersinia pestis* |
| Q9FX77    | B3 domain-containing protein At1g16640 | *Arabidopsis thaliana* (Mouse-ear cress) |
| P0AAN1    | Hydrogenase-2 operon protein HybE | *Escherichia coli* (strain K12) |
| Q57399    | Uncharacterized ABC transporter ATP-binding protein HI_1470 | *Haemophilus influenzae* (strain ATCC 51907 / DSM 11121 / KW20 / Rd) |
| Q58105    | Uncharacterized NOP5 family protein MJ0694 | *Methanocaldococcus jannaschii* (strain ATCC 43067 / DSM 2661 / JAL-1 / JCM 10045 / NBRC 100440) (Methanococcus jannaschii) |
| P76049    | Uncharacterized protein YqaY | *Escherichia coli* (strain K12) |
| P12307    | Mannose/glucose-specific lectine alpha 2 chain | *Lathyrus ochrus* (Yellow-flowered pea) (Pisum ochrus) |
| Q60381    | Uncharacterized nitrogen regulatory PII-like protein MJ0059 | *Methanocaldococcus jannaschii* (strain ATCC 43067 / DSM 2661 / JAL-1 / JCM 10045 / NBRC 100440) (Methanococcus jannaschii) |
| P9WFK1    | UPF0336 protein Rv0635 | *Mycobacterium tuberculosis* (strain ATCC 25618 / H37Rv) |
| P0A8J4    | UPF0250 protein YbeD | *Escherichia coli* (strain K12) |
| P07166    | Protein virC2 | *Agrobacterium fabrum* (strain C58 / ATCC 33970) (*Agrobacterium tumefaciens* (strain C58)) |
| P04489    | Probable early E4 11 kDa protein | *Human adenovirus C* serotype 5 (HAdV-5) (*Human adenovirus 5*) |
| P39332    | RutC family protein YjgH | *Escherichia coli* (strain K12) |
| P0AD21    | Uncharacterized protein YejG | *Escherichia coli* (strain K12) |
| O31697    | Uncharacterized protein YkzF | *Bacillus subtilis* (strain 168) |
**S1 PDBeFold analysis results**

Results summary of PDBeFold alignments between Aβ Peptide (1-42) (PDB ID 1z0q) or amyloid fibril (PDB ID 2nao) and all the structures associated to F1 capsule antigen protein are shown below.

RESULT SUMMARY

|   | Q-score | F-score | Z-score | RMSD | Algn Max Aaps Seq-% | Miss Nres-Q Max Q Miss-T Max-T | Query Target |
|---|---------|---------|---------|------|---------------------|-------------------------------|--------------|
| 1 | 0.05781 | 1.066   | 4.104   | 2.359| 13                  | 1                            | 1            |
| 2 | 0.05684 | 1.004   | 4.096   | 1.469| 13                  | 1                            | 1            |
| 3 | 0.05685 | 1.004   | 4.093   | 1.581| 13                  | 1                            | 1            |
| 4 | 0.05615 | 0.3422  | 2.083   | 2.601| 19                  | 1                            | 2            |
| 5 | 0.05477 | 1.508   | 5.101   | 2.516| 19                  | 1                            | 2            |

The following imagines show 3D structure of beta amyloid fibril (PDB ID 2nao) with the F1 capsule antigen (5 different PDB ID number) with highlighted amino acid positions involved in the homology.
S2 RCSB Sequence & Structure Aβ42-F1 Alignment analysis results

Alignment of Amyloid fibrils (PDB ID 2nao) with F1 capsule antigen using “Sequence and Structure Alignment” (https://www.rcsb.org/pages/analyze_features#Sequence) - algorithm JFATCAT rigid.

### Structure Alignment Results

| Alignment Details | Query: (orange/dark grey) | Subject: (cyan/light grey) |
|-------------------|---------------------------|----------------------------|
| **P-value**       | 9.68e-01                  |                            |
| **Score**         | 24.68                     |                            |
| **RMSD**          | 3.58                      |                            |
| **%Id**           | 0.0%                      |                            |
| **Similarity**    | 33%                       | 11%                        |

**Beta-amyloid protein 42**
- PDB ID: 2NAO
- Chain ID: A
- Length: 42
- Similarity: 33%

**F1 capsule antigen**
- PDB ID: 1Z9S
- Chain ID: C
- Length: 128
- Similarity: 11%

Align 2NAO.A.pdb Length1: 42 with 1Z9S.C.pdb Length2: 128
- P-value: 9.68e-01
- Equ: 14
- RMSD: 3.58
- Score: 24.68
- Align-len: 14
- Gaps: 0 (0.00%)
Identity: 0.00%
Similarity: 7.14%

9:A
|| . |
GYEVHHQKLVFFAE
.............
IGSKGGKLAAGKYT
| | . |
126:C

| ... Structurally equivalent and identical residues
: ... Structurally equivalent and similar residues
. ... Structurally equivalent, but not similar residues.

To calculate the coordinates of chain 2 aligned on chain 1 apply the following transformation:

\[
X_1 = (0.871949)X_{orig} + (-0.484268)Y_{orig} + (-0.072045)Z_{orig} + (28.995000) \\
Y_1 = (0.450925)X_{orig} + (0.851654)Y_{orig} + (-0.267118)Z_{orig} + (-81.550000) \\
Z_1 = (0.190714)X_{orig} + (0.200426)Y_{orig} + (0.960967)Z_{orig} + (-78.219000)
\]

Structure Alignment Results

Alignment Details: Query: (orange/dark grey)  Subject: (cyan/light grey)

**Beta-amyloid protein 42**  **F1 capsule antigen**

| PDB ID | Length | Chain ID | Similarity |
|--------|--------|----------|------------|
| 2NAO   | 42     | A        | 33%        |
| 3DPB   | 128    | C        | 11%        |

P-value: 9.67e-01  Score: 24.73  RMSD: 3.57  %Id: 0.0%
Align 2NAO.A.pdb Length1: 42 with 3DPB.C.pdb Length2: 128
P-value: 9.67e-01
Equ: 14
RMSD: 3.57
Score: 24.73
Align-len: 14
Gaps: 0 (0.00%)  
Identity: 0.00%
Similarity: 7.14%

9:A
|| . |
|GYEVH|QKL|FFAE|
|.........|
|IGSKGG|KLAAGKYT|
| . |
126:C

| ... Structurally equivalent and identical residues
| : ... Structurally equivalent and similar residues
| . ... Structurally equivalent, but not similar residues.
To calculate the coordinates of chain 2 aligned on chain 1 apply the following transformation:

\[
X_1 = (0.875637)X_{\text{orig}} + (-0.479433)Y_{\text{orig}} + (-0.058342)Z_{\text{orig}} + (-15.339000)
\]
\[
Y_1 = (0.449539)X_{\text{orig}} + (0.853220)Y_{\text{orig}} + (-0.264442)Z_{\text{orig}} + (-4.946000)
\]
\[
Z_1 = (0.176561)X_{\text{orig}} + (0.205328)Y_{\text{orig}} + (0.962635)Z_{\text{orig}} + (-59.838000)
\]

**Structure Alignment Results**

*Alignment Details: Query:* (orange/dark grey)  
*Subject:* (cyan/light grey)

|                  | PDB ID: 2NAO | PDB ID: 3DSN |
|------------------|--------------|--------------|
| P-value          | 9.54e-01     |              |
| Score            | 23.15        |              |
| RMSD             | 3.27         |              |
| %Id              | 0.0%         |              |
| Length           | 42           | 132          |
| Similarity       | 43%          | 14%          |

Align 2NAO.A.pdb Length1: 42 with 3DSN.C.pdb Length2: 132

P-value: 9.54e-01
Equ: 18
RMSD: 3.27
Score: 23.15
Align-len: 18
Gaps: 0 (0.00%)
Identity: 0.00%
Similarity: 16.67%

| |    .    |    . |
| |    .    |    . |
VFFAEDVGSNKGAIIGLM
:.................
IGSKGGKLAAAGKYTDAVT
| |    .    |    . |
| |    .    |
126:C        140:C

| ... Structurally equivalent and identical residues
: ... Structurally equivalent and similar residues
. ... Structurally equivalent, but not similar residues.

To calculate the coordinates of chain 2 aligned on chain 1 apply the following transformation:

\[
\begin{align*}
X_1 &= (0.949283)X_{orig} + (0.254346)Y_{orig} + (-0.184854)Z_{orig} + (-31.919000) \\
Y_1 &= (0.055223)X_{orig} + (0.443907)Y_{orig} + (0.894370)Z_{orig} + (-25.467000) \\
Z_1 &= (0.309537)X_{orig} + (-0.859218)Y_{orig} + (0.407347)Z_{orig} + (-49.574000)
\end{align*}
\]

Structure Alignment Results

Alignment Details:
Query: (orange/dark grey)  Subject: (cyan/light grey)

Beta-amyloid protein 42  F1 capsule antigen

P-value: 9.60e-01  PDB ID: 2NAO  PDB ID: 3DOS
Score: 23.19  Chain ID: A  Chain ID: C
RMSD: 4.29  Length: 42  Length: 135
%Id: 0.0%  Similarity: 52%  Similarity: 16%
Align 2NAO.A.pdb Length1: 42 with 3DOS.C.pdb Length2: 135
P-value: 9.60e-01
Equ: 22
RMSD: 4.29
Score: 23.19
Align-len: 30
Gaps: 8 (26.67%)

Identity: 0.00%
Similarity: 10.00%

1:A                        20:A
|           .    |    .    |    .    |
DAEF--------RHDSGYEVHHQKLVAE
..:...............:
VGDDVVLATGSDFFVRSIGKGGKLAAGK
| |    .    |    .    |
108:C      120:C

| ... Structurally equivalent and identical residues
: ... Structurally equivalent and similar residues
... Structurally equivalent, but not similar residues.

To calculate the coordinates of chain 2 aligned on chain 1 apply the following transformation:

\[
X_1 = (-0.707390)X_{orig} + (0.009306)Y_{orig} + (0.706762)Z_{orig} + (13.601000)
\]

\[
Y_1 = (-0.637529)X_{orig} + (-0.440174)Y_{orig} + (-0.632300)Z_{orig} + (73.362000)
\]

\[
Z_1 = (0.305214)X_{orig} + (-0.897864)Y_{orig} + (0.317307)Z_{orig} + (-33.218000)
\]

**Structure Alignment Results**

**Alignment Details:**

**Query:** (orange/dark grey)  
**Subject:** (cyan/light grey)  

| **Beta-amyloid protein 42** | **F1 capsule antigen** |
|-----------------------------|------------------------|
| **P-value:** 9.80e-01 | **Score:** 24.91 |
| **RMSD:** 6.32 | **PDB ID:** 2NAO |
| **%Id:** 10.5% | **PDB ID:** 1P5U |
| **Chain ID:** A | **Chain ID:** C |
| **Length:** 42 | **Length:** 130 |
| **Similarity:** 45% | **Similarity:** 15% |

Align 2NAO.A.pdb Length1: 42 with 1P5U.C.pdb Length2: 130

**P-value:** 9.80e-01

**Equ:** 19
RMSD: 6.32  
Score: 24.91  
Align-len: 19  
Gaps: 0 (0.00%)  

Identity: 10.53%  
Similarity: 15.79%  

6:A           20:A  
|   |    .    |  
HDSGYEVHHQKLVFFAEDV  
..|.............|  
VRSIGSKGGKLAAGKYTDA  
|      |    .    |  
123:C            140:C  
|   |    .    |  

| ... Structurally equivalent and identical residues  
: ... Structurally equivalent and similar residues  
. ... Structurally equivalent, but not similar residues.  

To calculate the coordinates of chain 2 aligned on chain 1 apply the following transformation:  

\[
x_1 = (-0.574353)x_{\text{orig}} + (-0.682623)y_{\text{orig}} + (0.451824)z_{\text{orig}} + (29.898000) \\
y_1 = (0.631490)x_{\text{orig}} + (-0.720681)y_{\text{orig}} + (-0.286075)z_{\text{orig}} + (40.508000) \\
z_1 = (0.520902)x_{\text{orig}} + (0.121014)y_{\text{orig}} + (0.844995)z_{\text{orig}} + (-60.018000) 
\]
S3 Bioinformatics analysis of 12III1 phage clone

S3.1 Sequence alignment 12III1 peptide-Aβ42-Caf1 by Clustal X2.1

| Alignment with highest score | Alignment score: 656.675 P-value: 0.00244419 |
|------------------------------|-----------------------------------------------|
| peptide: RWPPHF EWHD       | path: K16A L17A Q15A H14A H13A Y10A S8A H6A F4A E3A D1A |
| Alignment: RWPPHF EWHD     | KLQHHYS-HFED                                    |

S3.2 PepSurf and Mamitope epitope mapping of 12III1 onto Aβ42 and F1 capsular antigen

PepSurf analysis results of 12III1 exposed peptide with Aβ42 (PDB ID 2nao chain A, library type: random _AA):

Running Parameters:
Epitope Mapping Algorithm: MAPITOPE
PDB ID: 2nao
Chain identifier: A
Library Type: RANDOM_AA
Stop Codon Modification: TAG = GLN
The Distance Threshold value is: 9.0
The Statistical Threshold value is: 3.0
The Maximum gap "fill-in" is: 3

Best cluster 20-FAEDVG-25
Residues number: 4

PHE20:A
ALA21:A
GLU22:A
ASP23:A
VAL24:A
GLY25:A
Mamitope and PepSurf combined analysis results of 12III1 (exposed peptide with flanking pVIII sequence with Aβ42 (PDB ID 2nao chain A, library type : random _AA):

Cluster rank: 1 3-EFRH-6
Residues number: 4
intersects cluster number 1 of PepSurf with cluster number 1 of Mamitope

ARG5:A
GLU3:A
PHE4:A
HIS6:A
PepSurf analysis results of 12III1 exposed peptide with F1 capsular antigen (PDB ID chain C, library type: random _AA):

F1 (1p5u.C)

Cluster rank: 2
Residues number: 3

GLY49:C
ASP120:C
PHE122:C

Mamitope analysis results of 12III1 (exposed peptide with flanking pVIII sequence) with F1 (PDB ID 1p5u chain C, library type: random _AA):

Best cluster
Residues number: 4

PHE74:C
HIS82:C
GLN83:C
PHE84:C
ASP140:C

F1 (3dsn.C)

Cluster rank: 3
Residues number: 3

GLY49:C
ASP120:C
PHE122:C
Mamitope analysis results of 12III1 (exposed peptide with flanking pVIII sequence) with F1 (PDB ID 3dsn chain C, library type : random _AA):

Best Cluster
Residues number: 7

ASP92:C
SER93:C
ARG94:C
ASP95:C  92-DSRDFD-97  109-GDD-111
PHE96:C
ASP97:C
GLY109:C
ASP110:C
ASP111:C

Cluster rank: 2
Residues number: 4

PHE74:C
HIS82:C
GLN83:C  74-F  82-HQF-84  D-140
PHE84:C
ASP140:C

F1 (3dpb.C)

Cluster rank: 2
Residues number: 3

GLY49:C
ASP120:C
PHE122:C

Mamitope analysis results of 12III1 (exposed peptide with flanking pVIII sequence) with F1 (PDB ID 3dpbchain C, library type : random _AA):

Best cluster
Residues number: 4
Mamitope analysis results of 12III1 (exposed peptide with flanking pVIII sequence) with F1 (PDB ID 1z9 chain C, library type: random_AA):

Best cluster
Residues number: 4

PHE74:C
HIS82:C
GLN83:C
PHE84:C
ASP140:C
74-F   82-HQF-84   D-140

F1(1z9.C)
F1(3dos.C)

Cluster rank: 3
Residues number: 3

GLY49:C
ASP120:C
PHE122:C

Mamitope analysis results of 12III1 (exposed peptide with flanking pVIII sequence) with F1 (PDB ID 3dos chain C, library type: random _AA):

Best cluster
Residues number: 7

ASP92:C
SER93:C
ARG94:C
ASP95:C 92-DSRDFD-97 109-GDD-111
PHE96:C
ASP97:C
GLY109:C
ASP110:C
ASP111:C

Cluster rank: 2
Residues number: 4

PHE74:C
HIS82:C
GLN83:C 74-F 82-HQF-84 D-140
PHE84:C
ASP140:C
S3.3 Molecular docking prediction of 12IIII phage clone displayed peptide with Aβ fibrils

The following images show 3D structural modeled interaction between engineered 12III1-pVIII protein in wireframe style with displayed amino acid side positions and beta amyloid fibril in electrostatic surface style (A) and in backbone style coupled to energy map (B). Colors legend of electrostatic and steric clouds: i) Steric favorable non-polar amino acids are included in green regions; ii) Electrostatic favorable, red regions correspond to a nearby negative electro-static charge of amino acids, blue regions correspond to a nearby positive charge of amino acids; iii) Hydrogen donor favorable are yellow; iv) Hydrogen acceptor favorable are light blue.

The amino acids involved in the interaction are listed in the following tables.
**Table S2.** 12III1-pVIII amino acid residues involved in the interaction with beta amyloid fibril chains.

| Beta amyloid fibril chains | Amino acids of 12III1-pVIII involved in the interaction |
|----------------------------|-------------------------------------------------------|
|                            | Steric interaction | Electrostatic interaction |
| Chain A                    | none               | none                      |
| Chain B                    | Phe (11)*          | none                      |
| Chain C                    | Trp (7)*, Pro(8)*, Pro (9), His (10)*, Phe (11)* | none               |
| Chain D                    | Tyr (35), Ile (36), Tyr (38) | Glu (34)               |
| Chain E                    | Phe (11)*, Ala (32) | none                      |
| Chain F                    | Pro (9)*, His (10)*, Phe (11)*, Glu (12)*, Trp (13)*, Ala (24), Phe (25), Leu (28), Gln (29) | His (10)*, Glu (12)* |

*amino acid belonging to the engineered peptide displayed in 12III1-pVIII  
none = no interaction

**Table S3.** Amino acid residues of beta amyloid fibril chains involved in the interaction with 12III1-pVIII.

| Amino acids of beta amyloid fibril chains involved in the interaction |
|---------------------------------------------------------------|
|                  | Chain A | Chain B | Chain C | Chain D | Chain E | Chain F |
| H-bound          | none    | none    | Gly (37), Gly (38) | none    | none    | His (14), Gln (15) |
| Stearic interaction | none | Met (35), Val (36), Gly (37) | Met (35), Gly (37), Gly (38), Val (39), Val (40) | Phe (4), Glu (11), Val (12), His (13), His (14) | Phe (4), His (14) |
| Electrostatic interaction | none | none | none | His (14) | none | none |

none = no interaction