A Computational Method to Predict Disease-Specific Epitopes in Aβ, and Its Application to Oligomer-Selective Antibodies for Alzheimer’s Immunotherapy

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ABSTRACT

Oligomer-specific epitope predictions are presented for Aβ. Cyclic peptides of these epitope predictions are then computationally and experimentally generated, which constitute antigenic targets. Clustering analysis, curvature, exposure to solvent, solubility, dihedral angle distribution, and Ramachandran angle distributions are all used to characterize the conformational properties of predicted epitopes, which quantify the distinction between the antigenic profiles when presented in the context of the oligomer from that in either the monomer or fibril. A set of five oligomer-specific epitopes are proposed for Aβ. The computational epitope discovery approach has produced multiple Aβ oligomer-specific antibodies (see also poster #12185, session P4-14).

INTRODUCTION

Treatment for Alzheimer’s disease (AD) has faced the difficult challenge of effectively targeting and clearing toxic and/or presynapatic species of protein, which together lead to pathology and neurodegeneration. Current evidence points to a variety of different protein structures involved in cytotoxic beta-amyloid that is induced by modified Aβ oligomers [1]. A method for identifying antigens to Aβ that are conformationally-selective to the toxic oligomer, and which also have reduced toxicity to either Aβ monomer or fibril, is to identify a highly desired goal that holds significant promise for AD therapy [2-4].

METHODS AND MATERIALS

We employed computational simulations, using molecular dynamics with a standard force-field. An experimentally-validated structural model of a prion-fibrillar aggregate is globally stable away from its native conformation to be partially unfolded, using molecular dynamics with collective coordinates to yield it will be one of the least unphysical, can be used to define an ensemble of starting structures, which gives hints of the peptide’s preferred conformation.

RESULTS

Table 1. Antibody predictions

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Monomer</th>
<th>Fibril</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1A1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>M2A1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>M3A1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>M4A1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>M5A1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
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Figure 1. Schematic of Aβ monomer (left), oligomer (center), and fibril (right)

Figure 2. Computational method for epitope discovery

Note: The oligomer specific epitopes need to be guest to good predictions. For example, antibodies are selected to the oligomer model. Methods use a "collective coordinate" to globally bias the protein to unfold, i.e., to unfold the molecular model.

Figure 3. Contiguous regions in SCID that show an increased in solvent accessible surface area.

• We also tend to see that epitopes emerge persistently across different prion-fibrillized species, or "islands" of Alzheimer’s.
• This implies that Aβs raised to these epitopes may be generally useful across AD cases.

Figure 4. Epitope in SCID

As least 5 of these predicted regions should be conformationally stabilized in monomer, fibril, and/or cyclic peptides. For one conformation only, this gives a set of points in 3D space. For all 5 configurations, in the equilibrium ensembles of free, cyclic, and PDB.

Figure 5. Predicted epitope panel across several fibril morphologies.

Figure 6. Linear and cyclic peptide sequence. (58-63 in SODC with linear amino acids)

Oligomer-specific Epitopes

• Validate that the cyclic peptide equilibrium ensemble is distinct from the fibril or linear peptide ensemble, so that Aβs raised to it will be conformationally-selective.

Figure 7. Antigenic cluster analysis

• All the conformations of the linear peptide ensemble, and structurally align them to each other, i.e. by RDSS (least squares fit).
• The conformations are not completely disordered from each other, meaning they cluster around "cyclic structures", which give hints of the peptide’s preferred conformation.
• Find the centroid structure of the target clusters for linear, fibril, and cyclic peptide ensemble, and RDSS (least squares fit).

CONCLUSIONS

• We have predicted 5 conformational epitopes in Aβ.
• Computational analysis of these epitopes shows that these epitopes are conformationally distinct from the same sequence in either Aβ monomer or fibril.
• We have now raised over 500 antibody clones designed to be oligomer-selective against these 5 epitopes in both Aβ monomer and fibril.

REFERENCES


Figure 8. SPR results for the binding of mAbs to linear peptide of a predicted Aβ epitope sequence (above left), cyclic peptide (above center) and in vitro Aβ oligomer (above right).