# Design of antibody fragments specific for amyloidogenic aggregates

https://neurodegenerationresearch.eu/survey/design-of-antibody-fragments-specific-for-amyloidogenic-aggregates/

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**Country**

USA

**Title of project or programme**

Design of antibody fragments specific for amyloidogenic aggregates

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NIH (NIA)

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€ 1,218,924.77

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01/04/2014

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1

**The project/programme is most relevant to:**

Alzheimer's disease & other dementias

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Immunoglobulin Fragments, Amyloid beta-Protein, Complementarity Determining Regions, Amyloid, Linear Sequence Epitopes

**Research Abstract**
DESCRIPTION (provided by applicant): A grand challenge in biomolecular research is to rationally design antibodies that bind to target antigens with high affinity and specificity. The

goal of this proposal is to elucidate principles for designing the complementarity-determining regions (CDRs) of antibody fragments to mediate recognition of aggregated proteins with conformational and sequence specificity. Our proposal is based on our recent discovery that single-domain antibodies can be designed to recognize A?42 oligomers and fibrils using the same molecular interactions mediating A? aggregation associated with Alzheimer's disease (Perchiacca et al., PNAS, 2012). We find that hydrophobic A? peptides can be grafted into a single CDR loop, and the resulting Grafted AMyloid-Motif AntiBODIES (gammabodies) bind to A? oligomers and fibrils with nanomolar affinity. Based on these discoveries, we posit that additional A? peptides capable of mediating gammabody binding can be predicted based on their relative amyloidogenicity. We also hypothesize that the binding affinity of gammabodies will be maximal at small to intermediate CDR lengths that are sufficiently long to display A? self-recognition peptides but not long enough to disfavor binding due to increased entropy. In addition, we posit that our design approach is not limited to A? and can be extended to other amyloidogenic polypeptides, including IAPP (type 2 diabetes) and ?-synuclein (Parkinson's disease). Finally, we hypothesize that even higher-affinity gammabodies can be designed by grafting multiple amyloidogenic peptides into anti-parallel CDRs that are oriented in the same manner as the corresponding peptides at the growing (templating) ends of fibrils. Therefore, in Aim 1, we propose to determine how the length and sequence of CDR3 impacts the binding affinity and specificity for two A? gammabodies (A?15-24 and A?33-42). Then, in Aim 2, we propose to evaluate our predictions of additional A? peptides that mediate gammabody binding to A? aggregates when grafted into CDR3. Next, in Aim 3, we propose to extend the analysis performed in Aims 1 and 2 to evaluate our predictions of peptide segments from two other amyloid-forming polypeptides (?-synuclein and IAPP) that mediate gammabody binding to their corresponding aggregated conformers when grafted into CDR3. Finally, in Aim 4, we propose to evaluate whether the affinity of the A? and IAPP gammabodies developed in Aims 1-3 can be increased by grafting two different amyloidogenic peptides into anti-parallel CDRs to match the orientation of the corresponding peptides at the growing ends of fibrils. A significant outcome of our studies will be the elucidation of how self-complementary, amyloidogenic peptides can be used to mediate antibody-antigen recognition. We expect that our findings will lead to rules for designing of similar single- and multidomain antibodies with specificity for diverse amyloidogenic proteins, including those linked to human aggregation disorders such as Huntington's and prion diseases.

**Lay Summary**

PUBLIC HEALTH RELEVANCE: Antibodies that recognize toxic protein particles could be used to prevent or treat diseases such as Alzheimer's or prion diseases. We aim to understand how to rationally design antibodies that specifically recognize toxic protein particles.

**Further information available at:**

**Types:**

Investments > €500k

**Member States:**

United States of America

**Diseases:**

Alzheimer's disease & other dementias

**Years:**

2016

**Database Categories:**
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