

## Direct Correlation of Cell Toxicity to Conformational Ensembles of Genetic A $\beta$ Variants - DTU Orbit (08/11/2017)

### Direct Correlation of Cell Toxicity to Conformational Ensembles of Genetic A $\beta$ Variants

We report a systematic analysis of conformational ensembles generated from multiseed molecular dynamics simulations of all 15 known genetic variants of A $\beta$ <sub>42</sub>. We show that experimentally determined variant toxicities are largely explained by random coil content of the amyloid ensembles (correlation with smaller EC<sub>50</sub> values;  $R^2 = 0.54$ ,  $p = 0.01$ ), and to some extent the helix character (more helix-character is less toxic,  $R^2 = 0.32$ ,  $p = 0.07$ ) and hydrophobic surface ( $R^2 = 0.37$ ,  $p = 0.04$ ). Our findings suggest that qualitative structural features of the amyloids, rather than the quantitative levels, are fundamentally related to neurodegeneration. The data provide molecular explanations for the high toxicity of E22 variants and for the protective features of the recently characterized A2T variant. The identified conformational features, for example, the local helix-coil-strand transitions of the C-terminals of the peptides, are of likely interest in the direct targeting of amyloids by rational drug design.

### General information

State: Published

Organisations: Physical and Biophysical Chemistry, Department of Chemistry

Authors: Somavarapu, A. K. (Intern), Kepp, K. P. (Intern)

Number of pages: 7

Pages: 1990-1996

Publication date: 2015

Main Research Area: Technical/natural sciences

### Publication information

Journal: ACS Chemical Neuroscience

Volume: 6

Issue number: 12

ISSN (Print): 1948-7193

Ratings:

BFI (2017): BFI-level 1

Web of Science (2017): Indexed Yes

BFI (2016): BFI-level 1

Scopus rating (2016): CiteScore 3.72 SJR 1.504 SNIP 0.924

BFI (2015): BFI-level 1

Scopus rating (2015): SJR 1.808 SNIP 1.115 CiteScore 4.21

Web of Science (2015): Indexed yes

BFI (2014): BFI-level 1

Scopus rating (2014): SJR 1.681 SNIP 1 CiteScore 3.87

BFI (2013): BFI-level 1

Scopus rating (2013): SJR 1.634 SNIP 1.106 CiteScore 3.58

Scopus rating (2012): SJR 1.399 SNIP 0.98 CiteScore 3.15

Scopus rating (2011): SJR 1.152 SNIP 0.907 CiteScore 2.73

Original language: English

Alzheimer's disease, Amyloid beta, Coil, Structural ensembles, Toxicity

DOIs:

10.1021/acscemneuro.5b00238

Source: FindIt

Source-ID: 2286775200

Publication: Research - peer-review › Journal article – Annual report year: 2015