## Study Reveals Potential Target for Slowing Alzheimer's Disease

*By Nancy Parrish, Staff Writer*

One of the markers of Alzheimer's disease (AD) is accumulation of Aβ1-40 peptides that aggregate into fibrils in the brain. The multi-pathway of the assembly process is still controversial, according to Yifat Miller, Ph.D., Center for Cancer Research Nanobiology Program (CCRNP). However, she said, determining the full molecular structures of Aβ1-40 may lead to therapeutics that target Aβ1-40 fibril formation at an early stage of the disease.

Recently, solid-state nuclear magnetic resonance (ssNMR) measurements revealed a unique triangular structure of the Aβ1-40 fibril. This finding led to two significant discoveries by Miller and colleagues in CCRNP. Using the ssNMR data to create all-atom molecular dynamics simulations in explicit solvent, they found that (1) the unique Aβ1-40 triangular structure has a cavity along the fibril axis, and (2) the N-termini play a crucial role in the stability of the fibril by interacting with the U-turn or the C-termini domains. Miller and colleagues further illustrated polymorphic triangular structures due to the difference in the U-turn shape, as they had demonstrated for Aβ17–42 (Miller et al., *Biophys J* 97[4]:1168–1177, 2009).

"Our study illuminates the molecular features of the unique triangular Aβ1-40 fibrils and provides information that may encourage future work on an attractive target to disrupt this unique triangular fibrillar," Miller said. "Small molecules that can disrupt the interactions between the N-termini and the U-turn domains may be developed to interrupt the growth of the fibrils, and consequently, the fibrils' surface will be more accessible to drugs."

Miller, a visiting postdoctoral fellow in the Computational Structural Biology Group of CCRNP, received her doctorate in computational physical chemistry from the Hebrew University of Jerusalem in 2007. She joined CCRNP in 2008, and her work has focused on "the structural variability of potential conformations of Alzheimer's Aβ under various conditions and the self-assembly mechanism leading to ordered fibril formation," she said.

Yifat Miller, Ph.D., Center for Cancer Cancer Research Nanobiology Program, NCI-Frederick

Miller plans to return to Israel in September to become a senior lecturer in the chemistry department of the Ben-Gurion University of the Negev. ■

## The Unique Alzheimer's β-Amyloid Triangular Fibril Has a Cavity along the Fibril Axis under Physiological Conditions

Yifat Miller, Buyong Ma, and Ruth Nussinov
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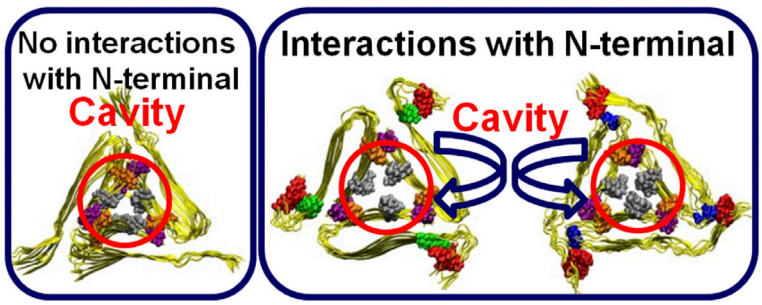
Elucidating the structure of Aβ1–40 fibrils is of interest in Alzheimer's disease research because it is required for designing therapeutics that target Aβ1-40 fibril formation at an early stage of the disease. M35 is a crucial residue because of its potential oxidation and its strong interactions across β-strands and across β-sheets in Aβ fibrils. Experimentally, data for the threefold symmetry structure of the Aβ9–40 fibril suggest formation of tight hydrophobic core through M35 interactions across the fibril axis and strong I31–V39 interactions between different cross-β units. Herein, on the basis of experimental data, we probe conformers with threefold symmetry of the full-length Aβ1–40. Our all-atom molecular dynamics simulations in explicit solvent of conformers based on the ssNMR data reproduced experimental observations of M35–M35 and I31-V39 distances. We revealed that the unique Aβ1–40 triangular structure has a large cavity along the fibril axis and that the N-termini can assist in the stabilization of the fibril by interacting with the U-turn domains or with the C-termini domains. Our findings, together with the recent cyroEM characterization of the hollow core in Aβ1–42 fibrils (Miller et al. PNAS, 107:14128-14133, 2010), point to the relevance of a cavity in Aβ1–40/1–42 oligomers, which should be considered when targeting oligomer toxicity. ■




Polymorphism in triangular Aβ1-40 fibril: M35 in the hydrophobic cavity and I31–V39 interactions between cross-β units. Left: The N-termini are flexible. Middle: F4–V12 interactions. Right: F4–G25 interactions.