Research & Design Phase Model Summary

St. Dominic Middle School SMART Team

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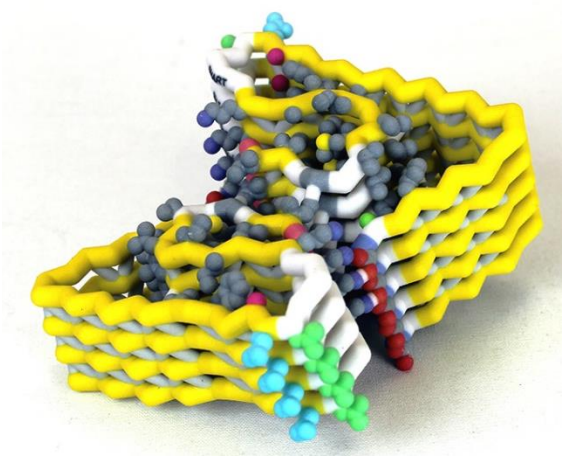
Amyloid Beta and Alzheimer Disease



PDB: 5oqv

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Format: Alpha carbon backbone

RP: Zcorp with plaster

Description:
According to the U.S. Centers for Disease Control, Alzheimer's disease (AD) is the sixth leading cause of American deaths, affecting 5.5 million people and striking one in ten people over age 65. The dementia characteristic of AD is associated with the over-production and aggregation of amyloid beta (Aβ), a 40-42 amino acid peptide clipped from the trans-membrane portion of the amyloid precursor protein (APP); a large membrane protein important for neural growth and repair. In a healthy brain, Aβ is recycled; while in AD, Aβ strands form neurotoxic aggregates outside neurons called senile plaques. A major component of plaques, Aβ fibrils are homodimers consisting of two protofilaments. The protofilaments are stacked, parallel, LS-shaped amyloid-β peptides connected to each other in a cross-beta sheet structure. Interactions of three groups of hydrophobic sidechains on neighboring Aβ strands stabilize each protofilament and maintain the N-terminus L-shape and C-terminus C shape. While over 50 mutations in the APP protein are associated with early onset AD, our model of the Aβ fibril highlights the six located on Aβ: Glu22Gln, Ala21Gly, Glu22Lys, Leu34Val, Ala2Thr, Glu22Gly, Asp23Asn, and Ala2Val. The St. Dominic Middle School SMART (Students Modeling A Research Topic) Team designed a model of an Aβ fibril using 3D printing technology to investigate structure-function relationships. Current research investigates peptides that can prevent the aggregation of Aβ. Research on Aβ could lead to the discovery treatments that prevent Aβ plaques from forming and killing neurons, which could greatly impact millions of lives.

Specific Model Information:

Amino acid sidechains involved in stabilizing the L-S structure:

- Ala2 – Chartreuse
- Val36 –cpk
- Phe4 –cpk
- Leu34 –cpk
- Leu17 –cpk
- Ile31—cpk
- Phe19—cpk
- Ala30 –cpk
- Ile32—cpk
- Met35—cpk
- Val40—cpk

Amino acid sidechains that are mutated in early onset Alzheimer's disease:

- Ala2 – Chartreuse
  Ala2Val (pathogenic mutation)
  Ala2Thr (Icelandic mutation thought to be protective against AD)
- Ala21—Magenta
  Ala21Gly (Flemish mutation)
- Glu22—Cyan
  Glu22Gly (Arctic mutation)
  Glu22Gln (Dutch mutation)
  Glu22Lys (Italian Mutation)
- Asp23—Springgreen
  Asp23Asn (Iowa Mutation)

Highlighted protein structures:

- Each of the 9 Amyloid-β subunits folds into an LS-shape.
  The N-terminus is L-shaped and the C-terminus is S-shaped.
- Each Amyloid-β subunit forms one strand of the cross beta sheets.
- Beta sheets: yellow
- Amino terminus of each amyloid-β strand: dodger blue
- Carboxy terminus of each amyloid-β strand: palevioletred
- H-bonds in beta sheets: lightgray

Supporting Features:

- Struts: white
- Hydrogen bonds: lighgray
- N-terminus of amyloid beta peptide: dodgerblue
- C-terminus of each amyloid beta peptide: palevioletred