Chemists show that nature could have used different protein building blocks

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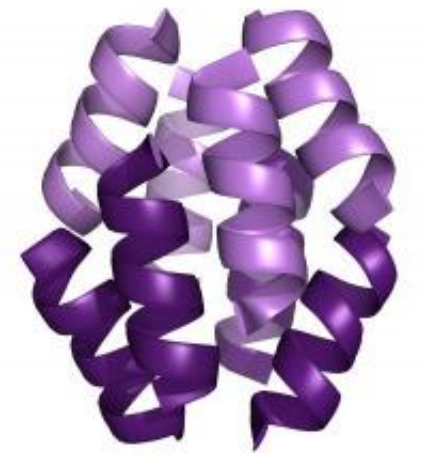
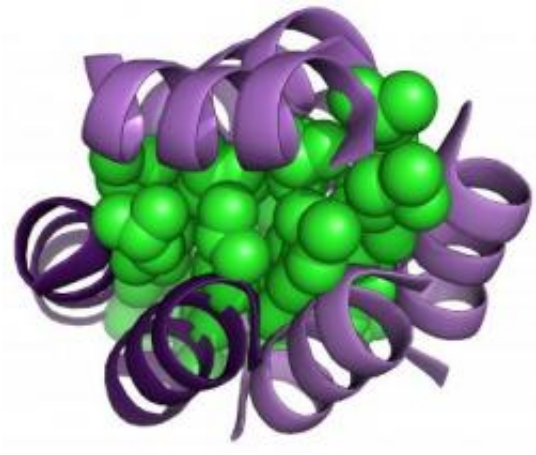


Beta-Bundles: Ribbon diagram representations of a beta-peptide bundle illustrating packing between helices and within the hydrophobic (green) core. Credit: Schepartz/Yale

Chemists at Yale have done what Mother Nature chose not to — make a protein-like molecule out of non-natural building blocks, according to a report featured early online in the Journal of the American Chemical Society.

Nature uses alpha-amino acid building blocks to assemble the proteins that make life as we know it possible. Chemists at Yale now report evidence that nature could have used a different building block – beta-amino acids — and show that peptides assembled from beta-amino acids

can fold into structures much like natural protein.



Beta-Bundles: Ribbon diagram representations of a beta-peptide bundle illustrating packing between helices and within the hydrophobic (green) core. Credit: Schepartz/Yale

"The x-ray structure featured in the report shows a molecule that shares many of the structural characteristics of natural proteins," said principal author Alanna Schepartz, the Milton Harris '29 Ph.D. Professor of Chemistry at Yale and a Howard Hughes Medical Institute Professor. "Related studies show that the physical properties of the molecule are also remarkably similar to natural proteins. In other words, the beta-peptide assembly looks and acts a lot like a real protein."

The ability to mimic natural proteins makes beta-peptides powerful new tools for basic research and drug discovery. Like a taped recording, their greatest value may be in their difference from a live performance.

"Since beta-peptides are not processed in the cell like natural peptides or proteins, it may be possible in the future to design beta-peptides that

perform better or in more locations than current protein drugs," said Schepartz. "They also may have unique properties as biomaterials."

Natural proteins are composed of linear chains of alpha-amino acids. Beta-peptides are composed of beta-amino acids, which have an extra carbon in their backbone. Like alpha-amino acids, beta-amino acids are generated under simulated pre-biotic conditions, are isolated from meteorites, and are byproducts of metabolism, but they are not genetically encoded like natural proteins, nor are they built into chains by cells.

Since the early 1990's, scientists have been able to assemble beta-peptides into isolated helices. Until now, however, creating a structure that mimics the larger size and complex folded architecture of a natural protein had been an elusive goal. Schepartz's team solved the dilemma by designing a molecule that could form a bundle using characteristics found in natural proteins — a greasy interior that repels water and a water-friendly exterior. This paper, which provides the first high-resolution picture of such a structure, shows a bundle of eight beta-peptides.

"The structure we see is intriguing, as it suggests that natural proteins could have been composed of beta-amino acids, but were not chosen to do so," said Schepartz.

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