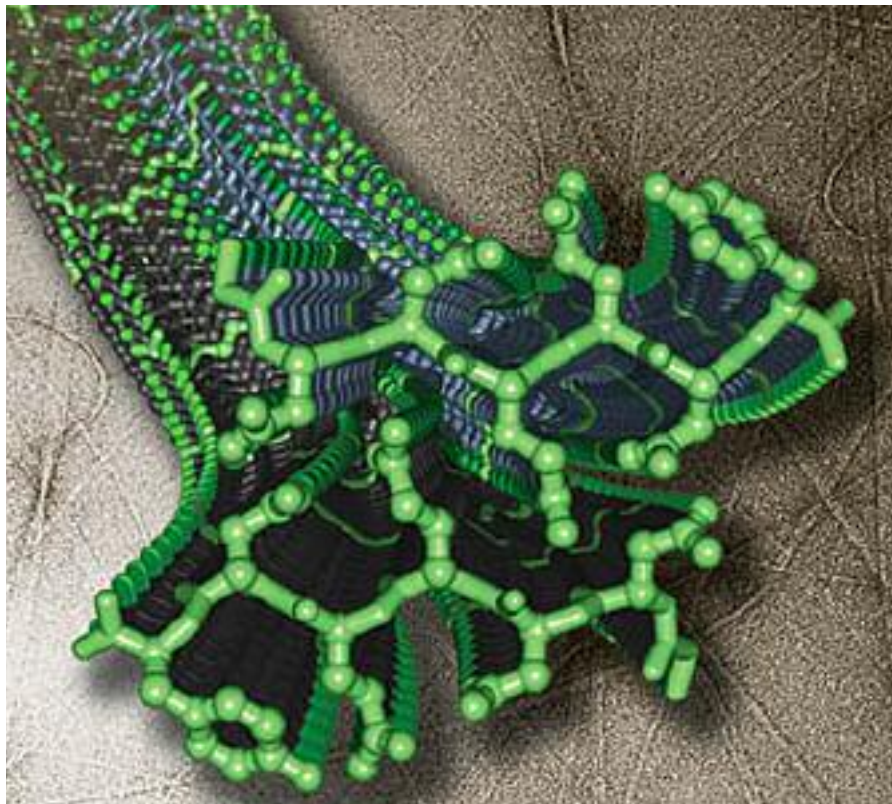


Hitting Pay Dirt on Amyloid Fibrils

An international collaboration helps solve the long-elusive structure of tiny proteins that figure in major diseases such as Alzheimer's.

DAVID EISENBERG, HHMI AT UCLA. IMAGE REPRINTED COURTESY OF NATURE, VOL. 435, PP. 773 TO 778.



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“When you have to shoot a bunch of crystals rather than a single one, not only are the data degraded, there’s too much data, which adds background noise.”



DAVID EISENBERG

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LEFT _ NEW STRUCTURAL STUDIES SHOW THAT THE FILAMENTS THAT MAKE UP AMYLOID DEPOSITS LOOK LIKE NEARLY-CLOSED STUCK ZIPPERS. ONCE AMYLOID FIBRILS FORM IN TISSUES AND CELLS, THEY RESEMBLE A TOWERING STACK OF ZIPPERS, EACH TIGHTLY BONDED TO THE ONE BELOW.

A CHANCE MEETING WITH AN OLD FRIEND helped solve a problem that had stymied David Eisenberg’s research team for years—and led to a breakthrough discovery. In 2000, the HHMI investigator’s group at the University of California, Los Angeles (UCLA), identified a short peptide chain from the yeast protein Sup35, which, like a full-length protein, could form amyloid fibrils—thread-like abnormal protein deposits involved in a host of deadly disorders, including Alzheimer’s disease, Parkinson’s disease, type II diabetes, and the human counterpart of mad cow disease.

The next logical step, says Eisenberg, was to determine the peptide’s atomic structure. This is a prerequisite to devising drugs that might prevent these lethal molecules from forming in the first place, says Jiri Safar, a scientist at the Institute for Neurodegenerative Diseases at the University of California, San Francisco (UCSF), “and developing diagnostic tools to detect their presence long before symptoms appear, to prevent irreparable damage.”

To decipher the three-dimensional structure of this biologically important molecule, Eisenberg coaxed the proteins into forming crystals. That way, he could use a technique known as x-ray crystallography, which relies on the ability to get proteins into a crystal form. But the task proved daunting because the microcrystals formed by the peptide, which is composed of just seven amino acids, were impractically tiny—some 50,000 times smaller than the crystals researchers normally work with.

The UCLA scientists spent several frustrating years pursuing initially promising technologies that ultimately led nowhere. “We tried a whole bunch of tools using traditional x-ray methods as well as other methods,” says Eisenberg, who is also director of the UCLA-DOE Institute for Genomics and Proteomics. “But when you have to shoot a bunch of crystals rather than a single one, not only are the data degraded, but there’s too much data, which adds background noise. So we weren’t getting a clear enough picture.”

All that began to change in July 2003, when Eisenberg attended a conference in Crete. Over lunch with Swedish scientist Carl-Ivar Brändén, he spoke of his dilemma. “There’s one person in the world who can help you,” Brändén immediately responded, “Christian Riekell.”

A crystallographer at the European Synchrotron Radiation Facility in Grenoble, France, Riekell had invented a highly focused x-ray camera capable of analyzing crystals as small as one micrometer in diameter—about 1/100th the width of a human hair—a technology 100 times more powerful than the best available in the United States. Another large plus was that a graduate student at the lab, Anders Madsen, had developed an effective way of manipulating microcrystals.

The UCLA team took their microcrystals to Riekell’s lab, where they recorded accurate x-ray diffraction patterns from an individual microcrystal. With this diffraction pattern in hand, the researchers looked for the position of

the zinc atom in the structure, knowing that microcrystals grow only in the presence of zinc. “When I found the zinc atom, finding the others was easy,” says Michael R. Sawaya, a research scientist at UCLA who contributed to the project. With the knowledge of the position of all the atoms, you can see the structure of the molecule. “Recognizing the features of the peptide was like seeing the familiar face of an old friend,” adds Sawaya.

There was much dancing around the lab when, after 8 years of hard work, the three-dimensional structure was known.

And the structure suggested to the researchers how the fibrils accumulate in brain tissue and why they are so infectious. At last they had all the puzzle pieces. The peptide molecules in the microcrystal assemble into a structure that resembles a tightly bound zipper that latches on to an identical structure, much in the manner of Velcro, which explains their great stability. This suggests how the amyloid fibrils keep growing: They latch on to either end of the structure, forming an almost indestructible spine-like chain. “This discovery is the pinnacle of years of hard work,” says UCSF’s Safar, “and is

a significant contribution in our understanding at the atomic level of the way amyloids form.”

The UCLA team hopes that unraveling the atomic structure will suggest ways to cap the growth of amyloids and pave the way toward formulating treatments that can inhibit this process. ■

-Linda Marsa-