Like a Chinese Finger Trap

**SCIENTISTS ZERO IN ON DISEASE-CAUSING AMYLOID STRUCTURE.**

In neurodegenerative diseases like Alzheimer’s, the needle-like fibers that accumulate in the brain are not the real damage-doers. The culprits are intermediate protein structures, called small amyloid oligomers, made of a few proteins that misfold and aggregate. But the oligomer’s fleeting existence—sometimes lasting only minutes before forming the longer fibers—make them nearly impossible to study. HHMI investigator David Eisenberg has at last pinned down the structure of an amyloid oligomer.

“We wanted to find the toxic agent,” Eisenberg, at the University of California, Los Angeles, says about his research published March 9, 2012, in *Science*. “You can’t design drugs if you don’t know the structure of the toxic agent.”

Though the oligomers in major amyloid diseases such as Alzheimer’s, Parkinson’s, and even type 2 diabetes are short-lived, Eisenberg found one that lasts longer. The needle-like amyloid fibers in some cataracts take decades to form, so the oligomer state of these misfolded proteins can be easily trapped. Eisenberg and graduate student Arthur Lagonowsky took advantage of these unhurried aggregates to study the cataract-forming protein, αβ crystalline (ABC).

Lagonowsky used a computational algorithm to find the segments of the ABC protein responsible for forming the fibers. He then confirmed that the ABC oligomer had antibody affinities and toxicity patterns similar to those in the major amyloid diseases. Finally, using x-ray diffraction, Lagonowsky saw that the small oligomer consists of a cylinder of six protein chains. They dubbed the structure “cylindrin.”

“This cylinder looks sort of like those toys you get in Chinatown, where you put your fingers in and realize they’re stuck,” says Eisenberg. “It has a structure unlike any of the 70,000 structures catalogued in the open-source Protein Data Bank.”

Eisenberg hopes that understanding the cylindrin structure may lead to new approaches to studying the structures of the more elusive oligomers associated with major diseases. “The fundamentals are absolutely critical to understanding medicine,” he says. “Work in structure and composition of amyloid diseases is just starting.”

**IN BRIEF**

Comparing autistic children’s genes to those of their parents, the scientists found more than 250 mutations unique to the children. Some mutations had been linked to autism in past studies; others were strong new candidates.

Analyzing the data further, the researchers found that the number of mutations increased with the father’s age, and that 39 percent of the mutations affected proteins within the same network.

“I was surprised to see so many of them as part of a highly interconnected set of proteins,” Eichler says. Skeptical at first, the scientists sequenced the exomes (the protein-encoding genes) of 50 nonautistic siblings; none carried the mutations found in the network. The research was published April 4, 2012, in *Nature*.

“Understanding how the mutations affect cells will require further experiments,” Eichler says, “but converging on a network is a step forward in the field of autism genetics.”

**IT DOES A BODY GOOD**

Milk may contain the calcium that helps build strong bones, but we rely on subtle biological interactions to absorb and make use of the mineral. In one of these interactions, called phosphorylation, a kinase enzyme affixes phosphates to proteins. With correct phosphorylation, proteins are able to bind calcium to form bones and teeth.

For over a century, scientists have known that the milk protein casein contains phosphate. In a study published June 1, 2012, in *Science*, researchers led by Jack E. Dixon, HHMI vice president and chief scientific officer, found that Fam20C—a member of the seldom-studied Fam20 family of proteins—is responsible for the phosphorylation of casein.

Scouring old scientific reports, the researchers also discovered something unexpected: mutations in Fam20C had been reported in patients with Raine syndrome—a fatal disease in which bones become too dense. Dixon’s team developed a cell line with the Raine syndrome mutations. “Every single one of these mutations inactivated the Fam20C kinase and prevented it from being secreted,” says Dixon. The mutations affected phosphorylation of casein as well as several other proteins involved in enamel and bone formation.

“What we’ve discovered isn’t just the casein kinase,” Dixon says. “It’s a whole new branch on the kinase tree that seems to play an important role in bone and teeth formation.”

**FOLLOWING CHI TO ITS PERFECT FORM**

Joe Noel calls chalcone isomerase, or CHI, the “perfect enzyme” because of its extreme speed.

Noel, an HHMI investigator at the Salk Institute, wanted to know how CHI evolved to catalytic perfection. He discovered that CHI likely evolved from a noncatalytic protein that played a completely different role in plants, and that CHI and its noncatalytic relatives coexist today.

CHI is crucial to production of flavonoids, which customize plants to varied terrestrial environments. Flavonoids provide UV screens, for example, and colors that lure pollinators.

Noel and colleagues combed through the genome of *Arabidopsis* and found that CHI shares genetic similarities with three members of the FAP protein family.

To learn how the two protein families were related, the scientists introduced FAP genes into E. coli bacteria, and then studied

The toxic agents in many neurodegenerative diseases are intermediate structures that form small cylindrical oligomers.