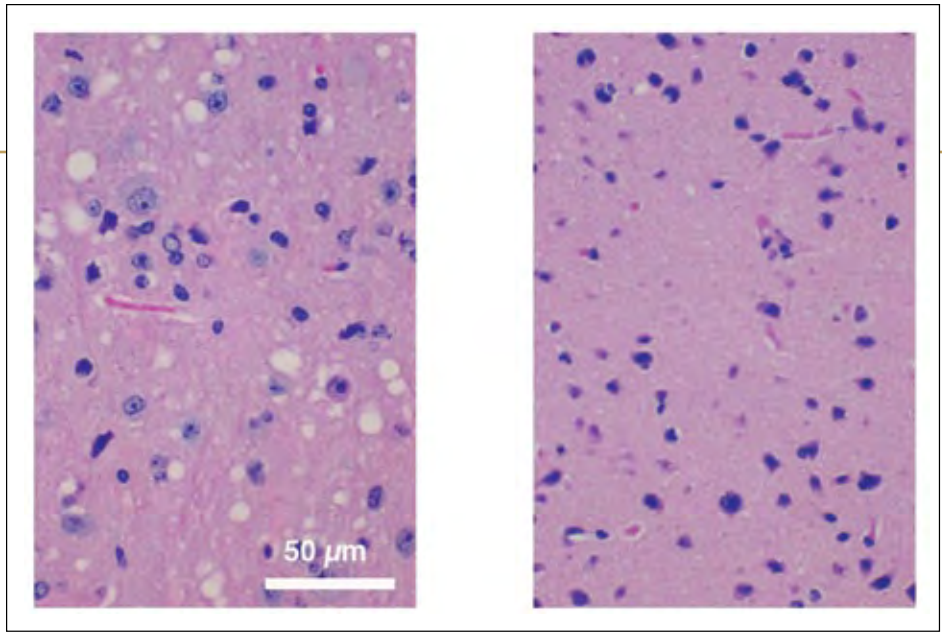
Rooting out a prion's sidekick



The combination of prion protein and a cofactor molecule can be disastrous for brain cells. Above, the image on the right shows mouse brain cells infected with only prion protein. On the left, mouse brain cells have been infected with prion protein and a cofactor molecule, causing degeneration and a sponge-like appearance. The numerous white spots on the left are holes in the brain that occur when neurons die. The blue spots in both images are the nuclei of various types of brain cells. Image courtesy of the lab of Surachai Supattapone.

Infectious prions have a trusty accomplice in causing disease, according to research by Geisel biochemist Surachai Supattapone, M.D., Ph.D. Normal, noninfectious prion proteins are usually found in the brain. But when prion proteins misfold, they can become infectious and trigger a number of fatal brain disorders, such as mad cow disease or Creutzfeldt-Jakob disease in humans.

What puzzles scientists is that infectious prions (simply called "prions"), unlike viruses, have no nucleic acids—no DNA or RNA—yet they are able to create distinct, self-propagating strains of prion diseases. Most scientists believe in a protein-only hypothesis in which prions create different strains of disease on their own, and many believe that the hypothesis may apply to other diseases as well, such as Alzheimer's and Parkinson's. But Supattapone is doubtful. If a prion contains just a single protein, without other essential molecules, "it's hard to explain why the strains exist first of all," he says. Another problem with the protein-only hypothesis, he adds, is that "nobody has been able to make infectious prions from just the prion."

Through a purification process, Supattapone, with Geisel biochemist Nathan Deleault, determined that when a noninfectious prion protein is mixed with a certain phospholipid molecule, named phosphatidylethanolamine (PE), the combination creates an infectious prion. This experiment was the first time anyone had formed infectious prions from only two components (prion protein and PE) and without any nucleic acids.

Next Supattapone and Deleault decided to test two things: whether PE is essential for prions to propagate disease in animals, and whether PE is needed to form different strains of prion disease. For the first step, his lab took purified noninfectious prion proteins without PE and a control group of noninfectious prion proteins with PE, mixed both groups with infectious prions, and then injected them into separate groups of mice. The researchers tested a variety of doses, from a full non-diluted dose to one one-millionth of a full dose. Even at the smallest dose the material with PE was infectious in the mice. Without the PE, the prions weren't infectious at any concentration, even at a full dose.

Supattapone's team then tried something new that had never been tested before—whether PE had any effect on the properties of strains of prion disease. They took three strains of infectious prions, mixed each of them with noninfectious prions and PE, and injected the combinations into different mice. In all of the mice, regardless of which combination had been injected, a new strain of prion disease emerged, and this strain was different from all of the parent strains. This gives strong evidence that the cofactor, PE, was instrumental in generating the new strain.

Based on these findings, Supattapone theorizes that prions are made up of at least two molecules—a normal prion protein and a cofactor, such as PE—and that each strain of disease is probably associated with its own set of cofactors. So PE, or another cofactor, allows prions to propagate but then forces those prions to become a single new strain of disease. The research is published in two separate articles in *Proceedings of the National Academy of Sciences*.

If this research holds up, Supattapone says, "it probably, in my mind, disproves the protein-only hypothesis." Matthew C. Wiencke