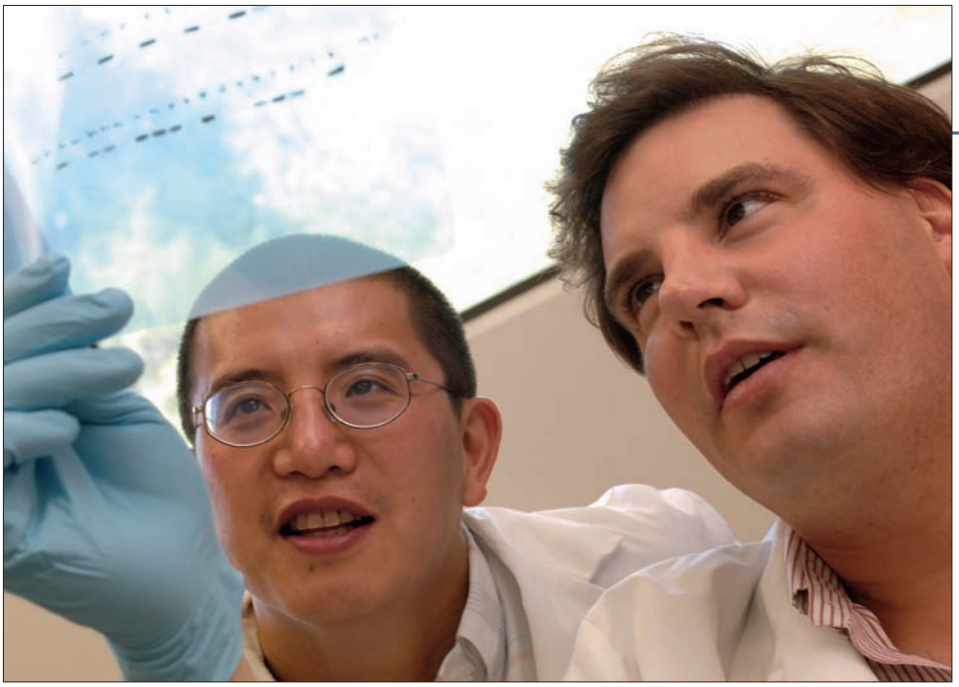

JON GILBERT FOX

Nick Orem, right, and Surachai Supattapone found that copper ions may keep prions from becoming infectious.

Lab is unraveling the mysteries of prions

Prion researcher Nicholas Orem, Ph.D., seems pretty calm for someone who has made a significant scientific discovery. He shrugs as if to say, "No big deal."

But biochemist Surachai Supattapone, M.D., Ph.D., head of DMS's prion lab, isn't reluctant to explain the importance of the finding. His postdoctoral fellow has determined that copper ions might prevent normal prions from becoming infectious.

Host: A prion is a normal mammalian protein that usually occurs in the brain and that becomes infectious when it misfolds. When infectious prions enter a susceptible host, they slowly convert normal prions to infectious ones, which then trigger any of several rare but frightening, fatal brain disorders called transmissible spongiform encephalopathies (TSEs). In cows, the disease is called bovine spongiform encephalopathy, or mad cow disease. In humans, it's called variant Creutzfeldt-Jakob disease (CJD).

People and animals who are stricken with TSEs gradually lose control of their bodies, descend into dementia, and die. Autopsies show their brains to be riddled with Swiss-cheese-like holes.

Supattapone has led DMS's prion lab since founding it in 2001. Before that, he spent six years in the lab of 1997 Nobel laureate and prion guru Stanley Prusiner, M.D., at the University of California at San Francisco. At DMS, Supattapone's team has been working to unravel the mysteries of prion disease in hopes of finding therapeutic strategies to combat them.

Orem remains calm as he recalls the day when his discovery became clear. He was researching the effects of copper, manganese, and zinc on the ability of infectious prions to force normal prions to convert. "The readout in the lab is what's called a Western blot," a method for identifying proteins, he explains. "You treat your sample with stuff called protease K. It's great at chewing up proteins and will chew up all the nonconverted [prions] and all the other proteins . . . leaving only converted prions."

Black line: Then the fragments are separated on a polyacrylamide plate and stained with an antibody that is specific for the infectious prion. "At the end of the day, you wind up with a picture where there is the protein you are staining for," says Orem. "There's a black line."

"I remember the day Nick got his results showing that copper was very potently inhibiting," enthuses Supattapone. "I remember [us] both being pretty happy to see that."

"Yes," admits Orem, "it's always exciting to have a clear result, and this was very clear." Still calm, but now visibly proud, he continues. "There were people who were trying to treat the disease with chelators, which are chemicals that bind up free copper—make it biologically unavailable. Clearly my work shows that would be the exact opposite of what you'd want to do. You'd want to treat with copper."

But only in the lab, not in humans, unfortunately. "Copper itself is toxic to the brain," Supattapone says. Besides, once patients exhibit symptoms of a prion disease, it would be too late to treat them.

Nevertheless, Supattapone believes that Orem's findings are significant and predicts that "Nick's paper is going to be well cited going into the future." One measure of the importance of a piece of research is how often it's cited by other papers in the field. Still, the researchers agree that the finding is nowhere near ready for clinical use.

Slowly: "It takes a while to discover rational treatments for human diseases like CJD," Supattapone explains. Many nonscientists don't appreciate the fact that medical research proceeds slowly, in small steps. "I think this is a great scientific result, with medical relevance whose significance will come more into play down the road, as we learn more." But, he adds, "unfortunately, there is still no effective therapy for prion disease."

Orem and Supattapone don't yet even understand *how* copper ions inhibit the conversion of normal prions to infectious ones. "Presumably, when copper binds, it changes the protein's shape enough that it is unable to adopt this pathogenic conformation," says Orem. He is now trying to determine if copper permanently disables the conversion process, or if removing it will restore an infectious prion's conversion powers.

In the meantime, he plans to remain . . . well, calm. LAURA STEPHENSON CARTER