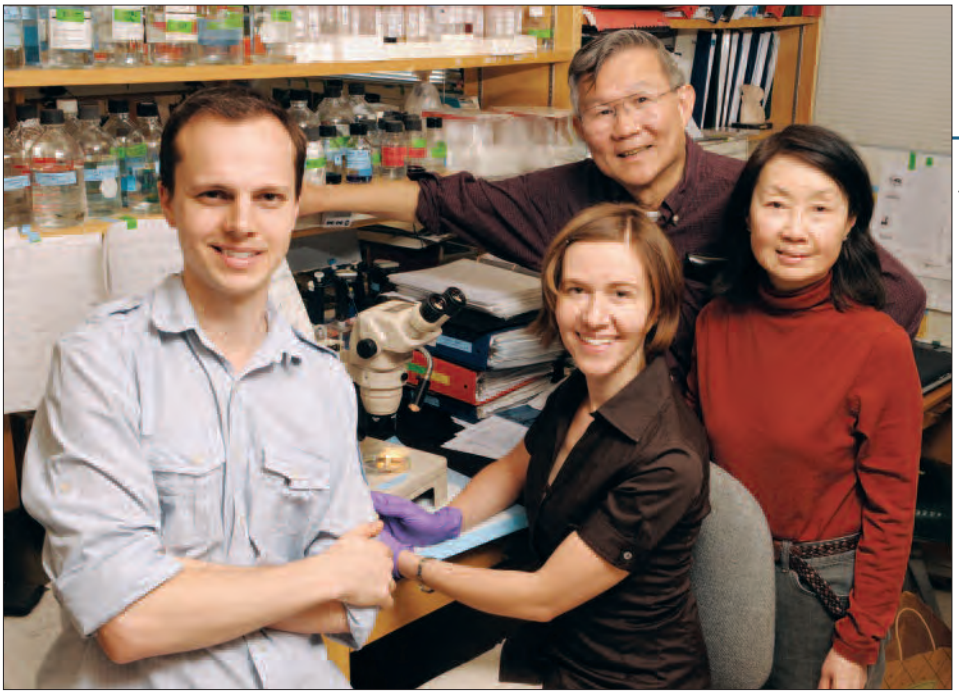

JON GILBERT FOX

From the left are Rogers, Bryleva, T.Y. Chang, and his wife, Catherine, also a coauthor on the lab's recent paper.

Putting some teeth in the attack on Alzheimer's

Attacking plaque on the teeth requires diligence with a toothbrush. Unfortunately, preventing or removing plaque in the brain is far more complicated. Such deposits, called amyloid plaque, have long been associated with Alzheimer's disease. If clumps of this plaque accumulate in the brain, small pieces can break off and float around, damaging nerve connections.

A DMS lab headed by biochemist Ta-Yuan Chang, Ph.D., reported in the *Proceedings of the National Academy of Sciences* that in mice with Alzheimer's, the removal of a gene known as ACAT1 reduces amyloid plaque and improves cognitive ability. Chang's lab cloned the first ACAT gene in 1993.

Genes: Mice and humans have two ACAT genes—ACAT1 and ACAT2. In mice, ACAT1 is more active. Both convert cholesterol in the brain into cholesterol esters, a storage form of the compound. Previous studies have shown cholesterol to be involved in Alzheimer's through modulation of the enzymes that produce a peptide called amyloid beta. When amyloid beta is cleaved from amyloid precursor protein (APP), it forms aggregates that create amyloid plaque.

Chang's team—including postdoctoral fellow Elena Bryleva, Ph.D., and graduate student Maximillian Rogers—knew from a study done at Harvard that ACAT inhibitors, which block ACAT enzyme activity, could reduce symptoms of Alzheimer's. But the mechanism of the inhibitors wasn't clear.

Types: So the DMS researchers tried a new tack and compared two types of mice. One was engineered to be born without the ACAT1 gene, while the other had the gene; both were designed to develop Alzheimer's when they were about four months old and both had a human form of APP.

The mice lacking ACAT1 had less plaque and better memory.

The mice lacking ACAT1 (known as A1-/AD mice) had 53% less human APP, less amyloid plaque, and much better memory function. The A1-/AD mice also had a 32% increase in a major oxysterol—a cholesterol metabolite—in their brains. It seemed that this oxysterol was responsible for many of the changes in these mice. With ACAT1 inactivated, the oxysterol was down-regulating an enzyme called HMGR that controls the rate of cholesterol synthesis. So "HMGR protein levels were decreased," says Rogers, "cholesterol synthesis levels were decreased, and total cholesterol in the brain was decreased." Since the brains of the A1-/AD mice also had less human APP, it looked as if the oxysterol was responsible for that drop, too.

To test this theory, Bryleva added the oxysterol to cultures of neurons from mice with the ACAT1 gene, to see if it generated the same effect as seen in the mice lacking ACAT1. It did. Both human APP and HMGR dropped.

The researchers are still not sure how the oxysterol causes human APP and HMGR to drop; it's an area they plan to study further.

Role: It may be of note that in the A1-/AD mice, as the oxysterol increases and HMGR decreases, the changes cause a drop in cholesterol biosynthesis. This makes a strong case that that particular oxysterol "plays a role in regulating cholesterol biosynthesis," says Bryleva. It's an important point, she adds, because researchers have long debated whether oxysterols play a role in regulating cholesterol synthesis in the brain.

There are many more questions that Chang's team wants to tackle. They've shown that knocking out the ACAT1 gene in a mouse with Alzheimer's reduces amyloid plaque buildup and improves cognitive ability, but this was done on a specific mouse model—one born without the ACAT1 gene and genetically engineered to develop Alzheimer's. "What we don't know is that when the mouse develops this disease, [if] then you take the ACAT1 gene out, whether [it] will still diminish the disease," says Chang. "We want to do that . . . find out whether [taking out] ACAT1 is preventive or therapeutic."

Mechanism: Chang also hopes to identify the mechanism by which the oxysterol prevents the accumulation of human APP. And a long-term goal is to move the findings from the lab bench to the clinical arena. "There's an urgent need to develop an ACAT1-specific inhibitor that has no side effects," says Chang, "for both Alzheimer's disease and atherosclerosis." MATTHEW C. WIENCKE