SCIENCE NEWS

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Compound Slows Key Step in Alzheimer's

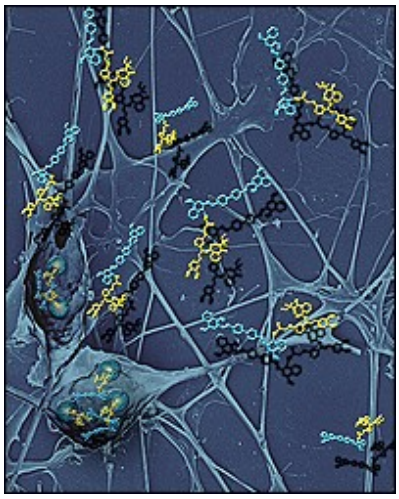

Image: COURTESY OF ISABELLA A. GRAEF

Small molecules make better drugs than large ones do, because they can more easily enter cells and gum up chosen chemically active sites. But their size makes it hard for them to stop larger molecules like proteins from interacting with one another, which is critical to many diseases. Now, borrowing a trick from soil bacteria, researchers have designed a small molecule that effectively forms a new drug on the spot by teaming up with a large protein that is common inside cells. As reported today in *Science,* the resulting complex binds to fragments of beta-amyloid protein and keeps them from sticking together to form the "plaques" that are a hallmark of Alzheimer's disease.

Scientists have previously found small molecules that stick to beta-amyloid, but they weren't good at preventing plaques. A small molecule between amyloid molecules is "like a grain of sand between strips of Velcro," says study co-author Isabella Graef of the Howard Hughes Medical Institute at Stanford University. Her aim was to "get that grain of sand to drag along a tennis ball." To do this, team member Jason Gestwicki chemically hooked one of the amyloid-binding molecules to another molecule that binds to a "chaperone," an abundant cellular protein that helps other proteins to fold properly. The new compound tethered bulky chaperones to the beta-amyloid fragments and prevented them from forming large clumps. When the researchers exposed cultured nerve cells treated with the compound to beta-amyloid, which ordinarily kills them, the cells survived.

The experiments are far from demonstrating a useful treatment for Alzheimer's disease. For one thing, the molecules can't cross the cell membrane. But the team is working to develop new compounds that can do that. Graef suggests that the technique might one day be used together with other drugs that reduce the amount of beta-amyloid present in the brain in the first place. She further notes that a drug strategy that inhibits interactions between proteins could be useful in a variety of other diseases, possibly including HIV and cancer. *--Don Monroe*

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