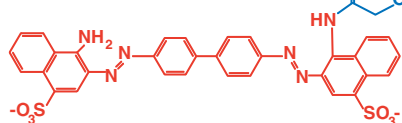


A Wily Recruiter in the Battle Against Toxic β Amyloid Aggregation

In Alzheimer's disease (AD), large, abnormal clumps of a peptide called β amyloid surround and clog the insides of neurons. These clumps are suspect because they kill cultured neurons, and several human mutations associated with early-onset AD are linked to problematic β amyloid. Hoping to retard the disease, researchers have tried using drugs to block such clumping, but with little success until recently.

The problem: Lilliputian drug molecules are no match for relatively massive amyloid peptides. Using them as blockers is like trying to prevent strips of Velcro from adhering by inserting grains of salt between them. But now Stanford researchers report a new blocking strategy that seems to work. On page 865, molecular biologist Isabella Graef, chemist Jason Gestwicki, and biologist Gerald Crabtree



Bully tactics. A new strategy to prevent clumping of β amyloid (micrograph) combines Congo red (red structure) with another molecule (blue) to maneuver a large cellular protein called FKBP in between amyloid peptides.

describe the synthesis of an ingenious drug that recruits a gargantuan cellular protein to insert itself between two amyloid peptides, preventing the formation of large, toxic β -amyloid clumps.

"It's very clever," says molecular biologist Roger Briesewitz of Ohio State University in Columbus. "By binding a small drug to an endogenous protein, the small drug becomes a large drug that can push away the protein that wants to bind to the drug target."

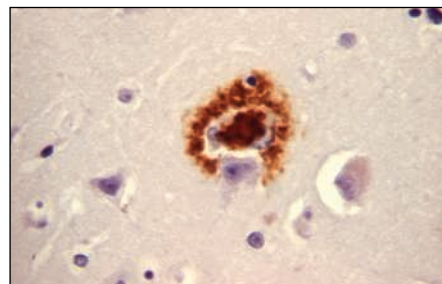
The method has not yet been tested in animals, and because the current form doesn't cross the blood-brain barrier, it has no clinical use in AD. But if the Stanford team's trick can be parlayed into therapy, it could lead to novel treatments for a variety of disorders—including perhaps other neurodegenerative ailments such as Parkinson's disease—in which protein-protein interactions are thought to play a key role. "We think the idea of fighting protein bulk with protein bulk is going to be general," says Gestwicki. "It's like fighting fire with fire."

The approach has a precedent in nature. For millions of years, soil bacteria have

made chemicals that cripple enzymes in bacterial foes by first binding to a giant cellular protein, which then walls off the enzyme from its usual substrate. A prime example is the immunosuppressant FK506. It inhibits the enzyme calcineurin by first recruiting a bulky protein chaperone—a protein that helps other proteins fold—called the FK506 binding protein (FKBP).

Graef was thinking about FK506's mechanism while reading an article about misfolded proteins in spring 2003. She immediately thought: "Why haven't we tried this as a way to block protein aggregation?" She thought β amyloid would be a good test protein because it has been so well studied.

Back in the lab, Graef recruited Gestwicki, who chemically tethered a synthetic ligand for FKBP to Congo red, a dye that sticks to β amyloid but doesn't block clumping except at high concentrations. The resulting



small molecule could grab FKBP on one end and β amyloid at the other and thus usher the bulky chaperone in between two amyloid peptides. Gestwicki made several versions of the drug, varying the length and flexibility of the section that linked Congo red to the FKBP ligand.

When added to tubes of β amyloid along with FKBP, Gestwicki's compounds either greatly delayed or completely prevented large clumps of β amyloid from forming, as detected by a fluorescent dye that binds to protein aggregates. The best compound blocked β -amyloid aggregation at concentrations 20-fold lower than any compound previously developed, Gestwicki says, a critical feature for a potential therapeutic. Without FKBP, however, the Stanford drug held no advantage, showing that the chaperone is critical to its *modus operandi*.

Under an electron microscope, Gestwicki saw that the β -amyloid aggregates that formed in the presence of his drug were much smaller than those in brains with ▶

NIH Tweaks Review Criteria to Include Clinical Research

In its first overhaul of grant-review criteria in 7 years, the National Institutes of Health (NIH) has reworded the rules to give more weight to projects that translate research results to patients.

The five grant-review criteria—significance, approach, innovation, investigators, and environment—will now "better accommodate interdisciplinary, translational, and clinical projects," NIH says in a 12 October announcement. For example, "innovation" can include challenging "clinical practice" as well as "existing paradigms." And overall, instead of advancing "a field," the work can "improve clinical decision or outcomes." Reviewers are also asked to review the research teams, not just the lead investigator. The changes, which take effect in January, are part of NIH Director Elias Zerhouni's Roadmap, a set of initiatives aimed at boosting translational research.

Although NIH can't say how the rules might change the mix of basic and clinical research it funds, NIH deputy director for extramural research Norka Ruiz-Bravo is "hopeful" that reviewers "will be even more thoughtful" about these projects.

Clinicians welcome the revisions. "It's going to shift [the mix] some," predicts Herbert Pardes, president of New York-Presbyterian Hospital in New York City, who served on a 1997 NIH panel on clinical research. "The more attention they pay to clinical research, the better."

—JOCELYN KAISER

Russian Parliament Clears Way for Kyoto Protocol

Russia's upper house of parliament was expected to ratify the Kyoto Protocol this week, guaranteeing that the landmark international pact to control greenhouse gas emissions will enter into force early next year. Last week, the Duma, parliament's lower house, voted 334–73 to approve the agreement, and Russian President Vladimir Putin is expected to sign the measure within weeks.

"We'll toast [Russia] with vodka tonight," Greenpeace climate campaigner Steve Sawyer told reporters after the 22 October Duma vote.

After years of debate, Russia's cabinet endorsed the protocol earlier this month (*Science*, 8 October, p. 209). To enter into force, Kyoto needed the backing of nations responsible for at least 55% of 1990 emissions. Russia, with a 17% share, put the pact over the threshold.

—DAVID MALAKOFF