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November 1, 2004
Vol. 82, Iss. 44
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November 1, 2004
Volume 82, Number 44
p. 7

DRUG DEVELOPMENT

How To Keep Proteins Apart

By recruiting another protein, bifunctional molecule prevents protein aggregation

[MAUREEN ROUHI](#)

Using small molecules to prevent protein-protein interactions is like using tiny spheres to separate the strands of cooked spaghetti. It generally doesn't work. But what if the small molecule recruits another protein to give it some bulk?



PROTEIN DEAGGREGATORS Crabtree (from left), Graef, and Gestwicki relax outside their lab.

COURTESY OF GERALD CRABTREE

That strategy works beautifully, according to Jason E. Gestwicki, Gerald R. Crabtree, and Isabella A. Graef at Stanford University Medical School. They have shown that a molecule with one part that binds tightly to a helper protein and another part that interacts with β -amyloid peptide prevents aggregation of the peptide into fibrils [Science, 306, 865 (2004)].

The formation of β -amyloid peptide fibrils is a key target in drug development for Alzheimer's disease. For decades, pharmaceutical companies have been looking for ways to prevent that aggregation, Crabtree says. But small molecules do not have enough steric bulk. So the Stanford team borrowed the surface area of another protein to help form a barrier between β -amyloid peptides.

The strategy is "ingenious," says Laura L. Kiessling, a chemistry professor at the University of Wisconsin, Madison. "It is often difficult to block protein-protein interactions because they involve the burial of large surface areas, and new inhibition strategies are needed."

To test the strategy, the Stanford team prepared a small molecule consisting of Congo red linked to a synthetic ligand that binds members of the FK506 binding protein (FKBP) family. Congo red, the targeting moiety, is known to bind to β -amyloid peptide. The synthetic ligand recruits endogenous FKBP. The team selected FKBP as helper proteins because they are abundant, about 1 million molecules per cell.

The small molecule bound to FKBP is far more effective in blocking aggregation of β -amyloid peptide than is the small molecule alone. In the presence of the FKBP-bound agent, β -amyloid peptide forms

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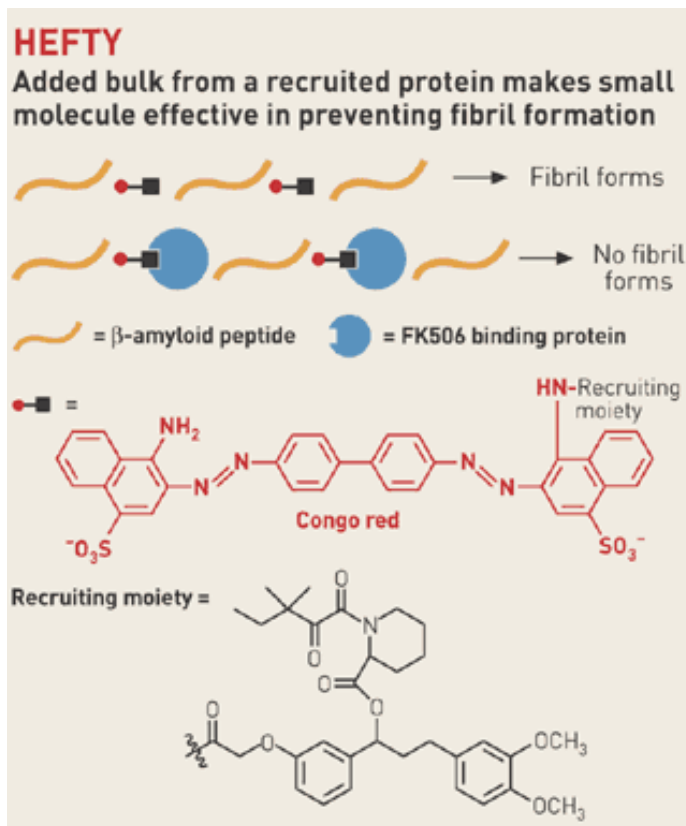
tetramers or pentamers instead of long fibrils, and neurons ordinarily killed by β -amyloid peptide aggregates are saved.

The efficacy can be optimized by using a variable linker to change the distance between the targeting and recruiting moieties. Further optimization could make development of therapeutics based on the bifunctional small molecules a real possibility.

The strategy is not just about Alzheimer's disease. "The pathogenesis of many diseases depends very much on protein-protein interactions," Crabtree says.

Because the strategy is modular, it could be general, Kiessling says. "In principle, both the targeting moiety and the protein-recruiting group can be altered. Thus other proteins might be targeted, and other protein surfaces might be recruited."

An intriguing target would be rapidly mutating viruses, such as HIV. With HIV, "the minute you have an inhibitor for a specific site, the virus evades by mutating at that site," Crabtree says. "Now, imagine that the small molecule is no longer small but very large because of the helper protein and contacts a large region of the HIV protein. HIV can mutate once to lose one interaction. But it's unlikely to mutate three or four times. By bringing in the entire surface area of the helper protein, we prevent the virus from escaping by a single-point mutation."



Chemical & Engineering News
 ISSN 0009-2347
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