

## NEUROBIOLOGY

# Untangling Alzheimer's by Paring Plaques Bolsters Amyloid Theory

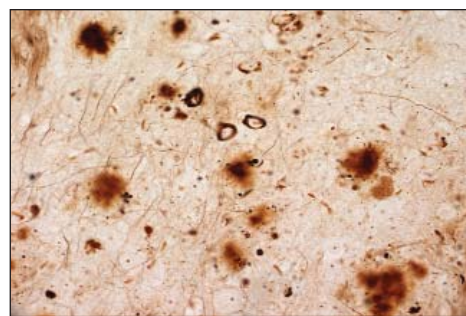
Consider it a potential biomedical bargain—two therapies for the price of one. New research in mice suggests that targeting one of the two molecular aggregates gumming up brains with Alzheimer's disease also rids tissue of the other, as long as treatment starts early enough. This finding and a recent analysis of an interrupted Alzheimer's vaccine trial in people have brought new life to the idea of immunotherapy for the debilitating disease.

An ongoing debate within the Alzheimer's disease community centers on the importance of brain plaques, extracellular clumps of a protein fragment called  $\beta$  amyloid, and tangles, filaments of the protein tau that form inside neurons. In the 5 August issue of *Neuron*, a team led by neuroscientist Frank LaFerla of the University of California, Irvine, reports that antibodies against  $\beta$  amyloid can wash mice brains free of amyloid plaques—and mutant tau before it tangles. Some researchers have argued that plaques instigate the formation of tangles, but there's been little solid evidence for that. "This is the most complete

confirmation that accumulation of  $\beta$  amyloid can lead to accumulation of tau and eventually to tangles," says neuroscientist Michael Hutton of the Mayo Clinic College of Medicine in Jacksonville, Florida.

Researchers have had difficulty testing the relative roles of plaques and tangles, because until last year, no one had generated mice that develop both. LaFerla and his colleagues recently endowed mice with a triple threat: a mutant copy of the gene for amyloid precursor protein (APP), a mutated gene for presenilin-1, which helps chop APP into  $\beta$  amyloid, and a mutant form of the tau gene. These rodents develop plaques and tangles in the cortex, amygdala, and hippocampus, just as people with Alzheimer's disease do. The plaques precede tangles, consistent with the idea that  $\beta$ -amyloid buildup starts brains off on the road to dementia.

In the new work, the team injected antibodies against  $\beta$  amyloid into the hippocampus of their transgenic mice once the animals were 1 year old. Three days after the in-



**Double trouble.**  $\beta$ -amyloid plaques (diffuse black structures) and tau tangles (open, black circles) mar this slice of mouse brain.

jection, plaques in the injected animals had disappeared. Between 5 and 7 days after the injection, tau, which in the mice had aggregated within neurons but not yet formed tangles, also had melted away.

LaFerla's group tested the antibody treatment on another set of triple-mutant mice; these animals have two copies of each mutant gene and develop tangles in under a year. The antibodies erased plaques in 6- and 12-month-old animals. They also cleared pre-tangle tau aggregates in the 6-month-old animals but couldn't budge the tangles in year-old mice. "Once tau forms tangles, it can't be removed," says LaFerla.

The rodent work seems to mirror recent findings in autopsies of brains from people involved in a vaccine trial for Alzheimer's disease. In 2000, investigators showed that immunizing mice with amyloid itself could rid mouse brains of plaques. In 2002, however, clinicians abruptly halted a human study of the vaccine when a small percentage of patients developed brain inflammation. Last month, at the 9th International Conference on Alzheimer's Disease and Related Disorders in Philadelphia, Pennsylvania, Sid Gilman of the University of Michigan, Ann Arbor, described the brains of four people with mild to moderate Alzheimer's disease who had received the vaccine and subsequently died from unrelated causes. Each brain showed an almost complete lack of  $\beta$  amyloid; the tangles remained, however.

LaFerla's work "goes hand-in-hand with the vaccine trial," says neurobiologist Virginia Lee of the University of Pennsylvania in Philadelphia. The mouse and human data suggest that a vaccine would be most therapeutic if researchers treat patients in very early stages of the disease, before tau forms tangles.

Still, Lee admits, that remains a bit of a "pipe dream," because such patients can't yet be identified. Nevertheless, biotech companies are redesigning amyloid vaccines to make them safer and considering new clinical trials. Apparently, the reported death of Alzheimer's disease immunotherapy was an exaggeration.

—MARY BECKMAN

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## NANOTECHNOLOGY

## Yellow Light for Nanotech

**LONDON, U.K.**—Although "gray goo" made of self-replicating "nanorobots" is unlikely to doom the planet, some kinds of nanomaterials could be hazardous and require a closer look, according to a 12-month study\* published last week by the U.K. Royal Society and the Royal Academy of Engineering. Overall, however, the report concludes that most nanotechnologies pose no new risk and no general moratorium is needed.

Many products that incorporate nanoparticles, such as computer chips and self-cleaning windows, are no cause for new concern, said Cambridge University mechanical engineer Ann Dowling, who led the study, at a press conference last week. But because some chemicals are more toxic in their nano form and can penetrate cells more readily, nanomaterials should be subjected to toxicity studies "without delay," she said. Panel member Anthony Seaton, an expert in occupational and respiratory medicine at Aberdeen University in the U.K., added, "At the moment, it would be wrong to pretend we know much about the toxicology of nanoparticles."

\* *Nanoscience and nanotechnologies: Opportunities and uncertainties.* [www.nanotec.org.uk/finalReport.htm](http://www.nanotec.org.uk/finalReport.htm)

The panel concluded that nanoparticles and nanotubes—tiny tubes of carbon that have many potential uses, such as in friction-reducing oil additives and electronic displays—should be tested and regulated as new chemicals under existing U.K. and E.U. legislation. "We believe no new bodies are needed to regulate nanotechnologies," Dowling said, but existing bodies should review their regulations, and manufacturers should publicly disclose test results. Only large quantities of new materials would need to be tested; small-scale producers such as laboratories would not be affected. Nanotechnologists seem pleased with the panel's conclusions. Physician Michael Horton of the London Centre for Nanotechnology says, "The report was entirely right in its optimistic caution."

U.K. science minister David Sainsbury commissioned the study in July 2003 following alarmist reports in the media about inhaling toxic particles and the perils of self-replicating gray goo. The Royal Society and the Royal Academy will hold a public meeting to discuss the report on 29 September, and the government says it will respond by the end of the year.

—FIONA PROFFITT