

PLAQUE BUILDUP IN THE BRAIN:

Leads to dementia // In Alzheimer's, amyloid-beta protein gets the blame // But is tau **the true culprit?**

Tangled Up in Tau

■ BY ANITA SLOMSKI // ILLUSTRATIONS BY HARRY CAMPBELL

Neurologist Bruce Miller calls tau—a floppy, free-form protein—“the holy grail of dementia.” That designation may come as a surprise to anyone who has even a passing interest in the science of end-of-life brain diseases. A different protein, amyloid-beta (A β), has become famous as the culprit responsible for the so-called senile plaques that gum up the brains of people with Alzheimer's disease. Yet tau also plays a role in Alzheimer's, by far the most prevalent type of dementia, and it's not A β but tau, escaping its proper place inside neurons, that attacks the brain in a host of similar diseases.

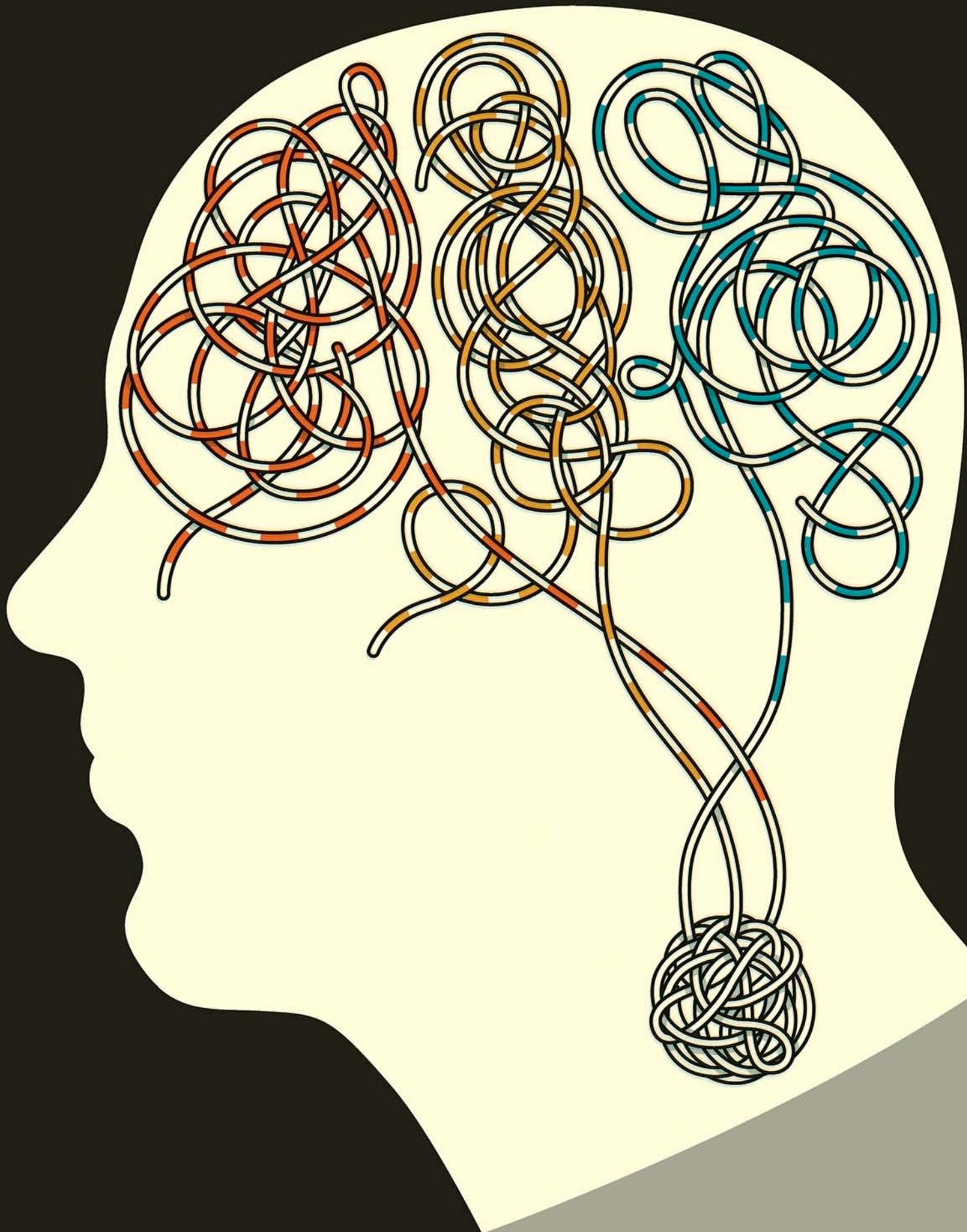
According to Miller, who heads the Memory and Aging Center at the University of California, San Francisco, and the Tau Consortium, an international research program, knowledge of A β emerged before much was known about tau. As a result, pharmaceutical companies have invested considerable sums developing therapies that target A β . Yet so far, all trials attempting to clear A β plaques from the brain have failed to slow down the disease or to produce any cognitive improvement in people with early stages of Alzheimer's disease.

As discoveries about tau were made, however, it became increasingly clear that the protein may be a major contributor to many kinds of dementia, which could be more closely related to one another than anyone had guessed. “We've gone from thinking of tau as not very interesting to understanding that tau pathology leads to multiple diseases that have different clinical symptoms based on which brain region and

type of neurons are affected,” says Michel Goedert, head of the neurobiology division at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England. In 1996, he and Bernardino Ghetti of Indiana University coined the term *tauopathy* to describe diseases that have tau inclusions as their common, defining denominator.

Among the more than two dozen tauopathies is frontotemporal dementia (FTD), which leads to impaired social skills, language loss and personality changes. Another, corticobasal degeneration, causes the rigidity and abnormal postures of Parkinson's disease as well as difficulty with speech and swallowing and the perception that an arm or a leg isn't part of your own body. There's also progressive supranuclear palsy, characterized by balance and eye problems, depression, apathy and dementia. Still another tauopathy—chronic traumatic encephalopathy—may arise in football players, war veterans and others who have suffered repeated concussions or other brain trauma.

The latest revelation about tau, in late 2012, helps explain why diseases of dementia progress slowly, with tau tangles destroying millions of neurons in a chain reaction that progresses from one region of the brain to the next. “That understanding gives us a whole panoply of new therapeutic targets,” says Bradley Hyman, director of the Memory Disorders Unit at Massachusetts General Hospital and one of the researchers who discovered how tau pathology spreads. It appears to be possible, for example, to use antibodies for clearing the neurofibrillary tangles or to come up with a way to block nerve cells from taking up the tangles and destroying themselves.



The possibility of eliminating abnormal tau offers hope for solving the riddles of several types of dementia. “I think we may find a cure for frontotemporal dementia before Alzheimer’s disease because we have a pure target in tau,” says Miller. The ability to go after tau problems in those diseases, by itself, could have an enormous impact. And while researchers are still in the early days of determining how tau interacts with A β in Alzheimer’s disease and deciding which protein is the more toxic at different stages of the disease, knowing how to get rid of tau tangles might also be one key to developing an effective therapy for Alzheimer’s disease.

Tau was identified in 1974 by cell biologist Marc Kirschner as one of several proteins that form a nerve cell’s microtubules (MTs), structures that are part of a neuron’s axon—a long projection that extends from the cell body to the synapses, the connections through which nerve impulses are transmitted from one neuron to the next. MTs transport nutrients and other substances into and out of the cell body, and tau’s role is to stabilize those vital structures. “Think of microtubules as the train tracks that carry cargo to the cells, with tau being the crossties that support them,” says neuropathologist John Trojanowski. He and his wife, biochemist Virginia Lee, are among the pioneers studying tau and head the Center for Neurodegenerative Disease Research and Center for Alzheimer’s Drug Discovery Program at the University of Pennsylvania’s Perelman School of Medicine.

Tau, which can leak out of neurons, shows up in cerebral spinal fluid—a phenomenon that might provide a way to diagnose tauopathies before symptoms appear.

Material produced in neurons gets shipped via MTs to the synapses, which enables the synapses to release neurotransmitters that carry signals to other neurons. “The neuron has engineered a just-in-time delivery mechanism to supply nerve terminals with everything they need to function, so they’ll be instantly ready if you have to quickly command your limbs to jump out of the way of a car, for example,” says Trojanowski.

And that cargo may have to travel a long way. Motor neurons, for example, have axons that stretch from the top of the head to the lower back. Strong, intact MTs are crucial if nerve cells are to communicate with one another.

By the late 1980s, scientists had identified tau as the protein forming the filaments that clump together within neurons to form tangles that, along with A β plaques, are pathological hallmarks of Alzheimer’s disease. A breakthrough came in 1998, when researchers found mutations on the tau gene that cause FTD. There are now more than 50 known mutations of the tau gene, which either impair the way tau binds to MTs or promote the aggregation of tau into filaments. Additional “susceptibility” genes are just starting to be sorted out, Miller says.

Fewer than one in 10 tauopathies can be traced to tau gene mutations. Nevertheless, the discovery that mutations on the tau gene cause FTD “put tau on equal footing with A β and meant it should no longer be considered an incidental or secondary disease process,” says Dennis Dickson, professor of Alzheimer’s disease research at the Mayo Clinic in Florida. What it did not do, however, was end conflicts between so-called BAPTists—researchers who maintained that A β (also

called beta-amyloid protein, or BAP) was the primary cause of Alzheimer’s—and the growing ranks of Tauists. “There were vituperative clashes about which protein was most important in Alzheimer’s disease,” says Trojanowski.

The BAPTists claimed that A β plaques form in the brain first and lead to problems with tau—and that getting rid of A β was a prerequisite for halting the progress of Alzheimer’s. For their part, the Tauists pointed out that a third of

elderly people without dementia have brains with numerous A β plaques when they die—and that therefore it must be tau, not A β , that is behind the neurodegeneration of Alzheimer’s.

But then came the failure of trial after trial of therapies designed to clear A β from the brains of people with mild cognitive impairment. Even approaches that succeeded in reducing the plaques did nothing to reduce Alzheimer’s symptoms, and

From One Protein, Many Diseases //

Among the two dozen known tauopathies, symptoms depend on where the tangles of tau protein occur and the type of neurons they affect. Here are four major examples.

DISEASE	SYMPTOMS	LOCATION	PREVALENCE
ALZHEIMER'S DISEASE	Memory difficulties; trouble solving problems; spatial/visual difficulties; social withdrawal; mood and personality changes; dementia.	Tau tangles start in the hippocampus and spread throughout the cerebral cortex. As neurons die, brain regions shrink. Deposits of amyloid-beta plaques are also a primary characteristic of the disease.	5.2 million Americans; likelihood of developing Alzheimer's disease doubles every five years beyond age 65. Alzheimer's disease accounts for 50% to 80% of all dementias.
CORTICOBASAL DEGENERATION	Difficulties with balance and walking, short-term memory, muscle control, speech and comprehension; eventual inability to walk; dementia.	Neurons and glia—the connective tissue that supports nerve cells—degenerate in the cerebral cortex and basal ganglia, predominantly on one side of the brain.	1 in 20,000 people between the ages of 60 and 80; may be more common in women.
FRONTO-TEMPORAL DEMENTIA (FORMERLY PICK'S DISEASE)	Dramatic changes in behavior and personality; inability to speak and understand language; loss of inhibitions.	Abnormalities arise in tau biochemistry and some inclusions appear in the frontal and temporal lobes.	50,000 to 60,000 Americans, with a typical onset in their 50s and 60s; accounts for 2% to 5% of all dementias, but 20% or more of dementias in those under age 65.
PROGRESSIVE SUPRANUCLEAR PALSY	Problems with gait and balance; difficulty controlling eye movements; difficulty with speech; depression; forgetfulness.	Neurofibrillary tangles appear in structures in the brain stem, such as in the substantia nigra, which is also involved in Parkinson's disease; both are characterized by similar motor problems.	20,000 Americans, or 1 in every 100,000 people over the age of 60; more common in men.

Hyman believes that a combination of treatments is likely to be needed, as has been the case in other diseases. “Lower cholesterol plays a big role in preventing heart attacks, but so does controlling blood pressure,” he says. “And to treat most cancers, you need a cocktail of chemotherapeutic agents. So it wouldn't be surprising if we need agents to tackle both A β and tau as well as maybe inflammation and other factors,” he adds.

But for all of the non-Alzheimer's tauopathies, the spotlight is on tau. Tau is a soluble protein that normally binds tightly to MTs and rarely clumps up. The problem comes when excessive and abnormal phosphate groups attach to the protein, causing it to loosen from the MTs and leading

to accumulation of tau inside the neuron. Those filaments of tau, now insoluble, attract other proteins, filling the neuron and eventually leading to death of the neuron. Meanwhile, lacking tau to stabilize them, the MTs unravel and the cell's transport system begins to fall apart. “The cell doesn't get its energy at the proper places at the right time, and the synapses start decaying,” says longtime tau researcher Eckhard Mandelkow of the Max Planck Institute in Hamburg and the German Center for Neurodegenerative Diseases in Bonn. With the synapses impaired, the neuron stops functioning and dies.

Where the tau tangles occur and what type of neurons they affect determine the symptoms of individual tauopathies. Tau deposits in the cerebral cortex are characteristic of FTD,

with symptoms of impulsivity, poor judgment and obsessive behavior. In people who have progressive supranuclear palsy, both neurons and support cells called astrocytes are affected in the brain stem and basal ganglia, causing rapidly progressing and disabling Parkinsonism and eye movement abnormalities. Tau in other brain regions, however, causes corticobasal degeneration. Different strains of tau appear to prefer certain brain regions and specific types of neurons.

Pathologists have long known that tau pathology spreads through the brain one region at a time. But how that occurs wasn't understood until recent mouse studies and cell culture experiments showed that abnormal tau escapes one neuron and is taken up by neighboring cells, a phenomenon not normally seen in cells. "Maybe tau has a tendency to aggregate in brain cells normally, but the healthy brain can get rid of it," says Goedert. "And the younger you are, the better that works."

When a tangle doesn't dissolve, a few particles break out of the cell membrane and into the spaces between neurons, giving tau an opportunity to infiltrate neighboring cells and generate a new tangle. The greater the number of tau aggregates in the brain, the worse the symptoms of dementia. Further proof that tau can leak out of neurons is that the protein shows up in cerebral spinal fluid—a phenomenon that might provide a way to diagnose tauopathies before symptoms appear.

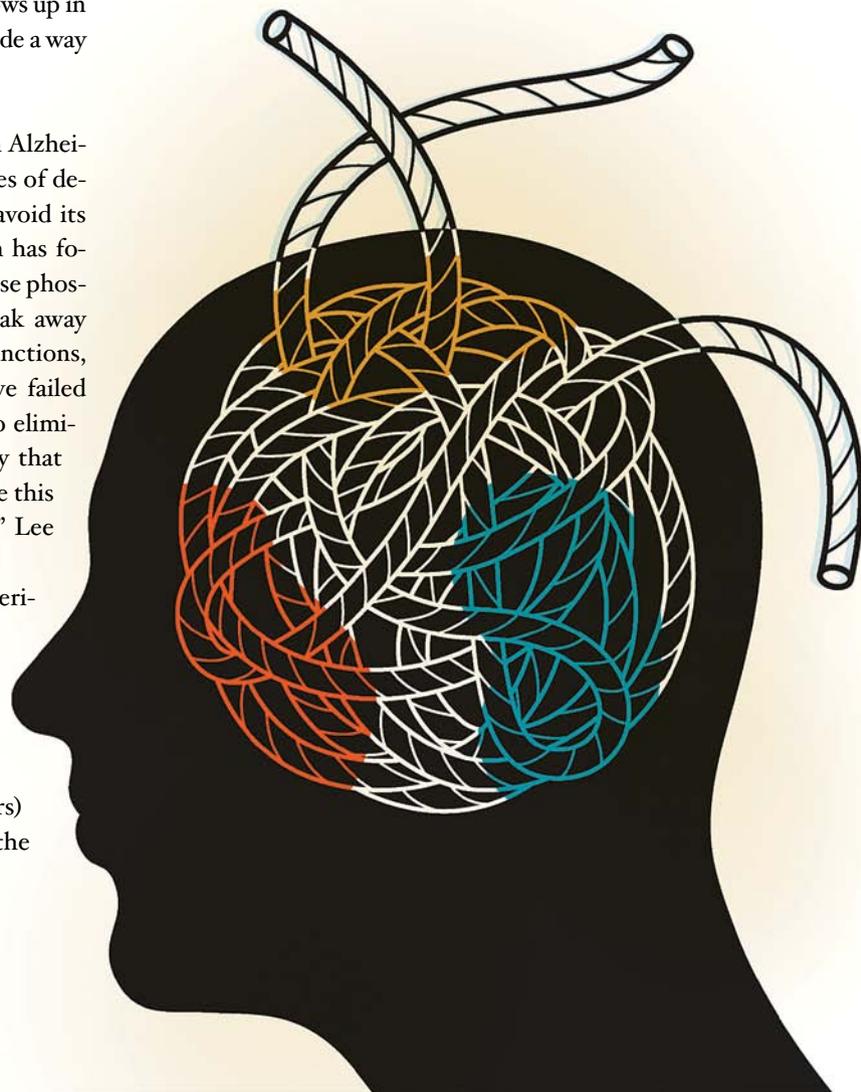
Knowing that problems with tau play a role in Alzheimer's disease as well as in so many other types of dementia puts a premium on finding ways to avoid its destruction. During the past decade, much research has focused on how to inhibit kinases, the enzymes that cause phosphates to accumulate around tau and lead it to break away from microtubules. But kinases have many other functions, and inhibitors designed to reduce their activity have failed in clinical trials, says Virginia Lee. Another idea is to eliminate tangles of tau by turning on cellular machinery that normally gets rid of protein waste. "But if you activate this garbage disposal, you might do damage to the cell," Lee says. "We need to find something more specific."

For several years, Lee and Trojanowski have experimented with using cancer drugs to stabilize MTs that are weakened when tau breaks away. As cancer treatments, such drugs work by preventing the normal disassembly of MTs that must occur so cells can divide—and because they can't replicate themselves, treated cancer cells (and many others) die. But neurons, which don't divide, are immune to the

toxicity of chemotherapy and might benefit from having their MTs shored up.

One problem with that approach is that most chemotherapy drugs can't get past the blood-brain barrier to reach neurons in the brain. But Lee and Trojanowski eventually found one that did, and in 2010 they used that agent, epothilone D, to treat mice they had engineered to develop memory deficits from tau tangles. First, the scientists gave the drug to very young mice that were just starting to develop cognitive impairments. The treatment increased the number of MTs and improved cognition. In a later study, involving older mice whose symptoms had become more severe, the drug not only succeeded at restoring MTs and cognition but also brought a "stunning reduction in tangle pathology, which we didn't expect," says Trojanowski.

Epothilone D and another drug designed to stabilize MTs are now being tested in human clinical trials. If the drugs prove effective at clearing tau tangles, patients would have to take them long term—normally a problem with toxic chemotherapy



“Apparently the brain can cope with tau aggregates for many years. So maybe it’s not too late for someone who has mild cognitive impairment.”

agents. But in mice, very small amounts of epothilone D—just 1% of what would be given to attack cancer—obliterated tau tangles. “Giving such a small dose once a week to people would be way below the threshold at which you would see toxicity and side effects,” Trojanowski says.

Halting tau production in the brain might be another way to reverse the ravages of tauopathies. Hyman’s team and other research groups recently showed that when they turned off the tau gene in mice for six months, nearly all of their tau tangles disappeared—a result that challenged long-held assumptions that tau lesions were irreversible. “But the mouse studies just establish biological plausibility,” says Hyman. “We don’t have the tools to turn off tau in people.”

One potentially better approach that would slow the aggregation involves a drug called methylene blue. Already approved by the FDA for conditions such as pediatric malaria and urinary tract infections, a modified form of the drug is being tested for FTD and mild to moderate Alzheimer’s disease. And Eckhard Mandelkow’s wife, Eva-Maria Mandelkow, also at the German Center for Neurodegenerative Diseases, has shown that the drug—which, like epothilone D, penetrates the blood-brain barrier—can prevent the damaging effects of tau in mice.

But the timing of treatment appears to be crucial. When Eva-Maria Mandelkow used methylene blue to treat mice that were 13 months old (the equivalent of about 40 years in humans) and had severe memory deficits, they didn’t improve. But when she gave the drug at nine months, just before the mice were starting to develop tau tangles and neuron loss, their memory and cognition were restored. “As long as you start before you have real cognitive decline, you have a chance to combat the memory loss,” she says. “Individuals who have a mutation in the tau gene may have pathology for 65 years and are fine until they suddenly develop cognitive decline. Apparently the brain can cope with these aggregates for many years. So maybe it’s not too late for someone who has mild cognitive impairment.”

Other researchers believe that the window of therapeutic opportunity comes when tau problems are localized in one

part of the brain and before symptoms arise. This is a time when immunotherapy—an approach that has been tried, unsuccessfully, to treat Alzheimer’s disease—might work to prevent widespread neurodegeneration. “Many studies with immunization against tau have shown beneficial effects in mouse models of tauopathy,” says Goedert.

Despite all of the advances that have been made in understanding tau, much more needs to be learned. “There is a vibrant debate about whether tau aggregates are the most toxic or if we should be going after oligomers, a pre-filament form of tau, or soluble tau fragments,” says Hyman.

But neither soluble nor insoluble forms of abnormal tau are good. “It’s like asking whether you’d rather have toxins all over your neighborhood or piled together in a toxic waste dump at the end of the block,” he explains. Emerging research may conclude that attacking a form of tau other than tangles is more effective. Yet the important point is that a clear therapeutic target now exists. “We have shifted away from trying to fix impaired memory in Alzheimer’s disease or eye movement problems in progressive supranuclear palsy,” says Hyman. “Now we’re focused on the cause, which clearly involves tau.” ■

→ DOSSIER

1. “Tau Pathology and Neurodegeneration,” by Maria Grazia Spillantini and Michel Goedert, *The Lancet Neurology*, June 2013. A comprehensive overview of the most recent research on the genetics of tau dysfunction, the role of tau in dementias, the way tau is thought to spread in the brain, and the interaction of amyloid-beta and tau in Alzheimer’s disease.
2. “Developing Therapeutic Approaches to Tau, Selected Kinases and Related Neuronal Protein Targets,” by Virginia M-Y Lee et al., *Cold Spring Harbor Perspectives in Medicine*, 2011. The authors speculate that ridding the brain of tau tangles—which occur when memory deficits start—may be more effective than purging the amyloid-beta plaques of Alzheimer’s disease, which form many years before symptoms do.
3. “Artistic Creativity and Dementia,” by Zachary A. Miller and Bruce L. Miller, *Progress in Brain Research*, Volume 204, 2013. A fascinating account of a subset of patients with frontotemporal dementia who develop new creativity in the visual or verbal arts.