An eye on…

Larry Goldstein, famous for his plainspoken attitude, is one of the few big names in the Alzheimer field who bucks the amyloid hypothesis.

Goldstein says the long-favored hypothesis, which proposes that the amyloid-beta protein is the initiating factor in the disease, doesn't adequately explain many observations—such as the poor correlation between the deposition of amyloid plaques and cognitive problems. "It's molecularly not explicit," he says. "What is it that amyloid does to neurons? Does it activate a receptor, poke a hole, activate kinases? There are a lot of different suggestions, but they're not precise."

Goldstein, a professor of cellular and molecular medicine and a Howard Hughes investigator at the University of California, San Diego, favors an alternate model that pins the start of the downward spiral in Alzheimer disease to transport defects in the axons of nerve cells. The resulting 'traffic jam' of motor proteins, organelles and vesicles causes the axons to swell, he says, and eventually leads to Alzheimer disease.

In a paper published last year, Goldstein and colleagues identified these defects in postmortem brains from individuals who showed early symptoms of the disease, but no amyloid plaques (*Science* **307**, 1282–1288; 2005). He also identified the defects in mouse models—more than a year before the mice developed classical disease pathology.

Goldstein says one of the big problems in the field is that there are no good animal models of the disease. He is instead turning to human embryonic stem cells that he has coaxed to differentiating into human neurons. "The problem is that humans are not just big mice," he says. "We don't know that the physiology and biochemistry of the human neuron is identical to that in animals."

Meredith Wadman, Washington D.C.

"Amyloid-beta is necessary and it's very early—and that's what makes it a beautiful target."

Indeed, most therapies in trials are aimed at reducing aggregates of the protein. Even if only one of them works, it would lend much-needed clinical credibility to the amyloid camp.

That resolution came tantalizingly close once before. In late 2001, Elan Corporation and Wyeth-Ayerst Laboratories set out to test an amyloid vaccine, AN-1792, in about 300 individuals. In animal models, the vaccine had effectively cleared plaques and improved memory. But in January 2002, the companies had to halt a phase 2 human trial after 18 participants developed meningoencephalitis, a potentially fatal inflammation of the brain.

Evidence from the trial showed that, as in the mouse models, the vaccine successfully cleared amyloid plaques from human brains. Whether it improved memory is more controversial, because the trial ended abruptly and there is limited information from follow-up studies of the participants. But at the very least, says Dale Schenk, chief scientific officer of Elan, "what that means is that at least one therapeutic approach extrapolates to patients, which is pretty darn great."

The company has since discontinued work on the vaccine, but is testing bapineuzumab, a monoclonal antibody to amyloid-beta, to treat the disease. Preliminary reports of the antibody's effects have been positive, and results from a phase 2 trial are expected by the end of this year.

Of mice and men

Every animal model for Alzheimer disease is based on the same premise—that overproduction of the amyloid-beta protein somehow triggers a cascade that eventually damages neurons and causes dementia.

Some of the mice have mutations seen in familial or early-onset Alzheimer disease and form the characteristic plaques seen in diseased brains. Others carry mutations in the protein tau and recreate the tangles, another hallmark of the disease.

"In that capacity, the animal models have been extremely successful and that's no trivial thing," notes Karen Duff, associate professor of neuroscience at New York University.

Research on the disease, for both mechanisms and treatments, has been based almost exclusively on these mice. But even their staunchest supporters acknowledge that there are glaring flaws.

For instance, only mice that carry two or more mutations reproduce all the physical features of an Alzheimer-addled brain. And most never exhibit the extent of neurodegeneration seen in people afflicted with the disease.

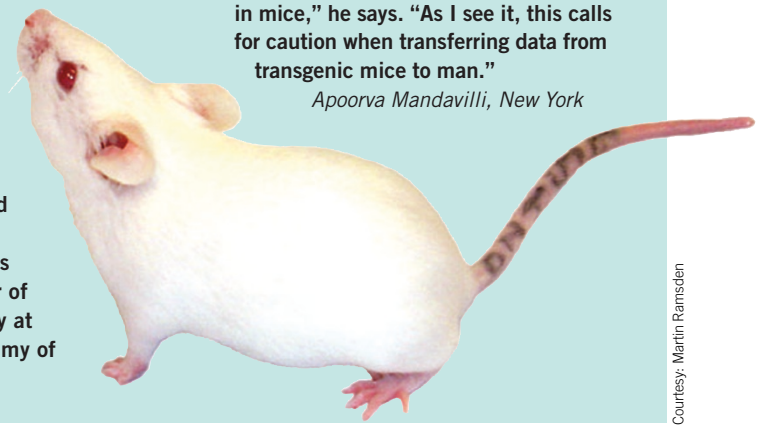
More important, the mice have never shed much light on the mechanisms involved in the disease, such as the relationship between amyloid-beta and tau, the two key molecules.

Because the mice are based on mutations in familial Alzheimer disease, it may be that they only model the rare form of the disease and not the more common sporadic form, suggests Kaj Blennow, professor of clinical neurochemistry at the Sahlgrenska Academy of Göteborg University.

Blennow notes that in the animal models, at least 47 molecules—a bizarre list ranging from cholesterol drugs and painkillers to blueberries and curry spice—have been shown to reduce the number of amyloid plaques.

"Hopefully, some of this is right, but I think there's a risk that there must be some difference between the mice and patients that makes it easier to improve things in mice," he says. "As I see it, this calls for caution when transferring data from transgenic mice to man."

Apoorva Mandavilli, New York



Courtesy: Martin Ramsden