~5% — Average lifetime risk of developing Alzheimer disease by age 65.
20–40% — Average lifetime risk of developing Alzheimer disease by age 85.

If drug companies have targeted amyloid-beta, it has less to do with an overwhelming belief in the hypothesis and more because it is the most practical strategy, says Schenk. "Let's be very frank, as long as something is a hypothesis, it's still in testing," he says. "It's really in the eye of the beholder."

Schenk says the series of molecular steps that lead to amyloid-beta, such as the enzymes that cleave the precursor protein, yield clear targets for drug development. At the same time, developing therapies has been far from easy because the main target is in the brain, one of the key enzymes has a difficult structure and another is likely to have wide-ranging effects in the body.

Companies are increasingly also looking for therapies based on tau—which binds and supports the microtubules that enable molecular transport down neurons—such as microtubule-stabilizing agents.

Tau tales

Not long ago, there was an acrimonious debate between two groups of researchers who called themselves BAPtists—or those who supported the amyloid-beta protein—and tauists, who believed that tau was the central molecule in Alzheimer disease.

"I was vocal about tau because I thought the field was putting too much emphasis on one 42–amino acid protein," says John Trojanowski, who along with his wife and fellow Alzheimer disease researcher Virginia Lee directs the Center for Neurodegenerative Research at the University of Pennsylvania (see Profile, page 752). "We don't know enough about the disease to put all of our eggs in one basket."

But the two groups have since settled their differences, merging their ideas into a central 'Unitarian' premise. According to this theory, amyloid-beta is involved at an early stage of the disease and triggers a series of steps, at some point involving the protein tau, that result in the plaques, tangles and memory loss.

One of the most credible criticisms of the amyloid hypothesis is that it has not yet been able to explain exactly how this happens. Critics raise various other points: for example, the most widely used mouse model, Tg2576, overexpresses the amyloid precursor protein—one of the mutations seen in familial disease—but doesn't form tangles and more closely resembles age-associated memory impairment than Alzheimer disease. And some tau models, which express little amyloid, develop the severe memory problems associated with Alzheimer disease.

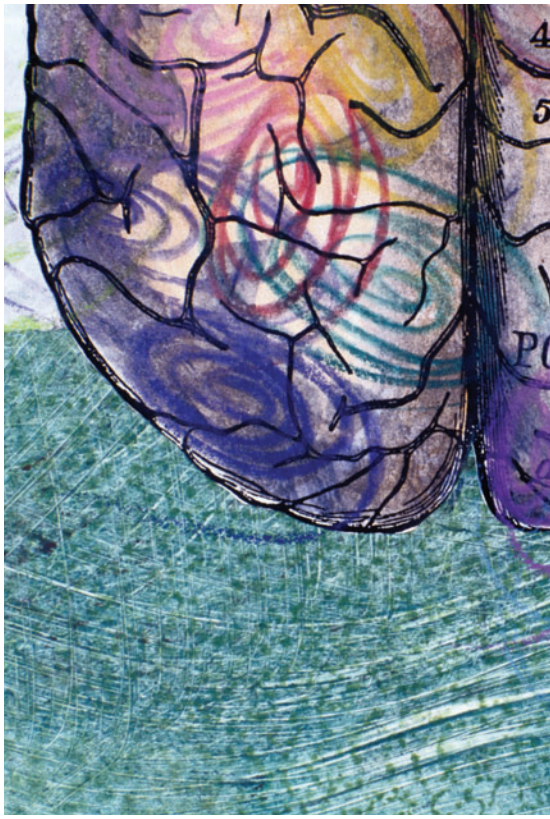
As a result of surprises like this, many sworn amyloid supporters have begun to work on tau. "I don't think amyloid-beta is sufficient to cause Alzheimer disease, that's why I'm interested in tau," says Ashe, who developed the Tg2576 and several dozen other mouse models.

Ashe and several others are trying to uncover the molecular links between amyloid-beta and tau that might explain how Alzheimer disease develops. The many trials based on removing amyloid aggregates might confirm—or refute—the amyloid hypothesis long before then.

But in the meantime, a small group of researchers continue to plead for greater attention to alternative theories. With a disease such as this, they say, the more ideas about how it all began, the better.

"You don't need a new religious leader," says Smith. "You need to tell all the followers to disband and get thinking."

Apoorva Mandavilli is senior news editor of Nature Medicine.



An eye on…

The thing **Mony de Leon** finds most disheartening about his job is watching healthy study volunteers develop Alzheimer disease.

A psychiatrist at New York University, de Leon is developing imaging tools and biomarkers to diagnose the debilitating disease before symptoms develop. In studies that can last 20 years, he often has to watch once-healthy individuals develop diseased brains.

In those afflicted with Alzheimer disease, abnormal forms of proteins called tau and amyloid-beta accumulate in the brain, and the hippocampus—the region of the brain responsible for memory—shrinks. But here's the rub: there are no clear estimates for how much of these proteins exist in a normal brain. The key to creating diagnostic tools, de Leon says, is to observe healthy people as young as age 50 and assess how these disease markers change over time. The results would help scientists set standards for comparison and start treatment early, when it is likely to be most effective.

Using data from his studies, de Leon says he can predict with 90% accuracy which individuals with mild cognitive impairment, a precursor to Alzheimer disease, will go on to develop the disease (*Neurobiol. Aging* **27**, 394–401; 2006). He hopes to collect enough information to be able to set standards for disease markers even in healthy, young people.

When de Leon began his career in the 1970s, few scientists recognized the difference between normal aging and cognitive disease. "Developing early diagnostic tools seemed so remote and so daunting a task," he says, "that I considered it the last thing I'd do before I died."

Emily Waltz, New York