

Alzheimer's Disease — How Long Before We Find a Cure?

By Raymond Barglow, Special to the Planet

Thursday February 25, 2010 - 08:46:00 AM

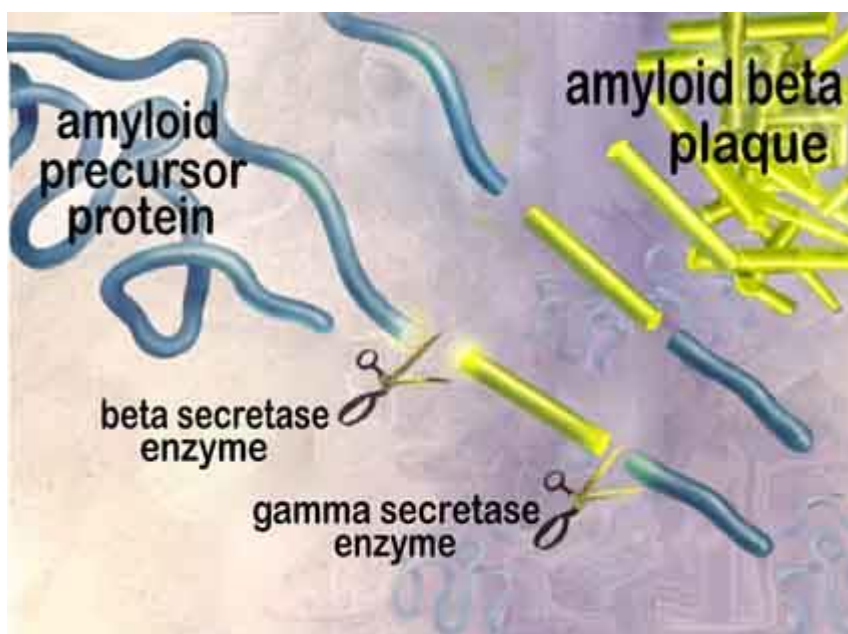
Today more than 5.5 million Americans have Alzheimer's, and 10 million caregivers will attend to them during the coming year. If we do not find a way of preventing this disease, there will be about 8 million cases by 2030 and as many as 16 million in 2050. Alzheimer's is economically as well as emotionally burdensome: direct and indirect costs of the disease amount to over \$100 billion annually, according to the National Institute on Aging.

What is to be done? It's been over a century since the German physician Alois Alzheimer described this disease in 1906. Will we remain unable to heal or prevent this fatal illness? This reporter spoke with scientists at UC Berkeley and elsewhere to better understand what we currently know and what we have yet to learn about this disease.

Were Alzheimer's caused by a germ, it would probably be much easier to remedy. Bacteria are a familiar kind of enemy, one that a traditional medical approach is designed to combat. You just ride into Dodge City and kill the bad guys. (Unfortunately, the "bad guys" often mutate and learn to survive the drugs we throw at them—but that's a story for another time.) Alzheimer's is a more complex adversary. Although we are learning to use imaging technologies to observe the havoc being wreaked in the brain, we haven't been able so far to clearly identify the responsible party or parties.

The most persuasive and widely accepted hypothesis about Alzheimer's is that it essentially involves the accumulation in the brain of a protein called "amyloid beta." A protein consists of one or several long strings of amino acids and routinely forms, folds, and unfolds under the guidance of enzymes and so-called "chaperone" molecules. Enzymes also slice protein strings, and it's this last action that appears to be implicated in the development of Alzheimer's disease.

Two enzymes, beta secretase and gamma secretase, clip an amyloid beta segment (colored yellow in the diagram) out of a larger, and entirely normal, parent molecule, amyloid precursor protein (blue). The clipped segments, in soluble form or clumped into plaques, damage neurons and synapses.



Because amyloid beta accumulation is a hallmark of Alzheimer's disease, it's an obvious therapeutic target. There are multiple points of possible intervention into the amyloid-related sequence of events—the so-called "amyloid cascade"—that eventually cripples the brain. Substances are being explored that could inhibit or halt the cleaving of the precursor protein by the beta and gamma secretases.

Another approach is to prevent the amyloid beta segments from attaching to one another. Yet another is to clear the plaque deposits from the brain, once they have formed.

All of this seems straightforward enough, and in the early nineties, when details of the amyloid cascade came to light, there was optimism that the seemingly inexorable processes leading to Alzheimer's could be interrupted.

Now, as a new decade gets under way, the story appears to be more complicated than many anticipated. Alzheimer's may turn out to be an illness that has multiple, interrelated molecular causes. Still, it's likely that the amyloid cascade plays an important role in the disease, and many scientists are trying to understand it.

Here at UC Berkeley, the bioengineering team of Dr. Teresa Head-Gordon is studying the self-assembly dynamics of proteins; this research may unlock the mysteries of many diseases in addition to Alzheimer's. In the UC Berkeley lab of Dr. Randy Schekman, graduate student Regina Choy is studying the "trafficking" (directed movement within the cell) of the precursor protein that may lead to Alzheimer's. Up on the hill, at the Lawrence-Berkeley National Laboratory, Dr. Bing Jap and his colleagues have been studying proteins that are active within cell membranes, including the gamma secretase enzyme mentioned above.

Such research has revealed a great deal about molecular processes that are characteristic of Alzheimer's disease. Advancing toward the discovery of effective remedies to the disease will also require, though, studies of living human subjects. But it has been difficult in the past for such studies to follow the disease in its early stages. By the time a person develops the tell-tale symptoms of the disease such as memory loss, a lot of neurological damage has already been done. Yet progress is being made on observing the disease further "upstream," as it were, years before the full-blown disease becomes manifest. The laboratory of Dr. William Jagust, a scientist at the UC Berkeley School of Public Health and at the Helen Wills Neuroscience Institute, uses PET scans and magnetic resonance imaging to measure amyloid deposits. That information can help to identify people whose cognition is currently intact but who—judging from their amyloid level and certain neural and behavioral measures—are at high risk for Alzheimer's. We can then study these individuals over time in order to learn more about the neurological changes that lead to the disease.

People who are likely to get Alzheimer's obviously make the best experimental subjects in clinical trials that seek to establish which preventive therapies work and which do not. But clinical trials of this kind, which could last a decade or longer, are going to be enormously expensive, requiring a level of funding far above what is currently available.

Given that Alzheimer's disease threatens to devastate our nation's health care system, the current level of support for research into the disease is very low. Zaven Khachaturian, former director of the NIH Office of Alzheimer's Disease Research and the chief architect of NIH Alzheimer's

research programs, told the Berkeley Daily Planet that "The amount of funding going into Alzheimer's research has been flat and is actually going down." The NIH provided less than half a billion dollars for the research in 2009. Cancer research, on the other hand, received 13 times more support.

There is a movement building to increase funding for Alzheimer's research. A Congressional Task Force established an "Alzheimer's Study Group" that proposed in 2009 that a project to overcome Alzheimer's be made an urgent national priority, and that an "Alzheimer's Solutions Project Office" be created within the federal government.

"Our effort has to be major, akin to the Manhattan Project or the Apollo project to land someone on the moon," according to Khachaturian. "We will ask President Obama for a commitment of this kind ... [aiming] to prevent the disease within the next decade, by the year 2020."

This sense of urgency is an appropriate one, even if we consider only the economic cost of the disease. However the current health care debate in this country is resolved, reform will fail unless Alzheimer's disease is defeated.

NOTES

I wish to thank the scientists and research advocates who discussed with me current directions and prospects of Alzheimer's research. Providing guidance early on was: Laurel Martin-Harris, graduate student at the Brain Research Institute, UCLA. Also very helpful were:

Regina Choy, graduate student, Department of Molecular and Cell Biology, UC Berkeley

Elizabeth Edgerly, Ph.D., Chief Program Officer, Alzheimer's Association

Teresa Head-Gordon, Ph.D., Department of Bioengineering, UC Berkeley

William Jagust, M.D., UC Berkeley School of Public Health and Helen Wills Neuroscience Institute in Berkeley

Bing Jap, Ph.D., Senior Staff Scientist, Lawrence Berkeley National Laboratory

Zaven Khachaturian, Ph.D., President, Prevent Alzheimer's Disease 2020;
Chief Editor, Alzheimer's & Dementia: the Journal of the Alzheimer's
Association; Senior Science Advisor to the Alzheimer's Association; Senior
Science Advisor to Cleveland Clinic Lou Ruvo Center for Brain Health

Edward Koo, MD, School of Medicine, UC San Diego