Working to change the course of Alzheimer's disease

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Alzheimer's Disease: A Century-long Challenge

In 1906, the German psychiatrist, Dr Alois Alzheimer, reported abnormalities in the brain of a patient, Frau "Auguste D," who died with severe dementia (Figure 1).[1] Over the last 100 years, great strides have been made toward understanding the disease that bears his name.

Alzheimer's disease (AD) is part of a group of disorders, known as dementias, that are characterized by cognitive decline and behavioral problems. AD accounts for most of the dementia cases diagnosed after age 65.[2]

Concerted efforts by scientists around the world have led to a more in-depth understanding of the biological basis of AD. These findings have paved the way for new interventions that target the pathophysiology of the disease, in the hope of slowing its progression or preventing it altogether.[3]

Despite these remarkable inroads, the final outcome for persons with AD has not changed significantly over the last 100 years. The prognosis for now is the same: AD remains a progressive, destructive, and fatal disorder with no known cure. Current treatments may offer temporary relief of symptoms.[5] However, in the absence of agents that can significantly modify the course of the disease, AD remains an area of exceptional clinical need.

Today, there is intense focus on developing new strategies for risk assessment along with better techniques for earlier detection of AD. In addition, major research is underway to develop disease-modifying drugs that, when used early in the disease process, hold the potential to delay or halt AD—a disease that is destined to reach epidemic proportions in the near future.

Figure 1. Dr Alois Alzheimer and his patient Frau "Auguste D." Courtesy of Professor Konrad Maurer.[4]

The Next 50 Years: An Explosion in the Elderly At-risk Population

The size of the elderly population is growing at an unprecedented rate worldwide and will more than double in the United States alone by the year 2050 when roughly 87 million people will be over the age of 65 (Figure 2).[6] Thanks in part to health education and advances in the treatment of chronic diseases, more and more people are living well into their 80s.[7] The sheer number of baby boomers and their increased life expectancy are the forces driving this explosion.

As age is a known risk factor for developing AD, these changing demographics predict an AD epidemic in the not-too-distant future. In fact, AD prevalence rates double every 4 years of life after age 65.[8] Today, there are an estimated 4.5 million persons in the United States with AD—a number that is expected to triple to 13.2 million by 2050 without major treatment advances (Figure 3).[9]

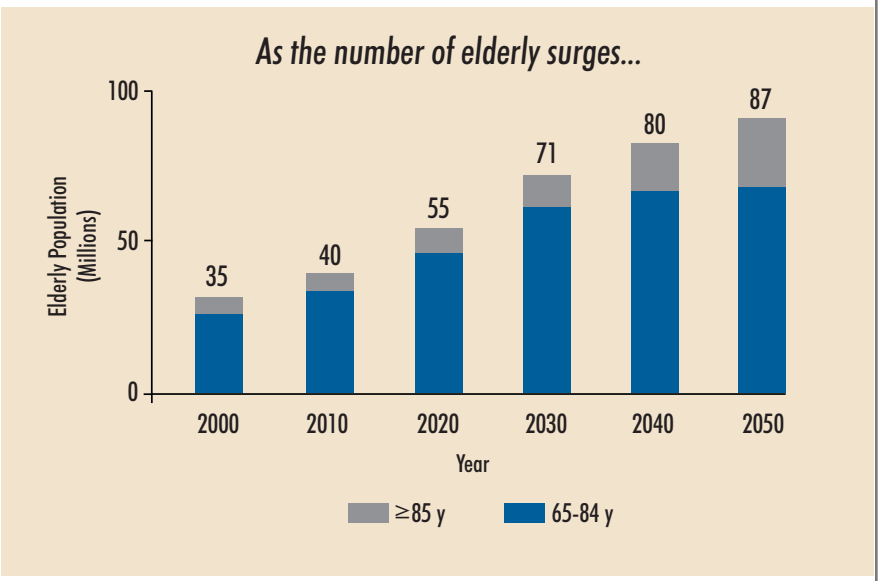


Figure 2. Projected population of the elderly in the United States: 2000 to 2050.[6]

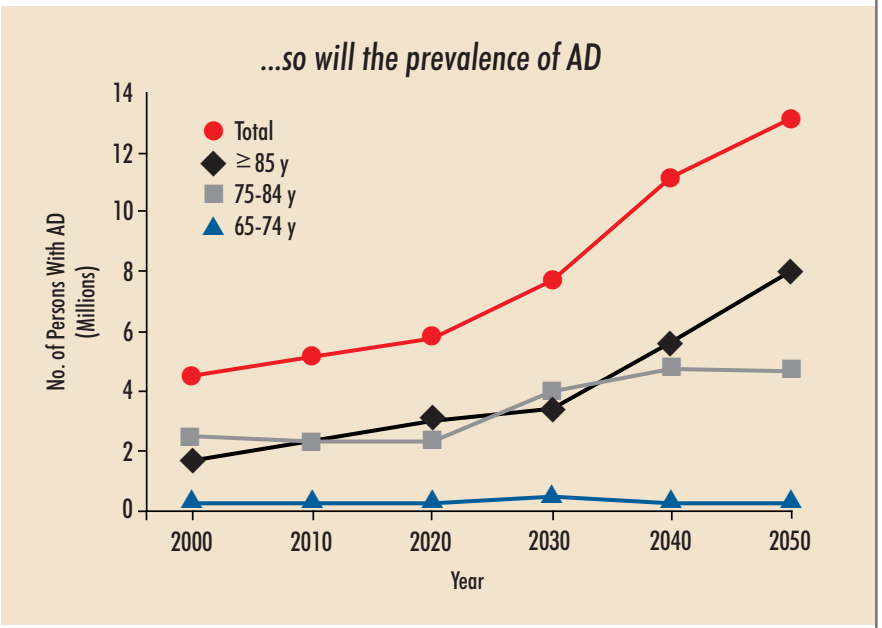


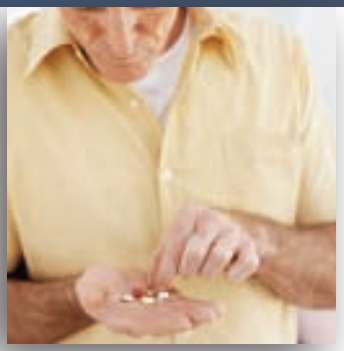
Figure 3. Projected growth in the number of Americans with AD through the year 2050. Reproduced with permission.[9]

The Far-reaching Economic Impact of AD

It is difficult to place a price tag on AD. However, the National Institutes of Health estimate a staggering cost of $100 billion per year in the United States alone. This makes AD as costly as cancer and third only after substance abuse and heart disease.[10] The cost to American business is $61 billion per year due to lost productivity, absenteeism, worker replacement for family caregivers, and overall health care costs.[11]

The financial burden for patients and their families is equally overwhelming. Many families choose to take care of their loved one at home for as long as possible, with yearly costs as much as $17,700 for severe dementia.[12]

Most persons with AD will eventually be institutionalized, which adds significantly to the overall financial burden to society as a whole. In 2005, the average price for a private room in a nursing home was $74,095 with specialized Alzheimer services costing even more.[13]



The Toll on Patients

The greatest costs to people suffering from AD have little to do with economics but instead speak to the fears of a foreshortened future and the eventual loss of dignity and independence. People with AD lose the very qualities that make them human—memory, reasoning, personality, and language.[3]

Many experts believe that AD first appears as a syndrome known as mild cognitive impairment (MCI), a transitional stage that is characterized by memory impairment without other signs of cognitive loss or impaired function.[14] It is estimated that 40% of those identified as having MCI will go on to a diagnosis of AD within 3 years.[2] As scientists and clinicians learn more about MCI, they will be better able to predict at-risk individuals who might benefit from early therapeutic intervention.

In patients who go on to develop dementia, the rate of deterioration varies. However, over the course of several years, impaired judgment, increasingly severe memory loss, and confusion inevitably ensue. Patients become less able to manage even the simplest tasks or perform their usual activities of daily living. They also often develop behavioral problems, such as agitation, delusions, wandering, and physical aggression. Eventually, full-fledged dementia occurs, motor and sensory skills are lost, and patients become bedridden and unresponsive to their environment.[5]

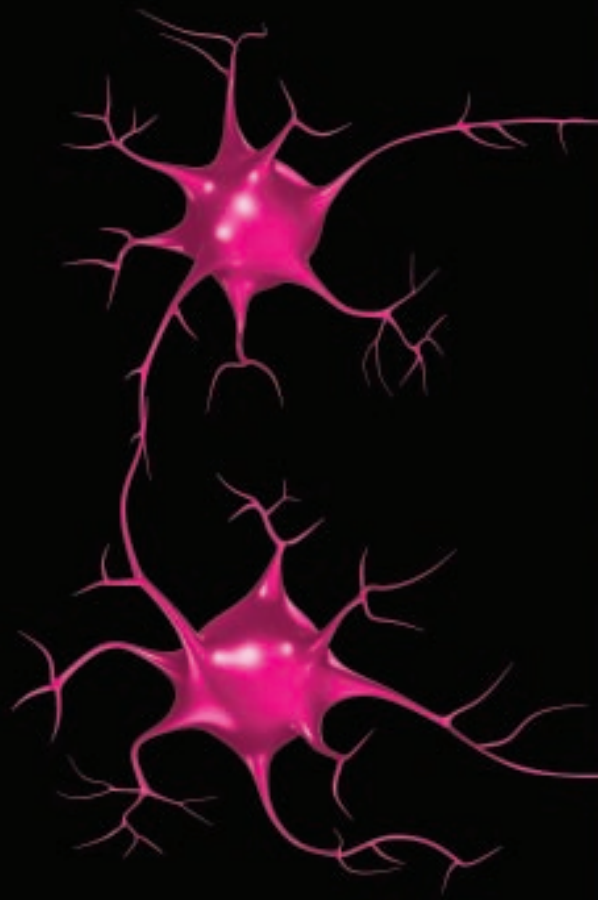
The Consequences for Caregivers

The 24-hour-a-day task of bathing, toileting, dressing, feeding, and ensuring the safety of a loved one is exhausting and often leads to psychological problems and medical illness for caregivers, some of whom are elderly and in poor health themselves.[15] Spouses of persons with dementia are at an approximately 25% higher risk of dying within a 9-year period vs persons whose spouses do not have dementia.[16]

Caregivers of parents with AD, who in many cases are working women, are also susceptible to personal or work-related problems.[17] A survey of caregivers conducted by the Alzheimer's Foundation of America found that those who were caring for a parent with AD felt abandoned by their extended family, had less time for their own family, and often had to resign from their job.[18] Indeed, caregiver distress, not patients' behavior problems or inability to care for themselves, is often the decisive factor leading to nursing home admission.[15]

Myriad: working to change the course of Alzheimer's disease...

inside & out



After a century of research, patients with AD and their families, along with health care professionals, can be encouraged that progress is indeed being made to impact the devastation caused by AD.

Myriad Pharmaceuticals, Inc., recognizing the tremendous unmet need to stem the tide of AD, is working at the interface of science and patients' lives to develop a novel intervention strategy for AD. The Company hopes that this work will change the course of AD from the inside (by slowing or preventing AD progression) and from the outside (by preserving cognitive and functional abilities) for patients worldwide.

MYRIAD®

*Researching a **SALA*** strategy for an Alzheimer's solution*

** **S**elective **A**β_{42}-**L**owering **A**gent*

Brain Changes in AD

Although physicians use a variety of criteria and techniques to reach a diagnosis of AD, diagnostic certainty can only be achieved at autopsy—thereby confirming brain atrophy (Figure 4) and the microscopic hallmark lesions of AD. These lesions, known as amyloid plaques (Figure 5) and neurofibrillary tangles (Figure 6), are found in specific areas of the brain, including those that control memory and cognition.[3,19]

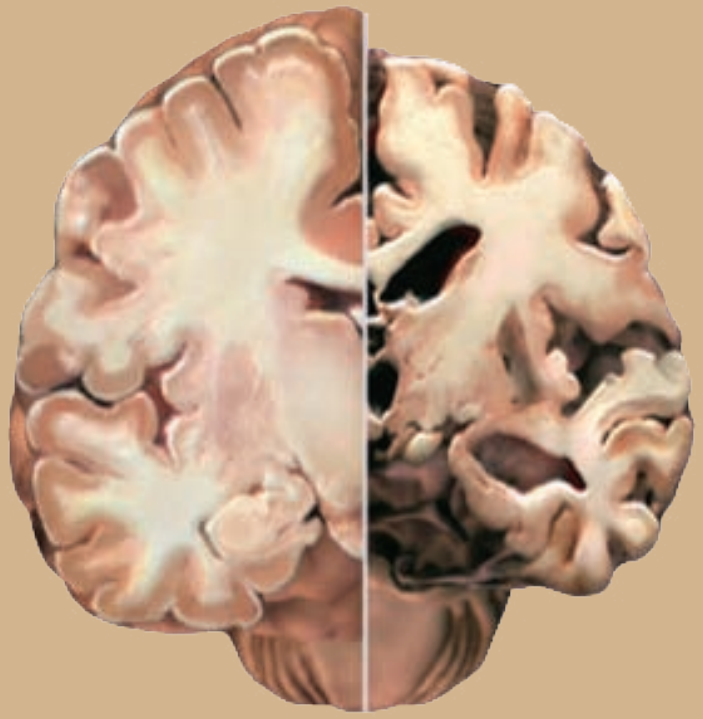


Figure 4. Cross-section of healthy brain (left) vs advanced AD brain (right) showing structural and brain volume changes. Used with permission from the Alzheimer's Association. ©2006.[20]

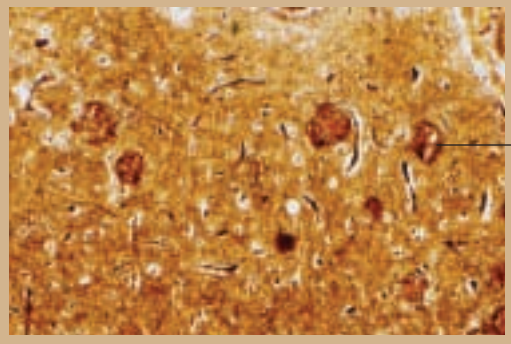


Figure 5. Amyloid plaques in a patient with AD. Photo courtesy of Daniel Christensen, MD. University of Utah, Salt Lake City, UT.

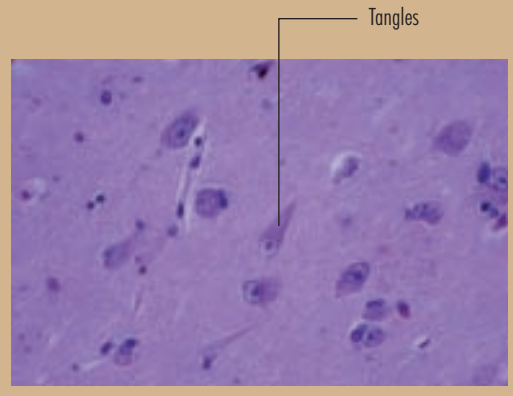


Figure 6. Neurofibrillary tangles in a patient with AD. Photo courtesy of Daniel Christensen, MD. University of Utah, Salt Lake City, UT.

Pathways to Pathology—The Amyloid Hypothesis

Research over the last 20 years has led to a better understanding of the basic biology of plaque and tangle formation. These findings, along with genetic evidence, strongly support the "amyloid hypothesis" as the leading theory for the cause of AD.[19,21]

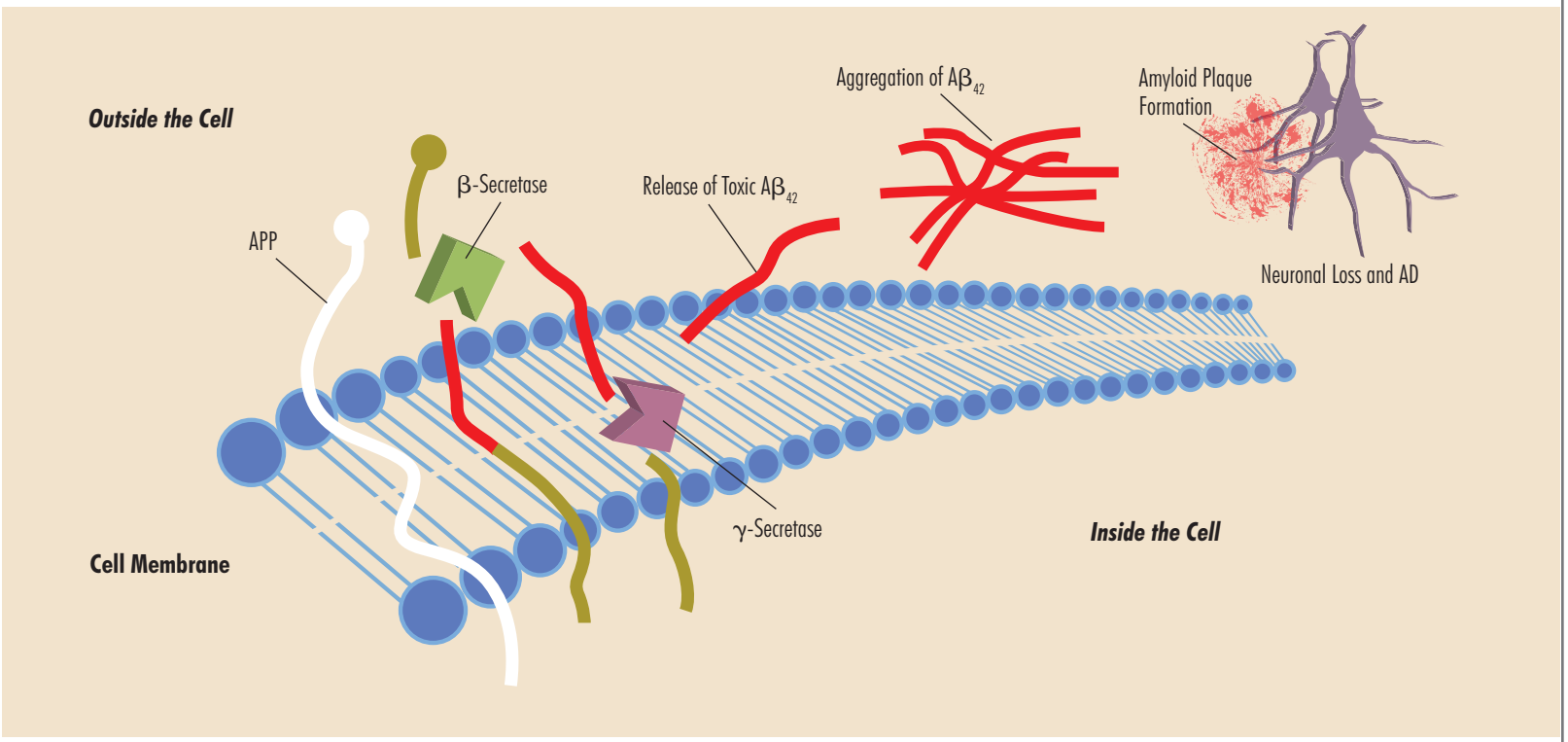


Figure 7. The process leading to amyloid plaque formation, neuronal loss, and AD.[23]

According to this hypothesis, it is altered production, aggregation, and deposition of the amyloid beta (Aβ) protein that results in amyloid plaque formation. This process initiates a cascade of pathological events leading to neuronal loss, impaired cell-to-cell communication, and ultimately the cognitive and behavioral dysfunction of AD.[19,22]

Amyloid plaque formation begins with the amyloid precursor protein (APP), a protein that is embedded in the cell membrane. In neuronal cells, APP can be processed by multiple pathways—one of which leads to development of AD. In this pathway-to-pathology, APP is cut first by the enzyme β-secretase and then by γ-secretase to form Aβ fragments of varying lengths. The fragment of most interest is the peptide known as $A\beta_{42}$. It is the accumulation and aggregation of the toxic $A\beta_{42}$ fragment that triggers a host of downstream processes that lead ultimately to neuronal cell death and AD (Figure 7).[19,21,23,24]

Amyloid-based Intervention Strategies—Stopping AD at the Start

Many researchers are focusing on attacking AD at its source by developing new drug candidates that interfere at various points along the amyloid cascade (Figure 8).[19,24]

It is their hope that successful intervention early in the disease process will prevent downstream pathological processes and delay the onset, slow the progression, or even stop AD before it starts. These so-called disease-modifying treatments may also help improve symptoms by rescuing surviving neurons.

Several anti-amyloid agents are already in various stages of testing to determine their safety, efficacy, and potential to modify the course of AD. These include:

1. **β-Secretase inhibitors**—to block the first enzymatic cleavage of APP[19,24]
2. **γ-Secretase inhibitors**—to block the second enzymatic cleavage of APP and the subsequent formation of Aβ and its toxic fragments[19,24]
3. **Selective $A\beta_{42}$-Lowering Agents (SALAs)**—to reduce production of the toxic $A\beta_{42}$ fragment through modulation of γ-secretase[19,24]
4. **Immunotherapies**—to stimulate the host immune system to recognize and attack Aβ or to provide antibodies that prevent Aβ plaque deposition or enhance plaque clearance[3,19,24]
5. **Anti-aggregation agents**—to prevent Aβ fragments from aggregating or to clear aggregates once they are formed[19,24]

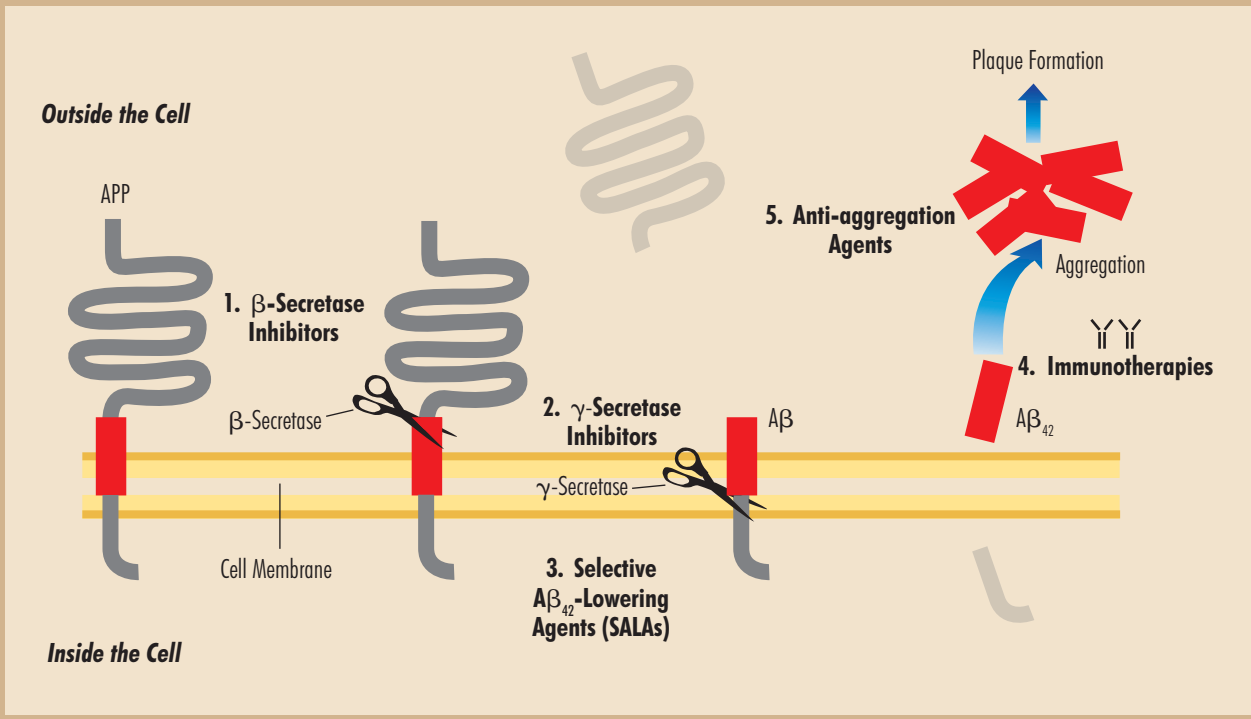


Figure 8. The Aβ pathway and targeted sites for anti-amyloid treatments that may have the potential to modify the course of AD. Adapted with permission.[24] ©2003. American Society for Clinical Investigation. All rights reserved.

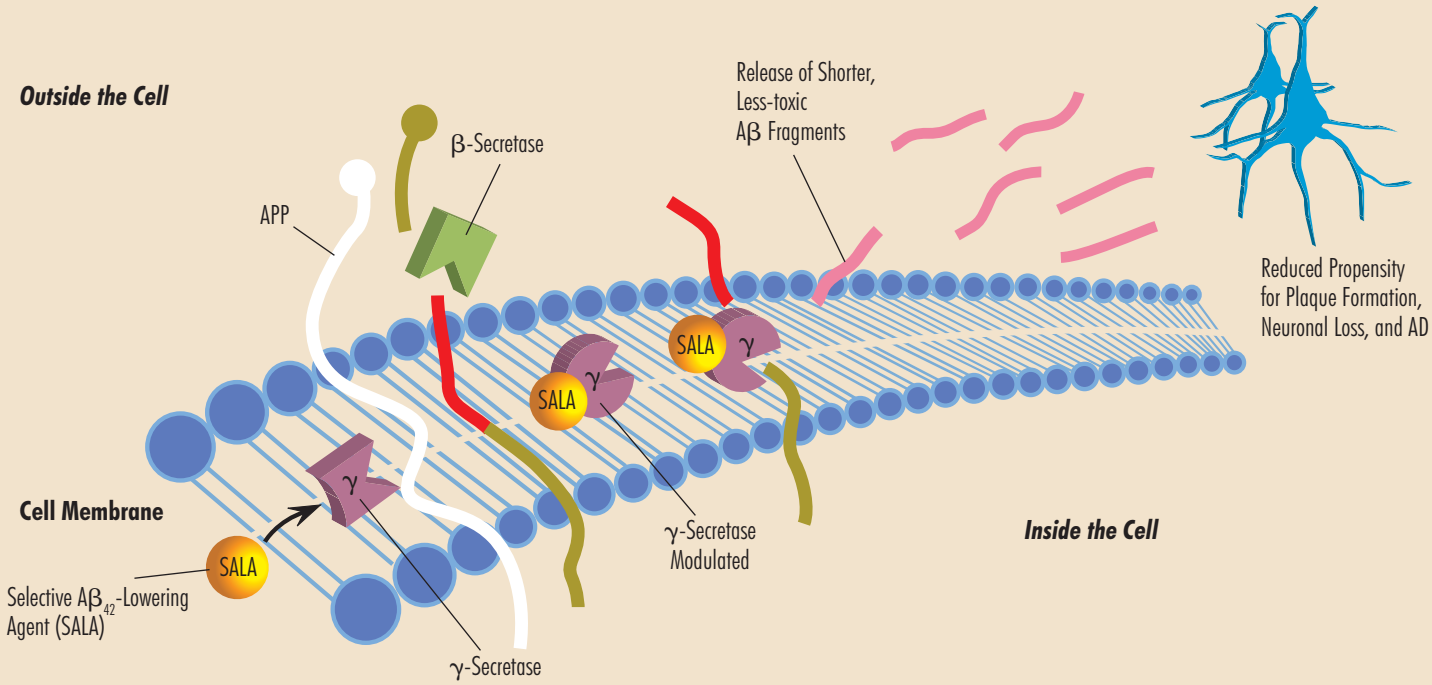


Figure 9. A SALA intervenes early in the disease process, modulating the activity of γ-secretase to form shorter, less-toxic Aβ fragments—thus reducing the risk of plaque formation, neuronal loss, and AD.[19,24-26]

Myriad—Working on a SALA Strategy for an Alzheimer's Solution

Myriad Pharmaceuticals, Inc., is currently developing a Selective $A\beta_{42}$-Lowering Agent (SALA) for the potential management of AD.

Research has shown that a SALA works by modulating, rather than inhibiting, γ-secretase to shift production away from $A\beta_{42}$ toward the generation of shorter, less-toxic fragments of Aβ (Figure 9). Reduced production of $A\beta_{42}$ would prevent development of amyloid plaques that are known to be associated with AD. In addition, unlike γ-secretase *inhibitors*, the *modulation* mechanism of a SALA does not appear to interfere with the function of other important γ-secretase activities.[19,24-26]

The ultimate goal is to determine if selective lowering of $A\beta_{42}$ will lead to an entirely new way of managing the cognitive and functional decline in patients with AD while also modifying the course of the disease. Clinical trials are ongoing to test this hypothesis.

Potential Benefits of Disease-modifying Therapies

The advent of new therapies designed to both treat the symptoms of AD and modify its course would represent a major advance in the field and could also reduce the overall number of people suffering from the disease. For example, if treatments that delay disease onset by 6.7 years were available by 2010, the number of persons with AD in the year 2050 would be reduced by 38%.[27] The economic benefits would be equally compelling—with a 1-year delay in disease onset resulting in a savings of billions of dollars per year.[28]

About Myriad

Myriad Genetics, Inc., develops diagnostics and therapeutics independently through its two subsidiaries: Myriad Genetic Laboratories, Inc., and Myriad Pharmaceuticals, Inc.

Myriad is located in the foothills of the Wasatch Mountains in Salt Lake City, Utah.

Myriad Genetic Laboratories, Inc., is a world leader in the prediction and prevention of disease through hereditary risk assessment. The Company's focus is on cancer predictive medicine, providing tests to determine increased risk of cancers including breast, ovarian, colon, endometrial, and melanoma.

Myriad Pharmaceuticals, Inc., is a leading biopharmaceutical company. The Company's strategy is to develop novel health care products in areas of critical need and to address some of the most pervasive diseases of our time. Myriad Pharmaceuticals, Inc., is currently developing therapeutics that include new drug candidates undergoing clinical trials for Alzheimer's disease and cancer.

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Disclaimer: Every effort has been made to ensure the accuracy of the information in this brochure via review of the published literature and through approval by a medical expert in Alzheimer's disease. The information provided should be critically assessed by health care professionals and is not intended to provide diagnostic or treatment recommendations.

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