

The amyloid hypothesis is too good to be true

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Abstract

According to the amyloid hypothesis, Alzheimer dementia begins in the brain with A β peptides accumulation and amyloid formation. The amyloid hypothesis has dominated Alzheimer research and clinical trials in the last 25 years. However, every trial, one by one and time after time, has failed to help anybody living with Alzheimer. Even worse, many trials even harmed the Alzheimer people. I revisit some of these trials to understand what went wrong, and review current ongoing preventive trials on asymptomatic people at high risk, or genetically determined, for developing Alzheimer. I argue, and explain, that these trials that may last till 2020, are going to fail too because brain A β amyloid is not the cause of Alzheimer.

Old men are children twice over – Aristophanes

Introduction

Alzheimer dementia [OMIM 104300] is detected first by slowly progressing and irreversible memory and mind problems, followed by remarkable behavioral and personality changes and, in the end, loss of self [1-3]. If we get Alzheimer, then the question is when and how, or why. Family history of dementia, advanced or old age, are the only major risk factors of Alzheimer. These are the risks we cannot do anything about. Other risks include diabetes, head trauma, obesity, psychiatric symptoms, stroke, and the APOE4 gene. 1% of Alzheimer is caused by inherited mutations in the APP, PS1 or PS2 gene [4-6]. Alzheimer is diagnosed every 3.7 seconds. Today 50 million people live with Alzheimer, tomorrow many more [7].

In the year 1900, in the US, there were 10,000 people at age 100 years or more. In 2050 there will be 1,000,000. In 2015, we spent \$640 million for Alzheimer research, and \$1 billion in 2016. In 2017, we spend \$1.4 billion and \$1.8 billion in 2018. We spend \$1 billion every day looking after 5.4 million Alzheimer people at homes and nursing homes. In 2015-2050, Alzheimer care will cost \$20 trillion [8,9].

Alzheimer

Aloisius 'Alois' Alzheimer was a psychiatrist and neuropathologist, and a great scientist from Frankfurt, Germany [10]. Alzheimer died in December 19, 1915 aged 51, in Breslau, Silesia (now Wrocław, Poland), where he had been a Professor of Psychiatry at the University of Breslau since 1912. Alzheimer published two papers in 1907 and 1911 describing 'amyloid plaques and neurofibrillary tangles' in the brain autopsies of his two presenile patients [11,12].

Alzheimer never suggested plaques and tangles were the cause of dementia. Indeed, this is what he wrote in 1911: "So scheint wirklich kein stichhaltiger Grund vorhanden, diese Fälle als durch einen besonderen Krankheitsprozeß verursacht zu betrachten" [12]. There is then no tenable reason to consider these cases as caused by a specific disease process" [13].

The amyloid hypothesis

Amyloid precursor protein (APP) is a membrane protein with one transmembrane domain. Proteinases called α -secretase and β -secretase

cleave APP outside the membrane releasing the extracellular soluble APP domain. γ -secretase cleaves APP in the middle of the transmembrane domain. γ -secretase is made of four proteins, with presenilin-1 or 2 (PS1 or PS2) as the dispartyl proteinase unit. APP proteolysis by β - and γ -secretase generates A β peptides, most often the A β 40 peptide, then the A β 42 peptide [14-16]. A β peptides are made inside the cell, in the endoplasmic reticulum (ER), where most of the γ -secretase activity is found [17].

Since 1991-1992, the amyloid hypothesis [18,19] has said Alzheimer dementia begins in the brain with the extracellular accumulation and aggregation of A β peptides in water soluble forms and insoluble β -sheet fibrillar forms of amyloid. Today, the amyloid hypothesis is strongly supported by the molecular data and genetics of the inherited forms of Alzheimer, which are caused by dominant mutations in the APP, PS1 or PS2 gene [20-23].

The amyloid hypothesis has dominated Alzheimer research and clinical trials for 25 years, most likely because it is simple and makes the A β peptides and brain amyloid an attractive target for therapeutic drug interventions and disease-modifying treatments. When the mutations in the 'Alzheimer genes' APP, PS1 or PS2 were found to increase A β peptides production or aggregation, or the A β 42/40 ratio, and brain amyloid formation, then to prevent, delay or stop Alzheimer was very simple: stop making A β peptides. So, what makes me think the amyloid hypothesis is too good to be true, 'too big to fail' as Rudy Castellani and Mark Smith said in 2011 [24]. I can think of five reasons:

1. Data on the A β peptides and brain amyloid are after the fact, after the Alzheimer diagnosis. The data are about correlation, and correlation is not about cause and effect. The same data could as well support a hypothesis that Alzheimer dementia causes brain amyloid formation. This is what Bishop and Robinson [25] also suggested 15 years ago. And this is what Davies *et al.* [26] wrote in 1988: "A circular

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definition has therefore arisen: clinical AD [Alzheimer dementia] depends upon histopathological criteria and pathologically defined AD depends upon clinical findings.”

2. The extent of brain amyloid formation and the natural history of memory and mind problems are not even correlated in Alzheimer progression, therefore cannot be caused one way or the other [27,28].

3. PET imaging of brain A β amyloid of mentally normal old people often looks the same as the Alzheimer people [29].

4. And this is an undisputed fact: careful autopsy examinations have shown 30% of people without Alzheimer have a typical brain ‘amyloid pathology’ [30,31].

5. In the past, all Alzheimer trials have failed. It should not take more than one experiment to prove a hypothesis wrong.

Trials and errors

Drug discovery and clinical development is a commercial enterprise peculiar of the pharmaceutical industrial-complex, which has both the physical stature and the financial imperative to deliver drugs for their stakeholders and investors alike [32]. In this paper I cite a few times *The New York Times* and other newspapers, because they have been the first to report on Alzheimer trials. Peer-reviewed papers in scientific journals take a very long time to appear in print or online.

In 2006-2008, Robert Green, Boston University School of Medicine, and his colleagues carried out the first Alzheimer drug trial targeting γ -secretase with **tarenflurbil** (clinical trials.gov identifier NCT0010554). Tarenflurbil (also called *R-flurbiprofen*, made by Myriad) is a nonsteroidal anti-inflammatory drug (NSAID) and a selective γ -secretase inhibitor (modulator), that is, it reduces A β 42 peptide production over the other A β peptides. Preclinical studies on the transgenic Tg2576 mouse model of Alzheimer had shown tarenflurbil reduced A β peptides in the blood, amyloid in the brain, and improved spatial learning of the Tg2576 mice in the Morris water maze test [33].

In 2009, it made no news when Green *et al.* [34] reported tarenflurbil did not delay mental decline and did not prevent the progressive loss of daily activities of people diagnosed with mild to moderate Alzheimer dementia. This phase 3 trial lasted 18 months, and was completed by 1,649 people at 133 sites in the US. Many of the Alzheimer people volunteering for this trial experienced ‘adverse events’, as they are called in clinical trials, such as dizziness, upper respiratory tract infection, and constipation. Even if the entrance of tarenflurbil from blood to cerebrospinal fluid (CSF) was known to be only 1%, it did not prevent neither Green or his colleagues, nor the U.S. Food and Drug Administration (FDA) approving the trial, going forward with the tarenflurbil trial.

In 2008, Eli Lilly and Co. (Lilly hereinafter) initiated a major Alzheimer drug trial with another γ -secretase inhibitor called **semagacestat** (Lilly). When the trial was stopped in August 2010, Lilly had enrolled 2,600 people in 31 countries [35]. The trial had to be stopped early because semagacestat did not help, it only made the Alzheimer people do worse in memory and mind tasks, and everyday living. Other adverse events included infections and skin cancers.

“A completely unexpected result” said Eric Siemers, medical director of the Alzheimer’s team at Lilly, and suggested the failed trial might indicate *too much* reduction of A β peptides production had harmed cognitive functions [35]. This is speculation at best and

tautology at worst, since in the Lilly trial it was not even shown if semagacestat entered the brain and inhibited γ -secretase, or whether brain amyloid was reduced.

Steven DeKosky, University of Virginia School of Medicine, consulting for Lilly at the time, said that Lilly’s failure *may have shown* that reducing brain amyloid does not help those with Alzheimer but it could still help prevent the disease, and suggested: “Having the drug fail doesn’t say the hypothesis is wrong that amyloid causes the disease” [35].

Brain entrance of drugs is a major problem in Alzheimer drug discovery and clinical development [36]. According to Anna Seelig (pers.com), semagacestat “is rather hydrophilic with a calculated LogP 0.39, it carries one –OH and two secondary amides, which all there strongly reduce the rate of passive diffusion. In addition it carries one tertiary amide and two carbonyl groups, which interact with P-glycoprotein. Hence, the molecule most likely does not permeate the blood-brain barrier very well.” P-glycoprotein, also called MDR1 (multidrug resistance-1), is a transmembrane protein powered by ATP that ‘reverses’ drug entrance to cells, a major problem in cancer chemotherapy [37].

I question the design of Lilly’s semagacestat trial, its approval by FDA and the Institutional Review Board (IRB) in the US and at each and every trial site in the 30 other countries, because a few studies on mice, published many years earlier, had already shown γ -secretase inhibition would impair learning and memory, and even worse, increase the risk for infections and skin cancers.

In 2001, Xi *et al.* [38] had shown that inhibiting γ -secretase activity by deleting the PS1 gene in transgenic mice increased β -catenin signaling and skin tumorigenesis. In 2004, Saura *et al.* [39] had shown deletion of the PS1 and PS2 genes in the postnatal forebrain of transgenic mice caused learning and memory problems, synaptic impairment, old age-dependent neuron cell death, and inhibited NMDA receptor signaling and the expression of CREB target genes, such as *c-fos*, important in learning amemory. In another 2004 paper [40], they had shown the learning and memory problems, and progressive neurodegeneration were not caused by brain amyloid, but were associated with increased levels of immune inflammatory biomarkers.

The results of Lilly’s semagacestat trial (NCT00594568) took three years to appear in print, in 2013, in *The New England Journal of Medicine* [41]. Was this 3-year delay due to a follow-up study to see if the adverse events discovered during the trial continued thereafter, which they did? In their paper, the Lilly authors wrote: “Semagacestat did not improve cognitive status, and patients receiving the higher dose had significant worsening of functional ability. Semagacestat was associated with more adverse events, including skin cancers and infections.”

The idea to inhibit γ -secretase activity was, and still is, a really bad idea because γ -secretase cuts (besides APP) some 100 other proteins such as Notch, a transmembrane signaling protein necessary for stem cell differentiation, embryonic growth and development [42,43]. To find drugs that modulate and inhibit γ -secretase activity on APP only is a zero-sum game no medicinal chemist would like to play.

Instead of using semagacestat, **gleevec** (Novartis) would have been a little better drug to inhibit γ -secretase, because gleevec reduces A β peptides production but does not inhibit Notch proteolysis [44]. Gleevec is a receptor tyrosine-kinase inhibitor, an FDA-approved drug for chronic myeloid leukemia (CML) treatment since 2001. Intriguingly enough, Sutcliffe *et al.* [45] have observed that, in the transgenic R1. 40

Alzheimer mice, gleevec inhibited A β peptides production in the liver, lowered A β peptides level in the blood and reduced amyloid formation in the brain. Gleevec does not enter the brain.

When the editors of *Nature Medicine* asked [46] the experts for their opinion of Lilly's failed semagacestat trial, and "how Alzheimer's researchers should move forward", here is something what they had to say:

Kaj Blennow and Henrik Zetterberg: "The study of primary biomarkers in early clinical phases will be essential to guide decisions to advance only compounds that target A β metabolism or clearance in humans into large and expensive phase 2 or 3 clinical trials."

Christian Haass: "Were the adverse events observed in the semagacestat trial predictable, and could they have been avoided? The answer is unfortunately yes, at least in part. We knew not only that γ -secretase is absolutely required for Notch signaling but also that the reduction of γ -secretase activity in animal models leads to skin tumors as well as alterations in lymphopoiesis and intestinal cell differentiation, symptoms closely related to those found in patients with AD treated with semagacestat."

Thomas Finucane: "A β plaques could be related to AD as charred furniture and water damage are related to house fires."

In comparison, Bart De Strooper [47] writing in *Cell* was very clear: "It seems clear that such a phase III trial was unlikely to test the amyloid hypothesis."

Recently, Doody *et al.* [48] were writing in *Alzheimer's Research & Therapy*: "The negative efficacy study examining... semagacestat in mild to moderate Alzheimer's disease" [Introduction], "Cognitive decline correlated with ventricular expansion [that is, brain swelling] and reduction in ptau" [Results], and finally "These findings may inform future studies of drugs targeting secretases involved in A β generation" [Conclusion].

Avagacestat (Bristol-Myers Squibb) is another γ -secretase modulator, it is 193-fold more effective in inhibiting APP over Notch proteolysis. Studies on rats and dogs had shown avagacestat reduced brain amyloid formation without any Notch-related adverse events [49].

In 2012, Coric *et al.* [50] reported on the first avagacestat trial on 209 people with mild to moderate Alzheimer, in a multicenter, global, randomized, double-blind, placebo-controlled, 5-arm, fixed-dose, parallel-group study, performed as a 24-week phase 2 trial (NCT00810147). There never was a phase 3 trial because December 4, 2012, Bristol-Myers Squibb cancelled further clinical research and development of avagacestat [51].

LY2886721 (Lilly) is an inhibitor of β -secretase activity. A phase 2 trial of LY2886721 on 6,000 people with mild cognitive impairment (MCI) or mild Alzheimer (NCT01561430) was stopped in June 2013, due to liver toxicity [52]. Liver toxicity was a surprise to Lilly, maybe because mice treated with LY2886721 did not show any liver toxicity, and transgenic mice without β -secretase had no liver problems. Therefore, Lilly suggested that the liver toxicity observed in humans was not due to anti- β -secretase activity of LY2886721 [52]. According to Peter Roberts of the University of Bristol, β -secretase is not "a nice selective target" because mice without β -secretase exhibit highly complex neurological abnormalities [53].

Today, in a 50% partnership with AstraZeneca, Lilly is experimenting

with another β -secretase inhibitor, **LY3311481/AZD3293**, in two FDA-approved 'fast track' phase 3 trials, called AMARANTH (NCT02245737) and DAYBREAK-ALZ (NCT02783573), on people aged 55-85 years with mild Alzheimer. These trials may last till 2020 [54].

AN1792 (Elan) was an uncharacterized fibrillar formulation of human A β 42 peptide. In 1999, Schenk, *et al.* [55] at Elan had shown AN1792 vaccination of PDAPP Alzheimer mice reduced brain amyloid formation. Next year, Janus *et al.* [56] and Morgan *et al.* [57] showed A β 42 peptide immunization (vaccination) prevented memory loss and improved the behavior of the PDAPP Alzheimer mice.

In 2005, Bayer *et al.* [58] reported on the first and only human trial of AN1792 vaccination of people aged 50-85 years with mild to moderate Alzheimer (NCT00021723). The trial was designed for the "evaluation of safety, tolerability, immunogenicity, and exploratory evidence of efficacy of AN1792." When their trial was stopped after 72 weeks, only 20% (59/300) of the vaccinated people had made antibodies to AN1792, and even so, did not differ in any way from the placebo vaccinated control people in memory and mind tasks or daily living measures. The trial had been stopped early because 6% of the AN1792 vaccinated Alzheimer people developed significant health problems including meningoencephalitis and death.

Three years earlier, March 2, 2002, *The Washington Post* first published the news of the human AN1792 trial suspension [59], and two months later Smith *et al.* [60] wrote in *The Lancet*: "it is no surprise that the inappropriate deposition of protein in the normal mouse brain because of massive overexpression of amyloid- β protein precursor modifies function, nor that its removal can then restore function, there is not, nor ever was, any evidence that interventions designed to remove or alter the deposition of amyloid- β would benefit patients with Alzheimer's disease."

In 2004, Robinson *et al.* [61] reviewed in useful details the AN1792 trials, on mice and men, and found "it extraordinary that justification for undertaking human trials of A β vaccines has been based exclusively on data obtained from transgenic mice" and then wrote: "new strategies treating AD should not be tested on humans until they have been extensively tested on non-murine species."

Bapineuzumab (Johnson & Johnson and Pfizer) is a humanized mouse monoclonal antibody against human A β peptides. July 2012, further clinical development of bapineuzumab was discontinued [62,63] because in two 78-week phase 3 trials (NC- T00575055 and NCT00574132) it did not help people living with mild to moderate Alzheimer, 1,121 people with and 1,331 without APOE4. The major adverse event was ARIA-E (amyloid-related brain imaging abnormalities with edema), which means brain swelling, a fatal condition if untreated.

Husseini Manji at Janssen Research and Development, a unit of Johnson & Johnson, said at the time that the failed trials did not mean researchers should abandon the *amyloid cascade* theory [62]. He also said: "While we are disappointed in the results of the two bapineuzumab studies, we believe that targeting and clearing amyloid remains a promising path to clinical benefits for people suffering from this disease." The cost of the failed bapineuzumab trials caused Johnson & Johnson to predict a loss of \$300-\$400 million in the third quarter of 2012 [62].

Later however, the two trials were continued in 26 countries to assess the "long-term safety, tolerability and clinical efficacy" of

bapineuzumab. These trials lasted 3 years before they were discontinued due to adverse events and lack of clinical efficacy of bapineuzumab. A report of these two trials by Ivanolu *et al.* [64] is a depressing read. In the 202 people with APOE4, treatment-emergent adverse events (TEAE) occurred in 71% of the people who originally had received placebo and 67% of those who had received bapineuzumab (NCT00998764). In the 492 people without APOE4, TEAE occurred in 82% and 68% in people who had received placebo and then bapineuzumab (0.5 mg/kg and 1.0 mg/kg), and in 73% and 64% who had received bapineuzumab and then bapineuzumab (NCT00996918). ARIA with edema or effusions were the main adverse events, occurring in 11% of placebo + bapineuzumab and 4% of bapineuzumab + bapineuzumab study groups. These trials “were conducted in accordance with principles set forth in the Declaration of Helsinki and according to good clinical practices established by the International Conference on Harmonisation”. Ivanolu *et al.* [64] finish the abstract of their paper by writing: “In these phase 3 extension studies, intravenous bapineuzumab administered for up to approximately 3 years showed no unexpected safety signals and a safety profile consistent with previous bapineuzumab trial.”

Solanezumab (Lilly) is a humanized mouse monoclonal antibody, which binds to the mid-domain of soluble A β peptides but not to the fibrillar form of insoluble A β amyloid. Solanezumab was used in two phase 3 trials on 1,012 and 1,040 people with mild to moderate Alzheimer (NCT00905372 and NCT00904683). November 2013, both trials of 18 months were stopped because the solanezumab vaccinated people showed no improvement in their mental activity or daily living. Reporting on these data in *The New England Journal of Medicine* [65] the Lilly authors wrote: “Data from these two phase 3 solanezumab trials did not show efficacy of this monoclonal antibody.” and “Cardiac diseases were numerically [*sic*] more common in patients who received solanezumab than in those who received placebo.” Other adverse events were ARIA-E and microhemorrhages, which means blood in the brain.

EXPEDITION3 was one more phase 3 trial of solanezumab by Lilly, this time on 2,100 people in 11 countries with mild Alzheimer (NCT01900665). When the trial was terminated in November 23, 2016, John C. Lechleiter, chairman, president and CEO of Lilly, said: “The results of the trial were not what we had hoped for and we are disappointed for the millions of people waiting for a potential disease modifying treatment for Alzheimer’s disease.” [53, 66-68]

Aducanumab (Biogen) is a fully humanized mouse monoclonal antibody “cloned from a healthy human subject that recognized the disease-causing fibrillar form of A β .” [69] July 22, 2015, Biogen disclosed the failure of aducanumab vaccination after a 54-week phase 1b trial on 166 people with mild to moderate Alzheimer [70]. Even if aducanumab had reduced brain amyloid, it failed to prevent or slow dementia progression. Two outcome measures of cognition, MMSE (Mini-Mental State Examination) and CDR-SB (Clinical Dementia Rating scale Sum of Boxes) were comparable to the ‘placebo effect’. Brain swelling was a major adverse event, and was observed most often in people with APOE4, with incidence of 5% in the 1 mg/kg and 3 mg/kg arms, 43% in the 6 mg/kg arm and 55% in the 10 mg/kg arm.

Biogen’s aducanumab trial (NCT01397539) was featured prominently at the AD/PD meeting in Nice, France, March 17-22, 2015, at the Alzheimer’s Association International Conference (AAIC) in Washington, DC, July 18-23, 2015, and at the Clinical Trials on Alzheimer’s Disease (CTAD) in Barcelona, Spain, November 5-8, 2015.

I was there and attended these meetings.

Biogen is continuing in recruiting thousands of asymptomatic people, and people with the early signs and symptoms of Alzheimer in the world for three more aducanumab trials (NCT01677572, NCT02477800 and NCT02484547) that may last till 2020.

Recently, Savigny *et al.* [71] published in *Nature* an interim progress report on their aducanumab trial NCT01677572, a double-blind, placebo-controlled, randomized 1b trial called PRIME, and wrote: “In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain A β in a dose- and time-dependent manner.” In contrast to their previous trial, this time they found aducanumab immunized people had less mental decline when measured with MMSE and CDR-SB instruments. However, when Savigny *et al.* [71] suggest: “These results justify further development of aducanumab for the treatment of AD”, my major concern is about their placebo control. Alzheimer patients immunized with placebo are not the right control for patients immunized with the aducanumab antibody.

Say no to Alzheimer drugs

The inconvenient truth today is this: whether or not in the pipelines of drug companies, we have not had any new Alzheimer drugs in 15 years. According to the Pharmaceutical Research and Manufacturers of America (pharma.org), there were 123 unsuccessful attempts in 1998-2014 to develop drugs to treat Alzheimer. Only four drugs made it to the market called ‘symptomatic Alzheimer’s treatment’ [72].

As of December 19, 2016, ClinicalTrials.gov had 1946 records on Alzheimer trials. A survey by Cummings *et al.* [73] of the records for 413 trials in 2002-2012 found a 99.6% failure rate, which is the worst in clinical therapeutic drug development ever. There must be a reason for this, this could not have happened by chance. When 141 of 215 trials were targeting brain A β amyloid, only one drug received FDA-approval for human use, which may explain the 0.4% ‘success’ rate of the trials. That drug is *memantine*, an inhibitor of NMDA receptor and synaptic glutamate signaling [74].

Long ago, in 1968, Lilly developed memantine (also called *namenda*) for the treatment of diabetes [74]. In 2003, memantine was ‘recycled’ and approved for the treatment of “mild- to-severe Alzheimer’s disease” in the US. Ten years later, EMA (European Medicines Agency) approved the use of memantine in Europe [75]. In 2014, memantine sold for \$1.2 billion in the US market. The three other FDA-approved Alzheimer drugs (*donepezil*, *galantamine* and *rivastigmine*) are acetylcholine esterase inhibitors, the stuff in the nerve gas [76].

Prevention is the only cure

Many Alzheimer drug trials, in my opinion too many trials, had to be stopped early because the drugs, often called investigational new drugs (IND), had no statistically significant clinical efficacy, only harmed the Alzheimer people. This gives Alzheimer research a bad name. This is not evidence-based science. This is amyloid hypothesis driven theology. I can only imagine the Alzheimer people, familial caregivers, friends and others having volunteered for these trials, their hopes and dreams all but dashed. How long do the people living with Alzheimer have to wait? There are no Alzheimer survivors.

Alzheimer trial failures cannot be explained, indeed, defended by saying ‘too little too late’ was done. That is, we were late with the treatment, at the time when dementia had already progressed beyond

the point of no return. What if the reason for the failures is this simple: our ideas of Alzheimer etiology, such as the amyloid hypothesis, are all wrong. If that is the case, then the outcome of Alzheimer trials should have been what it has been, nothing but failures. If that is the case, then the outcome of the ongoing preventive Alzheimer trials will be the same, nothing but failures.

Instead of cure, let's begin to think about prevention, and find ways to delay the onset, stop or slow the progression of dementia, and make Alzheimer history. Even a 5-year delay of Alzheimer onset would reduce health care costs by 50% [77]. In the US today, that would mean \$500 million a day.

Alzheimer does not come overnight. A lifetime may easily go by before the first signs and symptoms of memory and mind problems appear. In 1997, David Snowdon argued in his great 'Nun Study' that brain amyloid is not synonymous with dementia [78], and even suggested low linguistic ability early in the life is associated with a high risk for dementia later in the life [79]. In 2013, Elwood *et al.* [80] reported on the longest-running study ever on lifestyle and dementia. They had followed for 30 years 2,235 men living in Caerphilly, South Wales, UK, and found that healthy lifestyles could decrease dementia risk by 60%. If there ever were drugs that could do the same, they would be the best-selling drugs [81].

Dominantly Inherited Alzheimer Network (DIAN) is an international registry of families and family members with inherited dominant mutations in the APP, PS1 or PS2 gene, the genes that cause 1% of Alzheimer [82-84]. These unfortunate 0.5 million people in 517 families in the world are destined for developing Alzheimer at the early age of 22-55, at about the same age as their mother or father, and their mother or father. The exact timing of dementia onset is dictated by the particular mutation in the APP, PS1 or PS2 gene [85-88]. To me, the DIAN people are the best 'human model' to study and understand the mind and what the brain does as time goes by, to uncover the molecular details and cellular mechanisms at work in the mind and body many decades before Alzheimer begins.

The idea of preventing Alzheimer could not be any simpler than this: stop dementia, even before it begins [89-92]. However, concepts such as 'asymptomatic', 'preclinical', and 'prodromal' Alzheimer are as good as it gets walking on the dark side of the moon. When Ray *et al.* [93] studied blood proteins; they found 18 'signaling' proteins that could detect with 90% accuracy the people with MCI who would be diagnosed with Alzheimer 2-6 years later. Mapstone *et al.* [94] have found ten blood lipids, eight of them phosphatidylcholine (PC) lipids that predicted with 90% accuracy the time of MCI onset and 2-3 years later Alzheimer. When Bateman *et al.* [95] studied asymptomatic DIAN people with the PS1 mutation E280A, they found many changes in 'Alzheimer biomarkers' 10-25 years before the beginning of dementia symptoms, such as less A β peptides in CSF, more brain amyloid and less brain glucose uptake by PET imaging, and more brain atrophy by MRI. These findings are striking, since at the study time the DIAN people were cognitively normal. So, what do these biomarkers measure, if anything [93-100]? Intriguingly, Bateman *et al.* [95] also found an "impaired episodic memory" 10 years ahead of dementia. Compared to the other Alzheimer biomarkers, testing for episodic memory is noninvasive, takes no time, and costs nothing.

Even if the APP, PS1 or PS2 mutations increase A β peptides production, aggregation and brain amyloid formation, that cannot be the only effect of the mutations. What else they do we know absolutely nothing about. We know little, if anything, what APP or the A β

peptides do in cells and body, made of some 37 trillion cells [101]. Why we don't know why the APP mutation A673V causes the brain to lose 'its' memory and mind at age 36, when another mutation A673T of the same alanine decreases Alzheimer risk [102,103]. How can valine and threonine make all the difference from what the alanine does at the amino acid position 673 in APP, or at position 2 in the A β peptides [104]? If we don't study that, what hope we have to understand what goes on with Alzheimer.

How can it be that the E280A mutation in the PS1 gene you are born with causes you to lose your memory and mind when you are 49 years old [88]? Why it takes 49 years? Why not more or less? Why the age 49 is so predictable, that is, if your mother or father had Alzheimer at 49, so do you, no matter what you do. It simply cannot be due to more A β amyloid in your brain. And why the E280A mutation targets the mind but not the body? If there ever were genetics of the mind, this is it.

Recently, Sun *et al.* [105] studied the activity of γ -secretase they had reconstituted in liposomes with PS1 with 138 different mutations, one by one, many of which cause Alzheimer at different age. They could not find any correlation between the amount of A β peptides produced, or the A β 42/40 ratio, and the age of Alzheimer onset. What these data say is this: Alzheimer is not caused by A β peptides.

Alzheimer Prevention Initiative (API) is a \$100 million trial on DIAN people living in Medellin, Antioquia, on the Andes mountains in Colombia. They are 5,000 people in five families, and make the most extended Alzheimer family pedigree in the world. Some 1,500 family members have the PS1 mutation E280A [88]. In the trial (NCT01998841), 100 family members with the mutation are immunized with the anti-A β antibody **crenezumab** (Genentech, a member of the Roche Group). In control experiments, other family members with (100) or without (100) the mutation are immunized with placebo.

In the trial, the family members are studied in many ways to detect subtle alterations in their memory and mind and nonverbal reasoning, such as remembering words, naming objects, drawing complex figures, and knowing what time and place it is, and to see any irritability, sadness, crying, anxiety, impulsivity, and other emotions usually observed in Alzheimer people. The studies also use MRI for brain anatomy, PET imaging for brain amyloid and glucose uptake, and CSF measures for A β peptides and hyperphosphorylated tau, a 'diagnostic' protein marker of dead brain cells. "[T]hese tests may indicate in two years whether the drug [crenezumab] helps delay memory decline or brain changes", said Eric M. Reiman, executive director of the Banner Alzheimer's Institute (BAI), Phoenix, Arizona, who is leading the API trial [106], together with Pierre N. Tariot, director of the BAI. This trial may last till 2020.

Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) trial targets asymptomatic people at high risk for Alzheimer aged 65-85, with or without APOE4. This trial (NCT02008357) on 4,500 people in the US, Canada, Australia and Japan uses solanezumab, the same anti-A β antibody that has already failed in every clinical trial in the past. This \$ 140 million trial may last till 2020. At CTAD in San Diego, December 8-10, 2016, the A4 study leader Reisa Sperling updated on their progress: "As expected, 30% of clinically normal older individuals (mean age 72) show elevated amyloid levels on screening PET scans" [107]. She also said 58% of these individuals had APOE4, compared to only 24% of the individuals without elevated brain amyloid.

Isn't it peculiar that, when all the Alzheimer trials targeting A β

peptides in the blood or brain have already failed, all preventive trials today are doing the same with anti-A β antibodies, β -secretase or γ -secretase inhibitors, or other A β lowering drugs. Why not target α -secretase, a proteinase also called ADAM10, which cuts APP outside the membrane in the A β domain, and therefore prevents the generation of A β peptides [108]?

December 19, 2014, one of the first preventive Alzheimer trials by Roche (the SCarlet RoAD study) failed and was discontinued [109-111]. It was a phase 3 trial of **gantenerumab** immunization of 360 people in 15 countries (NCT02133937). Gantenerumab (Roche) is a novel fully humanized mouse monoclonal IgG1 antibody, optimized for binding to an A β peptide epitope found only in brain amyloid. In studies on mice, gantenerumab was shown to bind to A β peptides and reduce brain amyloid by T cell-mediated clearance.

Roche continues to evaluate gantenerumab in their Marguerite RoAD study, a phase 3 trial on people with mild Alzheimer (NCT01224106). In the past, since 1896, Roche has made important contributions to global health by developing 24 drugs included in the World Health Organization (WHO) Model Lists of Essential Medicines [109].

When Watt *et al.* [112] used SELDI-TOF-MS (surface-enhanced laser desorption-ionization time-of-flight mass-spectroscopy) to study the targeting specificity and affinity of the anti-A β antibodies being used in the preventive Alzheimer trials, here is what they found: bapineuzumab bound to A β peptides isolated from the brain amyloid, while solanezumab and crenezumab did not. Both solanezumab and crenezumab bound to some 200 other proteins unrelated to A β peptide. It is no wonder if Watt *et al.* [112] raised “questions as to whether solanezumab and crenezumab are suitable drug candidates for the preventive clinical trials for Alzheimer’s disease.” When Siemers *et al.* [113] at Lilly argued against these findings, Watt *et al.* [114] defended their findings.

When Jack de la Torre [115] was writing in *The New England Journal of Medicine*: “The question logically arises: when is a dead hypothesis really dead?” he was commenting on a piece written by Eric Karran and John Hardy (Antiamyloid therapy for Alzheimer’s disease are we on the right road? *N Engl J Med* 370, 377-378, 2014). Karran and Hardy were reviewing the high-profile failures of bapineuzumab and solanezumab trials and had said the trials “have provided valuable information” and that the trials of anti-A β antibodies should continue. At the same time, they had also written an impressively detailed, if not difficult to follow, account ‘defending’ Johnson & Johnson and Lilly on the failed trials [116]. They are absolutely right when they write: “The amyloid hypothesis has significantly influenced drug discovery and development, but no amyloidocentric therapeutic agent has reached its primary outcome measure.”

January 12, 2016, in London, John Hardy said of the new trials of solanezumab and aducanumab by Lilly and Biogen: “We’re hopeful, but we don’t want to overstate or mislead people. These trials will report in about 18 months, and if they are successful it tells us immediately we’re on the right road and that will lead a massive investment by those two companies and other companies to develop drugs that target amyloid in other ways. It will have a major effect”, and also said: “we are either very close [to] or very far away” from finding more successful treatments [117]. November 24, 2016, the day after Lilly’s EXPEDITION3 had failed, he said: “it would be important to look closely at the results to understand why it had failed” and that “the focus would now shift to ... inhibiting ... β -secretase” [53].

The year 2025 is near

Alzheimer’s Association (alz.org) has a vision of “a world without Alzheimer’s”.

January 4, 2011, in Washington, Mr. President Obama wrote his name with his left hand on the National Alzheimer’s Project Act (NAPA), a Public Law 111-375 (S.3036), to “prevent or effectively treat Alzheimer’s disease by 2025.” [118-120]. NAPA also says “The Project shall expire December 31, 2025”, at the *sunset*, as it is called in the law [118].

December 11, 2013, in London, the world leaders of G8 (now G7) countries agreed on their “commitment to identify a cure or a disease-modifying therapy for dementia by 2025” [121].

George Vradenburg, chairman and co-founder of USAgainstAlzheimers.org (since 2010 with “the bold and attainable goal of ending Alzheimer’s by 2020”), got it right by saying, to the effect, that the first Alzheimer’s patient cured is in clinical trials.

Todd Golde [122] has described many of the hurdles on the road to Alzheimer cure, and Cummings *et al.* [123] have written an important, impartial and well-reasoned paper on drug discovery and clinical development. If I read their papers between the lines, they say the same: there cannot be any new Alzheimer drugs by 2025, simply because it takes time and money, first to find the drugs, study the drugs in preclinical trials on animals, clinical trials on humans, then get the drugs, if any, approved by FDA for human use, and finally see if the drugs are right for Alzheimer people. That path to Alzheimer cure is ten or more years down the road.

What I say in this paper has been said in other words by many others [24,25,60,124-129]. I cite one more, a great paper by Banik *et al.* [130] who “critically reviewed past literature (1990-2014)” and argued Alzheimer research and clinical trials have been “hindered by the domination of the amyloid hypothesis”, and went on to write: “A greater variety of potential disease mechanisms must be entertained to enhance progress.” Karran and De Strooper [21] have described some such disease mechanisms like A β oligomerization, neuron cell cycle re-entry, dual pathway, metabolic disorders, mitochondrial loss-of-function, and cardiovascular impairment. Hill *et al.* [131] and Itzhaki *et al.* [132] have written on the ‘microbiome’ hypothesis of Alzheimer, and Area-Gomez and Schon [133] reviewed their intriguing Alzheimer MAM hypothesis. Recently, writing in *Cell*, De Strooper and Karran were somewhat enigmatic: “AD indeed is not a biochemical or molecular problem but a physiological one of disrupted cellular connectivity” [134].

What we need now are ‘high-risk high-reward’ funding organizations, science-educated policy makers, independent dementia scientists, doctors, nurses, family members, friends and other caregivers desperately seeking for novel ideas to better our research and care of Alzheimer people. It is time to get over the hype and hope, stigma and fear, and the myth of Alzheimer. What we need now is dementia-friendly society and Alzheimer’s cafés [1,8,135-141].

Today Alzheimer dementia is an incurable disease. Tomorrow is a new day. Let’s begin to care of cure of Alzheimer with passion. It’s about time. It’s about the human mind.

Alzheimer was right when he said dementia is a *peculiar* disease of the cerebral cortex, “eine *eigenartige* Erkrankung der Hirnrinde” [11]. How long it will take before we can prove Alzheimer wrong?

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References

- Whitehouse PJ, George D (2008) *The Myth of Alzheimer's*. St. Martin's Press, New York, USA
- Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, et al. (2016) Alzheimer's disease. *Lancet* 388: 505-517. [Crossref]
- Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, et al. (2015) Alzheimer's disease. *Nat Rev Dis Primers* 1: 15056. [Crossref]
- Tanzi RE, Bertram L (2005) Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. *Cell* 120: 545-555. [Crossref]
- Karch CM, Goate AM (2015) Alzheimer's disease risk genes and mechanisms of disease pathogenesis. *Biol Psychiatry* 77: 43-51. [Crossref]
- Van Cauwenberghe C, Van Broeckhoven C, Sleegers K (2016) The genetic landscape of Alzheimer disease: clinical implications and perspectives. *Genet Med* 18, 421-330. [Crossref]
- <https://www.alz.co.uk/research/statistics>
- Alzheimer's Association (2016) Alzheimer's disease facts and figures. *Alzheimers Dement* 12: 459-509. [Crossref]
- <https://www.nia.nih.gov/alzheimers/publication/stopping-alzheimers-disease-and-related-dementias/about-fy-2018-bypass-budget>
- Toodayan N (2016) Professor Alois Alzheimer (1864-1915): Lest we forget. *J Clin Neurosci* 31: 47-55. [Crossref]
- Alzheimer A (1907) Übereineigenartige Erkrankung der Hirnrinde. *Allg Z Psychiat* 64, 146-148
- Alzheimer A (1911) Übereigenartige Krankheitsfälle des späteren Alters. *Z Gesamte Neurol Psychiat* 4, 356-385
- Förstl H, Levy R (1991) On certain peculiar diseases of old age. *Hist Psychiatry* 2: 74-99. [Crossref]
- De Strooper B, Annaert W (2000) Proteolytic processing and cell biological functions of the amyloid precursor protein. *J Cell Sci* 113: 1857-1870. [Crossref]
- Bolduc DM, Montagna DR, Seghers MC, Wolfe MS, Selkoe DJ (2016) The amyloid-beta forming tripeptide cleavage mechanism of γ -secretase. *Life* 5. [Crossref]
- Wilkins HM, Swerdlow RH (2016) Amyloid precursor protein processing and bioenergetics. *Brain Res Bull.* [Crossref]
- Schreiner B, Hedskog L, Wiehager B, Ankarcrona M (2015) Amyloid- β peptides are generated in mitochondria-associated endoplasmic reticulum membranes. *J Alzheimers Dis* 43: 369-374. [Crossref]
- Hardy J, Allsop D (1991) Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends Pharmacol Sci* 12: 383-388. [Crossref]
- Hardy JA, Higgins GA (1992) Alzheimer's disease: the amyloid cascade hypothesis. *Science* 256: 184-185. [Crossref]
- Silk DJ, Hardy J (2016) The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med* 8: 595-608. [Crossref]
- Karran E, De Strooper B (2016) The amyloid cascade hypothesis: are we poised for success or failure? *J Neurochem* 139 Suppl 2: 237-252. [Crossref]
- Weitz TM, Town T (2016) Amyloid Cascade into Clarity. *Immunity* 45: 717-718.
- Tomita T (2017) Aberrant proteolytic processing and therapeutic strategies in Alzheimer disease. *Adv Biol Regul* S2212-4926: 30066-5. [Crossref]
- Castellani RJ, Smith MA (2011) Compounding artefacts with uncertainty, and an amyloid cascade hypothesis that is 'too big to fail'. *J Pathol* 224: 147-152. [Crossref]
- Bishop GM, Robinson SR (2002) The amyloid hypothesis: let sleeping dogmas lie? *Neurobiol Aging* 23: 1101-1105. [Crossref]
- Davies L, Wolska B, Hilbich C, Multhaup G, Martins R, et al. (1988) A4 amyloid protein deposition and the diagnosis of Alzheimer's disease: prevalence in aged brains determined by immunocytochemistry compared with conventional neuropathologic techniques. *Neurology* 38: 1688-1693. [Crossref]
- Vemuri P, Weigand SD, Przybelski SA, Knopman DS, Smith GE, et al. (2011) Cognitive reserve and Alzheimer's disease biomarkers are independent determinants of cognition. *Brain* 134: 1479-1492. [Crossref]
- Rosenberg RN (2015) Defining amyloid pathology in persons with and without dementia syndromes: making the right diagnosis. *JAMA* 313: 1913-1914. [Crossref]
- Mountz JM, Laymon CM, Cohen AD, Zhang Z, Price JC, et al. (2015) Comparison of qualitative and quantitative imaging characteristics of [^{11}C]PiB and [^{18}F]flutemetamol in normal control and Alzheimer's subjects. *Neuroimage Clin* 9: 592-598. [Crossref]
- Price JL, Morris JC (1999) Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann Neurol* 45: 358-368. [Crossref]
- Knopman DS, Parisi JE, Salviati A, Floriach-Robert M, Boeve BF, et al. (2003) Neuropathology of cognitively normal elderly. *J Neuropathol Exp Neurol* 62: 1087-1095. [Crossref]
- <http://blogs.barrons.com/stockstowatchtoday/2016/11/21/lilly-and-biogen-a-fertile-period-in-alzheimers-research/>
- Kukar T, Prescott S, Eriksen JL, Holloway V, Murphy MP, et al. (2007) Chronic administration of R-flurbiprofen attenuates learning impairments in transgenic amyloid precursor protein mice. *BMC Neurosci* 8: 54. [Crossref]
- Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, et al. (2009) Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. *JAMA* 302: 2557-2564. [Crossref]
- The New York Times, August 17, 2010, A1, edited for brevity and clarity, italics added.
- Pardridge WM (2009) Alzheimer's disease drug development and the problem of the blood-brain barrier. *Alzheimers Dement* 5: 427-432. [Crossref]
- Li-Blatter X, Beck A, Seelig A (2012) P-glycoprotein-ATPase modulation: the molecular mechanisms. *Biophys J* 102: 1383-1393. [Crossref]
- Xia X, Qian S, Soriano S, Wu Y, Fletcher AM, et al. (2001) Loss of presenilin 1 is associated with enhanced beta-catenin signaling and skin tumorigenesis. *Proc Natl Acad Sci U S A* 98: 10863-10868. [Crossref]
- Saura CA, Choi SY, Beglopoulos V, Malkani S, Zhang D, Shankaranarayana Rao BS, et al. (2004) Loss of presenilin function causes impairments of memory and synaptic plasticity followed by age-dependent neurodegeneration. *Neuron* 42, 23-36. [Crossref]
- Beglopoulos V, Sun X, Saura CA, Lemere CA, Kim RD, et al. (2004) Reduced beta-amyloid production and increased inflammatory responses in presenilin conditional knock-out mice. *J Biol Chem* 279: 46907-46914. [Crossref]
- Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, et al. (2013) A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med* 369: 341-350. [Crossref]
- Haapasalo A, Kovacs DM (2011) The many substrates of presenilin/ γ -secretase. *J Alzheimers Dis* 25: 3-28. [Crossref]
- Jorissen E, De Strooper B (2010) Gamma-secretase and the intramembrane proteolysis of Notch. *Curr Top Dev Biol* 92: 201-230. [Crossref]
- Netzer WJ, Dou F, Cai D, Veach D, Jean S, et al. (2003) Gleevec inhibits beta-amyloid production but not Notch cleavage. *Proc Natl Acad Sci USA* 100: 12444-12449. [Crossref]
- Sutcliffe JG, Hedlund PB, Thomas EA, Bloom FE, Hilbush BS (2011) Peripheral reduction of β -amyloid is sufficient to reduce brain β -amyloid: implications for Alzheimer's disease. *J Neurosci Res* 89: 808-814. [Crossref]
- Blennow K, Zetterberg H, Haass C, Finucane T (2013) Semagacestat's fall: where next for AD therapies? *Nat Med* 19: 1214-1215.
- De Strooper B (2014) Lessons from a failed γ -secretase Alzheimer trial. *Cell* 159: 721-726. [Crossref]
- Doody RS, Raman R, Sperling RA, Seimers E, Sethuraman G, et al. (2015) Peripheral and central effects of γ -secretase inhibition by semagacestat in Alzheimer's disease.

- Alzheimers Res Ther* 7: 36. [Crossref]
49. Albright CF, Dockens RC, Meredith JE Jr, Olson RE, Slemmon R, et al. (2013) Pharmacodynamics of selective inhibition of γ -secretase by avagacestat. *J Pharmacol Exp Ther* 344: 686-695. [Crossref]
 50. Coric V, van Dyck CH, Salloway S, Andreasen N, Brody M, et al. (2012) Safety and tolerability of the γ -secretase inhibitor avagacestat in a phase 2 study of mild to moderate Alzheimer disease. *Arch Neurol* 69: 1430-1440. [Crossref]
 51. <https://www.thepharmaletter.com/article/another-alzheimer-s-drug-hits-the-dust-as-bristol-myers-drops-avagacestat-development>
 52. Lahiri DK, Maloney B, Long JM, Greig NH (2014) Lessons from a BACE1 inhibitor trial: off-site but not off base. *Alzheimers Dement* 10: S411-419. [Crossref]
 53. Hawkes N (2016) Promise of new Alzheimer's drug is dashed after lack of evidence. *BMJ* 355: i6362. [Crossref]
 54. Sims et al (2016) OC4: Phase 3 study designs to evaluate treatment with a bace inhibitor LY3311481/AZD3293 in patients with early Alzheimer's disease. *J Prev Alzheimer Dis* 3: 269.
 55. Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, et al (1999) Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature* 400: 173-177. [Crossref]
 56. Janus C, Pearson J, McLaurin J, Mathews PM, Jiang Y, et al. (2000) A beta peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. *Nature* 408: 979-982. [Crossref]
 57. Morgan D, Diamond DM, Gottschall PE, Ugen KE, Dickey C, et al. (2000) A beta peptide vaccination prevents memory loss in an animal model of Alzheimer's disease. *Nature* 408: 982-985. [Crossref]
 58. Bayer AJ, Bullock R, Jones RW, Wilkinson D, Paterson KR, et al. (2005) Evaluation of the safety and immunogenicity of synthetic Abeta42 (AN1792) in patients with AD. *Neurology* 64: 94-101. [Crossref]
 59. The Washington Post, March 2, 2002, A3
 60. Smith MA, Atwood CS, Joseph JA, Perry G (2002) Predicting the failure of amyloid-beta vaccine. *Lancet* 359: 1864-1865. [Crossref]
 61. Robinson SR, Bishop GM, Lee HG, Münch G (2004) Lessons from the AN 1792 Alzheimer vaccine: lest we forget. *Neurobiol Aging* 25: 609-615. [Crossref]
 62. The New York Times, August 6, 2012, A1, edited for brevity and clarity, italics added.
 63. Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, et al (2014) Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med* 370: 322-333. [Crossref]
 64. Ivanoiu A, Pariente J, Booth K, Lobello K, Luscan G, et al. (2016) Long-term safety and tolerability of bapineuzumab in patients with Alzheimer's disease in two phase 3 extension studies. *Alzheimers Res Ther* 8: 24. [Crossref]
 65. Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, et al. (2014) Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med* 370: 311-321. [Crossref]
 66. The New York Times, November 23, 2016, A1
 67. Reardon S (2015) Alzheimer antibody drugs show questionable potential. *Nat Rev Drug Discov* 14: 591-592. [Crossref]
 68. Harrison JR, Owen MJ (2016) Alzheimer's disease: the amyloid hypothesis on trial. *Br J Psychiatry* 208: 1-3. [Crossref]
 69. Agadjanyan MG, Petrovsky N, Ghochikyan A (2015). A fresh perspective from immunologists and vaccine researchers: Active vaccination strategies to prevent and reverse Alzheimer's disease. *Alzheimers Dement* 11: 1246-1259. [Crossref]
 70. <https://www.fiercebiotech.com/story/setback-biogens-mid-range-dose- aducanumab-flops- alzheimers-study/2015-07-22>
 71. Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, et al. (2016) The antibody aducanumab reduces A β plaques in Alzheimer's disease. *Nature* 537: 50-56. [Crossref]
 72. phrma.org/sites/default/files/pdf/alzheimers-setbacks-and-stepping-stones.pdf
 73. Cummings JL, Morstorf T, Zhong K (2014) Alzheimer's disease drug development pipe-line: Few candidates, frequent failures. *Alzheimers Res Ther* 6, 37
 74. Robinson DM, Keating GM (2006) Memantine: a review of its use in Alzheimer's disease. *Drugs* 66, 1515-1534
 75. ema.europa.eu/docs/en_GB/document_library/EPAR_Summary_for_the_public/human/002766/WC500158285.pdf
 76. Rose S (1992) The Making of Memory. Bantam Books Ltd.
 77. Brookmeyer R, Gray S, Kawas C (1998) Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health* 88: 1337-1342. [Crossref]
 78. Snowdon DA (1997) Aging and Alzheimer's disease: lessons from the Nun Study. *Gerontologist* 37: 150-156. [Crossref]
 79. Riley KP, Snowdon DA, Desrosiers MF, Markesbery WR (2005) Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study. *Neurobiol Aging* 26: 341-347. [Crossref]
 80. Elwood P, Galante J, Pickering J, Palmer S, Bayer A, et al. (2013) Healthy lifestyles reduce the incidence of chronic diseases and dementia: evidence from the Caerphilly cohort study. *PLoS One* 8: e81877. [Crossref]
 81. Norman Doidge: "Brain, heal thyself." The Wall Street Journal, February 6, 2015, A3
 82. Bateman RJ, Aisen PS, De Strooper B, Fox NC, Lemere CA, et al (2011) Autosomal-dominant Alzheimer's disease: a review and pro-proposal for the prevention of Alzheimer's disease. *Alzheimers Res Ther* 3: 1. [Crossref]
 83. Morris JC, Aisen PS, Bateman RJ, Benzinger TL, Cairns NJ, et al. (2012) Developing an international network for Alzheimer research: The Dominantly Inherited Alzheimer Network. *Clin Invest (Lond)* 2: 975-984. [Crossref]
 84. Moulder KL, Snider BJ, Mills SL, Buckles VD, Santacruz AM, et al. (2013) Dominantly Inherited Alzheimer Network: facilitating research and clinical trials. *Alzheimers Res Ther* 5: 48. [Crossref]
 85. Ringman JM, Liang LJ, Zhou Y, Vangala S, Teng E et al; (2015) Early behavioural changes in familial Alzheimer's disease in the Dominantly Inherited Alzheimer Network. *Brain* 138: 1036-1045. [Crossref]
 86. Noroozian M (2016) Alzheimer's Disease: Prototype of Cognitive Deterioration, Valuable Lessons to Understand Human Cognition. *Neurol Clin* 34: 69-131. [Crossref]
 87. Bateman RJ, Benzinger TL, Berry S, Clifford DB, Duggan C, et al. (2017) The DIAN-TU Next Generation Alzheimer's prevention trial: Adaptive design and disease progression model. *Alzheimers Dement* 13: 8-19.
 88. Lalli MA, Cox HC, Arcila ML, Cadavid L, Moreno S, et al. (2014) Origin of the PSEN1 E280A mutation causing early-onset Alzheimer's disease. *Alzheimers Dement* 10: S277-277S283. [Crossref]
 89. Sindi S, Mangialasche F, Kivipelto M (2015) Advances in the prevention of Alzheimer's Disease. *FL1000 Prime Rep* 7: 50. [Crossref]
 90. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, et al. (2016) Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol* 15: 455-532. [Crossref]
 91. DeKosky ST, Growdon JH (2016) The Human Alzheimer Disease Project: Answering the Call. *JAMA Neurol* 73: 373-374. [Crossref]
 92. Bermejo-Pareja F, Llamas-Velasco S, Villarejo-Galende A (2016) Alzheimer's disease prevention: A way forward. *Rev Clin Esp* 216: 495-503. [Crossref]
 93. Ray S, Britschgi M, Herbert C, Takeda-Uchimura Y, Boxer A, et al. (2007) Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. *Nat Med* 13: 1359-1362. [Crossref]
 94. Mapstone M, Cheema AK, Fiandaca MS, Zhong X, Mhyre TR, et al. (2014) Plasma phospholipids identify antecedent memory impairment in older adults. *Nat Med* 20: 415-418. [Crossref]
 95. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, et al. (2012) Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* 367: 795-804. [Crossref]
 96. Fleisher AS (2014) The value of biomarker comparisons between autosomal dominant and late-onset Alzheimer disease. *JAMA Neurol* 71: 1087-1088. [Crossref]
 97. Toledo JB, Zetterberg H, van Harten AC, Glodzik L, Martinez-Lage P, et al. (2015) Alzheimer's disease cerebrospinal fluid biomarker in cognitively normal subjects. *Brain* 138: 2701-2715. [Crossref]
 98. Vos SJ, Fagan AM (2016) Alzheimer's disease biomarker states. *Lancet Neurol* 15: 25-26. [Crossref]
 99. O'Bryant SE, Mielke MM, Rissman RA, Lista S, Vanderstichele H, et al. (2017) Biofluid Based Biomarker Professional Interest Area (2016) Blood- based biomarkers

- in Alzheimer disease: Current state of the science and a novel collaborative paradigm for advancing from discovery to clinic. *Alzheimer Dement* S1552-5260: 33056-33064. [Crossref]
100. Reiman EM (2017) Alzheimer disease in 2016: Putting AD treatments and biomarkers to the test. *Nat Rev Rheumatol* [Crossref]
 101. Bianconi E, Piovesan A, Facchin F, Beraudi A, Casadei R, et al. (2013) An estimation of the number of cells in the human body. *Ann Hum Biol* 40: 463-471. [Crossref]
 102. Di Fede G, Catania M, Morbin M, Rossi G, Suardi S, et al. (2009) A recessive mutation in the APP gene with dominant-negative effect on amyloidogenesis. *Science* 323: 1473-1477. [Crossref]
 103. Jonsson T, Atwal JK, Steinberg S, Snaedal J, Jonsson PV, et al. (2012) A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. *Nature* 488: 96-99. [Crossref]
 104. Zheng X, Liu D, Roychoudhuri R, Teplow DB, Bowers MT (2015) Amyloid β -Protein Assembly: Differential Effects of the Protective A2T Mutation and Recessive A2V Familial Alzheimer's Disease Mutation. *ACS Chem Neurosci* 6: 1732-1740. [Crossref]
 105. Sun L, Zhou R, Yang G, Shi Y (2016) Analysis of 138 pathogenic mutations in presenilin-1 on the in vitro production of A β 42 and A β 40 peptides by γ -secretase. *Proc Natl Acad Sci USA*. [Crossref]
 106. Alzheimer Preventive Initiative trial marks milestone. banneralz.org/media/39622/bai_release.pdf
 107. Sperling et al (2016) OC27: The A4 study: Update on enrollment and preliminary tauPET analysis. *J Prev Alzheimer Dis* 3: 282.
 108. Habib A, Sawmiller D, Tan J (2016) Restoring soluble amyloid precursor protein functions as a potential treatment for Alzheimer's disease. *J Neurosci Res* [Crossref]
 109. <https://www.roche.com/media/store/releases/med-cor-2014-12-19b.html>
 110. <https://www.alzforum.org/news/research-news/end-road-gantenerumab-roche-declares-prodromal-alzheimers-trial-futile>
 111. <https://www.genomeweb.com/proteomics-protein-research/despite-scarlet-road-setback-roche-not-giving-gantenerumab-amyloid>
 112. Watt AD, Crespi GA, Down RA, Ascher DB, Gunn A, et al. Do current therapeutic anti-A β antibodies for Alzheimer's disease engage the target? *Acta Neuropathol* 127: 803-810. [Crossref]
 113. Siemers E, Dean RA, DeMattos RB, Hutton ML, Blennow K, et al. (2014) Anti-A β antibody target engagement: commentary regarding Watt et al. *Acta Neuropathol* 127: 803-810. [Crossref]
 114. Watt AD, Crespi GA, Down RA, Ascher DB, Gunn A, et al. (2014) Anti-A β antibody target engagement: a response to Siemers et al. *Acta Neuropathol* 128: 611-614. [Crossref]
 115. de la Torre JC (2014) Phase 3 trials of solanezumab and bapineuzumab for Alzheimer's disease. *N Engl J Med* 370: 1459-1460. [Crossref]
 116. Karran E, Hardy J (2014) A critique of the drug discovery and phase 3 clinical programs targeting the amyloid hypothesis for Alzheimer disease. *Ann Neurol* 76: 185-205. [Crossref]
 117. Hawkes N (2016) Amyloid plaques are still main target for Alzheimer's drugs. *BMJ* 352: i214. [Crossref]
 118. <https://www.govtrack.us/congress/bills/111/s3036/text>
 119. Snyder HM, Hendrix J, Bain LJ, Carrillo MC (2015) Alzheimer's disease research in the context of the national plan to address Alzheimer's disease. *Mol Aspects Med* 43-44: 16-24. [Crossref]
 120. <https://www.napa.alz.org/national-alzheimers-project-act-background>
 121. https://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=2363&page-Number=4
 122. Golde TE (2016) Overcoming translational barriers impeding development of Alzheimer's disease modifying therapies. *J Neurochem* 139 Suppl 2: 224-236. [Crossref]
 123. Cummings J, Aisen PS, DuBois B, Frölich L, Jack CR Jr, et al. (2016) Drug development in Alzheimer's disease: the path to 2025. *Alzheimers Res Ther* 8: 39. [Crossref]
 124. Hyman BT, Sorger P (2014) Failure analysis of clinical trials to test the amyloid hypothesis. *Ann Neurol* 76: 159-161. [Crossref]
 125. Morris eGP, Clark IA, Vissel B (2014) Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease. *Acta Neuropathol Commun* 2: 135. [Crossref]
 126. Castello MA, Jeppson JD, Soriano S (2014) Moving beyond anti-amyloid therapy for the prevention and treatment of Alzheimer's disease. *BMC Neurol* 14: 169. [Crossref]
 127. Drachman DA (2014) The amyloid hypothesis, time to move on: Amyloid is the downstream result, not cause, of Alzheimer's disease. *Alzheimers Dement* 10: 372-380. [Crossref]
 128. Herrup K (2015) The case for rejecting the amyloid cascade hypothesis. *Nat Neurosci* 18: 794-799. [Crossref]
 129. Ricciarelli R, Fedele E (2017) The amyloid cascade hypothesis in Alzheimer's disease: it's time to change our mind. *Curr Neuroparmacol* [Crossref]
 130. Banik A, Brown RE, Bamburg J, Lahiri DK, Khurana D, et al. (2015) Translation of Pre-Clinical Studies into Successful Clinical Trials for Alzheimer's Disease: What are the Roadblocks and How Can They Be Overcome? *J Alzheimers Dis* 47: 815-843. [Crossref]
 131. Hill JM, Clement C, Pogue AI, Bhattacharjee S, Zhao Y, et al. (2014) Pathogenic microbes, the microbiome, and Alzheimer's disease (AD). *Front Aging Neurosci* 6: 127. [Crossref]
 132. Itzhaki RF, Lathe R, Balin BJ, Ball MJ, Bearer EL, et al. (2016) Microbes and Alzheimer's disease. *J Alzheimers Dis* 51, 979-984. [Crossref]
 133. Area-Gomez E, Schon EA (2016) Mitochondria-associated ER membranes and Alzheimer disease. *Curr Opin Genet Dev* 38: 90-96. [Crossref]
 134. De Strooper B, Karran E (2016) The Cellular Phase of Alzheimer's Disease. *Cell* 164: 603-615. [Crossref]
 135. Joy Francis (2000) "Cafe complete". The Guardian.
 136. D'Alton S, Hunter S, Whitehouse P, Brayne C, George D (2014) Adapting to dementia in society: a challenge for our lifetimes and a charge for public health. *J Alzheimers Dis* 42: 1151-1163. [Crossref]
 137. Lin SY, Becker M, Belza B (2014) From dementia fearful to dementia friendly: be a champion in your community. *J Gerontol Nurs* 40: 3-5. [Crossref]
 138. Cahill S, Pierce M, Werner P, Darley A, Bobersky A (2015) A systematic review of the public's knowledge and understanding of Alzheimer's disease and dementia. *Alzheimer Dis Assoc Disord* 29: 255-275. [Crossref]
 139. Lin SY, Lewis FM (2015) Dementia friendly, dementia capable, and dementia positive: concepts to prepare for the future. *Gerontologist* 55: 237-244. [Crossref]
 140. Kenigsberg PA, Aquino JP, Bérard A, Gzil F, Andrieu S, et al. (2016) Dementia beyond 2025: Knowledge and uncertainties. *Dementia (London)* 15: 6-21. [Crossref]
 141. Sun F, Gao X, Brown H, Winfree LT Jr (2017) Police officer competence in handling Alzheimer's cases: The roles of AD knowledge, beliefs, and exposure. *Dementia (London)* [Crossref]

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