The amyloid hypothesis is too good to be true

Markku Kurkinen*
Wayne State University School of Medicine, Center for Molecular Medicine and Genetics, Detroit, Michigan 48201, USA

Abstract

According to the amyloid hypothesis, Alzheimer dementia begins in the brain with Aβ 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 Aβ amyloid is not the cause of Alzheimer.

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

Aloyuis ‘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 Wroclaw, 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 einenbesonderen 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 diasparty proteinase unit. APP proteolysis by β- and γ-secretase generates Aβ peptides, most often the Aβ40 peptide, then the Aβ42 peptide [14-16]. Aβ 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 Aβ 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 Aβ 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 Aβ peptides production or aggregation, or the Aβ42/40 ratio, and brain amyloid formation, then to prevent, delay or stop Alzheimer was very simple: stop making Aβ 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 Aβ 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
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 Aβ 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 NCT00103554). 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 Aβ42 peptide production over the other Aβ peptides. Preclinical studies on the transgenic Tg2576 mouse model of Alzheimer had shown tarenflurbil reduced Aβ 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 Aβ 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 MRD1 (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, Saara 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 important in 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, gleevac (Novartis) would have been a little better drug to inhibit γ-secretase, because gleevac reduces Aβ 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 Aβ peptides production in the liver, lowered Aβ 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 Aβ metabolism or clearance in humans into large and expensive phase 2 or 3 clinical trials.”

Christian Haas: “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: “Aβ 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 Aβ generation” [Conclusion].

Avagacestat (Bristol-Myers Squibb) is another γ-secretase modulator, it is 193-fold more effective in inhibiting APP over Notch pro teaseolyis. 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, LY33114814/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 Aβ42 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 Aβ42 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 Aβ 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 Aβ 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
biapineuzumab. These trials lasted 3 years before they were discontinued due to adverse events and lack of clinical efficacy of biapineuzumab. 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 biapineuzumab (NCT00998764). In the 492 people without APOE4, TEAE occurred in 82% and 68% in people who had received placebo and then biapineuzumab (0.5 mg/kg and 1.0 mg/kg), and in 75% and 64% who had received biapineuzumab and then biapineuzumab (NCT00996918). ARIA with edema or effusions were the main adverse events, occurring in 11% of placebo + biapineuzumab and 4% of biapineuzumab + biapineuzumab 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 noting: “In these phase 3 extension studies, intravenous biapineuzumab administered for up to approximately 3 years showed no unexpected safety signals and a safety profile consistent with previous biapineuzumab trials.”

Solanezumab (Lilly) is a humanized mouse monoclonal antibody, which binds to the mid-domain of soluble Aβ peptides but not to the fibrillar form of insoluble Aβ 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 Aβ.” [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/PT 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 Aβ 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 Aβ 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 Aβ 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 Aβ peptides production, aggregation and brain amyloid formation, that cannot be the only effect of the mutations. What else do they know absolutely nothing about. We know little, if anything, what APP or the Aβ 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 Aβ 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 Aβ 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 ages. They could not find any correlation between the amount of Aβ peptides produced, or the Aβ42/40 ratio, and the age of Alzheimer onset. What these data say is this: Alzheimer is not caused by Aβ 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-Aβ 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 Aβ 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-Aβ 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 Aβ...
peptides in the blood or brain have already failed, all preventive trials today are doing the same with anti-Aβ antibodies, β-secretase or γ-secretase inhibitors, or other Aβ lowering drugs. Why not target α-secretase, a protease also called ADAM10, which cuts APP outside the membrane in the Aβ domain, and therefore prevents the generation of Aβ peptides [108]?

December 19, 2014, one of the first preventive Alzheimer trials by Roche (the SCARLET RoA 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 Aβ peptide epitope found only in brain amyloid. In studies on mice, gantenerumab was shown to bind to Aβ peptides and reduce brain amyloid by T cell-mediated clearance.

Roche continues to evaluate gantenerumab in their Margaretue RoA 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 develope oping 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-Aβ antibodies being used in the preventive Alzheimer trials, here is what they found: bapineuzumab bound to Aβ peptides isolated from the brain amyloid, while solanezumab and crenezumab did not. Both solanezumab and crenezumab bound to some 200 other proteins unrelated to Aβ 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-Aβ antibodies should continue. At the same time, they had also written an impressively detailed, if not 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 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?
Acknowledgements

I have no conflict of interest, actual or potential. I thank Hans-Jürgen Apell, Simon D’Alton, Giovanna Buttice, Daniel George, Anton Scott Goslin, Leena Kiviluoma, Risto Kurkinen, Jerry Leszek, Kevin Peters, Anna Seelig, Anna Thuring, Jack de la Torre, Peter Whitehouse and David Woolls for their interest, understanding and help. Special thanks to Manuel Graeber for the two Alzheimer’s papers. I dedicate this paper to my aunt and godmother Liisa Niskanen (1930-2017) who lived with Alzheimer. I’ve been writing this paper many years in memory of Mark A. Smith (1965-2010).

References
20. Silk DJ, Hardy J (2016) The amyloid hypothesis of Alzheimer’s disease at 25 years. EMBO Mol Med. 8: 595-608. [Crossref]
22. Weitz TM, Town T (2016) Amyloid Cascade into Clarity. [Crossref]
24. 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]
44. De Strooper B (2014) Lessons from a failed γ-secretase Alzheimer trial. Cell 159: 721-726. [Crossref]
in Alzheimer disease: Current state of the science and a novel collabora-tive paradigm for advancing from discovery to clinic. Alzheimers Dement S1552-5266: 33056-33064. [Crossref]

100. Reiman EM (2017) Alzheimer disease in 2016: Putting AD treatments and biomarkers to the test. Nat Rev Rheumatol [Crossref]


106. 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]


111. Herrup K (2015) The case for rejecting the amyloid cascade hypothesis. Nat Neurosci18: 794-799. [Crossref]


114. Hill JM, Clement C, Pogue AI, Bhattacharjee S, Zhao Y, et al. (2014) Pathogenic microbicides, the microbiome, and Alzheimer’s disease (AD). Front Aging Neurosci 6: 127. [Crossref]


117. Hawkes N (2016) Amyloid plaques are still main target for Alzheimer's drugs. BMJ 352: 1214. [Crossref]

118. https://www.govtrack.us/congress/bills/111/s3036/text


120. https://www.napa.alz.org/national-alzheimers-project-act-background


124. Hyman BT, Sorger P (2014) Failure analysis of clinical trials to test the amyloid hypothesis. Ann Neurol 76: 159-161. [Crossref]