Observations

What Would It Take to Get an Effective Alzheimer's Drug?

Clinical trial failures kick off a search for new approaches

By Sam Gandy, Tamas Bartfai, Graham Lees, Mary Sano on July 17, 2017

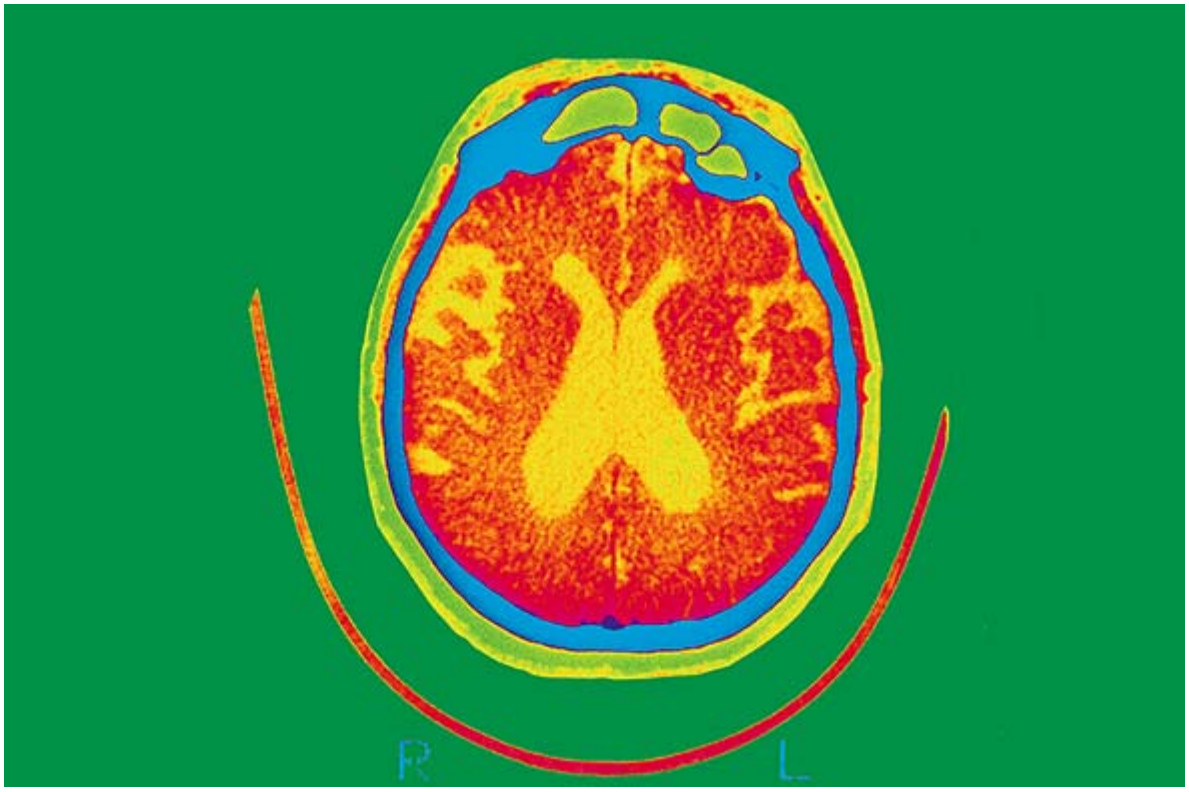
Credit: Dougal Waters Getty Images

Almost 47 million people live with dementia worldwide, and that number is expected to reach 131 million in 2050, according to Alzheimer's Disease International (ADI). Dementia due to Alzheimer's disease (AD) is estimated to account for 60 to 80 percent of cases. Dementia affects about half of the population age 85 years or older.

AD begins with progressively worsening dysfunction in memory, cognition and behavior, and culminates in loss of all higher brain function and, eventually, death due to immobility. There is no cure, and treatment of symptoms provides only limited, temporary relief. Hence, the full force of academic brain researchers and the pharmaceutical industry have focused on achieving measurable changes in the brain function of patients afflicted by AD. A status report of those efforts will be highlighted beginning July 16 as the leading annual meeting—The Alzheimer's Association International Conference—takes place in London.

The researchers at the meeting will spend a lot of time discussing one of the main strategies for intervention involving mitigation of the accumulation of aggregates formed mainly from amyloid beta (Aβ)—a peptide, or short chain of amino acids. Aβ appears in the cerebrospinal fluid, and its deposition in brain can be monitored via an imaging technique called amyloid positron emission tomography (aka "amyloid imaging" or "amyloid brain scanning"). Much of the pharmacological research is devoted to testing the hypothesis that reducing brain Aβ accumulation will prevent or slow the progression of memory problems. So far, the exclusive manipulation of Aβ levels in research and clinical trials has only resulted in a series of high-profile failures of drugs targeting Aβ.

In principle, the case for removing Aβ is strong. An Aβ mutation in certain Icelanders causes levels of that peptide to be reduced by half in the brain, blood and other tissues throughout their lives. These Icelanders virtually never develop AD. Current efforts at AD "prevention" trials—all of which target reduction of brain Aβ—begin at around age 60 in subjects with minimal or no memory complaints or other symptoms. Before they begin taking a drug, their brains are subjected to amyloid-imaging brain scans, and only those subjects already showing pathological accumulation of Aβ are admitted into the trial. This brain amyloid can be present and cause no memory loss or other symptoms for some 30 years or longer before symptoms begin and a diagnosis is made. In fact, the amyloid accumulation might *never* cause any symptoms. Some people die with full-blown Alzheimer's pathology but no symptoms.



Scan Of The Brain Of A Patient Affected By Alzheimer's Disease, Axial Section. Intersections Of Lateral Ventricles Are Dilated. Credit: BSIP Getty Images

What does this tell us? First, these data reveal the Aβ that has been studied for 30 years as the putative culprit in AD does not have a uniform effect across human populations. All clinical trials using molecules that reduce the accumulation of Aβ in the brain do not bring relief of AD symptoms and do not restore memory. The giant pharmaceutical companies—Pfizer, Lily, Novartis, Astra-Zeneca, Roche and, most recently, Merck—have experienced failed clinical trials, even in cases when the drug succeeds in in removing amyloid, as revealed by amyloid imaging.

Despite the lack of meaningful clinical benefit, the U.S. Food and Drug Administration and the pharmaceutical industry will continue to make slowing AD progression an important goal. Pharmaceutical companies cannot afford to turn their backs on AD because any successful drug would be a guaranteed blockbuster. But the cost of hundreds of millions of dollars per trial has markedly diminished interest in initiating new trials without a more complete understanding of the basic neuroscience and immunology of the disease. Another factor that weighs heavily in pharmaceutical company decisions is the fact that these trials take four to six years before producing results, as compared with the more usual drug discovery process in which the effectiveness of a drug, such as an antibiotic, can be established after, say, 48 hours or one week. Further, large, extended trials on aging people with multiple comorbidities like heart disease and diabetes are challenging for pharmaceutical companies because of the complications that

multiple comorbidities can cause. The challenge of diagnosing concurrent AD and vascular dementia, discussed in more detail below, presents a particular problem

Still, no major drug company wants to miss out on developing a drug that will be used for maybe 25 years by around 30 percent of the population. Many observers have argued convincingly that not enough resources have been devoted to non-Aβ–dependent basic AD research that focuses on inflammation and destruction of the synapses involved in communication among brain cells. When one considers that virtually every patient with high blood pressure or diabetes is treated by a combination of two to three drugs acting on different molecular targets, then an obvious conclusion would be that a patient's standard AD drug regimen would involve a cocktail of drugs prescribed to prevent or slow disease pathology. For the best chances of success, we are likely to require additional drugs that interact with other molecules besides Aβ. Recently, the scope of the research into promising non-Aβ drug targets has finally undergone expansion and acceleration. In contemplating what might be needed, we focus here on several approaches.

A first strategy might recognize that by age 85, half the population has at least the beginning symptoms or signs of cognitive impairment. To counter the organ's slow decline, simple math suggests that drug prevention of AD might ideally begin at the latest by 55 years of age, calculated from knowing the 50 percent risk of symptoms by age 85, then subtracting from that number the 30 years during which brain amyloid is often silent. Notably, age 55 roughly coincides with the midlife period when cardiovascular, physical, mental and lipid factors foster the still silent amyloid

pathology, causing progression toward the emergence of classical confusion and memory changes of AD. In the current prevention trial known as "A4" (for Anti-Amyloid Treatment of Asymptomatic Alzheimer's), only subjects who are 65 or older and have positive brain amyloid scans are offered entry into randomized trials of drugs that reduce brain Aβ accumulation. Thus, Aβ-reducing medication is being initiated at least 10 years later than the age likely to be optimum for preventing memory loss.

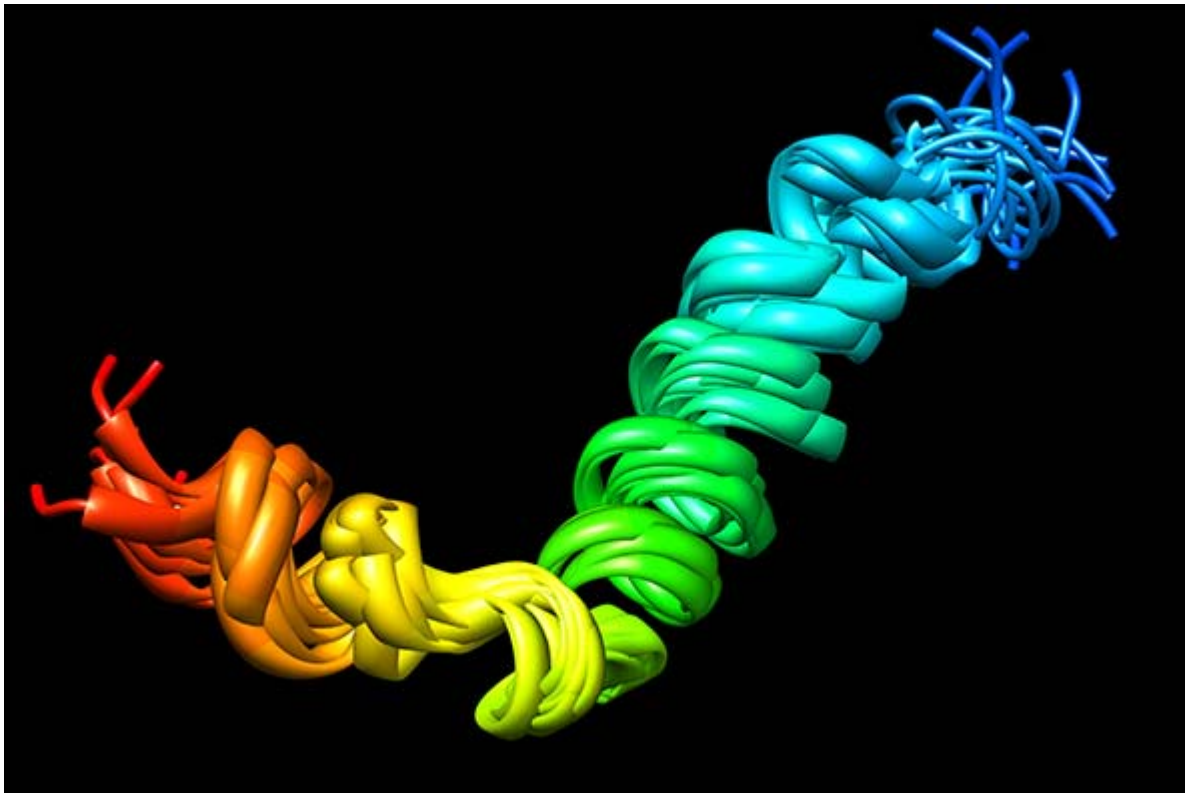
So, why are we beginning a prevention intervention 10 years later than one would predict to give the best chance of preventing memory symptoms? One answer is that the long-term safety and expense of Aβ-reducing interventions precludes trials in which clinically healthy, amyloid-harboring individuals with no memory complaints are exposed to risky and expensive medications for several decades.

BEYOND AMYLOID

There is no evidence so far to prove that current Aβ-lowering trials (beginning at age 65 or above) will show any meaningful benefit for memory or other brain functions. There is unlikely to be anytime soon a medicine (analogous to statins for cardiovascular disease and insulin for diabetes) that is administered for decades from midlife to death as a means of preventing AD. In the cases of statins and insulin, the FDA and society as a whole have agreed that their risk–benefit ratios are acceptable. Any new medication for AD that is worth the risk of ingestion for decades must be effective *and* must do no harm anywhere in the body. The Aβ-lowering drugs in the

current pipeline fall well short of this goal. As yet, there is no reason to expose patients to risky and expensive drugs showing only incremental benefits that are not meaningful. This Plan A is beginning to look like a dead end at least in the protocols employed so far.

Luckily, several new approaches to postponing the symptoms of AD—which might be grouped under a Plan B—are emerging. In AD the cytoskeleton in a neuron, which lends the cell its characteristic triangular shape, collapses to form tangles (aggregates of protein) at about the time that symptoms begin. New strategies involving medications or antibodies that reduce levels of the major tangle protein, known as tau, are entering phase II trials in patients with memory symptoms.



Molecular ribbon representation of the beta-amyloid peptide. The amyloid fibrillar form is the

primary component of amyloid plaques found in the brains of Alzheimer's disease patients. Credit: Pasieka Getty Images

There is at least one other opportunity for intervention during the period when brain amyloid is present but silent. Plan C calls for early initiation of surveillance by an amyloid PET scan of the brain and then initiation as soon as possible a safe drug that arrests disease progression and the onset of symptoms. When Andy Saykin at Indiana University and his team of geneticists used a powerful technique known as genome-wide association study (GWAS), they were able to identify genes that controlled both the rapidity with which PET scan–detectable brain amyloid progressed and symptoms appeared. The top "hit" encountered in this GWAS was a well-known inflammation-related gene known as *IL1RAP*. As a potential drug target, *IL1RAP* can now be tested in animal models in order to make sure the *IL1RAP*-reducing drugs are extremely safe, even if taken over decades. After safety is documented, then, as soon as possible, the drugs can be tested in humans with positive brain amyloid scans but few, if any, symptoms.

PROMISING GENES

Plan D would employ a computational analysis that can be used to analyze the expression of genes at various disease stages and in various regions of hundreds or thousands of AD patients' brains. Using this "big data" approach, Bin Zhang and Eric Schadt at Mount Sinai and colleagues identified entire networks of genes in which key molecules, known as hubs or drivers, appear to be controlling disease progression. By definition, when the level of expression of a

hub or driver gene changes, the expression levels of an entire network of genes changes along with it in the same direction—genes switch either on or off together. This approach has recently led to its first "hit": an immune-inflammatory gene called *TYROBP*, or *DAP12*. This gene is expressed in immune cells called dendritic cells and in "garbage collector" cells called microglia—the latter of which mop up cellular detritus (including Aβ). Is it a coincidence that *IL1RAP*, a gene that controls progression of the disease, and the network hub gene *TYROBP/DAP12* both modulate inflammation? Unlikely.

Recently, under the auspices of the U.S. National Institute on Aging Accelerating Medicines Partnership in AD, Jean-Vianney Haure-Mirande, Michelle Ehrlich and colleagues have validated the Schadt–Zhang breakthrough "hit" by showing that turning off the gene for *TYROBP/DAP12* completely normalizes the behavioral and electrical signal conductance defects caused by brain amyloidosis. Thus, at least in a mouse, reduction or elimination of *TYROBP/DAP12* can apparently prevent, arrest or reverse progression of amyloid-induced toxicity and symptoms even while the amyloid pathology remains in place. In theory, a drug targeting *TYROBP/DAP12* (or *IL1RAP*) could prevent onset or block disease progression and symptom appearance indefinitely. Screening for such a potent, brain-active, anti-inflammatory drug is already underway for *IL1RAP* because of its identity as a signaling component in some forms of leukemia.. Small molecules that are able to get into the brain and block *IL1RAP* signaling have already been developed and are being readied for study in AD.

Plan E would be to find a target amenable to active or passive

immunotherapy. At the moment this is a speculative goal, but it is not an avenue that should be neglected. Anti-tau antibodies —passive immunotherapy—constitute the next immunotherapeutic intervention on deck. Final results of these trials will appear around 2022, although interim analyses might give us a sooner peek at results. Active immunotherapy—vaccination—if safe, should be considered with each unique target under consideration.

Are these plans likely to help quell the Alzheimer's epidemic? If "progression arrest" were terrifically successful, we could drastically cut the number of new clinically emergent cases of AD symptoms. But there are several more issues to consider before we can reasonably hope to make a dent in the prevalence of most dementia.

First, about one third of patients with clinical AD and the pathology that precedes it—atrophy of brain tissue and abnormal glucose uptake by neurons—have negative amyloid imaging. What disease do they have? Is it possible there is both an "amyloid-first" form of AD, in which the peptide builds up prior to symptoms, and a separate "amyloid-later" form of AD, where pathology precedes the arrival of amyloid? Recent analyses of the evolution of brain amyloidosis reveals unexpected and unexplained variations in nature and time course. Do these different brain-region and time-course patterns signal separate pathways for generation of Aβ? Are these very different pathways that lead to the same final plaque and tangle pathology? Answers to these questions are sorely needed.

One more important unknown: the relationship linking cerebral atherosclerosis, vascular dementia and AD. What proportion of dementia involves coexistence of vascular dementia and AD? What

disease process links the two? How does vascular dementia increase the likelihood that concurrent AD will develop?

There is a need for a precision approach to be able to treat or prevent each subtype of dementia based on its molecular profile. For instance, treatments could be marshaled with different classes of drugs, some aimed at diminishing amyloid accumulation. Others could target brain blood vessel changes due to accumulation of amyloid or cholesterol in the blood vessel wall—and both classes might be useful in some patients. Tangle-reducing and/or inflammation-modulating drugs could be added to our cocktails if appropriate to the molecular profile.

A DECADE MORE

The new generation of drugs aimed at tau and inflammation are among the most promising strategies now on the drawing board, although we are not likely to know whether any of these is effective for another decade or two.

Dementia was recognized as an epidemic in the 1970s, and the Aβ peptide was discovered, sequenced and cloned in the 1980s. Now, over 40 years from the recognition of the epidemic nicknamed the "silver tsunami," we can reduce brain Aβ nicely. But we have not been able to translate Aβ reduction into meaningful benefit of memory improvement, perhaps because we cannot safely get amyloid-reducing drugs in patients early enough. Still, there is good reason to believe we will eventually have a meaningful impact on the major causes of dementia.

Many accomplished researchers are focusing their concentration on conquering the scourge of dementia. Nevertheless, unless there is a sustained increase in funding for novel "unconventional" approaches—those not exclusively focused on Aβ-lowering—then it may take at least a few more generations of effort. The current problem with research funding is that—until recently—relatively little was being spent on alternative targets to Aβ, but this situation is finally changing. The cost to the U.S. taxpayer of health care for dementia is estimated at well over $200 billion annually. Stimulus efforts from the administration of Pres. Barack Obama have recently enabled the U.S. National Institutes of Health to increase annual spending on AD research by $400 million per year to around $1.4 billion in the 2017 federal fiscal year. But these funds must be reallocated each year, and the Trump administration has already called for a 20 percent cut in the FY 2018 NIH budget.

DIY INTERVENTIONS

All may not be lost until funding suffices. There may be an interim strategy. Heart-healthy diet, lifestyle and cardiovascular status during midlife are important in determining when dementia appears in late life. Carriers of the Alzheimer's risk gene *APOE e4* who are runners have brain biomarkers including amyloid burdens that are indistinguishable from *APOE e4* noncarriers. Regular physical exercise has been reduced to a prescription standard—three 30-minute sessions of brisk walking or weight training per week. Physical exercise is perhaps the single most important factor that can have an impact on late-life dementia risk. The study of the

molecular basis for this benefit has been elevated to a serious research endeavor. Prescriptions for various forms of mental stimulation are also being studied. Training techniques are being quantified and are beginning to show some benefits, such as prevention of falls. Besides physical and mental stimulation, another focus involves allaying the social isolation that accelerates cognitive decline, leading physicians and families of patients to encourage participation in interactive social activities such as playing card games and musical instruments.

One challenge is that although observational studies suggest a benefit of these lifestyle interventions, randomized clinical trial of dietary and lifestyle intervention have had mixed results, some demonstrating an impact on rate of cognitive decline, others failing to show any benefit. Possibly the difference is that observational data reflect *midlife* and *lifelong* activities whereas clinical trials often do not take into account that interventions must begin in *midlife* to prevent the *late-life* emergence of cognitive impairment. Such trials will be very long and will take commitment of many stakeholders including patients, families and public health authorities to find support for this important effort. A U.S. National Academies of Sciences, Engineering and Medicine study recently declared that the possible cognitive benefits of modifying lifestyle and diet were promising but the current evidence for benefits of diet and lifestyle modification were insufficiently robust to warrant an endorsement for general public health recommendation and initiation of formal U.S. Preventive Services Task Force patient education programs. The Academies study focused on hypertension, physical exercise and cognitive stimulation, and encouraged continued study of diet and lifestyle benefits.

Credit: Joe deSousa Flickr

Another sign of hope has come from man's best friend. Dovetailing with diet and lifestyle studies in humans are studies in certain breeds of dog that develop an Alzheimer's-like aging-related pathology known as canine cognitive dysfunction (CCD). As in human AD, diet and lifestyle interventions in dogs have a substantial impact on the rate of cognitive decline in CCD. One hopes the close parallels between human dementia and its spontaneously occurring canine counterpart will provide the drug-discovery industry with an animal model that is more similar to human AD than are mouse models engineered with early-onset human Alzheimer's mutations. Also, our canine friends have large brains, a plus for imaging tissue changes. They can also be administered behavioral tests that we already use in humans to gauge different aspects of memory so that the effectiveness of any

drugs identified in canines might be directly translated into human patients. Through well-established animal protection programs that guarantee humane treatment, this would be an extraordinarily important advance because a major stumbling block in human drug research has been the challenge of translating Alzheimer's cures in mice into effective drugs for humans. Rodents are poor models of a disease where cognition is the main clinical feature and where most of our resources have been dedicated to studying rare early-onset mutations that may not correspond to common late-onset forms of AD. The unifying theme of all of these new research endeavors suggests the direction of the field needs to set off in a multitude of new directions.

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