

Alzheimer's Disease in Society: Research Efforts Investigate a Cure through Immunotherapy

Some degree of dementia associated with aging is not uncommon, especially in those individuals who are eighty years of age and older. This normal age-related dementia includes forgetfulness and minor memory loss (Swartzberg & Margen, 2001). However, this does not even begin to resemble the effects of Alzheimer's Disease, a dementia-related condition of the brain. Alzheimer's Disease is characterized by the gradual, irreversible progression of damage to the brain, and the ensuing effect it has on the functioning of those afflicted. Unlike age-related dementia, Alzheimer's Disease can make itself known early onset, which is classified in people 65 years of age and younger (Swartzberg & Margen, 2001). While loss of cognitive ability and physiological control of behavior are among the outwardly observable characteristics of AD, they are only symptoms that correspond to the accumulating effect of damage to the brain of the Alzheimer's—afflicted individual (Swartzberg & Margen, 2001). Pathologically, Alzheimer's Disease is characterized by the presence on the brain of amyloid-beta plaques and neurofibrillary tangles, that latter of which is due to the hyperphosphorylation of tau proteins (DaSilva, Brown, & McLaurin, 2009). Both the extent of damage to the brain and the complexity of the characteristic abnormal brain composition lends reasoning behind the vast body of literature and research that exists on Alzheimer's Disease.

Recent endeavors in the field of pathophysiological research in biology have been investigating the possibility of an Alzheimer's vaccine. As the research implies, the vaccine would prevent, slow the progress, and even possibly reverse the damage of Alzheimer's Disease via a pathway utilizing an immune response, essentially treating the disease with the ultimate goal of eliminating the acquiring of the disease altogether (Foster et al., 2008). While significant

and substantial research has been ongoing for approximately a decade now, the sheer complexity of the disease and its implications for the cognitive and physiological functioning of the individual have presented as incredibly time-consuming and extensive studies (Kayed & Jackson, 2009). Research, however, has shown strong promise for the future in regards to public availability of a proposed Alzheimer's vaccine. Many Phase I and Phase II clinical trials on the various different vaccination pathways being studied have been completed, and some Phase III trials are currently underway, showing just how far research into the vaccine has come in the years since the possibility was proposed (Matsuda, Kaminaka, & Nozaki, 2009). What is interesting about the vaccine research being done pertaining to AD is the variety of different biophysiological pathways that are showing success in preliminary studies. This implies that there may not be just one possibility for a vaccine to prevent or reverse the damage of Alzheimer's, in fact, there are many possible options that are being reserved thoroughly in order to ascertain which biological pathway and immune response creates the desired effect most efficiently, successfully, and above all, safely.

The Alzheimer's vaccine seeks to target the pathophysiological characteristics seen in the Alzheimer's damaged brain. Research into a possible vaccine pathway is centered around the two major characteristics of the disease on the brain: the beta-amyloid plaques and the neurofibrillary tangles (Kayed & Jackson, 2009). The majority of research has been focused on the beta-amyloid plaques, specifically, the removal or breakdown of the plaques, both soluble and insoluble, or aggregated, plaques (Foster et al., 2008). The reason that beta-amyloid plaque removal is the focus of most research, as opposed to the repairing of neurofibrillary tangles of tau protein, is due to the amyloid hypothesis of AD (Foster et al., 2008). This hypothesis states that it is the plaques that are the cause of the disastrous cognitive decline and impairment in

those with Alzheimer's Disease (Foster et al., 2008). This implies that if the plaques are destroyed and removed, the brain can then return to a state of normal functioning though healing itself, and it is hopeful that cognitive abilities would then be returned to the individual. Only recently have alternative approaches to the beta-amyloid vaccine been looked at, which seek to investigate the possibility of targeting tau, the protein that is responsible for creating neurofibrillary tangles (Kayed & Jackson, 2009). Early research with tau also represents promising input to the future of an Alzheimer's vaccine, but much more research has to be done with this pathological characteristic of Alzheimer's than does that on beta-amyloid plaque removal (Kayed & Jackson, 2009).

The vast majority of research has been centered on the removal of beta-amyloid plaques from the brain, in hopes that it will facilitate reversing of the cognitive deficits experienced by the patient via the brain naturally healing itself to function properly without the obstruction of the plaques. Though many different types of beta-amyloid vaccine pathways are being researched and studied in clinical trials, all have the same basic biological goal: stimulating an immune response to produce antibodies towards the beta-amyloid peptide which in turn prevents the further accumulation and aggregation of beta-amyloid into plaques and also breaks down the current plaques by the antibodies binding directly to the beta-amyloid (DaSilva et al., 2009). A few of the ways this method is being utilized in the beta-amyloid specific Alzheimer's vaccine is through passive immunization, active immunization, with and without different adjuvants (adjuvants act in much the same way for vaccines as catalysts do for enzymes; they aid the reaction in overall production of antibodies without causing an immune response themselves), and through DNA that encodes for the beta-amyloid peptide. Not only does each different method of breaking down the plaques have to be studied thoroughly with many accurate

replications of the study, but additionally the methods have to be compared to each other to see which technique offers the fewest side effects, most effective and efficient treatment, and most reliable and safest results.

The immunization technique of being active or passive refers to how the antibodies in the body are produced. In active immunotherapy, the focus is to get the body to produce its own antibodies against beta-amyloid, while in passive immunotherapy the antibodies are already prepared and are injected into the AD patient (Foster et al., 2008). As was already mentioned, the idea behind this method of immunization for the AD vaccine is that the beta-amyloid antibodies would bind to the beta-amyloid peptide and thus inhibit the further deposition of plaques and, additionally, breakdown the current plaques, both soluble and insoluble. This would hopefully halt further progression of the disease, and even return cognitive functioning. This type of immunization was utilized in one of the largest, most well-known, and earliest clinical trials of a beta-amyloid vaccine therapy (Foster et al., 2008). The 2000 study termed AN1792 was a phase I trial that took place in the UK; the initial results were very promising and represented early success with vaccine possibilities for AD (Foster et al., 2008). However, the clinical trials came to an abrupt halt when meningoencephalitis came up as a side effect of treatment (Zhang et al., 2009). This serious central nervous system inflammation was seen in 6% of the patients in the study, a total of 18 people (Foster et al., 2008). The impact of AN1792 on AD vaccine research stressed the importance of clinical trials first on mice, then on primates, then on humans.

A study by Zhang et al. introduced intramembranous fragments of beta-amyloid peptide with an adjuvant into mice in order to immunize them (2009). The potent adjuvant used was monophosphoryl lipid A/trehalose dicorynomycolate, or MPL + TDM, also known as Freund's adjuvant (Matsuda et al., 2009). The effects that were seen included moderate IgG antibody

production against beta-amyloid and neutralization of the neurotoxicity by the anti-sera (Zhang et al., 2009). Their work showed that intramembranous fragments of beta-amyloid do produce an immune response of antibody production and thus may be a possibility for use in an AD vaccine. However, this takes into consideration the fact that AN1792 used a potent adjuvant in its clinical trials, which has since then been established as one of the contributing causes of the induced meningoencephalitis seen in the patients (Matsuda et al., 2009).

Since use of an adjuvant in the beta-amyloid vaccines is not always optimal, because of the possible adverse side-effects previously explained, research has also been conducted to study the effectiveness of a beta-amyloid vaccine without an adjuvant. Matsuda et al. found that addition of a cysteine amino acid residue to the C terminus of the beta-amyloid peptide without an adjuvant increased the production of anti- beta-amyloid antibodies in AD model mice by several hundred times more than the peptide did without the additional cysteine residue (2009). Furthermore, this powerful increase in immune response was not seen with the addition of any other amino acid residue other than cysteine (Matsuda et al., 2009). An interesting aspect to the study also found that enhancement of the antibody production immune response was seen only with beta-amyloid peptides of certain lengths, specifically the longer chain peptides (Matsuda et al., 2009). These findings show that an adjuvant is not necessary for the effectiveness of the possible AD vaccine; other biological substances can increase the production of antibodies without the risk of dangerous side-effects.

Research on a vaccine that employs DNA encoding for beta-amyloid antibody production also shows the possibility for an effective AD vaccine without the use of an adjuvant (DaSilva et al., 2009). Plasmids that encoded for beta-amyloid provoked an immune response that produced anti beta-amyloid antibodies in mice, which decreased the degree of plaques by an average of

36%, insoluble plaques included (DaSilva et al., 2009). As can be understood from the many methods of vaccine research previously explained, the possibility for an AD vaccine may take the appearance of any one of these effective techniques for producing antibodies against beta-amyloid. Further research must replicate these studies with similar results again on mice, then take the studies to a level that can be more easily transferable to humans: primates. Future studies on these thus far effective methods of producing beta-amyloid antibodies would take the research one step closer to achieving a safe and effective vaccine for humans for reducing the beta-amyloid plaques in Alzheimer's patients.

While research has shown overwhelmingly consistent results of the various vaccine mechanisms being studied all showing results of producing antibodies and furthermore of clearing and breaking down beta-amyloid plaques, there are major related issues that are surfacing as significant concerns (Foster et al., 2008). The issues include neurotoxicity due to the breakdown of beta-amyloid plaques, which can accumulate to cause inflammation and swelling of the brain, hemorrhaging, and the fact that it has not yet been established whether breaking down and clearing the plaques will even result in improvement in the cognitive abilities of the Alzheimer's patient: the ultimate goal of the vaccine research (Foster et al., 2008). It is hopeful that with the successful attainment of a vaccine that clears the beta-amyloid plaques from the brain, which allows for the brain to be more comparable to that of a healthy brain as the abnormal plaques disappear, that it will then be obvious whether the beta-amyloid plaques are a source of the brain damage and cognitive impairment or rather have no significant effect on the symptoms accrued by the Alzheimer's patient.

Alzheimer's Disease is arguably one of the most devastating diseases for society, simply because of the widespread and intense impact it has on the loved ones of the person who is

afflicted. In the United States alone, those who are burdened by the emotional pain of caring for a loved one with Alzheimer's Disease is estimated at 4.5 million people (Foster et al., 2008). Watching a loved one slowly decline in mental ability and overall functioning as a person, in accordance with the progressive, worsening dementia that is AD, is almost unbearable for some. Loved ones must watch as the person they knew disappears; the Alzheimer-sufferer loses the ability to remember people, events, experiences, where they live, how to feed and bathe themselves, and basic personal grooming skills, which are just a few of the many unfortunate physiological and mental consequences of the disease. Those with AD in advanced stages are left utterly helpless and unaware of the world around them, essentially disengaged with the grasp on reality they once had. This is exactly why the finding of a successful Alzheimer's vaccine would have a tremendous impact on society. By slowing the progression of the disease, reversing the damage on the brain, and preventing the acquiring of the disease altogether, the vaccine would relieve people of the disastrous fate that Alzheimer's Disease has on a person, and by effect, their loved ones. Even preventing the furthering of damage to the brain in the form of beta amyloid plaques would mean that AD sufferers would not progress to the advanced stages of Alzheimer's in which they hold very few physiological functions and almost no cognitive or mental abilities. The vaccine would represent a culmination of an achievement at large for science and society together; relieving society and the people themselves from the pain and suffering of Alzheimer's Disease through biological research that produced a mechanism to stop the destruction of the brain that is the source of the suffering itself.

The future of the Alzheimer's Disease vaccine is not entirely certain yet, despite the volumes of promising research. Though it has been proven in many clinical trials that beta-amyloid plaques can be broken down via an antibody-inducing vaccine, it is not clear whether

this alone is enough to prevent the further progression of the disease, return of cognitive abilities, or prevention of the disease altogether (DaSilva et al., 2009; Foster et al., 2008). By determining whether the removal of beta-amyloid plaques in the brain via the proposed vaccine results in an improvement in cognitive faculties, research can see if the degenerative mental functioning of a person with AD is due to the presence of the plaques. If removal of the plaques does not result in return of cognitive abilities, it is likely that research will shift to targeting neurofibrillary tangles from tau protein to determine if repairing this pathological distinction of Alzheimer's will result in prevention of further damage, and even regaining of cognitive abilities. Long-term studies are key to the success of the possible vaccine, whichever mechanism or pathway it may take on. Time, however, is a factor that is not only of the utmost importance for the overall safety and effectiveness of a vaccine against AD, but also the first to be compromised when there is the looming pressure to come out with the answer as fast as possible to prevent the further affliction of this devastating disease on more people. Researchers are hopeful that the more that is learned from continuing studies of vaccine possibilities and long-term analysis of the effects of breaking down amyloid plaques, the greater the possibility that an Alzheimer's Disease vaccine will exist one day.

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