

Stealth Attack: Plaque-Specific Antibody Allows for Efficient A β Removal without Side Effects

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Anti-A β antibodies are being developed as potential treatments for Alzheimer's disease. Some have dose-limiting side effects and many do not robustly remove pre-existing amyloid plaques. In this issue of *Neuron*, DeMattos et al. (2012) demonstrate that an amyloid plaque-specific antibody removes existing A β aggregates without side effects.

Alzheimer's disease (AD) is the most common cause of dementia and we do not know as yet how to prevent, slow, or reverse the disease with currently available drugs. Amyloid- β (A β) is constantly produced in the brain, predominantly by neurons, and is secreted as a monomer. During most of our life, it is cleared and does not build up in the brain. However, in some people that go on to develop AD, it aggregates in the brain to form amyloid plaques and cerebral amyloid angiopathy (CAA). A β deposition and the subsequent aggregation of tau culminating in the formation of neurofibrillary tangles are two major pathological hallmarks of AD. By the time humans begin to have the earliest clinical symptoms and signs of AD, the amount of A β pathology in the brain is already substantial, probably close to the amount that will be present in the stage of advanced dementia due to AD (Jack et al., 2010; Perrin et al., 2009). Therefore, for those individuals who already have developed amyloid plaques and who are still asymptomatic or have very mild dementia, developing effective therapies that can effectively remove and decrease toxicity of pre-existing plaques and CAA without causing side effects is a major goal.

Many anti-A β antibodies are being developed as potential treatments for AD but success has been limited. A murine monoclonal antibody to A β , 3D6, was shown in several studies to decrease amyloid plaques and CAA when given soon after A β deposition began (Bard et al., 2000; Schroeter et al., 2008).

However, results from a recent phase III clinical trial using bapineuzumab (the human equivalent of 3D6) in patients with mild to moderate AD revealed disappointing results, including lack of clinical effects, no evidence of plaque removal (though it appears to have attenuated further increases in plaques), as well as provocation of side effects associated with CAA including edema and hemorrhages in the brain (Scheltens et al., 2012, Clinical Trials on Alzheimer's Disease, abstract) (Sperling et al., 2012). It is unclear whether this particular failure in a phase III clinical trial is due to inadequate timing of treatment (i.e., too late), lack of adequate target engagement, or both. Given that the most effective results on amyloid plaque and CAA removal in animal models have been obtained when anti-A β antibodies are started before A β pathology is fully formed in the brain (Das et al., 2001), discrepancies between the results from animal models and humans in plaque removal may stem from lack of efficacy of the anti-A β antibody being used in regard to its ability to actually remove existing A β aggregates. Thus, lack of target engagement along with side effects may have been a real issue with this antibody at the doses used in humans.

In this issue of *Neuron*, DeMattos et al. (2012) assessed the mechanism of action of an A β plaque-specific antibody, mE8, which specifically binds to pyroglutamate A β in amyloid plaques and which does not bind to soluble A β . Pyroglutamate A β is formed by truncation of the first two

N-terminal amino acids of A β and subsequent posttranslational modification of the third amino acid, glutamate, into pyroglutamate by glutaminy cyclase. Pyroglutamate A β is known to be more prone to aggregate, to form oligomers, and to be more toxic (Jawhar et al., 2011). Pyroglutamate A β is not normally present in vivo; it is, however, found in amyloid plaques (Saido et al., 1996). Herein, DeMattos et al. (2012) compared the effect of peripherally administered mE8 with effects of monoclonal antibody 3D6, which binds to both soluble and insoluble forms of A β in the brain in both preventive and therapeutic paradigms. When administered in a transgenic mouse model (PDAPP) at an age at which there are large amounts of A β plaque pathology in the brain as well as CAA, mE8 strongly decreased the amount of pre-existing, accumulated insoluble A β . This effect occurred without an increase in the amount of CAA or microhemorrhages (Figure 1, right). On the other hand, the 3D6 antibody did not decrease the amount of insoluble A β in the brain in old PDAPP mice with a large amount of pre-existing amyloid plaques, though it markedly increased CAA and CAA-associated microhemorrhages. Interestingly, 3D6 worked well in decreasing amyloid plaques and insoluble A β when given in a prevention mode, as has been shown previously (Figure 1, left). Studies like this, in which a compound is tested in a model in which the amount of A β plaques and accumulation in the brain is comparable to what is seen in humans

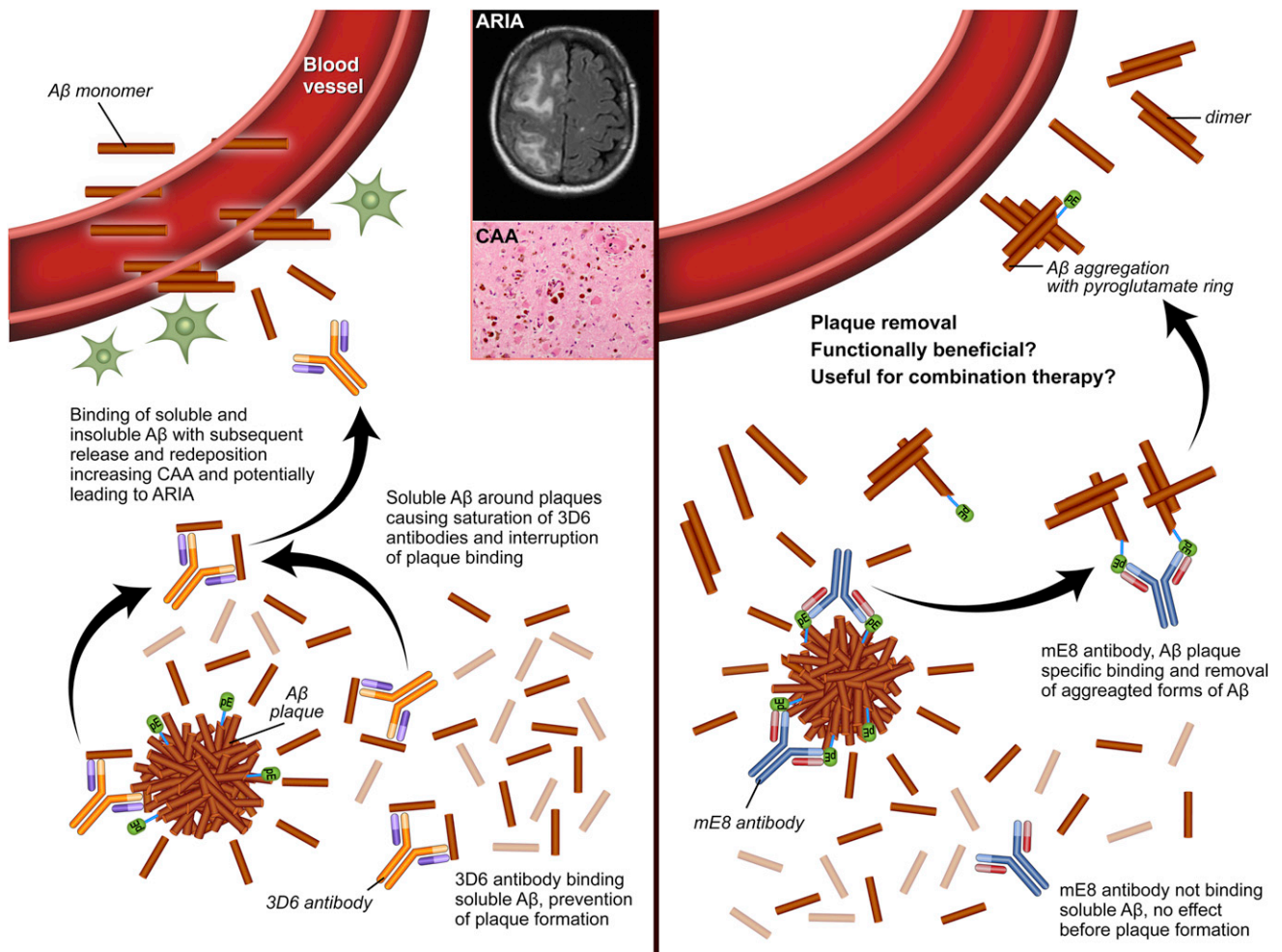


Figure 1. Aβ Plaque-Specific Antibody Removing Plaques without Increasing CAA

Plaque-specific antibody mE8 removes pre-existing Aβ plaques without causing increased CAA and ARIA (right). In contrast, 3D6 antibody prevented Aβ plaque formation but could not remove pre-existing plaques in the brain (left). Insets in the left panel are reprinted from Sperling et al. (2011). CAA, cerebral amyloid angiopathy; ARIA, amyloid-related imaging abnormalities.

with AD dementia, have not frequently been done in this field. The results strongly suggest that if one is targeting humans in clinical trials who already have substantial amyloid deposition, the design of such trials should be based on preclinical studies that mimic the human disease state that one is targeting. The preclinical results of DeMattos et al. (2012) would have predicted both little change in plaque load with bapineuzumab in humans and its effect of increasing CAA. Thus, utilizing mouse models can be useful, if similar stages of pathology are being compared to the human condition.

When administered prior to amyloid plaque formation, mE8 did not prevent Aβ plaque deposition. The lack of efficacy

in the prevention trial suggests that mE8 is not working by blocking seeding of soluble forms of Aβ. It does act on already formed Aβ deposits, presumably because pyroglutamate Aβ is generated after initial Aβ aggregation. In future studies, it will be important to combine therapies to both prevent and remove Aβ accumulation, for example, by combining drugs that inhibit Aβ production (e.g., gamma secretase inhibitors/modulators and β-site amyloid precursor protein-cleaving enzyme inhibitors) with therapies that remove existing plaques. The other consideration would be to combine therapeutic antibodies that lack CAA-associated side effects and can bind and neutralize the toxicity of soluble forms of

Aβ together with plaque-removing therapies. Such combinations might have the benefit of preventing new Aβ plaque formation and decreasing Aβ toxicity, while an antibody like mE8 could remove pre-existing plaques, a potential reservoir for toxic Aβ species.

This study raises some additional questions that will need to be addressed in future studies. Behavioral and/or functional studies were not performed in the DeMattos et al. (2012) study. Therefore, one cannot tell whether the decrease in levels of Aβ in the mice with pre-existing plaques are beneficial, neutral, or harmful to cognition or other brain functions affected by aggregated Aβ. The effect of the Aβ removal is very strong in this study

as assessed by biochemical analysis. However, the effect on actual plaque load as assessed by anti-A β staining was not significant in the 23-month-old PDAPP mice studied. This may be due to the fact that even though large amounts of A β were removed from the brain, the plaque load by staining was already so high, it would have taken longer to see an effect. It is of note that two other groups have seen effects on reducing A β plaques with anti-pyroglyutamate A β antibodies (Frost et al., 2012; Wirths et al., 2010), though these antibodies differ in their properties in comparison to mE8. In terms of the lack of efficacy of the 3D6 antibody in removing pre-existing plaques, DeMattos et al. (2012) interpreted this to being due to 3D6 becoming bound to monomeric A β with saturation in the microenvironment around the plaques, not allowing amyloid plaque binding and target engagement. Recent studies, however, suggest that the amount of monomeric, soluble A β in the interstitial fluid of the brain is decreased, not increased, in the presence of amyloid plaques (Hong et al., 2011; Roh et al., 2012). This is probably due to the sequestration of monomeric A β into plaques. It is possible that there are soluble monomeric or more likely oligomeric forms of A β that are bound or loosely associated with plaques that are not detected in the interstitial fluid of the brain with current methods. Theoretically, 3D6 could bind to these forms of A β , resulting in saturation and prevention of plaque binding. It is also possible that there is not more soluble A β around plaques preventing the effect of 3D6 but that the antibody simply has lower affinity

for certain forms of aggregated A β or lacks certain features that are needed to decrease existing plaques once a threshold level of A β accumulation is reached. Follow-up studies could be performed in which soluble forms of A β are measured in the interstitial fluid of the brain after administration of anti-A β antibodies to determine whether antibodies are influencing soluble A β differently in the presence or absence of amyloid plaques and to see whether this predicts in any way the effects of anti-A β antibodies on plaque removal or functional improvement.

The A β plaque-specific mE8 antibody might be an attractive candidate therapy to consider for secondary prevention trials for individuals with preclinical AD as well as for treatments of individuals with very mild dementia due to AD. Since those with preclinical AD and mild cognitive impairment or very mild dementia due to AD already have substantial A β deposition in their brain (Jack et al., 2010; Perrin et al., 2009), this type of treatment targeting pre-existing A β plaques might be quite promising as a disease modifying treatment.

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