

# Understanding amyloid beta and Alzheimer's disease: the key to helping AD patients

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## Efforts to prevent or treat Alzheimer's Disease (AD) by targeting Amyloid beta (A $\beta$ ) assemblies should be continued, but the strategies should be altered dramatically

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The most common error with the treatment of Alzheimer's Disease (AD) has been to confuse effects with causes. AD begins with small Amyloid beta (A $\beta$ ) assemblies, oligomers, that damage synaptic and organelle membranes. Pathogenic oligomers should be suppressed long before symptoms appear.

The root causes of Alzheimer's Disease (AD) are poorly understood and often misunderstood. Yes, everyone knows about plaques and tangles that contain amyloid beta (A $\beta$ ) and tau fibrils; these have been observed in the brains of most Alzheimer's patients since the 19th century. Billions have been spent to develop treatments that target these assemblies with almost no success. Just as war cannot be prevented by analyzing battlefield carnage, AD treatments based on analyses of plaques and tangles have failed. By the time they appear, it may be too late to avoid damage or halt the progression of AD.

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The following facts are less well-known and seldom publicized: (1) The severity of AD does not correlate with the presence of plaques. (2) Smaller A $\beta$  assemblies, called oligomers are more toxic than A $\beta$  fibrils or A $\beta$  monomers, (3) Levels of A $\beta$  and oligomers increase decades before symptoms, plaques, and tangles appear. (4) These increases can be detected. (5) A $\beta$  occurs in different isoforms; the most toxic, A $\beta$ 42, is two amino acid residues longer than the most common form, A $\beta$ 40. (6) The ratio of A $\beta$ 42 to A $\beta$ 40 is higher in AD patients. (7) Only A $\beta$ 42 oligomers form transmembrane channels in neurons. (8) Interaction of A $\beta$ 42 with synapses is facilitated by interaction with GM1 ganglioside lipid. (9) A $\beta$  has important biological functions that have not been well studied. (10) A $\beta$  oligomers occur both outside and inside neurons. (11) Intracellular A $\beta$  damages organelles, stimulates oxidation and triggers the formation of tangles. (12) Most neurological diseases, including AD, involve malfunction and destruction of mitochondria that power cells. (13) Damage to both synapses and mitochondria involve the passage of calcium ions through membranes, possibly through A $\beta$ 42 channels.

(14) Cellular garbage disposal mechanisms involving the Golgi apparatus and apolipoproteins are affected in AD. (15) A $\beta$  interacts with other amyloids, including  $\alpha$ -synuclein (Parkinson's Disease) and amylin (Type 2 diabetes); some of these interactions are pathogenic and others are protective.

## Why haven't these smaller Amyloid beta assemblies been targeted?

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A $\beta$  oligomers and their interactions with membranes are highly polymorphic; i.e., many forms of oligomers occur, and they often transition among these assemblies. Also, a common, somewhat misleading, conception is that A $\beta$  peptides and small assemblies are intrinsically disordered. This is almost certainly true under some circumstances, e.g. at early stages at relatively low concentrations in aqueous solutions when only a few peptides comprise the oligomers.

With time and increased concentrations, however, oligomers increase in size and become more structured. Their structural order increases in less hydrophilic environments, e.g. when detergents or organic solvents are present, when they interact with fatty acids or lipids, or when they bind to and penetrate membranes. Experimental studies and analyses of multisequence alignments support the hypothesis that some forms of A $\beta$  are functional; e.g., humans, snapping turtles, and finches have identical A $\beta$  sequences, and a sequence from bamboo sharks has only one highly conservative mutation. Highly conserved related proteins typically have similar highly ordered conformations and are typically functionally important. But which assemblies are functional and which are pathogenic remains unknown. And finally, the three-dimensional structures of most A $\beta$  oligomers have not been determined.

Our group develops structural models of A $\beta$  oligomers and channels. Some of our concentric  $\beta$ -barrel models are highly stable throughout relatively long molecular dynamic simulations, have sound energetic features, and are consistent with multiple experimental findings and well-established  $\beta$ -barrel theory. While hypotheses are not proofs, they are vital for hypothesis-based experimental approaches that can lead to proofs.

## Improved preventions and treatments for AD patients are the real goals

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We remain optimistic that effective treatments that target A $\beta$  can be developed. For example, interactions with some other amyloids such as humanin and the N1 peptide cleaved from the PRP prion protein are protective against Alzheimer's, as are some mutations such as those in rat A $\beta$ .

Efforts are already underway to develop vaccines against AD and to interfere with interactions of A $\beta$  with gangliosides. To nip these diseases in the bud, ideal treatments should have the following properties: (1) First do no harm. This includes not interfering with the vital functions of these peptides. Although a few studies have shown that A $\beta$  favorably affects synaptic activity, may be involved in lipid transport, and have antimicrobial properties; mechanisms underlying these processes are poorly understood and the effects of putative drugs on these mechanisms are seldom analyzed. (2) Treat the diseases at an early stage before the damage becomes irreversible. An increase in A $\beta$  concentration in cerebral spinal fluid can be detected long before symptoms appear, and genetic screening can detect mutations that increase the likelihood of Alzheimer's. (3) Treatments should target toxic forms of A $\beta$  without affecting vital forms.

## Encourage structural studies of pathogenic Amyloid beta assemblies

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Rational or structure-based drug design could be used if we only knew the structures of pathogenic forms. In spite of enormous progress in the single-particle determination of membrane protein structures, these methods have not yet produced atomic-scale structures of A $\beta$  assemblies. This may be because micrographs of these assemblies in membranes can appear hopelessly complicated due to the presence of multiple forms.

We find, however, that even in these cases important structural information can be gleaned from relatively low- resolution micrographs by identifying images of the same size and shapes and averaging these images. Also, high-resolution structures may not be required to develop antibodies and vaccines for crucial sites.

To summarize, we need to target the correct pathogenic assemblies well before symptoms appear. Relatively small channel-forming A $\beta$ 42 assemblies may be a major culprit: they are the most toxic form, occur more abundantly in AD patients, and the last thing you want to happen in synapses or mitochondria is for rouge proteins to increase calcium permeability of their membranes

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#### Amyloid Research Consultants

Amyloid Research Consultants enable research targeting root causes of diseases such as Alzheimer's, Parkinson's, and diabetes.

