Understanding what drives pathological pathways causing Alzheimer's disease (AD) is essential if we are to develop effective treatments for this devastating disorder. Our studies focus is the deposition of insoluble cerebral amyloid, a hallmark feature of the AD brain. High amyloid burdens trigger a cascade of harmful pathways that cause widespread neuroinflammation, neuronal death, and ultimately, dementia. Amyloid is generated in brain by the aggregation of a small protein called Aβ. Aβ is typically characterized as a functionless byproduct of catabolism. As such, the ability of Aβ to self-associate and generate insoluble amyloid is viewed as intrinsically abnormal and exclusively harmful. Since the discovery of Aβ over thirty years ago, this view of amyloid's origin has guided therapeutic strategies aimed at treating AD and the majority of drugs trialed to date target this protein. Treatments aim to reduce amyloidosis (deposition of amyloid) by lowering brain Aβ levels or blocking the protein from self-associating. Unfortunately, over 400 clinical trials have failed to yield a drug effective at slowing amyloidosis or AD progression.

While overwhelming genetic and biochemical data support the primacy of amyloid in AD, mounting data are inconsistent with the longstanding view of Aβ as an unfortunate functionless byproduct of metabolism. For example, Aβ is a very ancient protein (over 400 million years old) that continues to be expressed unchanged in most vertebrates. Such remarkable conservation over hundreds of millions of years strongly suggest Aβ has an important function in brain and that amyloid generation is key for the proteins normal physiological role. In 2010 we published a report identifying the possible normal function of Aβ. Aβ appears to be a member of a critically important group of immune proteins known as antimicrobial peptides or AMPs. AMPs are the foot soldiers of innate immunity, an ancient arm of the immune system. AMPs act like antibiotics and fight infections. The brain is immunoprivileged (antibodies and most immune cells are excluded) and AMPs are the central nervous systems primary defense against pathogens. In 2016 we reported data confirming expression of Aβ in genetically modified animal and cell culture models protects against fungal, bacterial, and viral infections, doubling host survival in some cases. Most pertinent to AD pathology, Aβ fights infection by entrapping and neutralizing invading pathogens within amyloid deposits. Acute infection lead to rapid and extensive amyloid deposition in our animal models. Thus, infection can seed amyloid deposition in brain. The new amyloid genesis model shifts the modality of amyloidosis from an unfortunate misbehavior of Aβ toward a dysregulated innate immune response. This insight has important implication for ongoing and future AD treatment strategies. Not least, it suggests microbes in the brain may accelerate, or possibly even initiate, the pathology thought key for neurodegeneration in AD- deposition of amyloid. We are currently exploring if microbes play a role in seeding amyloid deposition in human brain. Our recent findings suggest AD may not have a classical infectious disease etiology that involves a single pathogen mediating disease. Rather, the brains resident microbial population (microbiome) may be disrupted in AD. The microbiome imbalance leads to activation of Aβ/amyloid pathways as the brains innate immune system attempts to restore order. Long-term, microbe-induced amyloid deposition leads to amyloidosis, neuroinflammation, and eventually clinical AD. In this model, AD has parallels with inflammatory bowel disease and other disorders in which the gut microbiome is disrupted. Our brain microbiome model of amyloidosis remains provisional, and considerable additional data will be needed to confirm, or disprove, relevance to AD. However, our key finding that Aβ itself is not an incorrigible villain but also a protector has now been independently confirmed. Independent of what role microbes are found to play AD etiology, we believe the new emerging view of Aβ as an AMP to be an important advance that will help inform and shape ongoing and future therapeutic strategies aimed at treating this terrible disease.