

Treatment Developments in Alzheimer's Disease

An Expert Interview with Martin R Farlow

Department of Neurology, Indiana University School of Medicine, Indianapolis, IN, US

DOI: <https://doi.org/10.17925/USN.2018.14.1.17>



Martin R Farlow

Martin R Farlow is Professor of Neurology and Vice-Chairman of Research in the Department of Neurology at the Indiana University School of Medicine in Indianapolis. He is also Associate Co-Director of the Indiana Alzheimer's Disease Center in Indianapolis and leads a large Alzheimer's and related dementias clinical trials site, having led and/or contributed to over 150 clinical trials over the last 25 years. Dr. Farlow is a member of many professional associations including the American Academy of Neurology (AAN), American Neurological Association (ANA) and American Geriatrics Society (AGS). He is also a founding member in both the American Society of Experimental Neurotherapeutics and the International Society for CNS Clinical Trials and Methodology. Dr. Farlow has lectured on topics of aging, dementia, and Alzheimer's disease at more than 300 meetings, conferences, and hospitals/medical schools throughout the world. A prolific author, Dr. Farlow has presented more than 470 abstracts at professional meetings and has authored or co-authored more than 460 articles published in peer-reviewed journals. Dr. Farlow's research focuses on clinical trials of investigational drugs for the treatment of Alzheimer's disease and related dementias, being the lead investigator on major studies including tacrine, donepezil, rivastigmine, CAD106, and solanezumab. Dr. Farlow also has clinically characterized and helped determine genetic linkage for several familial dementias including the second mutation associated with autosomal dominantly inherited Alzheimer's disease, Gerstmann-Straussler-Scheinker disease, and multi-systems tauopathy with dementia.

Keywords

Aducanumab, Alzheimer's disease (AD), amyloid, tau, therapy, treatment

Disclosure: Martin R Farlow receives grant/research support from AbbVie, Accera, Biogen, Eisai, Eli Lilly, Genentech, Roche, Lundbeck, Boehringer Ingelheim, Novartis and Suven Life Sciences Ltd. He serves as a consultant/on advisory boards for Accera, Allergan, AstraZeneca, Avanir, Axovant, AZTherapies, Eli Lilly & Company, FORUM Pharmaceuticals, INC Research, KCRN Research, Kyowa Kirin Pharma, Longeveron, Medavante, Merck and Co. Inc., Medtronic, Proclara (formerly Neurophage Pharmaceuticals), Neurotrope Biosciences, Novartis, Sanofi-Aventis, Stemedica Cell Technologies, Inc., Takeda, United Neuroscience Inc. and vTV Therapeutics. He is also a patent holder with Elan (transgenic mouse model).

Review Process: This is an expert interview and as such, has not undergone the journal's standard peer review process.

Authorship: The named author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, takes responsibility for the integrity of the work as a whole, and has given final approval for the version to be published.

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Received: October 2, 2017

Published Online: February 16, 2018

Citation: *US Neurology*. 2018;14(1):17–18

Corresponding Author: Martin R Farlow, Department of Neurology, Indiana University School of Medicine, 355 West 16th Street, Suite 4700, Indianapolis, IN 46202, US. E: mfarlow@iupui.edu

Support: No funding was received in the publication of this article.

The annual Alzheimer's Association International Conference (AAIC) took place in London, UK in July 2017. In an expert interview, Martin R Farlow reflects on treatment development, one of the key themes of the meeting.

Q. A number of drugs in development for Alzheimer's disease (AD) have failed phase III clinical trials. Why do you think this is?

There have been a number of high-profile phase III clinical trial failures recently, raising the question why are these efforts not showing more promise? So far, there does not seem to be a single answer to this question. Certainly, a number of these trials used drugs that targeted either decreasing amyloid protein production or targeting fibrillary amyloid plaques with antibodies to assist the immune system in removing constituent proteins. With regard to decreasing amyloid production, both β -secretase and gamma-secretase inhibitors have failed. Potential reasons are: (i) adverse effects of these medications; (ii) targeting the disease in too late of a disease stage where progression is not reversible and several other neurodegenerative processes will continue whether or not amyloid is present; (iii) inhibiting amyloid production may inhibit disease process in dominantly inherited mutation-associated patients where there is excess amyloid production, but the vast majority of Alzheimer's patients have late-onset sporadic or late-onset familial forms of the disease where the mechanisms are more related to amyloid clearance failure; (iv) it may be that the amyloid hypothesis is wrong.

The other major approach is to use monoclonal antibodies targeting oligoclonal amyloid proteins and fibrillary proteins in plaques. A phase Ib aducanumab study has shown promise in patients with mild stage AD.¹ The protocol used pushed antibody to relatively high doses and accepted a relatively high level of amyloid-related imaging abnormalities (ARIA). ARIA has since proven to be less clinically significant and more manageable as an adverse effect than originally thought. It was then determined that most other anti-amyloid antibody studies that had been enrolling patients were greatly under dosing levels of antibodies required to achieve amyloid plaque removal and potential clinical efficacy. Several trials have since been modified or new trials initiated using higher levels of antibody dosing. There also has been a move to target Alzheimer's patients at earlier mild cognitive impairment (MCI), or even earlier, amyloid positive on PET scan, but pre-symptomatic stages.

Q. What are the limitations of targeting amyloid-beta peptide (A β) in AD?

The major limitations of targeting A β are as follows:

- (1) Too high a dose of antibody advanced too rapidly causes microhemorrhage and/or vasogenic edema.
- (2) Mild or moderate stages of disease may be too late with damage already done with other ongoing disease mechanisms continuing.
- (3) Drugs that inhibit amyloid production have had toxicities.
- (4) Expensive to select patients with amyloid present at baseline or measure amyloid removal (assessment requires lumbar puncture or amyloid positron emission tomography [PET]).
- (5) Very small percentage (typically <2%) of antibodies administered gets into the central nervous system limiting potential efficacy.
- (6) There are many other newly recognized targets, dozens of potential mechanisms of action or therapeutic targets for investigational

drugs, as a consequence of various genes recently discovered to cause Alzheimer's disease. The major effort is currently focused on anti-tau antibodies and/or drugs that interfere with tau metabolism and/or processing.

Q. What other therapeutic targets are being investigated in AD?

There is progressively more interest in microglia and various inflammatory-related pathways as major targets for future therapy of this illness.

Q. What agents in clinical development appear to be most promising?

The most promising agent currently publicly disclosed would be aducanumab. Other β -secretase inhibitors and anti-amyloid and/or anti-tau antibodies are still wait and see. □

1. Vigiotta V, O'Gorman J, Williams L, et al. P1-053 Change from baseline in clinical dementia rating scale cognitive and functional domains in PRIME, a randomized phase 1b study of the anti-amyloid beta monoclonal antibody aducanumab (BIB037). *Alzheimers Dement.* 2017;13 Suppl. P256-7.