Presentation Highlights

A Potential New Alzheimer's Treatment That May Function by Modulating the Gut Microbiota

Highlights from a Shanghai Green Valley Pharmaceutical co-sponsored presentation by Professor Jeffrey Cummings presented at the 13th annual Clinical Trials on Alzheimer's Disease conference, 29 November to 2 December, San Francisco, CA, USA

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SUPPLEMENT

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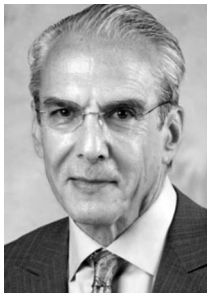
The Potential Role of Inflammation in Alzheimer's Disease

An Expert Interview with Jeffrey Cummings

Department of Brain Health, Chambers-Grundy Center for Transformative Neuroscience, University of Nevada, Las Vegas, NV, USA



Jeffrey Cummings

Jeffrey Cummings is the director of the Chambers-Grundy Center for Transformative Neuroscience, a centre devoted to using the tools of neuroscience and neurologic drug development to transform people's lives. He was a founding director of the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas and served as director of the Mary S. Easton Center for Alzheimer's Disease Research and the Deane F. Johnson Center for Neurotherapeutics, at the University of California, Los Angeles. He is a world-renowned Alzheimer's disease researcher and leader of clinical trials, with expertise in neuropsychiatric assessment, clinical trials, developing new therapies for brain diseases and the interface of neuroscience and society.

Keywords

Alzheimer's disease, brain–gut axis, gut microbiome, inflammation

Disclosures: Jeffrey Cummings has provided consultation to AB Science, Acadia, Alkahest, AlphaCognition, AriBio, Avanir, Axsome, Behren Therapeutics, Biogen, Biohaven, Cassava, Cerecin, Cortexyme, Diadem, EIP Pharma, Eisai, GemVax, Genentech, Green Valley, Grifols, Janssen, LSP, Merck, Novo Nordisk, Oligomerix, Ono, Otsuka, PRODEO, ReMYND, Renew, Resverlogix, Roche, Signant Health, Suven, United Neuroscience and Unlearn AI pharmaceutical, assessment, and investment companies. He owns the copyright of the Neuropsychiatric Inventory. Dr Cummings is supported by Alzheimer's Drug Discovery Foundation (ADDF), NIGMS grant P20GM109025; NINDS grant U01NS093334; NIA grant R01AG053798; NIA grant P20AG068053; and NIA grant R35AG71476.

Acknowledgements: Stuart Wakelin of Touch Medical Communications provided editorial assistance, funded by Shanghai Green Valley Pharmaceutical Co., Ltd.

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

Compliance with ethics: This article is an expert interview and does not report on new clinical data, or any studies with human or animal subjects performed by any of the authors.

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.

Received: 3 March 2022

Published online: 25 March 2022

Citation: *touchREVIEWS in Neurology.* 2022; 18(Suppl. 1):2–3

Corresponding author: Jeffrey Cummings, 1380 Opal Valley Street, Henderson, NV 89052, USA. E: jcummings@cnsinnovations.com

Support: The publication of this article was supported by Shanghai Green Valley Pharmaceutical Co., Ltd., who were allowed to review the essay for scientific accuracy before submission. Any resulting changes were made at the author's discretion.

Alzheimer's disease (AD) is the most common form of dementia, and causes a progressive decline in memory, language, executive and visuospatial function, personality and behaviour.[1] For many years, there have been only four approved medications to improve cognition in patients with AD, but these only address the symptoms, and do not affect the course of the underlying disease.[2–5] In an expert interview, Professor Jeffrey Cummings discusses the role of inflammation in AD and the upcoming GREEN MEMORY study (NCT04520412), a global randomized clinical trial investigating the use of GV-971 (sodium oligomannate) for the treatment of AD.[6,7]

Q. What are the key therapeutic targets in Alzheimer's disease?

The key targets in AD are amyloid, of course, which we've been working with for many years, and tau, which is associated with neurodegeneration and neurofibrillary tangles.

Q. What treatments are currently available for Alzheimer's disease?

Inflammation is increasingly recognized as an important target for AD therapeutics. Beyond that, metabolic factors and genetic factors are also being looked at.

The currently available therapies include the cholinesterase inhibitors and memantine, which we've had for many years. In 2021, aducanumab was approved in the USA. It is an anti-amyloid monoclonal antibody. In 2019, GV-971, or oligomannate, was approved in China and is on the market in China.

We increasingly recognize that inflammation has a critical role in neurodegeneration. The activities in the brain with amyloid and tau generate inflammation, and that exacerbates neuronal death.

Q. How might inflammation and gut homeostasis play a role in combating Alzheimer's disease?

One of the important sources that we now recognize is dysbiosis of the gut. So, by having inflammatory processes in the gut, one can measure inflammatory processes in the blood, and those inflammatory processes, in turn, influence inflammation in the brain.

Q. What is the GREEN MEMORY trial?

GV-971, or oligomannate, was approved in China and is on the market there following a successful phase III trial in China.[8] To determine the efficacy and safety of GV-971 in global populations, the GREEN MEMORY trial has been initiated. It includes sites in North America, in Europe and in China, and will explore the efficacy, the safety and the biomarker effects of GV-971. ❑

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A Potential New Alzheimer's Treatment That May Function by Modulating the Gut Microbiota

Including highlights from a Shanghai Green Valley Pharmaceutical co-sponsored presentation by Professor Jeffrey Cummings presented at the 13th annual Clinical Trials on Alzheimer's Disease conference, 29 November to 2 December, San Francisco, CA, USA

Stuart Wakelin

Touch Medical Communications, Ltd., UK

Alzheimer's disease (AD) is the most common form of dementia, and causes a progressive decline in memory, language, executive and visuospatial function, personality, and behaviour. For many years, there have been only four approved medications to help improve cognition in patients with AD, but these only address the symptoms, and do not affect the course of the underlying disease. Here we discuss information presented at the 13th and 14th Clinical Trials on Alzheimer's Disease conferences about the GREEN MEMORY trial (NCT04520412) of GV-971® (sodium oligomannate). This treatment, as well as the recently approved aducanumab, provides hope that new therapeutics with novel mechanisms of action may provide disease-modifying effects and help slow disease progression in people with AD.

Keywords

Alzheimer's disease, brain–gut axis, gut microbiome

Disclosures: Stuart Wakelin is a Medical Writer for Touch Medical Communications, Ltd.

Acknowledgements: Stuart Wakelin of Touch Medical Communications provided editorial assistance, funded by Shanghai Green Valley Pharmaceutical Co., Ltd.

Review process: Double blind peer review

Compliance with ethics: This article is a conference report and does not report on new clinical data, or any studies with human or animal subjects performed by any of the authors.

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.

Received: 24 September 2021

Accepted: 10 February 2022

Published online: 25 March 2022

Citation: *touchREVIEWS in Neurology.* 2022; 18(Suppl. 1):4–6

Corresponding author: Stuart Wakelin. Touch Medical Communications Ltd, Lancashire Gate, 21 Tiviot Dale, Stockport, Cheshire, SK1 1TD, UK. E: stuart.wakelin@touchmedicalmedia.com

Support: The publication of this article was supported by Shanghai Green Valley Pharmaceutical Co., Ltd., who were allowed to review the essay for scientific accuracy before submission. Any resulting changes were made at the author's discretion.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia.[1] It is characterized by two hallmark pathologies: the deposition of amyloid-β plaques and the neurofibrillary tangles of hyperphosphorylated tau.[1] The clinical presentation of AD includes a progressive decline in two or more cognitive domains, which include memory, language, executive and visuospatial function, personality, and behaviour.[1] These, in turn, can impair the ability to perform instrumental and/or basic activities of daily living.[1]

AD is a growing public health concern, which is predicted to affect 131 million people worldwide by 2050.[2,3] The global cost of AD is also substantial and rising, up to an estimated US$2 trillion by 2030.[2,3] As such, disease-modifying therapies in AD are urgently needed.[2]

Evolution of Alzheimer's disease treatment

Cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists

For many years, there have been only four approved medications to help improve cognition in patients with AD: the cholinesterase inhibitors donepezil, galantamine, and rivastigmine;[4–6] and the NMDA receptor antagonist memantine.[7] Cholinesterase inhibitors exert their therapeutic effect by increasing the concentration of acetylcholine at neurotransmitters through reversible inhibition of its hydrolysis by acetylcholinesterase.[4–6] Memantine exerts its therapeutic effect via uncompetitive binding to the NMDA receptor, thereby attenuating the persistent NMDA receptor activation that is thought to contribute to AD symptomatology.[7] While these treatments are effective in providing symptomatic relief for patients with AD, they are not disease-modifying treatments that can slow the progression of the disease.[4–7]

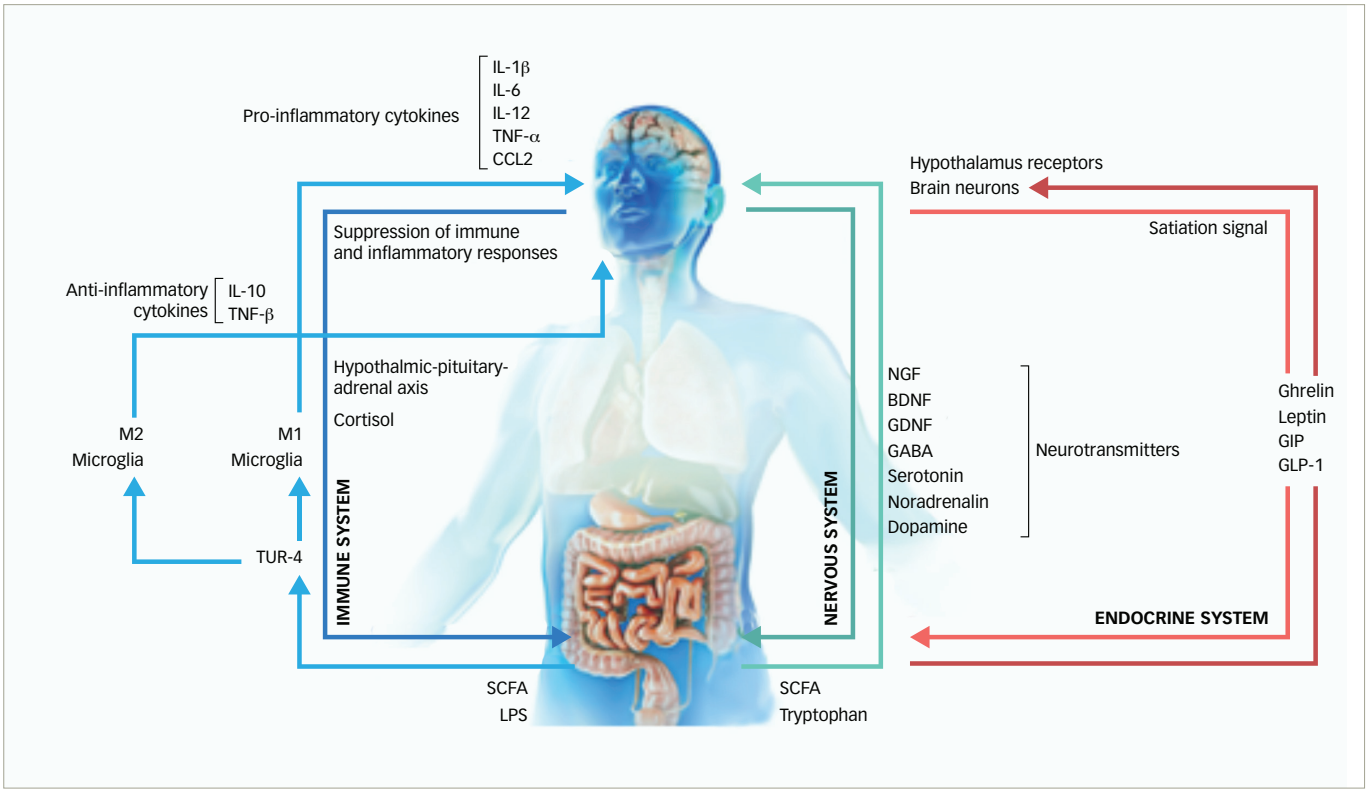
Therapies targeting amyloid-β and neurofibrillary tangles of hyperphosphorylated tau

Targeting the known pathological hallmarks of a disease is an established therapeutic strategy. Unfortunately, although there has been a great deal of research over past decades into AD treatments directed towards amyloid-β and neurofibrillary tangles, no clear advances have yet been made. Perhaps the most promising is the humanized monoclonal antibody aducanumab.[8]

Neuroinflammatory-directed therapies

Increasing evidence suggests that AD pathogenesis involves immunological mechanisms in the brain, with misfolded and aggregated proteins binding microglia and astrocytes.[9] These trigger innate immune responses and the release of inflammatory mediators, thereby contributing to disease progression and severity.[9] It seems increasingly likely that external factors, including systemic inflammation and obesity, can also interfere with the immunological processes of the brain and further promote disease progression.[9] While there has been some evidence of a

Figure 1: Schematic showing potential interactions between gut microbiota and the brain[12]



BDNF = brain-derived neurotrophic factor; GABA = gamma-aminobutyric acid; GDNF = glial-derived neurotrophic factor; GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1; IL = interleukin; LPS = lipopolysaccharide; NGF = nerve growth factor; SCFA = short chain fatty acid; TGF = transforming growth factor; TNF = tumour necrosis factor. Reproduced with permission from Bonfili et al., Microbiota modulation as preventative and therapeutic approach in Alzheimer's disease. FEBS J. 2021;288:2836–55.[12]

positive effect on cognitive decline in patients with AD receiving non-steroidal anti-inflammatory medications, these have not been replicated in later, larger trials.[9] Nevertheless, it is important to diversify how we approach AD and its interventions, and the recognition that the immune system contributes to AD pathogenesis and offers potential routes for disease-modifying therapies.[9]

The role of the gut microbiome

In recent years, the gut microbiome has increasingly become a focus of scientific investigation, and has been shown to play a key role in progressive neurodegenerative disorders, such as Parkinson's disease.[10,11] Central to this role is a dynamic interaction between the gut microbiota and the brain, termed the microbiota–gut–brain axis (*Figure 1*),[11,12] which may contribute to both the ageing process and the trajectory of neurodegenerative disorders.[10] This discovery led to research into the potential role of the microbiota–gut–brain axis in the pathogenesis and progression of AD, as well as the development of new therapeutic agents to target this mechanism and potentially slow the progression of the disease. There is now a growing body of evidence indicating a dysbiosis of gut microflora in patients with AD.[12,13] Not only have studies shown that the gut microbiota is altered in patients with AD, but also that these differences may play a role in AD pathogenesis.[14,15] Differences in gut genera have also been shown to be highly predictive of mild cognitive impairment, suggesting involvement at the very early stages of AD.[16] Of potential therapies, multi-strain and mono-strain probiotic formulae have shown some efficacy in slowing cognitive decline in animal models of AD.[11] Other potential therapeutic approaches aimed at modulating the gut microbiome include faecal microbiota transplantation, prebiotics, calorie restriction, digestion-resistant fibres and dietary supplementation.[12]

Recent developments

At the 13th and 14th Clinical Trials on Alzheimer's Disease (CTAD) conferences in 2020/2021 (as well as the Alzheimer's Association International Conference in 2021), there were many presentations of novel AD treatments related to amyloid-β, neuroinflammation and the gut microbiome. In one particular presentation by Professor Jeffrey Cummings, details of a planned global, phase III, multicentre, randomized, double-blind, placebo-controlled, 52-week trial (GREEN MEMORY [NCT04520412]) of the dietary compound sodium oligomannate (GV-971, Green Valley, Shanghai, China; 900 mg/day; capsule administration) in 2,046 patients with mild-to-moderate AD, were discussed.[17,18] Sodium oligomannate is a marine-derived oligosaccharide that stimulates specific gut microbiota.[19] The aim of the GREEN MEMORY study is to confirm the findings of a pivotal, phase III, double-blind, placebo-controlled, 36-week clinical trial in 818 Chinese patients with mild-to-moderate AD conducted at 34 Chinese sites.[19] In this study, patients with AD receiving oral sodium oligomannate (900 mg/day; capsule administration) showed a significant cognitive improvement compared with placebo after 36 weeks (mean modelled difference: -2.15 points on the 12-item Alzheimer's Disease Assessment Scale (ADAS-cog12); p<0.0001; unadjusted difference: -2.54 points), with a similar incidence of treatment-related adverse events (TRAEs; 73.9% and 75.4%, respectively).[19] Of the most common TRAEs, the incidence of hyperlipidaemia and nasopharyngitis appeared greater in the sodium oligomannate treatment group compared with the placebo group (7.1% versus 3.4% and 7.4% versus 5.6%, respectively); all other

common TRAEs were similar between groups.[19] The GREEN MEMORY study has now begun recruitment, with the first patient receiving their first treatment on February 3 2021. The study is expected to be completed in December 2025.[18]

The assessment of sodium oligomannate is of particular interest given the accelerated US Food and Drug Administration (FDA) approval in June 2021 of aducanumab – the first potentially disease-modifying treatment for AD.[20]

Summary

For many years, only four approved pharmacological treatments have been available for people with AD: donepezil, galantamine, rivastigmine and memantine. However, these only provide symptomatic relief. The accelerated approval of aducanumab, the GREEN MEMORY trial and information from the CTAD 2020 conference provide hope that new therapeutics with novel mechanisms of action may provide disease-modifying effects, and help slow disease progression in people with AD. ❑

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