FROM BENCH TO BEDSIDE
• Building on discoveries of the past
• Advancing research on early diagnosis, preventive methods and treatment
• Working towards finding a cure

FROM MAINSTREAM TO ALTERNATIVE APPROACHES

j-alz.com
Welcome Message

Twenty years of JAD. We have to thank all of the authors, editors, editorial staff and IOS Press, who have made JAD a dominant journal in the neuro field. At this point, we are publishing nearly 800 articles a year. We have the most citations of any journal of Alzheimer's disease in our field, publish more articles and have had more authors supporting us.

This first 20 years of JAD has been remarkable, and the next 20 years promises to be even more so. This year, our 20th year, we celebrated with a special issue – paying tribute to those who have contributed to JAD – as well as looking forward at what lies in store over the next 20 years, with Alzheimer’s Disease: New Beginnings. This new book looks at where we go from here, with new therapeutics and biomarkers, and other approaches to understanding the disease. Most of all, I have to thank all of those who have been so instrumental – Mark Smith† and all the other prime editors; Beth Kumar; and IOS Press – who have been so critical keeping JAD at the forefront of innovation.

Thank you to all.

George Perry, PhD
JAD Editor-in-Chief
Introduction

In 2018, the Journal of Alzheimer’s Disease (JAD) celebrates 20 years of publication.

The very first issue of the journal was published in March 2008 and – jump forward precisely 20 years – the 20th anniversary issue was also published in March, in 2018 (read more about this special issue on page 4).

At its launch, the journal was published annually as a single volume. The very first piece of research to appear focused on “Bursting Dense Microspheres in Alzheimer’s Disease” and this article, in fact all the content from the first issue, is freely available to read online (via j-alz.com).

JAD was launched based on the conviction of its founders that “researchers in the field of Alzheimer disease (AD) lacked an appropriate forum for the most innovative ideas necessary to advance the field.”
In this anniversary year, it is time to take stock of the impact that JAD has had – and continues to have – on research in the field and translating that research into clinical practice. This special 20th anniversary commemorative publication looks back, as well as forward, to the journey that lies ahead for AD research.

At the start of 2001, Editor-in-Chief George Perry was joined by Co-Editor-in-Chief Mark Smith† and by the end of the publication’s third year, the team was pleased to announce that JAD had established itself as a leading journal (which coincided with its acceptance into MEDLINE/PubMed) [J. Alzheimers Dis. 3 (6) (2001) 531].

By that time, the growth and vitality of AD research were readily apparent by the increasing number of articles and citations. While the launch of a new journal can be hampered by delayed acceptance by abstracting services and a slow influx of manuscript submissions, JAD was off to a strong start.

JAD has grown each year in number and quality of articles. In fact, this trend has continued and, over the course of 20 years, JAD has published more papers on AD than any other journal and received more citations than any other AD-focused journal.

† Mark Smith passed away in 2010 (in memoriam: j-alz.com/marksmith)
Looking Back at 20 Years of AD Research

JAD 20th Anniversary Special Issue

JAD’s 20th anniversary celebration officially started with the publication of a special anniversary issue (Volume 62, Issue 3) in March 2018. This landmark issue comprises fully open access content, which means it is freely available to read, download and share for all. To preview this issue, you’ll find a selection of abstracts on pages 5–7 of the top review articles, as selected by Editor-in-Chief George Perry.

This celebratory issue takes a look back at the AD research topics that have been instrumental in shaping the progress of AD research over the course of the journal’s lifetime. It features 35 review articles covering 20 years of AD research, plus personal perspectives from key researchers in the field.

In the Foreword for this issue, JAD’s Editor-in-Chief George Perry, PhD, recalls the early days of the journal: “The plan was to design a journal that reflected the field through creating community. Editorial structure, openness to novel topics, reviewer selection, scientometric analysis, awards programs, and historical compendiums were all focused on building a JAD community.”

In the special issue, it is the JAD community of authors that celebrates the past 20 years by writing of the journal’s role in developing the field. All content in this issue of JAD – co-edited by George Perry, PhD, Jesús Avila, MD, Massimo Tabaton, MD, and Xiongwei Zhu, PhD – has been specially commissioned. There are two personal perspectives: the first by Isidro Ferrer, MD, PhD, is a broad-ranging, historical perspective comparing the pursuit of AD research to art and in it we are reminded that “the feeling of beauty may also occur in science;” and the second by Thomas B. Shea, PhD, is a career-spanning perspective that includes “some of the more humorous and poignant twists along the way that some older players may find familiar and I hope might inspire some younger players to hang in there.” The remainder of the issue is made up of 35 review articles covering central aspects of AD research.

• Read more about the anniversary issue at: tiny.cc/JAD20celebration
• The open access issue can be accessed online at: tiny.cc/JAD-anniv

20th Anniversary Special Issue
Volume 62, Issue 3, 2018

Editors:
George Perry, PhD
Jesús Avila, MD
Massimo Tabaton, MD
Xiongwei Zhu, PhD
Both the incidence and the prevalence of dementia increase exponentially with increasing age. This raises the question of whether dementia is an inevitable consequence of aging or whether aging without dementia is achievable. In this review article, we sought to summarize the current evidence from epidemiological and neuropathological studies that investigated this topic. Epidemiological studies have shown that dementia could be avoided even at extreme old ages (e.g., centenarians or supercentenarians). Furthermore, clino-neuropathological studies found that nearly half of centenarians with dementia did not have sufficient brain pathology to explain their cognitive symptoms, while intermediate-to-high Alzheimer pathology was present in around one-third of very old people without dementia or cognitive impairment. This suggests that certain compensatory mechanisms (e.g., cognitive reserve or resilience) may play a role in helping people in extreme old ages escape dementia syndrome. Finally, evidence has been accumulating in recent years indicating that the incidence of dementia has declined in Europe and North America, which supports the view that the risk of dementia in late life is modifiable. Evidence has emerged that intervention strategies that promote general health, maintain vascular health, and increase cognitive reserve are likely to help preserve cognitive function till late life, thus achieving the goal of aging without dementia.

This paper in the 20th anniversary issue of the Journal of Alzheimer's Disease is a review on the development of cerebrospinal fluid (CSF) biomarkers, from early assay development to the current status with fully automated assays and the highest level of standardization, with focus on the most important, but also most troublesome, Alzheimer's disease (AD) biomarker; Aβ42. We also review the path from early clinical biomarker studies to the very extensive and consistent clinical validation of the diagnostic performance of the core AD CSF biomarkers we have today. Last, we give an update on recent developments, including biomarkers for synaptic proteins in CSF and the promise of blood biomarkers with potential application as screening tools.
Following our discovery of a fragment from the repeat domain of tau protein as a structural constituent of the PHF-core in Alzheimer’s disease (AD), we developed an assay that captured several key features of the aggregation process. Tau-tau binding through the core tau fragment could be blocked by the same diaminophenothiazines found to dissolve proteolytically stable PHFs isolated from AD brain. We found that the PHF-core tau fragment is inherently capable of autocatalytic self-propagation in vitro, or “prion-like processing”, that has now been demonstrated for several neurodegenerative disorders. Here we review the findings that led to the first clinical trials to test tau aggregation inhibitor therapy in AD as a way to block this cascade. Although further trials are still needed, the results to date suggest that a treatment targeting the prion-like processing of tau protein may have a role in both prevention and treatment of AD.
A Decade of Blood Biomarkers for Alzheimer’s Disease Research: An Evolving Field, Improving Study Designs, and the Challenge of Replication

L Shi, AL Baird, S Westwood, A Hye, R Dobson, M Thambisetty, S Lovestone

Blood-based biomarkers represent a less invasive and potentially cheaper approach for aiding Alzheimer’s disease (AD) detection compared with cerebrospinal fluid and some neuroimaging biomarkers. Acknowledging that many in the field have made great progress, here we review some of the work that our group has pursued to identify and validate blood-based proteomic biomarkers through both case control and AD pathology endophenotype-based approaches. Our focus is primarily to identify a minimally invasive and hopefully cost-effective blood-based biomarker to reduce screen failure in clinical trials where participants have prodromal or even pre-clinical disease. We summarize some of the key findings and approaches taken in these biomarker studies, while addressing the main challenges, including that of limited replication in the field, and discuss opportunities for biomarker development.

The Unexpected Role of $A_{\beta1-42}$ Monomers in the Pathogenesis of Alzheimer’s Disease

E Tamagno, M Guglielmotto, D Monteleone, G Manassero, V Vasciaveo, M Tabaton

Amyloid-$\beta$ ($A\beta$) has been proposed as a biomarker and a drug target for the therapy of Alzheimer’s disease (AD). The neurotoxic entity and relevance of each conformational form of $A\beta$ to AD pathology is still under debate; $A\beta$ oligomers are considered the major killer form of the peptide whereas monomers have been proposed to be involved in physiological process. Here we reviewed some different effects mediated by monomers and oligomers on mechanisms involved in AD pathogenesis such as autophagy and tau aggregation. Data reported in this review demonstrate that $A\beta$ monomers could have a major role in sustaining the pathogenesis of AD and that AD therapy should be focused not only in the removal of oligomers but also of monomers.

The Emergence of a New Conceptual Framework for Alzheimer’s Disease

B Dubois

The new criteria for the diagnosis of Alzheimer’s disease (AD), published by a group of experts in 2007, have resulted in a revolution in the comprehension of the disease. Before 2007, the diagnosis of AD dementia was done through a process of exclusion: it was considered in the case of patients with a dementia syndrome without identified etiologies. This traditional algorithm had three major limitations that penalize the disease. Since 2007, the disease has gained a clear definition based on positive evidence: a specific clinical phenotype (the amnestic syndrome of the hippocampal type) and the presence of biomarkers, considered as a biological signature of the disease. Thanks to these positive arguments, AD is a clinically and biologically well-delineated disease, no longer defined as “probable”. It is now possible to certify that a given patient has or does not have the disease. Like diabetes, cancer, hyperthyroidism or any other disorder, AD has now a clear definition with well-defined borders.
**Journal of Alzheimer's Disease (JAD)**

**Launch**
- **Mar 1998**: Launch of JAD, with George Perry as Editor-in-Chief - first issue is openly available
- **Jul 1999**: JAD becomes largest AD-specialized journal
- **Jul 2000**: First Alzheimer Award, presented to Suzanne De La Monte
- **Dec 1999**: JAD introduces rotating editorial board

**Firsts**
- **Mar 1998**: Launch of JAD, with George Perry as Editor-in-Chief - first issue is openly available
- **Jul 1999**: First perspective: “Dietary Links to Alzheimer’s Disease” by William B. Grant
- **Jan 2001**: Mark A. Smith becomes Co-Editor-in-Chief
- **2004**: JAD becomes largest AD-specialized journal

**Yearly Events**
- **2006**: JAD publishes over 100 articles annually
- **2008**: JAD publishes over 500 articles annually
- **2010**: JAD publishes over 500 articles annually
- **2013**: JAD publishes over 500 articles annually

**Highly-Cited Papers**
- **Dec 2005**: No.3 highly-cited paper (336 cites): “Insulin and Insulin-Like Growth” by Rivera et al.
- **Jan 2014**: No.5 highly-cited paper (146 cites): “Association of Mediterranean Diet with Mild Cognitive Impairment” by Singh et al.
- **Jan 2017**: Launch of the fully open access sister publication: Journal of Alzheimer’s Disease Reports

**Technical Milestones**
- **Feb 2011**: Launch of first sister publication: Journal of Parkinson’s Disease
- **Jun 2011**: No.4 highly-cited paper (274 cites): “Early Clinical PET Imaging with the Novel PHF-Tau Radioligand” by Chien et al.
- **Dec 2012**: No.5 highly-cited paper (149 cites): “Abnormal Hyperphosphorylation of Tau” by Wang et al.

**Book Series**
- **Feb 2013**: Landmark Book: Alzheimer’s Disease: Advances for a New Century (AIAD, Vol.3)
- **Mar 2016**: JAD celebrates 20th Anniversary with publication of open access special issue
- **Feb 2016**: Launch of the Alzheimer Funding Analyzer on j-alz.com
- **Jun 2016**: Launch of the JAD blog section on j-alz.com
- **Feb 2018**: Landmark Book: Alzheimer’s Disease: New Beginnings (AIAD, Vol.6)

**Editor Changes**
- **Jan 2001**: Mark A. Smith becomes Co-Editor-in-Chief
- **Dec 2010**: Mark A. Smith passes away

**Impact Factors**
- **Jun 2008**: JAD’s highest impact factor to date (5.101)
- **Jul 2015**: JAD receives its first impact factor (3.058)

**Supplements**
- **Jun 2006**: JAD receives its first impact factor (3.058)
- **Jun 2006**: JAD receives its first impact factor (3.058)
- **Jun 2013**: No.4 highly-cited paper (274 cites): “Early Clinical PET Imaging with the Novel PHF-Tau Radioligand” by Chien et al.

**Awards and Special Issues**
- **Feb 2015**: Launch of first sister publication: Journal of Alzheimer’s Disease Reports
- **Feb 2016**: Publication of JAD’s most-viewed “Microbes” Editorial
- **Feb 2016**: JAD's highest impact factor to date (5.101)

**Technical Awards**
- **Feb 2011**: Launch of first sister publication: Journal of Parkinson’s Disease
- **Jun 2011**: No.4 highly-cited paper (274 cites): “Early Clinical PET Imaging with the Novel PHF-Tau Radioligand” by Chien et al.

**Books**
- **Jan 2001**: Centennial Book: Alzheimer’s Disease: A Century of Scientific and Clinical Research – presented by George Perry to the Queen of Spain at the 2006 ICAD meeting (delegate copies sponsored by GlaxoSmithKline)
- **Jul 2006**: No.2 highly-cited paper (455 cites): “Identification of miRNA Changes” by Cogswell et al.
- **May 2009**: Paper: “Top 100 Investigators in AD” by JAD Scientometrics Editor, Aaron A. Sorensen
- **Jan 2017**: Launch of the fully open access sister publication: Journal of Alzheimer’s Disease Reports

**Technical Milestones**
- **Feb 2005**: First perspective: “Dietary Links to Alzheimer’s Disease” by William B. Grant
- **May 2009**: JAD publishes over 500 articles annually
- **Jun 2010**: Popular JAD supplement issue on “Therapeutic Opportunities for Caffeine” – open access
- **Jun 2010**: Accredited JAD supplement issue on “Mitochondria and Neurodegenerative Diseases” – open access
- **Dec 2012**: No.5 highly-cited paper (149 cites): “Abnormal Hyperphosphorylation of Tau” by Wang et al.

**Impact Factors**
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- **Dec 2005**: No.3 highly-cited paper (336 cites): “Insulin and Insulin-Like Growth” by Rivera et al.
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<th>Date</th>
<th>Landmark Publications</th>
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<tr>
<td>1998 Mar</td>
<td>Launch Issue, Editor: G Perry, Volume 1, Issue 1, Pages 1–70 – Openly Available</td>
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<tr>
<td>1999 Jul</td>
<td>First JAD perspective: Dietary Links to Alzheimer’s Disease: 1999 Update, Author: WB Grant, Volume 1, Issue 4/5, Pages 197–201</td>
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<td>2000 Jul</td>
<td>First Alzheimer Medal awarded to Suzanne De La Monte for the paper: Cerebrovascular pathology contributes to the heterogeneity of Alzheimer's disease, Authors: SM de la Monte, et al., Volume 1, Issue 2, Year 1998, Pages 119–134</td>
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<tr>
<td>2005 Feb</td>
<td>Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease – is this type 3 diabetes?, Authors: E Steen, et al., Volume 7, Issue 1, Pages 63–80 (no.1 highly-cited paper) (763 cites)</td>
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<tr>
<td>2005 Dec</td>
<td>Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: Link to brain reductions in acetylcholine, Authors: EJ Rivera, et al., Volume 8, Issue 3, Pages 247–268 (no.3 highly-cited paper) (336 cites)</td>
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<td>2008 May</td>
<td>Identification of miRNA changes in Alzheimer's disease brain and CSF yields putative biomarkers and insights into disease pathways, Authors: JP Cogswell, et al., Volume 14, Issue 1, Pages 27–41 (no.2 overall highly-cited paper) (455 cites)</td>
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<td>2012 Dec</td>
<td>Abnormal Hyperphosphorylation of Tau: Sites, Regulation, and Molecular Mechanism of Neurofibrillary Degeneration, Authors: JZ Wang, et al., Volume 33, Supplement 1, Pages S123–S139 (no.5 highly-cited paper) (149 cites)</td>
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<td>2013 Jun</td>
<td>Early Clinical PET Imaging Results with the Novel PHF-Tau Radioligand [F-18]-T807, Authors: DT Chien, et al., Volume 34, Issue 2, Pages 457–468 (no.4 highly-cited paper) (294 cites)</td>
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SCIENTOMETRICS

Insights from Aaron A. Sorensen, MA
JAD Scientometrics Editor

JAD has had a significant impact on the advancement of AD research over the last 20 years, and the translation of that research into clinical practice. Since its launch in 1998, it has published more papers on AD than any other peer-reviewed journal and received more citations than any other AD-focused journal. It has embraced publication of emerging and sometimes controversial lines of research, many of which later gained wide acceptance.

In 2009, Aaron A. Sorensen, MA, was appointed as JAD Scientometrics Editor. He works as Bibliometrics Engagement Leader at Digital Science and, for JAD, he has provided insights and expertise, contributing to several important AD analytics initiatives and papers. He provides some background: “As part of my job, I work with organizations that have the common interest of using advanced scientometrics to make strategic decisions regarding biomedical research. As a result of these interactions, I have developed, over time, a mental model of how one might conduct a comprehensive and innovative analysis within an entire investigative branch.”

Sorensen’s first investigation in relation to JAD was for the “Top 100 Investigators in AD” article, published in May 2009. The publication of this landmark study utilized both traditional and highly-innovative scientometric approaches to measure scientific productivity and impact. He comments: “As I began to consider which field I might choose as the first on which conduct an analysis, a conscious effort was made to include real examples of how the more innovative metrics might be employed and interpreted in order to stimulate hypothesis generation among the readership.”

During this, the 20th anniversary year of the journal, Sorensen has worked with other JAD editors on, not one, but two significant bodies of work. In the selection of the content to be covered in the anniversary issue looking back at the AD research over the last 20 years, and on the new book that looks to what might be the focus for the next 20 years, a combination of scientometric evaluations have contributed to the determination of the most significant areas and promising new approaches, respectively, in the major areas of AD research.

“A conscious effort was made to include examples of how the more innovative metrics might be employed and interpreted.”

Top Viewed JAD Articles*

1. Microbes and Alzheimer’s Disease, Authors: RF Itzhaki, et al., Vol.51, Iss.4, Pages 979–984 (2016) – Openly Available


*On the IOS Press Content website (in the last 3 years): content.iospress.com/journal-of-alzheimers-disease
Looking Forward to the Next 20 Years of AD Research

Alzheimer's Disease: New Beginnings

In JAD’s 20th anniversary year, a new book has been published that highlights the latest insights in Alzheimer’s disease (AD) research and, specifically, in areas in which major advances have been made and that are expected to impact future research approaches. This landmark publication includes 34 reviews and 10 original research articles. You’ll get a taste of what this volume has to offer in the featured content on pages 13–15.

This new volume Alzheimer’s Disease: New Beginnings is a companion to the book published on the centennial of Alois Alzheimer’s discovery – Alzheimer’s Disease: A Century of Scientific and Clinical Research – and of the publication Alzheimer’s Disease: Advances for a New Century, which focused on the developments in the 5 years since the centennial. The newest book looks to the future, with an emphasis on the development of novel approaches to understanding and treating Alzheimer’s and related diseases.

The editors George Perry, Jesús Avila, Paula I. Moreira, Aaron A. Sorensen, and Massimo Tabaton comment: “Now is the most exciting period of a generation in our field as old dogma makes way for new insight, whether it be: new approaches to clinical trials; improved biomarker-based diagnostics; population-based studies; prevention, metabolism; or further refinement of the role of inflammation, genetics, tau, and amyloid-β.” The topics selected for this volume were determined using sophisticated scientometric evaluations by the editors (read more about this on page 11).

The book is Volume 6 in the Advances in Alzheimer’s Disease (AIAD) book series, and the content is also published as JAD Volume 64, Supplement 1, Pages S1–S156, which can be accessed online at: tiny.cc/JAD64-s1.

The new book focuses on the future promise for therapeutic breakthroughs with the hindsight of failed clinical trials. The volume editors used a combination of scientometric evaluations to determine the most promising new approaches, as well as soliciting insights from leaders in each of the major areas of Alzheimer’s disease research. By combining these two approaches, they recruited authors from the entire outlook spectrum, from those who feel an elusive breakthrough might still be a few, well-placed tweaks away to those who feel that they are launching entirely new investigative paradigms. These scholars present an open-eyed path forward.

ORDER WITH DISCOUNT CODE: 20%AIAD2018
Use the code* to get a discount when ordering print copies of the book!
(*Valid until: December 31, 2018)
Clinical Trials for Disease-Modifying Therapies in Alzheimer’s Disease: A Primer, Lessons Learned, and a Blueprint for the Future

J Cummings, A Ritter, K Zhong

Review Article
Pages 1–20
Open Access

Alzheimer’s disease (AD) has no currently approved disease-modifying therapies (DMTs), and treatments to prevent, delay the onset, or slow the progression are urgently needed. A delay of 5 years if available by 2025 would decrease the total number of patients with AD by 50% in 2050. To meet the definition of DMT, an agent must produce an enduring change in the course of AD; clinical trials of DMTs have the goal of demonstrating this effect. AD drug discovery entails target identification followed by high throughput screening and lead optimization of drug-like compounds. Once an optimized agent is available and has been assessed for efficacy and toxicity in animals, it progresses through Phase I testing with healthy volunteers, Phase II learning trials to establish proof-of-mechanism and dose, and Phase III confirmatory trials to demonstrate efficacy and safety in larger populations. Phase III is followed by Food and Drug Administration review and, if appropriate, market access. Trial populations include cognitively normal at-risk participants in prevention trials, mildly impaired participants with biomarker evidence of AD in prodromal AD trials, and subjects with cognitive and functional impairment in AD dementia trials. Biomarkers are critical in trials of DMTs, assisting in participant characterization and diagnosis, target engagement and proof-of-pharmacology, demonstration of disease-modification, and monitoring side effects. Clinical trial designs include randomized, parallel group; delayed start; staggered withdrawal; and adaptive. Lessons learned from completed trials inform future trials and increase the likelihood of success.

Targeting Alzheimer’s Disease at the Right Time and the Right Place: Validation of a Personalized Approach to Diagnosis and Treatment

S Gauthier, KP Ng, TA Pascoal, H Zhang, P Rosa-Neto

Review Article
Pages 21–30
Open Access

Cautious optimism is appropriate for a near future (five years) time frame for a number of drugs acting on the different pathophysiological components of Alzheimer’s disease (amyloid deposition, tau hyperphosphorylation, neuro-inflammation, vascular changes, to name the most important known so far). Since the relative weight of these components will be different between individuals and will even change over time for each individual, a ‘one drug fit for all’ approach is no longer defensible. Precision medicine using biomarkers in the diagnosis and treatment of Alzheimer’s disease is the new strategy.
The amyloid-β oligomer (AβO) hypothesis was introduced in 1998. It proposed that the brain damage leading to Alzheimer's disease (AD) was instigated by soluble, ligand-like AβOs. This hypothesis was based on the discovery that fibril-free synthetic preparations of AβOs were potent CNS neurotoxins that rapidly inhibited long-term potentiation and, with time, caused selective nerve cell death (Lambert et al., 1998). The mechanism was attributed to disrupted signaling involving the tyrosine-protein kinase Fyn, mediated by an unknown toxin receptor. Over 4,000 articles concerning AβOs have been published since then, including more than 400 reviews. AβOs have been shown to accumulate in an AD-dependent manner in human and animal model brain tissue and, experimentally, to impair learning and memory and instigate major facets of AD neuropathology, including tau pathology, synapse deterioration and loss, inflammation, and oxidative damage. As reviewed by Hayden and Teplow in 2013, the AβO hypothesis "has all but supplanted the amyloid cascade." Despite the emerging understanding of the role played by AβOs in AD pathogenesis, AβOs have not yet received the clinical attention given to amyloid plaques, which have been at the core of major attempts at therapeutics and diagnostics but are no longer regarded as the most pathogenic form of Aβ. However, if the momentum of AβO research continues, particularly efforts to elucidate key aspects of structure, a clear path to a successful disease modifying therapy can be envisioned. Ensuring that lessons learned from recent, late-stage clinical failures are applied appropriately throughout therapeutic development will further enable the likelihood of a successful therapy in the near-term.
Over the last ten years, we have conducted research in Alzheimer’s disease (AD) using multimodal neuroimaging techniques to improve diagnosis, further our understanding of the pathological mechanisms underlying the disease, and support the development of innovative non-pharmacological preventive strategies. Our works emphasized the interest of hippocampal subfield volumetry in early diagnosis and the need for further development in this field including optimization, standardization, and automatization of the techniques. Also, we conducted several studies in cognitively intact at-risk elderly (e.g., subjective cognitive decline patients and APOE4 carriers) to better identify biomarkers associated with increased risk of developing AD. Regarding the physiopathological mechanisms, specific multimodal neuroimaging techniques allowed us to highlight the relevance of diaschisis, the mismatch between neurodegeneration and local Aβ deposition and the regional variation in the mechanisms underlying structural or functional alterations. Further works integrating other biomarkers known to play a role in the physiopathology of AD (tau, TDP-43, inflammation, etc.) in a longitudinal design would be useful to get a comprehensive understanding of their relative role, sequence, and causal relationships. Our works also highlighted the relevance of functional connectivity in further understanding the specificity of cognitive deficits in AD and how connectivity differentially influences the propagation of the different AD biomarkers. Finally, we conducted several studies on the links between lifestyle factors and neuroimaging biomarkers to unravel mechanisms of reserve. Further efforts are needed to better understand which lifestyle factor, or combination of factors, impact on AD pathology, and when, to help translating our knowledge to training programs that might prevent or delay brain and cognitive changes leading to AD dementia.

The past five years have seen an enormous development in the field of fluid biomarkers for Alzheimer’s disease (AD) and related disorders. The proteins that constitute the foundation for the cerebrospinal fluid (CSF) tests for the classical AD pathologies are now being explored as potential blood-based biomarkers, thanks to the recent implementation of ultrasensitive measurement technologies in academic and clinical laboratories worldwide. The current blood-derived data are still less clear than those obtained using CSF as the sample type, but independent research suggests that there are biomarker signals in blood that relate to plaque and tangle pathologies in AD, which are relevant to explore further. Additionally, neurofilament light has emerged as the first robust blood-based biomarker for neurodegeneration in a broad range of central nervous system disorders, as well as for acute brain injuries. Here, we briefly recapitulate the first and second waves of fluid biomarker analysis in AD, i.e., the development and validation of established and novel CSF biomarkers for the disorder, followed by a focused discussion on blood-based biomarkers for AD, which we describe as the third wave of fluid biomarker analysis that hopefully will gain further momentum during the coming five years.
2018 Alzheimer Award

Each year since 2000, the *Journal of Alzheimer’s Disease* has conferred the Alzheimer Award to the lead author of the best article published in the previous year.

Selected by the journal’s Associate Editors and members of the Editorial Board, this paper represents the highest level of scholarship and has the potential to positively impact diagnosis, prevention and treatment. The awardee is presented the Alzheimer Medal, a 3” bronze medal with the likeness of Alois Alzheimer and a cash award.

2018 Winner
The recipient of 2018 Alzheimer Award is Greg Kennedy, BSc, Swinburne University of Technology, Australia, in recognition of his research into how exercise might reduce the rate of age-related dementia.

The winning research paper offers a greater understanding of the mechanisms and their potential relationships with exercise and cognition, which will be invaluable in providing biomarkers for investigating the efficacy of differing exercise regimes on the outcome of cognitive functions.

Citation:

*How Does Exercise Reduce the Rate of Age-Associated Cognitive Decline? A Review of Potential Mechanisms*

G Kennedy, RJ Hardman, H Macpherson, AB Scholey, A Pipingas

DOI: 10.3233/JAD-160665


The article is openly available online: tiny.cc/2018award
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Aims & Scope

The Journal of Alzheimer’s Disease is an international multidisciplinary journal to facilitate progress in understanding the etiology, pathogenesis, epidemiology, genetics, behavior, treatment and psychology of Alzheimer’s disease (AD). This rigorously peer-reviewed journal publishes research reports, reviews, short communications, hypotheses, ethics reviews, book reviews and letters-to-the-editor. The journal is dedicated to providing an open forum for original research that will expedite our fundamental understanding of AD. Groundbreaking research that has appeared in the journal includes novel therapeutic targets, mechanisms of disease and clinical trial outcomes.

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