

**ORIGINAL ARTICLE**



## Bibliometric Analysis of Immunotherapy Interventions in Alzheimer's Disease: Insights and Trends

Tiantian Peng<sup>1#</sup>, Kexin Chang<sup>1#</sup>, Chengbang Liang<sup>1</sup>, Yu Shi<sup>1</sup>, Feng Yun<sup>2</sup>, Qian Hua<sup>1</sup>, Yan Tan<sup>1\*</sup>

<sup>1</sup>School of Life Sciences; School of Acupuncture and Moxibustion, Beijing University of Traditional Chinese Medicine, Beijing, 100029

<sup>2</sup>Peking University Third Hospital, 49 North Garden Rd., Haidian District Beijing 100191, P.R. China

<sup>#</sup>Tiantian Peng and Kexin Chang Contributed Equally to This Work.

Corresponding Author: Yan Tan

### Abstract:

The brain has traditionally been deemed to possess an 'immune privilege' on account of the presence of the blood-brain barrier. The understanding of the interaction between the brain and the immune system has, however, undergone a fundamental change with the discovery of the brain lymphatic network. Alzheimer's disease (AD) is a neurodegenerative disorder whose pathogenesis and pathogenic mechanisms are yet to be fully unraveled. Emerging research indicates that the immune system potentially plays a crucial role in the development and progression of Alzheimer's disease, influencing diverse aspects, for instance, cytokines, inflammatory reactions, and immune cells. The present study, therefore, aims to investigate the relationship linking Alzheimer's disease and the immune system and further scrutinizes the contributions made by various countries, institutions, journals, and authors in this domain, delving further into the research hotspots and trends.

We analyzed 1152 articles from the Web of Science database, revealing a slow growth trend in annual publications. The United States leads in publication volume and international collaborations, with Harvard University having significant influence. Key keywords include Alzheimer's disease, GFAP, A $\beta$ , and lymphocyte.

Our study underscores the potential importance of immune cells like microglia, astrocytes, and lymphocytes in AD pathology, highlighting them as targets for future research. General practices, immunotherapy, and plant therapies emerge as promising interventions. This bibliometric and visual analysis offers insights into the evolving landscape of AD research and the immune system's role, guiding future investigations and therapeutic strategies.

**Keywords:** Bibliometric analysis, AD, Immune system, Inflammatory, Lymphatic network.

### Introduction

AD is a progressive neurodegenerative disorder and the most common cause of dementia among elderly individuals. Its typical symptoms include decline in memory, cognitive impairment, behavioral and emotional changes, and ultimately leading to mortality. Early symptoms include difficulty in remembering recent conversations, names or events, apathy and depression, while late symptoms include communication barriers,

confusion, decline in judgment and behavior abnormalities<sup>1</sup>. It not only affects the patient, but also imposes physical, emotional and economic burden on their families and caregivers. The latest research data shows that globally, the prevalence of dementia is expected to triple by 2050, and this estimate increases to three times when considering a biological definition of AD. AD is the primary cause of dementia and is becoming a costly,

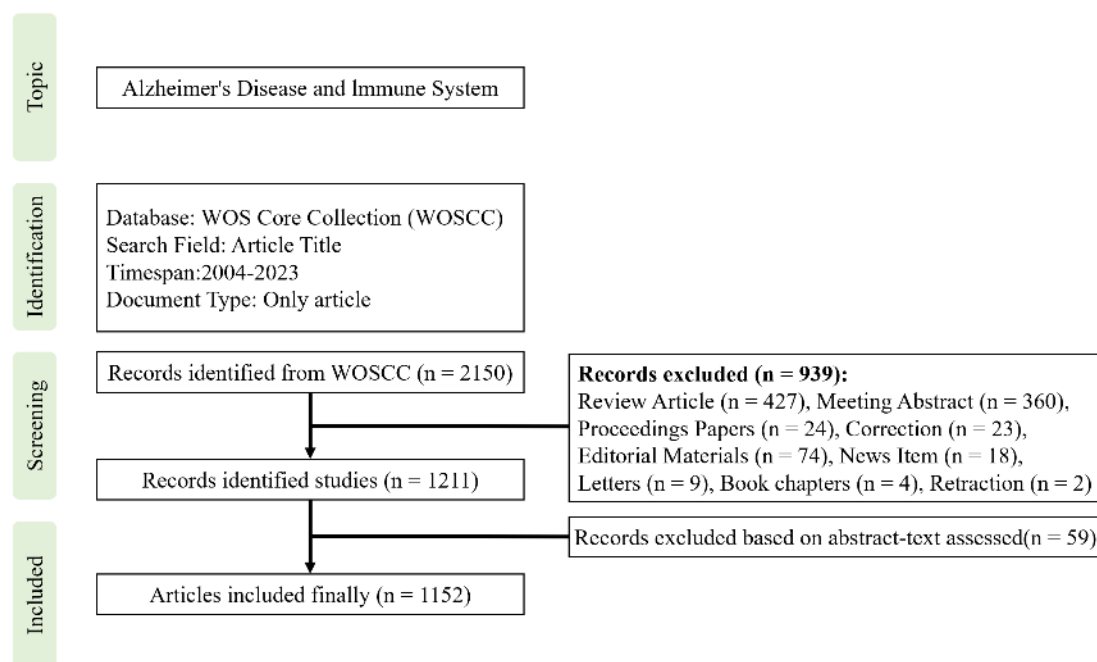
lethal, and burdening disease of this century<sup>2</sup>.

Various hypotheses have been proposed to explain the underlying mechanisms of the disease, which include the amyloid hypothesis<sup>3,4</sup>, tau hypothesis<sup>5</sup>, neuroinflammation hypothesis<sup>6-8</sup>, and oxidative stress hypothesis<sup>9</sup>, to name a few. Despite extensive research, there is currently no cure for AD<sup>10-12</sup>.

Recent discoveries and research have challenged the long-held belief that the brain is immune privileged, which is now recognized that a complex immune network exists within the brain that involves multiple peripheral immune players in addition to resident microglia cells, as well as this interaction allows the brain to modulate its immune activity in response to changes in the body's immune activity<sup>13,14</sup>. The impact of the immune system on the brain is being reconsidered in the context of brain development and aging, as

well as neurodegenerative diseases. This better understanding of the brain's immune system interactions may lead to the development of new treatments for diseases that affect the brain<sup>15</sup>.

Bibliometrics is a research discipline that analyses scientific publications to identify patterns and understand their impact on scholarly research. It involves different metrics, such as citation counts, author productivity, and journal ranking, to evaluate scholarly activity and develop funding and promotion strategies<sup>16</sup>. Recently, bibliometric studies have been adapted to include newer metrics, such as social media engagement and alternative metrics to measure scholars' impact beyond traditional metrics<sup>17</sup>. It is important that bibliometric methods remain transparent, reliable, and inclusive of emerging research trends and fields to ensure their continued relevance and accuracy in the evolving scholarly landscape<sup>18,19</sup>.



**Figure 1** Flow diagram of the inclusion process. The detailed process of screening and enrollment.

## Materials and Methods

### Data sources and search strategies

The Web of Science (WOS) database is considered one of the most authoritative academic literature search databases worldwide. Its extensive literature collection covers a wide range of academic disciplines, with content sourced from publishers, databases, and other sources from around the world which have undergone review and selection to ensure quality and

accuracy<sup>20-22</sup>. Therefore, we use the Web of Science database as a retrieval source for conducting bibliometric analysis on AD and neuroimmunology-related literature to gain an in-depth understanding of the latest developments in this scientific research field and literature.

All searches were conducted in a single day June 20, 2023 in order to avoid bias introduced by rapidly database renewal. The search strategies were presented as follows: #1 AND #2, Publication Date: 2004-01-01 to 2023-06-20

#1 ((((((((((((((((((((((TS=(immunity) OR TS=(immune)) OR TS=(immunology)) OR TS=(inflammation)) OR TS=(microglia)) OR TS=(astrocyte)) OR TS=(macrophage)) OR TS=(neutrophil)) OR TS=(NK cell)) OR TS=(natural killer cell)) OR TS=(dendritic cell)) OR TS=(lymphoid)) OR TS=(lymphocyte)) OR TS=(T cell)) OR TS=(T-cell)) OR TS=(B cell)) OR TS=(B-cell)) OR TS=(CD4)) OR TS=(CD8)) OR TS=(DC cell)) OR TS=(Myeloid-derived suppressor cell)) OR TS=(MDSC)

#2 ((TS=(Alzheimer's)) OR TS=(Alzheimer)) OR TS=(Alzheimers)

### Data Collection

The data was retrieved through “TS” algorithm (title) in WOS. To guarantee the retrieval ratio, we adopted the “remove duplicate (WOS)” function in CiteSpace to avoid double counting. Finally, 1152 documents were identified for further analysis and the data inclusion.

### Bibliometric analysis

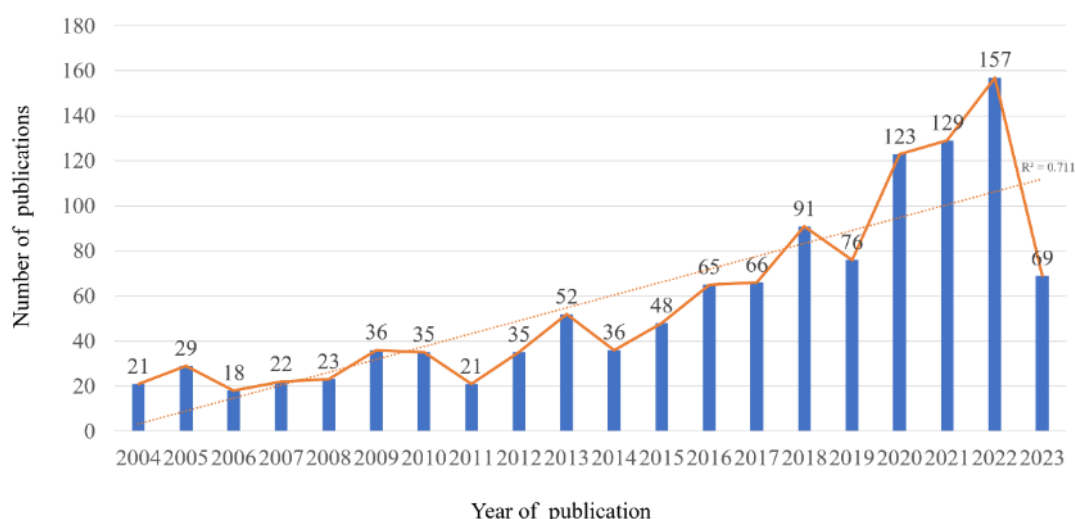
By using the basic features of WoSCC database, the number of papers, publication year and publication country are extracted and summarized, and the line chart, national document volume chart and international cooperation chart are drawn. We then import the data into CiteSpace

5.8. In the reworks format in R1, the time parameters are set to January 1, 2004 and August 31, 2023, the year per slice = 1, and other parameters are set to the default values, and the network hotspot map is drawn based on the actual situation.

## Results

### Growth trends of publications

As an important indicator, the change in the number of articles can directly reflect the research trend of AD and the immune system. After screening, a total of 1152 eligible articles were included (Figure 1). As can be seen from Figure 2, the number of articles in this research field was relatively few from 2004 to 2011 and continued to increase from 2015. From 2020 to 2022, the number of articles has increased rapidly, with an average annual number of more than 100. Among them, the highest number of articles was published in 2022, reaching 157. Since the literature retrieval time is limited to June 2023, the number of published papers in 2023 shows a decreasing trend. It shows that researchers pay more and more attention to AD and the immune system, and it will become one of the hot spots to conduct research on AD from the immune system in the future.



**Figure 2 Annual publication counts from 2004 to 2023 in the web of science core collection based on the search topic.**

### Analysis of keywords in publications on Alzheimer's and Immune System

The network visualization of the co-cited

keywords includes 1,152 items, divided into 6 major clusters and 17 minor clusters. The clustering module value  $Q=0.7299$  ( $Q>0.3$ ) and the average clustering contour value

S=0.8912(S>0.7) indicate that the clustering results are convincing(Figure 3). According to the keyword co-occurrence map and its detailed information, research hotspots in this field mainly focus on "microglia", "Alzheimer's", "curcuminoids", "astrocytes", "immunotherapy", "immune-related genes", "astroglia", "gene expression", "NF-kb ". This suggests that

microglia and astrocytes are the main target cells for current research in the field of AD and the immune system, and the hot population is AD patients. The intervention methods are mostly curcumin or immunotherapy, and the observation indicators are mostly immune-related genes, gene expression, and related immune factors, such as NF-kb and TNF- $\alpha$ .

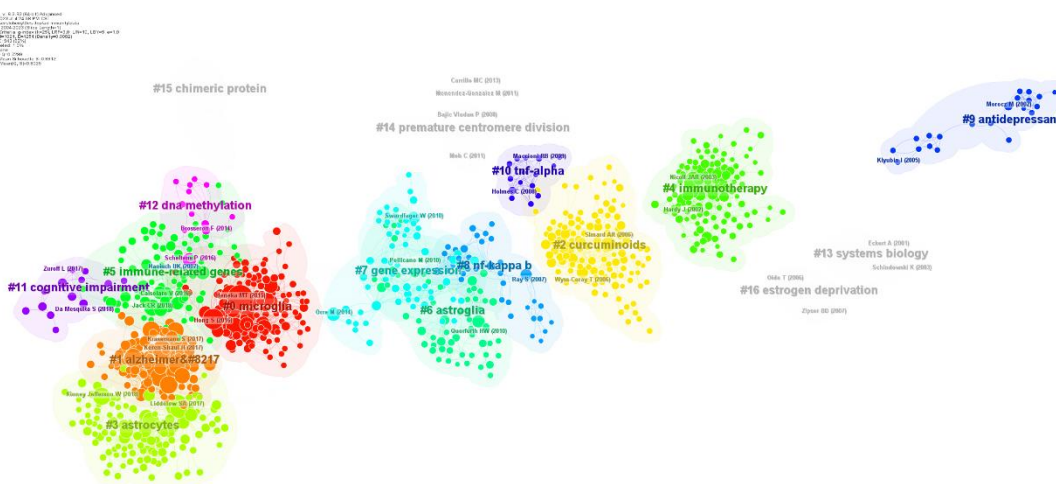


Figure 3 Landscape view of the co-citation network in from 2004 to 2023.

Table 1. Summary of the largest 17 clusters of research

Clust erID	Size	Silhouette	mean(Y ear)	Label (LSI)	Label (LLR)	Label (MI)
0	135	0.811	2013	alzheimer's disease; protein kinase ck2; casein kinase; interferon gamma; amyloid-beta peptide   amyloid; microglia; alzheimer's; inflammation; transcription factor	microglia (12.4, 0.001); neuroinflammation (12.19,0.001); confocal microscopy (7.15, 0.01); potassium channel (6.6,0.05); amyloid(5.04,0.05)	vorinostat (0.8); cx(3)cr1(creer/+):r26(dtr/+)
1	124	0.845	2018	alzheimer's disease; amyloid pathology; adaptive immune system; regulatory t cells; differential expression analysis amyloid beta; neural precursor cells; plaque-free microglia; lysosomal digestion; chronic	microglia (28.12, 1.0E-4); alzheimer' 17.19, 1.0E-4; trem2(9.59, 0.005);s disease (7.79,0.01); transcriptomics (7.79, 0.01)	systems biology (0.88); toxoplasma gondii (0.88);

2	121	0.903	2006	infection alzheimer's disease; monocyte chemotactic protein-1; beta-binding protein; neuron interaction; animal model apoptosis; macrophages; alzheimer; conophilic; angiopathy	curcuminoids (10.89, 0.001); bone marrow- derived mesenchymal stem cell (10.89, 0.001); mgat-iii (10.89, 0.001); amyloid- beta (10.1,0.005); macrophages (7.34 0.01)	monocyte chemotactic protein-1 (0.25); pd1 (0.25);
3	119	0.885	2018	alzheimer's disease; immune infiltration; differential genes; weight gene co- expression network; genetic biomarkers reactive astrocytes; glutamine synthetase; astrocytic morphology; redox alterations; perivascular space	microglia (23.49, 1.0E-4); astrocytes (20.18 1.0E-4); immune infiltration (11.36, 0.001); nrf2 (9.79,0.005); bioinformatics (9.79, 0.005)	c-11-acetate (0.97); chimera (0.97); dentate gyrus
4	111	0.947	2002	alzheimer's disease; beta peptide; amyloid beta; multivalent adenovirus vaccine; prime-boost strategies transgenic mice; t cell; multivalent adenovirus vaccine; immune response; virus-like particle	immunotherapy (19.16, 1.0E-4); vaccination a beta peptide (12.39, 0.001); adenovirus (12.39, 0.001); transgenic mice (8.67,0.005)	encephalitis (0.16); vaccines (0.16); macrophage/m
5	80	0.818	2016	alzheimer's disease; amyloid beta; myeloid dendritic cells; mesenteric lymphoid node; peyers patch t cell; regulatory t cell; effector t cell;	astrocytes (8.99, 0.005); immune-related genes (8.28, 0.005); alzheimer's (8.28, 0.005); amyloid-beta aggregation (8.28, 0.005); immune cell infiltration (8.28,0.005)	immune-infiltration analysis (0.57); ps1 transgenic

6	66	0.932	2010	transgenic mice; immune-related genes alzheimer's disease; monocyte chemoattractant protein-1; calcium-sensing receptor; human neuron; human astrocyte cerebral amyloid angiopathy-related inflammation; magnetic resonance maging; familial alzheimer's disease; transgenic animal models; rag2 knockout	astroglia (11.74, 0.001); cerebral amyloid angiopathy-related inflammation (11.74, 0.001); entorhinal cortex(11.74,0.001); rag2 knockout mice (5.86, 0.05); er stress (5.86,0.05)	rag2 knockout mice (0.19); er stress (0.19); ca2+d
7	63	0.944	2010	mice alzheimer's disease; immune response; posterior cingulate; rna sequencing; animal models gene expression; anima models; reactive glia; t-cell immune responses; neuronal precursors	gene expression (7.62, 0.01); anima animal models (0.14); models (6.4, 0.05); interleukin-2 (6.4, 0.05); entiviral vector (6.4, 0.05); a(6.4,0.05)	nterleukin-2 (0.14); lentiv
8	39	0.921	2008	alzheimer's disease; preclinical alzheimer's disease; immunobiological markers; systemic infection; mouse model mouse model; systemic infection; immune challenge; sporadic alzheimer's disease; gene expression pattern analysis	nf-kappa b (9.81,0.005); a beta-oligomers (0.11); 6.76,0.01); herpes simplex(6.76, 0.01); pathway (6.76, 0.01); p-pkc(6.76,0.01)	a beta-oligomers (0.11); nerpes simplex (0.11); pa
9	21	0.992	2001	alzheimer's disease; preclinical alzheimer's	antidepressant(17.69,1.0E-4);	alzheimer's disease (0.08);

				disease; immunobiological markers; systemic infection; mouse model mouse model; systemic infection; immune challenge; sporadic alzheimers disease; gene expression pattern analysis	lymphocytes (17.69, 1.0E-4); lymphocyte (13.9, 0.001); microarray (11.03,0.001); citalopram (8.8,0.005)	citalopram (0.03); e2f
10	15	0.979	2008	microarray analysis; astrocyte transcriptome; brain aging alzheimer disease; peripheral lymphocytes; alzheimers disease; alzheimers disease; amyloid beta; peripheral lymphocytes; orain aging alzheimer disease; microarray analysis	tnf-alpha (9.33, 0.005); p53 (9.33, 0.005); 8-oxo2dg (9.33, 0.005); brain aging alzheimer disease (9.33, 0.005); peripheral lymphocytes (9.33, 0.005)	alzheimers disease (0.08) microglia (0.03); tnf-a
11	13	0.98	2017	alzheimers disease; cognitive impairment; central nervous system; novel object recognition test; macrophage phagocytosis novel object recognition test; intrahippocampal injection; peripheral blood; cell therapy; morris	cognitive impairment (9.95, 0.005); peripheral sink of a beta (6.83, 0.01); stereology (6.83, 0.01); smad3 signaling (6.83, 0.01); fatty acid amide hydrolase (6.83,0.01)	peripheral sink of a beta (0.1); stereology (0.1);
12	12	0.992	2013	water maze alzheimers disease; dna methylation; dorsolateral prefrontal cortex; blood-brain barrier disruption;	dna methylation (15.54,1.0E-4); 5-hydroxymethylcytosine (5hmc)(7.74, 0.01); alzheimers disease biomarkers(7.74,0.01);	alzheimers disease (0.06); 5-hydroxymethylcytosine e

				hippocampal volume; hippocampal volume; alzheimers disease biomarkers; functional connectivity; default mode network; systemic inflammation	hippocampal volume (7.74, 0.01); dorsolateral prefrontal cortex(7.74, 0.01)		
13	7	1	2002		systems biology (NaN, 1.0); animal models (NaN,1.0); interleukin-2 (NaN, 1.0); vorinostat (NaN, 1.0); cx(3)cr1(creer/+):r26(dtr/+)(NaN, 1.0)	alzheimers disease (0.12); microglia (0.05); infla	
14	6	1	2009	dna damage; premature centromere division; sporadic alzheimer disease; peripheral blood lymphocytes	premature centromere division (12.44 0.001); sporadic alzheimer disease (9.67, 0.005); dna damage (9.67, 0.005); peripheral blood lymphocytes (9.67, 0.005); alzheimers disease (0.95,0.5)	alzheimers disease (0.11) microglia (0.05); infla	
15	6	0.987	2012	alzheimers disease; subunit vaccine; chimeric protein	immunotherapy (11.21,0.001); chimeric protein (10.23, 0.005); psd-95 (10.23, 0.005); subunit vaccine (10.23,0.005); dynimin 1(10.23,0.005)	alzheimers disease (0.09); microglia (0.03); infla	
16	5	1	2005	alzheimers disease; astrocytes; estrogen deprivation; oxidative stress; rats	estrogen deprivation (11.93, 0.001); rats (11.93, 0.001); oxidative stress (6.55,0.05); astrocytes (3.12,0.1); microglia (0.55,0.5)	alzheimers disease (0.11); microglia (0.04); infla	

### Authors publishing researches on AD and Immune System

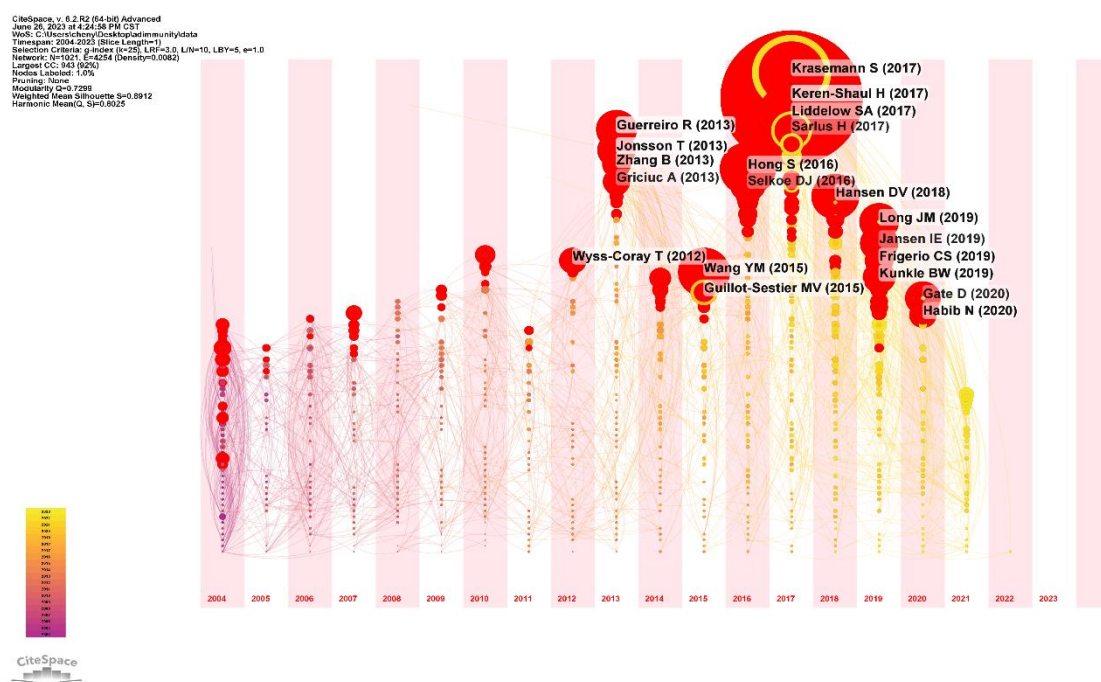
Among the authors of published studies on AD and the immune system, 1021 authors were included in our study. The research articles published in 2017 had the greatest impact and the

highest number of citations in further exploring the relationship between AD and the immune system(Figure 4). The top-ranked author is Shane Antony Liddelow, with a total of 14,867 citations. From 2020 to 2022, he has been consistently recognized as a Highly Cited Researcher in the Cross-Field category. The second-ranked author is

Keren-Shaul H, with a total of 11,464 citations. The third-ranked author, with a total of 9,270 citations, is Krasemann S. From 2004 to 2017, the number of published papers by authors in this field showed a gradual rising trend and reached a peak in 2017. Since 2017, the number of published papers by authors has gradually decreased (Figure 4). This may indicate that researchers have conducted more detailed studies building on previous research, refining their focus to the extent that it may not be accurately captured

by the terms 'AD' and 'immune system' in statistical analysis."

In summary, the research results indicate that nodes representing prolific authors in the annual statistics often overlap, suggesting frequent collaboration in their research efforts. This suggests that we can collaborate with other researchers to delve deeper into AD research from the perspective of the immune system, thereby increasing the influence of this field and providing more assistance to dementia patients.



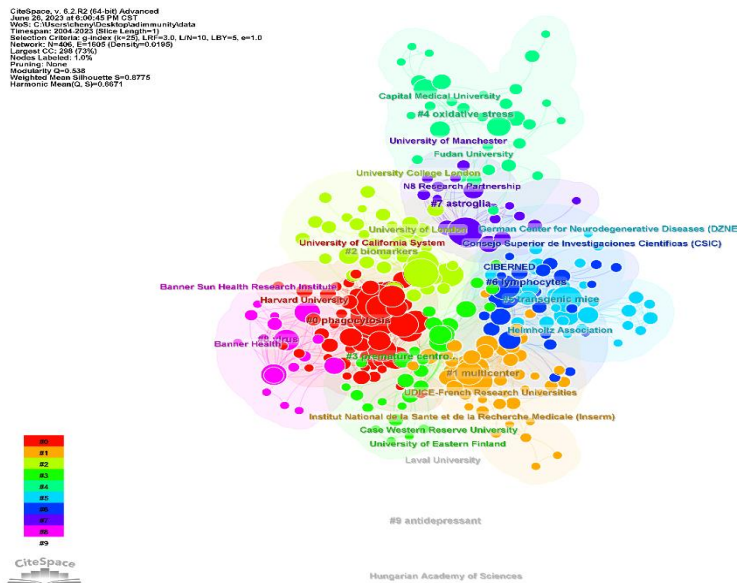
**Figure 4** Time zone view of author influence in AD and immune system.

### Institutions publishing research on AD and the immune system

The organization nodes were analyzed by CiteSpace software, and the cooperative network diagram was constructed. Nodes represent institutions, and connections represent cooperative relationships between institutions. The generated cooperative network diagram contains 406 nodes and 1605 lines, and the network density (density=0.0195) indicates that there is a certain degree of communication and cooperation between institutions.

According to the different research priorities of different institutions, we have listed the top nine research institutions in the world and their

corresponding keywords. Harvard University and the University of California System are responsible for the highest number of published papers among the world's institutions, using the keyword phagocytosis. UDICE-French Research Universities and Institut National de la Sante et de la Recherche Medicale (Inserm) rank second in global paper publication, with the dominant keyword "multicenter". The University of London ranked third in the number of published papers in the world, with a common keyword of "biomarker". Through a comprehensive analysis of publication quantity and centrality values, Harvard University emerges as the primary institution in this field, possessing the most extensive collaborative network.



**Figure:5** The distribution of institutions and their research keywords related to AD and the immune system.

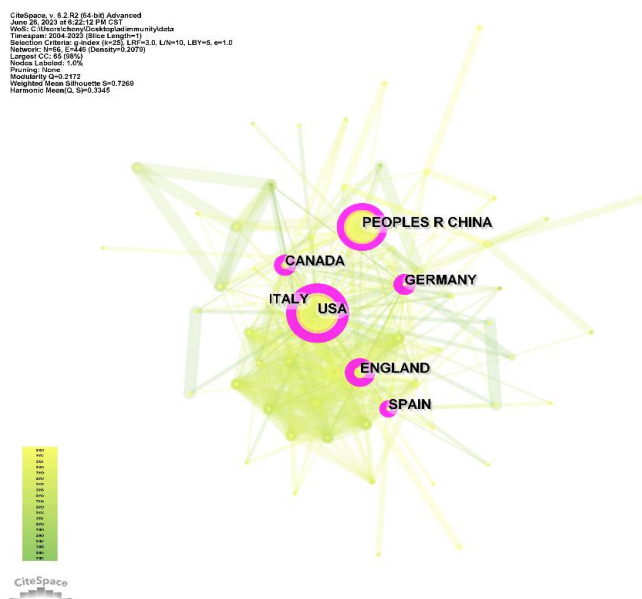
**Contribution of countries to global publications**

A total of 66 countries are involved in scientific research on AD and the immune system (Figure 6), and cooperation among countries in this field (Figure 8).

After Using CiteSpace to analyze country nodes, we found that, between 2004 and 2023, the top seven countries in terms of the number of published papers and centrality ranking are the USA, China, England, Germany, Canada, Spain, and Italy (Figure 6). The centrality values show a positive correlation with the number of

collaboration relationships.

Continuing with our analysis, we conducted a visual graph analysis of the keywords in national research (Figure 7). The top four frequently occurring keywords are "Alzheimer," "GFAP," "amyloid," and "lymphocyte." This suggests that the Aβ cascade hypothesis, related to the pathogenesis of AD, continues to be a focus of attention across various countries. It's noteworthy that the United States stands out in this field with the most extensive number of published papers, the highest centrality, the greatest influence, and the most collaborations.



**Figure 6** Top 10 authors with most publications in research scope of AD and Immune Systems.

The number of published papers in a country is represented by the size of nodes. The larger the node, the more papers are published. The lines

between nodes represent the cooperation between countries, and the width of the lines indicates the degree of cooperation.

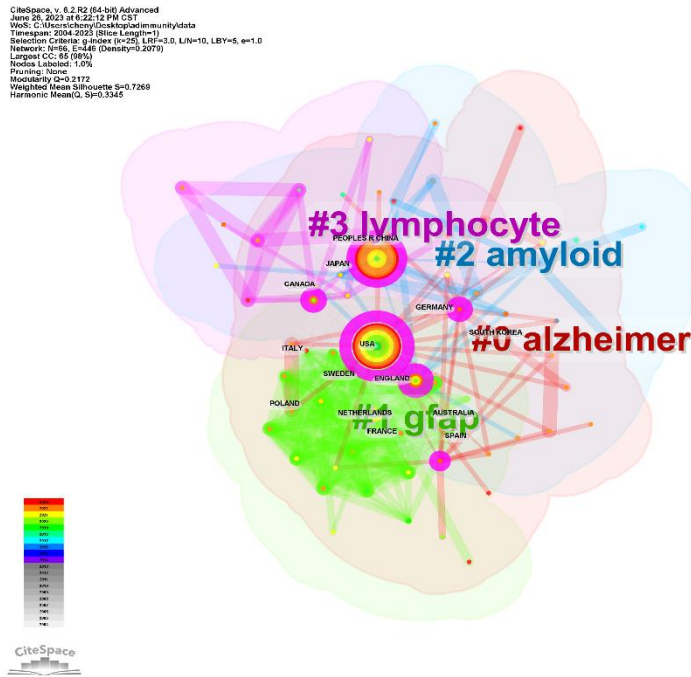


Figure 7 Top 4 keywords with most publications in research scope of AD and Immune Systems.

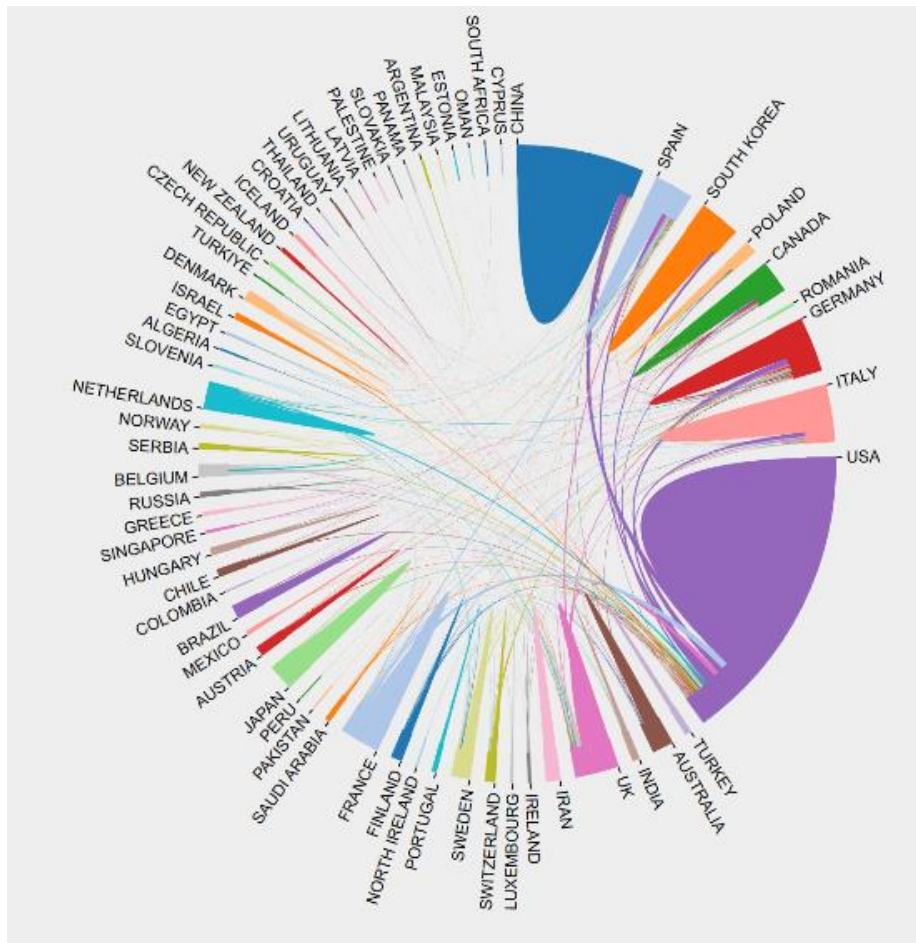


Figure 8 Cooperation between countries on Alzheimer's and the immune system from 2004 to 2023.

## Discussion

### Research trends in Alzheimer's and the immune system

An analysis of annual publications, international collaboration, and institutions indicates that in this research field, there is an overall trend of gradual growth in annual publications. The United States leads in the number of publications and displays the most frequent international collaborations. The research institutions in this field are predominantly universities, with Harvard University being the institution of the highest overall influence.

As indicated by the time curve, from 2004 to 2023, research regarding AD and the immune system has progressively increased. This signifies the growing recognition of the significance of the immune system in the onset and progression of AD. In 2015, Dr. Jonathan Kipnis, a neuroscience professor at the University of Virginia, and his team, primarily using mice as experimental subjects, identified previously undiscovered lymphatic vessels within the meninges (the thin membranes surrounding the brain and spinal cord)<sup>14</sup>. These lymphatic vessels transport blood and immune cells from the cerebrospinal fluid to clusters of lymph nodes in the neck, known as cervical lymph nodes<sup>23,24</sup>. This discovery fundamentally rewrote the textbooks and confirmed that the brain is not devoid of a lymphatic system. This study further elucidates how the immune system monitors the brain, filling a longstanding knowledge gap in this field.

In terms of authors, articles on AD and the immune system with the most significant impact have been published by Hadas Keren-Shaul from the Weizmann Institute of Science in Israel, Susanne Krasemann from Harvard University in the United States, and Shane Antony Liddelow from the New York University Medical Center in the United States. The paper titled "A Unique Microglia Type Associated with Restricting Development of AD," authored by Hadas Keren-Shaul, has been cited 1780 times, making it the most-cited paper in the related field. This research was published in *Cell* in 2017 and comprehensively mapped all the immune populations in the brains of both wild-type and Tg-AD (transgenic AD) mice. It described a novel microglial cell type, Trem2, associated with

neurodegenerative diseases (DAM)<sup>25</sup>. Susanne Krasemann and her team investigated the TREM2-APOE pathway, identifying it as a primary regulator of microglial cell functional phenotypes in neurodegenerative diseases. This pathway has been recognized as a novel target for restoring homeostatic microglial cells<sup>26</sup>. Shane Antony Liddelow is dedicated to researching the relationship between immune cells such as microglial cells, astrocytes, and oligodendrocytes, and their connection to AD and aging<sup>27</sup>. We believe that these researchers may play a unique and indispensable role in the scope of research on Alzheimer's disease and the immune system. Their contributions are likely to have a broad impact on the future development of this field and the prediction of its upcoming trends.

Among the top 9 institutions in research on AD and immune responses, over half of them are based in the United States, housing some of the world's most prestigious institutions. This partially explains why the United States has maintained a leading position in the field of AD and immune system research. Only two institutions, Capital Medical University and Fudan University, are located in China, indicating the urgent need for Chinese researchers to enhance the quality of their publications in the future.

### Research focuses on sepsis and Alzheimer's and the immune system

AD is the most common form of dementia in the elderly, characterized by an age-related neurodegenerative condition. Its features include progressive memory decline and cognitive impairment. Typically, it is histologically characterized by the substantial deposition of A $\beta$  plaques, the formation of neurofibrillary tangles, and neuroinflammation<sup>28-30</sup>. Currently, approximately 12 million people worldwide suffer from this disease, making it one of the globally recognized diseases<sup>10</sup>. In recent years, an increasing body of research suggests that there is a dysregulation in the peripheral and central immune systems in AD, which is related to cognitive function and clinical status and may change over time in a non-linear manner. There is also growing evidence that the roles of innate and adaptive immune processes vary with the pathological stages of AD<sup>31-33</sup>.

Combining high-frequency keywords, keyword

emergence, and keyword timeline analysis, we have found that the current targets of immunotherapy are A $\beta$  and microglial cells. In terms of institutional and country keywords, it has been discovered that in the last 19 years, the research focus in this field has mainly been centered on multicenter collaborations dedicated to investigating the impact of immune cells such as astrocytes and lymphatic endothelial cells in the brains of AD patients on the phagocytosis and clearance of large molecular toxins like A $\beta$ .

A substantial body of research suggests that immune cell types within the central nervous system (CNS) exhibit heterogeneity, as they play a dual role of both inhibiting and supporting the recovery of the nervous system<sup>34-36</sup>. These immune cells include microglial cells and astrocytes involved in innate immunity, as well as lymphocytes participating in adaptive immunity. Wyss Coray and his colleagues in their research on AD and other neurodegenerative diseases have pointed out that microglial cells or astrocytes within the immune system may disrupt neurons by releasing molecules that stimulate inflammation and trigger cell death<sup>37</sup>. Other researchers believe that T cells and other immune cells can have a protective role. For instance, Schwartz's research suggests that in AD mouse models, enhancing the immune response can clear amyloid plaques and improve cognitive abilities<sup>38</sup>.

Microglial cells migrate from the yolk sac to CNS around the 8th to 9th day of embryonic development. They undergo a stepwise developmental process that synchronizes with the development of the brain. Subsequently, they acquire a stable phenotype crucial for the protection and homeostasis of the brain<sup>39-41</sup>. In the brain, innate immunity is primarily represented by microglial cells. Once activated, microglial cells perform functions that include phagocytosis and clearance of debris and toxic substances within the brain<sup>42,43</sup>. However, many research reports have presented conflicting results regarding the contribution of tissue-resident microglial cells to the onset and progression of AD<sup>44,45</sup>.

Astrocytes are abundant cells in CNS<sup>46,47</sup>. In addition to performing various homeostatic maintenance functions, they also provide nutritional support to neurons, facilitate the formation and function of synapses, and trim

synapses through phagocytosis<sup>48,49</sup>. However, the proliferation of astrocytes can be a double-edged sword, as the barriers they form may also potentially inhibit the growth of neuronal dendrites<sup>50,51</sup>.

Adaptive immune cells infiltrating the brain parenchyma also appear to support the neuroinflammatory process, as evidenced by B lymphocytes and T lymphocytes<sup>35,52</sup>. B lymphocytes are endowed with a protective function against pathogens and trigger rapid, specific immune responses in the case of repeated infections induced by the same pathogen, as demonstrated<sup>53</sup>. Recent research indicates that in addition to immune cells in the brain, various immune cells also exist on the meninges<sup>24,54-56</sup>. The team led by Jonathan Kipnis has published findings that demonstrate the presence of lymphatic vessels on the surface of the brain's dura mater. These lymphatic vessels harbor immune cells and serve as transport channels for T lymphocytes, playing a crucial role in the onset and development of aging and AD<sup>56-58</sup>. In 2021, Jonathan Kipnis' team reported that these immune cells originate from the bone marrow within the skull<sup>59</sup>. When the CNS is damaged or when pathogens are present, signals carried by cerebrospinal fluid are transmitted to the bone marrow within the skull, prompting it to generate and release these mononuclear cells and neutrophils<sup>60</sup>.

Curcuminoids is the most commonly used intervention to study the relationship between AD and the immune system<sup>61,62</sup>. Curcuminoids are one of the most highly mentioned and cited chemicals in the phytomedicine literature and are a natural anti-inflammatory compound with neuroprotective properties<sup>63</sup>. Studies have shown that curcumin can inhibit the formation of toxic A $\beta$  oligomers<sup>64</sup>, inhibit the aggregation of A $\beta$  and tau *in vivo*<sup>65</sup>, and has anti-inflammatory<sup>66</sup> and antioxidant properties<sup>67</sup>, as well as inhibit specific enzymes such as acetylcholinesterase (AChE), butylcholinesterase (BChE) and  $\beta$ -secretase (BAC-1)<sup>68,69</sup>. The bioavailability of curcumin is very low. To improve the oral bioavailability of curcumin, various oral administration strategies have been developed, including solid dispersions, nano/microparticles, polymer micelles, etc. These drug strategies can increase the solubility of curcumin, improve the intestinal stability of

curcumin, change the absorption pathway of curcumin, and allow co-administration with other adjuvants<sup>70</sup>. Therefore, further exploration of curcumin targets or the development of novel drug delivery strategies will become the future research trend.

While these findings are enticing, research on immune cells, particularly border immune cells, and their role in the brain is still in its infancy, and we are far from a comprehensive understanding of what occurs in a healthy brain.

### Strengths and limitations

This article comprehensively and systematically included 1152 articles on AD and the immune system published from 2004 to 2023. The brain and the immune system should have a mutual influence on each other. However, due to the limited research on how the brain affects the immune system, we did not conduct an analysis or explanation of this research direction during our literature review. This also suggests that for a more comprehensive understanding of the relationship between the brain and the immune system, future research could focus on how the brain guides the immune system. This review paper systematically searched for literature on the relationship between AD and immunity from 2004 to mid-2023. However, it did not track articles from the second half of 2023 to 2024, indicating the need for further expansion of the literature search scope. Meanwhile, the discussion in this paper is focused on the lymphatic system, and further discussion on the lymph-like system is required in the future.

### Conclusions

In this study, the relationship between AD and the immune system was analyzed by bibliometric analysis. The results show that the United States has the highest number of published papers in this field, with the most frequent international collaborations, including emerging nations. Immunological cells such as microglia, astrocytes, and lymphocytes in the brains or meninges of dementia patients may become crucial research targets in the future study of AD. phytotherapy and immunotherapy are expected to be significant interventions in future Alzheimer's research. Therefore, unveiling the research targets for AD's impact on the immune system is crucial for subsequent drug development and patient

treatment.

### Abbreviations

**AD** Alzheimer's disease

**GFAP** glial fibrillary acidic protein

**A $\beta$**  amyloid-beta

**CNS** central nervous system

**DAM** neurodegenerative diseases

**BAC-1**  $\beta$ -secretase

**BChE** butylcholinesterase

**AChE** acetylcholinesterase

### Acknowledgements

This work was supported by the National Natural Science Foundation of China Project (Project No. U21A20414, No.82374175) and National Key Research and Development Program of China (2023YFE0203100).

### Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Author contributions

T.P. and K.C. mainly contributed to the Alzheimer's disease's impact on the immune system aspect. C.L. mainly contributed to the figure. Y.S. mainly contributed to the data collection aspect. Y.F. mainly oversaw the studies. Y.T. and Q.H. mainly contributed to the neurological diseases aspect.

### References

- 2023 Alzheimer's disease facts and figures. *Alzheimers Dement* **19**, 1598-1695 (2023). <https://doi.org/10.1002/alz.13016>
- Scheltens, P. *et al.* Alzheimer's disease. *Lancet* **397**,1577-1590 (2021). [https://doi.org/10.1016/S0140-6736\(20\)32205-4](https://doi.org/10.1016/S0140-6736(20)32205-4)
- Hardy, J. A. & Higgins, G. A. Alzheimer's disease: the amyloid cascade hypothesis. *Science* **256**,184-185 (1992). [https://doi.org:10.1126/science.1566067](https://doi.org/10.1126/science.1566067)
- Reiman, E. M. Alzheimer's disease: Attack on amyloid-beta protein. *Nature* **537**,36-37 (2016). <https://doi.org/10.1038/537036a>
- Busche, M. A. & Hyman, B. T. Synergy

- between amyloid-beta and tau in Alzheimer's disease. *Nat Neurosci* **23**, 1183-1193 (2020). <https://doi.org:10.1038/s41593-020-0687-6>
6. Hou, Y. *et al.* NAD(+) supplementation reduces neuroinflammation and cell senescence in a transgenic mouse model of Alzheimer's disease via cGAS-STING. *Proc Natl Acad Sci U S A* **118** (2021). <https://doi.org:10.1073/pnas.2011226118>
  7. Heneka, M. T. *et al.* Neuroinflammation in Alzheimer's disease. *Lancet Neurol* **14**, 388-405 (2015). [https://doi.org:10.1016/S1474-4422\(15\)70016-5](https://doi.org:10.1016/S1474-4422(15)70016-5)
  8. Calsolaro, V. & Edison, P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. *Alzheimers Dement* **12**, 719-732 (2016). <https://doi.org:10.1016/j.jalz.2016.02.010>
  9. Bai, R., Guo, J., Ye, X. Y., Xie, Y. & Xie, T. Oxidative stress: The core pathogenesis and mechanism of Alzheimer's disease. *Ageing Res Rev* **77**, 101619 (2022). <https://doi.org:10.1016/j.arr.2022.101619>
  10. Pleen, J. & Townley, R. Alzheimer's disease clinical trial update 2019-2021. *J Neurol* **269**, 1038-1051 (2022). <https://doi.org:10.1007/s00415-021-10790-5>
  11. Ossenkoppele, R., van der Kant, R. & Hansson, O. Tau biomarkers in Alzheimer's disease: towards implementation in clinical practice and trials. *Lancet Neurol* **21**, 726-734 (2022). [https://doi.org:10.1016/S1474-4422\(22\)00168-5](https://doi.org:10.1016/S1474-4422(22)00168-5)
  12. Walsh, S., Merrick, R., Milne, R. & Brayne, C. Aducanumab for Alzheimer's disease? *BMJ* **374**, n1682 (2021). <https://doi.org:10.1136/bmj.n1682>
  13. Mollgard, K. *et al.* A mesothelium divides the subarachnoid space into functional compartments. *Science* **379**, 84-88 (2023). <https://doi.org:10.1126/science.adc8810>
  14. Louveau, A. *et al.* Structural and functional features of central nervous system lymphatic vessels. *Nature* **523**, 337-341 (2015). <https://doi.org:10.1038/nature14432>
  15. Castellani, G., Croese, T., Peralta Ramos, J. M. & Schwartz, M. Transforming the understanding of brain immunity. *Science* **380**, eabo7649 (2023). <https://doi.org:10.1126/science.abo7649>
  16. Ninkov, A., Frank, J. R. & Maggio, L. A. Bibliometrics: Methods for studying academic publishing. *Perspect Med Educ* **11**, 173-176 (2022). <https://doi.org:10.1007/s40037-021-00695-4>
  17. Trueger, N. S., Yilmaz, Y. & Chan, T. M. Leveraging Tweets, Citations, and Social Networks to Improve Bibliometrics. *Jama Netw Open* **3** (2020). <https://doi.org:ARTN e201091110.1001/jamanetworkopen.2020.10911>
  18. Pessin, V. Z., Yamane, L. H. & Siman, R. R. Smart bibliometrics: an integrated method of science mapping and bibliometric analysis. *Scientometrics* **127**, 3695-3718 (2022). <https://doi.org:10.1007/s11192-022-04406-6>
  19. Gureyev, V. N. & Mazov, N. A. Bibliometrics as a promising tool for solving publication ethics issues. *Heliyon* **8** (2022). <https://doi.org:ARTN e0912310.1016/j.heliyon.2022.e09123>
  20. Singh, V. K., Singh, P., Karmakar, M., Leta, J. & Mayr, P. The journal coverage of Web of Science, Scopus and Dimensions: A comparative analysis. *Scientometrics* **126**, 5113-5142 (2021). <https://doi.org:10.1007/s11192-021-03948-5>
  21. Mongeon, P. & Paul-Hus, A. The journal coverage of Web of Science and Scopus: a comparative analysis. *Scientometrics* **106**, 213-228 (2016). <https://doi.org:10.1007/s11192-015-1765-5>
  22. AlRyalat, S. A. S., Malkawi, L. W. & Momani, S. M. Comparing Bibliometric Analysis Using PubMed, Scopus, and Web of Science Data bases. *Jove-J Vis Exp* (2019). <https://doi.org:ARTN e5849410.3791/58494>
  23. Jacobs, H. I. L. *et al.* The cerebellum in Alzheimer's disease: evaluating its role in cognitive decline. *Brain : a Journal of Neurology* **141**, 37-47 (2018). <https://doi.org:10.1093/brain/awx194>
  24. Da Mesquita, S. *et al.* Meningeal lymphatics affect microglia responses and anti-Abeta immunotherapy. *Nature* **593**, 255-260 (2021). <https://doi.org:10.1038/s41586-021-03489-0>
  25. Keren-Shaul, H. *et al.* A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. *Cell* **169**, 1276-1290.e1217 (2017). <https://doi.org:10.1016/j.cell.2017.05.018>
  26. Krasemann, S. *et al.* The TREM2-APOE Pathway Drives the Transcriptional Phenotype of Dysfunctional Microglia in

- Neurodegenerative Diseases. *Immunity* **47**, 566-581.e569 (2017). <https://doi.org/10.1016/j.immuni.2017.08.008>
27. Liddelw, S. A. *et al.* Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* **541**, 481-487 (2017). <https://doi.org/10.1038/nature21029>
  28. Hardy, J. & Selkoe, D. J. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* **297**, 353-356 (2002). <https://doi.org/10.1126/science.1072994>
  29. Vadukul, D. M. *et al.*  $\alpha$ -Synuclein Aggregation Is Triggered by Oligomeric Amyloid- $\beta$  42 via Heterogeneous Primary Nucleation. *J Am Chem Soc* **145**, 18276-18285 (2023). <https://doi.org/10.1021/jacs.3c03212>
  30. Hickman, S. E. & El Khoury, J. TREM2 and the neuroimmunology of Alzheimer's disease. *Biochem Pharmacol* **88**, 495-498 (2014). <https://doi.org/10.1016/j.bcp.2013.11.021>
  31. Bettcher, B. M., Tansey, M. G., Dorothee, G. & Heneka, M. T. Peripheral and central immune system crosstalk in Alzheimer disease - a research prospectus. *Nat Rev Neurol* **17**, 689-701 (2021). <https://doi.org/10.1038/s41582-021-00549-x>
  32. Ennerfelt, H. E. & Lukens, J. R. The role of innate immunity in Alzheimer's disease. *Immunol Rev* **297**, 225-246 (2020). <https://doi.org/10.1111/imr.12896>
  33. Jevtic, S., Sengar, A. S., Salter, M. W. & McLaurin, J. The role of the immune system in Alzheimer disease: Etiology and treatment. *Ageing Res Rev* **40**, 84-94 (2017). <https://doi.org/10.1016/j.arr.2017.08.005>
  34. Schwartz, M., Kipnis, J., Rivest, S. & Prat, A. How do immune cells support and shape the brain in health, disease, and aging? *J Neurosci* **33**, 17587-17596 (2013). <https://doi.org/10.1523/jneurosci.3241-13.2013>
  35. Clark, S. M., Vaughn, C. N., Soroka, J. A., Li, X. & Tonelli, L. H. Neonatal adoptive transfer of lymphocytes rescues social behaviour during adolescence in immune-deficient mice. *Eur J Neurosci* **47**, 968-978 (2018). <https://doi.org/10.1111/ejn.13860>
  36. Guillot-Sestier, M. V., Doty, K. R. & Town, T. Innate Immunity Fights Alzheimer's Disease. *Trends Neurosci* **38**, 674-681 (2015). <https://doi.org/10.1016/j.tins.2015.08.008>
  37. Paolicelli, R. C. *et al.* Microglia states and nomenclature: A field at its crossroads. *Neuron* **110**, 3458-3483 (2022). <https://doi.org/10.1016/j.neuron.2022.10.020>
  38. Baruch, K. *et al.* PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer's disease. *Nat Med* **22**, 135-137 (2016). <https://doi.org/10.1038/nm.4022>
  39. Condello, C., Yuan, P., Schain, A. & Grutzendler, J. Microglia constitute a barrier that prevents neurotoxic protofibrillar A $\beta$ 42 hotspots around plaques. *Nat Commun* **6**, 6176 (2015). <https://doi.org/10.1038/ncomms7176>
  40. Wang, Y. *et al.* TREM2-mediated early microglial response limits diffusion and toxicity of amyloid plaques. *J Exp Med* **213**, 667-675 (2016). <https://doi.org/10.1084/jem.20151948>
  41. Parhizkar, S. *et al.* Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE. *Nat Neurosci* **22**, 191-204 (2019). <https://doi.org/10.1038/s41593-018-0296-9>
  42. Pasciuto, E. *et al.* Microglia Require CD4 T Cells to Complete the Fetal-to-Adult Transition. *Cell* **182**,625-640.e624(2020). <https://doi.org/10.1016/j.cell.2020.06.026>
  43. Tarasoff-Conway, J. M. *et al.* Clearance systems in the brain--implications for Alzheimer disease. *Nature Reviews. Neurology* **12**, 248 (2016). <https://doi.org/10.1038/nrneurol.2016.36>
  44. Deardorff, W. J. & Grossberg, G. T. Targeting neuroinflammation in Alzheimer's disease: evidence for NSAIDs and novel therapeutics. *Expert Rev Neurother* **17**, 17-32 (2017). <https://doi.org/10.1080/14737175.2016.1200972>
  45. Guillot-Sestier, M. V. *et al.* Il10 deficiency rebalances innate immunity to mitigate Alzheimer-like pathology. *Neuron* **85**, 534-548 (2015). <https://doi.org/10.1016/j.neuron.2014.12.068>
  46. Linnerbauer, M., Wheeler, M. A. & Quintana, F. J. Astrocyte Crosstalk in CNS Inflammation. *Neuron* **108**, 608-622 (2020). <https://doi.org/10.1016/j.neuron.2020.08.012>
  47. Liddelw, S. A. & Barres, B. A. Reactive Astrocytes: Production, Function, and Therapeutic Potential. *Immunity* **46**, 957-967 (2017). <https://doi.org/10.1016/j.immuni.2017.06.006>

48. Burgaletto, C. *et al.* The immune system on the TRAIL of Alzheimer's disease. *J Neuroinflammation* **17**, 298 (2020). <https://doi.org/10.1186/s12974-020-01968-1>
49. Linnerbauer, M. & Rothhammer, V. Protective Functions of Reactive Astrocytes Following Central Nervous System Insult. *Front Immunol* **11**, 573256 (2020). <https://doi.org/10.3389/fimmu.2020.573256>
50. Endo, F. *et al.* Molecular basis of astrocyte diversity and morphology across the CNS in health and disease. *Science* **378**, eadc9020 (2022). <https://doi.org/10.1126/science.adc9020>
51. Zhou, B., Zuo, Y. X. & Jiang, R. T. Astrocyte morphology: Diversity, plasticity, and role in neurological diseases. *CNS Neurosci Ther* **25**, 665-673 (2019). <https://doi.org/10.1111/cns.13123>
52. Xie, L., Choudhury, G. R., Winters, A., Yang, S. H. & Jin, K. Cerebral regulatory T cells restrain microglia/macrophage-mediated inflammatory responses via IL-10. *Eur J Immunol* **45**, 180-191 (2015). <https://doi.org/10.1002/eji.201444823>
53. Engelhardt, B. *et al.* Vascular, glial, and lymphatic immune gateways of the central nervous system. *Acta Neuropathol* **132**, 317-338 (2016). <https://doi.org/10.1007/s00401-016-1606-5>
54. Louveau, A. *et al.* CNS lymphatic drainage and neuroinflammation are regulated by meningeal lymphatic vasculature. *Nat Neurosci* **21**, 1380-1391 (2018). <https://doi.org/10.1038/s41593-018-0227-9>
55. Antila, S. *et al.* Development and plasticity of meningeal lymphatic vessels. *J Exp Med* **214**, 3645-3667 (2017). <https://doi.org/10.1084/jem.20170391>
56. Da Mesquita, S. *et al.* Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. *Nature* **560**, 185-191 (2018). <https://doi.org/10.1038/s41586-018-0368-8>
57. Gadani, S. P., Walsh, J. T., Lukens, J. R. & Kipnis, J. Dealing with Danger in the CNS: The Response of the Immune System to Injury. *Neuron* **87**, 47-62 (2015). <https://doi.org/10.1016/j.neuron.2015.05.019>
58. Da Mesquita, S., Fu, Z. & Kipnis, J. The Meningeal Lymphatic System: A New Player in Neurophysiology. *Neuron* **100**, 375-388 (2018). <https://doi.org/10.1016/j.neuron.2018.09.022>
59. Cugurra, A. *et al.* Skull and vertebral bone marrow are myeloid cell reservoirs for the meninges and CNS parenchyma. *Science* **373** (2021). <https://doi.org/10.1126/science.abf7844>
60. Mazzitelli, J. A. *et al.* Cerebrospinal fluid regulates skull bone marrow niches via direct access through dural channels. *Nat Neurosci* **25**, 555-560 (2022). <https://doi.org/10.1038/s41593-022-01029-1>
61. Maiti, P., Bowers, Z., Bourcier-Schultz, A., Morse, J. & Dunbar, G. L. Preservation of dendritic spine morphology and postsynaptic signaling markers after treatment with solid lipid curcumin particles in the 5xFAD mouse model of Alzheimer's amyloidosis. *Alzheimers Res Ther* **13**, 37 (2021). <https://doi.org/10.1186/s13195-021-00769-9>
62. Chainoglou, E. & Hadjipavlou-Litina, D. Curcumin in Health and Diseases: Alzheimer's Disease and Curcumin Analogues, Derivatives, and Hybrids. *Int J Mol Sci* **21** (2020). <https://doi.org/10.3390/ijms21061975>
63. Xu, H. & Liu, Y. ROS-responsive nanomodulators downregulate IFITM3 expression and eliminate ROS for Alzheimer's disease combination treatment. *J Colloid Interface Sci* **645**, 210-218 (2023). <https://doi.org/10.1016/j.jcis.2023.04.139>
64. Bisceglia, F. *et al.* Prenylated Curcumin Analogues as Multipotent Tools To Tackle Alzheimer's Disease. *ACS Chem Neurosci* **10**, 1420-1433 (2019). <https://doi.org/10.1021/acchemneuro.8b00463>
65. Okuda, M. *et al.* PE859, A Novel Curcumin Derivative, Inhibits Amyloid- $\beta$  and Tau Aggregation, and Ameliorates Cognitive Dysfunction in Senescence-Accelerated Mouse Prone 8. *J Alzheimers Dis* **59**, 313-328 (2017). <https://doi.org/10.3233/jad-161017>
66. Chainoglou, E. & Hadjipavlou-Litina, D. Curcumin analogues and derivatives with anti-proliferative and anti-inflammatory activity: Structural characteristics and molecular targets. *Expert Opin Drug Discov* **14**, 821-842 (2019). <https://doi.org/10.1080/17460441.2019.1614560>
67. Akaishi, T. & Abe, K. CNB-001, a synthetic

- pyrazole derivative of curcumin, suppresses lipopolysaccharide-induced nitric oxide production through the inhibition of NF- $\kappa$ B and p38 MAPK pathways in microglia. *Eur J Pharmacol* **819**, 190-197 (2018). <https://doi.org/10.1016/j.ejphar.2017.12.008>
68. Yan, J. *et al.* Design, synthesis, and evaluation of multitarget-directed ligands against Alzheimer's disease based on the fusion of donepezil and curcumin. *Bioorg Med Chem* **25**, 2946-2955 (2017). <https://doi.org/10.1016/j.bmc.2017.02.048>
69. Kalaycıoğlu, Z., Gazioğlu, I. & Erim, F. B. Comparison of antioxidant, anticholinesterase, and antidiabetic activities of three curcuminoids isolated from *Curcuma longa* L. *Nat Prod Res* **31**, 2914-2917 (2017). <https://doi.org/10.1080/14786419.2017.1299727>
70. Ma, Z., Wang, N., He, H. & Tang, X. Pharmaceutical strategies of improving oral systemic bioavailability of curcumin for clinical application. *J Control Release* **316**, 359-380 (2019). <https://doi.org/10.1016/j.jconrel.2019.10.053>