*Chronic Diseases and Translational Medicine*

Chronic Diseases and Translational Medicine

REVIEW OPEN ACCESS

# Amyloid-Related Imaging Abnormality (ARIA) Beyond the APOE-ε4 Allele

Valentinus Besin[1] | Farizky Martriano Humardani[2] | Fenny Lanawati Yudiarto[3] | Paulus Anam Ong[4] | Sulistyo Emantoko Dwi Putra[5] | Ratih Asmana Ningrum[6]

[1]Faculty of Medicine, University of Surabaya, Surabaya, Indonesia | [2]Doctoral Program in Medical Science, Faculty of Medicine Universitas Brawijaya, Malang, Indonesia | [3]Department of Neurology, Diponegoro University, Semarang, Indonesia | [4]Department of Neurology, Universitas Padjadjaran, Bandung, Indonesia | [5]Faculty of Biotechnology, University of Surabaya, Surabaya, Indonesia | [6]Research Center for Genetic Engineering, National Research and Innovation Agency of The Republic of Indonesia (BRIN), Cibinong Sciences Center, Cibinong, Bogor, Indonesia

**Correspondence:** Farizky Martriano Humardani (farizky946@gmail.com)

**Received:** 10 February 2025 | **Revised:** 25 March 2025 | **Accepted:** 8 April 2025

**Funding:** The authors received no specific funding for this work.

**Keywords:** Alzheimer's disease | amyloid-related imaging abnormalities | monoclonal antibodies

## ABSTRACT

Monoclonal antibodies (mAbs) have made significant progress in the treatment of Alzheimer's disease (AD). However, mAbs are associated with adverse effects, including Amyloid-Related Imaging Abnormality (ARIA), which manifests as edema or effusion (ARIA-E) and hemorrhage (ARIA-H). The mechanisms behind these effects are not yet fully understood. Moreover, spontaneous ARIA has been insufficiently explored, and mAb therapies, particularly lecanemab, have mainly focused on patients with the *APOE-ε4* allele carrier. This review aims to address this gap by examining the mechanisms of spontaneous ARIA, ARIA induced by mAbs, and the influence of genetic variants on ARIA development. The autoantibody-Aβ-mediated immune response targets excessive Aβ deposits, increasing immune activity through microglial reactivity. The heightened immune response, driven by Aβ accumulation in blood vessels, promotes angiopathy and inflammation, potentially contributing to spontaneous ARIA. The *APOE-ε4* allele carrier is more strongly associated with ARIA-E because it redistributes Aβ deposition from the brain to blood vessels, influencing microglial reactivity. The redistribution enhances vascular integrity and reduces the risk of ARIA-H. However, it also increases the likelihood of ARIA-E due to Aβ accumulation in the vasculature, triggering inflammation. In contrast, the development of ARIA-H is linked to increased *TREM2* expression and microglial reactivity, leading to impaired vascular integrity and disrupted matrix remodeling, which worsens the condition. Additionally, the adverse effects of mAbs may extend beyond the *APOE-ε4* allele, possibly impacting other genetic variants involved in microglial reactivity, Aβ redistribution, and vascular integrity.

## 1 | Introduction

Anti-amyloid-beta (Aβ) monoclonal antibodies (mAbs) represent a promising class of therapeutics for Alzheimer's disease (AD). One such drug, lecanemab, has received FDA approval. BAN2401, further developed into lecanemab, is a second-generation immunoglobulin G1 (IgG1) monoclonal antibody humanized from the murine antibody mAb158 that targets Aβ protofibrils with high affinity [1]. A unique feature of lecanemab is its bivalent design (RmAb158-scFv8D3), which enables it to effectively clear soluble Aβ protofibrils at a dose ten times lower than RmAb158 alone while demonstrating ten times greater efficiency in eliminating its target from the brain [2]. Despite its structural properties, this results in monovalent binding to transferrin receptor 1 (TfR1), which facilitates highly efficient transport across the blood–brain barrier (BBB) [3, 4].

**Summary**

- Spontaneous ARIA versus mAb-Induced ARIA.
- Spontaneous ARIA Occurs in Late-stage AD.
- mAbs Accelerate the Occurrence of ARIA in early-stage AD.
- ARIA may extend beyond the *APOE-ε4* variant.

This breakthrough marks a significant advancement in the development of drugs that can cross the BBB, overcoming a longstanding challenge in the treatment of AD.

A meta-analysis has demonstrated that mAbs significantly increase the risk of side effects, such as amyloid-related imaging abnormality (ARIA), particularly in *APOE-ε4* allele carriers in AD [5]. The risk of ARIA is also higher in individuals with a history of stroke, infarct, or hemorrhage [6, 7]. and age is another contributing factor, as discussed in a separate review [8]. ARIA initially develops due to MRI abnormalities associated with mAb treatment in AD. However, ARIA has also been observed to occur spontaneously as a result of cerebral amyloid angiopathy (CAA), which was previously underreported because it lacked a clear definition [9]. ARIA is categorized into two types: cerebral edema or effusion (ARIA-E) and cerebral microhemorrhage with hemosiderosis (ARIA-H) [10].

The prevalence of ARIA is underrepresented in the population, particularly among different ethnic groups, due to several studies not focusing on its prevalence study. Previous studies have reported that the incidence of ARIA in AD is lower with lecanemab treatment (ARIA-E 9.9%–12.6%; ARIA-H 6.8%–17.3%) compared to aducanumab (ARIA-E 35%–36%; ARIA-H 19%–20%) and donanemab (ARIA-E 24%–26.7%; ARIA-H 19.7%–22.1%) [11]. This suggests that lecanemab has a better safety profile compared to aducanumab and donanemab. Interestingly, *APOE-ε4* allele carriers have about 3.5 times higher risk of ARIA-E than non-carriers [5]. The reasons for the differential risk of ARIA-E and ARIA-H between *APOE-ε4* allele carriers and non-carriers remain poorly understood. This review is the first to examine the mechanisms by which mAbs induce ARIA, the role of genetic factors, particularly the *APOE-ε4* allele carrier, in the development of ARIA, the occurrence of spontaneous ARIA, and the influence of genetic profiles on the adverse effects of mAbs. Additionally, it discusses the mechanism of action of current mAbs.

## 2 | Spontaneous ARIA

ARIA was identified following the detection of abnormalities on imaging associated with monoclonal antibody treatments, despite being asymptomatic in most cases (96.7%) of lecanemab therapy [12]. The finding has attracted significant attention from researchers and clinicians. However, ARIA can also occur spontaneously due to CAA [9]. The question arises as to whether a specific case of ARIA is attributable to spontaneous causes or to mAb treatment. However, limited evidence has been explored to address this issue.

As previously discussed, ARIA can occur spontaneously in cases of CAA, although it was not well-defined in earlier research [9]. Recent studies have identified spontaneous ARIA as a rare autoimmune encephalopathy characterized by ARIA suggestive of ARIA-E. This condition results from an autoantibody-mediated immune reaction against Aβ induced by CAA [13]. Several studies suggest that spontaneous ARIA can resolve within 3 months to 1 year with corticosteroids as initial therapy [7, 13, 14]. However, one case reported fatality after the patient initially underwent conservative management and was administered steroids only after clinical deterioration, with subsequent intolerance to increased steroid dosages [15]. Similar to ARIA caused by lecanemab, which has an incidence of less than 10% and typically resolves spontaneously within 3 months, the majority of cases are asymptomatic (97%) [16].

Studies have observed microglial activation during acute ARIA, characterized by elevated levels of anti-Aβ, Aβ40, Aβ42, Tau, and p-Tau181. In contrast, during remission, microglial activity returns to an inactive state, with biomarker levels returning to the normal range after recovery [13, 14]. Microglial activity exhibits two peaks of activation: one during mild cognitive impairment (MCI) and the other during late-stage AD [17, 18]. In MCI, microglial activation facilitates the clearance of Aβ and Tau through immune activation. However, over time, microglial activity declines. In late-stage AD, microglial aging becomes reactive, leading to increased pro-inflammatory responses [17, 18]. This is primarily due to the deposition of Aβ and Tau in the vasculature, a condition linked to cerebral amyloid angiopathy-related inflammation (CAA-ri). This is supported by evidence indicating that spontaneous ARIA frequently coexists with pre-existing CAA-ri [13], involving immune activation driven by CAA, which primarily contributes to the reduction of Aβ plaques [19].

Under normal conditions, the anti-Aβ antibody, also referred to as naturally occurring autoantibodies, facilitates the clearance of Aβ. In individuals with MCI, levels of anti-Aβ Immunoglobulin M (IgM) increase, whereas in AD, IgM levels decrease, while IgG levels rise [20, 21]. This is further supported by evidence of an increase in plasma B cells producing IgG against Aβ protofibrils (autoantibodies), which is elevated in late-stage AD but reduced against Aβ monofibrils (Figure 2A) [22]. IgG levels increase further in CAA-ri and closely resemble normal conditions during spontaneous ARIA remission [14]. IgG mediates Aβ clearance by initiating microglial phagocytosis through the activation of the fragment crystallizable (Fc) γ receptor (FcγR). Upon FcγR activation, Syk (spleen tyrosine kinase) is recruited to the receptor and undergoes autophosphorylation, triggering a cascade that leads to phagocytosis [23].

A single conserved N-glycosylation site in the heavy chain, with two asparagine-linked carbohydrates (N-glycans), is an integral part of the structure, co-forming with the disulfide bond that forms the IgG molecule [24]. IgG typically does not induce pro-inflammatory responses, as it is regulated to function in an anti-inflammatory phenotype [25]. In AD, alterations in N-glycosylation have been observed, and these changes can significantly modify immune responses, leading to a pro-inflammatory phenotype [26, 27]. These alterations include decreased sialylation and core fucosylation, along with

increased bisecting N-acetylglucosamine (GlcNAc) in the Fc domain [28]. The absence of core fucose and the presence of bisecting GlcNAc lead to a significantly increased binding to FcγR, while the lack of sialic acid results in an aberrant anti-inflammatory phenotype [24]. Alterations in N-glycosylation enhance the activation of antibody-dependent cell-mediated cytotoxicity (ADCC) and promote the release of pro-inflammatory cytokines (Figure 2B) [24, 28].

The proposed mechanism of spontaneous ARIA involves an autoantibody-Aβ-mediated immune response targeting excessive Aβ deposits. Furthermore, heightened immune activity, particularly involving IgG, driven by the accumulation of Aβ in the vasculature, promotes angiopathy, including CAA-ri and vasculitis, which are commonly observed in late-stage AD (Figure 2A). Alterations in N-glycosylation further exacerbate this process, leading to inflammation that manifests brain edema or effusion, characteristic of spontaneous ARIA (Figure 2B). Further investigations are needed to determine whether spontaneous ARIA is exclusively symptomatic or can also manifest asymptomatically. Additionally, further research is needed to determine whether spontaneous ARIA represents an advanced stage of CAA or arises from distinct pathological mechanisms. Current evidence suggests that spontaneous ARIA is similar to ARIA-E. Additional studies are required to investigate whether spontaneous ARIA occurs exclusively in ARIA-E or if it can also be associated with ARIA-H.

## 3 | Mechanism of Aβ Deposition and Mechanism of Action of Monoclonal Antibodies

The pathophysiology of AD is widely recognized to be closely associated with the production and clearance of Aβ. The amyloid precursor protein (APP) is cleaved by several proteases to generate Aβ, which then aggregates into soluble forms (monomers, oligomers, and protofibrils) and insoluble forms (fibrils, which accumulate to form plaques) [29]. Among this form, Aβ protofibrils are considered the most toxic form [30]. Under physiological conditions, astrocytes and other glial cells rapidly engulf large quantities of Aβ protofibrils. However, in AD, these cells store the ingested material rather than degrading it. The incomplete digestion leads to the accumulation of undigested Aβ, resulting in the secretion of extracellular vesicular truncated Aβ and lysosomal dysfunction. These changes increase ApoE levels in astrocytes, neurons, and oligodendrocytes and induce axonal swelling, vacuolization of neuronal cell bodies, and cholesterol deposits in lysosomal compartments. Ultimately, these processes lead to apoptosis in the neuronal cortex [31–33].

The mechanism of action of mAb drug clearance of Aβ is similar in principle, aiming to increase the clearance of Aβ but targeting different Aβ subtypes, such as soluble or insoluble forms. Aducanumab targets Aβ fibrils, while Gantenerumab targets aggregated forms of Aβ. Donanemab specifically targets β-amyloid plaques. In contrast, Bapineuzumab (3D6) does not specifically target monomeric or fibrillar Aβ but binds both with comparable affinity, including soluble and insoluble forms, while lecanemab targets Aβ protofibrils (Figure 1A) [34, 35]. These mAbs share a similar mechanism of binding Aβ through pathways independent of FcγR, enhancing phagocytosis and increasing the clearance of pathological Aβ by astrocytes and microglia. This process helps rescue neurons from secondary cell death (Figure 1A) [23, 36].

Triggering receptor expressed on myeloid cells 2 (TREM2) is believed to play a significant role in ARIA-H, while CAA is closely linked to the development of ARIA-E [37, 38]. A human IgG targeted at activating TREM2 (AL002) has been developed and tested in preclinical studies using monkeys over 4 weeks, demonstrating good tolerability in a 12-week clinical trial. This study showed increased microglial recruitment to Aβ deposits, driven by activated microglia enhancing phagocytosis [39, 40]. TREM2 levels reprogram microglia into a reactive state. Interestingly, the reprogramming of TREM2 is driven not only by direct agonist mAbs that influence TREM2 levels but also by mAbs like 3D6, which bind both soluble and insoluble forms of Aβ and enhance TREM2 levels [37]. This suggests that TREM2 activation is influenced not only by agonist TREM2-targeting mAbs but also by other mAbs that directly target specific Aβ subtypes.

The mAbs further enhance microglial-mediated phagocytosis of amyloid by increasing the expression of *TREM2* [37]. TREM2-containing microglial exosomes bind to Aβ, forming complexes that mitigate the inflammatory state surrounding Aβ and facilitate its recognition by microglia. This process promotes microglial engulfment and clearance of Aβ [41]. Additionally, TREM2 activation reprograms microglia into a reactive state, [42] enabling active phagocytosis through antibody-dependent cellular phagocytosis (ADCP) (Figure 1B).

## 4 | Mechanisms of ARIA Induced by Monoclonal Antibodies

Antibodies targeting Aβ represent a form of passive immunity designed to bind and aggregate Aβ, thereby reducing Aβ plaques. However, this therapy is associated with adverse effects, including ARIA-E and ARIA-H [11]. The underlying mechanisms behind these side effects remain unclear. A potential explanation for ARIA-E caused by mAbs is that certain treatments, such as aducanumab, bapineuzumab, donanemab, and gantenerumab, exhibit high binding affinity to CAA fibrils, which correlates with a higher incidence of ARIA-E (24%–35%). In contrast, lecanemab demonstrates a lower binding affinity to CAA fibrils and is associated with a lower incidence of ARIA-E (12.6%) [38]. This phenomenon is similar to spontaneous ARIA, where the binding of antibodies to CAA fibrils may trigger CAA-ri to clear Aβ, leading to inflammation and edema that result in ARIA-E.

TREM2 is predominantly expressed in macrophages and microglia but is also found in exosomes released by microglia. Under physiological conditions, TREM2-containing microglial exosomes bind to Aβ. These complexes reduce the inflammatory response surrounding Aβ by making it recognizable to microglia, promoting the microglial engulfment and clearance of Aβ [41]. ARIA-H has a distinct mechanism compared to physiological conditions. While Aβ immunotherapy helps in clearing Aβ, this process triggers an increased expression of TREM2 in macrophages, which contributes to vascular fibrosis,

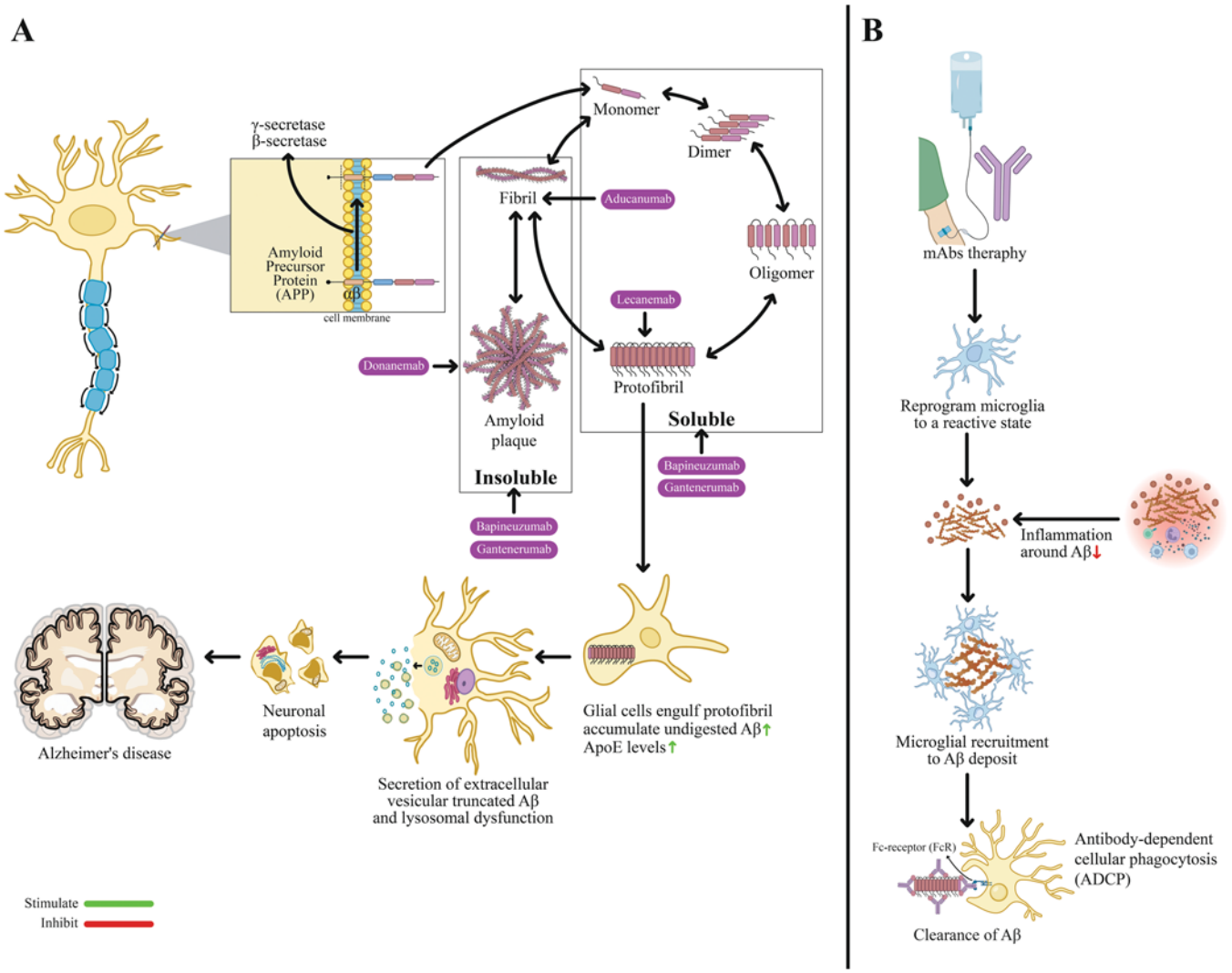



**FIGURE 1** | Mechanism of action of monoclonal antibodies targeting Aβ in the treatment of AD. (A) Targets of various mAbs. (B) Mechanism of monoclonal antibody-mediated clearance of Aβ. mAbs facilitate the clearance of Aβ by enhancing microglial-mediated phagocytosis through the upregulation of *TREM2* expression. Increased *TREM2* expression reduces inflammation surrounding Aβ deposits, allowing microglia to recognize and recruit these deposits. Additionally, TREM2 activation reprograms microglia into a reactive state, promoting active phagocytosis via antibody-dependent cellular phagocytosis (ADCP), thereby enhancing Aβ clearance.

microhemorrhages, smooth muscle cell damage, and compromised BBB integrity [37]. The expression of TREM2 is further exacerbated, as the negative regulator of natural antibodies against TREM2 is lower in AD [43].

In hepatic steatosis, TREM2-positive macrophages have been found to increase the production of *matrix metalloproteinase-12 (MMP-12)* while decreasing the expression of the tissue inhibitor of metalloproteinase-1 (*TIMP-1*), which normally inhibits MMP-12. Additionally, these macrophages reduce the expression of collagen type 1 alpha 1 (*COL1A1*) and collagen type 3 alpha 1 (*COL3A1*) [44]. Consequently, the increase in TREM2 levels induced by mAbs downregulates genes essential for maintaining vascular integrity, such as *COL1A1* and *COL3A1*, while also disrupting matrix remodeling by increasing *MMP-12* expression and decreasing *TIMP-1*. These changes collectively contribute to the development of ARIA-H. Unlike ARIA-E, which is characterized predominantly by edema or effusion, ARIA-H is associated with more extensive microhemorrhages (Figure 3) [37].

ARIA associated with mAbs differs from spontaneous ARIA. ARIA induced by mAbs typically occurs in individuals with early-stage AD, [12, 45], whereas spontaneous ARIA is more commonly observed in late-stage AD. As highlighted in the section on spontaneous ARIA, the difference arises from the increased accumulation of Aβ in late-stage AD, which activates inflammation through microglial reactivity. In contrast, ARIA associated with mAbs typically manifests earlier than spontaneous ARIA (Figure 2A). Further research is needed to better understand why inflammation leads to the development of distinct phenotypes, such as ARIA-E and ARIA-H.

## 5 | Mechanisms of *APOE* Variant Influence on the Occurrence of ARIA Subtypes

Apolipoprotein (Apo) has been extensively studied for its role in the clearance of Aβ. Among these, the *APOE-ε4* allele has received significant attention in neurodegeneration research, particularly

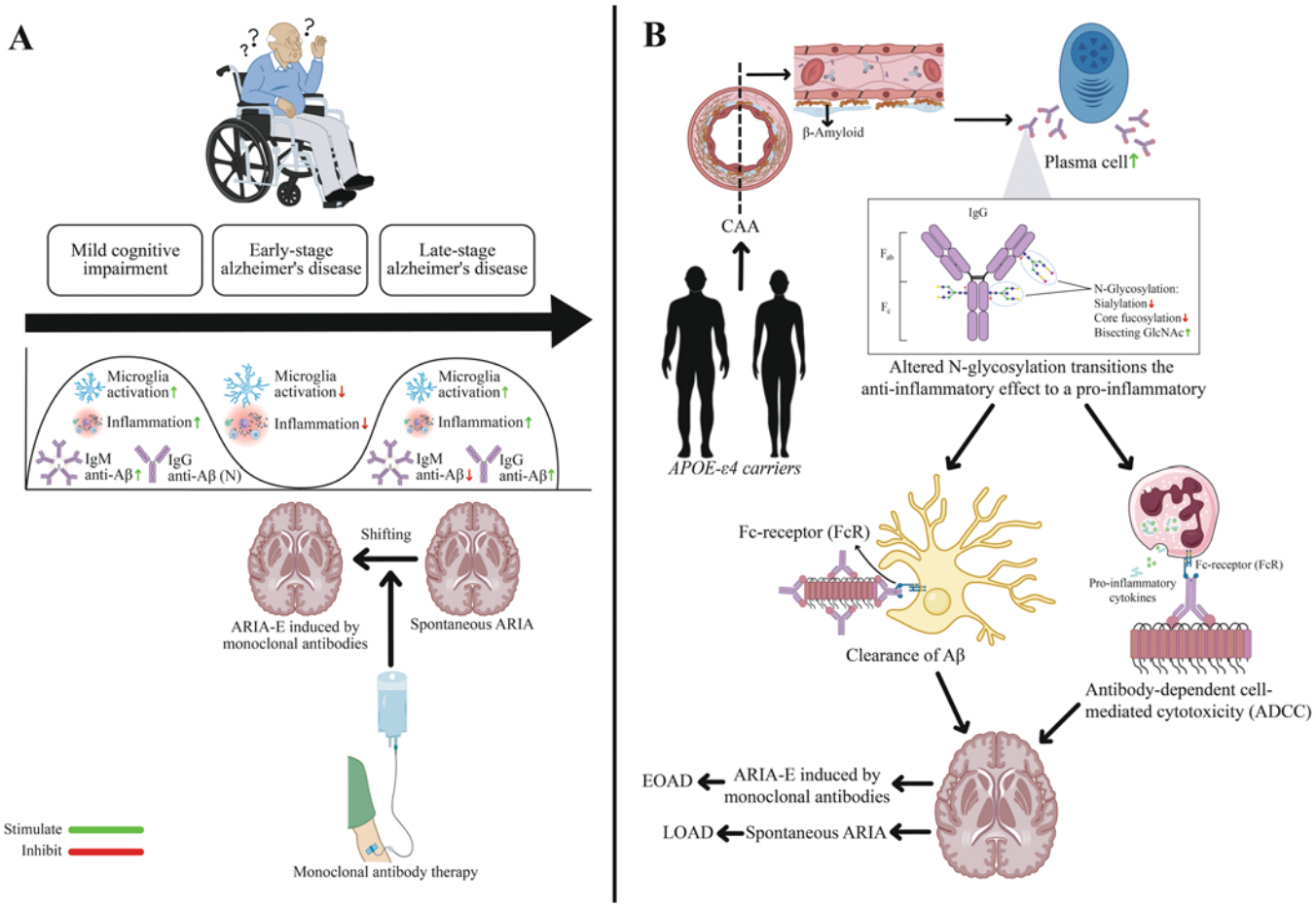



**FIGURE 2** | Mechanisms of ARIA-E induced by monoclonal antibodies. (A) Involvement of microglia, inflammation, and immunoglobulin levels is dependent on the stage of AD. In late-stage AD, high Aβ deposition leads to increased microglial activation, heightened inflammation, and elevated IgG levels, contributing to spontaneous ARIA. mAb therapies shift this phenomenon toward early-stage AD. (B) Heightened immune activity increases plasma cell proliferation, particularly involving IgG, driven by the accumulation of Aβ in the vasculature, known as cerebral amyloid angiopathy (CAA), leading to inflammation. The tendency to develop CAA is further exacerbated in *APOE-ε4* carriers. In AD, alterations in N-glycosylation include decreased sialylation and core fucosylation, along with increased bisecting N-acetylglucosamine (GlcNAc) in the Fc domain. These modifications enhance the activation of ADCC and promote the release of pro-inflammatory cytokines, contributing to spontaneous ARIA, which is frequently observed in late-stage AD. Meanwhile, mAb therapies may further accelerate this process in early-stage AD.

regarding the development of mAbs. Current guidelines also recommend assessing the *APOE* genotype before administering lecanemab to determine whether a patient is an *APOE-ε4* allele carrier [46]. This is crucial, as *APOE-ε4* allele carriers are known to have a 3.5-fold increased risk of developing ARIA-E [5].

The question arises as to why only *APOE*-ε4 is considered, while other genes are not. This may be due to the current research focus, particularly in the development of mAbs. To the best of our knowledge, the development of mAbs has predominantly focused on the *APOE-ε4* allele because previous studies have shown significant impacts on *APOE-ε4* allele carriers. Notably, the *APOE-ε2* allele has a protective role in AD, while the *APOE-ε3* allele does not have as significant an impact on AD as the *APOE-ε4* allele [47, 48]. However, the exclusive focus on the *APOE-ε4* allele overlooks the potential contributions of other genes that may also influence the efficacy and safety of mAb therapies.

Preclinical studies have demonstrated that the non-lipidated *APOE-ε4* allele carrier exhibits greater co-aggregation with Aβ compared to the non-lipidated *APOE-ε3* allele carrier. Additionally, the non-lipidated *APOE-ε4* allele induces higher secretion of cytokines and chemokines, following the order *APOE-ε4* > *APOE-ε3* > *APOE-ε2*. Glial cell engulfment is more pronounced in the non-lipidated *APOE-ε2* allele compared to the non-lipidated *APOE-ε4* allele. Notably, the non-lipidated *APOE-ε4* allele is more toxic than other isoforms. These findings suggest that the co-aggregation of the non-lipidated *APOE-ε4* allele with Aβ is slower to clear and induces greater inflammation compared to other *APOE* variants [47].

A possible explanation for the increased incidence of ARIA-E in individuals with the APOE-ε4 allele is that the genetic variant promotes the formation of CAA by redistributing Aβ deposition from the brain parenchyma to the blood vessels (Figure 3). However, this mechanism may simultaneously enhance vascular integrity and provide protection to the cerebrovascular system [49], with the redistribution of Aβ deposition potentially influenced by TREM2 (Figure 2B) [50]. In contrast, spontaneous ARIA observed in late-stage AD is primarily attributed to the excessive accumulation of Aβ, a hallmark feature of late-stage AD. mAb therapies may further accelerate this process in

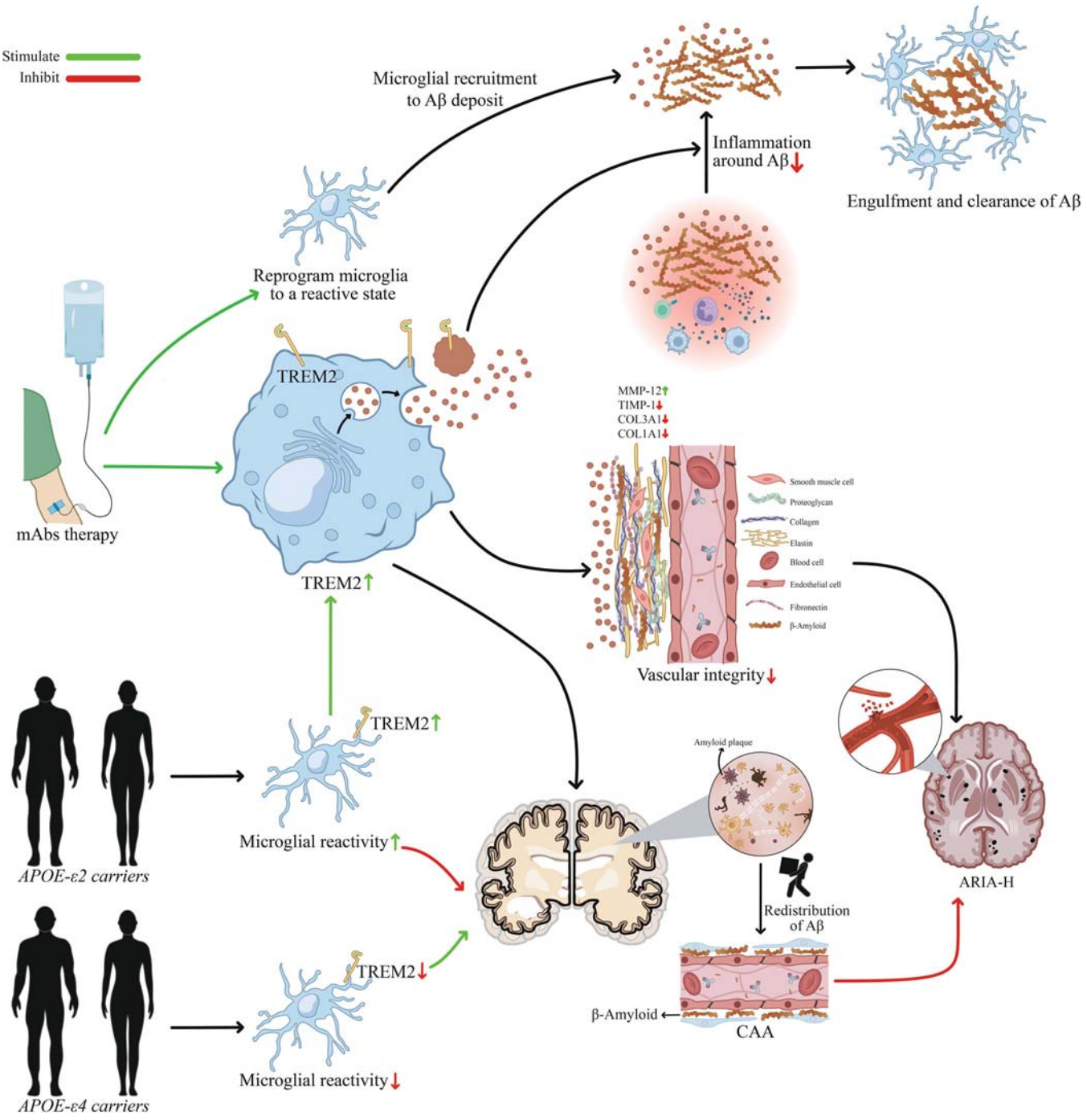



**FIGURE 3** | Mechanisms of ARIA-H induced by monoclonal antibodies. Increased microglial reactivity, driven by elevated TREM2 expression, exhibits allele-dependent effects, particularly in *APOE-ε4* and *APOE-ε2* carriers. In *APOE-ε4* allele carriers, increased *TREM2* expression leads to the redistribution of Aβ deposition from the brain parenchyma to blood vessels, enhancing vascular integrity. This reduces the occurrence of ARIA-H but increases the risk of ARIA-E. In contrast, *APOE-ε2* allele carriers exhibit the opposite effect. The heightened *TREM2* expression in *APOE-ε2* carriers, further amplified by mAb therapy, downregulates genes critical for vascular integrity, such as *COL1A1* and *COL3A1*, while disrupting matrix remodeling by increasing *MMP12* expression and decreasing *TIMP-1* expression, ultimately leading to microhemorrhage development. These vascular alterations contribute to ARIA-H progression. Additionally, increased *TREM2* expression reduces inflammation surrounding Aβ deposits, facilitating microglial recognition and recruitment to these sites. TREM2 activation further reprograms microglia into a reactive state, enhancing Aβ clearance.

early-stage AD, a condition that shares some pathological features with late-stage AD (Figure 2A).

Under AD conditions, TREM2 exhibits reduced activation in microglia [51]. Similarly, the loss of TREM2 in vascular regions results in nonreactive microglia that accumulate cholesterol, particularly ApoE, during the early stages of CAA [52]. The increase in TREM2 levels is linked with the occurrence of ARIA-H [37]. In *APOE-ε4* allele mice models, TREM2 levels are also reduced [53]. The reduction of TREM2 may explain the

lower prevalence of ARIA-H in *APOE-ε4* allele carriers, as the variant promotes the redistribution of Aβ from the brain parenchyma to the vasculature [49]. Conversely, another study showed that the absence of TREM2 in mouse models decreases CAA occurrence but increases Aβ accumulation in the brain while trapping microglia in a transitional state [50]. However, this study did not examine the differences between human *APOE-ε4* allele carriers and *APOE-ε4* allele carriers in mouse models. The contradictory findings may arise from these differences, as the mouse *APOE-ε4* allele carrier promotes Aβ deposition and CAA more effectively than the human *APOE-ε4* allele carrier [48, 54]. This disparity may be due to the approximately 70% similarity in amino acid sequences between the human and mouse *APOE-ε4* allele carrier.

A cohort study revealed that CAA without hemorrhage is more common in *APOE-ε4* allele carriers, while CAA with hemorrhage is more frequently observed in *APOE-ε2* allele carriers [55]. Additionally, a case study demonstrated that ARIA-H occurs more prominently in *APOE-ε2* allele carriers compared to *APOE-ε4* allele carriers. This was observed during lecanemab administration, which led to the development of ARIA-H in *APOE-ε2* allele carriers without progressing to intracranial hemorrhage (ICH) [56]. These findings suggest that the *APOE-ε2* allele carrier has a greater tendency to develop ARIA-H due to its unique characteristics. The *APOE-ε2* allele carrier is associated with enhanced engulfment of Aβ and a reduced ability to redistribute Aβ from the cerebral tissue to the vasculature (Figure 3) [47]. These factors collectively increase the likelihood of ARIA-H, particularly during monoclonal antibody therapy, offering insight into a possible mechanism by which mAbs induce ARIA, influenced by the differing characteristics of *APOE-ε4* and *APOE-ε2* allele carriers.

Reduced TREM2 levels might contribute to the progression of CAA while enhancing vascular integrity and reducing the risk of microhemorrhages. Microglial reactivity plays a key role in the differential occurrence of ARIA. Reduced microglial reactivity, driven by downregulated *TREM2*, is associated with ARIA-E, particularly in *APOE-ε4* allele carriers. This is supported by the contrasting microglial activity observed between *APOE-ε2* and *APOE-ε4* allele carrier, with the *APOE-ε2* allele carrier exhibiting higher activity compared to the lower activity seen in *APOE-ε4* allele carriers [57].

The high risk for *APOE-ε4* allele carriers to develop ARIA-E should be acknowledged, with symptoms including headache, cognitive dysfunction, and agitation, although more than half remain asymptomatic, and the condition can be recurrent with retreatment [58]. *APOE-ε2* allele carriers, on the other hand, are at higher risk for ARIA-H, but it is generally asymptomatic [56, 58]. Further research is needed to determine whether *APOE-ε4* and *APOE-ε2* allele carriers should receive differential treatment. It is also essential to monitor the risk of ARIA development, recognize its symptoms promptly, and establish appropriate criteria for initiating or discontinuing treatment. It is also important to be cautious of recurrent ARIA, particularly ARIA-E, and perform serial MRIs to detect ARIA, which may occur asymptomatically, especially early in treatment, as ARIA-H is often asymptomatic.

## 6 | Potential Occurrence of ARIA Based on Genetic Variants

The occurrence of ARIA-E and ARIA-H is potentially influenced not only by the *APOE-ε4* allele carrier but also by genetic variants that affect microglial reactivity, Aβ redistribution, and vascular integrity. Specifically, variants that influence apolipoprotein levels and TREM2 activity may play a role. Based on this evidence, we summarize the genetic variants that may either increase or decrease the occurrence of ARIA-E and ARIA-H (Table 1). However, further studies are needed to verify whether there are genetic variants, other than the *APOE-ε4* allele carrier, that have clinical significance in the occurrence of ARIA, especially regarding ARIA types.

Increased microglial reactivity, reduced Aβ redistribution from the brain to the vasculature, and impaired vascular integrity are associated with a higher occurrence of ARIA-H, while the opposite factors are linked to an increased occurrence of ARIA-E. Genetic variants that might increase the occurrence of ARIA-H include those associated with microglial reactivity, such as the *ABCA7* rs117187003 A allele, *ABI3* rs616338 T allele, *APOE-ε2* allele, *PLCG2* rs72824905 G allele, *TREM2* rs75932628 T allele, and *CD33* rs3865444 T allele; redistribution of Aβ from the brain to the vasculature, such as the *APOE-ε2* allele; and vascular integrity, such as the *APOE-ε2* allele, *APP* rs201729239 T allele, *LINC-PINT* rs10234094 C allele, and *MS4A4A* rs1582763 A allele. In contrast, other genetic variants listed in Table 1 are associated with an increased occurrence of ARIA-E.

The *CLU* variant shares similarities with the *APOE-ε4* allele carrier in its involvement in Aβ redistribution from the brain to the vasculature, potentially leading to CAA with reduced hemorrhage and inflammation in the absence of *CLU*. However, no direct association has been reported between *CLU* variants and CAA [65]. One study reported a higher occurrence of CAA in individuals with the *CLU* rs11136000 T allele [72]. This finding was further validated, showing that the variant increases *CLU* expression and exerts a protective role against AD [73]. The variant may promote the redistribution of Aβ from the brain to the vasculature, which could explain its protective role in AD while being associated with a higher occurrence of CAA. It may potentially increase the risk of ARIA-E while offering protection against ARIA-H, similar to what is observed in *APOE-ε4* allele carriers.

Genetic variants are influenced by ethnicity, although not all variants are exclusive to specific populations. The genetic profile can capture the majority of ethnicity-dependent variants and may be used for therapeutic grouping, potentially eliminating the need for individual genotyping or related tests. However, further research is needed to determine whether this genetic variant profile can be reliably used to assess ethnic influences, particularly in relation to other genetic variants that may impact mAb therapy and potentially induce ARIA, as we propose, which might influence mAb therapy. This approach is especially relevant for populations where mAbs are commonly used, such as Caucasians (*ABCA7* rs117187003 A allele [74], *TREM2* rs75932628 T allele [75], *APP* rs201729239 T allele [66], *LINC-PINT* rs10234094 C allele [69] and *UNC5C* rs28660566 T allele [71]), *APOE-ε2* [76] (Caucasian, African, and Hispanic), and *APOE-ε4* [76] (Asian, Caucasian, African, and Hispanic).

**TABLE 1** | Genetic variants associated with the pathophysiology of ARIA.

| Gene | SNPs | Allele | Phenotype | Reference |
|---|---|---|---|---|
| Microglial reactivity | | | | |
| *ABCA7* | rs117187003 | A | ↑ | [59] |
| *ABI3* | rs616338 | T | ↑ | [60] |
| *APOE-ε2* | rs429358 and rs7412 | ε2 | ↑ | [57] |
| *APOE-ε4* | rs429358 and rs7412 | ε4 | ↓ | [57] |
| *PLCG2* | rs61749044 | T | ↓ | [61] |
| *PLCG2* | rs72824905 | G | ↑ | [61] |
| *SORL1* | rs772677709 | G | ↓ | [62] |
| *TREM2* | rs75932628 | T | ↑ | [63] |
| *CD33* | rs3865444 | T | ↑ | [64] |
| Aβ redistribution | | | | |
| *APOE-ε2* | rs429358 and rs7412 | ε2 | ↓ | [47] |
| *APOE-ε4* | rs429358 and rs7412 | ε4 | ↑ | [47] |
| *CLU* | rs11136000 | T | ↑ | [65] |
| Vascular integrity | | | | |
| *APOE-ε2* | rs429358 and rs7412 | ε2 | ↓ | [49] |
| *APOE-ε4* | rs429358 and rs7412 | ε4 | ↑ | [49] |
| *APP* | rs201729239 | T | ↑ | [66] |
| *BIN1* | rs138047593 | C | ↓ | [67] |
| *CR1* | rs6656401 | A | ↑ | [68] |
| *LINC-PINT* | rs10234094 | C | ↓ | [69] |
| *MS4A4A* | rs1582763 | A | ↓ | [70] |
| *UNC5C* | rs28660566 | T | ↑ | [71] |

African and Caucasian populations exhibit genetic variants such as the *ABI3* rs616338 T allele and *PLCG2* rs72824905 G allele [77], while Asian and Caucasian populations have variants such as the *CD33* rs3865444 T allele [78], *CLU* rs11136000 T allele [79], and *CR1* rs6656401 A allele [80]. Hispanic and Caucasian populations show the BIN1 rs138047593 C allele [74]. Although the *PLCG2* rs61749044 T allele is found in Caucasians but lacks statistical significance for this ethnicity [61]. The genetic variant *SORL1* rs772677709 G allele is rare and has not been linked to a specific ethnicity [62]. Similarly, the *MS4A4A* rs1582763 A allele lacks ethnic specificity.

## 7 | Conclusion

The use of mAbs holds significant promise in the treatment of AD. However, their clinical application requires careful consideration, not only of the *APOE-ε4* allele carrier but also of other genetic variants that may influence treatment outcomes. Clinicians must also be cautious when diagnosing ARIA associated with mAb therapy, as distinguishing it from spontaneous ARIA presents a diagnostic challenge. Further research is needed to determine whether spontaneous ARIA is exclusively linked to ARIA-E or if it may also manifest as ARIA-H. Additionally, researchers should investigate the influence of TREM2 on the efficacy of mAbs, as TREM2 is closely associated with ARIA-H. In this review, we first introduce spontaneous ARIA, explore its association with mAbs, examine ARIA based on genetic profiles, and discuss how the *APOE-ε4* allele influences the occurrence of ARIA-E while potentially reducing the risk of ARIA-H.

### Author Contributions

Valentinus Besin and Farizky Martriano Humardani conceptualized the idea for the article. Fenny Lanawati Yudiarto, Paulus Anam Ong, and Ratih Asmana Ningrum conducted the literature search and performed the data analysis. Valentinus Besin and Farizky Martriano Humardani drafted the manuscript and prepared all the figures. Valentinus Besin, Sulistyo Emantoko Dwi Putra, Fenny Lanawati Yudiarto, Paulus Anam Ong, and Ratih Asmana Ningrum critically revised the work and editing. All authors read and approved the final manuscript.


### Acknowledgments

The authors have nothing to report.


### Ethics Statement

The authors have nothing to report.

### Conflicts of Interest

The authors declare no conflicts of interest.

## Data Availability Statement

The authors have nothing to report.

## References


1. M. Johannesson, L. Söderberg, O. Zachrisson, et al., "Lecanemab Demonstrates Highly Selective Binding to Aβ Protofibrils Isolated From Alzheimer's Disease Brains," *Molecular and Cellular Neuroscience* 130 (2024): 103949, https://doi.org/10.1016/j.mcn.2024.103949.

2. S. Syvänen, G. Hultqvist, T. Gustavsson, et al., "Efficient Clearance of Aβ Protofibrils in AβPP-Transgenic Mice Treated With a Brain-Penetrating Bifunctional Antibody," *Alzheimer's Research & Therapy* 10, no. 1 (2018): 49, https://doi.org/10.1186/s13195-018-0377-8.

3. V. Logovinsky, A. Satlin, R. Lai, et al., "Safety and Tolerability of BAN2401—A Clinical Study in Alzheimer's Disease With a Protofibril Selective A β Antibody," *Alzheimer's Research & Therapy* 8, no. 14 (2016): 1–10, https://doi.org/10.1186/s13195-016-0181-2.

4. T. Gustavsson, N. G. Metzendorf, E. Wik, et al., "Long - Term Effects of Immunotherapy With a Brain Penetrating Aβ Antibody in a Mouse Model of Alzheimer's Disease," *Alzheimer's Research & Therapy* 15 (2023): 90, https://doi.org/10.1186/s13195-023-01236-3.

5. D. Jeremic, J. D. Navarro-López, and L. Jiménez-Díaz, "Efficacy and Safety of Anti-Amyloid-β Monoclonal Antibodies in Current Alzheimer's Disease Phase III Clinical Trials: A Systematic Review and Interactive Web App-Based Meta-Analysis," *Ageing Research Reviews* 90 (2023): 102012, https://doi.org/10.1016/j.arr.2023.102012.

6. A. W. Gibson, H. Elser, M. Rosso, et al., "Ischemic Stroke Associated With Amyloid-Related Imaging Abnormalities in a Patient Treated With Lecanemab," *Alzheimer's & Dementia* 20, no. 11 (2024): 8192–8197, https://doi.org/10.1002/alz.14223.

7. L. Antolini, J. C. DiFrancesco, M. Zedde, et al., "Spontaneous Aria-Like Events in Cerebral Amyloid Angiopathy–Related Inflammation a Multicenter Prospective Longitudinal Cohort Study," *Neurology* 97, no. 18 (2021): E1809–E1822, https://doi.org/10.1212/WNL.0000000000012778.

8. S. J. Doran and R. P. Sawyer, "Risk Factors in Developing Amyloid Related Imaging Abnormalities (ARIA) and Clinical Implications," *Frontiers in Neuroscience* 18 (2024): 13266784, https://doi.org/10.3389/fnins.2024.1326784.

9. J. Barakos, R. Sperling, S. Salloway, et al., "MR Imaging Features of Amyloid-Related Imaging Abnormalities," *American Journal of Neuroradiology* 34, no. 10 (2013): 1958–1965, https://doi.org/10.3174/ajnr.A3500.

10. R. A. Sperling, C. R. Jack, S. E. Black, et al., "Amyloid-Related Imaging Abnormalities in Amyloid-Modifying Therapeutic Trials: Recommendations From the Alzheimer's Association Research Roundtable Workgroup," *Alzheimer's & Dementia* 7, no. 4 (2011): 367–385, https://doi.org/10.1016/j.jalz.2011.05.2351.

11. I. Terao and W. Kodama, "Comparative Efficacy, Tolerability and Acceptability of Donanemab, Lecanemab, Aducanumab and Lithium on Cognitive Function in Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Network Meta-Analysis," *Ageing Research Reviews* 94 (2024): 102203, https://doi.org/10.1016/j.arr.2024.102203.

12. L. S. Honig, M. N. Sabbagh, C. H. van Dyck, et al., "Updated Safety Results From Phase 3 Lecanemab Study in Early Alzheimer's Disease," *Alzheimer's Research and Therapy* 16, no. 1 (2024): 105, https://doi.org/10.1186/s13195-024-01441-8.

13. F. Piazza, S. P. Caminiti, M. Zedde, et al., "Association of Microglial Activation With Spontaneous ARIA-E and CSF Levels of Anti-Aβ Autoantibodies," *Neurology* 99, no. 12 (2022): E1265–E1277, https://doi.org/10.1212/WNL.0000000000200892.

14. F. Piazza, S. M. Greenberg, M. Savoiardo, et al., "Anti-Amyloid β Autoantibodies in Cerebral Amyloid Angiopathy-Related Inflammation: Implications for Amyloid-Modifying Therapies," *Annals of Neurology* 73, no. 4 (2013): 449–458, https://doi.org/10.1002/ana.23857.

15. N. S. Ryan, T. Lashley, T. Revesz, K. Dantu, N. C. Fox, and H. R. Morris, "Spontaneous ARIA (Amyloid-Related Imaging Abnormalities) and Cerebral Amyloid Angiopathy Related Inflammation in Presenilin 1-Associated Familial Alzheimer's Disease," *Journal of Alzheimer's Disease* 44, no. 4 (2015): 1069–1074, https://doi.org/10.3233/JAD-142325.

16. L. S. Honig, J. Barakos, S. Dhadda, et al., "ARIA in Patients Treated With Lecanemab (BAN2401) in a Phase 2 Study in Early Alzheimer's Disease," *Alzheimer's & Dementia (New York, N. Y.)* 9, no. 1 (2023): 12377, https://doi.org/10.1002/trc2.12377.

17. Z. Fan, D. J. Brooks, A. Okello, and P. Edison, "An Early and Late Peak in Microglial Activation in Alzheimer's Disease Trajectory," *Brain* 130, no. 3 (2017): 792–803, https://doi.org/10.1093/brain/aww349.

18. J. Appleton, Q. Finn, P. Zanotti-Fregonara, et al., "Brain Inflammation Co-Localizes Highly With Tau in Mild Cognitive Impairment Due to Early-Onset Alzheimer's Disease," *Brain* 148, no. 1 (2024): 119–132, https://doi.org/10.1093/brain/awae234.

19. S. Bogner, C. Bernreuther, J. Matschke, et al., "Immune Activation in Amyloid-β-Related Angiitis Correlates With Decreased Parenchymal Amyloid-β Plaque Load," *Neurodegenerative Diseases* 13, no. 1 (2013): 38–44, https://doi.org/10.1159/000352020.

20. A. Marcello, O. Wirths, T. Schneider-Axmann, M. Degerman-Gunnarsson, L. Lannfelt, and T. A. Bayer, "Circulating Immune Complexes of Aβ and IgM in Plasma of Patients With Alzheimer's Disease," *Journal of Neural Transmission* 116, no. 7 (2009): 913–920, https://doi.org/10.1007/s00702-009-0224-y.

21. L. M. De Plano, S. Carnazza, D. Franco, et al., "Innovative IgG Biomarkers Based on Phage Display Microbial Amyloid Mimotope for State and Stage Diagnosis in Alzheimer's Disease," *ACS Chemical Neuroscience* 11, no. 7 (2020): 1013–1026, https://doi.org/10.1021/acschemneuro.9b00549.

22. S. Söllvander, F. Ekholm-Pettersson, R. M. Brundin, et al., "Increased Number of Plasma B Cells Producing Autoantibodies Against Aβ 42 Protofibrils in Alzheimer's Disease," *Journal of Alzheimer's Disease* 48, no. 1 (2015): 63–72, https://doi.org/10.3233/JAD-150236.

23. T. Illouz, R. Nicola, L. Ben-Shushan, R. Madar, A. Biragyn, and E. Okun, "Maternal Antibodies Facilitate Amyloid-β Clearance by Activating FC-Receptor-Syk-Mediated Phagocytosis," *Communications Biology* 4, no. 1 (2021): 329, https://doi.org/10.1038/s42003-021-01851-6.

24. J. Krištić and G. Lauc, "The Importance of IgG Glycosylation—What Did We Learn After Analyzing Over 100,000 Individuals," *Immunological Reviews* 328, no. 1 (2024): 143–170, https://doi.org/10.1111/imr.13407.

25. Y. Kaneko, F. Nimmerjahn, and J. V. Ravetch, "Anti-Inflammatory Activity of Immunoglobulin G Resulting From Fc Sialylation," *Science* 313, no. 5787 (2006): 670–673, https://doi.org/10.1126/science.1129594.

26. Y. Kronimus, A. Albus, M. Hasenberg, et al., "Fc N-Glycosylation of Autoreactive Aβ Antibodies as a Blood-Based Biomarker for Alzheimer's Disease," *Alzheimer's & Dementia* 19, no. 12 (2023): 5563–5572, https://doi.org/10.1002/alz.13124.

27. L. Klarić, Y. A. Tsepilov, C. M. Stanton, et al., "Glycosylation of Immunoglobulin G Is Regulated by a Large Network of Genes Pleiotropic With Inflammatory Diseases," *Science Advances* 6, no. 8 (2020): eaax0301, https://doi.org/10.1126/sciadv.aax0301.

28. X. Zhang, H. Yuan, J. Lyu, et al., "Association of Dementia With Immunoglobulin G N-Glycans in a Chinese Han Population," *NPJ Aging and Mechanisms of Disease* 7, no. 1 (2021): 3, https://doi.org/10.1038/s41514-021-00055-w.

29. Y. Numaguchi, K. Tsukakoshi, N. Takeuchi, Y. Suzuki, K. Ikebukuro, and R. Kawano, "Real-Time Monitoring of the Amyloid

β1–42 Monomer-to-Oligomer Channel Transition Using a Lipid Bilayer System," *PNAS Nexus* 3, no. 1 (2024): pgad437, https://doi.org/10.1093/pnasnexus/pgad437.

30. Z. L. Chen, P. K. Singh, M. Calvano, E. H. Norris, and S. Strickland, "A Possible Mechanism for the Enhanced Toxicity of Beta-Amyloid Protofibrils in Alzheimer's Disease," *Proceedings of the National Academy of Sciences of the United States of America* 120, no. 36 (2023): e2309389120, https://doi.org/10.1073/pnas.2309389120.

31. S. Söllvander, E. Nikitidou, R. Brolin, et al., "Accumulation of Amyloid-β by Astrocytes Result in Enlarged Endosomes and Microvesicle-Induced Apoptosis of Neurons," *Molecular Neurodegeneration* 11, no. 1 (2016): 38, https://doi.org/10.1186/s13024-016-0098-z.

32. E. Nikitidou, P. E. Khoonsari, G. Shevchenko, M. Ingelsson, K. Kultima, and A. Erlandsson, "Increased Release of Apolipoprotein E in Extracellular Vesicles Following Amyloid-β Protofibril Exposure of Neuroglial Co-Cultures," *Journal of Alzheimer's Disease* 60, no. 1 (2017): 305–321, https://doi.org/10.3233/JAD-170278.

33. C. Beretta, E. Nikitidou, L. Streubel-Gallasch, M. Ingelsson, D. Sehlin, and A. Erlandsson, "Extracellular Vesicles From Amyloid-β Exposed Cell Cultures Induce Severe Dysfunction in Cortical Neurons," *Scientific Reports* 10, no. 1 (2020): 19656, https://doi.org/10.1038/s41598-020-72355-2.

34. J. W. Arndt, F. Qian, B. A. Smith, et al., "Structural and Kinetic Basis for the Selectivity of Aducanumab for Aggregated Forms of Amyloid-B," *Scientific Reports* 8, no. 1 (2018): 6412, https://doi.org/10.1038/s41598-018-24501-0.

35. R. B. DeMattos, J. Lu, Y. Tang, et al., "A Plaque-Specific Antibody Clears Existing β-Amyloid Plaques in Alzheimer's Disease Mice," *Neuron* 76, no. 5 (2012): 908–920, https://doi.org/10.1016/j.neuron.2012.10.029.

36. S. Söllvander, E. Nikitidou, L. Gallasch, et al., "The Aβ Protofibril Selective Antibody mAb158 Prevents Accumulation of Aβ in Astrocytes and Rescues Neurons From Aβ-Induced Cell Death," *Journal of Neuroinflammation* 15, no. 1 (2018): 98, https://doi.org/10.1186/s12974-018-1134-4.

37. X. Taylor, H. N. Noristani, G. J. Fitzgerald, et al., "Amyloid-β (Aβ) Immunotherapy Induced Microhemorrhages Are Linked to Vascular Inflammation and Cerebrovascular Damage in a Mouse Model of Alzheimer's Disease," *Molecular Neurodegeneration* 19, no. 78 (2024): 77, https://doi.org/10.1186/s13024-024-00758-0.

38. L. Söderberg, M. Johannesson, E. Gkanatsiou, et al., "Amyloid-Beta Antibody Binding to Cerebral Amyloid Angiopathy Fibrils and Risk for Amyloid-Related Imaging Abnormalities," *Scientific Reports* 14, no. 1 (2024): 10868, https://doi.org/10.1038/s41598-024-61691-2.

39. H. Long, A. Simmons, A. Mayorga, et al., "Preclinical and First-in-Human Evaluation of AL002, a Novel TREM2 Agonistic Antibody for Alzheimer's Disease," *Alzheimer's Research and Therapy* 16, no. 1 (2024): 235, https://doi.org/10.1186/s13195-024-01599-1.

40. S. Wang, M. Mustafa, C. M. Yuede, et al., "Anti-Human TREM2 Induces Microglia Proliferation and Reduces Pathology in an Alzheimer's Disease Model," *Journal of Experimental Medicine* 217, no. 9 (2020): e20200785, https://doi.org/10.1084/jem.20200785.

41. S. Huang, X. Liao, J. Wu, et al., "The Microglial Membrane Receptor TREM2 Mediates Exosome Secretion to Promote Phagocytosis of Amyloid-β by Microglia," *FEBS Letters* 596 (2022): 1059–1071, https://doi.org/10.1002/1873-3468.14336.

42. C. Y. D. Lee, A. Daggett, X. Gu, et al., "Elevated TREM2 Gene Dosage Reprograms Microglia Responsivity and Ameliorates Pathological Phenotypes in Alzheimer's Disease Models," *Neuron* 97, no. 5 (2018): 1032–1048.e5, https://doi.org/10.1016/j.neuron.2018.02.002.

43. D. Gu, L. Wang, N. Zhang, H. Wang, and X. Yu, "Decrease in Naturally Occurring Antibodies Against Epitopes of Alzheimer's Disease (AD) Risk Gene Products Is Associated With Cognitive Decline in AD," *Journal of Neuroinflammation* 20, no. 1 (2023): 74, https://doi.org/10.1186/s12974-023-02750-9.

44. T. Hendrikx, F. Porsch, M. G. Kiss, et al., "Soluble TREM2 Levels Reflect the Recruitment and Expansion of TREM2+ Macrophages That Localize to Fibrotic Areas and Limit NASH," *Journal of Hepatology* 77, no. 5 (2022): 1373–1385, https://doi.org/10.1016/j.jhep.2022.06.004.

45. S. Salloway, J. Wojtowicz, N. Voyle, et al., "Amyloid-Related Imaging Abnormalities (ARIA) in Clinical Trials of Gantenerumab in Early Alzheimer Disease," *JAMA Neurology* 82, no. 1 (2025): 19–29, https://doi.org/10.1001/jamaneurol.2024.3937.

46. M. S. Rafii, "Appropriate Use Recommendations for Lecanemab," *Journal of Prevention of Alzheimer's Disease* 10, no. 3 (2023): 356, https://doi.org/10.14283/jpad.2023.34.

47. Z. Xia, E. E. Prescott, A. Urbanek, et al., "Co-Aggregation With Apolipoprotein E Modulates the Function of Amyloid-β in Alzheimer's Disease," *Nature Communications* 15, no. 1 (2024): 4695, https://doi.org/10.1038/s41467-024-49028-z.

48. J. D. Fryer, K. Simmons, M. Parsadanian, et al., "Human Apolipoprotein E4 Alters the Amyloid-β 40:42 Ratio and Promotes the Formation of Cerebral Amyloid Angiopathy in an Amyloid Precursor Protein Transgenic Model," *Journal of Neuroscience* 25, no. 11 (2005): 2803–2810, https://doi.org/10.1523/JNEUROSCI.5170-04.2005.

49. M. Xiong, C. Wang, M. Gratuze, et al., "Astrocytic APOE4 Removal Confers Cerebrovascular Protection Despite Increased Cerebral Amyloid Angiopathy," *Molecular Neurodegeneration* 18, no. 1 (2023): 17, https://doi.org/10.1186/s13024-023-00610-x.

50. R. Zhong, Y. Xu, J. W. Williams, and L. Li, "Loss of TREM2 Diminishes CAA Despite an Overall Increase of Amyloid Load in Tg-Swdi Mice," *Alzheimer's & Dementia* 20, no. 11 (2024): 7595–7612, https://doi.org/10.1002/alz.14222.

51. Y. Okuzono, H. Sakuma, S. Miyakawa, et al., "Reduced TREM2 Activation in Microglia of Patients With Alzheimer's Disease," *FEBS Open Bio* 11, no. 11 (2021): 3063–3080, https://doi.org/10.1002/2211-5463.13300.

52. X. Taylor, P. Cisternas, Y. You, et al., "A1 Reactive Astrocytes and a Loss of TREM2 Are Associated With an Early Stage of Pathology in a Mouse Model of Cerebral Amyloid Angiopathy," *Journal of Neuroinflammation* 17, no. 1 (2020): 223, https://doi.org/10.1186/s12974-020-01900-7.

53. J. C. Park, J. W. Han, W. Lee, et al., "Microglia Gravitate Toward Amyloid Plaques Surrounded by Externalized Phosphatidylserine via TREM2," *Advanced Science* 11, no. 34 (2024): 2400064, https://doi.org/10.1002/advs.202400064.

54. F. Liao, T. J. Zhang, H. Jiang, et al., "Murine Versus Human Apolipoprotein E4: Differential Facilitation of and Co-Localization in Cerebral Amyloid Angiopathy and Amyloid Plaques in APP Transgenic Mouse Models," *Acta Neuropathologica Communications* 3, no. 1 (2015): 70, https://doi.org/10.1186/s40478-015-0250-y.

55. A. Charidimou, S. Martinez-Ramirez, A. Shoamanesh, et al., "Cerebral Amyloid Angiopathy With and Without Hemorrhage: Evidence for Different Disease Phenotypes," *Neurology* 84, no. 12 (2015): 1206–1212, https://doi.org/10.1212/WNL.0000000000001398.

56. S. Ji and M. Rosenbloom, "Intracerebral Hemorrhage Following Mild ARIA-H in an APOE ε2 Carrier Receiving Lecanemab," *Alzheimer's Research & Therapy* 16, no. 265 (2024): 265, https://doi.org/10.1186/s13195-024-01640-3.

57. N. Wang, M. Wang, S. Jeevaratnam, et al., "Opposing Effects of ApoE2 and ApoE4 on Microglial Activation and Lipid Metabolism in Response to Demyelination," *Molecular Neurodegeneration* 17, no. 1 (2022): 75, https://doi.org/10.1186/s13024-022-00577-1.

58. M. Filippi, G. Cecchetti, E. G. Spinelli, P. Vezzulli, A. Falini, and F. Agosta, "Amyloid-Related Imaging Abnormalities and β-Amyloid-

Targeting Antibodies: A Systematic Review," *JAMA Neurology* 79, no. 3 (2022): 291–304, https://doi.org/10.1001/jamaneurol.2021.5205.

59. C. A. Butler, A. Mendoza Arvilla, G. Milinkeviciute, et al., "The Abca7V1613M Variant Reduces Aβ Generation, Plaque Load, and Neuronal Damage," *Alzheimer's & Dementia* 20, no. 7 (2024): 4914–4934, https://doi.org/10.1002/alz.13783.

60. K. R. Ibanez, K. N. McFarland, J. Phillips, et al., "Deletion of Abi3/Gngt2 Influences Age-Progressive Amyloid β and Tau Pathologies in Distinctive Ways," *Alzheimer's Research & Therapy* 14, no. 1 (2022): 104, https://doi.org/10.1186/s13195-022-01044-1.

61. A. P. Tsai, C. Dong, P. B. C. Lin, et al., "Genetic Variants of Phospholipase C-γ2 Alter the Phenotype and Function of Microglia and Confer Differential Risk for Alzheimer's Disease," *Immunity* 56, no. 9 (2023): 2121–2136.e6, https://doi.org/10.1016/j.immuni.2023.08.008.

62. A. M. G. Jensen, J. Raska, P. Fojtik, et al., "The *SORL1* p.Y1816C Variant Causes Impaired Endosomal Dimerization and Autosomal Dominant Alzheimer's Disease," *Proceedings of the National Academy of Sciences of the United States of America* 121, no. 37 (2024): e2408262121, https://doi.org/10.1073/pnas.2408262121.

63. W. Liu, O. Taso, R. Wang, et al., "Trem2 Promotes Anti-Inflammatory Responses in Microglia and Is Suppressed Under Pro-Inflammatory Conditions," *Human Molecular Genetics* 29, no. 19 (2020): 3224–3248, https://doi.org/10.1093/hmg/ddaa209.

64. A. Griciuc, A. Serrano-Pozo, A. R. Parrado, et al., "Alzheimer's Disease Risk Gene cd33 Inhibits Microglial Uptake of Amyloid Beta," *Neuron* 78, no. 4 (2013): 631–643, https://doi.org/10.1016/j.neuron.2013.04.014.

65. A. M. Wojtas, S. S. Kang, B. M. Olley, et al., "Loss of Clusterin Shifts Amyloid Deposition to the Cerebrovasculature via Disruption of Perivascular Drainage Pathways," *Proceedings of the National Academy of Sciences of the United States of America* 114, no. 33 (2017): E6962–E6971, https://doi.org/10.1073/pnas.1701137114.

66. G. Nicolas, D. Wallon, C. Goupil, et al., "Mutation in the 3′ Untranslated Region of APP as a Genetic Determinant of Cerebral Amyloid Angiopathy," *European Journal of Human Genetics* 24 (2016): 92–98, https://doi.org/10.1038/ejhg.2015.61.

67. L. F. Garcia-Agudo, Z. Shi, I. F. Smith, et al., "BIN1K358R Suppresses Glial Response to Plaques in Mouse Model of Alzheimer's Disease," *Alzheimer's & Dementia* 20, no. 4 (2024): 2922–2942, https://doi.org/10.1002/alz.13767.

68. A. Biffi, J. M. Shulman, J. M. Jagiella, et al., "Genetic Variation at CR1 Increases Risk of Cerebral Amyloid Angiopathy," *Neurology* 78, no. 5 (2012): 334–341, https://doi.org/10.1212/WNL.0b013e3182452b40.

69. J. S. Reddy, M. Allen, C. C. G. Ho, et al., "Genome-Wide Analysis Identifies a Novel LINC-PINT Splice Variant Associated With Vascular Amyloid Pathology in Alzheimer's Disease," *Acta Neuropathologica Communications* 9, no. 1 (2021): 93, https://doi.org/10.1186/s40478-021-01199-2.

70. R. L. Winfree, E. Nolan, L. Dumitrescu, et al., "Variants in the MS4A Cluster Interact With Soluble TREM2 Expression on Biomarkers of Neuropathology," *Molecular Neurodegeneration* 19, no. 1 (2024): 41, https://doi.org/10.1186/s13024-024-00727-7.

71. H. S. Yang, C. C. White, L. B. Chibnik, et al., "UNC5C variants Are Associated With Cerebral Amyloid Angiopathy," *Neurology: Genetics* 3, no. 4 (2017): e176, https://doi.org/10.1212/NXG.0000000000000176.

72. A. Montañola, S. F. de Retana, A. López-Rueda, et al., "ApoA1, ApoJ and ApoE Plasma Levels and Genotype Frequencies in Cerebral Amyloid Angiopathy," *NeuroMolecular Medicine* 18 (2016): 99–108, https://doi.org/10.1007/s12017-015-8381-7.

73. I. F. Ling, J. Bhongsatiern, J. F. Simpson, D. W. Fardo, and S. Estus, "Genetics of Clusterin Isoform Expression and Alzheimer's Disease Risk," *PLoS One* 7, no. 4 (2012): e33923, https://doi.org/10.1371/journal.pone.0033923.

74. B. N. Vardarajan, M. Ghani, A. Kahn, et al., "Rare Coding Mutations Identified by Sequencing of Alzheimer Disease Genome-Wide Association Studies Loci," *Annals of Neurology* 78, no. 3 (2015): 487–498, https://doi.org/10.1002/ana.24466.

75. M. C. Dalmasso, L. I. Brusco, N. Olivar, et al., "Transethnic Meta-Analysis of Rare Coding Variants in PLCG2, ABI3, and TREM2 Supports Their General Contribution to Alzheimer's Disease," *Translational Psychiatry* 9, no. 1 (2019): 55, https://doi.org/10.1038/s41398-019-0394-9.

76. M. E. Belloy, S. J. Andrews, Y. Le Guen, et al., "APOE Genotype and Alzheimer Disease Risk Across Age, Sex, and Population Ancestry," *JAMA Neurology* 80, no. 12 (2023): 1284–1294, https://doi.org/10.1001/jamaneurol.2023.3599.

77. O. J. Conway, M. M. Carrasquillo, X. Wang, et al., "ABI3 and PLCG2 Missense Variants as Risk Factors for Neurodegenerative Diseases in Caucasians and African Americans," *Molecular Neurodegeneration* 13, no. 1 (2018): 53, https://doi.org/10.1186/s13024-018-0289-x.

78. X. Li, N. Shen, S. Zhang, et al., "CD33 rs3865444 Polymorphism Contributes to Alzheimer's Disease Susceptibility in Chinese, European, and North American Populations," *Molecular Neurobiology* 52, no. 1 (2015): 414–421, https://doi.org/10.1007/s12035-014-8880-9.

79. W. Du, J. Tan, W. Xu, J. Chen, and L. Wang, "Association Between Clusterin Gene Polymorphism rs11136000 and Late–Onset Alzheimer's Disease Susceptibility: A Review and Meta–Analysis of Case–Control Studies," *Experimental and Therapeutic Medicine* 12, no. 5 (2016): 2915–2927, https://doi.org/10.3892/etm.2016.3734.

80. J. Luo, S. Li, X. Qin, et al., "Meta-Analysis of the Association Between CR1 Polymorphisms and Risk of Late-Onset Alzheimer's Disease," *Neuroscience Letters* 578 (2014): 165–170, https://doi.org/10.1016/j.neulet.2014.06.055.

Volume 11 Issue 1 March 2025

ISSN 2095 - 882X
CN 10 - 1249/R

# Chronic Diseases® and Translational Medicine

慢性疾病与转化医学（英文）

Open Access

CITESCORE 6.7

ISSN 2095-882X

WILEY

PTIJ
Project for Enhancing International Impact of China STM Journals

Chronic Diseases® and Translational Medicine

## Editorial Board

### Editor-in-Chief

**Jun Wang**, M.D., Ph.D., *Peking University People's Hospital, Beijing, China*

Professor Jun Wang, Academician of Chinese Academy of Engineering, President of Peking University People's Hospital, Beijing, China. Professor Jun Wang is the chief of Department of Thoracic Surgery, Peking University People's Hospital and Chief of Minimal Invasive Thoracic Center, Peking University People's Hospital. He is also the president of Lung Cancer Committee of China Anti-Cancer Association, the Chair of Thoracic Committee of Chinese Research Hospital Association. He has published over 400 articles on peer reviewed journals, e.g. Am J Respir Crit Care Med, Sci Adv, J Thorac Oncol, Eur Respir J, Autophagy and Clin Cancer Res. As the founder of video-assisted thoracic surgery and minimally invasive thoracic surgery in China, his research interests include surgical treatment and molecular mechanism of lung cancer esophageal cancer and mediastinal tumor.

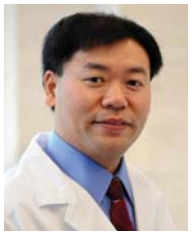
### Honorary Editor-in-Chief

**Dayi Hu**, Professor, *Peking University People's Hospital, Beijing, China*

Professor Dayi Hu is a national and Beijing municipal expert with outstanding contributions and an academician of the International Eurasian Academy of Sciences. His current roles include being the chairman of the Chinese Association on Tobacco Control, chairman of the Cardiovascular Disease Prevention and Rehabilitation Committee of the Chinese Association of Rehabilitation Medicine, and director of the Institute of Cardiovascular Diseases, Peking University People's Hospital. Prof. Hu was the first person in China to successfully cure tachyarrhythmia with radiofrequency ablation, and he he made great contributions to the treatment of acute myocardial infarction. He also launched a "Chest Pain Center" and has been actively promoting the integration of evidence-based medicine and clinical practice. With a focus on clinical epidemiological research, Prof. Hu organized the largest epidemiological cohort study on atrial fibrillation in China. Prof. Hu has published more than 500 articles in domestic and international scholarly journals and edited over 60 books. He has also won 6 Second Prizes of the State Science and Technology Progress Award.

## Cardiovascular and Cerebrovascular Section

### Associate Editors-in-Chief



**Yuxin Fan**, M.D., Ph.D., FACMG, *Texas Children's Hospital, Baylor College of Medicine, Houston, United States*

Dr. Yuxin Fan is Medical Director of John Welsh Cardiovascular Diagnostic Laboratory, Assistant Professor of Pathology & Immunology and Pediatrics, Baylor College of Medicine. His clinical interests mainly involve in the development and implantation of molecular genetic diagnosis of inherited human diseases, especially cardiovascular disorders using Sanger sequencing, next generation sequencing (NGS) and array-based comparative genomic hybridization (aCGH). I am also interested in developing viral testing for the molecular diagnosis of myocarditis and for the molecular monitoring of heart transplant rejection. His research interests have been focused on cardiovascular genetics, especially on the genetic screening for new genes related to cardiovascular disease and on the understating of mechanisms behind inherited cardiomyopathy using cellular and knock-in/out animal models.

**Dongfeng Gu**, M.D., Ph.D., *Southern University of Science and Technology, Shenzhen, China*

Dongfeng Gu is Academician of Chinese Academy of Sciences, Acting Vice President and Chair Professor of Southern University of Science and Technology (SUSTech) . Formerly as the Deputy Director of National Center for Cardiovascular Diseases, and the Vice President of Fuwai Hospital, Chinese Academy of Medical Sciences, he currently serves as the Vice President for both Chinese Preventive Medicine Association and China International Exchange and Promotive Association for Medical and Health Care. He is an expert for the World Health Organization prevention and control of cardiovascular and chronic diseases, a member of the expert consultation panel of Healthy China initiative, a committee member of Medical Science Department of Academic Advisory Committee of Chinese Academy of Medical Sciences, and the Deputy Director of Pharmaceutical Sciences, Health and Environment, Biomedical Engineering and Information Science Department of Academic Advisory Committee of Chinese Academy of Medical Sciences. Dr. Gu has been long devoted to and specialized in preventive cardiology, epidemiology, and medical genetics.

**Editorial Board**

**Li Su**, Ph.D., *University of Cambridge, Cambridge, United Kingdom*

**Xiao Tan**, Ph.D., *Uppsala University, Uppsala, Sweden*

**Kai Hu**, M.D., *University of Würzburg, Würzburg, Germany*

**Rongchong Huang**, M.D., Ph.D., *Beijing Friendship Hospital, Captial Medical University, Beijing, China*

**Gianfranco Parati**, M.D., *University of Milan-Bicocca and San Luca Hospital, Milan, Italy*

**Xiantao Song**, M.D., Ph.D., *Beijing Anzhen Hospital, Capital Medical University, Beijing, China*

**Hao Xue**, M.D., Ph.D., *General Hospital of the People's Liberation Army, Beijing, China*

**Guoping Peng**, M.D., Ph.D., *The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

**Fred C Lam**, M.D., Ph.D., FRCSC, *McMaster University Faculty of Health Sciences, Hamilton, Canada*

## Cancer Section

**Associate Editors-in-Chief**



### Why publish in Chronic Diseases and Translational Medicine?

- **Your research will be free to access**, making it available to read, download and share with ease.
- Publish open access at **no cost to you** - fees are waived for a limited period.
- **Your work will be discoverable and widely distributed** with indexing by PubMed Central, Scopus, Directory of Open Access Journals and Embase.
- Quality and impactful research governed by an international and distinguished editorial board.
- **Save time formatting** your manuscript with **Free Formatting submission.**
- An official journal of the Chinese Medical Association.

Posts by cdtm4

**Nianzeng Xing**, M.D., Ph.D., *Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China*

Professor Nianzeng Xing is the head of the Urology Department, Cancer Hospital of the Chinese Academy of Medical Sciences, National Cancer Center; he is also a member of the CPPCC National Committee. He has a doctorate from the Beijing Medical University and a postdoctoral degree from the Mayo Medical Center in the United States. Prof. Xing is both a national candidate of the "Baiqianwan Talent Program" and at national level one of the "Young and Middle-aged Experts with Outstanding Contributions". He currently serves multiple important academic positions, including being the vice president and director-general of the Urology Branch of the Chinese Medical Doctor Association, a member of the Urology Branch of the Chinese Medical Association, etc.

Having worked at the front line of clinical practice for a long time, Prof. Xing is famous for his rich clinical experience and outstanding surgical skills. He is good at the diagnosis and treatment of urinary tract tumors and is especially experienced in minimally invasive urinary surgery and comprehensive treatment. Prof. Xing has not only held consultations for surgeries at nearly 100 local hospitals but he has also performed dozens of surgical demonstrations in academic conferences at home and abroad. His other achievements include undertaking several important national and Beijing municipal projects. Prof. Xing has published nearly 300 professional papers in renowned domestic and international journals, of which more than 70 have been included in SCI. He has also won multiple science and technology progress awards.

**Jiafu Ji**, M.D., Ph.D., *Beijing Cancer Hospital, Beijing, China*

Professor Jiafu Ji has been engaged in clinical practice and scientific research on gastric cancer surgery for 36 years. He is not only the founder and promoter of the standardization of gastric cancer surgery and perioperative treatment in China but also the first Chinese expert to serve as the chairman of the International Gastric Cancer Association (IGCA). Prof. Ji's current roles include being the director of the Beijing Cancer Hospital (Peking University School of Clinical Oncology), director of the Beijing Institute for Cancer Research, director of the Key Laboratory of Malignant Tumor Pathogenesis and Translation of the Ministry of Education, and director of the Peking University Cancer Research Center. Prof. Ji's titles include professor, chief physician, doctoral supervisor, and expert who receives the state council special allowance. Prof. Ji also serves as the vice chairman of the Chinese Anti-Cancer Association, chairman of the Hospital Management Branch of the Chinese Anti-Cancer Association, vice chairman of the China International Exchange and Promotive Association for Medical and Health Care, standing director of the Chinese Medical Association, member of the Standing Committee and secretary-general of the Branch of Surgery of the Chinese Medical Association, as well as chairman of the Oncology Surgeon Committee of the Chinese Medical Doctor Association. In addition, Prof. Ji also serves as a member of the American College of Surgeons (FACS) and the Standing Committee of the Asian Surgical Association (ASA), and he is a Fellow of the Royal Colleges of Surgeons (FRCS).

**Lei Zheng**, M.D., Ph.D., *John Hopkins University School of Medicine, Baltimore, United States*

Dr. Lei Zheng is an oncologist in Baltimore, caring for patients with conditions such as pancreatic cancer and gastrointestinal cancers. Regarded as one of the world's top clinical specialists in pancreatic cancer, Dr. Zheng receives referrals from around the world. He is an internationally recognized expert in the tumor microenvironment of pancreatic cancer and in mouse models of pancreatic cancer and preclinical studies of combinational immunotherapies. Dr. Zheng serves as co-director of the Pancreatic Cancer Precision Medicine Center of Excellence Program at the Johns Hopkins School of Medicine.

**Editorial Board**



## Respiratory Section

**Associate Editors-in-Chief**

**Joe Y. Chang**, M.D., Ph.D., FASTRO, *The University of Texas MD Anderson Cancer Center, Houston, United States*

Joe Y. Chang (MD, PhD, FASTRO) is a tenured Professor, Director of Stereotactic Ablative Radiotherapy (SABR), MD Anderson Cancer Center. He is the Fellow of American Society of Radiation Oncology and received the award of "The Best Doctors in America". He is the current chair for American Radium Society/American College of Radiology (ACR) Thoracic Appropriateness Use Criteria Committee, chair of thoracic subcommittee of international Particle Therapy Co-Operative Group (PTCOG), NCCN Thoracic Guidelines Voting Committee Member; He served as a Section Chief of MD Anderson Thoracic Radiation Oncology, senior associate editor for International Journal of Radiation Oncology Biology Physics (Red Journal) and is an editorial board members for several international medical journals. He was the president and Chair of Board of Sino-American Network of Therapeutic Radiology and Oncology (SANTRO). He is an international renowned expert in radiotherapy and one of the pioneers in the field of proton therapy, stereotactic radiotherapy and immunotherapy in lung cancer. He is PI or Co-PI for many institutional, national and international clinical trials in lung cancer. He published more than 250 peer-reviewed SCI articles in the top oncology journals including Lancet Oncology, Nature Review Clinical Oncology, JAMA Oncology, JCO, JAMA Surgery, JAMA Network Open, Clinical Cancer Research, Cancer, Journal of Thoracic Oncology, Intentional Journal of Radiation Oncology Biology Physics and etc. He edited 5 books and published 24 book chapters related to image-guided radiation therapy, stereotactic ablative radiation therapy, intensity-modulated radiotherapy, proton therapy and combined immunotherapy with radiotherapy.

**Editorial Board**

**Yin Chen**, Ph.D., *University of Arizona, Tucson, United States*

**Qutayba Hamid**, M.D., Ph.D., *McGill University, Montreal, Canada*

**Bo Hang**, M.D., Ph.D., *Lawrence Berkeley National Laboratory, Berkeley, United States*

**Gang Liu**, M.D., Ph.D., *University of Alabama at Birmingham, Birmingham, United States*

**Xiangde Liu**, M.D., Ph.D., *University of Nebraska Medical Center, Omaha, United States*

**Yongzheng Wu**, M.D., Ph.D., *Institut Pasteur, Paris, France*

**Ting Yang**, M.D., Ph.D., *China-Japan Friendship Hospital, Beijing, China*

**Shugeng Gao**, M.D., Ph.D., *Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China*

**Dianhua Jiang**, M.D., Ph.D., *Cedars Sinai Medical Center, Los Angeles, United States*

**Chun Chang**, M.D., Ph.D., *Peking University Third Hospital, Beijing, China*

**Mengshu Cao**, M.D., Ph.D., *Nanjing Drum Tower Hospital, Nanjing, China*

**Lei Gao**, M.D., Ph.D., *Institute of Medical Biology, Chinese Academy of Medical Sciences, Beijing, China*

**Chaosheng Deng**, M.D., Ph.D., *Fujian Medical University, Fuzhou, China*

## Endocrine Section

**Associate Editors-in-Chief**

## Gastroenterology Section

### Associate Editors-in-Chief



Professor Shutian Zhang is the director of the Beijing Friendship Hospital, Capital Medical University, secretary-general of the National Collaborative Research and Innovation Alliance of Clinical Medicine, director of the National Clinical Research Center for Digestive Diseases, chairman of the Digestive Endoscopy Branch of the Chinese Medical Association, chairman of the Digestive Physician Branch of the Chinese Medical Association, and member of the Scientific Committee of the World Endoscopy Organization (WEO). His focus in clinical practice is on diagnosis and treatment using digestive endoscopy (minimally invasive), including endoscopic resection of early cancer, stent placement for advanced cancer, ligation and sclerotherapy for bleeding in liver cirrhosis, endoscopic hemostasis for bleeding ulcers, endoscopic removal of gallstones, and endoscopic treatment of pancreatitis. His focus in scientific research is the molecular mechanisms, intervention measures, and early diagnosis and treatment of precancerous diseases of the digestive system. Prof. Zhang has so far published more than 130 papers in international and domestic academic conferences and journals.



Professor Zhenning Wang is a standing member of the Party Committee and vice president of the China Medical University, as well as director, level-II professor, and doctoral supervisor of the Department of Gastrointestinal Cancer Surgery, First Affiliated Hospital of China Medical University. He is an expert with outstanding contributions to the National Health and Family Planning Commission, and a science and technology leader of the Innovative Talent Promotion Plan of the Ministry of Science and Technology. He also receives special government allowances from the State Council. Prof. Wang has hosted a special project of precision medicine of the National Major Science and Technology R&D Projects, a special research project of the 973 Program, 5 projects of the National Natural Science Foundation, a project of the Program for New Century Excellent Talents in University of Ministry of Education, and 21 other provincial and ministerial projects. His publications include 217 SCI papers, 131 of which he is either the first author or the corresponding author. Prof. Wang has also won 1 Second Prize of the State Science and Technology Progress Award, as well as 3 First Prizes, 4 Second Prizes, and 3 Third Prizes of the Provincial and Ministerial Science and Technology Progress Award.

### Editorial Board

## Nephrology Section

**Associate Editors-in-Chief**

**Editorial Board**

**Qi Cao**, Ph.D., *Westmead Institute for Medical Research, The University of Sydney, Sydney, Australia*

**Lihua Dong**, Ph.D., *University Hospital of Copenhagen Rigshospitalet, Copenhagen, Denmark*

**Ji Li**, Ph.D., *University of South Florida, Tampa Bay, United States*

**Song Rong**, M.D., *Hannover Medical School, Hannover, Germany*

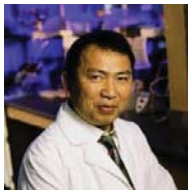
**Jian Yao**, M.D., Ph.D., *University of Yamanashi, Yamanashi, Japan*

**Hong Jiang**, M.D., Ph.D., *The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

**Wei Chen**, M.D., Ph.D., *The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China*

## Basic Medical Science and Life Science Section

**Associate Editor-in-Chief**



**Minghui Zou**, M.D., Ph.D., *Georgia State University, Center for Molecular and Translational Medicine, Atlanta, United States*

Ming-Hui Zou, M.D. Ph.D. is the eminent scholar in Georgia Research Alliance in Georgia, USA. Dr. Zou is the founding director, the Center of Molecular and Translational Medicine, and the Associate Vice President for Research, Georgia State University. Before he joined the Georgia State University, Dr. Zou was the George Lynn Cross Professor, Warren Endowed Chair in Diabetes Research, and Travis endowed Chair in Endocrinology in the University of Oklahoma Health Science Center, the Chief of Section of Molecular Medicine, and Vice Chair for Research in the Department of Medicine from 2005-2015. Dr. Zou has been instrumental in examining the role of nitric oxide and oxidative stress in the regulation of blood flow and vascular function. He performed elegant, state of the art, studies to show that the selective modification of two key proteins, prostacyclin synthase and endothelial nitric oxide synthase, is critical in the dysregulation of vessel function from nitric oxide and superoxide.

**Editorial Board**

**Igor Buzaev**, M.D., Ph.D., *GBUZ Republic Heart Centre, Ufa, Russia*

**Yong Du**, Ph.D., *The Royal Marsden Hospital/GenesisCare, London, United Kingdom*

**Zigang Ge**, M.D., Ph.D., *Peking University, Beijing, China*

**Qiushui He**, M.D., Ph.D., *University of Turku, Turku, Finland*

**Joseph T.F. Lau**, Ph.D., *The Chinese University of Hong Kong, Hong Kong, China*

**Myeong Soo Lee**, Ph.D., *The Korea Institute of Oriental Medicine, Daejeon, South Korea*

**Li Li**, M.D., *National Jewish Health/ University of Colorado Denver, Denver, United States*

**Junqi Qian**, M.D., *Virginia Urology Pathology Laboratory, Richmond, United States*

**Suimin Qiu**, M.D., Ph.D., *The University of Texas Medical Branch at Galveston, Galveston, United States*

**Jianyu Rao**, M.D., *University of California, Los Angeles, United States*

**Jiangning Song**, Ph.D., *Monash University, Biomedicine Discovery Institute, Melbourne, Australia*

**Jing Sun**, Ph.D., *Griffith University, Brisbane, Australia*

**Wei Wang**, M.D., *School of Medicine New York University, New York, United States*

**Lin Zhang**, Ph.D., *The Chinese University of Hong Kong, Hong Kong, China*

**Xiaofei Zhang**, M.D., Ph.D., *Beijing Tsinghua Changgung Hospital, Beijing, China*

**Xiangfeng Lu**, M.D., Ph.D., *National Center for Cardiovascular Diseases, Beijing, China*

**Yubin Zhou**, M.D., Ph.D., *College of Medicine, Texas A&M University, Houston, United States*

**Wei Wang**, M.D., Ph.D., FFPH, *Edith Cowan University, Perth, Australia*

## Managing Director

**Yi Cui**, *Chinese Medical Association Publishing House*

Yi Cui obtained his bachelor degree and master degree in Peking University Health Science Center, and has more than 12 years of experience in STM Journal publishing. He is also the deputy director of International Exchange and Cooperation Working Committee of China Editology Society of Science Periodicals (CESSP) and Member of Journal Publishing Professional Committee of China Anti-Cancer Association.

## Publisher

**Wanshu Zhang**, *John Wiley & Sons, Inc.*

Wanshu Zhang obtained her B.Sc. from the University of Science and Technology Beijing (USTB). She conducted her Ph.D. study at Peking University based on a cooperation project with USTB. After her post-doctoral research at Eindhoven University of Technology, she joined Wiley as a journal publishing manager. At present, she is Associate Publisher, Health Sciences and oversees a journal portfolio and strategic publishing project. Her responsibility also includes managing partnership journal business with Chinese societies.

## Publishing Assistant

**Siyue Xiao**, *John Wiley & Sons, Inc.*

Siyue Xiao received her MSc from University of Warwick, Coventry, UK, with major in e-Business Management, and further acquired a Postgraduate Diploma in Asian Arts from SOAS, University of London, London, UK, in pursuing her interests in art history. She has worked in a literature agency handling foreign book rights for 2.5 years before she joined Wiley as a Journal Publishing Assistant in Health Sciences team.

Chronic Diseases® and Translational Medicine

## Early View

Online Version of Record before inclusion in an issue

Export Citation(s)

## REVIEW

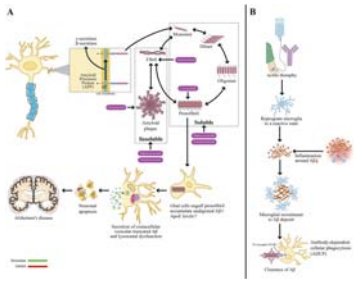
Open Access

### Amyloid-Related Imaging Abnormality (ARIA) Beyond the APOE-ε4 Allele

Valentinus Besin, Farizky Martriano Humardani, Fenny Lanawati Yudiarto, Paulus Anam Ong, Sulistyo Emantoko Dwi Putra, Ratih Asmana Ningrum

Version of Record online: 24 April 2025

https://doi.org/10.1002/cdt3.70006



Mechanism of action of monoclonal antibodies targeting Aβ in the treatment of AD. (A) Targets of various mAbs. (B) Mechanism of monoclonal antibody-mediated clearance of Aβ. mAbs facilitate the clearance of Aβ by enhancing microglial-mediated phagocytosis through the upregulation of *TREM2* expression. Increased *TREM2* expression reduces inflammation surrounding Aβ deposits, allowing microglia to recognize and recruit these deposits. Additionally, TREM2 activation reprograms microglia into a reactive state, promoting active phagocytosis via antibody-dependent cellular phagocytosis (ADCP), thereby enhancing Aβ clearance.

Abstract | Full text | PDF | References | Request permissions

## STUDY PROTOCOLS

Open Access

### Evaluation of NaTto Red Yeast Rice on Regulating Blood Lipid (ENTRY) Study: A Multicenter, Double-Placebo, Double-Blinded, Randomized Controlled Trial in Chinese Adults

Shufeng Chen, Fangchao Liu, Jinyue Li, Fengchao Liang, Jianxin Li, Jie Cao, Donghua Liu, Keyong Huang, Hongfan Li, Xiangfeng Lu, Jianfeng Huang, Dongfeng Gu

Version of Record online: 24 April 2025

https://doi.org/10.1002/cdt3.70005

Study flow chart of the ENTRY study.

Abstract | Full text | PDF | References | Request permissions

## REVIEW

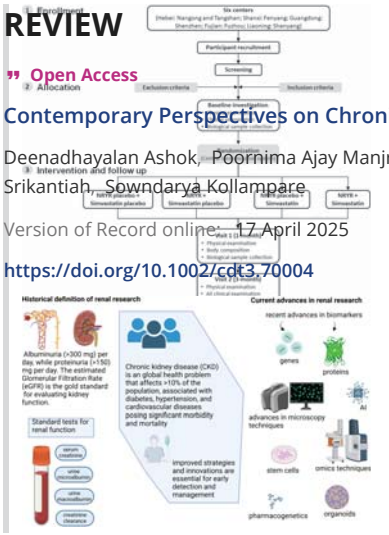
Open Access

### Contemporary Perspectives on Chronic Renal Disorders

Deenadhayalan Ashok, Poornima Ajay Manjrekar, Bhushan C. Shetty, Sujina S. S, Rukmini Mysore Srikantiah, Sowndarya Kollampare

Version of Record online: 17 April 2025

https://doi.org/10.1002/cdt3.70004




Abstract | Full text | PDF | References | Request permissions

## ORIGINAL ARTICLE

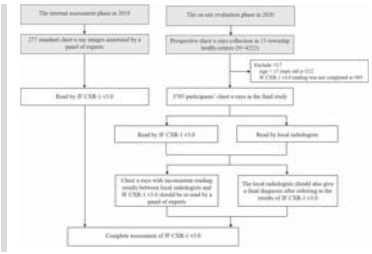
Open Access

### Performance of Computer-Aided Detection Software in Tuberculosis Case Finding in Township Health Centers in China

Xuefang Cao, Boxuan Feng, Bin Zhang, Dakuan Wang, Jiang Du, Yijun He, Tonglei Guo, Shouguo Pan, Zisen Liu, Jiaoxia Yan, Qi Jin, Lei Gao, Henan Xin

Version of Record online: 02 April 2025

https://doi.org/10.1002/cdt3.70001



Flow chart of the study implementation.

Abstract | Full text | PDF | References | Request permissions

## CORRECTION

Open Access

### Correction to “Alignment of Human Aquaporin 4 and ß-Amyloid Proteins May Indicate Involvement of ß-Amyloid in Brain Water Homeostasis and Prevention of Brain Edema”

Version of Record online: 27 March 2025

https://doi.org/10.1002/cdt3.70003

This article corrects the following:

Alignment of human aquaporin 4 and ß-amyloid proteins may indicate involvement of ß-amyloid in brain water homeostasis and prevention of brain edema

Steven Lehrer, Peter H. Rheinstein

Volume 9, Issue 2, Chronic Diseases and Translational Medicine | pages: 177-181 |
First Published online: March 29, 2023

Full text | PDF | Request permissions

Open Access

### Correction to “Alignment of Human KAT2A (GCN5) Histone Acetyltransferase and SARS-CoV-2 Orf8 Viral Proteins”

Version of Record online: 19 March 2025

https://doi.org/10.1002/cdt3.70002

This article corrects the following:

Alignment of human KAT2A (GCN5) histone acetyltransferase and SARS-CoV-2 Orf8 viral proteins

Steven Lehrer, Peter H. Rheinstein

Volume 9, Issue 3, Chronic Diseases and Translational Medicine | pages: 263-265 |
First Published online: December 30, 2022

Full text | PDF | Request permissions

## ORIGINAL ARTICLE

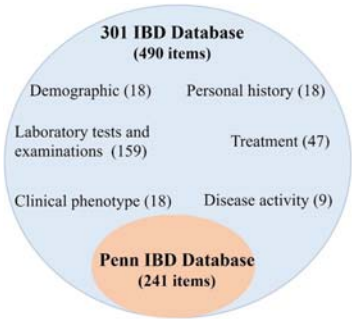
Open Access

### Development and Initial Use of a New Inflammatory Bowel Disease Clinical Database Integrating Both Eastern and Western Clinical Characteristics

Jingshuang Yan, Rongrong Ren, Ruqi Chang, Wanyue Dan, Xiaohan Zhang, Fei Pan, Bin Yan, Hongzhe Lee, Ni Josie, Gang Sun, Lihua Peng, Gary D. Wu, Yunsheng Yang

Version of Record online: 14 February 2025

https://doi.org/10.1002/cdt3.70000




Abstract | Full text | PDF | References | Request permissions

## SHORT COMMUNICATION

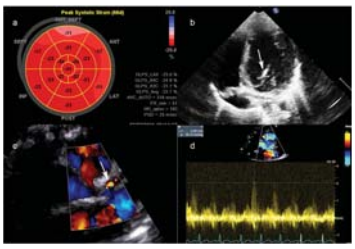
Open Access

### Overlap of Takayasu Arteritis and Kawasaki Disease in Infants

Jingya Li, Yan Sun, Liyuan Xu, Shanshan Li, Ning Ma

Version of Record online: 27 January 2025

https://doi.org/10.1002/cdt3.157



Echocardiography showed the myocardial ischemia presentation of an 8-month-old boy.

Abstract | Full text | PDF | References | Request permissions

## REVIEW

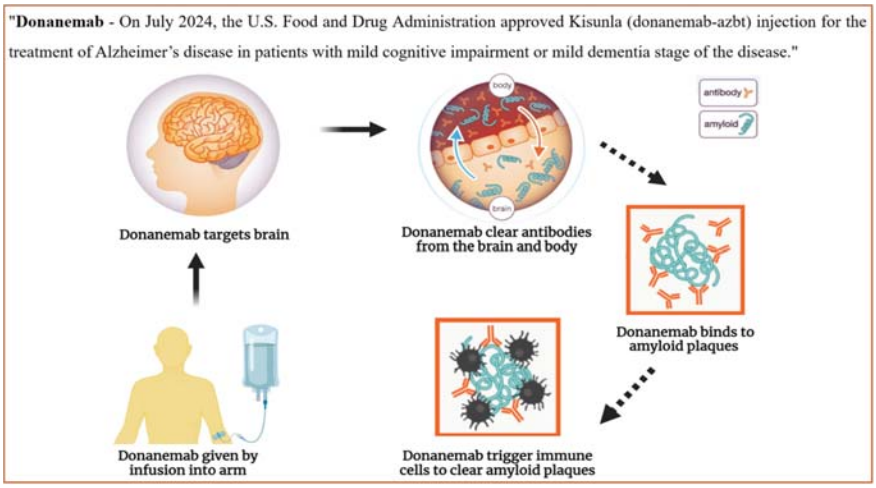
Open Access

### Translational Medicine in Alzheimer's Disease: The Journey of Donanemab From Discovery to Clinical Application

Nandhini Jayaprakash, Karthikeyan Elumalai

Version of Record online: 16 December 2024

https://doi.org/10.1002/cdt3.155




Abstract | Full text | PDF | References | Request permissions

## PERSPECTIVE

Open Access

### Wearable Technology in the Management of Chronic Diseases: A Growing Concern

Victor Abiola Adepoju, Safayet Jamil, Mohammad Shahangir Biswas, ABM Alauddin Chowdhury

Version of Record online: 10 December 2024

https://doi.org/10.1002/cdt3.156

Abstract | Full text | PDF | References | Request permissions

## ORIGINAL ARTICLE

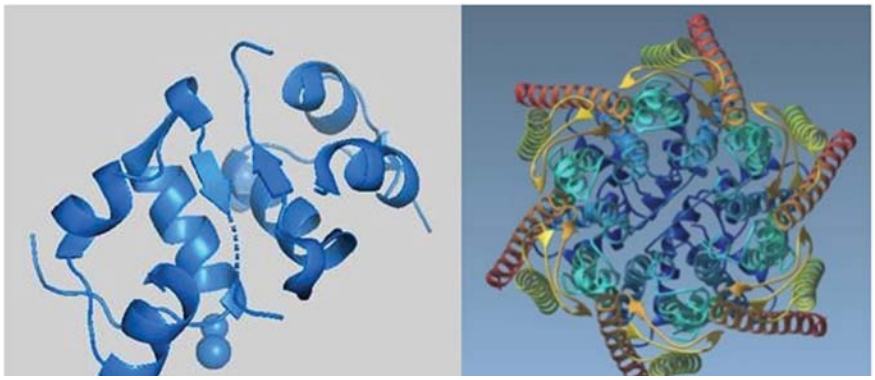
Open Access

### Insulin and Metformin are Associated With Reduced Risk of Amyotrophic Lateral Sclerosis

Steven Lehrer, Peter H. Rheinstein

Version of Record online: 30 June 2024

https://doi.org/10.1002/cdt3.141



Human insulin heterodimer (A). Human insulin heterodimer (dark blue) docked within center of Cx43 channel (B)

**Abstract** | **Full text** | **PDF** | **References** | **Request permissions**

# Chronic Diseases and Translational Medicine

| COUNTRY | SUBJECT AREA AND CATEGORY | PUBLISHER | SJR 2024 |
|---|---|---|---|
| United States<br>Universities and research institutions in United States<br>Media Ranking in United States | Medicine<br>Medicine (miscellaneous) | John Wiley and Sons Inc | 0.663 Q2<br>H-INDEX<br>23 |

| PUBLICATION TYPE | ISSN | COVERAGE | INFORMATION |
|---|---|---|---|
| Journals | 2095882X | 2018-2025 | Homepage<br>How to publish in this journal<br>Cdtm@cmaph.org |

SCOPE

Chronic diseases have become a major challenge to human health globally. The aim of CDTM is to promote the prevention, diagnosis and treatment of chronic diseases by providing a forum for communicating the latest research advances from preclinical, translational, and clinical researchers from all established and emerging disciplines relevant to chronic diseases.

Join the conversation about this journal

Quartiles

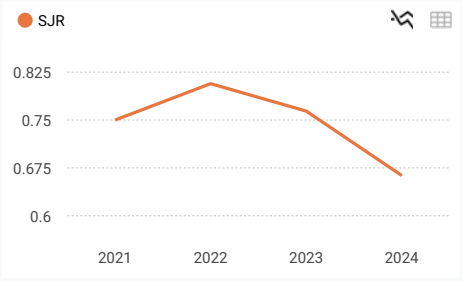
FIND SIMILAR JOURNALS

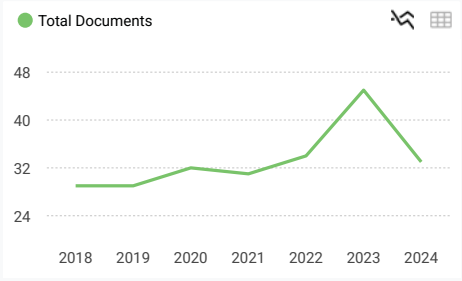
1
**Journal of Investigative Medicine**
USA
**69%**
similarity

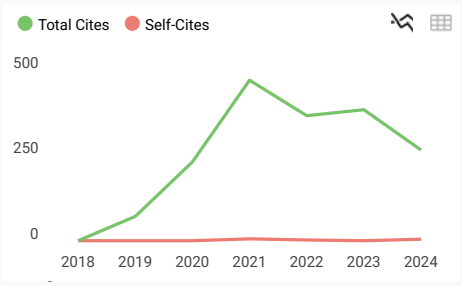
2
**Annals of Medicine**
GBR
**63%**
similarity

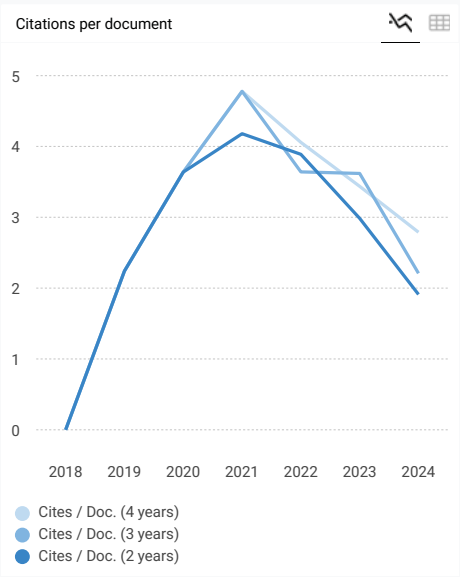
3
**Chinese Medical Journal**
CHN
**62%**
similarity

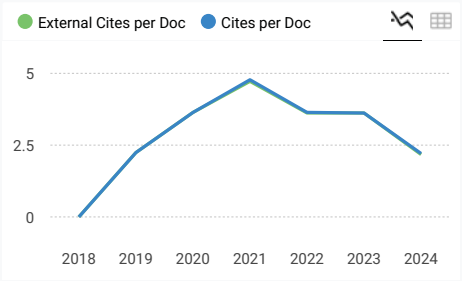
4
**Journal of Internal Medicine**
GBR
**61%**
similarity

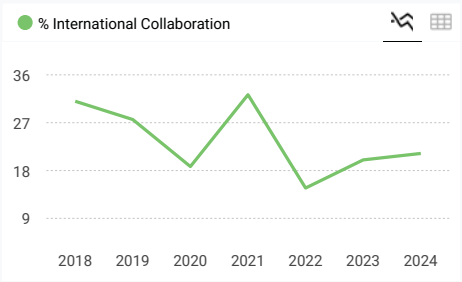


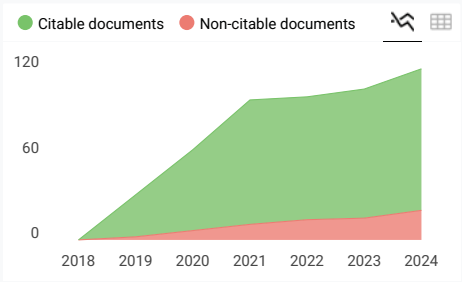



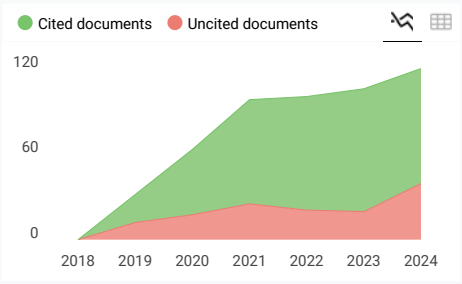



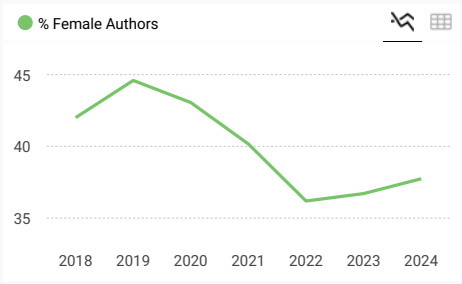



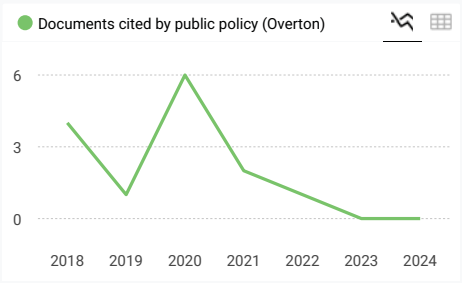



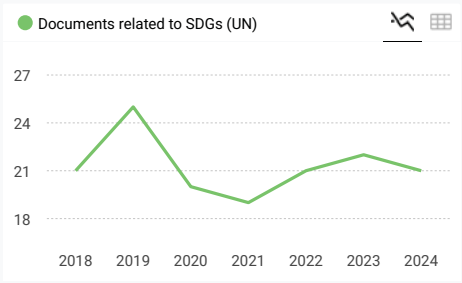



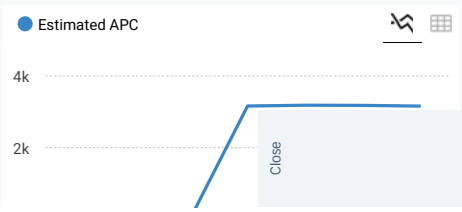



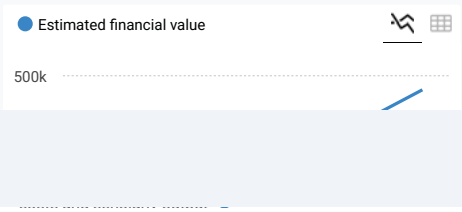



Email
(will not be published)

Submit

The users of Scimago Journal & Country Rank have the possibility to dialogue through comments linked to a specific journal. The purpose is to have a forum in which general doubts about the processes of publication in the journal, experiences and other issues derived from the publication of papers are resolved. For topics on particular articles, maintain the dialogue through the usual channels with your editor.

# Source details

## Chronic Diseases and Translational Medicine

Years currently covered by Scopus: from 2018 to 2025

Publisher: John Wiley & Sons

E-ISSN: 2095-882X

Subject area: Medicine: General Medicine

Source type: Journal

View all documents > | Set document alert | Save to source list

CiteScore 2023
6.7

SJR 2023
0.764

SNIP 2023
0.875

CiteScore | CiteScore rank & trend | Scopus content coverage

### CiteScore 2023

$$6.7 = \frac{760 \text{ Citations } 2020 - 2023}{113 \text{ Documents } 2020 - 2023}$$

Calculated on 05 May, 2024

### CiteScoreTracker 2024

$$4.6 = \frac{503 \text{ Citations to date}}{110 \text{ Documents to date}}$$

Last updated on 05 April, 2025 • Updated monthly

### CiteScore rank 2023

| Category | Rank | Percentile |
|---|---|---|
| Medicine<br>General Medicine | #60/636 | 90th |

View CiteScore methodology > | CiteScore FAQ > | Add CiteScore to your site

Feedback

## About Scopus

What is Scopus

Content coverage

Scopus blog

Scopus API

Privacy matters

## Language

日本語版を表示する

查看简体中文版本

查看繁體中文版本

Просмотр версии на русском языке

## Customer Service

Help

Tutorials

Contact us

ELSEVIER



Feedback