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Amyloid-β Seeds in Alzheimer's Disease: Research Challenges and Implications

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ABSTRACT

The amyloid cascade hypothesis, proposed over 30 years ago, places amyloid-β (Aβ) at the center of Alzheimer's disease (AD) pathogenesis. Though controversial, recent clinical successes with Aβ-targeting therapies have reinforced its importance. However, these treatments have shown only modest clinical benefits in line with a two-stage AD progression: an early phase driven by Aβ-seed and a later phase that progresses at least partly independently of Aβ. Evidence of Aβ seed transmission in humans raises both therapeutic potential and biosafety concerns. This review explores current understanding of Aβ seeds, including challenges in studying such seeds, model systems to study Aβ seeds, and biosafety issues when working with Aβ seeds.

1 | Introduction

Since the proposal of the amyloid cascade hypothesis more than 30 years ago, the amyloid beta peptide (Aβ) has been at the center of debates about the main cause of Alzheimer's disease (AD) (Selkoe and Hardy 2016; Kepp et al. 2023). These discussions have not been without controversy, even to the extent of rejecting a possible role for Aβ in AD pathology (Herrup 2015). However, recent positive outcomes of large phase III clinical studies targeting Aβ aggregates, along with the approval of Aβ-based immunotherapies in many countries around the world, have positioned Aβ as a leading target for disease-modifying AD therapies (van Dyck et al. 2023; Hampel et al. 2021). Nevertheless, the effects of Aβ immunotherapy on the clinical progression of the disease were small, and a large body of evidence now suggests that AD progresses in two phases: an early phase in which pathogenesis is driven by Aβ aggregation, and a later phase in which AD progression becomes at least partly independent of the massive amount of Aβ deposition that is present in this later phase (Jucker and Walker 2023; De Strooper and Karran 2016). For these reasons, the focus of Aβ-centered research and clinical intervention is shifting from the relatively large Aβ plaques, which represent an endpoint in the aggregation cascade, to Aβ seeds, much smaller bioactive assemblies that propagate throughout the brain and are thought to be a critical early driver of AD pathogenesis. Research in animal models has shown that this pathogenic process closely resembles the endogenous action of prions in neurodegenerative prionopathies such as Creutzfeldt-Jakob disease (Jucker and Walker 2018, 2024; Uhlmann et al. 2020). In addition, substantial evidence has been provided for the transmission of Aβ

Abbreviations: AD, Alzheimer's disease; APP, β-amyloid precursor protein; Aβ, amyloid beta; CAA, cerebral amyloid angiopathy; c-hGH, cadaver-derived human growth hormone; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; FAD, familial Alzheimer's disease; ICH, intracerebral hemorrhages; iPSC, induced pluripotent stem cells; PIA, potentially infectious agents; PMCA, protein misfolding cyclic amplification assay; PSEN, presenilin 1; RT-QuIC, real-time quaking-induced conversion; TG, transgenic; YFP, yellow fluorescence protein.

seeds in humans (Gomez-Gutierrez and Morales 2020; Banerjee et al. 2024). A better understanding of the prion-like properties of Aβ seeds and, especially, how and where the propagation of aberrant Aβ starts in the brain is key to designing novel therapeutic approaches targeting the initial stage of AD. However, the prion-like molecular mechanism of Aβ propagation also has raised several safety questions about how to handle human and synthetic Aβ seed-containing samples.

Here we summarize the current knowledge on the nature and propagation of Aβ seeds. We also highlight the difficulties of studying Aβ seeds and review current model systems to study pathogenic Aβ assemblies. Finally, we provide an update on the transmission of Aβ seeds and the biosafety issues.

2 | Aβ Seeds and the Initial Stage of AD

Aβ misfolding propagates through the brain by a prion-like mechanism in which small seeding-active nuclei template the misfolding and aggregation of naïve Aβ monomers into higher aggregation states, ranging from small soluble oligomers to large mature plaques (Figure 1). Therefore, such seeding-active nuclei (i.e., seeds) might represent the smallest pathogenic unit in the aggregation and deposition of Aβ (Hampel et al. 2021; Jucker and Walker 2018).

In AD, Aβ aggregation and deposition in the brain starts more than 20 years before the onset of symptoms, potentially offering a wide timeframe for preventive Aβ-based therapies (Jia et al. 2024; Bateman et al. 2012). However, the variety of Aβ aggregates, together with other characteristics such as the existence of conformationally distinct strains, makes it difficult to select the proper molecular target for the initial stage of Aβ aggregation (Lau et al. 2021; Panza et al. 2019). In mouse models and AD brain, Aβ aggregates at early amyloid stages show a higher seeding potency when compared with aggregates found at later stages (Condello et al. 2022; Ye et al. 2017). Not only the disease stage is important for seeding activity but also the aggregation state of Aβ. Small soluble oligomers seem to be the most seeding-active Aβ species, being crucial for the initial stage of Aβ aggregation (Katzmarski et al. 2020; Langer et al. 2011). Such seeding-active oligomers have been termed "on-pathway" to differentiate them from oligomers that are not part of the aggregation process (termed "off-pathway") (Muschol and Hoyer 2023; Oren et al. 2021) (Figure 1). Remarkably, soluble Aβ oligomers are present in the brain (Sideris et al. 2021) and CSF (Blömeke et al. 2024) of early-stage AD patients, although it is unclear whether such oligomers are seeding active, as is the case for soluble oligomers from late-stage AD patients (Song et al. 2025). The importance of soluble aggregates in AD pathogenesis may be in line with the assumption that Lecanemab, the recently approved anti-Aβ immunotherapy, binds preferentially to oligomeric forms of Aβ aggregates (van Dyck et al. 2023; Söderberg et al. 2023; Meilandt et al. 2019; Ostrowitzki et al. 2022; Fertan et al. 2024).

The aggregation of Aβ follows a nucleation-dependent model that begins with a lag phase in which small seeding-active nuclei (Aβ seeds) are formed, but Aβ deposition cannot be detected yet (Jarrett and Lansbury 1993; Arosio et al. 2015). Consistent with such in vitro findings, pre-amyloid Aβ seeds have been detected in the brains of transgenic (tg) mouse models overexpressing the β-amyloid precursor protein (APP) (Uhlmann et al. 2020). Acute immunotherapy of pre-depositing APP tg mice with an

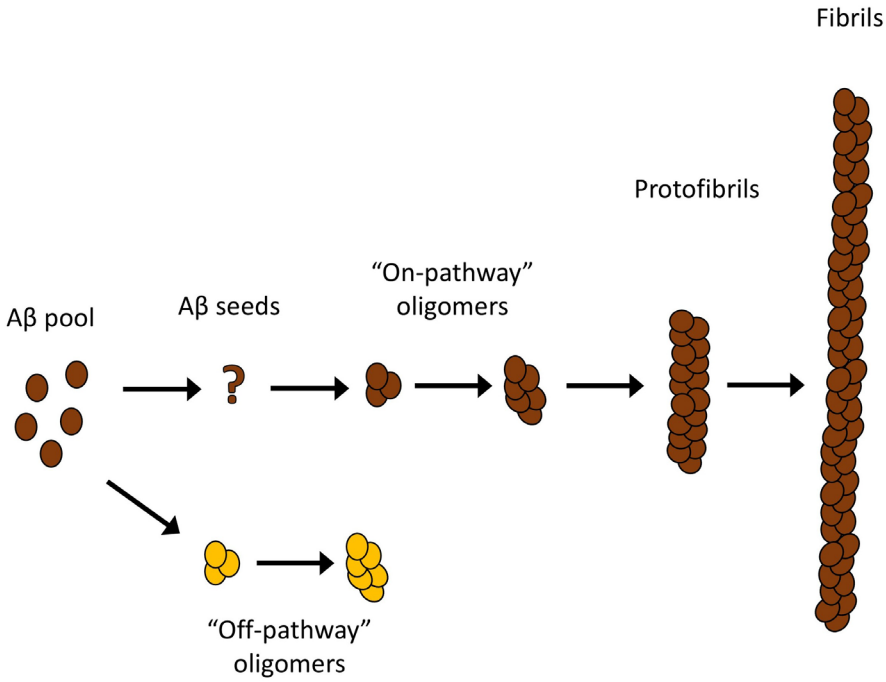

FIGURE 1 | Aggregation of amyloid beta (Aβ). Amyloid aggregation of Aβ is represented in brown. Aβ seeds form through nucleation from Aβ monomers and initiates the aggregation process that leads to the formation of amyloid fibrils. Different aggregation states are shown, including "on-pathway" oligomers which will grow into a fibril state. It should be noted that the exact nature of Aβ seeds is unknown although current evidence suggests a soluble oligomeric conformation. Alternatively, "off-pathway" oligomers can form from Aβ monomers. Such oligomers will not convert into fibrils, but they compete with the formation of amyloid fibrils by depleting the Aβ monomers pool.

Aβ antibody (Aducanumab) led to a significant reduction of Aβ deposition and associated neurodegeneration later in life (Uhlmann et al. 2020). This finding indicates that bioactive Aβ seeds already exist during the lag phase of protein aggregation in the brain, and that their targeting and removal might represent the most suitable therapeutic target for AD prevention.

3 | Nature of Aβ Seeds

The exact molecular nature of Aβ seeds is currently elusive, posing a major challenge for scientists working in the AD field. In vivo experiments have repeatedly demonstrated that Aβ aggregation can be induced in the brains of young APP transgenic mice by intracerebral injection of Aβ-laden brain homogenates (Langer et al. 2011; Jucker and Walker 2013; Meyer-Luehmann et al. 2006). However, no specific conformation can currently be assigned to Aβ seeds, as different aggregate forms can trigger seeding—albeit with sometimes large differences in their respective efficiency. There is evidence that intracerebral Aβ aggregation can be induced by small, soluble Aβ seeds from the brain parenchyma (Langer et al. 2011), by Aβ seeds isolated from various cellular compartments and intracellular membranes (Marzesco et al. 2016), by purified Aβ fibrils from the brain, and by aggregated synthetic Aβ (Stöhr et al. 2012; Novotny et al. 2016; Kollmer et al. 2019). While Aβ in the brain forms the most active seeds, Aβ from the cerebrospinal fluid of transgenic mice and AD patients seems to be inert (Fritschi, Langer, et al. 2014). Interestingly, however, a recent publication reported seeding activity of plasma Aβ (Jia et al. 2022). Since several Aβ assemblies with different aggregation states are capable of acting as seeds, it is difficult to assign a specific conformation to Aβ seeds, although a soluble oligomeric nature of the Aβ seed might be the most plausible entity.

Aβ seeds can persist in the living brain for months following exogenous injection (Ye, Fritschi, et al. 2015). To this end, *App*-null mice were inoculated with Aβ seeds. Up to 6 months later, brain extracts from these inoculated *App*-null mice were still seeding actively. Thus, Aβ seeds can successfully escape parenchymal degradation and clearance mechanisms for at least 6 months, which is a substantial time in a mouse's lifespan. How Aβ seeds escape degradation remains unclear. Aβ aggregates injected into the peritoneal cavity could be detected in blood monocytes up to 1 week after initial seed inoculation, but the seeding activity of the material in monocytes was not tested (Eisele et al. 2014). Aβ aggregates can be degraded by cells of the monocyte lineage (Ye, Fritschi, et al. 2015; Majumdar et al. 2008; Zaghi et al. 2009). Whether Aβ seeds are transported by monocytes and released before the degradation processes are complete or whether seeds can resist degradation in monocytes is unknown.

The observation that Aβ seeds can exist in the brain at levels below their detectability by routine methods is problematic (Uhlmann et al. 2020). Although new, ultrasensitive ELISA-based detection methods might help to overcome this problem (Yang et al. 2015), the major problem remains that the molecular composition of seeds remains unknown. What is known is that brain-derived Aβ seeds exhibit a much higher biological activity compared to the seeds from synthetic Aβ (Stöhr et al. 2014). It would be of considerable importance to establish where Aβ seeds initially emerge and from where they start the pathological seeding cascade that ultimately results in AD.

4 | Cellular Origin of Aβ Seeds

A neuronal origin for Aβ seeds and their propagation throughout neural networks has been demonstrated in tg mice with neuronal expression of APP on an endogenous *App*-deficient background (Eisele et al. 2014; Calhoun et al. 1999). Evidence for both extracellular and intraneuronal Aβ seed formation has been provided (Ye et al. 2017; Eisele and Duyckaerts 2016; Olsson et al. 2018). More recently, oligodendrocytes, microglia, and neuronal lysosomes have been suggested as a source of Aβ seeds.

Oligodendrocytes produce Aβ with an elevated 42/40 amino acid ratio, which suggests a high capacity to form oligomers (Rajani et al. 2024; Kuperstein et al. 2010). Indeed, Aβ from oligodendrocytes contributes to cerebral Aβ deposition, as shown by the reduction of Aβ plaque burden after selective suppression of the Aβ rate-limiting generating protease BACE1 specifically in oligodendrocytes (Rajani et al. 2024; Ishii et al. 2024; Sasmita et al. 2024). Nevertheless, also in these models, it appears that neuron-derived Aβ is responsible for the initial seeding and propagation of Aβ, while oligodendrocyte-derived Aβ might be involved in further Aβ seed propagation and plaque growth.

Microglia are well-known contributing factors to AD risk and pathology by their role in neuroinflammation (Hampel et al. 2021). In addition to their role in neuroinflammation (Botella Lucena and Heneka 2024), there is evidence that microglia are involved in Aβ seed formation. Non-plaque-associated microglia accumulate Aβ aggregates within their lysosomes that can be released after cellular death, potentially contributing to plaque formation (although the seeding activity of such lysosomal aggregates has not been demonstrated) (Spangenberg et al. 2019). Besides, it has been suggested that microglia can contribute to Aβ pathology by carrying Aβ seeds and propagating them through the brain (Huang et al. 2021; d'Errico et al. 2022). Moreover, ASC specks, which are structures released by microglia after inflammasome activation, bind to Aβ, increasing aggregation and deposition (Friker et al. 2020; Venegas et al. 2017). Recently, ApoE has emerged as a potential mediator of the role of microglia on Aβ aggregation (Kaji et al. 2024). In a series of elegant experiments, Kaji et al. showed that ApoE aggregates can act as seeds for Aβ aggregation inside microglial lysosomes. Interestingly, ApoE co-aggregates with Aβ in the initial stage of Aβ aggregation but not in later stages (Xia et al. 2024).

Although the association of neuronal lysosomes with the intracellular accumulation and aggregation of Aβ has been known for years (Olsson et al. 2018; Gouras et al. 2000; Hu et al. 2009; Yang et al. 2011), new research has brought these organelles into focus again. In normal conditions, the autophagic pathway clears Aβ through lysosomes, whereas in AD this pathway is impaired (Nixon 2024). In mouse models of amyloid pathology, lysosomal deficiencies arise at an early stage, leading to poorly acidified lysosomes where APP-β-C-terminal fragment and Aβ build up. This accumulation leads to perinuclear amyloid that might be the origin of Aβ plaques (Lee et al. 2022). This finding

brings back the idea of an intracellular origin for Aβ seeds (Hu et al. 2009; Nilsson et al. 2013; Gouras et al. 2014). However, recombinant Aβ oligomerization seems to be enhanced by the lysosomal low pH in normal conditions (Schützmann et al. 2021), which is somewhat in contrast to the proposed role of faulty acidification in Aβ aggregation, although such lysosomal oligomerization may refer to "off-pathway" Aβ oligomers (see above). Hence, faulty acidification might shift Aβ kinetics from "off-pathway" Aβ oligomers toward fibrillization, with initial seed formation and subsequent perinuclear aggregation. More research is needed on the role of lysosomes in the formation and propagation of Aβ seeds.

5 | Models to Study Aβ Seeds

Aβ research has mainly focused on the use of APP transgenic (tg) rodent models. Although these models only replicate certain aspects of AD pathology, they are ideal to study Aβ seeding (Sasaguri et al. 2017; Ulm et al. 2021). APP tg rodent models provide information on how Aβ seeds propagate throughout anatomical structures of the brain, how plaque conformation is influenced by the conformation of the original seeds, and how differences in susceptibility to Aβ inoculation depend on the host environment, that is, the specific model used (Figure 2).

Aβ seeding is usually initiated with intracranial injection of aggregated Aβ-laden brain material or synthetic aggregated Aβ into the hippocampus or cortex of tg rodent models (Meyer-Luehmann et al. 2006; Ye, Fritschi, et al. 2015; Rasmussen et al. 2017; Li et al. 2022; Yue et al. 2021; Hérard et al. 2020; Ye, Hamaguchi, et al. 2015). The chosen injection site of Aβ seeds is crucial for the subsequent pathological protein aggregation. While the induction of Aβ aggregation is usually abundant in the vicinity of the injection site, it is also detectable in

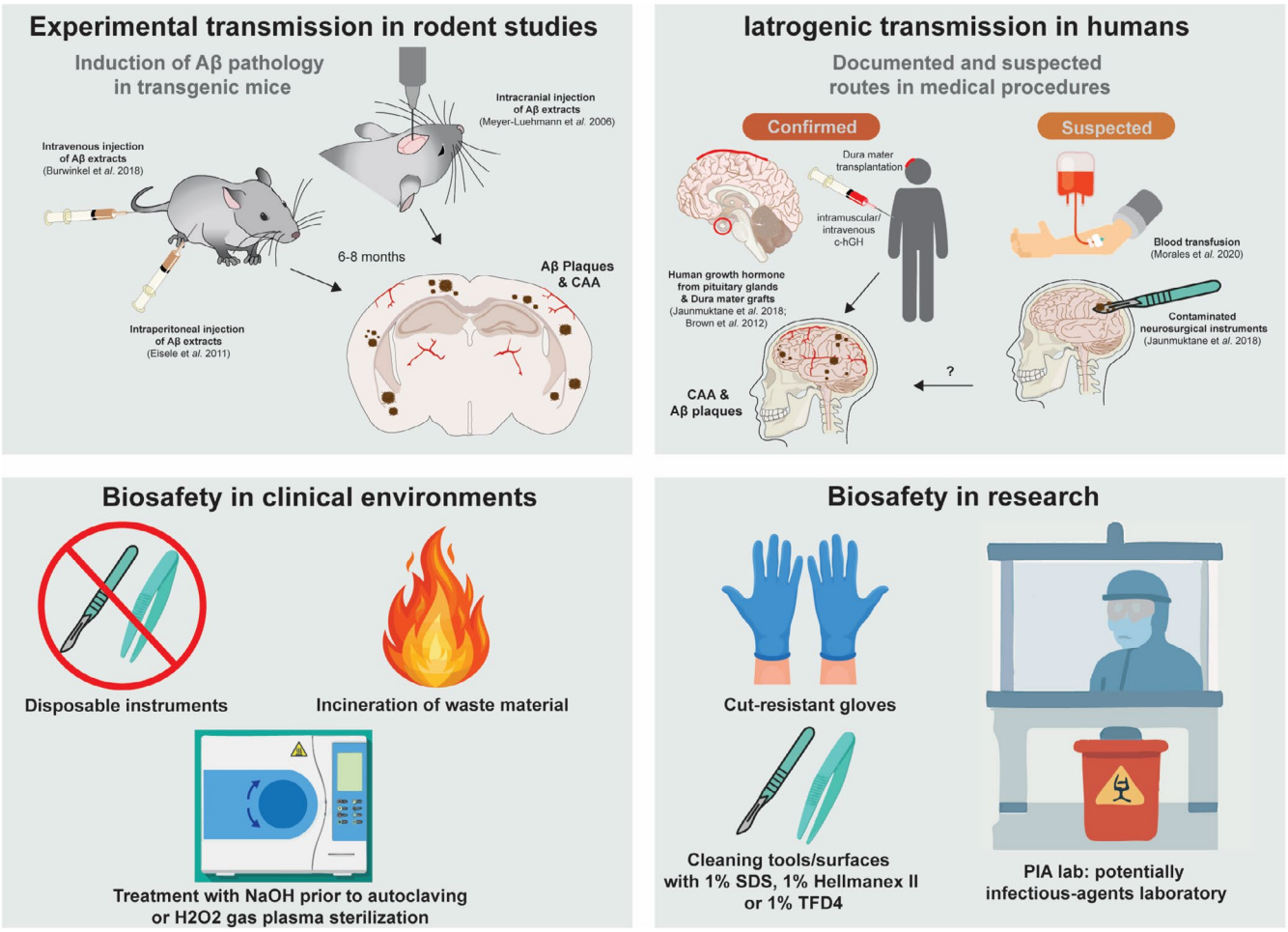

FIGURE 2 | Transmission and biosafety of amyloid beta (Aβ) seeds. Experimental transmission: Animal models can be used to study Aβ seeding by intracerebral, intraperitoneal, or peripheral inoculation with brain extracts containing misfolded Aβ. These experiments help reveal the mechanisms and timelines of pathology spread. Iatrogenic transmission in humans: Documented in rare cases following exposure to contaminated human-derived biological materials (e.g., cadaveric dura mater grafts, pituitary-derived hormones, and surgical instruments). Evidence comes from neuropathological examinations showing early-onset Aβ pathology in individuals decades after exposure. Potential routes of exposure: Includes neurosurgical instruments, endoscopes, or other reusable medical devices that may come into contact with nervous tissue. Contamination is resistant to standard sterilization and may require prion-specific decontamination protocols. Biosafety measures: Implement WHO-recommended prion decontamination procedures for high-risk tissues. Use disposable instruments when feasible. Segregate instruments used in high-risk procedures. Maintain strict traceability and staff training to prevent inadvertent transmission.

connected brain regions (Eisele and Duyckaerts 2016; Eisele et al. 2011; Walker et al. 2002). The specific spreading may involve passive diffusion at the injection site as well as active transport along axonal connections (Eisele et al. 2011, 2009). Importantly, the regional Aβ production—according to the promotor used in each mouse line—plays an important role in the spatial aggregation process and underlines also the importance of the host environment for the spreading and propagation of Aβ seeds (Jucker and Walker 2018). In human postmortem brain, there is an impressive spatiotemporal evolution of Aβ accumulation. Protein aggregation appears to start in the neocortex and further spreads to the rhinencephalon, the brainstem, and the cerebellum (Hampel et al. 2021; Thal et al. 2002). The vulnerability of distinct brain regions to Aβ aggregation is not fully understood (Grothe et al. 2018; Yao et al. 2024).

Apart from intracranial injection, peripheral application routes of Aβ seeds involve intraperitoneal, intravenous, and intramuscular application as well as administration of Aβ-laden eye drops. In general, the efficiency of peripheral administration routes requires more time and is less efficient than that of intracerebral injections (Eisele et al. 2011; Morales et al. 2012).

5.1 | Animal Models

The most common experimental animal models to study Aβ seeding and β-amyloidosis are tg mice overexpressing human APP containing mutations associated with familial early-onset forms of AD (FAD), either alone or in combination with mutated human presenilin (PSEN) (Drummond and Wisniewski 2017). Several studies have investigated the dynamics of Aβ seeding in such models—mostly APP23, APP/PS1, and 5× FAD—as well as human APP-knock-in mouse models (Katzmarski et al. 2020; Langer et al. 2011; Meyer-Luehmann et al. 2006; Eisele et al. 2009; Heilbronner 2013; Burwinkel et al. 2018; Ruiz-Riquelme et al. 2018). Differences in the regional vulnerability and progression of seeded Aβ pathology, plaque morphology, and susceptibility to Aβ inoculation were found, underlying the importance of the host and type of seed for the induction and propagation of Aβ pathology.

The APP23 mouse model expresses human APP with the Swedish double mutation ($APP^{K670N/M671L}$) under the Thy1 promoter (Sturchler-Pierrat and Stauffenbiel 2000; Sturchler-Pierrat et al. 1997). APP23 mice display large and both diffuse and compact plaques and abundant cerebral amyloid angiopathy (CAA). Upon Aβ inoculation, the APP23 mouse model exhibits a slow and spatially restricted seeding response. When brain homogenate containing Aβ aggregates is injected into the hippocampus or other regions such as the neocortex or striatum, the spread of pathology follows known limbic connectivity pathways (Ye, Hamaguchi, et al. 2015; Heilbronner 2013).

Mouse models expressing both APP and PSEN FAD mutations (APP/PS1 transgenic mice) typically show earlier plaque deposition and high concentrations of $Aβ_{42}$ due to the PSEN mutations (Radde et al. 2006; Holcomb et al. 1998). The plaque morphology in these models is characteristically dense-core and congophilic. These models are particularly responsive to exogenous Aβ seeds and demonstrate robust seed propagation over time (Heilbronner 2013). The disadvantage of such rapid models to study seeding is that the endogenous Aβ deposition emerges so rapidly that it becomes more difficult to distinguish seed-induced from endogenously induced Aβ deposits at later time points.

The heterogeneity in Aβ plaque morphology and the biochemical composition of the plaques among tg mice allows for the study of strain-like behavior of Aβ seeds. As an example, the injection of brain material from APP23 mice (compact and diffuse plaques) into APP/PS1 mice leads to the appearance of both diffuse Aβ and dense plaques, which contrasts with the typical dense-core-plaque-only morphology observed in (unseeded) APP/PS1 mice (Heilbronner 2013).

APP knock-in models (e.g., APP^{NL-F} mice) have the advantage that they avoid potential artifacts of unphysiological APP overexpression, but their response to seeding is only moderate because the endogenous Aβ generated is less than that of their tg counterparts. Upon injection of Aβ aggregates into the cortex, Aβ pathology emerges gradually and remains rather localized. The native plaque morphology in these mice is largely diffuse in early stages, although more compact plaques can emerge with age or following strong seeding stimuli (Ruiz-Riquelme et al. 2018; Saito et al. 2014).

To date, Aβ seeding in wildtype mice has not been successful. This is likely due to three amino acids that differ in the Aβ sequence of mice and humans (R5G, Y10F, and H13R) (Krohn et al. 2015; Xu et al. 2015). Thus, the expression of human-sequence Aβ peptide appears necessary for the formation of Aβ plaques in the murine brain parenchyma. Interestingly, however, mice with overexpression of murine APP with FAD mutations have been reported to deposit amyloid, demonstrating that murine Aβ can also form amyloid plaques (Xu et al. 2015).

Aβ seeding in the hippocampus of 5×FAD mice not only accelerated amyloid pathology but also led to an early decline in hippocampus-dependent memory, as shown by impaired performance in the Morris Water Maze (Ziegler-Waldkirch et al. 2018). Injection of Aβ seeds into the olfactory bulb, as an alternative to hippocampal injections, to directly assess functional consequences to olfaction revealed deficits in odor detection and discrimination once seeded Aβ deposits had reached a certain threshold (Ziegler-Waldkirch et al. 2022). These findings provide evidence that Aβ seeding in the olfactory bulb can drive olfactory dysfunction, linking pathology in this region to a clinically relevant behavioral outcome.

Together, these findings underscore the importance of model selection in Aβ seeding experiments. While models like APPPS1 and 5×FAD offer rapid and widespread pathology for mechanistic or therapeutic studies, knock-in models such as APP^{NL-F} provide a more physiological context for investigating early-stage amyloid pathology. Moreover, the choice of brain region for seed injection significantly influences both the anatomical spread and morphological features of the resulting plaques, offering a valuable approach for dissecting circuit-specific vulnerability in AD.

5.2 | Cell Culture Models

In 2019, Aoyagi et al. developed a cellular assay for measuring the prion-like seeding activity of Aβ using HEK293T cells that express $A\beta_{40}$ or $A\beta_{42}$ constructs N-terminally fused to yellow fluorescent protein (YFP). Upon addition of postmortem AD brain tissue homogenate or synthetic Aβ fibrils, seeding activity can be determined from the number of cells showing yellow-fluorescent puncta. This assay has been used to quantify the seeding activity of brain samples from patients suffering from AD or other neurodegenerative diseases. An application for antemortem detection of pathological Aβ seeding activity in the CSF or blood of patients could be an important diagnostic tool and may even be able to measure the efficiency of treatment approaches (Aoyagi et al. 2019).

In addition, organotypic hippocampal slice cultures provide an ex vivo model that preserves the cytoarchitecture and connectivity of the hippocampus while allowing experimental manipulation. These cultures have been used to investigate Aβ aggregation and seeding, as well as the spread of pathology across neuronal networks, thereby bridging the gap between simplified cell-based assays and in vivo models (Novotny et al. 2016; Panagiotakopoulou 2025).

The development of induced pluripotent stem cells (iPSCs) made it possible to use experimental models that are derived from human tissue (Takahashi et al. 2007). Cultures of human iPSCs and cerebral organoids derived from FAD and sporadic AD show increased production of Aβ and tau phosphorylation (Yagi et al. 2011; Muratore et al. 2014; Kondo et al. 2013; Israel et al. 2012; Raja et al. 2016; Choi et al. 2014; Vanova et al. 2023; Urrestizala-Arenaza et al. 2024). Limitations of using iPSC culture and cerebral organoids to study Aβ seeds include: (i) the interplay between the various brain cells and the neurovascular interface is not well recapitulated in the cultures, and the spreading and propagation of Aβ seeds may differ; (ii) aging, the greatest risk factor for AD, is not well represented in cell culture models.

6 | Transmission of Aβ Seeds

The experimental transmission of Aβ pathology in mouse models is well established; a single intracerebral injection of minute amounts of Aβ seed-containing brain extracts (from an aged APP tg mouse) induces Aβ deposition in susceptible host mice (Meyer-Luehmann et al. 2006; Eisele et al. 2009) (Figure 2). The misfolding and deposition of the host Aβ is thought to occur through a templating mechanism as described for prion diseases (Jucker and Walker 2013). When such inoculations are done intraperitoneally, the induction of Aβ deposition in the brain takes longer and has been reported (at least in the first phase) to be predominantly associated with the vasculature (Eisele et al. 2014, 2011).

Under rare circumstances, prion diseases such as Creutzfeldt–Jakob disease (CJD) have been transmitted between humans (Figure 2). Unfortunately, such patients received prion-contaminated cadaver-derived human growth hormone (c-hGH) or gonadotropin in their youth, and years to decades later developed CJD. Similarly, in the past and very rarely, patients with brain injury received cadaver-derived prion-contaminated dura mater transplants, and years later have developed CJD (Brown et al. 2012, 2000; Heath et al. 2006; Thadani et al. 1988). Given the similarities between Aβ seeds and prions, there were concerns regarding the potential for iatrogenic Aβ transmission. Indeed, based on autopsy reports, it was found that young adult patients who died of (iatrogenic) CJD after c-hGH treatment had prominent Aβ deposits in the brain predominantly in the form of CAA (Jaunmuktane et al. 2015). In a follow-up study, it could be shown that such c-hGH contains Aβ and can induce Aβ deposition in mice (Purro et al. 2018). Additionally, numerous other cases have been reported with Aβ pathology after cadaveric dura mater grafts (Banerjee et al. 2024; Raposo et al. 2020; Hervé et al. 2018). Recently, it was reported that some patients who had received c-hGH injections developed signs of early-onset AD. The possibility that the iatrogenic transmission of Aβ seeds might not only induce Aβ pathology but also initiate the entire AD pathogenic cascade is now under investigation (Jucker and Walker 2024; Banerjee et al. 2024).

Transmission of Aβ pathology via contaminated neurosurgical instruments is an obvious, albeit difficult to prove, alternative route of transmission. Four patients were reported who underwent neurosurgical procedures early in life and developed CAA-related intracerebral hemorrhage three decades later (Jaunmuktane et al. 2018). Due to the small numbers and the difficulty of ruling out the effect of trauma from neurosurgery on the formation of CAA, this finding remains controversial. However, Aβ transmission via Aβ seed-contaminated stainless-steel wire has been demonstrated in mice (Eisele et al. 2009) and thus, transmission of Aβ pathology by contaminated surgical instruments is possible.

CJD transmission via blood has been demonstrated under exceptional and rare conditions and prior to the current use of leukapheresis (Seed et al. 2018; Pozzo di Borgo et al. 2023). Whether Aβ seeds can be transmitted via blood has been widely discussed and there is some evidence from animal work (Morales et al. 2020). A retrospective study analyzed data from blood banks in Denmark and Sweden and found an increased risk of intracerebral hemorrhages (ICH) in patients who received blood from donors who later had multiple ICH (Zhao et al. 2023). Since ICH is frequently associated with CAA, this finding led to the suspicion that Aβ seeds could be transmitted through blood transfusions. However, there is no direct histological or imaging evidence that these donors and recipients had CAA. Also, ICH appeared already after a couple of years after the blood transfusion, which contrasts somewhat with the observation that it takes decades for iatrogenic CAA to develop. Moreover, it cannot be ruled out that other blood factors and not Aβ are the cause of the observed rise in ICH.

7 | Aβ Seeds and Biosafety

Although the likelihood of β-amyloid or even AD transmission under normal circumstances appears remote, it is important to take all possible biosafety measures to prevent transmission.

7.1 | Precautions to Avoid Aβ Transmission During Medical Procedures

Growth hormone extraction from the pituitary gland of cadavers and dura mater grafts from diseased people was discontinued in the mid-1980s and mid-1990s, respectively, and therefore they no longer pose a risk of iatrogenic transmission (Lauwers et al. 2020). Similar to prions, Aβ seeds are resistant to conventional sterilization methods such as heating (95°C), γ-ray irradiation, and formaldehyde (Meyer-Luehmann et al. 2006; Fritschi, Cintron, et al. 2014; Sakudo et al. 2022; Nakano et al. 2022). In 2000, the World Health Organization (WHO) endorsed prion decontamination methods during medical procedures. These include the utilization of disposable instruments and incineration of waste materials. For instruments that cannot be disposed of, soaking in a solution of sodium hydroxide or sodium hypochlorite prior to autoclaving is recommended (World Health Organization 2000) (Figure 2).

These guidelines for prions can also be applied to reduce the risk of Aβ seeds being transmitted through medical devices. Additionally, sterilization methods using hydrogen peroxide gas plasma can inactivate Aβ seeds sticking to stainless steel wires (Eisele et al. 2009). This method, which is commonly used in hospitals (Sakudo et al. 2022; Okpara-Hofmann et al. 2005; Kyi et al. 1995), applies an electric field to the gas that evaporates from a concentrated hydrogen peroxide solution in a closed chamber and creates a sterilizing environment (Fichet et al. 2007; Rogez-Kreuz et al. 2009). The Thioflavin T fluorescence assay has shown that autoclaving at 135°C for 90 min rather than under conventional conditions (121°C, 30–60 min) was more effective in eliminating Aβ seeding activity (Nakano et al. 2022).

To evaluate the efficacy of a cleaning method, it is essential to detect residual trace amounts of Aβ seeds. Both the protein misfolding cyclic amplification assay (PMCA) and real-time quaking-induced conversion (RT-QuIC) were originally designed to identify prion seeds (Saborio et al. 2001; Atarashi et al. 2011). In both processes, the seeds interact with normal soluble monomeric proteins, converting them into fibrils of misfolded Aβ. The difference between the two methods is that PMCA uses repeated sonication, while RT-QuIC employs shaking to fragment the fibrils into new seeds for amplification cycles. Once sufficient aggregates have been obtained, the misfolded proteins are detected by biochemical assays in PMCA, or fluorescent dyes in RT-QuIC (Kulichikhin et al. 2021). Applying these amplification methods for Aβ has been difficult. An Aβ-PMCA assay has been reported to detect oligomeric Aβ in CSF (Salvadores et al. 2014) but it needs replication and has not been tested for detection of Aβ seeds on medical devices.

7.2 | Precautions to Avoid Aβ Transmission in Research Laboratories

Although there is no evidence of laboratory transmission of Aβ to date, there are at least two cases of accidental transmission of prions in lab settings. Moreover, Aβ seeds are often concentrated in laboratories for experimental purposes and thus increase the risk of transmission. Biosafety measures are now being implemented in laboratories around the world (e.g., UK Department of Health and Social Care (Department of Health and Social Care, UK 2021)). Our laboratories have also established protocols for handling Aβ seeds (Table 1 and Figure 2). Specifically, a dedicated space has been established (the potentially infectious-agents laboratory (PIA lab)) to limit exposure to Aβ seeds. Wearing protective glasses and a

TABLE 1 | Biosafety measures for working with Aβ seeds in PIA labs.

The setup of PIA lab
1. Doors of the PIA labs must always stay closed.
2. Equipment in the PIA lab stays in the PIA lab.
3. Lab coats used in the PIA lab stay in the PIA lab. (Once no longer needed or dirty move them to the laundry collection bag in the PIA lab for autoclaving and washing).
4. Cover the bench with an absorbing paper, and trash it in waste baskets that remain in the PIA lab until autoclaving.
Personal protection when working in PIA lab
1. Wear a lab coat, shoe protection, surgical mask, protective glasses and gloves (preferentially double) at all times.
2. When using sharp tools (e.g., TEM tweezers, scalpels and blades for microtome and cryostat) wear anti-cut gloves.
3. When handling potentially Aβ seeds-containing tissue always work in a biosafety cabinet and use disposable scalpels and tweezers.
4. Open tubes with Aβ containing materials in the safety cabinet and avoid splashing.
Decontamination
1. Cleaning the bench with 1% SDS (preferentially wetted for 1 h).
2. Immersing the reusable tools completely in 1% SDS for 2 h.
3. Autoclaving all waste from PIA lab.

Abbreviation: PIA, potentially infectious-agent.

surgical mask and working under the fume hoods when exposed to potential aerosols in the PIA lab minimizes exposure to Aβ or other proteopathic seeds. When handling Aβ-rich tissues (both from humans and mice), disposable instruments and cut-resistant gloves are used to limit potential transmission via cuts from sharp instruments. Cleaning all reusable tools and contaminated surfaces with a solution of 1% SDS, 1% Hellmanex II, or 1% TFD4 dissolved in milliQ water is used to inactivate putative Aβ seeds (Fenyi et al. 2018) while autoclaving all waste from the PIA lab can prevent the spread of Aβ seeds outside the laboratory (Table 1).

8 | Conclusion

Prion diseases and other proteopathic neurodegenerative diseases, among them AD but also Parkinson's disease, ALS, Huntington's disease, and many others (Jucker and Walker 2018) are characterized by the misfolding and seeded propagation of specific proteins. The complex and still incompletely understood mechanism by which these proteins aggregate and trigger a pathological process is of fundamental importance for the development of disease-modifying treatments. Much depends on clarifying the mechanisms by which seeds originate, spread, and proliferate throughout the brain. New ultrasensitive methods for detecting very low amounts of Aβ seeds in the brain, CSF, and blood have the potential to clarify some of these mechanisms. Elucidating the role of the host and actors such as oligodendrocytes and microglia is equally important.

As our understanding of the prion-like properties of Aβ seeds has grown, it is now reasonable to ascribe recent reports of iatrogenic CAA and possibly AD to the introduction of Aβ seeds via contaminated biologics. While there is not yet compelling evidence for the transmission of Aβ proteopathy by other means, the potential for such infectivity and lessons learned from long-standing research on prions argue for taking reasonable precautions when working clinically and scientifically with potentially infectious proteins. Such precautionary measures have therefore been introduced in recent years, similar to those followed when working with prions. In the future, the implementation of biosafety measures must go hand in hand with advances in research on Aβ seeds to ensure that all possible risks are taken into account.

Author Contributions

Natalie Beschorner: writing – original draft, writing – review and editing. **Ying Xu:** writing – original draft, writing – review and editing. **Mathias Jucker:** writing – review and editing. **Alejandro Ruiz-Riquelme:** writing – original draft, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this review because no new data were created or analyzed.

Peer Review

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