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# Aβ Seeding as a Tool to Study Cerebral Amyloidosis and Associated Pathology

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Misfolded proteins can form aggregates and induce a self-perpetuating process leading to the amplification and spreading of pathological protein assemblies. These misfolded protein assemblies act as seeds of aggregation. In an *in vivo* exogenous seeding model, both the features of seeds and the position at which seeding originates are precisely defined. Ample evidence from studies on intracerebal injection of amyloid-beta (Aβ)-rich brain extracts suggests that Aβ aggregation can be initiated by prion-like seeding. In this mini-review article, we will summarize the past and current literature on Aβ seeding in mouse models of AD and discuss its implementation as a tool to study cerebral amyloidosis and associated pathology.

**Keywords: Alzheimer's disease, cerebral amyloidosis, amyloid plaques, Aβ seeding, cross-seeding**

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## HISTORY OF SEEDING: FROM *IN VITRO* TO *IN VIVO*

Protein aggregation is a common feature of many neurodegenerative diseases that is assumed to play a central role in the pathogenesis. The aggregation of Aβ has been described as a nucleation-dependent polymerization process, including an initial slow nucleation phase, also called lag-phase, followed by a rapid growth phase (Jarrett and Lansbury, 1993; Jarrett et al., 1993; Harper and Lansbury, 1997; Walsh et al., 1997). The nucleus or seed formation in the nucleation phase is the rate-limiting step and thermodynamically unfavorable (Jarrett and Lansbury, 1993). The addition of stable seeds, e.g., aggregates generated by fragmentation of fibrils (Jarrett and Lansbury, 1993; Falsig et al., 2008; Knowles et al., 2009; Xue et al., 2009), accelerate the polymerization process and shorten significantly the lag-phase in a process termed "seeding" (Jarrett and Lansbury, 1992, 1993; Harper and Lansbury, 1997). These preformed seeds serve as a template for polymerization of respective aggregates (Jarrett and Lansbury, 1992) and can either have the same nature as the nuclei leading to a homologous seeding or be made from a different protein inducing heterologous seeding (Morales et al., 2009, 2013). Several *in vitro* and *in vivo* aggregation studies have provided the essential proof for a seeded-nucleation model of Aβ (Jarrett et al., 1993; Lomakin et al., 1996, 1997; Harper and Lansbury, 1997; Kane et al., 2000; Walker et al., 2002; Petkova et al., 2005; Meyer-Luehmann et al., 2006; Knowles et al., 2009; Paravastu et al., 2009; Eisele et al., 2010; Cohen et al., 2013).

The nucleation-dependent polymerization process gives rise to several Aβ assemblies such as oligomers, protofibrils and fibrils (Glenner and Wong, 1984; Harper et al., 1997; Lambert et al., 1998). Soluble Aβ oligomers were proposed to be the most toxic species of Aβ (Walsh et al., 2002; Wang et al., 2002; Cleary et al., 2005; Lesné et al., 2006; Townsend et al., 2006; Shankar et al., 2008), as it was already demonstrated for small assemblies of the prion protein (PrP; Silveira et al., 2005). Intracerebroventricular injections of media containing naturally secreted Aβ oligomers into rats led to inhibition of hippocampal long-term potentiation (LTP) and disrupted cognitive function (Walsh et al., 2002; Cleary et al., 2005). Moreover, soluble Aβ oligomers such as dimers isolated from human AD brains and Aβ*56 isolated from APP-transgenic (APP-tg) mouse brain were shown to impair synaptic plasticity and memory when administered to rodents and rat hippocampal slices (Lesné et al., 2006; Shankar et al., 2008). Hyperaggregation of soluble Aβ into higher aggregates was shown to be protective against Aβ mediated toxicity (Cohen et al., 2009). Despite the fact that soluble oligomers represent the most toxic species of Aβ, the presence of insoluble Aβ amyloid plaques leads to disruption of neocortical synaptic transmission, neuronal deformation and neuronal dysfunction (Stern et al., 2004; Tsai et al., 2004; Meyer-Luehmann et al., 2008, 2009).

The intracerebral injections of PrP-containing human brain homogenates into animals have led to the discovery of the transmissible prion disease approach (Gajdusek et al., 1966; Gibbs et al., 1968; Gajdusek, 1977; Hadlow et al., 1980; Prusiner, 1982). Since PrP and the Aβ peptide share similar biological and molecular features regarding the pathogenic self-assembly, misfolding and spreading within the brain, the question whether this concept could also be applied to other neurodegenerative diseases such as Alzheimer's disease with Aβ peptide as potential trigger of the disease has been under discussion for quite some time (Prusiner, 1984; Rasmussen et al., 2017a).

Initial *in vivo* Aβ seeding experiments were performed by intracerebral inoculation of brain extract from AD patients in non-human primates that yielded inconsistent results (Goudsmit et al., 1980; Manuelidis and Manuelidis, 1991). Later attempts to seed Aβ pathology were successful in wild-type marmosets (Baker et al., 1993, 1994; Ridley et al., 2006), a New World monkey that express human-type sequence of Aβ (Heuer et al., 2012). Intracerebral infusion of brain tissue material from an AD patient resulted in Aβ deposits that could not be observed in control animals (Baker et al., 1993, 1994; Ridley et al., 2006). Interestingly, the distribution pattern of exogenously induced plaques was similar to those of elderly uninjected controls that developed cerebral amyloidosis (Maclean et al., 2000). However, the use of marmosets as a model for AD was considered impractical (Baker et al., 1993, 1994; Maclean et al., 2000; Ridley et al., 2006).

It is worth highlighting that compared to other mouse models for α-synuclein and tau, it is not possible to induce cerebral amyloid deposition in non-transgenic mice within its normal life span (Meyer-Luehmann et al., 2006; Luk et al., 2012; Guo et al., 2016), due to three amino acid difference between the mouse- and human-derived Aβ sequence (Otvos et al., 1993).

The strongest piece of evidence for "prion-like" seeding of misfolded Aβ aggregates *in vivo* was documented in experiments carrying out the inoculation of diluted brain extracts derived from confirmed AD patients into young, pre-depositing APP-tg mice (Kane et al., 2000; Walker et al., 2002; Meyer-Luehmann et al., 2006). APP-tg mice inoculated with AD brain extracts displayed remarkable Aβ deposition as well as mice injected with brain homogenate from control patients due to similar Aβ production levels (Kane et al., 2000; Walker et al., 2002; Meyer-Luehmann et al., 2006; Szaruga et al., 2015), while attempts to seed Aβ pathology *in vivo* using cerebrospinal fluid (CSF) from AD patients failed, although Aβ concentrations were significantly higher than the ones present typically in brain homogenates (Fritschi et al., 2014b). Whether some cofactors or a specific conformation of Aβ is missing in CSF compared to brain homogenates is currently not clear (Fritschi et al., 2014b). Further studies confirmed that APP-tg mouse brain extracts were equally efficient to seed Aβ aggregation in APP-tg mice as the ones prepared from human AD brains (Meyer-Luehmann et al., 2006; Eisele et al., 2009; Watts et al., 2011; Morales et al., 2012; Rosen et al., 2012). Most of those Aβ seeding studies are carried out in tg mice overexpressing mutant human APP, although Aβ deposits can also be induced *de novo* in rodents after comparable longer incubation periods that would never exhibit Aβ plaque pathology spontaneously within their normal lifespan (Morales et al., 2012; Rosen et al., 2012). This is a strong indication that exogenously applied seeds act as a template for misfolding of endogenous Aβ and that seeding is not solely promoting the premature deposition of amyloid. Importantly, the overexpression of APP seems not essential for the prion-like propagation of seeded Aβ aggregates within the brain (Ruiz-Riquelme et al., 2018).

## NATURE OF Aβ SEEDS AND SEED-INDUCED Aβ DEPOSITS

The injection of autopsy-derived, brain extracts from young control individuals into APP-tg mice with no seed-induced Aβ deposits suggested that the presence of Aβ in the brain extract is crucial for *in vivo* seeding (Kane et al., 2000; Walker et al., 2002). To substantiate this hypothesis, depletion of Aβ and Aβ aggregates from the brain extracts prevented induction of Aβ deposits in host mice as well as formic acid treatment of the inoculum (Meyer-Luehmann et al., 2006; Duran-Aniotz et al., 2014). On the other hand, synthetic, multimeric Aβ fibrils have also been used to determine the essential seeding factor. Original experiments using synthetic Aβ in different composition displayed only poor seeding capacity (Meyer-Luehmann et al., 2006), while higher amounts of synthetic Aβ fibrils were indeed seed-competent but not as efficient as Aβ-containing human or mouse brain homogenates (Stöhr et al., 2012, 2014). Using hippocampal slice culture model, Novotny et al. revealed that synthetic Aβ can be converted into seeds able to induce β-amyloidosis *in vivo* (Novotny et al., 2016). Whether a particular conformation of the Aβ or additional factors is needed to induce seeding is not yet clear. To assess the stability of Aβ seeds *in vivo*, APP-null mice have been

used as recipient mice that fail to induce Aβ pathology because of absent Aβ production. Six-months post-incubation, brain homogenates of these mice successfully induced Aβ deposition in APP-tg hosts, suggesting that Aβ seeds are highly robust and are able to retain their seeding activity for months (Ye et al., 2015a). Furthermore, Aβ-rich extracts prepared from human AD and APP-tg mice brains after formaldehyde treatment for 1–2 years were still able to seed Aβ deposits in APP-tg mice (Fritschi et al., 2014a). Nonetheless, the question still remains which Aβ species in brain homogenates is essential for the seeding activity in APP-tg mice and what cofactors are required. Indeed, another study revealed that Aβ seeds do not consist of only one type of Aβ aggregate, but are rather a mixture of small soluble or insoluble (in 100,000× *g* ultracentrifuged supernatant or pellet fraction) and proteinase-K (PK)-sensitive or PK-resistant Aβ species (Langer et al., 2011). Interestingly, sonication and thus fragmentation of the insoluble fraction into smaller and more soluble Aβ seeds, enhanced the seeding activity of the inoculum, consistent with results from fragmentation studies (Jarrett and Lansbury, 1993; Falsig et al., 2008; Knowles et al., 2009; Xue et al., 2009). In line with the previous mentioned studies, Aβ oligomers seem to be important for the initiation of Aβ aggregation especially for the early phase of the seeding process (Katzmarski et al., 2019). According to another study, the Aβ seeding potency of the brain extracts is highest at the very early stage of cerebral amyloidosis (Ye et al., 2017).

As demonstrated before, Aβ can aggregate into polymorphic shapes (Fändrich et al., 2009; Levine and Walker, 2010; Eisenberg and Jucker, 2012). Aβ isolated from AD patients were shown to trigger synthetic Aβ to adopt corresponding structural "strains" (Lu et al., 2013; Qiang et al., 2017). Also molecular differences in Aβ between non-demented and AD cases were pointed out (Piccini et al., 2005; Portelius et al., 2015), supporting the hypothesis of defined Aβ "strains" that probably correspond to the development of AD pathology. "Strain-like" variations of Aβ were observed in *in vitro* (Petkova et al., 2005; Nilsson et al., 2007; Paravastu et al., 2008; Meinhardt et al., 2009; Spirig et al., 2014) as well as *in vivo* studies using AD mouse models (Meyer-Luehmann et al., 2006; Heilbronner et al., 2013; Stöhr et al., 2014; Watts et al., 2014; Condello et al., 2018). Moreover, these "strain-like" variations in the molecular structure of Aβ aggregates were shown to be transmissible between APP-tg donor and recipient (Meyer-Luehmann et al., 2006; Heilbronner et al., 2013). Interestingly, the morphology and the biochemical composition of the seed-induced Aβ deposits represented histopathological features of the plaques present in donor and host mice. The respective brain region and thus the local environment seem to play a crucial role with regard to the morphology of the exogenously induced Aβ plaques (Eisele et al., 2009; Ye et al., 2015b). While infusion of brain homogenate into the hippocampus yielded compact and diffuse plaques, injections into striatum led to the formation of merely diffuse plaques (Eisele et al., 2009). Finally, "strain-like" features of Aβ aggregates present in different human familial AD cases could be partially recapitulated in mouse models by exogenous seeding (Watts et al., 2014; Rasmussen et al., 2017b; Condello et al., 2018) that were even maintained after multiple passages (Watts et al., 2014).

## SPREADING

The induction of Aβ plaque pathology as consequence of exogenous seeding appears initially in the proximity to the injection site, where the highest concentration of seeds due to administration has been assumed (Kane et al., 2000; Walker et al., 2002; Meyer-Luehmann et al., 2006; Eisele et al., 2009; Hamaguchi et al., 2012; Ye et al., 2015b). Within the first day, injected material is still measurable before the Aβ signal usually becomes immunohistochemically undetectable for several months (Ye et al., 2015b). Importantly, seed-induced Aβ deposits present after several months of incubation were evidently not the injectate itself (Kane et al., 2000; Meyer-Luehmann et al., 2006; Eisele et al., 2009). Moreover, the diffusion of the injected Aβ material away from the injection site within a 7 day time-frame revealed that the initial Aβ distribution pattern in the affected regions resembled the pattern of seeded aggregation appearing 5 months after injection (Walker et al., 2002). Although seed-induced Aβ deposition close to the injection site has been shown to increase over time, it expands also to more distant and axonally interconnected brain regions (Kane et al., 2000; Walker et al., 2002; Meyer-Luehmann et al., 2006; Hamaguchi et al., 2012; Rönnbäck et al., 2012; Ye et al., 2015b), suggesting that neuronal pathways are essential for the trafficking of Aβ seeds through the brain. It was further postulated that Aβ was traveling non-randomly and depositing mostly along structures corresponding to the limbic connectome (Ye et al., 2015b). So far, there is no evidence for active transport of Aβ along neurons *in vivo*, even though it is thought to be a plausible mechanism for the spreading of Aβ pathology based on results from *in vitro* studies (Nath et al., 2012; Domert et al., 2014; Song et al., 2014; Brahic et al., 2016). Furthermore, the occurrence of intraneuronal Aβ in mice, as well as human brains, supports the hypothesis of neuronal involvement in Aβ pathology dissemination (Gouras et al., 2000; LaFerla et al., 2007). Most likely the mechanism responsible for the distribution of seeded Aβ deposits is a combination of both, passive diffusion and active transport mechanisms (Eisele and Duyckaerts, 2016). The exact cellular mechanisms involved in spreading of Aβ have not yet been elucidated. Recent studies suggested the involvement of endosomes/lysosomes or intracellular assemblies of Aβ to be crucial factors (Hu et al., 2009; Marzesco et al., 2016).

Since the transmission of Aβ seeds resembles a prion-like mechanism, the systemic routes relevant for transmission of prion diseases from periphery to CNS were also taken into account (Blättler et al., 1997; Mabbott and MacPherson, 2006; Aguzzi et al., 2008). Induction of Aβ pathology by means of oral, intraocular or intranasal routes was excluded due to absent Aβ seeding in inoculated APP-tg mice (Eisele et al., 2009). However, intraperitoneal (Eisele et al., 2010, 2014) or intravenous (Burwinkel et al., 2018) administration of Aβ-rich brain extracts induced intracerebral β-amyloidosis especially in

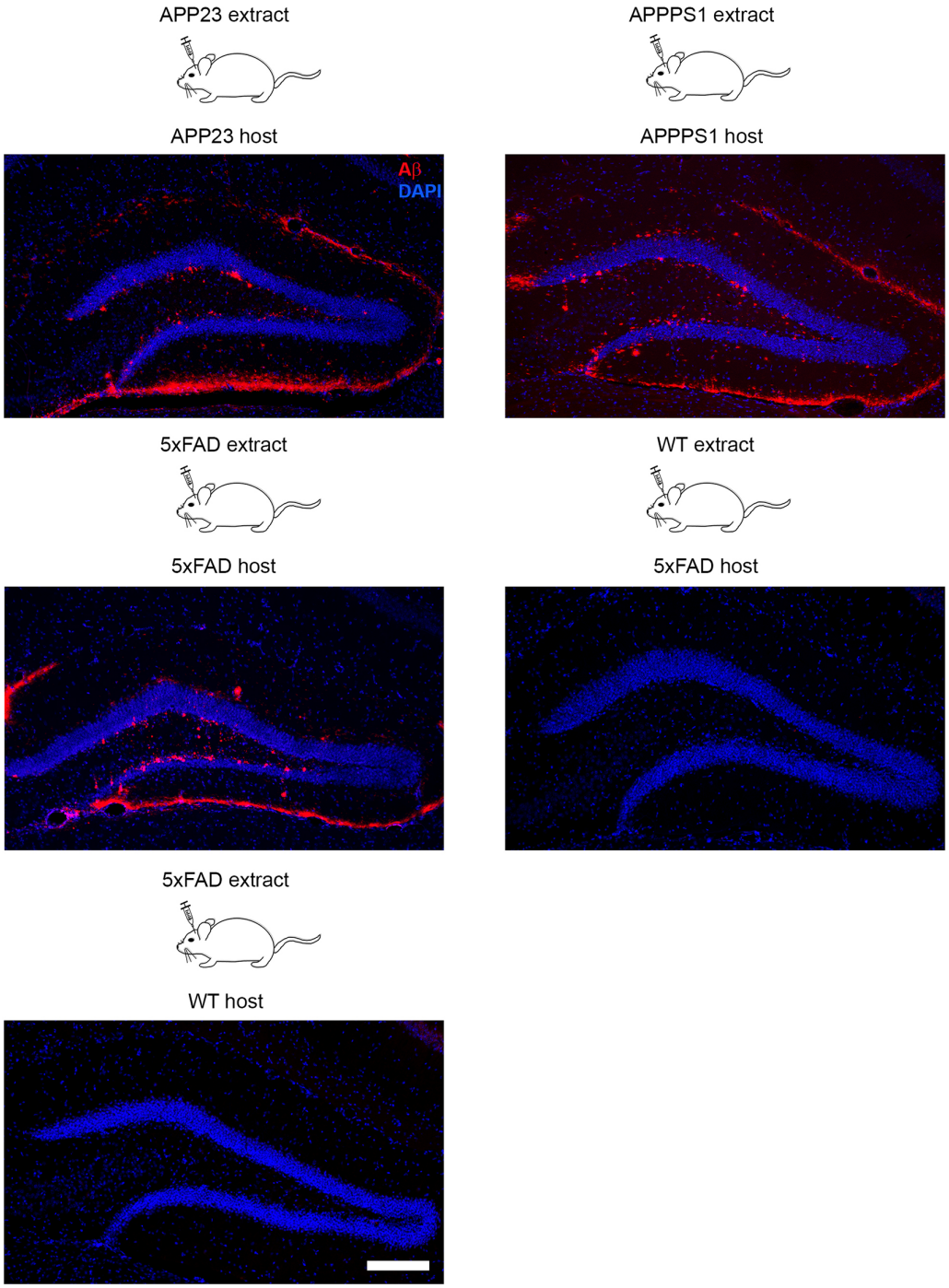


**FIGURE 1 |** Intracerebral inoculation of brain extracts from APP23, APPPS1 and 5xFAD mice into the hippocampus of young APP-transgenic (APP-tg) host mice with genetically identical background induced seeding of Aβ pathology. In contrast, infusion of brain homogenate from a wild-type mouse into a 5xFAD tg host and vice versa failed to induce cerebral β-amyloidosis due to the lack of Aβ either in the brain extract or host animal. Fluorescence microscopy of Aβ (6E10, red) and cells (DAPI, blue). Scale bar represents 100 μm.

the walls of the blood vessels in form of cerebral amyloid angiopathy (CAA). In contrast to CAA, Aβ aggregates become manifest in amyloid plaques in the brain parenchyma (Thal et al., 2015). CAA is an age-related vessel disorder that can occur in the brain of AD patients as well as non-demented elderly people and is associated with vascular dementia (Thal et al., 2012, 2015). The occurrence of CAA after administration of Aβ-rich extracts in spatially different brain regions indicates as

well a role for the vascular system (Meyer-Luehmann et al., 2006; Eisele et al., 2009) or perivascular drainage channels (Weller et al., 1998; Thal et al., 2007) as possible propagation route for Aβ seeds. Whether parenchymal and vascular seed-induced Aβ deposits are generated by the same or *via* different pathways is still unknown. Nevertheless, these results provided sufficient evidence for the spread of Aβ seeds possibly *via* vascular routes. Transport of Aβ from the periphery to the brain by immune cells such as macrophages was also proposed (Eisele et al., 2014; Cintron et al., 2015), but the precise mechanisms remained unclear.

## CROSS-SEEDING

Several studies have proven the overlap of different neuropathological lesions such as neurofibrillary tangles (NFTs; tau), Lewy bodies (α-synuclein) or prions with Aβ pathology in brains of patients with neurodegenerative diseases like AD, PD, Dementia with Lewy Bodies (DLB) and Creutzfeldt-Jakob disease (CJD) (McKeith et al., 1996; Braak and Braak, 1997; Hamilton, 2000; McKeith, 2000, 2006; Ferrer et al., 2001; Tsuchiya et al., 2004; Debatin et al., 2008; Hyman et al., 2012; Jaunmuktane et al., 2015). *In vitro* and *in vivo* studies have demonstrated that tau, α-synuclein and prion proteins can interact with Aβ and thus influence the onset and course of the respective disease (Hamilton, 2000; McKeith, 2000; Götz et al., 2001; Lewis et al., 2001; Masliah et al., 2001; Tsigelny et al., 2008; Lasagna-Reeves et al., 2010; Morales et al., 2010).

Since several years, there has been a debate on the interaction between Aβ peptide and tau protein and its influence on the pathogenesis of AD. Both pathologies, amyloid plaques and NFTs containing hyperphosphorylated tau, are necessary for the accurate diagnosis of AD (Hyman et al., 2012). Tau pathology was also shown to be directly inducible *in vivo* in wild-type and tau tg mice after injections of tau-containing brain extracts or synthetic tau fibrils (Clavaguera et al., 2009, 2013; Lasagna-Reeves et al., 2012; Iba et al., 2013; Guo et al., 2016). According to the amyloid cascade hypothesis, amyloid deposition precedes NFT formation and posits that changes in amyloid-β lead to widespread tau pathology (Hardy and Selkoe, 2002). Early results from *in vitro* studies gave already a hint on the potency of Aβ to induce phosphorylation and aggregation of tau (Busciglio et al., 1995; Ferrari et al., 2003; Pennanen and Götz, 2005; Lasagna-Reeves et al., 2010). Infusion of synthetic Aβ fibrils, pre-aggregated Aβ or Aβ-rich extracts into the hippocampus of tau-transgenic (tau-tg) mice indeed resulted in enhanced NFT formation (Götz et al., 2001; Bolmont et al., 2007; Vasconcelos et al., 2016), similar to the effects seen in double-transgenic mice exhibiting both Aβ and tau pathology (Lewis et al., 2001; Pooler et al., 2015). Injections of human derived-tau in mice with a high Aβ plaque load developed enhanced induced tau pathology, suggesting that Aβ plaques might trigger the propagation of tau (He et al., 2018).

Furthermore, in about 50% of AD patients the presence of α-synuclein aggregates has been verified (Hamilton, 2000; Uchikado et al., 2006). Previous studies have implicated a direct interaction of Aβ and α-synuclein (Tsigelny et al., 2008). It has also been demonstrated that Aβ can trigger α-synuclein polymerization *in vitro* and overexpression of human APP/Aβ fostered the accumulation of α-synuclein and associated disease phenotype *in vivo* (Paik et al., 1998; Masliah et al., 2001). Besides, α-synuclein has been identified as a major protein accumulating in neurites in APP-tg mice, implying that Aβ might be causal for this aggregation (Yang et al., 2000). Surprisingly, APP-tg mice intracerebrally injected with α-synuclein-derived extract were devoid of seeded Aβ deposition, suggesting that α-synuclein is not able to cross-seed Aβ plaques *in vivo* (Bachhuber et al., 2015). Instead, the presence of α-synuclein even hampered amyloid plaque formation in APP-tg mice (Bachhuber et al., 2015). Moreover, brains of APP-tg mice lacking α-synuclein exhibited a significant increase in Aβ plaque load, suggesting as well a suppressive role of α-synuclein on the progression of Aβ plaque pathology (Kallhoff et al., 2007).

Finally, a role for prion protein to interact with Aβ aggregates has also been proposed. Intraperitoneal injection of prion proteins into APP-tg mice seemed to promote mature Aβ plaque formation and prion pathology was enhanced in presence of Aβ (Schwarze-Eicker et al., 2005; Morales et al., 2010). However, no cross-seeding was observed after intracerebral inoculation of infectious prions into the hippocampus of APP-tg mice (Rasmussen et al., 2018).

## CONCLUSION

The seeding model of AD pathology in mice is a widely used tool to study plaque formation *in vivo* at its very early stage and within a defined time period (Kane et al., 2000; Meyer-Luehmann et al., 2006). In general it is a very robust model that was applied in many different APP-tg mouse models (Tg2576, APP/PS1, APP23, 5xFAD) with only slight variation with regard to the onset of seeding (first sign of seed-induced Aβ deposits after intracerebral inoculations) and affected brain areas (Kane et al., 2000; Meyer-Luehmann et al., 2006; Duran-Aniotz et al., 2014; Ziegler-Waldkirch et al., 2018) (**Figure 1**). Although seeding experiments were performed mainly in the hippocampus, the induction of Aβ deposits was additionally demonstrated in several different brain areas such as parietal cortex, striatum or olfactory bulb (Eisele et al., 2009). The greatest advantage of this model is that the accelerated Aβ plaque formation reduces the incubation time (Meyer-Luehmann et al., 2006). Furthermore, the age of the newborn plaques is easily determinable due to the predictability of the model. Characterization of seed-induced Aβ deposition and its effect on the environment at the injection side as well as areas affected by spreading of Aβ seeds can be studied as well. Recently, the consequence of Aβ seeding on adult neurogenesis and cell death was demonstrated (Ziegler-Waldkirch et al., 2018), supporting the notion that seed-induced Aβ deposits may also be a source of toxicity. Future experiments will need to test the consequences of Aβ seeding on other cell types and unravel in detail the origin of Aβ-mediated toxicity. Finally, *in vivo* seeding as a model can assist to identify factors impacting or accelerating AD progression such as microglia-derived ASC specks (Venegas et al., 2017) or the Trem2 receptor

on microglia (Parhizkar et al., 2019) that might in turn contribute to the development of appropriate AD treatment.

## AUTHOR CONTRIBUTIONS

MF and MM-L wrote, read and approved the final manuscript.

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**Conflict of Interest**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.