Positron emission tomography in animal models of Alzheimer’s disease amyloidosis

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Abstract: Animal models of Alzheimer’s disease amyloidosis that recapitulate cerebral amyloid-beta pathology have been widely used in preclinical research, and have greatly enabled the mechanistic understanding of Alzheimer’s disease and the development of therapeutics. Comprehensive deep phenotyping of the pathophysiological and biochemical features in these animal models are essential. Recent advances in positron emission tomography have allowed the non-invasive visualization of the alterations in the brain of animal models as well as in patients with Alzheimer’s disease. These tools have facilitated our understanding of disease mechanisms, and provided longitudinal monitoring of treatment effect in animal models of Alzheimer’s disease amyloidosis. In this review, we focus on recent positron emission tomography studies of cerebral amyloid-beta accumulation, hypoglucose metabolism, synaptic and neurotransmitter receptor deficits (cholinergic and glutamatergic system), blood-brain barrier impairment and neuroinflammation (microgliosis and astrocytosis) in animal models of Alzheimer’s disease amyloidosis. We further propose the emerging targets and tracers for reflecting the pathophysiological changes, and discuss outstanding challenges in disease animal models and future outlook in on-chip characterization of imaging biomarkers towards clinical translation.
1. Introduction

Alzheimer’s disease (AD) is the most common cause of dementia, afflicting 50 million people worldwide [1]. AD is pathologically featured by amyloid-beta (Aβ) plaques and neurofibrillary tangles formed by hyperphosphorylated tau, gliosis, neurotransmitter deficits, and neuronal loss leading to cognitive impairment [2,3]. Aβ is produced from through sequential cleavages of amyloid precursor protein (APP) by β-secretase and γ-secretase. An imbalance in the production and clearance of Aβ leads to its abnormal cerebral accumulation of Aβ in different forms (oligomers, protofibrils, fibrils and amyloid plaques)[4]. The abnormal accumulation of Aβ deposits, especially the neurotoxic oligomeric Aβ plays a crucial role in the disease pathogenesis in animal models and in patients with AD [5-8]. Recent advances in positron emission tomography (PET) using [18F]fluorodeoxyglucose (FDG), tracers for Aβ pathology and tauopathy, structural magnetic resonance imaging and cerebrospinal fluid biomarkers have provided valuable insights into the time course of pathophysiology of AD continuum, assisted the early and differential diagnosis, and facilitated the development of therapeutics for AD [9-13]. A range of molecular imaging tracers for neuroinflammation, synaptic density and neurotransmitter receptor deficits have been developed and provided comprehensive picture of AD [13-16]. Disease animal models recapitulating AD amyloidosis have been developed including transgenic APP/PS1, APP23, APPswe, J20, PS2APP, arcAβ, 5xFAD, 3×Tg mice, TgF344 and McGill-R-Thy1-APP rats [17-24], 2nd generation AppNL-G-F, Apphu/hu knock-in mice [25,26], 3rd generation mouse models [27,28] as well as non-human primate model [29]. The animal models accumulate cerebral Aβ pathology, develop gliosis, metabolic and synaptic deficits and cognitive impairment assessed by behavior tests, facilitated the understanding of disease mechanisms and the development of treatment strategies. In this review, we focus on the recent development in PET imaging for Aβ, alterations in cerebral glucose metabolism, synaptic neurotransmitter receptors, blood-brain barrier as and neuroinflammation in rodent models of AD amyloidosis.
2. Amyloid imaging

*Ex vivo* immunohistochemistry in brain tissues from amyloidosis mouse or rat models has revealed that Aβ pathology initiates first in the cortical region, and spreads to the limbic region and finally to the cerebellum [30], in a animal line-dependent manner. More pronounced load of Aβ deposits was observed in 5xFAD mice compared to that in APPswe mice [30-32]. In addition to the parenchymal Aβ plaques, cerebral amyloid angiopathy (CAA) is also observed in different amyloidosis animal models especially in the APPDutch mice, Tg-SwDI, APP/London, APP23, arcAβ and APPswe mice [33,34].

Several Aβ imaging tracers have been developed and applied in animal models of amyloidosis, including benzothiazole derivatives [11C]PiB, [18F]flutemetamol, [18F]florbetaben, [18F]FIBT, [18F]florbetapir, [11C]AZD2184, [18F]FC119S and [18F]flutafuranol, benzofuran derivatives [18F]FACS and [18F]FPZBF-2, benoxazole derivatives [11C]BF-227 and [18F]MK3328, benzoselenazole derivative [18F]fluselenamyl. hydroxyquinoline derivative [18F]CABS13, imidazopyridine derivative [18F]DRKXXH1, as well as [64Cu]labelled 8a′–8d and HYR-17 [35-52] (Table 1). In addition, single-photon emission computed tomography (SPECT) tracers imidazopyridine derivative [125I]DRK092, [125I]CQ-PBCA nanoparticles, [125I]DRM106 [53-56] and multi-modal imaging tracer [18F]CDA-3 [57-59] have been evaluated in amyloidosis rodent models. Higher cortical amyloid PET tracers uptake were observed in various transgenic or knock-in animal models compared to wild-type littermates and validated by the *ex vivo* immunohistochemical stainings. Longitudinal comparative imaging studies across amyloidosis mouse lines have detected distinct Aβ spreading patterns *in vivo*. Snellman *et al.* showed a greater Aβ tracer dynamic range in the brain of APP23 model compared with that of APPswe and APP/PS1 models by PET imaging using both [11C]PiB and [18F]flutemetamol [42,60]. Brendel *et al.* compared four amyloidosis mouse strains (PS2APP, APPswe/PS1G384A, APP/PS1, APPswe) and found that PS2APP mice demonstrated greater dynamic changes in the longitudinal [18F]florbetaben
imaging study [61] (Fig. 1d). Moreover, comparative studies of amyloid imaging tracers have been performed in a head-to-head manner in animal models, such as comparing $^{[11]C}$PiB, $^{[18]F}$florbetaben, and $^{[18]F}$FIBT [40], and comparing $^{[18]F}$florbetaben and $^{[18]F}$flutemetamol [62]; Similar patterns of tracer detection of cerebral Aβ distribution in the animal models have been reported in general. Sacher et al. showed an asymmetry and hemispheric predominance of Aβ accumulation detected by using $^{[18]F}$florbetaben accompanied by microglial activation assessed by using $^{[18]F}$GE-180 in five mouse lines including APP/PS1, PS2APP, APP-SL70, APPswe transgenic mice and App$^{NL-G-F}$ knock-in mice [63].

As the commonly used amyloid tracers cannot differentiate parenchymal Aβ plaques and CAA [64], efforts have been made to develop CAA specific tracers such as resorufin derivatives [65], $[^3H]1, 2$ [66], and $[^{99m}Tc]$hydroxamamide complexes [67]. One of the unsolved question in Aβ imaging is the detection towards small forms of Aβ aggregates. Biechele et al. recently indicated that the non-fibrillar Aβ (positive for 3552 antibody) in addition to the Thiazine red stained fibrillar Aβ significantly impacted the $^{[18]F}$florbetaben PET signal in App$^{NL-G-F}$ and APP/PS1 mice from 3-12 month-of-age [68]. In addition to the small chemical dyes, PET using Aβ antibodies conjugated to a transferrin receptor antibody, such as $[^{125}I]$RmAb158-scFv8D3, $[^{124}I]$8D3-F(ab’)2-h158 have been developed to detect cerebral accumulation of small forms of Aβ. These tracers habor an improved blood-brain barrier permeability and have been demonstrated in several transgenic mouse models of amyloidosis [53,69,70]. Meier et al. demonstrated that the uptake of $[^{125}I]$RmAb158-scFv8D3 and $[^{124}I]$8D3-F(ab’)2-h158 was significantly higher in the cortical regions of transgenic ArcSwe mice compared with non-transgenic littermates. In addition, the distribution pattern of PET using $[^{124}I]$8D3-F(ab’)2-h158 differs from that by PET using $^{[11]C}$PiB in the brain of tg-ArcSwe mice, indicating preference to different types of Aβ by these two tracers (Figs. 1a-c)[70]. Given the quantitativeness of in vivo microPET, non-invasive
imaging using $^{18}$Fflorbetaben and $^{18}$Fflorbetapir for Aβ load have been applied for longitudinal monitoring of the treatment effect in animal models, such as using γ-secretase modulator, and β-secretase 1 inhibitor [71-73]. Xu et al. recently demonstrated using $[^{11}]$CSGSM-1560 for in vivo detection of an increased level of γ-secretase in 5×FAD compared to wild-type mice [74] (Figs. 2 h-j).

3 Cerebral glucose metabolism imaging

Brain glucose dysregulation plays an important role in AD [75]. Post-mortem studies reported higher levels of brain tissue glucose concentration, lower levels of glucose transporter 3, and glycolytic flux in brain from patients with AD compared to controls, associating with the severity of AD pathology [75]. Accumulating evidence also indicates a link between diabetes and AD [76]. $^{18}$FFDG PET have been routinely used for detecting the reduced cerebral glucose metabolism (CMRglc) in disease specific brain regions in patients with AD, Frontotemporal dementia and Parkinson’s disease to improve the diagnostic accuracy [11,77]. In lab settings, $^{18}$FFDG PET have been assessed along with Aβ imaging in various amyloidosis rodent models such as APPswe mice, 5×FAD, APP/PS1, 3×Tg, Tg4-42, TASTPM mice, and McGill-R-Thy1-APP rats [47,78-84] (Table 2). Most of the studies in rodent amyloidosis models reported a global reduction in CMRglc, although few exception of increased CMRglc (associating with gliosis) was also reported [85]. Several studies have reported the longitudinal temporal and spatial association between the reginal patterns of reduced $^{18}$FFDG uptake and Aβ deposition using $[^{11}]$CPiB or $^{18}$Fflorbetaben [86,87], and with microglial activation such as using $^{18}$FGE-180 [87] (Figs. 1e-h), and $^{18}$FDPA-714 in animal models [88]. Tsukada et al. reported reduced $^{18}$FFDG measures of CMRglc, increased $[^{11}]$CPiB measures of Aβ deposition, increased $[^{11}]$CDPA-713 for microglia activation, and reduced $^{18}$FBCPP-EF for mitochondrial complex 1 in brain of aged monkeys [89]. However $^{18}$FFDG uptake is known to be highly sensitive to the experimental conditions such as anesthesia, and handling, as well as genotype, age and gender of the animal models [90].
4 Synaptic and neurotransmitter receptor deficits

4.1 Synaptic vesicle glycoprotein 2A

Synapse loss is reported in *post-mortem* frontal cortex of patients with AD, correlating with cognitive severity [91]. Imaging biomarkers reflecting the synapse damage or loss are thus highly desired [92]. Amyloidosis animal models show cortical, hippocampal atrophy and enlargement of ventricle assessed by using structural magnetic resonance imaging, although to a less extent compared to that in tauopathy animal models [93]. Synaptic vesicle glycoprotein 2A (SV2A) is located at the synapses across the entire brain and is the binding site for the antiepileptic drug levetiracetam [94]. Higher loads of cerebral Aβ deposits have been reported in the brain of SV2A knock out mice compared to control littermates [95]. Several SV2A PET imaging tracers have been developed including $[^{11}C]UCB-J$, $[^{18}F]UCB-H$ [96], $[^{18}F]SynVesT-1$ [97], $[^{18}F]SDM-8$ [98] and $[^{18}F]MNI-1126$ [99] (*Table 2*). A reduction of approximately 40% of SV2A signal by PET using $[^{11}C]UCB-J$ was observed in the hippocampus in patients with AD compared with cognitively normal control cases [100,101]. PET measures of Aβ deposition associated with regional synaptic density measured by $[^{11}C]UCB-J$ in patients with early AD [100,102]. Few studies have reported on SV2A imaging in AD animal models. Bertoglio *et al.* demonstrated that $[^{11}C]UCB-J$ bound specifically to SV2A in mouse brain, and that the radioligand binding can be quantified by kinetic modeling using an image-derived input function [103]. Toyonaga showed that *in vivo* $[^{11}C]UCB-J$ detected reduced levels of SV2A in APP/PS1 mice, and the treatment effects of tyrosine kinase Fyn inhibitor Saracatinib in mitigating the $[^{11}C]UCB-J$ reduction [104]. Xiong *et al.* recently compared the $[^{11}C]UCB-J$ binding in tg-ArcSwe and wild-type mice [105], and did not observe clear difference between the two groups. $[^{18}F]SynVesT-1$, $[^{18}F]$analog of $[^{11}C]UCB-J$, has demonstrated favourable *in vivo* brain uptake in non-human primate [106]. Sadasivam *et al.* showed a lower $[^{18}F]SynVesT-1$ standard uptake value (SUV) across the whole brain of APP/PS1 mice compared to non-transgenic...
mice [107]. The results from a static (30-60 min post-injection) $[^{18}\text{F}]$SynVesT-1 PET scan was found comparable to kinetic modeling results [107].

### 4.2 Glutamate receptors

The glutamate receptors are classified into the $N$-methyl-D-aspartate receptor (NMDAR), $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)-kainate receptor, and metabotropic glutamate receptors (mGluRs). The glutamate receptors mediate excitatory neurotransmission, involve in multiple second messenger systems and are essential in learning and memory [108,109]. Glutamate excitotoxicity, and disruption of the glutamate receptor mediated normal signaling are implicated in AD [110,111]. Aβ reduces glutamatergic transmission and inhibits synaptic plasticity [112,113]. Direct interaction between Aβ oligomers and glutamate receptors including NMDAR [114], mGluR subunit mGluR5 [115], AMPA receptor subunit GluA3 [116] and GluA1 [117] have been demonstrated, leading to impaired synaptic plasticity in the animal models [118]. Chronic pharmacological inhibition of mGluR5 has been shown to prevent the cognitive impairment and reduce pathological development in APP/PS1 mice [119]. Thus glutamate receptors have been important target for AD therapeutics. Several imaging tracers for glutamate receptors have been developed including $[^{11}\text{C}]$K-2 [120] and $[^{11}\text{C}]$HMS011 [121] for AMPA receptor, $[^{18}\text{F}]$GE-179 [122] and $[^{18}\text{F}]$PK-209 for NMDAR [123], $[^{11}\text{C}]$Me-NB1 [124] for NMDAR GluN1/GluN2B subunits [125], as well as $[^{18}\text{F}]$FPEB, $[^{11}\text{C}]$ABP688 and $[^{18}\text{F}]$PSS232 for mGluR5 [126-128]. In patients with AD, PET using $[^{18}\text{F}]$FPEB [129] and $[^{11}\text{C}]$ABP688 [130] revealed consistent reductions in regional mGluR5 binding in the hippocampus and amygdala compared to non-demented controls. So far only mGluR5 imaging have been reported in amyloidosis animal models and showed conflicting results probably due to different animal models utilized (Table 2). Lee et al. demonstrated an age-dependent 35% decrease in the level of $[^{18}\text{F}]$FPEB measures of mGluR5 in the cortical and subcortical brain areas in 5×FAD mice at 9 month compared
to 3 month-of-age, validated by ex vivo assessment of mGluR5 protein expression level [131]. However Varlow et al. showed that $[^{18}F]$FPEB uptake increased in the brain of 10 month-old APP/PS1 mice compared with controls [132]. Fang et al. reported similar levels of $[^{18}F]$FPEB uptake in the brain of Tg-ArcSwe mice compared to control mice at different ages [133]. However immunoblotting results indicated that the level of mGluR5 in Tg-ArcSwe mouse brain lysate was higher compared to control mice, at 12 month-of-age, not at 8 and 16 month-of age [133]. Further studies are needed to elucidate the dynamic alteration in glutamate receptors in AD animal models.

4.3 Cholinergic system

The cholinergic system is essential for learning, memory formation, attention, for regulating inflammation [134]. The cholinergic system includes nicotinic acetylcholine receptors (nAChR), muscarinic acetylcholine receptors (mAChR), acetylcholinesterase (AChE), and butyrylcholinesterase (BChE). $\alpha_7$ nAChR and $\alpha_4\beta_2$ nAChR are the most abundant nAChR subtypes in the brain. The cholinergic system is impaired early in AD associating with the cognitive, behavioral and global functioning decline [134-136]. Reduced basal forebrain cholinergic neurons, increased levels of $\alpha_7$ nAChR [137,138] and reduced levels of M1 mAChR [139] were reported in the cortical regions of post-mortem brain from AD patients compared to control. Interaction between $\alpha_7$ as well as $\alpha_4\beta_2$ nAChR and different forms of Aβ aggregates have also been reported [140-143]. Several recent PET tracers, including $[^{11}C]$NS14492 [144], $[^{11}C]$(R)MeQAA [145], and $[^{18}F]$ASEM for $\alpha_7$ nAChR [146], $[^{11}C]$(+)-3-MPB [147] and $[^{18}F]$fluorobenzyl-dexetimide [148] for mAChR, $[^{11}C]$LSN3172176 [149] for M1 mAChR, and $[^{11}C]$MK-6884 for M4 mAChR [150] have been developed (Table 2). PET using $[^{11}C]$nicotine imaging showed that the cortical nAChR binding correlated with the cognitive function of attention in patients with mild AD [151]. Few in vivo PET studies for cholinergic system have been performed in AD models. Nishiyama et al. demonstrated higher $[^{11}C]$(R)-MeQAA brain uptake in the thalamus, hippocampus, striatum, and cortical regions, along with increased $[^{11}C]$PiB detection of Aβ
load and impaired $[^{18}\text{F}]$BCPP-EF binding to mitochondrial complex 1 in brain of aged monkey [145]. Chaney et al. demonstrated a lower levels of $[^{18}\text{F}]$ASEM in TgF334 rats compared to wild-type at 18 month-of-age [152]. Rejc et al. recently reported increased levels of BChE along with Aβ accumulation using $[^{11}\text{C}]$4 and $[^{18}\text{F}]$florbetaben respectively in brain of 5×FAD mice at 4-12 months-of-age compared to wild-type mice [153] (Figs. 3c-e). In comparison, comparable levels of AChE were observed in APP23 compared to wild-type mice at 10-13 months-of-age assessed by PET using $[^{11}\text{C}]$MP4A [154].

5 Blood-brain barrier

Blood-brain barrier (BBB) is impaired at an early disease stage in AD [155,156]. Whether the BBB dysfunction is secondary to Aβ pathology or a causal factor has not been fully elucidated. In amyloidosis animal models of AD, BBB disruption is observed in mouse models such as arcAβ, APP/PS1, but not prevalent in certain mouse line such as PS2APP line [157,158]. Several receptors presented in the BBB have been explored as PET imaging targets, such as adenosine triphosphate-binding cassette (ABC) transporter ABCC1, ABCG2, ABCB1 (P-glycoprotein, P-gp), and receptor for advanced glycation endproducts (RAGE). P-gp plays an important role in the clearance and efflux of Aβ from the brain into the blood across the brain endothelial luminal membrane [159]. The levels of P-gp expression and activity were found decreased in the brains of AD patients compared to that in control cases, as well as in APP mouse model compared to wild-type mice [160]. Several P-gp tracers such as (R)-O-$[^{18}\text{F}]$fluoroethylnorverapamil, (R)-N-$[^{18}\text{F}]$fluoroethylverapamil, (R)-$[^{11}\text{C}]$verapamil, $[^{11}\text{C}]$tariquidar, $[^{11}\text{C}]$metoclopramide, and $[^{18}\text{F}]$MC225 have been developed [161-168] (Table 2). Zoufal et al. demonstrated an age-dependent reduction in the cerebral P-gp function in APP/PS1 mice compared to wild-type mice assessed by PET using (R)-$[^{11}\text{C}]$verapamil [161] (Figs. 2d-g) and by using $[^{11}\text{C}]$metoclopramide [162]. However (R)-$[^{11}\text{C}]$verapamil showed suboptimal brain uptake, and further
Improvement and evaluation of P-gp function using novel tracers with improved properties are needed. In addition, PET using 6-bromo-7-[\(^{11}\)C]methylpurine (\([^{11}\)C]BMP) showed an increased level of ABCC1 along with \([^{11}\)C]PiB detection of increased level of Aβ pathology in the brain of APP/PS1 mice compared to wild-type mice [165]. The increase in the ABCC1 level has been assumed relating to upregulation of its expression in astrocytes as a protective mechanism. Imaging of ABCG2 by PET using \([^{11}\)C]erlotinib have been reported in APP/PS1 mice: no alteration in the level of ABCG2 compared to wild-type mice was observed [166].

Receptor for advanced glycation end products (RAGE) is a BBB transporter, and a binding site for advanced glycation end products, and mediates Aβ transportation across the BBB into the brain [169,170]. The expression level of RAGE was found increased in post-mortem AD brains compared to that in control cases [169]. RAGE tracers such as \([^{11}\)C]FPS-ZM1 [171], \([^{18}\)F]RAGER [172], \([^{18}\)F]InRAGER [173], and \([^{64}\)Cu]Rho-G4-CML nanoparticle (multimodal) have been developed [174]. The only imaging study conducted in AD animal model by Luzi et al. showed that \([^{11}\)C]FPS-ZM1 uptake in the brain of APPswe was similar compared to that of wild-type mice [175]. Further development and studies are needed to evaluate RAGE imaging tracers in AD animal models and in patients with AD.

6 Neuroinflammation imaging

Several recent articles have provided thorough reviews on neuroinflammation PET imaging in AD patients and AD animal models [16,176-180]. Thus here we discuss briefly the recent development in neuroinflammation imaging in AD amyloidosis animal models. Neuroinflammation plays an important role in the pathogenesis of AD and appears early in the disease development [181-183]. Microglia are the resident macrophages in the central nervous system, engulf Aβ plaques and are important for maintaining the brain homeostasis [183,184]. Recent single cell sequencing and transcriptomics have
demonstrated a transcriptionally-distinct and neurodegeneration-specific profile of microglia termed disease-associated-microglia (DAM) [185-187]. The 18 kDa translocator protein (TSPO) that located on the outer mitochondria membrane of microglia has been the most investigated target for microgliosis PET imaging. Three generations of TSPO tracers have been developed with improved properties, from the 1st generation (R)-[^11]CPK11195 [188]; 2nd generation[^11]C]PBR28 [189], [125]I]CLINDE [54], [^18]F]FEDAA1106 [190], [^18]F]DPA-714 [88] to the 3rd generation [^18]F]GE-180 [87] (Figs. 1e-h) and [^11]C]ER176 [191]. PET using various 18 kDa translocator protein (TSPO) tracers have demonstrated an early microgliosis preceding the Aβ deposition in several animal models of amyloidosis including APP23, hAPP-J20, APPSL70, AppNL-G-F and PS2APP mice [184,192-197]. Due to the diverse cellular location of TSPO expression on astrocytes and endothelial cells in addition to that on microglia, tracers specific for microglial expression and of disease-associated profile are of high interest [198-200]. Emerging targets and tracers include[^11]C]SW125M139 for purinergic P2X7 receptor [201,202], [^124]I] mAb1729-scFv8D3CL for triggering receptors expressed on myeloid cells (TREM) 2, [^11]C]AZD1283 for purinergic P2Y12 receptor [203], [^11]C]CPPC [204] and [^11]C]GW2580 [205] for colony stimulating factor 1 receptor, [^11]C]KTP-Me for cyclooxygenase 1 [206] etc have been developed and been evaluated in AD animal models. Meier et al. showed a higher expression level of TREM2 in brain from ArcSwe mice compared to wild-type mice at 24 h, 48 h, and 72 h post-injection by autoradiography using [^124]I] mAb1729-scFv8D3CL [207] (Figs. 3f-l).

7 Discussion

In addition to the aforementioned targets, many emerging targets show potential as indicators for pathological alterations in AD, and are yet to be further investigated in amyloidosis animal models, such as 1) metal dysregulation and copper trafficking e.g. using [^64]Cu]GTSM [208]; 2) reactive oxygen species [209] and pH alterations [210]; 3) microtubule using [^11]C]MPC-6827, [^11]C]HD-800, [^11]C]WX-132-18B[211-213]; 4) sigma 1 receptor using [^11]C]HCC0929, [^18]F]FTC-146, [^18]F]IAM6067 and
Astrocytes are essential for maintaining the homeostasis, synaptic plasticity and inflammatory response in the central nervous system [220]. Astrocytes play key roles in the onset and progression of AD. Reactive astrocytes show disease-associated profiles and exert dynamic functions (neuroprotection and neurotoxicity) in AD [221-225]. Few studies have been reported on PET imaging of astrocytosis in AD animal models. PET using irreversible mono-amine oxidase B (MAO-B) inhibitors \[^{11}\text{C}]\text{deuterium-L-deprenyl (DED)} showed an early astrocytosis preceding the $\text{A}\beta$ accumulation assessed by using \[^{11}\text{C}]\text{AZD2184} in the brain of APPswe at 6 months-of-age compared to wild-type mice (Figs. 3a, b). Similar finding of an early increase in \[^{11}\text{C}]\text{DED} binding was reported in Tg-ArcSwe mice compared to wild-type littermates [226]. Several novel MAO-B tracers have been developed including \[^{11}\text{C}]\text{SMBT-1} [227] based on (S)-\[^{18}\text{F}]\text{THK5117} structure [228] and \[^{18}\text{F}]\text{6} [229]. In addition, novel astrocytic tracer \[^{11}\text{C}]\text{BU99008}, which targets imidazoline-2 binding sites (I2BS), has showed specific and high-affinity binding property in post-mortem characterization [230]. *in vivo* PET in patients with AD [231,232].

*In vivo* longitudinal imaging in animal models of AD amyloidosis has provided valuable insights on the spatiotemporal links between different pathophysiology. The challenges in bridging the translational gaps of PET imaging in rodent models and in patients with AD may include:

- Animal model: Different rodent models of AD demonstrated divergent time courses and patterns of pathophysiological development [32,233,234]. Thus rational selection of optimal animal model and age for investigation are thus critical in PET imaging studies in tracer evaluation [235]. In addition, species difference in cell types, protein expression level, available binding sites, post-translational
modification of the target added to the complexity [236]. For example, the Aβ deposits formed in the APP mouse models and in aged primates are structurally different from that in the brain from patients with AD [237]. Thus, models that better recapitulate the human AD pathology will greatly boost the AD research, such as the recent Aβ-KI mouse model of late-onset AD [28], 3rd generation mouse model [27]; Moreover, databases of comprehensive deep phenotyping in disease animal models such as “MODEL-AD” by the Alzheimer consortium think tank [238,239] (www.model-ad.org/) are instrumental in facilitating the translational research. Systems biology approaches including single cell sequencing, transcriptomics, biochemical characterization, and behavioural assessments along with in vivo imaging data will provide accurate interpretation of the readouts [240-243].

Conclusions

We provide an overview of PET imaging in animal models of AD amyloidosis, highlighting recent development in visualizing Aβ, cerebral glucose metabolism, synaptic and neurotransmitter receptor deficits, BBB impairment and neuroinflammation, and proposed outstanding challenges for future development to increase the translational power of preclinical PET in AD.

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.

Author Contributions

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Figure legends

Figure 1. Imaging of amyloid-beta accumulation, translocator protein and cerebral glucose metabolism in amyloidosis animal models of Alzheimer’s disease (a-c) PET images and quantification of $[^{11}\text{C}]$PiB (40-60min after injection) and $[^{124}\text{F}]$RmAb158-scFv8D3 scans (72 h after injection) expressed as standardized uptake value (SUV). (a): Comparison of representative SPECT and PET images of $[^{125}\text{I}]$RmAb158-scFv8D3 and $[^{11}\text{C}]$PiB of App$^{\text{NL-G-F}}$ and wild-type mice. (b, c): Retention of $[^{125}\text{I}]$RmAb158-scFv8D3 and $[^{11}\text{C}]$PiB in different brain regions of App$^{\text{NL-G-F}}$ and wild-type mice. Reproduced from [70] with permission from Society of Nuclear Medicine and Molecular Imaging; (d) Multi-modal analysis of the four AD mouse strains in cross-sectional $[^{18}\text{F}]$florbetaben PET study. Images indicate group averaged sagittal PET slices, normalised to the cerebellum as well as ex vivo autoradiography. Dots indicate PETSUVR$_{\text{cortex/cerebellum}}$ in individual mice. Dashed lines express the estimated time dependent progression in PS2APP (red); APPswe/PS1G384A (green); and APP/PS1 (purple) mice, fitted with a polynomial function. Reproduced from [61] with permission from PLOS One; (e-h) $[^{18}\text{F}]$GE-180, $[^{18}\text{F}]$florbetaben, and $[^{18}\text{F}]$FDG PET imaging at different ages of PS2APP animals. (e) Coronal planes of mean SUVR maps projected on an MRI mouse atlas (gray scale). (f-h) Correlations between the different forebrain radiotracer SUVR for all PS2APP mice. Reproduced with permission [87] with permission from Society of Nuclear Medicine and Molecular Imaging.

Figure 2. In vivo imaging of synaptic density, blood-brain barrier and gama-secretase in amyloidosis animal models of Alzheimer’s disease. (a-c) Representative $[^{11}\text{C}]$UCB-J PET image and time-activity curve in APP/PS1 mice. (a) Static SUV image (30–60 min after injection) overlaid on atlas brain MR image. (b, c) Hippocampal SUVRs in wild-type and APP/PS1 mice during baseline, treatment, and washout phases: whole brain SUVR, (b) and brain stem SUVR (c). Reproduced from
[104] with permission Society of Nuclear Medicine; (d-g) Imaging of P-glycoprotein (P-gp, ABCB1) using (R)-[11C]verapamil; (d) Sagittal PET summation images (0–60 min) of wild-type and APP/PS1 mice aged 50, 200 and 380 days and Aeb1a/b(+/−) mice pre-treated i.v. with vehicle or tariquidar (4 mg/kg) at 2 h before start of the PET scan. (e-g) Whole brain region is highlighted as a white line (d, e). Whole brain-to-plasma radioactivity concentration ratios at the end of the PET scan (Kp,brain). Lines indicate mean ± standard deviation. Ns: not significant, *P < 0.05, **P < 0.001. Reproduced from [161] from Sage Publication. (h-j) PET-CT imaging of γ-secretase in 5xFAD and wild-type mice. (h) PET-CT image of 5xFAD mice (n = 2) after i.v. injection of [11C]SGSM-15606. (i) PET-CT image of wild-type mice (n = 2) after i.v. injection of [11C]SGSM-15606. (j) Time activity curve of whole brain uptake of [11C]SGSM-15606 in h and i. Data are expressed as the percentage of injected dose per cubic centimeter (% ID/cc). Reproduced from [74] with permission from Rockefeller University Press.

Figure 3. In vivo imaging of astrocytosis, butyrylcholinesterase and triggering receptors expressed on myeloid cells (TREM) 2 in amyloidosis animal models of Alzheimer’s disease. (a, b) [11C]deuterium-l-deprenyl ([11C]DED) microPET imaging in APPswe and wild-type (WT) mice. (a) [11C]DED microPET coronal parametric BPND maps images. (b) [11C]DED binding in the cortex and hippocampus, expressed as BPND, obtained from simplified reference tissue model of [11C]DED using the cerebellum as a reference region, in three groups of APPswe mice aged 6, 8–15 and 18–24 months and two groups of wild-type mice aged 8-15 and 18–24 months. Significant differences between groups are indicated by *p < 0.05. Reproduced from [244] with permission from Springer Nature. (c-e) PET images for BChE imaging in 5xFAD mice. (c, d) axial view of PET images in 5xFAD and wild-type mice after i.v. administration of [11C]4 at different ages. (e) Staining for BChE enzymatic activity in 4, 8 and 12-month-old brains of wild-type (A, C and E) and 5xFAD mice (B, D and F) using the Karnovsky-Roots method. BChE staining showed increase of enzyme activity in the
cerebral cortex of 5×FAD at different ages in comparison to wild-type (A to F) mice. Magnified images show the co-occurrence of plaques with BChE enzyme activity in different regions of the cerebral cortex (B, D and F) Reproduced from [153] with permission from Ivyspring International Publisher. (f-I) SPECT imaging of TREM2 level in ArcSwe, Swe and wild-type mice. (f) Representative SUV scaled sagittal SPECT images with $[^{124}\text{I}]\text{mAb1729-scFv8D3CL}$ at 24 h, 48 h, and 72 h after injection. (g) Radioligand distribution in brain tissue displayed in sagittal ex vivo autoradiography images in ArcSwe, Swe, and wild-type animals at 24 h and 72 h after injection (g). (h) Binding comparison of $[^{125}\text{I}]\text{mAb1729-scFv8D3CL}$ and unlabelled mAb1729-scFv8D3CL by using ELISA. Percent of injected dose (i) and SUV (j) of $[^{125}\text{I}]\text{mAb1729-scFv8D3CL}$ in brain 2 h, 24 h, and 72 h after injection. (k) Level of $[^{124}\text{I}]\text{mAb1729-scFv8D3CL}$ in blood which was sampled 1 h, 3 h, 24 h, 48 h, and 72 h after injection. (l) sTREM2 levels in TBS extracted brains of ArcSwe, APPSwe, and wild-type mice at the age of 18 months. Reproduced from [207] with permission from Springer Nature.
Table 1. Amyloid-beta PET imaging in animal models of Alzheimer disease amyloidosis

| Tracer | Animal models | References |
|--------|---------------|------------|
| [11C]PiB | APPswe mice | [41,60,245] |
| | 5×FAD mice | [85] |
| | APP/PS1 mice | [40,60,82,86,246-248] |
| | 3×Tg mice | [249] |
| | APP23 mice | [37,60,190] |
| | Aged non-human primate | [89,145] |
| | 5×FAD mice | [81,85] |
| | TASTPM mice | [250] |
| | APP/PS1 mice | [73,251] |
| | PS2APP mice | [61,252] |
| | APPswe mice | [61,253] |
| | AppNL-G-F mice | [68,192,197,252,254] |
| | APPswe/PS1G384A mice | [61] |
| | APP-SL70 mice | [252,255] |
| | TgF334 rats | [152] |
| | APP/PS1 mice | [61,68,82,256] |
| | APP/PS1 mice | [257] |
| | McGill-R-Thy1-APP rats | [47] |
| | APPswe mice | [46] |
| | APP23, APPswe, APP/PS1 | [41,42] |
| | APP/PS1 mice | [40] |
| | 5×FAD, APP/PS1 mice | [38,39] |
| | APP/PS1 mice | [258,259] |
| | APP/PS1 mice | [260] |
| | Tg-ArcSwe, AppNL-G-F mice | [70] |
| | APP/PS1 mice | [53] |
| | APPswe mice | [57] |
| | 3×Tg mice | [54] |
| | 5×FAD mice | [43] |
| | 5×FAD mice | [48] |
| | APP/PS1 mice | [44] |
| | APPswe mice | [55] |
| | APP/PS1 mice | [56] |
| | APP/PS1 mice | [45] |
| | Tg-ArcSwe mice | [66] |
| | APPswe mice | [67] |
Table 2. PET imaging in of neurotransmitter receptors, blood-brain barriers, enzymes, metabolism and synaptic density in animal models of Alzheimer disease amyloidosis

| Target       | Tracer          | Animal models                                      | References            |
|--------------|-----------------|---------------------------------------------------|-----------------------|
| CMRglc       | $[^{18}F]$FDG   | 3×Tg mice                                          | [83,263-267]          |
|              |                 | APPswe mice                                        | [79]                  |
|              |                 | APP/PSwe mice                                      | [73,82,88,250,268-270]|
|              |                 | Tg4-42 mice                                         | [78,271]              |
|              |                 | 5×FAD mice                                          | [81,85,256,272,273]   |
|              |                 | 3×Tg rats                                           | [274]                 |
|              |                 | APP23 mice                                          | [275]                 |
|              |                 | McGill-R-Thy1-APP rats                              | [47]                  |
|              |                 | TASTPM mice                                         | [250,276]             |
|              |                 | Aged monkey                                         | [89]                  |
|              |                 | Striatal-lesioned rats                              | [14,103,104]          |
| SV2A         | $[^{11}C]$UCB-J | APP/PSwe mice                                      | [104]                 |
|              |                 | ArcSwe, Tg-L61 mice                                 | [105]                 |
|              | $[^{18}F]$SynVesT-1 | APP/PSwe mice                                      | [107]                 |
|              | $[^{18}F]$FPEB  | 5×FAD mice                                          | [131,277]             |
| mGluR5       | $[^{11}C]$ABP688 | APP/PSwe mice                                      | [132]                 |
|              | $[^{11}C]$MeQAA | Tg-ArcSwe mice                                      | [133]                 |
|              | $[^{18}F]$ASEM  | Aged monkey                                         | [145]                 |
| $\alpha 7nAChR$ | $[^{11}C]$flumazenil | APP/PSwe mice                                      | [154]                 |
|              | $[^{11}C]$MP4A  | APP23 mice                                          | [154]                 |
|              | $[^{11}C]$4     | 5×FAD mice                                          | [153]                 |
| GABAR        | $[^{11}C]$flumazenil | APP/PSwe mice                                      | [154]                 |
|              | $[^{11}C]$SGSM-1560 | 5×FAD mice                                        | [74]                  |
| IIa HDAC     | $[^{18}F]$TFAHA | 3×Tg mice                                           | [278]                 |
| GLP-1R       | $[^{18}F]$FBEM-Cys$^{39}$-exendin-4 | 3×Tg mice                                         | [267]                 |
|              | $[^{18}F]$fallypride | 3×Tg, 5×FAD mice                                   | [267,277]             |
| D2R          | $[^{18}F]$fallypride | Aged monkey                                        | [89,145,217,279]     |
| MC1          | $[^{18}F]$BCPP-EF | SAMP10 mice                                        | [208]                 |
| Copper       | $[^{64}Cu]$GTSM | TASTPM mice                                         | [213]                 |
| MT           | $[^{11}C]$MPC-6827 | J20 mice                                          | [213]                 |
| GSK3β        | $[^{11}C]$OCM-44, $[^{3}H]$PF-367 | APPswe mice                                  | [280]                 |
|              | $[^{11}C]$2     | 3×Tg mice                                           | [218]                 |
|              | $[^{18}F]$RAGER | Rats                                                | [172]                 |
|              | $[^{18}F]$InRAGER | LPS-treated mice                                   | [173]                 |
| RAGE         | $[^{11}C]$FPS-ZM1 | APPswe mice                                        | [175]                 |
|              | $[^{64}Cu]$Rho-G4-CML NP | Murine model of hindlimb ischemia             | [174]                 |
| ABCC1        | $[^{11}C]$BMP   | APP/PSwe mice                                       | [165]                 |
| ABCG2        | $[^{11}C]$erlotinib | APP/PSwe mice                                    | [166]                 |
|              | $[^{11}C]$tariquidar | APP/PSwe mice                                    | [166]                 |
| Compound                        | Species                        | REF   |
|--------------------------------|--------------------------------|-------|
| [11C]metoclopramide (R)-O-[18F]fluoroethynorverapamil | APP/PS1 mice                     | [162] |
| [18F]fluoroethylverapamil      | Mdr1a/b<sup>−/−</sup>, Bcrp1<sup>−/−</sup> mice, rats | [164] |
| [18F]MC225                     | Non-human primates, rats        | [167,168] |
| (R)-[11C]verapamil             | APP/PS1 mice                     | [161] |

ABC: ATP-binding cassette transporter; α7 nAChR: α7 nicotinic acetylcholine receptor; AChE, acetylcholine esterase; BChE: butyrylcholinesterase; CMRglc: cerebral metabolic rate of glucose; D2: dopamine receptor D2; FDG: fluorodeoxyglucose; GABAR: gamma-Aminobutyric acid receptor; GLP-1R: glucagon-like peptide-1 receptor; GSK3β: glycogen synthase kinase-3β; GSM: γ-secretase modulator; IIa HDAC: class IIa histone deacetylases; LPS: Lipopolysaccharide; MC1: mitochondrial complex 1; mGluR5: metabotropic glutamate receptor type 5; MT: microtubule; NP: nanoparticle; P-GP: P-Glycoprotein; SV2A: synaptic vesicle glycoprotein 2A;
Fig. 1
**Fig. 2**

(a) Time Activity Curves

(b) Hippocampus (normalized by whole brain)

(c) Hippocampus (normalized by brain stem)

(d) Wild-type, APPtg, Abcb1a/b
d(e)  

(f)  

(g) % Kp,brain increase
