We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

10

Amyloid Imaging PET Ligands as Biomarkers for Alzheimer's Disease, Preclinical Evaluation

Marie Svedberg[1,2], Ewa Hellström-Lindahl[2], Obaidur Rahman[3] and Håkan Hall[1,2]
[1,2]*Uppsala University, Uppsala*
[1]*Department of Public Health and Caring Sciences, Molecular Geriatrics*
[2]*Department of Medicinal Chemistry, Preclinical PET Platform*
[3]*Norwegian Medical Cyclotron Center, Oslo University Hospital, Oslo*
[1,2]*Sweden*
[3]*Norway*

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia in the aging population. It is a complex disease that affects many brain functions and is characterized by a progressive impairment of cognitive abilities, such as memory, learning and social skills. AD was first described over hundred years ago by the German psychiatrist Dr. Alois Alzheimer, reporting of the in due course characteristic pathological changes postmortem discovered in his 56 years old patient Auguste D (Alzheimer, 1907). The disease is obviously devastating for the patients and affects everyday life for both patients and their families, but it also generates economical challenges for the heath-care system and the society as the elderly population is growing (Wimo & Winblad, 2008). Although research regarding AD is intensive worldwide and new results do get a greater understanding of the causes of the disease, the exact mechanisms and underlying cause behind AD are still unsolved. The disease progresses over decades leading to premature death. There are no disease-modifying therapies for AD available, and the current treatment might provide symptomatic relief and slower disease progression.

The new imaging technologies based on structural and functional processes in the brain enable early diagnosis and may also differentiate between types and severity of neurodegeneration. Mild cognitive impairment (MCI) is closely related to AD and can be considered as a transitional stage between normal cognition and dementia. MCI is characterized by either isolated memory impairment or impairment in several cognitive domains, but not of sufficient severity to meet diagnostic criteria for AD (Petersen et al., 2001). Although MCI is associated with an increased risk of developing AD, about half of MCI patients progress to AD at a rate of approximately 10%–15% per year, but approximately half do not develop AD even after follow-up periods as long as 10 years (Ewers et al., 2010; Ganguli & Petersen, 2008; Ganguli et al., 2011).

A clinical diagnosis of AD is assessed by several investigations including medical history and neuropsychological criteria such as the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association) (McKhann et al., 1984), but a definite diagnosis of AD can only be done postmortem. Therefore, development of efficient prevention therapies for AD would greatly benefit from a diagnosis at a prodromal stage of the disease. Positron emission tomography (PET) is considered a unique diagnostic tool that enables early detection of pathology that facilitates prediction of AD and following the progression *in vivo* (Långström et al., 2007). Highly specific and sensitive biomarkers are of great value to assess therapeutic efficacy clinically and in terms of clearance of histopathological lesions and decelerated neurodegeneration.

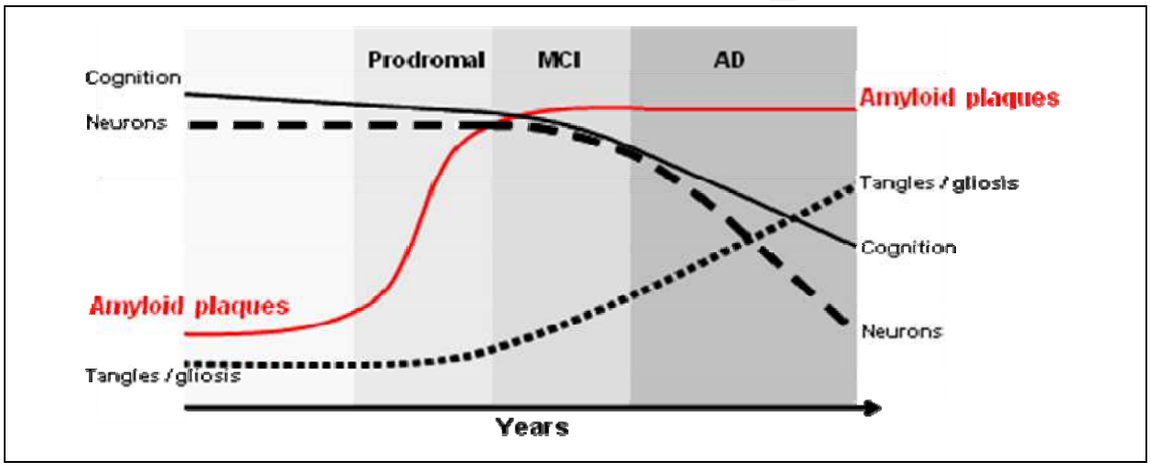


Fig. 1. Model of the temporal pattern of neuropathologic changes in AD neocortex. The figure shows that there is increase in amyloid plaques (Aβ) in the prodromal phase, followed by a progressive loss of neurons and a formation of neurofibrillary tangles in parallel with deteriorating cognitive capacities in the intermediate cognition state, MCI and later in AD. Figure adapted from Långström et al. (2007).

2. Pathology

AD is characterized neuropathologically by cerebral neuronal loss and the main histopathological hallmarks are intracellular neurofibrillary tangles consisting of hyperphosphorylated tau and extracellular β-amyloid (Aβ) deposits found as senile plaques in the brain parenchyma. These plaques are formed from insoluble Aβ peptides, fibrils and oligomers, that originate through processing of the larger Amyloid Precursor Protein (APP) (Selkoe & Schenk, 2003).

2.1 Pathological protein, Aβ

The Aβ containing plaques induce cell death and are formed during early disease progression long before the patient feels any symptoms in the prodromal phase of the disease (Braak et al., 1998; Ingelsson et al., 2004) (figure 1). Whether the formation of plaques is the major underlying event of the neurogenerative process in AD is a matter of debate. The amyloid cascade hypothesis is today one of the leading theories and suggests that Aβ

depositions in the brain are the central lesion in the pathogenesis of AD (Korczyn, 2008). However, although the Aβ plaques appear in the brain prior to the neurofibrillary tangles, it has been demonstrated that the neurofibrillary tangles are better correlated with neuronal loss and cognitive decline than to Aβ plaques (Schönheit et al., 2004). Furthermore, plaques are present in cognitively normal elderly subjects without any signs of neurodegeneration (Hellström-Lindahl et al., 2004; Villemagne et al., 2008). Nonetheless, there is evidence that amyloid are associated with severity of dementia (Näslund et al., 2000).

Since it became possible to measure Aβ *in vivo* in the brain by PET (Klunk et al., 2004), Aβ plaques has became a disease-defining pathologic marker of AD. However, the plaques might play an important role in the pathophysiological mechanisms of the disease. Various strategies to prevent aggregation, increase Aβ clearance or alter APP metabolism sought for the development of new treatment strategies of AD

2.1.1 Amyloid imaging

Amyloid imaging using PET has developed rapidly in recent years. With the development of the amyloid-imaging PET tracer [^{11}C]PIB (N-methyl-[^{11}C]-2-(4-methylaminophenyl)-6-hydroxy-benzothiazole), a derivate of the widely used dye for plaques thioflavin-T, the possibility to study the presence of amyloid in the brains of AD patients in early stages of the disease with PET became an important tool (Archer et al., 2006; Klunk et al., 2004; Mintun et al., 2006; Nordberg, 2004). [^{11}C]PIB has a high affinity for aggregated Aβ, crosses the blood brain barrier (BBB) easily, has low toxicity and makes it possible to visualize plaque and vascular amyloid deposits in the brain. [^{11}C]PIB is today the most commonly used radioligand in the assessment of amyloid plaques in the living human brain using PET, although several new compounds are under development (see table 1) (Henriksen et al., 2008; Ono, 2009). However, the exact nature of the mechanism for the binding of [^{11}C]PIB and other amyloid ligands to Aβ in the form of β-pleated sheets is still unknown.

One of the central issues regarding the PIB-amyloid binding in the AD brain is thus to understand the mechanisms and binding properties of the ligand. It has been demonstrated that [^{11}C]PIB has high affinity for fibrillar Aβ and binds to the β-sheet structure of the Aβ fibrils (Klunk et al., 2003). It has also been shown that [^{11}C]PIB in nanomolar concentrations does not bind to neurofibrillary tangles (Bacskai et al., 2007; Ikonomovic et al., 2008; Kadir et al., 2011; Rosen et al., 2011).

2.1.2 Neuroinflammation (gliosis)

The widespread cellular degeneration and neuronal loss in AD is accompanied by reactive gliosis (Kadir et al., 2011). Close to the amyloid plaques both astrocytes and microglia are clustered, probably as a result of a starting neuroinflammatory process (Akiyama et al., 2000). Activated microglia accumulate in order to remove the plaques by phagocytosis (Streit, 2004). However, the cluster of microglia produce a number of various neurotoxic substances thereby inducing inflammatory processes, possibly contributing to the neurodegeneration process (Akiyama et al., 2000; Streit, 2004). Astrocytes proliferate as a reaction to neuronal insults, and astrogliosis is thus also a phenomenon in the AD brain (Porchet et al., 2003). Moreover, astrocytes may impair the efficacy of microglia to remove the plaques (Akiyama et al., 2000).

Molecular imaging of the entities involved in neuroinflammation process that follows plaque formation is today possible, as a result of the development of a number of new different radiotracers labeling microglia or astrocytes (Akiyama et al., 2000). For the study of activated microglia, ligands labeling the peripheral benzodiazepine receptor (translocator protein 18 kDa) are used, such as PK11195 and analogues (Banati, 2002; Cagnin et al., 2002). Astrocytes, which also are involved in the neuroinflammatory process, may be studied using a tracer labeling the monoamine oxidase B (MAO-B) enzyme, such as deprenyl. However, deprenyl is rapidly metabolized *in vivo*, which can be diminished by using a di-deuteriated deprenyl (Bergström et al., 1998; Fowler et al., 1988; Logan et al., 2000).

3. Chemistry

The highly conjugated fluorescent staining agents Congo red and chrysamine G (figure 2) were the first selected target molecules for the development of Aβ imaging ligands. However, those compounds were not suitable *in vivo* due to their low brain penetration ability (Klunk et al., 1994; Klunk et al., 1995). A number of other compounds with various chemical structures and promising Aβ binding abilities have been developed during last couple of years (Henriksen et al., 2008; Ono, 2009). Among those the most successful one so far is [^{11}C]PIB or [^{11}C]6-OH-BTA-1. All these compounds are small molecules with a central lipophilic group, a secondary or tertiary amine at one end and a polar or non-polar group at the other end. The terminal amine group and the middle lipophilic group which are the common features of all so far published molecules might have some impact on their amyloid binding properties. A list of available Aβ imaging PET ligands together with their chemical names and structures is presented in table 1.

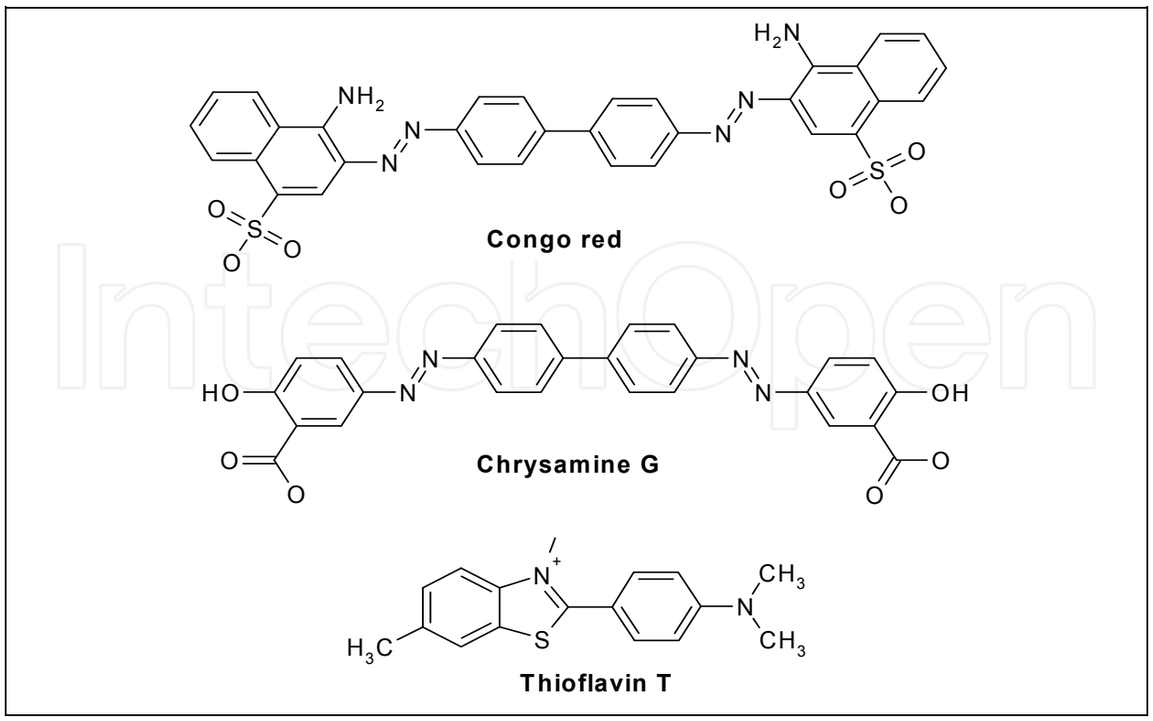
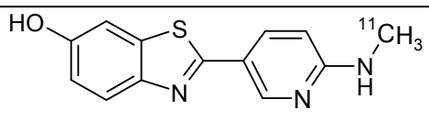
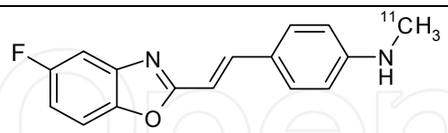
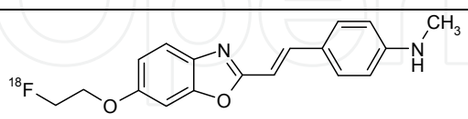
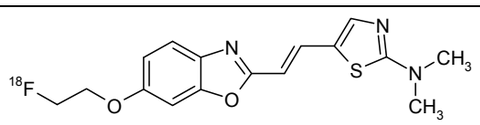
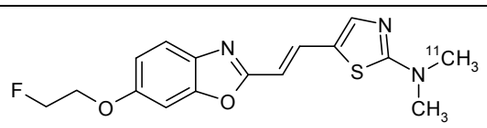
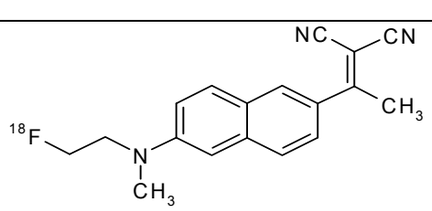
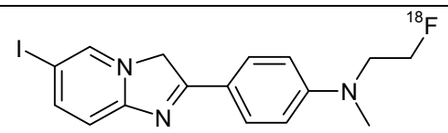
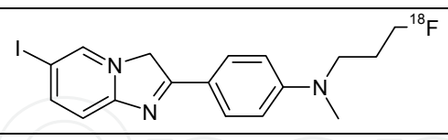
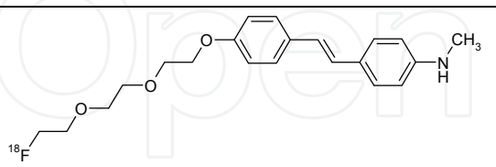
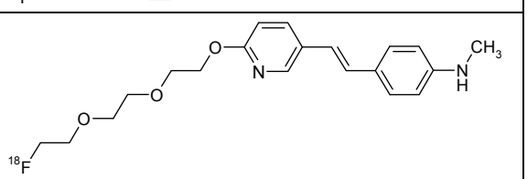
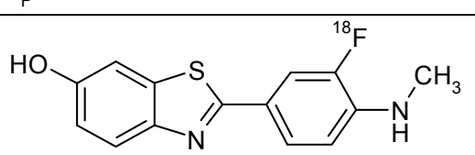


Fig. 2. Chemical structures of Congo red, chrysamine G and thioflavin T.

Short names	Chemical names	Structures
[^{11}C]AZD2184	*N*-[^{11}C]methyl)-2-(6-methylamino-pyridin-3-yl)-benzo[d]thiazol-6-ol	
[^{11}C]BF-145	2-(4-[*N*-Methyl-^{11}C]methylaminostyryl)-5-fluorobenzoxazole	
[^{18}F]BF-168	2-(4-methylaminostyryl)-6-(2-[^{18}F]fluoroethoxy)benzoxazole	
[^{18}F]BF-227	2-(2-[2-dimethylaminothiazol-5-yl]ethenyl)-6-(2-[^{18}F]fluoroethoxy)benzoxazole	
[^{11}C]BF-227	[^{11}C]2-(2-[2-dimethylaminothiazol-5-yl]ethenyl)-6-(2-fluoroethoxy)benzoxazole	
[^{18}F]FDDNP	2-(1-(2-(*N*-(2-[^{18}F]fluoroethyl)-*N*-methylamino)naphthalene-6-yl)ethylidene)malononitrile	
[^{18}F]FEM-IMPY	6-iodo-2-[4´-*N*-(2-[^{18}F]fluoroethyl)methylamino] phenyl-imidazo[1,2-a]pyridine	
[^{18}F]FPM-IMPY	6-iodo-2-[4´-*N*-(2-[^{18}F]fluoropropyl)methylamino] phenyl-imidazo[1,2-a]pyridine	
[^{18}F]florbetaben ([^{18}F]BAY94-9172)	4-(*N*-methylamino)-4´-(2-(2-(2-[^{18}F]fluoroethoxy)-ethoxy)-ethoxy)-stilbene	
[^{18}F]florbetapir ([^{18}F]AV-45)	*N*-{4-[2-(4-{2-[2-(2-[^{18}F]fluoroethoxy)ethoxy] ethoxy}-phenyl)vinyl]phenyl}-*N*-methylamine	
[^{18}F]flutemetamol	2-[3-[^{18}F]fluoro-4-(methylamino)phenyl]1,3-benzothiazol-6-ol	

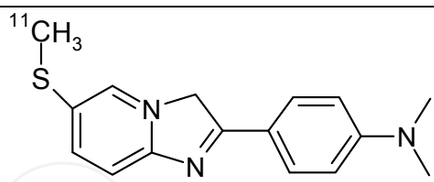
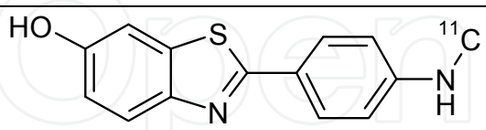
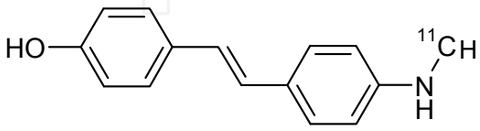
Short names	Chemical names	Structures
[^{11}C]MeS-IMPY	[*S*-methyl-^{11}C]*N*,*N*-dimethyl-4-(6-(methylthio)imidazo[1,2-a]pyridine-2-yl)aniline	
[^{11}C]PIB	[^{11}C]-2-4-(methylaminophenyl)-6-hydroxybenzothiazole	
[^{11}C]SB-13	[^{11}C]4-*N*-methylamino-4´-hydroxystilbene	

Table 1. Aβ imaging PET ligands

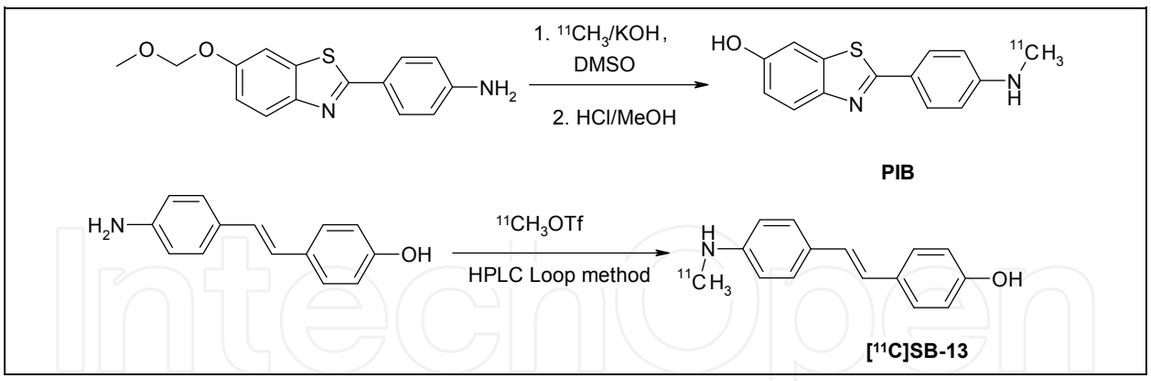
3.1 Synthesis of ^{11}C-and ^{18}F-labeled Aβ binding PET ligands

The Aβ binding PET ligands have been labeled with the ideal positron emitting radionuclides ^{11}C or ^{18}F, and the terminal amino or hydroxyl group of the molecule is mainly selected as the suitable ^{11}C or ^{18}F-labeling position. In case of [^{18}F]flutemetamol, the labeling strategy was different and one of the aromatic ring of the lipophilic part of the molecule was selected for that purpose.

3.1.1 Synthesis of ^{11}C-labeled ligands

The commonly used method for the synthesis of ^{11}C-labeled Aβ binding PET ligands is the methylation using [^{11}C]methyl iodide or [^{11}C]methyl triflate. The cyclotron produced [^{11}C]carbon dioxide is first converted to [^{11}C]methyl iodide or [^{11}C]methyl triflate which react with the desmethyl precursor of the corresponding target molecule to give the final ^{11}C-labeled product. A typical example of methylation using [^{11}C]methyl iodide is the synthesis of [^{11}C]PIB or [^{11}C]6-OH-BTA-1. *N*-Methylation of methoxymethyl (MOM) protected BTA using [^{11}C]methyl iodide in presence of potassium hydroxide followed by deprotection of MOM by treating with 50:50 mixture of methanol and concentrated hydrochloric acid gave the target compound [^{11}C]PIB (Scheme 1) (Mathis et al., 2003). Other Aβ binding PET ligands prepared by methylation using [^{11}C]methyl iodide are [^{11}C]AZD2184 (Andersson et al., 2010), [^{11}C]BF-145 (Shimadzu et al., 2004) and [^{11}C]MeS-IMPY (Seneca et al., 2007).

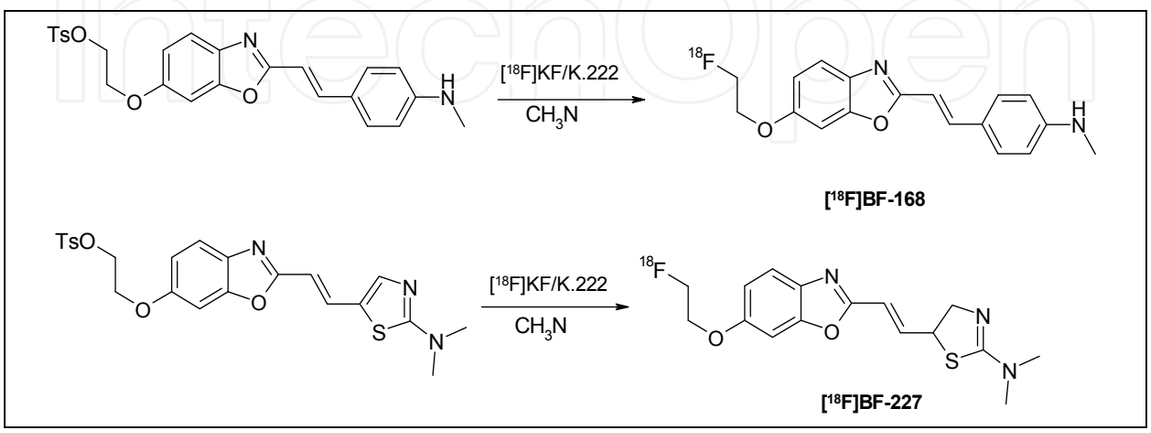
The synthesis of the ^{11}C-labeled stilbene derivative [^{11}C]SB-13 is an example of methylation using [^{11}C]methyl triflate. The synthesis was performed in a HPLC sample loop (Scheme 1) (Ono et al., 2003). Some other known Aβ binding PET ligands prepared by methylation using [^{11}C]methyl triflate are [^{11}C]BF-227 (Kudo et al., 2007), [^{11}C]IMPY (Cai et al., 2008), benzofuran derivatives (Ono et al., 2006) and analogues of aminophenylbenzothiazoles with a fluorine substituted phenyl ring (Henriksen et al., 2007).



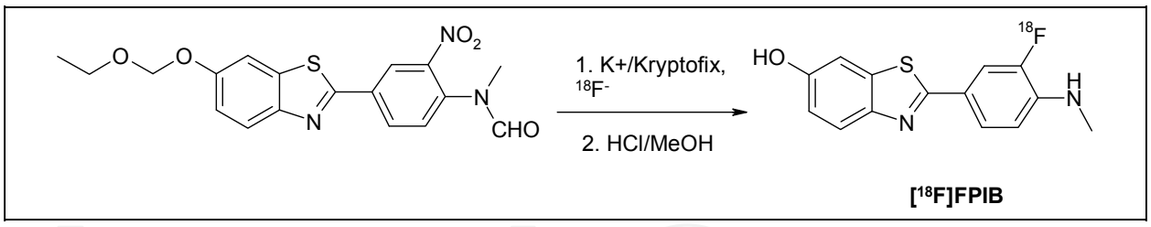
Scheme 1. Synthesis of [^{11}C]PIB and [^{11}C]SB-13

3.1.2 Synthesis of ^{18}F-labeled ligands

The commonly used ^{18}F-labeling strategy for Aβ binding PET ligands is the aliphatic nucleophilic fluorination of the corresponding tosylate or mesylate precursors of the target molecules using non carrier added [^{18}F]fluoride. A number of ligands have been prepared using this method and the followings are examples of such Aβ ligands. Two benzoxazole derivatives [^{18}F]BF-168 (Shimadzu et al., 2004) and [^{18}F]BF-227 (Okamura et al., 2007) were prepared by aliphatic nucleophilic fluorination of the corresponding 6-(2-tosyloxyethoxy)-benzoxazole derivatives using [^{18}F]fluoride ion in presence of potassium carbonate and kryptofix (Scheme 2). Other ^{18}F-labeled Aβ ligands prepared by aliphatic nucleophilic fluorination are [^{18}F]fluoropegylated stilbene derivatives [^{18}F]florbetapir ([^{18}F]AV-45) (Yao et al., 2010) and [^{18}F]florbetaben ([^{18}F]BAY 94-9172) (Wang et al., 2011; Zhang et al., 2005), amino naphthalene derivative [^{18}F]FDDNP (Klok et al., 2008; Liu et al., 2007), and phenylimidazole derivatives [^{18}F]FEM-IMPY and [^{18}F]FPM-IMPY (Cai et al., 2004). Only one of all amyloid binding ligands published so far has been prepared by aromatic nucleophilic fluorination. This ligand is a ^{18}F-labeled analogue of BTA known as [^{18}F]flutemetamol (or [^{18}F]FPIB, [^{18}F]GE-067). The precursor contains a nitro group situated ortho to a carboxamide group on one of the aromatic ring which is substituted by no-carrier added [^{18}F]fluoride to give the target compound (Scheme 3) (Koole et al., 2009; Storey et al., 2007).



Scheme 2. Synthesis of [^{18}F]BF-168 and [^{18}F]BF-227



Scheme 3. Synthesis of [^{18}F]flutemetamol ([^{18}F]FPIB)

4. Evaluation of amyloid binding PET ligands

An important part of the development of new potential tracers for visualizing amyloid with PET is the preclinical evaluation of these compounds. Several complementary *in vitro* and *in vivo* animal techniques are used for the evaluation which has to be performed before the new tracer can be given to humans. These techniques aim at finding compounds with optimal affinity for the target (Aβ), while having as low binding as possible to other targets. Moreover, the kinetics needs to be suitable for PET, i.e. the binding equilibrium should be reached in the time frame of a PET experiment. These and other important criteria for a suitable PET ligand need to be studied in the preclinical evaluation phase.

Homogenate binding assay is a standard technique for the determination of affinity and selectivity of any compound. However, many of the parameters obtained in homogenate binding studies can also be obtained using *in vitro* cryosection autoradiography. After the process of evaluating the binding properties of a compound to be developed into a tracer to be used in PET or SPECT, homogenate binding studies may be used for determining of the absolute density of amyloid plaques in a tissue homogenate.

Autoradiography is a commonly used method in the study of radioligands for use in PET or SPECT, as direct comparisons of *in vitro* autoradiography images can be made with *in vivo* PET images labeled with ^{11}C and ^{18}F. Autoradiography gives information on distribution, selectivity and nonspecific binding, as well as a number of kinetic parameters which all are parameters indicative of usefulness for *in vivo* molecular imaging. With regard to visualization of amyloid plaques *in vivo*, cryosection autoradiography is often used in comparison of different potential ligands, for example in structure activity relationship studies. Furthermore, the much higher resolution with *in vitro* autoradiography as compared with *in vivo* PET makes the former technique a complementary technique.

It is obvious that certain parameters can be determined solely by an *in vivo* administration. For example, of great importance with regard to visualization of amyloid plaques *in vivo* is the extent of BBB penetration. In this case, "*ex vivo*" autoradiography could be preferred. Here "*ex vivo*" is defined as administration of the radioligand *in vivo* followed by autoradiography *in vitro*, and at least some of the above mentioned parameters can be determined. On the other hand, some parameters might be very difficult, if not impossible, to determine *in vivo*, such as to determine if an interaction really is saturable or not. Many of the compounds developed as tracers cannot be given in high enough concentrations to determine this, due to known toxicity or lack of toxicity information. For example, in spite of the numerous clinical studies performed with [^{11}C]PIB, saturating amounts of [^{11}C]PIB cannot be given to living subjects, and from *in vivo* PET it is not known if all [^{11}C]PIB binding can be blocked by excess unlabeled PIB *in vivo*. Using *in vitro* autoradiography the

binding was blocked totally by adding 1000-fold higher concentration with unlabeled PIB (figure 3) (Långström et al., 2007; Svedberg et al., 2009).

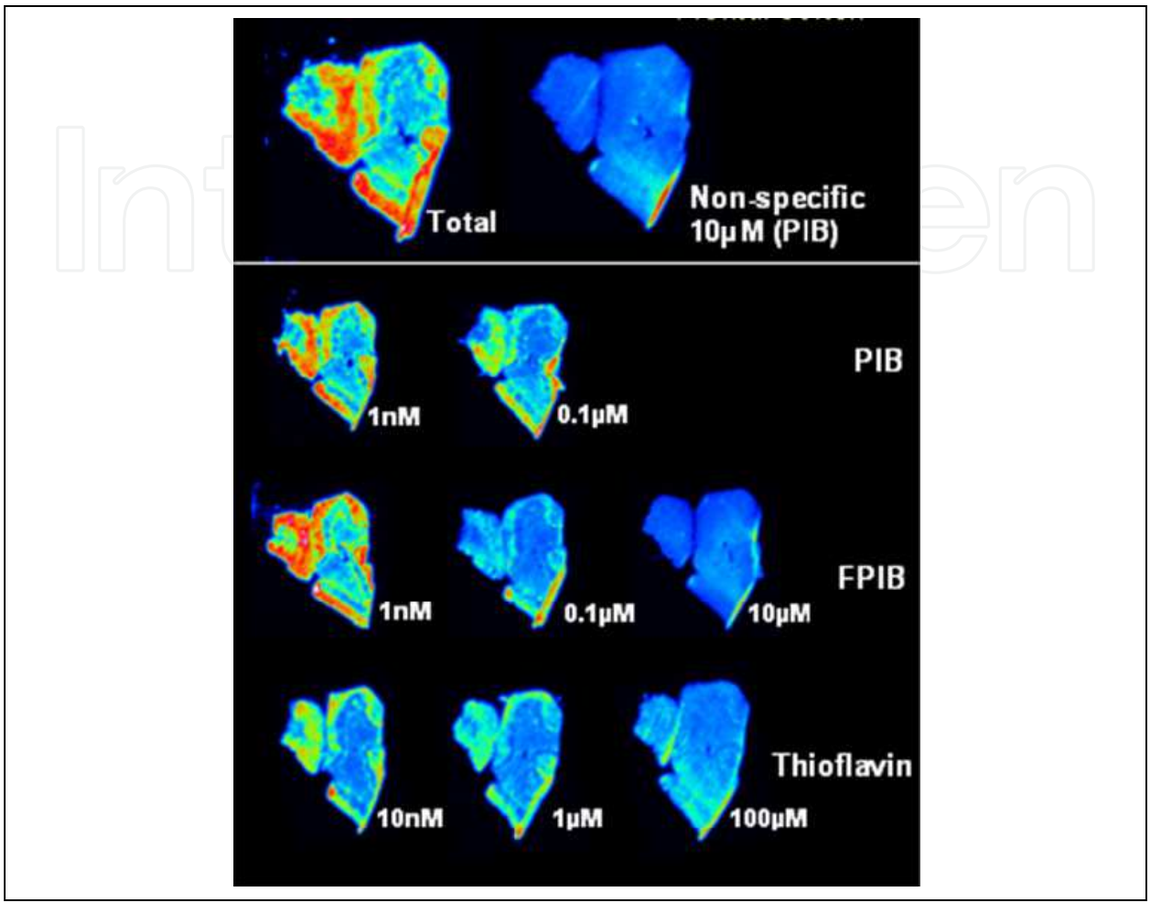


Fig. 3. Autoradiograms showing effects of PIB, flutemetamol (FPIB) and thioflavin on [^{18}F]flutemetamol binding to sections of the temporal cortex of an AD patient.

5. Results

5.1 *In vitro* binding of PIB to postmortem AD brain

Binding of [^{3}H]PIB binding to insoluble Aβ deposits in postmortem brain obtained from AD patients has been reported by several investigators. *In vitro* studies have shown that the Kd for [^{3}H]PIB binding to AD brain (3-4 nM) is similar to the Kd for binding synthetic Aβ1-40 and Aβ1-42 fibrils (1 nM) (Fodero-Tavoletti et al., 2007; Ikonomovic et al., 2008; Kadir et al., 2011; Klunk et al., 2005). In some AD and control brain homogenates as well as with Aβ synthetic fibrils a lower-affinity [^{3}H]PIB binding site with Kd values of 75-250 nM have been observed (Ikonomovic et al., 2008; Klunk et al., 2005). However, these low-affinity sites would not contribute significantly to *in vivo* binding at [^{11}C]PIB concentrations around 1 nM. No significant correlation of [^{3}H]PIB binding with soluble Aβ peptides has been observed (Ikonomovic et al., 2008; Klunk et al., 2005). The requirement that Aβ be in fibrillar form for PIB binding was verified by showing that the highly fluorescent PIB derivative 6-CN-PIB

labeled both Aβ42 -and Aβ40-immunoreactive plaques whereas no labeling was detected in tissue sections pre-treated with formic acid which disrupts β-pleated sheets (Ikonomovic et al., 2008).

Several studies have reported correlations between *in vivo* [^{11}C]PIB retention and with region-matched postmortem quantification of [^{3}H]PIB binding, Aβ plaque loads and Aβ peptide levels but not with neurofibrillar tangles (Bacskai et al., 2007; Ikonomovic et al., 2008; Kadir et al., 2011; Rosen et al., 2011). In addition, a direct correlation between [^{11}C]PIB binding and insoluble Aβ levels determined by ELISA in homogenates of AD brain has been observed (Ikonomovic et al., 2008; Kadir et al., 2011; Klunk et al., 2005; Rosen et al., 2011; Svedberg et al., 2009).

Although several clinical PET studies with [^{11}C]PIB have been performed (Engler et al., 2003; Engler et al., 2006; Klunk et al., 2003; Klunk et al., 2004), *in vitro* evaluation studies have provided us with important new information. In agreement with others (Fodero-Tavoletti et al., 2007; Klunk et al., 2005; Rosen et al., 2011) our recent *in vitro* study (Svedberg et al., 2009) revealed significantly higher binding of PIB in AD brain compared to control brain when using [^{11}C]PIB autoradiography and [^{11}C]PIB radioligand assay. Moreover, we observed no specific [^{11}C]PIB binding in the cerebellum which is often used as a reference region for quantification of [^{11}C]PIB retention in PET studies. For example, the distribution of [^{11}C]PIB was investigated using autoradiography on tissue from patients that suffered from AD (Svedberg et al., 2009), which demonstrated that the binding is confined to external layers of the cerebral cortex, which due to a lower resolution is not seen in PET (figure 4).

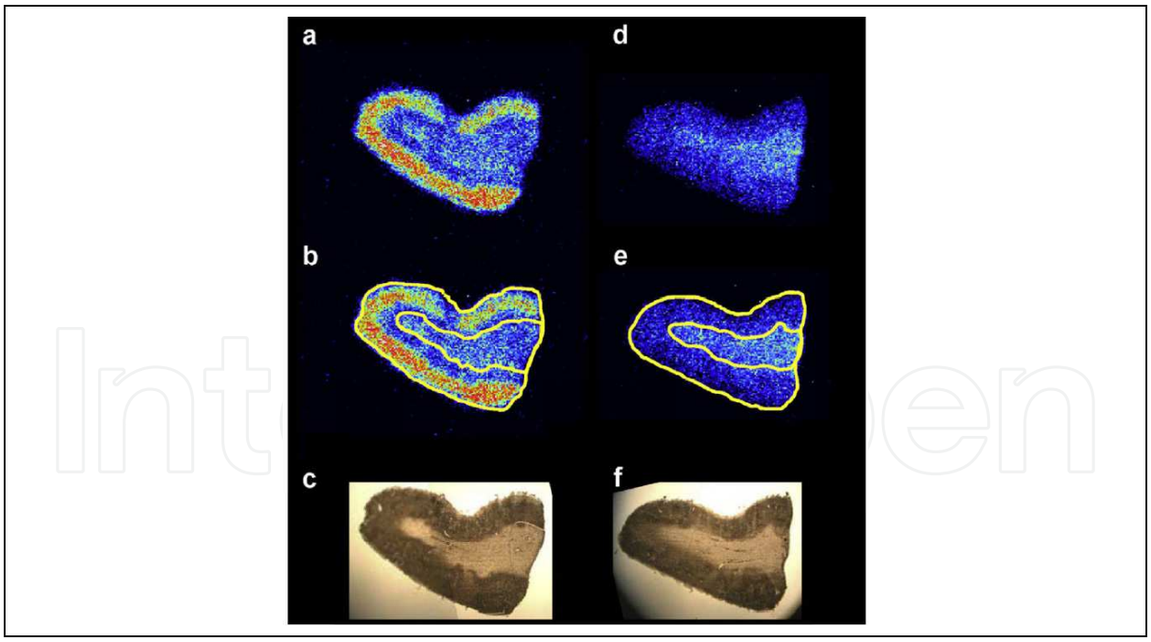


Fig. 4. [^{11}C]PIB binding in the temporal cortex of an AD patient and microscopic images of the sections used. Autoradiograms depicting total (a and b) and nonspecific binding (d and e) of [^{11}C]PIB in the temporal cortex of a patient with AD and microscopic images of the sections used (c and f). The yellow lines in B and E were drawn as regions of interest; the gray and the white matter area, respectively, on the microscopic images and were transferred to the autoradiograms. From Svedberg et al. (2009).

By using a combination of autoradiography and histochemical techniques Lockhart et al. (2007) showed that PIB, in addition to binding senile plaques (dense core plaques) also bound to cerebral amyloid angiopathy (CAA) and some diffuse plaques. In contrast to senile plaques where Aβ42 are much more abundant (Hellström-Lindahl et al., 2004; Näslund et al., 2000), the major amyloid peptide species in CAA is Aβ40 with less amounts of Aβ42 (Mann et al., 1996). CAA is present in 80% or more of AD patients (Jellinger, 2002) and may therefore contribute significantly to the *in vivo* [^{11}C]PIB signal and *in vitro* binding of PIB (Bacskai et al., 2007; Johnson et al., 2007; Svedberg et al., 2009).

PIB binds only weakly to Aβ deposits in nonhuman species (Klunk et al., 2005; Rosen et al., 2011). Recently, Rosen et al (2011) showed that despite levels of Aβ in cortical extracts that sometimes exceeded those in AD brain, high-affinity [^{3}H]PIB *in vitro* binding in nonhuman primates (aged chimpanzees, rhesus macaques, and squirrel monkeys) was strikingly less than that in humans with AD. Similarly, less [^{3}H]PIB binding was detected in homogenates of transgenic PS1/APP mouse brain compared to AD brain, despite higher Aβ levels (Klunk et al., 2005). A substantial difference in the intensity of [^{11}C]PIB labeling between AD brain and APP transgenic mice has also been shown by ex vivo autoradiography (Maeda et al., 2007).

5.2 *In vivo* animal studies

Two major *in vivo* modalities are of importance in the evaluation of new PET ligands. One is organ distribution studies in normal mice or rats, which gives information on to where the compound and its metabolites distribute. Organ distribution studies are also used in calculation of dosimetry, i.e. how much of a radiolabeled compound can be given without reaching radioactive doses that may risk damages due to radiation.

A more obvious modality is the use of animal PET. In order to study binding to Aβ plaques transgenic animals are required, as plaques are not found naturally in old rats or mice (Philipson et al., 2010). Transgenic mouse models have become an important and valuable research tool in neurodegenerative disorders like AD. Attempts to model and study in detail longitudinal pathological processes in living brains and molecular mechanisms involved in the pathogenesis of the disease can provide insight into disease progression in AD patients.

Transgenic mice of different types have been developed, all with amyloid plaques in the brain (Elder et al., 2010; Lannfelt et al., 1993; Morrissette et al., 2009). In the early animal PET studies using transgenic animals no binding of [^{11}C]PIB was seen, in spite of a high amyloid load in the animal brains (Klunk et al., 2005; Toyama et al., 2005; Ye et al., 2006), The inconsistency between AD patients and transgenic mice models was for long unclear and explained by fewer binding sites or lower binding affinity of [^{11}C]PIB for Aβ plaques in transgenic mice (Klunk et al., 2005; Toyama et al., 2005) and/or that the Aβ containing plaques in the mice resembles synthetic Aβ, where low [^{11}C]PIB binding was demonstrated (Ye et al., 2006). It was demonstrated that intrinsic mouse Aβ is formed and deposited in significant amounts in the brain of an AD mouse model and is deposited together with human Aβ, and this might also explain the low efficacy of PIB binding in transgenic mice brain tissue (van Groen et al., 2006). Few years later it was demonstrated that the specific radioactivity of the tracer significantly contributed to the detection of the amyloid deposits in the mouse brain. High-level retention of [^{11}C]PIB in APP transgenic mice brain regions known to contain amyloid was obtained when high-specific activity [^{11}C]PIB was

administrated (Maeda et al., 2007). It might also depend on the type of transgenic animal used, as ex vivo studies using [^{3}H]PIB and a new transgenic animal model, ARTE10, clearly showed intense labeling of the amyloid in these animals (Willuweit et al., 2009).

Senile plaques are generally enriched in Aβ 1-42 species and are additionally subjected to a wide range of post-translational and post-deposition modifications, such as N-and C-terminal truncation, oxidation, and isomerization (Lockhart, 2006). The N-terminally truncated and modified Aβ, AβN3-pyroglutamate, has been identified in AD brain (Wirths et al., 2010) and suggested to be a major contributor to PIB binding (Maeda et al., 2007). Compared to AD brain, this Aβ subtype is not so abundant in transgenic mice (Güntert et al., 2006; Kawarabayashi et al., 2001), and the levels of AβN3-pyroglutamate may therefore provide another plausible explanation for the difference in [^{11}C]PIB binding between humans and mice.

5.3 Clinical PET

[^{11}C]PIB, developed in collaboration between Uppsala University in Sweden and University of Pittsburgh School of Medicine, PA, USA, was the first tracer to detect Aβ in the brain of living patients (figure 5) (Klunk et al., 2004). The results demonstrated an increased [^{11}C]PIB retention in several brain regions known to contain Aβ in AD and none in controls (Klunk et al., 2004). The [^{11}C]PIB signal in the cortex was approximately 1.5-2 fold higher in the AD patients compared to the control subjects (Klunk et al., 2004). Interestingly enough, postmortem studies of the same patients that showed elevated [^{11}C]PIB retention *in vivo* during their life correlates significantly with regional *in vitro* measures of Aβ pathology found at autopsy (Ikonomovic et al., 2008; Kadir et al., 2011).

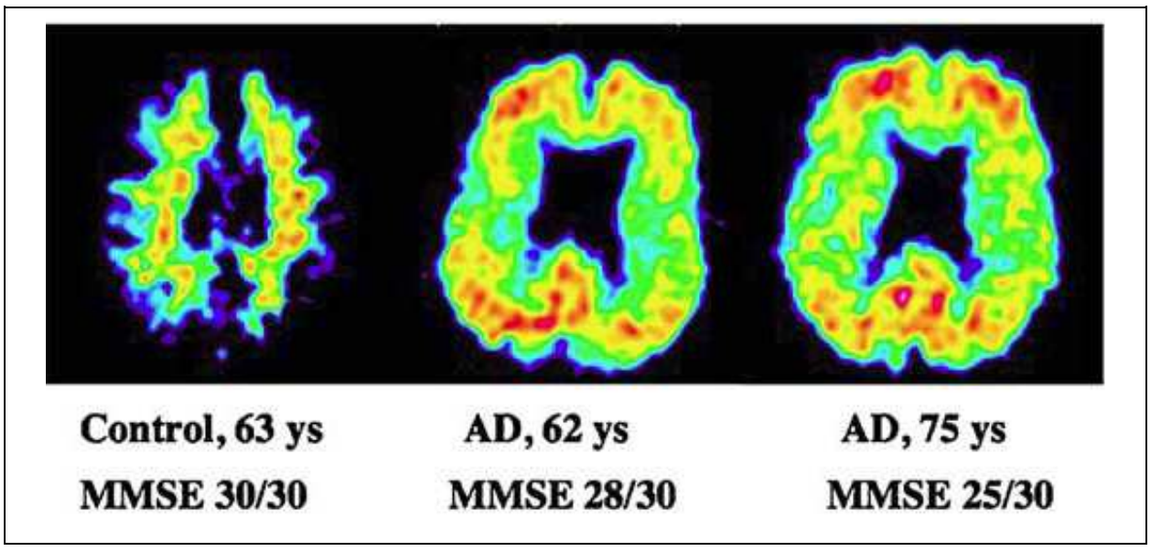


Fig. 5. [^{11}C]PIB amyloid binding to the brains of two AD patients and one healthy control (sagittal sections). Red indicates high, yellow medium, blue low [^{11}C]PIB retention. MMSE Mini-Mental- State-Examination, vs. years. Figure adapted from Nordberg (2008).

Since the study reported by Klunk et al. (2004) several selective amyloid ligands are under study or have been studied *in vivo* in living patients (see table 1). Regardless of compelling

results with [^{11}C]PIB the short half-life limits the use of PIB and other ^{11}C-ligands. This emphasizes the need for ^{18}F-ligands, with longer half-life, to implement a broader Aβ PET imaging. Recently, [^{18}F]AV-45 PET imaging was performed in AD patients and control subjects (Wong et al., 2010). The results revealed an increase in [^{18}F]AV-45 retention in the cortical gray matter in the AD patients, areas that expected to have high Aβ accumulation and none in the control subjects (Wong et al., 2010) similar to previously reported for [^{11}C]PIB.

6. Conclusion

The development of plaques are very early events in the course of events leading to AD (Ingelsson et al., 2004; Långström et al., 2007), and imaging plaques in early stages of the disease would be of great value for the treatment. However, the "ceiling effect", i.e. that the amount of amyloid plaques reaches maximum already early in the disease (Engler et al., 2006; Nordberg, 2007), makes it difficult to follow the slow progression of the disease using *in vivo* imaging of amyloid plaques. The large number of compounds that are under development or are today used in *in vivo* PET or SPECT investigations of amyloid plaques all aim at visualizing the same entities, and will hardly overcome this problem. New ligands that visualize the formation of plaques earlier in the course of disease are therefore needed. The presently available compounds bind to plaques, but some are also binding to earlier stages in the formation of plaques, such as to fibrils and oligomers, and might therefore be of great value for finding new treatment of AD and thus also for the individual patients.

There is also great interest in finding a specific radioligand for the visualization of neurofibrillary tangles, which is another hallmark seen in AD. Some of the ligands binding to the amyloid plaques also bind to some extent to tangles, and further development of these compounds may lead to ligands also labeling tangles (see e.g Barrio et al., 2008; Okamura et al., 2005; Shoghi-Jadid et al., 2002; Åslund et al., 2009). The development of tracers labeling tangles should be complementing the tracers labeling amyloid discussed above.

It can be concluded that the use of PET in the evaluation of AD has alleviated the diagnosis of the disease considerably. The development of new tracers with even better properties and tracers labeling amyloid fibrils and neurofibrillary tangles is therefore still a highly prioritized research area.

7. Acknowledgment

We are grateful for valuable discussions with Prof. Bengt Långström and our colleagues at Uppsala University. This study was performed when authors OR and HH were employed at Uppsala Applied Science Lab, GE Healthcare. We are grateful to a SAMBIO funding from Vinnova, Sweden.

8. References

Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G.M., Cooper, N.R., Eikelenboom, P., Emmerling, M., Fiebich, B.L., Finch, C.E., Frautschy, S., Griffin, W.S., Hampel, H., Hull, M., Landreth, G., Lue, L., Mrak, R., Mackenzie, I.R.,

McGeer, P.L., O'Banion, M.K., Pachter, J., Pasinetti, G., Plata-Salaman, C., Rogers, J., Rydel, R., Shen, Y., Streit, W., Strohmeyer, R., Tooyoma, I., Van Muiswinkel, F.L., Veerhuis, R., Walker, D., Webster, S., Wegrzyniak, B., Wenk, G. & Wyss-Coray, T. (2000) Inflammation and Alzheimer's disease. *Neurobiology of Aging,* Vol. 21, No. 3, pp. 383-421, 0197-4580 (Print), 0197-4580 (Linking).

Alzheimer, A. (1907) Über eine eigenartige Erkrankung der Hirnrinde. *Allegemeine Zeitschrift für Psychiatrie und Psychisch-Gerchtliche Medizin,* Vol. 64, No. pp. 146-148.

Andersson, J.D., Varnäs, K., Cselenyi, Z., Gulyas, B., Wensbo, D., Finnema, S.J., Swahn, B.-M., Svensson, S., Nyberg, S., Farde, L. & Halldin, C. (2010) Radiosynthesis of the candidate beta-amyloid radioligand [^{11}C]AZD2184: Positron emission tomography examination and metabolite analysis in cynomolgus monkeys. *Synapse,* Vol. 64, No. 10, pp. 733-741.

Archer, H.A., Edison, P., Brooks, D.J., Barnes, J., Frost, C., Yeatman, T., Fox, N.C. & Rossor, M.N. (2006) Amyloid load and cerebral atrophy in Alzheimer's disease: an ^{11}C-PIB positron emission tomography study. *Annals of Neurology,* Vol. 60, No. 1, pp. 145-147, 0364-5134 (Print), 0364-5134 (Linking).

Bacskai, B.J., Frosch, M.P., Freeman, S.H., Raymond, S.B., Augustinack, J.C., Johnson, K.A., Irizarry, M.C., Klunk, W.E., Mathis, C.A., Dekosky, S.T., Greenberg, S.M., Hyman, B.T. & Growdon, J.H. (2007) Molecular imaging with Pittsburgh Compound B confirmed at autopsy: a case report. *Archives of Neurology,* Vol. 64, No. 3, pp. 431-434.

Banati, R.B. (2002) Visualising microglial activation in vivo. *Glia,* Vol. 40, No. 2, pp. 206-217, 0894-1491 (Print), 0894-1491 (Linking).

Barrio, J.R., Kepe, V., Satyamurthy, N., Huang, S.C. & Small, G. (2008) Amyloid and tau imaging, neuronal losses and function in mild cognitive impairment. *The Journal of Nutrition, Health & Aging,* Vol. 12, No. 1, pp. 61S-65S, 1279-7707 (Print), 1279-7707 (Linking).

Bergström, M., Kumlien, E., Lilja, A., Tyrefors, N., Westerberg, G. & Långström, B. (1998) Temporal lobe epilepsy visualized with PET with ^{11}C-L-deuterium-deprenyl--analysis of kinetic data. *Acta Neurologica Scandinavica,* Vol. 98, No. 4, pp. 224-231, 0001-6314 (Print), 0001-6314 (Linking).

Braak, H., de Vos, R.A., Jansen, E.N., Bratzke, H. & Braak, E. (1998) Neuropathological hallmarks of Alzheimer's and Parkinson's diseases. *Progress in Brain Research,* Vol. 117, No. pp. 267-285.

Cagnin, A., Gerhard, A. & Banati, R.B. (2002) In vivo imaging of neuroinflammation. *European Neuropsychopharmacology,* Vol. 12, No. 6, pp. 581-586, 0924-977X (Print), 0924-977X (Linking).

Cai, L., Chin, F.T., Pike, V.W., Toyama, H., Liow, J.S., Zoghbi, S.S., Modell, K., Briard, E., Shetty, H.U., Sinclair, K., Donohue, S., Tipre, D., Kung, M.P., Dagostin, C., Widdowson, D.A., Green, M., Gao, W., Herman, M.M., Ichise, M. & Innis, R.B. (2004) Synthesis and evaluation of two ^{18}F-labeled 6-iodo-2-(4'-N,N-dimethyl-amino)phenylimidazo[1,2-a]pyridine derivatives as prospective radioligands for β-amyloid in Alzheimer's disease. *Journal of Medicinal Chemistry,* Vol. 47, No. 9, pp. 2208-2218.

Cai, L., Liow, J.-S., Zoghbi, S.S., Cuevas, J., Baetas, C., Hong, J., Shetty, H.U., Seneca, N.M., Brown, A.K., Gladding, R., Temme, S.S., Herman, M.M., Innis, R.B. & Pike, V.W. (2008) Synthesis and evaluation of N-methyl and S-methyl ^{11}C-labeled 6-

methylthio-2-(4'-N,N-dimethylamino)phenylimidazo[1,2-a]pyridines as radioligands for Imaging β-amyloid plaques in Alzheimer's disease. *Journal of Medicinal Chemistry,* Vol. 51, No. 1, pp. 148-158.

Elder, G.A., Gama Sosa, M.A. & De Gasperi, R. (2010) Transgenic mouse models of Alzheimer's disease. *Mount Sinai Journal of Medicine,* Vol. 77, No. 1, pp. 69-81, 1931-7581 (Electronic), 0027-2507 (Linking).

Engler, H., Lundberg, P.O., Ekbom, K., Nennesmo, I., Nilsson, A., Bergström, M., Tsukada, H., Hartvig, P. & Långström, B. (2003) Multitracer study with positron emission tomography in Creutzfeldt-Jakob disease. *European Journal of Nuclear Medicine and Molecular Imaging,* Vol. 30, No. 1, pp. 85-95, 1619-7070 (Print), 1619-7070 (Linking).

Engler, H., Forsberg, A., Almkvist, O., Blomquist, G., Larsson, E., Savitcheva, I., Wall, A., Ringheim, A., Långström, B. & Nordberg, A. (2006) Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. *Brain,* Vol. 129, No. Pt 11, pp. 2856-2866.

Ewers, M., Walsh, C., Trojanowski, J.Q., Shaw, L.M., Petersen, R.C., Jack, C.R., Jr., Feldman, H.H., Bokde, A.L., Alexander, G.E., Scheltens, P., Vellas, B., Dubois, B., Weiner, M. & Hampel, H. (2010) Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. *Neurobiology of Aging,* Vol. No. pp. 1558-1497 (Electronic), 0197-4580 (Linking).

Fodero-Tavoletti, M.T., Smith, D.P., McLean, C.A., Adlard, P.A., Barnham, K.J., Foster, L.E., Leone, L., Perez, K., Cortes, M., Culvenor, J.G., Li, Q.X., Laughton, K.M., Rowe, C.C., Masters, C.L., Cappai, R. & Villemagne, V.L. (2007) In vitro characterization of Pittsburgh compound-B binding to Lewy bodies. *Journal of Neurochemistry,* Vol. 27, No. 39, pp. 10365-10371, 1529-2401 (Electronic), 0270-6474 (Linking).

Fowler, J.S., Wolf, A.P., MacGregor, R.R., Dewey, S.L., Logan, J., Schlyer, D.J. & Långström, B. (1988) Mechanistic positron emission tomography studies: demonstration of a deuterium isotope effect in the monoamine oxidase-catalyzed binding of [^{11}C]L-deprenyl in living baboon brain. *Journal of Neurochemistry,* Vol. 51, No. 5, pp. 1524-1534, 0022-3042 (Print), 0022-3042 (Linking).

Ganguli, M. & Petersen, R.C. (2008) Mild cognitive impairment: challenging issues. *American Journal of Geriatric Psychiatry,* Vol. 16, No. 5, pp. 339-342, 1545-7214 (Electronic), 1064-7481 (Linking).

Ganguli, M., Blacker, D., Blazer, D.G., Grant, I., Jeste, D.V., Paulsen, J.S., Petersen, R.C. & Sachdev, P.S. (2011) Classification of neurocognitive disorders in DSM-5: a work in progress. *American Journal of Geriatric Psychiatry,* Vol. 19, No. 3, pp. 205-210, 1545-7214 (Electronic), 1064-7481 (Linking).

Güntert, A., Döbeli, H. & Bohrmann, B. (2006) High sensitivity analysis of amyloid-beta peptide composition in amyloid deposits from human and PS2APP mouse brain. *Neuroscience,* Vol. 143, No. 2, pp. 461-475, 0306-4522 (Print), 0306-4522 (Linking).

Hellström-Lindahl, E., Mousavi, M., Ravid, R. & Nordberg, A. (2004) Reduced levels of Abeta 40 and Abeta 42 in brains of smoking controls and Alzheimer's patients. *Neurobiology of Disease,* Vol. 15, No. 2, pp. 351-360.

Henriksen, G., Hauser, A.I., Westwell, A.D., Yousefi, B.H., Schwaiger, M., Drzezga, A. & Wester, H.-J. (2007) Metabolically stabilized benzothiazoles for imaging of amyloid plaques. *Journal of Medicinal Chemistry,* Vol. 50, No. 6, pp. 1087-1089.

Henriksen, G., Yousefi, B.H., Drzezga, A. & Wester, H.-J. (2008) Development and evaluation of compounds for imaging of beta-amyloid plaque by means of positron emission tomography. *European Journal of Nuclear Medicine and Molecular Imaging,* Vol. 35, No. Suppl 1, pp. S75-S81.

Ikonomovic, M.D., Klunk, W.E., Abrahamson, E.E., Mathis, C.A., Price, J.C., Tsopelas, N.D., Lopresti, B.J., Ziolko, S., Bi, W., Paljug, W.R., Debnath, M.L., Hope, C.E., Isanski, B.A., Hamilton, R.L. & DeKosky, S.T. (2008) Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. *Brain,* Vol. 131, No. Pt 6, pp. 1630-1645, 1460-2156 (Electronic).

Ingelsson, M., Fukumoto, H., Newell, K.L., Growdon, J.H., Hedley-Whyte, E.T., Frosch, M.P., Albert, M.S., Hyman, B.T. & Irizarry, M.C. (2004) Early Abeta accumulation and progressive synaptic loss, gliosis, and tangle formation in AD brain. *Neurology,* Vol. 62, No. 6, pp. 925-931.

Jellinger, K.A. (2002) Alzheimer disease and cerebrovascular pathology: an update. *Journal of Neural Transmission,* Vol. 109, No. 5-6, pp. 813-836, 0300-9564 (Print), 0300-9564 (Linking).

Johnson, K.A., Gregas, M., Becker, J.A., Kinnecom, C., Salat, D.H., Moran, E.K., Smith, E.E., Rosand, J., Rentz, D.M., Klunk, W.E., Mathis, C.A., Price, J.C., Dekosky, S.T., Fischman, A.J. & Greenberg, S.M. (2007) Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. *Annals of Neurology,* Vol. 62, No. 3, pp. 229-234, 0364-5134 (Print), 0364-5134 (Linking).

Kadir, A., Marutle, A., Gonzalez, D., Scholl, M., Almkvist, O., Mousavi, M., Mustafiz, T., Darreh-Shori, T., Nennesmo, I. & Nordberg, A. (2011) Positron emission tomography imaging and clinical progression in relation to molecular pathology in the first Pittsburgh Compound B positron emission tomography patient with Alzheimer's disease. *Brain,* Vol. 134, No. Pt 1, pp. 301-317, 1460-2156 (Electronic), 0006-8950 (Linking).

Kawarabayashi, T., Younkin, L.H., Saido, T.C., Shoji, M., Ashe, K.H. & Younkin, S.G. (2001) Age-dependent changes in brain, CSF, and plasma amyloid (beta) protein in the Tg2576 transgenic mouse model of Alzheimer's disease. *Journal of Neuroscience,* Vol. 21, No. 2, pp. 372-381.

Klok, R.P., Klein, P.J., van Berckel, B.N.M., Tolboom, N., Lammertsma, A.A. & Windhorst, A.D. (2008) Synthesis of 2-(1,1-dicyanopropen-2-yl)-6-(2-[^{18}F]-fluoroethyl)-methylamino-naphthalene ([^{18}F]FDDNP). *Applied Radiation and Isotopes,* Vol. 66, No. pp. 203-207.

Klunk, W.E., Debnath, M.L. & Pettegrew, J.W. (1994) Development of small molecule probes for the beta-amyloid protein of Alzheimer's disease. *Neurobiology of Aging,* Vol. 15, No. pp. 691-698.

Klunk, W.E., Debnath, M.L. & Pettegrew, J.W. (1995) Chrysamine-G binding to Alzheimer and control brain: Autopsy study of new amyloid probe. *Neurobiology of Aging,* Vol. 16, No. 4, pp. 541-548.

Klunk, W.E., Engler, H., Nordberg, A., Bacskai, B.J., Wang, Y., Price, J.C., Bergström, M., Hyman, B.T., Långström, B. & Mathis, C.A. (2003) Imaging the pathology of Alzheimer's disease: amyloid-imaging with positron emission tomography. *Neuroimaging Clinics of North America,* Vol. 13, No. 4, pp. 781-789, ix.

Klunk, W.E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D.P., Bergström, M., Savitcheva, I., Huang, G.F., Estrada, S., Ausen, B., Debnath, M.L., Barletta, J., Price,

J.C., Sandell, J., Lopresti, B.J., Wall, A., Koivisto, P., Antoni, G., Mathis, C.A. & Långström, B. (2004) Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Annals of Neurology,* Vol. 55, No. 3, pp. 306-319.

Klunk, W.E., Lopresti, B.J., Ikonomovic, M.D., Lefterov, I.M., Koldamova, R.P., Abrahamson, E.E., Debnath, M.L., Holt, D.P., Huang, G.F., Shao, L., DeKosky, S.T., Price, J.C. & Mathis, C.A. (2005) Binding of the positron emission tomography tracer Pittsburgh compound-B reflects the amount of amyloid-beta in Alzheimer's disease brain but not in transgenic mouse brain. *Journal of Neuroscience,* Vol. 25, No. 46, pp. 10598-10606.

Koole, M., Lewis, D.M., Buckley, C., Nelissen, N., Vandenbulcke, M., Brooks, D.J., Vandenberghe, R. & Van Laere, K. (2009) Whole-body biodistribution and radiation dosimetry of ^{18}F-GE067: a radioligand for in vivo brain amyloid imaging. *Journal of Nuclear Medicine,* Vol. 50, No. 5, pp. 818-822, 0161-5505 (Print).

Korczyn, A.D. (2008) The amyloid cascade hypothesis. *Alzheimers & Dementia,* Vol. 4, No. 3, pp. 176-178, 1552-5279 (Electronic), 1552-5260 (Linking).

Kudo, Y., Okamura, N., Furumoto, S., Tashiro, M., Furukawa, K., Maruyama, M., Itoh, M., Iwata, R., Yanai, K. & Arai, H. (2007) 2-(2-[2-Dimethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy)benzoxazole: a novel PET agent for in vivo detection of dense amyloid plaques in Alzheimer's disease patients. *Journal of Nuclear Medicine,* Vol. 48, No. 4, pp. 553-561, 0161-5505 (Print), 0161-5505 (Linking).

Lannfelt, L., Folkesson, R., Mohammed, A.H., Winblad, B., Hellgren, D., Duff, K. & Hardy, J. (1993) Alzheimer's disease: molecular genetics and transgenic animal models. *Behavioural Brain Research,* Vol. 57, No. 2, pp. 207-213, 0166-4328 (Print), 0166-4328 (Linking).

Liu, J., Kepe, V., Zabjek, A., Petric, A., Padgett, H.C., Satyamurthy, N. & Barrio, J.R. (2007) High-yield, automated radiosynthesis of 2-(1-{6-[(2-[^{18}F]fluoroethyl)(methyl) amino]-2-naphthyl}ethylidene)malononi trile ([^{18}F]FDDNP) ready for animal or human administration. *Molecular Imaging and Biology,* Vol. 9, No. pp. 6-16.

Lockhart, A. (2006) Imaging Alzheimer's disease pathology: one target, many ligands. *Drug Discovery Today,* Vol. 11, No. 23-24, pp. 1093-1099.

Logan, J., Fowler, J.S., Volkow, N.D., Wang, G.J., MacGregor, R.R. & Shea, C. (2000) Reproducibility of repeated measures of deuterium substituted [^{11}C]L-deprenyl ([^{11}C]L-deprenyl-D2) binding in the human brain. *Nuclear Medicine and Biology,* Vol. 27, No. 1, pp. 43-49, 0969-8051 (Print), 0969-8051 (Linking).

Långström, B., Andrén, P.E., Lindhe, Ö., Svedberg, M.M. & Hall, H. (2007) In vitro imaging techniques in neurodegenerative diseases. *Molecular Imaging and Biology,* Vol. 9, No. 4, pp. 161-175, 1536-1632 (Print), 1536-1632 (Linking).

Maeda, J., Ji, B., Irie, T., Tomiyama, T., Maruyama, M., Okauchi, T., Staufenbiel, M., Iwata, N., Ono, M., Saido, T.C., Suzuki, K., Mori, H., Higuchi, M. & Suhara, T. (2007) Longitudinal, quantitative assessment of amyloid, neuroinflammation, and anti-amyloid treatment in a living mouse model of Alzheimer's disease enabled by positron emission tomography. *Journal of Neuroscience,* Vol. 27, No. 41, pp. 10957-10968, 1529-2401 (Electronic), 0270-6474 (Linking).

Mann, D.M., Iwatsubo, T., Ihara, Y., Cairns, N.J., Lantos, P.L., Bogdanovic, N., Lannfelt, L., Winblad, B., Maat-Schieman, M.L. & Rossor, M.N. (1996) Predominant deposition of amyloid-beta 42(43) in plaques in cases of Alzheimer's disease and hereditary

cerebral hemorrhage associated with mutations in the amyloid precursor protein gene. *American Journal of Pathology,* Vol. 148, No. 4, pp. 1257-1266.

Mathis, C.A., Wang, Y., Holt, D.P., Huang, G.F., Debnath, M.L. & Klunk, W.E. (2003) Synthesis and evaluation of ^{11}C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents. *Journal of Medicinal Chemistry,* Vol. 46, No. 13, pp. 2740-2754.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. & Stadlan, E.M. (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology,* Vol. 34, No. 7, pp. 939-944.

Mintun, M.A., Larossa, G.N., Sheline, Y.I., Dence, C.S., Lee, S.Y., Mach, R.H., Klunk, W.E., Mathis, C.A., DeKosky, S.T. & Morris, J.C. (2006) [^{11}C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. *Neurology,* Vol. 67, No. 3, pp. 446-452.

Morrissette, D.A., Parachikova, A., Green, K.N. & LaFerla, F.M. (2009) Relevance of transgenic mouse models to human Alzheimer disease. *Journal of Biological Chemistry,* Vol. 284, No. 10, pp. 6033-6037, 0021-9258 (Print), 0021-9258 (Linking).

Nordberg, A. (2004) PET imaging of amyloid in Alzheimer's disease. *Lancet Neurology,* Vol. 3, No. 9, pp. 519-527.

Nordberg, A. (2007) Amyloid imaging in Alzheimer's disease. *Current Opinion in Neurology,* Vol. 20, No. 4, pp. 398-402.

Nordberg, A. (2008) Amyloid plaque imaging in vivo: current achievement and future prospects. *European Journal of Nuclear Medicine and Molecular Imaging,* Vol. 35 Suppl 1, No. pp. S46-50, 1619-7070 (Print), 1619-7070 (Linking).

Näslund, J., Haroutunian, V., Mohs, R., Davis, K.L., Davies, P., Greengard, P. & Buxbaum, J.D. (2000) Correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline. *JAMA, The Journal of American Medical Association,* Vol. 283, No. 12, pp. 1571-1577.

Okamura, N., Suemoto, T., Furumoto, S., Suzuki, M., Shimadzu, H., Akatsu, H., Yamamoto, T., Fujiwara, H., Nemoto, M., Maruyama, M., Arai, H., Yanai, K., Sawada, T. & Kudo, Y. (2005) Quinoline and benzimidazole derivatives: candidate probes for in vivo imaging of tau pathology in Alzheimer's disease. *The Journal of Neuroscience,* Vol. 25, No. 47, pp. 10857-10862, 1529-2401 (Electronic).

Okamura, N., Furmoto, S., Funaki, Y., Suemoto, T., Kato, M., Ishikawa, Y., Ito, S., Akatsu, H., Yamamoto, T., Swada, T., Arai, H., Kudo, Y. & Yanai, K. (2007) binding and safety profile of novel derivative for in vivo imaging of amyloid deposite in Alzheimer's disease. *Geriatrics & Gerontology International,* Vol. 7, No. pp. 393-400.

Ono, M., Wilson, A., Nobrega, J., Westaway, D., Verhoeff, P., Zhuang, Z.-P., Kung, M.-P. & Kung, H.F. (2003) ^{11}C-Labeled stilbene derivatives as A-beta aggregate specific PET imaging agents for Alzheimer's disease. *Nuclear Medicine and Biology,* Vol. 30, No. pp. 565-571.

Ono, M., Kawashima, H., Nonaka, A., Kawai, T., Haratake, M., Mori, H., Kung, M.-P., Kung, H.F., Saji, H. & Nakayama, M. (2006) Novel benzofuran derivatives for PET imaging of .beta.-amyloid plaques in Alzheimer's disease brains. *Journal of Medicinal Chemistry,* Vol. 49, No. 9, pp. 2725-2730.

Ono, M. (2009) Development of positron-emission tomography/single-photon emission computed tomography imaging probes for in vivo detection of β-amyloid plaques

in Alzheimer's brains. *Chemical & Pharmaceutical Bulletin,* Vol. 57, No. 10, pp. 1029-1039.

Petersen, R.C., Doody, R., Kurz, A., Mohs, R.C., Morris, J.C., Rabins, P.V., Ritchie, K., Rossor, M., Thal, L. & Winblad, B. (2001) Current concepts in mild cognitive impairment. *Archives of Neurology,* Vol. 58, No. 12, pp. 1985-1992.

Philipson, O., Lord, A., Gumucio, A., O'Callaghan, P., Lannfelt, L. & Nilsson, L.N. (2010) Animal models of amyloid-beta-related pathologies in Alzheimer's disease. *FEBS Journal,* Vol. 277, No. 6, pp. 1389-1409, 1742-4658 (Electronic), 1742-464X (Linking).

Porchet, R., Probst, A., Bouras, C., Draberova, E., Draber, P. & Riederer, B.M. (2003) Analysis of glial acidic fibrillary protein in the human entorhinal cortex during aging and in Alzheimer's disease. *Proteomics,* Vol. 3, No. 8, pp. 1476-1485, 1615-9853 (Print), 1615-9853 (Linking).

Rosen, R.F., Walker, L.C. & Levine, H., 3rd. (2011) PIB binding in aged primate brain: enrichment of high-affinity sites in humans with Alzheimer's disease. *Neurobiology of Aging,* Vol. 32, No. 2, pp. 223-234, 1558-1497 (Electronic), 0197-4580 (Linking).

Schönheit, B., Zarski, R. & Ohm, T.G. (2004) Spatial and temporal relationships between plaques and tangles in Alzheimer-pathology. *Neurobiology of Aging,* Vol. 25, No. 6, pp. 697-711.

Selkoe, D.J. & Schenk, D. (2003) Alzheimer's disease: molecular understanding predicts amyloid-based therapeutics. *Annual Review of Pharmacology and Toxicology,* Vol. 43, No. pp. 545-584, 0362-1642 (Print), 0362-1642 (Linking).

Seneca, N., Cai, L., Liow, J.-S., Zoghbi, S.S., Gladding, R.L., Hong, J., Pike, V.W. & Innis, R.B. (2007) Brain and whole-body imaging in nonhuman primates with [^{11}C]MeS-IMPY, a candidate radioligand for .beta.-amyloid plaques. *Nuclear Medicine and Biology,* Vol. 34, No. 6, pp. 681-689.

Shimadzu, H., Suemoto, T., Suzuki, M., Shiomitsu, T., Okamura, N., Kudo, Y. & Sawada, T. (2004) Novel probes for imaging amyloid-b: F-18 and C-11 labeling of 2-(4-aminostyryl)benzoxazole derivatives. *Journal of Labelled Compounds and Radiopharmaceuticals.,* Vol. 47, No. pp. 181-190.

Shoghi-Jadid, K., Small, G.W., Agdeppa, E.D., Kepe, V., Ercoli, L.M., Siddarth, P., Read, S., Satyamurthy, N., Petric, A., Huang, S.C. & Barrio, J.R. (2002) Localization of neurofibrillary tangles and β-amyloid plaques in the brains of living patients with Alzheimer disease. *The American Journal of Geriatric Psychiatry,* Vol. 10, No. 1, pp. 24-35, 1064-7481 (Print).

Storey, A.E., Jones, C.L., Bouvet, D.R.C., Lasbistes, N., Fairway, S.M., Williams, L., Gibson, A.M., Nairne, R.J., Karimi, F. & Långström, B. (2007) Process for fluorination of anilides. *PCT international applications WO 2006-GB3009 20060811,* Vol. No. pp. 45.

Streit, W.J. (2004) Microglia and Alzheimer's disease pathogenesis. *Journal of Neuroscience Research,* Vol. 77, No. 1, pp. 1-8, 0360-4012 (Print), 0360-4012 (Linking).

Svedberg, M.M., Hall, H., Hellström-Lindahl, E., Estrada, S., Guan, Z., Nordberg, A. & Långström, B. (2009) [^{11}C]PIB-amyloid binding and levels of Abeta40 and Abeta42 in postmortem brain tissue from Alzheimer patients. *Neurochemistry International,* Vol. 54, No. 5-6, pp. 347-357, 1872-9754 (Electronic).

Toyama, H., Ye, D., Ichise, M., Liow, J.S., Cai, L., Jacobowitz, D., Musachio, J.L., Hong, J., Crescenzo, M., Tipre, D., Lu, J.Q., Zoghbi, S., Vines, D.C., Seidel, J., Katada, K., Green, M.V., Pike, V.W., Cohen, R.M. & Innis, R.B. (2005) PET imaging of brain with the beta-amyloid probe, [^{11}C]6-OH-BTA-1, in a transgenic mouse model of

Alzheimer's disease. *European Journal of Nuclear Medicine and Molecular Imaging,* Vol. 32, No. 5, pp. 593-600, 1619-7070 (Print), 1619-7070 (Linking).

van Groen, T., Kiliaan, A.J. & Kadish, I. (2006) Deposition of mouse amyloid β in human APP/PS1 double and single AD model transgenic mice. *Neurobiology of Disease,* Vol. 23, No. 3, pp. 653-662.

Wang, H., Shi, H., Yu, H., Jiang, S. & Tang, G. (2011) Facile and rapid one-step radiosynthesis of [^{18}F]BAY94-9172 with a new precursor. *Nuclear Medicine and Biology,* Vol. 38, No. pp. 121-127.

Villemagne, V.L., Pike, K.E., Darby, D., Maruff, P., Savage, G., Ng, S., Ackermann, U., Cowie, T.F., Currie, J., Chan, S.G., Jones, G., Tochon-Danguy, H., O'Keefe, G., Masters, C.L. & Rowe, C.C. (2008) Abeta deposits in older non-demented individuals with cognitive decline are indicative of preclinical Alzheimer's disease. *Neuropsychologia,* Vol. 46, No. 6, pp. 1688-1697, 0028-3932 (Print), 0028-3932 (Linking).

Willuweit, A., Velden, J., Godemann, R., Manook, A., Jetzek, F., Tintrup, H., Kauselmann, G., Zevnik, B., Henriksen, G., Drzezga, A., Pohlner, J., Schoor, M., Kemp, J.A. & von der Kammer, H. (2009) Early-onset and robust amyloid pathology in a new homozygous mouse model of Alzheimer's disease. *PLoS One,* Vol. 4, No. 11, pp. e7931, 1932-6203 (Electronic), 1932-6203 (Linking).

Wimo, A. & Winblad, B. (2008) Economical aspects of dementia. *Handbook of Clinical Neurology,* Vol. 89, No. pp. 137-146, 0072-9752 (Print), 0072-9752 (Linking).

Wirths, O., Bethge, T., Marcello, A., Harmeier, A., Jawhar, S., Lucassen, P.J., Multhaup, G., Brody, D.L., Esparza, T., Ingelsson, M., Kalimo, H., Lannfelt, L. & Bayer, T.A. (2010) Pyroglutamate Abeta pathology in APP/PS1KI mice, sporadic and familial Alzheimer's disease cases. *Journal of Neural Transmission,* Vol. 117, No. 1, pp. 85-96, 1435-1463 (Electronic), 0300-9564 (Linking).

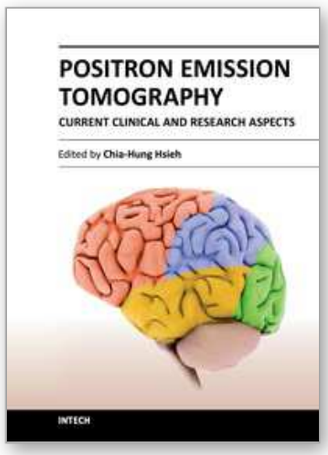
Wong, D.F., Rosenberg, P.B., Zhou, Y., Kumar, A., Raymont, V., Ravert, H.T., Dannals, R.F., Nandi, A., Brasic, J.R., Ye, W., Hilton, J., Lyketsos, C., Kung, H.F., Joshi, A.D., Skovronsky, D.M. & Pontecorvo, M.J. (2010) In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand ^{18}F-AV-45 (florbetapir [corrected] F 18). *Journal of Nuclear Medicine,* Vol. 51, No. 6, pp. 913-920, 1535-5667 (Electronic), 0161-5505 (Linking).

Yao, C.-H., Lin, K.-J., Weng, C.-C., Hsiao, I.-T., Ting, Y.-S., Yen, T.-C., Jan, T.-R., Skovronsky, D., Kung, M.-P. & Wey, S.-P. (2010) GMP-compliant automated synthesis of [^{18}F]AV-45 (Florbetapir F-18) for imaging beta-amyloid plaques in human brain. *Applied Radiation and Isotopes,* Vol. 68, No. pp. 2293-2297.

Ye, L., Morgenstern, J.L., Lamb, J.R. & Lockhart, A. (2006) Characterisation of the binding of amyloid imaging tracers to rodent Aβ fibrils and rodent-human Aβ co-polymers. *Biochemical and Biophysical Research Communications,* Vol. 347, No. 3, pp. 669-677.

Zhang, W., Oya, S., Kung, M.P., Hou, C., Maier, D.L. & Kung, H.F. (2005) F-18 stilbenes as PET imaging agents for detecting beta-amyloid plaques in the brain. *Journal of Medicinal Chemistry,* Vol. 48, No. 19, pp. 5980-5988, 0022-2623 (Print), 0022-2623 (Linking).

Åslund, A., Sigurdson, C.J., Klingstedt, T., Grathwohl, S., Bolmont, T., Dickstein, D.L., Glimsdal, E., Prokop, S., Lindgren, M., Konradsson, P., Holtzman, D.M., Hof, P.R., Heppner, F.L., Gandy, S., Jucker, M., Aguzzi, A., Hammarström, P. & Nilsson, K.P. (2009) Novel pentameric thiophene derivatives for in vitro and in vivo optical imaging of a plethora of protein aggregates in cerebral amyloidoses. *Acs Chemical Biology,* Vol. 4, No. 8, pp. 673-684, 1554-8937 (Electronic), 1554-8929 (Linking).



Positron Emission Tomography - Current Clinical and Research Aspects

Edited by Dr. Chia-Hung Hsieh

ISBN 978-953-307-824-3
Hard cover, 336 pages
Publisher InTech
Published online 08, February, 2012
Published in print edition February, 2012

This book's stated purpose is to provide a discussion of the technical basis and clinical applications of positron emission tomography (PET), as well as their recent progress in nuclear medicine. It also summarizes current literature about research and clinical science in PET. The book is divided into two broad sections: basic science and clinical science. The basic science section examines PET imaging processing, kinetic modeling, free software, and radiopharmaceuticals. The clinical science section demonstrates various clinical applications and diagnoses. The text is intended not only for scientists, but also for all clinicians seeking recent information regarding PET.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen