Amyloid Plaque Imaging from IMPY/SPECT to AV-45/PET

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The formation and deposition of β-amyloid (Aβ) plaques are the earliest pathological changes in Alzheimer's disease (AD). Molecular imaging of Aβ plaques could serve as a surrogate marker in early diagnosis and neuropathogenesis studies of AD. Several radionuclide labeled ligands have recently been developed for noninvasive visualization of Aβ plaques in the brains of AD patients using single photon emission computed tomography or positron emission tomography (PET). There has been rapid progress in the field of imaging for plaque pathology. AV-45 was the first plaque imaging agent to enter multi-center, investigational new drug clinical trials in the US, and has now been studied in dozens of trials with more than 1,000 subjects ranging from cognitively normal individuals to those with AD dementia. "Imaging to autopsy" phase III studies further confirmed and validated the specific imaging signal correlated to the plaque burden in living subjects. With these promising and confirmed characteristics of AV-45, the Alzheimer's Disease Neuroimaging Initiative (ADNI) under common consensus decided on AV-45 as the emerging standard PET imaging agent for evaluating the progression of plaque pathology in patients with AD or mild cognition impairment, and even healthy controls. With the wide availability of AV-45 for plaque imaging, the ultimate goal of the ADNI is global clinical trials for disease detection and progression. This review presents recent experience with Aβ-targeting radiotracers at Chang Gung University and Chang Gung Memorial Hospital. *(Chang Gung Med J 2012;35:211-8)*

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Alzheimer's disease (AD) is a brain disorder resulting in progressive memory loss and other cognitive loss. One of the pathological landmarks found postmortem in the brains of patients is an abundance of senile plaques containing β-amyloid (Aβ) peptides.[1,2] While the exact mechanisms underlying the pathology of AD are not fully understood, reducing deposition of amyloid plaques is believed to be potentially useful to patients.[3,4] Currently, inhibition of β- and γ-secretases responsible for Aβ formation and Aβ immunization to reduce Aβ plaques have been proposed as potential treatments for AD.[5,6] The pivotal role of Aβ aggregates in AD thus provides a strong impetus to search for specific Aβ-aggregate-binding agents to target this devastating disease.[2] When labeled with appropriate radioiso-

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topes, these molecular imaging agents might play important roles serving as *in vivo* diagnostic tools to detect plaque pathology and monitor the progression of Aβ aggregates in the brain. Advances in *in vivo* detection of β-amyloid formation and aggregation could further facilitate drug development for the disease by providing critical information on plaque burden in the living brain.

IMPY Study

Among dozens of radioiodinated ligands developed and reported, IMPY [6-iodo-2-(49-dimethylamino-)phenyl-imidazo[1,2-α]pyridine] (Fig. 1) labeled with ^{125}I or ^{123}I showed the most desirable in vitro and in vivo characteristics to target amyloid plaques.[7,8] Binding studies of [^{125}I]IMPY to the Aβ plaque-like structures in doubly transgenic mice (PSAPP) were fully evaluated.[9] The feasibility of using [^{123}I]IMPY in conjunction with micro single photon emission computed tomography (microSPECT) imaging to detect Aβ plaque-like structures in the living brain of PSAPP mice was attempted. However, results of the microSPECT imaging studies were not very encouraging (unpublished result). Several studies further indicated that there is no good, appropriate animal model with plaques resembling those in human brains.[10,11] Subsequent clinical studies of [^{123}I]IMPY in healthy subjects and AD patients showed a distribution pattern which was not similar to that of [*N*-methyl-1-^{11}C]-2-(4'-metnylaminophenyl)-6-hydrozybenzothiazole ([^{11}C]PIB), a well characterized and studied PET tracer for plaques, but there was a more perfusion-like pattern, even with a higher accumulation in AD brains compared with age-matched controls (unpublished data). Moreover, the signal-to-noise ratio for plaque labeling of [^{123}I]IMPY was not as robust as that of PIB (PIB showed a S/N ratio of about 2.5 while IMPY displayed a ratio of 1.8 to 2.0, between 30-50 min after intravenous injection). Because of the fast brain and plasma clearance of [^{123}I]IMPY observed in AD as well as in healthy subjects, it was believed that the in vivo metabolism/instability of [^{123}I]IMPY may ultimately lead to a decreased signal. Taken together, [^{123}I]IMPY did not meet the criteria of a potential plaque imaging agent.

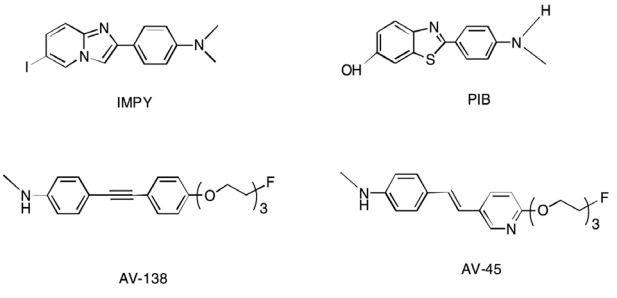

Fig. 1 Structures of PIB, IMPY, AV-138 and AV-45.

Despite the disappointing results observed for in vivo SPECT imaging with [^{123}I]IMPY, the ^{125}I labeled tracer [^{125}I]IMPY became the most desirable radiotracer for in vitro characterization of plaque binding. High affinity (in nM range) and high capacity [^{125}I]IMPY binding were obtained in cerebellar homogenates prepared from postmortem AD brains.[8] The location and density of the specific signal detected by [^{125}I]IMPY correlated with the distribution of amyloid plaques in brain specimens, as confirmed by thioflavin-S (TF-S) staining.[8] Most importantly, [^{125}I]IMPY has been used as the standard radiotracer in competitive binding experiments for screening of potential plaque binding agents.

When molecular imaging for neurodegenerative disease, i.e. the AD project, was initiated at Chang Gung Memorial Hospital (CGMH) and Chang Gung University (CGU) in Taiwan in late 2007, [^{125}I]IMPY was introduced as the first radiotracer targeting amyloid plaques. [^{125}I]IMPY was successfully prepared at CGU with high specific activity of 2,200 Ci/mmol and greater than 95% radiochemical purity. In addition to laying the foundation for tracer preparation, the screening methodology using [^{125}I]IMPY for in vitro plaque binding as well as brain section labeling (*in vitro* autoradiography) was established at CGU. The capability to perform these preclinical evaluations was essential for later follow-up screening and validation of newly introduced radiotracers.

AV-138 Study

For a decade, development of SPECT imaging tracers for amyloid plaques met with limited success. In contrast, positron emission tomography (PET) plaque imaging with PIB has demonstrated the feasibility of clearly visualizing plaques in living human brains.[12] Plaque pathology can be detected not only in patients with AD, but also those with mild cognition impairment (MCI) and even some control sub-

jects who show positive pathology with PIB.[13] However, the short half-life (20 min) of ^{11}C in PIB limits its usefulness for widespread clinical application. With the recent successful development of several PET plaque imaging agents labeled with ^{18}F ($t_{1/2}$ = 109 min),[14-18] the urgent need to move on to new ^{18}F -labeled plaque imaging agents at CGMH/CGU was immediately realized and work in this area proceeded. Under the sponsorship of a small biotech company, Avid Radiopharmaceuticals, Inc.[19] several ^{18}F -labeled plaque imaging agents originally developed at the University of Pennsylvania[14,15] were subsequently demonstrated to be potentially useful preclinically. Under an agreement with Avid, the first ^{18}F -labeled PET tracer targeting amyloid plaques, [4-((4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)phenyl)-ethynyl)-*N*-methylbenzenamine] (AV-138) was introduced at CGMH/CGU in early 2008.

AV-138 belongs to a series of fluoropegylated diphenlacetylene derivatives based on a triple-bonded structure (Fig. 1). Consistent with data reported previously,[20] the high binding affinity of nonradioactive AV-138 with K_i values of 2.4 ± 0.7 nM was confirmed side by side with nonradioactive IMPY (K_i = 4.0 ± 2.5 nM) for Aβ aggregates (Fig. 2).[21]

To ensure timely delivery of radiofluoro-labeled AV-138 and to comply with the guidelines of PET tracer manufacturing for further clinical application, a one-step, one-pot radiofluorination approach was used. The Sumitomo automated modules at the cyclotron facility of CGMH were used for radiosynthesis following a method described previously with some modifications.[21]

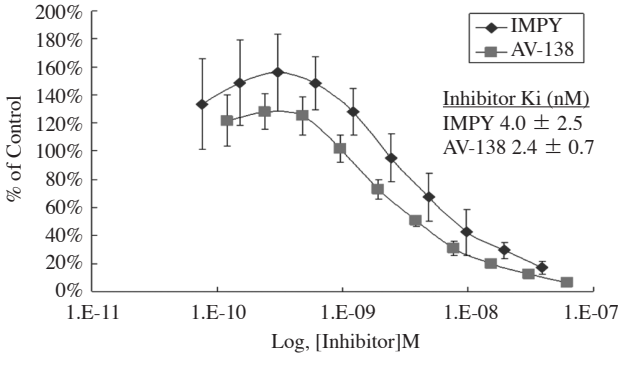

Fig. 2 Comparison of IMPY and AV-138 in [^{125}]IMPY binding in AD brain homogenates. AV-138 shows a binding affinity similar to IMPY with K_i values of 4.0 ± 2.5 and 2.4 ± 0.7 nM, for IMPY and AV-138, respectively. Each value was determined three times with a duplicate for each measurement.

As expected, specific binding of AV-138 was clearly observed mainly in AD gray homogenates (plaque-enriched region), with a low signal in AD white homogenates (minimal plaques present). The ratio between gray and white homogenates reached as high as 10 (Fig. 3).[21] In contrast, there was very low binding signal present in both control gray and white homogenates. The huge binding signal difference between AD gray and control gray homogenates was related to the presence of significant amounts of measurable Aβ plaques present in AD gray but not in control gray tissues. Thus, the phenylacetylene ligand AV-138 is desirable, based on the higher Aβ plaque signal and the lower nonspecific binding that are comparable to PIB and other ^{18}F labeled tracers.[22]

Using a high-resolution FLA-5000 phosphor imager to replace traditional film autoradiography, excellent images (FujiFilm, Tokyo, Japan) of Aβ plaque labeling with both [^{125}I]IMPY and AV-138 could be detected (Fig. 4A). Fluorescence signals from plaques stained with TF-S on the brain sections could readily be visualized (Fig. 4B). A fused image

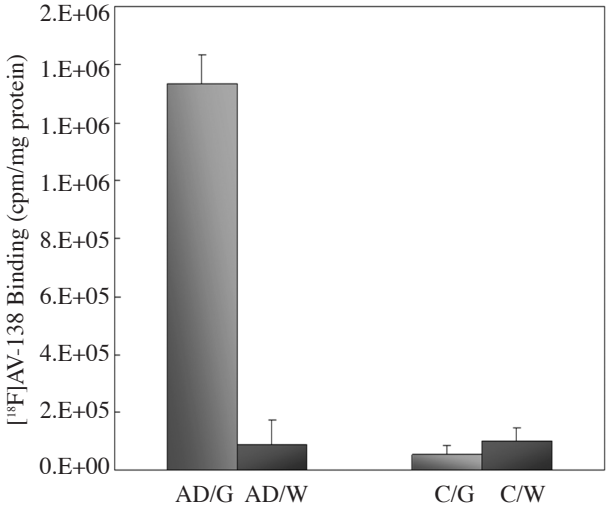

Fig. 3 Binding of AV-138 to β-amyloid plaques in postmortem brain homogenates in pooled AD patients and controls. Specific binding can be clearly seen in the AD gray matter (AD/G) homogenates, but not in the AD white matter (AD/W) and control brain homogenates (C/G and C/W). Data are expressed as mean ± SD and are the average of three independent experiments with duplicate values for each measurement.

shown in Fig. 4C confirmed the consistency and the match for these two different labels.[21]

During the radiofluorination of AV-138, we faced a low yield (3.3%-8.5%, decay corrected) and an unexpected sticking problem associated with this ^{18}F tracer. Several attempts to improve the automation synthesis were not successful. Because this unfavorable property could ultimately decrease the widespread clinical application of the automated synthesis, we looked for other potential tracers as possible replacements.

AV-45 Study

With exploratory investigational new drug (IND) guidance (approved Jan, 2006 from the Food and Drug Administration in the United States) in effect, Avid quickly began human trials of more than a dozen potential ^{18}F PET imaging agents which were selected based on various preclinical criteria targeting amyloid plaques.[19] AV-45, (*E*)-4-(2-(6-(2-(2-(2-fluoroethoxyethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methyl benzenamine, and AV-138 were among the final four tracers with the best pharmacokinetics and pharmacodynamics for imaging brain amyloid deposits in humans. AV-45, similar to AV-138, is a fluoropegylated PET tracer (Fig. 1) with a double bond (instead of the triple bond in AV-138) connecting phenyl and pyridine rings (AV-138 has two phenyl rings instead). With this unique structure, AV-45 displayed relatively fast kinetics (brain uptake and background washout) resulting in the best imaging contrast (plaque signal vs. white matter background) less than one hour after tracer injection.[19]

Although successful automated synthesis of AV-138 was readily achieved at CGMH,[21] excellent imaging results were observed for AV-45,[19,23,24]

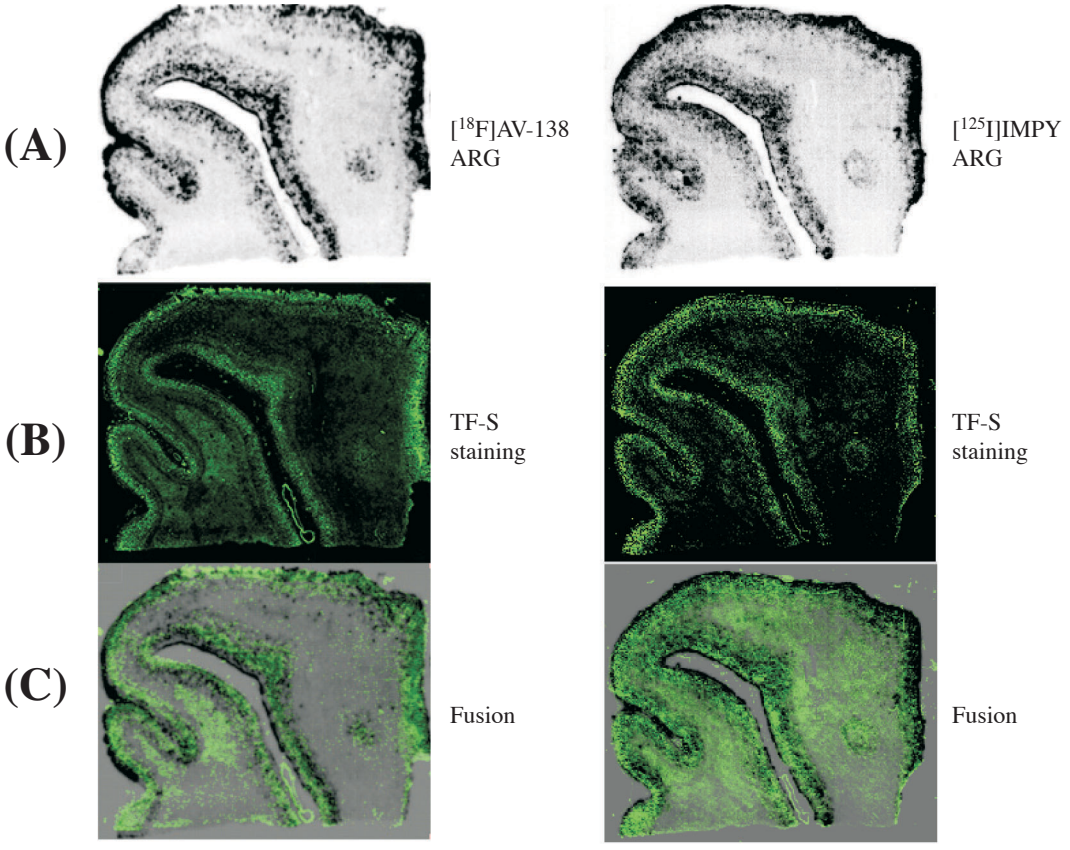

Fig. 4 *In vitro* autoradiography of postmortem AD brain sections with [^{125}I]IMPY or AV-138. The same section was fluorescently stained with Th-S. Both nuclear and fluorescent images were analyzed and quantified with a high-resolution phosphor imager. (A) AV-138 or [^{125}I]IMPY imaging; (B) Thioflavin-S (TF-S) staining; (C) Fusion imaging.

which prompted us to quickly switch to this agent for future clinical studies. We chose to carry out more detailed evaluations for institutional production and validation of AV-45 for clinical imaging studies targeting Aβ plaques. The goal of timely delivery of AV-45 for possible widespread clinical applications complying with the guidelines of PET tracer manufacturing was quickly achieved at CGMH.

The properties of the generated AV-45 under good manufacturing practice-compliant automated synthesis was further validated for specific Aβ plaque binding. Saturated binding with high affinity (K_d = 2.59 nM) and high capacity (B_{max} = 9,326 fmol/mg protein) was observed in AD gray homogenates (Fig. 5). The binding signal was observed mainly in AD gray homogenates, with low signal in AD white homogenates (minimal plaques present) reaching a high contrast of 8 (data not shown).

With the production of the radiopharmaceutical AV-45 in place, a phase I human study began at CGMH. The pilot study focused mainly on the in vivo biodistribution, safety, and radiation dosimetry of AV-45 in human subjects. PET AV-45 amyloid imaging was also performed in a group of patients with AD and healthy elderly controls without dementia.

AV-45 did not show any noticeable pharmacological effects in any of the subjects. High absorbed doses were found in the gallbladder wall, liver, and upper large intestine wall.[27] The critical organ was the gallbladder wall, which received 58.7 Gy/MBq. The effective dose equivalent and effective dose for AV-45 were 23.37 ± 2.54 Sv/MBq and 16.87 ± 0.60 Sv/MBq, respectively.[26]

PET brain imaging of AV-45 demonstrated that its localization in the frontal, parietal and precuneus cortex in AD patients but not in the brains of control patients was consistent with the pattern of amyloid distribution (Fig. 6). A high standardized uptake value ratio of the frontal cortex to the cerebellum was reached between 50-60 min after injection of the radiopharmaceutical.

The results of this pilot phase I study showed that AV-45 is a safe PET tracer for studying amyloid plaque distribution in the brain. The administration of AV-45 leads to a reasonable radiation burden in investigated subjects which does not preclude longitudinal studies.

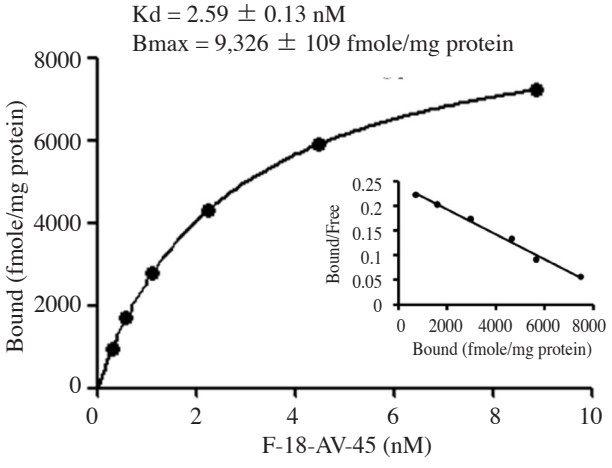

Fig. 5 Representative saturation and Scatchard plots of AV-45 in AD gray homogenates showing high binding affinity and high capacity.

Conclusion

There has been rapid progress in the field of imaging for plaque pathology. AV-45 was the first

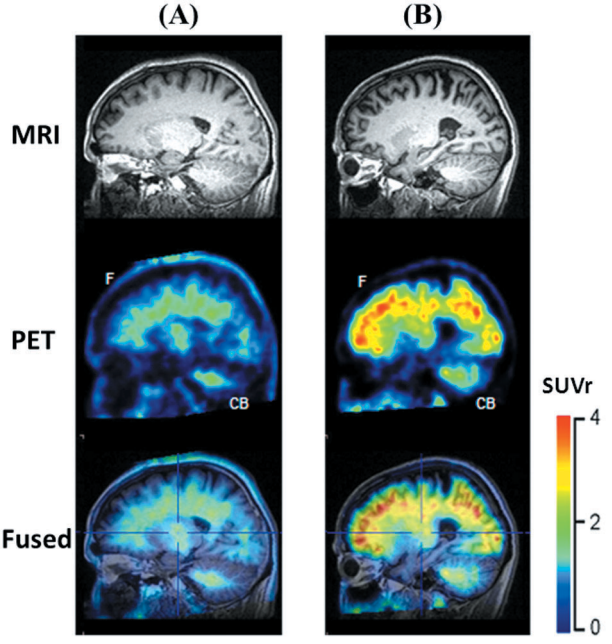

Fig. 6 AV-45 brain images of a healthy control (A), and AD patient (B) at time intervals of 50-60 min postinjection. The color scale was normalized to the cerebellum cortex for comparison. Abbreviations used: F: frontal cortex; CB: cerebellum.

plaque imaging agent to enter multicenter, IND clinical trials in the US, and has now been studied in dozens of trials with more than 1,000 subjects ranging from cognitively normal individuals to those with AD dementia. "Imaging to autopsy" phase III studies further confirmed and validated the specific imaging signal correlated to the plaque burden in living subjects. With these promising and confirmed characteristics of AV-45, the Alzheimer's Disease Neuroimaging Initiative (ADNI) under common consensus decided on AV-45 as the standard PET imaging agent for evaluating the progression of plaque pathology in patients with AD or MCI, and even healthy controls. With the wide availability of AV-45 for plaque imaging, the ultimate goal of the ADNI is global clinical trials for disease detection and progression.

The production of the PET plaque tracer AV-45 in Taiwan, particularly in CGMH, is ready for clinical trials. Likely, there will be another site steadily producing AV-45 for distribution. With the joint efforts of neurologists and nuclear medicine physicians as well as radiochemists and medical physicists, a bright future using AV-45 for PET plaque imaging in Taiwan is expected.

Acknowledgements

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從 IMPY/SPECT 到 AV-45/PET 探索類澱粉腦癡造影

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腦內乙型類澱癡塊的形成與沉積是阿爾茲海默氏病最早期的病理變異。針對乙型類澱粉癡塊的分子影像可以作爲阿爾茲海默氏病早期診斷與神經病理機轉研究的一項替代指標。迄今已有多種放射性標幟藥物被研發作爲以單光子放射電腦斷層掃描 (SPECT) 或正子放射斷層掃描 (PET) 等非侵入方式檢測阿爾茲海默氏病患者腦內乙型類澱粉癡塊的造影劑。本文回顧長庚大學與長庚紀念醫院近年探索乙型類澱粉癡塊核醫造影劑的經驗歷程。(長庚醫誌 2012;35:211-8)

關鍵詞：乙型類澱粉癡塊，阿爾茲海默氏病，AV-45，AV-138，IMPY

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