

## GUEST EDITORIAL

# Imaging biomarkers for amyloid: a new generation of probes and what lies ahead

### Introduction

Since the original 1984 criteria for Alzheimer's disease (AD), put forth by a work group jointly established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann *et al.*, 1984), important advances have occurred in our ability to detect AD pathophysiology, with the incorporation of biomarkers – defined as anatomic, biochemical, or physiologic parameters that provide *in vivo* evidence of AD neuropathology (Cummings, 2011) – that can improve the certainty of AD diagnosis. Use of imaging biomarkers such as positron emission tomography (PET) with amyloid ligands, particularly in asymptomatic and pre-dementia stages of AD, however, has been the subject of debate (Dubois *et al.*, 2013), with arguments both for and against the biomarker driven diagnosis of AD.

### Revised conceptualization of AD: the role of amyloid imaging

In contrast to the original 1984 criteria the recently proposed revisions put forth by the International Working Group (IWG; Dubois *et al.*, 2007) and the National Institute on Aging/Alzheimer's Association (NIA-AA; Sperling *et al.*, 2011a) redefine AD as a clinicobiological entity, comprising a semantic and conceptual distinction between AD neuropathology and resulting clinical phenomenology. Currently, AD is conceptualized as a progressive pathophysiological process in which  $\beta$ -amyloid pathology is thought to accumulate during a silent “preclinical” phase followed by a dynamic cascade of neurodegenerative events including tau pathology, which ultimately cause cognitive impairment and dementia. This amyloidocentric framework incorporates the use of imaging biomarkers for amyloid in the form of abnormal PET amyloid tracer retention. The slow progression of  $\beta$ -amyloid deposition in AD supports the idea that amyloid pathology occurs very early in the

disease process and tends to reach a plateau by the onset of the first clinical signs of dementia.

As novel amyloid directed therapeutics enter clinical trials, the role of amyloid imaging is increasingly clear given that its ability to allow for accurate, reliable, and reproducible quantification of both regional and global amyloid burden, and the growing consensus emerging from longitudinal studies that disease-modifying therapies targeting amyloid must be administered early on in the disease course (Sperling *et al.*, 2011b). In addition to serving as a diagnostic biomarker to guide population enrichment strategies, amyloid imaging can be used to calculate sample size and to increase statistical power via population stratification or through use as baseline predictors (Wu *et al.*, 2011). In parallel, amyloid-imaging outcomes can serve as endpoint biomarkers to monitor the rate of disease progression, as well as response to therapy.

### First generation of amyloid probes: $^{11}\text{C}$ Pittsburgh Compound B

The  $^{11}\text{C}$  labeled thioflavin T derivative Pittsburgh Compound B (PIB) is the benchmark PET amyloid-imaging agent, demonstrating high sensitivity and specificity for *in vivo* quantification of fibrillar  $A\beta$  in both plaques and related  $A\beta$  containing lesions, such as diffuse plaques and cerebral amyloid angiopathy (Price *et al.*, 2005; Lockhart *et al.*, 2007; Cohen *et al.*, 2012). Importantly, on the basis of concentrations achieved during PET studies, cortical retention of  $^{11}\text{C}$ -PIB has been shown to reflect  $A\beta$  load as opposed to Lewy bodies or tau pathology (Fodero-Tavoletti *et al.*, 2007; Lockhart *et al.*, 2007; Ikonovic *et al.*, 2008). In addition to accelerating current understanding of cerebral amyloidosis and advancing detection of AD pathology to an earlier stage (Klunk *et al.*, 2004; Mintun *et al.*, 2006; Rowe *et al.*, 2007; Cohen *et al.*, 2012),  $^{11}\text{C}$ -PIB has contributed to improvements in the differential diagnosis of neurodegenerative diseases (Ng *et al.*, 2007; Rabinovici *et al.*, 2007; Rowe *et al.*, 2007). However, the short 20-minute half-life of carbon-11 probes limits their use to imaging centers possessing an onsite cyclotron and

a radiochemistry department with expertise in the synthesis of  $^{11}\text{C}$ ; the cost of  $^{11}\text{C}$ -PIB studies has precluded its routine use in clinical settings.

### Second and third generation amyloid probes: $^{18}\text{F}$ -labeled radiopharmaceuticals

In order to address short half-life limitations a number of  $^{18}\text{F}$  labeled amyloid PET radiopharmaceuticals have been developed with a 110-minute half-life. Radiopharmaceuticals like [ $^{18}\text{F}$ ]3'-F-PIB (flutemetamol; Wolk *et al.*, 2011), [ $^{18}\text{F}$ ]AV-45 (florbetapir; Clark *et al.*, 2012), [ $^{18}\text{F}$ ]-AV-1 or [ $^{18}\text{F}$ ]-BAY94-9172 (florbetapen; Rowe *et al.*, 2008; Vallabhajosula, 2011), and [ $^{18}\text{F}$ ]AZD4694 or NAV4694 (Jureus *et al.*, 2010; Cselenyi *et al.*, 2012; Rowe *et al.*, 2013) can facilitate the integration of PET into routine clinical use by allowing for centralized production and regional distribution (Rowe and Villemagne, 2013).

While  $^{18}\text{F}$ -florbetapir,  $^{18}\text{F}$ -florbetaben, and  $^{18}\text{F}$ -flutemetamol allow for clear differentiation of AD patients from healthy controls, cortical retention of  $^{18}\text{F}$ -florbetapir and  $^{18}\text{F}$ -florbetaben are inferior to that of  $^{11}\text{C}$ -PIB (Villemagne *et al.*, 2012) and are characterized by a more narrow dynamic range of standardized uptake value ratios (SUVRs), associated visually with elevated non-specific white matter (WM) binding (Vandenberghe *et al.*, 2010). Moreover, novel  $^{18}\text{F}$  amyloid tracers are associated with the loss of gray-white matter demarcation (Rowe and Villemagne, 2011), in contrast to  $^{11}\text{C}$ -PIB, where gray matter retention is visibly greater relative to subjacent WM uptake (Rowe and Villemagne, 2013). Though it has yet to pass through phase II trials,  $^{18}\text{F}$ -AZD4694 (NAV4694) is similar to  $^{11}\text{C}$ -PIB, possessing rapid kinetics, low non-specific WM binding, and a wider dynamic range when comparing AD to healthy control individuals (Cselenyi *et al.*, 2012; Zimmer *et al.*, 2013). In a head-to-head comparison study with  $^{11}\text{C}$ -PIB among healthy controls and patients with AD and frontotemporal lobar degeneration (FTLD),  $^{18}\text{F}$ -NAV4694 showed an  $r$  of 0.98 and a slope of 0.95, indicating significant overlap with  $^{11}\text{C}$ -PIB (Rowe *et al.*, 2013).

### Criteria for appropriate use of amyloid PET imaging

Given that  $^{18}\text{F}$ -florbetapir is now approved by the Food and Drug Administration (FDA) for the clinical assessment of individuals with cognitive impairment, with additional  $^{18}\text{F}$  tracers likely to become available in the coming years, appropriate use criteria (AUC) are of chief importance owing to

(1) the potential for harm if scans are performed for inappropriate reasons, are misinterpreted, and/or the information obtained incorrectly applied; and (2) the high cost associated with such investigations. Apropos the first instance, a suitable example is the disclosure of amyloid positivity in an individual without cognitive impairment. Given positive findings in close to 30% of cognitively normal individuals over the age of 70 – and the lack of sufficient longitudinal data to adequately characterize the potential risk of future cognitive decline – premature diagnosis of AD on the basis of a positive  $\text{A}\beta$  scan alone has been categorized as inappropriate given the potential for detrimental social, psychological, employment, lifestyle, and financial consequences (Rowe and Villemagne, 2013). In addition, among patients with cognitive complaints, precipitous conclusions could lead to lack of appropriate treatment for underlying alternative causes, such as depression. Moreover, from an economic perspective, the lack of established disease-modifying therapies necessitates a careful cost-benefit analysis, with the likelihood of improved diagnostic accuracy and altered treatment guiding a decision to opt for amyloid imaging. In short, amyloid findings must be situated within the context of a comprehensive investigatory framework, interpreted by a physician with requisite expertise, and, where possible, supported by additional markers suggestive of AD such as an amnesic syndrome of the hippocampal type (Dubois and Albert, 2004), hippocampal atrophy on magnetic resonance imaging (MRI), or a parietotemporal pattern of hypometabolism on  $^{18}\text{F}$ -FDG PET.

Assembled in late 2012 by the Alzheimer's Association (AA) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the Amyloid Imaging Taskforce (AIT) was charged with delineating AUC for amyloid PET imaging using available literature and a consensus-based approach among dementia experts. On the basis of this approach amyloid imaging was deemed appropriate in the following clinical contexts: (1) patients exhibiting unexplained mild cognitive impairment (MCI) that is persistent or progressive, (2) patients fulfilling core criteria for possible AD yet with a clinical course that is atypical or an etiologically mixed presentation, and (3) patients with rapidly progressive dementia and atypically young age at the onset. In a sister publication (Johnson *et al.*, 2013b), clarification and expansion of three topics were discussed in the original publication (Johnson *et al.*, 2013a), including the practical identification of physicians possessing the expertise required for appropriate integration of amyloid PET imaging; the importance of identifying

the specific subset of MCI individuals for whom amyloid PET imaging would prove appropriate; and the creation of developing education programs aiming to augment awareness of the amyloid PET AUC and how best to integrate this technique into clinical decision-making algorithms.

### Potential ethical issues tied to disclosure of amyloid positivity

With the increasing paradigmatic shift toward the uncoupling of AD pathophysiology from resulting clinical phenomenology – with the attendant implication of a diagnosis of AD issued during the presymptomatic/minimally symptomatic phase – appropriate legal revisions must occur in parallel to guard against privacy and confidentiality infringements (Karlawish, 2011). Guidelines must also be put in place to address the well-established stigma tied to AD, and to guide assessment of the potential for negative psychological sequelae in a given individual following disclosure of biomarker information conferring an elevated risk of AD (e.g. amyloid positivity).

Although researchers are currently not under obligation to disclose biomarker findings to research participants owing to uncertainty regarding the clinical utility of this information – a case in point being the Alzheimer's Disease Neuroimaging Initiative's (ADNI) "no return policy" – a move toward clinical trials and increasing calls for disclosure of research results from the public (Shalowitz and Miller, 2008) makes clear the need to accelerate the development of appropriate guidelines. This reorientation toward disclosure has been, furthermore, strengthened by recent findings suggesting that ADNI investigators support disclosure of amyloid imaging results – as well as, more generally, other biomarker findings – to ADNI participants (Shulman *et al.*, 2013). In addition, despite a lack of evidence supporting the predictive value associated with imaging biomarkers, some clinicians have already begun incorporating IWG and NIA-AA research diagnostic criteria for asymptomatic at risk and MCI/prodromal into clinical practice (Gauthier and Rosa-Neto, 2013).

As the field of AD moves rapidly forward, a growing need exists in terms of the incorporation of procedures addressing disclosure of biomarker findings into large-scale studies and the encouragement of research addressing the impact of disclosure of biomarker findings (Gauthier and Rosa-Neto, 2013). Importantly, those ADNI investigators who endorsed disclosure likewise, in a majority of cases, highlighted the importance of developing standardized protocols and participant

educational materials addressing disclosure, as well as longitudinal outcome studies to assess the effects of this information on the well-being of participants (Shulman *et al.*, 2013).

### Future directions

In research, amyloid-imaging agents can serve to enrich clinical trial populations, monitor disease progression, or assess the effect of amyloid-targeted interventions. While PET amyloid probes have yet to find application in routine general clinical practice, FDA approval of <sup>18</sup>F florbetapir – with approval of additional <sup>18</sup>F compounds likely in the coming years – requires careful adherence to, and promulgation of, current AUC. Moreover, as new data are gathered, and, in particular, should new effective therapies emerge, these criteria will likely require re-evaluation and, possibly, redefinition. In the interim, special care must be paid to the potential consequences associated with inappropriate use of amyloid PET imaging. Further, given the increasing attitudinal shift toward disclosure of research results it is vital that psychosocial research keep pace with developments in the area of AD biomarkers.

ANTOINE LEUZY,<sup>1,2,\*</sup>

EDUARDO RIGON ZIMMER,<sup>1,2,3,\*</sup> VENKAT BHAT,<sup>4</sup>  
PEDRO ROSA-NETO<sup>1,2</sup> AND SERGE GAUTHIER<sup>2</sup>

<sup>1</sup>Translational Neuroimaging Laboratory (TNL), McGill Center for Studies in Aging (MCSA), Douglas Mental Health Research Institute, Montreal, Canada

<sup>2</sup>Alzheimer's Disease and Related Disorders Research Unit, McGill Center for Studies in Aging (MCSA), Douglas Mental Health Research Institute, Montreal, Canada

<sup>3</sup>Department of Biochemistry, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, Brazil

<sup>4</sup>Department of Psychiatry, McGill University, Montreal, Canada

\*Both authors contributed equally to this work.

Email: serge.gauthier@mcgill.ca

### References

- Clark, C. M. *et al.* (2012). Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: a prospective cohort study. *Lancet Neurology*, 11, 669–678. doi:10.1016/S1474-4422(12)70142-4.
- Cohen, A. D., Rabinovici, G. D., Mathis, C. A., Jagust, W. J., Klunk, W. E. and Ikonovic, M. D. (2012). Using Pittsburgh Compound B for in vivo PET imaging of fibrillar amyloid-beta. *Advances in Pharmacology*, 64, 27–81. doi:10.1016/B978-0-12-394816-8.00002-7.

- Cselenyi, Z. *et al.*** (2012). Clinical validation of 18F-AZD4694, an amyloid-beta-specific PET radioligand. *Journal of Nuclear Medicine*, 53, 415–424. doi:10.2967/jnumed.111.094029.
- Cummings, J. L.** (2011). Biomarkers in Alzheimer's disease drug development. *Alzheimer's & Dementia*, 7, e13–e44. doi:10.1016/j.jalz.2010.06.004.
- Dubois, B. and Albert, M. L.** (2004). Amnestic MCI or prodromal Alzheimer's disease? *Lancet Neurology*, 3, 246–248. doi: 10.1016/S1474-4422(04)00710-0.
- Dubois, B. *et al.*** (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurology*, 6, 734–746. doi:10.1016/S1474-4422(07)70178-3.
- Dubois, B., Gauthier, S. and Cummings, J.** (2013). The utility of the new research diagnostic criteria for Alzheimer's disease. *International Psychogeriatrics*, 25, 175–177. doi:10.1017/S1041610212002098.
- Fodero-Tavoletti, M. T. *et al.*** (2007). In vitro characterization of Pittsburgh compound-B binding to Lewy bodies. *The Journal of Neuroscience*, 27, 10365–10371. doi:10.1523/JNEUROSCI.0630-07.2007.
- Gauthier, S. and Rosa-Neto, P.** (2013). Dementia: disclosure of results to participants in dementia research. *Nature Reviews Neurology*, 9, 608–609. doi:10.1038/nrneuro.2013.213.
- Ikonomovic, M. D. *et al.*** (2008). Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. *Brain*, 131, 1630–1645. doi:10.1093/brain/awn016.
- Johnson, K. A. *et al.*** (2013a). Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *Alzheimer's & Dementia*, 9, e1–e16. doi:10.1016/j.jalz.2013.01.002.
- Johnson, K. A. *et al.*** (2013b). Update on appropriate use criteria for amyloid PET imaging: dementia experts, mild cognitive impairment, and education. *Journal of Nuclear Medicine*, 54, 1011–1013. doi:10.2967/jnumed.113.127068.
- Jureus, A. *et al.*** (2010). Characterization of AZD4694, a novel fluorinated Abeta plaque neuroimaging PET radioligand. *Journal of Neurochemistry*, 114, 784–794. doi:10.1111/j.1471-4159.2010.06812.x.
- Karlawish, J.** (2011). Addressing the ethical, policy, and social challenges of preclinical Alzheimer disease. *Neurology*, 77, 1487–1493. doi:10.1212/WNL.0b013e318232ac1a.
- Klunk, W. E. *et al.*** (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Annals of Neurology*, 55, 306–319. doi:10.1002/ana.20009.
- Lockhart, A. *et al.*** (2007). PIB is a non-specific imaging marker of amyloid-beta (Aβ) peptide-related cerebral amyloidosis. *Brain*, 130, 2607–2615. doi:10.1093/brain/awm191.
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and 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*, 34, 939–944.
- Mintun, M. A. *et al.*** (2006). [11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. *Neurology*, 67, 446–452. doi:10.1212/01.wnl.0000228230.26044.a4.
- Ng, S. Y., Villemagne, V. L., Masters, C. L. and Rowe, C. C.** (2007). Evaluating atypical dementia syndromes using positron emission tomography with carbon 11 labeled Pittsburgh Compound B. *Archives of Neurology*, 64, 1140–1144. doi:10.1001/archneur.64.8.1140.
- Price, J. C. *et al.*** (2005). Kinetic modeling of amyloid binding in humans using PET imaging and Pittsburgh Compound-B. *Journal of Cerebral Blood Flow & Metabolism*, 25, 1528–1547. doi:10.1038/sj.jcbfm.9600146.
- Rabinovici, G. D. *et al.*** (2007). 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. *Neurology*, 68, 1205–1212. doi:10.1212/01.wnl.0000259035.98480.ed.
- Rowe, C. C. and Villemagne, V. L.** (2011). Brain amyloid imaging. *Journal of Nuclear Medicine*, 52, 1733–1740. doi:10.2967/jnumed.110.076315.
- Rowe, C. C. and Villemagne, V. L.** (2013). Brain amyloid imaging. *Journal of Nuclear Medicine Technology*, 41, 11–18. doi:10.2967/jnumed.110.076315.
- Rowe, C. C. *et al.*** (2007). Imaging beta-amyloid burden in aging and dementia. *Neurology*, 68, 1718–1725. doi:10.1212/01.wnl.0000261919.22630.ea.
- Rowe, C. C. *et al.*** (2008). Imaging of amyloid beta in Alzheimer's disease with 18F-BAY94–9172, a novel PET tracer: proof of mechanism. *Lancet Neurology*, 7, 129–135. doi: 10.1016/S1474-4422(08)70001-2.
- Rowe, C. C. *et al.*** (2013). Head-to-head comparison of 11C-PIB and 18F-AZD4694 (NAV4694) for beta-amyloid imaging in aging and dementia. *Journal of Nuclear Medicine*, 54, 880–886. doi:10.2967/jnumed.112.114785.
- Shalowitz, D. I. and Miller, F. G.** (2008). Communicating the results of clinical research to participants: attitudes, practices, and future directions. *PLoS Medicine*, 5, e91. doi:10.1371/journal.pmed.0050091.
- Shulman, M. B., Harkins, K., Green, R. C. and Karlawish, J.** (2013). Using AD biomarker research results for clinical care: a survey of ADNI investigators. *Neurology*, 81, 1114–1121. doi:10.1212/WNL.0b013e3182a55f4a.
- Sperling, R. A. *et al.*** (2011a). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7, 280–292. doi:10.1016/j.jalz.2011.03.003.
- Sperling, R. A., Jack, C. R., Jr. and Aisen, P. S.** (2011b). Testing the right target and right drug at the right stage. *Science Translational Medicine*, 3, 111cm133. doi:10.1126/scitranslmed.3002609.
- Vallabhajosula, S.** (2011). Positron emission tomography radiopharmaceuticals for imaging brain Beta-amyloid. *Seminars in Nuclear Medicine*, 41, 283–299. doi:10.1053/j.semnuclmed.2011.02.005.
- Vandenberghe, R. *et al.*** (2010). 18F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: a phase 2 trial. *Annals of Neurology*, 68, 319–329. doi:10.1002/ana.22068.
- Villemagne, V. L. *et al.*** (2012). Comparison of 11C-PiB and 18F-florbetaben for Aβ imaging in ageing and

Alzheimer's disease. *European Journal of Nuclear Medicine and Molecular Imaging*, 39, 983–989. doi:10.1007/s00259-012-2088-x.

- Wolk, D. A. et al.** (2011). Association between in vivo fluorine 18-labeled flutemetamol amyloid positron emission tomography imaging and in vivo cerebral cortical histopathology. *Archives of Neurology*, 68, 1398–1403. doi:10.1001/archneurol.2011.153.
- Wu, L., Rosa-Neto, P. and Gauthier, S.** (2011). Use of biomarkers in clinical trials of Alzheimer disease: from concept to application. *Molecular Diagnosis & Therapy*, 15, 313–325. doi:10.2165/11595090-000000000-00000.
- Zimmer, E. et al.** (2013). [18F]NAV4694 shows higher binding and wider dynamic range compared with [11C]PiB in Alzheimer's disease postmortem tissue. *Alzheimer's & Dementia*, 9, P22–P23. doi:10.1016/j.jalz.2013.05.1161.