It is almost exactly 10 years since the first report of a PET ligand that specifically bound to a pathological protein in the brain was published (Klunk et al., 2004). This tracer, $^{11}$C-Pittsburgh compound B (PIB), detected fibrillar aggregated forms of amyloid-$\beta$, the major constituent of the Alzheimer’s disease plaque and, according to many, the initiating event in Alzheimer’s disease pathogenesis. This report was soon followed by several amyloid imaging tracers that were radio labelled with the longer half-life positron-emitting nuclide $^{18}$F, opening the door to commercial manufacture and clinical application. Several of these tracers are now approved by worldwide regulatory agencies including the US Food and Drug Administration and the European Medicines Agency, although reimbursement for clinical use remains problematic. In this issue of Brain, Okamura and colleagues report the first human PET studies with a new tracer for tau, $^{18}$F-THK5105, and reveal that retention of this tracer correlates with dementia severity and brain atrophy in Alzheimer’s disease (Okamura et al., 2014).

Because it is difficult to develop, test and validate a new PET imaging agent, it may have seemed overly optimistic 10 years ago to conclude that a new era in human brain imaging had begun, but it had. The latest developments are a series of PET tracers that bind to the microtubule-associated protein tau that is aggregated as neurofibrillary tangles in Alzheimer’s disease. Tau-related diseases also include the group of tauopathies often referred to as frontotemporal lobar degenerations, and the highly publicized chronic traumatic encephalopathy. Tau would seem to be a difficult target for PET imaging: it may be intracellular thus requiring tracer passage across both the blood–brain barrier and cell membranes; it is found in the brain at lower concentrations than amyloid-$\beta$; and it is characterized by different isoforms reflecting alternative splicing with either three (3R) or four (4R) repeated microtubule binding domains. The first PET tau imaging agent to be reported, $^{18}$F-FDDNp, was not specific for tau and showed relatively low uptake. However, in the past few years, three research groups have investigated separate molecular structures resulting in three series of compounds that are promising tau-binding PET tracers. One of these, $^{11}$C-PBB3 (Maruyama et al., 2013), has shown in vitro binding to tau in the form of neurofibrillary tangles, neuritid threads and plaque neurites in Alzheimer’s disease brain tissue, and also in vitro binding to tau inclusions in tissue from patients with Pick’s disease (a 3R tauopathy), or progressive supranuclear palsy and corticobasal degeneration (4R tauopathies). PET studies showed hippocampal uptake in cognitively normal older people, and extensive cortical binding in patients with Alzheimer’s disease that appeared largely consistent with the pathological staging proposed by Braak and Braak (1991). Another series of compounds includes the $^{18}$F-labelled T807 and T808 (Chien et al., 2013, 2014); these compounds both demonstrate tau binding to Alzheimer’s disease brain tissue without labelling amyloid-$\beta$. They show good in vivo brain penetration in humans and patterns of retention on PET scans that again are consistent with Braak staging.

The third group of $^{18}$F-labelled compounds comprises the ‘THK’ series developed at Tohoku University. The first of this series, $^{18}$F-THK523, was reported by Fodero-Tavoletti et al. (2011), and although tissue studies indicated good selectivity for tau over amyloid-$\beta$, subsequent human PET experiments showed low cortical binding compared to binding in white matter, making signal detection difficult. Okamura and colleagues now report the first human PET studies of the related compound $^{18}$F-THK5105 (Okamura et al., 2014). They studied eight patients with Alzheimer’s disease and eight older control subjects with $^{18}$F-THK5105 and $^{11}$C-PIB. $^{18}$F-THK5105 data acquired over 2 h showed that tracer activity in the cerebellar cortex washed out similarly in patients and control subjects, whereas tracer retention occurred in the temporal lobe in patients with Alzheimer’s disease. By 90 min post-injection, ratios in cortex to cerebellum averaged 1.32 in the inferior temporal lobe of patients (the neocortical region with highest retention) compared with 1.09 in control subjects. Although other cortical regions generally showed higher retention in patients than controls, the highest brain signal was seen in pons, and this was similar in both patients and control subjects. Other subcortical brain regions showing high uptake included putamen and white matter, which did not differ between patients and control subjects. In controls, tracer retention in medial temporal regions was higher than in neocortex, suggesting the presence of medial temporal lobe neurofibrillary tangles, a common finding in ageing. $^{11}$C-PIB uptake revealed a very different pattern, with highest uptake in precuneus and frontal cortex; uptake of the two tracers was not statistically correlated. In addition, associations were found between $^{18}$F-THK5105 retention and both cognitive and magnetic resonance volumetric measures that were not seen with $^{11}$C-PIB.

These data are very supportive of the use of $^{18}$F-THK5105 in the study of Alzheimer’s disease, with a number of important potential applications. Okamura et al. (2014) note that...
\[^{18}\text{F}-\text{THK5105}\] retention in the inferior temporal cortex showed no overlap between patients and control subjects, suggesting that tau imaging could be diagnostically useful, although the samples are still quite small. Reports that the related compound THKS23 did not bind to tau deposited in the tauopathies of corticobasal degeneration, progressive supranuclear palsy, and Pick’s disease (Fodero-Tavoletti et al., 2014) may be good news if we are looking for a disease-specific biomarker, but bad news if we are looking for a biomarker to image frontotemporal lobar degeneration syndromes. The findings that brain \[^{18}\text{F}-\text{THK5105}\] paralleled both clinical measures of severity and magnetic resonance measures of atrophy, though preliminary, are consistent with observations that post-mortem measures of neurofibrillary tangle pathology are among the best correlates of disease severity in patients with Alzheimer’s disease and suggest that tau imaging could be a staging method that might also be useful in detecting response to a therapeutic agent. Recent attempts to develop PET amyloid imaging as surrogate markers of treatment efficacy have been disappointing in failing to show either a strong relationship with dementia severity or prediction of clinical therapeutic response (Salloway et al., 2014). Because tau pathology correlates with symptoms, tau imaging could be a potential surrogate outcome for any therapy that has clinical benefit and would certainly be a useful biomarker in a trial of a therapeutic agent targeted to tau itself, an especially important goal in relation to frontotemporal lobar degeneration.

In addition to potential applications to clinical trials, tau imaging will be of major benefit for understanding the pathological progression of Alzheimer’s disease and differentiating it from normal ageing. Current models of Alzheimer’s disease are problematic in many respects, one of which is the difficulty in defining the relative importance of neurodegeneration as opposed to amyloid-\(\beta\) deposition. Although early models of biomarker change in Alzheimer’s disease posited that amyloid-\(\beta\) was an initiating event, evidence of neurodegeneration in the absence of amyloid-\(\beta\) has resulted in a pathological framework that admits the possibility of independent and early tauopathy in Alzheimer’s disease (Jack et al., 2013). The suggestion that all of the tau imaging agents are retained in the medial temporal lobes of old control subjects offers the promise that the relationship between medial temporal tau and neocortical amyloid-\(\beta\) can be disentangled, as well as the relationships between both of these proteins and brain atrophy, hypometabolism and cognition.

We now have at least three distinct ligands for human tau imaging. PET imaging of neurodegenerative diseases is rapidly evolving and there will undoubtedly be new tau imaging agents on the way, along with additional agents for other proteins such as \(\alpha\)-synuclein. In fact, Okamura et al. (2014) note that they have developed another related compound, \[^{18}\text{F}-\text{THK5117}\], which has more favourable pharmacokinetic and binding properties. There are no data for comparison of the THK series compounds with \[^{18}\text{F}-\text{T807}\] and \[^{11}\text{C}-\text{PBB3}\], although the \[^{11}\text{C}\] label of PBB3 will limit its use to institutions with PET radiochemistry programs unless an \[^{18}\text{F}\] label can be developed. Which of these compounds is ‘best’ is a complex determination that will have to be defined by the intended use and additional data that accrue in this rapidly developing field. No PET ligand is perfect, and these tau ligands are likely to differ by specificity (do they bind to different forms of tau and to non-tau targets?), sensitivity (how much tau signal can be detected compared to non-specific background binding?), pharmacokinetics (is brain penetration high and steady state achieved early enough to yield good images?) and other factors. The implications for understanding Alzheimer’s disease and developing effective treatments are important, and as we learn more about the behaviour of different ligands we may open up new avenues to the study of non-Alzheimer’s disease tauopathies and chronic traumatic encephalopathy. The pace of scientific discovery is accelerating and the end result will be more tools and more information that should result in more effective treatments.

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