increase the possibility to identify a drug effect on the conversion rate to Alzheimer disease.

Disease-modifying drugs may slow down the degenerative process, but are not expected to have any immediate symptomatic effect. Thus, large patient populations and extended treatment periods will be needed to identify an effect on cognition. Imaging Aβ has the potential to be a surrogate biomarker to directly monitor an effect on plaque deposition in trials of new anti-Aβ drug candidates. Such an effect could probably be identified in relatively small patient populations and short treatment periods. Biological data suggesting that a drug has positive effects on plaque deposition would be of great value to make a go–no-go decision for an expensive clinical trial with clinical improvement as the endpoint. The importance of a surrogate marker of amyloid that can be used in living individuals with Alzheimer disease is supported by the finding that PIB does not label plaques in mouse models of Alzheimer disease[6], despite the huge Aβ load in these models[9]. This suggests that there may be differences in the secondary structure, or other modifications, of the deposited Aβ between mouse models of Alzheimer disease and individuals with Alzheimer disease, which also may raise concerns about studying pathogenic mechanisms and evaluating new treatments in these Alzheimer disease models.

Many questions remain about the clinical usefulness of amyloid imaging. The diagnostic performance has to be evaluated in large series of Alzheimer disease cases, controls and cases with other dementia disorders. Further, there is as yet no study on the predictive power of amyloid PET to identify incipient Alzheimer disease in a large cohort of MCI cases. Nevertheless, the study by Klunk and coworkers lays the foundation for the use of amyloid imaging as a diagnostic and surrogate marker for Alzheimer disease.

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The author's perspective

This project took over 10 years, and there were periods when success did not seem likely. One issue was that transgenic mouse studies indicated that the PiB compound was not going to be effective, and we had to come to a decision to not let what we thought were flawed animal studies outweigh the clearly positive preclinical data we had from *in vitro* human tissue studies and pharmacokinetic studies in wild-type mice. We have always felt fortunate that PiB works in humans and not in transgenic mice, rather than the other way around. After all, our goal was to image individuals with Alzheimer disease, not just transgenic mice. Another interesting thing was that there was a 'Pittsburgh Compound-A' that was far along in development for human studies, which was replaced in the eleventh hour by PiB as a result of a very fortunate refocusing on normal brain clearance properties in animal models.

It was difficult to get the paper published. It was rejected by three journals because of the prior press releases following oral presentations as well as the reviewers' expectation that we include data on many more subjects and complete detailed pharmacokinetic modeling of the compound. We have recently accomplished the latter, more than two years after the initial publication. Currently, in collaboration with GE Healthcare, we are developing a ^{18}F–labeled version of PiB because the current ^{11}C–labeled PiB is only accessible to the approximately 10% of existing PET facilities with the necessary expertise and accessibility to an on-site cyclotron required for its production. It is clear that many see PiB as a valuable early diagnostic aid or an aid to confirm diagnosis in clinically confusing cases. Importantly, several pharmaceutical companies are including pre- and post-treatment amyloid imaging studies in their trials of antiamyloid therapies.

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Highly cited research papers on Alzheimer disease published in 2003[a]

Reference	Times cited
Kayed, R. *et al.* Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. *Science* **300**, 486–489	326
Edbauer, D. *et al.* Reconstitution of γ-secretase activity. *Nat. Cell Biol.* **5**, 486–488	183
Takasugi, N. *et al.* The role of presenilin cofactors in the γ-secretase complex. *Nature* **422**, 438–441	179
Oddo, S. *et al.* Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Aβ and synaptic dysfunction. *Neuron* **39**, 409–421	177
Phiel, C.J. *et al.* GSK-3α regulates production of Alzheimer's disease amyloid-β peptides. *Nature* **423**, 435–439	150
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Ehehalt, R. *et al.* Amyloidogenic processing of the Alzheimer β-amyloid precursor protein depends on lipid rafts. *J. Cell Biol.* **160**, 113–123	138
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Gong, Y. *et al.* Alzheimer's disease-affected brain: presence of oligomeric Aβ ligands (ADDLs) suggests a molecular basis for reversible memory loss. *Proc. Natl. Acad. Sci. USA* **100**, 10417–10422	130

[a]Number of citations as of 13 June 2006. Table includes all primary research articles that have the terms 'Alzheimer' or 'Alzheimer's' in their title, abstract or keywords, and that have been cited at least 125 times. Table does not include reviews. Data source: *Scopus*