

Faster Alzheimer's detection in sight

Approval of imaging agent would enable earlier diagnosis of the disease, potentially paving way to better therapies

By Ed Silverman

In the often fruitless world of central nervous system disease research, particularly for cognitive disorders such as Alzheimer's disease, rare advances in the field are usually embraced, even if their path to ultimately benefiting patients is not altogether smooth. One example is the imaging agent, **Amyvid**, designed to detect beta amyloid plaque associated with Alzheimer's. The late-stage product, despite being attached to a pair of recent regulatory setbacks, including a disappointing vote by an FDA advisory committee and a subsequent complete response letter issued by the agency, finally appears close to fruition and its pending approval is seen as a watershed moment in the use of imaging to combat the withering brain disease.

Amyvid, under development by **Eli Lilly and Co.** (lilly.com), would be used to find beta amyloid plaque in the brains of living people who undergo a positron emission tomography scan. Beta amyloid is a toxic protein believed to be a major hallmark of Alzheimer's disease. **Amyvid** was first developed by **Avid Radiopharmaceuticals Inc.** (avidrp.com), which was purchased last winter by Lilly as part of the company's bet on making Alzheimer's disease a key part of its product portfolio.

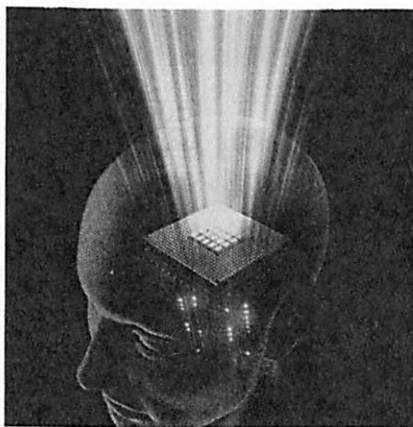
Lilly has been negotiating with FDA about concerns doctors may have difficulty being able to consistently read and interpret **Amyvid** scans. An FDA advisory panel earlier this year had recommended that any agency approval of the dye, also called florbetapir, be conditioned upon a reader training program.

"There is an expectation that [**Amyvid**] will soon be approved," says James

Barrett, Ph.D., a former VP of neuroscience discovery research at Wyeth, who is now a professor in the Department of Pharmacology and Physiology at Drexel University.

"This would be the first technique for *in vivo* imaging of the plaques," Dr. Barrett says. "If the plaques are involved, you can monitor their presence and quantify them so you can initiate and monitor dissolution."

The progress is in stark contrast to just a year ago, when the likelihood of an approved imaging agent remained less certain. Consequently, the push to combat Alzheimer's and other forms of dementia seemed caught in a conundrum. On one hand, without useful imaging techniques to illuminate the existence and progression of the disease, drug development remains



hard to reach. At the same time imaging would be still more useful if therapies were more beneficial in treating patients.

The problem has been that different types of drugs currently in development have so far failed or disappointed and, increasingly, researchers believe one important reason is that the therapies were given to patients when Alzheimer's symptoms were too advanced. An FDA-approved imaging agent would, presumably, open the door to a faster and more rewarding diagnosis that would allow for drug development to begin at a more useful phase.

"This [approval] would be a significant development and certainly a major

step from just a year ago," says Richard Hargreaves, Ph.D., the worldwide head of discovery neuroscience, **Merck & Co.** (merck.com). "Amyloid PET tracers have been used to select patients for clinical trials with a high amyloid burden and can distinguish Alzheimer's from other types of dementia."

An approved imaging agent would be critical in testing the popular but oft-questioned hypothesis that amyloid plaques are a telltale sign of Alzheimer's disease, according to Dr. Hargreaves. Currently, a firm correlation between the amount of amyloid plaque in the brain and cognitive impairment is unclear. Though existing tools can detect amyloid plaque, they do little to explain the severity of the disease that may have manifested itself in an Alzheimer's patient, says Gregory Goldmacher, M.D., Ph.D., associate director of medical and scientific affairs, **Icon Medical Imaging**, a unit of the contract research organization, **Icon Plc.** (iconplc.com).

"Even with the best diagnostic imaging in the world, the treatment options are still pretty limited," Dr. Goldmacher says. "You can detect, but at this point, it won't change the course of the disease."

To that end, an FDA approval of **Amyvid** would mean that an agent that has been confined to use in clinical trials may suddenly have wider application. For the first time, clinicians would have a sanctioned tool with which to identify pre-clinical stages of Alzheimer's. This, in turn, would help provide data for drugmakers as they develop drugs that could have a higher probability of success. Lilly is not the only manufacturer nearing this milestone. **GE Healthcare** (gehealthcare.com) and **Bayer AG** (bayer.com) are close behind.

"Right now, researchers have to use an unapproved imaging agent with any drug under an [investigational new drug application] and this slows things down, which makes it harder to do the studies," says Richard Walovitch, Ph.D., president, **WorldCare Clinical LLC** (wcclinical.com), a CRO that specializes in imaging

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for clinical trials. "But over the last year or so, the FDA has held discussions with these companies, which is very significant, although we still don't have what we want yet."

Drug development in this area is moving in fits and starts. Three patients who were treated with an Alzheimer's medication being developed by **Bristol-Myers Squibb Co.** (bms.com) wound up with a brain-swelling condition known as vasogenic edema. A dozen cases were also found in a closely watched 2008 Phase II study of the monoclonal antibody **bapineuzumab**, which is being developed by **Pfizer Inc.** (pfizer.com) and **Johnson & Johnson** (jnj.com). And last year, Lilly halted two studies of a gamma secretase inhibitor, the same type of mechanism as the Bristol-Myers Squibb drug, after worsening dementia symptoms appeared in late-stage clinical trials.

Steps are being taken, however, that may hasten drug-development efforts in Alzheimer's disease. Recently, a group of academic and industry experts convinced FDA to ease safety restrictions on clinical trials for Alzheimer's drugs, which were imposed after vasogenic edema appeared in the 2008 bapineuzumab study. The new guidelines will allow some patients who develop swelling to stay in clinical trials. The old guidelines restricted patients from having more than two incidents of cerebral microhemorrhages, or tiny leaks of blood in the brain, before they enter a study. And frequent MRI scans were required to check for swelling or other problems that might be caused by experimental medicines.

At the same time, studies being run by the Alzheimer's Disease Neuroimaging Initiative (adni-info.org) are successfully advancing the use and understanding of biomarkers, including brain atrophy and neuron loss measured with magnetic resonance imaging, and neurodegeneration detected by the rise of tau and synaptic dysfunction, which can be measured by fludeoxyglucose-PET scans. "The holy grail is to slow progression," Dr. Hargreaves says. "These markers may show the slope that tells you whether you're slowing disease."

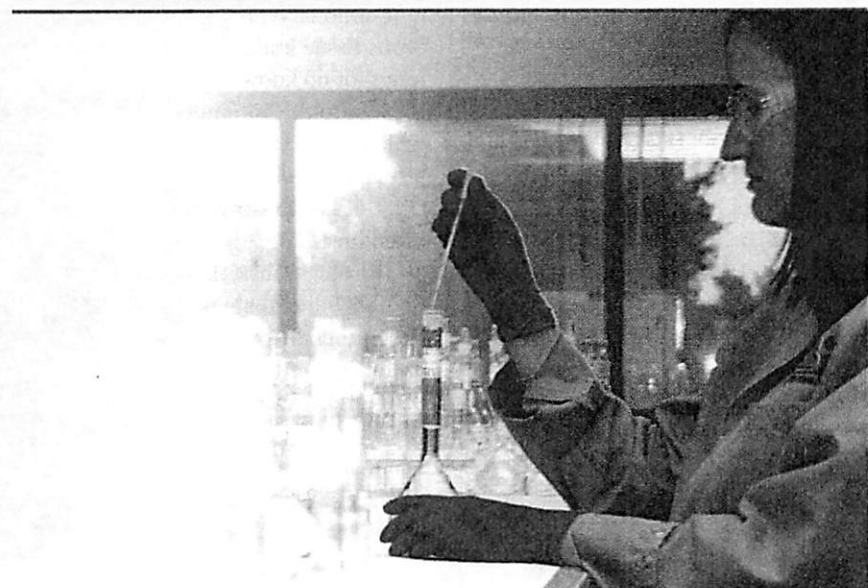
Meanwhile, a new categorization of Alzheimer's patients is emerging that may allow drug testing to begin sooner.

A recent paper published in the journal *Alzheimer's & Dementia* by a group of leading neurologists proposed a preclinical classification that would predict the risk of progression from so-called normal cognition to mild cognitive impairment and then to Alzheimer's disease and other forms of dementia.

"Identifying the preclinical stage means patients don't have cognitive impairment,

but imaging may yield changes [that are important to detect]," Dr. Walovitch says. "If I start treating [those patients] now, drugs can be [developed that are] more efficacious, because I'm getting at the disease at an earlier stage. If people can home in on this at the preclinical stage and understand collectively all the biomarkers that give you a profile, then therapies may become more effective." **R&D**

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