

Alzheimer's: molecular marker could support earlier and better diagnosis

# Protein hunters in the brain



*Alzheimer's disease today can only be identified once a patient's mental capacity is already severely limited. Researchers at Bayer HealthCare are working on a molecule that could enable psychiatrists and neurologists to make an earlier diagnosis of the disease and distinguish it better from other forms of dementia. While the molecule could help to gain more time for treating patients, its manufacture and supply to clinical studies is a compelling race against time.*

The shuttle is ready and waiting; its journey can begin. Its mission: reconnaissance. Its destination: the human brain. There it tracks down one of the most important signs of Alzheimer's disease: amyloid plaques, protein deposits that disrupt the function of nerve cells and cause inflammation. "Our goal is to identify a central indicator of the disease in the living brain, for the first time in the history of Alzheimer's research," explains Dr. Rainer Braun, a chemist in the Pharmaceutical Development department of Bayer HealthCare's Bayer Schering Pharma Division, where he is responsible for developing the "shuttle,"

a PET tracer referred to as BAY 94-9172 (florbetaben). In the process, fluorine-18, a radioactive variation of natural fluorine, is bound to a molecule that accumulates on amyloid plaques in the body. After injection, the molecule is transported through the bloodstream to the plaques in the brain. As the radioactive fluorine-18 decays, it releases positrons. By means of positron emission tomography (PET), the site of decay can be localized and the plaques imaged for doctors to see.

Plaques can only be diagnosed today in tissue samples from deceased patients. The PET technology could provide



indications of Alzheimer's long before the first symptoms of the disease become apparent.

For hospitals and doctors to use this innovative diagnostic technique, practical methods for manufacturing and supplying PET tracers must be developed. This is where the technical drug development activities of Bayer Schering Pharma's Pharmaceutical Development team come into play. "Our objective is to develop a marketable – and by that I mean economical and robust – manufacturing process for the PET tracer, in order to ensure a reliable supply of florbetaben for patients," says Braun, describing the task facing his team.


### Every second is vital during production of the molecule

The new diagnostic method is based on the radioactive decay of fluorine-18, a relatively short-lived radioisotope. "Fluorine-18 has a half-life of 110 minutes," Braun explains. In other words, after two hours, only half of the precious substance remains. This means, too, that the Bayer specialists cannot produce PET tracers in large quantities at one location and ship them all over the world for use. The tracer cannot be loaded with its radioactive cargo until immediately prior to use, and this must be done in the direct vicinity of a hospital or doctor's office.

Professor Osama Sabri, Director of the Clinic and Polyclinic for Nuclear Medicine at Leipzig University Hospital, has gathered practical experience with florbetaben: "We were the first in Europe to apply the method." Braun describes the current status: "The manufacturing process is so efficient now that we can supply the substance from Leipzig to other hospitals. Because fluorine-18 is so short-lived, we have a maximum of eight hours from production to application."

At Leipzig University Hospital, the required fluorine-18 isotopes are generated in a cyclotron right before production of the tracer begins. The fluorine-18 is then conveyed via transport lines directly to the manufacturing area. This is when the clock starts ticking. The subsequent steps take a total of approximately one to two hours. This is followed by delivery, for which a maximum of five hours remain because another one to two hours must be allowed for final patient preparation at the hospital. Finally, no more than eight hours after it was manufactured at Leipzig University Hospital, the doctor can send the tracer on its journey through the brain.

To supply the clinical development program with the substance, Braun's team has set up a global network of suitable supply sites. Each site can supply a number of hospitals with the Bayer tracer. From a technical and logistical point of view, nothing else stands in the way of the next, most crucial part of the project: a Phase III study scheduled to begin in late 2009 that will provide the data required for the licensing process. Once licensing has been granted, doctors all over the world can send the florbetaben shuttle on its mission: the early diagnosis of abnormal protein deposits in the brain.

 [www.alzheimers-research.org.uk](http://www.alzheimers-research.org.uk)  
*This site offers current research results and other information on the symptoms of Alzheimer's.*

Making Alzheimer's visible: Dr. Marianne Patt (large photo) opens the cyclotron, in which radioactive fluorine-18 is produced. The protein deposits that can be identified with the new radiopharmaceutical florbetaben are regarded as a potential trigger of the disease. Professor Osama Sabri from Leipzig University Hospital is collecting practical experience with the Bayer tracer (photo below). Dr. Andreas Schildan from Leipzig University Hospital and Dr. Rainer Braun (photo right, left to right) prepare the synthesis of florbetaben.

