Measuring the hippocampus, the brain structure most vulnerable to Alzheimer's, helps track the disease.

PERSPECTIVE

In search of biomarkers

New methods to follow changes in the brain or blood associated with Alzheimer's disease are critical for developing and testing drugs, says **Neil S. Buckholtz**.

This commentary starts from my frustration that no new drugs to combat Alzheimer's disease have been approved by the US Food and Drug Administration (FDA) since 2003. The few medications currently available address the symptoms of cognitive loss, but they do not delay or modify disease progression, and they work for only a limited time. In some people, they offer no relief at all.

It can take more than 10 years and almost US\$2 billion to bring a new drug into clinical use. Failure rates are high, especially for drugs that target the brain. And research into Alzheimer's disease is still stuck on a fundamental question. Although abnormal brain deposits of two proteins — amyloid- β and tau — are hallmarks of the disease, we do not know if they are a cause or a by-product of the disorder.

Some Alzheimer's researchers believe that recently tested drugs might have failed because they were evaluated in people in the later stages of disease, when irreversible damage had already occurred and removing amyloid- β was no longer beneficial. To modify disease progression, therapies need to be applied earlier and be targeted at the disease mechanisms occurring in the brain at that stage. We therefore need better biomarkers to provide insight into disease progression and to help target drugs to the right pathological processes at the right time.

We are making strides. This year, the National Institute on Aging (NIA), which is part of the US National Institutes of Health (NIH), and the Alzheimer's Association jointly introduced a different way of thinking about Alzheimer's disease. These new diagnostic guidelines — the first in 27

years — should not only guide research but also enhance the development and testing of interventions. They present three stages of Alzheimer's disease: preclinical¹, mild cognitive impairment² (MCI), and dementia³.

The guidelines also address whether changes in the brain, blood and cerebrospinal fluid (CSF) are associated with Alzheimer's disease. Researchers often use such biomarkers to detect the onset of disease and track its progression, but they cannot become

routine in clinical diagnosis without further testing and validation. I hope that testing and validation of biomarkers under the revised guidelines will result in improved diagnosis and treatment of Alzheimer's disease. Importantly, the guidelines will inform discussions about clinical trials for disease prevention (see 'Prevention is better than cure', page S15).

Another effort relating to biomarkers is the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI is a public-private partnership comprising scientists from academia and from pharmaceutical and diagnostics companies. ADNI is identifying the best methods — such as clinical and neuro-psychological tests, magnetic resonance imaging (MRI, see top image), positron emission tomography (PET), genetic screening, and blood and CSF markers — to evaluate the progression from normal cognitive ageing to MCI, from MCI to mild Alzheimer's dementia, and from

mild to severe dementia, and to use these markers for early diagnosis. These biomarkers are being incorporated into clinical trials to assess the ability of new drugs to modify disease progression. The ADNI data are freely available to the international scientific community.

However, there is more work to be done. In preclinical drug discovery and development, biomarkers must provide a bridge to clinical studies to allow accurate prediction of treatment response in humans, as animal models are currently poor predictors of outcomes in human clinical trials. In the clinical arena, the major problem arises in the transition from phase II to phase III clinical trials — many failures in phase III had a positive signal in phase II. New biomarkers are needed to ensure that a drug candidate is engaging the correct target and that the proper dose has been selected at phase II.

The NIA has established a variety of funding mechanisms to meet these challenges. Many of the efforts involve biomarkers: preclinical translational biomarkers that help predict clinical therapeutic potential, and clinical biomarkers that indicate target engagement and dose selection. In the best of all worlds, the same neuroimaging (MRI, PET) and fluid (blood, CSF) biomarkers could be used for both preclinical and clinical use.

I believe that cooperation between public and private organizations in the preclinical arena — equivalent to ADNI's clinical role — will ease the transition from preclinical to clinical work. This idea is fairly radical for a preclinical setting and would require new ways of thinking from the private sector; in particular, companies would need to share information with one another, as well as with academia. This kind of sharing, perhaps brokered by the NIH and the Foundation for the NIH (which manages the private partners in ADNI), could advance the use of biomarkers with the goal of developing a standard set of criteria for assessing preclinical drug efficacy and aiding clinical decision-making. The greater use of biomarkers made possible by this strategy should help to advance the discovery of new drugs — and benefit the patients and families who desperately need them.■

Neil S. Buckholtz is chief of the Dementias of Aging Branch in the Division of Neuroscience at the National Institute on Aging in Bethesda, Maryland.
e-mail: buckholn@nia.nih.gov

1. Sperling, R. A. et al. *Alzheimer's & Dement.* **7**, 280–292 (2011).
2. Albert, M. S. et al. *Alzheimer's & Dement.* **7**, 270–279 (2011).
3. McKhann, G. M. et al. *Alzheimer's & Dement.* **7**, 263–269 (2011).