Plasma lipids: harbingers of AD?

By Michael J. Haas, Senior Writer

A panel of plasma lipids could represent a new diagnostic tool for identifying patients likely to develop Alzheimer's disease before symptoms appear, according to new clinical findings from a team of U.S. researchers.[1] Although the lipid panel could help enrich clinical trials of AD therapeutics for likely responders, validation studies will need to confirm its specificity for AD over other forms of dementia.

Diagnosis of AD and its precursor, mild cognitive impairment (MCI), currently involves detecting changes in biomarkers that often occur together with or after the onset of neurocognitive symptoms. In addition, measuring levels of the key biomarkers—β-amyloid (Aβ) and its peptides, and microtubule-associated protein-τ (MAPT; tau; FTDP-17)—requires invasive procedures such as lumbar puncture or costly and time-consuming methods such as PET imaging or functional MRI scans.

Simple blood tests to detect AD noninvasively before the onset of symptoms have become the Holy Grail for diagnosing the disease. Several studies have tried to correlate the progression of MCI to AD with blood levels of small molecules, Aβ peptides, tau or other proteins.[2–4] However, none has identified blood markers that could predict which cognitively normal individuals are at risk of developing AD.

To bridge this diagnostic gap, a team headed by Mark Mapstone and Howard Federoff conducted a 5-year clinical study to look for plasma markers in individuals age 70 or older with no cognitive impairment that could predict which of them would develop AD or amnestic MCI (aMCI)—the memory-related form of MCI that most often progresses to AD.

Mapstone is an associate professor of neurology and neurogeriatrics at the **University of Rochester Medical Center School of Medicine and Dentistry**. He co-led the team with Howard Federoff, EVP of health sciences at **Georgetown University** and executive dean of the **Georgetown University School of Medicine**.

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The team included researchers from the **Unity Health System**, **Rochester General Hospital** and the **University of California, Irvine School of Medicine**.

Panel power

The team enrolled 525 participants with no history of major neurological, psychiatric or blood disorders. Blood samples were withdrawn and cognitive tests performed at the start of the study and every year thereafter.

Of the 74 patients who were identified with symptoms of AD or aMCI during the study, 46 already had symptoms at the start of the study but had never been diagnosed with aMCI or AD. The other 28 became symptomatic during the study's course. The average time for the latter group—labeled 'converters'—to show symptoms was 2.1 years.

From the original 525 participants, another 73 age-matched individuals with no cognitive impairment were selected as normal controls.

The team performed lipidomic and metabolomic analyses of the plasma samples and found a panel of 10 lipids whose levels were significantly lower in the normal-functioning converters before they developed symptoms than in the control group. The lipid levels remained low after the converters showed signs of cognitive impairment and were comparable to levels in the 46 patients with AD or aMCI.

The lipid panel included eight phosphatidylcholines and two acylcarnitines, all of which are components of cell membranes in multiple cell types. The team proposed that the observed changes in plasma lipids might reflect a breakdown of neuronal cell membranes that precedes the onset of subtle cognitive changes. Their hypothesis was based on multiple studies that identified associations between AD and low phospholipid levels in plasma and the CNS.[5–10]

Finally, the team developed a mathematical model that used the 10 lipid markers to predict which initially unaffected individuals would develop aMCI or AD with 90% sensitivity and 90% specificity.

According to the paper's authors, the findings suggest that the panel of lipid markers could be used to identify cognitively normal individuals who would convert to a diagnosis of aMCI or AD within two or three years.

The study was published in *Nature Medicine*.

Lipid AD-vances

"The study potentially opens a new door in biomarker development for Alzheimer's disease," said Stephen Salloway. "Having a plasma profile that is associated with the disease and that can predict its progression would be a major advance."

Salloway is director of neurology and the Memory and Aging Program at **Butler Hospital** and a professor of neurology and psychiatry at **The Warren Alpert Medical School of Brown University**.

According to Norman Foster, director of the Center for Alzheimer's Care, Imaging and Research, senior investigator at The Brain Institute and a professor of neurology at **The University of Utah**, "The ability to predict the onset of clinical symptoms in two to three years would definitely advance the field by allowing the benefits of treatments to be identified over a very short time."

Xiaoming Guan added that the markers should be tested in a younger population to see whether the changes in these lipids can be detected even earlier. Guan is senior director of the Neurodegeneration Discovery Performance Unit at **GlaxoSmithKline plc**'s R&D center in Shanghai.

GSK has three compounds in the clinic to treat AD: rilapladib (SB 659032), a small molecule inhibitor of lipoprotein-associated phospholipase A_2 (PLA_2G7; PAFAH; Lp-PLA_2), is in Phase IIa testing; SB-742457 (742457), a serotonin ($5\text{-}HT_6$) receptor antagonist, is in Phase II trials; and 2647544, an Lp-PLA_2 inhibitor, is in Phase I testing. In addition, GSK and **Affiris AG** have three vaccines against Aβ in Phase I to Phase II testing to treat AD.

According to Richard Pither, CEO of **Cytox Ltd.**, the ability to detect which presymptomatic patients are likely to develop AD could be particularly beneficial for companies developing disease-modifying therapies.

"This panel of markers could help get those compounds into the right patients," he said.

Cytox develops diagnostic tests for identifying patients at risk of AD or other forms of dementia.

However, Howard Fillit said that in addition to validating the findings in a larger patient population, the team needs to establish that the markers are specific for AD.

Fillit is executive director and CSO of the **Alzheimer's Drug Discovery Foundation** and a clinical professor of geriatrics, medicine and neuroscience at **Mount Sinai Hospital**.

Because the team did not use cerebrospinal fluid (CSF) markers or PET imaging scans to diagnose MCI and AD in the converters, it is not certain that they actually had the diseases, he said.

Indeed, Salloway and Foster said that it would be useful to examine whether the changes in plasma lipid levels coincide with changes in CSF or PET imaging markers for AD.

Foster added that the findings should be replicated in other populations, using Aβ and/or tau markers to show whether the lipids in the panel are altered when there is evidence of AD pathology.

Determining whether the lipid markers correlate with CSF and imaging markers for AD would also help rule out—or rule in—Lewy body dementia and other forms of non–AD-related dementia in the converters, Pither said. "Looking at these lipids in patients who have other forms of dementia could also help determine whether the markers are AD specific or not."

Fillit added that because most people aged 70 and older have comorbidities such as atherosclerosis, vascular abnormalities in the brain or other cardiovascular conditions, "the altered lipid levels might just be markers for cognitive impairment due to vascular inflammation, not Alzheimer's disease."

Mapstone agreed that the lipid markers need to be validated in a larger and more demographically diverse population than was used in the study. But he countered Fillit's concerns about comorbidities by pointing out that the same risk factors for MCI unrelated to AD were probably present in the controls as well as the converters.

"We haven't looked at those comorbidities in our cohort, but I think that if we did, we wouldn't see major differences in them between the converters and controls—just as we saw no differences in the frequency of apolipoprotein E ε4 between the two groups," he said. "But we did see differences in the lipid levels."

Last week, the **Alzheimer's Association** issued a statement noting that the findings were preliminary and required replication and validation in larger, more diverse populations. The organization declined *SciBX*'s request for further comment.

Road map for markers

The team's immediate next step is to validate the lipid markers in a larger, retrospective study using banked plasma samples—such as those from the Alzheimer's Disease Neuroimaging Initiative (ADNI), Mapstone told *SciBX*. Once the samples are in hand, he expects to be able to complete the validation within a few months.

ADNI is a public-private partnership launched in 2004 that includes the Alzheimer's Association and the **Foundation for the National Institutes of Health**.

In the meantime, the researchers are continuing to follow the 21 converters who developed aMCI to see whether they go on to develop full AD.

In addition, Mapstone told *SciBX* that although the lipid panel is not ready for use as a routine AD screening test, it could be used to assist patient selection in clinical trials in AD.

"Our approach could enrich the trial population with a larger fraction of potential converters than other markers such as apolipoprotein E ε4, which carries a 30% risk of AD," he said.

"Potential converters would be randomized between the placebo and treatment arms. We would expect the converters in the placebo group to progress to MCI or AD, thus providing validation of the markers. We would also monitor the individuals identified as nonconverters to confirm that they did not develop MCI or AD, which would further validate the markers," he said.

To monitor treatment responses and track disease progression, the trial would use CSF and PET imaging markers because they are considered the gold standards, he added.

Mapstone said that a forthcoming paper by the team will report data from transcriptome analysis of plasma from its study cohort and integrate those findings with the lipid data reported in *Nature Medicine*.

Ultimately, the team aims to use a systems biology approach—incorporating lipidomic, transcriptomic and genomic data from the study cohort—to identify cognitively normal individuals who will develop MCI and AD.

Other efforts to identify markers for early detection of AD and for monitoring disease progression include the ADNI. The study has enrolled more than 1,000 participants, including patients with AD or MCI, individuals at risk of developing AD and controls who have no memory problems.[11]

Mapstone said that Georgetown and the **University of Rochester**

have filed a patent application covering the *Nature Medicine* findings. The technology will be available for licensing once the validation study on banked samples has been completed.

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REFERENCES

1. Mapstone, M. *et al. Nat. Med.*; published online March 9, 2014; doi:10.1038/nm.3466
   Contact: Howard J. Federoff, Georgetown University, Washington, D.C.
   e-mail: hjf8@georgetown.edu
2. Irizarry, M.C. *NeuroRx* **1**, 226–234 (2004)
3. Ray, S. *et al. Nat. Med.* **13**, 1359–1362 (2007)
4. Doecke, J.D. *et al. Arch. Neurol*. **69**, 1318–1325 (2012)
5. Nitsch, R.M. *et al. Proc. Natl. Acad. Sci. USA* **89**, 1671–1675 (1992)
6. Schaefer, E.J. *et al. Arch. Neurol.* **63**, 1545–1550 (2006)
7. Mulder, C. *et al. J. Neural Transm.* **110**, 949–955 (2003)
8. Walter, A. *et al. Neurobiol. Aging* **25**, 1299–1303 (2004)
9. Prasad, M.R. *et al. Neurochem. Res.* **23**, 81–88 (1998)
10. Pettegrew, J.W. *et al. Neurochem. Res.* **26**, 771–782 (2001)
11. Weiner, M.W. *et al. Alzheimer's Dement.* **9**, e111–e194; published online Aug. 7, 2013; doi:10.1016/j.jalz.2013.05.1769

COMPANIES AND INSTITUTIONS MENTIONED

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