

Is Shape of A β an Early Blood Biomarker for Alzheimer's?

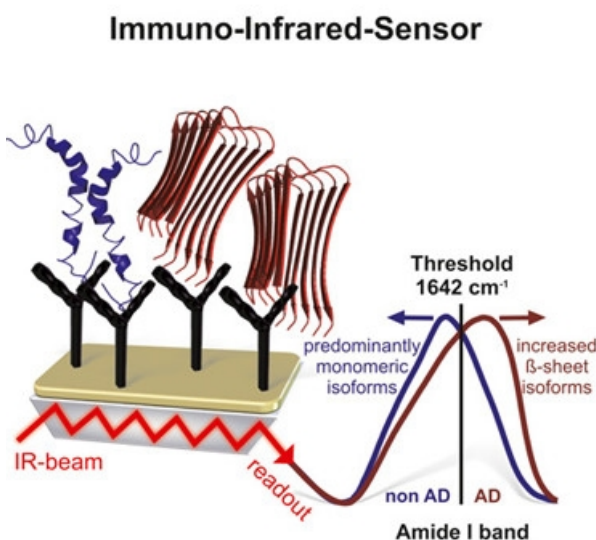
12 Apr 2018 Within the past nine months, researchers developed assays that correlate reduced concentration of soluble A β in the blood with amyloid plaques in the brain. Now a group led by Klaus Gerwert, Ruhr-University Bochum, Germany, suggests that changes in the structure of plasma A β might herald Alzheimer's disease. Using infrared spectroscopy to measure the ratio of β -sheet to α -helical forms of A β in plasma, the researchers distinguished people with prodromal AD from healthy controls. In a longitudinal study, normal people who tested positive for the β -sheet form were nearly eight times more likely to be diagnosed with Alzheimer's during the next eight years. Gerwert published the findings in the April 6 EMBO Molecular Medicine.

- Infrared sensor detects β -sheet structures in A β peptides from blood.
- The signal can discriminate prodromal AD from controls.
- Positive-testing individuals were nearly eight times more likely to develop AD, an average of eight years later.

"The results with this novel technique are very encouraging," wrote Colin Masters, University of Melbourne, Australia. Hilal Lashuel, École Polytechnique Fédérale de Lausanne, Switzerland, also welcomed the findings. "It is a very promising development in the right direction, moving beyond measuring total levels [of A β] to detecting and quantifying pathogenic species," he said. "However, it still requires refinement to improve sensitivity."

For decades, scientists struggled to measure a difference between levels of A β peptide in the plasma of patients and controls ([April 2016 news](#); [Blennow and Zetterberg, 2018](#)). Success finally came in the form of mass spectrometry-based assays, which increased accuracy and precision over previous measures, and an ELISA ([Jul 2017 conference news](#); [Feb 2018 news](#); [Fandos et al., 2017](#)).

Previously, Gerwert and colleagues used infrared spectroscopy to search for the β -sheet type of A β found in fibrillar plaques associated with AD. They capitalized on a change in the vibration of amide bond carbonyl groups as the peptide morphs from α -helix to β -sheet. This changes absorption of infrared light, which manifests as a shift within the infrared spectrum (see image at right). This approach enabled Gerwert to discriminate between blood samples from healthy controls and AD patients with a sensitivity of 75 percent



Shape-Shift Sensor.

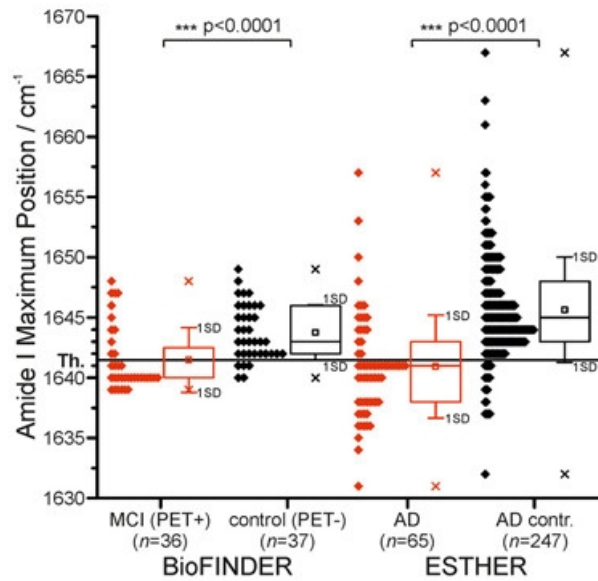
Antibodies trap α -helical (blue) and β -sheet (red) conformations of A β from the blood (left). The β -sheet form, detected by an infrared spectral shift (right), is indicative of AD. [Courtesy of Nabers et al., EMBO Mol Med, 2018.]

and a specificity of 88 percent (Nabers et al., 2016; Nabers et al., 2016).

Now co-first authors Andreas Nabers, Ruhr-University Bochum, and Laura Perna, German Cancer Research Center (DKFZ), Heidelberg, used the same method to test samples from people at earlier disease stages. As in the 2016 study, they used a pan-A β antibody, β -Amyloid [13-28], to capture, in theory, all A β peptides, including α -helical monomers and protofibril oligomers, and then measured the infrared spectrum of the trapped material. They first examined blood from the prospective Swedish Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably study. BioFINDER samples came from 36 patients with mild cognitive impairment who had abnormal [18F]-flutemetamol PET scans, and 37 cognitively healthy controls with normal amyloid scans.

In the prodromal AD samples, infrared absorption indicated A β sheet, as expected (image below). The spectral shift distinguished PET-positive people from PET-negative with a sensitivity and specificity of 69 and 86 percent, respectively.

Next, Nabers and Perna tested earlier stages of disease using baseline samples collected between 2000 and 2002 from ESTHER, a population-based longitudinal cohort of nearly 10,000 healthy older adults from Germany. Follow-up questionnaires, medical records, and biological samples were collected every three years, and incident dementia recorded. During an average of eight years of follow-up, 70 volunteers were diagnosed with AD, of whom 65 had a clean baseline blood sample and an unambiguous diagnosis. Nabers and Perna matched these 65 cases with 247 controls based on age, gender, and education level, and compared their blood A β spectra. The assay distinguished AD sample from controls with a sensitivity and specificity of 71 and 91 percent, respectively. Overall, people who were diagnosed with AD were 7.9 times more likely to test positive.



Predicting AD.

A shift in plasma A β amide I absorption distinguished PET-positive from PET-negative volunteers (left), and AD patients from controls (right). [Courtesy of Nabers et al., EMBO Mol Med, 2018.]

The authors also compared samples from 66 cases of vascular dementia and 36 cases of mixed dementia with 311 and 149 matched controls, respectively. Both sets of samples tested negative. Gerwert cautioned, however, that the difficulty of diagnosing vascular and mixed dementia limits the interpretation of these results.

“This is a completely new aspect of A β monitoring,” said Henrik Zetterberg, University of Gothenburg, Sweden. He also noted that the results add to a growing number of studies indicating that A β measured in blood is relevant to what is happening in the brain.

The overall accuracy of the test is moderate, however. Gerwert predicts better performance with technical tweaks, including better antibodies to trap A β . Zetterberg noted that the motley collection of peptides captured by the antibody used may explain the large overlaps between groups. He said antibodies specific for aggregate-prone A β 42 may yield cleaner data. Although the signal might be too low to detect in plasma, it could work in CSF, he predicted. Lashuel had a different take. He liked the concept of capturing all forms of A β , but noted that the epitope recognized by β -Amyloid [13-28] may be buried in some A β configurations. “The low sensitivity of the assay might be due to missing A β species,” he said. He suggested reconstituting known A β

structures in vitro, and then testing if they are recognized by the sensor. Masters wondered if β -Amyloid [13-28] might be capturing not only A β , but other proteins bound to the peptides. Gerwert said he cannot exclude this possibility but, based on his earlier work, thinks it unlikely.

The source of the β -sheet-enriched peptides in blood also puzzled some. Katsuhiko Yanagisawa, National Center for Geriatrics and Gerontology in Aichi, Japan, wondered whether the peptides derive from the brain or from peripheral cells.

Zetterberg noted the assay may be capturing a transition from a benign to toxic A β conformation that maybe relevant beyond a plasma assay. He thinks such a transition may explain why A β 42:A β 40 ratios in human CSF fall into two separate groups, high and low, and rarely in between. "There's a lack of people in the gray zone," he said. "This must mean that something happens quickly, perhaps within months, to deplete CSF A β 42 even though amyloid build-up is gradual." That something could be a switch to a soluble β -sheet formation, said Zetterberg.

Going forward, all agreed that replication and validation are needed if the test is to be used for trial selection or screening for probable AD prior to more expensive tests, such as amyloid PET.
—Marina Chicurel

COMMENTS

No Available Comments

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REFERENCES

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| Meta-Analysis of 21 Years of Alzheimer's Fluid Biomarker Research 8 Apr 2016 | 2017 |
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Antibody Citations

[A \$\beta\$ 42:A \$\beta\$ 40 Ratio in Blood and CSF of Cognitively Normal Individuals](#) (BAM90.1)

Paper Citations

Blennow K, Zetterberg H. [The Past and the Future of Alzheimer's Disease Fluid Biomarkers](#). *J Alzheimers Dis*. 2018;62(3):1125-1140. [PubMed](#).

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FURTHER READING

No Available Further Reading

PRIMARY PAPERS

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