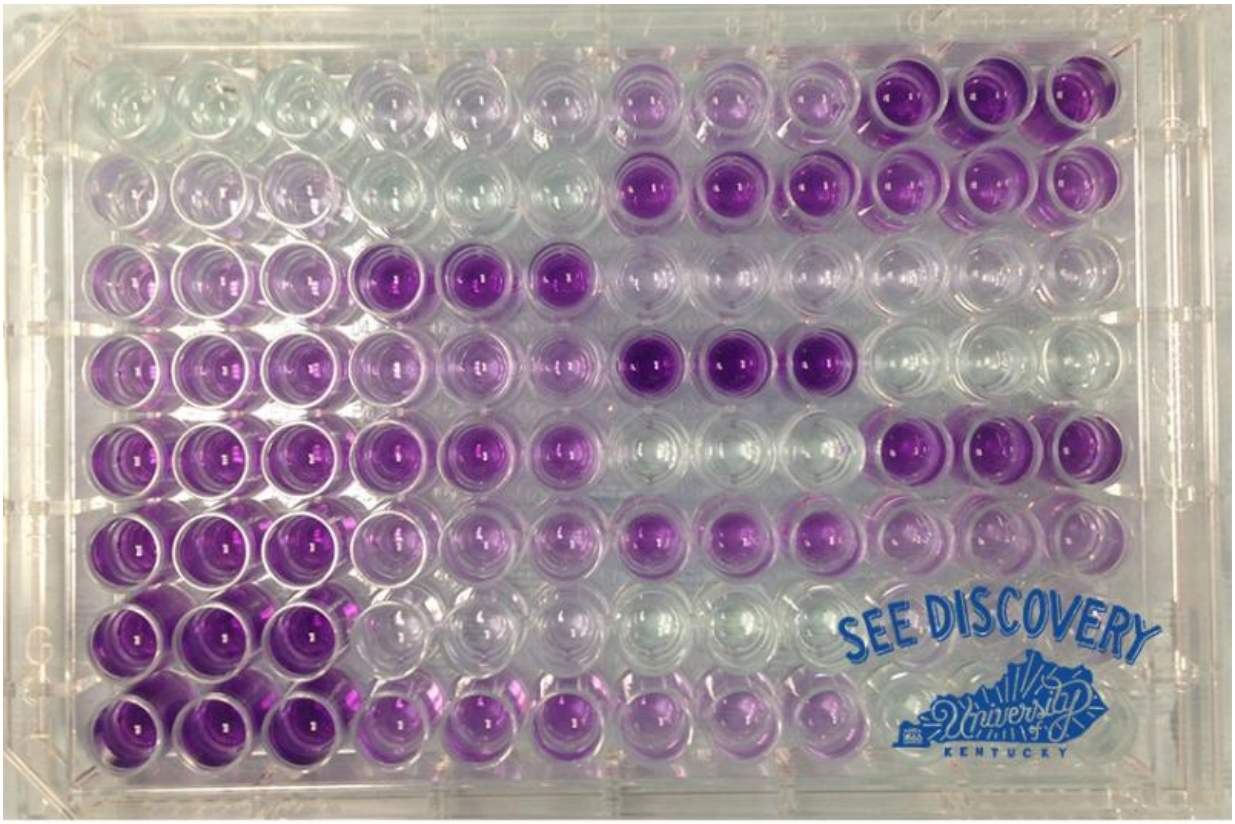
Identifying biomarkers key to early intervention in Alzheimer's disease

July 22 2015, by Laura Dawahare



Although the term didn't surface until the 1980s, the concept of biomarkers has been around for almost a century. Today, doctors routinely test blood for signs of anemia or the antigen associated with

prostate cancer. Urine samples can hint at the presence of infection or diabetes, and EEGs diagnose electrical abnormalities in the brain.

But scientists are now advancing the concept, looking for ways to identify a host of diseases early in the process to provide opportunity for early intervention and improve the chances that treatment will be effective.

This is particularly true for Alzheimer's disease (AD), where evidence points to the fact that the disease process begins long before someone has clinical symptoms, and the ramifications of the disease – both financial and emotional – are disastrous.

At the University of Kentucky's Sanders-Brown Center on Aging, researchers are looking for biomarkers that might serve as an early warning system for AD. The process is not without complications, but these scientists possess a collective "Rosie the Riveter" spirit.

Mark Lovell is one of them. According to Lovell, the only definitive way to diagnose AD is through autopsy, though other options, such as PET imaging to identify the presence of AD pathology, are becoming more widely used. The challenge, explains the bioanalytical chemist and Jack and Linda Gill Professor of Chemistry, is finding a biomarker that 1) is an accepted predictor of the disease and 2) can easily be identified by a physician at the clinic level.

"Multiple studies show alterations in levels of the proteins associated with AD – tau and beta amyloid— in cerebrospinal fluid, but a spinal tap to obtain that fluid is often a hard sell for patients", Lovell said. "Furthermore, there appears to be variability in the data connecting the levels of these proteins in CSF and the diagnosis of AD, which has limited the use of beta amyloid and tau clinically."

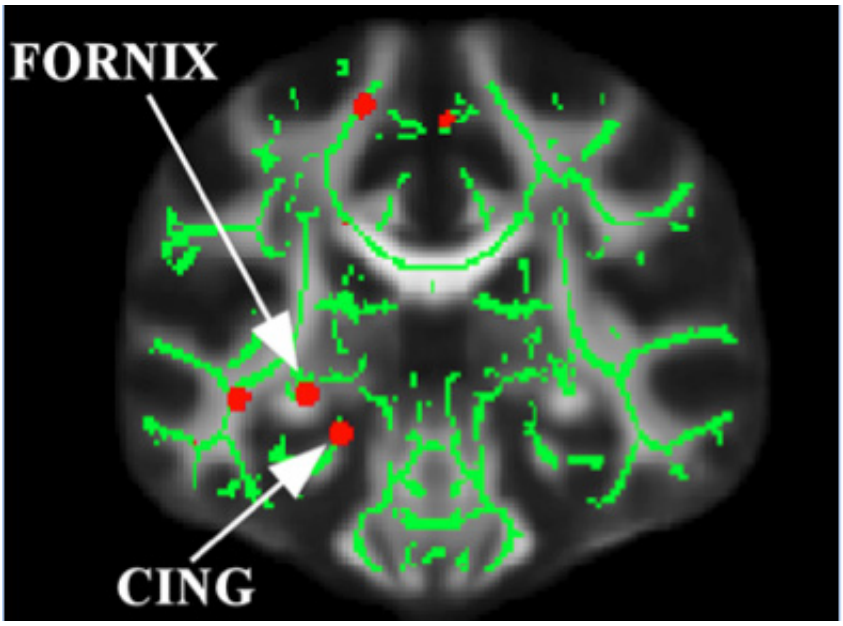
But in the spirit of Sanders-Brown's iconic first director and Lovell's research mentor, William Markesbery, Lovell is willing to explore unconventional ideas so he started searching for alternative biomarkers.

Working with Bert Lynn, director of UK's Mass Spectrometry Center, Lovell began to sort proteins in CSF samples by weight. As the results came in, two particular proteins (transthyretin and prostaglandin-d-synthase) caught his attention.

"We were able to tease out that these two proteins, when subjected to oxidative damage, tended to stick together and fractionate at a higher molecular weight than expected," said Lovell.

Further study suggested that these proteins may signal dysfunction in the choroid plexus, a brain region responsible for the production and filtration of cerebrospinal fluid.

Since, in AD, current data suggest there are changes in the transfer capacity of the choroid plexus it made sense to Lovell and Lynn that these two proteins might make a good biomarker for AD.



The red areas of these DTI results indicate portions of the brain where associations were found between microstructural tissue properties and CSF biomarkers of Alzheimer's disease (AD). Two of these areas (labeled fornix and cing, short for cingulum) are white matter pathways that connect key portions of the brain's memory circuitry known to be affected in AD.

The next step, says Lovell, was to go "downstream" to blood or urine, for example to determine whether this same protein combination appears there as well.

"I've historically been skeptical that blood can be as strong a predictor of Alzheimer's disease as cerebrospinal fluid (CSF), but I was pleasantly surprised to see that there was a reasonable correlation in samples of CSF and blood taken from the same patients," Lovell said.

Lovell cautions that further evaluation in larger sample populations is necessary before this can be called a definitive success, but if the hypothesis is borne out, "we will have a blood based biomarker that might be more predictive than amyloid beta peptide."

Ultimately, Lovell thinks AD will be diagnosed by a panel of three or four biomarkers, rather than a single "up or down" test. And that's where

Brian Gold comes in.

Gold, a cognitive neuroscientist, is fascinated by CSF protein biomarker findings of Lovell and others and is conducting his own research in the hopes of using brain imaging to find non-invasive AD biomarkers. However, up until now, Gold explains, most MRI studies of preclinical AD have been restricted to structural volumetric characteristics of the brain.

"We've instead been focusing on microstructural brain changes detectable with a form of MRI called diffusion tensor imaging (DTI), which assesses the diffusion of water molecules in the brain," said Gold. "As cellular structures begin to degenerate, tissue barriers degenerate as well, allowing for increased water diffusion DTI-based changes in the brain are thus somewhat analogous to hairline cracks in a house's foundation that precede visible structural damage."

Gold and his colleagues are one of just a handful of U.S. groups exploring how CSF protein biomarkers correlate with microstructural brain changes using DTI and dynamic physiological changes using functional MRI.

His work, published last year in the *Neurobiology of Aging*, found tantalizing correlations between reduced white matter microstructure in the brain and the presence of CSF markers of AD.

"In other words, if our findings using DTI and functional MRI are highly correlated with Lovell's CSF biomarkers, we have potentially uncovered a minimally invasive way to diagnose pre-clinical AD."

While Gold and Lovell look prospectively for the Holy Grail, others at Sanders-Brown are taking a retrospective look using big data.

Dick Kryscio and Erin Abner help manage the Alzheimer's Disease Center (ADC) database, a collection of thousands of data points from more than 1300 research volunteers enrolled in the Biologically Resilient Adults in Neurological Studies cohort. With literally thousands of blood samples, CSF samples, results from cognitive testing, medication history, physical and neurologicalexaminations, and medical history, the database size probably approaches the inventory of a mid-sized grocery store. Abner and Kryscio troll the reams of data looking for consistencies that might constitute an early warning of disease.

Kryscio notes that biomarkers serve two purposes—as a predictor of disease and as a means to a diagnosis. While most biomarkers today serve the latter function, "a marker truly earns its keep when a person is on his or her way to disease," he says.

And, while not a biomarker in the strictest sense, their most promising work in predicting disease has been in the area of self-reported memory complaints.

Both Abner and Kryscio have published studies in *Neurology* and *Journal of Prevention* demonstrating a link between self-reported memory complaints and the development of cognitive impairment later in life.

"In other words, people usually are the best judges of their own memory—they can detect subtle problems years before there are more obvious symptoms," says Abner. She points out that it's an enormous oversimplification. "You aren't likely to have AD just because you can't remember where you put your keys one day," she said but added it has potential as a candidate for the "panel of tests."

Abner and Kryscio's efforts have international ramifications, as they are two of the gatekeepers for the ADC biospecimens, which are shared

worldwide.

"The number of data parameters, and the longitudinal nature of the data available, makes this database world-class, but there are nonetheless a finite number of studies for which we can provide specimens before the supply is exhausted," Kryscio said. "It's a service to our research participants to help researchers with a study design that eliminates waste and maximizes the quality of the science, and we don't take that responsibility lightly."

Regardless of the path—whether looking forward or backward—the ability to detect AD at its earliest stages will have huge ramifications on the race to treat and eventually cure the most expensive malady currently known to man.

Provided by University of Kentucky