Study underlines potential of new technology to diagnose disease

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Researchers at The Scripps Research Institute (TSRI) in Jupiter, FL, have developed cutting-edge technology that can successfully screen human blood for disease markers. This tool may hold the key to better diagnosing and understanding today's most pressing and puzzling health conditions, including autoimmune diseases.

"This study validates that the 'antigen surrogate' technology will indeed be a powerful tool for diagnostics," said Thomas Kodadek, PhD, a professor in the Departments of Chemistry and Cancer Biology and vice chairman of the Department of Chemistry at TSRI, whose group developed the technology.

The latest study, published in the journal *Chemistry & Biology* on March 21, 2013, shows how the technology accurately identified human blood markers for neuromyelitis optica (NMO), a rare autoimmune disorder resembling multiple sclerosis that can result in blindness and paralysis. Following a similar study on mouse models for multiple sclerosis two years ago, the work confirms that the technique can also be successfully applied to humans.

Finding the Needle in a Haystack

The blood is filled with molecules called "antibodies" released by the immune system to defend the body against disease. Many autoimmune diseases produce antibodies specific to that disease. Identifying these

disease-specific antibodies among the millions of other similar yet non-disease-specific antibodies in the blood, however, is much like finding a needle in a haystack.

Many current diagnostic methods detect disease-specific antibodies by using part of the virus, bacteria or cellular component targeted by the antibody in a patient's body, essentially "fishing" for the antibody using its distinct target as bait. Unfortunately, many disease-specific antibodies and their targets are currently unidentified.

Kodadek and his colleagues have found a way to sidestep this conundrum by substituting these unknown antibody-binding targets with biologically unnatural molecules called "peptoids." Peptoids are chain-like molecules tethered to tiny beads and extended "link by link" by the sequential addition of small chemical subunits. By using different subunits and randomizing their order, chemists can produce libraries of thousands and even millions of different peptoids quickly and easily.

These vast libraries are screened for peptoid "hits" that bind exclusively to antibodies found only in patients known to have a specific disease. "We find disease biomarkers differently [than anyone else]," explained Kodadek. "This enables new disease biomarker detection." Additionally, by using these peptoid hits to "fish" for disease-specific antibodies, the system enables disease-specific antibody detection without first knowing the antibodies' natural binding targets.

A Diagnostic Revolution

Using this technology, the group identified several peptoids that bound exclusively to antibodies in NMO patient blood serum and not healthy patients or patients with similar diseases, including multiple sclerosis, lupus, Alzheimer's disease and narcolepsy. At least one of the peptoids bound to an antibody that is well known to be associated with NMO.

The study builds on technology that the group successfully used to identify disease markers in mouse models for multiple sclerosis, introduced in a January 2011 publication in the journal *Cell*. "[Our latest study] is proof positive that our technology works in complex human systems as well," explained Kodadek.

Kodadek noted the new study also introduced a technical advance that increases the technology's utility, significantly improving the peptoid library screening process. This step initially involved the time-consuming and painstakingly tedious task of removing peptoids from beads and refixating them to a different solid support, called a microarray.

"This is the first time we screened peptoid libraries directly on the beads [on which they were made] instead of using microarrays," said Bindu Raveendra, PhD, staff scientist who was a first author of the study with postdoctoral researcher Wu Hao. "Previously, we could screen thousands of peptoids at a time; now, we can now screen millions. That just wasn't feasible using microarrays."

More information: "Discovery Of Peptoid Ligands For Anti-Aquaporin 4 Antibodies" *Chemistry & Biology*, 2013.

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