Peptoid prognostics

By Lev Osherovich, Senior Writer

Florida and Texas researchers have devised a screening technology that uses peptoids to identify antibodies that could detect Alzheimer's disease.¹

Opko Health Inc. has in-licensed the platform and last month partnered with **Bristol-Myers Squibb Co.** to develop a test for early AD based on the approach.

Peptoids are peptide-like chains in which amino acids are connected to the peptide backbone at the nitrogen position rather than at their natural carbon position. The molecules superficially resemble natural proteins, but their different backbone structure causes them to form distinct shapes that are not possible with ordinary peptides.²

In 2004, Thomas Kodadek and colleagues devised a way to synthesize large peptoid libraries³ and have been exploring the potential of the molecules in a range of diagnostic and therapeutic applications. Kodadek is a professor of chemistry and cancer biology at **Scripps Florida**.

Now, his team has used microarrays of peptoids to probe serum for antibodies linked to two neurological disorders—AD and multiple sclerosis (MS).

Kodadek said diseases with immunological or inflammatory involvement such as MS, AD and many cancers have distinct disease-associated

antigens and corresponding antibodies that recognize these antigens. These antibodies are absent in healthy individuals, so detecting them in the serum of presymptomatic patients could theoretically aid early diagnosis.

The challenge is to find the right diagnostic antibodies when their corresponding antigens are unknown. Conversely, it is hard to identify antigens without corresponding antibodies in hand.

Kodadek's method dispels this chicken-egg problem.

He hypothesized that some of the peptoids in his library resembled the shape of natural, disease-linked antigens closely enough to bind and capture disease-associated antibodies. Kodadek reasoned that pep-

toids deposited onto a microarray and coupled to an ELISA-like fluorescence detection system could serve as probes for disease-associated antibodies whose true antigens are unknown (see **Figure 1, "Disease biomarker screening with peptoid arrays"**).

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Scripps Florida

Brain probe

To validate the approach, Kodadek's team ran serum from a mouse model of MS over a microarray bearing 4,608 peptoids. A trio of peptoids bound to antibodies from the MS mice but not to those from healthy controls.

Figure 1. Disease biomarker screening with peptoid arrays.

Reddy *et al.* describe a way to identify disease-associated antibodies from patient serum using microarrays of peptoids, which are small N-substituted oligoglycine molecules. The technology is being developed by **Opko Health Inc.** for early detection of cancer and neurodegenerative disease.

Microarrays bearing a library of peptoids [a], including ones that mimic disease-associated antigens (in red), are treated with serum from healthy controls and patients. Various peptoids bind an assortment of antibodies in both control and patient samples, while disease antigen-mimicking peptoids capture a distinct set of disease-associated antibodies (in purple) [b]. Addition of a fluorescently labeled secondary antibody leads to a distinct fluorescent pattern on patient microarrays compared with control microarrays. Disease-specific signals are shown in purple and common signals are shown in green [c].

The team then probed a larger, 15,000-peptoid array with serum from 6 AD patients as well as serum from age-matched healthy controls and controls with Parkinson's disease (PD), a mechanistically unrelated neurodegenerative condition.

The group identified three peptoids that bound selectively to antibodies in all six AD patients compared with those in controls. Data were published in *Cell*.

Kodadek said his team has since gone on to show that these 3 peptoids recognized antibodies in serum from a larger cohort of 200 AD patients but not antibodies in serum from controls.

"The sensitivity and specificity of the test are holding up beautifully," he said.

ADded value

One use for Kodadek's AD-linked peptoids could be as a tool to identify the actual antigens that trigger antibody responses in AD patients.

"It's an open question if these antigens are something that's critical in the development of disease," said Kodadek. He added that evidence thus far suggests it is unlikely that these antigens are well-known AD-associated proteins like β -amyloid (A β) or microtubule-associated protein- τ (MAPT; TAU; FTDP-17).

To find the antigens, the team is now working backward—using the peptoids to isolate the antibodies that bind them and then using the antibodies to fish out antigens from AD patient serum.

In addition, Kodadek thinks the microarray could be useful for identifying and validating prognostic peptoids in other diseases in a clinical setting. He is trying to scale up and improve the screening and detection procedure to increase throughput.

Kodadek's previous institution, **The University of Texas Southwestern**

Medical Center at Dallas, has patented the technique and out-licensed it to Opko in 2009.

"We're a holding company with interest in various areas" including diagnostics and vaccine development, said Opko chairman and CEO Phillip Frost. "We're interested in a large number of diagnostic tests across the board for lung and pancreatic cancer, as well as AD and PD."

The Kodadek study shows that "at least in AD we have some indication that this [technique] can be diagnostically useful," said Frost.

In January, Opko partnered with BMS to collaborate on a serum test for AD using the peptoid technique.

"The BMS agreement involves validating our method for making an early diagnosis in select AD trials" of undisclosed BMS compounds, said Frost.

BMS's most advanced AD compound is BMS-708163, a γ -secretase inhibitor in Phase II testing.

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COMPANIES AND INSTITUTIONS MENTIONED

Bristol-Myers Squibb Co. (NYSE:BMJ), New York, N.Y.

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