Welcome to the peptidome

By Tim Fulmer, Senior Writer

U.S. researchers have developed a peptide-based screen for identifying autoantigens associated with autoimmune diseases.¹ The researchers believe the screen could save time and money compared with other proteomic screens and plan to use the method to identify autoantigens associated with multiple sclerosis, type 1 diabetes and rheumatoid arthritis.

Accurately identifying autoantigens has been challenging because peptide or protein libraries that represent the full human proteome have not been generally available. Moreover, there were no methods for rapidly analyzing hundreds of thousands of autoantigen-autoantibody interactions in human serum.

Now, a team led by Stephen Elledge, professor of genetics at **Harvard Medical School**, has designed an autoantigen screen to meet those challenges.

First, the researchers constructed an autoantigen library representing the entire human proteome. To do that, they used the human genome sequence to generate a peptidome of more than 400,000 overlapping 36-amino-acid peptides that corresponded to the 24,239 predicted protein-encoding regions of the human genome.

Next, the researchers optimized a phage immunoprecipitation protocol that allowed them to rapidly identify and sequence those autoantigen peptides that bound autoantibodies in complex mixtures such as patient serum and cerebrospinal fluid.

With the screening library and sequencing protocols in hand, the researchers used the platform to analyze the cerebrospinal fluid of a 63-year-old cancer patient who was diagnosed with paraneoplastic neurological disorders (PNDs), a CNS autoimmune disease with previously characterized autoantigens.

The peptidome screen identified seven autoantigen candidates in the patient, including one that had been previously identified by an independent autoantigen screen. Subsequent screens of cerebrospinal

fluid from two additional patients who had PND symptoms identified more autoantigen candidates.

The findings were published in *Nature Biotechnology*.

Besides Harvard, the team included researchers from the **Massachusetts Institute of Technology**, the **University of California, San Diego** and **Agilent Technologies Inc.**, which specializes in the synthesis of screening libraries and helped construct the library used in the paper.

Agilent declined to comment on the paper.

Automating autoantigen discovery

Corresponding author Elledge told *SciBX* the findings represent “the first synthetic human proteome and a method to rapidly analyze it.”

Unlike other proteomic screening protocols such as cDNA phage display and protein arrays, the peptidome platform “requires a minimal amount of technical expertise for a successful screen of patient antibodies. There’s no longer the need to perform multiple, time-consuming rounds of phage selection, and by looking at the whole peptide library at once, we increase the amount of information gained from a single experiment and reduce screening time,” said Elledge.

Elledge and colleagues plan to use the peptidome screening platform “to discover which autoantigens are commonly found in some of the more prevalent autoimmune diseases, including multiple sclerosis, type 1 diabetes and rheumatoid arthritis. In all those cases, identifying common autoantigens would be immediately useful for diagnostic purposes and could eventually lead to new therapies as

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—Stephen Elledge,
Harvard Medical School

well,” he said.

Elledge said the peptidome library is available for licensing from Harvard Medical School. He declined to comment on the patent status of the findings.

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