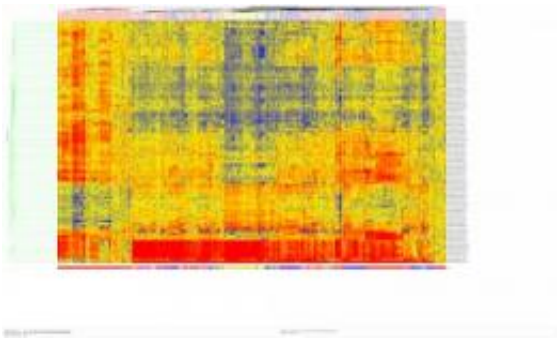
Harnessing the immune system's diagnostic power (w/ Video)

June 8 2010, by Richard Harth



In immunosignaturing, a chemical marker causes the antigen-antibody pair to fluoresce, with the magnitude of fluorescence indicating the strength of antigen-antibody binding (red is strong binding, blue is weak). A single drop of blood, containing an individual's complete set of antibodies, is spread across an array of 10,000 random sequence peptides, imprinted on a microarray slide, revealing the immune system's complete pattern of activity after exposure to a pathogen, a vaccine or any other factor provoking a change in the antibody portrait. Credit: The Biodesign Institute at Arizona State University

An inexpensive system for earlier disease diagnosis could save innumerable lives. It would also have a profound impact on the nation's healthcare industry, currently buckling under the strain of spiraling costs.

Now Bart Legutki, a researcher at the Biodesign Institute at Arizona State University has pioneered a method for profiling the immune system, using clues provided by antibody activity to track an individual's

state of health. The work was done in collaboration with Stephen Albert Johnston, director of the Institute's Center for Innovations in Medicine.

The new technique, known as immunosignaturing, could provide rapid, pre-symptomatic diagnosis for a broad range of ailments, from infectious diseases to chronic afflictions to varied forms of cancer, offering the best hope for successful treatment. Immunosignaturing also shows potential as a low-cost alternative for vaccine evaluation, currently a lengthy and expensive undertaking.

As Legutki explains, the immune system is exquisitely sensitive to any alterations in an individual's state of health resulting from infection or disease, registering these changes through subtle fluctuations in antibody activity. "The body has already done the hard work of figuring out what is going on inside us," he says, adding, "We just need to interpret the message."

The immunosignature can be thought of as a snapshot of an individual's immune system activity at the point in time the test is taken. The test involves a tiny sample of blood that is spread across a slide, with a resulting image that appears as a pattern of colored spots. The team demonstrated that a baseline immunosignature of antibody activity could be established and then compared with an immunosignature following exposure to a vaccine or pathogen.

In the current study, a distinctive shift in the immunosignature pattern was observed in both mice and humans, following vaccination for influenza. Further, the picture of activity appeared to be pathogen-specific—the immunosignature for influenza displayed a characteristic pattern easily distinguishable from that produced by tularemia exposure. The group's findings recently appeared in the journal *Vaccine*.

Johnston notes that most existing diagnostic blood tests used to evaluate

host-pathogen response target a single disease component. "With traditional tests, you're only analyzing the immune response to very defined things," he says. This is true for example with ELISA, one of the most popular tests, which looks at an antigen or collection of antigens extracted from a whole virus or other pathogen. Once the antigen has been isolated, it is spread out on a slide and exposed to a sample of blood—generally several microliters. ELISA and similar immunoassays test antibodies one by one and generally require the pathogen of interest to be known in advance.

The chemical binding of antibody and disease antigen provides the tell-tale signal detected in the test. In the case of tests like ELISA, an antigen is affixed to a surface, and a specific antibody that binds to the antigen is applied. A chemical marker causes the antigen-antibody pair to fluoresce, with the magnitude of fluorescence indicating the strength of antigen-antibody binding.

By contrast, immunosignaturing provides a universal platform, capable of detecting subtle transformations over the entire antibody profile, regardless of the underlying cause. In order to accomplish this, a single drop of blood, containing an individual's complete set of antibodies, is spread across an array of 10,000 random sequence peptides, imprinted on a microarray slide.

These peptides—chains of amino acids—are capable of selectively binding with antibodies contained in blood, revealing the immune system's complete pattern of activity under normal conditions. The pattern may then be compared with an immunosignature recorded after exposure to a pathogen, a vaccine or any other factor provoking a change in the antibody portrait.

Legutki and Johnston stress that the random nature of the peptides used to probe the antibody landscape is central to the technique's

effectiveness. They have found that a library of 10,000 random peptides, each 20 amino acids in length, arranged on a microarray are sufficient to probe the full repertoire of antibodies present in blood, estimated at a staggering 109 discreet proteins.

Results of the study revealed a characteristic immunosignature in mice following vaccination for influenza and persisting for 211 days post immunization. 283 peptides specific to influenza increased their activity subsequent to immunization. Later, seven human patients were also tested following vaccination for seasonal flu and likewise displayed a characteristic immunosignature indicating activation of the immune system following vaccination.

"We asked which peptides were the same and which went up, 21 days after the immunization," Johnston says, noting that 30 peptides in the human subjects consistently reacted with antibodies from immunized people, and the response reflected degree of antibody activity. "We could tell which of the donors tested represented day 21 post-vaccination and which were day zero. So it's a very effective way to show that the vaccine did indeed take."

The group, which includes Biodesign researchers D. Mitchell Magee and Phillip Stafford, has tested the method on some 20 diseases, in each case observing a distinctive signature.

While the era of personalized medicine is already underway in terms of tailoring treatments based on individual health traits, immunosignaturing takes the model a step further, by personalizing diagnostics. The beauty of the technique is that changes in antibody profile are measured against each individual's unique baseline, rather than comparing antibody response with a one-size-fits-all index.

"One of the projects in my center has been to develop a way for healthy

people to continuously monitor their health in a comprehensive way so that they can detect any aberration, anything that starts to go wrong," Johnston says. "If we do that early, we can act early. This is also the most important thing we can do in terms of health economics. "

Provided by Arizona State University

Citation: Harnessing the immune system's diagnostic power (w/ Video) (2010, June 8) retrieved 10 April 2024 from https://medicalxpress.com/news/2010-06-harnessing-immune-diagnostic-power-video.html

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