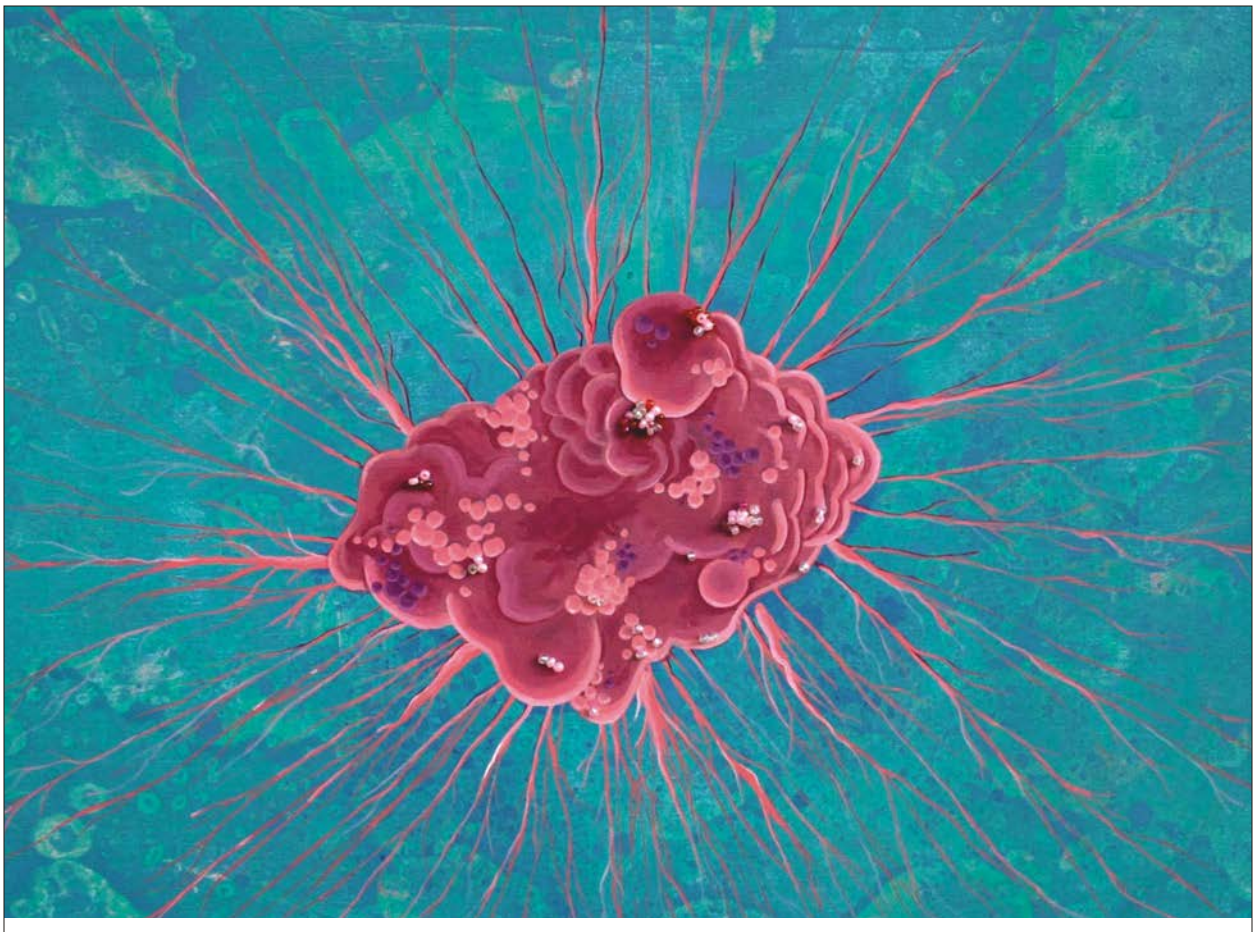

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Powerful Biomarker Panel for the Early Detection of Breast Cancer Discovered

In the war on cancer, perhaps there is nothing more powerful in a physician's arsenal than early detection. Despite recent advances in early detection and treatment, breast cancer remains a common and significant health problem in the United States and worldwide. Approximately one in ten women will get breast cancer in their lifetime and more than half of women with late stage cancer (II and III) have no cure or effective therapeutic available.

Using a new, powerful method for rapidly screening molecules associated with disease, proteomics expert Joshua LaBaer and colleagues from the Biodesign Institute at Arizona State University have identified a broad panel of 28 early predictors, or biomarkers, that may one day aid in the early diagnosis of breast cancer.

"We do not have any available blood markers for breast cancer," said LaBaer, a Virginia G. Piper Chair in Personalized Medicine at ASU who directs the Center for Personalized Diagnostics at the Biodesign Institute. "Our hope is to combine a new type of blood test with mammography screening to aid in the early detection of breast cancer."

The findings represent the first demonstration of a custom protein array technology deployed to find biomarkers in breast cancer patients before they were clinically diagnosed for cancer. These biomarkers were specific for breast cancer patients and not in healthy women or women with a benign form of breast disease.

Their findings appear in the American Chemistry Society's Journal of Proteome Research.

The LaBaer lab is involved in a quest for biomarkers that detect early disease and distinguish benign breast disease from invasive cancers to guide patient and doctor decisions. LaBaer is an expert in a burgeoning field that strives to understand the global role of protein function, called proteomics, that plays a powerful and relevant role in the discovery of biomarkers -- unique molecular fingerprints of disease -- that is part of a large scale Biodesign Institute effort to identify biosignatures that can provide early warning for those at risk of major illnesses, including cancer and diabetes.

To develop new biomarkers for the early detection of breast cancer, LaBaer's team explored the intersection between cancer and our bodies' primary defense mechanism against invaders, the immune system. Previous studies have shown that proteins produced by cancers can trigger the body to produce antibodies that are not found in healthy individuals. These "autoantibodies" can be measured in the blood and used to betray the presence of a hidden cancer.

The challenge faced by researchers is to determine which antibodies among millions are specific for breast cancer.To accomplish this, the team used a novel protein microarray technology, called Nucleic Acid Protein Programmable Array (NAPPA), which was invented in LaBaer's Harvard Institute of Proteomics lab in 2004.

Protein microarrays display thousands of different candidate proteins lined up in rows and columns on a single microscopic slide. A tiny drop of blood was added to the microarray to look for proteins that are recognized by the antibodies from the cancer patients but not from the healthy women.

To narrow down the list of candidates, several successive screens were performed that compared the immune responses in women with early-stage breast cancer, those without cancer, and those with benign abnormalities in their breasts. The patients and controls were also matched for age and location.

Three phases of screens were performed, using increasingly rigorous statistical selection standards that narrowed down the number of potential biomarkers candidates from 5,000 to 761, which showed any measurable difference between healthy and disease populations, to 119, which showed a

clear statistical difference.Finally, these were then tested in a blinded study (where the researchers did not know which samples were from breast cancer patients and which ones were from controls) to find the final 28 biomarkers. The group not only looked at how each individual biomarker fared during the screening, but also how the entire panel of biomarkers worked together.

This was the first time the group has utilized NAPPA technology to identify the parts of the immune response that are activated during cancer, and the first serum biomarker panel developed for the discrimination of benign breast disease from invasive breast cancers. The group was pleased to confirm that many of the candidate biomarkers have also been described as important in breast cancer tumor biology and pathology.

"We were surprised at how hard it is to find biomarkers like this," said LaBaer. "The changes are subtle and rare, which is a real warning shot to those investigating breast cancer research. The key is a team approach that combines many different types of scientific expertise to tackle the problem."

In addition, LaBaer's team has a broad interest in identifying autoantibody biomarkers in patients that can be readily used for the detection of many other cancers, such as ovarian cancer, prostate cancer, and lung cancer as well as autoimmune diseases such as diabetes and arthritis.

Samples used in these analyses were obtained from Fox Chase Cancer Center (FCCC), the Duke University Medical Center (DUMC), and the Dana-Farber Cancer Institute (DFCI) with support from the National Cancer Institute (NCI) Early Detection Research Network and the NCI Breast SPORE program. LaBaer's research is supported by grants from the NCI branch of the National Institutes of Health and a $35 million philanthropic gift from the Virginia G. Piper Charitable Trust.

Karen S. Anderson, Sahar Sibani, Garrick Wallstrom, Ji Qiu, Eliseo A. Mendoza, Jacob Raphael, Eugenie Hainsworth, Wagner R. Montor, Jessica Wong, Jin G. Park, Naa Lokko, Tanya Logvinenko, Niroshan Ramachandran, Andrew K. Godwin, Jeffrey Marks, Paul Engstrom, Joshua LaBaer. Protein Microarray Signature of Autoantibody Biomarkers for the Early Detection of Breast Cancer. Journal of Proteome Research, 2010; : 101123131642093 DOI: 10.1021/pr100686b