New biomarker method could increase the number of diagnostic tests for cancer

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A team of researchers, including several from UCSF, has demonstrated that a new method for detecting and quantifying protein biomarkers in body fluids may ultimately make it possible to screen multiple biomarkers in hundreds of patient samples, thus ensuring that only the strongest biomarker candidates will advance down the development pipeline. The researchers have developed a method to increase accuracy in detecting real cancer biomarkers that is highly reproducible across laboratories and a variety of instruments so that cancer can be detected in its earliest stages.

The results of the Clinical Proteomic Technology Assessment for Cancer (CPTAC) study, which is sponsored by the National Cancer Institute (NCI) appear online June 28, 2009, in Nature Biotechnology.

From UCSF, the co-authors include Susan J. Fisher, PhD, a professor in the Department of Obstetrics, Gynecology & Reproductive Sciences and Faculty Director of the Sandler-Moore Mass Spectrometry (SMMS) Core Facility; Simon Allen, PhD, an Assistant Researcher in Department of Obstetrics, Gynecology & Reproductive Sciences; Steven C. Hall, a professor in the Department of Obstetrics, Gynecology & Reproductive Sciences and Director of Operations of the SMMS Core Facility; Eric B. Johansen, PhD, Laboratory Manager of the SMMS Core Facility; and Richard K. Niles, PhD, Bioinformaticist in the SMMS Core Facility. Co-authors from the Buck Institute for Age Research who are a part of the UCSF CPTAC team include Bradford Gibson, PhD, Professor and Director of the Chemistry Core; Michael P. Cusack, Intern; Jason M.

Held, PhD, Postdoctoral Fellow' and Birgit Schilling, Staff Scientist. Drs Fisher and Gibson and Joe Gray (Lawrence Berkeley National Laboratory) are Co-PIs of the UCSF portion of the CPTAC.

"These findings are significant because they provide a potential solution for eliminating one of the major hurdles in validating protein biomarkers for clinical use. Thousands of cancer biomarkers are discovered every day, but only a handful ever makes it through clinical validation. This is a critical roadblock because biomarkers have the potential to allow doctors to detect cancer in the earliest stages, when treatment provides the greatest chances of survival," said John E. Niederhuber, M.D., NCI director. "The critical limiting factor to date in validating biomarkers for clinical use has been the lack of standardized technologies and methodologies in the biomarker discovery and validation process, and this research may solve that dilemma."

The collaborative and multi-institute nature of this work was critical because many other technologies have yielded test results that vary greatly from one laboratory to the next. The Clinical Proteomic Technologies for Cancer (CPTC) program was established to help solve this problem. The five institutes that participated in this research as part of the NCI-sponsored CPTAC include the Broad Institute of the Massachusetts Institute of Technology and Harvard, Cambridge, Mass.; Vanderbilt-Ingram Cancer Center, Nashville, Tenn.; University of California, San Francisco; Purdue University, West Lafayette, Ind., and Memorial Sloan-Kettering Cancer Center, New York City.

Proteomics studies interactions between proteins, which often work in a tag-team fashion to send important signals within a cell. Most proteomic technologies have been based on mass spectrometry, a decades-old technology that determines which proteins are in a specimen based on the mass and electric charge of fragments of each protein.

The current biomarker discovery process typically identifies hundreds of candidate biomarkers in each study using small numbers of samples, leading to very high rate of invalid biomarkers. The biomarkers that are actually valid -- that is, true biomarkers -- must be culled from lengthy lists of candidates, a time-consuming and not always accurate process.

The CPTAC center network study demonstrates that new applications of existing proteomic techniques show promise of greater accuracy. The findings suggest that two technologies -- multiple reaction monitoring (MRM) coupled with stable isotope dilution mass spectrometry (SID-MS), which is a technique used by protein scientists to measure the abundance of a particular protein in a sample -- may be suitable for use in preclinical studies to rapidly screen large numbers of candidate protein biomarkers in the hundreds of patient samples necessary for verification.

MRM provides a rapid way to determine whether a candidate biomarker is detectable in blood. This is critically important for clinical use, as well as in being able to assess whether changes in a candidate biomarker correspond with the presence or stage of a disease. A sophisticated type of mass spectrometry, MRM is designed for obtaining the maximum sensitivity for quantifying target compounds in patient samples.

"Our work demonstrates that this technology has the potential to transform how candidate protein biomarkers are evaluated. SID-MRM-MS, combined with complementary techniques, could provide the critical filter to assess protein candidate performance without the immediate need for other detection or quantification tests. This would provide the critical missing component for a systematic biomarker pipeline that bridges discovery and clinical validation," said senior author Steven Carr, Ph.D., director of the Proteomics Platform at the Broad Institute. "This is an important step forward for the field of proteomics, one that would not have been possible without the

collaborative efforts of the CPTAC partners."

In this study, the researchers demonstrated that MRM is highly sensitive and specific, important characteristics that ensure the detection of real disease-specific biomarkers. In addition, using common samples and standardized protocols, they found that MRM is highly reproducible across laboratories and technology platforms. Clinical Proteomic Technologies for Cancer will make common samples and standardized protocols available through its reagents data portal, which can be accessed at http://proteomics.cancer.gov.

More information: Addona T, Abbatiello SE, et al. A multi-site assessment of precision and reproducibility of multiple reaction monitoring-based measurements by the NCI-CPTAC Network: toward quantitative protein biomarker verification in human plasma. Online June 28, 2009, *Nature Biotechnology*.

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