Major cancer study aims to identify protein markers for early-stage disease

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A team led by Bay Area scientists is one of five nationwide to receive a major grant from the National Cancer Institute (NCI) to refine and standardize the technologies for identifying biomarkers in the blood -- specific proteins, and the patterns they make -- for the early detection of cancer.

The grants, which signal the NCI's strategic shift toward studies aimed at early detection of cancer, are designed to lead to the discovery of many such biomarkers, the scientists say.

The grants have been issued under the NCI's Clinical Proteomic Technology Assessment for Cancer program, part of its five-year Clinical Proteomic Technologies Initiative for Cancer.

The team is directed by Susan Fisher, PhD, UCSF professor of cell and tissue biology, director of the UCSF Biomolecular Resource Center Mass Spectrometry Facility, a member of the UCSF Comprehensive Cancer Center and a visiting scientist in Berkeley Lab's Life Sciences Division.

Co-principal investigators are Joe W. Gray, PhD, associate laboratory director for life and environmental sciences at the Department of Energy's Lawrence Berkeley National Laboratory, UCSF professor of laboratory medicine, and co-leader of the breast oncology program at the UCSF Comprehensive Cancer Center, and Bradford W. Gibson, PhD, a professor and director of chemistry at the Buck Institute for Age

Research and UCSF adjunct professor of pharmaceutical chemistry.

The team also includes key co-investigators at California Pacific Medical Center in San Francisco, M. D. Anderson Cancer Center in Houston, and University of British Columbia in Vancouver.

The team will work to establish the best method for conducting mass spectrometry in the context of cancer biomarker discovery. Mass spectrometry is a technique used to detect and measure the precise molecular weight of proteins. A critical second step will involve consolidating the data and analyzing it, with the goal of piecing together the fragments of proteins identified in the research into recognizable molecules, and identifying patterns of proteins within given blood samples.

The need to standardize mass spectrometry is great. Currently, the technology produces varying results in different labs. Research in one lab may suggest certain proteins are associated with a given blood sample, while research in another lab may point to other proteins.

The capacity to detect proteins in fluids is of intense interest to cancer researchers because cancerous tumors "leak" proteins and other molecules into blood, urine and other accessible bodily fluids early on in their development.

This knowledge is already being applied in the clinic: Elevated levels of prostate specific antigen (PSA) hint at the presence of prostate cancer, while elevated levels of cancer antigen 125 (CA-125) suggest possible cancer of the ovary or other organs. However, both tests have "false negatives" or "false positives," making them unreliable.

If mass spectrometry can be refined and standardized, scientists say, it could revolutionize the detection of cancer and lead to earlier

interventions with current therapies -- surgery, radiation, chemotherapy and targeted drug therapy. The technique could also be used to monitor a cancer's response to treatment and to detect the recurrence of cancer after treatment.

"This is an extraordinarily exciting endeavor," says Fisher.

"We truly believe in this project, and that it is going to help people. We think that the methods we're proposing will work."

The UCSF component of this research initiative will be carried out in two phases. Initially, scientists will study blood samples from mice that have been transplanted with human breast cancer cells. Later they will study blood samples from patients with various stages of the actual disease.

The researchers will focus specifically on a phase in protein development known as "post-translational modifications," which occur after the code for a gene has been translated into a protein. Initially, the protein is a "naked scaffold," says Fisher, but over time it becomes decorated, much like a Christmas tree. This is the stage of "modification."

It is known, says Fisher, that cancer cells decorate proteins very sloppily. "We want to use this knowledge against cancer cells," she says, "working to purify these poorly decorated proteins so that we can identify them as biomarkers in blood samples."

Analyzing the complex data produced by mass spectrometry using advanced computing techniques – a science known as bioinformatics -- will be critical for making sense of the information, says Fisher. Part of the challenge will be the need to piece together data on fragments of individual proteins, rather than whole molecules, a result of a limitation

of mass spectrometry:

The instrumentation is not able to weigh an entire protein. The protein must first be cut, with an enzyme, into pieces. Once enough pieces of the puzzle are inputted into the database, it is expected that order will appear. The result could be the identification of biomarkers associated with early-stage cancer of the breast.

Source: University of California - San Francisco