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## Questions and Answers: Proteomics and Cancer

### Key Points

- Proteomics is the study of the proteins in a cell, tissue or organism. (Question 1)
- Only a small percentage of the thousands of proteins in human cells have been sequenced or identified. (Question 2)
- Proteomics technology is being explored for potential use in cancer diagnosis and treatment. This research involves searching for proteins that may serve as biomarkers of early disease, responsiveness to therapy, or the likelihood of relapse after treatment. (Question 3)
- A high priority of current research efforts is the application of proteomics technology to improving patient care. (Questions 4 and 5)
- There is no validated proteomic technology currently available for the clinic. (Questions 6 and 8)

### 1. What is proteomics?

The term 'proteome' was first coined in 1994, and refers to all the proteins in a cell, tissue, or organism. Proteomics refers to the study of the proteome. Because proteins are involved in almost all biological activities, the proteome is a rich source of biological information.

Protein scientists have diverse interests. These include determining the function and amino acid sequence of proteins; their three-dimensional structure; how the addition of sugar, phosphate, or fat affects protein function; and how proteins interact with other molecules, including other proteins. Some researchers are focused on the proteins present in particular parts of the cell such as the outer cell membrane, the nucleus, the cytoplasm (the region of the cell outside the nucleus), or the nuclear membrane; others are analyzing protein-protein interactions in a particular cell or organism; some are studying the differences between the proteins present in diseased vs. healthy cells (1).

### 2. How does studying the proteome compare to studying the genome? What are some of the challenges in proteomics research?

The total number of proteins in human cells is estimated to be between 250 to 500 thousand, and only a small percentage have been sequenced or identified. The complete proteome has not been characterized for any organism. In contrast, the genome or the entire set of genes for several organisms has been sequenced, including humans. The human genome is estimated to contain about 35,000 protein-encoding genes (<http://www.genome.gov/10002192>).

Besides the difference in quantity, another important difference between the genome and proteome is that the genome is static and relatively unchanged from day to day. Cellular proteins, on the other hand, are continually moving and undergoing changes such as binding to a cell membrane, partnering with other proteins, gaining or losing a chemical group such as a sugar, fat, or phosphate, or breaking into two or more pieces. Proteins play a central role in the complex communication network within and between cells and are constantly responding to the needs of the organism.

Several other properties of proteins add to their complexity:

- Proteins and/or modified proteins may vary among individuals, between cell types, and even within the same cell under different stimuli or different disease-states.
- One gene can produce more than one protein and one protein can be modified in multiple ways, which may change its behavior. This can happen when the cell uses a single gene DNA template to produce several different messenger RNAs, which are then used as templates to make different proteins, or it may happen when a protein is modified by cellular processes after it is created. The result is that instead of one gene producing one protein, one gene can produce as many as 1,000 different proteins. On average, however, a gene produces five to ten different proteins from its messenger RNAs (2).
- The quantity of different proteins can vary greatly. For example, in human blood, the concentration of the protein albumin is more than a billion times greater than another protein, interleukin-6.
- There is no laboratory amplification technique for proteins like there is for amplifying genes. This means that it is not possible to make copies of proteins that are present in very small amounts.

### 3. What are the approaches used in the development of clinical proteomics?

The goal of clinical proteomics is to develop proteomics technology for the benefit of patient care. This new research technology is now being used in clinical research studies ranging from cancer to cardiovascular disease and organ transplants (3). Researchers are searching for proteins that can be used as early biomarkers of disease, or that may predict response to therapy or the likelihood of relapse after treatment in blood, urine, or diseased tissue. (4, 5).

#### **Ovarian Cancer**

Ovarian cancer is a major focus of early biomarker discovery because it is usually diagnosed at an advanced stage with a five-year survival rate of about 20 percent. To evaluate the potential use of proteomics as a diagnostic tool, a group of researchers from the National Cancer Institute (NCI) in Bethesda, Md., collected serum from 50 ovarian cancer patients and 50 controls and used a computer algorithm to search for the protein patterns that distinguished cancer from non-cancer. When they tested this pattern with a set of blinded serum samples, the test pattern correctly identified all 50 patients with cancer, and was able to discriminate them from 63 out of 66 patients who were unaffected or had benign disease (6). Using the same approach, two other groups reported similar results (5,6).

#### **Prostate cancer**

A similar proteomic analysis of prostate cancer patients vs. healthy controls was carried out by looking for differences in protein patterns between the two groups. Using blood samples from 167 prostate cancer patients, 77 patients with benign prostate hyperplasia and 82 healthy men, the computer was able to develop a classification system that correctly classified 96 percent of the samples as either prostate cancer or non-cancer (benign prostate hyperplasia/healthy men) (9). Another proteomic approach is to determine whether the changes in specific phosphoproteins

(proteins with phosphate groups attached) believed to be important in cellular signaling events and cancer progression in prostate cancer patients can serve as a biomarker of early disease (10).

### **Breast Cancer**

A combination of three candidate proteins in the blood were found to be useful in discriminating between 169 patients at various stages of breast cancer compared to women with benign breast disease and healthy controls (11). In three other studies, nipple aspirate fluid was used to identify tumor marker candidates (12-14). Nipple aspirate fluid has a higher concentration of breast specific proteins than blood. Mammary ducts are thin tubes that lead to the nipples and are where 70 percent to 80 percent of breast cancers originate.

### **Lung and Bladder**

Several laboratories have successfully analyzed tumor tissue from patients with lung and bladder cancer and discovered protein patterns that could discriminate diseased from healthy tissue (15). Likewise, preliminary results using a proteomic approach to detect bladder cancer have been promising (16).

### **Future Use**

At this point, none of the above described proteomics analyses is mature enough to be used in the clinic as a screening tool. However, these exploratory studies point to the promise of proteomics as a diagnostic marker (See Question 5). Validation in clinical trials in large groups of patients is necessary before proteomics patterns can be used routinely in the clinic as biomarkers for early disease.

#### **4. What proteomics studies are underway at NCI?**

The former NCI-Food and Drug Administration (FDA) Proteomics Program was launched in 1997 under the leadership of Lance Liotta, M.D., Ph.D., formerly of NCI's Center for Cancer Research, and Emanuel Petricoin, Ph.D., formerly of FDA's Center for Biologics Evaluation and Research (CBER).

The general strategy of the proteomics program was to extract proteins from blood or tissue, analyze them with mass spectrometry to create patterns of protein fragments, sort through the patterns with an artificial intelligence computer program in order to discover differences that distinguish, for example, cancer patients vs. healthy controls, or patients who respond to therapy vs. those or who do not respond.

A high priority of the program was to develop research discoveries so that they could be tested in clinical trials and ultimately applied to patient care. The potential benefits to patients might include:

- Diagnosing cancer earlier than was possible;
- Improving the understanding of tumors at the protein level, leading to better treatments.
- Developing individualized therapies for each patient; and
- Determining the toxic and beneficial effects of treatments before administering them to patients.

### **Blood Test for Ovarian Cancer**

Liotta, Petricoin, and their colleagues invented or refined several key technologies used in proteomic analysis and in the process identified hundreds of proteins in breast, ovary, prostate, and esophagus tissue that change in amount as the cells in these tissues grow abnormally. In 2002, they discovered

patterns of proteins found in the blood of ovarian cancer patients that may be useful as an early biomarker of disease (6). Using the patient's blood and an analysis that can be completed in 30 minutes, researchers were able to differentiate between serum samples taken from patients with ovarian cancer and those from unaffected individuals.

### **Artificial Intelligence**

The discovery of protein patterns that distinguished ovarian cancers patients from those without disease relied on a sophisticated artificial intelligence computer program developed by Correlogic Systems, Inc., Bethesda, Md. Scientists were able to "train" the computer to identify a pattern of only a handful of small proteins from thousands of candidates found in the blood that could distinguish cancer patients vs. control samples. Once these patterns were found, they were tested on other blinded samples from patients with and without cancer. Fifty out of 50 cancers and 63 of 66 non-cancer samples were correctly identified. These results suggested that proteomic technology may help clinicians diagnose the disease much earlier than current methods.

### **Improvements in Blood Test**

A 2002 Lancet paper (6) reported that the proteomic test performed with 100 percent sensitivity and 95 percent specificity for that set of serum samples. Sensitivity measures the proportion of people with the disease who test positive; specificity measures the proportion of the people without the disease who test negative. A specificity of 95 percent means that 5 percent of those who did not have cancer would test positive, which is far too high a false-positive rate for commercial use.

In another study, which involved a larger group of ovarian cancer patients and controls, the scientists tested archived blood samples with a higher resolution instrument and a different protein pattern compared to the 2002 paper (17, 18). Despite the report of nearly 100 percent sensitivity and specificity, in this study, validation in a very large clinical group is needed before a commercial test for this technique can become available.

### **Discovering New Proteins**

Although it is not necessary, in theory, to know the identity of the proteins that may detect early disease or response to treatment, many of these proteins have now been identified and are leading to an understanding of the molecular pathways involved in disease. For more information, please go to: <http://bpps.nci.nih.gov><sup>1</sup>

### **Other Cancers**

In addition to ovarian cancer, similar techniques are being applied to other cancers. Researchers are looking for protein patterns in the blood that are diagnostic for early stage prostate and breast cancers, as well as patterns that can predict risk for prostate, melanoma, and pancreatic cancers (19,20).

### **Proteins in Tissues**

In addition to analyzing proteins in the blood, another thrust of proteomics research is to compare the proteins in tumor tissue vs. healthy tissue. Using this approach, researchers are probing tissues for phosphorylated proteins known to be important in carcinogenesis and are looking for useful diagnostic patterns. The work is yielding new insights about molecular pathways that are altered in cancer progression (21).

## Role of Albumin

The NCI-FDA team also discovered that the low-molecular proteins, useful for early detection of ovarian cancer, accumulate in the blood carried by larger proteins such as albumin. This piggy-backing ensures the smaller proteins a longer life in the circulating blood (22, 23, 24). Knowing this, scientists can obtain a greater concentration of potential biomarker proteins by isolating the carrier protein fraction from albumin. Some groups are working to create a synthetic carrier protein that could be used to standardize diagnostic protein patterns.

## Refining the Technology

Experts are continuing to test alternative mass spectrometry platforms and computer algorithms that they hope will yield clinically useful patterns (25).

### 5. Are there any ongoing clinical trials using proteomics as a diagnostic test?

A NCI-sponsored ovarian cancer clinical trial, involving ten sites, is scheduled to start in Fall 2005. Because over 80 percent of advanced stage epithelial ovarian cancer patients see their cancer return after being treated with standard chemotherapy, biomarkers are needed for predictors of persistent disease and relapse. CA-125, the only FDA-approved ovarian cancer relapse marker, will become elevated in some, but not all, of the approximately 80 percent of advanced stage patients for whom it was increased at initial diagnosis. Elevation in CA-125 may precede clinical evidence of relapse by as much as six to 10 months or lag behind clinical relapse by the same time intervals, making it a less than satisfactory clinical tool.

Researchers have identified a protein signature pattern that sensitively and specifically recognizes the presence of ovarian cancer (stages I-IV) in blood from affected women. Furthermore, the pattern can distinguish between affected women and unaffected women and those with the presence of non-malignant disease. Investigators hypothesize that significant changes in proteomic signature patterns can be defined and that these will be reliably predictive of relapse. Further, they hypothesize that the protein signature pattern changes will be as good as or better than CA125 as a single marker alone or in combination with CA125 monitoring. A serum repository of samples from women with ovarian cancer will be created in order to develop and validate the multiple biomarkers and proteomics tests being created for ovarian cancer recurrence and screening.

The purpose of this trial is to determine sensitivity and specificity for detection of cancer in patients who are in remission for their disease. This study is an expansion of efforts that were initiated in 2000 by Elise Kohn, M.D., NCI, with the "Pilot Study of Proteomic Evaluation of Epithelial Ovarian Cancer Patients in First Clinical Remission: Development of a Protein Fingerprint Profile Associated With Relapse, NCI 00-C-0018." The earlier study enrolled about 25 patients towards a ceiling of 40. Research results are not available to date because the proteomics work will begin when researchers have an adequate number of samples to create a training set.

For more details, visit:

(<http://clinicaltrials.gov/ct/gui/search?term=proteomics&submit=Search>)

### 6. What are some of the technologies used in proteomics research?

Traditionally, proteomics experiments have been done using two-dimensional gel electrophoresis (2DE), a process by which large mixtures of proteins are separated by electrical charge and size. In the first dimension, the proteins migrate through a gel-like substance until they are separated by their charge; for the second dimension, they are transferred to a second semi-solid gel and are separated by size. The advantage of this method is that a large number (3,000 to 10,000) proteins can be visually

separated. The drawback is that certain kinds of proteins such as membrane proteins, proteins present in very small amounts, or very large or very small proteins are difficult or impossible to visualize by 2DE.

In the last ten years or so, mass spectrometry (MS) has increasingly become the method of choice for analyses of complex protein samples. Mass spectrometry is a technique that measures two properties: the mass-to-charge ratio ( $m/z$ ) of a mixture of ions (particles with an electric charge) in the gas phase under vacuum; and the number of ions present at each  $m/z$  value. The end product is a mass spectrum or chart with a series of spiked peaks, each representing the ion or charged protein fragment present in a given sample. The height of the peak is related to the abundance of the protein fragment. The size of the peaks and the distance between them are a fingerprint of the sample and provide a clue to its identity (26).

The mass spectrometer consists of an ionization source, a mass analyzer, and a detector:

- The ionization source ionizes the proteins or protein fragments present in the sample. Ionizing means removing electrons from protein fragments resulting in positively charged particles.
- The mass analyzer measures the mass-to-charge ratio of the ionized protein fragments in the sample
- The detector registers the number of ions at each  $m/z$  value. The end product is a mass spectrum described in the previous paragraph.

### **Ionization Sources**

Two ionization techniques, MALDI and ESI, have had a major impact on protein biochemistry because they are able to produce ions in the gas phase without fragmenting the proteins too extensively, a problem with older methods. MALDI (Matrix-assisted laser desorption ionization) produces ions by sublimating (transforming a solid to a gas) and ionizing the proteins out of a dry, crystalline stage. ESI (electrospray ionization) ionizes the protein mixtures out of a liquid. MALDI is normally used to analyze relatively simple peptide mixtures while ESI is preferred for more complex samples. However, a variant of MALDI, where the surface of the MALDI target has been modified, is used with more complex mixtures. Known as surface-enhanced laser-desorption ionization (SELDI) MS, this technique is widely used in cancer proteomics. Only a small fraction of protein fragments in the sample bind to the SELDI surface because they have an affinity for the substances on the surface (26).

### **Mass Analyzer and Detector**

Once the ions are produced, the mass analyzer/detector separates them by the mass-to-charge ratio and produces a mass spectrum, or a series of spiked peaks, which are used to identify the proteins. The mass of the protein peaks increases from left to right; the height of each peak is proportional to the number of ions at that particular mass-to-charge ratio. Four types of mass analyzers are commonly used: ion trap, time of flight (TOF), quadrupole, and Fourier transform ion cyclotron (FT-MS)(26).

### **Ionizers, Analyzers, and Detectors**

The ionization method, MALDI, is commonly coupled to TOF mass analyzers, while ESI is most often coupled to ion-trap or quadrupole spectrometers. Most serum protein mass spectrum data have been generated by using the Ciphergen Biosystems (Fremont, Calif.) ProteinChip array surface-enhanced laser-desorption ionization-time-of-flight (SELDI-TOF) MS system. In this system, specific substances are applied to the surface of the SELDI chip array to capture peptides in the sample. Once captured, the proteins are detected by TOF MS.

Examples of commercially available statistical tools used to analyze mass spectra are: PROTEOME QUEST (Correlogic Systems, Bethesda, Md.); PROPEAK (3Z Informatics, Mount Pleasant, S.C.); BAMF (Eclipse Diagnostics, Vacaville, Calif); and Biomarker Wizard (CIPHERGEN Biosystems, Fremont, Calif).

#### 7. What are some of the advantages of using mass spectrometry techniques in clinical research?

The great advantage of mass spectrometry (MS) over other technologies for detecting and monitoring subtle changes in substances in the body is the ability to measure rapidly and inexpensively thousands of elements in a few drops of blood. Unlike 2DE, MS patterns generated from the thousands of proteins present in blood are difficult to analyze visually. However, the powerful computational ability of today's computers makes it possible to analyze MS spectra rapidly and distinguish subtle differences in patterns between diseased and healthy people.

Mass spectrometry-based proteomics analysis is extremely rapid. The entire process, from collecting blood to analyzing the MS spectrum, can occur in less than one minute. In addition, hundreds of samples can be analyzed sequentially, and extremely small amounts of protein can be detected.

#### 8. What are some of the challenges to proteomics research?

Proteomics data are being collected at a faster pace than the ability of the researchers to validate, interpret, and integrate them with other known data. There is a great need to make data portable and comparable. Software tools are needed in all areas of data analysis, including data collection, storage, searching, analysis, classification, management, archiving, and retrieval.

In June 2005, NCI's Board of Scientific Advisors (BSA) approved a Clinical Proteomics Technologies Initiative, a \$104 million program aimed at optimizing current proteomics technologies and developing new technologies, reagents, and systems to significantly advance the field of cancer proteomics research. This initiative is not specific to the National Institutes of Health Bethesda campus, which housed the program in which Petricoin and Liotta worked and Kohn currently works. Rather, it is open to the broad cancer research community. The initiative builds on a 2-year process that sought feedback from the research community through workshops and meetings.

The initiative encompasses a three-pronged strategy:

- Establishment of Clinical Proteomic Technology Assessment Consortia, which will be comprised of multidisciplinary teams from different institutions focused on evaluating tools, such as proteomic technologies and reference reagents; developing protocols and performing cross-laboratory studies of common sample sets; and also providing consultative services and training to the community.
- Support of research into overcoming barriers to protein/peptide feature detection, identification, and quantification; and development of mathematical, computational, and predictive approaches for analysis of large scale data.
- Creation of a virtual, centralized clinical proteomics reagents resource, which will include resources such as antibodies, peptides, and proteins.

In the future, scientists expect that by combining both the genomic and proteomic data, they will be able to create a mathematical model of the molecular pathways in cells. With these models, researchers will be able to predict previously unknown interactions and verify the predictions experimentally. Novel proteins, cellular functions, and pathways will also be discovered. It is hoped that understanding the connections between cellular pathways will greatly reduce the suffering and loss of life due to cancer.

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## Related Resources

Because the proteome is constantly changing, standardizing the conditions of proteomic analyses is a very important, and is necessary for comparisons between investigators. The Human Proteome Organization (HUPO: [www.HUPO.org](http://www.HUPO.org) <sup>2</sup>), along with the Plasma Proteome Project (<http://www.plasmaproteome.org/>), have been formed to address this issue, as well to promote new research.

## NCI Resources

NCI-FDA Clinical Proteomics Program Web site:  
<http://www.ncifdaproteomics.com>.

To visit NCI's Web site:  
<http://www.cancer.gov>

For information about research currently supported by NCI:  
<http://researchportfolio.cancer.gov/>

For information about clinical trials:  
<http://www.clinicaltrials.gov>

For general information:  
**Cancer Information Service:** 1-800-4-CANCER (1-800-422-6237)

## Table of Links

1 <http://bpp.nci.nih.gov>

2 <http://www.HUPO.org>