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OncoLog

Proteomics May One Day Revolutionize Cancer Detection, Staging, and Prognosis

by Katie Prout Matias

Many cancers progress silently, not making themselves known until they reach an advanced stage. For example, in 75% of women with ovarian cancer, the disease has already advanced beyond the earliest and most treatable stages by the time it is diagnosed. The five-year survival rates of patients with ovarian cancer who were diagnosed early and those diagnosed later—90% versus 35%, respectively—underscore the need for an effective early detection method.

(*Continued on* **next page**)

Dr. Gordon Mills, *a professor in the Department of Molecular Therapeutics, and his colleagues have identified protein biomarkers in ovarian and breast cancers that may one day be used in screening blood tests.*

THE UNIVERSITY OF TEXAS
MD ANDERSON
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Proteomics May Revolutionize Cancer Detection, Staging, and Prognosis

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But what if a simple finger prick could be used to detect ovarian cancer, as well as every other kind of cancer? The beginnings of what could become a revolution in cancer screening can be seen in studies like those being performed at The University of Texas M. D. Anderson Cancer Center in which researchers have been able to detect cancer by the presence of patterns of abnormal proteins in the blood.

According to Gordon Mills, M.D., Ph.D., a professor in the Department of Molecular Therapeutics at M. D. Anderson, every tumor comes into contact with the bloodstream, so it should be possible to detect in a person's blood the proteins produced by the tumor as well as the subtle changes in other proteins caused by the tumor cells.

A wealth of information lies hidden inside the proteome—a universe of proteins even more vast and fluid than the genome—and proteomic discoveries have the potential to affect the entire spectrum of cancer research and care.

At M. D. Anderson, researchers are studying the modifications, functions, and interactions of the estimated one and a half million proteins in the human body and are exploring how protein biomarkers and patterns might be used to detect, stage, and predict the outcomes of tumors, as well as to enhance drug efficacy and develop novel targeted therapies.

Detection

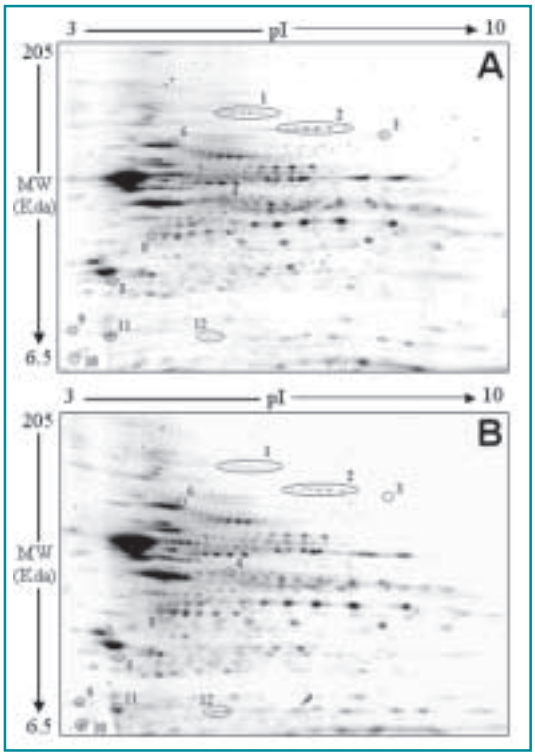
In a study of the early detection of ovarian cancer, Dr. Mills and researchers from the National Cancer Institute (NCI) and the Food and Drug Administration (FDA) compared protein patterns in the blood of patients with ovarian cancer with those in the blood of healthy volunteers. Using the abnormal protein patterns they found in the patients with cancer, the researchers developed a test that correctly identified all 50 cases of ovarian cancer in their study, including those in the earliest stages.

"The question that hasn't been resolved is how many different proteins one will have to look at," Dr. Mills said. In the ovarian cancer study, the investigators were able to identify the presence of cancer in most of the malignant cases by looking at just five proteins.

Preliminary research shows that there may be as many as ten protein biomarkers of breast cancer, said Dr. Mills, who collaborated with the same teams from the NCI and the FDA as well as with researchers from Duke University and M. D. Anderson to investigate protein markers in breast cancer. Dr. Mills said a blood test for these markers might one day be used in place of mammography or in cases where the mammographic results are in question.

Protein blood tests might also one day replace invasive screening techniques such as colonoscopy.

"Having the general population of the United States undergo colonoscopy—an invasive procedure that requires an anesthetic and has complications associated with that and, occasionally, with the procedure itself—for a disease that has a total prevalence in the population of about 6% is not a very satisfying situation," said Stanley Hamilton, M.D., professor and head of the Division of Pathology and Laboratory Medicine at M. D. Anderson. Dr. Hamilton is researching the use of proteomic serum screening to detect protein markers in colorectal cancer. People who have the protein markers would then undergo a colonoscopy, but those who did not could be spared the procedure.



Dr. Howard Gutstein, *an associate professor in the Department of Anesthesiology, is studying protein changes in brain cells that mediate opiate tolerance. Here, rat cells treated with morphine (panel B) show different protein expression levels than do control cells treated with saline (panel A).*

Staging and prognosis

Prostate cancer is the only cancer for which a blood protein screening test is already commonly used. But although the prostate-specific antigen (PSA) test is remarkably good at detecting prostate cancer, it is a very poor marker of prognosis, said Wadih Arap, M.D., Ph.D.

In a recent study, Dr. Arap and Renata Pasqualini, Ph.D., both professors of medicine and cancer biology in the Department of Genitourinary Medical Oncology, screened patients with prostate cancer for patterns of antibodies against a certain protein and found that high levels of the antibodies correlated with a poor prognosis as well as with advanced disease.

"The novel aspect of this work is that we're not looking at the expression of the gene or the protein but at how the body is responding to it by producing antibodies," said Dr. Pasqualini.

Using protein antibody production to determine whether a tumor is aggressive or likely to metastasize would allow clinicians to create tumor profiles and tailor therapy accordingly. In the case of prostate cancer, oncologists could decide to forgo a prostatectomy in cases where the disease is too advanced for the procedure to be curative, said Dr. Arap.

Dr. Renata Pasqualini *(left) and* **Dr. Wadih Arap**, *professors of medicine and cancer biology at M. D. Anderson, retrieve samples from a cell line bank stored in liquid nitrogen to use in an experiment. In a recent study, they found that high levels of antibodies against a certain protein correlated with a poor prognosis as well as with advanced disease in patients with prostate cancer.*

Drug efficacy

All too often, drugs given to patients with cancer do not perform as hoped in some patients or lose their effectiveness after some initial activity. By looking at what happens to proteins before, during, and after drug administration, researchers hope to understand how a drug works or why it does not work.

For example, Howard Gutstein, M.D., an associate professor in the Department of Anesthesiology at M. D. Anderson, is studying protein changes that occur in the cells that mediate opiate tolerance. "[Cancer pain] destroys whatever quality of life patients have, and opiates are the best drugs we have to treat that pain. They've been in use for thousands of years," Dr. Gutstein said. Knowing the mechanisms involved in opiate tolerance would allow researchers to selectively prevent tolerance to the analgesic effects of the drug but not to adverse effects such as depressed breathing, said Dr. Gutstein.

In the case of therapeutic drugs, clinicians could avoid giving unnecessary, toxic treatments if they knew beforehand whether the drug would work in a particular patient based upon his or her specific protein patterns.

"The goal is to find out if a patient has resistance to certain drugs or if chemotherapy will work. If we can find a marker before starting treatment, that would be helpful in preventing unnecessary treatments for certain patients," said Ryuji Kobayashi, Ph.D., a professor in the Department of Molecular Pathology and director of the Proteomics Program at M. D. Anderson. Dr. Kobayashi is researching biomarkers in pancreatic, breast, and ovarian cancers and in glioblastoma.

Monitoring a drug's effects on proteins during treatment could help clinicians determine if the right amount of the drug is getting to the tumor and even identify new therapies. Studying the drug's mechanism and the proteomic changes may reveal new molecular targets upstream or downstream of the intended target, said Dr. Hamilton.

Challenges ahead

The proteome dwarfs the genome in size and complexity. Because it took many years and people working around the clock to map the human genome, "trying to do a proteome project boggles the mind," said Dr. Gutstein, who pointed out that an estimated 10,000 to 15,000 proteins are expressed in every cell in the body and that the proteome differs in every cell type and between healthy and sick individuals.

Furthermore, proteins can be altered in many ways, and their multiple interactions with other proteins as well as with genes adds to the complexity of mapping the proteome. In fact, Drs. Arap and Pasqualini think it would be impossible to list all the proteins in the body. "The same protein may have 20,000 different forms," said Dr. Arap.

According to Dr. Kobayashi—who improved the in-gel digestion technique, which is now the standard technique used in proteomics, and proved the method several years before the term "proteomics" was born—continuing to develop extremely sensitive and high-throughput technologies that can analyze many proteins simultaneously will be the key to progress.

"The rapidly emerging technologies around proteomics have the potential to give us a much greater window on both normal and abnormal cellular function," Dr. Mills agreed. "That window will provide incredible data of what is happening in the cancer cells: What are the predisposing events? What are the early initiating events? What are the events that allow that cell to progress? Can the cell metastasize? The ability to start looking at things on a much more global basis is producing a level of excitement we have not had in the past." ●

FOR MORE INFORMATION, *contact Dr. Mills at (713) 792-4687, Dr. Hamilton at (713) 792-2040, Dr. Arap at (713) 792-3871, Dr. Pasqualini at (713) 792-3872, Dr. Gutstein at (713) 792-5037, or Dr. Kobayashi at (713) 745-3363.*

Depression in Patients with Cancer

by David Galloway

It is perfectly normal for someone with cancer to be sad, to cry, to grieve, and to be angry. Physicians expect these reactions to a cancer diagnosis or news of disease progression. But when such reactions persist, it should raise a red flag.

"There is no such thing as a 'rational' or 'understandable' major depression—ever," said Laura Sherman, M.D., an assistant professor in the Department of Neuro-Oncology, Section of Psychiatry, at The University of Texas M. D. Anderson Cancer Center. "Just because a depression might have been triggered by cancer does not mean that it should not be treated as a separate medical problem."

"It's like saying, 'I hit you on the head, so of course you have pain. You have a reason for your pain, so I'm not going to give you a Tylenol. If you didn't have a reason, I would treat it,'" Dr. Sherman said. "And that makes no sense."

Using the rigid criteria usually applied in psychiatry, the rate of depression in patients with cancer could be as low as 5%, said Michael J. Fisch, M.D., M.P.H., an assistant professor in the Department of Palliative Care and Rehabilitation Medicine at M. D. Anderson. The actual rate is between 15% and 25%, however, because diagnosing depression in patients with advanced cancer calls for a slightly different application of the criteria. "If you are used to doing office-based psychiatry, and you are not used to caring for people in the last few months of life, then you may have trouble applying what you know to those kinds of patients," Dr. Fisch said. The diagnosis can be complicated by the fact that some of the usual symptoms of depression can be mimicked or concealed by the effects of cancer and cancer therapy.

Debra Sivesind, *M.S.N., (standing) a clinical nurse specialist in the Department of Palliative Care and Rehabilitation Medicine, leads a guided imagery class at the Place… of wellness at M. D. Anderson. Guided imagery, a complementary therapy that can help some people relax and manage stress, is sometimes recommended for patients with depression.*

Some physicians are uncomfortable asking their patients about depression. "It's safe to ask about it," Dr. Fisch said, adding that asking opens the door for a patient to discuss the issue. The physician can then decide whether the severity of the symptoms expressed indicates a need for counseling or medication.

Still, it can be a challenge to get some patients to open up. A patient who is asked about feeling depressed or hopeless in the presence of his wife might fear that acknowledging such feelings would send the message that he had given up or that he didn't think his marriage and family were good enough reasons to strive to live longer. Another patient might think that an expression of hopelessness would make her oncologist decide aggressive treatment of her cancer was no longer worthwhile.

Symptoms of Major Depression

Depression is indicated if one or more of the following symptoms is present for at least two weeks:

- A depressed mood for most of the day and on most days
- Diminished pleasure or interest in most activities
- Significant change in appetite and sleep patterns
- Psychomotor agitation or slowing
- Fatigue
- Feelings of worthlessness or excessive, inappropriate guilt
- Poor concentration
- Recurrent thoughts of death or suicide

Source: National Cancer Institute

Is a Separate—and Treatable—Illness

To medicate or not to medicate

If the criteria for diagnosing depression in patients with cancer are unclear, the rules of thumb for deciding whether to prescribe antidepressants are even less firmly established.

"When to give medication? I think that every clinician might have a little different threshold," said Debra M. Sivesind, M.S.N., R.N., C.S., a clinical nurse specialist in the Department of Palliative Care and Rehabilitation Medicine at M. D. Anderson.

The types of medications used to treat depression in patients with cancer include selective serotonin reuptake inhibitors, tricyclic antidepressants, and to a limited extent, analeptic agents such as amphetamines.

Several factors should be considered when prescribing antidepressants to patients with cancer. First, the antidepressant treatment chosen should target the specific distressing symptoms the patient is experiencing. Also, any adverse effects of the medication should be minimized and should not worsen the patient's health or exacerbate any coexistent medical problems. Finally, the patient's other medications should be evaluated before antidepressant therapy is begun to avoid any potentially harmful drug interactions.

Many modes of treatment

Treating depression means more than writing a prescription, however. Studies have shown that the treatment of depression is optimized when medication is combined with psychotherapy or supportive counseling.

While Dr. Sherman calls herself a "better-living-through-chemistry person," she embraces all modalities of treatment. "If psychotherapy is going to be helpful, great. If going to a support group is up this person's alley, fabulous. Some people really like tai chi or hypnotism. There are many different avenues for treatment," she said.

Among the complementary therapies that can help some patients with depression is guided imagery, which

"If you are used to doing office-based psychiatry, and you are not used to caring for people in the last few months of life, then you may have trouble applying what you know to those kinds of patients."

– Michael J. Fisch, M.D., M.P.H., assistant professor, Department of Palliative Care and Rehabilitation Medicine

Sivesind teaches through M. D. Anderson's Place…*of wellness*. Guided imagery exercises stimulate the creation of positive mental images, which helps some patients manage stress and relax.

"Guided imagery can be used to stimulate all of the five senses," Sivesind said. "When I'm leading a group in guided imagery, I will ask them to imagine either a beach or the mountains, something that's comforting and relaxing for most people. So, in going to the beach, you can taste the salt air, you can feel the wind on your skin and the warmth of the breeze, you can feel the sand beneath your feet, you can hear the waves, you can see the clouds and sailboats."

Experiencing pleasant images does two things for the patients, Sivesind said. First, it gives them control over something. "In the midst of being out of control, their life getting absolutely turned upside down with cancer, this kind of exercise is a way to be in control," she said. Second, guided imagery can trigger the relaxation response, a state of deep rest that alters physical and emotional responses to stress. It brings about decreases in the heart rate, blood pressure, and muscle tension. "A relaxed body is a healthy body," Sivesind said. "A relaxed body is probably in a better place for healing, in a better place for the chemotherapy to work."

However, Sivesind cautions that guided imagery is not for everyone. "When people get relaxed, guess what? That is where our emotions live," she said. "Some people don't want to touch those emotions, but these exercises may be used to release emotions, which can be healing."

Different cancer, different depression

The symptoms of depression may vary according to the type of cancer a patient has. Patients with pancreatic cancer, for example, may show a blunted affect and pronounced anhedonia, a lack of interest or joy in things, Dr. Sherman said. In contrast, a woman with breast cancer may undergo a sudden chemotherapy-induced menopause that triggers a depression with marked emotional lability.

The incidence of depression also varies by cancer type. Depression accompanies breast cancer, certain gynecologic cancers, and head and neck cancers more frequently than other cancers. It is not yet known whether those associations result from the chemistry of the tumors themselves or from the chemotherapy regimens patients receive.

Depression does not always follow cancer. Sometimes, it precedes it. "In pancreas cancer, there's a pretty good

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Depression in Patients with Cancer

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"Some people will say you can't treat depression when a patient is dying. Yes, you can. You absolutely can."

– Laura Sherman, M.D., assistant professor, Department of Neuro-Oncology, Section of Psychiatry

wealth of data showing that many of these people, maybe up to 50%, have a prodromal depression that happens to them before they ever start having other physical symptoms," Dr. Sherman said. "About six months before, sometimes even longer, out of the blue, people who never had depression before suddenly have a full-blown major depression."

More than a mental problem

Depression not only subjects a patient to greater suffering in and of itself but also hinders cancer treatment, Dr. Fisch said. He cited a study by Musselman and colleagues (*New England Journal of Medicine*, March 29, 2001) that compared paroxetine with placebo in patients receiving high doses of interferon as adjuvant therapy for melanoma. "The people who got the antidepressant were not only less depressed but were more likely to stay on their therapy," Dr. Fisch said. "That is, depression interfered with cancer treatment."

Potentially even more important is the idea that some depression medications also help fight other cancer symptoms. Mirtazapine helps reduce nausea and weight loss, and Dr. Sherman is developing a protocol to evaluate its use in fighting cachexia in patients with pancreatic cancer.

Most important is that treating depression in patients with cancer might actually increase survival rates. Studies have shown that patients with untreated depression do poorly, but it is not clear whether that is a result of a lack of compliance or something else. Other studies have suggested a link between psychosocial interventions and survival. Dr. Sherman plans to look at the possibility of a survival benefit in her pancreatic cancer protocol.

No need to be miserable

The treatment of depression in dying patients is not a losing battle, Dr. Sherman said. "Some people will say you can't treat depression when a patient is dying," she said. "Yes, you can. You absolutely can." Fast-acting antidepressants such as paroxetine and citalopram can be administered in combination with psychostimulants such as methylphenidate to elevate a patient's mood within just a few days, Dr. Fisch said.

"There is nothing that says we have to absolutely be miserable as we die," Dr. Sherman said. "A lot of the people I've worked with feel almost fortunate in a way. They say, 'I know that I have this time to make up with people I've had arguments with, I have this time to be close to my family.' They focus on what is important in life. For some people, it's a very rich, rewarding experience. Just because they've got a terminal illness doesn't mean they can't enjoy life." ●

FOR MORE INFORMATION, *contact Dr. Sherman at (713) 792-7546, Dr. Fisch at (713) 792-3936, or Debra Sivesind at (713) 745-4556.*

Risk Factors for Depression in Patients with Cancer

Cancer-Related Risk Factors:

- Depression at time of cancer diagnosis
- Poorly controlled pain
- Advanced stage of cancer
- Additional concurrent life stressors
- Increased physical impairment or discomfort
- Pancreatic cancer
- Being unmarried and having head and neck cancer
- Treatment with certain chemotherapeutic agents, including the following:
  - Corticosteroids
  - Procarbazine
  - L-Asparaginase
  - Interferon-α
  - Interleukin-2
  - Amphotericin B

Risk Factors Not Due to Cancer:

- History of depression:
  - Two or more episodes in a lifetime
  - First episode early or late in life
- Lack of family support
- Family history of depression or suicide
- Previous suicide attempts
- History of alcoholism or drug abuse
- Concurrent illnesses that produce depressive symptoms (i.e., stroke or myocardial infarction)
- Past treatment for psychological problems

Source: National Cancer Institute

HOUSE•CALL

Facing Fatigue When You Have Cancer: What Can You Do?

Even a minor illness, like a cold, can drain a person's energy. So it's no wonder that the fatigue that accompanies cancer can sometimes be as debilitating as the disease itself. Patients with cancer often describe the way they feel as "completely exhausted" or "drained." They talk about being mentally "sluggish" and "easily distracted." Their fatigue, they say, occurs after the slightest exertion and is rarely relieved by rest. Fortunately, not everyone with cancer experiences this type of fatigue, and those who do can take steps to combat its effects.

What causes fatigue?

Cancer-related fatigue has many causes. One source is the disease itself; for example, tumors can produce toxic substances that interfere with normal body functions. Chemotherapy and radiation therapy can lead to nausea, dehydration, loss of appetite, difficulty breathing and sleeping, infection, anemia, pain, and changes in metabolism, all of which are potential sources of fatigue. Hypothyroidism, the decrease in physical activity that frequently follows a diagnosis of cancer, and medications for pain and depression may cause fatigue. Finally, the anxiety, stress, and depression that often accompany cancer and its treatment can result in fatigue.

How does fatigue take its toll?

People with cancer are affected by fatigue in many ways. For example, they may be too tired to perform daily tasks, to eat as they should, or to get to a clinic or hospital for treatment. Extreme fatigue may cause them to miss work or quit altogether, which can affect their insurance coverage and their finances. They may not have the energy to interact socially, causing them to withdraw from friends and family when they most need support.

What can be done to combat fatigue?

No magic pill exists to cure cancer-related fatigue. However, if you are coping with debilitating fatigue, there are things you can do to lessen the effects:

1 Communicate with your medical team and insist on getting help.

Some medications can help increase energy. Your doctors and other health-care professionals can treat the symptoms of fatigue and often the source, but first they must be aware of how you feel.

2 Take charge of your own well-being.

- If possible, exercise lightly. Light exercise such as walking can actually decrease fatigue. Exercise can also improve your appetite and self-esteem.
- Get plenty of sleep and rest. Take naps if you need to, but don't sleep so much during the day that you can't sleep at night.
- Eat as well as you possibly can. Eat several small meals a day if eating three large ones makes you uncomfortable. And drink lots of liquids.
- Be realistic about what you can do. Accept that you need to conserve your energy for what is most important. Prioritize your activities. Plan your day so that you are active when you have the most energy.
- Find ways to enjoy yourself and the company of your family and friends.
- Stay under your doctor's care after your treatment has ended.
- Try to stay positive, and remember that for most people, the fatigue does go away in time.
- Consider trying complementary therapies such as relaxation techniques, self-hypnosis, meditation, or yoga.

3 Accept the help of others.

Your family and friends no doubt want to help you and may not know how, so accept their offers to run errands and take care of whatever they can. Find out what your community offers in the way of transportation to and from treatments and appointments. And consider joining a support group; being with others who have similar issues can be helpful to you and to your loved ones. ●

Cancer-Related Fatigue Information Sources

- Fatigue Clinic at M. D. Anderson Cancer Center
  (713) 792-2340
  (*Patients must be referred by a physician.*)
- National Cancer Institute*
  (800) 422-6237 (Cancer Information Service)
  www.cancer.gov
- American Cancer Society*
  (800) 227-2345 (National Hotline)
  www.cancer.org
- National Comprehensive Cancer Network*
  (888) 909-6226
  www.nccn.org
- The Oncology Nursing Society
  www.cancersymptoms.org
- Cancer Care*
  www.cancercare.org

**Information also available in Spanish.*

For more information, contact your physician or contact the M. D. Anderson Information Line:

(800) 392-1611 *within the United States, or*

(713) 792-6161 *in Houston and outside the United States.*

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DiaLog

Proteomics: The Creation of a New Field of Study

Ryuji Kobayashi, Ph.D.
Professor, Department of Molecular Pathology
Director, Proteomics Program

Exactly 50 years after Watson and Crick reported their discovery of the structure of DNA, the Human Genome Project was completed. The project, which identified about 28,000 human genes, has had an enormous influence on the biological sciences. In the 1990s, scientists spent more time in the laboratory cloning new genes. Now, with genome sequencing and highly sensitive and high-throughput mass spectrometry techniques, scientists have more time for functional studies, including the study of proteomics.

The term "proteome" was coined less than ten years ago to describe the set of proteins encoded by the genome. Proteomics, the study of the proteome, started from the large-scale identification of proteins separated by two-dimensional gel electrophoresis. Proteomics now includes not only the analysis of all expressed proteins but also the traditional study of proteins, such as protein identification in complexes and functional studies related to protein structure.

M. D. Anderson Cancer Center's Proteomics Program, launched in the fall of 2001, is involved in many basic science and clinical research projects because of the state-of-the-art instrumentation and technology it offers. In the area of translational research, the program's focus is to discover new biomarkers for early diagnostic and drug sensitivity screening.

The availability of genome sequences brought about new technological developments in protein analysis, most notably mass spectrometry, which rapidly replaced the Edman degradation technique after nearly 50 years of dominance. Mass spectrometric methods match the masses of fragmented peptides with the calculated masses from fragments of proteins in the DNA-protein database. The use of mass spectrometry also merged the fields of protein chemistry, physics, chemistry, biomedical sciences, and clinical research. History teaches us that new insights and discoveries often arise from the interface of different fields of science.

Mass spectrometry is very sensitive, but techniques utilizing immune reactions are even more sensitive. Therefore, current goals in protein biomarker research are finding the markers in blood or body fluid using mass spectrometry, identifying the peptide or protein, and then making antibodies to validate the protein and to use for clinical testing. An alternative method is to obtain protein profiles or fingerprints by mass spectrometry, which statistical bioinformaticians can analyze to identify cancer-specific patterns.

We in the Proteomics Program begin our collaborations with clinicians by listening to their needs and explaining what we can do. Together, we develop research plans and any new technologies needed to put the plans into action. Through this and other team efforts at M. D. Anderson, we hope to one day be able to control cancer or eliminate it altogether.

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