Chemotherapy offers a standard treatment for many types of cancer. However, not everyone's cancer responds to the standard treatment. To better treat and understand these resistant cancers, a new science, morphoproteomics, is being developed and used by the Consultative Proteomics team at the Department of Pathology and Laboratory Medicine at McGovern Medical School at UTHealth.

Morphoproteomics examines the specific properties and biology of a cancer tumor that is not responding to treatment, allowing scientists to suggest alternative therapies specific to the tumor and patient.

Morphoproteomics were brought in to help Melissa Weiss, who was diagnosed with an extremely rare cancer. Healthy and active, 24-year old Melissa was used to going to the gym and teaching school in San Antonio. But in the summer of 2010, she suddenly began losing weight and experiencing pain in her knees. Her symptoms progressed over the next few months — losing hair, developing blood blisters and heart palpitations.

Her doctors in San Antonio were stumped. An internist suggested kidney problems; an endocrinologist said it was Cushing's syndrome. An MRI provided the correct answer — a tumor on her right adrenal gland and part of the right liver lobe.

Diagnosed with this extremely rare cancer, Melissa was referred to Houston to MD Anderson Cancer Center for care. Starting chemotherapy in March 2011, the cancer shrunk and was surgically removed in November 2011.
The cancer returned a few months later, this time on the left side of her liver and lung. And as it returned, it resisted the standard chemotherapy.

“We believe that tumors adapt over time to resist therapy, and that the tumor’s molecular profile suggests ways to control or stop that adaptation and the recurrence of the disease,” says Robert E. Brown, M.D., medical director of the Department of Pathology and Laboratory Medicine’s Consultative Proteomics, vice chair, and Harvey S. Rosenberg Chair in Pathology and Laboratory Medicine.

Using morphoproteomics, Dr. Brown and his team completed a rigorous analysis on a sample of Melissa’s tumor, which defined the tumor’s biology and its signature biologic pathways.

Based on the analysis, Dr. Brown recommended potential therapy agents to target some of the resistant pathways. With this detailed information about the tumor, Melissa's oncologist was able to construct a personalized therapeutic plan, effectively treating the cancer.

Five years later, Melissa is cancer free and has two children, Paislie, 2 (10/13), and August, 1 (11/15), with her husband, Dustin Engelke. “My oncologist told me he only had one patient who made it to 5 years – but I’m past 5 years and going strong!” Melissa says.

Thanks to the work of McGovern Medical School pathologists, Melissa may not be the only one who survives this milestone.

“As a result of the profiling of her different tumors, we were able to create a schematic that would be available and adaptable to many, many patients who have adrenocortical carcinoma,” explains Dr. Brown. “So, actually, Melissa Weiss should feel good not only because her tumor has subsided and she is apparently free of disease at this moment, but also because she's made a contribution to fellow patients who might be afflicted with the same type of tumor.”

Morphoproteomics also has been successful in two patients with a very rare cancer of the nasal cavity and sinuses. Referred to the Consultative Proteomics team by their oncologists, the pathologists thoroughly reviewed the tissues and recommended a targeted chemotherapy using a combination of drugs never before used in the treatment of these tumors.

The patients’ tumors responded to this new chemotherapy combination, and it has been identified as a new effective treatment for sinonasal undifferentiated carcinoma.

“Combined with our extensive research, expert analysis and optional genomic data, Consultative Proteomics reports guide the patient and physician to treatments supported by the underlying biological protein patterns in the tumor,” Dr. Brown says.
Did you ever see that movie, “The Fantastic Voyage?” In the 1960s sci-fi, a group of scientists shrinks down and goes exploring in a submarine through a human body. Take that concept one step further – what if scientists could explore the structures that comprise human cells? That is precisely what Dr. Jun Liu and his research team are doing with high-tech 3-D modeling – without the miniature submarine part. When you think of 3-D, you may think of plastic glasses and movie popcorn. But for Jun Liu, Ph.D., associate professor of pathology and laboratory medicine, 3-D brings to mind colorful cellular infrastructure and molecular machines – bringing micro-organisms to life.

Dr. Liu’s lab is focused on high-throughput cryo-electron tomography – which allows the creation of 3-D structures and functions of the molecular machines found in living cells, such as rotating flagella and viruses walking across a cell.

“A living cell can be viewed as a miniature factory that contains a large collection of dedicated molecular machines,” Dr. Liu explains. “These machines, optimized by billions of years of evolution, orchestrate nearly every major process in the cell.”

Cryo-electron microscopy has been hailed as the “research method of the year 2015” by Nature. By freezing specimens in their native state then viewing them under a special microscope, researchers are able to discern incredible details of molecules, even down to individual ions, and then map them to a 3-D structure. With support from the National Institutes of Health, school leadership, and pathology faculty, including James Stoops, Ph.D., McGovern Medical School has been using this developing technology for the last decade.

Understanding cellular organization and protein structure is vital to comprehending cellular function in order to develop targeted therapies. By seeing how the cells work, scientists can develop drugs to disarm the harmful intruders and keep the body healthy.

The high-throughput cryo-electron microscopy system allows UTHealth

Gram-negative bacteria secrete a wide range of proteins, nutrient acquisition, virulence, and efflux of drugs and other toxins. Among those secretion systems, the Type III secretion systems (T3SS) are essential virulence determinants for many Gram-negative pathogens. The injectisome, also known as the needle complex, is the central T3SS machine required to inject effector proteins from the bacterium into eukaryotic host cells.
researchers to investigate the molecular basis of many infectious diseases, such as Lyme disease, syphilis, and food-borne illnesses, with a goal of creating drug-therapy targets.

Dr. Liu joined McGovern Medical School in 2007, previously serving as a scientist at the National Cancer Institute, National Institutes of Health. Hereceived his Ph.D. in physics from the Institute of Physics, Chinese Academy of Sciences, Beijing, and completed postdoctoral training at Florida State University.

A hands-on course at UTHealth, the New Investigator Development Program led by Kevin Morano, Ph.D., associate dean for faculty affairs, put Dr. Liu on the fast track to winning multi-year research grants from the National Institutes of Health to pursue cryo-electron microscopy.

"I'm so grateful for the grant training. It made a huge difference for me then as a new investigator," Dr. Liu says. "I believe these studies made possible by the grants have really kicked off my career as a scientist."

Dr. Liu and his lab have developed two 3-D cellular model systems, in Lyme disease and E. coli, to study the tiny structures in their native cellular environment. This work has been accomplished in collaboration with Steve Norris, Ph.D., Greer Professor and vice chair for research for pathology; Bill Margolin, Ph.D., professor of microbiology and molecular genetics; and many other McGovern Medical School colleagues.

The investigators have developed the unique procedure to visualize hundreds of cells at molecular resolution within one week, using a combination of automated Cryo-ET data collection and high-throughput image processing.

"The ability to rapidly produce and process hundreds of tilt series has improved both the throughput and the quality of the resulting 3-D reconstructions. It's becoming possible to generate a high-resolution 3-D structure of molecular nano-machines in situ within a month," Dr. Liu says.

The researchers were the first to model the unprecedented detailed changes in the structure of a virus as it infects an E. coli bacterium, showing how the tail of the virus extends into the host — the very action that allows it to infect a cell with its DNA.

"Powered by recent breakthroughs in cryo-EM, I expect that our projects will continue to thrive in next five years and beyond," Dr. Liu says.

Bacteriophages direct the evolution of bacterial pathogenicity by imposing selection for resistance to infection and by horizontal gene transfer of host genes to new bacteria. Most phages utilize elaborate tail machines to eject their genome into a host cell. In addition, these highly sophisticated molecular machines are responsible for host-cell recognition, attachment, and cell envelope penetration. Understanding how tailed phages infect their bacterial hosts will not only provide insight into the evolution of bacterial pathogenicity, but will also illuminate basic biological problems such as molecular recognition, protein-protein, protein-DNA, protein-membrane interactions, and the transport of large macromolecules across cell membranes.

This project is supported by NIH/NIGMS.
Blood. It’s not something most people like to think about, but it’s something we can’t live without.

During surgery, those in the operating room think about blood—how much blood will the patient need? Is the patient at risk for bleeding?

This is where the Division of Hemotherapy and Transfusion Medicine comes in. A board-certified subspecialty of pathology, this five-person team at McGovern Medical School focuses on blood disorders and blood needs of patients, providing real-time data to surgeons and anesthesiologists, providing the best care to patients.

Brian Castillo, M.D., joined the hemotherapy team in July.

“Patients undergoing more complicated procedures with a high risk for bleeding, such as a heart transplant and left ventricular assist device cases, we provide real-time coagulation monitoring to provide personalized immediate transfusion support. This also extends to any cardiac surgery patient in the postoperative period with acute bleeding or significant coagulopathy,” he explains.

This burgeoning personalized approach provides the best transfusion support for patients at Memorial Hermann-Texas Medical Center, providing care for patients pre-op and well as inter-operatively, if bleeding becomes an issue, and post-op.

Karen Malinowski, Clinical Trial Program Manager, who recently had a heart pump implanted for giant cell myocarditis, is one of the patients who has been helped by this team.

“They made things so easy,” says Malinowski, who works in the Department of Pathology and Laboratory Medicine as the clinical trial program manager. “I went to the ER because I kept collecting fluid, couldn’t walk, couldn’t eat, and then I woke up a week later with doctors telling me I had acute heart failure and needed a heart transplant.”

Until Malinowski gets the call for a new heart, a left ventricular assist device, a battery-powered pump, keeps her heart beating.

Audrey Wanger, Ph.D., professor of pathology and laboratory medicine and friend, says the service, led by Kim Klein, M.D., assistant professor of pathology and laboratory medicine, really helped Malinowski’s surgical process. “Kim went with us to donate blood at the Gulf Coast Regional Blood Center and told us what we had to do, how much blood Karen was expected to need based on the surgery and her personalized factors. Kim arranged everything—she had it all organized and made such a difference.”

Dr. Wanger says Malinowski will rely on the hemotherapy service again as she prepares for her heart transplant. “We can only donate blood every certain number of weeks, and Kim has it all figured out how we will rotate to make sure Karen has enough blood products, and the right products on hand when it’s time,” she says.

McGovern Medical School’s Department of Cardiothoracic and Vascular Surgery, which provides care for a number of patients who require surgery for complex aortic disease, including aortic dissections and extensive thoracic abdominal aortic aneurysms, has come to depend on the hemotherapy team.

“These patients, many of whom are redo operations, present difficult management issues related to perioperative coagulopathies,” explains Steven Eisenberg, M.D., FACS. “The Hematopathology Division of the Department of Pathology, under the leadership of Dr. Klein, has provided invaluable consultation services in the management of these very challenging patients. The HemPath service has made direct contributions, which have resulted in the survival of our patients.”

It’s that direct patient impact that inspired Dr. Castillo to join the specialty.

“I was a resident here and early on thought I’d do surgical pathology. In my third year this service began to take shape and I loved how engaging it was to see the real-time interpretation of data being applied clinically and seeing a difference it could make at the patient’s bedside,” he says.

Dr. Wanger says she has seen the need for the service grow.

“When they were first starting out, I thought hemotherapy was an annoyance—they were pulling our residents away for rotations, and they didn’t have enough business. Now I can see the value added, and I think it’s going to grow a lot,” she says.

The Hemotherapy team includes Dr. Brian Castillo, from left, Dr. Alice Chen, Dr. Hlaing Tint, (back) Dr. Paul Allison and Dr. Kimberly Klein.
Scientists can devote a lifetime investigating a single structure, disease, or chemical reaction.

Sudhir Paul, Ph.D., professor of pathology, has spent more than 25 years at McGovern Medical School investigating the possibilities of formulating a vaccine to combat HIV, the virus that causes AIDS. Eradicating HIV by worldwide vaccination has remained the Holy Grail for AIDS researchers ever since discovery of the HIV virus in the 1980s.

HIV is no longer a death sentence in the United States as it was in the 1980s. However, the World Health Organization estimates 34 million people have died from AIDS-related causes, and that more than 2 million people became infected with HIV in 2014.

For more than two decades and with the support of over $30 million in funding, Dr. Paul and his lab have discovered what he believes the best hope to target the chameleon-like AIDS virus: catalytic antibodies. Catalytic antibodies, a discovery of the Dr. Paul lab, are much more potent than regular antibodies. “They not only bind to a target, but also chop it up,” Dr. Paul explains.

“The virus has yogic flexibility, and we have to adjust our vaccine approach accordingly.”
– Dr. Sudhir Paul

“We are focused on the Achilles heel of the virus. We target a small but constant region of the ever-changing virus known as HIV,” Dr. Paul says. “The virus has yogic flexibility, and we have to adjust our vaccine approach accordingly.”

The HIV vaccine Dr. Paul and his lab have developed mimics a specific virus area that lock onto human immune cells through high energy covalent binding. “This creates a chemical reaction, which is completely new for a vaccine,” Dr. Paul explains, adding that the vaccine works by sharing electrons with the immune cell receptors. “This a reaction is like a bomb going off, empowering immune cells to produce catalytic antibodies with specificity that is not feasible with conventional vaccines.”

The vaccine has been tested in mice and monkeys, and the vaccine-induced antibodies protect against infection against various HIV strains that cause infection around the world, Dr. Paul says. “I am fortunate to have always had the support of my chairman Dr. Robert Hunter who has backed my work and encouraged me to persist with my dream even in difficult times,” he says.

Catalytic antibodies, for which Dr. Paul and his lab have been issued more than 15 U.S. patents, have been designed to target Alzheimer’s, Parkinson’s disease, and spinal stenosis, in addition to HIV. Alzyme, which fights Alzheimer’s plaque, wipes out amyloid in the mouse model with no inflammation. And Stenzyme, which fights spinal stenosis, erases the stenosis in the bone tissue.

“Our work now has reached the stage where it’s ready for large-scale manufacturing and clinical trials,” Dr. Paul says.

Dr. Paul and his lab, headed up by Stephanie Planque, Ph.D., assistant professor of pathology and laboratory medicine, have external support from the NIH, Alzyme Research Foundation, and the CEO of a for-profit company Richard Massey.

“We are partnering with a company to create catalytic antibodies to any target. We want to have a clinical trial for the HIV e-vaccine, and I imagine a day when we have a targeted gene delivery of the catalytic antibody for Alzheimer’s. So, we can not only treat diseases but also prevent them at low cost,” he says.

Dr. Paul says his research is paying off. The new basic science rules on catalytic antibodies for which his lab is known are finding their way into the scientific textbooks, and studies in animals and human tissue have shown promising results.

“Very few people took catalytic antibodies seriously 25 years ago. Only now is there growing conviction that they are important, and we will be missing out on something important if we don’t act urgently. I have grown old doing innovative things that people don’t believe initially, and then taking years persuading them to take the work seriously,” Dr. Paul adds with a wry smile.