

Target-and-Control STRATEGIES to Battle CANCER

Researchers pursue new approach instead of traditional search-and-destroy methods to deal with cancer.

by JANE M. SANDERS

After an inconclusive mammogram followed by months of watching and worrying, Missy noticed a sudden change in the hardened lump in her right breast.

A biopsy followed, and a few weeks later, the 38-year-old found herself being wheeled into surgery for a mastectomy. Scared and uncertain about her prognosis, she expected the worst.

Indeed, Missy's tumor was an aggressive one, and doctors recommended six months of chemotherapy and a long course of the anti-estrogen drug Tamoxifen, which induced menopause-like symptoms and increased her risk of uterine cancer. Myriad side effects followed – nausea, vomiting, hair loss, infections – accompanied by anger and anxiety.

"I was mad as a hornet," she recalls. "I resented the fact that at 38, I had lost my breast and went into early menopause. I think I could've gotten by with fewer chemo treatments."

Missy – now cancer free, but still anxious – was one of the 1.3 million cancer patients a year



PHOTO BY GARY MEEK

Inset: Missy was 38 when she was diagnosed with breast cancer. Now disease-free, she is an active "Relay for Life" American Cancer Society fundraiser at the metro Atlanta high school where she teaches science. Fundraising activities include bake sales and sponsored walks.

who are treated under a "search-and-destroy" method of fighting the disease. That strategy depends upon radiation and chemotherapy to kill cancer cells, but it also kills healthy cells. Patients often get sicker before they can get better.

But cancer research is changing this paradigm to a broader one aimed at targeting and controlling the disease. Not only should doctors be able to detect cancer cells, but also find genetically abnormal cells that are predisposed to becoming cancerous, explains Georgia Institute of Technology Professor of Biology Al Merrill, who heads the university's Cancer Research Council.

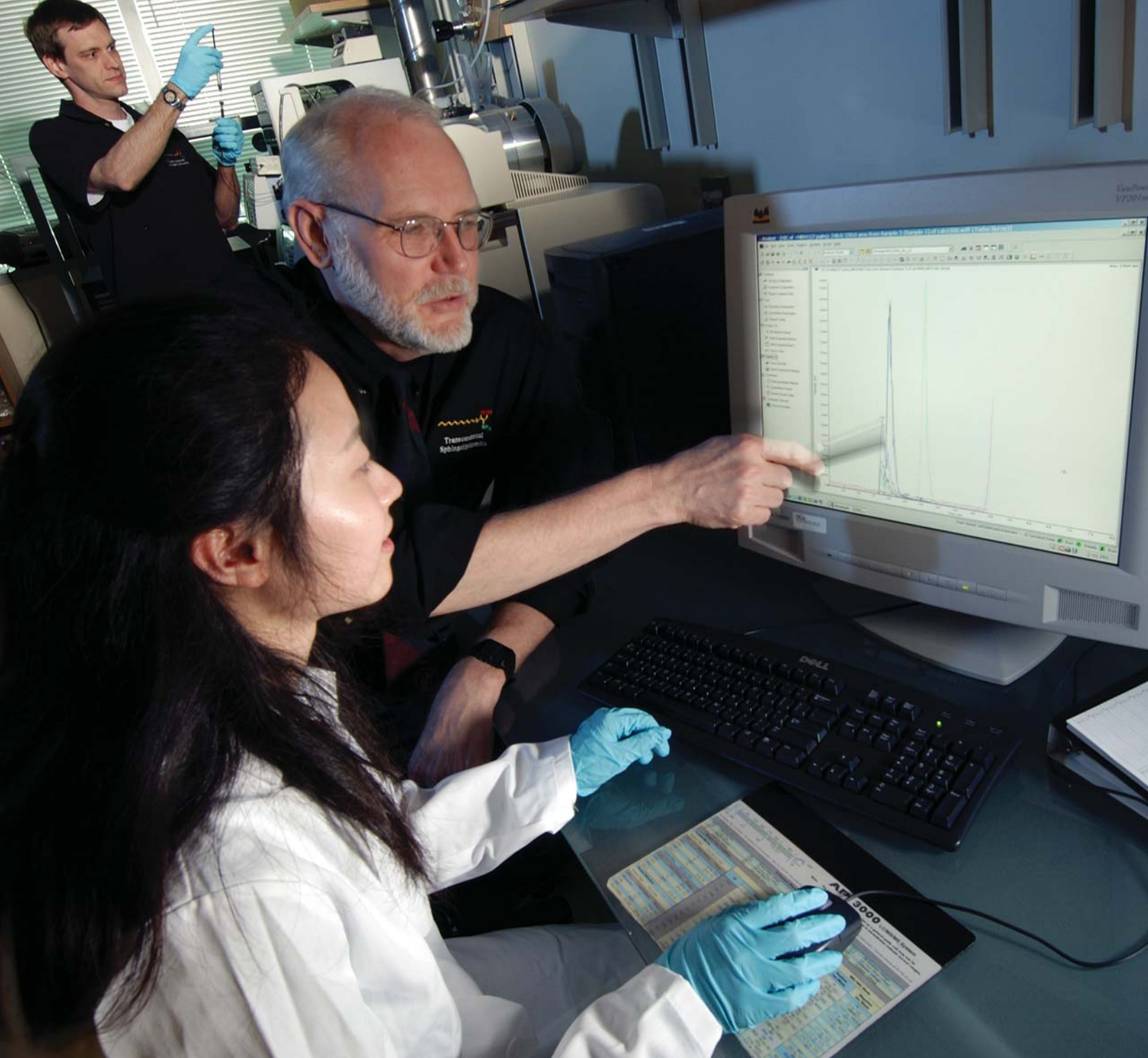


PHOTO BY GARY MEEK

“Target and control goes after abnormal cells at an early stage. Better than killing them, we want to control them, to find out what’s wrong with them,” Merrill explains. “Often it’s a signaling pathway that’s abnormal. So maybe, there’s a way – a drug or a nutrient — to make these cells normal again.”

The “poster child” for the target-and-control approach is a new leukemia drug called Gleevec, which targets an abnormal cell signaling pathway called the bcr-abl protein signaling receptor. This abnormality causes the pathway to lose its ability to signal cell growth. The drug blocks this specific

receptor and allows cells to behave normally. This treatment approach does not kill cells; it goes after a molecular defect.

“Restoring natural processes to cells is an attractive idea – a paradigm change to which our research is contributing,” says Merrill, the Smithgall Chair in Molecular Cell Biology, whose expertise is in cell signaling.

He and several dozen multidisciplinary experts at Georgia Tech and Emory University in Atlanta are investigating target-and-control strategies on basic and applied research fronts. Funded locally by the Georgia Cancer Coalition and nationally by

Georgia Institute of Technology Professor of Biology Al Merrill, center, heads the institute’s Cancer Research Council. Here, he is assisted by biology graduate students Jia Wei, foreground, and Chris Haynes.

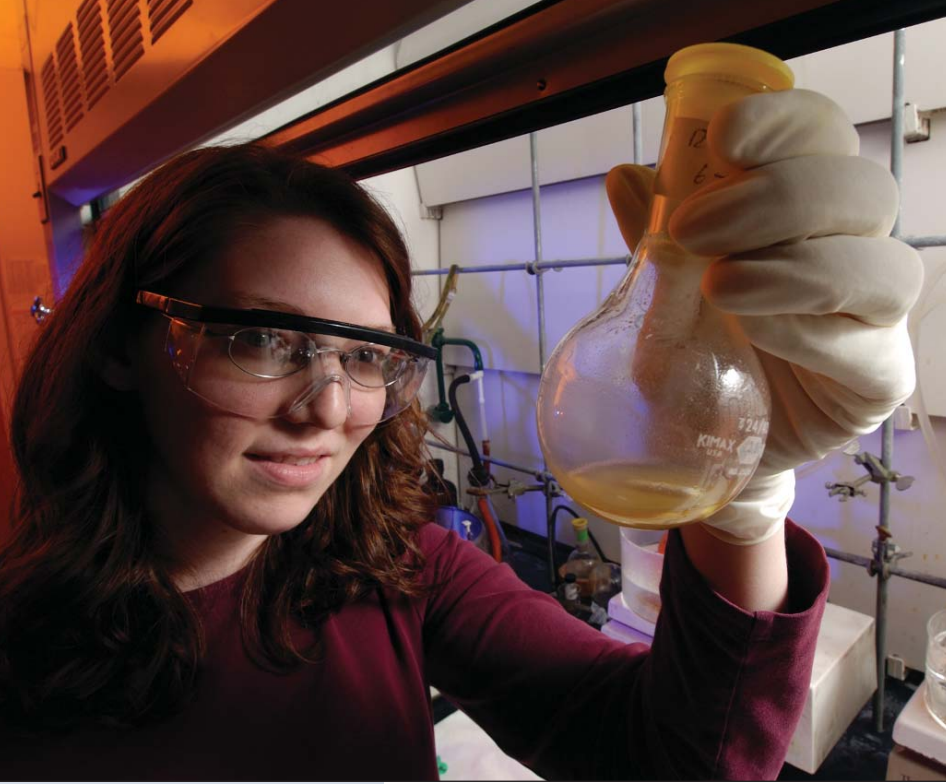


PHOTO BY GARY MEEK

Ph.D. student Sylvia Shadinger works with Regents Professor Jim Powers' research team to design and synthesize small-molecule inhibitors for five classes of proteases. One of their primary research interests relates to the design and synthesis of inhibitors for cysteine proteases, which include the papain family. Papain proteases are characterized by their role in digesting proteins.

Shown, below, is an artist's rendition of normal cells on one side and cancer cells on the other showing the characteristic structures of each.

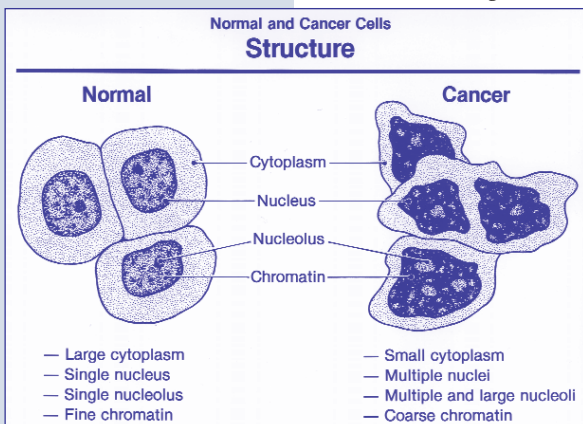


ILLUSTRATION BY PAT KENNY, COURTESY OF NATIONAL CANCER INSTITUTE

such organizations as the National Institutes of Health and the National Science Foundation, the researchers are finding clues and engineering solutions to fight the war that cancer wages against humans.

Studies include basic cancer biology research, design of new intervention methods, and development of detection and monitoring technologies in bioinformatics, biosensing and bioimaging. Research addresses many types of cancer, including breast, prostate, ovarian and colon.

Cancer researchers at Georgia Tech and Emory contribute expertise in multiple disciplines, including cancer biology, bioinformatics, chemistry and biochemistry, biomedical engineering, radiation biology and nuclear engineering, systems engineering, and electrical and computer engineering. And, as importantly, their efforts are being combined with clinicians working with all types of cancer patients.

"There is a genuine commitment to join forces

to combat cancer in new ways," Merrill says. To support these new initiatives, researchers are applying for federal grants and conducting fundraisers, among other efforts. One recent fundraiser was the first Jimmy V Atlanta Celebrity Golf Classic. It benefited Emory's

Winship Cancer Institute, Georgia Tech and The V Foundation for Cancer Research.

Bringing this diverse group together is the Georgia Tech Cancer Research Council, formed by Provost Jean-Lou Chameau in 2002 and chaired by Merrill. Its initial purpose has been to collect information on cancer-related research already under way and find additional studies and/or technologies that could be applied to the field. The council is building a network of researchers at Georgia Tech, Emory and throughout the state. Merrill envisions an international network for the future.

"We want to create better connections for the faculty doing this kind of work," Merrill says. "We want to spread the word that this is an exciting area of research, and Georgia Tech students and faculty are the people to be doing it."

The council organized a cancer research symposium in 2003 for Georgia researchers and also developed a course for graduate students and undergraduate seniors to introduce students to cancer biology, clinical practices and new biotechnologies to treat cancer. Other organizations are now creating courses patterned after this one, Merrill notes.

"A multi-disciplinary approach like this is so important because the technology is evolving as the basic scientific discoveries are unfolding," Merrill says. "We now know the whole human genome. We have the technology to view thousands of genes at once to help us understand protein abnormalities. What used to take a decade to understand, we can now discover in six months. This allows us to make strategic decisions on where to focus our attention."

Hopes are high for cancer diagnosis and treatment breakthroughs. Seven-year cancer survivor Missy, now an active fundraiser for research through the American Cancer Society, says: "I want women to survive breast cancer and be around to raise their grandbabies like I will be."

■ Contact Al Merrill at 404-385-2842 or al.merrill@biology.gatech.edu. For more of cancer survivor Missy's story and the mind-over-matter battle waged by stomach cancer patient Jeff Saunders, see www.gtresearchnews.gatech.edu/cancer. Links are also listed to previously published articles on Georgia Tech cancer research projects.

Mining **BREAST** Imaging Data **CANCER**

Software will provide key indicators of breast cancer in seconds.

In the seconds it takes to do a Google search, a software tool under development at Georgia Tech could provide key indicators drawn from medical imaging data to help doctors making a diagnosis and prognosis of breast cancer.

The image-enabled data mining system, which could be expanded to find other diseases, would be a support tool for breast-imaging radiologists, as well as medical researchers. The work is being supported, in part, by the Georgia Cancer Coalition (GCC).

"The software could help a radiologist better diagnose breast cancer," says Christopher Barnes, an associate professor of electrical and computer engineering in Georgia Tech's Regional Engineering Program in Savannah, Ga. "If the doctor finds a suspicious area on a mammogram, this software tool might help the physician decide what to do next and how urgently action is required."

Barnes' software would find relevant case histories over the entire archived database – even one including millions of patient records.

"This tool would look at the radiologist's region of concern in the current patient's mammogram and, using the mammogram's pixels as a query, determine all relevant, on-line case histories – that is, others who have had suspicious mammograms with similar micro-calcification clusters," he explains. "The purpose is to find relevant case histories – with their recorded indicators, diagnosis, prognosis and outcomes – to support a diagnosis and post-diagnosis decisions for the current patient."

The front end of the system (i.e., the doctor's interface) would run on a desktop computer, while the database would reside on another, more powerful computing system. The doctor would submit an image of the suspicious

portion of a patient's mammogram as a query to the clinic's archive.

"The tool would help answer questions like: 'What is the likelihood of a malignancy based on all the relevant case histories? Is there enough concern to order a biopsy?' We're trying to reduce the rate of unnecessary biopsies," Barnes explains.

"Right now, as many as four in five biopsies prove a patient to be cancer free," he adds. "Although a cancer-free diagnosis is wonderful news, the doctor's order for a biopsy incurs medical risks, emotional trauma and unnecessary expense. They are ordered based on a doctor's review of the patient's mammogram. We'd like to get the biopsy rate down to two or three in five by helping the radiologist use comparative analysis tools. The software won't be successful unless it can improve the unnecessary biopsy rate without increasing the missed detection rate. That is the goal for the level of care in a clinic."

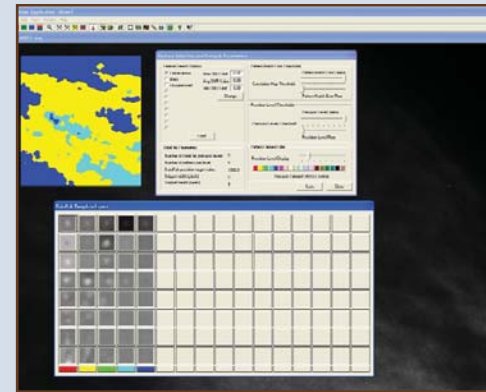
A doctor might also use this software to determine what treatment methods are most suitable based on relevant case histories. "The query results might indicate which ordered procedures have resulted in the past in the best outcomes," Barnes explains.

Barnes' software also has a clinical research application because of its potential ability to search based on multiple criteria, including imagery, patient information, diagnosis, treatment procedures, outcome history and even genomic-related clinical data, including DNA microarray results, which might indicate specific sub-types of cancer.

Barnes began development of his software in the mid-1990s at the Georgia Tech Research Institute. The GCC grant awarded in 2003 will help him move the software toward clinical trials.

— Jane M. Sanders

■ Contact Chris Barnes at 912-966-7927 or chris.barnes@gtrep.gatech.edu.



Data mining color code results indicate the availability of on-line similar case histories.

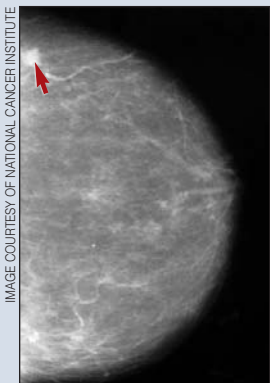


IMAGE COURTESY OF NATIONAL CANCER INSTITUTE

Left: Shown on this mammogram is a small cancerous lesion indicated by an arrow, as well as calcific deposits in the veins.

Molecular Complexity

Researcher explores the molecular events that turn on genes that are overexpressed in some cancers.

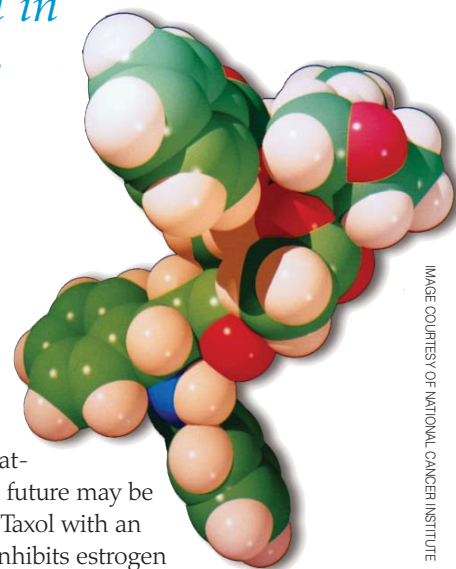


IMAGE COURTESY OF NATIONAL CANCER INSTITUTE



PHOTO BY GARY MEEK

Above: Assistant Professor of Biology Marion Sewer studies the genes that encode a subset of cytochrome P450 enzymes that make steroid hormones such as estrogen. Her research team included recent graduate Houman Khalili, pictured here.

Above right: In breast cancer, the current treatment is a chemotherapy drug called Taxol (model of a Taxol molecule shown here), which inhibits the ability of estrogen to turn on genes. A more effective treatment in the future may be to combine Taxol with an agent that inhibits estrogen production in the breast only.

In breast and other types of cancer, genes that encode the cytochrome P450 family of enzymes are overexpressed, creating an overproduction of these proteins. Under normal conditions, cytochrome P450s perform a variety of functions – from ridding the body of toxic compounds such as air pollutants and pharmaceutical drugs to producing essential biological molecules, such as cholesterol and hormones.

Georgia Tech Assistant Professor of Biology Marion Sewer studies the genes that encode a subset of cytochrome P450 enzymes that make steroid hormones such as estrogen, testosterone and cortisol (the “stress” hormone). Sewer primarily investigates the molecular events that turn on these genes in response to chronic stresses.

“This research is complex at the molecular level in terms of the steps involved in turning on genes, given all the proteins and pathways that are involved,” Sewer notes.

But Sewer is now extending this basic research to studies of cancers that are “hormone dependent” – that is, their progression is linked to an overproduction of hormones. For example, estrogen is overproduced in breast cancer, and testosterone is overproduced in prostate cancer. This expanded research program was funded in 2003 with a five-year grant from the Georgia Cancer Coalition.

In breast cancer, the current treatment is a chemotherapy drug called Taxol, which inhibits the ability of estrogen to turn on other genes. A more

effective treatment in the future may be to combine Taxol with an agent that inhibits estrogen production in the breast only, Sewer notes. Her research could contribute to the development of such a drug, she adds.

But Sewer must first conduct more basic research on the P450 gene that converts estrogen to a toxic compound that binds to DNA and leads to cancer. This particular gene is overexpressed in more than 95 percent of cancerous breast tissue. Though this gene has a documented role in causing other cancers – including stomach cancer and smoking-related lung cancer – its function is not clearly understood in breast cancer, Sewer says. If her research team can learn why this gene is turned on at such a high level, then they might be able to identify a way to turn it off in the breast.

At this stage in their research, Sewer and her team of six undergraduate and graduate students are characterizing different regions of this gene and how those regions affect expression.

She estimates that it will be at least 15 years before her research would lead to human trials of potential pharmaceutical agent that might be developed from her team’s findings.

— Jane M. Sanders

■ Contact Marion Sewer at 404-385-4211 or marion.sewer@biology.gatech.edu.

A drug that may treat a common side effect of chemotherapy and diabetes is being tested by Georgia Tech and Emory University researchers. They have found the compound, developed about a decade ago at Georgia Tech, is effective in treating neurodegenerative disease and stroke in animal models.

Researchers believe the compound, dubbed AK295, could be used to treat peripheral neuropathy – the condition of tingling and numbness in a person’s outer extremities, says its developer Jim Powers, a Regents Professor in the Georgia Tech School of Chemistry and Biochemistry. Peripheral neuropathy occurs in about 40 percent of breast cancer patients taking the chemotherapy drug Taxol. It also affects about half of diabetics.

“It’s not always clear in the early stages of testing whether a compound will be useful,” Powers says. “But we now know AK295 works in head injury and stroke models in animals.”

AK295 is an inhibitor for the calpain protease, a member of the papain family of proteases. Proteases are enzymes that cleave (basically, cut) proteins. Proteases have numerous physiological functions, including roles in digestion, blood clotting and hormone activity. Proteases also have a role in metastasis in cancer, Powers notes. Some tumors secrete proteases to chew up surrounding tissue so they can expand. In breast cancer, for example, a protease called cathepsin B is present in the leading edge of invasive tumors.

Powers and collaborator Jonathan Glass at Emory University have been testing AK295 with internal funding. Now they are seeking funding to move the testing into human clinical trials, a step that may take another five years, Powers says. He and Glass have received numerous patents related to their research, and they are seeking a licensee for AK295.

In addition to AK295, Powers designs and synthesizes other small-molecule inhibitors for five classes of proteases. One of his primary research interests relates to the design and synthesis of inhibitors for cysteine proteases, which include the papain family.

“We do a lot of computer modeling of enzymes,” Powers explains. “It is structure-based drug design.”

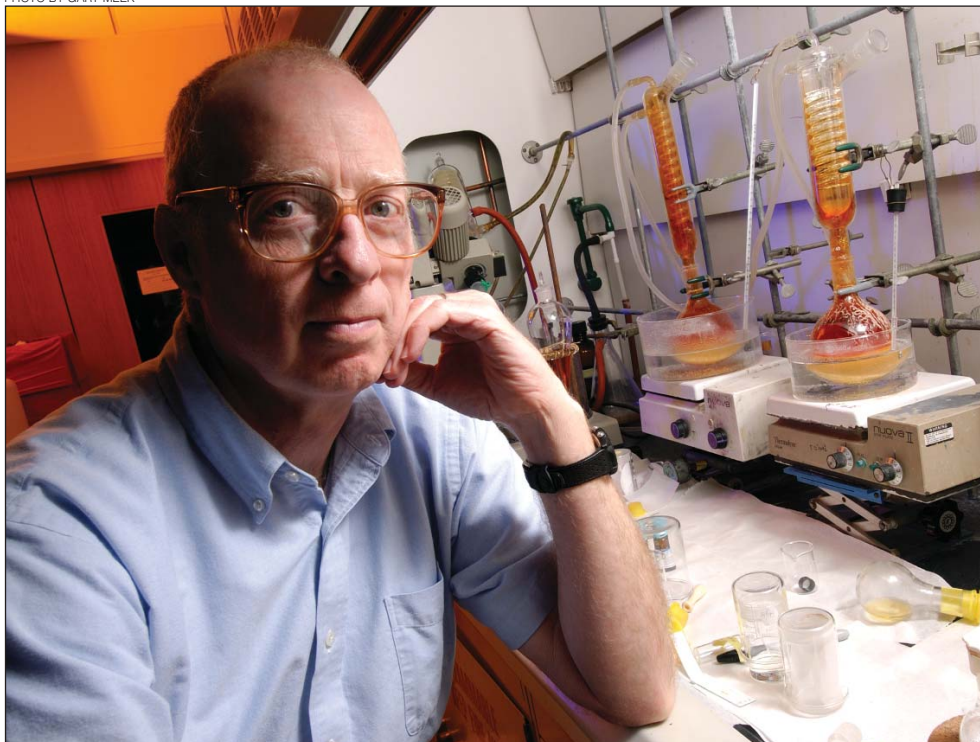
— Jane M. Sanders

■ Contact Jim Powers at 404-894-4038 or james.powers@chemistry.gatech.edu.

Treating a CHEMOTHERAPY Side Effect

Protease inhibitor developed at Georgia Tech shows promise for treating numbness in the extremities.

PHOTO BY GARY MEEK



Regents Professor Jim Powers and his research team are testing a compound he developed called AK295. It could be used to treat peripheral neuropathy – the condition of tingling and numbness in a person’s outer extremities.

Right: These images are models of how Regents Professor Jim Powers and his research team expect their caspase inhibitors to interact with caspases enzymes.

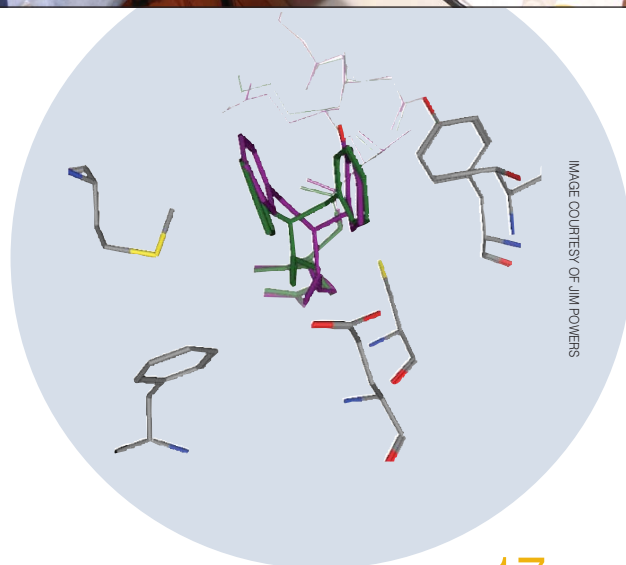


IMAGE COURTESY OF JIM POWERS

Catching Cancer Before it → SPREADS

Georgia scientists pursue early-stage diagnostic test for ovarian cancer.

In a quest to develop an early-stage diagnostic test for ovarian cancer is a “virtual” research institute of Georgia-based academic experts in molecular biology, biochemistry and bioinformatics.

Led by John McDonald, a former University of Georgia professor of genetics who became chairman of the Georgia Tech School of Biology in July 2004, the researchers are studying the same tissue samples from ovarian cancer patients and are comparing their results with each other and with patient data files.

Studying the same tissue samples – obtained from the non-profit, Atlanta-based Ovarian Cancer Institute (OCI) — gives the group a distinctive insight, says McDonald. He is the chief scientific officer for OCI, which was founded in 2001 by noted gynecologist Benedict Benigno of the Southeastern Gynecologic Oncology Group.

“We’re beginning to establish some correlations now,” McDonald notes. “We’re providing the biologists with high-quality tissue to analyze. They are comparing results, and we hope within a year to see some significant outcomes.”

Ovarian cancer causes almost no symptoms in the early stages and is often misdiagnosed when symptoms – such as weight gain and digestive problems – occur. When symptoms become severe, the cancer has usually progressed to Stage 3 and has spread to surrounding organs. The five-year survival rate at that point is only 25 percent. But if caught before it spreads, the survival rate jumps to 95 percent.

Researchers working under the auspices of OCI are funded by various organizations, including the Georgia Cancer Coalition and the National Institutes of Health. McDonald brings funding to ovarian cancer research on several fronts.

First, OCI researchers are exploring the possibility that every type of tissue contains adult stem cells that regenerate damaged tissue. Some evidence exists that these cells are present in ovarian tissue.

“It is possible that malignant cells may be derived from aberrant adult stem cells and not epithelial cells, which are observed when you examine tumors,” McDonald explains. “If this is true, it’s important because chemotherapy is often used to reduce the size of tumors – some as large as 25 pounds – before surgery. Chemotherapy kills epithelial cells and is effective, but tumors often recur.

“One hypothesis we’re pursuing is that stem cells are not affected by chemotherapy and that they are regenerating more cancer cells after the chemo,” he adds. “So we want to isolate and characterize the stem cells and then determine their response to chemotherapy. Then perhaps we can design a therapy to inhibit the stem cells.”

In a related research effort, McDonald and his team are using molecular technologies, such as microarray analyses, to create molecular profiles of tumors. This information would assist pathologists as they identify ovarian cancer subtypes and assign a stage to a tumor.

“We hope to find a molecular profile of ovarian cancers and identify subtypes,” McDonald adds. “Different subtypes may respond differently to chemotherapy. So it’s a more refined approach. We already have good preliminary data on this.”

— Jane M. Sanders

■ Contact John McDonald at 404-894-3735 or john.mcdonald@biology.gatech.edu.

Development of an early-stage diagnostic test for ovarian cancer is the goal of group of Georgia scientists led by John McDonald, right, a former University of Georgia professor of genetics who became chairman of the Georgia Tech School of Biology in July 2004.

This micrograph depicts adenocarcinoma, or ovarian cancer.

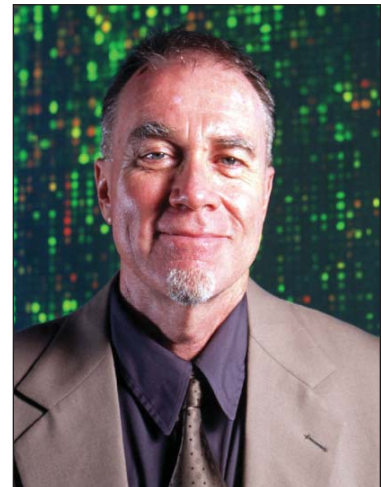
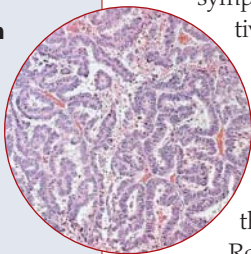


PHOTO BY PAUL EFLAND, COURTESY OF UGA

SENTINEL AGAINST Ovarian Cancer

Basic research on the organic molecule LPA could lead to new diagnostic tools and drugs to treat ovarian cancer.

One member of a family of fat-like molecules called lysophospholipids strongly promotes ovarian and uterine cancer tumor cell growth and metastasis. This compound – called lysophosphatidic acid, or LPA – is being studied by researchers at Georgia Tech.

Its role is important to scientists searching for an early detection marker and new drugs to treat the often-lethal ovarian cancer, which has few or no symptoms in its early stage.

The Georgia Cancer Coalition is funding Harish Radhakrishna, an assistant professor of biology who began a one-year pilot study on LPA last year, to gather more data on his recent findings.

Radhakrishna's investigation was prompted by a 1999 Cleveland Clinic study comparing LPA levels in the blood and body cavity fluid of ovarian cancer patients at varying stages of the disease. Researchers found that, at all stages of the cancer, patients had elevated levels of LPA compared to healthy individuals. They further discovered that LPA stimulates growth and metastasis of various tumor cell types, including lung, breast, prostate and ovarian.

"Although LPA has a normal physiological function, such as stimulating the contraction of muscles and participating in normal cell growth, cancer cells often subvert that good role," Radhakrishna explains. His team's investigation narrowed when Radhakrishna and his Ph.D. student Mandi Murph found that application of LPA to breast and lung cancer cells greatly diminished the activity of a critical "sentinel" protein, p53, which is mutated in half of all human cancers.

"This is important because all cells have several 'guard posts' set up to ensure that only normal cells can divide," Radhakrishna explains. "The p53 protein is one of the most important 'sentinels' in normal cells; it makes sure the cell does not divide if its DNA is damaged."

If the DNA in a cell is damaged, p53 stops the cell from dividing and triggers a pathway to fix the damage and then lets the cell continue to divide. But if the DNA is damaged beyond repair, p53 triggers the destruction of the cell through a process called programmed cell death or apoptosis.

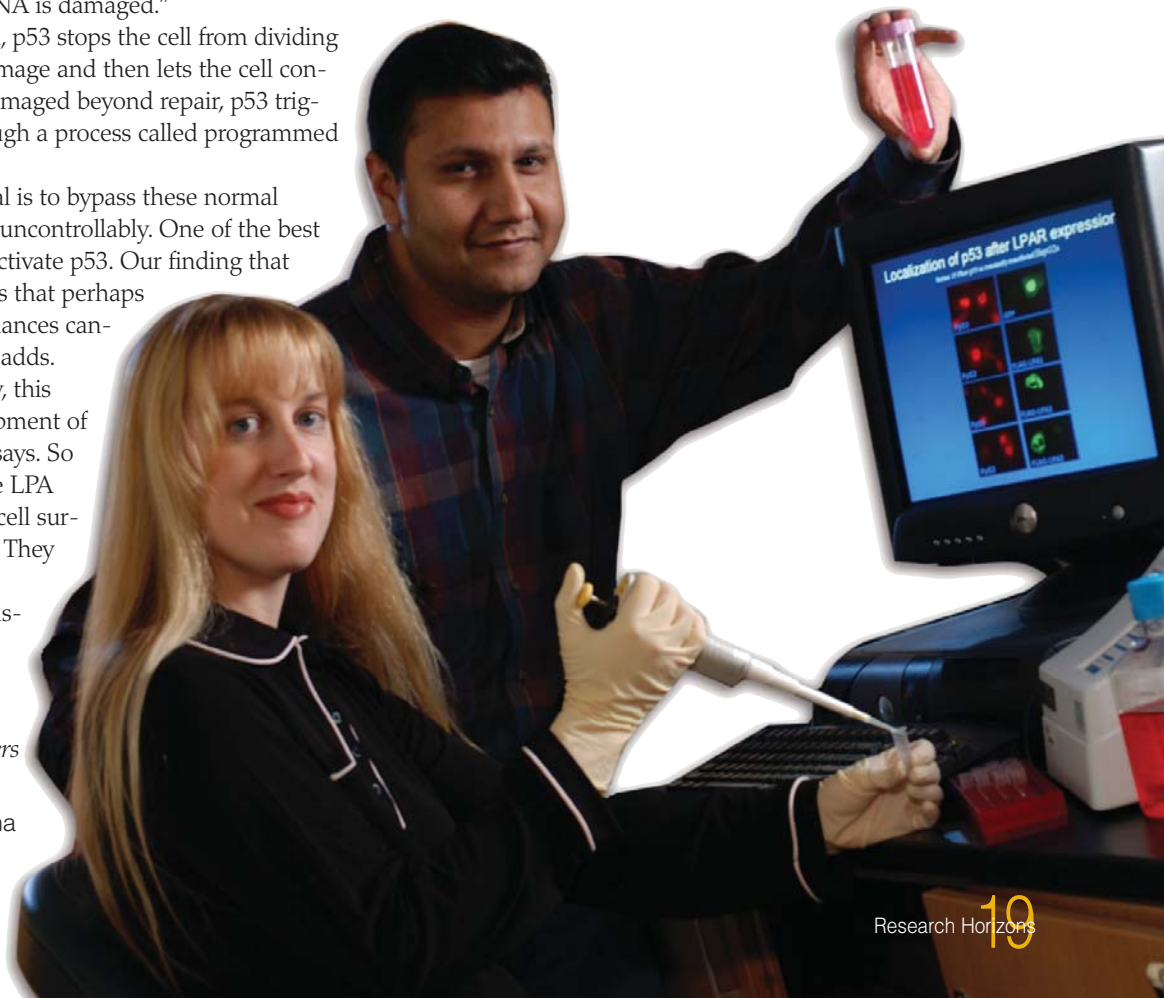
"If you're a cancer cell, your goal is to bypass these normal 'checkpoints' so that you can divide uncontrollably. One of the best ways to do this is to mutate and inactivate p53. Our finding that LPA decreases p53 function suggests that perhaps this is one of the ways that LPA enhances cancer cell proliferation," Radhakrishna adds.

For the pharmaceutical industry, this process could be a target for development of an anti-cancer drug, Radhakrishna says. So he and Murph are studying how the LPA signal gets from the receptor at the cell surface to the point of inactivating p53. They have found that LPA enhances the destruction of p53 and are now focusing on the steps it takes to accomplish that task in breast, lung and ovarian cancer cells.

— Jane M. Sanders

■ Contact Harish Radhakrishna at 404-385-1312 or harish.radhakrishna@biology.gatech.edu.

Assistant Professor of Biology Harish Radhakrishna and his Ph.D. student Mandi Murph found that application of the fat-like molecule LPA to breast and lung cancer cells greatly diminished the activity of a critical "sentinel" protein, p53, which is mutated in half of all human cancers.



PEERING into the BODY

Magnetic resonance technology being refined and applied in new ways.

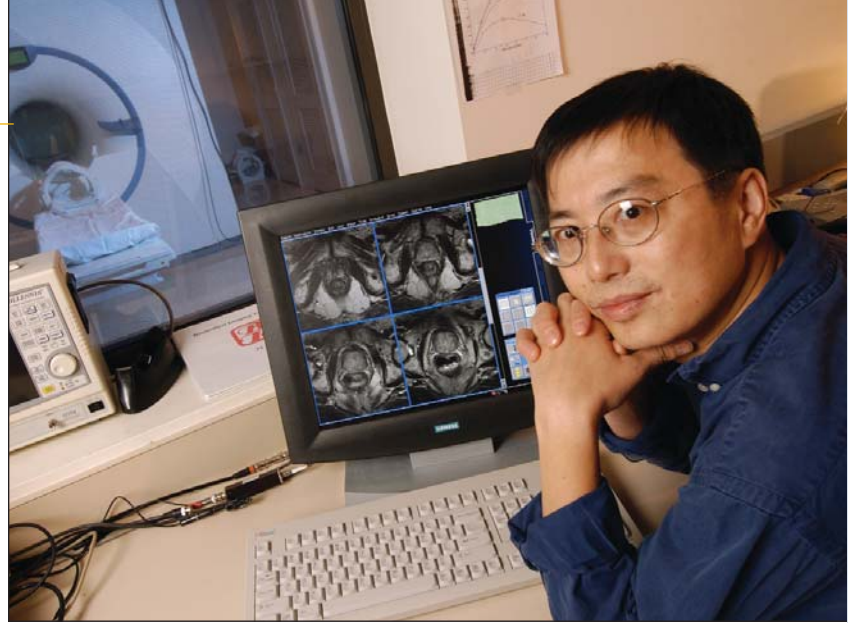


PHOTO BY GARY MEEK

Professor Xiaoping Hu is using magnetic resonance imaging and magnetic resonance spectroscopy, which provides chemical information, to develop a new way of imaging prostate cancer.

Magnetic resonance imaging has been used in medicine for decades to study human gross anatomy and diagnose or monitor disease. More recently, physicians have been using magnetic resonance imaging (MRI) and spectroscopy to study physiological function.

“The key advantage of magnetic resonance technology is that it’s non-invasive and physicians can use it to follow patients over time,” explains Xiaoping Hu, a Georgia Research Alliance Eminent Scholar in Imaging and professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University.

Magnetic resonance (MR) technology can be employed in the research, diagnosis and treatment of cancer and other diseases. Specifically, MRI technology allows doctors to follow the evolution of cancerous lesions and tumors to see if treatment is working and how the tumor is affecting the surrounding anatomy. Also, MRIs provide researchers and clinicians with physiological function information, such as information about nutrient-carrying blood flow to a tumor over time.

But MR technology still poses many problems in the manipulation of data. So Hu is addressing the technical issues, as well as developing new applications for the technology.

In collaboration with Department of Biomedical Engineering colleagues Shuming Nie, Gang Bao and Ravi Bellomkonda, Hu is helping develop target-specific MR

contrast agents to allow more specific and sensitive diagnostic imaging.

And in another project funded by the Coulter Foundation, Hu is using MRI and MR spectroscopy, which provides chemical information, to develop a new way of imaging prostate cancer. For now, patients must undergo an extremely uncomfortable endorectal probe procedure to obtain prostate images, which are often of poor quality. Hu and his colleagues at Emory Radiology are using an external probe to image the prostate with minimal patient discomfort and substantially improved image quality.

“Our preliminary findings using MRI show the external probe works well, but the spectroscopy study is inconclusive and needs further study to increase its sensitivity,” Hu says.

He and his collaborators in the Emory University School of Medicine are seeking NIH funding to continue this work. They need more patient volunteers who agree to undergo both the endorectal probe, as well as the two MR procedures. And they hope to purchase better hardware to enhance the research.

Meanwhile, Hu is setting up a new MR instrument for animal imaging. Hu expects the new instrument to be available for use by Georgia Tech and Emory researchers by the end of this year. Hu also uses MR technology to study normal brain function and neuropsychiatric diseases such as schizophrenia, Parkinson’s, Alzheimer’s, depression and drug abuse. This research is funded by the National Institutes of Health.

— Jane M. Sanders

■ Contact Xiaoping Hu at 404-712-2615 or xhu3@emory.edu.

Below is a magnetic resonance image of a prostate. It was obtained with an external probe that is much less uncomfortable to the patient than an endorectal probe.

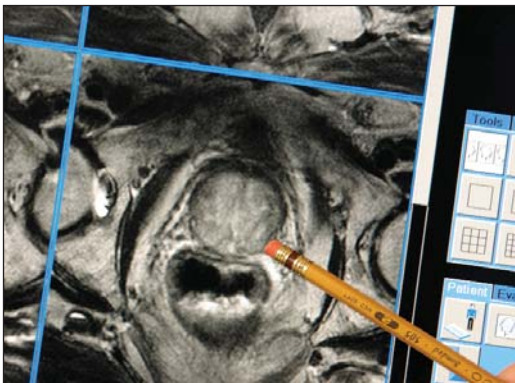


PHOTO BY GARY MEEK

Slippery Path


A special kind of fat can change cell signaling pathways and block cancer in animals.

Cancer cells want to live forever, and, in fact, they lose the ability to die on their own as normal cells do. Georgia Tech Professor of Biology Al Merrill wants to figure out how to fix them.

To that end, Merrill is applying his expertise in cell signaling — the processes cells use to let information in from the outside to induce intracellular changes ranging from nutrient handling to cell division, and even cell death. He focuses on a group of signaling molecules called sphingolipids, which work at the intersection where cells decide whether to grow or die.

“Sphingolipids are mostly involved in cell structure and signaling,” says Merrill, who holds the Smithgall Chair in Molecular Cell Biology. “They help define the cell membrane — a functional wall that interacts in specific ways with the cell surface proteins and other components. These interactions often turn proteins on and off.”

Also, cells use sphingolipid molecules to receive extracellular stimuli that tell the cell to change its behavior. “This signaling pathway is very important to a cell’s life cycle,” Merrill explains.

 “If it is interrupted by an enzyme-induced remodeling of the cell membrane, cancer may result.”

About 10 years ago, Merrill hypothesized that foods containing sphingolipids, a special kind of fat – if delivered via natural digestion in the right amounts and combinations – could enter the body and tap the relevant signaling pathway. Merrill and his collaborators have shown that this process could normalize cell function and block several types of cancer – colon, breast and prostate — in several animal models.

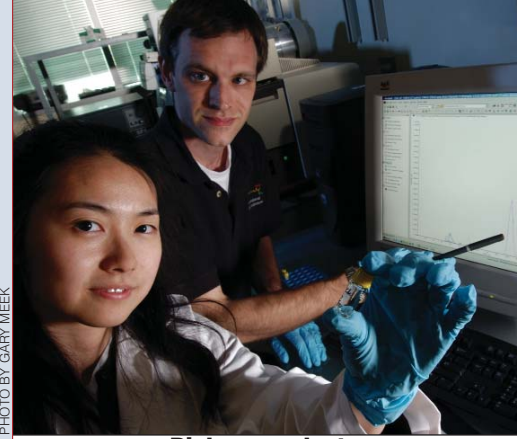
“We know we can change the signaling pathway with this molecule,” Merrill says. “We can do it in mice, and we hope to do it in people someday.” While animal studies continue, Merrill and his research team are beginning to pursue the steps necessary for FDA approval of human trials using sphingolipids.

For now, Merrill is testing the suppression effects of sphingolipids on human prostate cancer cells in mice with a team of investigators that includes Cameron Sullards at Georgia Tech and Professors Dennis Liotta, Dirck Dillehay, David Pallas and Frank McDonald at Emory University. Funded by a National Cooperative Drug Discovery grant from the National Cancer Institute, the researchers are moving away from the difficult-to-control diet-based delivery of sphingolipids to drug-based intervention. Preliminary results from tests of sphingolipid analogues are promising, Merrill adds.

— Jane M. Sanders

■ Contact Al Merrill at 404-385-2842 or al.merrill@biology.gatech.edu.

PHOTO BY GARY MEEK



Biology graduate students Jia Wei, left, and Chris Haynes use mass spectrometry to explore a potential link between vitamins, lipids and cancer.

PHOTO BY GARY MEEK



Cancer cells want to live forever, and, in fact, they lose the ability to die on their own as normal cells do.

Biology graduate student Chris Haynes and other researchers at Georgia Tech and Emory University are testing the suppression effects of sphingolipid analogues on human prostate cancer cells in mice. Preliminary results are promising. Here, Haynes inspects samples ready for mass spectrometry testing.

Left: Just like scientists cracked the human genome, researchers at Georgia Tech are helping develop mass spectrometry methods to identify and quantify all the small molecules in cells – collectively called the “metabolome.”

FINDING THE NEEDLE in the Haystack

Researcher is probing gigabytes of data for molecular profiles of cancer.

Current imaging technologies and biopsy analyses – though they have advanced significantly – cannot slow the cancer death rate without some additional diagnostic tools because cancer is just too complex, says May D. Wang, an assistant professor focusing on bioinformatics and bioimaging research in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University.

Physicians need cancer-specific molecular profiles to assist in early detection, prognosis decisions and the development of more effective therapies. So Wang's research team is designing algorithms to analyze gene and proteomic data obtained from high-throughput technologies — such as DNA microarray analysis and mass spectrometry — to find cancer-specific molecular profiles and to reconstruct and study functional pathways.

She is also developing a new bioinformatics system to archive, retrieve and process the molecular imaging data. And Wang is creating a real-time, human anatomy simulation tool to predict biological behavior, from the whole body down to the cellular and molecular levels.

"This is a long-term research program," Wang notes. "It will be some time before we have a complete archive of all the population's molecular profiles and clinical records, so we work at the current stage of technology using a limited sample of data."

Wang is encouraged, however, by her team's progress. In one experiment, Wang and her team analyzed data from a published study of 70 prognosis-related genetic signatures derived from 25,000 genes present in 78 cancer patients. Wang used her algorithm to reduce the number of signatures to 13, effectively yielding better predictions.

Georgia Tech researchers are developing a user-friendly computing environment for real-time analysis of human anatomical 3-D image data from the Visible Human Project at the National Institutes of Health.

Once the molecular profiles are found, the next challenge is to reconstruct the underlying biological functional pathways. Wang's group has proposed a new modeling framework to study metabolic and signaling pathways. Wang has filed provisional patents on the molecular profiling and functional pathway modeling.

She has also developed a biological function mining system called GOMiner and a powerful Web-enhanced version called EGOMiner. The system simultaneously searches 17 databases to identify the function of individual genes or proteins. EGOMiner can also group genes based on their functional category and indicate which genes are regulated up or down, or remain unchanged. Further, it performs statistical analyses and is integrated with other bioinformatics tools to determine cell signaling pathways and molecular structure and find related published studies.

"This is an all-in-one tool to automate the research process," Wang explains. "We think it's having a significant impact on the research community."

GOMiner, developed initially for the National Cancer Institute (NCI), took only five minutes to yield the genetic information that it previously took NCI scientists six months to reconstruct, Wang notes.

In a related research effort, Wang and her team are developing a user-friendly computing environment for 3-D, real-time navigation of human anatomical image data from the Visible Human Project at the National Institutes of Health. The system will also navigate through 3-D cell and molecular imaging data acquired by bionanotechnology techniques.

The project is benefiting from a recent \$400,000-plus donation from Hewlett Packard of a powerful 68-CPU computing system and eight digital projectors.

To support her work, Wang recently received a Georgia Cancer Coalition Distinguished Cancer Scholar award for translational cancer bioinformatics and bioimaging research.

PHOTO BY GARY MEEK



PHOTO BY GARY MEEK



— Jane M. Sanders

■ Contact May Wang at 404-385-2954 or maywang@bme.gatech.edu, or visit www.miblab.gatech.edu.

3-D Modeling

Researchers creating in-vitro, 3-D model of prostate cancer with tissue engineering.

Researchers led by Assistant Professor May Wang are designing algorithms to analyze gene and proteomic data obtained from high-throughput technologies, such as DNA microarray analysis, to find cancer-specific molecular profiles. This information will assist physicians in the early detection of cancer.

Researchers currently rely on animal models and two-dimensional (2-D) cultures of human cells to study cancer and test potential drugs.

Yet these models have two major problems: Human cells behave differently in a 2-D environment than their natural 3-D state, and animal physiology isn't the same as humans.

"We can cure all kinds of cancer in mice, but there's no guarantee the same drug will work for humans," says Yadong Wang, an assistant professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. "In fact, many anticancer drugs shine in both tests but fail in human trials."

Wang, who focuses on biomaterials and tissue engineering, is working on a new approach to testing — an in-vitro, 3-D model of human prostate cancer created through tissue engineering. Funded through the Georgia Cancer Coalition, Wang is collaborating with Leland Chung, director of Emory University's Molecular Urology and Therapeutics Program and an expert in prostate cancer.

"An in-vitro, 3-D cellular structure will mimic the human physiology better because it encourages cells to maintain their natural behavior," Wang says. "We hope this will bridge the gap between a 2-D culture and the patient."

Although other researchers have attempted in-vitro, 3-D models by layering human cells or growing them in collagen gels, these models haven't been thick enough or lasted more than a few weeks.

"Cancer is not something that happens overnight," Wang says. "To get a more complete picture, you need to study it long term. For example, metastasis occurs in the later stages of cancer development."

Wang's first step is to build a biological scaffold that provides structure and support for cells until the new tissue can assume that function. One challenge is using the right material. Most scaffolding materials are stiff, hard polymers, but because the prostate is a soft tissue, the researchers are using poly(glycerol sebacate), a biocompatible and biodegradable elastomer.

After constructing the scaffold and seeding the cells, the researchers will study prostate-cancer cells in the in-vitro, 3-D model and contrast their behavior with cancer cells in a 2-D model.

Although initially focused on prostate cancer, this in-vitro, 3-D model could be expanded to other diseases, such as breast, ovarian and lung cancer. "If successful, this 3-D model will enable in-vitro studies of human cancer cells in a more natural environment and provide a method for high-throughput testing of anticancer drugs," Wang says.

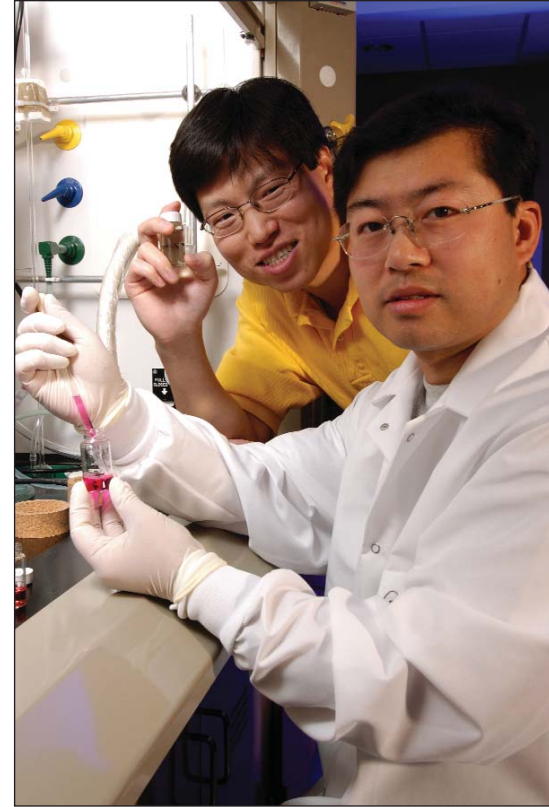


PHOTO BY GARY MEEK

A new approach to cancer drug testing is an in-vitro, 3-D model of human prostate cancer created through tissue engineering by Assistant Professor of Biomedical Engineering Yadong Wang, left, and his research team, including Jin Gao, a postdoctoral associate working on the project.

We can cure all kinds of cancer in mice, but there's no guarantee the same drug will work for humans.

— T.J. Becker

■ Contact Yadong Wang at 404-385-5027 or yadong.wang@bme.gatech.edu.



Associate Professor Chris Wang and his collaborators are developing a new generation source of neutrons for neutron brachytherapy, a type of radiation treatment for cancer. The smaller neutron source delivers radiation more uniformly inside a tumor.

The new Cf-252 neutron source, left, under development by Georgia Tech and other researchers is 20 times smaller in volume and five times stronger in intensity than older neutron sources, right, used in radiation therapy for cancer.

PHOTOS COURTESY OF CHRIS WANG



Zapping Cancer with New Neutron-Based Therapies

Researchers are developing more effective radiation methods.

The battle in radiation therapy has always been about minimizing damage to normal tissue, says Chris Wang, an associate professor in Georgia Tech's School of Mechanical Engineering, who is developing new neutron-based methods for treating cancer.

Traditional radiation treatment uses gamma rays or X-rays. Yet neutrons can be more effective because they deposit more concentrated energy at the subcellular level.

"But the damage neutrons cause is more difficult for cells to repair," Wang says. "That's good for the cancer cells, but bad for surrounding normal tissue."

In fast neutron therapy (FNT), patients are treated with an external beam of high-energy neutrons produced by a particle accelerator. The neutron energy destroys the tumor, but there's a "late effect" in that normal tissue may deteriorate within a few months, Wang explains. Thus, FNT can only be used for certain cancers, such as salivary gland cancer.

A more promising method is neutron brachytherapy (NBT) where patients receive neutrons via the insertion of a sealed, miniature, neutron-emitting isotope. Because NBT uses an internal delivery method, radiation is more concentrated in the tumor area and poses less risk to normal tissues.

Yet adoption of NBT has been limited because existing neutron sources are too large and weak to be distributed evenly throughout a tumor.

Wang has been collaborating with the U.S. Department of Energy's Oak Ridge National Laboratory and Isotron Inc., an Alpharetta, Ga.-based start-up company, to develop a new generation source of neutrons for NBT. In a recent advance, the researchers have encapsulated a neutron source that is 20 times smaller in volume and five times stronger in intensity.

"The smaller the neutron source, the better, because it can be administered more uniformly inside the tumor," Wang says. He is developing the delivery system for NBT, and clinical trials are about a year away.

With funding from the Georgia Cancer Coalition, Wang is also studying a new group of chemical compounds for treating prostate cancer. The disease is often treated with neutron capture therapy (NCT). A patient is first injected with a neutron-sensitive compound that targets cancer cells; then an external beam of low-energy neutrons irradiates the tumor.

Though promising, NCT's success relies on having the ideal compound. "If you miss some of the tumor cells, it won't be effective," Wang says. "And the biological pathways of a human body are too complex for this to occur."

With this in mind, Wang is working on a new approach that he calls "boron-enhanced neutron brachytherapy"—a combination of NBT and NCT. The idea is to administer boron, a neutron-capture agent, to target tumor cells before the neutron-emitting isotope is inserted.

"In this case you wouldn't need a perfect compound," Wang explains. "The compound would act as an enhancement as opposed to relying completely on it."

— T.J. Becker

■ Contact Chris Wang at 404-894-3727 or chris.wang@nre.gatech.edu.

Calculating Dosage

Computational methods will allow more precise radiation dose.

Researchers at Georgia Tech and Emory University are combining their expertise in nuclear engineering and medical imaging to advance dosage accuracy in radiation therapy.

"Calculations in radiation dose have not kept pace with improvements in delivery systems," says Farzad Rahnema, chairman of Georgia Tech's Nuclear and Radiological Engineering/Medical Physics Program in the Woodruff School of Mechanical Engineering.

Rahnema is working with Tim Fox, director of Emory's Medical Physics Division in the Department of Radiation Oncology, to develop a new computational tool that will more precisely calculate radiation dose and where it will be deposited.

Existing methods don't account for the intricate geometry of the human body; different tissues, air cavities and bones affect how radiation deposits its energy. Also, a patient's posture and diet prior to treatment can also influence the location of tumor.

"If we can track tumors more accurately, then the number of treatments can be reduced, which would allow radiation dose to be escalated," Fox explains. "This would improve tumor control while reducing dose to normal tissue structures."

With funding from the Georgia Cancer Coalition, Rahnema and Fox are developing a tool that combines the strengths of two different computational methods — stochastic (Monte Carlo) and advanced deterministic (coarse mesh transport) methods.

Their idea: Divide patient anatomy and the radiation beam head into subregions. Stochastic algorithms, which can handle complex geometric problems, will be used to predict how each subregion responds to the flow of radiation and how photons and electrons exit the area. Because stochastic methods require long running times to reduce error from statistical noise,

Above: Existing methods for calculating radiation dosage don't account for the intricate geometry of the human body; different tissues, air cavities and bones affect how radiation deposits its energy.

Right: This illustration shows shaped radiation beams used to treat a brain tumor with external beam radiation.

this data will be computed in advance and stored in a data library. Then deterministic methods, which are more efficient, will use the library to tie subregions together and calculate a precise dose distribution in the tumor and surrounding tissues.

"We've had good success using these methods in 2-D nuclear criticality problems," Rahnema says. "Now we'll extend them to 3-D geometry to handle the radiation therapy problem."

One challenge will be working with a different type of radiation. "With nuclear reactors, we're only dealing with neutrons," Rahnema explains. "With radiation therapy, we're working with electrons and photons, which have different characteristics. Since the radiation types are different, it might create different numerical problems."

Yet Rahnema and Fox are optimistic that their system could reduce dose errors to less than 2 percent. (Current methods are inaccurate by 5 to 10 percent, depending on where the tumor is located in the body.)

In addition to increasing dose accuracy, this software tool would enable treatment planning to become more efficient. "That's significant because improved accuracy and speed don't usually go hand in hand," Fox adds.

— T.J. Becker

■ Contact Farzad Rahnema at 404-894-3731 or farzad.rahnema@nre.gatech.edu; or Tim Fox at 404-778-2304 or tim@radonc.emory.org.



PHOTO BY MICHAEL ANDERSON, COURTESY OF NATIONAL CANCER INSTITUTE

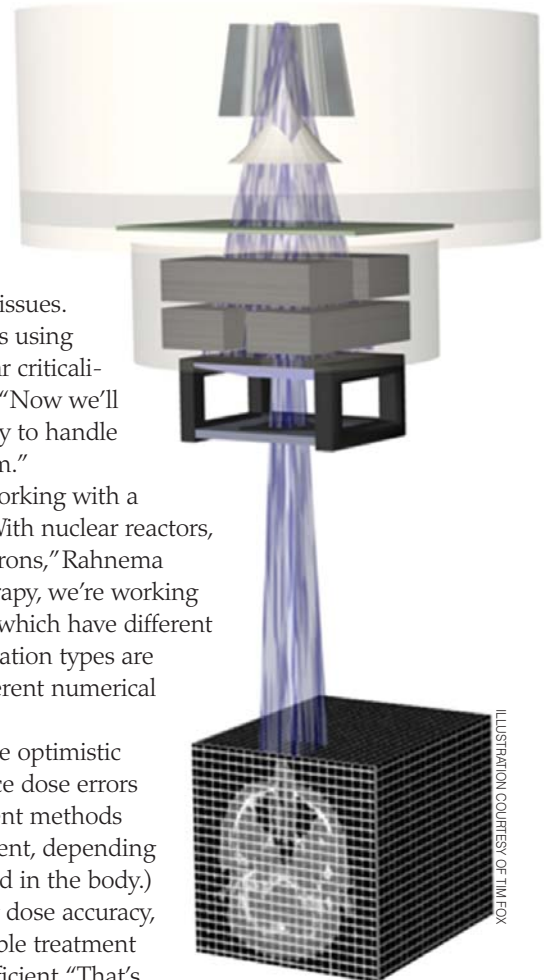


ILLUSTRATION COURTESY OF TIM FOX

Above: This illustration depicts a new computational tool that will more precisely calculate radiation dose and where it will be deposited in cancer treatment. It is under development by Professors Farzad Rahnema at Georgia Tech and Tim Fox at Emory University.

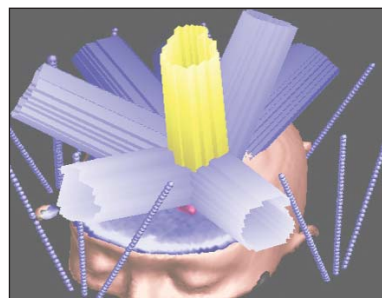
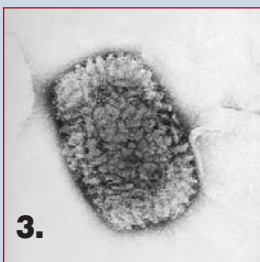
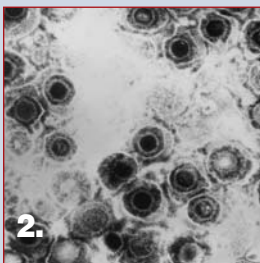
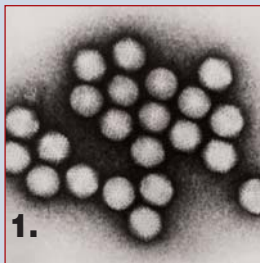


ILLUSTRATION COURTESY OF TIM FOX

Fighting Disease with Disease

Mathematical modeling may help answer questions about using viruses to treat cancer.



IMAGES COURTESY OF CDC

Among emerging cancer treatments are natural and genetically engineered oncolytic viruses — viruses that kill cancer cells while sparing normal cells. Types of virus being studied for this use are the 1.) adenovirus, 2.) herpes simplex virus, and 3.) vaccinia virus.

Among emerging cancer treatments are natural and genetically engineered oncolytic viruses — viruses that kill cancer cells while sparing normal cells.

Although virotherapy appears promising, there are many unanswered questions, such as how to administer the virus to the tumor, says Joseph Wu, an assistant professor in Georgia Tech's School of Industrial and Systems Engineering. Named a 2003 Georgia Cancer Coalition Distinguished Cancer Scholar, Wu is using mathematical models to help advance virotherapy.

Controlling viral replication and release are among issues that Wu is studying.

"The longer the virus can replicate inside the cell, the larger the burst size, which means more virus particles will be released to infect cancer cells," Wu explains. "At the same time, the longer the virus replicates inside the cell, the more time the immune system has to clear the infected cell and destroy the unreleased virus particles. We hope that mathematical modeling can help us determine an optimal infection cycle time."

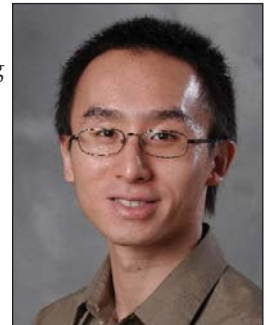
Wu is also investigating combination treatments — using virotherapy or angiogenic inhibitors to enhance traditional radiotherapy or chemotherapy. Angiogenic inhibitors are compounds that kill cancer cells indirectly by blocking the development of new blood vessels supplying the tumor's nutritional needs. Although it's unlikely that angiogenic inhibitors will be powerful enough to be a singular treatment, they might enable doctors to reduce radiotherapy and chemotherapy dosage so patients suffer less.

"Engineers can use mathematical models to help medical researchers see things quantitatively and predict outcomes," Wu says. "Mathematical modeling doesn't generate a singular solution, but it's a powerful tool to help formulate hypotheses and design experiments."

This is especially true when there is an exponential number of strategies or drugs to analyze. Mathematical modeling is a cost-effective way to narrow down the most promising treatments to take to clinical trials.

"For example, anti-HIV cocktails were designed primarily through use of mathematical models," Wu says. "Those models helped researchers avoid testing every drug combination in clinical trials. The same approach can be used to design test schedules for combination cancer therapies."

PHOTO BY NICOLE CAPPELLO



Although fighting cancer using viruses appears promising, there are many unanswered questions, such as how to administer the virus to the tumor. Assistant Professor Joseph Wu is using mathematical models to help advance this type of therapy.

■ Contact Joseph Wu at 404-894-0054 or joewu@isye.gatech.edu.

— T.J. Becker

OPTIMIZING Radiation Therapy

Software applies mathematics and engineering principles to medicine.

Through externally-applied beams or “seed” implants, radiation therapy provides a valuable tool for treating cancer. But its effectiveness depends on the ability to target cancer cells with appropriate radiation doses while sparing healthy tissues.

Associate Professor Eva Lee is using mathematical optimization techniques originally developed for the industrial world to help doctors produce the best results from radiation therapy. Her work has already produced a software planning tool that helps physicians optimize the placement of radioactive seed implants used to treat prostate cancer.

Licensed to California medical software company Prowess, Inc., the software is now undergoing U.S. Food and Drug Administration review and could be available for clinical use within months. The system, to be known as Panther™ Inverse Brachy, would be integrated into operating room computers to help plan brachytherapy operations and analyze their progress in real time.

“We can improve the local tumor control from 65 percent with traditional planning techniques to 95 percent with our automated planning software,” says Lee, who holds a joint appointment at Georgia Tech’s School of Industrial and Systems Engineering and Emory University’s Department of Radiation Oncology. She has collaborated with New York’s Memorial Sloan Kettering Cancer Center on the optimal cancer therapeutics.

Using complex mathematical algorithms, the software helps ensure that prescribed levels of radiation reach tumor cells while minimizing exposure to nearby bodily structures. Connected to an ultrasound probe that detects the location of each seed, the system allows physicians to re-optimize the placement plan while the operation is under way. Future enhancements would account for variations in the prostate shape and volume caused by swelling, and for actual location of cancer cells within the gland.

“Right now, everybody has to treat the prostate as a homogenous mass,” Lee notes. “We will be able to tailor the plan to target where the cancer is located within the prostate.”

Pioneered for prostate cancer therapy, the optimization tools could also be used in treating breast, cervical, brain and other cancers using seeds, as well as to improve the effectiveness of external beam radiation. By customizing treatment for specific patients, the software could reduce outcome differences related to the experience of physicians.

Beyond treatment planning, Lee is working with researchers at Emory’s Department of Cardiology to analyze changes in the body’s vascular system as a potential early warning for tumor development. As they grow, tumors need new capillaries to feed them nutrients and oxygen. By using pattern recognition software to study abnormal capillary changes, researchers might be able to detect early signs of cancer.

The technique – which uses fluorescence microangiography images – could also help with diagnosing heart disease, diabetes and other conditions that cause changes in the microvascular system. “The capillary system tells you a lot about what’s happening in the body – what is growing, what is dying and how things are evolving,” she explains.

Lee’s research has been supported by the National Science Foundation, the National Institutes of Health and the Whitaker Foundation.

— John Toon

■ Contact Eva Lee at 404-894-4962 or eva.lee@isye.gatech.edu.

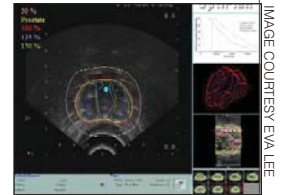


IMAGE COURTESY EVA LEE

Research under way at Georgia Tech and Emory University has already produced a software planning tool that helps physicians optimize the placement of radioactive seed implants used to treat prostate cancer.

We can improve the local tumor control from 65 percent with traditional planning techniques to 95 percent with our automated planning software.

Left: Associate Professor Eva Lee uses mathematical optimization techniques originally developed for the industrial world to help doctors produce the best results from radiation therapy. Here, she holds an ultrasound image of a prostate.



PHOTO BY GARY MEER