INNOVATIONS IN CANCER BIOLOGY, DETECTION AND TREATMENT

- Understanding Cancer’s Origins
- Detecting Cancer in New Ways
- Improving Cancer Therapy
At Georgia Tech, one of our primary goals, and indeed our passion, is to pursue research that improves the human condition.

A significant area of interdisciplinary research at Georgia Tech is advancing cancer treatment, prevention and early detection. This work is conducted in a highly collaborative environment that permeates the institute. Our scientists and engineers are working with clinicians to make discoveries in cancer research that transcend the boundaries of the laboratory bench to make a difference at the bedside. We are pleased to provide this special compilation of cancer research articles, previously published in Research Horizons, the research publication of Georgia Tech.

Researchers conducting this work have been honored for their excellence and impact. Ten of our researchers have been named Georgia Cancer Coalition Distinguished Cancer Scholars and nine Georgia Cancer Coalition Cancer Research Awards have been presented to faculty members investigating how to prevent, treat and cure cancer. In addition, ten of our faculty members who conduct cancer research hold endowed chairs through the generous gifts of alumni and friends.

We are committed to translating research results into clinical use. Through support from the State of Georgia, the Georgia Research Alliance, the Georgia Cancer Coalition, our collaborative partners at Emory University and Children’s Healthcare of Atlanta, and the generous philanthropic support of many alumni and friends, we have created an innovation ecosystem that translates multidisciplinary research into unique solutions for difficult challenges, such as cancer diagnosis and treatment. We are recognized globally for translating inventions into viable licensing and startup company opportunities through our Advanced Technology Development Center (ATDC) technology accelerator and other programs that support entrepreneurs.

This work directly supports the economic development and competitiveness goals of our state. By leveraging our intellectual capital with proven commercialization techniques, we serve as an economic engine creating jobs and partnerships delivering technologies that have a global impact on human health.

I hope you find this special issue on cancer research to be of interest. If you would like to learn more, please feel free to contact me.

Stephen E. Cross, Ph.D.
Executive Vice President for Research
Georgia Institute of Technology
Understanding the Origins of Cancer:

Scientists Investigate the Molecular Changes that Lead to Disease

Cancer is the most-feared of human diseases, often striking without warning and seemingly without identifiable cause. Decades into the nation’s war on cancer, we have learned that the disease is far more complex than we originally believed.

At the Georgia Institute of Technology, researchers are pursuing many different directions in their quest to understand how cancer arises. They are adding their findings to a deepening understanding of the complex molecular pathways that turn a normal cell into a malignant one. Ultimately, that knowledge may lead to new strategies for preventing cancer, new diagnostic techniques for finding it early – and to drugs and other agents that may provide cures.

This article describes Georgia Tech research into the origins of cancer including:

- The potential role of non-mutational changes, called epigenetics;
- An integrated approach to studying ovarian cancer;
- Mechanisms for repairing double-strand DNA breaks;
- Predicting where DNA will break, and how often it will break; and
- Understanding the role of cell-signaling molecules such as sphingolipids.

This is the first in a series of three reports that will focus on cancer research at Georgia Tech. The other two will highlight efforts to develop new diagnostics and new treatments.

Investigating the Role of Epigenetics in Cancer

While many biologists investigate cancer genetics – mutations in DNA sequences that cause the disease – a growing group of biologists is examining the role of cancer epigenetics, which are changes that contribute to malignancy without causing changes in DNA sequences.

Yuhong Fan, an assistant professor in Georgia Tech’s School of Biology, believes that the scientific field of epigenetics may help shape the future of cancer diagnosis and treatment.

“Cancer cells have drastically different epigenetic patterns compared to normal cells,” explains Fan, who is also a Georgia Cancer Coalition Distinguished Cancer Scholar. “Many epigenetic changes may appear prior to the development of invasive cancer, so I think that doctors might one day be able to detect epigenetic markers for cancer before a tumor appears.”

Epigenetic studies concentrate on the way the genome is marked and packaged inside a cell’s nucleus. Much of Fan’s research focuses on the role of H1 linker histones, a family of 10 proteins that helps to package the DNA within chromosomes.

Fan and Arthur Skoultchi, chair of the Department of Cell Biology at the Albert Einstein
College of Medicine at New York’s Yeshiva University, previously observed the effects of partially reducing H1 levels in mice. The work showed that H1 histones are important to an organism’s normal development. Expanding on these findings, Fan recently teamed with John McDonald, chief scientist of the Ovarian Cancer Institute and associate dean for biology development in the School of Biology, to determine if the multiple H1 subtypes are regulated differently in benign and malignant ovarian cancer tissues.

“We found that some of the H1 subtypes were expressed at significantly higher levels in the cancerous tissue compared to the benign tissue and some were expressed at significantly lower levels,” notes Fan. “The most remarkable finding was that these differences, whether increases or decreases, were consistent among multiple samples.”

With this knowledge, Fan’s next step is to find out what genes and functions are affected by changes in expression of each subtype. To do this, her group plans to change the level of each H1 subtype in cancer cell culture and monitor what happens to cell growth and cell fate.

“We hope that measuring the expression level of one or more of these H1 subtypes can be used as an epigenetic biomarker for the cancer diagnosis of the future,” adds Fan. “Since the expression patterns are consistent, you could easily measure a few epigenetic characteristics, rather than looking at thousands of genes.”

Funding for Fan’s research is provided by the National Institutes of Health and the Georgia Cancer Coalition.
Examining How Ovarian Cancer Develops

Unlike many cancer biology researchers who investigate general processes underlying many cancers, John McDonald focuses his investigations broadly on one type of cancer – ovarian.

Ovarian cancer is the most lethal gynecological cancer, with the American Cancer Society predicting that in the United States alone each year, more than 20,000 women will be diagnosed with ovarian cancer and 16,000 will die from it.

“Ovarian cancer is called the silent killer because by the time symptoms arise and it’s detected, it has typically spread throughout the body,” says McDonald, chief scientist of the Ovarian Cancer Institute and associate dean for biology development in the School of Biology. “Our laboratory takes an integrated approach to studying ovarian cancer by investigating its causes, establishing accurate and reliable diagnostic tests, and developing novel and effective therapies.”

One focus of McDonald’s research is to determine how cancer cells develop in the ovaries. While it is estimated that up to 90 percent of ovarian carcinomas are derived from ovarian surface epithelial cells – cells that create the thin layer of tissue that covers the ovaries – the behavior of these cells differs from other epithelial-derived carcinomas because they become more specialized as malignancy progresses.

To investigate this behavior in more detail, McDonald and Nathan Bowen, a research scientist and Georgia Cancer Coalition Distinguished Cancer Scholar, compared the gene expression profiles of ovarian surface epithelial cells isolated from the surface of healthy ovaries with those of malignant ovarian tumors collected by the Ovarian Cancer Institute.

The results showed that more than 2,000 genes were expressed at significantly different levels in the two sample types. Genes associated with adult stem cell maintenance were expressed at a much higher level in the cells isolated from healthy ovaries.

“We found that changes in the expression of genes involved in maintaining the inertness and stem cell nature of epithelial surface ovarian cells may be instrumental in the initiation and development of ovarian cancer,” explains McDonald.

The results also showed that the surface of the ovary exhibits the characteristics of an adult stem cell niche, which is a protected environment where stem cells remain inactive until a signal triggers their cell cycle and they differentiate.

Expanding on these results, McDonald, Bowen and postdoctoral fellows Roman Mezencev and Lijuan Wang are currently examining the sensitivity of ovarian cancer stem cells and differentiated cancer cells to existing chemotherapy agents.

“The preliminary results indicate that existing chemotherapy agents may effectively kill cancer cells but not touch these cancer stem cells, which could be why ovarian tumors and other cancers frequently recur,” adds McDonald.

This work was supported by the Ovarian Cancer Institute, Georgia Cancer Coalition, Golfers Against Cancer Foundation, Ovarian Cycle Foundation, Robinson Family Foundation and Deborah Nash Harris Foundation.
Investigating DNA Repair Mechanisms

Exposure to environmental carcinogens such as tobacco smoke and ultraviolet radiation can result in various types of DNA damage and subsequently lead to the development of cancer if the damage is not repaired.

Double-strand breaks, in which both strands in the DNA double helix are severed, are particularly hazardous to cells because they can lead to genome rearrangements. And their repair is intrinsically more difficult.

Biologists typically believed that double-strand breaks could only be repaired by homologous intact DNA – until recently, when Francesca Storici, an assistant professor in Georgia Tech’s School of Biology, showed that RNA could be used as a template to directly repair DNA in yeast cells. This contradicted the dogma that genetic information had to flow from DNA to RNA.

"Using RNA that naturally resides inside a cell to repair damaged DNA could represent an additional line of defense against DNA damage," says Storici, who is also a Georgia Cancer Coalition Scholar. "The capacity of RNA to record itself into DNA could be the basis of a wholly unexplored process of RNA-driven DNA evolution."

These unique RNA functions may have important implications in gene targeting and gene therapy because RNA molecules mimicking RNA oligonucleotides could be generated directly in the nucleus of targeted cells via transcription from vectors.

Since her initial discovery in yeast, Storici has used RNA to repair broken chromosomal DNA in human cells in culture and to correct a base defect in the genome of bacterial cells, suggesting that RNA-templated DNA repair is a more general mechanism. She is currently examining exactly how this direct transfer of RNA information to DNA occurs.

"While we can gain a lot of insight from understanding how a cell can repair its DNA, we can also use that information to create a better method for correcting genetic defects," notes Storici.

Her goal is to develop a tool to correct a particular mutation on a specific chromosome while causing minimal damage to the DNA. One way to do that, Storici says, might be to search for factors that facilitate delivery of the targeting molecule to the nucleus and promote the exchange of DNA strands.

To test the tool she develops, Storici is working with and constructing different human cell lines, and monitoring the repair of specific genetic defects with a simple flow cytometry assay.

Given the ability of RNA to transfer genetic information to chromosomal DNA and the possibility of amplifying RNA within cells at will, Storici plans to continue investigating new directions in gene targeting and treatment of cancer and other genetic diseases.
Understanding the Role of Sphingolipids in Cancer Development

For almost 30 years, Georgia Tech professor Alfred Merrill has been studying lipids – the fats, oils, cholesterol and certain vitamins that our bodies need to grow and survive. Today, his expertise lies in a subgroup of lipids called sphingolipids, which influence cell structure, signaling and interaction.

“The lipid backbones of sphingolipids are important cell-signaling molecules that turn on and turn off intracellular proteins that are involved in cell growth, death, and an interesting process called autophagy that has recently gained much attention in the cancer research field,” says Merrill, who is also the School of Biology’s Smithgall Chair in Molecular Cell Biology.

Autophagy – meaning “self-eating” – involves the degradation of cellular compartments, called organelles, and cellular proteins. During this process, a cell forms a vesicle that encapsulates its cytoplasm and some of the organelles and then fuses with digestive enzymes that degrade the contents of the vesicle and make them available for cell nutrition.

Interestingly, autophagy has been implicated in both cancer cell death and survival. Since Merrill’s research has shown that sphingolipid signaling is essential for creating autophagy vesicles, these metabolites may be involved in both promoting and limiting tumor growth.

Autophagy promotes cancer cell survival by allowing cells to respond to changing environmental conditions, such as nutrient deprivation. During starvation, autophagy allows cells to degrade proteins and organelles and thus obtain a source of nutrients that would not be available otherwise.

“Cancer cells use autophagy because as they are developing they have a period in which they go into a nutrient crisis because they haven’t established their own blood and nutrient flow, so they use autophagy as a way to survive in the meantime,” explains Merrill.

However, this same process of gaining nutrients can lead to tumor cell death as well. Merrill’s laboratory found that a number of anti-cancer agents promote the formation of these vesicles through sphingolipid signaling.

“Preliminary data supports the theory that the autophagic vesicles in cancer cells are unstable, so if one of their components—the sphingolipids—is out of balance, this can cause them to break apart and spill out their toxic contents, killing the cancer cell,” adds Merrill.

While the mechanism through which autophagy inhibits tumor development is still unclear, graduate student Kacee Sims is examining the role of sphingolipid pathways in the conversion of autophagy from a cancer cell survival pathway to a cell death pathway.

The project described was supported by Award No. U54GM069338 from the National Institute of General Medicine Sciences (NIGMS). Any opinions, findings, conclusions or recommendations expressed are those of the researcher and do not necessarily reflect the views of the NIGMS or the National Institutes of Health. Significant funding to support this research was also provided by the Smithgall Endowment to Georgia Tech.
Investigating the Complexity of Chromosome Breaks

Everyone has fragile sites on their chromosomes that are particularly prone to breaking, making them hot spots for rearrangements that can lead to hereditary diseases and cancer. Georgia Tech School of Biology associate professor Kirill Lobachev is trying to understand what’s special about these regions, the consequences of the breaks, and the pathways that are involved in promoting and repairing these breaks.

“It is becoming clear that the fragile sites often contain unstable repetitive sequences that can adopt unusual DNA structures,” says Lobachev. “We think that everyone is probably a carrier of these unstable motifs that can cause chromosomes to break anytime, so we ultimately want to be able to predict where a chromosome is going to break and how frequently this break will occur, and determine if we can prevent it.”

Determining whether a particular chromosomal region is predisposed to breakage requires knowledge about the structural parameters of the unstable sequences that make chromosomes fragile, such as their size or composition of the genetic sequences they contain. Using the yeast *Saccharomyces cerevisiae* as a model organism, Lobachev’s laboratory has been able to mimic some of the structural instability that cancer cell chromosomes exhibit.

In a recent study, Lobachev and colleagues demonstrated that DNA replication machinery sometimes stalls when it reaches a long sequence of palindromes—sequences that read the same way backward and forward. Further analysis has shown that chromosomes break when DNA replication is slowed or altered.
“Long palindromes were known to change the shape of DNA from a double helix into a hairpin or cruciform structure, but this was one of the first studies to show that these changes could affect DNA integrity,” explains Lobachev.

In addition, Lobachev and post-doctoral fellow Vidhya Narayanan determined that palindromic sequences induce a particular type of DNA break that is a precursor to a process involved in cancer called gene amplification. Amplification of genes involved in metabolism or inactivation of drugs can lead to chemotherapy resistance, and amplification of genes that turn normal cells into cancer cells are known to occur in several late-stage cancers.

They showed that gene amplification depends on the location of an oncogene relative to the break – called a hairpin-capped double strand break – and the end of the chromosome. The study indicated that restricting breakage of the unstable sequences may be a promising strategy for pharmaceutical cancer prevention and treatment.

In the future, knowing what genetic sequences are more likely to lead to chromosomal fragility and being able to explore genetic pathways involved in this process may help researchers identify persons who might be prone to developing cancer, adds Lobachev.

---

CONTACTS

Yuhong Fan  
404.385.1312  
yuhong.fan@biology.gatech.edu

Kirill Lobachev  
404.385.6197  
kirill.lobachev@biology.gatech.edu

John McDonald  
404.385.6630  
john.mcdonald@biology.gatech.edu

Alfred Merrill  
404.385.2842  
al.merrill@biology.gatech.edu

Francesca Storici  
404.385.3339  
francesca.storici@biology.gatech.edu

---

Collaboration with the Georgia Cancer Coalition

The Georgia Cancer Coalition’s (GCC) mission is to reduce the number of cancer deaths in Georgia. One key initiative toward accomplishing that goal is naming Georgia Cancer Coalition Distinguished Cancer Clinicians and Scientists. In concert with Georgia’s academic universities, the GCC supports the recruitment of national leaders in cancer research to Georgia. At Georgia Tech, 10 researchers are Distinguished Cancer Scholars, including:

- Ravi Bellamkonda, professor, biomedical engineering
- Nathan Bowen, senior research scientist, biology
- Yuhong Fan, assistant professor, biology
- Melissa Kemp, assistant professor, biomedical engineering
- Valeria Tohver Milam, assistant professor, materials science and engineering
- Shuming Nie, professor, biomedical engineering
- Manu Platt, assistant professor, biomedical engineering
- Francesca Storici, assistant professor, biology
- Dongmei “May” Wang, associate professor, biomedical engineering
- Ming Yuan, associate professor, industrial and systems engineering

The Georgia Cancer Coalition has also awarded nine Cancer Research Awards to Georgia Tech faculty members investigating how to prevent, treat and cure breast, ovarian and prostate cancers. Michelle Dawson, an assistant professor in Georgia Tech’s School of Chemical and Biomolecular Engineering, received one of these grants for her research into the development of specialized cells designed as gene delivery vehicles to target and treat breast cancer.

Ali Adibi, professor in the School of Electrical and Computer Engineering, received one of the 2011 grants to study label-free prostate cancer biomarkers for the detection and treatment of prostate cancer.

Elizabeth Mynatt, professor in the School of Interactive Computing, also received a grant to support the development of a distributed model of the pediatrics system in Georgia. The goal is to better understand how care processes, information and resources flow through the system.
More than a third of all Americans – some 120 million people – will be diagnosed with cancer sometime during their lives. Because the odds of survival approach 90 percent if the disease is found early, scientists worldwide are on a quest to develop ways to detect and diagnose cancer early.

At the Georgia Institute of Technology, researchers are pursuing many different directions into cancer detection and diagnostic techniques including:

- Using gold nanoparticles to locate and kill cancer cells inside the body;
- Creating software programs that improve the process of identifying cancer biomarkers from gene expression data;
- Collecting and characterizing tumor cells in a person’s bloodstream with microfluidic devices;
- Determining which gases exhaled in a person’s breath indicate the presence of breast cancer;
- Detecting ovarian cancer from patterns of metabolites found in a drop of blood; and
- Enhancing the detection of circulating tumor cells with gold nanoparticles.

This is the second in a series of three reports focusing on cancer research at Georgia Tech. The first, published in the Winter/Spring 2009 issue of Research Horizons, highlighted efforts to understand how cancer arises. The third report will highlight new cancer treatments.

Using the Power of Gold Against Cancer

A precious metal long used for jewelry, gold may soon be considered precious for cancer detection and treatment.

“Once you cut the size of gold down to a few nanometers, its properties change and it reacts with other elements, catalyzes reactions and interacts with light, which makes it valuable for medical applications,” says Mostafa El-Sayed, the Julius Brown Chair and Regents’ Professor in the Georgia Tech School of Chemistry and Biochemistry.

While his wife was fighting breast cancer – a battle she ultimately lost – El-Sayed began reading journal articles about cancer research and realized that the properties of gold might make it useful for detecting and killing cancer cells. To investigate the possibility, he began collaborating with his son, Ivan El-Sayed, a head and neck cancer surgeon at the University of California, San Francisco.

Mostafa El-Sayed designed nanometer-sized spheres of gold and attached them to antibodies targeting specific receptors on cancer cells, which were provided by his son. Using dark-field imaging, they were able to detect the cancer cells to which the antibodies had attached. They could see the cancer cell surfaces and distinguish them from healthy cells due to the strong scattering of light from the gold nanoparticles.

Then the father-son team observed that these metal nanoparticles could also act as light-activated...
heaters for killing cancer cells. By shining visible laser light on cells, they were able to selectively destroy cancer cells with much lower power than was required to kill healthy cells.

“During these experiments, we realized that gold nanoparticles have advantages over other nanostructures because they can achieve both diagnostics and therapy simultaneously,” notes Mostafa El-Sayed.

After seeing the clinical potential of gold nanospheres on cells, the researchers conducted mouse experiments in collaboration with John McDonald, associate dean for biology program development at Georgia Tech, and Erin Dickerson, formerly a research scientist in McDonald’s laboratory. Xiaohua Huang, a postdoctoral fellow at Georgia Tech and Emory University, and graduate student Erik Dreaden also contributed to this research.

By changing the shape of the nanospheres to cylindrical gold nanorods, the researchers were able to use near-infrared laser light to detect malignant tumors hidden more deeply under the skin and selectively destroy them without harming the healthy cells. Currently, research is being conducted to investigate the effects of gold nanoparticles on animals to clear the way for human clinical trials.

“The unique ability to tune the gold nanoparticle properties by varying their size, shape, composition and medium has allowed us to design nanostructures geared for specific bio-applications,” explains Mostafa El-Sayed. “Since light converted into heat selectively kills cancer cells, this treatment can be used for different kinds of cancers, avoids normal drug resistance and does not require invasive surgery, thus avoiding post surgery infections.”

This work was funded by grant number DE-FG02-97ER14799 from the U.S. Department of Energy (DOE). The content is solely the responsibility of the principal investigator and does not necessarily represent the official view of the DOE or the United States Government. Significant funding to support this research was also provided by the Julius Brown endowment to Georgia Tech.

**CONTACTS**

Charlene Bayer  
404.407.6361  
charlene.bayer@gtri.gatech.edu

Mostafa El-Sayed  
404.384.0292  
mostafa.el-sayed@chemistry.gatech.edu

Facundo Fernandez  
404.385.4432  
facundo.fernandez@chemistry.gatech.edu

Bruno Frazier  
404.894.2030  
bruno.frazier@ece.gatech.edu

John McDonald  
404.385.6630  
john.mcdonald@biology.gatech.edu

Shuming Nie  
404.712.8595  
snie@emory.edu

May Dongmei Wang  
404.385.2954  
maywang@bme.gatech.edu

**Photo: Gary Meek**

Mostafa El-Sayed (left) and Wei Qian shine laser light on cells with gold attached, allowing selective destruction of cancer cells.
Cancer Biomarker Identification Software Tools Earn Certification

The explosive growth of genomic and proteomic data has ushered in a new era of molecular medicine in which cancer detection, diagnosis and treatment are tailored to each individual's molecular profile. But this personalized medicine approach requires that researchers discover and link biomarkers — such as genes or proteins — to specific disease behaviors, such as the rate of tumor progression and different responses to treatments.

Two new software programs that help address that challenge have recently earned silver-level compatibility certification from the National Cancer Institute's cancer Biomedical Informatics Grid®, also known as caBIG®.

Developed by May Dongmei Wang and her team in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University, the programs — caCORRECT and omniBioMarker — remove noise and artifacts, and identify and validate biomarkers from microarray data. Funding to develop the programs was provided by the National Institutes of Health — primarily the Emory-Georgia Tech National Cancer Institute Center for Cancer Nanotechnology Excellence (CCNE), the Georgia Cancer Coalition, Microsoft Research and Hewlett-Packard.

“Certification by caBIG means the tools can be easily used by everyone in the cancer community to improve approaches to cancer detection, diagnosis, treatment and prevention,” says Wang, an associate professor in the Coulter Department, a Georgia Cancer Coalition Distinguished Cancer Scholar and director of the CCNE biocomputing and bioinformatics core.

daCORRECT — chip artifact CORRECTion — is a software program that improves the quality of collected microarray data, ultimately leading to improved biomarker selection. Because each microarray chip contains thousands of spots, it is easy for a few spots to become marred due to experimental variations by different laboratory technicians or errors that create scratches, edge effects and bubble effects on the data.

daCORRECT removes the noise and artifacts from the data, while retaining high-quality genes on the array. The software can also effectively recover lost information that has been obscured by...
Building Microdevices That Separate and Analyze Cancer Cells

Microfluidic devices developed at Georgia Tech are enabling cancer researchers to collect and characterize tumor cells in a person’s bloodstream. Analyzing the quantity and diversity of the cancerous cells allows for early detection of tumors and cancer metastasis, as well as the monitoring of treatment. The analysis can also indicate the type of cancer, its aggressiveness and its receptiveness to particular treatments.

“Microfluidic devices have advantages over many typical laboratory analysis systems like flow cytometry because they cost less, require only a small population of cells, demand less time and can be combined for multiple sequential analyses,” says Georgia Tech School of Electrical and Computer Engineering professor Bruno Frazier.

Frazier and graduate student Youngdo Jung designed a microfluidic device that attracts and collects magnetically labeled cells into a center channel while allowing untagged cells to travel along outer channels. To test the device with cancer cells,
they teamed with Emory University researchers Lily Yang, an associate professor of surgical oncology research; Georgia Chen, an associate professor of hematology and oncology; and Dong Shin, a professor of hematology and oncology.

Because the proteins located on the surfaces of cancer and normal cells are different, the researchers selectively targeted the proteins on the cancer cell surfaces and tagged them with magnetic nanoparticles. In experiments, the researchers were able to collect 86 percent of the tagged cancer cells in the center outlet and 95 percent of the non-tagged red blood and white blood cells in the side outlet, with a flow rate of 100 microliters per hour.

Excited with the experimental results, Frazier’s team combined the microseparator with a downstream impedance spectroscopy microsystem, which traps a single cell in an analysis cavity and measures its electrical impedance.

“This impedance spectroscopy system allows us to determine the heterogeneity of a tumor, including the percentages of normal cells and different stage cancer cells, which is information that can be used to create a personalized treatment regimen,” explains Frazier.

In experiments with normal and cancerous breast cells, the researchers observed significant differences in the magnitude and phase of the impedance signal, enabling them to easily classify the cells. The technique can distinguish normal human breast tissue cells, early-stage breast cancer cells, invasive breast cancer cells and metastasized breast cancer cells.

Since completing the cellular experiments, the Georgia Tech and Emory researchers have begun testing the microsystems with blood and tissue samples from breast and head/neck cancer animal models.

“We believe that the microfluidic devices we’ve built will eventually play a key role in numerous aspects of cancer diagnosis and treatment, including detecting and evaluating metastatic disease, selecting and individualizing initial surgical and medical therapies, monitoring disease progression and understanding the fundamental biology of metastasis,” notes Frazier.

This work was funded by grant number ES10846 from the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH). The content is solely the responsibility of the principal investigator and does not necessarily represent the official view of the NIEHS or the NIH.
Breath Test Studied for Detecting Breast Cancer

Early breast cancer detection can significantly improve survival rates. However, current diagnostic tests expose women to the potentially harmful effects of radiation—and often fail to detect cancer in the earliest stages.

A team of researchers from Georgia Tech, Emory University and the University of Ulm in Germany are using a portable, non-invasive device to determine which biomarker gases exhaled in a person’s breath indicate the presence of breast cancer.

“Scientists know that it’s possible to detect different chemical compounds from a person’s breath and relate them to illness,” explains Charlene Bayer, principal research scientist at the Georgia Tech Research Institute (GTRI). “Yet they haven’t been able to quantify results—such as determining a patient has a tumor because he or she has X amount of Y compounds in his or her breath.”

Breath biomarkers are volatile organic compounds originating in the lower lungs. Certain compounds are related to oxidative stress, the body’s response to inflammation, and are often an indication of disease.

As a patient breathes into the device, these compounds are trapped and examined by a sensor. The researchers’ sensing methodology combines gas chromatography—a technique for separating complex compounds—with mass spectrometry, which identifies the chemical makeup of a substance. Specific patterns in the compounds are then found and used to confirm the presence or absence of the disease.

The team recently conducted a clinical study analyzing more than 300 volatile organic compounds in breath samples of 20 healthy women over the age of 40 and 20 women recently diagnosed with stage II-IV breast cancer and who had not received treatment. The results showed that the breath analysis was able to determine whether the sample came from a cancer patient or healthy subject 78 percent of the time.

The researchers are currently adding to their clinical database of breath data and trying to determine which compounds are most important for detecting breast cancer. That could help reduce the number of compounds tested.

Because it can offer immediate results right in a physician’s office, Bayer expects the device will help increase early detection among those who do not have the resources for a mammogram, more easily conduct interval testing for those with a genetically high risk for breast cancer, and facilitate recurrence testing after breast cancer treatment.

Other researchers involved in this project include Brani Vidakovic, a professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University; Sheryl G.A. Gabram, a professor of surgery in the Division of Surgical Oncology at Emory University; and University of Ulm professor Boris Mizaikoff.
Creating an Ovarian Cancer Detection Tool

Scientists at Georgia Tech are using patterns of metabolites found in a drop of blood to detect ovarian cancer. Using an analytical technique called mass spectrometry, the researchers have been able to differentiate between serum samples taken from patients with ovarian cancer and those from unaffected individuals.

“Ovarian cancer is the fourth leading cause of death in women, but it is a relatively rare cancer, so a functionally useful diagnostic test has to be 99 percent accurate or you are going to get too many false positives,” says John McDonald, chief scientist of the Ovarian Cancer Institute and associate dean for biology development in the School of Biology.

McDonald teamed with mass spectrometry expert Facundo Fernandez, an associate professor in the Georgia Tech School of Chemistry and Biochemistry, to sort molecules in the serum based on their weight and electrical charge.

“We focused on metabolites as opposed to proteins or peptides because we get better quantification and higher resolution for the smaller molecules that comprise the human metabolome,” explains Fernandez.

With the help of Alexander Gray, an assistant professor in the Georgia Tech College of Computing’s Computational Science and Engineering Division, the research team was able to detect patterns of key metabolites in the blood. Using a sophisticated artificial intelligence computer program, they were able to “train” the computer to distinguish patterns of small metabolites found in the blood of cancer patients from those of control subjects.

The scientists first used serum samples from known cancer patients and unaffected individuals to establish metabolomic patterns that were present at different levels in the two groups. The machine learning program identified a pattern consisting of only a few dozen metabolites, among thousands of candidates, which could be used to distinguish between women with ovarian cancer and women with non-cancerous conditions.

Once these patterns were identified, the researchers tested the patterns of the same metabolites in a different set of serum samples from other patients with and without cancer. The researchers identified the samples with 99 percent accuracy.

The identity of the key metabolites and the role they may play in ovarian cancer is still under investigation, but the development of an accurate and reliable diagnostic test will save lives when combined with existing therapies, according to McDonald.

“Another great thing about this approach is that it may be possible to extend it for the early detection of any type of cancer or any disease from a droplet of blood,” adds McDonald.

This work is supported by the Ovarian Cancer Institute, Deborrah Nash Harris Endowment Fund, the Ovarian Cycle Foundation and the Georgia Research Alliance VentureLab program.
Tiny gold particles can help doctors detect tumor cells circulating in the blood of patients with head and neck cancers, researchers at Emory University and Georgia Tech have found.

The detection of circulating tumor cells (CTCs) is an emerging technique that can allow oncologists to monitor patients with cancer for metastasis or to evaluate the progress of their treatment. The gold particles, which are embedded with dyes allowing their detection by laser spectroscopy, could enhance this technique's specificity by reducing the number of false positives.

The results were published in the March 2011 issue of the journal *Cancer Research*.

One challenge with detecting CTCs is separating out signals from white blood cells, which are similarly sized as tumor cells and can stick to the same antibodies normally used to identify tumor cells. Commercially available devices trap CTCs using antibody-coated magnetic beads, and technicians must stain the trapped cells with several antibodies to avoid falsely identifying white blood cells as tumor cells.

Emory and Georgia Tech researchers show that polymer-coated and dye-studded gold nanoparticles, directly linked to a growth factor peptide rather than an antibody, can detect circulating tumor cells in the blood of patients with head and neck cancers.

"Nanoparticles could be instrumental in modifying the process so that circulating tumor cells can be detected without separating the tumor cells from normal blood cells," said Shuming Nie, a professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. "We’ve demonstrated that one tumor cell out of approximately 1 to 10 million normal cells can be detected this way."

In collaboration with oncologists at Winship Cancer Institute, researchers used nanoparticles to test for CTCs in blood samples from 19 patients with head and neck cancer. Of these patients, 17 had positive signals for CTCs in their blood. The two with low signals were verified, by a different technique, to have no circulating cells.

"Although the results have not been compared or validated with current CTC detection methods, our 'one-tube' surface-enhanced Raman scattering technology could be faster and lower in costs than other detection methods," said Dong Moon Shin, professor of hematology and oncology and otolaryngology, associate director of academic development for Winship Cancer Institute and director of the Winship Cancer Institute Chemoprevention Program. "We need to validate this pilot study by continuing with larger groups of patients and comparing with other tests."
Cancer treatment typically involves surgery, radiation therapy, chemotherapy, hormone therapy or biological therapy. An oncologist may use one therapy or a combination of methods, depending on the type and location of the cancer, whether the disease has spread, the patient’s age and general health, and other factors.

At Georgia Tech, researchers are pursuing many different directions toward improving existing cancer treatment methods and developing new therapeutic techniques, including:

- Attacking cancer stem cells;
- Improving radiation therapy;
- Including motion and biological information in planning treatment;
- Assessing a tumor’s ability to create new blood vessels;
- Developing a new approach to targeted cancer therapy;
- Increasing responses to chemotherapy;
- Enabling personalized drug delivery;
- Analyzing gene expression data to predict response to drugs;
- Predicting the age of T cells to improve cancer immunotherapy;
- Capturing free-floating cancer cells to reduce metastasis;
- Aiding surgeons in detecting the edges of tumors; and
- Designing a brain tumor treatment that captures migrating cancer cells.

Recent evidence suggests that certain cancers may persist or recur after treatment because a few cells – called cancer stem cells – survive existing therapy and then seed new tumors. These stem cells can be particularly resistant to chemotherapy and radiation.

“In the future, effective cancer therapy may require the detection and elimination of cancer stem cells in tumors,” said Gang Bao, the Robert A. Milton Chair in Biomedical Engineering in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. “Developing a method to detect cancer stem cells is challenging because evidence suggests there is only one cancer stem cell for every 100,000 to 1 million cancer cells in tumor tissue, so the method must be very sensitive.”

Bao and postdoctoral fellow Won Jong Rhee recently developed a new method that effectively discriminates cancer stem cells from other cancer cells by locating protein markers on the surface of stem cells and stem cell-specific genes inside cancer stem cells. The work was published on April 2, 2009, in the journal BMC Biotechnology.

The researchers located live stem cells by simultaneously detecting the presence of the stem cell surface protein marker SSEA-1 with dye-labeled antibodies and stem cell-specific mRNA – called
Oct-4 – inside the stem cells using molecular beacons.

“By fluorescently imaging the level of Oct-4 mRNA in the cytoplasm of live stem cells with molecular beacons, we were able to increase the detection sensitivity and specificity,” explained Bao, who is also a Georgia Tech College of Engineering Distinguished Professor.

Since initially developing this method for detecting and isolating stem cells, the research team has been improving the method’s efficiency and specificity by targeting multiple mRNAs and cell surface markers using molecular beacons and antibodies. According to Bao, the next stage for this research is to isolate cancer stem cells from human tumor tissue samples.

“After we isolate the cancer stem cells, we still need to learn more about them, including the pathways or genes responsible for their development and whether they behave the same when isolated from different patients. Then we need to identify drug molecules that can kill them,” he added.

Funding for this research is provided by the Emory-Georgia Tech National Cancer Institute Center for Cancer Nanotechnology Excellence (CCNE).

Improving Radiation Therapy

One critical challenge in radiation therapy has always been how best to minimize damage to normal tissue while delivering therapeutic doses to cancer cells. Intensity-modulated radiation therapy (IMRT) is an advanced type of radiation treatment that utilizes computer-controlled linear accelerators to deliver precise radiation doses to tumors while avoiding critical organs. Clinicians can use IMRT to treat difficult-to-reach tumors – such as tumors in the brain, head, neck, prostate, lung and liver – with new levels of accuracy.

“Constructing an IMRT treatment plan that irradiates the cancerous tumor without

CONTACTS

Shabbir Ahmed
shabbir.ahmed@isye.gatech.edu

Gang Bao
gang.bao@bme.gatech.edu

Ravi Bellamkonda
ravi@gatech.edu

Melissa Kemp
melissa.kemp@bme.gatech.edu

Eva Lee
eva.lee@isye.gatech.edu

John McDonald
john.mcdonald@biology.gatech.edu

Valeria Milam
valeria.milam@mse.gatech.edu

Shuming Nie
snie@emory.edu

Adegboyega “Yomi” K. Oyelere
aoyelere@gatech.edu

Lakeshia Taite
lakeshia.taite@chbe.gatech.edu

Ming Yuan
ming.yuan@isye.gatech.edu
impacting adjacent normal structures is challenging," explained Shabbir Ahmed, an associate professor in the Stewart School of Industrial and Systems Engineering at Georgia Tech. "Because of the many possible beam geometries and the range of intensities, there are an infinite number of treatment plans and many metrics to assess their quality."

To develop better treatment plans faster, Ahmed began working with School of Industrial and Systems Engineering professor Martin Savelsbergh and graduate student Halil Ozan Gozbasi, as well as collaborators Ian Crocker, Timothy Fox and Eduard Schreibmann from the Emory University School of Medicine's Department of Radiation Oncology. Funding for this research was provided by Emory University.

The Georgia Tech researchers built on an existing model and developed a fully automated program that simultaneously generates several high-quality treatment plans satisfying the clinician-provided requirements. The optimization program uses three-dimensional computed tomography images of the patient and information about (1) the type, location and size of the tumor; (2) maximum allowable doses to non-cancerous organs; and (3) the patient’s health.

"Previous models would produce one treatment plan in an hour and then if it was not exactly what the clinician wanted, someone would have to change the requirements and rerun the program to create a new treatment plan," explained Ahmed. "Our program produces several optimized solutions in a fraction of the time."

The technology, which has been tested successfully on real brain, head/neck and prostate cancer cases, produces clinically acceptable treatment plans in less than 15 minutes.
Including Motion and Biological Information in Treatment Planning

Intensity-modulated radiation therapy (IMRT) treatment planning is challenging because some organs, such as the prostate, move due to normal daily volume changes in the bladder and rectum. In addition, a tumor can change shape during radiation treatment, which typically lasts five days a week for five to 10 weeks.

Eva Lee, an associate professor in the Georgia Tech School of Industrial and Systems Engineering, and Joseph Deasy, a professor and director of the Division of Bioinformatics and Outcomes Research in the Department of Radiation Oncology at Washington University in St. Louis, are addressing motion issues with liver and lung cancer patients.

By collecting computed tomography images over time, the researchers can track every spatial point of interest in the tumor and surrounding area during each phase of the breathing cycle. This allows them to develop treatment plans that account for breathing, motion and shape changes throughout the treatment regimen.

“Accounting for motion in the image-guided treatment planning dramatically improves under-dosing the tumor tissue and even reduces the dose to normal tissue and critical organs,” noted Lee, who is also director of the Center for Operations Research in Medicine and HealthCare at Georgia Tech.

In lung cancer cases, that means reducing the average dose of radiation to the normal lung tissue, heart and esophagus. For liver cancer, the researchers have reduced the radiation delivered to normal liver and non-liver tissues.

In another project, Lee and Marco Zaider, an attending physicist and head of brachytherapy physics in medical physics at Memorial Sloan-Kettering Cancer Center in New York, are incorporating biological information into treatment planning for prostate cancer IMRT and brachytherapy – the placement of radioactive “seeds” inside a tumor.

Using magnetic resonance spectroscopy, the researchers identified regions of the prostate that had denser populations of tumor cells. These areas could then be targeted with an escalated radiation dose, while maintaining a minimal dose to critical and normal tissues.

“One of our main concerns is avoiding normal tissue toxicity, so by targeting only the ‘bad’ pockets of tumor cells, we hope to improve the outcome,” said Zaider. “Biological optimization attempts to target tissue that is potentially responsible for metastatic spread.”

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

This project was partially supported by Award No. 0800057 from the NSF and Award No. S1UL1RR025008-02 from the NIH. The content is solely the responsibility of the principal investigator and does not necessarily represent the official views of the NSF or NIH.

Assessing a Tumor’s Ability to Create New Blood Vessels

Cancer manifests itself in different ways – some cancers proceed slowly, while others spread aggressively. These differences have led clinicians to believe that personalized cancer therapies might be the best solution for treating the disease.

Now, new research, published in the June 2009 issue of the journal PLoS ONE, is providing insight into the aggressiveness of tumors. This information could facilitate development of a personalized treatment regimen.

Because aggressive tumors create more new blood vessels to sustain their growth, researchers designed long-circulating nanoparticles that were 100 nanometers in diameter and contained a contrast agent that could only seep into tumors from blood vessels that were growing and therefore leaky.

“We exploited the fact that the nanoparticles are too big to leak out of normal blood vessels, but they can leak out of newly forming tumor vessels because these immature vessels have bigger holes in them,” explained lead author Ravi Bellamkonda, a professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University.

The study showed that the degree of “leakiness” of tumor blood vessels to the nanoprobe correlates to its expression of vascular endothelial growth factor (VEGF), a protein that stimulates the growth of new blood vessels in tumors.
Clinical studies have shown that VEGF expression varies among tumors, with higher levels of VEGF expression correlating with unfavorable prognosis, but scientists haven’t been able to non-invasively determine VEGF expression levels in individual tumors until now,” said Bellamkonda, who is also a Georgia Cancer Coalition Distinguished Scholar.

After injecting the contrast-containing nanoprobes into rats with six-day-old breast cancer tumors, the research team visualized the levels of nanoprobe accumulation in the tumor using digital mammography. The results showed increased “leakiness,” nanoprobe accumulation and tumor growth rates in tumors with higher levels of VEGF. Similar-size tumors showed various degrees of angiogenesis and blood vessel permeability, which caused them to behave differently, emphasizing the inherent variability in tumors and the need for a personalized approach to each tumor.

“In the future, instead of just measuring the size of a tumor, clinicians can quantify the leakiness of tumor blood vessels to determine the extent of angiogenesis in each tumor and decide which patients should undergo anti-angiogenic therapy or other aggressive treatment regimens,” added Bellamkonda.

Collaborators on this research include Efstatios Karathanasis, formerly a Coulter Department postdoctoral fellow and currently an assistant professor in the Department of Biomedical Engineering at Case Western Reserve University; Carl D’Orsi and Ioannis Sechopoulos of the Department of Radiology and Winship Cancer Institute at the Emory University School of Medicine; and Ananth Annapragada, an associate professor of health information sciences at the University of Texas, Houston.

This project is supported by the National Science Foundation (NSF) (Award Nos. 0401627 and ERC-EEC-9731643), the Nora Reed Foundation, the Wallace H. Coulter Foundation and the Georgia Cancer Coalition. The content is solely the responsibility of the principal investigator and does not necessarily represent the official view of the NSF.
Developing a New Approach to Targeted Cancer Therapy

A new therapeutic strategy for cancer treatment is to inhibit enzymes called histone deacetylases, which play an important role in the regulation of gene expression. Vorinostat (SAHA) – a histone deacetylase inhibitor – was approved by the U.S. Food and Drug Administration in 2006 to treat an immune system cancer called cutaneous T-cell lymphoma.

While these inhibitors are clinically valuable, they typically inhibit many of the 18 different histone deacetylase subtypes, a process that can be harmful to essential cell functions throughout the body.

“Our goal is to create inhibitors for these enzymes that target specific cancerous organs so that we can exploit their anti-cancer activity in the cancerous tissue areas only and not negatively affect other areas of the body,” said Adegboyega “Yomi” K. Oyelere, who holds the Blanchard Assistant Professorship in the Georgia Tech School of Chemistry and Biochemistry.

In the January 22, 2009, issue of the *Journal of Medicinal Chemistry*, Oyelere and Georgia Tech biology assistant professor Yuhong Fan described a new class of potent non-peptide histone deacetylase inhibitors that can be selectively accumulated in the lungs. To create them, the researchers modified the amine sugar portion of common antibiotics such as azithromycin and clarithromycin with a histone deacetylase inhibiting structure. Experiments have shown that the new compounds are more potent than SAHA and are lung-specific. As a result of these preliminary findings, Oyelere was recently awarded a five-year, $1.5 million grant from the National Institutes of Health to continue this lung cancer research.

Oyelere is also designing histone deacetylase inhibitors that...
Chemical and biomolecular engineering assistant professor Lakeshia Talte is investigating ways to smuggle powerful chemotherapeutic drugs and chemical compounds into tumor cells, thus increasing the drugs’ cancer-killing activities and reducing their toxic side effects on healthy cells.
Increasing Responses to Chemotherapy

Lakeshia Taite is investigating ways to smuggle powerful chemotherapeutic drugs and chemical compounds into tumor cells, thus increasing the drugs’ cancer-killing activities and reducing their toxic side effects on healthy cells.

As an assistant professor in the Georgia Tech School of Chemical and Biomolecular Engineering, Taite is developing cancer drug delivery vehicles composed of a gold nanoshell core with dendrimers attached to the surface. Dendrimers are polymers that exhibit a tree-like structure with many branches and cavities where chemotherapy drugs can be encapsulated.

The dendrimers are synthesized with targeting molecules on their surfaces that can seek out and bind to cancer cells. Introduced into the body, they bind to cancer cells, and when near-infrared light shines on the body, the gold nanoshell heats up. That heat leads the dendrimers to shrink, the drug to be released, and the tumor cells are exposed to both the heat and drug therapies.

“In some cases, ablation takes place at temperatures that can be uncomfortable to the patient, so we are trying to develop dendrimers that require lower transition temperatures to release the drug,” said Taite. “We believe that even if the lower temperature does not kill all of the cancer cells, it will still damage them enough that they will become extremely vulnerable to the drug, ultimately still leading to cell death.”

Amanda Lowery, a research fellow in radiation oncology at Vanderbilt University, is collaborating with Taite on this research.

Taite is also designing another delivery vehicle to carry and release nitric oxide for the treatment of aggressive brain tumors. She is focusing on nitric oxide because it has the ability to cross the blood-brain barrier and help other molecules cross both the blood-brain barrier and the blood-tumor barrier.

“Nitric oxide has been shown to increase the sensitivity of certain tumors to chemotherapeutics and radiation, so we are working to form materials that can be attached to imaging particles and a chemotherapeutic that can be targeted to specific tumors. That would significantly enhance current tumor treatment approaches,” explained Taite.

The targeted nitric oxide delivery system will be used to study the efficacy of using nitric oxide to sensitize brain tumors to treatment and improve patient prognosis.

“My ultimate goal in designing all of these drug delivery systems is to improve patient quality of life and reduce cancer recurrence,” added Taite.

Enabling Personalized Drug Delivery

The search is on for drug delivery systems that allow treatment to be tailored to an individual patient and a particular tumor. Researchers at Georgia Tech are contributing to the pursuit by developing ways to program the assembly and disassembly of multi-particle drug delivery vehicles.

“Cancer is a complicated disease, and we wanted to find a way that we could simultaneously deliver many different particles to the tumor site as a package and, upon arrival, break open the packages so that the individual particles could then carry out their particular functions,” said Valeria Milam, an assistant professor in the Georgia Tech School of Materials Science and Engineering.

Individuals benefit from this type of personalized treatment through the increase in the drug’s cancer-killing power and the reduction of its toxic side effects.

Milam and her students are using short nucleic acid polymers called oligonucleotides to connect the particle surfaces for simultaneous delivery of different therapeutic and diagnostic agents to the tumor site.

“To assemble the pieces, we are using short oligonucleotides as the glue because they have a weak, yet sufficient affinity for their partner strand,” explained Milam, who is also a Georgia Cancer Coalition Distinguished Cancer Scholar. “This allows us to direct particles A and B to attach to particle C through oligonucleotide linkages, while keeping particles A and B unconnected to one another.”

Then, to disassemble the particle package, a competitive oligonucleotide – one with a stronger affinity as a partner strand – is introduced into the system. These competitive strands displace the original partner strands, allowing the package to break open. Milam and her team are further improving the drug delivery vehicle so that it can be initially camouflaged to avoid any host response that would...
clear it out of the body before arriving at the tumor site.

“Our ongoing work involves initially masking the presence of the therapeutic carriers by applying a stealth coating to the vehicle surface,” noted Milam. “Then, after the desired circulation time, the coating will be shed to reveal cancer-targeting ligands.”

While Milam’s experiments are still at the laboratory stage, her ultimate goal is to develop materials that can be used in the clinical setting to treat cancer. Former Georgia Tech students Christopher Tison and Sonya Parpart, and current graduate students James Hardin and Bryan Baker, also worked on this research. This work is currently supported by the Georgia Cancer Coalition, a National Science Foundation CAREER award, and the U.S. Army. It was previously supported by the Emory-Georgia Tech National Cancer Institute Center for Cancer Nanotechnology Excellence (CCNE).

This material is based upon work supported by the U.S. Army (Award No. W911NF-09-1-0479), National Institutes of Health (NIH) (Award No. U54CA119338) and National Science Foundation (NSF) (Award No. CMSR-0847436). Any opinions, findings, conclusions or recommendations expressed are those of the principal investigator and do not necessarily reflect the views of the U.S. Army, NIH or NSF.

Analyzing Gene Expression Data to Predict Drug Response

The major clinical goals in applying gene expression profiling to cancer are to develop predictors of drug response that will guide more individualized therapies.

Ming Yuan, an associate professor in the Stewart School of Industrial and Systems Engineering at Georgia Tech, is using computational and mathematical approaches to analyze how gene expression evolves over time in individuals with breast cancer and whether these patterns can predict treatment outcome. Specifically, Yuan is studying how gene expression evolves during the menstrual cycle and whether there is any association between these patterns and cancer relapse.

“Our goal is to weed out the genes that just change expression level due to a woman’s menstrual cycle and not because of tumor progression or treatment,” explained Yuan, who is also a Georgia Cancer Coalition Distinguished Cancer Scholar. “We want to know which genes are abnormally expressed over time and behave differently than the majority of genes because that would make them likely drug targets.”

Better predictors of relapse risk could help cancer patients make better treatment decisions in consultation with their physicians. Yuan is working with William Hrushesky of the University of South Carolina and the Dorn Veterans Affairs Medical Center on this research.

In another project, Yuan is collaborating with two University of Wisconsin professors, Alan Attie and Christina Kendzierski, to conduct expression quantitative trait loci (eQTL) studies. This analysis allows the researchers to identify genomic hot spots that regulate gene transcription and expression on a genome-wide scale. “We want to determine which regions of the genome are most predictive of expression variations, but it’s challenging because there are a vast range of possible regulatory loci and many of them are correlated, making it hard to differentiate which is actually responsible for a given effect,” said Yuan.

Yuan’s analysis will determine the hot spots as well as how those genes are connected to each other, but ultimately, the proposed genes will need to be studied further by biologists.

Yuan’s research is supported by the National Science Foundation and the Georgia Cancer Coalition.

This work was partly funded by grant number DMS-0846234 from the National Science Foundation (NSF). The content is solely the responsibility of the principal investigator and does not necessarily represent the official view of the NSF.
Professor Allen Tannenbaum displays the computer program he developed to extract the prostate (shown in blue) from magnetic resonance images.

James Hardin, Valeria Milam and Bryan Baker (left to right) display multi-particle drug delivery vehicles designed to allow cancer treatment to be tailored to an individual patient and a particular tumor.
Predicting Age of T Cells to Improve Cancer Immunotherapy

Manipulation of cells by a new microfluidic device may help clinicians improve a promising cancer therapy that harnesses the body’s own immune cells to fight such diseases as metastatic melanoma, non-Hodgkin’s lymphoma, chronic lymphocytic leukemia and neuroblastoma.

The therapy, known as adoptive T cell transfer, has shown encouraging results in clinical trials. This treatment involves removing disease-fighting immune cells called T cells from a cancer patient, multiplying them in the laboratory and then infusing them back into the patient’s body to attack the cancer. The effectiveness of this therapy, however, is limited by the finite lifespan of T cells — after many divisions, these cells become unresponsive and inactive.

“Our statistical model, enabled by the data generated with the microfluidic device, revealed an optimal combination of extracellular and intracellular proteins that accurately predict T cell age,” said Melissa Kemp, an assistant professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University and a Georgia Cancer Coalition Distinguished Cancer Scholar. “Knowing this information will help facilitate the clinical development of appropriate T cell expansion and selection protocols.”

Being able to assess the age and responsiveness of T cells — and therefore transfer only young functional cells back into a cancer patient’s body — offers the potential to improve the therapeutic outcome of several cancers.

For their study, Kemp, electrical engineering graduate student Catherine Rivet and biomedical engineering undergraduate student Abby Hill analyzed CD8+ T cells from healthy blood donors. To obtain biomarker and dynamic signaling-event measurements, the researchers ran the donor T cells through a microfluidic device designed in collaboration with Hang Lu, an associate professor in the Georgia Tech School of Chemical & Biomolecular Engineering.

They acquired information from 25 static biomarkers and 48 dynamic signaling measurements and found a combination of phenotypic markers and protein signaling dynamics — including Lck, ERK, CD28 and CD27 — to be the most useful in predicting cellular age.

With the donor T cell data, the researchers developed a model to assess which biomarkers or dynamic signaling events best predicted the quality of T cell function. The model found the most informative data in predicting cellular age to be the initial changes in signaling dynamics.

Details on the microfluidic device and statistical model were published in the March 2011 issue of the journal Molecular & Cellular Proteomics. This work was supported by the National Institutes of Health, Georgia Cancer Coalition and Georgia Tech Integrative BioSystems Institute.

This project is supported in part by the National Institutes of Health (NIH) (Grant No. R21CA134299). The content is solely the responsibility of the principal investigator and does not necessarily represent the official views of the NIH.
Capturing Free-Floating Cancer Cells to Reduce Metastasis

A paper published in the January 2011 issue of the journal *Nanomedicine* could provide the foundation for a new ovarian cancer treatment option – one that would use an outside-the-body filtration device to remove a large portion of the free-floating cancer cells that often create secondary tumors.

Researchers have formed a startup company and are working with a medical device firm to design a prototype treatment system that would use magnetic nanoparticles engineered to capture cancer cells. Added to fluids removed from a patient’s abdomen, the magnetic nanoparticles would latch onto the free-floating cancer cells, allowing both the nanoparticles and cancer cells to be removed by magnetic filters before the fluids are returned to the patient’s body.

In mice with free-floating ovarian cancer cells, a single treatment with an early prototype of the nanoparticle-magnetic filtration system captured enough of the cancer cells that the treated mice lived nearly a third longer than untreated ones. The researchers expect multiple treatments to extend the longevity benefit, though additional research will be needed to document that and determine the best treatment options.

“Almost no one dies from primary ovarian cancer,” said John McDonald, a professor in Georgia Tech’s School of Biology and chief research scientist of Atlanta’s Ovarian Cancer Institute. “You can remove the primary cancer, but the problem is metastasis. A good deal of the metastasis in ovarian cancer comes from cancer cells sloughing off into the abdominal cavity and spreading the disease that way.”

The removal system being developed by McDonald and postdoctoral fellow Ken Scarberry – who is also CEO of startup company Sub-Micro – should slow tumor progression in humans. It may reduce the number of free-floating cancer cells enough that other treatments, and the body’s immune system, could keep the disease under control.

“If you can reduce metastasis, you can improve the lifespan of the person with the disease and get a better chance of treating it effectively,” said McDonald.

Though much more research must be done before the technique can be tested in humans, McDonald and Scarberry envision a system very similar to what kidney dialysis patients now use, but with a buffer solution circulated through the peritoneal cavity to pick up the cancer cells.

The research has been supported by the Georgia Research Alliance (GRA), the Ovarian Cancer Institute, the Robinson Family Foundation and the Deborah Nash Harris Endowment. A member of Georgia Tech’s ATDC startup accelerator program and a GRA VentureLab company, Sub-Micro has also raised private funding to support its prototype development.
Aiding Surgeons in Detecting Edges of Tumors

Biomedical engineers are developing a hand-held device called a SpectroPen that could help surgeons see the edges of tumors in human patients in real time during surgery.

Scientists at Emory University, Georgia Tech and the University of Pennsylvania describe the device in an article published in October 2010 in the journal *Analytical Chemistry*.

What a patient with a tumor wants to know after surgery can be expressed succinctly: "Did you get everything?" Statistics indicate that complete removal, or resection, is the single most important predictor of patient survival for most solid tumors.

“This technology could allow a surgeon to directly visualize where the tumors are, in real time. In addition, a post-surgery scan could check tumor margins,” said Shuming Nie, a professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. “A major challenge is to completely remove the tumor as well as identify lymph nodes that may be involved.”

The SpectroPen can be used to detect fluorescent dyes, and also scattered light from tiny gold particles, a technology that Nie and his colleagues have been refining.

The particles consist of polymer-coated gold, coupled to a reporter dye and an antibody that sticks to molecules on the outsides of tumor cells more than it sticks to normal cells. Through an effect called surface-enhanced Raman scattering, the gold in the particle greatly amplifies the signal from the reporter dye. Nie and his team have been able to show that the particles can detect tumors smaller than one millimeter grafted into rodents.

The SpectroPen combines a near-infrared laser and a detector for fluorescence or scattered light. It is connected by a fiber optic cable to a spectrometer that can record fluorescence and Raman signals.

The research was carried out by an interdisciplinary team of senior investigators including May Wang, Coulter Department at Georgia Tech and Emory University; Sunil Singhal, University of Pennsylvania; and James Provenzale and Brian Leyland-Jones, Emory University.

Provenzale and surgeons at the University of Georgia College of Veterinary Medicine are currently using this device to operate on dogs with naturally occurring tumors. Singhal is applying to conduct clinical trials involving patients with lung cancer.

The research was supported by a Grand Opportunities (GO) grant from the National Cancer Institute (NCI) and the NIH Director’s Office, and by the NCI Centers of Cancer Nanotechnology Excellence (CCNE) at Emory and Georgia Tech.
Designing a Brain Tumor Treatment That Captures Migrating Cancer Cells

In August 2010, the Georgia Institute of Technology received a EUREKA grant from the National Institutes of Health (NIH) to design a new way to treat invasive brain tumors by capturing the migrating cells that spread the disease. The EUREKA — Exceptional, Unconventional Research Enabling Knowledge Acceleration — program helps scientists test new, unconventional ideas or tackle major methodological or technical challenges.

The research team plans to develop a system that will excavate brain tumor cells by directing them away from their location in the interior of the brain to a more external location where they can be removed or killed. Nanofiber-based polymer thin films coated with biochemical cues will be aligned in the brain to provide a corridor for tumor cells to follow to a gel-based ‘sink’ where they will be captured and safely removed or encouraged to die through chemical signaling.

“We believe this is the first attempt to exploit the invasive, migrating properties of brain tumors by engineering a path for the tumors to move away from the primary site to a location where treatment can occur,” said lead investigator Ravi Bellamkonda, a professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University.

Collaborating with Bellamkonda on this project are Tobey MacDonald, director of the pediatric neuro-oncology program at the Aflac Cancer Center and Blood Disorders Service of Children’s Healthcare of Atlanta and an associate professor of pediatrics at the Emory University School of Medicine; and Barun Brahma, a pediatric neurosurgeon at Children’s Healthcare of Atlanta.

The National Cancer Institute is providing more than $1 million for the EUREKA grant. For the project, Bellamkonda, MacDonald and Brahma are focusing on treating medulloblastomas — highly malignant brain tumors that account for more than 20 percent of pediatric brain tumors. The five-year survival rates for children with this cancer only range from 50 to 70 percent and the majority of survivors have a significantly reduced quality of life as a result of treatment-related toxicities.

This EUREKA grant aims to address the urgent need to develop therapies to safely treat invasive medulloblastomas in children. If successful, this approach could open a new avenue for the treatment of other invasive solid tumors, such as brain stem tumors. These cancers are incurable because they are located in an inoperable region and/or they are resistant or inaccessible to the delivery of chemotherapy agents.

With a grant from the National Cancer Institute, biomedical engineering professor Ravi Bellamkonda plans to design a new way to treat invasive brain tumors by capturing the migrating cells that spread the disease.
Georgia Tech Administration
Stephen Cross, Executive Vice President for Research
Stephen Fleming, Vice President and Executive Director of the Georgia Tech Enterprise Innovation Institute
Robert McGrath, Vice President and Director of the Georgia Tech Research Institute

STAY IN TOUCH WITH GEORGIA TECH RESEARCH NEWS

Georgia Tech’s Research News Office has a new online home that will make keeping track of our research discoveries easier than ever.

The URL may seem familiar (gtresearchnews.gatech.edu), but the site has been completely redesigned to help you find the stories you need as quickly as possible. We have also added four new ways to automatically track new research news stories and feature articles:

- Email notification;
- RSS feeds;
- Our popular Twitter feed @gtresearchnews;
- Our Facebook page: www.facebook.com/gtresearchnews

The new site allows searching by research topic/category, and includes a monthly archive, downloadable Research Horizons PDFs, and a listing of other stories you may be interested in. News releases and articles dating back to 1995 are still available.

gtresearchnews.gatech.edu

Biology professor John McDonald’s laboratory takes an integrated approach to studying ovarian cancer. Here is an image from his work showing ovarian cancer cells clustered together on the left (purple) and non-cancerous stroma surrounding them (brown). (Image: L. DeEtte Walker)