Extracts

College of Medicine

Device Can Analyze Genes At Patients' Bedside

Knowing the genomic signature of a cell population can help doctors diagnose diseases and may allow them to predict how individual patients will respond to trauma and what treatments to order.

University of Florida researchers have helped to develop a device that quickly identifies genes and proteins in body fluids — a technique that could make a vital difference to the patients doctors treat.

In a study published in a recent issue of *Nature Medicine*, scientists describe how they developed and tested a new way to isolate cells from patient samples and analyze them to help predict outcomes after severe trauma. The technology, called a microfluidic cassette, allows precise analysis of very small volumes of fluids and can be used to study patients' genes and proteins.

"Theoretically, you can isolate any cell population, under any disease, and rapidly get nucleic acids to produce a genomic signature," said Lyle L. Moldawer, a professor and vice chairman of research in the UF College of Medicine's Department of Surgery.

The approach also could be used with patients who have cancer or other conditions.

Moldawer, a co-author of the paper who also directs the department's Laboratory of Inflammation Biology and Surgical Science, said the team that developed and tested the cassette did so to isolate neutrophils, the first type of white blood cell on the scene of an infection, and to analyze the proteins they produce. These proteins indicate how genes that regulate the immune system respond to trauma, which may allow health-care providers to quickly identify patients more likely to develop serious complications.

The device was constructed by a team at Massachusetts General Hospital and sent to UF for initial testing, spearheaded by Elizabeth Warner, a surgical resident researcher and a co-author of the paper. Scientists from several other institutions, including Stanford University, the University of Rochester, the University of Washington, Pacific Northwest National Laboratory, Harvard University and Washington University in St. Louis also co-authored the paper.

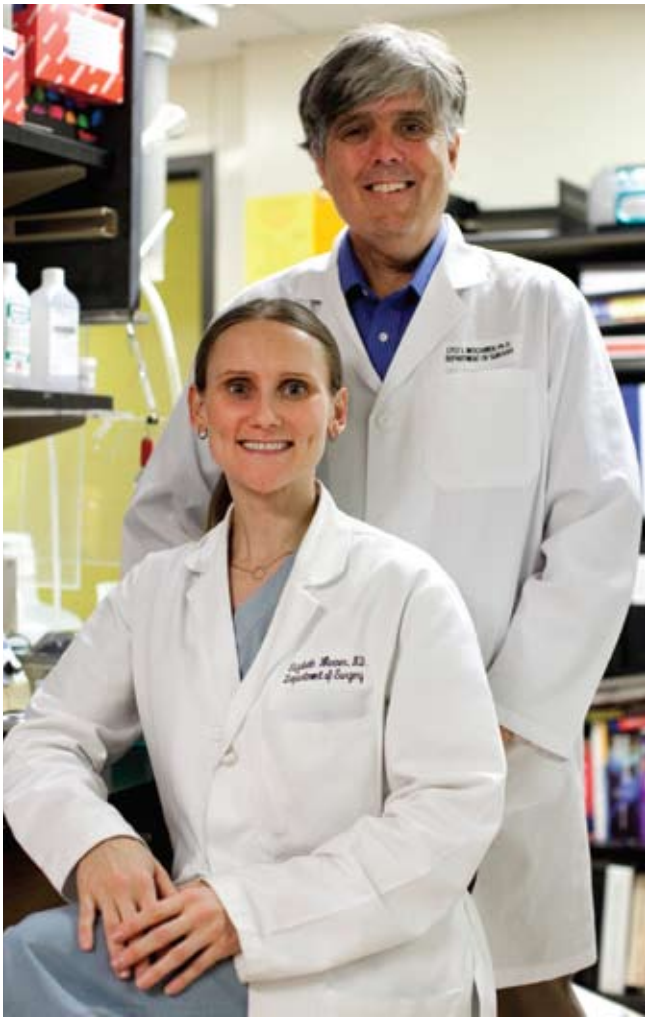
"We've identified 63 genes that are differentially expressed," Moldawer said, "so that when you are admitted to the emergency room after severe trauma, we can hopefully tell with better certainty whether you're going to have a good or bad outcome (by looking at these genes)."

The genes in question regulate functions of the immune system. Patients whose expression of these genes is abnormal, he said, are less likely to return to their normal immune function within days of trauma, as most patients do. This leaves them more vulnerable to infections and a myriad of related complications.

Previous devices required 4 to 8 milliliters of fluids, the work of a highly skilled technician and several hours to complete analysis.

Kenneth Kotz, a research fellow in the department of surgery at Massachusetts General Hospital, built the device, which is laced with antibodies that capture the individual cells when a sample of fluid, such as blood or urine, is pumped through it. Nucleic acids or proteins from the cells are then extracted from the cassette, allowing researchers to analyze how specific genes are expressed.

Testing showed the device yielded pure samples of neutrophils, and their gene expression pattern was consistent with results from tests performed in earlier studies.



Maria Farias

Lyle L. Moldawer, a professor and vice chairman of research in the UF College of Medicine's department of surgery, and Elizabeth Warner, M.D., a surgical resident researcher.

Lyle Moldawer,
moldawer@surgery.ufl.edu

Laura Mize

Tyler Jones

"Sanitation, of course, contributes to produce safety. But now that we know that there's also biology behind these interactions, it's important to clearly understand that it's not always the fault of the farmers and the producers and packers."

— Max Teplitski

Institute of Food and Agricultural Sciences

Salmonella Responds To Tomato Varieties, Ripeness

University of Florida researchers have discovered that tomato variety and maturity influence the ways salmonella bacteria respond to the fruit.

The findings, published in August by the online, open-access journal *Public Library of Science (PLoS) ONE*, suggest researchers may be able to develop tomato cultivars more resistant to salmonella contamination.

Also, by monitoring tomato ripeness, it may be possible to reduce fruit's susceptibility to contamination during and after harvest, said Max Teplitski, an associate professor in soil microbiology.

And finally, he said, the findings support the idea that salmonella contamination isn't solely due to hygiene problems on the picking or handling end — although such workers are often the first blamed.

"Sanitation, of course, contributes to produce safety. But now that we know that there's also biology behind these interactions, it's important to clearly understand that it's not always the fault of the farmers and the producers and packers," Teplitski said. "Even though our studies have been limited in scope, these results give us a realistic expectation that we can identify or develop a tomato variety that is high yielding and also less susceptible to salmonella contamination."

Salmonella infection is among the most common foodborne illnesses, often spread by raw or undercooked meat, poultry or eggs, but sometimes a result of eating contaminated produce. Its symptoms can include abdominal pain, fever, nausea and vomiting.

In 2008, federal health officials erroneously blamed a salmonella outbreak on domestically grown tomatoes, but later said imported contaminated peppers were responsible. Growers in Florida and other states lost an estimated $100 million in sales.

Teplitski notes that less than 1 percent of supermarket produce contains salmonella or *E. coli* and the contamination becomes a problem only when this produce contaminates other food, or is consumed raw.

"The chances of encountering it are very low," he said. "Even so, the producers are not satisfied with less than 1 percent. They want to have 0 percent."

The study, funded by the Florida Tomato Committee and Center for Produce Safety, began after Teplitski said his research team noticed that oblong Roma tomatoes seemed more often linked to salmonella than round varieties, and wondered if this was more than coincidence.

The researchers inserted "reporter" salmonella into tomatoes of varying maturity and type so they could see how the gene would react. The reporter salmonella emit a fluorescent light as they multiply inside the tomato. That fluorescence showed researchers salmonella distinguishes between tomato varieties and among fruit of varying ripeness.

Team member and UF postdoctoral researcher Jason Noel is now screening a greenhouse full of tomato varieties to give growers information about which are most resistant to salmonella contamination. They also plan to look at field irrigation and fertilization practices, to see if they affect produce safety.

Max Teplitski, maxtep@ufl.edu

Mickie Anderson

Extracts

McKnight Brain Institute

Human Link Found Between Memory And Nerve Cell Production

Production of new nerve cells in the human brain is linked to learning and memory, according to a new study from the University of Florida.

The research is the first to show such a link in humans. The findings, published in the journal *Brain*, provide clues about processes involved in age- and health-related memory loss and reveal potential cellular targets for drug therapy.

The researchers studied how stem cells in a memory-related region of the brain, called the hippocampus, proliferate and change into different types of nerve cells. Scientists have been unsure of the significance of that process in humans.

"The findings suggest that if we can increase the regeneration of nerve cells in the hippocampus we can alleviate or prevent memory loss in humans," said Florian Siebzehnrubl, a postdoctoral researcher in neuroscience in the UF College of Medicine, and co-first author of the study. "This process gives us what pharmacologists call a 'druggable target.'"

Over the past two decades, several studies have shown that new nerve cells are generated in the hippocampus. In animal studies, disrupting nerve cell generation resulted in the loss of memory function, while increasing the production of new nerve cells led to improved memory.

To investigate whether the same is true in humans, the UF researchers, in collaboration with colleagues in Germany, studied 23 patients who had epilepsy and varying degrees of associated memory loss. They analyzed stem cells from brain tissue removed during epilepsy surgery, and evaluated the patients' pre-surgery memory function.

In patients with low memory test scores, stem cells could not generate new nerve cells in laboratory cultures. But in patients with normal memory scores, stem cells were able to proliferate. That showed, for the first time,

Chemical Engineering

Electrical Charge Eliminates Surface Tension In Nanowires

Surface tension isn't a very powerful force, but it matters for small things — water bugs, paint and, it turns out, nanowires.

Nanowires are so tiny that a human hair would dwarf them — some have diameters of just 150 billionths of a meter. Because of their small size, surface tension that occurs during the manufacturing process pulls them together, limiting their usefulness. This is a problem because the wires are seen as a potential core element of new and more powerful microelectronics, solar cells, batteries and medical tools.

But in a paper in the journal *ACS Applied Materials & Interfaces*, a University of Florida engineering researcher says he has found an inexpensive solution.

Kirk Ziegler, an assistant professor of chemical engineering, said nanowires are most often made today with a process that involves the immersion of the wires.

When complete, each wire is supposed to poke up right next to the other from a flat surface, like bristles on a Lilliputian toothbrush. But Ziegler said the wires are so tiny and so flexible that surface tension clumps them up when dried.

Manufacturers use extremely high pressure to reduce the surface tension, but Ziegler said that process is difficult, expensive and not conducive to large-scale production.

Ziegler and doctoral student Justin Hill realized that they needed to introduce a force that counteracted that of the surface tension. They came up with a process simple enough to be achievable with a nine-volt battery. The researchers apply an electrical charge to the nanostructures during the manufacturing process, charging each tiny wire and making it repel its neighbor.

"As the two nanowires pull toward each other because of the surface tension, the like charges at the tips act to push them apart," Ziegler said. "The aim is to get a net zero force on the structure, so the nanowires stand straight."

Tests of microscope-slide-sized surfaces, each containing trillions of nanowires, showed that the procedure effectively prevents clumping, Ziegler said.

Nanowires have not found wide commercial applications to date, but Ziegler said that as engineers learn how to make and manipulate them, they could underpin far more efficient solar cells and batteries because they provide more surface area and better electrical properties.

"Being able to pack in a higher density of nanowires gives you a much higher surface area, so you start to generate higher energy density," he said.

Ziegler said that biomedical engineers are also interested in using the wires to help deliver drugs to individual cells, or to hinder or encourage individual cell growth. The University of Florida has applied for a patent on the process, he added.

Kirk Ziegler, kziegler@che.ufl.edu

Aaron Hoover

clear correlation between patients' memory and the ability of their stem cells to generate new nerve cells.

The work is potentially applicable beyond epilepsy, but first more studies have to be done with larger numbers of patients and more detailed testing of related brain structures and function, the researchers said. In addition, researchers still need to figure out how exactly the newly generated nerve cells contribute to learning and memory.

"The study gives us insights on how to approach the problem of cognitive aging and age-related memory loss, with the hope of developing therapies that can improve cognitive health in the aging," said J. Lee Dockery, M.D., a trustee of the McKnight Brain Research Foundation, which has teamed with the National Institute on Aging to promote research on age-related memory loss.

Florian Siebzehnrubl,
florians@mbi.ufl.edu

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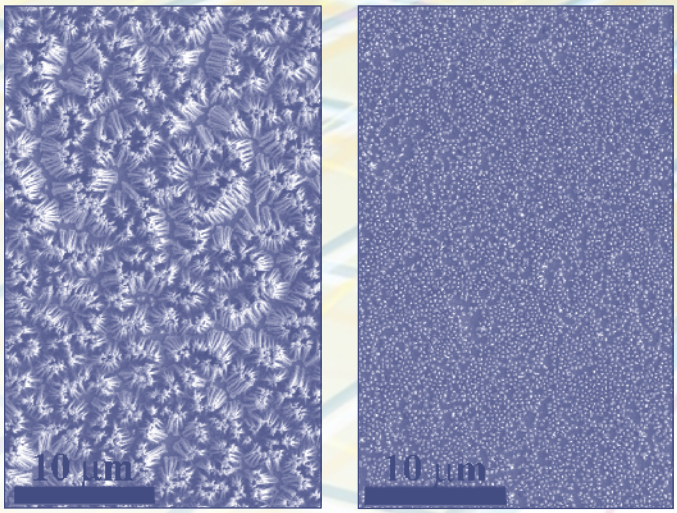


As the electron microscope image on the left illustrates, nanowires can clump up during the manufacturing process, limiting their usefulness. But by applying a small electrical charge, UF chemical engineers were able to make the wires stand up straight.

Surgeon Studying Link Between Colitis and Colon Cancer

Emina Huang, an associate professor of surgery in the College of Medicine, has received a $1.52 million grant from the National Institutes of Health to fund her research into the origins of colon cancer.

Emina Huang

The five-year grant will allow Huang to investigate whether "there's a way to prevent the progression from benign ulcerative colitis to cancer," she said.

"We asked the question: Are tumor-initiating cells present in ulcerative colitis?" said Huang. "We found the answer is 'yes,' and we've been able to identify those and work with them."

Approximately 700,000 people have colitis in the United States, according to the Crohn's & Colitis Foundation of America. The National Cancer Institute estimates that cancer of the colon and rectum will claim the lives of about 50,000 people this year.

"Prolonged inflammation due to colitis has been shown to contribute to the development of colon cancer and we are looking at the mechanisms involved in this process," said Elizabeth Butterworth, a biological scientist in the department.

Interleukin-8 is an immune system protein thought to contribute to cancer growth, and Butterworth said the team will examine cells affected with ulcerative colitis "to elucidate whether interleukin-8 plays a role in the number or type of divisions present in our samples."

They also will generate and analyze cancer "stem" cell lines for proteins key to tumor development, and investigate how and why metastasis occurs. Cancer stem cells are those thought by some researchers to be responsible for the generation of new cancerous cells.

Robert C. Fisher, a research scientist in the Department of Surgery, said the team will examine "fundamental stem cell properties, including clonality and self-renewal, along with metastatic potential" to determine the role these cells may play in cancer development. The research could eventually allow doctors "to predict patients who will progress to cancer from benign disease" and to find ways to stop the change from happening in the first place, said Huang.

Emina Huang, emina.huang@surgery.ufl.edu

Laura Mize

Extracts

College of Medicine, College of Engineering

Surgeons, Particle Engineers Team Up On New Breast Cancer Treatments

A University of Florida medical and engineering team is developing new ways to deliver treatment to breast cancer patients.

The researchers recently received three U.S. Department of Defense Breast Cancer Concept Awards and a research foundation grant totaling nearly $600,000 to continue their three potential delivery methods that may one day allow doctors to target tumors in hard-to-reach places without damaging healthy cells nearby. All three projects rely on nanotechnology.

"Right now what we do is we image cancer, and then we design a treatment for it," said surgeon Stephen Grobmyer, who is also a member of the UF Shands Cancer Center. "With theranostics, which nanotechnology is enabling, you can combine the diagnosis and treatment all into one modality."

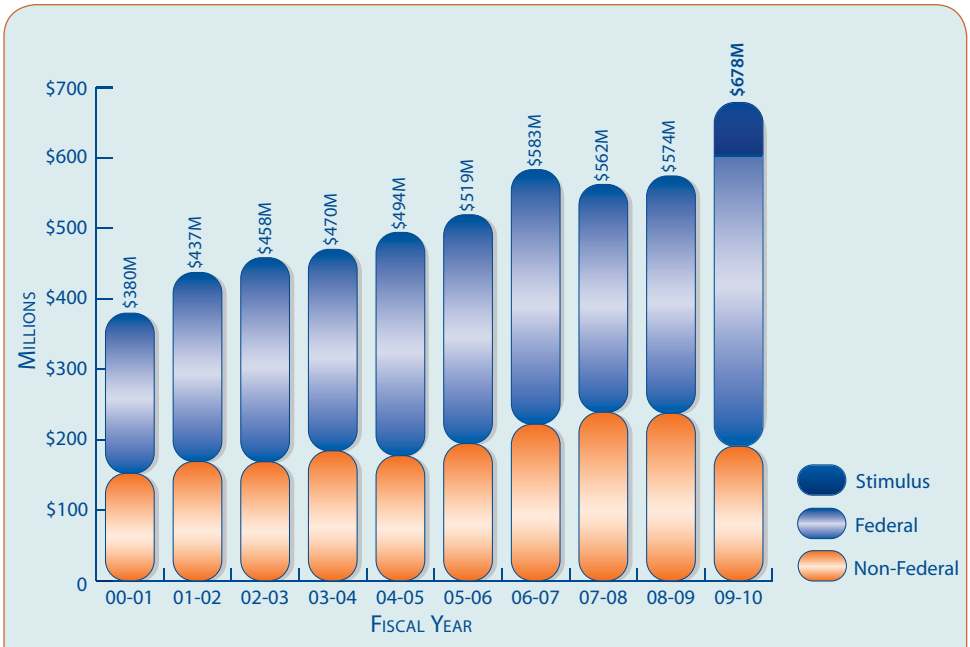
Landenberger Research Foundation has awarded Grobmyer $250,000 for two years.

One delivery method the team will investigate would require attaching treatment or imaging nanoparticles to glucose molecules and injecting the combined materials into the patient. Because cancer cells consume much more glucose than healthy ones do, tumors will take in many of the glucose cells and accompanying nanoparticles. Grobmyer and Scott Brown, a research assistant scientist in the College of Engineering's Particle Engineering Research Center, are co-principal investigators on this project.

Another potential method would envelop nanoparticles inside malignant cells that have been removed from the patient and treated with radiation so they cannot reproduce. These cells would then be injected back into the patient. Data from previous studies show malignant cells within a patient find and attach themselves to active tumors, thus delivering any treatment or imaging nanoparticles they are carrying.

Brown, the principal investigator on this project, said the method could be especially helpful for patients with cancers that have just begun to metastasize. He is hopeful some of the reinjected tumor cells would find small groups of active malignant cells growing in the patient, ones too small to be effectively targeted by traditional imaging methods for imaging or therapy.

"Right now a problem is detection. If you have metastatic disease, basically it's a waiting game," he said. "You wait until you can actually get something to show up on a PET, CT or an MRI. But with this, if it's effective, any patient who gets a tumor removed who may be at risk for metastatic disease may just take an injection and



Sponsored Research Awards 2001—2010

"Our success at competing for federal research grants positions us well to maintain our growth as the stimulus funding winds down and state and private funding rebound."

— Win Phillips

Jesse Jones

Medical and engineering researchers, from left, Scott Brown, Luke Gutwein, Stephen Grobmyer, Brij M. Moudgil and Parvesh Sharma.

later undergo whole body imaging."

Deactivated tumor cells from cancer patients have been used in previous research on cancer vaccine development, but using them for treatment delivery is a novel approach, Grobmyer said.

"If you change your approach and say, 'OK, we're not going to modify the particle but we're going to use the patient's own tumor to deliver the particles,' it might be a way to get around some of the issues related to delivery," he said.

The third project proposes using polyhydroxy fullerenes, soccer-ball-shaped carbon molecules modified by UF engineers, to deliver nanoparticles to tumors for treatment and magnetic resonance imaging.

"The beauty of the nanotechnology is you separate the delivery from the treatment," Grobmyer said. "The treatment actually becomes the easy part, in a way, because we can kill cancer cells a bunch of ways. We just have to be able to specifically get the material we want there."

The Department of Defense funded only about 5 percent of the 1,238 Concept Award applications it received. In addition, the Philadelphia-based Margaret Q. Landenberger Research Foundation has awarded Grobmyer $250,000 for two years.

Stephen Grobmyer,
stephen.grobmyer@surgery.ufl.edu

Laura Mize

Office of Research

Research Funding Hits Record $678 million

Research awards to University of Florida faculty increased $104 million last year to a record $678 million, thanks primarily to a 45-percent increase in federal funding.

Federal awards rose $151 million from $336.5 million to $487.5 million, with the increase almost evenly split between regular and economic stimulus funding through the American Recovery and Reinvestment Act. The university secured $77 million in stimulus funding by the end of the fiscal year on June 30.

UF President Bernie Machen credited the faculty for their efforts in his annual State of the University speech to the Faculty Senate, calling the increase "my best piece of news today."

Win Phillips, UF's vice president for research, said the faculty were "flexible, responsive and aggressive" in pursuing stimulus funding under tight deadlines.

"Equally impressive was the $74 million increase in non-stimulus federal funding," Phillips added. "Our success at competing for federal research grants positions us well to maintain our growth as the stimulus funding winds down and state and private funding rebound."

State funding was down $25.4 million and industry funding was down $8.6 million.

The UF Health Science Center received $394.3 million, including the largest award ever to the university — $64 million from the National Institutes of Health to the Institute on Aging. The grant was for researchers to study the impact of exercise and health lifestyles on the mobility of senior citizens. About half of that award came from stimulus funds. The Institute on Aging also received a separate stimulus award of $15 million to help pay for a new building.

"The Institute on Aging initiative is very important to the state and the nation," Phillips said. "This building will provide a central location where seniors participating in a wide variety of research studies can interact with faculty from throughout the university."

The Institute of Food and Agricultural Sciences received $101.2 million, the College of Engineering received $78 million and the College of Liberal Arts and Sciences received $42.4 million. All of the other colleges received a combined $62.4 million.

Joseph Kays

Extracts

Unmanned Plane Captures Environmental Data

On an airboat on Lake Okeechobee, four University of Florida researchers prepare to launch an airplane — by hand.

They check its altitude and attitude, turn the 11-pound plane side to side, lift its nose and lower it. They test wind speed, direction, the plane's GPS system and autopilot.

"Three … 2 …1," the plane gets a shove from doctoral student John Perry and it's airborne, flying in laptop computer-controlled patterns over the lake. Passing about 650 feet overhead, it sounds like a vacuum cleaner from a neighbor's home. Farther off, it makes no noise at all. When it lands next to the airboat a half-hour later, it barely makes a splash.

The plane is the result of a decade's worth of work by a multidisciplinary research team headquartered at UF's Institute of Food and Agricultural Sciences. There has been a near-constant honing of what's called the Unmanned Aerial System before researchers settled on today's aircraft, which is durable, watertight, and takes incredibly sharp GPS-pinpointed photographs.

Later, those photographs create elaborately detailed maps, which provide data not available anywhere else for scientific research. In this case, the goal is to help gather information on plant life, but researchers say the tiny plane offers a vastly safer and more accurate way to conduct all kinds of environmental monitoring.

Despite its high gee-whiz quotient, said Larry Taylor of the U.S. Army Corps of Engineers, what's important isn't how nifty a gadget the plane is: It's what it can do.

During the 30-minute flight, the plane takes and stores about 750 photographs. With the help of global positioning technology, the researchers know with startling accuracy the location of the area shown in each photo.

The possibilities for this technology to help wildlife biologists are nearly endless, the researchers say. They include being able to count wading birds' nests or even the eggs inside; counting the alligators in a swamp and documenting landscape components, such as trees or vegetation.

Aquatic vegetation was the focus of the team's Lake Okeechobee outing. Members sent the plane up to photograph water lettuce and hyacinths left in a roughly 1/3-mile square of lake surface after federal officials used herbicide to thwart the invasive plants six weeks earlier.

There are three flights this day — two taking standard color photographs and a third to get color-infrared images. The only apparent disturbance to nature occurs during one of the landings, which startles a water bird enough to make it scoot to another spot.

The airplane flies using a lithium battery, so there's no exhaust to pollute the air or hurt wildlife.

"It's a green system," Perry said. "It replaces the alternatives of manned aircraft such as helicopters and low-flying planes, and it produces better data."

Tyler Jones

UF doctoral student John Perry (left) launches an unmanned airplane over Lake Okeechobee. Ground station monitor Thomas Rambo, seated, controls the launch via laptop computer as Brandon Evers looks on.

The plane is just a couple of years away from being available for general use, said Franklin Percival of the UF-affiliated Florida Cooperative Fish and Wildlife Research Unit, who's led the team since it began.

"We've concentrated all these years on the plane and payload, and now we've got all of those things right," he said.

Taylor, sitting atop a nearby airboat on the morning of the Lake Okeechobee launches, said the plane's evolution in the last few years is nothing short of miraculous.

"With the previous airframe, it was like, 'Please, God, let it get back down,'" he said. "But this one is just completely different."

Franklin Percival, percivaf@ufl.edu

Mickie Anderson

The *Washington Post* described the work of two UF professors, Augusto Oyuela-Caycedo and Michael Heckenberger, whose archaeological research examines historical ecology and anthropology in the Amazon. In their recent expeditions to Peru, Bolivia and Brazil, the anthropologists say they are debunking one commonly held assertion that parts of this vast forest were too dense to be home to more than just small tribes of indigenous people.

"There is a gigantic footprint in the forest," Oyuela-Caycedo told the Post, adding that 20 million people may have inhabited these regions centuries ago.

The researchers have found evidence of ceramics, canal systems and semi-domesticated fruit trees in areas once considered uninhabitable. UF geographer Nigel Smith, also mentioned in the article, contributed to the on-site analysis of these findings.

A new spray-on polymer developed by a team of UF scientists was featured in *Discovery News*, the cable channel's online news site.

UF chemistry professor John Reynolds, UF physics professor Andrew Rinzler and their colleagues on the team say that the spray can help reflect or transmit any color of light when applied to hard glass or flexible plastic. The polymer, when combined with solar technology, could also power portable electronics.

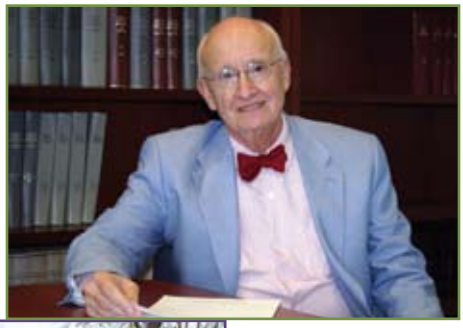
The news site touted the technology's promise:

"Over the last several years the Florida scientists, in conjunction with BASF, have developed a range of color-changing polymers. The technology could lead to full-color e-readers, color-changing billboards and signs, or any number of other applications."

MSNBC.com posted an article about the research of UF biology Professor Todd Palmer, who studies the symbiotic relationship between ants and trees of the African savanna. The ants that live in the Acacia drepanolobium trees and eat the sugary nectar from its leaves protect the species by crawling inside and biting the sensitive snouts of elephants, thus deterring the giants from devouring much of the tree as a tasty snack. "We found the elephants like to eat the 'ant plant' trees just as much as they like to eat their favorite tree species," Palmer said. "And that when either tree species had ants on them, the elephants avoided those trees like a kid avoids broccoli."

Often perceived by family members as depression, those who suffer from Alzheimer's may, in fact, have a reduced ability to experience emotion, according to a recent study by UF researchers featured in *USA Today* and published in the Journal of Neuropsychiatry and Clinical Neurosciences. "Emotion and memory go together," said Kenneth Heilman, a professor of neurology at the UF McKnight Brain Institute and senior author of the study. "The more emotion you can attach to an event, the more likely you are to remember. I think what this paper is telling us is that the disease is causing the emotional response to become more and more shallow over time."

The *New York Times* examined the efficacy of early breast cancer diagnosis and whether the tests currently administered can adequately distinguish benign lesions and early-stage breast cancer. The Times quoted Dr. Shahla Masood, head of pathology at the University of Florida College of Medicine in Jacksonville, who said that there "is a 30-year history of confusion, differences of opinion and under- and overtreatment. There are studies that show that diagnosing these borderline breast lesions occasionally comes down to the flip of a coin."



Dr. Kenneth Heilman

UF and Brazilian anthropologists excavate a site in South America as part of research indicating that the Amazon basin may once have been home to large civilizations.