

Partnerships: High-Tech, High-Touch

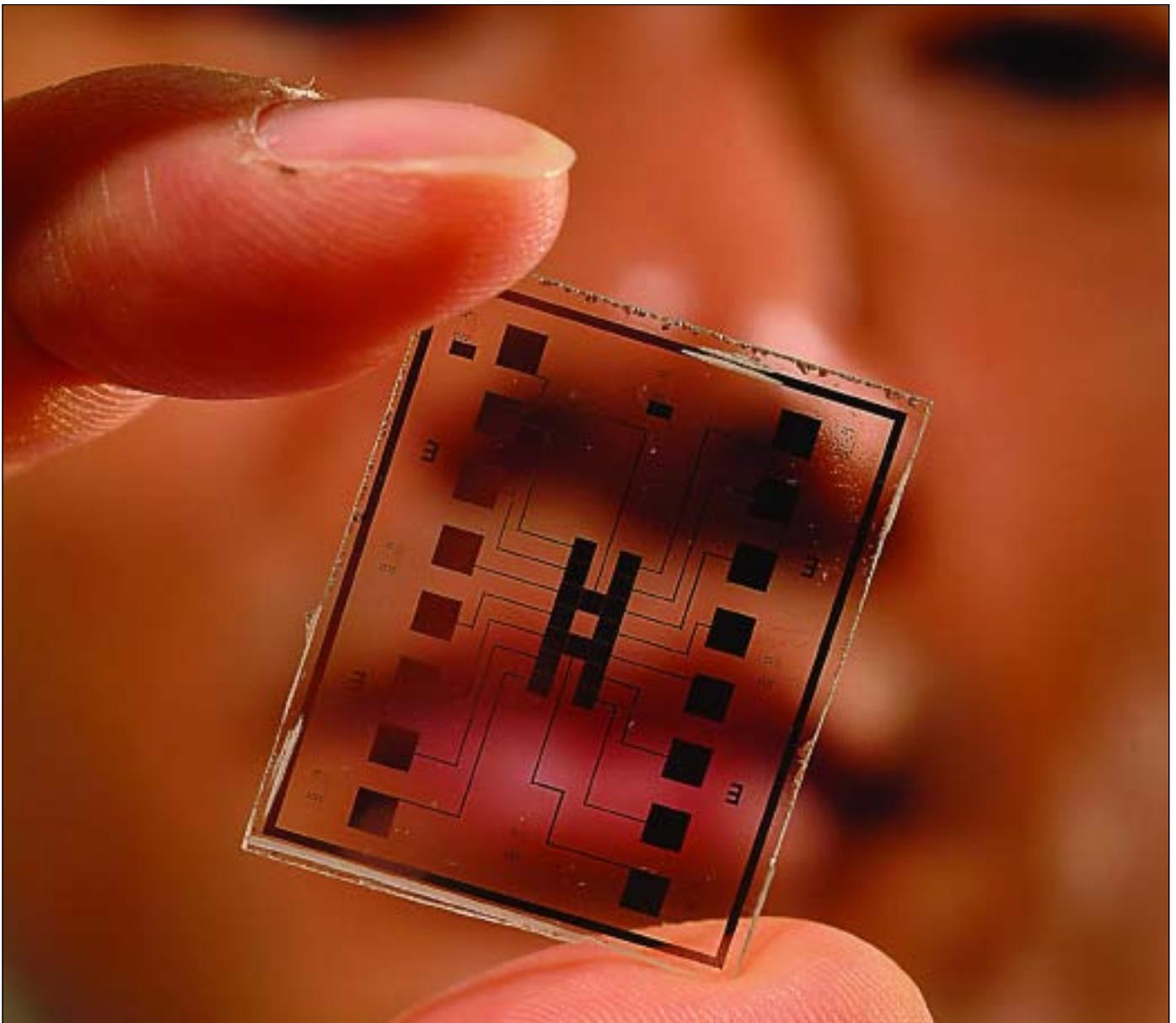
By Kim Irwin

Imagine a medical clinic in rural China or sub-Saharan Africa serving poor patients from outlying areas without the benefit of state-of-the-art testing and sophisticated lab equipment. The patient population is at high risk for liver cancer, which kills more than half a million people worldwide every year. But the ability to test these patients to see if they're at risk or to diagnose them at an early stage is hampered by geography and economics.

Yet all that may change with a single drop of blood placed inside a space-aged device no larger than a shoe box. In less than an hour, a doctor in that remote clinic may be able to determine whether a patient carries a tumor marker in their blood that indicates significant risk for liver cancer.

The room-sized laboratory needed to process such a test in the past is being reduced to a computer chip the size of a small Post-It note thanks to the emerging fields of nanotechnology and fluidics and a unique partnership between the Jonsson Comprehensive Cancer Center and the NASA-supported Institute for Cell Mimetic Space Exploration (CMISE) at UCLA.

"This is a new paradigm," said Chang-Jin "CJ" Kim, a professor of mechanical and aerospace engineering and leader of the sys-



tematics group at CMISE. “No such machine now exists. There are lots of blanks to fill in, but overall the picture makes sense.”

Elsewhere on campus, researchers in the cancer center and the UCLA School of Public Health are working to discover subtle variations in the human genetic blueprint that predispose some individuals to develop cancer after contact with environmental pollutants.

The research partnership seeks to explore, for example, why some individuals exposed to second-hand cigarette smoke develop lung cancer while others do not. Bringing together the best environmental researchers and molecular biologists at UCLA, the program will shed new light on how pollutants interact with genetics to cause a variety of cancers.

“We will investigate the molecular mechanisms by which pollutants cause cancer and why certain sub-populations of people are more sensitive than others,” said Dr. Zuo-Feng Zhang, a professor of public health and epidemiology and co-director of the environmental genomics program. “What we learn may help us develop improved biomarkers of exposure and susceptibility, identify people at increased risk and design nutritional and chemical interventions to counteract the development of cancer, especially in those with increased sensitivity.”

In other laboratories, researchers from a variety of scientific disciplines are focusing on chemical genomics, which will screen thousands of chemicals in large groups to determine which compounds have the potential to disrupt the abnormal cell signaling that serves as the flashpoint for cancer.

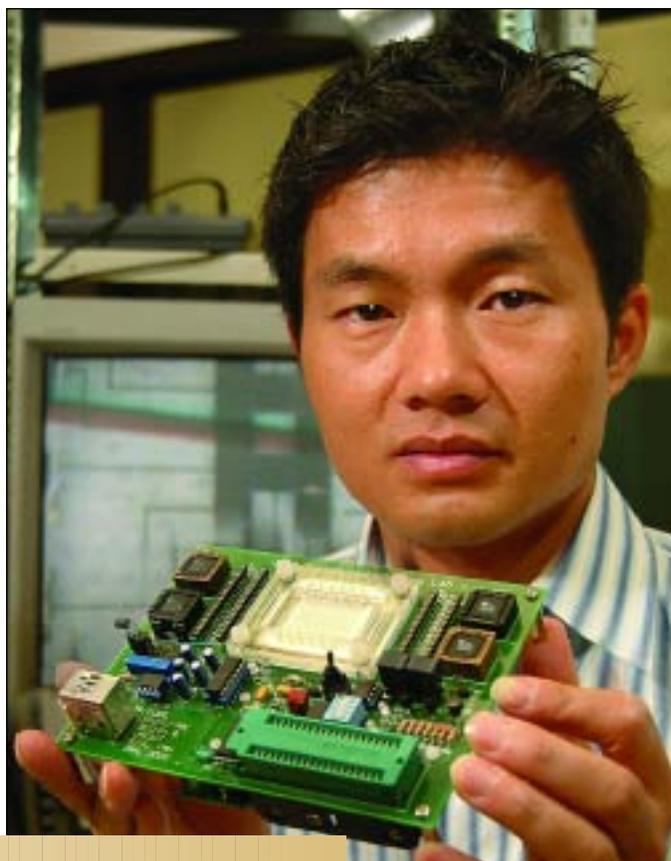
This program, a partnership between the Jonsson Cancer Center, David Geffen School of Medicine, Howard Hughes Medical Institute, California NanoSystems Institute and the departments of Pharmacology and Microbiology, Immunology and Molecular Genetics, allows scientists to examine small molecules—smaller than proteins—that can inhibit cellular functions that may result in cancer.

“The primary purpose of this effort is to foster basic research. What we may discover here could be the starting point for developing new anti-cancer drugs later on,” said John Colicelli, profes-

sor C. Gasson, director of the Jonsson Cancer Center and the driving force behind the leading-edge partnerships. “We’ve now evolved beyond that and are partnering with other units on campus.”

And UCLA is uniquely positioned to foster such partnerships. Unlike many institutions across the nation, UCLA’s school of medicine and its colleges are located in one place, providing an environment that is ripe for collaboration.

“I used to envy free-standing cancer centers, because the whole institution is dedicated to cancer research,” said Gasson, a professor of medicine and biological chemistry. “But university-based cancer centers do have advantages in the partnership paradigm as we go



“Size matters. Things don’t work the same way on the micro-scale. Surface tension is strong on the micro-scale and people tried hard to figure a way to get around that to make micro machines. I approached with an opposite mindset and started to dream up machines run by surface tension.”

—Chang-Jin “CJ” Kim, Ph.D.

sor and vice chairman of biological chemistry at UCLA. “We’re among the top institutions in the country taking this highly interdisciplinary approach.”

These diverse programs represent the new direction of cancer research at UCLA—partnerships between engineers and molecular biologists, between toxicologists and nutritionists, between biological chemists and epidemiologists to uncover new and better ways to prevent, detect and treat cancers.

“Science is changing from the way it was a couple of decades ago, when an individual was working in a lab doing research,” said Judith

forward. We have access to experts in mathematics, engineering and computer science right here on campus.”

Such partnerships not only are crucial to discovery, they’re essential if UCLA is to survive as a research institution, said Dr. Owen Witte, an

investigator in the Howard Hughes Medical Institute and a professor of microbiology and molecular genetics.

“We have to find ways to collaborate,” Witte said. “Without that, we will not be competitive in the world. There’s no way an independent department or individual could accomplish these programs on their own.”

“And there’s an undercurrent of value to these partnerships that cannot be measured,” he added. “How many interactions will occur because of these programs? How many new ways of thinking will emerge from these interactions? It’s hard to quantify, but it’s palpable.”

Leonard Rome, a professor of biological chemistry and UCLA's senior associate dean for research, said most medical schools across the country are not doing these types of partnerships.

"We're unique here at UCLA in that we have the combination of nanotechnology with the cutting edge of engineering, medicine and the physical sciences," Rome said. "There's a certain ease to these cross-campus collaborations at UCLA that you can't find in other places."

And these collaborations have the potential to catapult UCLA and the Jonsson Cancer Center to the forefront of research.

Lab on a Chip



A collaboration between UCLA and NASA, CMISE is combining advances in biology and engineering to create miniscule monitoring systems for use in research projects in space and on earth.

Blending micro-technology mechanics and biology, the researchers at CMISE are developing sensor systems to monitor, sense, control and prevent damage to an astronaut's body as it travels through space. Though tiny in size, these systems have the potential to carry out the complex functions of a full laboratory, creating what is essentially a lab on a chip.

Researchers in the university's dental school were already working with scientists in engineering to develop a system to detect tumor markers in saliva when Gasson attended a meeting for UCLA's organized research units in July 2003. The meeting was a show-and-tell of sorts and inspiration struck Gasson as she listened to Chih-Ming Ho, director of CMISE, talk about his work with NASA. If this system can monitor the physiologic changes of astronauts in space, might it not be possible to develop a system to detect tumor markers in a drop of blood? And if that was possible, couldn't the lab on a chip be used to help people all over the world who might be at risk for cancer but who don't have access to sophisticated testing and laboratories?

"With this technology, it might be possible to do a blood test in places where there are no labs and no electricity and screen high-risk individuals who could later be referred to urban centers for further diagnosis and treatment," Gasson said.

The lab on a chip is made possible through advances in nanotechnology and micro/nano fluidics, said Ho, who holds the Ben Rich-Lockheed Martin Professorship at UCLA's Henry Samueli School of Engineering and Applied Science. Nanotechnology allows the manipulation of objects at the level of molecules and atoms—with the length scale at nanometers, about a hundred thousand times smaller than the width of a human hair. Advances in fluidics resulted in the ability to move liquids around on the nanoliter to microliter scale without pumps and valves, instead manipulating the fluid with electric forces.

"We're now able to detect cancer biomarkers at extremely sensitive levels," said Ho, "even at the single molecule level."

Liver cancer was chosen as the pilot project for lab on a chip because it is the fourth most common cancer worldwide, developing usually as a late complication of hepatitis B and C and cirrhosis. Worldwide, about 400 million people currently are infected with hepatitis B, and another 100 million have hepatitis C.

The lab on a chip is designed to detect a tumor marker called

Alpha-Fetoprotein, or AFP, which is present in increased levels in patients with liver cancer. The lab on a chip would process a drop of blood no bigger than the tip of a ball point pin and mix it with a chemical probe designed to detect AFP. In less than an hour, the testing physician would have the results. The probe will fluoresce or light up when AFP is present.

"The probe is like a key designed to fit into a lock," Ho said. "The lock only recognizes that one key. If the key fits, the protein is detected and the 'light' goes on."

Although the concept may sound simple, the execution was not.

Mixing fluids on the microliter level was not easy until the last decade because scientists could not find a way to perform the delicate process until the advent of MEMS, or Microelectromechanical Systems, a micro machine with minute parts.

"Mixing fluids with chemical reactants was difficult before at this small a scale," Ho said. "It was like putting cream in honey—the two would not mix well. With micro/nano fluidic technologies, the mixing process is much easier."

CJ Kim, a MEMS expert, took on the gargantuan task of shrinking and automating a room-sized lab filled with technicians, beakers, pipettes and samples. He developed the techniques necessary to move liquids on the sub-microliter scale, breaking new ground with a method that is simple and reliable.

The blood droplets and chemical probes may be moved on a grid on the Post-It note-sized computer chip using electric signals. The key was the surface tension of liquid. An ant can get trapped in a water droplet, yet humans have no trouble exiting a tub full of water. Why?

"Size matters. Things don't work the same way on the micro-scale," Kim said. "Surface tension is strong on the micro-scale and people tried hard to figure a way to get around that to make micro machines. I approached with an opposite mindset and started to dream up machines run by surface tension."

He eventually succeeded, using electric signals powered by batteries. It took a year for Kim to perfect the process, to move water droplets on the grid and get them to mix. Now he's working to accomplish the same thing with blood samples and chemical probes.

"I never thought our technology would be used for cancer research," Kim said. "When this was proposed, it was a dream. Enough people out there thought this would never happen. Now we have it."

Ho and Kim estimate the lab on a chip will be in use within two years. And it would not have happened without the molecular biologists detecting cancer-causing mutations in genes and the protein expressions that are linked to disease, the mechanical engineers like Kim conquering surface tension to develop fluidics or the advances in monitoring sensors that allow the detection of proteins like AFP in fluids.

"When you work with people in other disciplines, it opens your eyes," Ho said. "You can see beyond your own field, see new ways of doing research, new ways of thinking about a problem. There are no boundaries."

Gasson said the lab on a chip, made possible in part with philanthropic support from Ken and Wendy Ruby, may someday be used to detect tumor markers for other cancers in blood, saliva and urine. Screening tests for cancer may one day be a simple procedure performed in a doctor's office on a battery-operated device no bigger than a Palm Pilot.

Environmental Genomics

The \$1 million Ann Fitzpatrick Alper program in Environmental Genomics, made possible with a leadership gift from Pacific Palisades resident Art Alper in memory of his wife, is emerging at a time when molecular epidemiology and genetics are becoming the major focus in environmental related cancer risk assessment.

This focus demands multidisciplinary collaborations between epidemiologists, molecular biologists, toxicologists and experts in nutrition and statistical genetics, Zhang said.

“We’ll need to work together to focus on the etiology of cancer and to explain the lure of the genes and environmental exposures on the development of cancer,” he said.

The program seeks to uncover the veiled mechanisms behind environmental cancers. Why do some people exposed to pollutants develop cancers when others do not? Is some genetic alteration present in those more at risk? If so, can it be targeted with therapies or other strategies to prevent the cancers from developing?

At present, the environmental genomics program is focusing on four research projects that seek to:

- ✱ Characterize genetically the effects of air pollution particles on the makeup of human cells.
- ✱ Understand the relationship of environmental exposures and a non-smoker’s susceptibility to lung cancer.
- ✱ Investigate the molecular mechanism responsible for higher incidence of prostate cancer for men exposed to pesticides in California.
- ✱ Characterize the mechanism that makes boron a dietary element that appears to prevent or reduce the risk of prostate cancer.

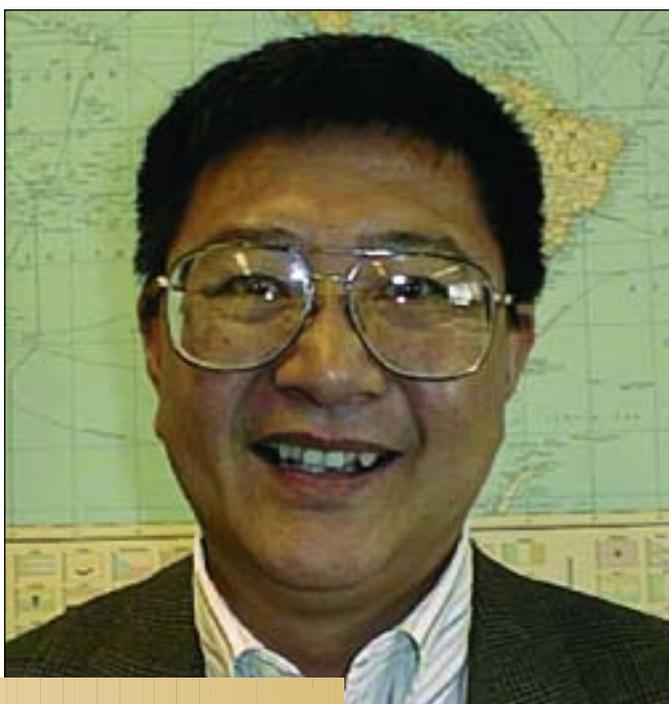
“This promises to be a unique effort that we hope will unravel many of the mysteries surrounding the interaction of genes and environment,” Gasson said.

Understanding the processes and genetic alterations involved in the development of various cancers has already resulted in targeted therapies that attack what is broken in cancer cells, leaving healthy tissues alone and resulting in less toxic treatments for patients. The same promise holds true for the environmental genomics program, Rosenstock said.

“Perhaps by understanding the genetic risks posed by environmental pollutants, we can tailor drugs to help prevent cancer,” she said. “Or, more likely, we can try to control the environmental factors for those people at risk for cancer.”

An environmental activist who drove a hybrid car, Ann Fitzpatrick Alper developed lung cancer although she had not smoked since the early 1950s.

About 90 to 95 percent of the nearly 1.4 million Americans



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—Dr. Zuo-Feng Zhang

Cancer occurs when changes in our genetic blueprint, or DNA, cause certain genes to become altered in cells, which then grow out of control. In some people, exposure to environmental pollutants may trigger these changes or genetic mutations.

“Before we had the new tools of the genome revolution, disease was considered to be either environmentally or genetically caused,” said Linda Rosenstock, dean of the UCLA School of Public Health, who oversees the program. “But now we know that most diseases are the result of an interaction between genetics and the environment. At UCLA, we are fortunate to have the top scientific minds in both environmental research and molecular biology, which uniquely positions us to tackle these emerging issues.”

who will be diagnosed with cancer this year have no known genetic predisposition to the disease. Researchers believe these people develop malignancies due to complex interactions between their genes and the environment. If

scientists can uncover the chemical and biological cascade that results in cancer, they can potentially stop the disease before it occurs. The goal is to discover what specific combination of an individual’s genetics and factors such as diet, air pollution, exposure to tobacco, sensitivity to sunlight, etc., result in disease.

“The key to the future is to understand why certain people develop certain cancers,” Zhang said. “Through this kind of research, merging environmental factors and molecular genetics, we may be able to find the answers.”

The Alper gift is being augmented with gifts from the Kenneth Jonsson Family Foundation and UCLA’s Jonsson Cancer Center.

Chemical Genomics

Tinkering with something to examine how it works is a time-honored tradition in science. Such is the goal of chemical genomics.

Combining chemistry and cell biology, chemical genomics seeks to investigate processes inside a cell using small molecules aimed at the signaling pathways that influence cell behavior. Researchers hope to identify biologically active compounds that can be used to modulate gene function and expression in cells, improving their understanding of the biologic pathways involved in human health and disease.

This can be a tall order at academic institutions like UCLA.

Pharmaceutical companies have the resources to purchase large libraries of chemical compounds and screen them with an eye towards developing new therapeutics. In contrast, academic scientists don't always have such easy access to these libraries, which can be very expensive. However, a new partnership between six departments and institutes at UCLA is seeking to change that by developing the Molecular Screening Shared Resource.

"The goal is to provide small molecule chemical libraries that will be screened by multiple investigators from different disciplines on campus," said Witte, who heads up the new shared resource.

The partners—Jonsson Cancer Center, David Geffen School of Medicine, Howard Hughes Medical Institute, California NanoSystems Institute and the departments of Pharmacology and Microbiology, Immunology and Molecular Genetics—each provided "tremendous financial and moral support," for the new resource, Witte said.

With financial contributions in excess of \$2 million to date, the Molecular Screening Shared Resource was able to purchase the nec-

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essary equipment and have funds to buy existing chemical libraries. The program also will tap into UCLA-established libraries, as well as develop new libraries in conjunction with UCLA chemists. Space, at a premium on the UCLA campus, was provided by the Microbiology, Immunology and Molecular Genetics Department.

The development of this resource provided the solid foundation UCLA scientists needed to apply for further funding to establish the W. M. Keck Epithelial Cell Cancer Biology Program, which will probe the origins of the majority of solid tumors (See related story on page 9).

The process by which a healthy cell becomes cancerous cell involves a complex cascade of molecular interactions.

Normal cells can develop abnormal signaling, which can cause them to grow too much or invade other organs, leading to cancer. These signals are based on complex protein interactions, which are like puzzle pieces that need to fit together in just the right way. Small molecules may block or break apart those protein interactions and stop or interrupt the development of cancer.

Chemical genomics, also called chemical screening, used to be

done one compound at a time in a laborious process that took months and years. It now can be done using what is called high-throughput screening, a process that allows scientists to test hundreds of small molecules—alone and in combination—simultaneously.

"These small molecules, smaller than proteins and therefore more likely to be taken up into cells, may inhibit a process that is required for cancer cells," Colicelli said.

Testing can be done in what is called an assay array, in which cancer cells or proteins are placed in wells and a different small molecule is added to each well.

"Then we'll see what reactions occur, how the cells or proteins behave. We'll see what processes are inhibited and what proteins are activated, whether the cells grow and divide," Colicelli said. "This information will provide clues about how cancers develop and how we might stop that development without harming normal cells."

And unlike the pharmaceutical companies, which operate in secrecy, what UCLA scientists discover by studying these interac-



tions will be public information.

"That's very important," Colicelli said. "UCLA won't be developing drugs, but we may discover something that puts us at the starting point for a new therapeutic, and a pharmaceutical company is then welcome to step in and develop those compounds into useful drugs."

The development of the revolutionary leukemia pill Gleevec is an example of that process. Witte and his research team discovered a mutation in a gene called Bcr-Abl and linked it to the development of chronic myeloid leukemia (CML). That discovery provided drug companies with a target for a new drug. A compound was developed to molecularly target the mutant Bcr-Abl protein that causes CML and that drug was then tested in academic medical centers and ultimately approved for use.

"It's the role of a university to do this vital basic research," Colicelli said, "to shed new light on the function of various genes and the roles those genes may play in pathways crucial to biological function." ★