

The Next New Thing

By Kim Irwin

Researchers from across the UCLA campus are teaming up to use the science of the very small to understand the origins of the majority of solid tumor cancers.

The interdisciplinary W. M. Keck Epithelial Cell Cancer Biology Program will use the emerging field of nanotechnology to uncover the complex nature of tumors that share an epithelial cell origin, including breast, colon, prostate, lung, bladder and pancreatic cancers. What they learn could lead to new molecular diagnostics and therapies.

Funded with a \$1.5 million grant from the W. M. Keck Foundation, the epithelial cell cancer biology program is taking giant leaps of faith and science, testing theories considered too risky to garner traditional grant funding and along the way challenging

conventional approaches while making strides towards the development of innovative and powerful new biomedical techniques.

“We wanted something out there,” said Leonard Rome, professor of biological chemistry, UCLA’s senior associate dean for research and the program’s principal investigator. “We wanted the next new, new thing. A program like this would not have been funded by the National Institutes of Health. The science is not mature enough.”

Owen Witte, an investigator in the Howard Hughes Medical Institute and a professor of microbiology and molecular genetics, cautiously characterizes the effort as “high-risk science.”

“It’s a grand plan,” Witte said. “It’s likely not to work, but there’s a big payoff if it does.”





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Like all visionaries, the Keck program scientists have their focus fixed firmly on the horizon, at the edge of the leading-edge of research. They’re willing to take the big leap because the potential reward is huge—new and better ways to detect and treat deadly cancers that strike more than 700,000 Americans each year, killing more than 275,000 of them.

“This is the untried. We’re proposing to do something that hasn’t been done,” Rome said. “The methodology we’re using is only just now being developed. If this works, we’re going to have some very exciting data.”

Nanotechnology helps scientists study the building blocks of cancer at atomic, molecular or macromolecular levels. The epithelial cell cancer biology program will use three technologies still in their embryonic stage and apply them to a very basic problem—what cell functions go awry that may result in cancer—in the hopes of opening up new approaches to diagnosis and treatment of cancers, said John Colicelli, professor and vice chairman of biological chemistry at UCLA.

These three modalities, called the technology triangle, will be employed to help researchers identify novel genes and proteins and visualize individual molecules. These innovative technologies are:

Quantum dot molecular imaging or Q-dot imaging: A new way of seeing biologic processes with a fluorescent microscope. Probes can be attached to a given protein to monitor it and see what other proteins it interacts with, what part of the cell it is in and what signaling pathways the protein may use.

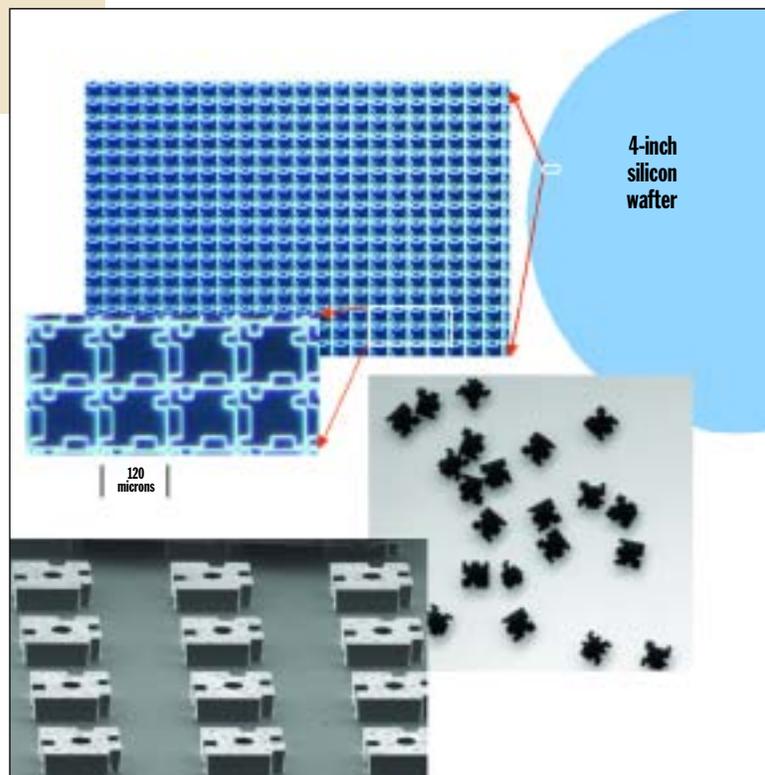
Shape-encoded particles: A novel, automated technology using distinctly shaped particles cut from a silicon wafer. Each particle carries a specific chemical or biological probe. The probes are attached to the unique microscopic shapes, with the shape of the carrier particle becoming the identification code for the attached probe. Thousands of these shape-encoded particles carrying different tumor cells or proteins can be mixed together in one tube for simultaneous, or multiplexed, analysis.

Chemical genomics: Combining chemistry and cell biology, this technology investigates processes inside a cell using small molecules aimed at the signaling pathways that influence cell behavior. The goal is to identify biologically active compounds that can be used to modulate gene function and expression in cells, improving our understanding of the biologic pathways involved in human health and disease.

“Each of these approaches is a very important technology,” Rome said. “However, used together they bring a whole new dimension to the arsenal of weapons we have to understand how cancer begins.”

UCLA leads the nation in Q-dot imaging and shape-encoded

Shape-encoded particles cut from a silicon wafer carry a specific chemical or biological probe. These probes help researchers identify novel genes and proteins and visualize individual molecules.



particles technologies, Colicelli said. The epithelial cell cancer biology program builds upon the strengths of the W. M. Keck Proteomics Center at UCLA, and will enhance scientific collaborations among researchers from UCLA’s Jonsson Comprehensive Cancer Center, the California NanoSystems Institute, the College of Letters and Science and the Henry Samueli School of Engineering and Applied Sciences.

“Prior to this, we analyzed tumor cell lines or tumor tissues one at a time,” Colicelli said. “Now, using these three technologies, we see an opportunity to analyze many samples at the same time and get more meaningful data more quickly, to see if different tumor tissues perhaps have similar genetic alterations.”

Tumor cells are characterized by multiple, accumulated alterations in signaling pathways. The Keck program seeks to uncover these alterations in cancers that share an epithelial cell origin.

Epithelial cells are the cells that form the body’s coverings and linings, including cells on the surface of the skin and the mucous membranes. These cells play a central role in the function of tissues such as lung, colon, kidney, pancreas, liver, breast, cervix and prostate. Epithelial cells also give rise to epithelial cancers, the major category of solid tumor cancers.

Although they are the same basic type of cells, epithelial cells will be different in each of the tissues and cancers being studied, Colicelli said. However, they may also have some things in common—a protein expression for example—that perhaps could be found across several cancer types. That shared protein expression may provide a target for a therapy that could be effective in both a breast and a lung cancer patient.

The Keck program will look at all aspects of epithelial cancers, with an initial focus on pancreatic cancer, a particularly deadly form of cancer that kills 98 percent of those who contract it. This year alone, more than 31,860 people will be diagnosed with pancreatic cancer. Of those, 31,270 will not survive beyond five years. In an effort to shed some light on this deadly disease, three biochemical mechanisms known to contribute to pancreatic cancer will be examined—the receptor tyrosine kinase (RTK), the RAS proteins and G proteins. Each biochemical mechanism is controlled by multiple components, Colicelli said, and not all of them have been analyzed.

“We know bits and pieces, but not the whole story,” he said.

The Keck program seeks to flesh the story out, using the technology triangle to identify the cell signaling signatures that may contribute to pancreatic cancer. Using standard methodologies, it would not be possible to analyze all the potential factors that may lead to pancreatic tumors.

“We’ll combine the power of these technologies to examine previously unanswered questions and gain insight into pancreatic cancer,” Colicelli said.

Among the earliest identified cancer-causing oncogenes were representatives of the RTK family. Over-expression of certain RTKs can lead to tumor formation. Because of this, many RTKs serve as cancer drug targets. Herceptin, Gleevec, Iressa, Erbitux, Avastin and Tarceva are among the new therapies that target these types of receptors. As part of the Keck program, researchers will evaluate the activity levels of RTKs in pancreatic cancer cell lines and see what happens in the cell signaling pathways using shape-encoded particles and Q-dot imaging technologies.

What researchers uncover could lead to the discovery of new compounds that may inhibit the cell signaling pathways that result in pancreatic cancer. That, in turn, could lead to the development of new targeted therapies. Their findings also may provide new diagnostic tools to help detect cancer earlier, when it is easier to treat.

The family of RAS proteins plays a central role in the regulation of signaling that governs cell proliferation and differentiation. Mutations in the RAS genes result in the transformation of normal cells into cancerous cells that grow rapidly and form tumors. In epithelial cancer cells, activation of RAS genes is one of the most common genetic alterations. In pancreatic cancer, RAS is activated in about 95 percent of cases. It is found to a lesser degree in lung and colorectal cancers as well. Keck researchers will focus on about 50 members of the RAS gene family, studying the protein activity levels in each tumor cell type to see what alterations occur.

G protein-coupled receptors, one of the largest receptor families, have been among the most effective targets for drugs. Half of all drugs available today, including antihistamines and antidepressants, are directed against these types of receptors. G proteins,

which function as molecular switches, play a role in regulating cell growth and they are prominent in epithelial cell cancers such as pancreatic cancer, said Enrique Rozengurt, a professor of digestive diseases, a cancer researcher and holder of the Ronald S. Hirshberg Chair in Translational Pancreatic Cancer Research.

Rozengurt has worked with G proteins in both lung and pancreatic cancers, “two devastating cancers where virtually nothing can be done,” he said.

G protein receptors sit on the cell membrane and form a pocket where hormones or neurotransmitters can bind. The binding induces a change in shape, which is transmitted to the G protein, which then becomes active in cell signaling that results in cell division or migration, which can lead to cancer.

“If we can interrupt the binding and occupy that pocket with substances that bind but don’t trigger a shape change or cell signaling, we might be able to interrupt the development of cancer,” said Rozengurt, who is heading up the G-protein research in the Keck program.



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But there are several such pockets on the cell membrane. Is blocking one enough? Researchers think not. Rozengurt will use the Keck technology triangle to seek new molecules that will bind to the G-protein receptor but not initiate the dangerous cell signaling. He’ll be looking for molecules that antagonize multiple G-protein receptors. Such compounds might one day be used to develop the same sort of cocktail therapy approach that has been so successful in AIDS treatment.

“The idea is that two or three or more molecules will act at different points of the growth signaling pathway in a cell,” Rozengurt said. “If we can attack at multiple points, we may be able to contain the disease.”

Like his colleagues, Rozengurt agrees that what the Keck program is attempting to accomplish is “very ambitious.”

“We’ve tried approaches with chemistry and biology that have not yielded the results we expected,” he said. “Increasingly, there’s the realization that it is the interactions of biochemistry, cell biology, genetics, chemistry and physics that come together in a way that are bringing us new possibilities for drug discovery.”

Joining Rome as director of the Keck Epithelial Cell Cancer Biology Program are co-directors Witte, Colicelli, Rozengurt, Stanley Nelson, a professor of human genetics, and Shimon Weiss, a professor of chemistry and biochemistry. ★