

# Science Driven by Inquisitive Minds

Science has seen an enormous explosion in technology in the past three decades, advances that have changed the way experiments are conducted in laboratories and how discoveries that can save lives are made.

In a monumental project that spanned 10 years, the human genome was revealed as scientists identified and mapped the 20,000 to 25,000 genes that make up each individual. Although work on interpreting the data is still in its scientific infancy, it is anticipated that detailed knowledge of the human genome will open up new, unimagined avenues for advances in medicine. The mapping also has led to easier methods for genetic testing, which can now tell a woman if she is at higher risk for breast or ovarian cancer.

Advances in imaging technology – Positron Emission Tomography (PET) and the development of new imaging probes to be used with it - allow scientists to watch the immune system as it recognizes and responds to cancer in the body. Using PET, researchers are testing a method that would track cancer treatments inside a patient's body in real time as the therapy finds and kills the diseased tissue. In another project, a non-invasive approach is being developed that may one day allow doctors to evaluate a tumor's response to a drug before therapy is even prescribed, allowing a treatment to be personalized to the patient's unique biochemistry.

Automated, computerized molecular screening technology allows up to 100,000 small molecules to be screened in one day to gauge their ability to fight cancer, a task that used to take years when done by hand in a laboratory. (See story on page 10.)

In addition to looking for new, more effective and less toxic cancer treatments, the technology also allows scientists to find out what's going on

inside a cancer cell, which signaling pathways are activated and interacting in a way that may be promoting disease.

Gene expression microarrays are a powerful technology that allow millions of different probes to be designed throughout the human genome so that every gene can be simultaneously assessed. That data can be quickly assessed to determine whether individuals genes are on or off in cancers and other cell types. This information, unavailable a decade ago, gives biologists critical information about which genes within the genome are active in the development of cancer.

The identification of cancer stem cells in several types of cancer may result in the development of new treatments to target and kill these cells, which are the very root of the disease. It is thought that without the cancer stem cells, these cancers could not come back, a stage when they're much more deadly and harder to treat.

Lab-on-a-chip technology is on the cusp of changing the way cancer is diagnosed. The room-sized laboratory needed to process such a cancer diagnostic test in the past is being reduced to a computer chip the size of a stamp due to the emerging fields of nanotechnology and fluidics. One day, a single drop of saliva placed on a cell phone-sized machine in a dentist's office may be able to determine whether a patient has head and neck cancer, well before it is obvious on a physical exam.

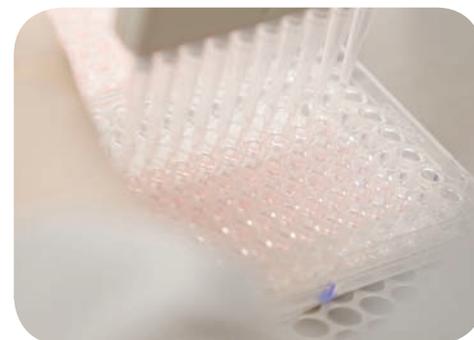
But as much as those advances and others are changing the face of basic science, what really drives discovery has remained constant – a driven, curious person with a burning biological question that must be answered.

"The fundamental unit of scientific discovery is still and will always be the inquisitive mind," said Dr. Owen



Witte, who has been conducting basic research at UCLA for more than 40 years and whose science has led to the development of new drugs to treat leukemia. "What really drives scientific advances is the people who have to, must, know the answer to a question and that should never change."

And that one question then leads to another and another, taking the basic scientist on a journey down a road often times with no specific destination but whose twists and turns could result in a discovery that may lead to new and better ways to treat cancer.



## Basic Science...

### TRANSLATION

It used to be that basic scientists labored with their teams in a lab, seldom crossing paths with the physicians who one day might be working with the treatments that sprang from their research.

Today, in another transition that is altering the face of science, basic researchers often collaborate with physician scientists on translational projects that move discovery from the lab bench to the patient bedside.

"Basic scientists were so far removed from the clinical context that those intellectual bridges could not be crossed," said Dr. Harvey Herschman, director of basic research for UCLA's Jonsson Comprehensive Cancer Center, who also has been a scientist for more than 40 years. "The gulf between the two was so great, there was no way to translate the work."

But as knowledge of some of the fundamental aspects of cell biology has expanded, and clinics have started more and more to measure biochemistry and metabolic processes to monitor the efficacy of treatment, the unbridgeable gulf is narrowing, Herschman said.

"Opportunities to reach across the gulf and join hands are much more prevalent today," he said. "Basic research discoveries in the lab are continuing to accelerate and amaze, and as an added bonus we are more and more able to exploit this new knowledge and collaborate with clinicians to change the standard of care."

Indeed, painstaking, intensive work in Jonsson Cancer Center laboratories has resulted in new and better therapies to treat cancer.

Gleevec, for chronic myeloid leukemia, was based on a discovery made by Witte linking the Bcr-Abl gene and its mutant protein to the cancer. Sprycel,

which treats Gleevec-resistant cancer, had its origin in basic research labs at UCLA. Even while patients were beginning to become resistant to the new drug Gleevec, basic scientists in UCLA labs were studying how the cancer was able to get around the drug. Much of the pre-clinical work on the drug Avastin, now approved for advanced colorectal, breast, brain and kidney cancers, was conducted by Jonsson Cancer Center basic scientists.

And the molecularly targeted breast cancer drug Herceptin, perhaps one of the most widely used drugs today, was the result of work in a lab at UCLA. In that lab, belonging to physician-scientist Dr. Dennis Slamon, researchers conducting basic research linked a particularly aggressive and deadly form of cancer to a mutation called HER-2/neu. Because of that finding, women with this form of cancer, who used to have the very worst prognoses, now have among the best chance to beat their disease.

And all those advances, which today are saving lives, began with an idea, a question that a scientist wanted to answer, had to answer.

## Scientist Stories



### UTPAL BANERJEE

Utpal Banerjee knew from the time he was five that he wanted to be a scientist. Later, simple experiments performed in high school chemistry

labs held him enrapt. Chemistry kits featuring bottles filled with dangerous fluids like mercury were like a siren song.

"There was no question," he recalls. "I knew that I would become a scientist."

Banerjee attended St. Stephen's College in New Delhi, India, for his

undergraduate work and there earned both a bachelor's and master's degree in physical chemistry. He then came to Pasadena as a student and obtained his doctorate degree in chemistry at Caltech. In his post doctoral work, also at Caltech, Banerjee made a big change in his focus and started working in genetics.



"I always wanted to work on live systems," said Banerjee, now chairman of the department of molecular, cell and developmental biology at UCLA. "And I hadn't had an opportunity earlier to do that."

In his quest to explore genetics, Banerjee studied with the renowned Seymour Benzer at Caltech, and it was there that he first began his work with *Drosophila*, the common fruit fly. He focused on a particular gene called *sevenless*, which functions in the fruit fly's eye and shares a similarity to many genes that have implications in cancer development. In his own laboratory at UCLA, Banerjee then studied another member of this oncogenic pathway, which he named *Son of sevenless*, or *Sos*.

Banerjee studied the basic normal development of the eye, what cellular pathways were at work in that development and what happened when that development went awry.

## Basic Science...

"If you want to understand cancer, and have a chance to actually cure cancer, you have to first understand how the gene works," Banerjee said. "Then you can understand what happens when it doesn't work the way it should."

And Banerjee has studied that extensively over the years, in fruit flies, zebrafish, and now in stem cells.

In the zebrafish blood, Banerjee found a new gene that may have implications in transforming normal blood cells into leukemic cells, a pilot study funded by the Jonsson Cancer Center.

A second aspect of Banerjee's work is on the development of blood cells and in understanding their function as stress signal sensors. In a recent study published in the journal *Nature*, Banerjee focused on reactive oxygen species (ROS), the oxygen-containing free radicals that result from oxidative stress and that are commonly known to damage cells. Elevated levels of ROS, therefore, are extremely harmful. However, Banerjee and his team found that in the fruit fly, as perhaps in humans, some blood precursors have moderately elevated levels of ROS and this could be a very good thing.

These small molecules can act as an internal communicator, signaling certain blood precursor cells, or blood stem cells, to differentiate into immune-bolstering cells in reaction to a threat. After the progenitor cells differentiate, the ROS levels return to normal, ensuring the safety and survival of the mature blood cells.

Banerjee discovered that when ROS was taken away in the blood stem cells, they failed to differentiate into the immune-bolstering cells, called macrophages. On the other hand, when levels of ROS were further increased by genetic means, the blood stem cells "differentiated like gang busters," Banerjee said, making a large number of macrophages.

The ROS, Banerjee said, acted as a signaling mechanism that kept the blood stem cells in a certain "sensitized" state – when levels rose, it was a message to the cell to differentiate.

The implications from the finding are several fold, Banerjee said. The blood stem cells are stress sensing cells, their function is to sense conditions that increase oxidative stress and react with an immune response. Keeping their ROS levels slightly elevated puts the cells on alert, sensitive and ready to respond to any threat quickly.



### LUISA IRUELA-ARISPE

Scientist Luisa Iruela-Arispe sees endless opportunities for basic scientists in the future. Technology will continue

to advance and in her laboratory and throughout the Jonsson Cancer Center, she encounters young researchers with a "true enthusiasm for moving science forward in a way that makes an impact on health."

"I see a lot of excitement in basic research," said Iruela-Arispe, whose own youthful passion and curiosity drew her into the field. "With today's technology, you can take huge creative leaps forward."

That evolution of technology – the ability to image cells, examine their signaling pathways and quickly analyze whole genomes – has allowed researchers to ask very specific questions and obtain very precise answers.

"Before, we would analyze data in the context of what others have done and interpret results in a far more speculative manner," she said. "Now we can be more definitive and move ahead more quickly, which is important because every question leads to 50 other questions."

These tools hadn't yet been conceived when science first piqued Iruela-Arispe's interest. Since she can remember, she's had questions she wanted answered, what she calls the "why, why, why of things." Even as a young girl, she was more likely to dissect a dead insect she found on the sidewalk than scale a jungle gym.

Those questions led Iruela-Arispe to science, where she now studies the normal and abnormal development of blood vessels and how that plays a role in cancer. She came to UCLA from Harvard more than a dozen years

"There was no question.

I knew that I would become a scientist."

– Utpal Banerjee

In fruit flies, he's now studying cell metabolism and its link to cancer. When cells start growing out of control, which happens in cancer, they need a larger amount of energy to fuel that growth. Cancer cells find alternate ways to create that energy to feed themselves, and those pathways may provide targets to block that metabolic activity and thereby starve the cancer.

His work involves changing the status of the mitochondrion, which act as the cell's power plants. This can be done by genetic means or by the application of drugs. He's focusing on a cell signaling pathway that causes cells to grow fast and increases the number of mitochondria in the cell. If that pathway could be blocked, cancer cells might lack the extra energy they need to grow and spread.

"If we can take the energy away from the cells, it might be a way to attack the cancer," he said.

## Basic Science...

ago, and has since made important discoveries about angiogenesis, the physiological process involving the growth of new blood vessels from pre-existing vessels.

Solid tumors cannot grow larger than a pinhead without creating an independent blood supply to provide the oxygen and nutrients they need to grow and spread. Researchers had posited that interrupting the development of that blood supply could result in starving, and hopefully killing, the tumors.

Iruela-Arispe's lab was among the first to develop the concept of naturally occurring angiogenesis inhibitors. She explored the idea that natural inhibitors of this process were responsible for regulating the ability of blood vessel to expand and might be useful in fighting cancer. ([Click here to watch Iruela-Arispe talk about her work.](#))



She was the first to clone METH-1 and METH-2, two potent, naturally occurring human proteins that inhibit angiogenesis. They act by inhibiting the growth of endothelial cells, which line the inside of blood vessels and are key to new blood vessel formation.

Her idea, then a novel concept, proved to be prescient. A little more than a decade after her observations, the angiogenesis inhibitor Avastin is approved for use in metastatic colorectal, non-small cell lung cancer and breast and kidney cancers, as well as glioblastoma, a deadly brain cancer.

In the years since - her work funded in part by a seed grant from the Jonsson Cancer Center - Iruela-Arispe has continued to study how normal vasculature develops. Looking at the "normal" system has helped her gain information on how things go awry in cancer. She and her team developed genetic tools to play with the gain and loss of endothelial cell function in the normal system to see what occurred.

That work led her to study blood stem cells, the cells that give rise to all the cells in the bloodstream. Four years later, that work led to another important finding. Iruela-Arispe proved definitively that blood stem cells are made during mid-gestational embryonic development by endothelial cells. Her discovery put to rest a long-standing controversy over whether blood stem cells were created, or born, in the endothelium or originated from another cell type in a nearby location.

The finding ultimately could lead to new therapies for certain blood disorders and cancers, said Iruela-Arispe, a professor of cell, molecular and developmental biology and director of the cancer center's Cancer Cell Biology Program Area.

Blood stem cells currently cannot be grown outside of the body without losing their "stemness," their ability to differentiate into the different blood cell types. If blood stem cells can be grown outside the body from endothelial cells and be programmed to only self-renew, or make more of their own kind, researchers may one day be able to produce blood stem cells to replace the bone marrow in transplants or the mutated blood cells that result in diseases like leukemia.



### SIAVASH KURDISTANI

The journey to science for Dr. Siavash Kurdistani was not an easy one. He was born in Tehran, and fled the

social and political turmoil sweeping his country after the 1979 revolution and the eight-year war with Iraq that followed.

At 17, and not permitted to emigrate, Kurdistani fled his country with the aid of smugglers. Over 10 days, he traveled by car and hiked over mountains to reach Pakistan, where he was jailed for being in the country illegally.

Designated by the United Nations as a refugee, Kurdistani was able to relocate to Austria and, later, to New York City. Living with a cousin in a basement apartment next to an elevated subway track in Brooklyn, Kurdistani studied diligently and rapidly progressed through his English as a Second Language courses. Soon he was able to graduate from high school. After graduating, he traveled west and attended Santa Monica College for two years, then transferred to UCLA, where he graduated summa cum laude with a bachelor's degree in biochemistry.

Armed with a medical degree from Harvard, where he graduated magna cum laude, Kurdistani returned to UCLA for his residency.

## Basic Science...

Today, Kurdistani studies epigenetics, a field focused on inherited information other than that encoded on DNA. Specifically, he studies chemical modifications of proteins called histones, which are found in nearly all eukaryotic organisms whose cells contain complex, membrane-bound structures such as a nucleus.

"My research involves the study of processes that are associated with DNA, but don't involve genetic mutations," said Kurdistani, an assistant professor of biological chemistry who joined the UCLA faculty five years ago.

DNA, which carries all the instructions for a cell, wraps itself around histones, which serves as a kind of scaffold that allows for the compaction of the long DNA molecules. The complex of the DNA and the histones is called chromatin, the physiologically relevant form of the genome in humans.

The chemical modification of these histones, which is the basis of Kurdistani's work, is crucial because they regulate such processes as gene transcription, DNA repair and other DNA-related functions.

Kurdistani is studying how histone modifications are exploited by cancer cells to support their unregulated growth, although alterations of histone modifications are involved in many disease processes, he said.

What Kurdistani has found in the lab is that loss of histone modifications is associated with cancers that behave more aggressively. Patients with these types of cancers had poorer prognoses, decreased survival rates and increased chances for recurrence. The finding allowed him to develop a tool, a type of clinical test, to distinguish between cancers that are less aggressive versus those that are more aggressive.

"This is important because it allows an oncologist to tailor therapies to the specific traits of the cancer," said Kurdistani. "Patients with more aggressive cancer could get more aggressive therapies, while those with more indolent cancers could be spared the most aggressive regimens and the side effects that come with them."

The assay, which still needs further development, can be used in cancers of the glandular tissues, including breast, lung, kidney, prostate and pancreas.

Like his contemporaries, Kurdistani has benefited from the explosion in technology that has helped to speed the basic research process. The advances are great, he said, but what is most vital to the research process is creativity.

"First, you have to have a good idea," he said. "Creativity is helped by having the space and time to be able to think, to let ideas develop on their own. It also is helped by interactions and collaborations with other scientists in a multidisciplinary environment. UCLA is a great place for that."



### STEPHEN SMALE

For scientist Stephen Smale, the genomics era has - literally - changed everything in basic research and the study of gene regulation. One of his projects focusing

on the inflammatory response in the cancer microenvironment, in fact, could not be done without the advent of the study of the genome.

"The emergence of sequencing, evaluating and studying the genome did not exist prior to 2001," said Smale, a professor of microbiology, immunology and molecular genetics and director of the cancer center's Gene Regulation Program Area. "Basic research will be

divided into two eras - pre-genomics and post-genomics. There's a lot more to study now, we can move faster and the value of what we're learning is greater. We can see the broader relevance of what we're doing much more easily in the post-genomics era."

Prior to genomics, scientists could only study gene regulation by looking at one gene at a time in great detail with the hope that the results obtained would be relevant to a much broader set of genes. It was informative, but slow and frustrating, Smale said.

Further complicating the science, different researchers focusing on different model genes believed to be similarly regulated often came up with disparate results.

"The question was, is one researcher right and one wrong or is there some underlying logic we're missing?" Smale said. "Now, with genomics, we can look at a broad set of genes at the same time and immediately gain insight. We can find specific sets of genes regulated by a given strategy, which increases the value of the information and allows us to interpret our findings much more effectively."

A UCLA professor for 20 years - a period he said has "flown by" - Smale studies the molecular mechanisms of gene regulation in cells of the immune system.

In addition to gene regulation associated with an inflammatory response, Smale studies the development of the immune system. Blood stem cells give rise to lymphocytes, red blood cells, macrophages, neutrophils and other immune cell types in the bone marrow. Studies of immune development are very important for understanding many types of leukemia and lymphoma, Smale said, because these cancers are derived from immature immune cells undergoing development.

## Basic Science...

One focus of Smale's work on immune system development is a transcription factor called Ikaros, which Smale co-discovered in 1991. Ikaros is a protein that binds to specific DNA sequences and Smale has been studying how it regulates genes during immune system development.

It appears to work, he said, through an unusual mechanism and, while his lab and others have gained insights, they still haven't uncovered how it operates. Ikaros is mutated in more than 85 percent of certain types of acute lymphoblastic leukemia (ALL) and if he could uncover how it works, it would be a giant leap forward in understanding the molecular basis of these ALL subtypes, an understanding that could be translated into new and more effective therapies for the disease.

Smale's work on inflammatory responses in the cancer microenvironment employs genomics to uncover the selective regulation of different genes involved in inflammation.

"The reason this is important for cancer is that within the tumor microenvironment, some inflammation molecules enhance tumor growth, while others stimulate an immune response to fight the tumor. If we could identify strategies for inhibiting the genes that promote tumor growth without inhibiting those that promote the immune response, we may have a new way to fight cancers."



### OWEN WITTE

Even though the math works out, Dr. Owen Witte still sounds a bit incredulous when he states that he's been doing basic science at UCLA for 30 years. He's

seen many changes over the years, but he has no trouble stating the crucial ingredient in research – an idea out of left field, a question that just has to be answered.

In his illustrious career, Witte has answered many questions and some of those answers have led to remarkable discoveries that were translated into clinical uses - new drugs to treat chronic myeloid leukemia (CML), understanding of immune disorders like X-Linked Agammaglobulinemia (XLA), defining a surface antigen in prostate cancer that led to clinical trials of a monoclonal antibody, and the development of a new probe for Positron Emission Tomography scanning that will allow modeling and measuring the immune system in action and monitoring response to new cancer therapies.

"The fundamental unit of scientific discovery is still and will always be the inquisitive mind."

– Dr. Owen Witte

Witte discovered the Bcr-Abl oncogene as a tyrosine kinase produced from the Philadelphia chromosome and its mode of action in CML. His work provided a target for a new therapeutic and as a result the drug Gleevec was tested and approved for use in patients with CML. Prior to the discovery and the development of Gleevec, patients were given Interferon, which had serious side effects. In some patients, Gleevec stopped the cancer dead in its tracks. The basic defect in XLA is a failure of B-lymphocyte precursors to mature into B-lymphocytes, and ultimately, into plasma cells. Since they lack the B lymphocytes that are responsible for producing protective antibodies, XLA patients often have severe and chronic infections. In his lab, Witte discovered that in patients with XLA, the BTK gene is missing from the lymphocytes, defining for the first time that a genetic

immune deficiency was caused by a loss of function of a specific tyrosine kinase. That finding has led to the development of a class of targeted drugs, which are being tested in clinical trials to control B cell growth in malignancy and autoimmunity.

Witte has also discovered surface antigens in prostate cancer that may be important in the development and treatment of the disease. Among the most important is a surface antigen in prostate cancer called Prostate Stem Cell Antigen, or PSCA, which Witte and several colleagues helped to uncover. That finding led to development of a monoclonal antibody targeting PSCA that is now being tested in clinical trials.

Most recently, Witte and colleagues modified a common chemotherapy drug to create a new probe for Positron Emission Tomography (PET), which enables scientists to monitor the immune system – at the whole body level in 3D – as it tries to fight some cancers or when it goes awry as it does in autoimmune diseases. Called FAC, the small molecule was created by slightly altering the molecular structure of one of the most commonly used chemotherapy drugs, gemcitabine. The team then added a radiolabel so the cells that take in the probe can be seen during PET scanning.

The probe is based on a fundamental cell biochemical pathway called the DNA Salvage Pathway, which acts as a recycling mechanism that helps with DNA replication and repair. All cells use this pathway to different degrees. But in lymphocytes and macrophages, the cells of the immune system that initiate an immune response, the pathway is activated at very high levels. Because of that, the probe accumulates at high levels in those cells.

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"None of the projects started began with the sole intention of making therapeutic or diagnostic tools," he said. "We had a question and asked it. We found an answer and then had a second question to ask. And so it goes."



### HONG WU

When Dr. Hong Wu began her career in basic science more than 20 years ago, discoveries were made slowly by a

scientists working alone in a laboratory on a project. Today, basic research is much more multidisciplinary, with researchers from different disciplines collaborating on projects, using leading-edge technologies to shine a new light on science.

And so it is for Wu at UCLA, where her work on the biological function of a tumor suppressor gene in cancer development has led to very fruitful collaborations with a team from UCLA's soft tissue sarcoma and pancreatic cancer programs, where she shares insights with clinicians who are treating patients in the clinic.



A professor of molecular and medical pharmacology and an expert in cell signaling and animal models, Wu has focused her research on the PTEN gene, the second most frequently deleted human tumor suppressor gene. When it's missing in a cell, it divides out of control and the result is cancer. She and her team use both a genetic model and a cellular model to study how PTEN functions in humans and the pathways it uses, which may provide future targets for therapeutics.

PTEN was cloned about a decade ago, about the same time that Wu came to UCLA from the Whitehead Institute at MIT. PTEN was the first tumor suppressor gene shown with phosphatase activity, so Wu was able to study how its enzymatic activity controls tumorigenesis.

"We now know PTEN plays an essential role in the PI3 kinase pathway and know the mutation of it will lead to resistance to certain therapies," she said.

For example, a patient with a PTEN deletion will not respond well to treatment with an inhibitor targeting the epidermal growth factor receptor (EGFR). So that could be used as a prognosis marker for breast cancer patients with that mutation, she said.

In a lung cancer trial, a similar conclusion was reached – patients with PTEN mutations do not respond to EGFR therapies.

PTEN itself does not provide a target for therapy, but the pathways it controls may prove to be targets for therapy, including the pathways mTOR, AKT and PI3 kinase. Wu is also studying what effect PTEN might have in controlling stem cell activity in leukemia, brain and prostate cancers, which also could lead to new and more effective therapies.

By analyzing cells and animal models lacking the PTEN tumor suppressor, Wu and her colleagues have demonstrated that PTEN negatively affects stem cell self-renewal, proliferation and survival. The finding provides a strong link between stem cell biology and cancer biology, and suggests that tumors may originate through the transformation of stem cells. If that transformation could be targeted or interrupted, it might provide yet another new and more effective way to treat these cancers.

"For someone like me, trained in and conducting basic research for the past 20 years, the big challenge and next step is to integrate and work with physician-scientists."

– Hong Wu

"For someone like me, trained in and conducting basic research for the past 20 years, the big challenge and next step is to integrate and work with physician-scientists," Wu said. "With this collaboration, you realize your basic research can have a real impact on patients."

Wu also is credited with establishing animal models for various human cancers, including leukemia, brain and prostate cancer models. These animal cancer models offer unique tools for exploring the molecular mechanism underlying human cancers and for the development of new therapies.