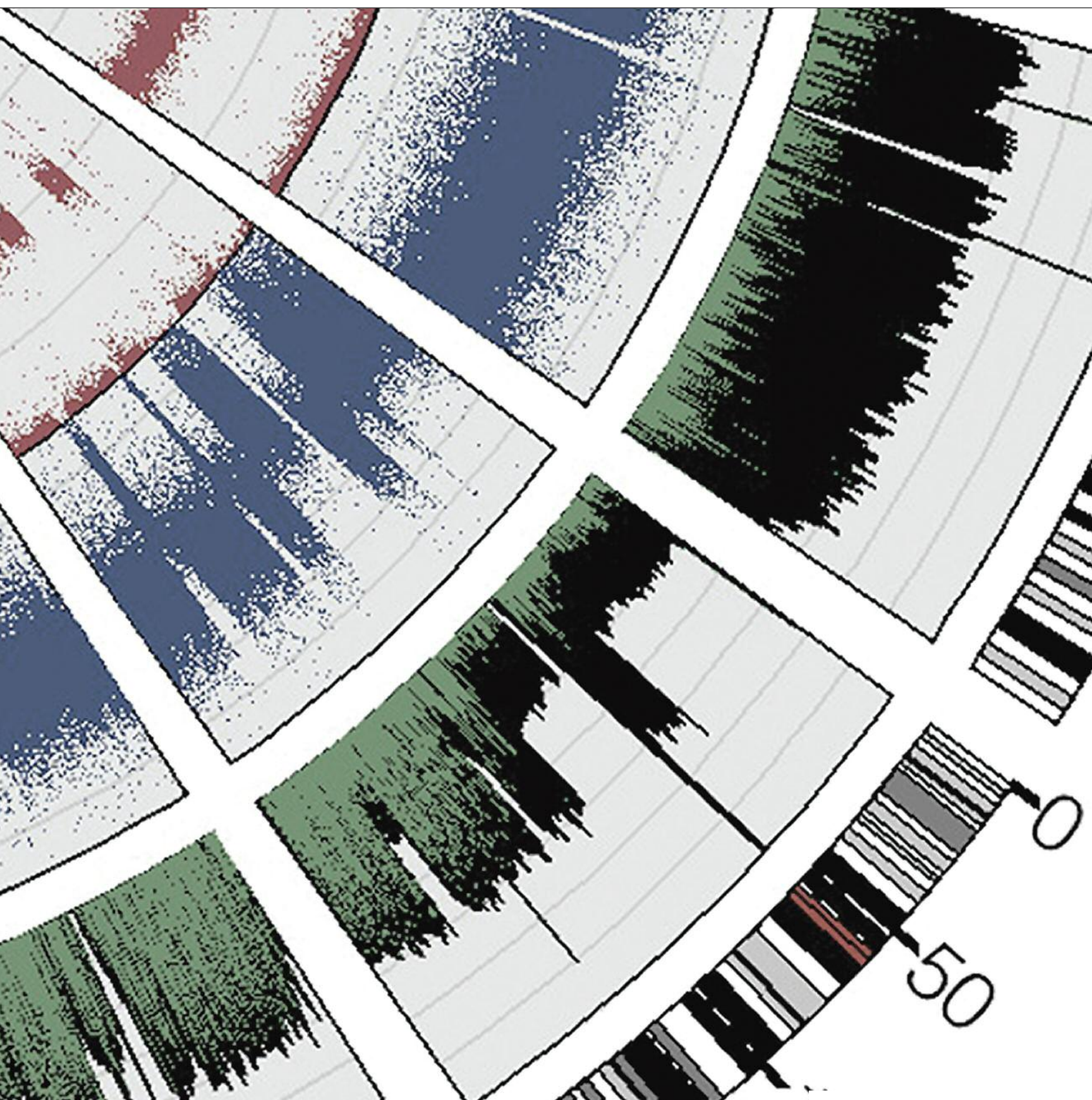


# UCLA Pathology and Laboratory Medicine 2012 Annual Report



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# Four Tales of Imagination

In Los Angeles, we have just completed the year-long *Pacific Standard Time: Art in L.A. 1945-1980*, a collaboration of more than 60 cultural institutions across Southern California to celebrate the birth of the L.A. art scene ([www.pacificstandardtime.org](http://www.pacificstandardtime.org)). The Martian dining lounge of LAX, opaque divers and Mulholland pools of David Hockney, the waffle Bunche building at UCLA, the interior whorls of Ed Ruscha, the gothic spires of the Watts Towers. A reminder of how today's Los Angeles was built on creativity, playfulness, dreams.

As they planned our 2012 Annual Report, our enterprising editor and co-editor, Sharon Webb and Justin Perry, captured the stories of four faculty, whose creativity and energy are shaping our own department today.

Jonathan Said, himself at the center of the revolution in hematopathology, has gathered at UCLA an extraordinary team of clinicians, scientists, and trainees. A Boswell of contemporary music and Johnson of extreme travel, subliminal adventure is always at the edge of Dr. Said's community.

Richard Gatti, an ebullient raconteur and Julliard-trained pianist, has tenaciously pursued the dream of therapeutic genomics. From the co-discovery of the ATM gene to creation of read-through pharmacotherapy now poised for clinical trials, Dr. Gatti's work provides a precedent and rationale for the launch this year of the UCLA Clinical Genomics Center. This center, an unprecedented partnership of Pathology, Pediatrics, and Human Genetics, provides patient-centered genome-based diagnostics and clinical care for patients with Mendelian disease.

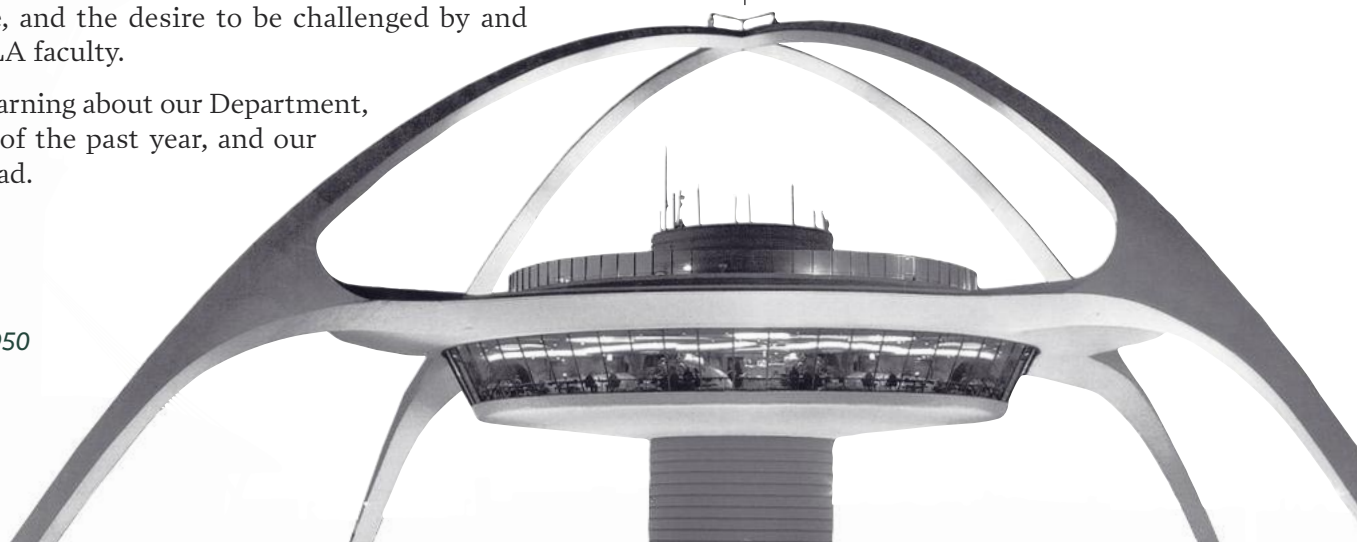
Sarah Dry, a discerning clinical scholar of both soft-tissue sarcomas and gastrointestinal surgical pathology, has precociously emerged at UCLA as an imaginative and incisive leader of the health system-wide initiative to integrate molecular translational research with patient-centered clinical care.

Education is embedded in all our Department's activities, but with the logarithmic increase in information, and the kaleidoscope of its interpretation, we need new strategies for organizing and disseminating it to our trainees inside the university, and the community around us. Robert Trelease is turning this process inside out, with interactive portals for medical information and learning that can be accessed by anyone with a tablet or smartphone, and the desire to be challenged by and engaged with the UCLA faculty.

So, please join us in learning about our Department, its accomplishments of the past year, and our plans for the year ahead.

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Theme Building, LAX, 1950





# A Reflection on Hematopathology

Dr. Jonathan Said's interest in hematopathology — the branch of medicine concerned with nature, function, and diseases of the blood — began when he left his childhood home in the South African Highveld as a naïve intern to enter the somewhat Dickensian atmosphere of the Boston City Hospital (BCH). In those days it was possible for a foreign medical school graduate to get a residency without even an interview. He chose the Mallory Institute of Pathology at BCH because of its rich history in pathology training and the pioneering work done there on Hodgkin's lymphoma by Dr. Frank Mallory. In addition, authors of the influential and enduring text *Pathologic Basis of Disease*, Drs. Stanley Robins and Ramzi Cotran, taught there. Dr. Cotran would go on to later serve as Said's first mentor in pathology. It was an ideal environment for an aspiring pathologist, and there where his life-long love affair with the art and science of pathology began.

Said's early years of training were marked by rapid scientific advances in the field of hematopathology. His chief resident, Dr. Helmut Renke, an enthusiastic teacher and now celebrated nephropathologist, had trained in Germany under the esteemed Dr. Karl Lennert — the grand old man of hematopathology. "It was clear from Dr. Lennert's studies and those of Dr. Robert Lukes at USC that we were on the threshold of a revolutionary approach to diagnosing and treating hematopathologic malignancies based on novel immunologic concepts," Said recalls. "These concepts met at a nexus that identified lymphomas as tumors of the immune system."

The following year, Cotran left Boston City Hospital to become chair of pathology at the Peter Bent Brigham Hospital (later Brigham and Women's Hospital), and asked that Said accompany him to his new post. "The Brigham was in all respects different from the Boston City Hospital. At the Brigham there was a heady atmosphere of research into immunologic diseases, and lymphoma diagnosis and treatment," Said explained. The Brigham and Dana Farber Cancer Center, with its pioneering work on leukemia chemotherapy by Dr. Sidney Farber, had been at the forefront of the newly evolving approach to cancer as a curable disease.

There Said began working with Dr. Emil Unanue, a brilliant, albeit intimidating, immunologist originally from Havana, Cuba, on immune complex disorders of the kidney. "Emil taught me basic immunology skills that stood me in good stead when I applied them to the study of lymphoma," Dr. Said recalls. At the same time, he was fortunate to work with Stuart Schlossman at the Dana Farber Cancer Center who was producing the first monoclonal antibodies against the malignant T-cells of lymphoblastic leukemia, and with legendary clinicians such as William Moloney, George Cannellos and Lee Nadler, then a precocious hematology fellow. "As a junior trainee it was an awesome experience to present the pathology for lymphoma cases at tumor boards and play a role in patient care alongside those luminaries in the early days of effective lymphoma and leukemia chemotherapy, which until then had been fatal diseases," he added.

Having trained with the best, Dr. Jonathan Said continues his quest to treat and cure diseases of the blood and lymph nodes.



“Our department includes some very gifted hematopathologists. They have the unique expertise to diagnose many of the most complex blood, bone marrow, and lymphatic conditions that exist.”

—DR. JONATHAN SAID

Still riding what he referred to as a wave of good fortune, Said teamed up with his next mentor, Dr. Geraldine Pinkus. They were able to obtain funding to apply newer immunologic techniques to the study of lymphoreticular malignancies. “In those days before flow cytometry, I spent countless hours in the dark hand-counting fluorescent cells in cell suspensions and performing arcane T- and B-cell assays using sheep red cell rosettes. In fact, one late night session ended in a narrow escape as the old fashioned light source in the fluorescent microscope exploded from overheating,” he recalls with a grin.

Reports had been coming out of the laboratory of David Mason in Oxford, England that immunohistochemistry could be performed on paraffin sections, which allowed application of immunologic tumor markers to tissues from patient biopsies. Said and Pinkus were fortunate to have learned this technique from Dr. Clive Taylor, who had just left the UK to take a position at USC. “We set up the tests in Tupperware containers from Geri’s kitchen alongside our microscopes as we signed out cases, and were amazed to get positive results,” Said recalls. “Pinkus and I published one of the first papers that used this method in *The American Journal of Pathology* in 1977, and the technique, albeit in a highly automated and sophisticated form, is now standard in all pathology laboratories.”

“At about the same time,” Said continued, “we were able to benefit from a callus on the toe of one of the pathology residents. He scraped off some of its superficial crust, and together with his scientist wife Susan, used it to develop a primitive polyclonal keratin antibody, which turned out to be one of the first keratin stains and still one of the mainstays of tumor diagnosis in differentiating lymphoid cancers from carcinomas.

Following his residency and research fellowship in hematopathology, Said joined the faculty at the Brigham where he might have remained if Dr. Michael Fishbein, currently chief of Decedent and Cardiac Pathology at UCLA, had not tempted him to Southern California on one of the bleakest winter days in Boston. Despite the obvious temptations, the decision to leave was a difficult one. “I can remember one of my collaborators shaking his head while looking at my scrawny frame and saying, ‘Does he look like he belongs in California?’” he recalls with a smile. “Nevertheless, coming to UCLA gave me an opportunity to develop my own program in hematopathology, with my own laboratories that included an immunohistochemistry lab and electron microscopy lab.”

Said began establishing partnerships and making scientific contributions upon arrival at UCLA. It was during those early days on campus that he met Dr. Peter Shintaku, who had just completed a PhD in microbiology from UCLA. The two formed a vital professional relationship that lasts to this day. “Shintaku remains my right-hand man after almost 30 years,” according to Said. “He has developed into a superbly talented immunohistochemist, who currently serves as director of the Immunohistochemistry Laboratory in the Department of Pathology and Laboratory Medicine at UCLA.”

While working in the Los Angeles area, Said quickly became fascinated by a baffling spectrum of lymphoproliferative disorders that were beginning to become frighteningly common in young, predominantly male patients. This trend, he realized in retrospect, was actually the beginning of the AIDS epidemic. “Notwithstanding the tragic dimensions of the disease, this was a unique opportunity to study a new disease that can be considered a model of the immune system in disarray and its effect on the pathogenesis of lymphoreticular neoplasms,” he explained.



## THE ROLE OF miRNA IN LYMPHOMAS AND LEUKEMIAS

Dinesh S. Rao, MD, PhD, is working with cellular molecules that were first discovered in 1993. These molecules, called miRNA, are short strands of ribonucleic acid found in blood cells that have a nucleus. His goal is to take these molecules and clarify their structure, function, and relationship with other molecules in the cell. Specifically, he hopes to identify their role in the hematopoietic system, especially as it relates to the onset and spread of lymphoma and leukemia.

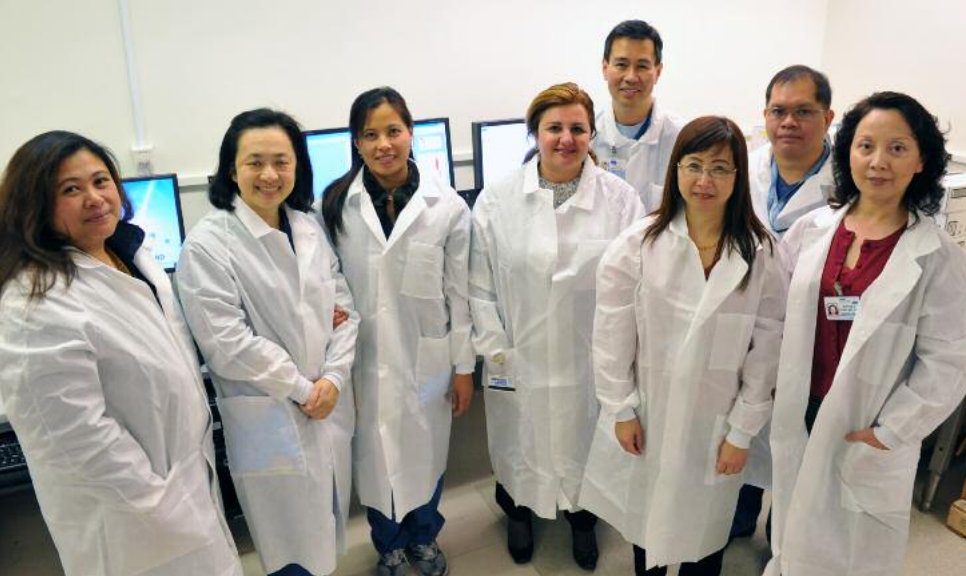
Dr. Rao came to UCLA as a hematopathology fellow, under the mentorship of Dr. Jonathan Said. His thesis work was completed in the laboratory of Dr. David Baltimore, a renowned scientist and Nobel laureate, at the California Institute of Technology. “It was there that I combined my interest in hematopoiesis and other lymphoid problems with my interest in miRNA,” he said. There his work focused on the role of miRNA in normal B-cell development and lymphoma pathogenesis. He established the identity of a novel miRNA involved in the differentiation of B-lymphocytes into plasma cells. This same miRNA appears to be an effector of the tumor suppressor protein p53, thereby linking it to cancer initiation or progression.

As a newly minted assistant professor in the Department, his research on the topic continues to flourish. He has become an important investigator nationally, working on the role of miRNA in the immune system. “My lab is now trying to understand how these miRNAs affect the formation of hematological malignancies (i.e., cancer that affects blood, bone marrow, and lymph nodes), and whether we can leverage them in diagnosis and care. As a physician who is an active member of the hematopathology service, this is the ultimate goal of what we do here,” he explained. This translational research is carried out using advanced technologies, including molecular profiling microarrays, high-throughput sequencing, and flow cytometry.

Dr. Rao and his team have recently made important inroads into miRNA-dependent regulation of B-cell differentiation and myeloid cell differentiation in the hematopoietic system. His work promises to reveal interconnections between important pathways in hematopoietic development and cancer, with the potential of developing new therapeutic possibilities. It has both practical and biomedical applications and is an exploration of important problems in gene expression and cellular differentiation. “We are looking into whether returning lost or damaged miRNA would stop or slow growth of leukemia or lymphoma,” he continues. “In short, we’re trying to use basic science findings to improve care in the clinical setting, which is ambitious. We think we are on the right path, and only time will tell if it fully translates to the bedside.”

*ABOVE: Dr. Rao reviews experimental results with laboratory personnel. “The unexpected result is the one that may be groundbreaking,” says Dr. Rao. “So it’s very important to have a hand in what happens daily in the lab. It’s also critical to make the connections between lab work and the clinical problems that we try to address as physicians.”*





## A DECADE OF PROGRESS: UCLA CLINICAL FLOW CYTOMETRY

As an integral component of hematopathology, clinical flow cytometry has evolved rapidly over the past two decades as a result of technological advancements, as well as development of the World Health Organization's (WHO) classifications and international consensus. UCLA's clinical flow cytometry program was not keeping pace with other high quality programs throughout the country.

Dr. Sophie Song was hired as medical director of the UCLA Clinical Flow Cytometry Lab in 2002 to accomplish one major objective—to create a “robust” outreach program for the Clinical Flow Cytometry Lab and Hematopathology Program. According to the Department's mission, Dr. Song first developed a comprehensive business plan with help of an outside consultant. “It was clear that we had to overhaul the entire technical procedures and interpretative approaches that we

were using, as well as operations of the lab, including personnel, organization of shifts, etc.,” she explained. In working with the hospital management, Department, and medical staff, significant changes were made in all major aspects of the clinical service. Over 20 new SOPs were deployed, and brand new teaching curricula of clinical flow cytometry were developed for pathology residents and fellows. In addition, “We extended our operating hours and increased staffing to accommodate any samples that came in late or over the weekend.” According to Dr. Song, these changes have significantly improved the quality and turnaround time, increasing the lab's volume by approximately 10 to 20 percent annually.

Furthermore, Dr. Song led efforts to update the current testing platform for flow cytometry by designing new antibody combinations and proposing new instrumentation for the lab. “This new equipment will add two- to four-dimensions in identifying target cell populations and therefore dramatically increase sensitivity and specificity of the testing,” she continued. The lab space is also being configured to accommodate the new equipment. “This new testing platform will continue to improve our efficiency and productivity, and bring our already high quality to an even higher level,” continued Dr. Song. “We can now compete with the best academic and commercial flow cytometry labs in the country, and serve our physicians and their patients faster and more effectively than ever.”

**ABOVE: The Clinical Flow Cytometry Team (from left to right): Syndette Fabello, Gina Balatico, Angie Manzanilla, Roya Hariri, Ritchie Mendoza, Qingfeng Kong, Erick Redor, and Dr. Sophie Song. (absent from the photo: Dindo Maglonzo and Grace Peralta)**

With this new model, his team, collaborating with cytopathologist Dr. Ann Walts, identified a new kind of lymphoma in AIDS patients that was only present in body fluids. Concurrently, two scientists from Columbia University identified a novel carcinogenic herpes virus now called herpesvirus 8 (HHV8). Said subsequently received a phone call from Drs. Daniel Knowles and Ethel Cesarman, researchers at Cornell University, who had also recognized the same effusion-based lymphomas, now called primary effusion lymphoma (PEL). “To our astonishment the HHV8 virus was only found in effusion-based lymphomas and appeared to play a direct role in its pathogenesis, one of the rare examples of an oncogenic virus actively produced by and transforming the malignant B-cells.”

In further studies, with the aid of Dr. Phillip Koeffler from the UCLA Jonsson Comprehensive Cancer Center, Said and his colleagues produced an immortal cell line called KS1 taken from the cells of a patient with primary effusion lymphoma. This turned out to be an important resource for producing pure HHV8, which has numerous research and practical applications including development of an ELISA assay that can be used to screen blood and other examples

for exposure to the virus. The virus was also shown to be the cause of a lymphatic cancer, Kaposi's sarcoma, solving one of the great riddles of tumor pathogenesis.

In addition to his interests in hematopathology, Said has been accepted as an expert in diagnostic hematopathology as an author of chapters on Hodgkin's disease (2006) and Primary Effusion Lymphoma and Lymphomas associated with HIV infection (2010). He is currently president of the Society for Hematopathology, and together with Drs. Sophie Song, Scott Binder, and Stephen Lee, organized an international workshop on cutaneous lymphomas in 2011.

Furthermore, Said has ushered in significant growth and success to the department, especially in regard to the hematopathology program. “Under the leadership of our chair Dr. Jonathan Braun, we have an unparalleled environment for the study of hematologic diseases, lymphomas and leukemias, including accomplished basic researchers, gifted hematopathologists, and a succession of talented and productive trainees from our fellowship program.” Said has seen these three areas in the hematopathology program—clinical services, research, and education—significantly expand and, more importantly, become intertwined.

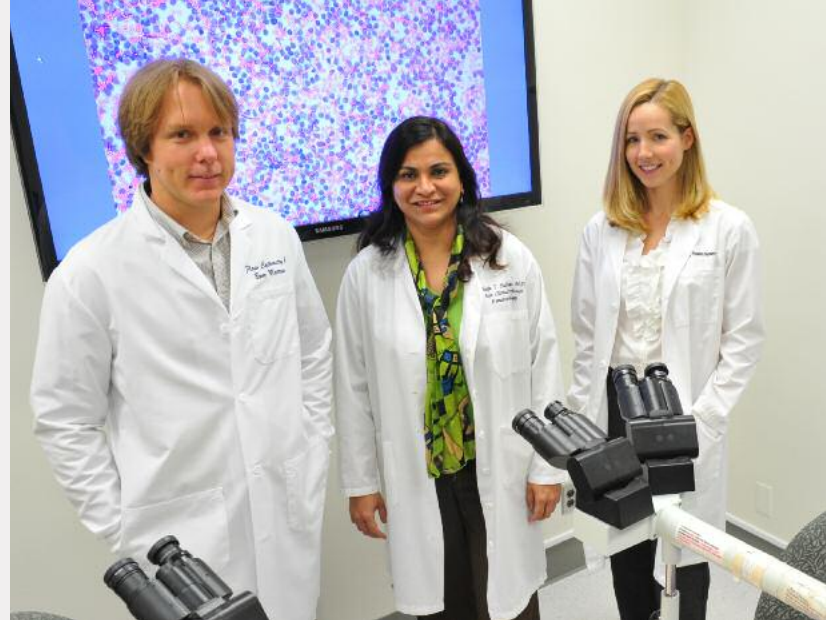


“Our department consists of some very gifted hematopathologists,” he remarks proudly, which means a lot coming from someone who has worked alongside the giants of the field. “They have the unique expertise to diagnose many of the most complex blood, bone marrow, and lymphatic conditions that exist.”

Furthermore, the hematopathologists are part of a team providing care to patients both at UCLA and in the community, with outstanding clinicians such as Drs. Fred Rosenfelt, Peter Rosen, Sven de Vos, Lauren Pinter Brown, and John Timmerman. “We are able to help enroll patients in clinical trials so that they receive cutting edge cancer therapy, particularly patients who may have relapsed or failed conventional therapy in the community,” Said comments.

Said has also experienced the maturation of a successful research program in hematopathology at UCLA. Departmental research currently focuses on the pathogenesis of malignant lymphomas using a transgenic model with Dr. Sven deVos in the UCLA Hematology Oncology Department, virus associated B-cell lymphomas including EBV and HIV, and characterization of T-cell lymphomas with a multi-institutional pathology consortium. Said is also personally involved in multiple clinical trials as part of the pathology committee for the NIH clinical trial consortium CALGB. Other researchers and clinicians within the department are also involved in collaborative clinical trials taking place at UCLA and beyond. He continues, “We are also able to take advantage of the outstanding cytogenetics and molecular laboratories run by Drs. Nagesh Rao and Wayne Grody respectively in order to perform state-of-the-art testing on patient samples. This allows us to provide the best treatment for the individual patient with leukemia and lymphoma.”

Medical education and training in hematopathology have also continued to improve. In October 2011, the Department hosted the Society for Hematopathology/European Association for Haematopathology (SH/EAHP) Workshop 2011. Said and colleagues Drs. Sophie Song, Scott Binder and Stephen Lee served as members of the organizing committee. It was the largest international conference hosted and organized in Department history, with more than 430 physician attendees worldwide. Said has also played a critical role in transforming the fellowship program in hematopathology. These fellows receive advanced training in the field using state-of-the-art supportive diagnostic techniques, in a broad spectrum of pediatric and adult morphologic hematopathology. In short, these are the hematopathologists of the future. “Ultimately,” commented Said, “I hope we are able to create an environment where these young, inquisitive minds can share the passionate quest to understand, diagnose, and cure hematologic diseases.”



## THE ELITE: HEMATOPATHOLOGY FELLOWSHIP TRAINING PROGRAM

“Hematopathology is the study of blood-associated diseases and encompasses a vast range of intriguing and complex disorders which often demand subspecialty expertise,” explains Dr. Sheeja Pullarkat, director of the Department’s hematopathology fellowship program. A continually evolving field at the intersection of cutting edge diagnostic techniques and fascinating therapeutic trials, hematopathology requires both a breadth of knowledge and exceptional attentiveness to detail, qualities which are developed through the Department’s rigorous fellowship program.

Each year increasingly competitive applicants from around the country, who have already completed four years of medical school and a pathology residency, compete for two coveted positions as hematopathology fellows in the Department. Those chosen undergo a rigorous year immersed in high volume, expert level pediatric and adult hematopathology cases, including referrals sent as far away as China.

Fellows eventually master a myriad of diagnostic modalities including morphology, immunohistochemistry, cytogenetic and molecular diagnostics, flow cytometric analysis and telepathology, all with the goal of providing the most accurate and personalized diagnostic results for a variety of adult and pediatric patients. According to Dr. Pullarkat, the fellows see as many as 1,300 bone marrow cases and 1,400 lymph node cases per year, with numbers continually expanding given the addition of international telepathology consultations. Fellows also have numerous opportunities to participate in translational research while at UCLA. “In addition to their keen diagnostic skills as pathologists, our graduates have the research experience to make them well prepared for careers in academia,” continues Dr. Pullarkat. The graduates are also well represented in private practice settings and subspecialty reference labs. “In all, our graduates are elite specialists who are prepared to succeed in whatever professional setting they choose, while continuing to push the limits of our knowledge regarding blood diseases.”

**ABOVE:** Left to right: Phillip Starshak, hematopathology fellow; Sheeja Pullarkat, Program Director; Brit Shackley, hematopathology fellow





# The Pedigree of a Disease

**T**he back corner of Dr. Richard Gatti's office is piled high with "pedigrees" of families with children suffering from Ataxia telangiectasia (A-T). His right wall is covered with photos of children he has helped diagnose and treat. He has spent the last 25 years of his career, as he says, "trying to understand the universe of genetic changes that leads to A-T." He has spent considerably longer arming himself with the scientific tools to do so.

A-T is a very rare, neurodegenerative genetic disorder that causes severe physical disability, usually leaving its victims in a wheelchair from lack of coordination. Patients tend to lose their ability to fight infections and form coherent speech in early childhood. They are up to 70 percent more likely to develop cancer in their lifetime, especially lymphomas, and are hypersensitive to X-rays. "These patients are constantly battling health issues, and tend to die much too young," Gatti explained. "My career has led me from pediatrics to immunology to molecular genetics in this search to understand how a single genetic "typo" or random mistake in DNA can lead to such devastating consequences in children."

While completing his clinical training in pediatrics, Gatti became intrigued with the unique relationship between immunodeficiency and cancer. It was evident from his early training that children with weakened immune systems were more likely to develop cancer. His interest in this relationship ultimately motivated him to pursue a research fellowship at the University of Minnesota under the mentorship of Dr. Robert Good, who is often considered the father of clinical immunology. While studying the complexities of the human immune system, Gatti and his colleagues were able to transplant bone marrow stem cells into patients with severe combined immune deficiency (SCID)—the first successful bone marrow transplantation. These stem cells, once inside the transplant recipient, possess the remarkable ability to restore normal blood and immune function in the immune-compromised individual. In fact, this first successful transplant patient is still living and thriving, a father of four. Gatti still receives Christmas cards each year from members of the family. Today, more than 50,000 bone marrow transplants are performed annually on immune-compromised individuals.

His research interests then took him to the Karolinska Institute in Stockholm, where some of world's most advanced research on cancer immunobiology was being performed in the laboratories of Dr. Georg Klein, then considered the most preeminent tumor immunologist. At the institute, he sought to combine his knowledge of immunology with a basic science background in cancer biology and genetics. "This plan backfired on me," he admitted candidly, "because I learned that cancer is not primarily a disease of the cell surface, where most immunologists focus, but a language within the nucleus of a cell. Cancer is primarily a genetic disease."

This discovery, in conjunction with his clinical and research training, ultimately led him to focus on A-T. As a primary immunodeficiency disorder, A-T encompassed his interests in immunology, cancer, and genetics. He reasoned at the time that because it was caused by the mutation of a single

Dr. Richard Gatti  
has stalked Ataxia  
telangiectasia  
throughout his  
career and across  
many disciplines.  
Now he may have  
a treatment.



### THE MUSICAL MEDIC (1967)

It's rare that one has the talent to carry them through a brilliant career. It is even more rare to be blessed with two gifts and have the opportunity to choose the direction your life will take. Such was the case for Dr. Richard Gatti.

A master pianist, at age 15 Gatti was the winner of the "Stars of Tomorrow" competition sponsored by a New York radio station. Two years later, he won a New York Times-sponsored competition. He performed solo at radio stations around the New York area. Ultimately, he earned a scholarship to the renowned Julliard School of Music.

But at age 17, Gatti decided that his true calling was medicine. He withdrew from Julliard to join Columbia College, where he majored in pre-medical sciences and musicology.

While in the Army, Gatti held concerts to entertain patients, to raise money for pediatric care in remote areas of Ethiopia where he was stationed, and to support orphanages and clinics.

Today, his love for music remains strong. "I made the right choice," said Gatti. "My love for music has enriched lives, but my work in medicine has saved lives and will save many more. It was the right choice for me."

gene, cloning the gene for A-T would provide insights into all three disciplines. "We started by collecting genetic pedigrees of ethnic groups in the U.S. — such as the Amish — where A-T was more prevalent," Gatti explained. "Because the disease is so rare that only 1,500 cases exist in the U.S., we ultimately had to collect pedigrees from over 20 countries."

Enlisting the help of Dr. Kenneth Lange, currently Chair of the UCLA Department of Human Genetics, he began tracking the genetic thread that connected families with A-T. In their seventh year of searching, they mathematically located the gene (ATM gene) on chromosome 11q23 and published tour de force findings in the prestigious journal *Nature*. Although finding the specific location of the gene was a huge discovery, there was still much research to be done. "There was no Human Genome Project map at the time of our discovery," Gatti reiterates, "so it took another seven years and an international team of Britons, Israelis and our American lab to "fine map" the region and isolate the gene. The Israelis were the first to clone it."

The ability to clone the gene really served as a watershed moment, as it finally allowed researchers to study A-T in a controlled laboratory environment. Within three years, Gatti and collaborators at Charité-Universitätsmedizin in Berlin and Benaroya Institute in Seattle had cloned another closely related DNA repair gene, that of Nijmegen Breakage Syndrome (NBS), on chromosome 8q21. NBS was originally considered to be a variant form of A-T. These children have a "bird-like" pointed face and mental retardation and tend to look more like one another than like members of their own family. And the risk of cancer is even higher in NBS than in A-T patients. As an unexpected bonus, the molecular methods the team developed for their research also made for excellent diagnostic tests, which ultimately led to the creation of the UCLA Diagnostic Molecular Pathology Laboratory. As one of the first facilities of its kind in the country, the laboratory has pioneered applications of DNA-based genetic testing that allowed for definitive diagnoses of a wide variety of genetic and neoplastic diseases.

For the past decade, Gatti's lab has continued to trace the steps that lead from a mutation in the A-T gene to the devastation of spending one's entire adult life in a wheelchair. "We believe that some mutations are due to a kind of 'typo' in the DNA (genetic code), like placing a period in the middle of a sentence," Gatti explained. "These are called nonsense mutations." In short, a gene is a stretch of DNA that encodes instructions for producing a protein. Our bodies produce countless proteins (antibodies, enzymes, etc.), all of which serve very specific functions in various cellular processes. A mutation occurs when DNA instructions are altered in such way that the structure and function of the protein are altered so as to make it non-functional. The non-functional ATM protein is then promptly destroyed. Research has shown that cells without the functional ATM protein do not respond normally to DNA damage, which makes A-T patients more vulnerable to cancer, as well as to the effects of the X-rays that are often used to treat it.

For the past nine years, his laboratory's goal has been to identify a compound that would allow ribosomes to ignore the nonsense typos in the ATM gene and read through them. This would allow patients with a faulty ATM gene to still produce functional ATM protein. To date, Gatti's lab has screened more than 70,000 compounds in hopes of finding the genomic detour in the misinformed translation process. These new compounds are called small molecular read through (SMRT) drugs. "Finding a safe and effective SMRT drug treatment for A-T would be a very fulfilling achievement after 25 years of work," he commented. With a glance back to his wall of pedigrees, he notes. "It would culminate a long career of translating basic science research into diagnosis and treatment." ✨



## STOPPING ANGIOGENESIS TO PREVENT TUMOR GROWTH

Angiogenesis—the process by which new blood vessels are formed—is an important process in the growth and development of our body. It helps heal wounds, restore blood to tissue after injury, and prepare a mother's womb for pregnancy. Unfortunately, it also plays a significant role in the growth of tumors. A tumor, like any tissue, needs to constantly receive nutrients and remove waste to survive. Adequate blood supply via angiogenesis provides the mechanism by which tumors can grow and ultimately metastasize. Thus, any method that reduces blood supply (anti-angiogenic therapies) to a tumor could potentially serve as an effective therapeutic intervention.

Madhuri Wadehra, PhD, an assistant professor in the department, has focused her research efforts on better understanding this component of tumor biology. She has recently identified a tetraspan protein, epithelial membrane protein-2 (EMP2), as one promising marker in a number of cancers. Recent data suggests that EMP2 functions as an oncogene—a gene that has the potential to cause cancer—in a number of tumors including endometrial, ovarian, breast, and primary CNS malignancies. In mice, she has found that upregulation of this protein promotes tumor formation and more aggressive, highly vascularized tumors. Similarly, data has shown that upregulation of EMP2 expression in patients is associated with metastasis and poor prognostic outcome.

In response to these findings, her team is interested in determining if EMP2 can be a diagnostic and/or therapeutic target in the battle against cancer. For this purpose, she is developing a personalized antibody therapy strategy. Specifically, antibodies are being created that bind to and destroy the tumor. Research has shown that these antibodies exhibit strong anti-proliferative and pro-apoptotic activity against endometrial, ovarian, breast, and glioblastoma cell lines. More importantly, her research has shown that these recombinant EMP2 antibodies reduce tumor load *in vivo* in all four cancer models, and, just as importantly, they do not appear to exhibit any toxicity against endogenous tissue. This work has already resulted in two publications, and two more manuscripts have been submitted. Overall, her goal is to create a novel cancer therapy based on EMP2 expression to improve patient survival.



## UCLA CLINICAL GENOMICS CENTER

Utilizing their expertise in Pediatrics, Human Genetics, and Pathology, the UCLA Clinical Genomics Center, led by Stanley F. Nelson, MD, provides a comprehensive analysis and diagnostic interpretation of a patient's entire protein-encoding genome by searching through 37 million base pairs in 20,000 genes to potentially locate the single DNA change responsible for the patient's disorder. The only academic institution on the West coast to offer this unique service, the Center provides pre- and post-test genetic counseling and utilizes next generation sequencing technology (clinical exome sequencing), state-of-the-art computational and bioinformatic resources, and integrated laboratory information systems to deliver a precise genetic diagnosis for benefit of patients and physicians.

Clinical exome sequencing is performed within the CLIA-certified, CAP-accredited, multi-state licensed UCLA Molecular Diagnostics Laboratories. It is intended for use in conjunction with the clinical presentation and other markers of disease progression for the management of patients with rare genetic disorders. Even though there are over 2,000 Mendelian diseases caused by known DNA variants, many patients suspected to have rare genetic disorders do not receive a molecular diagnosis, often due to genetic heterogeneity and the relative inefficiency of the current sequencing technology. It is widely accepted that about 85% of known disease-causing variants occur within 1% of the genome of which the exome is comprised. Surveying this portion alone is an efficient and powerful clinical diagnostic tool for individual patients. It is also more cost-effective than traditional gene panels which provide the clinician with relatively limited information for nearly the same or greater cost. In practice, about 50% of the patients have a clearly causal DNA variant identified. When no clearly causal DNA variant is identified, these possible disease-causing variants are stored for future re-analysis and potential correlation to disease as new findings are published in the literature.

The Center's inaugural symposium, *Clinical Applications of Genome-Wide Testing*, was held last January. An impressive roster of speakers, which included event Chair Wayne Grody, MD, PhD, and Co-Chair Fabiola Quintero-Rivera, MD, provided compelling presentations to an audience of more than 125. The 2nd annual symposium is scheduled for January 25, 2013.

## STUDYING GERMINAL CENTER B CELLS DURING IMMUNE RESPONSES

Our body's immune system protects us against disease. It must be able to detect the invasion of foreign agents, distinguish them from the healthy cells of our own body, and then attack without harming those same healthy cells. It is a complex process that is vital for our own survival.

Lymphocytes—a type of white blood cell—are the major components of our body's immune system. There are two types of lymphocytes in our blood, B cells and T cells. B cells are responsible for generating antibodies (humoral immunity) and are regulated by T cells, which also can kill infected tissue cells directly (cell-mediated immunity). Some infectious agents and vaccines stimulate an immune response characterized by T cells helping B cells to produce high-affinity antibodies. During this T-dependent immune response, B cells are recruited into structures called germinal centers within lymphoid tissues, such as lymph nodes, tonsils, and the spleen. The generation of these high affinity antibodies within germinal centers requires breaking of immunoglobulin gene DNA by the AID enzyme, followed by repair of the breaks.

Recently, members of Dr. Mike Teitell's laboratory discovered a new component of this *AID-induced DNA damage repair mechanism* in which DNA double-stranded breaks activate a new signal transduction pathway. In this new pathway, the damage-sensing kinase ATM is activated, which in turn activates a second kinase, the tumor suppressor LKB1, and a third kinase that leads to inactivation of a transcriptional regulator, CRTC2. Inactivation of CRTC2 results in the repression of a gene transcription program that is required for

the differentiation of germinal center B cells into antibody-secreting plasma cells. Defects in this pathway have been identified in human B cell lymphomas that originate from germinal center B cells, suggesting that this pathway needs to function properly to provide for a robust antibody response and also to oppose the development of B cell malignancies.

Furthermore, LKB1—the tumor suppressor kinase mentioned above—has been identified as an important protein that regulates cell metabolism and polarity. Interestingly, LKB1 mutations cause the heritable condition Peutz-Jeghers Syndrome, which consists of benign gastrointestinal polyps, mucosal hyperpigmentation, and an increased risk of cancer. Sporadic mutations of this protein have also been linked to lung and cervical cancer. Studies from the Teitell lab, as described above, indicate a new role for LKB1 as a responder to genetic damage within germinal center B cells that requires further investigation.

Nicole Walsh, a senior doctoral student in the Teitell laboratory, is studying the role(s) of LKB1 in the normal development of germinal center B cells during immune response. To do this, she has generated a mouse model lacking LKB1 expression specifically in B cells. This model enables the examination of how B cells develop and function during an immune response in the absence of LKB1. Her work will help fill an important gap in current knowledge of B cell biology, specifically addressing whether DNA damage itself promotes the differentiation of germinal center B cells into antibody-secreting plasma cells. Her research will also provide new insights into how dysregulated B cell functions contribute to, or can be targeted in the treatment of, B cell malignancies and autoimmune diseases.



Michael Teitell, MD, PhD,  
and Nicole Walsh





## MOLECULAR ALTERATIONS IN THE DEVELOPMENT AND PROGRESSION OF PANCREATIC CANCER

The fourth leading cause of cancer mortality, pancreatic cancer accounts for approximately 40,000 deaths each year in the United States. It is a highly aggressive malignancy for which there are only limited treatment options of marginal benefit. The development of more effective treatments for this devastating disease primarily hinges on an improved understanding of the full complement of genetic and molecular events that drive pancreatic cancer growth and metastasis.

Towards this goal, recent deep sequencing efforts of the pancreatic cancer exome (the portion of the genome that encodes for genes) have shown that pancreatic cancer is genetically heterogeneous and complex. Each tumor averages mutations in more than 60 genes that differ considerably from one patient to the next. While these genetic changes are numerous and diverse, when integrated based on their functional activity they define thirteen core biological pathways uniformly altered in all pancreatic tumors. One of these core pathways is Wnt signaling, the primary focus of research in the laboratory of Dr. David Dawson, a gastrointestinal pathologist and assistant professor in the Department of Pathology and Laboratory Medicine. Initially supported by a career development award from the American Association for Cancer Research/Pancreatic Cancer Action Network, Dawson is a recent recipient of a highly competitive Research Scholars Grant from the American Cancer Society, which will allow him to continue his studies of Wnt signaling and its role in pancreatic carcinogenesis.

The Wnt pathway is important for normal embryonic development, stem cell regeneration, and the maintenance of healthy adult tissues. It is also abnormally regulated in many types of cancer. Having shown already that Wnt signaling promotes pancreatic cancer growth and spread, Dawson has begun to unravel the key genes and proteins responsible for inappropriately high levels of Wnt signaling in pancreatic cancer cells. This is a daunting task, as the Wnt pathway is extraordinarily complex with well over 100 genes and proteins known to dictate its levels of activation in various tissues and disease states.

Although well-described mutations in a few key genes are responsible for abnormal Wnt activity in certain tumors such as colon cancer, these mutations are not seen in pancreatic cancer. Instead, he has identified alternative genes whose inappropriate expression results in elevated Wnt activity in pancreatic tumors. Taking advantage of his experience and exposure as a gastrointestinal pathologist in the department, Dawson has also pursued translational work that has revealed the Wnt pathway to be a critical determinant of pancreatic cancer survival in the clinical setting. Based on this important observation, he is exploring how key molecular events responsible for altered Wnt pathway signaling in pancreatic cancer might be leveraged as useful clinical biomarkers and targets of drug therapy. In this regard, Dawson is pursuing the ultimate goal of “personalized medicine” in which patient-specific, targeted molecular therapy is used to effectively treat this highly lethal cancer. This basic and translational research approach illustrates the evolving role of the clinician-scientist and pathologist in the utilization of new technologies and delivery of patient care in the 21st century.





# The Educational Computer

**D**r. Robert Trelease is a hacker. He's a techno-wizard. He's an entrepreneur. He's the self-described (tongue-in-cheek) "Al Gore of educational computing" in the David Geffen School of Medicine at UCLA. He is also a professor in the Department's Division of Integrative Anatomy.

Seeing him, tucked in an office that is difficult to find in the hidden corridors of the Center for the Health Sciences, you may not immediately place him in this role. But when he talks the lights come on and you find yourself trying to up keep with his words with little success, as his ideas fly quickly past you.

Before Microsoft Windows and PowerPoint, Trelease was already using computers to give lectures in anatomy. However, the process of preparing and making a presentation was much different than we know it today. In the early days of computing, anatomical images had to be painstakingly scanned with a custom-interfaced camera, one by one. The slides were then programmed with an early video presentation scripting language, which only few managed to master. Finally, a specially interfaced Amiga computer and surplus video projector were dragged into the lecture hall or lab to give students visual checkpoints during lectures. In all, it could take up to 80 hours to prepare a single presentation.

When Dr. Luann Wilkerson was hired as Senior Associate Dean for Medical Education for the School of Medicine, she quickly became aware of Trelease's computer ambitions. They began an ongoing, 15-year dialogue on how computers could be used to improve medical education. By the mid-1990s, the Dean's Office was preparing to support the first generation of PowerPoint-based computer lectures and digital projection in its renovated lecture halls.

"The next milestone in computer-assisted anatomy education was the eruption of computer-accessible Internet," explained Trelease. "Everything changed, from the economy to commerce, and it quickly became evident that computers would be very viable educational tools." To capitalize on these events, the School of Medicine formed the Instructional Design and Technology Unit (IDTU) in 1996, with Trelease serving as faculty advisor, and later as webmaster and continuing associate director. IDTU was designed to be a focal point for technology assistance, focusing primarily on learning and teaching. For the past 15 years, the site's team has created education tools, managed online resources (e.g., ANGEL course management [CMS] and podcasting), and studied the effectiveness of technology on the overall learning process of medical students. The goal has always been to improve student and faculty communication, enhance classroom and lab instructional methods, explore alternative learning delivery methods, and provide faculty, staff and students access to important electronic learning resources. At the time IDTU was founded, the UCLA School of Medicine was one of the first in the U.S. to adopt a medical student computer ownership requirement, which ultimately allowed the resources provided by the IDTU to be accessible by all medical students.

Dr. Robert Trelease  
can't wait for new  
technology to  
help his anatomy  
students. So he  
creates it himself.

## GROSS ANATOMY LAB UNDERGOES TECHNICAL UPGRADE

For a time, it had been all planning, working, and waiting. But finally, the DGSOM Gross Anatomy Lab has been transformed into a fully-equipped “telemedicine lab” with the capability to broadcast live teaching events to adjacent classrooms, other areas in the hospital, even other campuses throughout the U.S. “We finally have both the teleconferencing capabilities and lab infrastructure that make it possible for each attendee, no matter their location, to benefit from the anatomy education provided by our faculty,” explained Dr. Elena Stark, director of UCLA’s Integrative Anatomy Division and vice-chair for Medical and Dental Education in the Department of Pathology and Laboratory Medicine.

The lab consists of 30 cadaver stations for the study of basic, clinical, radiological, and surgical anatomy—components that often serve as the foundation of any medical and dental education, and also components that are essential in pre-clinical and clinical training of applied anatomy specialties such as general surgery, urology, obstetrics and gynecology, orthopedics and other surgical specialties. More importantly, the lab is now outfitted with audiovisual equipment capable of broadcasting to the highest resolution plasma screens throughout the lab and hospital. This allows students who aren’t at a specific cadaver station, or even in the lab, to view the same high-resolution anatomy as the students who are on site.



“If there is interesting anatomical variation found at one particular station, we now have the ability to broadcast it to all our students through the high resolution monitors,” remarked Stark. It also allows the faculty to incorporate novel teaching approaches, for example, demonstrating structures on the “model cadaver” and allowing students to work in groups and teams (team-based learning) to learn the same structures from the specimen at their table. In residency trainings and other surgical anatomy courses, it also offers the faculty the possibility of demonstrating procedures the students can easily

follow at their stations by either looking at the large plasma screen or by following the procedure at their station, which is located next to their cadaver table. It will support and facilitate lab activities, team-based learning, and problem-based learning groups, among other strategies. In all, it allows the transmission of anatomy education to more people and, in the future, may enable them to revisit it at their convenience.

Furthermore, “UCLA students on rotation at off-site locations or traveling no longer have to miss important lectures or presentations,” Stark continued. If needed, these students can now watch the same lecture or demonstration from their computer, either as a live stream or archived video file. This could have an immediate impact on medical education at UCLA Riverside, where a small group of UCLA medical students complete part of their training. With this technology, these students have access to additional learning activities broadcasted from the UCLA campus.

The technology is also expected to have a national and international draw. “Because we have world-class experts in areas like organ transplants, plastic surgery, and orthopedics, we expect others to be very interested in what we have to say. The sky is really the limit with this technology, and we’re very excited to begin expanding its application here,” concluded Stark.





To ensure that medical students took full advantage of available technology, Wilkerson and the Dean's Office wanted each student to have a personal digital assistant (PDA). Trelease was responsible for identifying crucial server technology and prototyped applications that would allow IDTU to leverage its web resources for these PDAs. The PDA requirement was implemented in 2001 for third and fourth year student clerkships. Their PDAs were loaded with a variety of information from the Dean's Office (such as how to navigate at off-site rotations like Cedars-Sinai, what to do in case of an accidental needle stick, etc.), as well as a pharmacopeia reference with drug dosing information, medical terminology, and clinical decision-support software. Trelease published several papers about the successes of the PDA as used by medical students at UCLA. The technology was later adopted by other academic institutions, including national leaders like Harvard, Stanford, and Yale.

The PDAs also proved important for the school's periodic evaluations by accrediting groups such as the Liaison Committee on Medical Education (LCME) and the Association of American Medical Colleges (AAMC). Accrediting groups request data on the demographics and illnesses of patients encountered during clerkship rotations, data that was often difficult to provide in the past. However, while on their clerkships UCLA medical students entered these data into their PDAs, which then could easily be downloaded onto the school's servers and processed by the IDTU staff. This was such a novel practice that the UCLA School of Medicine received an award from the AAMC for innovative use of technology in gathering and storing information. The trophy now hangs on a wall on the fourth floor of the Biomedical Library.

**T**echnology continued to evolve quickly as the Internet matured into the new millennium and smartphones started to spread to the broad populace. PDAs became less useful as students began self-selecting the iPhone for many tasks in their daily lives. "In this case, the school's technology requirement adapted to our student's behavior," explained Dr. Trelease. "We adopted a general smartphone requirement in 2009."

The next generation of advances brought the iPad, which has become an ideal mobile platform for viewing medical records and files with detailed graphics. With this big-screen, high-resolution, high-capacity device, Trelease saw the ideal format for anatomy education. Working with Elsevier publishers, he began incorporating images by the renowned anatomical artist Dr. Frank Netter into a "just-in-time" mobile learning resource for medical student surgical clerkships and for general surgery residents.

"Many educators think anatomy should be taught across all four years of medical school," continued Trelease. "It's difficult to do that when third and fourth year students are running from clinic to clinic. They can't carry a textbook into the operating room while they observe gall bladder surgery, but they can easily refer to their iPhone or iPad or small reference guide while the surgeon is explaining crucial surgical anatomy, blood supply, etc."

Elsevier, starting with a conservative approach, published Trelease's book, *Netter's Surgical Anatomy Review P.R.N.*, in 2010, as a portable volume that could be carried in a lab coat pocket. "I also pitched the project as an iPhone application that could be downloaded," he added. To make this happen he had to learn iPhone programming. "This was something like translating Mandarin into Russian and then writing the message in German. The language has words that are a foot long. It got so I had so much language and so much anatomy in my head that I sometimes found it difficult to converse at a normal level." The print version was released in summer of 2010.

Trelease had registered as an Apple developer in 2008, and, despite his teaching load, completed the iPhone version of the book during the 2010 fall term.

"Third- and fourth-year students are running from clinic to clinic. They can't carry a textbook into the OR while they observe gall bladder surgery, but they can refer to their iPhone or iPad."

—DR. ROBERT TRELEASE



### TELEPATHOLOGY: CLINICAL CARE AND MEDICAL EDUCATION SPANNING THE GLOBE

The field of radiological sciences has been using digital images (X-ray, MRI, CT, and ultrasound) for diagnostic purposes for more than 25 years. Until recently, the field of pathology had been unable to perform similar digital analyses on pathological cases because the images were of such poor quality that diagnosis could not confidently be made. However, the recent development of scanning technology that produces high-quality, digitized images has enabled pathologists to make more diagnoses over ever longer distances—24 hours a day, 7 days a week.

Under the leadership of Scott Binder, MD, senior vice chair for Clinical Services, the department continues to expand its pathology expertise via telepathology. Binder is leading work, in conjunction with the University of California (UC) Office of the President, on a UC system-wide initiative to implement this new technology to a network of 8–10 remote hospitals throughout the state of California. These sites would have the ability to send high quality images of pathology slides to UCLA pathologists over a secure Internet connection, which would enable a group of pathologists without subspecialty expertise to consult with the department's expert team of pathologists for advanced diagnostic purposes. This technology also produces a windfall of educational opportunities for medical students, residents, and fellows in the David Geffen School of Medicine. It enhances clinical training by providing greater exposure to some of the world's most complex pathological cases. It also benefits the UCLA scientific community by providing material for research

and esoteric testing. For example, the challenging cases sent for telepathology consultations are being used to enhance and expand the Department's molecular pathology and emerging genomics programs.

The department also continues to develop a successful telepathology exchange with a prestigious health center in China. This partnership was developed and fostered by Jianyu Rao, MD, director of Cytopathology in the department, and currently consists of a mutually beneficial exchange of challenging diagnostic cases and bi-directional educational interactions. The prestigious Second Affiliated Hospital Zhejiang University (SAHZU) currently sends an increasing number of challenging digitized slides/cases to UCLA Pathology for diagnostic purposes.

In addition, SAHZU has been sending their pathologists to UCLA for intensive exposure to technology and testing not currently available in China. On the other hand, UCLA pathologists have been regularly visiting SAHZU to learn from their wealth of experience with the large number of patients they have encountered in the past decade. The goal is to collaborate even more closely over the next few years, and the result of this collaboration may be a new joint diagnostic center using the advanced technologies of telepathology, molecular pathology and genomics to create the most advanced cancer diagnostic center in China, under the leadership of both UCLA and SAHZU pathologists.

**ABOVE: Inaugural Ceremony and Video Conference of Telepathology Agreement between UCLA-Second Affiliate Hospital of Zhejiang University**



“I’ve been historically part of a cost center in the School of Medicine,” remarked Trelease. “But I’m now making money on my books and applications, and effectively on my software development services. The IDTU offers its clients help with course support, application development, multimedia production, and educational tool design services. All this helps to offset our educational costs and overhead.” He continues, “The University is pushing us to be more entrepreneurial, and this has always been natural for me. I’m willing to share my expertise, which is why I helped build IDTU and all its learning resources over the last two decades. I’ve given countless presentations and written papers to inform our colleagues at other institutions about what I see coming and how it can be used to improve medical education.”

## PARTNERSHIP: UCLA PATHOLOGY AND RADIOLOGY JOIN FORCES

The development of the UCLA Radiology Pathology Center (RadPath) is a joint venture between the UCLA Departments of Radiology and Pathology that is bringing together industry-leading experts in radiologic imaging and tissue diagnosis for enhanced diagnostic reporting and research development. In this new era of personalized medicine, the center seeks to develop a single, integrated report encompassing both radiological and pathological diagnostic modalities for better evaluation of a disease process. Scott Binder, MD, W. Dean Wallace, MD, and Kingshuk Das, MD, were responsible for designing the pathology service with the capacity to combine clinical staging, pathologic diagnoses, molecular prognoses and response prediction in patients for evaluation and treatment of their malignant disease.

An electronic version of the report that is dynamic and facilitates synthesis of the different studies with access to digital images from the various radiology and pathology studies is currently being developed. Review of the integrated images will provide clinicians and patients with a better understanding of their diseases, as well as contribute to education of medical students and residents in training.

“We are very proud to be able to offer this new diagnostic service, which, to our knowledge, is the first of its kind in the nation,” remarked Wallace, Chief of Pulmonary Pathology. The U.S. Department of Health and Human Services has invited them to contribute to a white paper titled “The Importance of Radiology and Pathology Communication in the Diagnosis and Staging of Cancer,” available at <http://aspe.hhs.gov/sp/reports/2010/PathRad/index.shtml>.

RAD-PATH REPORTING SYSTEM – APRIL 10, 2011 10:06pm PDT
MAIN MENU | MESSAGES | HELP | LOG OUT


UCLA

Health System

Department of Radiological Sciences | Department of Pathology and Laboratory Medicine

Rad-Path: Integrated Summary

Print Report

Patient Name MRN DOB   Sex Referring Physician	Encounter Radiology Accession # Pathology Specimen # Collection Date Receipt Date Location RRU4MC	
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Integrated Summary

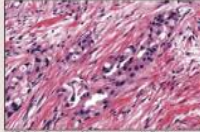
Pathology Summary

Radiology Summary

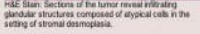
[-] SURGICAL PATHOLOGY SUMMARY

Specimen  
Origin  
Histology  
Differentiated  
Nuclear grade  
Comments

Right upper lobe nodule  
Lung  
Adenocarcinoma with BAC features  
Moderate  
Intermediate  
The patient's prior tumor pathology has been reviewed and demonstrates similar histologic features. Mutation analysis for EGFR gene performed.



All Available Detail  
Gross description  
Microscopic exam  
Immunohistochemistry  
Pending  
Mutation analysis  
Gene Expression  
Virtual microscopy



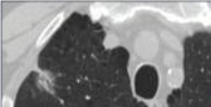
H&E Stain: Sections of the tumor reveal infiltrating glandular structures composed of atypical cells in the setting of chronic desmoplasia.

[-] RADIOLOGY SUMMARY

CT-Guided Core Biopsy Lung  
Diagnostic CT

Primary Finding  
Features

23 x 18 mm nodule in right upper lobe.  
Mixed solid and ground glass attenuation  
> 2 cm from carina  
No atelectasis  
Contacted visceral pleura  
Satellite micronodule in same lung



All Available Detail  
Key Images  
Key Images  
Key Images  
Pending  
Quantitative Analysis





# Sharing Samples and Skills Around the World

**A**natomic pathology is concerned with the study and diagnosis of disease based on the examination of *human tissue*. Much like biofluids, human tissue has long been a wealth of information in the clinical setting. It gives physicians important insight into disease processes, and often serves as the most important diagnostic, prognostic, and therapeutic tool in patient care.

More recently, human tissue has proved just as valuable to the biomedical research community. There is a growing need among investigators for tissue that can be used for a wide range of molecular, biochemical, and tissue analyses. Since 1996, these services have been provided by the UCLA *Translational Pathology Core Laboratory (TPCL)*. This lab collects, processes, stores, and distributes human remnant tissue from routine surgical resections for use by investigators in basic science, translational and clinical research studies.

“In the past, there was no central resource for translational pathology services on campus,” explained Sarah Dry, MD, associate professor in the Department and director of the TPCL. Instead, individual research teams would tackle the tedious process of identifying, procuring, processing, and storing their own tissue specimens. It was a difficult and time consuming process that few researchers managed to master. To address this, the Department of Pathology and the Jonsson Comprehensive Cancer Center together supported the creation of TPCL.

The value of banking (storing) tissues for future use has been recognized for some time. However, biobanking as a specialty only came to be recognized in the last decade. Until then the process of cataloging frozen tissue samples was considered primitive by current standards. Samples sat at room temperature for unknown lengths of time prior to stabilization through snap freezing or formalin fixation. Storage space was limited and unreliable. The tracking system often consisted of hand-written notes kept in a journal or taped to a freezer. It was unorganized and greatly jeopardized the integrity and security of important tissue specimens.

In comparison, TPCL biobanking operations are now highly organized, similar to clinical laboratory operations. In fact, TPCL will become the first College of American Pathologists accredited biorepository in California, and one of the first 20 nationally, once it passes inspection this summer. TPCL now snap-freezes tissue samples within minutes of receipt. Each tissue is logged into the UCLA IRB-approved biobanking database, given a barcode, and precisely stored in a secure freezer. Each specimen is catalogued by tissue type, and diagnosis in a biobanking database. This database greatly facilitates searches by TPCL staff for specific researcher requests for samples.

The TPCL also serves to protect the patients. “A pathologist or pathology assistant examines all specimens that are removed as part of routine medical care and selects only those samples for TPCL that are not required for diagnosis,” explained Dr. Dry. More importantly, the remnant tissue is not distributed for research use until the clinical diagnosis has been confirmed for that patient.

With the technology she controls, Dr. Sarah Dry can preserve tissue samples through time and send them in highest resolution through space.

“Digital analysis offers a great tool to pathologists, however, it remains essential for pathologists to manually interpret the images.”

—DR. SARAH DRY

Furthermore, researchers must first have appropriate UCLA Institutional Review Board (IRB) approval before they can access any banked tissue. “The primary goal of our IRB is to ensure the protection of human research subjects,” she continued. The IRB reviews ensure that proposed research protocols meet federal and local standards for human subjects research.

Since its inception, the Department’s biorepository has had an immediate and growing impact on research at the institution. Researchers have had improved access to remnant tissue for the study of infectious diseases, central nervous system disorders, tumors, auto-immune conditions, among others. In many cases, malignant and matched normal tissue sample have been available for conducting cancer research.

The Department continues to expand its biobank operations. As one of the most comprehensive and advanced healthcare systems in the world, the UCLA Medical Center treats some of the rarest and most complex diseases in the world. Although clinical diagnosis is always the priority, any remnant samples from these cases would be invaluable to the research community.

As the bank grows, “we will also be better equipped to study common diseases such as hypertension and diabetes,” continued Dr. Dry. “These diseases are multifactorial, so large numbers of samples are required to cover all aspects of presentation and progression.” A bank that can organize and store large quantities of biosamples better lends itself to these large-scale studies.

**T**PCL was one of the earliest adopters of digital imaging and analysis. Since 2008, the TPCL has offered state-of-the-art virtual microscopy and digital pathology services to the UCLA research community. In virtual microscopy, whole glass slides are converted to high resolution digital images that can be viewed over a web-based interface. Similar to a microscope, users can change magnification and move around the slide. This system eliminates any delay, damage, or loss of often irreplaceable slides during shipping or storage. Instead, digital images are able to be archived, stored indefinitely, and easily retrieved. While glass slides may fade with time, the digital image remains robust.

More importantly, this technology allows people to come together to discuss histology images via the web. These images or portions of them can be sent electronically to other clinicians, researchers, or students for real-time viewing, discussion, and analysis. Scientific collaboration is made possible by this technology, and greatly enhances the pathologist’s impact on the research community.

Digital pathology is viewed as the next step in virtual microscopy. This technology makes quantitative analysis of high resolution digital images possible. Rather than simply viewing the digital image, the TPCL uses image analysis tools to derive objective quantification measures from the digital slides. This often includes quantitative immunohistochemistry and analysis of other cellular characteristics.

As Dr. Dry explains, “Digital analysis programs utilize complex algorithms to evaluate different parameters. The most sophisticated programs permit users to evaluate structures in relation to each other and are particularly useful for research applications. There are algorithms being used today for clinical testing that can show, for example, what percentage of breast tumor cells show Her-2 staining.” The images and information can be included in the physician report, and communicated to the family who may need to choose a different treatment option or inform other potential patients, such as siblings or offspring. Yet, this technology will not supplant pathologists any time soon. “Digital analysis offers a great tool to pathologists, however, it remains essential for pathologists to manually interpret the images. Automated interpretation of Ki-67 is a good example of this. The algorithm may not be able to distinguish Ki-67 staining of non-tumor lymphocytes from the staining in the cancer, but a pathologist will.” ✱





## UCLA IMMUNOGENETICS CENTER

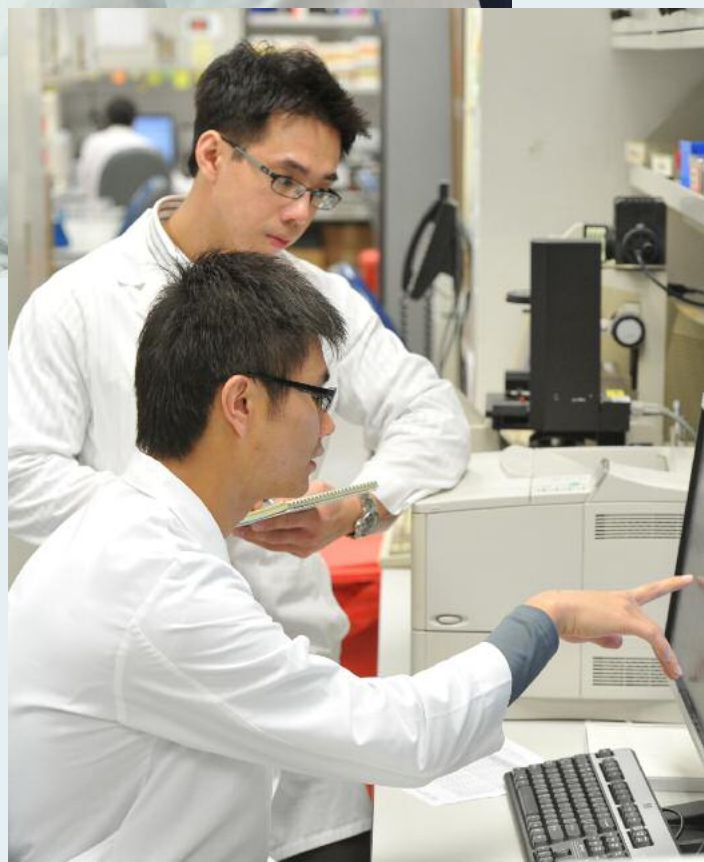
As the field of transplant science continues to grow in capability and complexity, the issue of standardization has taken a central place in assuring ongoing quality and safety. The UCLA Immunogenetics Center's reputation for international leadership in transplantation is augmented by its reference programs, which provide well-characterized reference samples of blood, lymphocytes, DNA, and serum to labs throughout the U.S. and around the world. Of all the lab's functions, standardizing samples and the language used to describe them is at the core of its role.

The UCLA International Cell Exchange, one of the center's premier referencing programs, was established to standardize the practice of HLA typing and histocompatibility testing. Through this initiative, samples are now sent to over 200 laboratories world-wide for HLA typing and antibody testing. Results are returned to UCLA, where they are collated and re-issued as a single report for comparison and discussion. By offering a forum for data exchange and discussion, the Cell Exchange has been instrumental to international standardization. "Not only does this help labs keep pace with current standards, but it provides standardized nomenclature for use in the field," explained Dr. Elaine Reed, director of the Immunogenetics Center. "Without this standardization, region-wide organ sharing would not be possible."

"As new technologies or immunologic questions have arisen that are important to safe transplantation science, our goal has been to provide the reference reagents to validate the technology and reagents used at our partner institutions around the world," remarked Dr. Rajalingam Raja, associate director of the laboratory. "One thing we've done longest, and still do best, is send out rare examples of HLA typing so that our sister centers can determine whether or not their reagents can adequately identify those rare polymorphisms. If we didn't do this, the field of transplantation would be severely limited."

The lab has many other claims to fame, including the development of a new program allowing "chain" organ donation, or "paired kidney donation" (PKD). The chain starts with one volunteer, who gives an organ. The recipient in turn donates to a match recipient on the list, and so on. The PKD can extend to as many as 30 links. "This procedure began here, and is now being done at 52 centers across the world," remarked Dr. Jennifer Zhang, also an associate director of the laboratory.

UCLA's legacy in transplant science is legendary. "Beginning with the pioneering work of Dr. Paul Terasaki and extending through our current faculty such as Drs. J. Michael Cecka, Rajalingam Raja, and Jennifer Zhang, our leadership in the science of transplantation forms its own chain of excellence," said Reed.



**TOP:** Ching Liv (back); Arlene Locke (front)  
**ABOVE:** Peter Phan (front); David Nguyen (back)

## HIGH-THROUGHPUT CLINICAL PROTEOMICS CORE

James LeBlanc, PhD, is director of the High-Throughput Clinical Proteomics (HTCP) Core Laboratory at UCLA. This core facility provides research support—in the field of proteomics—to investigators across the UCLA campus. Proteomics is the large-scale study of proteins in attempt to determine the concentration and identity of proteins in a given sample. Proteins are vital to both the structure and function of living organisms, especially at the cellular level. Cells can increase or decrease the expression of a particular protein depending on environmental stresses or disease. The goal of proteomics is to detect protein expression changes for differing clinical samples. Identifying protein differences between healthy and diseased cells has the potential to serve as diagnostic, prognostic, and/or therapeutic tools in the clinical setting.

With clinical samples having hundreds to many thousands of proteins, this protein sorting and assessment can be a considerable challenge. The HTCP is a mass spectrometry core facility designed specifically for profiling large numbers of clinical samples for changes in content. It is equipped to handle all clinical samples types—urine, plasma, CSF, and cell lysates. Using mass spectrometry, the first step is to find clinically relevant differences in protein content in the samples. The next step is to then isolate and identify those proteins and peptides deemed significant. Once specific proteins are identified researchers can begin to investigate how these proteins function in various cellular processes.

Using these methods, the core has made important strides in isolating diagnostic markers associated with inflammatory bowel disease (IBD), which includes such conditions as ulcerative colitis and Crohn's disease. In collaboration with researchers at UCLA and Cedars-Sinai Medical Center, it was found that the constant inflammation associated with IBD can lead to bowel disease. According to LeBlanc, the inappropriate inflammatory response was likely the driver of the response, and “we were interested to see if we could detect signs of these diseases from protein content in clinical samples, without doing an invasive biopsy.”

In treating this patient population, Cedars-Sinai began by examining a specific section of the intestinal tract, cleaning it with a saline wash, and then taking a biopsy for examination under a microscope. As part of the research, the saline wash was collected from specific sites of the bowel, where the HTCP would then examine it as a source of human proteins, bacterial proteins, yeast proteins, and fungus from the disease site. They found specific proteins—also referred to as biomarkers—indicative of ulcerative colitis and Crohn's disease in the wash. “The current wash is obtained during a sigmoidoscopy, but our long-term hope is that stool or saliva could be viable, both of which can be obtained non-invasively,” said LeBlanc.

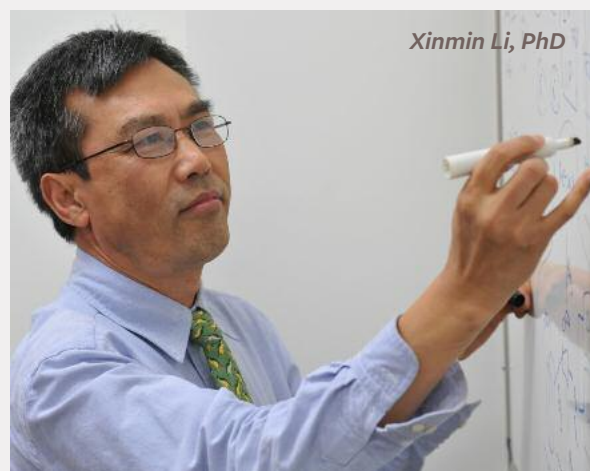
One goal for the upcoming year is to examine cross-sections of the bowel to determine whether the proteins seen in the saline wash are visible in surrounding tissue. The laboratory of Dr. Jonathan Braun is “also interested in the connection between the disease and the immune response,” explained LeBlanc. “Working together to locate precisely where these proteins are located will allow us to better understand the dynamics of the disease,” he concluded.

## CLINICAL MICROARRAY CORE

The UCLA Clinical Microarray Core (CMC) is a fully automated, high-throughput genomic facility equipped to provide next-generation sequencing and microarray-based genotyping services for prevention, early diagnosis, and management of major human diseases. This core facility, directed by Xinmin Li, PhD, helps researchers examine gene expression under particular physiological and pathological conditions. This provides insight to gene function, mechanisms of disease and aid in identifying disease-related signatures or profiles that can be applied to diagnosis, prognosis, and treatment.

Already one of the premier laboratories of its kind in the country, the CMC has improved its next-generation sequencing (NGS) capabilities with the recent acquisition of the Illumina HighSeq2000 and Ion Torrent Personal Genome Machine. The Illumina HiSeq2000 sequencing system is an industry leading NGS platform that enables researchers to obtain 30-fold coverage of two human genomes or perform gene expression profiling on 200 samples. The Ion Torrent PGM, also a revolutionary NGS platform, combines semiconductor technology with natural biochemistry to directly translate chemical information into digital data. Both sequencing systems provide better sequencing scalability and flexibility for various applications.

Microarray is a powerful technology that is used to identify complex biomarkers for challenging cancers. Recently, the CMC and Dr. Scott Binder's group developed a multiplex PCR-based test to distinguish between pseudoepitheliomatous hyperplasia (PEH) and squamous cell carcinoma (SCC). In clinical practice, it is often extremely difficult to distinguish between the benign PEH and malignant SCC. In fact, there are no reliable immunohistochemical, molecular or other methods that can resolve this significant clinical problem. This new test utilizing microarray technology will replace the current non-quantitative and subjective diagnostic methods.



Xinmin Li, PhD





## CLINICAL & TRANSLATIONAL RESEARCH LABORATORY

The newly developed UCLA Clinical and Translational Research Laboratory (CTRL) serves the larger laboratory testing needs for clinical and translational research at UCLA. “The lab is designed to meet the testing needs of any research protocol or clinical trial on campus, with results that are equivalent to those obtained from the Clinical Laboratory at the Ronald Reagan UCLA Medical Center,” explained Dr. Anthony Butch, director of the CTRL. Services include routine clinical laboratory testing, processing, short-term storage and, if necessary, shipping of samples to other facilities for highly specialized testing. The lab recently moved into a new 5,200 square foot space on the A-level of the Center for Health Sciences building.

The idea, according to Butch, is to service the entire UCLA enterprise. “Say you have a clinical trial for a new drug and want to look at whether the drug is working or not based on chemistry and hematology tests,” he explained. “We now have the ability to perform this testing in our lab, as opposed to sending the samples to the hospital for processing.” Their biggest growth over the past quarter has been moving clinical and research protocols from the Clinical Laboratory at the hospital to the new facility, where they are now capturing an estimated 80 percent of the available business. According to Butch, the lab is also beginning to service more clients outside of UCLA—an aspect of the business that continues to grow.

More importantly, the lab is organized to offer a full spectrum of testing needs. This includes routine chemistry tests, thyroid function tests, fertility tests, tumor marker tests, basic coagulation testing and routine urinalysis, as well as flow cytometric assays and tests of immune function, both in real-time and as batch testing. “If we cannot meet your needs, we will do the processing ourselves and send the samples somewhere that can,” he continued. As an example, the lab will begin offering an assay to measure iohexol, a compound that can be used to measure kidney glomerular filtration rate (GFR). Whereas other tests for GFR are labor-intensive and require the use of nuclear medicine, the use of iohexol is easier and detecting clearance by the kidneys only requires a few simple blood draws, after which the patient can return home. This test was specifically tailored for a nephrology group at UCLA. “If there is a real need for new tests, we can develop them quickly to meet the need of our investigators,” continued Butch. “We have the expertise, highly trained staff, and the extended operating hours to meet the need of any research study. The represents a real move into the future,” especially as it relates to clinical and translational research.

**ABOVE: Anthony Butch, PhD (left); Najib Aziz, MD**

# Department in Depth: Listings

## EXECUTIVE LEADERSHIP

Jonathan Braun, MD, PhD  
Chair  
Scott Binder, MD  
Senior Vice Chair, Clinical Services  
Linda Baum, MD, PhD  
Vice Chair, Academic Affairs  
Kenneth Dorshkind, PhD  
Vice Chair, Research  
Thomas Drake, MD  
Vice Chair, Information Systems  
Charles Lassman, MD, PhD  
Vice Chair, Clinical Education  
Elaine Reed, PhD  
Vice Chair, Research Services  
Elena Stark, MD, PhD  
Vice Chair, Medical and Dental Education  
Arnold Scheer, MPH  
Chief Administrative Officer

## CLINICAL LEADERSHIP

Scott Binder, MD  
Medical Director, Clinical Outreach Services  
Linda Baum, MD  
Medical Director, UCLA Clinical Laboratories  
Steven Hart, MD  
Medical Director, Santa Monica-UCLA Medical Center  
Thomas Drake, MD  
Associate Medical Director, UCLA Clinical Laboratories  
Nora Ostrzega, MD  
Medical Director, UCLA Olive-View County Medical Center  
Robert Morin, MD  
Medical Director, Harbor-UCLA Medical Center  
Kim Mislick, MD  
Medical Director, Northridge Hospital  
Tamar Baruch-Oren, MD  
Medical Director, Olympia Medical Center

## DIVISION CHIEFS

Jonathan Said, MD  
Anatomic Pathology  
Linda Baum, MD, PhD  
Laboratory Medicine

## SECTION CHIEFS

Michael Fishbein, MD  
Autopsy/Decedent Affairs  
Sophia Apple, MD  
Breast Pathology  
Michael Fishbein, MD  
Cardiac Pathology  
Anthony Butch, PhD  
Clinical Chemistry  
Michael Lewinski, PhD  
Clinical Microbiology

Nagesh Rao, PhD  
Cytogenetics  
Jianyu Rao, MD  
Cytopathology  
Scott Binder, MD  
Dermatopathology  
Jiaoti Huang, MD, PhD  
Genitourinary Pathology  
Galen Cortina, MD, PhD  
Gastrointestinal Pathology  
Jianyu Rao, MD  
Gynecologic Pathology  
Sunita Bhuta, MD  
Head and Neck Pathology  
Stephen Lee, MD  
Hematology  
Elaine Reed, PhD  
Immunogenetics  
Charles Lassman, MD, PhD  
Liver Pathology  
Wayne Grody, MD, PhD  
Molecular Pathology and Clinical Genomics  
Harry Vinters, MD  
Neuropathology

Ben Glasgow, MD  
Ophthalmic Pathology  
Wayne Grody, MD, PhD  
Orphan Disease Testing  
Michael Teitell, MD, PhD  
Pediatric and Neonatal Pathology  
W. Dean Wallace, MD  
Pulmonary Pathology  
Charles Lassman, MD, PhD  
Renal Pathology  
Scott Nelson, MD, PhD  
Skeletal and Soft Tissue  
Alyssa Ziman, MD  
Transfusion Medicine  
Anthony Butch, PhD  
Toxicology

## FELLOWSHIP PROGRAMS

Michael Fishbein, MD  
Director, Cardiopulmonary Program  
Michael Lewinski, PhD  
Director, Clinical Microbiology Program  
Nagesh Rao, PhD  
Director, Cytogenetics Programs  
Sophia Apple, MD  
Director, Cytopathology Program  
G. Peter Sarantopoulos, MD  
Director, Dermatopathology Program  
Galen Cortina, MD, PhD  
Director, GI and Liver Program  
Sheeja Pullarkat, MD, PhD  
Director, Hematopathology Program  
Wayne Grody, MD, PhD  
Director, Molecular Pathology Program

Wayne Grody, MD, PhD  
Director, Molecular Genetics Program  
William Yong, MD  
Director, Neuropathology Program  
Charles Lassman, MD, PhD  
Director, Surgical Pathology Program  
Nora Ostrzega, MD  
Director, Surgical Pathology Program (Olive View)  
Alyssa Ziman, MD  
Director, Transfusion Medicine Program

## RESIDENCY PROGRAM

Charles Lassman, MD, PhD  
Director  
Alyssa Ziman, MD  
Associate Director  
Peggy Sullivan, MD  
Associate Director  
Dinesh Rao, MD, PhD  
Associate Director

## MEDICAL AND DENTAL EDUCATION

Elena Stark, MD, PhD  
Director, Division of Integrative Anatomy  
Thread Chair, Anatomy and Histopathology, School of Medicine  
Thomas Drake, MD  
Block 1 Chair, School of Medicine  
Joseph Miller, PhD  
Director, Anatomy, School of Dentistry  
Lee Goodglick, PhD  
Director, Pathology and Histology, School of Dentistry

## CENTERS AND LABORATORIES

Anthony Butch, PhD  
Director, Olympic Analytical Laboratory  
Director, Clinical and Translational Research Laboratory  
David Seligson, MD  
Co-Director, Biomarker Innovations Laboratory  
Director, Tissue Array Core Facility  
Elaine Reed, PhD  
Director, Immunogenetics Center  
James LeBlanc, PhD  
Director, High Throughput Clinical Proteomics  
King Das, MD  
Director of Operations, Genetic Medicine  
Associate Director, Diagnostic Molecular Pathology Laboratory

Michael Teitell, MD, PhD  
Director, Cancer Nanotechnology Program Area (JCCC)  
Romney Humphries, PhD  
Director of Operations, Clinical Microbiology  
Sarah Dry, MD  
Director, Translational Pathology Core Laboratory  
Director, Center for Pathology Research Services  
Scott Binder, MD  
Director, Biomarker Innovations Laboratory  
Sophie Song, MD, PhD  
Director, Clinical Flow Cytometry Laboratory  
Director, Bone Marrow Laboratory  
Stanley Nelson, MD, PhD  
Director, Clinical Genomics Center  
Sunita Bhuta, MD  
Director, Transmission Electron Microscopy Laboratory  
W. Dean Wallace, MD  
Director, Laboratory Safety  
Wayne Grody, MD, PhD  
Director, Diagnostic Molecular Pathology Laboratory  
Director, Orphan Disease Testing Laboratory  
Director, Genetic Medicine  
Xinmin Li, PhD  
Technical Director, Clinical Microarray Core Laboratory

## ADMINISTRATION

Kelly Bartlone  
Manager, Surgical Pathology Reporting and Transcription Office  
Heather Boczek  
Manager, Sales & Services and Procurement Activities  
Pam Bumerts  
Manager, Transfusion Medicine  
Debra Cobb  
Director of Operations, Clinical Laboratories  
Paul Colonna  
Manager, Microbiology, Cytogenetics and Molecular Pathology  
Diana Crary  
Manager, Core Laboratories and Point of Care Testing  
Elisa DeRobles  
Manager, Billing and Outreach Services  
Assistant to Vice Chair, Clinical Services  
Geri Goodeliunas  
Manager, Santa Monica-UCLA Medical Center & Orthopaedic Hospital Laboratories  
Sharon Higgins  
Director of Operations: Space, Facilities, Safety and Compliance

David Islas  
Manager, Research Administration  
David Jaquez  
Director, Personnel and Payroll  
Timothy Kares  
Director of Finance  
Nina Ladbbon-Khatibi  
Manager, Clinical Finance  
Christina Kim  
Manager, Student Affairs and Training Activities  
Debra Lacava  
Manager, UCLA Immunogenetics Center  
Mary Levin  
Program Director, School of Cytotechnology  
Mary Alice Mita  
Administrative Director, Clinical Services  
Justin Perry  
Manager, Research Services  
Justine Pomakian  
Manager, Special Projects  
Marivic Visico  
Manager, Regulatory Affairs, Compliance, Education and Safety  
Merian Raz  
Manager, Clinical Support Services  
Ann Shadler  
Director of Operations, Anatomic Pathology  
Dennis Sunseri  
Manager, Pathology Information Systems  
Nora Warschaw  
Manager, Molecular Diagnostic Laboratories  
Sharon Webb  
Director of Business Development

## FULL PROFESSORS

Sophia K. Apple, MD  
Raymond Barnhill, MD  
Linda G. Baum, MD, PhD  
Sunita M. Bhuta, MD  
Scott W. Binder, MD  
Jonathan Braun, MD, PhD  
Anthony W. Butch, PhD  
David S. Chia, PhD  
Alistair John Cochran, MD  
Galen R. Cortina, MD, PhD  
Gay M. Crooks, MD, M.S., FRACP  
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Thomas A. Drake, MD  
Rita B. Effros, PhD  
Michael D. Fishbein, MD  
Richard A. Gatti, MD  
David W. Gjertson, PhD  
Ben J. Glasgow, MD  
Wayne W. Grody, MD, PhD  
Oliver Hankinson, PhD



Sharon L. Hirschowitz, MD  
 Jiaoti Huang, MD, PhD  
 Kathleen Ann Kelly, PhD  
 Charles R. Lassman, MD, PhD  
 Stephen Lee, MD  
 Xinmin Li, PhD  
 Shaleen Metten, PhD  
 Paul Mischel, MD  
 Scott D. Nelson, MD  
 Jian Yu Rao, MD  
 Nageshwara P. Rao, PhD  
 Elaine F. Reed, PhD  
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 Marie Elena Stark, MD, PhD  
 Michael Alan Teitell, MD, PhD  
 Peter John Tontonoz, MD, PhD  
 Robert B. Trelease, PhD  
 Harry V. Vinters, MD  
 Hanlin L. Wang, MD, PhD  
 William H. Yong, MD

#### **ASSOCIATE PROFESSORS**

Tamar Baruch-Oren, MD  
 Nicole Ann Dawson, MD  
 Sarah M. Dry, MD  
 Lee A. Goodglick, PhD  
 Chi Kien Lai, MD  
 Xin Liu, MD, PhD  
 Qun Lu, MD  
 Michael A. Lewinski, PhD  
 Joseph Miller, PhD  
 Neda A. Moatamed, MD  
 Sheeja Pullarkat, MD  
 Fabiola Quintero-Rivera, MD  
 Rajalingam Raja, PhD  
 David B. Seligson, MD  
 Sophie X. Song, MD, PhD  
 W. Dean Wallace, MD  
 Bo Wei, PhD  
 Jonathan J. Wisco, PhD  
 Alyssa Ziman, MD

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 Chandra Nicole Smart, MD  
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 Yin Sun, PhD  
 Carlos Tirado, PhD  
 Madhuri Wadehra, PhD  
 Aparche Yang, MD  
 Qiuheng Zhang, PhD

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 Daljit S. and Elaine Sarkaria  
 Chair in Diagnostic Medicine  
 Michael Fishbein, MD,  
 Frances and Albert Piansky  
 Chair in Anatomy  
 Jerzy Kupiec-Weglinski, MD, PhD  
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 Chair in Immunobiology and  
 Transplantation  
 Paul Mischel, MD,  
 Lya and Harrison Latta  
 Endowed Chair in Pathology  
 Michael E. Phelps, PhD  
 Norton Simon Chair in Biophysics  
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 Chair in Pathology  
 Richard Gatti, MD,  
 Rebecca Smith Chair in A-T  
 Research  
 Benjamin Glasgow, MD,  
 Wasserman Professor of  
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 Carmine Clemente, PhD  
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 Nora Sun, MD  
 Mitsuo Takasugi, PhD  
 M. Anthony Verity, MD  
 Julien L. Vanlancker, MD  
 Faramarz Naeim, MD  
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 Primary Dept: Medicine  
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 Primary Dept: Medicine  
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 Science  
 Anna Wu, PhD  
 Primary Dept: Pharmacology

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 Hane Lee  
 Sangderk Lee  
 Fang Li  
 Feng Liu  
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 Vei Hsien Mah  
 Javier Mestas  
 Encarnacion Montecino-Rodrigue  
 Kotoka Nakamura  
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#### **POST-DOCTORAL SCHOLARS**

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 Mandana Amiri  
 Beata Berent Maoz  
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 Peter Hoang Bui  
 Jinkuk Choi  
 Jenny Elizabeth Davies  
 Boxiao Ding  
 Thilini Ranga Fernando  
 Jessica Aaron Fowler  
 Omai B. Garner  
 Carmen Giltner  
 Beatrice Gini

Nathan Stewart Hageman  
 Sara Haghighyegh Zavareh  
 Ayaka Ito  
 Marius Ciprian Jones  
 Yoko Kidani  
 Dhong Hyun Lee  
 Laureanne Pilar el Lorenzo  
 Kenta Masui  
 Tomoo Matsutani  
 Ian H. McHardy  
 Leili Mirsadraei  
 Kiyoko Miyata  
 Albert Brian Mochon  
 Saleem Sandoval  
 Sandra Thiemann  
 Claudio J. Villanueva  
 Haolei Wan  
 Kevin Jason Williams  
 Ting-Hsiang Sherry Wu  
 Sohila Zadrán  
 Thomas Andrew Zangle  
 Li Zhang

#### **GRADUATE STUDENT RESEARCHERS**

David Akhavan  
 Michael Dawson Arensman  
 Joseph P Argus  
 Jennifer Ping Chou  
 Jennifer K Chun  
 Mary C Clark  
 Jorge Rafael Contreras  
 Jeffrey Nels Dock  
 Jeanette Grant  
 Daniel S. Halperin  
 Ronik Khachatourian  
 Jonathan Jacobs  
 Airie Kim  
 William Sang Kim  
 Woojin Kim  
 Lisa Kohn  
 Sandy Li  
 Xiaoxiao Li  
 Lin Lin  
 Nathan Thomas Martin  
 Brian J McMorran  
 Nicole Rodriguez  
 Norma Rodriguez-Malave  
 Xin Rong  
 Olivia Teresa Schontzler  
 Eriko Christine Shimada  
 Maomeng Tong  
 Cynthia Tran  
 Nicole Valenzuela  
 Christine Marie Van Horn  
 Nicole C. Walsh  
 Jiexin Wang  
 Autumn Gabrielle York  
 Jin Zhang

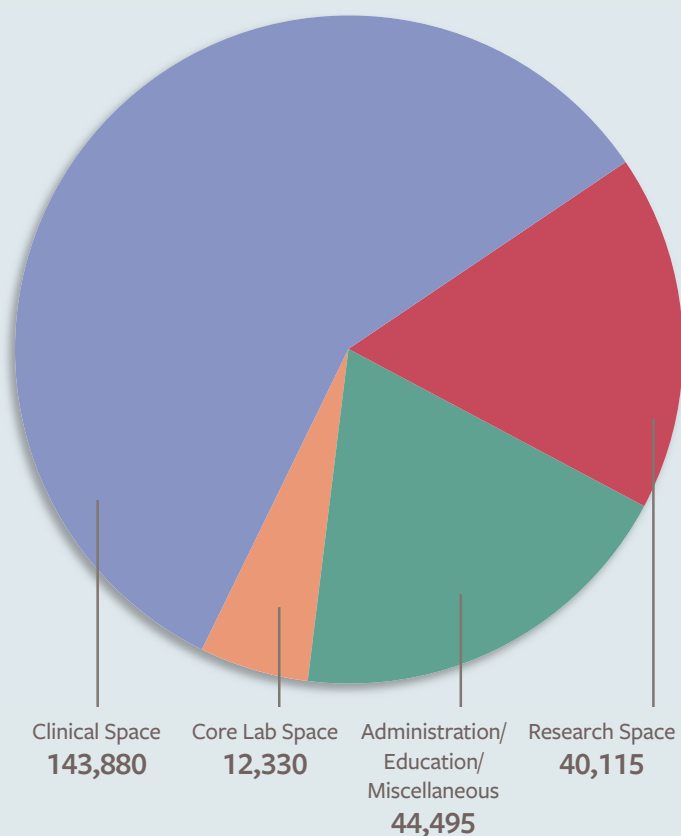
## Department in Depth: Metrics



### Facilities

Total number of square feet of clinical research, and teaching space

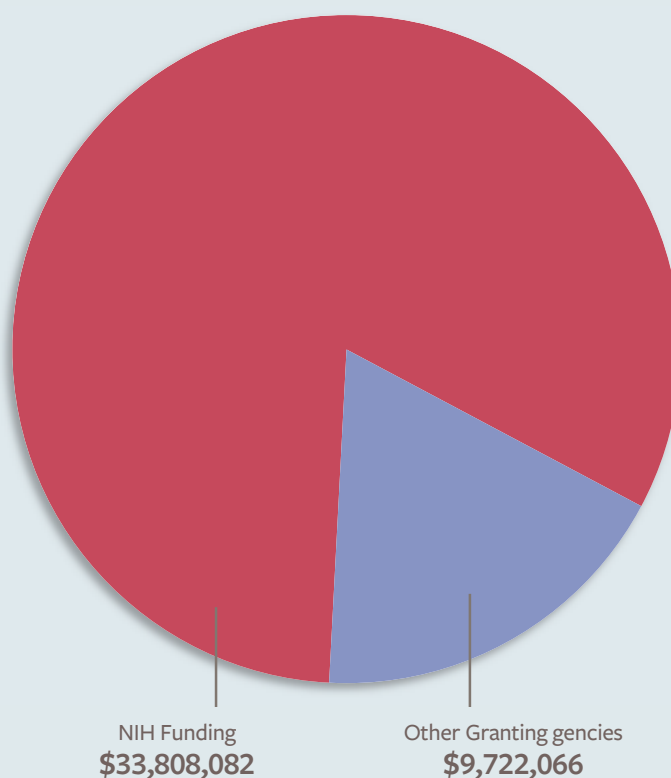
240,820



### Research Funding

Total contracts and grants research funding

\$43,530,148



### People

Total number of faculty, staff, residents/fellows, post doctoral researchers and graduate student researchers

1,195

Faculty  
105

Staff  
971

Residents/  
Fellows  
34

Postdoctoral  
Researchers  
34

Graduate  
Student  
Researchers  
29

Professional  
Research  
Series  
22



### Clinical Metrics

FY 2012 (projected)



#### Outreach

approx. **55,000** cases  
9.5% are second-opinion consults



#### Cytology

approx. **37,200**  
(gyn and non-gyn)



#### Surgical Pathology, Westwood

approx. **24,000**



#### Surgical Pathology, Santa Monica

approx. **8,400**



#### Molecular Pathology

approx. **920**



#### Cytogenetics

approx. **24,800**



#### Clinical Lab tests

approx. **5,813,400**



# Department in Depth: Publications

Kumar A, **Li XX**, **LeBlanc J**, Farmer DG, Elashoff D, **Braun J**, Ziring D. Proteomic Analysis Reveals Innate Immune Activity In Intestinal Transplant Dysfunction. *Transplantation*. 2011; 92(1):112-9. PMID: 21527871.

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Abi-Rached L, Jobin MJ, Kulkarni S, McWhinnie A, Dalva K, Gragert L, Babrzadeh F, Gharizadeh B, Luo M, Plummer FA, Kimani J, Carrington M, Middleton D, **Rajalingam R**, Beksac M, Marsh SG, Maiers M, Guethlein LA, Tavoularis S, Little AM, Green RE, Norman PJ, Parham P. The shaping of modern human immune systems by multiregional admixture with archaic humans. *Science*. 2011 Oct; 334(6052):89-94. PMID: 21868630.

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Agnihotri S, Gajadhar A, Ternamian T, Gorlia T, Diefes K, **Mischel PS**, Kelly J, McGown G, Thorncroft M, Carlson B, Sarkarai J, Margison G, Alsape K, Hawkins C, Heti M, Guha A. Alkylpurine-DNA-glucosylase confers resistance to temozolomide and xenograft models of glioblastoma multiforme and is associated with poor survival in patients. *J Clin Invest*. 2012 Jan; 122(1):253-66. PMID: 22156195.

Andorsky DJ, Yamada R, **Said JW**, Betting GS, Timmerman JM. Programmed death ligand 1 (PD-L1) is expressed by non-Hodgkin lymphomas and inhibits the activity of tumor-associated T cells. *Clin Cancer Res*. 2011 Jul; 17(13):4232-44. PMID: 21540239.

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Angst E, **Dawson DW**, Stroka D, Gloor B, Park J, Candinas D, Reber HA, Hines OJ, Eibl G. N-myc Downstream Regulated Gene-1 Expression Correlates with Reduced Pancreatic Cancer Growth and Increased Apoptosis in Vitro and in Vivo. *Surgery*. 2011 May; 149(5):614-24. PMID: 21236457.

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