UCLA PATHOLOGY AND LABORATORY MEDICINE

2015 Annual Report

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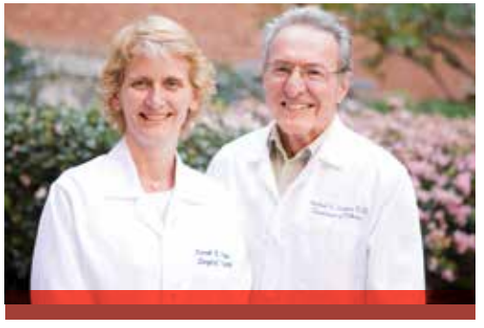

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EL NIÑO

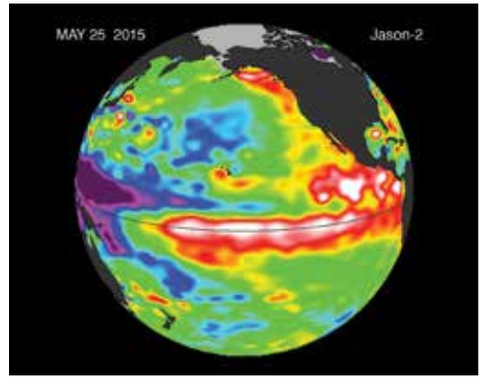
Los Angeles is a city of dreamers. The Chumash ancestors trekked in search of a life elevated by protected bays and oak woods. The Spaniards sailed here to shape dreams of faith and empire. Artists and directors gathered to transfer reality into cinema. It is everywhere an aspiring city, from millennial NoHo and Venice to the cultural mosaic of PV and Koreatown. These are places where many from our department live and meld work and community.

The only thing Los Angeles doesn't have is water. Nine years of drought has brought water in California to an historic low. We adopt immediate adjustments — how to differently keep the interiors and exteriors of our homes and public places. And, we wrestle with the surprising sociology in its wake: grass lawns are the new fur coats. But we dream about El Nino, the mid-Pacific vortex, absent this past decade, that directs rain to our parts. And indeed, as I write to you, El Niño is again forming, with its promise of change for the good.

"HOW CAN PATHOLOGY CREATE THE EL NIÑO WE NEED FOR QUALITY INNOVATION AND ACCESS TO CARE?"

The health of Americans is also in drought due to access, cost, and limits of contemporary medicine to restore health and avert disease. However, we are dreamers. In these pages, read about Drs. Romney Humphries and Omai Garner, who are finding how to use the Accountable Care Act to improve cancer surveillance and care of hepatitis as well as care access (and in their spare time, working hands on to care for prospective Ebola patients). Dr. Scott Binder, Lee Flores, and the exceptional team of BURL have flipped the model of clinical care, delivering UCLA clinical testing at affordable cost to patients where they receive their care across the 20,000 squares miles of the City of Los Angeles. Exciting new care delivery models, including RadPath (integrated radiology and pathology) and international partnerships (CTI) are bringing new access to quality care on an affordable basis to our region and to partner communities in Zhezhiang Province and Shanghai.

To restore health, Dr. King Das is creating ways to get ahead of decompensation in COPD care, and with Dr. Valerie Arboleda and others, using nexgen sequencing to diagnose and manage congenital disease. Linking department research and molecular diagnostics to match treatments to individual cancers through molecular features is a blossoming enterprise of Drs. Dean Wallace and King Das (lung cancer), Sophie Song and Dinesh Rao (leukemia), Hanlin Wang (colorectal cancer), David Dawson (prostate cancer), and Elaine Reed (organ transplant and chronic inflammatory disease management). And, Drs. Sarah Dry and Michelle Li have created the UCLA Portal, that opens access to these remarkable capabilities to the



Radar altimetry image from the OSTM/Jason-2 satellite

disease research community within UCLA and nationally. And for the generation ahead, Dr. Elena Stark links pathology to the aspirations of our medical students, and Dr. Tony Butch to the welfare of our nation's athletes.

Read on, and see how Pathology is helping build the El Nino for the health of our national community.

Jonathan Braun

Dr. Jonathan Braun,
Professor and Chair
Department of Pathology and Laboratory Medicine

CLINICAL SERVICES

PATHOLOGY DEPARTMENT PLAYING KEY ROLE IN UCLA HEALTH'S ACCOUNTABLE CARE ORGANIZATION IMPLEMENTATION

The United States leads the world in per capita spending on healthcare – paying approximately $8,745 per person in 2012, according to the Organization for Economic Cooperation and Development – but ranks poorly among high-income countries in quality and outcome measures. Research has shown that barely more than half of patients receive the recommended care for their condition. "There has been a recognition that our system is inefficient, siloed, and poorly organized," says Romney Humphries, PhD, an assistant professor and chief of clinical microbiology within the UCLA Department of Pathology and Laboratory Medicine. "We're very good at taking care of patients with acute illnesses, but not as good when it comes to chronic diseases in which patients need follow-up care and appropriate management throughout their lives."

That concern is being addressed nationally through the development of Accountable Care Organizations (ACOs) – groups of doctors, hospitals, and other healthcare providers who come together voluntarily to deliver coordinated, high-quality care. Initiated by the U.S. Centers for Medicare and Medicaid Services as part of the Patient Protection and Affordable Care Act of 2010, ACOs aim to ensure that patients – especially those with chronic illnesses – receive the right care at the right time, while avoiding unnecessary duplication of services and preventing medical errors. "It's about sharing accountability for patient care through a structure that promotes coordination, quality improvement and population management to improve patient outcomes, ensure patient safety, and reduce cost," Dr. Humphries explains.

UCLA Health has moved quickly to develop its own ACOs – an effort that has been recognized in the Becker's Hospital Review list of "100 Accountable Care Organizations to Know," which features some of the most advanced ACOs in the country. Approximately half of UCLA's patients are part of a UCLA ACO. And as UCLA Health continues to develop its ACO infrastructure, the Department of Pathology and Laboratory Medicine is playing a key role.

Romney Humphries, PhD, represents the department on the hospital's quality improvement committee.

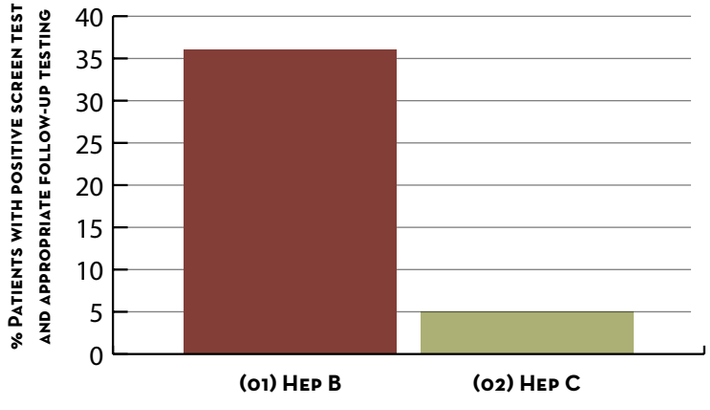
"There is a great deal that we can contribute from the lab perspective to quality improvement efforts, from eliminating unnecessary tests to ensuring that patients receive medically necessary tests for their care," says Dr. Humphries, who represents the department on the hospital's quality improvement committee. In addition to taking a hard look at utilization to determine and address the overuse and underuse of tests, Dr. Humphries and colleagues are focusing on improving how pathologists communicate test results to physicians so that they are interpreted properly.

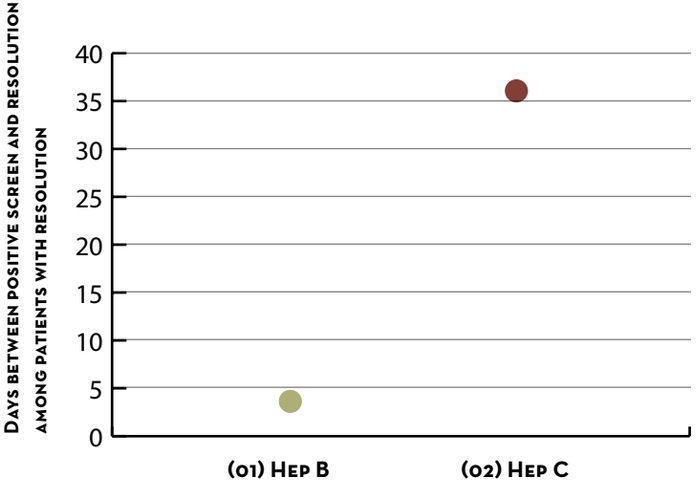
The effort includes an emphasis on ensuring that UCLA physicians follow evidence-based practices in their care of patients. As part of the ABIM Foundation's Choosing Wisely campaign, medical specialty organizations have issued lists of recommendations for appropriate research-driven care. Through pop-up alerts when clinicians are using the electronic medical record system to order a test that may not be appropriate, UCLA Health plans to address areas in which overutilization is seen as a potential concern. Within the Department of Pathology and Laboratory Medicine, one such area involves blood utilization, given that blood products are among the leading laboratory-related costs to the hospital, and are often ordered unnecessarily. Through the slogan "One Is the New Two," the department is encouraging clinicians to follow evidence-based guidelines and not order extra units of blood for hospitalized patients when they aren't needed.

In the area of underutilized tests, the department is piloting a decision-support structure for complicated conditions that involve multiple lab tests, starting with hepatitis B and hepatitis C infection. Examination of data at UCLA found that only 30 percent of patients with a positive screening test for hepatitis B or C were receiving the recommended follow-up testing. "With both of these infections, there are many different tests that can be ordered, but in reality you need only a few to get the patients to the point where they can be referred to a specialist," Dr. Humphries says. The department is launching an algorithm-based program to streamline the process, guiding the testing process based on the results to ensure that patients receive the appropriate tests on the same visit.

With these and other efforts, Dr. Humphries says, "The Department of Pathology and Laboratory Medicine has the expertise to provide valuable decision support. It is critical that we seize this opportunity to be leaders in supporting high-quality, high-efficiency care." ▲

"THE DEPARTMENT IS LAUNCHING AN ALGORITHM-BASED PROGRAM TO STREAMLINE THE PROCESS, GUIDING THE TESTING PROCESS BASED ON THE RESULTS TO ENSURE THAT PATIENTS RECEIVE THE APPROPRIATE TESTS ON THE SAME VISIT". — Romney Humphries, PhD





Confirmatory Testing Performed at UCLA for Patients who Screen Positive for Hepatitis B and C

FIT SCREENING PROGRAM DETECTS COLORECTAL CANCERS AT EARLY, TREATABLE STAGE

COLON CANCER, the third most commonly diagnosed cancer in the United States, is 90-percent curable when detected early. Regular colorectal cancer screening is recommended by the American College of Gastroenterology. Occult blood in the stool is an early warning sign of colorectal cancer or precancerous adenomas; early diagnosis by fecal occult blood screening and treatment of these problems has been shown to significantly reduce mortality from colorectal cancer. But conventional test methods used for the detection of fecal occult blood do not provide a high degree of accuracy. Immunological tests developed to detect human hemoglobin are more accurate, and do not require special dietary restrictions for patients.

In 2014, the UCLA Department of Pathology and Laboratory Medicine launched the Fecal Immunochemical Test (FIT) for occult blood diagnosis. Unlike the other fecal occult blood test (guaiac card), which detects the peroxidase activity of heme, FIT detects globlin. Because of this, FIT offers numerous advantages over guaiac cards, including:

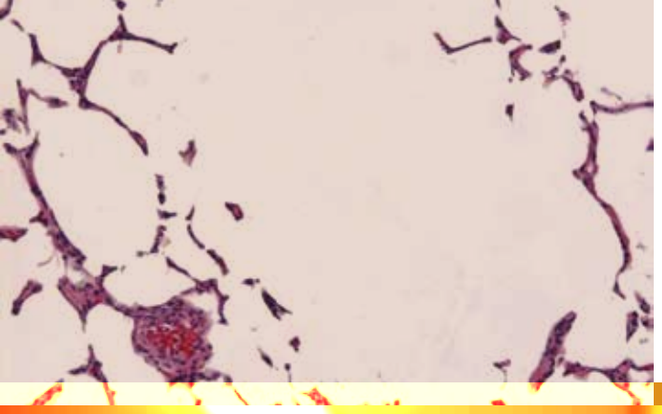
- Less risk for false positives or negatives due to diet and/or drugs vs. fecal occult blood, which can be affected by peroxidases found in raw fruit and vegetables, vitamin C, or dietary heme from red meat.
- Heightened specificity for lower GI bleeding vs. fecal occult blood, which can detect bleeding from any site in the gastrointestinal track.
- Heightened sensitivity for advanced adenoma and colorectal cancer in clinical trials as compared to occult blood.

FIT IS NOW RECOMMENDED BY THE AMERICAN COLLEGE FOR GASTROENTEROLOGY AS THE PREFERRED CANCER DETECTION TEST OVER GUAIAC CARDS IN PATIENTS WHO DECLINE COLONOSCOPY.

FIT is now recommended by the American College for Gastroenterology as the preferred cancer detection test over guaiac cards in patients who decline colonoscopy. The challenge is to identify and screen all of the UCLA patients who do not visit their doctors on a regular basis for colorectal cancer screening by FIT testing. In the fall of 2014, Dr. Omai Garner and Sharon Webb helped to launch a colorectal cancer screening program by FIT with Dr. Mark Grossman and Dr. Sam Skootsky of the UCLA Faculty Practice Group (FPG). Physicians from the FPG developed a letter for a group of 5,000 targeted patients – all of whom required colon cancer screening – explaining the necessity of screening. The letter contained a FIT sampling kit for easy at-home collection of a sample for occult blood testing. The kit contained a pre-addressed postage-paid return envelope so that the FIT kit could be mailed back to the lab and tested.

A fellow in the Division of Digestive Diseases analyzed the results of the 2014 Colon Cancer Screening project. Approximately 18 percent of the mailed fit kits were returned to UCLA for testing, matching national averages for this type of mailer screening program. In addition, 1,123 patients who received the letter either completed the FIT screen or had colorectal cancer screening performed by another method (sigmoidoscopy or colonoscopy). One positive case of cancer and seven cases of precancerous adenomas were recognized – all of which may have not been diagnosed without this multi-departmental initiative. The successful effort will continue into 2015, building upon the success of the pilot program by targeting an additional 50,000 UCLA patients who are due for colorectal cancer screening but do not have yearly contact with their physicians. ▲

Omai Garner, PhD



Above: Alveolar tissue destruction in emphysema.

Below: Kingshuk Das, MD, spearheaded the initiative in collaboration with UCLA Pulmonologist Dr. Christopher Cooper.

TARGETED LABORATORY ORDER SETS STANDARDIZE PROCESSES FOR OPTIMAL MANAGEMENT OF COPD

AS PART OF ITS LARGER EFFORT to support UCLA Health's quality improvement strategy, the Department of Pathology and Laboratory Medicine has worked with the Department of Medicine's Division of Pulmonology to help standardize the management of patients with chronic obstructive pulmonary disease (COPD).

The goal of the effort is to ensure that COPD patients treated at UCLA receive the appropriately high level of care they need. "Healthcare is best delivered when it is standardized and founded by scientific evidence – and we are instituting protocols and clinical pathways based on evidence from clinical trials that this is the best way to manage COPD," says Kingshuk Das, MD, associate director of the Molecular Diagnostics Laboratory, who has spearheaded the initiative for the pathology department in collaboration with noted COPD expert and UCLA pulmonologist Dr. Christopher Cooper.

Dr. Das notes that certain diagnostic algorithms are more or less effective depending on the severity of the patient's COPD, which allows personalized treatment and follow-up of patients to reduce hospitalizations and improve outcomes. Utilizing this knowledge, targeted laboratory order sets have been assembled for use in CareConnect, UCLA Health's electronic medical record system, as part of the UCLA clinical pathway for COPD management. The project is part of a larger quality improvement initiative being undertaken by UCLA called MOVERS (Mortality, Outcomes, Value, Experience, Readmissions, Safety), which involves the development of appropriate clinical pathways to decrease mortality, improve outcomes, increase patient value, gain experience, reduce hospital readmissions, and increase patient safety.

The clinical pathway for treating COPD at UCLA will begin with a dedicated outpatient COPD/airway diseases clinic, including post-discharge appointments for recently hospitalized patients, spirometry testing and imaging, in addition to algorithmic laboratory testing, to optimize outpatient care and prevent hospitalizations.

COPD was chosen as an initial focus for developing standardized clinical pathways because of the potential for positive impact on the care of a large number of patients, Dr. Das says, as COPD affects 3-9% of the U.S. population. The Department of Pathology and Laboratory Medicine intends to support such quality improvement efforts across the UCLA Health system. "The vast majority of clinical management decisions are supported by laboratory testing, and our clinical colleagues at UCLA are renowned leaders in their fields," Dr. Das says. "This is a collaboration that combines our strengths to benefit our patients." ▲

UCLA RADPATH USES *IT* TO STREAMLINE, ENHANCE DIAGNOSTIC CONSULTATION FOR CANCER PATIENTS

A **COLLABORATIVE EFFORT** between UCLA's Department of Pathology and Department of Radiology has resulted in a first-of-its-kind clinical service that uses information technology to deliver a Web-based, integrated diagnostic platform to bring together full range of radiology and pathology reports – a process designed to streamline and enhance the diagnostic consultation for cancer patients.

By allowing all of the diagnostic studies of a patient's cancer – from CT scans to reports on genetic mutations – to be easily accessed from a single source, UCLA RadPath is able to increase the speed and accuracy of evaluations, according to W. Dean Wallace, MD, associate professor and chief of pulmonary pathology in the pathology department.

"Ultimately, the RadPath report will be able to move patients from time of definitive diagnosis to definitive treatment much more quickly," says Dr. Wallace, who, along with Dr. Corey Arnold from UCLA Medical Imaging Informatics and Dr. Fereidoun Abtin from the Department of Radiology, has been a leader of the platform's development team, which has also included numerous other faculty and staff from both departments.

Dr. Wallace explains that the need for RadPath stems from the rapid accumulation of diagnostic tools and other sources of information in both pathology and radiology. "This results in more challenges for our clinical colleagues in collecting all of this information, synthesizing it, and coming up with their own coherent picture of the disease in question," he says. "But now, patients who come to UCLA for evaluation and treatment of lung lesions can rely on very sophisticated coordination between the diagnostic clinicians and very strong lines of communication with the treating clinicians because of the effectiveness of the workflow and the very contextualized diagnostic information in the UCLA RadPath reporting platform."

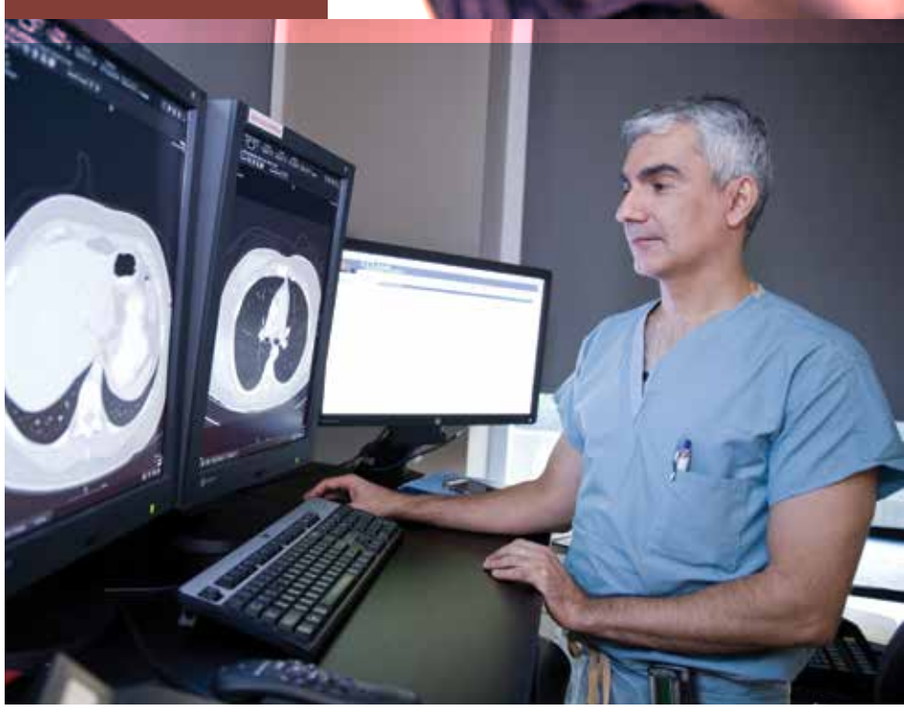
The combined reporting platform brings these disparate information sources together into one portal. RadPath can significantly reduce the time it takes for clinicians to find what they need before seeing a patient, as well as introducing technologies that wouldn't readily be included in conventional reporting systems – such as linking to literature references, and enabling email communication among doctors in a setting in which all of the information from the patient's studies are available.

Perhaps the most significant innovation generated by the RadPath platform is the correlation of pathology with radiology findings to catch and prevent any errors of interpretation, Dr. Wallace says.

RadPath is currently being used exclusively for lung cancer cases, with the ultimate goal of expanding it to other cancers. Early feedback from pathologists, radiologists and clinical colleagues has been highly favorable. "By combining the expertise of our two departments, UCLA RadPath delivers the most comprehensive, yet concise and practical, diagnostic report in the world," Dr. Wallace says. ▲

"ULTIMATELY, THE RADPATH REPORT WILL BE ABLE TO MOVE PATIENTS FROM TIME OF DEFINITIVE DIAGNOSIS TO DEFINITIVE TREATMENT MUCH MORE QUICKLY..."

– W. Dean Wallace, MD



Above: W. Dean Wallace, MD

Below: UCLA Radiologist Fereidoun Abtin, MD

BURL OUTREACH CLINICAL LABORATORY MEETING THE NEEDS OF GROWING UCLA OUTPATIENT POPULATION

The BURL Outreach Clinical Laboratory, a partnership between UCLA Health and the Department of Pathology and Laboratory Medicine, continues to thrive as it enters its third year of offering state-of-the-art outpatient pathology clinical services throughout Southern California.

"We are offering services at a low cost with an excellent turnaround time and superb quality – all of which is very hard to match in the community," says Scott Binder, MD, professor and senior vice chair of pathology and laboratory medicine, and director of the department's outreach services.

BURL is being driven by the expansion of UCLA Health clinics in communities from as far north as Ventura County and as far south as the South Bay. That has been accompanied by a dramatic expansion in the pathology department's outreach program, an integral part of which involves offering laboratory services for UCLA Health patients in the outpatient clinics.

When UCLA had no outreach laboratories, Dr. Binder notes, patients were being billed at hospital rates for outpatient services. Although the quality and sophistication of the analyses were state-of-the-art, the costs of tests were prohibitive compared to what patients could expect in the community.

"We needed an alternative," Dr. Binder says. "Without BURL, we would have to partner with a large commercial reference laboratory in order to provide these services. But there are advantages to not having to do that."

By opening BURL, owned by the Regents of the University of California but with a separate license to enable a community fee schedule, UCLA and the pathology department can offer the growing number of outpatients a convenient and competitively priced service along with the expertise for which UCLA is known.

BURL accepts specimens for all tests, ranging from routine blood draws to the most complex genomic testing for Mendelian disorders. The partnership with the hospital means that specimens received at BURL can be sent to the hospital for more complicated testing as needed. While other reference laboratories do excellent work, Dr. Binder says, they typically don't have the same level of pathology expertise on staff. As a core part of BURL's mission, pathologists work closely with the community-based UCLA physicians to assist in interpreting the tests. Among other things, BURL is supporting physicians by analyzing their lab utilization and steering them toward best practices for improving outcomes and minimizing costs.

"We continue to see more emphasis on diagnostics as a means to select the best therapy – so-called personalized medicine," says Dr. Binder. "We want to make sure that is available to patients well beyond the physical confines of our hospital." ▲

Above: Scott Binder, MD

Below: BURL staff (left to right): Maggie Barragan, Vincent Lee, Raul Briones, Kavita Doshi, Natalie Lopez, Evelyn Azcuna, Sarah Jones, Ryan Padayao, James Raffin, Lee Flores, Stacie McConnell, Dominque Cruz, Amelia Ludovico, Michael Dizon, Vicky Cruz, Robin Bituin, Crisa Noblejas, Pia Berina

UCLA PATHOLOGY INVOLVED IN JOINT EFFORT TO OPEN STATE-OF-THE-ART CLINICAL LABORATORY IN CHINA

The UCLA Department of Pathology and Laboratory Medicine is helping to lead an effort that will bring a much-needed new clinical laboratory to Shanghai, China. The 32,000-square-foot facility, the first of its kind in China, is scheduled to open this year. It will offer genetic and molecular diagnostics and other sophisticated tests that exceed the scope of the average lab in China, where quality pathology services have been lacking, according to Scott Binder, MD, professor and vice chair of pathology at UCLA and director of pathology laboratory services for UCLA Health.

The University of California and UCLA Department of Pathology and Laboratory Medicine signed an agreement last year with Centre Testing International Corp., a Chinese firm, to create a jointly owned company, UCLA Health/CTI Medical Laboratories, to operate the laboratory in support of clinical trials and the enhancement of medical care for Chinese patients.

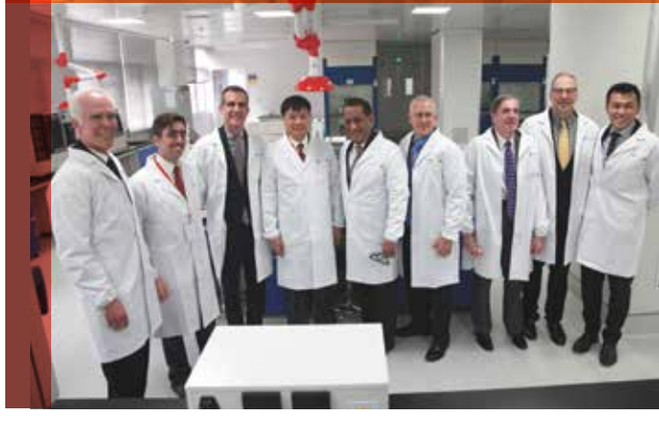
As part of the joint venture, CTI will provide the capital and hire the lab technicians, while UCLA will provide the professional and technical expertise, including training of the Chinese lab technicians and ensuring that quality standards are being met. The laboratory will be electronically and digitally linked with UCLA, enabling physicians and patients to consult with UCLA pathologists.

It was Dr. Binder who proposed the idea of a joint effort to establish such a laboratory in China, where pathology has traditionally been undervalued as a specialty. "China has a shortage of pathologists trained to diagnose and interpret complex test results in specialized fields of medicine," Dr. Binder says. "Our partnership gives CTI and UCLA the opportunity to save lives by changing that."

For several years, Dr. Binder and colleagues have worked with Zhejiang University School of Medicine in Hangzhou, China as part of a telepathology program in which digitalized slide images are sent from China to UCLA for assistance with challenging cases. UCLA pathologists have consulted with physicians at the university's teaching hospital on more than 2,000 cases, and Dr. Binder and others have traveled to China multiple times for consultations. Through that collaboration, Dr. Binder concluded that UCLA could help to make more of an impact by establishing a laboratory that could better handle challenging cases in China.

"If the diagnosis isn't correct, patients are going to either be overtreated or undertreated, and that's devastating either way," Dr. Binder says. "It's nice to help out with 2,000 diagnoses, as we have done, but we want to help improve the overall quality of care in China. By ensuring quality in a lab that's testing for a drug that could benefit millions of people, for example, we can affect many more lives." ▲

EXPLORE Clinical Laboratory in China at pathology.ucla.edu/news.



Above: At the ceremonial new logo unveiling are (left to right) Mike Bonin, Dr. Serge Alexanian, Dr. Jianyu Rao, Gil Cedillo, Dr. Scott Binder, Eric Garcetti, Sangem Hsu, Gil Garcetti, Tim Lou, Dr. Qinlong Zheng, Rick Jacobs, and Paul Fasi.

Middle: At the ribbon cutting ceremony in front of the medical laboratory are (from left to right) Dr. Jianyu Rao, Gil Cedillo, Sangem Hsu, Mayor Eric Garcetti, Dr. Scott Binder, Mike Bonin, and Dr. Serge Alexanian.

Below: Within the laboratory's anatomic pathology processing area are (from left to right) Gil Garcetti, Dr. Serge Alexanian, Mayor Eric Garcetti, Dr. Qinlong Zheng, GilCedillo and Mike Bonin, Dr. Scott Binder, Rick Jacobs and Stephen Cheung.

UCLA OLYMPIC ANALYTICAL LABORATORY TESTING AND RESEARCH CONTRIBUTE TO THE FIGHT AGAINST DOPING IN SPORTS

Olympic Analytic Laboratory Senior Supervisory Staff (left to right): Ron Gonzalez Joe Ramnarain, Yulia Kucherova, Brian Ahrens, Anthony Butch, PhD, Boro Starcevic, and Louise Laden.

THE UCLA OLYMPIC ANALYTICAL LABORATORY, the largest accredited anti-doping laboratory in the world, was established in 1982 by a grant from the Los Angeles Olympic Organizing Committee and has performed drug testing for three Olympic Games (Los Angeles 1984, Atlanta 1996, and Salt Lake City 2002), as well as other major sporting events such as soccer's World Cup. The laboratory, in the UCLA Department of Pathology and Laboratory Medicine, provides state-of-the-art drug testing in the fight against doping in sports. To accomplish this, the laboratory uses sound scientific principles and the most advanced technologies to detect the presence of prohibited substances in urine and blood. Under the leadership of Dr. Anthony Butch, the staff of more than 40 employees tests about 40,000 urine and blood samples each year for the presence of drugs of abuse and performance-enhancing substances.

For urine samples collected in competition, the laboratory screens for the presence of more than 300 prohibited substances. These include anabolic agents, peptide hormones, growth factors, beta-2 agonists, hormone and metabolic modulators, diuretics and masking agents, stimulants, narcotics, cannabinoids (synthetic and natural), glucocorticoids, and beta-blockers. Dr. Butch explains that the majority of drug tests use methods known as gas chromatography mass spectrometry and liquid chromatography with tandem mass spectrometry detection. Synthetic testosterone and testosterone precursor use (DHEA) is detected by gas chromatography-combustion-isotope ratio mass spectrometry. To detect erythropoietin-stimulating agents (darbepoietin, erthyropoietins, etc.) isoelectric focusing and sarcosyl polyacrylamide gel electrophoresis techniques are used for separation and identification.

"Samples that screen positive for a prohibited substance must undergo repeat testing to confirm the results from the original screen before the sample is considered positive," Dr. Butch says. "Documentation is then provided to support positive test results and the laboratory is often called upon to defend and explain the scientific data at appeals and arbitration hearings when the athlete challenges the doping violation." Positive tests can result in sanctions ranging from a verbal warning to up to two years, depending on the testing authority and the circumstances regarding the positive result.

To continue to develop cutting-edge technologies in the fight against doping in sports, the Olympic Analytical Laboratory has a robust research program focused on developing and validating new testing strategies to improve existing methods and identify designer compounds as they become available through the black market," Dr. Butch notes. Previous research efforts by the laboratory have resulted in the identification of norbolethone, tetrahydogestrinone and desoxymethyltesosterone, designer steroids that are now routinely identified in screening methods used by all accredited laboratories.

More recently, the laboratory developed an immunoextraction method followed by tandem mass spectrometry detection of tryptic peptides to detect different isoforms of human chorionic gonadotropin (hCG) in urine samples. The laboratory is currently developing cutoffs for each of the hCG isoforms in order to detect doping with the different formulations of hCG. Other projects include the development of a top-down and bottom-up approach to detect doping with insulin-like growth factor 1, and validation of a biomarker test with a 1-2 week window to detect the use of human growth hormone. ▲

LABORATORY INITIATIVES SEEK TO IMPROVE PATIENT CARE

The Clinical Laboratory is always seeking to improve patient care through process improvement. To support this endeavor, process review committees have been established within each functional area of the Department of Pathology Clinical Laboratory. These committees gather process-improvement ideas from staff and present them to management. Suggestions can be related to any area of work, including ideas for increasing efficiency, reducing costs, decreasing result turnaround time, and enhancing clinician and patient satisfaction – all toward the common goal of improving patient care.

To meet the growing regulatory requirements in the Clinical Laboratory, a quality monitor has been designated from each lab section. Quality monitors are responsible for ensuring adherence to policies within the Clinical Laboratory Quality Manual, and for thorough documentation as defined by the quality assurance program.

Two process improvements were implemented in Transfusion Medicine to improve patient safety and patient care. The Blood Administration module was employed to streamline the process of ordering, releasing, and documenting transfusions. The patient safety features of the module include barcode scanning and dual nursing signoff to ensure that the correct patient receives the correct blood product. The Massive Transfusion Protocol (MTP), which is used by clinicians to treat severely injured trauma patients, was redesigned to immediately provide thawed plasma when the patient arrives at the Emergency Department. "By providing Universal Group A Plasma units at the outset of all severe trauma cases, we are improving survivability; conserving the more precious, rare blood types; and reducing our overall blood product usage," explains Paul Colonna, director of clinical laboratories operations.

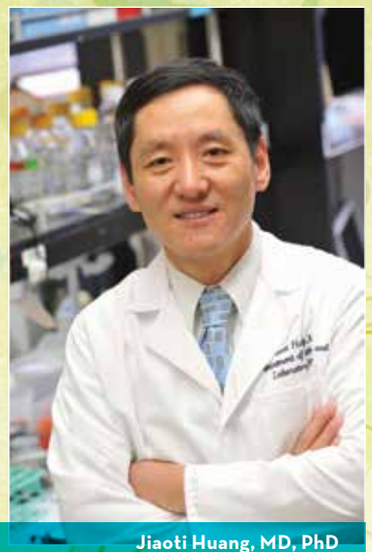
Sepsis, which can occur in response to infection and can quickly become life-threatening, is difficult to predict, diagnose and treat, and puts patients at increased risk of complications and death. To improve the clinical microbiology laboratory's ability to identify potential pathogens in these patients, the lab has implemented a new blood culture system. The system utilizes blood culture bottles with special resins that inhibit the activity of some antimicrobials while allowing recovery of bacteria and appropriate treatment choices for the patient. Another process improvement saw the implementation of a testing algorithm for a positive microbiology urinalysis with reflex to bacterial culture; this algorithm can improve clinical care by reducing the number of contaminated urine cultures, minimizing the number of patients treated for asymptomatic bacteriuria based on culture results alone, and minimizing the number of urine specimens unnecessarily cultured, saving patient expense. Furthermore, a new methodology for detection of Mycobacterium tuberculosis by polymerase chain reaction (PCR) has been initiated. "Results from conventional culture methods can take 2-8 weeks, while the more specific and sensitive PCR method can produce results within hours," Colonna explains. "This test has enabled more rapid recognition of patients infected with TB and more rapid rule-out for patients suspected of having the disease, allowing a reduced length of stay in the hospital." ▲

PROCESS REVIEW COMMITTEES AND QUALITY MONITORS ARE THE FOUNDATION OF NUMEROUS IMPROVEMENT INITIATIVES THROUGHOUT THE DEPARTMENT.

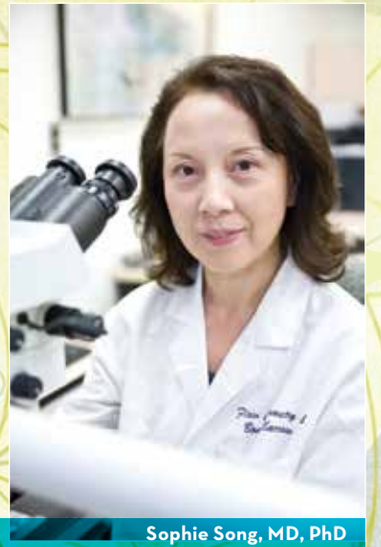
Clinical Laboratory Management Team (left to right): Cynthia Toy, Paul Colonna, Diana Crary, Anthony Johnson, Marivic Visico, Lucy Garrido.

RESEARCH GUIDES THE WAY TO NEW AND IMPROVED DIAGNOSTIC TOOLS

DELVING FURTHER INTO THE MECHANISM OF MALIGNANCY



Jiaoti Huang, MD, PhD



Sophie Song, MD, PhD

Dinesh Rao, MD, PhD

David Dawson, MD, PhD

The Department of Pathology and Laboratory Medicine offers a menu of hundreds of tests that are used to monitor the health status of individuals, formulate diagnoses, and customize treatment choices for patients. Each month, approximately 500,000 samples are analyzed to guide the care of patients in the UCLA Health system, along with those in UCLA's regional and national referral networks.

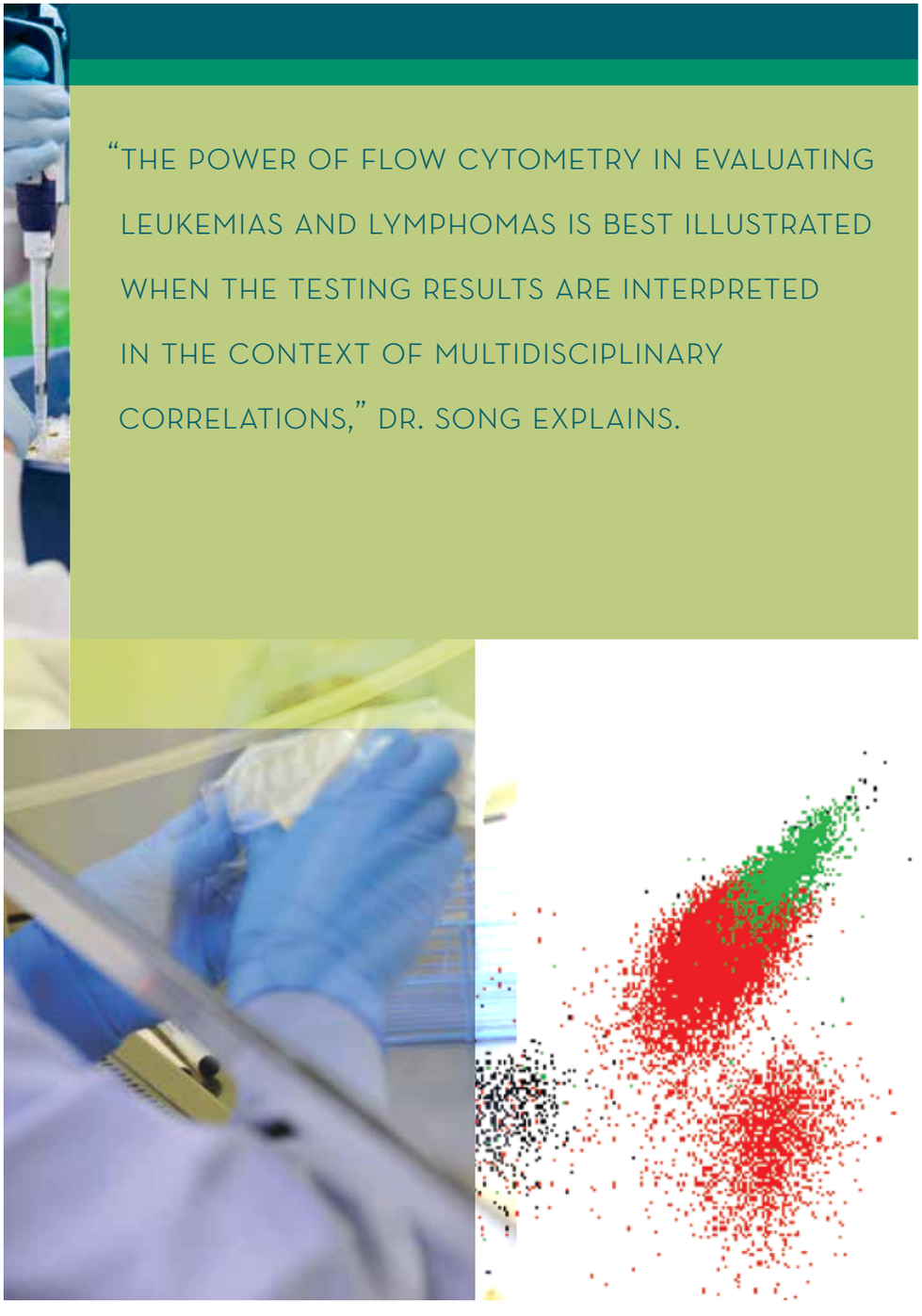
This ability to delve into pathological processes affecting patients and ensure that they are properly cared for is dependent on painstaking laboratory studies by department investigators. "It's easy to take the availability of these tests for granted," says Kenneth Dorshkind, PhD, the department's vice chair for research, "but they would not be possible without a large body of research into the normal development and function of cells and tissues, often conducted over decades."

As an example, Dr. Dorshkind points to the efforts of the department's Flow Cytometry Core, directed by Dr. Sophie Song, in diagnosing leukemias and lymphomas. "The now-routine analyses performed in the core, equipped with state-of-the-art flow cytometers, is based on decades of work in immunology and hematology," Dr. Dorshkind notes.

While flow cytometry and other genetic analyses have greatly improved the ability to diagnose blood cell cancers, additional tests to predict survival and the response to therapy are still needed. Dr. Dorshkind believes that research in the laboratory of Dr. Dinesh Rao, a hematopathologist in the department, may lead to their development. "Dr. Rao and members of his laboratory are defining the role of novel molecules, referred to as non-coding RNAs, in the normal and dysregulated development of blood cells," Dr. Dorshkind explains.

In other instances, the value of current tests that have been used routinely to diagnose disease has been questioned, necessitating the need to develop more accurate assessments. Dr. Jiaoti Huang is doing just that through research aimed at identifying biomarkers to predict prostate cancer.

Finally, new testing is needed for certain diseases to improve early detection and therapeutic approaches. A prime example of this is pancreatic cancer. "By the time of ini-



"THE POWER OF FLOW CYTOMETRY IN EVALUATING LEUKEMIAS AND LYMPHOMAS IS BEST ILLUSTRATED WHEN THE TESTING RESULTS ARE INTERPRETED IN THE CONTEXT OF MULTIDISCIPLINARY CORRELATIONS," DR. SONG EXPLAINS.

Dot plot of immunophenotypic analysis using 6-color 8-parameter flow Cytometry

tial clinical symptoms, pancreatic cancer is typically at an advanced, non-operable stage with only limited and modest treatment options," Dr. Dorshkind says. These challenges are the focus of research in Dr. David Dawson's laboratory that seeks a better understanding of pancreatic cancer progression, which in turn could lead to improved approaches to early detection and treatment.

Drs. Song, Rao, Huang, and Dawson illustrate the multi-dimensional role of physician-scientists in the department. "On the one hand, these physicians are responsible for interpreting the results of various tests ordered by healthcare providers in the UCLA network," Dr. Dorshkind says. "However, they are also conducting groundbreaking research that will further elucidate the mechanisms of disease and identify more effective ways to diagnose it."

SOPHIE SONG: USING FLOW CYTOMETRY TO DIAGNOSE BLOOD CELL CANCERS

Developing and mature white blood cells express surface and intracellular molecules in combinations that enable immunophenotypic identification of the cell type and its maturation status. The expression of these molecules is detected by labeling cells with antibodies to the surface and intracellular determinants, then analyzing them with an instrument referred to as a flow cytometer. This immunophenotypic analysis, now routine in diagnostic laboratories around the world, is based on decades of research.

Flow cytometry is used by basic scientists to identify different types of blood cells and determine how their number and immunophenotypes may be affected by experimental variables. In the clinical settings, flow cytometry has emerged as a valuable diagnostic tool for various blood cell cancers, and is an integral component of managing leukemias and lymphomas according to the current practice standards. The department's Clinical Flow Cytometry Laboratory provides state-of-the-art multiparametric testing on a daily basis. The laboratory is directed by Dr. Sophie Song, a hematopathologist, who received her MD from Capital Medical University in China and a PhD in Biochemistry from the University of Kansas.

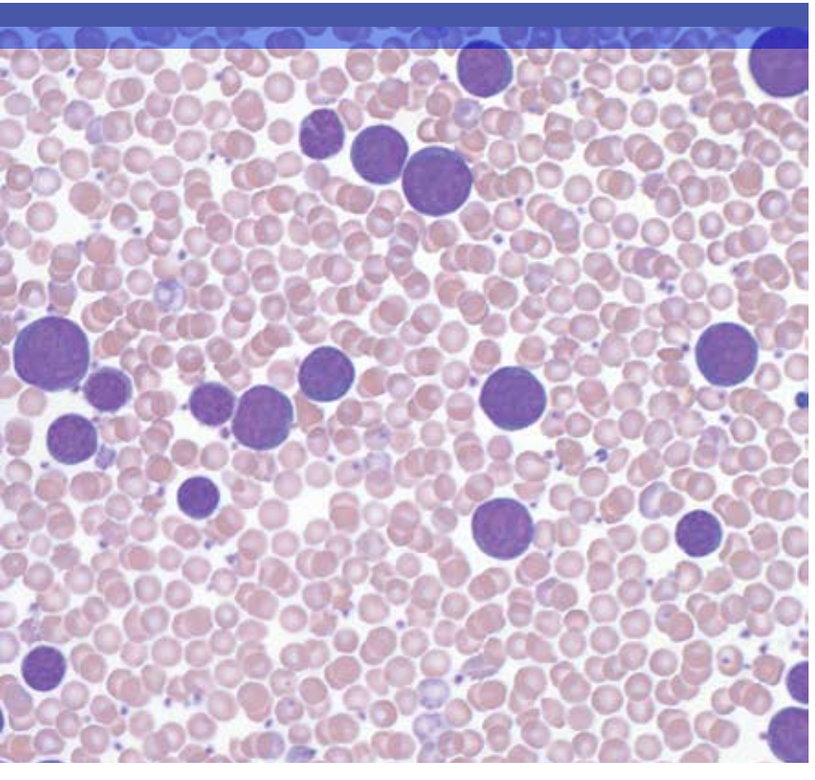
"The power of flow cytometry in evaluating leukemias and lymphomas is best illustrated when the testing results are interpreted in the context of multidisciplinary correlations," Dr. Song explains. "Making an accurate diagnosis by flow cytometry requires skillful integration of clinical information, morphologic findings, immunohistochemical and cytochemical studies, as well as cytogenetic and molecular genetics analyses."

DINESH RAO: THE ROLE OF NON-CODING RNAS IN LEUKEMIA

Dr. Dinesh Rao routinely uses the full arsenal of testing available when making a diagnosis, including flow cytometry. However, as a practicing hematopathologist, he is also aware that there are times when he would like to have additional information about a tumor in order to better understand the prognosis, or to recommend a course of treatment.

Dr. Rao, who received his MD from Case Western University School of Medicine and

completed his PhD in the laboratory of Nobel Laureate Dr. David Baltimore at the California Institute of Technology, heads a laboratory that is conducting basic research that promises to provide such information. Dr. Rao and colleagues are seeking to better understand normal and dysregulated blood cell development, which would lay the groundwork for the next generation of clinical laboratory testing for leukemia and lymphoma.



Leukemia

Funded by several grants from the National Institutes of Health, the Rao laboratory is delving into the physiology of non-coding RNAs. Their name reflects the fact that this relatively new class of molecules does not code for any protein in the cell. Instead, non-coding RNAs regulate gene expression, which in turn influences the types of proteins synthesized by the cell.

"REMARKABLY, THE REDUCTION OF NONCODING RNA IN EXPERIMENTS IN LEUKEMIA CELLS LED TO AN INCREASED RESPONSE TO THE TREATMENT," DR. RAO NOTES.

The goal of the Rao laboratory is to determine how non-coding RNAs regulate the development of a type of white blood cell referred to as a B lymphocyte. These are the cells that secrete the antibodies that attack foreign invaders in the body. Emerging studies point to abnormalities in the expression and/or function of non-coding RNAs in the development of various hematopoietic malignancies, including those affecting B lineage cells.

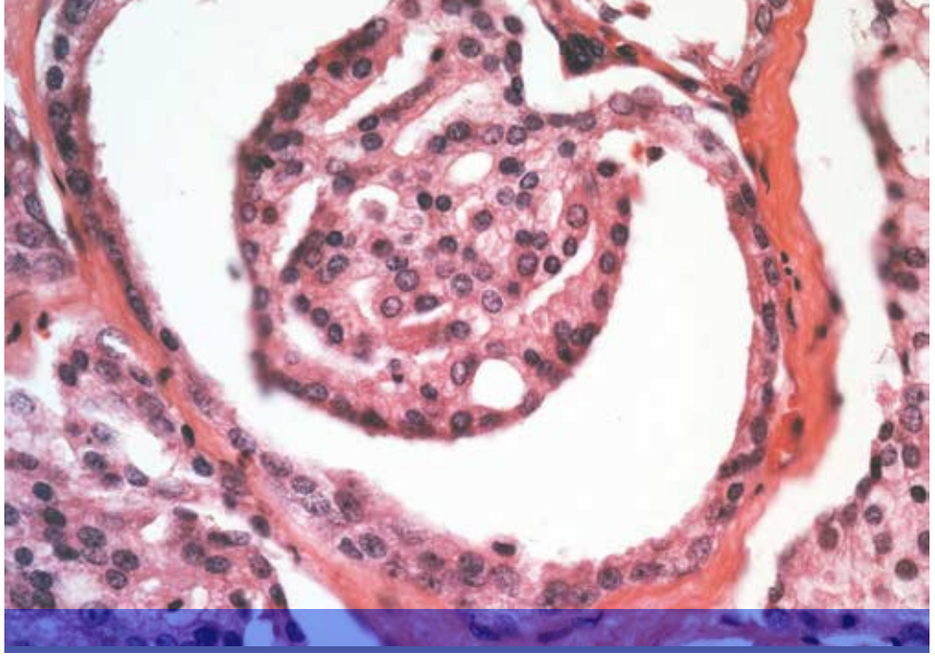
In one recently published study, Dr. Rao's laboratory discovered a noncoding RNA that was highly expressed in a type of B-cell malignancy, called acute lymphoblastic leukemia, when compared with normal B-lymphocytes. When high levels of this molecule were detected in the leukemia cells, patients had a poor response to one of the treatments for this disease. "Remarkably, the reduction of this noncoding RNA in experiments in leukemia cells led to an increased response to the treatment," Dr. Rao notes. "This study highlights that there are yet-undiscovered molecules in the cell that can influence the clinical behavior of these blood cancers."

There are both therapeutic and diagnostic implications to Dr. Rao's work. The lab continues to investigate which non-coding RNAs contribute to cancer and how they do so. Next steps include developing tests that could detect these molecules on a routine basis, which could lead to a new diagnostic and treatment-guiding paradigm in leukemia. Moreover, understanding the basis of their development can pave the way to the development of targeted therapeutics for patients who currently have few options.

EXPLORE Research Enterprise at pathology.ucla.edu/ResearchEnterprise

JIAOTI HUANG: DEVELOPING NEW DIAGNOSTICS FOR PROSTATE CANCER

THE PROSTATE-SPECIFIC ANTIGEN (PSA) test has been one of the most widespread screens used to evaluate patients for prostate cancer.



However, the value of PSA testing has come into question in recent years. PSA screening results in approximately 1 million prostate biopsies a year. Because of the test's poor specificity, only about one in four patients with PSA levels in the gray zone are found to have cancer on the biopsy.

Among men with elevated PSA but negative biopsies, many have benign conditions such as benign prostatic hyperplasia or chronic prostatitis, while some have cancer that was missed by the biopsy. Since the two possibilities cannot be accurately distinguished, all men with elevated PSA and negative biopsies are subject to repeat PSA tests and biopsies, resulting in unnecessary pain, anxiety and expense in many men who turn out not to be at risk for prostate cancer. These issues with low specificity of PSA screening and poor sensitivity of biopsy underscore the fact that improvements in the detection of prostate cancer are needed.

The laboratory of Dr. Jiaoti Huang, the department's chief of surgical pathology, is leading the way through his service responsible for the gross and microscopic examination of surgical specimens and biopsies. He holds an MD from Anhui Medical University in Hefei, China, and a PhD from New York University; he completed his residency in anatomical and clinical pathology at NYU Medical Center, and fellowship in oncologic surgical pathology from Memorial Sloan-Kettering Cancer Center.

The major research focus of the Huang laboratory is on different aspects of prostate cancer, including the molecular mechanisms of carcinogenesis, biomarkers, histological diagnosis, immunohistochemical profiles, the mechanism of tumor progression to the castration-resistant stage, and novel therapeutic strategies. Specifically, Dr. Huang and his colleagues are actively working to identify biomarkers in negative biopsy tissue that predict the likelihood of harboring unsampled cancer in patients. "Our goal is to use such biomarkers to stratify these patients so that men with high risk are offered immediate re-biopsy while those with low risk can be spared unnecessary procedures," Dr. Huang explains.

Another important problem is the inability to predict the biological behavior of prostate cancer when only small-volume, low-grade cancer is present on biopsy. "Many of these patients have cancers that are indolent, while some have aggressive cancers that were not well sampled," Dr. Huang says. "Because of this, many men elect to undergo radical treatment such as surgery or radiation to deal with the uncertainty, resulting in over-treatment in many whose disease would not have affected life expectancy or quality of life." To solve this problem, Dr. Huang's laboratory is seeking to identify biomarkers that can predict the biological behavior of the tumor so that patients are appropriately managed.

"OUR GOAL IS TO USE SUCH BIOMARKERS TO STRATIFY THESE PATIENTS SO THAT MEN WITH HIGH RISK ARE OFFERED IMMEDIATE RE-BIOPSY WHILE THOSE WITH LOW RISK CAN BE SPARED UNNECESSARY PROCEDURES," DR. HUANG EXPLAINS.

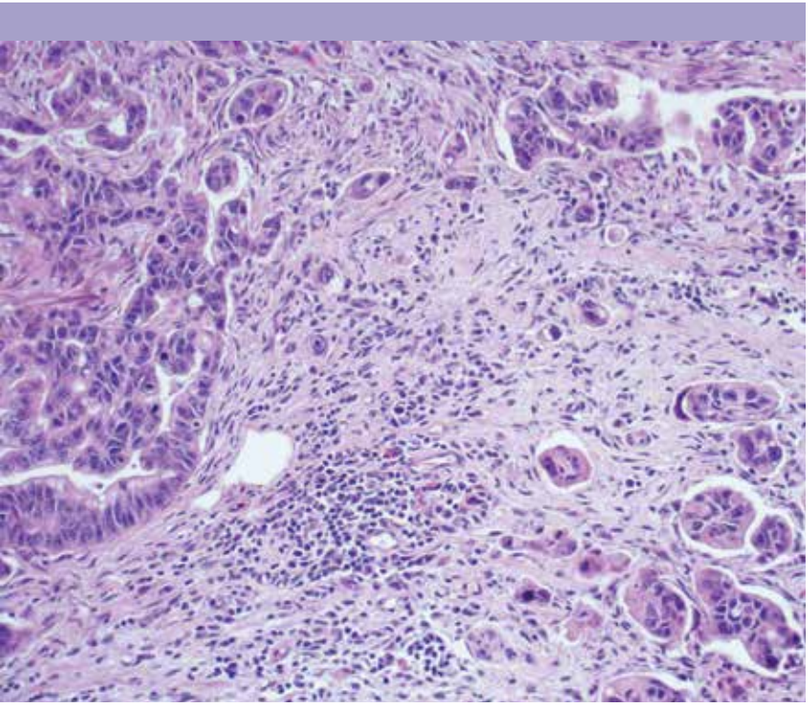
DAVID DAWSON: THE CHALLENGES IN DIAGNOSING PANCREATIC CANCER

Pancreatic cancer arises when cells in the pancreas, a glandular organ located behind the stomach, begin to multiply out of control. It is a devastating disease for two reasons. First, by the time symptoms of pancreatic cancer appear it is typically at an advanced stage. Second, the disease almost invariably responds poorly to chemotherapy or radiation treatment.

The laboratory of Dr. David Dawson is focused on delineating the role of growth

Above: An interesting case of prostate cancer with the so-called "glomerulation" pattern.

signaling pathways and transcriptional networks involved in pancreatic carcinogenesis. Dr. Dawson is a cancer biologist and practicing surgical pathologist who joined the UCLA David Geffen School of Medicine faculty in the Department of Pathology and Laboratory Medicine in 2006. Dr. Dawson earned his MD and PhD in Molecular Biology and Genetics at Northwestern University and completed residency training in anatomic pathology and a subspecialty fellowship in gastrointestinal pathology in the Department of Pathology and Laboratory Medicine at UCLA.



Pancreatic Cancer

Through comprehensive transcriptional,epigenetic and proteomic profiling of patient tumors and cell lines, the Dawson laboratory has identified several molecular alterations linked to tumor progression and patient survival in pancreatic cancer. Many of these alterations are candidate biomarkers that could be deployed as clinical tests for the detection and treatment of pancreatic cancer. Further integrative analyses of these alterations reveal the important role certain growth signaling pathways play in pancreatic cancer. Among these, the Dawson laboratory is focused on the Wnt signaling pathway, which is critical in normal embryonic development and frequently deregulated in numerous types of cancer.

THROUGH COMPREHENSIVE TRANSCRIPTIONAL, EPIGENETIC AND PROTEOMIC PROFILING OF PATIENT TUMORS AND CELL LINES, THE DAWSON LABORATORY HAS IDENTIFIED SEVERAL MOLECULAR ALTERATIONS LINKED TO TUMOR PROGRESSION AND PATIENT SURVIVAL IN PANCREATIC CANCER.

Work from the Dawson laboratory and many others indicate that abnormal activation of the Wnt pathway is an early event crucial for the development of pancreatic cancer, and is key mediator of tumor aggressiveness, including its capacity to spread elsewhere in the body. The Dawson lab has identified several key factors that drive abnormal Wnt signaling in pancreatic cancer and is addressing how these factors may be used as biomarkers to identify a subset of patient tumors more dependent on the Wnt pathway for their growth and spread.

"The ability to detect an activated Wnt signature in clinical specimens could influence our management of pancreatic disease," says Dr. Dawson. "Such a signature may prove useful in distinguishing between a benign versus precancerous lesion such as cysts that could inform a decision to undergo prophylactic surgery prior to the development of cancer. Likewise, such a signature could be used to identify a subset of patients whose pancreatic cancer is most likely to respond to Wnt-based therapy. This is exciting, given that several Wnt inhibitors are now finally in early-phase clinical trials for pancreatic cancer and other malignancies." ▲

IDENTIFICATION OF A NOVEL CONGENITAL SYNDROME SHOWS POWERFUL IMPACT OF NEXT-GENERATION SEQUENCING

CLINICAL EXOME SEQUENCING – a next-generation DNA sequencing technology that enables researchers to query all genes in a single test – is making a powerful impact at the specialized centers such as UCLA that offer it. Among the latest examples is the first-ever report implicating mutations in a gene known as KAT6A as the cause of a clinical syndrome for which there was previously no diagnosis. The report, from the UCLA Clinical Genomics Research Center, was led by clinical pathology resident Valerie A. Arboleda, MD, PhD, and Stanley Nelson, MD, and was published in the March 5, 2015 issue of the *American Journal of Human Genetics*.

Dr. Arboleda explains that before the advent of next-generation sequencing technologies, genetic diseases were diagnosed based on phenotype – looking at patients' clinical features and symptoms and attempting to match them with previously described syndromes. "That works well for relatively common disorders such as Down syndrome, but not for diseases that occur in one of every 100,000 patients – so that most physicians will never see more than one case in their lifetime," Dr. Arboleda says.

She notes that with most genetic diseases, the clinical presentation can vary significantly between patients and even within the same family. Clinical exome sequencing enables experts to take a patient with multiple symptoms – in the case of the patients reported on by Dr. Arboleda's group, this included developmental delay, dysmorphic facial features, difficulty swallowing, cardiac defects, and hearing loss – and definitively identify a single genetic mutation as the culprit.

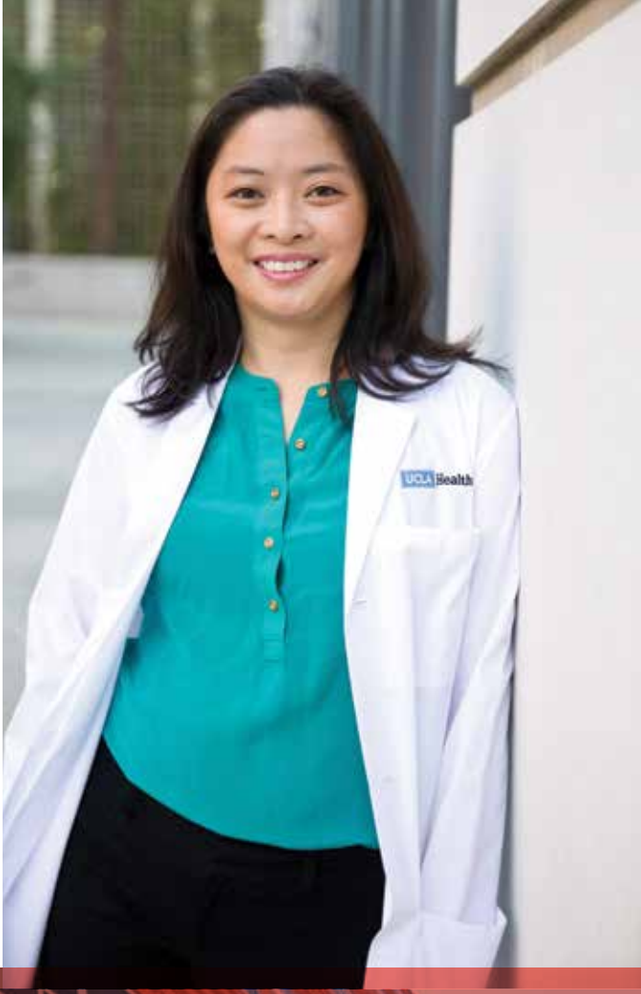
Although there is often no cure or even specific treatment designed for such patients, the diagnosis can be extraordinarily important for several reasons, Dr. Arboleda explains. For one, it puts an end to what has been called the "diagnostic odyssey," in which the families of patients with extremely rare genetic disorders are sent from one specialist to the next in an emotionally and physically exhausting effort to find an answer for unexplained and persistent symptoms. "Knowing there is a diagnosis and that other families are dealing with similar issues can provide a source of comfort and strength," Dr. Arboleda says.

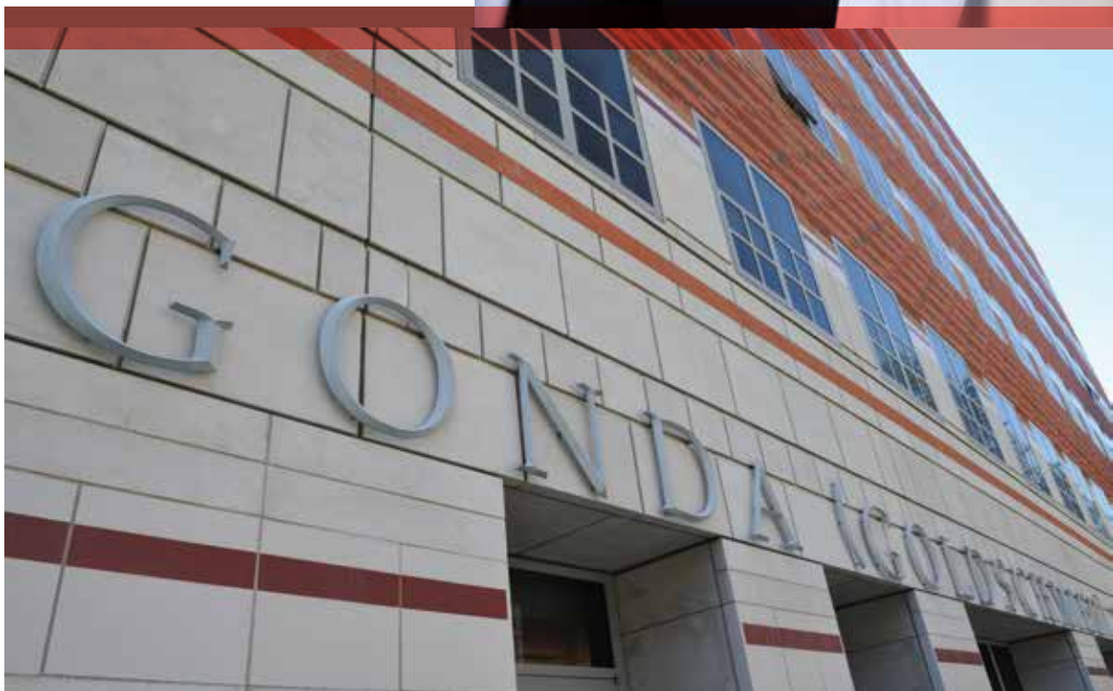
Moreover, by describing multiple patients with KAT6A mutations in the literature, Dr. Arboleda and colleagues have opened the door to a number of other families coming forward who turn out to have the same diagnosis. One family has begun to organize those with a KAT6A mutation in an effort to learn more about how symptoms develop over time so that families have a better idea of what to expect, as well as how symptoms may differ from one patient to another.

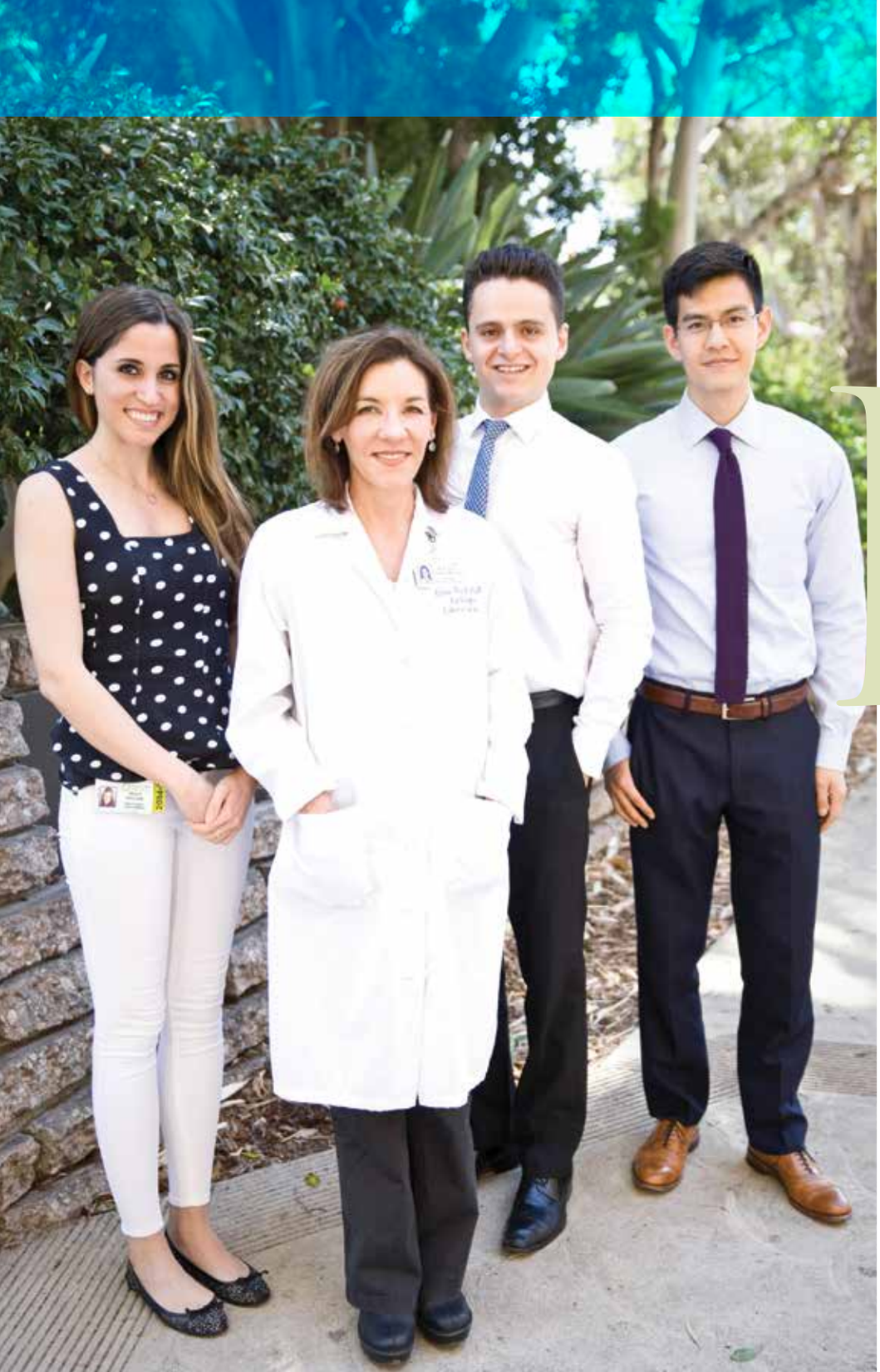
Finally, says Dr. Arboleda, even if there are no effective treatments now, "understanding the pathophysiology is the first step toward identifying rational targeted therapies for any genetic disease." ▲

"KNOWING THERE IS A DIAGNOSIS AND THAT OTHER FAMILIES ARE DEALING WITH SIMILAR ISSUES CAN PROVIDE A SOURCE OF COMFORT AND STRENGTH."

– Valerie Arboleda, MD, PhD







PATHOLOGY INTEREST GROUP WIDENS STUDENTS' HORIZONS THROUGH VENUE TO EXPLORE THE SPECIALTY

Hollywood's influence on the public perception of the pathology specialty has been significant – even among medical students.

"Many of them think pathology is all about the CSI work," says Elena Stark, MD, PhD, professor and vice-chair for medical and dental education for the Department of Pathology and Laboratory Medicine at UCLA, referring to the various long-running CSI: Crime Scene Investigation television series focusing on forensics. "They're not aware of the many different alternatives within pathology in the areas of diagnostics, patient care, education and research."

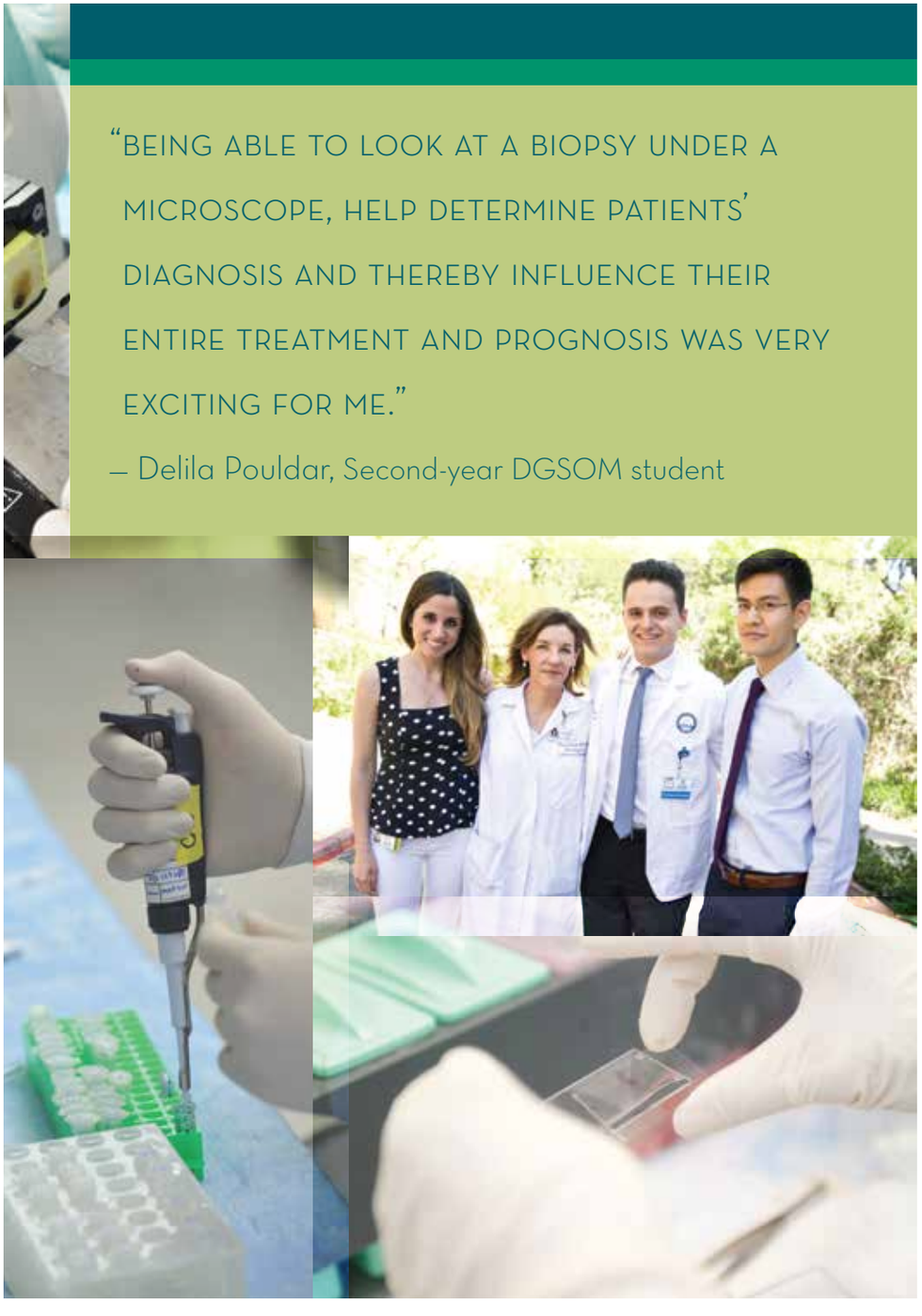
The Pathology Interest Group (PathIG), now in its third year, is changing that by educating and inspiring UCLA David Geffen School of Medicine (DGSOM) students about the various roles in pathology and their impact on the medical field, while offering a venue for interested students to explore the field further.

"This is a very successful interest group that has given our department a great deal of visibility within the medical student population," says Dr. Stark, the group's faculty advisor. "It widens their horizons and gives them a sense of the possibilities as they are considering specialties, and it helps the department to attract talented and enthusiastic students and residents."

Dr. Stark with members of the Pathology Interest Group (left to right), Delila Pouldar, Elena Stark, MD, PhD, Sina Rabi, Kevin Terashima

Interest groups within the DGSOM are driven by students for the purpose of going deeper into a discipline through activities ranging from mixers and lunches with faculty to informal seminars and shadowing opportunities. "During the first year of medical school, many students become excited after spending time in our curricular histology labs learning about normal and abnormal histological findings," Dr. Stark says. "We hope to help translate that enthusiasm into thinking about future careers."

PathIG seeks to do that by enhancing students' understanding of what the pathology specialty entails. Students learn why pathologists are often described as "the doctors' doctor." Says Dr. Stark: "Nowadays, many final diagnoses are made by the pathologist. When a patient is suspected of having cancer, for example, even if the tumor can be seen through imaging, typically it's only through a biopsy analyzed by a pathologist that we can understand the type of tumor and how the patient should be treated."



"BEING ABLE TO LOOK AT A BIOPSY UNDER A MICROSCOPE, HELP DETERMINE PATIENTS' DIAGNOSIS AND THEREBY INFLUENCE THEIR ENTIRE TREATMENT AND PROGNOSIS WAS VERY EXCITING FOR ME."

— Delila Pouldar, Second-year DGSOM student

Students whose perception of pathology's role may have been clouded by popular culture learn about the many avenues available to pathologists, and about the slew of cutting-edge research tools and technology emerging from pathology departments such as UCLA's. Sessions dispel the myth that pathology is a solitary specialty. "Some people think pathologists are in their labs looking through microscopes all day or that the only thing they do is autopsies, and that's not the case at all," Dr. Stark says. "Most pathologists have close relationships and interactions with many other clinicians and specialists."

PathIG opens each academic year with a luncheon that serves as an introduction to pathology, featuring an informal round-table discussion in which UCLA pathologists covering a variety of roles discuss their daily research, education and clinical activities. The second event is an introduction to dermato pathology (in collaboration with the Dermatology Interest Group) – a field within pathology that appeals to many students.

During the year, microscope sessions supplement the medical school curriculum by providing interested students with the opportunity to go through the paces of a pathologist as they utilize the power of multi-head microscopes in small group sessions; these have become so popular they have to be repeated several times to accommodate all interested students, Dr Stark notes. Shadowing opportunities are also offered throughout the year, wherein students follow UCLA pathologists to get a better grasp of their daily activities. At the annual Pathology Research Fair, faculty present a brief overview of their studies and then students can approach them to learn more about specific projects and opportunities to join their research group.

Delila Pouldar, a second-year DGSOM student and one of the PathIG coordinators, says her interest in pathology was initially piqued during the histopathology coursework in her first year. "Being able to look at a biopsy under a microscope, help determine patients' diagnosis and thereby influence their entire treatment and prognosis was very exciting for me," she says. "It was through the Pathology Interest Group that this interest was further cultivated as I learned the diverse and indispensible role of pathology in whatever subspecialty I ultimately end up going into."

Dr. Stark, who teaches most of the curricular histology classes at DGSOM, says she has seen a tremendous difference in the enthusiasm and knowledge base of her students since PathIG was established. "They are much more motivated and have a better understanding of the big picture," she says. "The students who have attended PathIG events are able to connect what they are learning in the classroom with what they have seen or heard about from our pathologists, which has increased the excitement around our field." ▲

Dr. Stark with members of the Pathology Interest Group (left to right), Delila Pouldar, Elena Stark, MD, PhD, Sina Rabi, Kevin Terashima

PATHOLOGY PLAYS KEY ROLE AT THE OUTSET OF MEDICAL SCHOOL AT UCLA

BEGINNINGS ARE IMPORTANT – setting the tone for the time ahead. This is especially the case for students at the David Geffen School of Medicine at UCLA (DGSOM), whose journey begins with "Foundations of Medicine I," an eight-week integrated block in which Department of Pathology and Laboratory Medicine faculty are responsible for much of the teaching. Notwithstanding the department's Division of Anatomy, this active role at the outset is atypical of a traditional medical school curriculum, where pathology is generally taught in the second year. But for DGSOM's innovative curriculum, which aims to bridge basic science and clinical medicine from the start, pathology takes on a vital role.

Chandra Smart, MD and first year DGSOM Medical Students.

"Block 1" of the curriculum is tasked with covering foundational topics that are common to most organ systems, beginning with introducing basic principles of genetics. Interactive lab sessions use current molecular and cytogenetic diagnostic techniques and clinical situations to reinforce these basic principles. Week 2 addresses embryology and development as well as histology, which begins the year-long involvement of the Anatomy Division. The subsequent four weeks are largely devoted to core basic pathology concepts that underlie disease mechanisms in all organ systems – cell and tissue injury, inflammation and immune processes, and cancer.

Histopathology labs supplement lectures to help students learn to recognize basic pathologic processes histologically and associate basic principles with specific clinical situations, using skin disorders as examples. In the later weeks, gross anatomy begins with a focus on the peripheral and autonomic nervous systems, along with external anatomy features. The latter includes a unique exercise in which students perform skin biopsies on cadavers. These are processed for histology just like clinical biopsies, and are evaluated as unknowns by the students in a final histopathology lab to demonstrate the role of pathology in clinical diagnosis in a hands-on manner. Over the course of the block, students are also introduced to the immune and hematopoietic (blood) systems, during which students draw blood from each other and make "peripheral smear" slides to learn to recognize blood cells histologically. As part of their preparation, students observe expert phlebotomists from the department perform blood drawing on UCLA patients in the outpatient laboratory.

The deep engagement of the department's faculty and staff in this course introduces medical students from day one to pathology and laboratory medicine as being at the core of diagnostic medicine in a patient-centered health system. ▲

… (STUDENTS') JOURNEY BEGINS WITH "FOUNDATIONS OF MEDICINE I", AN EIGHT-WEEK INTEGRATED BLOCK IN WHICH DEPARTMENT OF PATHOLOGY AND LABORATORY MEDICINE FACULTY ARE RESPONSIBLE FOR MUCH OF THE TEACHING.

EXPLORE the David Geffen School of Medicine at UCLA at pathology.ucla.edu/education

NEW PROGRAM ENGAGES RESIDENTS IN DEPARTMENT'S QI EFFORTS

A NEW QUALITY IMPROVEMENT (QI) PROGRAM initiated by the UCLA Department of Pathology and Laboratory Medicine will provide all residents with important experiences participating in one of the department's QI projects as a leader or team member.

The Resident Education Quality Improvement Program, Pathology and Laboratory Medicine (REQIPP), scheduled to be implemented beginning in July, is an outgrowth of the department's QI program headed by Romney Humphries, PhD (see page 2). REQIPP will engage pathology residents and fellows in evaluating and developing QI programs within the department, according to Dawn Ward, MD, assistant professor in the department and director of REQIPP.

"REQIPP will help facilitate the department's QI priorities and identify new QI initiatives," Dr. Ward explains. "It will help us to meet Accreditation Council for Graduate Medical Education and American Board of Pathology milestones, as well as contributing to standardizing and improving outcomes for UCLA patients – all while giving invaluable experiences to our trainees."

REQIPP HAS FOUR COMPONENTS:

QI CURRICULUM. The curricular portion consists of a question-based learning program, along with periodic QI-focused lectures and mini-workshops to expose residents to the theory behind quality improvement.

QI PROJECTS. Residents will work with faculty and lab staff to either lead or participate as part of a team on projects that identify and measure process improvements. "Measuring a specific change is essential because it forces us to look at our systems in ways that allow us to develop ways to improve them, then test whether the interventions that are implemented lead to an improvement," Dr. Ward explains.

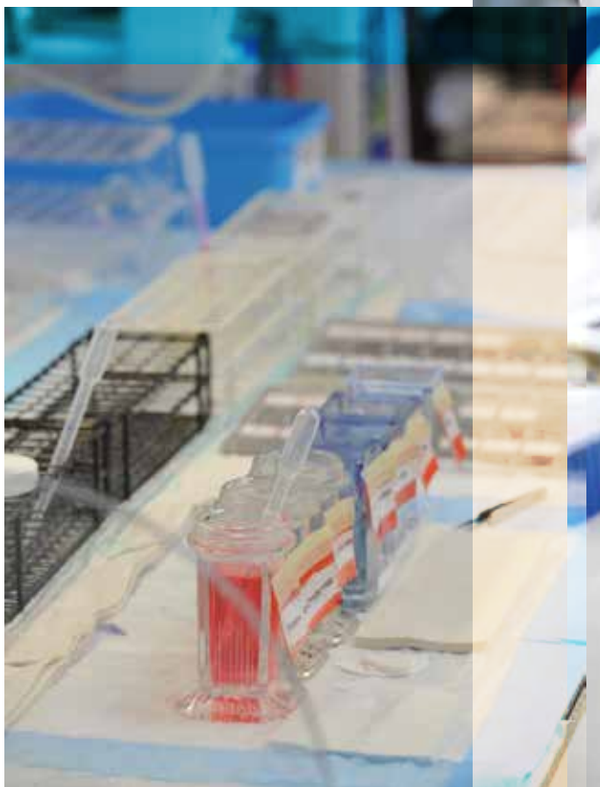
QI SCHOLARSHIP. Residents will have the opportunity to be acknowledged and rewarded for their work on projects by applying for awards through an existing UCLA house-staff scholarship program that is available to residents. Other opportunities will be identified through the department and professional societies.

QI LEADERSHIP. In addition to leading QI projects, residents will be encouraged to represent the department on multidisciplinary hospital-wide projects and to participate on the hospital's house staff QI council. Residents will also have the opportunity to submit articles on their projects to academic journals, as well as submitting abstracts and presenting posters at professional conferences.

"REQIPP this will contribute to improving care for UCLA patients," Dr. Ward says. "But beyond that, engaging our residents in the development and evaluation of quality improvement programs will bring more visibility to the department within the hospital and help to increase our participation in multidisciplinary QI projects that will be hospital-wide. For the residents, this will equip them with the tools they will need to help implement QI projects in their careers as they seek to continue to improve healthcare for patients." ▲

EXPLORE our Residency Program at pathology.ucla.edu/education/residencyprogram

Dawn Ward, MD



HELPING MD/PHD STUDENTS SUCCESSFULLY TRANSITION TO THEIR CLINICAL EXPERIENCES

Michael Teitell, MD, PhD

ONE OF THE MAJOR CHALLENGES for students matriculating through an MD/PhD program is going from medical student to doctoral student and back. "You spend two years with your medical school classmates, and then, as your peers are going on to the wards, you begin accumulating knowledge in the lab as you work toward your PhD," says Michael Teitell, MD, PhD, professor in the UCLA Department of Pathology and Laboratory Medicine. "After you defend your PhD thesis, you go back to the clinics, and it may have been four or five years since you were last exposed, full-time, to medicine. It's a different culture, you're with a different class, and you are suddenly preparing for residency. It can be a difficult transition."

As associate director of the UCLA-Caltech Medical Scientist Training Program (MSTP), Dr. Teitell's role is to help UCLA's MD/PhD students make a successful transition to their clinical experiences. He does so in part by meeting with students as they are in the final stages of their PhD program and providing consultation as they begin the process of returning to medical school. Dr. Teitell makes himself available for mentoring MSTP students who are uncertain about their path, or want to ensure that they follow the best possible course for their final two years of medical school so that they are well prepared for residency.

Dr. Teitell, along with MSTP leadership, has also worked closely with the medical school in pursuit of greater flexibility for when the MSTP students can return, to better accommodate those who finish early or need time after the start of the academic year to complete their PhD studies. In addition, a new clinical reintroduction course for MSTP students is designed to assist with the process of becoming re-acclimated to the wards through shadowing and mentoring.

> "WITH THE REMARKABLE ADVANCES WE'RE MAKING IN PERSONALIZED DIAGNOSTICS AND TARGETED MEDICINE, IT'S MORE IMPORTANT THAN EVER TO HAVE PEOPLE WHO ARE ACTIVE IN BOTH CLINICAL CARE AND RESEARCH,"
>
> – Michael Teitell, MD, PhD

Dr. Teitell is committed to supporting the MSTP mission of preparing exceptionally qualified young people for careers in academic medicine as physician-scientists. Last year, a National Institutes of Health advisory panel reported that the U.S. faces a looming shortage of practicing MD/PhDs. "With the remarkable advances we're making in personalized diagnostics and targeted medicine, it's more important than ever to have people who are active in both clinical care and research – and thus understand both the limits of care and how to go about breaking through those barriers," Dr. Teitell says. "We need to help students who are pursuing that type of career have the best possible educational experience." ▲

EXPLORE the Medical Scientist Training Program at mstp.healthsciences.ucla.edu

TRAINING THE LABORATORY STAFF OF THE FUTURE

"**Training resources** must be directed toward occupations that are in high demand by health employers, as opposed to simply targeting resources toward jobs that require minimal training and preparation."

As part of this recommendation, published in 2014 by the California Hospital Association based on a 2013 statewide hospital survey, clinical laboratory scientists were identified as a critical allied-health occupation. The California Hospital Association reported that among the hospitals responding to the survey, 40 percent of the clinical laboratory scientist workforce is over the age of 55. The report came as no a surprise to the UCLA Department of Pathology and Laboratory Medicine, which has long recognized that it would need to expand its existing laboratory-based Clinical Laboratory Scientist training program to offset its own aging laboratory workforce.

The department has a long history of providing training and educational programs for the next generation of leaders in pathology and clinical laboratory medicine. Although a well-established clinical laboratory scientist training program has been in place for many years, to bolster the existing program Clinical Laboratory Scientist limited-license training programs were developed, helping to fulfill staffing needs in specific areas of the laboratory.

THE DEPARTMENT HAS A LONG HISTORY OF PROVIDING TRAINING AND EDUCATIONAL PROGRAMS FOR THE NEXT GENERATION OF LEADERS IN PATHOLOGY AND CLINICAL LABORATORY MEDICINE.

The limited-license programs were created to help fill the void in the specialty clinical laboratory sections of cytogenetics, clinical genetic molecular biology, immunohematology and microbiology. While a licensed clinical laboratory scientist is able to perform testing in each of these specialty sections, the unique skills and additional training requirements to work in the area have made recruitment into the respective specialty fields difficult. The limited-license training programs offer an opportunity for those with an interest and educational background in the specialty field to become licensed. For a full year, one to two trainees in each specialty training program are provided the post-baccalaureate clinical experience required for licensure. The limited-license training program also offers a career-growth opportunity for non-licensed staff who are highly motivated to maintain their association with UCLA Health.

The department's commitment to delivering leading-edge education has also led to the establishment of a Pathology Assistant training program. In affiliation with Quinnipiac University's Master Degree Pathology Assistant program, the department provides clinical training in anatomical pathology for two students. Working "hand and eye" with pathologists, pathology assistants perform the necessary tissue examinations and provide the clinical data for pathologists to make a clinical diagnosis.

As was noted in the statewide survey, many programs that are supported solely by local hospitals make tremendous impacts on the lives of individuals, families, and communities. ▲

Above: Voicu Suciu, graduated from the Clinical Immunohematology Scientist program (Blood Bank Limited License program) in January.

Middle: PA's and PA Students: Carmen Giorgioni, PA (ASCP), Zhongyi Zhang, PA (ASCP), Tony Ruiz, PA (ASCP), Tyler Burdick, PA student, Quinnipiac University

Below: Clinical Microbiology Scientist (CMS) students, Mary Sladek and Stephanie Horiuchi.

IMMUNOHISTOCHEMISTRY, MOLECULAR TESTING CHANGE THE DIAGNOSTIC LANDSCAPE, IMPROVE OUTCOMES

When Michael C. Fishbein, MD, was getting started as a pathologist, the process of cancer diagnosis often involved a measure of guesswork.

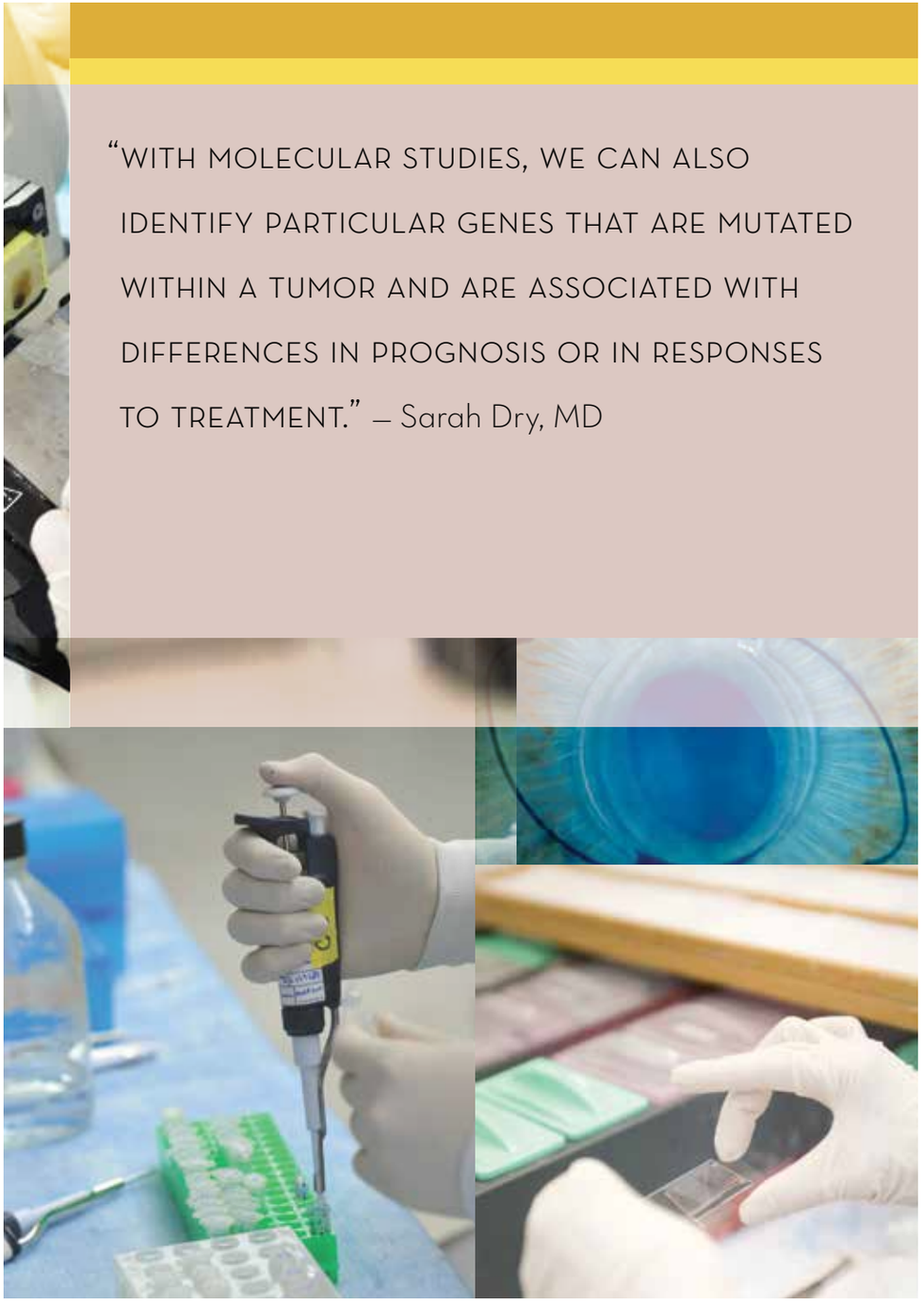
"We had electron microscopy and histochemistry – techniques that helped with some types of tumors, but not all," recalls Dr. Fishbein, a professor in the UCLA Department of Pathology and Laboratory Medicine. "Often, when you were stumped as a pathologist, you would show what you were analyzing to the oldest person in the department, he would make the diagnosis and you would say 'Wow, that was brilliant.' Of course, you had no way of knowing whether or not the diagnosis was correct."

Everything changed with the advent of immunohistochemistry (IHC), Dr. Fishbein says. First described in the late 1980s and brought into widespread use in the 1990s, the diagnostic technique, which uses antibodies that attach to particular proteins of interest within biological tissues, marked the first time pathologists could positively identify specific diseases in patients, such as a metastatic cancer from a specific organ or site. "It took the guesswork out of the process of characterizing tumors and saying where they came from," Dr. Fishbein says.

Sarah Dry, MD and Michael Fishbein, MD

IHC continues to be widely used, but in recent years there has been an explosion of new molecular tests that are changing the landscape once again. "Molecular testing, for both tissues and fluids, has redefined testing strategy and improved patient outcomes," says Sarah M. Dry, MD, professor in the department and director of the Center for Pathology Research Services.

Dr. Dry notes that as recently as 15-20 years ago, pathologists often couldn't distinguish between a lymphoma and a soft-tissue sarcoma – her area of focus. "Now these IHC stains enable us to identify, in many cases, the cell of origin – such as a B-cell lymphoma or a pre-B-cell lymphoma," she notes. "And with molecular studies, we can also identify particular genes that are mutated within a tumor and are associated with differences in prognosis or in responses to treatment – for example, BRAF mutations in melanomas. We've gone from this broader category of tumors to something much more specific, using far less tissue than we did 20 years ago." For many soft-tissue sarcoma cases, Dr. Dry says, she won't make



"WITH MOLECULAR STUDIES, WE CAN ALSO IDENTIFY PARTICULAR GENES THAT ARE MUTATED WITHIN A TUMOR AND ARE ASSOCIATED WITH DIFFERENCES IN PROGNOSIS OR IN RESPONSES TO TREATMENT." — Sarah Dry, MD

a final diagnosis without molecular studies because they have become so integral to the treatment strategy.

Testingforchromosomalabnormalities–typically through fluorescence in situ hybridization (FISH) performed on paraffin blocks by specialists in cytogenetics – now provides definitive diagnoses on even small-needle core biopsies. In soft-tissue sarcoma diagnosis, Dr. Dry says, FISH has largely replaced immunohistochemistry in terms of importance. For certain tumors, such as synovial sarcomas – characterized by a translocation involving chromosome 18 and chromosome X – demonstration of the translocation alone is enough to make a conclusive diagnosis and direct clinicians toward the appropriate treatment.

Indeed, by guiding treatment strategy, the more precise diagnoses resulting from the molecular tests are improving outcomes. In lung cancer, the leading cause of cancer death, molecular testing can identify certain mutations in tumors that point the way toward new targeted drugs that can be effective only when the mutation is present. Similarly, testing for genetic mutations – typically through sequencing by molecular pathologists – can guide treatment in colon cancer (see the article on page 27).

Genetic testing is helping to much more rapidly identify pathogens than prior methods of growing pathogens in culture in a microbiology lab, Dr. Dry adds. This allows for earlier targeted treatment and appropriate isolation – as well as reducing the costs associated with unnecessary isolation of patients who do not have certain pathogens, such as tuberculosis. Genetic testing is now also being used to identify and track outbreaks of highly resistant bacteria in healthcare settings. A case in point is the recent outbreak of carbapenem-resistant Enterobacteriaceae (CRE) linked to contaminated duodenoscopes that was identified at UCLA by bacterial sequencing when traditional epidemiological investigations failed.

Advances in immunology testing have also made a significant difference for transplant patients. Dr. Dry explains that research has led to the development of IHC antibodies used on tissue sections, as well as to the development of testing of blood for antibodies that become elevated – particularly in chronic rejection. "Ten years ago it was often very difficult to diagnose evolving chronic rejections," Dr. Fishbein says. "This has been an important advance in the management of these patients."

IHC has advanced significantly in the last two decades. "When we first started we basically had one general marker to diagnose carcinoma, one to diagnose melanoma, and one that we thought to be good for sarcomas," Dr. Dry says. "Now we have close to 200 antibodies in our IHC lab that we consider to be routine." However, a new era is underway. "Molecular tests are still used in a minority of cases," says Dr. Dry. "But as the research progresses we are going to see them used with increasing frequency." ▲

GROWTH IN MOLECULAR TESTING ENHANCES VALUE OF DEPARTMENT'S TRANSLATIONAL PATHOLOGY CORE LABORATORY TO RESEARCHERS

Kingshuk Das, MD

"WITH NEW AND EMERGING TECHNOLOGY WE ARE ABLE TO GENETICALLY ANALYZE EVEN MINUTE SPECIMENS IN A VERY NIMBLE AND SCALABLE WAY." – Kingshuk Das, MD

THE EXPONENTIAL GROWTH in molecular testing in recent years has enhanced the value of the Translational Pathology Core Laboratory (TPCL) as a research facility within the UCLA Department of Pathology and Laboratory Medicine.

"With microarray analysis, next-generation sequencing and other technologies, the sophistication of the testing available for specimens in the TPCL tissue bank has greatly increased, to the point that it is now a resource for genomic-scale testing of specimens for a wide range of patient-centered studies," says Kingshuk Das, MD, an associate director of the department's Molecular Diagnostics Laboratory, which conducts testing for the TPCL in its mission to support basic, translational and clinical researchers at UCLA through pathology-related services.

The molecular tests of archived specimens offered by the Molecular Diagnostics, Clinical Microarray, and Cytogenetics laboratories range from more targeted analysis by fluorescence in situ hybridization (FISH), a cytogenetic test that provides an up-close view of chromosomal abnormalities; to genome-wide analyses at low resolution such as microarray testing, or at high resolution at the single base level using next-generation sequencing, Dr. Das notes. "We can sequence single genes, panels of genes, or even the entire exome (all protein-coding regions of the genome), transcriptome (all messenger RNAs), or genome," he explains.

The power of the technology has increased to the point that for a typical test now used for lung cancer patients, in which 49 genes are sequenced at once – an arduous task for any lab as recently as five years ago, Dr. Das says – the Molecular Diagnostics Laboratory can run the entire test on 10 nanograms of DNA, which amounts to less than 1/10,000th the mass of a grain of table salt.

"With new and emerging technology we are able to genetically analyze even minute specimens in a very nimble and scalable way," Dr. Das says. "For instance, if a researcher is interested in screening patient specimens for a particular drug target, or is interested in discovering prognostic genetic signatures from a set of specimens, he or she can contact the TPCL and initiate a study, which has made this an invaluable resource." ▲

EXPLORE the Transitional Pathology Core Laboratory at pathology.ucla.edu/TPCL

EXPANDED LUNG CANCER TESTING PLATFORM PROVIDES MORE PRECISE DIAGNOSIS, GUIDING TREATMENT

DOCTORS AT UCLA are now able to better diagnose and treat patients with lung cancer thanks to innovations developed by the UCLA Department of Pathology and Laboratory Medicine. The UCLA Molecular Diagnostics Laboratory recently expanded its testing platform for lung cancer to include not only all clinically important molecular genetic tests, but also many more for clinical trials of newer lung cancer treatments currently in development.

The standard of care for pathologic analysis of lung cancer now includes genetic evaluation for mutations and abnormalities in genes coding for EGFR (epidermal growth factor receptor) and ALK (anaplastic lymphoma kinase) in advanced-stage lung adenocarcinoma, explains W. Dean Wallace, MD, chief of pulmonary pathology in the UCLA Department of Pathology. "At UCLA, the pathologists, oncologists and surgeons have worked together to develop new and state of the art genetic tests to more comprehensively evaluate lung cancer cases to improve cancer care for our patients by increasing their treatment options to target specific genetic changes in their tumors," Dr. Wallace says.

UCLA was one of the sites that participated in the nationwide multicenter Lung Cancer Mutation Consortium that developed a large panel of molecular tests, including those for EGFR, ALK, KRAS, NRAS, AKT1, PIK3CA, BRAF, HER2, MEK1, RET, MET and ROS1. "Any single mutation is relatively infrequent, but when all mutations were evaluated, a mutation was found in approximately 60 percent of patients enrolled in the consortium," Dr. Wallace notes. Some of these mutations are strongly associated with response to specific treatment, especially EGFR, ALK and ROS1. In patients with lung cancer who have one of these abnormalities, treatment can markedly shrink the tumor and prolong life. For other mutations, there are clinical trials that may benefit the patient, but the results are too preliminary to draw firm conclusions on the effectiveness of the treatments. "Nevertheless," Dr. Wallace says, "the ability to better evaluate and understand lung cancer from examining the genetic changes in the DNA of tumors holds the promise of better treatment options and outcomes for patients now and in the future." ▲

> "AT UCLA, THE PATHOLOGISTS, ONCOLOGISTS AND SURGEONS HAVE WORKED TOGETHER TO DEVELOP NEW AND STATE OF THE ART GENETIC TESTS TO MORE COMPREHENSIVELY EVALUATE LUNG CANCER CASES TO IMPROVE CANCER CARE FOR OUR PATIENTS BY INCREASING THEIR TREATMENT OPTIONS TO TARGET SPECIFIC GENETIC CHANGES IN THEIR TUMORS." — W. Dean Wallace, MD

W. Dean Wallace, MD

Hanlin Wang, MD, PhD

MOLECULAR TESTING EXPANDS ROLE OF PATHOLOGY IN COLORECTAL CANCER CASES

THE ADVENT OF MOLECULAR TESTING of patients diagnosed with colorectal cancer has ushered in the era of personalized medicine in the treatment of the third-leading cause of cancer death in the United States – and has greatly expanded the role of the pathologist, says Hanlin L. Wang, MD, PhD, professor and director of gastrointestinal pathology in the UCLA Department of Pathology and Laboratory Medicine.

> "WE ARE EXPERIENCING A PARADIGM SHIFT. IN THE PAST, PATHOLOGISTS SIMPLY TOLD THE CLINICIAN, 'THIS IS COLON CANCER.' BUT NOW WE KNOW THAT COLON CANCER ISN'T A SINGLE DISEASE THAT SHOULD ALWAYS BE TREATED THE SAME WAY." – Hanlin Wang, MD, PhD

Dr. Wang notes that at UCLA, pathologists are now doing much more than simply rendering a diagnosis for colorectal cancer patients. They are also serving as clinical consultants to gastroenterologists, colorectal surgeons, oncologists and medical geneticists – guiding appropriate treatment, prognostic assessment, and family counseling.

"We are experiencing a paradigm shift," says Dr. Wang. "In the past, pathologists simply told the clinician, 'This is colon cancer.' But now we know that colon cancer isn't a single disease that should always be treated the same way. We have targeted treatments, and we know that some patients respond better to some therapies than others. Through molecular testing we can provide that type of information in advance, as well as genetic information that can be very valuable for screening of the patient's family members."

Dr. Wang and his UCLA pathology colleagues now routinely perform two sets of tests to assist treating physicians in making therapeutic decisions for patients with colorectal cancer. The first, which is given to all colorectal cancer patients, tests for the expression of DNA mismatch repair proteins using immunohistochemistry. For selected patients, microsatellite instability by polymerase chain reaction is also performed. In addition to providing information used for patient prognosis, the tests can predict the effectiveness of treatment with 5-fluorouracil, a front-line colorectal cancer chemotherapy drug. The tests are additionally used to identify patients with Lynch syndrome, also known as hereditary non-polyposis colorectal cancer – an inherited disorder that increases the risk of colorectal cancer as well as other cancers. A positive test can point toward the need for earlier and more frequent screening of the patient's family members, Dr. Wang says.

For patients with metastatic colorectal cancer, UCLA pathologists perform molecular testing for KRAS gene mutations, as well as mutations of other genes in the same signaling pathway. Such testing helps to predict the effectiveness of therapies that target the epidermal growth factor receptor (EGFR), which can be effective, in conjunction with chemotherapy, for a subset of patients. "By knowing in advance which patients are likely to respond to the anti-EGFR therapy, we can help direct clinicians toward the best treatment for their patients," Dr. Wang explains, adding: "As we learn more about other molecular mechanisms involved in cancer it will continue to lead to new targeted therapies, and new molecular tests that pathologists can conduct for the benefit of patients and their families." ▲

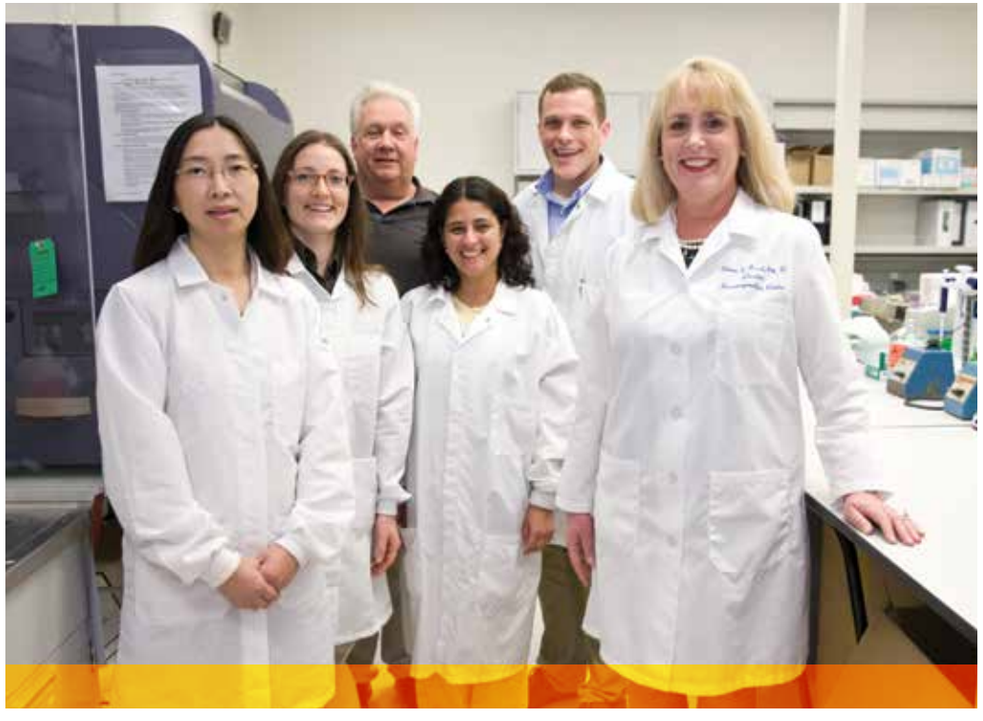
IAC BRIDGES RESEARCH AND CLINICAL CARE THROUGH EXPERTISE, CUTTING-EDGE TECHNOLOGIES FOR IMMUNE ASSESSMENT

The Immune Assessment Core (IAC), based in the Immunogenetics Center in the Department of Pathology and Laboratory Medicine, is a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory that bridges clinical and research spheres by providing expertise and cutting-edge technologies for immune assessment in the fields of transplantation, autoimmunity, hematopoiesis and beyond. "The IAC leverages the extensive experience of the Immunogenetics Center in assay development and standardization, and couples it with a savvy combination of multi-parameter analyses and systems biology approaches to obtain a comprehensive characterization of a patient's immune system at the genetic, phenotypic and functional levels," explains Dr. Elaine F. Reed, director of the center.

IAC scientists Dr. Maura Rossetti and Dr. Ping Rao work in close collaboration with UCLA professor of biostatistics and pathology Dr. David Gjertson and computational immunologist Dr. Alexander Hoffman to identify signatures across multiple immune-phenotyping and functional assays, toward the goal of understanding mechanisms of disease and ultimately improving patient outcomes. "Our multidisciplinary team believes the time has come for precision medicine whereby a simple blood test will not only provide critical information for the diagnosis of immune and inflammatory diseases, but will also inform the choice of immunotherapy for their prevention and treatment," Dr. Reed says.

Cytomegalovirus (CMV), the most common infectious pathogen encountered in solid organ and bone marrow transplantation, is a significant cause of morbidity and mortality in transplant patients because of the immunosuppressive therapy they receive to minimize graft rejection. The IAC is collaborating with Dr. Matthew Albert and his team at the Pasteur Institute in a multi-center effort to characterize the immune response to CMV in heart, lung and renal transplant recipients. Together, the collaborating research teams are performing longitudinal assessment of the immune response to CMV using a novel, standardized blood collection and antigen stimulation system called the TruCulture whole-blood collection system. Following CMV stimulation using the TruCulture system, CMV-specific immunity is determined using high-throughput genomic and multiparameter flow cytometry assays coupled with detailed clinical characterization. The main goal of this research is to achieve superior stratification for risk of CMV primary infection or reactivation, Dr. Reed explains. The effort also seeks to gain new insights into how CMV contributes to chronic allograft rejection and identify new approaches to patient management and therapy. "On a larger scale, we believe that the major deliverable of this project is the creation of a comprehensive database of highly annotated clinical, phenotypic and multidimensional -omics data on the immune response to CMV during vaccination, primary infection and reactivation – a unique resource to be mined to find answers to questions still to be asked in the field," Dr. Reed says.

The IAC is also identifying molecular and cellular biomarkers of advanced heart failure in collaboration with Dr. Mario Deng, director of the UCLA Heart Failure and Heart Transplant program. Heart failure is a leading cause of morbidity and mortality worldwide. Implantation of mechanical circulatory support devices may serve as an alternative therapy to heart transplantation. But this strategy is not effective in all patients, as some develop multi-organ system dysfunction (MOD), a serious side effect that can lead to a patient's death. IAC researchers discovered that non-invasive, multi-parameter immune-phenotyping of peripheral blood T cells sheds light into the mechanism of MOD and identifies patients at high risk of mortality. "We expect these discoveries will contribute to detection, prediction and improved treatment of heart failure across the disease spectrum," Dr. Reed says.



Left to right: Ping Rao, PhD, Maura Rossetti, PhD, David Gjertson, PhD, Diana Arango-Saenz, Nicholas Harre, Elaine F. Reed, PhD

Inflammatory bowel disease (IBD), a chronic and relapsing inflammatory condition of the gut, is intimately linked to the type and activity of gut-resident microbial communities. Intestinal microbes shape the reactivity

Continued on page 29

Continued from page 28

of human immune cells by releasing metabolites that dampen or enhance their activation. Because these metabolites are of microbial origin, they can be targets of intervention with potentially fewer side effects. The IAC is collaborating with Dr. Jonathan Braun, an expert in IBD and chair of the Department of Pathology and Laboratory Medicine, to identify and validate microbial metabolites driving aberrant T cell activation and disease. As an outgrowth of this work, IAC researchers expect that the identification of pathogenic metabolites will lead to the generation of new therapies focused on dietary intervention.

Finally, the IAC is at the forefront of the diagnosis of rare pediatric immunodeficiency diseases, including chronic granulomatous disease (CGD), common variable immunodeficiency (CVID), and others. "Timely diagnosis is critical to ensure that patients get immediate, life-saving treatment," Dr. Reed says. The IAC has implemented assays to probe the function of various immune-cell subsets involved in these diseases, including B cells, T cells and granulocytes. These assays are also fundamental for proper immune monitoring upon hematopoietic bone marrow transplantation, the optimal therapy currently available for most of these genetic diseases. "Because many of these assays are time-sensitive, it is critical to have a clinical lab offering this type of testing close to the clinic where patients receive care," Dr. Reed notes. "The IAC aims to become the center of reference for advanced clinical testing for immunodeficiency and beyond in Southern California." ▲

CLINICAL APPLICATION OF HLA GENOTYPING USING NEXT-GENERATION SEQUENCING – FROM BENCH TO BEDSIDE

OVER THE PAST YEAR, Dr. Jennifer Qiuheng Zhang, assistant professor of pathology and laboratory medicine and associate director of the UCLA Immunogenetics Center; and Dr. James Lan, a fellow in the laboratory director training program, have been busy transforming their first-of-its kind next-generation sequencing method for human leukocyte antigen (HLA) typing from the development phase to direct clinical application. Deciphering the genetic blueprint of the highly diverse HLA genes has broad medical implications, including donor-recipient matching in transplantation, prediction of certain autoimmune diseases, and "personalized" risk assessment of adverse drug reactions.

Since the early 1990s, several sequencing methods have been made available to study HLA genes, which are known for their critical immune-regulatory functions as well as marked sequence complexity. However, all of these traditional techniques have significant limitations in their throughput, typing resolution, and cost; consequently, these barriers have precluded widespread uptake and efficient utilization of HLA sequence information. In 2013, UCLA researchers applied next-generation DNA sequencing technology (NGS) – wherein millions to billions of DNA fragments are sequenced in unison – to elucidate the intricate structure of HLA genes. This initial effort was bolstered by key partnerships with the National Marrow Donor Program (NMDP) and collaborators from the private sector (One Lambda Inc., Canoga Park; Omixon Inc., Hungary). The end product of this enormous teamwork is a powerful and streamlined methodology "ready for prime time" in the clinical arena.

Left to right: James H. Lan, MD, Jennifer Qiuheng Zhang, PhD, David A. Nguyen, Yuxin Yin, PhD

To set the stage for clinical implementation, the center introduced several upgrades to its robotics and sequencing instruments. While NGS is recognized as an extremely powerful assay, the upstream work required to "prepare" DNA fragments into sequence-ready templates is exceptionally involved and time-consuming. To streamline this process and minimize the amount of hands-on time, the center has installed two automation robots. In addition, the center is fully equipped with three state-of-the-art sequencing instruments to meet the high-throughput demand of certain clinical applications.

As a pioneering laboratory of the NGS-HLA method, the center is the first in the world to report high-resolution, full-length gene data to the NMDP registry. Due to various technical limitations, classical sequencing methods analyze only certain HLA regions that are traditionally perceived as "clinically important," resulting in gaps in the curated reference sequences. However, new research examining other HLA territories increasingly supports the clinical relevance of interrogating additional gene-regulatory sites. The center has delivered comprehensive HLA information on unique cheek-swab specimens collected from more than 2,000 bone marrow donors. This important milestone has not only filled in many of the pre-existing reference sequence gaps, but also contributes to the discovery of novel variants and fundamental knowledge of HLA genetics. ▲

CENTER FOR PATHOLOGY RESEARCH SERVICES ASSISTS UCLA SCIENTISTS IN ACHIEVING GOALS

AMID RAPIDLY GROWING DEMAND within the UCLA scientific community, the Center for Pathology Research Services (CPRS) has grown significantly in the last year, according to Michelle Li, PhD, manager of research services for the Department of Pathology and Laboratory Medicine and for the center, which is directed by Dr. Sarah Dry.

The CPRS was established in 2013 to serve as a centralized resource for UCLA investigators seeking to access and utilize the extensive services offered by the department's clinical labs and core facilities. The need for such a resource is driven primarily by two trends, Dr. Li explains. One is the increased volume of research involving human subjects in recent years. "At any given time, UCLA has approximately 1,800 ongoing Institutional Research Board-approved studies, roughly 80 percent of which require pathology services," Dr. Li notes.

Beyond the growing volume, the research is increasingly complex, requiring the coordination and expertise of a resource such as CPRS. "With the advances in personalized medicine, studies often involve large sample sizes with parallel testing of multiple specimen types, including blood, tissue and other biospecimens," Dr. Li explains. "Therefore, research is typically conducted at multiple study sites, requiring services from a number of different clinical labs and core facilities in our department."

She points to advances in genomics as an example of the increased complexity. "In the past, we would look at one particular gene, but with next-generation sequencing technology, we can now look at thousands of genes at the same time using either blood or tissue samples – increasing the complexity of the studies as well as the demand for research services."

CPRS provides hands-on services and support at all stages of research, from study planning to the project's completion. That includes assistance with issues of project feasibility review; study set-up and coordination; cost analysis and budget development; providing pricing and billing governance; and ensuring regulatory compliance. The center also assists researchers in navigating through the extensive service menu offered by the Department of Pathology and Laboratory Medicine, and in transitioning to the ongoing changes in the healthcare information technology landscape at UCLA.

The most recent addition to CPRS is the Pathology Research Portal (PRP), which was established as a centralized processing and storage lab for bio-fluid samples. As with the other core facilities that are part of CPRS, the purpose is to support the UCLA research community. "This is not a cookie-cutter approach," says Dr. Li. "The services these facilities provide are highly customizable. We are here to support the UCLA research mission and help our researchers achieve their goals." ▲

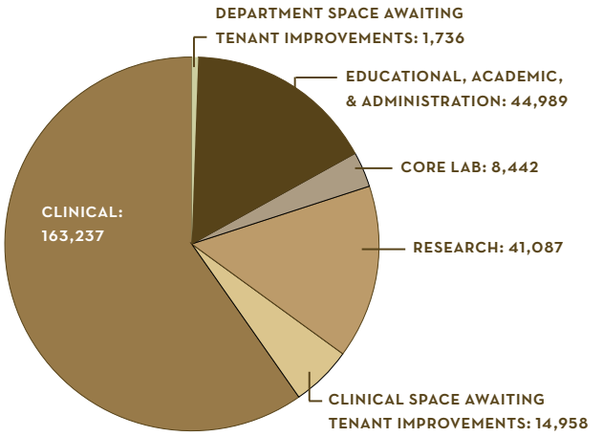
Above: Michelle Li, PhD, Manager of Pathology Research Services

Below: Pathology Research Portal Staff (left to right), Rufino Juta, Sydney Brown, Michelle Li, PhD, Amalia Reina, Josie Maria Goldchin

FACILITIES

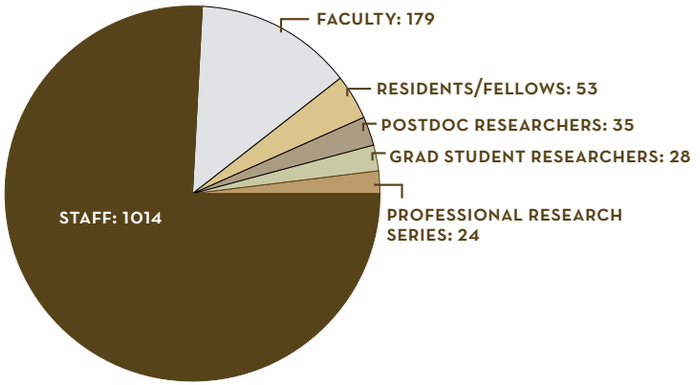
TOTAL SPACE IN SQUARE FEET = 257,755

Total number of square feet of Clinical, Research, and Teaching space



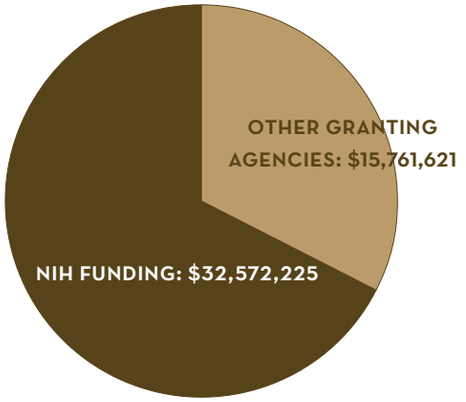
DEPARTMENT OF PATHOLOGY

TOTAL = 1333



RESEARCH FUNDING

TOTAL = $48,333,846



13 DEPARTMENT INVENTIONS IN 2014

32,268 SURGICAL PATHOLOGY CASES

463 EXOME (GENOMICS) CASES

5,860 MOLECULAR PATHOLOGY CASES

43,095 CYTOLOGY CASES

26,353 CYTOGENETICS CASES

360 MICROARRAY CASES

nearly 6 million CLINICAL LAB TESTS

GROWTH

OVERALL TEST VOLUME INCREASED IN 2014 BY MORE THAN 3% (APPROXIMATELY 200,000 TESTS ANNUALLY).

PATHOLOGY AND LABORATORY MEDICINE IN THE COMMUNITY

EBOLA PREPAREDNESS

Drs. Linda Baum, Romney Humphries and Omai Garner, with input from other faculty and staff from the UCLA Department of Pathology and Laboratory Medicine and in consultation with the ID/Infection Control and Disaster Planning teams, are coordinating the department's Clinical Laboratory Ebola preparedness effort.

An essential part of the effort is to teach and reinforce to all physicians and staff, especially in the emergency department, that no blood should be drawn on any suspected patient until the patient is in the isolation unit – a section of one of the medical ICUs that has been designated as such. Once the patient is in the isolation unit, there will be point-of-care (POC) testing only, in a defined alcove in the patient's room. No samples will be sent to any area of the UCLA Clinical Laboratories. The infectious disease clinicians have agreed to this limited POC testing, as this is in compliance with Centers for Disease Control and Prevention (CDC) guidelines.

POC testing will include blood gases, electrolytes, glucose, bilirubin, creatinine, PT, CBC, and malaria testing, because many Ebola patients in West Africa are also infected with malaria. There will be a portable laminar flow hood in the testing area and as much testing as possible will be done in the hood over a bleach soaked pad to absorb and neutralize any drips or spills. Instruments that do not fit in the hood will be on a cart adjacent to the hood.

Until UCLA receives an Ebola patient, the instruments will remain in the Ronald Reagan UCLA Medical Center Core Lab, where training, proficiency and competency testing, and instrument maintenance can be easily performed. The instruments will move to the isolation area in the ICU if a patient suspected of having Ebola is admitted. Once a patient is confirmed as being infected with Ebola, the instruments will not leave the patient's room, and daily quality control will be performed in the ICU area. Reagents will be stored in the ICU area. The only blood that will leave the patient isolation area will be two plastic tubes, packaged in that area, which will be picked up the Los Angeles County Department of Public Health (LADPH). One tube will be tested for Ebola by PCR at LADPH and one tube will be shipped by LADPH to the CDC for confirmatory PCR testing.

THE DEPARTMENT COLLABORATES WITH ID/INFECTION CONTROL TO COORDINATE THE CLINICAL LABORATORY EBOLA PREPAREDNESS EFFORT.

Nine Clinical Laboratory volunteers are learning all POC techniques and methodology, including instrument maintenance, and being trained in donning/doffing of special personal protective equipment, including Tyvek suits. If an Ebola patient is admitted at UCLA, these volunteers will be working in pairs in 12-hour shifts, with a supporting faculty member available throughout the shift to back up the clinical laboratory scientist staff.

MORE THAN 250 STUDENTS HAVE COMPLETED THE PROGRAM; 95 PERCENT HAVE GRADUATED FROM HIGH SCHOOL AND 87 PERCENT HAVE PURSUED SECONDARY EDUCATION.

PATHOLOGY DEPARTMENT TEAMS WITH SOCIAL JUSTICE LEARNING INSTITUTE TO ENHANCE OPPORTUNITIES FOR URBAN COMMUNITIES OF COLOR

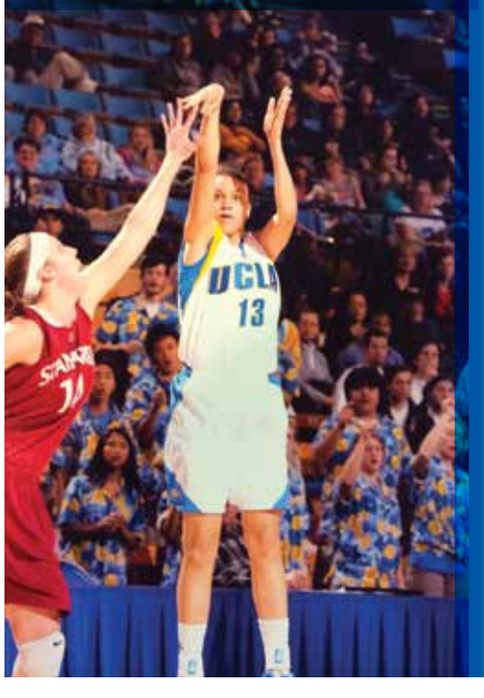
The Social Justice Learning Institute (SJLI), founded in 2008 by Omai Garner, PhD, and D'Artagnan Scorza, PhD, is a nonprofit organization dedicated to improving the education, health and well-being of youth and communities of color by empowering them to enact social change through research, training, and community mobilization. SJLI works with youth, residents, local schools, districts, and city officials to increase educational opportunities through innovative programs and sustainable practices focused on education, health, and environmental justice.

A critical component of SJLI is the Urban Scholars Program, which supports the personal and academic development of youth. This program is integrated into the academic curriculum at several California high schools. Its goals include helping youth gain and maintain a minimum grade-point average of 3.0, helping youth achieve a proficient score on the California Standards Test, assisting in applications for college and vocational training, and helping youth become leaders and change agents. More than 250 students have completed the SJLI-led Urban Scholars Program at seven different high schools in Southern California; 95 percent of these Urban Scholars students have graduated from high school and 87 percent have pursued secondary education.

In July of 2014, the UCLA Department of Pathology and Laboratory Medicine hosted students in the Urban Health Scholars Program. During the five-week program, 15 high school students came to UCLA over six days, hosted by faculty members Dr. Linda Baum and Dr. Omai Garner. One group of students spent time with Dr. Garner in the Clinical Microbiology Laboratory, learning the basics of microbial pathogenesis and touring the Brentwood lab. Another group spent time with faculty members Dr. Dawn Ward and Dr. Alyssa Ziman in the Donor Center, Component Processing, and Blood Bank areas of Transfusion Medicine, where they met donors, followed a unit from donation through processing, and learned the steps involved in blood typing and cross-matching. All students participated in a Career Day, where representatives of various allied health fields spoke with about the training required for different types of careers and the types of jobs available in these fields. Elsa Tsukuhara presented on career paths for phlebotomists, medical laboratory technologists and clinical laboratory scientists. The students were excited to learn about the different opportunities for a career in lab medicine – as one said, "I didn't even know these careers existed!" The pathology department and SJLI will continue to provide these types of educational opportunities.

SJLI is looking to expand and replicate its proven models of success, and to lead the state and national discourse on what is possible for all urban communities of color. For more information or to become involved, visit sjli.org.

PATHOLOGY AND LABORATORY MEDICINE IN THE COMMUNITY



PROMOTING THE WELFARE OF STUDENT-ATHLETES AS UCLA'S FACULTY ATHLETICS REPRESENTATIVE

As an undergraduate at UCLA in the 1980s, Dr. Michael Teitell held a paid position tutoring student-athletes. Through that experience, he realized the extraordinary demands many faced. "There's a misperception that they are somehow coddled, but my observation was that many are stressed and overworked, with extraordinary time demands," says Dr. Teitell. "They're trying to compete at the highest levels academically and athletically. They're spending hours on the practice field and doing other things related to their sport, while also being in the classroom with many exceptional UCLA students who can devote most or all of their time to studying. And something like 96 percent of student-athletes will never see a paycheck related to their sport – with a few exceptions, they depend on the education they receive here for their career success."

Today Dr. Teitell is a member of the UCLA faculty – a professor in the Department of Pathology and Laboratory Medicine, where he runs a busy research laboratory with multiple active grants from the National Institutes of Health and more than a dozen papers published in peer-reviewed journals in the last year. But he is also passionate about contributing to the campus community at the institution where he has spent most of his adult life. So in 2008, Dr. Teitell accepted an invitation to serve on the Intercollegiate Athletics Committee, which is designed to look after the welfare of student-athletes. And last year, he was appointed to serve as UCLA's faculty athletics representative – a National Collegiate Athletic Association (NCAA)-mandated position reporting directly to the chancellor.

Above: Erica Tukiainen, Third-Year student at UCLA DGSOM
Below: Erica Tukiainen as Captain UCLA Women's Basketball Team

> "IT WAS THROUGH THE UCLA ATHLETICS PROGRAM THAT I MET DR. TEITELL, WHO HELPED ME PREPARE FOR MEDICAL SCHOOL."
>
> — Erica Tukiainen, third-year student at UCLA DGSOM

The faculty athletics representative provides faculty input, guidance, and oversight of the athletics program, working with the athletic director and Department of Athletics leadership to ensure that the program maintains the high standards and reputation of the university and its academic programs. It's a varied role in which Dr. Teitell is involved in everything from mentoring or finding other experts to assist student-athletes, to representing UCLA in votes on initiatives coming out of the NCAA or Pac-12 conference.

Erica Tukiainen, now a third-year student at the David Geffen School of Medicine at UCLA, was among those who benefited from Dr. Teitell's role. "It was an honor to play all four years and serve as the captain on the UCLA women's basketball team," says Tukiainen, who majored in French while completing her pre-medical studies as a UCLA undergraduate. "It was through the UCLA athletics program that I met Dr. Teitell, who helped me to prepare for medical school. I am forever thankful for his guidance and mentorship that helped me to find my path to medicine."

Dr. Teitell notes that a sea change is under way in college athletics, with a host of legal actions and legislation that will give student-athletes a greater voice and more rights. In consultation with UCLA Chancellor Gene Block and the Department of Athletics leadership, Dr. Teitell will be representing the university in regional and national discussions on potential new policies. "Part of my role is to help figure out what's best for the student-athletes and at the same time what's best for the university," he says.

ASSISTING MOZAMBIQUE IN ESTABLISHING SAFE BLOOD SUPPLY, EVIDENCE-BASED TRANSFUSION PRACTICES

In Mozambique, one of the world's poorest countries, there are 10 million children under the age of 15 – but fewer than 50 pediatricians, and only two pediatric surgeons.

Alyssa Ziman, MD, associate professor and director of transfusion medicine for the UCLA Department of Pathology and Laboratory Medicine, is assisting Mozambique's Ministry of Health and medical community in addressing one of the country's serious public health concerns – the need to establish protocols for a safe, reliable blood supply and evidence-based blood-transfusion practices to decrease transfusion-associated infections.

Dr. Ziman's work is part of a larger initiative by Partners for Pediatric Progress, a collaborative effort among the Program in Global Health and Center for World Health of the David Geffen School of Medicine at UCLA to improve the health of children in some of the most resource-poor regions of the world, through focused training of the partner countries' healthcare professionals. Partners for Pediatric Progress established its first collaboration with Mozambique in 2008, and has worked closely with colleagues at the country's top medical school and teaching hospital in Maputo, the nation's capital, to address many concerns.

Two years ago, UCLA medical students conducting a study as part of the collaboration found that many children were being transfused inappropriately, mostly because of the lack of a reliable blood supply. "The surgeons and anesthesiologists wanted the pediatric patients to go into the operating room with a higher hemoglobin concentration than would otherwise be necessary because of their concern that if the child needed blood during the operation, it might not be available," Dr. Ziman explains. "The problem is the risks associated with transfusion. For example, the rate of HIV-positive units is about one in 1,000, which means a significant risk of transfusion-transmitted HIV."

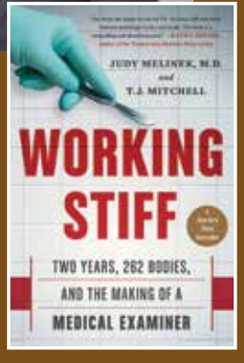
> MANY CHILDREN WERE BEING TRANSFUSED INAPPROPRIATELY, MOSTLY BECAUSE OF THE LACK OF RELIABLE BLOOD SUPPLY.

Dr. Ziman was recruited to assist. She initially went to Mozambique and met with the Ministry of Health to discuss how Partners for Pediatric Progress could best support the country's efforts. Several months later, the leader of Mozambique's national blood collection operations came to UCLA for a four-month fellowship to learn about UCLA's donor center and transfusion service before returning to open a blood collection center in Maputo. In addition, Dr. Ziman and her UCLA colleagues held a blood-banking seminar in Mozambique to educate physicians, and continue to assist efforts to promote transfusion medicine education and blood donation, and to train staff.

"These physicians are highly capable, but they have such limited resources and haven't had the experience or benefit of someone to share the knowledge with them about these practices," says Dr. Ziman. "By helping them to better understand the appropriate transfusion indications and risks associated with transfusion, along with how best to develop a blood collection program that both brings in donors and instills confidence, we can make a great impact."

Above: Alyssa Ziman, MD
Below: Dr. Olegario Muanantatha, Director, National Blood Reference Center, Mozambique

ALUMNI



Above: Alumnus, Dr. Judy Melinek, MD with husband and co-author, T. J. Mitchell.

ALUMNUS DR. JUDY MELINEK PENS BESTSELLER

Alumnus, Dr. Judy Melinek trained at UCLA in Pathology, graduating in 1996. She started her forensics fellowship at the New York City Office of the Chief Medical Examiner in July 2001, two months before the Sept. 11 attacks.Dr. Melinek wrote a *New York Times* best-selling memoir about her forensic training, co-authored by her husband T.J.Mitchell, entitled "Working Stiff: Two years, 262 Bodies &the Making of a Medical Examiner" (Scribner 2014). She currently works at the Alameda County Coroner's Office as a contract physician, and is an Associate Clinical Professor at the UCSF Depaertment of Pathology. She has qualified as an expert on forensic pathology, neuropathology and wound interpretation over 100 times in civil and criminal courts. She is also the CEO of a private medico-legal practice called Pathology Expert Inc.

ALUMNI UPDATE

The Clinical and Research Alumni groups have continued to expand our networks. We regularly communicate with alumni via a quarterly newsletter, which includes spotlight articles on featured clinical and research alumni, as well as through online mechanisms such as LinkedIn. We hope to be able to provide a directory of alumni contact information in the future. Possible upcoming activities this year include an alumni-resident picnic, and we look forward to continue engaging our alumni in 2015 and beyond.

KEEP IN TOUCH!

UCLA Pathology Alumni

Pathology Research Alumni

To learn more or subscribe to our newsletter, **EXPLORE** pathology.ucla.edu/alumni

AWARDS & RECOGNITION

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Fellow, of American Association for the Advancement of Science

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2015 Society for Cardiovascular Pathology Distinguished Achievement Award

Wanwisa Himakhun
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David Rimoin Award for Research Excellence in *Medical Genetics*

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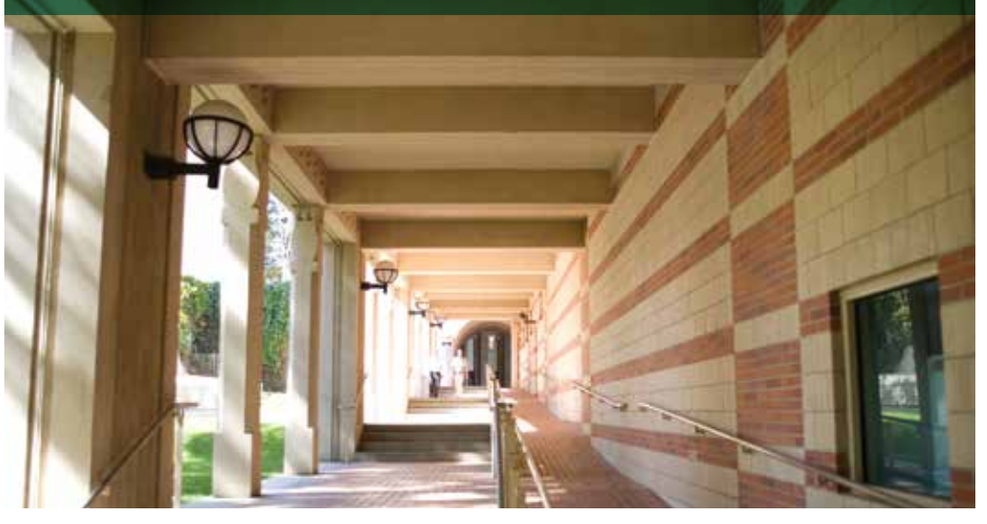
2014 Johnny Mercer Award for Brain Cancer Research



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OPPORTUNITIES FOR GIVING

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Teaching Awards:	**$100,000**
Summer Youth Trainee:	**$10,000**

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- Pathway Diagnostics
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- Advances in Transfusion Medicine
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- Controlling Inflammation-Mediated Atherosclerosis

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