On the cover: HeLa cells (pictured) belong to the oldest, most commonly used human cell line in medical research. Extraordinarily robust and prolific, these cells have been broadly used for research in cancer, HIV/AIDS, vaccine development, gene mapping and many other scientific efforts.

Image courtesy of Thomas Deerinck of the National Center for Microscopy Imaging and Research at UC San Diego

Medicine has always been personal.

That fact is evident in UC San Diego Health System’s vision to create a healthier world — one life at a time — through new science, new medicine and new cures.

But, as you will read in this year’s issue of Discoveries, advances in human genetics have helped redefine “personalized medicine,” reflecting a paradigm shift that will improve the delivery of effective, cost-efficient health care.

For example, the Institute for Genomic Medicine — a collaboration of the UCSD School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences — brings together diverse labs in an overarching pursuit of translating basic research into clinical care. Through the promise of “omics,” academic medicine is transforming all of medicine, and UC San Diego scientists and doctors, as described in the story “Ome Builders,” are at the forefront.

Personalized medicine is the aim of the newly created Center for Personalized Cancer Therapy at Moores Cancer Center. No two cancers are alike. The Center will match identified mutations or abnormalities in each patient’s genetic profile with specifically tailored therapies designed to produce the optimal benefit with the least adverse effect. This is the future of cancer care.

Recently, San Diego philanthropists Joan and Irwin Jacobs helped get us one step closer, donating $1 million to molecular profiling research. You can read more about the Center and its director, Dr. Razelle Kurzrock, in the story “Re-examining Cancer.”

In 2010, you might recall, the Jacobs pledged $75 million to build UC San Diego Jacobs Medical Center. Jacobs Medical Center physically embodies the future of personalized medicine. Comprised of three new hospitals — the Hospital for Cancer Care, the Hospital for Advanced Surgery and the Hospital for Women and Infants — it will allow us to provide leading-edge technologies, investigational therapies and minimally invasive surgical procedures for our patients. It’s scheduled to open in 2016.

Adjacent to the Jacobs Medical Center will be the Altman Clinical and Translational Research Institute (CTRI) building, recognizing leadership donors Lisa and Steve Altman. Also set to debut in 2016, the Altman CTRI will further accelerate UC San Diego Health Sciences’ efforts to deliver new drugs, technologies and procedures. As UC San Diego Chancellor Pradeep Khosla stated at the groundbreaking ceremony in January, “This building is going to be a bridge to our future.”

These state-of-the-art facilities will help us fulfill our vision and redefine medicine. In the following pages, you can read stories about how faculty and students of UC San Diego Health Sciences are redefining medicine as well — both in grand terms and personally — one life at a time.

Sincerely,
David A. Brenner

Vice Chancellor, Health Sciences and Dean, School of Medicine
University of California, San Diego
Open your eyes and uncountable photons stream into and through them, smacking against the retina — a postage-stamp-sized patch of light-sensitive cells at the back of each eye — where they are almost instantaneously converted into electrical impulses sent to the brain.

When everything is working, it’s a sight to behold.
IN DISEASES LIKE RETINITIS PIGMENTOSA AND AGE-RELATED MACULAR DEGENERATION, however, the retina’s photoreceptor cells — its critical rods and cones — degenerate and die. Light signals aren’t detected and vision is impaired, perhaps lost altogether.

For decades, researchers have labored to create an artificial retina that might restore sight. Though progress has been made, the technology is limited and comparatively crude, consisting of a tiny, eyeglass-mounted camera that beams data wirelessly to a watch battery-sized electronic array implanted inside the user’s eye. Electrodes in the array stimulate existing retinal cells, resulting in the brain “seeing” rough patterns of blacks, whites and grays. Resolution is insufficient for functional vision; it’s a shadow of the real thing.

A collaborative team of doctors, scientists and engineers from the Jacobs Retina Center and in the UCSD Departments of Bioengineering and Electrical Engineering are bundling together infinitesimally tiny optoelectronic nanowires, 50 to 100 per retinal cell. (These wires can be 0.2 to 5 micrometers in diameter and 1 to 50 micrometers in length. By comparison, the typical human cell is 10 micrometers wide.) Each nanowire can detect approximately 50 percent of passing photons and transmit that data directly to biological retinal neurons that have attached themselves to the artificial retina.

“We can easily fit thousands of these nanowires into an artificial retina, which means resolution is not an issue,” said William R. Freeman, MD, Distinguished Professor of Ophthalmology and director of the Jacobs Retina Center. “We can make more megapixels of visual information than the brain has ever seen or the retina could handle.”

Leaping beyond current micro-electronic technologies, researchers at the Jacobs Retina Center and in the UCSD Departments of Bioengineering and Electrical Engineering are bundling together infinitesimally tiny optoelectronic nanowires, 50 to 100 per retinal cell. (These wires can be 0.2 to 5 micrometers in diameter and 1 to 50 micrometers in length. By comparison, the typical human cell is 10 micrometers wide.) Each nanowire can detect approximately 50 percent of passing photons and transmit that data directly to biological retinal neurons that have attached themselves to the artificial retina.

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It’s not simply progress writ amazingly small, added Gabriel A. Silva, PhD, an associate professor of bioengineering and ophthalmology and project co-leader. At this scale, the physics and chemistry of the interface between the device and biology involves fundamental molecular interactions that do not occur at larger microscales, he said. Many current technical hurdles become irrelevant.

For example, because the nanowires require relatively little energy to function, Silva said much less heat is generated and external batteries may not be needed or, if required, could be small enough to be implanted alongside the eye and changed just once or twice a year. Every aspect of this nano-based retinal prosthesis is designed to help get it to the millions of Americans suffering from degenerative retinal disease faster. The surgical implantation techniques, for example, are minimally invasive and well-tested. The wires themselves are made of inert materials that do not provoke an immune response. “They don’t corrode. There’s nothing for enzymes to digest,” Freeman said.

“I think we’re 10 years away from the first clinical trials,” said Silva. “No single person or lab has the expertise to carry out this type of work on their own, but collectively, we can use our expertise. We’re all very close and we work together. It just makes things happen more quickly.”

Freeman said a nano-based artificial retina would be complementary to related biological research, such as exploratory efforts to rebuild retinas using stem cells. While that approach may one day yield meaningful results, Freeman said it’s easier and faster to engineer a device to meet specific needs than it is to manipulate live cells or develop drugs.

“Right now, we’re still doing animal studies, but things are moving pretty fast. I think we’ll be in clinical trials in five years with a first- or maybe a second-generation device.”

According to the American Macular Degeneration Foundation, age-related macular degeneration affects more than 10 million Americans. It’s the leading cause of blindness among people aged 55 and older.

“We can make more megapixels of visual information than the brain has ever seen or the retina could handle.”

William R. Freeman, MD, Distinguished Professor of Ophthalmology
Discoveries in medical science are rarely made overnight; rather, pieces of the puzzle fall into place over years, often decades, of research. Perhaps even more elusive is a discovery that fundamentally changes how medicine is practiced.

Change of Heart

Redefining the treatment of coronary heart disease

Photographs by David ATMoth
NEARLY 45 YEARS AGO, DANIEL STEINBERG, MD, PHD, CAME TO UC SAN DIEGO TO HEAD THE DIVISION OF METABOLIC DISEASE.

It was a fledgling university campus then, perched on the bluffs of La Jolla, overlooking the Pacific — and the UCSD School of Medicine had just been established.

“I had heard about San Diego from a colleague at the National Institutes of Health who had come back all aglow after a visit to this new university,” said Steinberg, now a Professor Emeritus of Medicine at UC San Diego. “I remember my first visit to my new lab in 1968. It was a nice, sunny day and the equipment consisted of an ashtray and a wastebasket.”

Despite modest beginnings, Steinberg and colleagues would become instrumental in changing how physicians look at coronary disease. But first would come an enormous battle to prove the hypothesis — that high cholesterol is a major contributing factor in the development of atherosclerosis and coronary heart disease.

THE CHOLESTEROL WARS

To some, it may be surprising that what today seems common sense — lowering blood LDL cholesterol to reduce the risk of coronary heart disease and stroke — would have once been so controversial. As early as 1961, the American Heart Association had accepted a causal relationship and recommended that people at high risk be advised to modify their diet and avoid heart attacks. However, few physicians were paying much attention, and in 1968, the war between scientists who claimed that elevated blood cholesterol caused heart disease, and those equally respected scientists who found the idea “untenable,” was in full engagement.

In 1979, Steinberg invited Joseph L. Witztum, MD, of Washington University in St. Louis to join the UCSD School of Medicine faculty. In coming years, Witztum would become internationally recognized for his work, in collaboration with Steinberg, on the role of oxidized LDL as a major contributing factor in atherosclerosis. But in 1979 — despite an ever-increasing number of epidemiological studies, experimental animal studies and additional interventional studies here and elsewhere around the country linking high cholesterol with heart disease — “there was still no ‘you-can’t-argue-with-this’ type of study, a blockbuster,” said Steinberg.

In 1984, with Steinberg heading the nationwide study of 3,800 men at 12 centers around the country funded by the National Institutes of Health, and Witztum leading the clinical trial unit here at UC San Diego, the pair was instrumental in launching the Coronary Primary Prevention Trial. This study — the first large randomized, double-blind study to show a statistically significant decrease in heart disease as a result of lowering cholesterol levels through drug therapy — would change how physicians treated the condition.

By 1985, while naysayers among scientists and cardiologists still existed, newspaper headlines read “Cholesterol: No more doubt about dangers.”

HOW LOW DO WE GO?

In his 2007 book, The Cholesterol Wars, Steinberg recalls, “This continuing controversy over the years made it very much an uphill battle to convince practitioners, including the cardiologists (perhaps especially the cardiologists) to pay attention to hypercholesterolemia. …Today, of course, aggressive treatment of the condition has become standard medical practice, largely due to statin drugs, which became available in the late ’80s.”

Witztum went on to make the seminal observation that oxidation of LDL renders it immunogenic, and he has played a key role in the recognition that immune mechanisms are an integral part of the process leading to atherosclerosis.

“In the 1980s, we also showed that oxidation of LDL converted it into a more dangerous form,” said Witztum. “Our work since then has been to understand how this happens. We don’t yet know how to prevent the process, but we have discovered that oxidized LDL is recognized by the body’s immune system as abnormal, so now we know that atherosclerosis is actually an inflammatory disease.”

In an important set of studies, Witztum and fellow UC San Diego cardiologist Sam Tsimikas, MD, have shown that oxidized phospholipids (oxidized fats found in oxidized LDL) are toxic and cause chronic inflammation in the artery. In 2005, Tsimikas published a seminal study in the New England Journal of Medicine, describing a novel blood test that could measure levels of oxidized phospholipids in the bloodstream, thus reflecting the amount of blockage in the coronary artery.

“We have identified antibodies that bind to oxidized LDL and can perhaps prevent it from being taken up by the macrophages — large white blood cells that play an important role in the body’s immune system,” said Witztum. “We theorize that such antibodies could be protective.” His lab is working to develop a vaccine approach that could inhibit atherosclerosis and has already succeeded in animal models. Though a human vaccine could be many years away, this is the hoped-for next important step in the treatment of heart disease.

Both Steinberg and Witztum consider the other to be a world leader in solving one of the Western world’s biggest health problems. They are proud of the work that has resulted from a nearly 20 percent decrease in the rate of heart attacks in the decades since their landmark Coronary Primary Prevention Trial. They both now believe that coronary heart disease could be further reduced by treating high cholesterol levels at a very young age — perhaps beginning in adolescence.

“The question now isn’t whether low blood cholesterol levels prevent heart attacks,” said Witztum. “The question for physicians is, how low do we go?”

Discoveries by Steinberg, Witztum and colleagues have changed how cardiologists treat patients at UC San Diego Sulpizio Cardiovascular Center and around the world.
Standing atop Mt. Kilimanjaro, Dr. Anna Kulidjian paused to marvel at the sprawling, gorgeous African plains below. Somewhere in the misty distance lay the Kenyan village of Chyulu Hills — the reason Kulidjian had climbed the world’s tallest free-standing mountain.

**An Ambulance Named Anna**

THOUGH SHE COULDN’T SEE IT, KULIDJIAN KNEW THE MAASAI VILLAGE WELL. Situated on protected land, the village is surrounded by national parks, abundant with forests, rivers and wildlife. What the residents of Chyulu Hills lack is medical care.

Kulidjian is trying to remedy that. An orthopedic surgeon at UC San Diego Health System, she is working with colleagues, organizations and donors to set up medical services in Chyulu Hills. The trek up the 20,000-foot Kilimanjaro, arranged in collaboration with the Maasai Wilderness Conservation Trust, was designed to raise money to buy an ambulance for the village.

“From donating medical equipment to raising money for an ambulance, our team has made it their professional and personal mission to organize health care projects around the world that help educate surgeons and improve patient care,” Kulidjian said.

In the case of Chyulu Hills, an ambulance was desperately needed to transport patients with life-threatening conditions and to reach remote areas not currently served by health care facilities.

“The village names all its vehicles as a reflection of gratitude,” said Kulidjian. “When the community health leader told me they named the ambulance ‘Anna,’ I was truly honored.”

“Anna” the ambulance has quickly proven its value, said Kulidjian. It was recently used to save the life of a mother and her premature baby who likely would not have survived without fast emergency transportation.

“Stories like that touch me deeply and give me the energy to continue our grass-roots efforts,” she said.

The ambulance is just part of the story, however. Kulidjian and her team have also successfully performed 24 hip replacement surgeries in Armenia — a landlocked, mountainous country in the South Caucasus region of Eurasia.

Joint replacement surgeries in Armenia have been plagued by high infection and dislocation rates. Kulidjian’s visiting team of surgeons and doctors worked around the clock for a week teaching the Armenian orthopedic surgeons new techniques and practices related to device placement, physical therapy, anesthesia and operating room safety for sterilization.

The result: Patients who thought they would never walk again are now fully mobile.

“I was born in Armenia, so this experience was very personal to me,” Kulidjian said. “It was challenging, both emotionally and physically, and I realized what a privilege it was to have been educated in the United States. The patients were calling us ‘angels from heaven,’ and I will never forget the meaning of that trip.”

ALWAYS MORE TO BE DONE

Kulidjian applies the lessons and professional skills learned through her humanitarian efforts overseas to her work at UC San Diego Health System. “These missions have given me more compassion for patients and have taught me how to be more resourceful and a stronger team player. They’ve also built up my confidence level when dealing with complex surgical problems,” she said.

She is currently working on a formal collaboration with UC San Diego Health System and the Maasai Wilderness Conservation Trust for an “Adopt a Village” program that will continue to bring education and medical care to underserved areas.

“Whether climbing Africa’s tallest mountain or holding the hand of an Armenian grandmother who is walking for the first time in years, I am always appreciative of everything around me and am hit with the reality that there is always more that can be done around our world,” Kulidjian said.
Ome Builders

UC San Diego researchers help science construct the big picture

In the beginning, it was the great unkome.

Then came the Human Genome Project (1990–2006), which famously employed the word “genome,” a term combining the words “gene” and “chromosome,” originally coined in 1920 to describe all of the genetic material in a sperm or an egg. In the Project, of course, “genome” also represented the complete genetic instructions for making a person. It would also be the start of something even larger: the age of omes.

At last count, there were more than 400 different fields of study containing either ome or omics in their name. These are endeavors to encapsulate all that is known about something within a single enterprise. In the life sciences, they range from metabolomics (all of the molecular players in metabolism — sugars, fats, nucleotides and amino acids, each of which has its own subset omes) to how molecules interact in a cell (interactomics) or neurons in the brain (connectomics).

And researchers at UC San Diego are asking a lot of those questions, often in new ways. The UCSD Institute for Genomic Medicine (IGM), for example, is a collaboration between the School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences. It brings together diverse labs in a singular pursuit of genetic and genomic research that can be translated into clinical care.

“The historic mode of biology was to look at one gene or one protein at a time, to study everything about it, to go very deep,” said Trey Ideker, PhD, a professor of medicine and chief of the Division of Medical Genetics, and professor of bioengineering in the Jacobs School of Engineering at UC San Diego. “The omics mode is complementary. You look at all 30,000 proteins or genes in a cell and see what they’re doing. It’s a new way to ask questions.”

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The UCSD Institute for Genomic Medicine (IGM), for example, is a collaboration between the School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences. It brings together diverse labs in a singular pursuit of genetic and genomic research that can be translated into clinical care.

“Our multidisciplinary teams integrate genomic, transcriptomic, proteomic, metabolomic and signaling approaches to understand and treat genetic contributions to human disease,” said Al La Spada, MD, PhD, professor of pediatrics and cellular and molecular medicine and associate director of the IGM.
Omics means doing science differently — at least some of the time. Christopher Glass, an IIM faculty member and professor of cellular and molecular medicine, recalls studying the regulation of gene expression one gene at a time through most of the 1990s. He still does that, but technological advances now allow him and colleagues to study large sets of genes in a single experiment and, more pointedly, to investigate the roles and functions of all RNA molecules — the so-called transcriptome.

Advanced technologies and the omics approach, Glass declared, “have had a transformative effect on the field of molecular biology.”

Likewise for LIPID MAPS — a multi-institutional initiative led by researchers at UC San Diego — to account for the thousands of fat species involved in virtually every metabolic function and interaction.

“LIPID MAPS was started in 2003 and funded for 10 years by the National Institute of General Medical Sciences to develop the subject of lipidomics,” said Director Edward A. Dennis, PhD, Distinguished Professor of Pharmacology, Chemistry and Biochemistry. “Starting from scratch, this whole field has developed in the last decade and has contributed to a fundamental change in how research on lipid metabolism and signaling is approached and understood. There are now lipidomics initiatives in many other countries, all over the world.”

AN EXPLOSION OF SCIENTIFIC DATA

The emergence of omics and omics reflects an unprecedented explosion of scientific data and the need to find ways to make sense of it — and use it. It is not, however, the end of the story. Beyond that big picture is an even larger one: How do these omics fit together?

“If omics allowed us to move from studying one gene at a time to studying all genes, the next question is how do these genes and their products interact and work together to produce the functions of biology,” said John Kelsoe, MD, a professor of psychiatry who studies the influence of genetic variation on drugs used to treat mental illnesses like bipolar disorder and schizophrenia. “This is the next step in comprehensive biology — and ‘systems biology’ is its name.”

Three years ago, the National Institutes of Health helped UC San Diego take that next step, funding creation of the National Resource for Network Biology (NRNB). Combining the expertise and data of numerous research centers on campus and elsewhere, the NRNB’s mission is to help clinicians analyze the wealth of complex biological data that exists and apply that knowledge to real problems and diseases.

“The emergence of omics is changing everything as people gather big datasets, not just cells in dishes, but patients in hospitals,” said Ideker, who is also the NRNB’s principal investigator. “But the big, end-all, isn’t just knowing a lot, it’s knowing how to help people.”

Rarely does the disease strike the young. However, in 2012, a 34-year-old mother arrived at UC San Diego Health System unable to speak, paralyzed on her right side and unconscious. On the National Institutes of Health Stroke Scale, her score was a grim 25; strokes scored over 15 are usually either severely disabling or fatal.

“The patient had fibromuscular dysplasia, a genetic disease that causes weakening or a tear in the wall of arteries that reach the brain,” said Alexander Khlessi, MD, director of endovascular neurosurgery at UC San Diego Health System. “The patient’s dominant carotid artery was torn and completely blocked — what we call a spiral dissection. In effect, her brain was being starved of blood and oxygen.”

Khlessi and his team opted to rebuild the artery through an endovascular approach, a minimally invasive procedure in which a catheter is inserted into the blood vessel. Normally, catheters and wires fed from an artery in the leg are used to cross the blockage and reconstruct the artery using a series of stents. This patient, however, required a more elaborate approach; her artery was so damaged that crossing the blockage from below was impossible.

“With a blocked artery, every second counts. Her life was in the balance, so we were forced into the unconventional,” said Khlessi. The surgeons placed a second catheter in the opposite carotid artery, guiding it through small connections between the arteries of the brain itself, and down the damaged left carotid to cross the damaged area from above — literally going over the top.

During the two-hour procedure, Khlessi successfully reconstructed the entire length of the left carotid artery using four telescoping stents. The gateway to the repair was the anterior communicating artery, a very tiny artery deep in the brain.

Within 24 hours, the patient was speaking. Today, she has fully recovered and returned to caring for her children.

CHANGING HOW SURGERY IS DONE

The Comprehensive Stroke Center at UC San Diego Health System is one of only a few locations in the country to offer complete surgical and neuro-critical care for complex stroke patients.

“Beyond the availability of novel devices that have revolutionized our ability to open arteries in the brain, recent studies demonstrate that restoration of blood flow is only one piece of the puzzle,” said Khlessi. “The benefits of having an entire team that rapidly makes the diagnosis with sophisticated imaging and gets the patient to the angiography suite quickly cannot be overstated.”

The Center for the Future of Surgery at the UCSD School of Medicine further allows Khlessi to direct physician training courses for surgical devices central to advancements in stroke care. Beyond serving as a national destination for pre-clinical and simulator training, the Center has become an important clearinghouse for new device development in the field.

“Working here goes beyond providing leading-edge care to our patients,” said Khlessi. “I value training the next generation of surgeons and changing the way surgery is done. From driving national conversations in health care delivery to developing new techniques and devices, we are given the opportunity — every day — to make medicine better.”
A Model of Compassion

UC San Diego Student-Run Free Clinics

They come from diverse places, with different stories and varying circumstances. But all who arrive here — at two churches and two elementary schools — come with the same, shared needs.

$157K

Amount students have pledged to date from future earnings to support the free clinics

Since 1997, the UC San Diego Student-Run Free Clinics have provided health, social and legal assistance to thousands of men, women and children unable to afford or obtain services through more traditional means.

“These are among society’s neediest,” says Ellen Beck, MD, clinical professor of family and preventive medicine at UC San Diego and clinic founder. “This is a clinic for patients who have fallen through the cracks, and who don’t have anywhere else to go.”

Although Beck and a team of School of Medicine faculty members act as advisors, the clinics are largely run by students from the UCSD School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences, with help from local doctors, dentists, legal advisors, social workers and interpreters — all of whom volunteer their time and expertise.

The clinics have been a marked success since the first clinic opened inside a church-based homeless shelter in Pacific Beach. Not just for the approximately 2,000 patients seen each year, treated for everything from poor nutrition or an aching tooth to diabetes, asthma and heart disease, but also for the future doctors and pharmacists who choose to serve the underserved.

“Outbound clinics are an opportunity to learn the mechanics of creating and operating a student-run free clinic. At last count, there were more than two dozen similar clinics in operation around the country. Closer to home, UCSD School of Medicine students have started a free clinic in Tijuana, Mexico, in collaboration with the medical school at Universidad Autonoma de Baja California. Farther away, Skaggs students are helping start a free clinic in Awka, Nigeria, partnering with Nnamdi Azikiwe University.

For participating medical students, the clinics are a chance to apply classroom teaching to real people and real-world situations. The rewards are psychic as well.

Mann, the second-year medical student, recalls treating two patients with serious health problems linked to excessive weight. He prescribed diet and exercise programs. “It was a fantastic collaborative experience,” said Tony Kuleto, a 34-year-old former Secret Service agent turned second-year medical student, “It’s a hands-on experience to work over the summer and during winter breaks even though they do not receive academic credit. These are moments they’ll remember long after graduation.”

The students have already launched a campaign to pledge part of their future earnings to help keep the clinics alive and well. So far, they’ve raised more than $157,000. That’s putting money where their heart is.

“More than anything else, my experience in the Free Clinic has really helped accelerate my skills as a physician. I ask more targeted questions, formulate hypotheses quicker and know how to better advocate for my patients now.”

Jeremy Egnatios
First-year medical student

Photographs by David Ahrnhoer
A Fertile Future

Like 15-year-olds everywhere, Christina Montana spends much of her day pondering things like the nature of boys, the latest trends in jeans, the anticipatory joys of having a driver’s license and who might ask her to prom.

Unlike her friends and classmates, though, Christina must often do her thinking from a chair in the infusion center at UC San Diego Moores Cancer Center, where she receives chemotherapy to battle Hodgkin’s lymphoma.

Though her big brown eyes and quick, stunning smile rarely reveal it, Christina’s year-long fight — she was diagnosed at 14 with the cancer of the lymph node system — has been difficult. “My family keeps me positive,” she said. “I miss school and the social interaction of learning, but I text my friends like a typical teenager.”

Nonetheless, the fight has made Christina mature beyond her years, most notably when she was confronted recently with news that her cancer had flared out of remission. “There was a 15 percent chance of recurrence,” said Christina’s father, Jesus Montana. “She’s now being treated more aggressively.”

The support of her family has helped Christina make some life-changing decisions that most girls her age never think about. Nationwide, only 30 to 40 percent of young patients newly diagnosed with cancer receive counseling on how cancer therapies might impact their future fertility and their ability to have children. Fewer than 10 percent of them undergo a fertility preservation procedure.

Christina has thought about these things — and she’s taken action.

“My family had many in-depth conversations about preserving my eggs when I was diagnosed,” she said. “I want to have children someday and decided I’d rather be safe than sorry.”

Working with Irene Su, MD, an assistant professor in the Department of Reproductive Medicine at UC San Diego Health System, Christina opted to bank eggs for future use. Su said it was a smart and brave decision.

“Christina absolutely amazes me,” Su said. “It was surprising how certain she was at her age to undergo all the injections and blood draws for egg banking. Her family’s openness to speak about fertility preservation is inspiring.”

Indeed, Su said Christina has energized the clinical and research teams to work even harder to find new and better ways to preserve fertility in young patients. Su noted that egg-freezing technologies have significantly improved in recent years and the process is no longer considered experimental.

That bodes well for Christina and others who look forward to having families of their own. “Since her cancer came back, we are relieved to know our daughter will have the option of having her own biological children,” said Jesus. “As parents, you want only the best for your children.”

Someday, Christina hopes to say the same.

For more information on the UC San Diego Fertility Preservation Program, go to http://cancer.ucsd.edu/coping/fertility or phone 858-822-2660.
Discoveries Magazine

For Men of a Certain Age, Prostate-Specific Antigen (PSA) Screening is Almost a Rite of Passage. It’s a simple blood test, easily done, but if PSA levels are deemed too high, the next step is frequently a biopsy — the actual plucking of tissue from the prostate, a walnut-sized gland located just below the bladder.

Prostate biopsies are not casually conducted. They can be painful and involve complications, but health experts have long argued that their potential benefit — an accurate assessment of the presence and scope of any cancer in the prostate — outweighs their risks and potential problems.

But what if the biopsy actually makes the cancer worse?

Michael Karin, PhD, Distinguished Professor of Pharmacology at UC San Diego School of Medicine, is one of biomedical science’s most-cited authors, notably for his pioneering research elucidating how inflammation can fuel the development and growth of tumors. Much of this work has involved explaining how chronic conditions like obesity generate immune responses that aid and abet cancer cell survival and growth. But Karin and colleagues have also gathered evidence indicating that inflammation also promotes the progression of prostate cancer to a more aggressive and incurable disease. Such inflammation could be initiated by a prostate biopsy.

“Our findings suggest that promoting inflammation of the cancerous tissue can hasten progression to metastatic disease, in which the cancer is spread to other parts of the body,” Karin said. “We have shown that the proteins produced by inflammatory cells are the ‘smoking gun’ behind prostate cancer metastasis.”

Karin and colleagues hope to soon launch clinical trials of a drug that ablates inflammatory B cells, improving prostate cancer therapy.

“Researchers need to work on developing non-invasive methods to monitor the presence and development of prostate cancer.”

Michael Karin, PhD

For more than 40 years, medical science has waged a steady, expensive war against cancer, with mixed results. The overall death rate from cancer is down — dropping approximately 1 percent a year since 1990. Still, almost 575,000 Americans die from the disease annually.

Cancer is, in fact, many diseases. It’s different in every patient. It defies easy explanation. To find answers, researchers must sometimes re-examine their data and assumptions, promote provocative positions or simply demand things be done differently.

Meet three such scientists: Michael Karin, Thomas Kipps and Razelle Kurzrock.
“CLL is a complex and confounding disease. If we untangle its secrets, we have clues to the secrets of many other cancers.”

Thomas Kipps, MD, PhD

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) IS A CANCER OF THE BLOOD AND BONE MARROW, characterized by the growth of abnormal white blood cells that ultimately crowd out healthy cells, wreaking havoc on the immune system. Patients weaken, increasing the chance they will develop severe or life-threatening complications.

Like all cancers, CLL is distinct. Nonetheless, says Thomas Kipps, MD, PhD, professor of medicine and deputy director of research at UC San Diego Moores Cancer Center, CLL might hold the key to understanding and treating many kinds of cancer, including solid tumors.

Kipps has spent almost three decades investigating and treating CLL. He is among the nation’s leading experts in the disease and serves as director of the multi-institutional CLL Research Consortium, based at UC San Diego.

“CLL is a complex and confounding disease,” said Kipps, “but its basic biology and nature make it the low-hanging fruit on the tree of cancer discovery. If we untangle its secrets, we have clues to the secrets of many other cancers.”

AN IMPORTANT CANCER MODEL

Several factors make CLL a pre-eminent cancer model.

First, it can be diagnosed easily and early, based on simple blood tests. That makes studying it comparatively uncomplicated. “Unlike solid tumor research, in which there’s often no easy access to the primary tumor except through surgery, we can focus direct, repeated and regular attention on CLL cells by just taking a blood sample,” Kipps said.

Second, CLL tends to grow slowly. Some patients lack symptoms for years, even decades. Initial treatment is often to simply watch and wait, which means researchers and doctors can focus on investigating fundamental, still unresolved questions: What caused the cancer? How does it progress? What changes, when and where? Why does the same cancer behave differently in different patients?

“The opportunity to do research is important,” said Kipps. “In acute leukemias and other cancers that typically act and kill quickly, there is little time to reflect upon the nature of the disease or study it. Your most pressing goal is to save the patient.”

Last, CLL appears to share many qualities with solid tumor cancers, such as sarcomas, carcinomas and lymphomas. “In fact, much of what we’ve learned about solid tumors in recent years derives from leukemia research.”

For example, Kipps and colleagues discovered in 2004 that microRNAs — short sequences of ribonucleic acid that turn on and off hundreds of different genes — play a major role in causing CLL. “No one had previously suspected microRNAs,” he said.

In 2010, Kipps followed up with colleagues David Cheresh, PhD, Sudarshan Anand, PhD, and others at UC San Diego Moores Cancer Center, identifying a microRNA that regulated blood vessel growth, which is essential to the development and spread of tumors.

Of course, a better understanding of CLL doesn’t eliminate the need for continued research into solid tumors and other cancers. “The war on cancer has many fronts,” Kipps said. But CLL presents an unrivaled path for progress — and perhaps an eventual victory.

IMAGINE THAT YOU TRIED TREATING PNEUMONIA WITH INSULIN, says Razelle Kurzrock, MD, the senior deputy director for clinical science at UC San Diego Moores Cancer Center.

“It wouldn’t work, and you might soon come to the conclusion that insulin was a bad drug, which it obviously isn’t. It’s a very effective treatment for diabetes. It’s just wrong for pneumonia.”

Something similar happens daily with the search for new cancer treatments. Every year, scores of compounds and molecules with suspected anti-cancer properties are tested in long, complex clinical trials — looking to narrow down candidates to the very few with the broadest therapeutic effect. It often doesn’t matter if benefits are marginal, at best.

In the process, Kurzrock said countless drug candidates that might significantly benefit a small subset of patients are ignored or discarded, perhaps lost forever. “Nowhere is that reality more obvious and painful than in the long fight against cancer.”

As scientists have painstakingly parsed its secrets, they have learned one lesson over and over: It’s never the same enemy. Mutations and causative factors vary by cancer type and patient, and a therapy that effectively receives a different treatment.

“Call PREDICT (Profile-Related Evidence Determining Individualized Cancer Therapy),” she said. “In 10 or 20 years, people will look back and wonder why we thought this was so novel.”

Targeted, personalized medicine

Before coming to Moores Cancer Center last year, Kurzrock developed a hugely successful Phase 1 clinical trials program at the University of Texas MD Anderson Cancer Center that emphasized targeted, personalized medicine.

Called PREDICT (Profile-Related Evidence Determining Individualized Cancer Therapy), the approach employs leading-edge molecular technologies to identify specific mutations in patients — Kurzrock calls them “actionable abnormalities” — and uses that information to match patients to the drugs and treatments most likely to work for them.

“The potential for greater efficacy is huge,” she said, “because we’ll know what works for different situations. We’ll understand the mechanisms involved, which means fewer adverse side effects.”

This brings us back to the way clinical trials are conducted. Instead of focusing on the drug, she says, trials need to focus on strategy, testing how to best combine diagnoses with drug combinations. “Every person, in effect, becomes his or her own trial.”

Kurzrock wants Moores Cancer Center to be at the forefront of this effort. She concedes there are a lot of hurdles, not least among them how to approve drugs if every patient effectively receives a different treatment. But she believes these challenges can be resolved and that they must be resolved.

“I think we’re almost set for a revolution in cancer care,” she said. “In 10 or 20 years, people will look back and wonder why we thought this was so novel.”
With good reason, the human brain is called the most complex object in the known universe. Aside from its billions of neurons and trillions of connections and the mind-bending notion that it’s an object seeking to comprehend itself, there’s the fact that the human brain almost never gives up its secrets easily.

Nowhere is that more painfully evident than in the cases of Alzheimer’s disease (AD) and autism, two distinctly different neurological disorders that share the confounding trait of being extraordinarily difficult to study — let alone diagnose or treat.

Alzheimer’s disease, for example, is nearly impossible to diagnose before symptoms appear late in life. By then, said Larry Goldstein, PhD, professor in the UCSD Departments of Cellular and Molecular Medicine and Neurosciences, abnormal or dying brain cells have accumulated years, even decades, of damage.

Autism, on the other hand, strikes early, but no less mysteriously. Toddlers who were on a seemingly normal course of development suddenly display neurological and behavioral symptoms of the disease, from diminished or lost communication skills to obsessive-compulsive behaviors.

To find a cure for these disorders — none currently exists for either — scientists must unravel what’s happening to an afflicted brain at the cellular and molecular level. Until quite recently, that’s been basically impossible.

“We’re dealing with the human brain. You can’t just do a biopsy on living patients,” said Goldstein, who also directs the UC San Diego Stem Cell Program and is scientific director of the Sanford Consortium for Regenerative Medicine, which is comprised of five San Diego-based research institutions. “Instead, researchers have had to work around, mimicking some aspects of the disease in non-neuronal human cells or by using limited animal models. Neither approach is really satisfactory.”

Last year, though, Goldstein and colleagues announced a potentially profound advance in AD research: They created stem cell-derived in vitro models of both hereditary and sporadic AD neurons.

“Creating highly purified and functional human Alzheimer’s neurons in a dish — this has never been done before,” Goldstein said. “These aren’t perfect models. They’re proof of concept. But now we know how to make them.”

More importantly, the stem cell-derived AD neurons present the possibility of not just examining their cellular biology, but using them to directly test new therapies. Currently, no drugs exist that can change the course of the disease.

“At the end of the day, we need to use cells like these to better understand Alzheimer’s and find drugs to treat it,” Goldstein said. “We need to do everything we can because the cost of this disease is just too heavy and horrible to contemplate. Without solutions, it will bankrupt us — emotionally and financially.”
Goldstein and colleagues created “Alzheimer’s in a dish” by extracting fibroblasts (a kind of skin cell) from patients with heritable familial AD and with sporadic AD — the latter of which is more common but its cause unknown. The fibroblasts were then reprogrammed into induced pluripotent stem cells (iPSCs) that could be differentiated into working neurons that display biochemical indicators of AD.

Alysson R. Muotri, PhD, assistant professor of pediatrics and cellular and molecular medicine, and colleagues did something similar in 2010 when they used iPSCs from patients with Rett syndrome to create the first functional human cellular model for studying the development of autism spectrum disorder.

“This work is important because it puts us in a translational mode,” Muotri said. “It helps expand and deepen our understanding of autism, from a behavioral disorder to a developmental brain disorder. We can now look for and test drugs and therapies and see what happens at a cellular and molecular level. We will learn what kind of drugs work in what types of autism. That’s something we’ve never been able to do before.”

Rett syndrome (RTT) is a neurological disorder in which affected children display normal development until the age of six to 18 months, after which physical and behavioral symptoms begin to emerge, from low muscle tone and progressive motor dysfunction to diminished or disappearing socialization abilities. It is one of the most aggressive forms of autism. RTT is caused by mutations to a gene that encodes for a protein implicated in other types of psychiatric disorders. Affected neurons have fewer synapses, reduced spine density and signaling defects. In other words, they don’t work very well.

In a preview of the possible, Muotri’s research showed how iPSCs might offer a future human treatment. He exposed his newly created human RTT-iPSCs to a protein growth factor called IGF-1, which has shown some beneficial effects in mouse models. The protein appeared to rescue some RTT-iPSCs, clearing away some neuronal defects, though researchers don’t yet understand exactly how it happens. IGF-1 is currently in clinical trials for patients with RTT.

“This suggests that the synaptic deficiencies of Rett syndrome, and likely other autism spectrum disorders, may not be permanent,” he said.

In other words, it might be possible to develop drugs that halt and reverse neuronal deficiencies in autism, Alzheimer’s and other degenerative neurological conditions. That achievement is a long way off, of course, but the creation of these induced, impaired neurons marks a big step in that direction.

About Alzheimer’s and Autism

More than 30 million people worldwide (almost 6 million in the U.S.) are afflicted with Alzheimer’s, a devastating degenerative disease that eats away at cognitive functions, such as memory. It’s harder to know how many people suffer from autism spectrum disorder, partly because it encompasses a wide range of conditions and partly because recordkeeping varies by country. In the United States, the Centers for Disease Control and Prevention estimates roughly 1 million American children have diagnosed autism spectrum disorder. The worldwide number, including diagnosed and undiagnosed, is likely in the tens of millions.
Being a teen with CF presents daily challenges that impact long-term survival. Suddenly faced with managing all aspects of their care, some rebel. They stop taking their medications, resist using their airway clearance devices and skip needed therapies.

“The timing creates a perfect storm”, said Kevin Shaw, MD, co-director of the Adult Cystic Fibrosis Clinic at UC San Diego Health System. “We see drastic changes in our patients’ health, especially among college students around the time of final exams.”

National data shows that teenage patients with CF undergo a dramatic drop in pulmonary function. This may not be the natural course of the disease, but instead, a function of being young and wanting to hang out with friends, rather than being a patient.

To reach this vulnerable population, UC San Diego Health System has launched a regional effort to improve the quality of care of CF patients who are transitioning into adulthood.

“GROWING UP
“Our goal is to proactively identify and track CF patients long before they leave pediatric care,” said Jessica Goggin, RN, a nurse at UC San Diego Health System. “Often, patients are advised to transition to an adult center but they fear doing so, sometimes waiting up to a year to seek care. We want to help these patients. It’s better to have a first-time visit in clinic rather than in the emergency department.”

Shaw and the CF team visit local pediatric hospitals to meet in advance with parents of young CF patients, after which the patients themselves are contacted to help set up a UC San Diego Health System appointment within 30 days of their pediatric care ending.
“One of the first things we ask them when we see a new patient is, ‘What do you know about cystic fibrosis?’” said Shaw. “Do you know why you take this medicine? Do you know what it does? We also talk about compliance and adherence.”

Shaw estimates that few of these young patients, even after years of treatment, understand why they have CF or what the disease is. “I’d say that nine out of 10 patients under the age of 18 cannot offer a definition of cystic fibrosis. They are just beginning to be old enough to understand the science of their disease, so education becomes a priority,” said Shaw.

The Adult Cystic Fibrosis Clinic at UC San Diego Health System was established in 1995. Since 2007, the number of patients has more than doubled. The clinic now sees more than 220 patients.

Shaw and his team hope to make use of a closed social media network or private teleconferencing with CF patients. “In the near future, we’d like to Skype with any patient for the initial intake instead of making a phone call,” said Shaw. “By seeing the patient and talking to them, we can get a health history and better interpret the state of the disease with visual clues as well as verbal information. If possible, we’d like to facilitate video calls in group settings to provide psycho-social support.”

While communication can be lifesaving, direct contact with other CF patients is risky. At one time, summer camps were a way for patients to connect, until it was learned that harmful bacteria was passed between patients. Social media now serves as a virtual camp for patients. “On Facebook, we call each other cysters and fibros,” said Ashley. “We talk every day. The website helps me to meet others my age. If I’m on a new med, I post about it and ask about side effects. People look for solutions with insurance carriers. It’s good for moms, too.”

Shaw and his team hope to make use of a closed social media network or private teleconferencing with CF patients. “With CF, you can actually see progress each year in the history of the disease. Fifteen years ago, life expectancy was in the late 20s. Now, a patient’s life expectancy, on average, is close to 40,” said Goggin. “There is progress in seeing these tangible improvements. With CF, we see it in the numbers.”

“Right now, our oldest patient in clinic is 68 years old,” said Shaw. “I do believe we will see patients in their 70s and 80s. With the right funding, research and clinical care, it will happen.”

Facts
Cystic fibrosis is an inherited chronic disease that affects the lungs and digestive system of about 70,000 children and adults worldwide. A defective gene and its protein product cause the body to produce unusually thick, sticky mucus that clogs the lungs and leads to life-threatening lung infections. It also obstructs the pancreas and stops natural enzymes from helping the body break down food and absorb nutrients.

Most patients with CF are diagnosed before the age of two. Due to frequent hospital visits, surgical interventions and massive amounts of prescriptions, kids with CF often self-identify as a patient first, before thinking of themselves as a boy or girl, son or daughter.
The new Altman Clinical and Translational Research Institute (CTRI) building officially broke ground in January. Slated to open in 2016 and named for San Diego philanthropists Steve and Lisa Altman, the building will create a unique, multidisciplinary environment that brings together laboratory scientists and clinical investigators to better understand disease, develop new methods of treatment and translate clinical research results into clinical practice.

Gary S. Firestein, MD, professor of medicine, dean and associate vice chancellor of Translational Medicine at UC San Diego Health Sciences, is CTRI director.

In December 2012, UC San Diego Medical Center was named one of the first five facilities in the country, and the first center in San Diego County, to be certified as a Comprehensive Stroke Center. This is the newest level of certification for advanced stroke care awarded by The Joint Commission, recognizing the significant differences in resources, staff and training that are necessary for the treatment of complex stroke cases.

In March 2013, the National Comprehensive Cancer Network (NCCN) announced the election of UC San Diego Moores Cancer Center as the first and only San Diego-based NCCN Member Institution, joining 22 Member institutions across the country dedicated to improving the quality, effectiveness and efficiency of care provided to patients with cancer.

Napoleone Ferrara, MD, PhD, the molecular biologist credited with helping decipher how tumors grow, and with development of new treatments for both cancer and age-related macular degeneration, was named recipient of The Economist magazine’s 2012 Innovation Award for bioscience. Ferrara joined the UCSD School of Medicine in December as a professor of pathology and senior deputy director for basic science at UC San Diego Moores Cancer Center. In February, Ferrara was also named one of 11 recipients of the inaugural Breakthrough Prize in Life Sciences, which comes with a $3 million cash award.

Maike Sander, MD, professor of pediatrics and cellular and molecular medicine, was named director of UC San Diego’s Pediatric Diabetes Research Center (PDRC), which brings together top-ranked physicians and research scientists to investigate the causes of, and help find a cure for, type 1 diabetes. Sander has served with the PDRC since its inception in 2008.

UC San Diego Health System is collaborating with Qualcomm Life, a wholly owned subsidiary of Qualcomm Technologies, Inc., to pilot the 2net Platform and Hub for remote patient monitoring. Qualcomm Life’s innovative 2net technology collects patients’ clinical information from wireless medical devices and transmits it to UC San Diego Health System physicians, to supplement information already available. This system provides a rapid, automated way to collect patient data in near real-time, analyze the readings and suggest follow-up actions with the patient, if needed.

“The Altman CTRI is a building that is going to be a bridge to our future; where we are going to define new cures, where we are going to define how medicine should be practiced.”

Pradeep K. Khosla
UC San Diego Chancellor
UC San Diego Health Sciences comprises one of the nation’s top research-intensive schools of medicine; the Skaggs School of Pharmacy and Pharmaceutical Sciences; and UC San Diego Health System, the region’s only academic health system.