CityofHope® CityofHope® VOL. 31 NO. 1 SPRING 2020

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CITY OF HOPE RESPONDENCE

The Road Ahead

City of Hope Scientists Look Toward the Future

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VOL. 31 NO. 1 | SPRING 2020



Facing a formidable foe





THE ROAD AHEAD *10*

City of Hope scientists offer predictions.





Peerless surgeons wield the latest techniques.



City of Hope is transforming the future of health. Every day we turn science into practical benefit. We turn hope into reality. We accomplish this through exquisite care, innovative research and vital education focused on eliminating cancer and diabetes. © 2012 City of Hope

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LEADERSHIP MESSAGE

A NEW VISION

Dear Friends,

City of Hope has always served as a haven of healing and hope for people suffering from life-threatening illness. Today, even as we navigate the COVID-19 pandemic, our vision remains the same: to bring tomorrow's discoveries to the people who need them today.

As one of the world's leading cancer centers, City of Hope has a long history of caring for people who are the most vulnerable. Immunocompromised cancer patients are particularly susceptible to infection, and we are one of the best-equipped organizations to help them through the current crisis due to our deep expertise in research, prevention and treatment of infectious disease.

In this issue of City News, you will find advice and perspective from leading City of Hope experts on COVID-19 and cancer, news on City of Hope affiliate TGen's rapid-response COVID-19 testing kit, and remarkable stories about the next generation of cancer care and discovery.

Conventional wisdom holds that character is formed in a crisis such as the COVID-19 pandemic. I disagree. Instead, I believe that situations like this allow the true character of organizations and individuals to be revealed, and I could not be more proud of how our organization, our people and the patients we serve have risen to the occasion. Hope is in our organization's DNA.

Since our very beginning over 100 years ago, we have combined the best science has to offer with the comforting power of human compassion. That focus, and the courage and resolve it inspires in patients, caregivers and staff, sets us apart.

As always, thank you for your commitment and support. You have made possible everything you will read in the coming pages.

ROBERT STONE *President and Chief Executive Officer City of Hope*

NEWHOLE

NEW FACES · ADVANCING SCIENCE · BEGINNINGS

Eileen P. Smith, M.D.

Eileen P. Smith, M.D., assumed the role of the Francis & Kathleen McNamara Distinguished Chair in Hematology and Hematopoietic Cell Transplantation at City of Hope late last year. She is also a clinical professor and associate director of the Clinical Research Program. In addition, Smith is medical director of the City of Hope Alpha Stem Cell Clinic.

Smith's focus on improving the transplantation process, coupled with her devotion to compassionate patient care, are what made her the ideal candidate to lead City of Hope's renowned Department of Hematology & Hematopoietic Cell Transplantation. Replacing former chair Stephen Forman, M.D., after 32 years, Smith is the first woman to lead the department.

"My first reaction was it was just too overwhelming to even consider," Smith said. "I'm grateful I've had the opportunity to work at City of Hope with Dr. Forman and grateful that he had confidence and faith in me to lead the department." Smith began at City of Hope in 1988 as a fellow in medical oncology and bone marrow transplantation.

"The core vision is to carry on the legacy of excellence and innovation and caring for patients with hematologic cancers and other life-threatening diseases and to also make sure we honor the legacy that led us to this place," Smith added. "We're growing and will need to make changes, but the vision is to never lose track of core values, which is all about putting patients first."

Smith received her medical degree from University of Southern California, where she also did a fellowship in hematology. She served in the National Health Service Corps and is active in PRIM&R: Public Responsibility in Medicine & Research.

Stanley Hamilton, M.D.

Stanley R. Hamilton, M.D., joined City of Hope as chair of the Department of Pathology from Houston's MD Anderson Cancer Center in February 2020. He brings more than four decades of expertise to City of Hope in his new role.

"We've been looking at glass slides for hundreds of years," Hamilton said of the practice of pathology, "but in the last 30 to 40 years the whole field has changed completely." It's a change driven by the digital revolution, the sequencing of the human genome and the explosion of precision medicine: molecular and DNA-based tumor analysis. Pathology is "now a major contributor to driving therapy," he said.

> Having helped transform MD Anderson's pathology department over the last two decades, Hamilton means to do it again at City of Hope, where the process is already underway.

He hopes to advance and extend the digital transformation now taking place, bringing access to state-of-the-art pathology to every patient at every City of Hope community practice site, as well as improving and enhancing the biomarker data used in clinical trials, and further integrating digital pathology into the overall informatics of the institution.

"Pathology is central to achieving success in many of our strategic priorities," said Michael Caligiuri, M.D., president of City of Hope National Medical Center and the Deana and Steve Campbell Physician-in-Chief Distinguished Chair, "including precision medicine, cellular therapy, biomarker discovery and clinical research. Dr. Hamilton's strength as a clinician, researcher and collaborator will be critical as we continue our pursuit to sequence every cancer patient here at City of Hope in order to best understand and treat their disease."

• CUTYBUZZ



Arthur Riggs, Ph.D., is joined by longtime colleague and collaborator Keiichi Itakura, Ph.D., at the unveiling of the insulin molecule sculpture.

Riggs Honored at Symposium

Arthur Riggs, Ph.D., the Samuel Rahbar Chair in Diabetes & Drug Discovery, was honored for his 50 years at City of Hope at the Arthur Riggs Symposium held on Aug. 27, 2019. A sculpture of the 3D structure of the insulin molecule was unveiled that will permanently reside in the Anthony F. Markel Family City of Hope Museum.





Hope Floats

"The Power of Hope" was the theme of City of Hope's Rose Parade float this year, an ambitious display that took home the "Past President Award" from the Tournament of Roses judges for "most outstanding innovation in the use of floral and non-floral materials."

Seven City of Hope patients rode on this year's float: Kaysen Camat-Toki, Jeff Carpenter, Ivan Garcia-Burgos, Annie Tighe, Cierra Danielle Jackson, Donna McNutt and Leif Voeltz.





Staples

FOR

Celebrities, survivors, superheroes, supporters and slobbery pups were among this year's Walk for Hope participants.

Walk for Hope

Thousands of survivors and supporters converged on the Duarte, California, campus on Sunday, Nov. 3, 2019, for the 23rd annual Walk for Hope. The 2K/5K walk raises funds to step up cures for women's cancers. Last year's event was the most successful Walk for Hope since it began, raising more than \$1.5 million.



Nurse Denise Ramos gives patient Steve Finley an infusion at the Judy & Bernard Briskin Center for Clinical Research.

COVID-19 and Cancer Patients

BY SAMANTHA BONAR AND ABE ROSENBERG

ike other medical centers in the region and across the country, City of Hope has never faced a challenge like the COVID-19 global pandemic. With their immune systems compromised due to the cancer itself and treatments such as chemotherapy and stem cell transplant, cancer patients are particularly vulnerable to infection. As a center specializing in cancer treatment, however, City of Hope has decades of experience in studying, preventing and treating infectious disease.

Some cancer patients are at particularly high risk. According to Sanjeet Singh Dadwal, M.D., chief of City of Hope's Division of Infectious Diseases, "The risk is likely to be higher in patients with hematologic malignancies such as acute and chronic leukemias, lymphoma and multiple myeloma, and those who have undergone bone marrow transplantation, especially those who have chronic graftversus-host disease that requires treatment to suppress the immune system. Patients undergoing active treatment (chemotherapy, radiation or surgery) are also likely to be at high risk for complications from this infection."

City of Hope has strict and evolving protocols in place to protect patients, family members and staff, including screening patients for illness and recent travel out of the country, as well as travel limitations and mandatory quarantine rules for staff. The institution has developed detailed guidelines for diagnosing and treating its most vulnerable patients — those with hematological malignancies and those who have received bone marrow transplants (BMT). (The institution banned all visitors on March 25 to protect patients and staff.)

In addition, City of Hope scientists are working around-the-clock on their own version of a COVID-19 vaccine, while City of Hope's affiliate Translational Genomics Research Institute has developed a rapid-response test.

HOW COVID-19 AFFECTS CANCER PATIENTS

"We are still learning how this virus may

impact those getting infected with it who have cancer. So far, data from China suggests that patients with cancer have the highest risk of complications," said Dadwal, who specializes in treating cancer patients who develop infections. "This includes events such as admission to the ICU, need for ventilator support and poor outcomes. The risk is higher in patients with more than one chronic medical condition."

"Patients who are undergoing active treatment for cancer are presumably at higher risk than those who are in remission," Dadwal added. "Patients who are in the first year after stem cell transplantation or CAR T cell therapy could be at higher risk for complications if they get infected with COVID-19. Those who are beyond one year after BMT and are still considered to be immunocompromised may remain at an elevated risk for complications."

This makes prevention key for cancer patients, survivors and their caregivers and family members, he said. Patients should not panic, however. "It is most likely that this virus will be circulating in the community for some time, increasing the likelihood of acquisition," Dadwal said. "However, by employing frequent hand hygiene, environmental disinfection, social distancing (including of family members if they are ill) and avoidance of travel and crowded places, you can minimize the chances of contracting COVID-19."

RACING TO DEVELOP A VACCINE

Alarm bells went off early for Don J. Diamond, Ph.D., professor in the Department of Hematology & Hematopoietic Cell Transplantation. A 31-year City of Hope veteran specializing in infectious diseases, Diamond has developed numerous vaccines to combat everything from breast cancer to birth defects to cytomegalovirus, which can be lethal in BMT patients.

Diamond tasked Assistant Research Professor Felix Wussow, Ph.D., to formulate a plan of action to take on the novel coronavirus, which came together quickly after examining the virus's genetic sequence. "In a very short period of time he developed a highly sophisticated and incredibly meticulous strategy for a vaccine," said Diamond.

First, leveraging the DNA information and commercially available technology, researchers are synthesizing key components of the coronavirus ("Not the virus itself," emphasized Diamond) to build a complex, inert virus capable of making proteins that will teach the body's immune system to fight off COVID-19. To deliver this anti-COVID-19 weapon, scientists are grafting it onto a new version of a proprietary platform developed at City of Hope.

"We think our delivery system is very powerful," he emphasized.

Diamond hopes to begin phase 1 clinical trials in fall 2020. He expects the full process to take "18 months minimum," much like the timeline for other COVID-19 vaccine projects now going on. It's likely the Food and Drug Administration will grant compassionate-use status to any effective vaccine, bypassing the multiyear phase 3 step. "This is normal when the disease is dire enough," he said.

In the meantime, City of Hope researchers are pursuing their goal nonstop, putting in 12-hour days, seven days a week. They sense a double urgency to their work. Aside from the obvious, many researchers have put aside other projects — every one of them important — to focus on COVID-19. The sooner they succeed, the quicker they can return to those previous missions. "There's a lot at stake here. I can't think of a better way to spend my time," declared Diamond.

He is both amazed and impressed by what he sees taking place all around him.

"We are blessed to have this facility, this knowledge base and these extraordinary people. We're in kind of a David-and-Goliath scenario.

"We may not be the biggest, but we aim to be the best."

Donors and Volunteers Respond to COVID-19

BY JAY FERNANDEZ



San Gabriel Lions Club President Dr. Debby Pyng Lou (front, left), West Covina Mayor Tony Wu (right) and volunteers

City of Hope got its start when a courageous group of volunteers came together to provide care and dignity to patients battling a deadly respiratory disease. Though our focus has shifted in the decades since from tuberculosis to cancer and diabetes, that foundation of generosity and hard work on the part of volunteers holds strong today in the face of a new medical crisis. City of Hope's robust community of donors and volunteers near and far has leapt into action with in-kind donations to protect patients and their caregivers.

Valuable donations of supplies and personal protective equipment (PPE) have been coming from patients, friends and supporters. Apple, a philanthropic partner to City of Hope over many years, has pledged to donate 50,000 KN95 masks; MGA Entertainment CEO Isaac Larian has also made a significant equipment donation. Peggy and Andrew Cherng, co-founders and co-CEOs of Panda Express restaurants and longtime supporters of City of Hope, have donated 90,000 Food and Drug Administration-registered KN95 and single-use masks through their charitable foundation, Panda Cares' COVID-19 Community Care Fund.

Industry partners Smart & Final and Marron Foods have also stepped up, with donations of powdered milk. Laura Dorr-Uyemura, director of Clinical Nutrition Services, explained that the milk is used in high-protein shakes and smoothies, a popular source of nutrition for patients, which were in danger of being eliminated due to shortages.

Patient connections are yielding generous donations, too. A gift of protective hoods, coveralls, boots and masks for City of Hope staff have come from the volunteer-run Orange County Chinese Ladies Group, coordinated by nurse practitioner Michelle Leon and Stephen J. Forman, M.D.

At the time of this writing, significant donations of masks have come from West Covina Mayor Tony Wu in partnership with San Gabriel Hope Lions Club President Dr. Debby Pyng Jou; masks and hand sanitizer from Samantha Phan, Angels of Hope member; and a shipment of PPE from the San Marino Lions Club, coordinated by President Vivian Lu.

"With high demands but limited supply, we wanted the PPE to be utilized where it is most needed," said Jing Chen of the Orange County Chinese Ladies Group. She noted the special vulnerabilities City of Hope patients face, even as many medical centers are seeking supplies.

For more information about donating medical supplies, please contact Sree Duggineni at sduggineni@coh.org.

The Best Is Yet to Come

BY ABE ROSENBERG

ancer care is changing rapidly, and the pace of change is accelerating. In 2019, major advances in precision medicine, gene-based therapy, immunotherapy and many other areas brought new hope to countless patients.

Those breakthroughs align with some fantastic news that the American Cancer Society announced in January of this year: the cancer death rate in the United States showed its largest singleyear drop ever reported, falling 2.2% from 2016 to 2017. Over the last three decades, the rate has dropped 29%, which translates to about 2.9 million fewer cancer deaths than would have occurred if the mortality rate had remained constant.

The decline is largely attributed to reduced smoking rates and advances in lung cancer treatment. In addition, new therapies for melanoma have helped extend life for many people, including those with metastatic disease.

On the downside, progress has slowed for those cancers that can be found through screening such as colorectal, breast and prostate, according to the report. Experts attribute this to the rising rate of obesity among Americans, as well as significant racial and geographic disparities in access to health care. And still, cancer remains the third leading cause of death, after the novel coronavirus and heart disease, in both men and women.

Nonetheless, City of Hope clinicians and researchers are brimming with optimism as 2020 begins. Here are some of their predictions for the latest innovations in understanding, detecting and treating cancer.

NO-SCALPEL BIOPSY

So-called "liquid" biopsies can detect tumor DNA in the blood, making for a much less invasive method for detecting cancer. As our DNA knowledge base and know-how continue to grow, liquid biopsies are becoming ever more accurate, at ever earlier stages. While it's unlikely they'll replace conventional biopsy

— where physical tumor tissue is extracted — anytime soon, the prospects are exciting.

"Our crystal ball is very clearly showing an increased trend for patients to be monitored with liquid biopsies," said Stephen Gruber, M.D., Ph.D., M.P.H., director of the Center for Precision Medicine at City of Hope. "Liquid biopsies detect early progression or resistant disease faster than other methods. And this is likely to be increasingly used in the U.S. for measuring residual disease and recurrence."

"A simple blood test can now detect disease recurrence up to one year before it can be detected by imaging or other routine tumor markers," said colorectal cancer specialist Marwan G. Fakih, M.D., "allowing not only tumor detection at an early stage but also helping track tumor evolution and allowing physicians to adapt and modify their treatments based on tumor molecular changes."



"These methods,"

added stomach cancer

surgeon Yanghee Woo, M.D., "will identify patients who have stomach cancer through supersensitive and accurate blood-testing methods. These will be especially important in early detection of stomach cancer in high-risk patients."

In addition, detailed cancer screenings using gene-based tools can discover a proclivity for the disease even before it develops, identifying people at risk.

"Many entities are introducing new products into the market in 2020. Everyone wants to allow better access to genetic testing for people with both a family history of cancer, as well as patients newly diagnosed with cancer," Gruber said.

"Given the advances made in genomic sequencing, in the coming years, we're going to see next-generation diagnostics being used," agreed Ajay Goel, Ph.D., M.S., chair of the Department of Molecular Diagnostics and Experimental Therapeutics. "Expect to see more blood-based tests that can measure circulating DNA, RNA or proteins that can be used as routine diagnostic testing for people whose family/ genetic history put them at high risk for certain diseases.

"These tests will become a lot more affordable. Cancer will be diagnosed earlier, which means physicians can intercept earlier and provide treatments earlier, resulting in better survival and treatment outcomes."

Imaging technology will play a role, too, with significant advances taking place. Stomach cancer specialist Woo is excited about "biomarker-directed imaging that not only can show us that there is a mass in the patient, but also inform us whether or not it is cancer, and more details as to what type of molecular biomarker it expresses to help determine the therapeutic response with specific treatments."

THERANOSTICS: THE ALL-IN-ONE SOLUTION

The relatively new field of theranostics — a combination of "therapeutics" and "diagnostics" — makes it possible to diagnose and treat cancer at the same time. One example is to use a radioactive agent in the imaging process to "light up" cancer cells, then immediately deploy a second agent to attack those cells.

"We will see a further role of image-guided management in diseases including prostate cancer," predicted radiation oncologist Arya Amini, M.D., "where we can utilize imaging to detect microscopic disease that routine scans would not be able to identify. This work will likely grow from prostate cancer into other areas, including colorectal cancer."

"I believe the theranostics approach, and more broadly the use of radioactive-targeted compounds, will make a big impact in prostate cancer beginning soon," agreed prostate cancer specialist Tanya Dorff, M.D. She calls theranostics a "big breakthrough" and predicts "the use of imaging to show a phenotype of a cancer that could be targeted with a radioactive compound, i.e. Lu177-PSMA (lutetium-based prostate-specific membrane antigen therapy, often used in advanced cases). Further radioisotopes and targeting antibodies are being explored."

There's also great interest in "radioimmunotherapy," said diagnostic radiologist Ammar Ahmed Chaudhry, M.D., explaining that clinicians "will combine theranostic agents with immunotherapy to deliver optimal high-powered treatment to aggressive forms of cancer that are generally resistant to conventional therapies."



GENE THERAPY: "OFF THE SHELF" AND INTO THE FUTURE

Perhaps no recent advance has created more excitement than CAR T cell therapy — when a patient's own immune cells are reengineered to seek out and attack cancer. The Food and Drug Administration (FDA) has approved two CAR T cell products for treating blood cancers, and clinical trials continue for a broad array of solid



tumors. More will follow, along with new ideas; Woo predicts we'll see "CAR T therapy in combination with other immune therapies targeting specific stomach cancer biomarkers."

Because each CAR T cell treatment originates from a patient's own cells, the process is slow and very expensive. But efforts are underway to develop "off-the-shelf" CAR T treatments created with donor cells that are specially treated to eliminate the possibility of rejection. Gene therapy pioneer John A. Zaia, M.D., the Aaron D. Miller and Edith Miller Chair for Gene Therapy, predicts "an off-the-shelf CAR T cell will show promise in early studies" in 2020. Zaia also predicts at least three more gene therapy products will receive FDA approval in 2020, and he expects to see the first human clinical trials for gene therapy to combat sickle cell disease.

Clinical geneticist Thomas P. Slavin, M.D., believes we've barely scratched the surface in genetic research and treatment, and yet a major shift is already taking place. Together with City of Hope affiliate Translational Genomics Research Institute, researchers are taking a critical step beyond analyzing a tumor's genetic makeup. They are pairing that information with each patient's "germline" — the inherited genetic characteristics that make each individual unique. "This will be a very important step toward driving the use of genomics in oncology to help patients and their families," predicted Slavin, because of all the added data it will provide, especially regarding a person's risk of developing future tumors.

"We are right on the cusp of this being very obvious," he added. "City of Hope will be among the first to roll out 'paired tumor germline sequencing,' and it will quickly become the standard of care."

ARTIFICIAL INTELLIGENCE. REAL CURES.

More and more elements of the patient experience are now being converted into digital information. This opens the door to using big data and artificial intelligence to mine that treasure trove of material for insights few could have imagined only a few years ago.

"The digitization of electronic medical records, radiology and pathology will allow application of artificial intelligence (AI) in precision medicine," said diagnostic radiologist Chaudhry. "AI can help find a needle in a haystack. Synthesis of this information will allow for early detection and patient-specific treatment optimization."

"Mathematics and computational biology will continue to increase its influence and role in basic and translational research in cancer," said mathematical oncologist Russell Rockne, Ph.D., director of the Division of Mathematical Oncology and a contributing researcher in the Gehr Family Center for Leukemia Research, who recently authored a paper on cancer and Einstein's theory of relativity. "I also predict that mathematical modeling and machine learning will continue to merge together."

"Technology is advancing at such a rapid pace," said Woo. "We pioneer the translating of these tools to ensure the safety, efficacy and oncologic benefit to our patients."

BETTER RADIATION TREATMENT

Much of the fanfare these days may go to "miracle" drugs born in the genome-sequencing era, but radiation oncology — now more than a century old — is racking up its share of leading-edge breakthroughs. Radiation oncologist Amini is looking forward to an "exciting" 2020. He expects to see a high-dose form of radiation called SBRT (stereotactic body radiation therapy) taken beyond its traditional use in early-stage cancers to be deployed in cases where cancer has spread to multiple locations. "You will see a much greater role for radiation in Stage 4 cancers, which has changed the paradigm of our field," he said.



INHIBITORS: MOLECULAR WEAPONS

As the era of targeted therapy expands, a variety of "inhibitors" — agents that block the growth factors that allow cancer cells to multiply — are showing promise in new areas.

Fakih, co-director of the Gastrointestinal Cancer Program, reports that a specific EGFR (epidermal growth factor receptor) inhibitor will gain acceptance "as a proven treatment option for second or third line treatment of BRAF-V600E mutated colorectal cancer," a significant breakthrough because patients with BRAF-V600E mutations tend to



respond poorly to other treatments. Using this inhibitor as part of a trio of inhibiting agents "has proven superior to chemotherapy in the second line (and beyond) treatment in this patient population" and is expected to receive regulatory approval soon, he said.

There is similar good news regarding PARP (poly-ADP ribose polymerase, a cell protein) inhibitors and prostate cancer, said Dorff, head of the Genitourinary Cancers Program. Many prostate cancer treatments target the androgen receptor (AR) in an effort to deprive tumors of the testosterone they need to grow. Dorff believes PARP inhibitors "will be the first targeted therapy not targeting AR to be approved in prostate cancer. This will hopefully just be the first of many more individualized approaches to enter the prostate cancer treatment paradigm."

PALLIATIVE CARE FOR EVERYONE

City of Hope's Department of Supportive Care Medicine will do much more in 2020 than simply work with patients on end-of-life issues. "Right now," explained Chandana Banerjee, M.D., M.P.A., "some physicians are still reluctant to start working with supportive care medicine because there is a stigma involved with discussing end-of-life care."

That stigma, Banerjee believes, is fading and could largely disappear in 2020 because of the proactive efforts of City of Hope's staff.

"We're going to see hematologists and oncologists place more attention on palliative medicine," she said, adding that palliative efforts will begin much earlier, perhaps even at initial diagnosis. It makes sense for both patients and physicians. "The reality is that working with supportive care medicine early can provide symptom relief for patients. Supportive care medicine can become an ally with the primary team to help the primary team execute their treatment plan."

In other words, tending to the patient, body and soul — City of Hope's core philosophy — will remain every bit as important as any research breakthrough, surgical advancement or DNA-based wonder drug.

Moving the Needle Toward a Cure for Ovarian Cancer

ust before his first wife, Sue, passed away from ovarian cancer in 2008, Anthony "Tony" Markel and then-City of Hope President and Chief Executive Officer Michael A. Friedman, M.D., created the City of Hope Markel-Friedman Accelerator Fund for Ovarian/Peritoneal Cancer Research to accelerate investigations into a cure for the disease. That mission has taken on new force with the hiring of Lorna Rodriguez-Rodriguez, M.D., Ph.D., former chief of Gynecologic Oncology at the Rutgers Cancer Institute of New Jersey and an expert in ovarian cancer.

"I'm very impressed with her credentials, her zest and zeal," said 78-year-old President and Chief Executive Officer Michael Markel, whose funding supports Rodriguez-Rodriguez's work. "She's identified a very strong team to lead a much more aggressive initiative in ovarian and peritoneal cancer research. We've stepped it up a notch. I'm very confident that they'll be able to move the needle."

Though it is rare, ovarian cancer remains the most lethal gynecologic cancer. Rodriguez-Rodriguez, professor in the Division of Gynecologic Oncology at City of Hope, is determined to find a cure by using breakthrough immunotherapies and advancing genomic technologies for testing at Translational Genomics Research Institute (TGen), where she is an adjunct professor. "The key word is urgency," said Rodriguez-Rodriguez, who joined City of Hope in 2019 and has seven teams working on the ambitious project. "We want results fast. The Markel-Friedman funding means we can accelerate the research. We can do big clinical trials in unknown areas that are more high-risk but also higher return."

"It's only through research and discovery and translation that we go from a death sentence to hope to, ultimately, a cure," said Michael A. Caligiuri, M.D., the Deana and Steve Campbell Physician-in-Chief Distinguished Chair, president of City of Hope National Medical Center and the one tasked with recruiting Rodriguez-Rodriguez. "Speed matters when you have cancer. That's very important to Mr. Markel. He wants projects that are potentially transformative. And Lorna is a world-class expert in ovarian cancer. She is completely turned on by science. Her eyes light up."

Markel helped grow the Virginia-based Markel Corporation, which was founded by his grandfather, into one of the largest property and casualty insurance companies in the United States. He has been an integral part of raising money for City of Hope through the National Insurance Industry Council, which honored him with its *Spirit of Life®* Award in 2006. Markel went on to serve as national chair of City of Hope's Power of Hope campaign, which raised an astounding \$1 billion for research.

"Individuals and corporations that have been fortunate enough to do really well have an obligation to support their communities," said Markel. "The employees are gratified when they see their employers stepping up and trying to solve social issues and being philanthropic toward medical charities. It should be part of the mantra of every successful organization."

Operating Room Ock Stars

PHOTO BY VERN EVANS

BY ABE ROSENBERG

City of Hope surgeons are artists in their own right. Going beyond cancer removal, they use their advanced skills and knowledge to restore patients to their former form and function, aided by the latest technologies and techniques.



hen orthopedic oncologist J. Dominic Femino, M.D., meets a new bone cancer patient, he sets out immediately to calm fears.

"I see a lot of scared patients," said Femino, chief of City of Hope's Division of Orthopaedic Surgery and associate director of its Musculoskeletal Tumor Program. Many of his patients are teenagers. While childhood cancers are rare, sarcomas — cancers of the bone and soft tissue — are among the most common.

Not too long ago, a teen with cancer in his leg faced amputation — or worse. That's changed.

"Bone sarcoma is very treatable," Femino said. "Survival rates are excellent, and 90% of the time we can save the patient's limb."

But saving a limb is only part of the challenge with a still-growing child. If cancer has settled in the "growth plates" — located at the ends of each long bone — excising it impacts the young leg's future development. Simply implanting a rigid prosthesis won't do. "We have to equalize the lengths of both legs as the patient continues to grow," Femino explained.

In the past, this would require multiple surgeries over the years to replace the prosthesis with progressively larger ones, a less-than-ideal solution considering the risks of surgery, plus the downtime and rehab after each procedure.

An alternative single-surgery method implants a compressed spring inside of a plastic housing. As the patient grows, doctors heat the leg to partially "melt" the plastic, enabling the spring to expand. But with each "melt," the system weakens.

MAGNETIC MASTERS

Surgeons now use a more versatile and precise device: a telescoping metal rod manipulated by an external magnet that extends the implant a millimeter or so at a time. "It's a more durable and reliable system," said Femino, and City of Hope is one of the few institutions with the skill and knowledge to employ it.

The next advance takes the magnetic concept to another level while capitalizing on the body's own healing abilities.

Femino's partner, Lee M. Zuckerman, M.D., has pioneered the use of these magnetic nails in orthopedic oncology. He was the first surgeon in the world to use the technique to reconstruct large defects with donated bone. The nails can both expand and compress, and using these nails to compress the donated bone to the patient's own bone results in a higher rate of the donated bone healing compared to standard methods. He has reconstructed defects as large as 11 inches with this method. The nails also can be used to lengthen the bone, and enable children who develop a leg-length discrepancy due to their cancer treatment to reach their natural height. Zuckerman has used this technology to lengthen the bone over 6 inches when a child's growth has been affected. Currently, he is only one of about 10 surgeons in the world using this technology for bone transport in orthopedic oncology, which involves cutting the bone and slowly moving it so new bone forms and fills in the defect. He has reconstructed defects as large as 7 inches.

"I'm excited by these advances," said Femino, himself the son of an orthopedic surgeon. He's known since age 12 that he would follow in his father's footsteps, and he took the additional step into orthopedic oncology because "it forces me to be creative. No two tumor defects are the same.

"And unlike regular orthopedics [where patient and surgeon likely spend only a brief time together], I really enjoy the long-term relationships I've developed with my patients."

TITANIUM TAG TEAM

Cancer surgeries can be incredibly complex, especially when tumors invade intricate areas involved with speaking, breathing, eating and swallowing: the tongue, throat, jaw, tonsils, larynx — all grouped together under "head and neck cancer." Surgeons in this challenging field must have expertise not only in removing cancer, but also in rebuilding complicated systems to restore normal function as fully as possible.

And sometimes, two surgeons may be better than one.

Such is the case with Thomas J. Gernon, M.D., and Robert S. Kang, M.D., M.P.H. Friends since their residency days, each is highly trained in all aspects of head and neck surgery and perfectly capable of completing entire removal reconstruction procedures on their own.

Nevertheless, they decided to work together on each operation, dividing the duties according to their respective strengths. Gernon, an expert in microvascular procedures, prefers to focus on extracting diseased tissue, while Kang, who completed a fellowship in facial plastic and reconstructive surgery, harvests healthy material — part of a leg bone to replace a diseased jaw, for example — then implants it.

"It streamlines the process," explained Gernon. Working in tandem can significantly shorten total operating time, which normally runs as long as 12 hours. Both surgeons join forces for the final stage connecting the tiny blood vessels of the implant to their new location. "Always good to have an extra pair of hands under the microscope," said Kang.

"It's a real team effort," agreed Gernon, pointing out that the community of head and neck surgeons in the U.S. is quite small, making this two-doctor partnership even more of a rarity.

Their tag team exploits also take advantage of several newer advances in the field.

Robotics, for one. A robotic probe entering through the mouth can reach tumors at the back of the tongue and in the tonsils, areas that would require major incisions if removed conventionally.

To replace a jawbone, Kang and Gernon are excited by the latest titanium-based templates. Before, a surgeon had to take a rigid piece of the metal, bend and twist it into the approximate shape, and secure it to the skull before attaching a transplanted fibula (leg bone) and soft tissue refashioned into a new jaw. "It takes awhile," noted Kang.

Now it's possible, long before anyone enters the operating room, to send a computed tomography scan of the patient's jaw to a fabricating company that creates a custom-made titanium shell that's ready and waiting to receive the replacement implant when surgery begins. It's more precise and a real time-saver.

Leg bones make ideal jaw replacements because the bone density is similar. "You can even put teeth into it," noted Kang. For other, thinner parts of the skull — cheeks, eye sockets, etc. — there's no comparable material elsewhere in the body, so Kang and Gernon turn to PEEK, or polyether etherketone, a synthetic substance that can also be preshaped in advance.

Both surgeons look forward to the day when they won't need to transplant bones or use any foreign substances at all.

"Perhaps we'll grow replacement bones from stem cells," suggested Kang.

Or perhaps advanced drugs will eliminate most surgeries.

"The real excitement," said Gernon, "is in developing biomarkers, profiling more tumors and targeting them with personalized drugs. That will make a huge difference."

In the meantime, they'll keep working together, a microcosm of the uniquely City of Hope-style team mentality.

"Everybody here really cares," observed Gernon. "They're really good at what they do. The level of detail across the board is amazing. And everybody gives each patient everything they've got."

From left, head and neck oncology surgeon Robert S. Kang, M.D., M.P.H.; orthopedic oncology surgeon Lee M. Zuckerman, M.D.; orthopedic oncology surgeon J. Dominic Femino, M.D.; and head and neck oncology surgeon Thomas J. Gernon, M.D.

City of Hope scientists discuss how they developed and tested the first chimeric antigen receptor (CAR) T cell using chlorotoxin, a component of scorpion venom, to direct T cells to target brain tumor cells.

> Highly Potent Death Stalker Scorpion Venom Component Could Be Lifesaving Treatment for Brain Cancer

by LETISIA MARQUEZ

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Christine Brown, Ph.D.

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ity of Hope scientists have developed and tested the first chimeric antigen receptor (CAR) T cell therapy using chlorotoxin (CLTX), a component of scorpion venom, to direct T cells to target brain tumor cells, according to

a preclinical study published March 4 in Science Translational Medicine.

CARs commonly incorporate a monoclonal antibody sequence in their targeting domain, enabling CAR T cells to recognize antigens and kill tumor cells. In contrast, the CLTX-CAR uses a 36-amino acid peptide sequence first isolated from death stalker scorpion venom and now incorporated into the CAR to serve as its recognition domain.

Glioblastoma (GBM), the most common type of brain tumor, is also among the most deadly of human cancers, according to the American Cancer Society. It is particularly difficult to treat because the tumors are disseminated throughout the brain. Efforts to develop immunotherapies, including CAR T cells, for GBM must also contend with a high degree of heterogeneity within these tumors.

For the study, City of Hope researchers used tumor cells in resection samples from a cohort

⁶⁶Much like a scorpion uses toxin components of its venom to kill its prey, we're using the chlorotoxin to direct the T cells to target the tumor.⁹⁹

of a CAR using chlorotoxin to target GBM cells. The peptide has been used as an imaging agent to guide GBM resection surgery, and to carry radioisotopes and other therapeutics to GBM tumors.

"Much like a scorpion uses toxin components of its venom to target and kill its prey, we're using chlorotoxin to direct the T cells to target the tumor cells with the added advantage that the CLTX-CAR T cells are mobile and actively surveilling the brain looking for appropriate targets," Barish said. "We are not actually injecting a toxin but exploiting CLTX's binding properties in the design of the CAR. The idea was to develop a CAR that would target T cells to a wider variety of GBM tumor cells than the other antibody-based CARs.

"The notion is that the higher the proportion of tumor cells that one can kill at the beginning of treatment, the greater the probability of slowing down or stopping GBM growth and recurrence," Barish added.

Dongrui Wang, Ph.D., a graduate student in City of Hope's Irell & Manella Graduate School of Biological Sciences, was the lead scientist to establish and optimize the CLTX-CAR T cell platform and to determine that cell surface protein matrix metalloprotease 2 (MMP2) is

required for CLTX-CAR T cell activation. He added that "while people might think the chlorotoxin is what kills the GBM cells, what actually eradicates them is the tumor-specific binding and activation of the CAR T cells."

of patients with GBM to compare CLTX binding with expression of antigens currently under investigation as CAR T cell targets, including IL13R α 2, HER2 and EGFR. They found that CLTX bound to a greater proportion of patient tumors and cells within these tumors.

CLTX binding included the GBM stem-like cells thought to seed tumor recurrence. Consistent with these observations, in preclinical studies, CLTX-CAR T cells recognized and killed broad populations of GBM cells while ignoring nontumor cells in the brain and other organs. The study team demonstrated that CLTX-directed CAR T cells are highly effective at selectively killing human GBM cells in cell-based assays and in animal models without off-tumor targeting and toxicity.

"Our chlorotoxin-incorporating CAR expands the populations of solid tumors potentially targeted by CAR T cell therapy, which is particularly needed for patients with cancers that are difficult to treat such as glioblastoma," said Christine Brown, Ph.D., City of Hope's Heritage Provider Network Professor in Immunotherapy and deputy director of the T Cell Therapeutics Research Laboratory. "This is a completely new targeting strategy for CAR T therapy, with CARs incorporating a recognition structure different from other CARs."

Michael Barish, Ph.D., City of Hope professor and chair of the Department of Developmental and Stem Cell Biology, initiated the development

Michael Barish, Ph.D.

Based on the promising

findings of this study, the study team intends to bring this therapy to patients diagnosed with GBM with the hope of improving outcomes against this thus far intractable cancer. With recently granted Food and Drug Administration approval to proceed, the first-in-human clinical trial using the CLTX-CAR T cells is now screening potential patients.

This work was supported by the Ben & Catherine Ivy Foundation of Scottsdale, Arizona, and the clinical trial will be supported by The Marcus Foundation of Atlanta.

City of Hope has treated nearly 500 patients since its CAR T program started in the late 1990s. The institution continues to have one of the most comprehensive CAR T cell clinical research programs in the world — it currently has 29 ongoing CAR T clinical trials, including CAR T trials for HER-2 positive breast cancer that has spread to the brain, and PSCA-positive bone metastatic prostate cancer. It was the first and only cancer center to treat GBM patients with CAR T cells targeting IL13R α 2, and the first to administer CAR T cell therapy locally in the brain, either by direct injection at the tumor site, through intraventricular infusion into the cerebrospinal fluid, or both. In late 2019, City of Hope opened a first-in-human clinical trial for patients with recurrent GBM combining IL13R α 2-CAR T cells with checkpoint inhibitors nivolumab, an anti-PD1 antibody, and ipilimumab, blocking the CTLA-4 protein.

Where No contract of the second secon

BY MAXINE NUNES

Markus Kalkum, Ph.D.

an terrestrial microbes survive in outer space — and if so, how do they do it? These are some of the questions that researchers at City of Hope, working with NASA's Jet Propulsion Laboratory, set out to answer. Their discoveries are shedding new light on a range of subjects, from human health to the origins of life on Earth.

The study, part of a long-term collaboration with NASA, was led by City of Hope graduate student Abby Chiang, Ph.D., under the supervision of Markus Kalkum, Ph.D., professor and director of the Mass Spectrometry and Proteomics Core at Beckman Research Institute of City of Hope. Chiang was awarded her doctorate in part as a result of this work, and the results were published in June 2019 by the American Society for Microbiology.

BACTERIA VOYAGE INTO SPACE

The idea for this project began when JPL's Kasthuri Venkateswaran , Ph.D., found that certain strains of bacteria, including *Bacillus pumilus* and *Bacillus horneckiae*, were especially hardy. They were isolated in cleanrooms where spacecraft are built, and were also found to survive when exposed to the environment outside of the International Space Station (ISS). The spores of

these hardy microbes were also found to withstand treatment with peroxide and ultraviolet rays.

"If future space missions ever try to look for life on other planets, the spacecraft doing the searching have to be very clean. We don't want to go to other planets and look for life only to find that we brought it with us," said Kalkum.

To study what happens to microbes in space, *Bacillus pumilus* spores were placed in a special container on the outside of the ISS and kept there for 18 months.

"The conditions were quite extreme — microgravity, the



Certain strains of bacteria have been found to survive when exposed to the environment outside of the International Space Station.

vacuum of space, exposure to UV and UVC rays, cosmic radiation and particle radiation," said Chiang. "And when the spores were brought back to Earth, some of them were very much alive."

HOW DID THE SPORES SURVIVE SUCH EXPOSURE?

Chiang and Kalkum used mass spectrometry, which analyzes the structure of molecular compounds, and proteomics, a method of studying proteins the same techniques that are being used to study the biological mechanisms in cancer. And they made some fascinating discoveries. The metabolism of the spores had greatly slowed down, the protein coat that protects them was bigger and they had stronger virulence factors. No relevant changes to their DNA were found, which meant that the changes were most likely not genetic mutations.

This new information could now help inform the development of a more effective method of cleaning space hardware. Keeping an eye on what microbes are on the space station and learning how they adapt in microgravity continues to help us understand how best to protect astronaut health.

But the experiment has other important implications as well. By understanding the mechanisms by which bacteria protect themselves and grow stronger, we can also learn how to strengthen "good" bacteria, the probiotics that play such an important role in health. In fact, Chiang and Kalkum also worked on a National Cancer Institutefunded study of the probiotic *Lactobacillus reuteri*, a strain of bacteria that inhibits gut inflammation, which when chronic can lead to colon cancer.

"Probiotic bacteria can be flimsy," said Kalkum. "But if you can make them more hardy by learning the mechanisms they need to resist extreme environment, you could engineer them to live better inside humans in a way that is beneficial to the humans as well."

If NASA wants to send astronauts to explore the moon and Mars, this type of research would be essential.

MEANWHILE, INSIDE THE SPACE STATION ...

Bacteria aren't the only microbes of concern on the ISS. Several types of fungi have been discovered living inside it, particularly on wet surfaces. In an earlier City of Hope/NASA collaboration, Chiang and Kalkum found that, like the bacteria, the fungi had more robust growth than their counterparts on Earth.

One strain of fungus found on the ISS, *Aspergillus fumigatus*, is an opportunistic pathogen, and life aboard the space station made it even more virulent than its clinical counterpart CEA10, a type of *Aspergillus*

sometimes found in hospitals that can cause illness in immunosuppressed patients.

The adaptive mechanism that strengthened it, however, was exactly the opposite of what happened to the bacteria. Where bacteria reduce their energy consumption and slow their metabolism, fungi inside the space station speed up their metabolism. Some fungal species also produce a protective coating of melanin — as if they were making their own sunscreen.

Understanding these mechanisms is crucial if we are to eliminate them in clinical settings as well as in space, where they could be harmful to astronauts on long-term missions, and even simply to do good science as robotic explorers study extraterrestrial bodies.

However, other fungi found growing on the space station, like $\ensuremath{\textit{Pennicillium}},$ are our allies.

"Some of these fungi can produce useful things, like antibiotics for treating diseases," Kalkum said. "So on the space station they could actually use these as chemical machines to produce useful compounds during space travel."

THE ORIGINS OF LIFE ON EARTH

"Are you familiar with the panspermia hypothesis?" Kalkum asked.

Panspermia is a Greek word that means "seeds everywhere," and this theory posits that seeds, or microscopic organisms, traveling through space might have carried these seeds to Earth and been the origin of life here.

"In the early days of the solar system, there was much more activity with meteoroids and asteroids, and if some microorganisms or biosignatures might have been able to survive space travel long enough, it could have been the way that life was brought to Earth," said Kalkum. "We don't have evidence, but this study raises the possibility because some of these organisms are very hardy and resistant to extreme conditions."

What began as a graduate student project for Chiang is not only helping us understand how microbes survive in space, it may be one small but important step toward finding an answer to an age-old question: Is there life elsewhere in the universe?

Fighting Cancer One Cell at a Time

BY ABE ROSENBERG

A City of Hope scientist demonstrates how toxins can change cells on the cellular level, leading to cancer.

f the future of cancer treatment lies in precision medicine — individualized drugs for each patient and malignancy, developed at the cellular level — then a team of researchers led by City of Hope scientists has just moved the science a significant step forward.

Using tools that didn't exist a decade ago,

result of 'defective' genes," said Shiuan Chen, Ph.D., professor and chair, Department of Cancer Biology, and the Lester M. and Irene C. Finkelstein Chair in Biology. "Environmental factors play a role, and now we have this detailed mechanism that shows how cells are affected."

That "detailed mechanism" is single cell RNA sequencing, or "scRNA-seq," a relatively new

TOXIN EFFECTS

Environmental toxins can cause changes on a cellular level that can lead to cancer. For example, cells might grow faster or change their pathways.



researchers have demonstrated — with greater precision than ever — how external elements such as certain toxic chemicals can fundamentally change a cell's composition and behavior in ways that may lead to cancer.

"We're showing that cancer is not always the

process with considerable advantages over older, less precise and more biased methods like gene expression microarrays. scRNA-seq produces reams of digital data, is more versatile and was previously unavailable but now made possible by advances in techniques to analyze single cells and in bioinformatics analysis, a field in which



City of Hope has invested heavily.

"It's a new, very exciting technology, and it's still evolving," said Chen.

In this study, the first of its kind in the area of environmental carcinogenesis, Chen and his team focused on breast cancer that strikes women who are going through menopause, "a critical window of [cancer] susceptibility," he explained, "when normal hormone levels drop" and the mammary glands become supersensitive to any added estrogen or estrogen mimics in the environment.

Because millions of women take estrogen to deal with side effects of menopause, it made sense to examine any cellular changes this may cause. Several studies link estrogen therapy to increased



"We're showing that cancer is not always the result of 'defective' genes," said Shiuan Chen, Ph.D., above right. "Environmental factors play a role."

risk of breast cancer, but the exact cellular mechanism isn't fully understood.

Using mouse models, the researchers deployed scRNA-seq to examine changes in menopausal mammary gland cells when they are exposed to increased levels of estrogen (E2).

At the same time, they also looked at cellular changes caused by the presence of chemical compounds known as polybrominated diphenyl ethers (PBDEs). Once commonly used as flame retardants, PBDEs have been banned in the U.S. since 2004, but they can linger in the body for many years after exposure.

Mammary glands are complex structures with many different varieties of cells, and scRNA-

seq made it possible to examine all of them. Several displayed profound changes in this study, especially when E2 and PBDEs were both present. Some cells grew faster. Others changed their pathways or physical parameters, making it easier for cancer to take hold. Still others, like immune cells, saw those immune properties altered.

"Our findings support that E2 + PBDE increase the risk of developing breast cancer through the expansion of estrogen-responsive luminal epithelial cells and immune modulation," wrote Chen in the study, which was published in the journal Communications Biology on Nov. 5.

Understanding how an individual cell changes is

a vitally important step, said Chen, because this knowledge "can help us identify new targets and design drugs that will attack those targets."

The scRNA-seq process that enables this deep cellular dive is growing rapidly in popularity, a fact recognized by the National Institutes of Health, which funded this study.

Chen and his colleagues see many more potential applications for scRNA-seq going forward. Several important studies are already underway, examining cancer at different stages of development and also moving past mouse models to look at human tumors, especially those that tend to recur or resist conventional treatment. City of Hope opens its first Orange County facility in Newport Beach.

City of Hope opens its first facility in Orange County

BY NATHAN LAMMERS

From left, City of Hope Chief Medical Officer Vijay Trisal, M.D.; Newport Beach Mayor Will O'Neill; City of Hope President and CEO Robert Stone; Annette M. Walker, president of City of Hope Orange County; Rep. Harley Rouda (D-Laguna Beach); City of Hope patient Kandace McMenomy; Ravi Salgia, M.D., Ph.D.

ity of Hope fulfilled its promise of speeding lifesaving treatments to Orange County with the opening of its Newport Beach, California, site on Jan. 27.

The Newport Beach location is the first phase of City of Hope's plans to invest \$1 billion to develop and operate

a comprehensive cancer campus of the future in Irvine and network of care in Orange County.

"With the opening of our Newport Beach site, we launch a new era of cancer care in Orange County, delivering pioneering research and highly specialized care to our communities. This is what our patients asked us to do, and we are honored to answer the call," said Annette M. Walker, president of City of Hope Orange County. "I'd like to thank the site activation teams, the construction and design teams, all the physicians and all the staff, who lent their hearts and hands into transforming a medical office building into a sacred place for hope and healing."

LOCAL ACCESS TO CITY OF HOPE'S WORLD-CLASS PHYSICIANS

The patient-centric, future-focused facility at 1601

Avocado Ave. offers stand-out features, including a state-of-the-art infusion center with calming ocean views.

The opening of the Newport Beach location is the first time Orange County residents will have local access to our world-renowned compassionate care, personalized therapies and highly specialized physicians. Led by Ravi Salgia, M.D., Ph.D., professor and chair of the Department of Medical Oncology & Therapeutics Research and the Arthur & Rosalie Kaplan Chair in Medical Oncology, the specialty team includes an internationally recognized researcher in multiple myeloma treatment, a pioneer in kidney and bladder cancer, and one of the country's leading experts and researchers on colorectal cancer.

"Each cancer is unique, which is why we assembled a roster of outstanding researchers and physicians who provide targeted treatments for specific cancer diagnoses," Salgia said. "These clinician-scientists are among the best in their fields and are transforming laboratory breakthroughs into treatments to offer the best hope for our patients."

Also unique to Newport Beach is the innovative Precision Prevention and Early Detection program overseen by Laura Goetz, M.D., M.P.H., assistant clinical professor in the Department of Medical Oncology & Therapeutics Research. The program will inform patients and their families of their risk factors based on state-of-the-art techniques such as genetic risk assessments, biomarker panels and environmental exposure surveys.

"There are a lot of things that people don't realize about what they can do personally for cancer prevention, and 50% of all cancers are preventable, so that's a huge number of people who really don't need to be getting cancer," Goetz said. "What I want to do with the Newport Beach facility is really turn the tables on how people think about cancer and how they think about what they can do to decrease their risks for cancer."

A 'NECESSITY' FOR CANCER PATIENTS

City of Hope's presence in Orange County meets a critical need for what is the sixth-most populous county in the nation. Nearly 20% of Orange County cancer patients have been leaving the area for advanced cancer care, including 3,200 patients who are coming to City of Hope's main campus in Duarte each year. That can mean up to a two-hour commute each way for treatment treatment they can now get much closer to home.

"Having City of Hope in Orange County is not just a convenience for cancer patients," said Leslie Seigel, a City of Hope patient who lives in Newport Beach and is a breast cancer survivor who sought treatment at the Duarte campus. "It is an absolute necessity."

Kandace McMenomy commuted to Duarte from Newport Beach regularly during her diagnosis and treatment for Stage 2 breast cancer. "I knew I wanted a leader in cancer care, which is why I turned to City of Hope for my treatment," said McMenomy, whose personal fitness studio is just a half-mile from the new location in Newport Beach. "Having these services closer to home will mean so much to all who are impacted by cancer. This is a great thing for our community."

Todd Kennedy is another patient who was commuting to Duarte for treatment of advanced multiple myeloma. "I am so grateful, and frankly, relieved, that City of Hope is in Orange County," he said.

PART OF A LARGER \$1 BILLION VISION

Last year, City of Hope announced a plan to invest \$1 billion to develop and operate a 21stcentury comprehensive cancer campus in Irvine and a network of care that will provide residents unprecedented access to leading-edge medicine. Leaders and volunteers are engaging the philanthropic community to help make this vision a reality.

The Irvine campus will be on 11 acres at FivePoint Gateway, housing a comprehensive clinical hub for specialized cancer care, phase 1-3 clinical trials, precision medicine, early detection and prevention programs, and more. Orange County's first hospital dedicated



The 12,500-square-foot patient-centric and future-focused facility is located at 1601 Avocado Ave.

exclusively to treating and curing cancer is planned for the Irvine site in 2025.

"With Newport Beach now open, our clinical network across Southern California grows to 30 locations," said Vincent Jensen, chief executive, City of Hope Medical Foundation. "Most importantly, our expansion into Orange County allows patients to receive City of Hope care where they want to be — closer to home and closer to their loved ones. This is at the heart of our goal to deliver patient-centered care."

"We are excited to have a new partner who is dedicated to improving the health and wellbeing of our community," said Newport Beach Mayor Will O'Neill. "City of Hope will be an important health resource, making a difference in cancer care and prevention, and working toward eradicating this terrible disease from our lives."

Longterm Friends, Visionary Giving

ity of Hope continues its mission to support the community as it engages in a \$1 billion expansion, both in Duarte and on a new campus in Irvine. But we could never achieve our grand ambitions without the backing of those with equal vision.

Longtime National Business Products Industry (NBPI) member Jess Beim and his wife, Lill, are just such philanthropic visionaries. "We feel so fortunate to be able to support a quality organization whose important, meaningful work heals the sick and moves toward finding cures for cancer, diabetes and other life-threatening diseases," said Lill and Jess. "We were fortunate to be successful in business, and that enabled us to help others."

A New Jersey native, Jess met Lill, his wife of 62 years, at UCLA during the time that they were presidents of their fraternity and sorority. Jess and Lill have lived in Southern California ever since, as do their two children and grandchildren. After graduating college, Jess immediately entered into the family business, K&M Company, growing it into a successful office products and school supplies enterprise that was eventually acquired by Avery Dennison US.

Jess first got involved with City of Hope when he attended a *Spirit* of Life[®] event sponsored by the National Office Products Industry. He followed up by taking annual industry tours of the campus. As a

leader in the office products business, Jess had the ability to network with senior industry executives at City of Hope events, which helped strengthen his support of the organization. "The quality of care and expertise of the medical professionals was so impressive," said Jess, "And as K&M Company grew, we became more involved in City of Hope."

Jess served for many years on the NBPI Council that focused on the financial support of City of Hope's Center for Biomedicine & Genetics and its accompanying Chemical GMP Synthesis Facility. He was awarded the industry's *Spirit of Life* Award in 2007, raising an unprecedented amount of money at the time. Jess's honor followed in the tradition of his close friend Irwin Helford, the founder of Viking Office Products, whose gift resulted in the state-of-the-art City of Hope Helford Clinical Research Hospital.

Since its inception in 1983, NBPI has raised more than \$200 million for research and treatment. "City of Hope offers a unique approach by focusing on comprehensive treatment for the whole person," said Lill. "They not only offer the best medical care available, they also work with the entire family in an atmosphere of kindness and compassion."

Jess and Lill Beim

40Yearsof Wisdom Wonder

BY ABE ROSENBERG

t comes as a surprise.

Ask John A. Zaia, M.D., why he chose to study viruses early in his career, and he morphs from medical man to wide-eyed wonder, explaining his affinity

for microscopic parasites in much the way Monet might have considered his Giverny garden.

"The first time I looked at one of those tissue cultures under a microscope," he recalled, "I could see their beauty. It was remarkable!"

To the average person, "beauty" is probably not

"He's never lost his

sense of wonder."

and mobility to deliver a new generation of precision medicine and gene therapy.

Relaxed in his unassuming office in an out-ofthe-way alcove of the Familian Science Building where he's worked since day one, the calm, self-effacing Zaia seems perfectly situated, surrounded by favorite things: jam-packed bookshelves, stacks of papers, a baseball on the desk, a bat on the wall, mementoes from numerous fly-fishing trips and plenty of family photos (he has three grown children, including a daughter who followed in Dad's footsteps and became a doctor herself).

> From this quiet space, the multi-titled Zaia (Aaron D. Miller and Edith Miller Chair in Gene Therapy; director, Center for Gene Therapy; program director, City of Hope Alpha Stem Cell Clinic)

Stephen J. Forman, M.D.

the first thing that comes to mind when thinking about the bugs that cause AIDS, Ebola or the common cold.

But then, "average" is the last thing anyone would say about the physician-scientist now marking 40 years at City of Hope.

"He's a wonderful human being, an excellent doctor and a great scientist," said hematologist Stephen J. Forman, M.D., a colleague and longtime friend. "He's never lost his sense of wonder. And he has wisdom. When people are losing their heads, he's the calm one in the room."

In those four decades, Zaia has leveraged his wisdom and wonder into a keen understanding not only of how viruses work, but also how best to control their destructive properties and, now more than ever, how to harness their hardiness has earned renown as a premier virologist and gene therapy pioneer. He is recognized worldwide for his breakthrough efforts to eradicate HIV.

And he was famous long before he set foot in Duarte, California.

A Massachusetts native and son of a physician ("I always knew I was going to be a doctor. I didn't see anything else."), Zaia took his Harvard M.D. degree and focused on infectious diseases in children.

His started with chickenpox.

Working with outdated blood from the Massachusetts blood bank, Zaia helped advance the research that eventually made a widespread vaccine feasible. He also became known as the go-to person for treating kids with leukemia who contract chickenpox, a life-threatening situation when chemotherapy weakens the immune system.

Zaia also studied cytomegalovirus (CMV), a common bug that's usually harmless but can be lethal in newborn infants, with their still-incomplete immune systems.

Today CMV remains a major area of research for Zaia and his lab because of its potentially deadly effects on other vulnerable populations, such as people undergoing stem cell transplants and those with HIV.

When it comes to battling HIV and AIDS, few can match Zaia's achievements.

Arriving at City of Hope in 1980 just as the epidemic was exploding, Zaia the virologist recognized the potential "home run" before him: AIDS was the curse, the challenge and the opportunity of a lifetime.

Forty years later, he's still at it. But so much has changed.

"People with HIV can now live a normal lifespan, thanks to antiviral drugs," he said. "But that's not the same as a normal life. They still have to take meds every day."

He's determined to fix that, and he's getting close. His goal is to create a "functional cure" in which HIV, though it remains in the body, is incapable of doing harm.

He's testing several approaches. Using the gene-editing system known as zinc finger nuclease (ZFN), "we genetically modified blood cells to resist HIV, then used those cells for transplants." Though early ZFN procedures succeeded barely 1% of the time, nextgeneration models are showing greater promise.

Another strategy employs a lentivirus — in effect, using a virus to stop a virus. Even CMV — his old nemesis — is capable of being weaponized to stimulate dormant HIV so it can be recognized and attacked by chimeric antigen receptor (CAR) T cells.

He's especially excited about CAR T's potential. Plans are underway for the first clinical trials to employ CAR T cell therapy to fight AIDS. Step one is to create those modified immune cells from a patient's own blood, but ultimately Zaia hopes to see "off the shelf" CAR T products whose "foreign-ness" has been deactivated, eliminating the risk of rejection or graft-versus-host disease.

Beyond AIDS, Zaia said that the total number of gene therapy drugs is growing rapidly, and the trend is accelerating. He's predicting major progress in 2020 for gene therapies to treat lymphoma and sickle cell disease, among others.

Zaia's focus remains strong. Having worked at the Centers for Disease Control and taught at Harvard Medical School, he says he "fell in love" with City of Hope right from the start, and all these years later he knows he's where he belongs.

"City of Hope is the ideal place to do my work," he said. "I enjoy every single day."



TGen Develops COVID-19 Test

City of Hope affiliate's infectious disease lab provides critically needed testing for Arizona

BY SAMANTHA BONAR

Since mid-January, Translational Genomics Research Institute (TGen), an affiliate of City of Hope, has been part of the worldwide effort to develop testing for the SARS-CoV-2 virus causing COVID-19 disease. Acting as genomic first responders, Arizona-based TGen is using advanced biomedical technologies to study this disease, while also working to help establish a statewide tracking network for COVID-19.

In early March — after receiving Emergency Use Authorization from the Food and Drug Administration for its genomic-based test — TGen began working with federal, state, county and tribal governments, private health care providers and others to expand testing for COVID-19 in Arizona, part of a concerted effort to get out in front of this global health threat.

TGen's testing uses RNA analysis to confirm the existence of the virus.

"These types of tests are essentially what the Centers for Disease Control developed and what others are developing around the world, and they look at respiratory samples, the nasal swabs that people have been hearing about," David Engelthaler, M.D., co-director of TGen's Pathogen and Microbiome Division (infectious diseases) in Flagstaff, explained in a late-March podcast.

"We can actually take that swab, extract the genetic material — that takes about half an hour to an hour to process — and then we get it into our PCR machines, which can give us results back in about 45 minutes. The whole process takes less than an hour and a half," he explained. But because TGen is testing up to hundreds of samples at a time, the current turnaround time is 24 hours, he added. As of April 1, TGen's CLIA lab was able to process up to 300 samples a day, he said.

TGen is receiving patient respiratory samples daily to get some idea of the general population incidence of the virus. TGen is also conducting analysis of samples from suspected and symptomatic individuals for COVID-19 from select communities, including Native American communities, and special populations such as long-term health care centers and jail populations to help provide support to these often-underserved groups who are most in need.

Finally, through TGen, Arizona is moving to establish a comprehensive public health testing program for high-risk but asymptomatic individuals, such as health care workers, who could be a dangerous reservoir for the virus.

"We're trying to find the virus where it's present before it's starting to cause the severe cases, so we better understand where it is and where to focus public health resources," Engelthaler said.

A bonus is that TGen has the capability to do genomic sequencing on the entire virus, which may help us understand it better.

"The great thing about TGen is the 'gen' in TGen, the genomics," Engelthaler said. "As soon as we identify any presumptive positive samples, we can put those samples straight into our genomic sequencing laboratory, sequence out the whole genome and better understand the virus. We can look to see where the virus strains are coming from, how they're moving around the community, which ones are more related to others, and watch and understand this new pathogen as it evolves in front of us."

Stephen and Joyce Hasper: "Hope Is Our Favorite Word"

"Hope was our favorite word even before I was told I had cancer," shares Stephen Hasper, who received a diagnosis of multiple myeloma in March 2014. In the months ahead, he and his wife, Joyce, would discover that their favorite word was more important to their lives than ever as they learned about City of Hope and soon became a patient family. Stephen received an autologous stem cell transplant at City of Hope in January 2015. Today, they are volunteers and donors, helping others when their lives have been impacted by cancer.

A married couple of 51 years, Stephen and Joyce volunteer with the Patient and Family Advisory Council, where they share their experience and mentor new patients and caregivers. Stephen talks to new patients who will be receiving stem cell implants because they want to hear from someone who has "been through it." And Joyce meets with caregivers who are concerned about supporting their family members, noting that her husband reminds her, "it can be harder to be the caregiver."

Stephen's words of wisdom have helped countless patients and families. As a City of Hope Speakers Bureau member, he shares his journey with five words: shock, confusion, pain, adventure and beauty. "There is shock when you receive a diagnosis. Sometimes, there is confusion about the best treatments and other decisions. There was and continues to be some pain involved with my illness and treatment. I tell people who are newly diagnosed: 'Welcome to the adventure you never intended to take. But now that you're here, you're going to meet some wonderful people.' Lastly, I encourage others to find beauty every day. Joyce and I do this by spending time with our six grandchildren."

The Haspers experience as patient family volunteers inspired them to include City of Hope in their estate plans and become Legacy of Hope Society members. "City of Hope kept me alive and has given me a high quality of life — including time with Joyce and my grandkids. Every day, the doctors and researchers

are providing care, making discoveries, and doing research that is helping people and giving them hope. We feel privileged to be a part of this place and to make it part of our legacy."

Learn about ways to create your legacy of hope at myplanwithcoh.org.

Stephen and Joyce Hasper

CITY OF HERCES

To the doctors and nurses everywhere, tirelessly sacrificing To the caregivers going above and beyond To the researchers in their relentless pursuit of answers To the patients and families remaining courageous To the supporters giving their time and more To the communities coming together

Thank you.





Two new deans have taken the helm of City of Hope's graduate program, determined to attract the best and brightest

BY SAMANTHA BONAR

Yilun Liu, Ph.D., and David Ann, Ph.D.

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wo new deans took the helm of City of Hope's graduate program on Oct. 1, 2019, determined to attract the best and brightest students from around the nation and the globe, risk-takers who will carry the institution's most ambitious visions for understanding, treating and curing disease into the future.

David Ann, Ph.D., dean and the Morgan & Helen Chu Dean's Chair of the Graduate School of Biological Sciences, and Yilun Liu, Ph.D., the program's inaugural vice dean, are new to their graduate program roles but not the institution.

Ann joined City of Hope in 2006 and is a professor and associate chair of the Department of Diabetes Complications & Metabolism and co-leader of the Molecular and Cellular Biology of Cancer Program. He has served as chair of the Admissions Committee of the graduate school for the last seven years (and as associate dean for admissions since 2017), taught graduate level courses and mentored new faculty, graduate students and postdoctoral fellows. Ann is also director of the Eugene and Ruth Roberts Summer Student Academy at City of Hope.

He obtained his B.S. in medical technology from National Taiwan University and his Ph.D. degree in biochemistry from Purdue University. His research focuses on oncogenesis, metastasis and cancer metabolism.

"We want to train students in critical thinking, analytical skills with rigor, reproducibility and responsibility. We call these the 3R's."

David Ann, Ph.D.

Liu, a professor and associate chair of the Department of Cancer Genetics and Epigenetics, came to City of Hope in 2011. That year, she joined the Irell & Manella Graduate School of Biological Sciences as an associate chair and was appointed a full professor in 2018. Liu has extensive experience in teaching students at both undergraduate and graduate levels both at City of Hope and Yale University.

In 2018, Liu took on the role of associate dean and co-director of the Master of Science Program in Translational Medicine, a newly created joint educational venture between the Irell & Manella Graduate School of Biological Sciences and the Henry E. Riggs School of Applied Life Sciences at the Keck Graduate Institute.

Liu received her B.S. in biology from MIT and Ph.D. in molecular biophysics and biochemistry from Yale. Her research deals with understanding how dysfunctions in DNA replication and transcription contribute to genomic instability that leads to cancer and premature aging.

Increasing City of Hope's graduate program's visibility is a priority, and Ann and Liu have already instituted such simple tweaks as a more easily recognizable logo and adding a link to the graduate school (which offers both a master's in translational medicine and a doctorate in biological sciences) to the City of Hope homepage.

"I personally didn't even know there was a graduate school until I came here," Ann said.

"We need the outside world to know that this is a wonderful program here," Liu concurred. "A lot of people just know about this as a hospital, a cancer center, and they don't even know about the research going on."

Overhauling the curriculum is a top goal. "We want to train students in critical thinking, analytical skills with rigor, reproducibility and responsibility. We call these the 3R's and

they are the most important things for biomedical researchers," Ann said.

"We need to create a very innovative curriculum. Cutting-edge knowledge must be combined with state-of-art technology," Liu added. "We need students to know that they will get the best training here to meet their future career goals."

One of the top benefits of the program is being on the same campus with the hospital, Ann said. "This is a major selling point because there's no barrier between the basic science and the clinical science. The academic and the clinical are integrated here. You feel like you are not just in graduate school. You're a part of a cancer center."

Indeed, the program mostly appeals to students interested in cancer and/or diabetes research. "The students we attract are more interested in cancer-relevant research. They are interested in the translational approach; to apply what they learn from the basic science into disease-solving or disease care," Liu said.

Founded in 1994 with a class of just four, the Irell & Manella Graduate School of Biological Sciences at Beckman Research Institute of City of Hope is accredited by the Western Association of Schools and Colleges. Students in the Ph.D. program have full financial support and pay no tuition.

> Since conferring its first doctoral degree in 1997, the program has grown steadily to over 90 students and 110 faculty members. Currently the graduate school admits about 15 students per year, and Ann insists the quality of the student body is more important than the quantity.

Alumni work at major medical and veterinary schools, in biotech and pharmaceutical industries, in artificial intelligence, pharmacogenomics, bioinformatics and molecular diagnostics.

In 2018, the school added the two-year Master of Science Program in Translational Medicine jointly with

the Keck Graduate Institute. This program is aimed at providing students with applied research experience and in-depth understanding of how to translate basic research into medical products from the perspectives of both academic research and downstream commercial development. The goal for the master's program is to eventually expand to 20 students, or about double its current number, Ann said.

Currently 96 students are enrolled in City of Hope's graduate program, 87 students in the doctoral program and nine in the master's. (With 121 combined faculty in the doctoral and master's programs, that is a greater than 1-1 faculty-student ratio, which allows for "a lot of individual attention," according to Liu.) About 75% of the students are American, while 25% are international students from Asia to Europe.

"The graduate school has a large population of people who come from overseas — there's a certain richness to that," said Morgan Chu, a partner at Irell & Manella LLP and longtime supporter of the school. "Here, students get personal attention. They're not one of many faceless students in a large institution. They are individuals."

City of Hope researchers also host about 250 postdoctoral students from top-tier institutions at any one time. "The postdocs and the grad students are some of the most vibrant parts of our workforce," said Mark LaBarge, Ph.D., director of the postdoctoral training office and a professor in the Department of Population Sciences. "They are the ones doing the most high-risk research, pushing into the unknown. They are the boots on the ground that will get us to the next treatment innovation."

While already strong, Ann and Liu look forward to seeing the graduate program become even more robust and exciting for its young scholars. "I always enjoy working with young people," Liu said. "It's a privilege to see young people learn, mature, then develop into a biomedical scientist or scholar."

BY STEPHEN J. FORMAN, M.D.

ur campus is usually a place bustling with activity, a culture of caring for people with cancer and their families, and research focused on the development of

new therapies for all who come to us for help. Every day, there is a palpable and visible energy reflecting the essence of City of Hope, making it exciting to come to work. But since the beginning of the coronavirus pandemic and the need for social isolation, our mission has shifted to how to continue our work while being mindful of the safety of our patients, their loved ones and our staff. Cancer ignores the viral threat and makes no accommodations for our patients.

The social isolation has also affected the way in which we care for people, since the journey for our patients has become lonelier than it already was. We are used to having families and friends all around, helping in the care of their loved ones. Hugging, touching and embracing



An employee undergoes a body temperature scan as part of now-routine coronavirus screening at City of Hope Helford Clinical Research Hospital.

are essential acts of comfort in the care of our patients suffering from cancer, and this extends even to our staff. Yes, we do hug in our workplace, supporting patients, families and each other, too. In many ways, the most difficult and sometimes personally painful part for all of us — patients, families and staff — has been witnessing and experiencing the separation when patients come to the clinic or are admitted, and not knowing when and if they will ever be together again. For our inpatients in particular, the staff has become their new family, and we are all spending more time with each patient throughout the day.

Even with the threatening clouds of the pandemic, we have continued to accept new patients, performed transplants, made CAR T cells, done essential surgery, enrolled people on hematology and medical oncology clinical trials, and collected blood and platelets. Our nurses, therapists, support staff, housecleaning, security, dietary technicians and physicians all leave the safe environment of their homes to come to work, knowing the risk they may be taking, but also feeling that this is our collective calling.

As I walk through the units day after day to round on inpatients, and see patients in the clinic, it is obvious that the care of the patient remains

paramount, and our nurses are professional, calm and kind, smiling with their eyes ("smize!") over their masks with patients and with each other. And despite the limits on visitors, I can see how many patients are grateful for what we are doing, and how much we care about them.

In some ways, the pandemic has made it even clearer who we are as an organization and our uniqueness in caring for people while at the same time coming to work each day to find a better way. Through the haze of the viral threat, we have stood together and heard a higher calling.

Many of the staff are working from home, and have discovered how effective Zoom can be in continuing our work. We wonder how our lives will be different when the pandemic ebbs. We know changes will come, but our identity remains the same, and is likely even clearer to all. There are so many small events and stories that emerge each day, including acts of courage, kindness and love that exemplify who we are, and in these times, show that we are one. And for that, I am both grateful and proud.





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"City of Hope gave me my life back. With young children, I am taking advantage of this blessing I was given. I'm not just living, I'm thriving."

— Manuel Espinosa

Adriana and Manuel Espinosa, Legacy of Hope Society members, with their sons, Julian and Cristian. The Espinosas have named City of Hope as a beneficiary of their life insurance policy.

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