CITY OF HOPE

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INSIDE THE BMT REUNION
PAGE 04

‘WITHIN MY LIFETIME’
PAGE 10

CANCER’S SWEET TOOTH
PAGE 16

QUEST FOR A CURE

INSIDE CITY OF HOPE’S MISSION TO CURE TYPE 1 DIABETES IN SIX YEARS
CONTENTS

VOL. 28 NO. 3 | SPRING/SUMMER 2017

QUEST FOR A CURE
08
Inside City of Hope’s mission to cure type 1 diabetes in six years.

BETA TESTING
14
New study flips the script on the cause of type 1 diabetes.

‘WITHIN MY LIFETIME’
10
The incredible legacy of diabetes researcher Arthur Riggs, Ph.D.

CANCER’S SWEET TOOTH
16
Researchers discover the sugar addiction of cancer cells.

FRONT COVER:
On the cover (from left to right): Rama Natarajan, Ph.D.; Defu Zeng; Bart Roep, Ph.D.; Fouad Kandeel, M.D., Ph.D.; Arthur Riggs, Ph.D.; Debbie Thurmond, Ph.D.

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. © 2017 City of Hope

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KATIE NEITH
ABE ROSENBERG
SUSAN YATES

Photographers
THOMAS BROWN
VERN EVANS
CRAIG TAKAHASHI
To many people, City of Hope is known primarily as one of the world’s foremost cancer research and treatment centers. But fighting cancer is only part of our story.

For 40 years, we have been making history against another illness that can be just as shattering to patients and their families. Diabetes.

Quietly, without fanfare, City of Hope researchers have made breakthrough discoveries and created technologies that have changed millions of lives. Today, the Diabetes & Metabolism Research Institute at City of Hope is committed to developing a cure for type 1 diabetes within six years, fueled by a $50 million funding program led by the Wanek family.

In this issue, you will read about the many ways that cancer and diabetes are interrelated, making it even more important for City of Hope to focus on both of these complex, multifaceted diseases. Meet a true pioneer, Dr. Arthur Riggs, the man who co-led the team responsible for the technology that led to the development of synthetic insulin.

Learn about our latest studies that explain how critical beta cells go wrong and trigger their own destruction.

The Wanek gift reinforces what we’ve always understood at City of Hope. Talent, knowledge and dedication, in partnership with your ongoing support, can indeed produce miracles. I look forward to everything we will achieve together.

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For the past 41 years, City of Hope has hosted an annual reunion for bone marrow transplant (BMT) survivors. What began with a birthday cake and a single candle representing a patient’s first year free from cancer has grown into an annual extravaganza that draws more than 4,000 survivors, donors and families from around the world, as well as the doctors, nurses and staff who helped them through the lifesaving treatment process.

The emotional highlight of every BMT Reunion is the point at which patients are introduced to the donors who quite literally saved their lives. Many bone marrow recipients, though overwhelmed with curiosity and the need to express their gratitude, can only dream of meeting the strangers who gave the gift of life. City of Hope makes that dream come true for two patients every year.

“The reunion highlights what research and exceptional nursing and physician care have accomplished to save the lives of patients,” said Stephen J. Forman, M.D., the Francis & Kathleen McNamara Distinguished Chair in Hematology and Hematopoietic Cell Transplantation at City of Hope. “It emphasizes we are all connected to each other, and the many joys in life that a patient is able to experience once they have been cured by a transplant.”

BY JOSH JENISCH
Anthony Stein, M.D., jumps from the stage during a performance with the Marrowettes.

Young violinist Alexander Fried.

The Marrowettes — comprised of City of Hope doctors and nurses — perform.

Two Laker Girls pose with City of Hope nurses.
Christopher Sistrunk, Ph.D.

Christopher Sistrunk, Ph.D., has joined City of Hope as assistant professor in the Department of Population Sciences. Prior to joining City of Hope, he was a postdoctoral fellow in medical oncology at Duke University, where he developed specific biomarkers for the initiation of triple-negative breast cancer. Sistrunk is studying the epigenetic effects linked to the chronic exposure of high levels of heavy metals in drinking water.

Nadia Carlesso, M.D., Ph.D.

Nadia Carlesso, M.D., Ph.D., joined Beckman Research Institute of City of Hope as professor in the Department of Hematology & Hematopoietic Cell Transplantation and as associate director of basic research at the Gehr Family Center for Leukemia Research. Carlesso and her team will lead efforts to identify novel therapeutic approaches simultaneously targeting the leukemia cells and the leukemic microenvironment. She has been continuously funded by the National Institutes of Health since 2001.

Markus Müschen, M.D., Ph.D.

Hailed as one of the best researchers of his generation, Markus Müschen, M.D., Ph.D., has joined City of Hope as the holder of The Norman and Sadie Lee Foundation Professorship in Pediatrics, and founding chair of the Department of Systems Biology at Beckman Research Institute of City of Hope. Müschen also serves as the new associate director of pediatric oncology of the comprehensive cancer center.

Kevin Morris, Ph.D.

Kevin Morris, Ph.D., associate director of the Center for Gene Therapy at City of Hope, was the first to recognize unique properties of noncoding RNA and is considered an international leader in the field. The goal of his work, in his words, is “to understand the role of noncoding RNA in life, evolution and selection” and to use that knowledge to develop novel therapies for AIDS, cancer and other diseases.
A diabetes powerhouse made even stronger — City of Hope's Diabetes & Metabolism Research Institute. Here, major breakthroughs have changed the lives of millions of diabetes patients around the world. One of the biggest, synthetic human insulin, was developed through research conducted at City of Hope, which is a direct result of work pioneered by Art Riggs, Ph.D., our institute director, and his team. And now we are looking to the future. The near future. With a goal of curing type 1 diabetes in six years. We aim to do that thanks to a transformative gift from the Wanek family and the generosity of countless others. The Wanek Family Project for Type 1 Diabetes at City of Hope: committed to finding a cure for type 1 diabetes. To learn more about our groundbreaking work in diabetes, visit CityofHope.org/t1d
Ron Wanek, founder and chairman of Ashley Furniture Industries (at the microphone), announces a generous gift to City of Hope

**QUEST FOR A CURE**

BY LETISIA MARQUEZ
INSIDE CITY OF HOPE’S MISSION TO CURE TYPE 1 DIABETES

It’s an extraordinary goal powered by an extraordinary gift.

City of Hope’s Diabetes & Metabolism Research Institute is committed to developing a cure for type 1 diabetes (T1D) within six years, fueled by a $50 million funding program led by the Wanek family.

It seems an audacious goal for a comprehensive cancer center, but City of Hope has a long history of groundbreaking work in diabetes. Research conducted by City of Hope led to the development of synthetic human insulin, which is still used today by many of the estimated 1.5 million Americans with type 1 diabetes (T1D) and 27 million with type 2 diabetes (T2D).

“City of Hope is best positioned to take on this challenge,” said Robert W. Stone, president and chief executive officer of City of Hope. “This is thanks to our 40-year institutional legacy of pioneering treatment and research advances in diabetes.”

The funding for the transformative research needed to embark on such an endeavor is led by a gift from the Wanek family, which owns Ashley Furniture Industries, the world’s largest home furniture manufacturer.

“City of Hope scientists’ research has revolutionized the understanding and treatment of diabetes,” said Todd Wanek, chief executive officer of Ashley Furniture, speaking on behalf of his family. “It continues today as physicians and scientists gain systemic understanding of diabetes as a complex, multifaceted disease.”

Through the generosity of the family and gifts from an anonymous donor, City of Hope will be able to devote more than $50 million over the next six years to an unprecedented research effort: The Wanek Family Project for Type 1 Diabetes.

A MULTIFACETED APPROACH

The Wanek Family Project will result in the creation of a series of highly focused programs at City of Hope. The idea is to attack the problem of T1D in an integrated way. Novel immunotherapy approaches will be investigated, as will insulin-secreting beta cells and ways to keep the body from rejecting those cells during transplantation.

The City of Hope goal to cure T1D will focus on three core areas, each of which is crucial in treating both types of diabetes.

**IMMUNE MODULATION**

Research is already underway at City of Hope to unlock the immune system’s role in diabetes, including T cell modulation and stem cell-based therapies that may reverse the autoimmune attack on islet cells in the pancreas, which is the cause of T1D. City of Hope’s Bart Roep, Ph.D. the Chan Soon-Shiong Shapiro Distinguished Chair in Diabetes, previously worked at Leiden University Medical Center in the Netherlands, where he was instrumental in launching a phase 1 clinical trial for a vaccine that aims to spur the immune system to fight — and possibly cure — T1D. Plans are being developed for a larger phase 2 trial to launch in the future at City of Hope.

**BETA CELL EXPANSION AND REPLACEMENT**

T1D and T2D both develop due to the dysfunction and demise of insulin-secreting beta cells. Researchers will work to improve methods of boosting and replacing beta cells to encourage long-term survival. Studies associated with the Wanek Family Project will derive new innovations to correct the beta cell dysfunction in diabetes.

**PREVENTING DIABETES COMPLICATIONS**

Both T1D and T2D are associated with similar complications: accelerated heart, kidney, neural and eye diseases greatly increase morbidity and mortality rates in both diseases. Scientists will work on intervening at the genetic level to reverse complications and will seek ways to predict the development of complications in order to prevent them from occurring.

“City of Hope is extremely grateful for the Wanek family’s significant gift that will enable the institution to forward type 1 diabetes research, the results of which will have worldwide impact,” said Stone.

“Our family is extremely confident that City of Hope is the institution that will find a cure for the more than 1 million Americans who battle type 1 diabetes disease every day,” Wanek said.
Arthur Riggs, Ph.D., the Samuel Rahbar Chair in Diabetes & Drug Discovery and director of the Diabetes & Metabolism Research Institute at City of Hope, is rounding third in his quest for a cure for type 1 diabetes. Now, thanks to a new $50 million funding program led by the Wanek family, he is only picking up the pace. “I’m very excited,” he said. “I continue to be amazed and excited about the progress that the entire field is making, and very pleased that we are right there at the forefront, particularly in the fields of cellular therapy and immunotherapy.”
A LEGACY OF BREAKTHROUGHS

Riggs is no newcomer to this task — he has been working on better treatments for diabetes since joining City of Hope nearly 50 years ago in 1969.

Although not as well-known as its cancer program, “City of Hope has had a very significant research program in diabetes since 1970,” Riggs said.

Perhaps most significantly, Riggs co-led the team that laid the groundwork for the development of the first synthetic human insulin for patients — from E. coli bacteria — in 1978. He received the Juvenile Diabetes Foundation Research Award the following year for that breakthrough, which led to the formation of Genentech and the biotechnology industry. Today, the medication has become the standard of care for diabetes, helping over 4 million people worldwide.

City of Hope scientists have been responsible for several other leaps forward in diabetes treatment, including development of the HbA1C blood sugar test and pancreatic islet (insulin-making clusters of beta cells) transplantation.

MODERN DEVELOPMENTS

In 2014, City of Hope established the Diabetes & Metabolic Research Institute, integrating basic, translational and clinical research with innovative care and comprehensive education.

The work done there has resulted in exciting developments in cell transplantation, gene regulation and immune tolerance, and in gaining systemic understanding of diabetes as a complex, multifaceted disease.

“We’ve become one of the best diabetes research institutes in the world,” Riggs said.

ACCELERATING PROGRESS

Type 1 diabetes is an autoimmune disorder in which immune cells that normally protect people from infections and cancer mistakenly attack the insulin-producing beta cells found in the pancreas, leaving the patient dependent on insulin injections.

The new infusion of funds “will accelerate our progress [against the disease], especially in clinical trials,” Riggs said. “It will accelerate the transfer to patient care.”

Current trials involve manipulating the immune system via a vaccine and an improved method of bone marrow stem cell transplantation to replace the diabetic patient’s compromised immune system with a healthy one. Both of these techniques “have the promise of stopping [type 1] diabetes even once it has started. Preclinical work will be started right away. We’ll find out right away whether or not they’ll work,” Riggs said.

Other experiments involve improving islet cell transplantation techniques and using nanoparticles that are derived from stem cells to improve the function and survival of transplanted islet cells. Still other trials will be focused on preventing the complications of diabetes.

RENEWED PURPOSE

Ironically, “I did not intend to study diabetes,” Riggs admitted. “The early work was an accident. Really we were trying to make genes. We asked ourselves, ‘What useful gene can we make?’ The gene that we decided to make that we thought would be useful was human insulin.”

However, “Around 2000, I did take it upon myself as a goal to cure diabetes within my lifetime. I’m comfortable with the goal of curing [type 1] diabetes within the next six years,” Riggs said. “I’m very excited about the way things have developed.”

In more good news, Riggs pointed out that “there is a lot of overlap between type 1 and type 2 diabetes” — the latter by far the more common manifestation — “and all of the research about beta cells that we’re doing applies to both type 1 and type 2 diabetes.”

However, even though Riggs sees a cure within sight, “That will just be the beginning. It will take longer for it to go into common practice. But I’m confident we will learn how to stop diabetes in its tracks within six years.”

“We are already moving forward. We’re off with a running start,” he said.
SIDES OF THE SAME COIN

Cancer and diabetes have more in common than you think

BY ABE ROSENBERG
City of Hope recently announced its goal to cure type 1 diabetes within six years, made possible in part through a generous gift from the Wanek family. The announcement raises a natural question:

Why should City of Hope, a renowned cancer center, devote so much time, effort and resources to the study and treatment of diabetes? Aren’t they very different diseases?

Well, yes and no.

To begin with, a great many people struggle with both diabetes and cancer at the same time.

People with type 2 diabetes (the most common form) are twice as likely to develop liver or pancreatic cancer. They also run a higher-than-normal risk of developing colon, bladder and breast cancer. Diabetic women with breast cancer have a higher mortality rate than women with breast cancer alone. (Oddly, diabetic men run a lower risk of developing prostate cancer.)

Ever-growing research strongly suggests that none of this is random or coincidental. Rather, it’s clear that, from biology to risk factors to treatment options, cancer and diabetes are intimately related in many ways.

“Cancer and diabetes are two sides of the same coin,” asserted Debbie Thurmond, Ph.D., chair of the Department of Molecular and Cellular Endocrinology at the Diabetes & Metabolism Research Institute at City of Hope. “They are disruptions of the body’s normal metabolism.”

That may help explain why obesity is a major risk factor for both diseases. Excess fat may begin that disruption process, as well as increase inflammation, a known trigger for diabetes as well as cancer. Fat deposits located around internal organs secrete chemicals and send signals which make cells more aggressive, initiating tumor growth, while also creating insulin resistance, leading to type 2 diabetes.

And one illness may feed on the other. Some studies suggest that abnormally high levels of insulin, typical in type 2 diabetes, can cause cancer. At the same time, a buildup of blood sugar is exactly what some cancer cells are waiting for.

“Cancer cells love glucose,” added Rama Natarajan, Ph.D., chair of the Department of Diabetes Complications and Metabolism, as well as an expert in molecular oncology. “It’s their primary fuel, and we’ve known this since 1930, when the Warburg effect was identified.”

Nobel Laureate Otto Warburg demonstrated that cancer cells consume and metabolize glucose at 200 times the normal rate. In fact, positron emission tomography scans are designed to detect the presence of cancer in the body by locating areas of high glucose consumption.

In theory then, a medication that lowers blood sugar levels in diabetes could also potentially fight cancer, by “starving” malignant cells to death. Which is why many cancer researchers are looking closely at metformin, the No. 1 drug for treating type 2 diabetes. There is evidence that diabetics who take metformin may be less likely to develop cancer, and, should they contract the disease, significantly less likely to die from it.

Some treatments, however, may fight one disease while making the other worse.

“There are forms of chemotherapy that induce insulin resistance, bringing on symptoms of diabetes,” said Arthur Riggs, Ph.D., director of the Diabetes & Metabolism Research Institute at City of Hope. It was Riggs’ pioneering work in the 1970s that led to the development of synthetic human insulin.

Worse, immunotherapy, one of the most exciting advances in cancer treatment, may actually bring on the less-common type 1 diabetes, which is essentially an autoimmune disorder. With immunotherapy, the body’s immune system is “unleashed,” and it may attack critical insulin-producing cells in the pancreas.

“Immunotherapy,” said Riggs, “can cause permanent diabetes. It’s a serious complication.” Serious enough for some of Riggs’ colleagues to wonder if they’ve crossed the “Do No Harm” line. Riggs doesn’t think so. “It’s progress,” he said. “Immunotherapy can save someone’s life, and the diabetes it leaves behind is treatable.”

All of which points to the logic, even the necessity, of experts in both cancer and diabetes working together. City of Hope has understood this for 40 years, culminating in 2014 with the opening of its Diabetes & Metabolism Research Institute, and then in 2017 with the establishment of The Wanek Family Project for Type 1 Diabetes. The opportunities for collaboration are enormous, and the need for such cross-pollination is clear.

“We need to be worried about each other,” said Thurmond, the Ruth B. & Robert K. Lanman Chair in Gene Regulation and Drug Discovery Research, “exactly because treating one disease may wreak havoc with the other, so we need to communicate and share information, and that’s exactly what we do.”

“It’s an educated guess,” said Riggs, the Samuel Rahbar Chair in Diabetes & Drug Discovery, “but I’d say the majority of our diabetes researchers are also working on cancer, and many of our cancer biologists are doing work relevant for diabetes.”

Perhaps nowhere is that collaboration more critical than in islet cell transplantation, a promising experimental treatment for type 1 diabetics. Cell clusters from a donor pancreas are implanted, in the hope that they’ll begin to produce insulin and regulate blood sugar, and reducing the need for insulin injections.

When embarking on such complex transplant surgery, it’s invaluable to be able to confer with colleagues who’ve performed over 13,500 bone marrow and stem cell transplants to treat leukemia and other blood cancers.

“Rejection, for example, is always a possibility with any transplant, so you need to suppress the immune system” said Riggs. “The bone marrow folks on the cancer side know more about immunosuppression than anybody else.”

It works both ways. Diabetes researchers are developing a treatment that may one day cure the disease, and carry an added benefit: It may also halt graft-versus-host disease, a serious consequence of bone marrow transplants.

Other ongoing collaborations may bear fruit in the near future. Among them:

1. Searching for a possible link between the receptor for advanced glycation end product and some brain tumors. “We’ve seen that gliomas grow faster in diabetic mice,” said Natarajan, the National Business Products Industry Professor in Diabetes Research. “Our team is working with (City of Hope neurosurgeon) Dr. Behnam Badie to examine this.”

2. A National Institutes of Health grant will explore whether insulin resistance is a key factor in the high rate of triple-negative breast cancer in obese women of color.

3. A training program for postdoctoral students is being created to address the diabetes-metabolic disorder-cancer connections.

Ultimately of course, the common goal is to eradicate both cancer and diabetes. While no one can say how long that will take, it’s reasonable to believe that, with both camps working side by side, they just may pull it off. One step at a time.

“Yes, to a researcher, ‘cure’ is a four-letter word,” said Thurmond. “We don’t like to send out false hopes. For now though, curing diabetes within a decade, without making cancer worse … that’s the plan!”
BETA TESTING

NEW STUDY FLIPS THE SCRIPT ON CAUSE OF TYPE 1 DIABETES

BY KATIE NEITH

For decades, scientists believed that the root cause of type 1 diabetes (T1D) was the immune system mistakenly identifying insulin-secreting beta cells as a potential danger and, in turn, destroying them.

This is because T1D — a disease that affects an estimated 1.5 million Americans and was previously known as juvenile diabetes — is the result of the unexplained loss of cells in the pancreas that produce insulin.

Now, a study led by City of Hope’s Bart Roep, Ph.D., the Chan Soon-Shiong Shapiro Distinguished Chair in Diabetes and professor and founding chair of the Department of Diabetes Immunology, turns that idea on its head.

“Our findings show that type 1 diabetes results from a mistake of the beta cell, not a mistake of the immune system,” said Roep, who is director of The Wanek Family Project for Type 1 Diabetes, which was recently created with gifts from the Wanek family and anonymous donors to support the institution’s goal of curing T1D in six years. “The immune system does what it is supposed to do, which is respond to distressed or ‘unhappy’ tissue, as it would in infection or cancer.”

Roep, along with researchers from the Leiden University Medical Center in the Netherlands, published study results showing this outcome in the Feb. 27 issue of the journal, Nature Medicine.

In the paper, the team outlined a mechanism by which stressed beta cells are actually causing the immune response that leads to their own demise. When beta cells are destroyed, the body no longer makes insulin and therefore cannot distribute glucose — a simple sugar we get from eating that is used by the body for energy — causing T1D and, ultimately, the need to artificially supplement insulin.

To gain a better understanding of why the immune system attacks the body’s own source of insulin — the pancreatic beta cells — the team took some clues from cancer molecules that are also targeted by the immune system after successful treatment of the cancer with immunotherapy.

One of these cancer targets is a so-called “nonsense” protein, a nonfunctional protein that is the result of a misread DNA sequence. It turns out that the same type of protein error is also produced by the beta cells in T1D.

Roep and the other researchers believe it is a “wrong read” of the insulin gene itself that causes problems. This faulty product of the insulin gene is created when beta cells are stressed, said Roep.

“Our study links anti-tumor immunity to islet autoimmunity, and may explain why some cancer patients develop type 1 diabetes after successful immunotherapy,” he said. “This is an incredible step forward in our commitment to cure this disease.”

The results of the study give Roep new insight, he said, for his work — and for other scientists in the Diabetes & Metabolism Research Institute at City of Hope — in developing new vaccines to desensitize the immune system so that it will tolerate islets again, as well as for research into combining immunotherapy with more traditional diabetes treatments to reinvigorate islets.

“Our goal is to keep beta cells happy,” Roep said. “So we will work on new forms of therapy to correct the autoimmune response against islets and hopefully also prevent development of type 1 diabetes during anti-cancer therapy.”
Acute lymphoblastic leukemia (ALL) represents the most frequent type of cancer in children and young adults. Despite a good general prognosis and increased survival rates over the past decades, outcomes have not improved for the approximately 25 percent of patients who relapse after initially successful treatment. More than 60 percent of patients who experience ALL bone marrow relapse will die from their disease.

Now, a team led by City of Hope’s Markus Müschen, M.D., Ph.D., founding chair of the Department of Systems Biology and holder of The Norman and Sadie Lee Foundation Professorship in Pediatrics, thinks that sugar uptake and energy supply may play a key role in the relapse of ALL.

A paper published in the Feb. 13 issue of the journal, Nature, outlines their findings, which point to increased glucose as the driver of the energy needed for specific cells to transform into malignant cancer cells. ALL typically arises from B cells, which are known for producing antibodies in the human immune system. B cells can also transform into childhood leukemia when something goes wrong in their development.

By taking a closer look at how B cells are regulated, Müschen and colleagues found that factors that determine B cell identity can also restrict glucose — or sugar — and energy supply. Hence, B cells have much lower energy levels than any other cell type.

“While transformation to cancer and childhood leukemia takes large amounts of energy, we discovered that the low energy levels in B cells protect them from malignant transformation toward leukemia and cancer,” said Müschen, who recently joined Beckman Research Institute of City of Hope.

“The low energy levels in normal B cells are simply too low to allow transformation to cancer and leukemia,” said Lai Chan, Ph.D., the study’s first author and assistant professor in the Department of Systems Biology.

The team also found that deletion of genes that encode B cell-determining factors occur in almost all cases of childhood leukemia. Conversely, they saw that the addition of large amounts of sugar can make B cells susceptible to malignant transformation by giving them the energy needed for tumor formation.

Müschen says these results back up a previous finding that obese children with high blood sugar levels are much more likely to develop drug-resistant leukemia and experience relapse than children who are not overweight. The findings also indicate that dieting could be an important consideration for children who have survived leukemia.

“Avoiding obesity and excessive energy supply, or sugar, may help to decrease the risk of leukemia relapse,” he said.

To test that theory, Müschen plans to perform experiments in animal models to evaluate the efficacy of dietary restriction on patient-derived childhood leukemia cells.

He also plans to assess the activity of drugs that reduce the ability of leukemia cells to take up glucose and energy supply.

Since future relapse patients are indistinguishable from patients who will respond well to standard chemotherapy, many of the approximately 110,000 childhood ALL survivors in the U.S. would benefit from milder forms of chemotherapy, yet are treated with an aggressive regimen and will suffer late effects from unnecessary toxicity, said Müschen.

“We found that these drugs strongly work together with existing anti-leukemia drugs, and preclinical safety studies suggest that these drugs can be given to patients without any additional toxicity or adverse side effects,” he said.
Markus Müschen, M.D., Ph.D.
Let’s say you’re a carpenter, and you’re building a cabinet. No problem, you’re pretty good at it. But suppose you happen to meet a computer whiz with a modeling program that can design a super gorgeous cabinet? And what if the two of you then bump into a chemist with a formula for treating wood that’ll make that cabinet practically indestructible? Then, what if the three of you meet up with a mathematician with an algorithm enabling you to build bigger, better and cheaper? Wouldn’t that be amazing? All that help from folks who never picked up a hammer in their lives!

Chasing cancer from all angles

BY ABE ROSENBERG
Welcome to the future of cancer research.
Scientists and clinicians alike have figured out that in this era of precision, targeted therapy that digs down into the very DNA of disease, it’s necessary to venture beyond their own labs for answers.

Tomorrow’s breakthroughs will require a multidisciplinary approach: medical people working hand-in-hand with physical scientists, data crunchers, nanotechnologists, digital imaging specialists and more. Pulling together such a disparate team requires a special kind of vision and leadership.

And few people do it better than Peter Lee, M.D.

“I try to take a ‘big picture’ approach to solving problems,” said Lee, the Billy and Audrey L. Wilder Professor in Cancer Immunotherapeutics who chairs City of Hope’s Department of Immuno-Oncology. “So many traditional scientists begin with something complex and break it down to just one thing, in isolation. That doesn’t translate into real-world help for patients.”

He’s been helming multidisciplinary teams for more than a decade, starting with a U.S. Army grant in 2005 for which he brought together statisticians, computer scientists and clinicians to study breast cancer.

In his latest “big picture” project, Lee directs a diverse, far-flung team that’s examining breast tumors’ so-called “microenvironment,” or the noncancerous cells that surround and support the tumor, and how they affect the immune system.

It’s this kind of ambitious, never-before-trying approach that truly excites Lee, and he’s found kindred spirits at the Stand Up To Cancer (SU2C) Foundation, which is funding his team — along with the Breast Cancer Research Foundation, the V Foundation and Bristol-Myers Squibb — in a kind of “combo” grant.

“Lee is a serious guy who really cares,” said Arnold J. Levine, Ph.D., a SU2C scientific advisor and supervisor of Lee’s team, pointing out that Lee takes what he learns from his patients and reintegrates it into his lab. “Not every clinician does science the way he does.”

Levine isn’t the only one who believes Lee is onto something.

“We’ve only begun to understand how the tumor microenvironment modulates cancer both from a growth and suppression perspective,” said David Horne, Ph.D., vice provost and associate director of Beckman Research Institute of City of Hope. “The more we can unravel these complex interactions, the more we’ll understand how to develop more effective therapies involving the tumor microenvironment, rather than just the tumor itself.”

For Lee, all this is validation, as well as incentive. But results are what matter most to him.

“What matters to me most,” he said, “is the focus on the patients. I want to bring them the results of my research.”
A Journey of Hope

The enduring legacy of City of Hope’s Japanese-American scientists

BY LETISIA MARQUEZ
CITY OF HOPE'S RICH HISTORY IS FILLED WITH STORIES OF CELEBRATED RESEARCHERS WHO HELPED SHAPE THE COURSE OF MODERN MEDICINE.

But lesser known are the stories of the Japanese-American scientists who came to City of Hope and contributed greatly to the advancement of cancer and genetic research, helping the institution develop into the internationally renowned center it is today.

And though decades have passed since their arrival, one City of Hope scientist is making sure that their contributions are not forgotten.

PRESERVING THE PAST

Yoko Fujita-Yamaguchi, Ph.D., professor emeritus in the Diabetes & Metabolism Research Institute at City of Hope, has written a book in Japanese that delves into the contributions of Japanese-American scientists at City of Hope. Her next step: working closely with Steve Novak, former director of City of Hope's graduate program and a trained archivist, to write a version of the book in English.

"A tremendous amount of history was made by two distinguished City of Hope scientists, Dr. Riojun Kinosita and Dr. Susumu Ohno, but few people know about it," Yamaguchi said. "We do not want their contributions to be forgotten. We want to pay homage to what they did and how they helped advance cancer and genetics research."

A RISING STAR

Before he became head of the newly formed City of Hope Cancer Research Institute in 1952, Kinosita, a Japanese native, was already well-known for his groundbreaking research on carcinogens. In the 1930s, chemical procedures had evolved so that individual compounds could be linked to cancer. But little was known about direct links until researchers such as Kinosita conducted research on the topic.

In 1936, Kinosita reported that something known as butter yellow, a chemical used to color food, induced cancer in the liver of rats when it was taken with food. In 1939, Kinosita was invited by the prestigious Jane Coffin Childs Memorial Fund for Medical Research to deliver a lecture titled, "Studies on the carcinogenic compounds," at Yale University School of Medicine.

American newspapers reported on Kinosita's visit to the United States in 1948 to give lectures about his research. At the time, World War II had just ended and anti-Japanese sentiment was still strong. But Kinoshita, president of the Japanese Cancer Society, was given a passport to the U.S. to present his findings to cancer experts through a special arrangement made by the American Cancer Society.

Yamaguchi meticulously searched for articles about Kinosita's lectures in newspaper archives. She found them and keeps them tucked away in a folder, with the hope to include them in the English-language book.

FINDING HOPE

In 1952, City of Hope and the UCLA medical school combined forces to launch a joint research effort at City of Hope's Duarte, California, campus. Known as the Cancer Research Institute, the fledging operation quickly attracted progressive scientists such as Kinosita, who had worked at UCLA and came to City of Hope to lead research efforts.

Kinosita's impact was swiftly felt. In fact, a small basic research unit that he started in 1952 has since grown and earned international renown. It became the City of Hope Beckman Research Center in 1982.

As head of the Cancer Research Institute in 1952, Kinosita recruited a young researcher, Susumu Ohno, who was born to Japanese parents in Korea. Ohno was a young postdoctoral fellow at the time, but his research would also make waves in the scientific community.

In the 1978 obituary for Kinosita, Ohno wrote, "He shall long be remembered for his brilliant series of experiments that proved that a number of azo dyes were hepatocarcinogens of varying strengths (1932 to 1937)" and "As professor of pathology first at Hokkaido and then at Osaka (Imperial) Universities, he cultivated the next generation of leaders in Japanese cancer research."

THE PRODIGY

Ohno, at the time of his recruitment to City of Hope, held a doctor of veterinary medicine degree and became Kinosita's last graduate student in 1953. He earned his Ph.D. in 1961 from Hokkaido University.

Ohno had a brilliant career at City of Hope, highlighted by numerous fundamental findings in genetics, epigenetics and molecular evolution. However, he is probably most famous for having written "the book" on evolution by gene duplication. He also discovered the phenomenon of X chromosome inactivation where, in females, one of the two X chromosomes becomes condensed and nonfunctional. As a result, the cells of both males and females have only one functioning X chromosome.

In recognition of these and many other discoveries, Ohno was elected to the National Academy of Sciences and received the Armory Prize for Reproductive Biology from the American Academy of Arts and Sciences. He retired from City of Hope in 1996.

PASSION AND ENERGY

Arthur D. Riggs, Ph.D., director of the Diabetes & Metabolism Research Institute at City of Hope, director emeritus of Beckman Research Institute of City of Hope and the Samuel Rahbar Chair in Diabetes & Drug Discovery, said that Yamaguchi and Novak's book will highlight early scientific breakthroughs at City of Hope, which younger generations may have forgotten.

Many of those early leaders have passed away, Riggs said, so it's crucial that the history be recorded now.

"Yoko is the one who has had the energy to document the history, so we are extremely grateful for her work and passion," he added.

In addition to the book, the researchers are organizing a special symposium in honor of Kinosita that will take place on Feb. 28, 2018. Panelists will discuss research aimed at understanding how exposure to chemicals and radiation in the environment leads to cancer.

"A lot of the incredibly important discoveries made by City of Hope scientists were made early on in the 1950s, '60s, '70s and '80s, and few people know about them," Riggs said. "What's also striking is how well the Jewish community embraced Japanese scientists just a few years after World War II, and how important those scientists were in developing our renowned research department."

"We are forever indebted to them."

“We do not want their contributions to be forgotten.”

Yoko Fujita-Yamaguchi, Ph.D., professor emeritus in the Diabetes & Metabolism Research Institute at City of Hope
‘BEING A NEUROSURGEON IS NOT ENOUGH’

BY DENISE HEADY

It had already been a long day for Behnam Badie, M.D.

He’d spent 12 hours on his feet surgically removing three aggressive brain tumors from three different patients — but he wasn’t ready to slow down.

Badie, chief of neurosurgery and director of the Brain Tumor Program at City of Hope, went from the operating room back to his office to review scans of a patient who was enrolled in a promising clinical trial for which he is a principal investigator. He and his colleagues are studying the potential of CAR-T cell therapy as a way to treat glioblastoma, an aggressive and fast-growing type of brain tumor.

BEYOND THE OPERATING ROOM

Glioblastoma, Badie said, is one of medicine’s most heartbreaking diseases. The average lifespan for someone who has been diagnosed with glioblastoma is often measured in months, not years. Not much progress has been made on the treatment of the disease over the past two decades.

While about 25 percent of brain tumors are malignant (cancerous), nearly 60 percent of Badie’s patients have a malignant brain tumor.

“No matter how well the surgery goes, how skillful you are as a neurosurgeon, malignant tumors still come back right at the surgical area,” said Badie. “It is always difficult to go to patients and tell them their surgery was successful, but there’s a good chance the tumor will recur in a few months.”

Driven in part by the plight of his patients, Badie spends nearly as much time in the laboratory as he does in the operating room. He wants to help not just today’s patients, but tomorrow’s.

“I’ve realized being a neurosurgeon is not enough,” said Badie. “The only way to truly beat this awful disease is through science and technology. And that’s one of the reasons I came to City of Hope.”

A DEFINING MOMENT

Ten years into his career as a neurosurgeon, Badie’s world was turned upside down when he learned his father, the family patriarch, had a malignant brain tumor.

“I remember seeing his brain MRI and I knew right away what was going to happen to him,” said Badie. “It was a turning point in my life.”

Badie’s father lived for almost a year after the initial diagnosis. And looking back, Badie finds it ironic that it was his dad who actually encouraged him to go into medicine.

“Before that I was a mere surgeon,” said Badie. “I’d done thousands of brain surgeries and many of them were the same. But after that experience, I saw the other side of having a brain tumor. I saw the family’s side. My dad gave me a better understanding of what the families and the patients go through; the sense of desperation and urgency — I think that really completed me as a neurosurgeon. It has motivated me to do more than just surgery.”

Badie is now working to transform brain tumor treatment using nanoparticles, engineered T cells, engineered stem cells and other novel treatments. But he has seen the most encouraging results with CAR-T therapy, during which a patient’s immune cells are reprogrammed to attack tumors. During one clinical trial, Badie was shocked to see a glioblastoma patient’s tumors appear “melt away.”

WHAT IT MEANS FOR THE FUTURE

What Badie and his team have achieved may be just the beginning.

“Treating brain tumors is very challenging,” said Badie. “There are many limitations and obstacles. They are very invasive, so it’s hard to remove the entire tumor without damaging the brain. And getting drugs into the brain has always been a major challenge because the blood-brain barrier, a natural defense system, keeps many drugs out.”

City of Hope researchers see enormous potential for CAR-T therapy. They remain encouraged that the treatment greatly improves quality of life by preserving patients’ neurological function and minimizing the toxic side effects of other treatments.

“We still have a lot of work to do, but just having that positive result from the low dose of the CAR-T cells is really, really promising,” said Badie. “Demonstrating that this technology works in a handful of patients gives us hope that CAR-T cell therapy will change the way we treat brain tumors.”

A treatment like this is something Badie wishes he’d had for his father.

“It’s very common for patients to ask me, ‘What would you do if it was you or your family?’ And I tell them I’ve been there with my father. He had the same cancer 11 years ago and I wish I had this option for him at that time — but I didn’t.”

“There’s no question in my mind that what we’re doing now will impact a lot of lives.”
BLOOD BROTHERS
Bone marrow donor and recipient meet each other for the first time

BY LETISIA MARQUEZ

As Evan Braggs played basketball one day in the summer of 2004, he ran out of breath and fell to the ground.

“I had to lie down for like 15 minutes,” he recalled. The next morning, his father took him to a local hospital, where medical staff tested his blood twice because they wanted to make sure the diagnosis was correct.

Braggs’ hemoglobin levels were so low that he was immediately admitted to the intensive care unit and given a blood transfusion.

“One of the nurses mentioned to me I was about two weeks away from having a heart attack,” he added.

The diagnosis shocked Braggs, who is now 32 and lives in Rancho Cucamonga, California. He had never had as much as a broken bone and, at the time, he ran hurdles for the Mt. San Antonio College track team. He also played basketball and worked out every day.

“Looking at me, you would not have known how sick I was,” he added.

At City of Hope, Ryotaro Nakamura, M.D., associate professor of hematology and hematopoietic cell transplantation, treated Braggs with two serums in
Mike Cook was stationed at Quantico, the Marine Corps base in Virginia, in the early 2000s when he attended a blood drive. A volunteer for bone marrow donation asked if he would join a registry. Cook didn’t hesitate.

“I thought about my nephew, who was sick at one time. He had a brain tumor when he was 18 months old,” said Cook. “He was helped, and I thought, ‘If I can do anything to help someone, I will do it.’”

Like many people who join the registry, Cook didn’t think about donating again until he received a call in 2005, letting him know that a patient matched his bone marrow.

He recalls visiting a hospital in Washington, D.C., to make the donation. There was a long line of people waiting for various procedures. Cook checked into the hospital, and told the receptionist he would sit down and wait.

“No, you’re a special case,” the receptionist told him and waved him right into the donation area. “It made me feel like what I was doing was truly special.”

On April 28, hundreds of other people — strangers for the most part — made Cook feel special. In an emotional reunion, Cook meet the patient whose life he helped save — Evan Braggs — at City of Hope’s Bone Marrow Transplant Reunion.

“I was ecstatic to know that this person actually wanted to meet,” said Cook, who served in the U.S. Marine Corps for nearly 21 years, seeing combat in Bahrain and then in Desert Shield/Desert Storm. Today, he is a reverend in charge of the men’s ministry at Shiloh New Site Baptist Church in Stafford, Virginia.
When Sergio Ramirez came to City of Hope in early 2013, the acute lymphoblastic leukemia (ALL) he thought he had overcome after three years of treatment had recently returned. And it had come back stronger.

A biopsy revealed that 82 percent of his bone marrow cells were leukemic cells. The Los Angeles father of three boys was terrified about what loomed ahead.

“If the first three years of chemotherapy and maintenance did not work, I thought, “What am I going to go through now?”’ said Ramirez, 34, who knew that patients whose ALL has relapsed have only a roughly 40 percent chance of survival. ALL is a cancer that starts in white blood cells, produces cancerous cells and can quickly spread to a body’s organs.

“I was terrified but I didn’t show that because of my kids. I just wanted them to see that Daddy was strong and that he was going to be there for them,” he added.
Ramirez’s doctor had referred him to City of Hope to take part in an immunotherapy trial led by Anthony Stein, M.D., co-director of the Gehr Family Center for Leukemia Research.

Ramirez took two 28-day cycles of a drug, which spurred his immune cells to attack the leukemia cells and put his cancer in remission. But Ramirez still needed a bone marrow transplant so he could remain cancer-free, and received one a few weeks later. He’s thought often about the unrelated donor who came forward to save the life of a person he had never met.

On April 28, Ramirez finally thanked his donor, Michael Palacios, 27, of Los Angeles, at City of Hope’s 41st annual Bone Marrow Transplant Reunion.

To say Ramirez is appreciative would be an understatement.

“I’m here with my kids, thanks mostly because of his generosity,” said Ramirez, who recalled that a donor who had first been identified didn’t go through with the donation. “My biggest fear was that my sons would lose their dad. It was also my biggest motivation to keep on fighting.”

***

The night before he was scheduled to donate bone marrow, Michael Palacios couldn’t sleep.

He was too restless and excited. He kept thinking about the City of Hope patient with a terminal illness, lying in a hospital bed anxiously waiting for Palacios’ bone marrow.

“I was so excited to get this done and be a part of someone’s life, to give them a second chance at life,” said Palacios, who was 24 at the time of the donation in 2013.

Palacios has thought often about the patient whose life he helped save.

“I can’t imagine how happy he is to celebrate life, and to be with his family,” he added. “It’s an indescribable feeling. It’s something that actually came out of my flesh, out of my own body, and I gave it to someone else.”

Palacios signed up to be a donor in 2011. At the time, he was a volunteer at Children’s Hospital Los Angeles, where he played games, read books and provided other entertainment to children being treated at the hospital. A volunteer supervisor suggested to Palacios that he sign up for the Be the Match bone marrow registry. Eager to help, he joined that same day.

“As far back as I can remember, I’ve loved to help people,” he said.

He recalled that as a 5-year-old, his mother would take him to visit her friends, many of them young mothers like her.

“Their babies would cry and I would try to comfort them by putting toys in their cribs,” he said.

In high school, Palacios volunteered with churches to feed the hungry. In college, he helped make meals for homeless men and women, as well as adults going through alcohol and drug rehabilitation at a Hollywood church.

But knowing that he helped save someone’s life through bone marrow donation is the highlight of his young life.

“Donating was a very exciting and humbling experience,” he added. “It showed me that a lot of people are working very hard on a daily basis to save people’s lives and to inspire others.”

As noted above, Palacios met the patient he helped save, Sergio Ramirez, at City of Hope’s Bone Marrow Transplant Reunion.

“I still haven’t fully processed what I actually did,” Palacios said. “I’ve done a lot of things over the years — working with nonprofit organizations, different churches and doing missionary work in different countries. But I can legitimately say I saved someone’s life.”
WONDER WOMAN
JEANETTE BAITY

Cancer survivor Jeanette Baity may not have an invisible plane or a golden lasso, but she shares two other traits with Wonder Woman, her favorite superhero: courage and determination.

During treatment she “got Wonder Woman stickers and temporary tattoos and I really just tried to embrace everything that character stands for,” she said. “I tried to project a really strong female persona. In my head I was asking, ‘If Wonder Woman got cancer, what would she do?’”

By her 35th birthday in October 2015, Baity was declared cancer-free. But her determination didn’t end there. She decided to raise money from friends and family for City of Hope’s “Take It Personal” campaign, using its peer-to-peer fundraising platform called ourHope.

“I first heard about ourHope on the City of Hope website,” Baity said. “I just went on the ourHope page, wrote a quick bio and met my goal, so of course I was really impressed with all of my friends and family not thinking twice about donating.”

The “Take It Personal” campaign runs from June 1 to July 31 of this year and is a meaningful way to share your story and make an impact for City of Hope. Plus, every dollar raised in June and July will be matched up to $100,000. Creating a page is simple, just go to CityofHope.org/ourHope to share your story and set up your site.

On the heels of a transformational gift to City of Hope to establish The Wanek Family Project for Type 1 Diabetes, Ashley Furniture Industries staff gathered at the Bellagio Hotel in Las Vegas in January to honor Ron Wanek, founder and chairman of the board, for his 55 years in the furniture industry.

Inspired by his personal philanthropy, 580 marketing specialists raised $32,000 to commemorate this milestone anniversary and to celebrate his success in building the world’s leading furniture company. Wanek designated the gift to City of Hope.

“When we heard about the Waneks’ commitment to City of Hope in the fight to cure type 1 diabetes, we wanted to do something,” said Chris Roberts, Ashley Motion Division marketing specialist.

Ashley Furniture Industries has a strong history of community giving. The Wanek family, which founded and owns Ashley Furniture Industries, have long supported City of Hope through their leadership in the International Home Furnishings Industry.
CREATING TOMORROW’S MIRACLES

Sam Richardson with his wife, Sarah, and their children

Sam Richardson’s successful career is the result of his great drive and professional commitment. He has worked for three companies that are longtime supporters of City of Hope’s National Business Products Industry. It’s no surprise that he, too, has become a dedicated supporter. What is surprising is how that connection to City of Hope has changed the future for his entire family.

Richardson’s father was diagnosed with an aggressive form of bladder cancer.

“He called me and told me he had three months to live,” Richardson recalled. “I sought out the doctors at City of Hope because I knew they could provide essentially that: hope. And they did.”

Long past his initial three-month prognosis, Richardson’s father is still alive.

Richardson and his wife, Sarah, arranged to leave a gift for City of Hope through their whole life insurance plan.

“We were taught that you give what you can and we want to send that same message to our children,” said Richardson. “That’s why we’ve left a gift of life insurance to City of Hope. It’s an easy way to provide for our daughters and leave a legacy that gives hope to future families.”

Watch the Richardson’s tell their story and learn about easy ways to create your legacy of hope at myplanwithcoh.org/Richardson.

ELLA FITZGERALD:

Celebrating 100 Years of Song

BY MICHAEL EASTERLING

Ella Fitzgerald, known the world over as the First Lady of Song, would have celebrated her 100th birthday on April 25. A friend of City of Hope, her legacy lives on in areas of our Duarte, California, campus honoring her for her generous support of our diabetes research through the Ella Fitzgerald Charitable Foundation. City of Hope is the only medical institution that the foundation funds for diabetes research. Fitzgerald died from complications of the disease in 1996.

Fitzgerald, of course, lives on through her timeless music. Surviving challenging times and poverty in her youth, she went on to win 13 Grammy Awards, countless Downbeat Jazz Awards, the Kennedy Center Honor, the Presidential Medal of Freedom and the National Medal of Arts. She performed her last concert at Carnegie Hall in 1991.

“She truly believed in the work that City of Hope is doing,” said Fran Morris-Rosman, executive director of the foundation, based in Los Angeles. “In Ella’s later years, she was an insulin-dependent type 2 diabetic, suffering from many complications. Through the charitable foundation that Ella herself established, she wanted to support research that is focused on finding a cure for the disease that claimed her life. She would be very pleased with the progress that’s been made in the past 21 years.”

Fouad Kandeel, M.D., Ph.D., professor and chair of City of Hope’s Department of Clinical Diabetes, Endocrinology & Metabolism, and chair, Department of Translational Research and Cellular Therapeutics, recently benefited from the foundation’s yearly funding, which supported diabetes research programs he oversees, including the diabetes fellowship program.

“The Ella Fitzgerald Foundation has also been instrumental in funding the research of young investigators at City of Hope. The foundation started the careers of our scientists and their scientific endeavors,” Kandeel said.

LET’S BE FRANK

When Frank DiBella was diagnosed with Stage 4 bladder cancer in 2014, doctors at two hospitals told him he had only two to four months to live.

But DiBella — a successful business consultant, tax advisor and accountant whose string of celebrated clients included Liberace and Arnold Schwarzenegger — is accustomed to a challenge. He’d already beat kidney cancer 20 years earlier, and so he started polling his contacts for the next best step. The answer: City of Hope, and Sumanta Pal, M.D., an internationally recognized leader in genitourinary cancers.

“I’m a lucky man. Dr. Pal saved my life,” DiBella said.

Now he’s returning the favor.

A longtime fundraiser for the Muscular Dystrophy Association, DiBella has shifted his philanthropic focus to support City of Hope and Pal’s research into novel therapeutic approaches. This March marked the third annual “Let’s Be Frank About Cancer” gala in Orange County, California, chaired by DiBella. So far it has raised $4.5 million for City of Hope.

DiBella has a bigger dream: extending City of Hope to Orange County “so more people can benefit,” he said. He turns 72 this August, in time to celebrate six years since that two-month prognosis.

“When you go to City of Hope,” he said, “that’s what it is all about: hope.”

Frank DiBella (right) with Sumanta Pal, M.D.
In 1978, Keiichi Itakura, Ph.D., Arthur Riggs, Ph.D., the Samuel Rahbar Chair in Diabetes & Drug Discovery, David Goeddel, Ph.D., and Roberto Crea, Ph.D., in collaboration with Genentech scientists, revolutionized diabetes treatment. They believed they could use DNA chemistry and recombinant DNA technology to synthesize a human hormone, such as insulin. A year earlier, they had successfully programmed a bacteria to act as a “factory” to produce the hormone somatostatin. On Aug. 24, 1978, the Riggs-Itakura-Genentech team succeeded in creating synthetic human insulin using E. coli bacteria as the “factory.” This discovery led to the development of Humulin®, the brand name for synthetic human insulin. This scientific breakthrough carried out in a City of Hope lab was a medical miracle for patients dependent on insulin to manage their diabetes.
ourHOPE is City of Hope’s personal fundraising website and a way for you to directly support the cause closest to your heart.

OURHOPE MAKES IT EASY TO RAISE MONEY FOR CITY OF HOPE

When Art was diagnosed with a grade 3 terminal brain tumor at age 38, our whole world turned upside down. We never knew how much time we had left as a family, but we were grateful for every day. During special events such as our children’s birthdays, we knew that we didn’t necessarily need more gifts.

The one thing we desperately needed was progress toward a cure for brain cancer. That is why we chose to create an ourHope page for our friends and family to donate toward something more meaningful for our family, and for our ultimate goal: survival.

— Flora and Art Chong

TO GET STARTED, GO TO

CityofHope.org/ourhope

STEP 1 — Sign up and personalize your fundraising page

STEP 2 — Share your story and start fundraising

STEP 3 — Help find cures and care for patients

TO MAKE A GIFT

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New York City/Philadelphia/
Washington D.C.
800-344-8169

Northwest Region
San Francisco
800-732-7140

Seattle/Portland
800-934-9196

Southeast Region
Florida
Atlanta/Nashville
800-584-6709

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SEE YOUR BENEFITS

To receive a no-obligation example of the income and tax savings you would receive based on your donation amount* and your age† please contact us:

800-232-3314 | plannedgiving@coh.org
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* Our minimum donation amount is $25,000.
† The minimum age to establish a City of Hope gift annuity is 65.