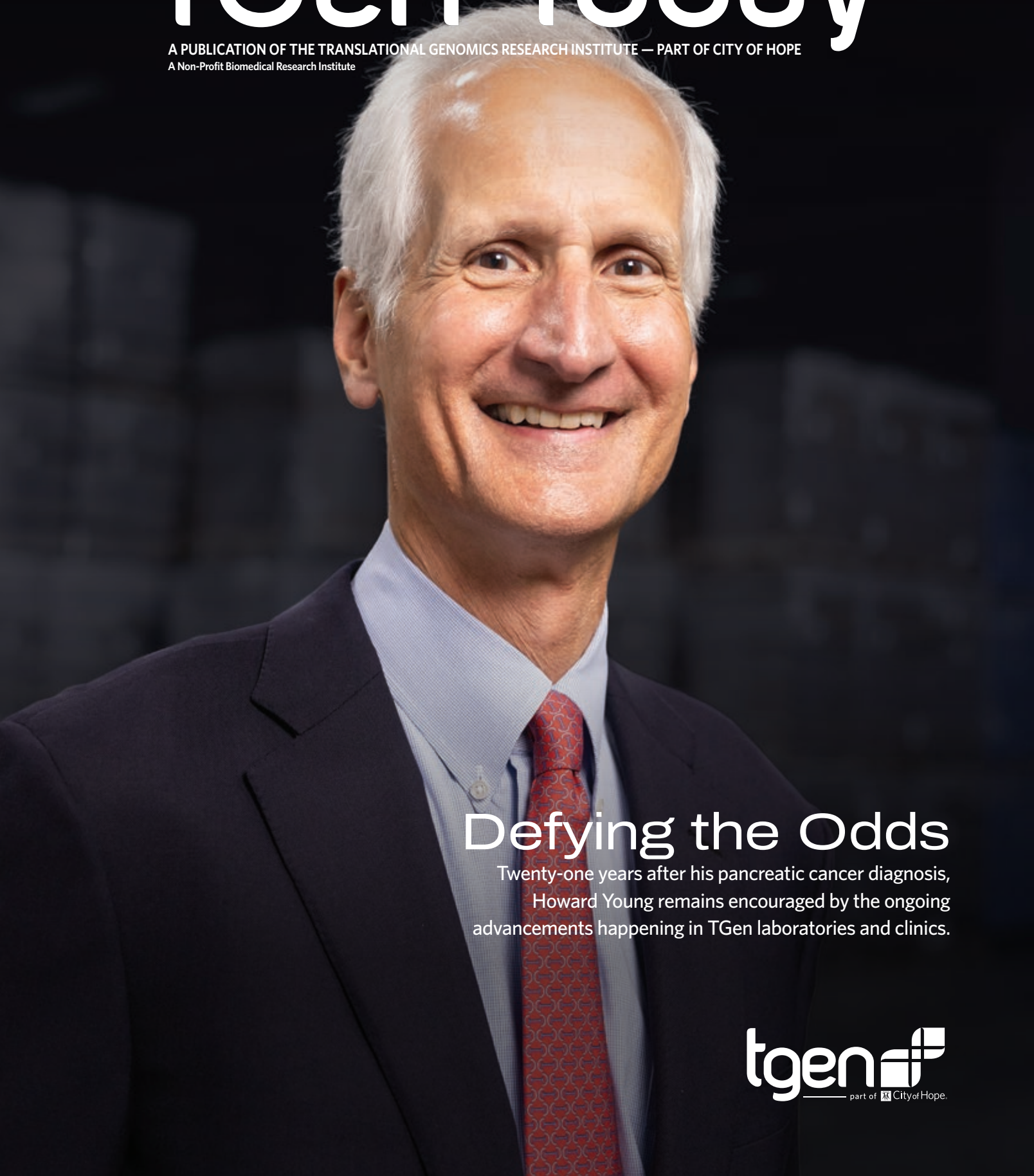


TGen Today

DECEMBER | 2023

A PUBLICATION OF THE TRANSLATIONAL GENOMICS RESEARCH INSTITUTE — PART OF CITY OF HOPE
A Non-Profit Biomedical Research Institute



Defying the Odds

Twenty-one years after his pancreatic cancer diagnosis, Howard Young remains encouraged by the ongoing advancements happening in TGen laboratories and clinics.

tgen 
part of  City of Hope.

A Look Inside...



Dear Friends,

If we have learned anything from two decades of research, it is that change is a constant and, when paired with discovery, often brings about improvements that touch our lives in profound ways.

This edition of *TGen Today* highlights change as a positive by detailing how biomedical science intersects with our everyday lives and how technology provides the tools necessary to answer many of the questions we ask in our laboratories as we set out to conquer disease; answers that often hold the promise to improve lives and alter outcomes.

That is certainly true for Howard Young, who has defied the odds as a pancreatic cancer survivor for over two decades. Howard has witnessed the remarkable evolution in cancer therapy, which has allowed him to experience moments and create memories that once seemed unattainable at the time of his diagnosis.

Howard's story can serve as an inspiration to others, showing that even when confronted with adversity, individuals can summon the strength and courage to endure. His story also underscores the ongoing progress in research and healthcare, at TGen, with our colleagues at City of Hope, and our collaborators around the world. This progress holds the promise of enhanced treatments and, ultimately, cures for countless others like Howard, and we are proud to stand at the forefront of this moment in time.

Our work in microbiome research, under the direction of Keehoon Lee, Ph.D., and his colleagues at TGen North, has significantly expanded our understanding of genomics and health by uncovering the deeply entwined relationships between the human genome and the genomes of those microorganisms living in and on our bodies. Beyond disease risk, the microbiome plays a role in nearly all aspects of our lives and can impact our immune system, mental health, inflammation, gut health, skin and oral health, and so much more.

This knowledge holds the potential to revolutionize healthcare. It enables the development of new precision medicine approaches, improved therapeutics, and offers a deeper comprehension of the complex interplay between humans and their environment. As we uncover the secrets of the microbiome, we are forging a path toward a healthier and more individualized approach to treatment and prevention.

TGen's Jonathan Keats, Ph.D., takes us inside the world of genome sequencing, a technology that has evolved significantly since the first human genome was sequenced. The improvements in sequencing have enhanced accuracy, speed, cost-effectiveness, and accessibility. These advancements have ushered in a new era of research, clinical diagnostics, and patient care. In doing so, they have driven innovation and discoveries in ways only imagined less than a decade ago.

The theme of change, when combined with discovery, enriches our lives and holds the promise of a brighter future. Beyond change, however, lies a simple truth: we cannot succeed without your ongoing belief in TGen and your support for our work in precision medicine. Each gift, regardless of its size, matters. For that, we are profoundly grateful.

Enjoy the read.

Best,

Erin Massey
Chief Development Officer, TGen Foundation
Vice President of Philanthropy, City of Hope



TGen, the Translational Genomics Research Institute, part of City of Hope, is an Arizona-based, nonprofit medical research institute dedicated to conducting ground breaking research with life-changing results. We work to unravel the genetic components of common and complex diseases, including cancer, neurological disorders, infectious disease, and rare childhood disorders. By identifying treatment options in this manner, we believe medicine becomes more rational, more precise and more personal.

TGen Today



2 Sequencing at Your Service

TGen's Collaborative Sequencing Center is continually upgrading its equipment and software to provide the most efficient, accurate and inexpensive next-generation sequencing. These advancements help the diagnosis of diseases in patients that we were previously unable to identify.



4 Journey to the Microbiome

Keehoon Lee, PhD, investigates the vast and intricate ecosystem of the human body.



10 Defying the Odds for Pancreatic Cancer

Twenty-one years after his diagnosis of pancreatic cancer, Howard Young is encouraged by the ongoing advancements happening in laboratories and clinics.



15 TGen Fashions a Future Without Cancer

TGen's third annual Runway for Research, organized by the TGen Foundation in collaboration with Neiman Marcus and Scottsdale Fashion Square raised more than \$320,000, setting a Runway record.



16 TGen In-Brief

News and noteworthy.



www.tgen.org



facebook.com/helptgen



x.com/tgen



youtube.com/tgenvideo



tgen.org/donate

TGen Talks is a monthly podcast that explores our latest science and discoveries. Find *TGen Talks* on the tgen.org homepage, through iTunes or on SoundCloud.



Sequencing at Your Service

An outbreak of bird flu became the catalyst that turned Jonathan Keats, Ph.D., toward a career in cancer research.

The Ph.D. advisor he wanted to study with at the time had gone to Hong Kong to investigate the outbreak, leaving Keats time to ponder whether he really wanted to dedicate his life to flu research. The answer came back no. Instead, Keats shifted his focus to genetic research on cancers, but he was determined to work directly with biopsies from patients, rather than just using mice or isolated cell lines in the lab.

"I didn't want to be someone who conducted research that might help people in 20 years. I wanted to make an immediate impact," he says. He also notes that this is why he enjoys working at TGen, as they share the same ethos: "Help someone today" he adds. "That's definitely a TGen motto."

ILLUMINATING THE "DARK" PARTS OF THE GENOME

Today, Keats is an assistant professor in TGen's Integrated Cancer Genomics Division and directs TGen's Collaborative Sequencing Center (CSC), a service center that provides next-generation sequencing for researchers around the world. Curious about the collection of genetic mutations within a patient's tumor? Want to sequence a child's entire genome and compare it with the whole genomes of her parents to find the cause of a rare disease? Hope to take a closer look at how RNA influences gene expression in a single cell? The CSC can help.

The state-of-the-art center draws on an array of advanced machines and analysis platforms to perform next-generation sequencing. Next-generation sequencing uncovers the genetic sequence of a patient's sample by sequencing billions of gene fragments at once, instead of determining the sequence one section of the genome at a time.

The center is continually upgrading its equipment and software to provide the most efficient, accurate and inexpensive next-generation sequencing, "so that the questions we want to ask can be addressed with the best technology we have today," Keats says.

There are different ways of sorting through the secrets of a genome, each with its own bespoke technology, he explains.

There's short-read sequencing, which gives a highly accurate readout of 50 to 300 "letters" or base pairs in a piece of DNA. TGen has been a leader in pushing short-read data into the clinic, using it to detect the "needle in a haystack" mutation that could affect a patient's response to therapy or determine whether a cancer patient has no detectable mutation after treatment.



"I didn't want to be someone who conducted research that might help people in 20 years. I wanted to make an immediate impact."

– Jonathan Keats, Ph.D.



This spring, the center installed its first long-read sequencer, the Oxford PromethION, which allows researchers to sequence a much longer string of DNA, up to the megabase or million base pair-long segments. The longer read allows a better glimpse at the DNA surrounding an interesting part of the genome but is less accurate than short reads.

Along with DNA sequence data, the long read can also identify modifications to genes that change their expression—a phenomenon called epigenetics. If a clinician is wondering why a patient stops responding to a particular cancer therapy, the long read can provide an answer as to whether the therapy has deleted the targeted gene or modified it in a way that prevents its expression. “It’s nice to be able to do all that in one test,” Keats notes.

In September, the center added another sequencer that looks at intermediate length DNA. “It breaks DNA into pieces of about 20,000 base pairs and makes a circle of it, and then the sequencer goes around and around and reads the circle over and over again,” explains Keats, “giving us the kind of accuracy that we can get from a short-read sequencer.”

Back in 2001, the first draft human genome sequence was assembled for about \$3 billion and had numerous gaps in its data. Today, “our two new instruments together let us do human genome assemblies that are gapless for less than \$10,000,” Keats notes.

The new platforms shine light on the “dark regions of the human genome,” he says. “We can now diagnose diseases in a patient that we couldn’t before because we now realize that the genetic error in this patient is in a piece of DNA that we didn’t even appreciate exists in the human species.”

Cancer sometimes occurs by what Keats calls “structural events”—occurrences that involve the deletion, repetition, flipping end to end, or swapping of a piece of DNA between chromosomes. Short-read sequencing doesn’t always pick up on these events, he says.

For 15 years, Keats worked on cells from a cancer patient trying to figure out why his cells appeared as they did. “And then this summer we did long-read sequencing and all of the sudden it made perfect sense.”

“Before we weren’t seeing what we thought we should be seeing, because there ... happened to be two structural events side by side,” he explains. “The short-read sequencing would only show us one but never showed us the second one.”

The solution presented itself with the help of a new sequencer and work done in part by a Helios Scholar summer intern, Keats says.

“I think that’s what makes me excited, because I know when we apply these sequencers to patient material, it’ll help us understand things we haven’t before.”

A RESEARCH UNICORN

Keats is also the Scientific Director of the Judy and Bernard Briskin Center for Multiple Myeloma Research at City of Hope. A relatively rare cancer—about 0.8 percent of Americans will get the disease in their lifetime—multiple myeloma occurs in plasma cells in the bone marrow, where the affected cells appear under the microscope like a malevolent batch of sunny-side up eggs.

When Keats turned from influenza to cancer research, he began working with a former professor who happened to study myeloma. “And now I realize how lucky I was, because it’s a unicorn disease when it comes to genetic research and research in general,” he says.

Researchers studying the genetics of cancers like breast cancer, for instance, analyze patient samples that sometimes only contain about 50 percent tumor material, Keats notes. It’s standard practice in multiple myeloma to enrich the material taken from a patient’s bone marrow, however, “so every sample I work on is about 95 percent tumor content or greater.”

With such pure material at hand, scientists can explore genetic aspects of cancer that have been difficult to confirm. For instance, Keats and his colleagues have learned that RNA measurements in a tumor are highly reproducible across studies and over time—something that was very difficult to see in solid tumors.

“I do think myeloma is sending a strong signal that if you can get rid of the contaminating normal that just adds noise to the system, that we will be able to learn a lot more about your disease,” he says.

And since plasma cells secrete certain

antibodies, scientists can use the antibodies produced by myeloma cells as a kind of natural biomarker. “You can basically track the amount of that antibody in the blood and that reflects the mass of tumor that exists in the body,” Keats explains. “We can readily monitor outcomes with a simple blood test.”

TGen scientists, among others in the cancer community, have long worked toward this goal of a simple way of monitoring tumors and how they respond to treatment. “But we’ve been doing this in myeloma for decades,” Keats says.

Keats is the lead researcher on the Multiple Myeloma Research Foundation’s Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile (CoMMpass) study, the largest single sequencing study of newly diagnosed multiple myeloma patients to date.

CoMMpass confirmed that there are two main groups of myeloma patients: one group with extra copies of chromosomes in their tumor cells, and another group with specific rearrangements in their chromosomes.

But the researchers have also uncovered multiple subtypes within these two groups, each with its own genetic quirks. These subtypes and specific genetic events help clinicians choose the therapy that best targets a patient’s tumor—and avoid costly, time-consuming therapies that don’t match—as Keats and his colleagues reported recently in a study published in *Nature Medicine*.

ANSWERS IN 48 HOURS

Those kinds of therapeutic decisions could get a lot easier with the TGen Clinical Laboratory’s 48-hour whole genome test service, debuting early next year.

The lab will offer the service for patients with the blood cancer acute myelogenous leukemia (AML) and then patients with multiple myeloma. A clinician at City of Hope, for example, could draw a blood or bone marrow sample from a patient and send it overnight to TGen. At the TCL, scientists will isolate, sequence and analyze DNA or RNA from the sample before sending a report back to the clinician.

Keats says that tracking down enough patient samples to validate each test the lab performs to achieve certification as patient-

ready has been one of the most challenging aspects of setting up the 48-hour service.

“It takes a team and a lot of effort to build something like this lab,” Keats says. “TGen’s really good at team science, so it builds on the strengths that we have here.”

Where the lab will really shine “is therapeutic decision-making—is a target gene still present, is it deleted, is it mutated,” he says, “so that physicians can make informed decisions on whether a therapy is likely to work for a patient or not.”

“ONE OF THE STRENGTHS OF TGEN’S SEQUENCING CENTERS, KEATS SAYS, IS THAT ITS SCIENTISTS HAVE WORKED WITH PATIENTS FROM A WIDE RANGE OF RACIAL AND ETHNIC BACKGROUNDS AND CAN APPRECIATE THE IMPORTANCE OF THAT 0.1 PERCENT.”

Studies show that people are 99.9 percent identical in their genetic makeup, so cancer genome researchers have long compared their patient samples to a “reference human genome,” made up of DNA sequences from multiple individuals.

But it’s that 0.1 percent that could prove useful in learning more about which individuals will respond to specific treatments. One of the strengths of TGen’s sequencing centers, Keats says, is that its scientists have worked with patients from a wide range of racial and ethnic backgrounds and can appreciate the importance of that 0.1 percent.

As it becomes easier and cheaper to assemble a whole human genome, researchers might start tracing the genetic roots of a patient’s tumor by comparing it against their own reference genome, rather than a reference genome that’s a mixture of multiple people. When we can do that, Keats notes, “there’s going to be things we discover that we would completely miss otherwise.”

With all these possibilities ahead, this is the most excited he’s been since the advent of next-generation sequencing about the potential of cancer genetics to change lives, Keats says.

“We used to talk about getting here and knowing we couldn’t, not without \$50 million for each patient,” he recalls. “Now it’s official that the world is your oyster and if you want to, you can do it.”



Journey to the Microbiome

Keehoon Lee, Ph.D., investigates the vast and intricate ecosystem of the human body

In a world teeming with organisms too small to see with the human eye, a deeper understanding of microbiology has long fascinated scientists. These tiny life forms, collectively known as microbes, have an outsized impact on our planet's ecosystems, our health, and even our daily lives.

For scientists such as TGen's Keehoon Lee, Ph.D., the relatively new field of integrated microbiomics seeks to fully understand the microbial realm by shedding light on the intricate web of connections between microorganisms and their hosts.

"We often speak of the microbes that cause disease as free-floating, solo agents of destruction, whether it's the bacteria behind a hospital infection or the fungus that infects the lungs in Valley fever," says Lee, a research assistant professor in TGen's Pathogen and Microbiome Division and co-director of the TGen Integrated Microbiomics Center (TIMC), "but the way we study microbes in the lab differs vastly from how they appear in nature."

Microbes are microscopic organisms such as bacteria, viruses, and fungi. They are ubiquitous, found everywhere from the depths of the ocean to the human gut, from the soil beneath our feet to the skies above. While many are harmful and cause diseases, a vast majority are beneficial, playing essential roles in various ecosystems and supporting life as we know it.

"Before, all of microbiology study was of the single, pure forms," says Lee. "Scientists would study one microbe at a time, such as *E. coli*, rarely, if ever, considering that microbe as part of a larger microbial community."

Today, the microbiome is the focus of

intense clinical interest. But 15 years ago, it was a word that was only just appearing in the scientific literature. For Lee, it all began with a sticky film of bacteria he encountered in a Northern Arizona University lab.

Sometimes bacteria from one or two species will aggregate in a slimy matrix, called a biofilm. Most often studied in medicine, biofilms also cause problems in places like the oil and gas industry where they can clog pipelines, and in transportation where they cling to and corrode the hulls of ships.

At NAU, Lee learned more about how biofilms cause chronic infections. For example, *Pseudomonas aeruginosa* bacteria, commonly found in burn victims, results from *Pseudomonas* biofilms, which adhere to the skin's surface and contribute to persistent infections.

"It's hard to clear or kill these biofilms with traditional antibiotic treatment, as the antibiotic resistance increases on the order of 1000-fold," Lee says. "That really caught my interest, to see how they act differently in their community."

THE EARLY YEARS

When Lee first started his research, the primary method for studying biofilms required him to take on the role of an amateur gardener, skillfully encouraging different species to thrive together and form new biofilms within the laboratory setting. "But it's a lot harder than it sounds," he says. "Biofilms that form in nature are usually not just one species, they also have all kinds of bacteria, fungus or other microbes in there."

“ We often speak of the microbes that cause disease as free-floating, solo agents of destruction, whether it's the bacteria behind a hospital infection or the fungus that infects the lungs in Valley fever. ”

— Keehoon Lee, Ph.D.



TGen North microbiome tech, Briana Coyne (left) reviews data with Keehoon Lee, Ph.D., assistant professor in TGen's Pathogen and Microbiome Division.

Luckily, genomic sequencing was coming into its own at that time, sparing Lee from those tedious experiments. Sequencing could swiftly identify and analyze not just the few genomes contained in a biofilm but the entire microbiome of an environment, such as the nose, throat or gut.

"Whether skin or slime on a river rock, sequencing allows us to define what's in there," he explains. "We changed the method of study by looking at their genomes instead of actually growing samples to analyze."

Lee and his colleagues now had a new way to glimpse the complex workings of a mostly hidden and poorly understood microbial world. But what would they see?

THE BRAIN, THE GUT AND EVERYTHING IN BETWEEN

The TIMC is a research service center, explains Lee, who has served as its co-director for almost two years. He and his colleagues work with scientists and clinicians to design studies that look deeper into a particular microbiome contained in fecal matter and urine and in the case of medical studies, tissue. Staff at the center sequence the genomes of the microbes that make up that microbiome's community and sometimes analyze the function of specific genes within those genomes.

Often the goal is to compare and contrast: what does a healthy gut microbiome look like compared with the gut microbiome of a person with colitis, for example? If researchers can pinpoint differences in the types of microbes or the way the microbes behave in each community, they could design therapies to nudge the diseased microbiome back toward health.

At the moment, there is only one FDA-approved microbiome treatment, to treat infection of the colon by *C. difficile* bacteria. Patients with this condition, sometimes called *C. diff*, receive a donor's fecal transplant that carries a healthy gut microbiome.

Treating *C. diff* with surgery or antibiotics proved successful 30- to 45 -percent of the time. "With the microbiome transplant, we saw a 90- to 95 -percent cure rate," Lee says. "It was extremely effective and resulted in few relapses."

A recent surge in microbial studies revealed the sophisticated connection between the gut microbiome and various diseases extends beyond the gastrointestinal tract, encompassing the central nervous system, conditions such as depression, and even cardiovascular diseases.

The link between brain and gut has been one of the more astonishing connections

discovered in microbiome studies. Scientists have found that bacteria in the gut can produce chemicals like serotonin, for example, that travel the long vagus nerve connecting the gut and brain to impact illnesses such as depression.

Some scientists believe that disruptions in the gut microbiome may initiate or worsen the inflammation observed in disorders like Alzheimer's disease and heart disease. Some gut bacteria produce molecules known as short-chain fatty acids, which possess protective and anti-inflammatory properties.

"These molecules can reinforce the barrier that the brain uses to protect itself," says Lee. "But if you have an unhealthy gut microbiome that has low short-chain fatty acids and more inflammatory molecules, they can go to the blood-brain barrier and increase its permeability."

Is there a way to tilt the health of the gut microbiome back toward normal?

The scientists who collaborate with TIMC want to answer that question. They are looking at possible probiotic treatments that add an essential microbe, or the molecules it produces, back into a microbiome. But they are also studying prebiotic approaches, looking for diets that lead to a healthy microbiome. For instance, the TIMC is helping a team of Finnish and City of Hope researchers

determine whether a high-fat diet —like the Ketogenic diet— can be beneficial for patients with bowel disease.

CANCER AND VALLEY FEVER

Researchers from TGen and City of Hope recently collaborated to examine how the microbiome can trigger certain cancers, such as the link between the HPV virus and cervical cancer, or how cancer drugs or immunotherapy interact with these microbiomes. At City of Hope, for instance, Sumanta Pal, M.D., co-director of City of Hope's Kidney Cancer Program, has been collaborating with Lee and Center researchers to learn how a patient's microbiome might respond to immunotherapy for metastatic renal cell carcinoma.

"We know that some microbiome members render these therapies very inactive, but some microbiomes can enhance the efficacy of these drugs," says Lee.

One example is the role of short-chain fatty acids in colon cancer. Scientists are also exploring the restoration of the microbiome after radiation therapy in rectal cancer and assessing whether probiotics can reduce side effects and enhance outcomes in immunotherapy for multiple cancers. Physicians also share information about the inflammatory molecules they see in their patients, or patient outcome data, for a particular type of cancer or treatment. This allows TIMC staff to dig deeper into the exact

relationship between a specific cancer and the microbiome data.

The center also actively partners with public health officials throughout the Southwest, actively monitoring the spread of the fungus responsible for causing Valley fever in both people and dogs. In Arizona's Maricopa County, the Center conducts air microbiome sampling at various locations to actively track potential outbreaks.

Fungal genome sequencing is a challenge, Lee says, capturing only about 50 percent of the data in a sample. But the center is working on a new sequencing technique, "and I'm confident that we're going to increase the accuracy of fungal microbiome studies," he notes.

Beyond cancer and Valley fever, Lee and his colleagues are proactively seeking new opportunities to apply their expertise. He sees potential in collaborating with TGen's Center for Rare Childhood Disorders, or maybe offering a microbiome sampling kit to patients enrolled in the precision aging studies led in part by TGen researchers.

In an era where the smallest entities are making the biggest impacts, integrated microbiomics provides a gateway to unlocking the secrets of the microbial world—a world that has always been with us yet remains largely unseen.

"With each breakthrough," says Lee, "we inch closer to a deeper understanding of the tiny organisms that shape our lives in ways we could never have imagined."



TGen North bioinformatician Brett Van Tassel (left) and microbiome technician, Briana Coyne (center) review data with TGen North assistant professor Keehoon Lee, Ph.D.

A recent surge in microbial studies revealed the sophisticated connection between the gut microbiome and various diseases extends beyond the gastrointestinal tract, encompassing the central nervous system, conditions such as depression, and even cardiovascular diseases.



DEFYING THE ODDS FOR PANCREATIC CANCER

“When you see experts at TGen, you’re going to get the latest standard of care at the very minimum, but you may be getting what is the future standard of care, like I did, and it could save your life, like it has mine.”

– Howard Young

Howard Young is someone a lot of people call after they’re diagnosed with pancreatic cancer. He gets calls from the husbands, wives, children and friends of patients as they support a loved one fighting the disease. Over the past two decades, hundreds of individuals struggling in their darkest hours have reached out to him for guidance, inspired by his cancer journey and the hope he brings.

People may find their way to Howard through church or through business connections. He’s the longtime co-owner and vice president of General Wholesale Company, a leading beverage distributor based in Atlanta. He has also led countless fundraising events for pancreatic cancer research, often partnering with other prominent community leaders. At these events – and in support groups, interviews and other settings – Howard is open about sharing his story, hoping to encourage others who are navigating or may one day have to contend with their own battles with cancer.

It has now been nearly 21 years since Howard first received his diagnosis of pancreatic cancer – a disease with the lowest survival rate of all major cancers. Rather than accept these odds, he found his way to TGen and Daniel D. Von Hoff,

M.D., who helped him not only survive the disease but also beat back three Stage 4 recurrences.

Howard advises people to ignore the frightening statistics. He urges them to seek out the best specialists, get genomic testing and participate in clinical trials. He connects many people to his own care team at TGen. When asked about other types of cancer, Howard often checks with his friends at TGen to track down the names of the top experts in those areas.

“You cannot afford to not get the best care,” he tells people. When you see experts at TGen, “you’re going to get the latest standard of care at the very minimum,” he explains, “but you may be getting what is the future standard of care, like I did, and it could save your life, like it has mine.”

Howard’s knowledge of research progress at TGen runs deep. Not only has he participated in clinical research as a patient, but he has also served as a patient advocate for three Stand Up To Cancer grants headed by Dr. Von Hoff, helping secure significant funding that drove development of new treatment regimens, including one for refractory pancreatic cancer. Howard also serves on the TGen Foundation board and chairs TGen’s National Advisory Council for Pancreatic Cancer Research.



Howard Young relaxes at home with his wife, Becky, (top left) and his five grandchildren.

His long association with TGen dates back almost to the organization's inception in 2002, when Howard's life took a surprising turn.

AN OMINOUS DIAGNOSIS

Howard didn't know a lot about cancer in 2002. It might have been the furthest thing from his mind. He was 42 years old, in the prime of life and otherwise in great health.

He and his wife, Becky, had three active girls. He was leading a successful family business. The holidays were approaching.

Then after a month of indigestion, he scheduled an appointment with his internist, thinking he might have picked up a bug during a recent trip to Mexico. He was completely unprepared for

the news he received. On December 19, 2002, after a CT scan, his doctor told him he had pancreatic cancer. Surgery was scheduled for the day after Christmas. But even if the procedure was a complete success, they said, he'd still have only a 20 percent chance of surviving for six months.

Howard had six days to get his affairs in order. His daughters were 12, 15 and 17 at the time.

He remembers looking at them thinking, "Will I ever see them graduate from high school, much less get married or have a child?"

He and Becky chose their words carefully when they talked to the girls. They downplayed the urgency and explained that there was "a mass" in his pancreas that had to be removed.

It was their youngest daughter who

asked, Could it be cancer? "We didn't tell them there was a 90 percent chance it was," Howard said. "But we said, well, yes, it very well could be."

Howard's surgery was followed by painful complications that brought him back to the hospital. He lost 35 pounds over just a few weeks. Then came months of intense chemotherapy followed by radiation.

YOU NEED TO TALK TO DAN VON HOFF

Howard sought a couple of second opinions during this time. Then, through a friend, he met someone who was battling pancreatic cancer himself who told Howard that the best person in America that he could see would be Daniel Von Hoff. "He said you might not be able to

get through to him," Howard recalled, "but you ought to try."

Howard called Dr. Von Hoff's office that same day and right away was invited to Arizona.

Dr. Von Hoff spent a full hour with Howard and Becky, and he assured them they had done everything they should do. "Now here's the great news," Dr. Von Hoff said, and he told them about molecular profiling.

Each person's cancer is unique to that individual, Dr. Von Hoff explained, and it can vary a great deal. Using a sample of Howard's tumor tissue that had been collected during his surgery the year before, Dr. Von Hoff and his team at TGen set out to look for known markers that could be treated with targeted therapies. These targeted treatments were often non-toxic and less debilitating than traditional chemotherapy and radiation.

Analyzing Howard's tumor sample, Dr. Von Hoff identified several known markers they began to attack with targeted therapies in an effort to destroy any lingering cancer cells. One treatment, for instance, targeted the epidermal growth factor receptor, which can contribute to cancer growth in a variety of cancers. They put Howard on a therapy that blocked this receptor in order to inhibit tumor growth.

After completing a series of targeted therapies, Howard was feeling like himself again and Dr. Von Hoff thought he was in a good place. Howard continued to travel to Arizona for monitoring every three months at first, then every six months.

JUST IN TIME FOR A TRANSFORMATIONAL CLINICAL TRIAL

In 2008, after years of monitoring, one of Howard's routine scans showed cavitory nodules on both lungs. Dr. Von Hoff ordered robotic surgery to biopsy one of the nodules, and this procedure confirmed that Howard had Stage 4 metastatic pancreatic cancer.

The timing, however, was fortuitous.

Dr. Von Hoff was in the midst of a clinical trial for the treatment of advanced pancreatic cancer that was showing great promise. He put Howard on the two-drug regimen of gemcitabine and nab-paclitaxel that he was testing, and the results were phenomenal. Within three months, Howard's nodules were no longer visible on a CT scan. After a six-month course of the drugs, Howard was once again cancer free and back to routine monitoring.

On December 19, 2002, after a CT scan, his doctor told Howard he had pancreatic cancer. Surgery was scheduled for the day after Christmas. But even if the procedure was a complete success, they said, he'd still have only a 20 percent chance of surviving for six months.

When the nodules returned in 2013, the two-drug combination that Howard had previously taken had just received FDA approval as one of two standards of care for pancreatic cancer. Further, Dr. Von Hoff now had evidence that patients who'd responded well to the regimen the first time tended to respond similarly well in the face of a recurrence. Sure enough, Howard's nodules disappeared just as quickly as before.

With each recurrence, Howard said he and his family put on their "battle gear" and maintained their faith. "It's a real emotional thing to shift gears," he said. "Every time, you think, is this the one?" Then each time he got to ring the bell signaling he was all-clear, he would start to settle back into normal life.

A REVELATION FROM GENOMIC PROFILING

Following his treatment in 2013, Howard was ready to declare that cancer was behind him. But the bad news came again in 2015. This time, it looked different.

Howard now had a mass in his lung that looked like it might be lung cancer. They scheduled surgery in Phoenix to remove a portion of Howard's left lower lobe and biopsy the mass. Again, it proved to be Stage 4 metastatic pancreatic cancer.

After surgery, Howard was put on the "TGen triple," the two-drug combination he had taken previously, paired with cisplatin, a form of platinum. Howard had recently been part of a Stand Up To Cancer grant which allowed Dr. Von Hoff to prove that this additional ingredient helped inhibit the ability of pancreatic cancer cells to repair their DNA, causing them to self-destruct. The "TGen triple" was now a recommended treatment by the National Comprehensive Cancer Network, and Howard responded favorably to it.

This time, Dr. Von Hoff said he wanted to map both Howard's genome and the genome of his tumor. This level of mapping was a relatively new practice, as TGen was getting the technology down to a fairly affordable undertaking. Today, City of Hope is performing an even more advanced level of genomic profiling for 90% of its patients to reveal potential treatment targets and contribute to the development of new diagnostics and therapies.

The analysis revealed that Howard's genome has an overamplification of one gene called GATA6. This increased number of genes, Dr. Von Hoff speculated, may help explain why Howard responds so well to treatment. A colleague on the Stand Up To Cancer grant, Michael Barrett at the Mayo Clinic in Arizona, conducted a global research study of long-term pancreatic cancer survivors, and many shared with Howard this overamplification of GATA6, suggesting it may be an indicator for a better prognosis in patients.



Howard, pictured with Dr. Daniel D. Von Hoff, who presented him with TGen's John S. McCain Leadership Award in 2016.

In the beginning, Howard asked friends to sponsor him in the 10K Peachtree Road Race. "I wanted people to know that you could recover from pancreatic cancer. You could go run a race," he said. "I wasn't winning it, but I ran the whole way."

Soon after, as his story became known, he partnered with others in the Atlanta area to raise funds in support of TGen's work. To date he has helped raise over \$6 million in support of Dr. Von Hoff and his pancreatic cancer research and clinical trials.

Howard joined TGen Foundation's board in 2009, the same year he began serving as a patient advocate on the first of three Stand Up To Cancer grants. In 2016, he was honored for his service with TGen's John S. McCain Leadership Award.

Today, as chair of TGen's National Advisory Council for Pancreatic Cancer Research, Howard is helping lead TGen's Relentless Pursuit initiative, an effort to establish The Daniel D. Von Hoff, M.D. Endowed Chair in Cancer Research and to raise support for pancreatic cancer clinical trials and early detection. Howard said the Council wants to ensure that some of the best and brightest scientists follow in the footsteps of Dr. Von Hoff, pushing the boundaries of innovation in the fight against pancreatic cancer.

Howard is encouraged by the continued progress being made in the laboratories and in the clinics. "Where once there seemed little hope," he said, "we now are seeing success."

He is particularly optimistic about the work Dr. Von Hoff and his colleagues are doing to develop a blood test to detect pancreatic cancer at its earliest stages when it is highly susceptible to treatment. The vision is that, in a few years, when individuals go to their primary care doctors, those with the highest risk profile will start to get a routine blood screening for early, curable pancreatic cancer.

Howard is also excited about the application of genomic analysis across City of Hope. "It's revolutionizing the treatment of cancer," Howard said. "City of Hope CEO, Robert Stone, and TGen president, Jeff Trent, Ph.D., have put together an all-star team that is rewriting the treatment of cancer globally. It's changing lives."

"Howard is such a great person who has given so much to the fight against cancer," Dr. Von Hoff said. "And we're starting to see more Howards out there. When patients see we've got people like Howard who've made it this far, they realize, I could be one of those, too."

That's a message that Howard likes to share, as well, with the many people who reach out to him. "I tell them, I'm alive in year 21. Why can't you be here 21 years from now?"

LIVING A FULL LIFE

It has now been eight years since Howard's last recurrence. He's looking forward to his 40th wedding anniversary. He has walked all three daughters down the aisle and recently welcomed his fifth grandchild. "I'm feeling pretty good," he said, "but I'm knocking on wood as I say this."

Howard has continued to get regular scans in Phoenix. He now sees Dr. Erkut Borazanci, one of Dr. Von Hoff's protégés who has taken over many of his patients, leaving Dr. Von Hoff more time to focus on research. At Howard's most recent appointment, Dr. Borazanci said he felt it was safe for Howard to go down to one scan a year.

"That's the first time anyone has said that to me in 20 years," Howard said.

GIVING BACK

Since the early days of his cancer journey, Howard said, "I wanted to find a way to raise money and awareness for pancreatic cancer. And I tell people I don't know where you can have more of an impact than TGen and Dr. Von Hoff."

Dr. Von Hoff's clinical trial work has now led to 3 of the 4 regimens approved by the FDA for treatment of patients with advanced pancreatic cancer.

TO SUPPORT THE DANIEL D. VON HOFF, M.D. ENDOWED CHAIR IN CANCER RESEARCH, PANCREATIC CANCER CLINICAL TRIALS AND EARLY DETECTION, VISIT: [TGEN.ORG/RELENTLESS](https://www.tgen.org/relentless)



TGEN FASHIONS A FUTURE WITHOUT CANCER

A diverse group of fashion enthusiasts, community members, and supporters gathered October 13 at Scottsdale Fashion Square for TGen's third annual Runway for Research, organized by the TGen Foundation in collaboration with Neiman Marcus and Scottsdale Fashion Square. The event celebrates cancer survivors and inspires hope while raising vital funds to support women's cancer research at TGen, part of City of Hope.

The two-hour event and fashion show turned Fashion Square's Luxury Wing into a runway, where guests received a first-class experience while treating themselves to an insider's preview to this year's hottest trends.

Erin Massey, Chief Development Officer at TGen and Vice President of Philanthropy

at City of Hope, emphasized the significant impact of the event on TGen's research in women's cancers.

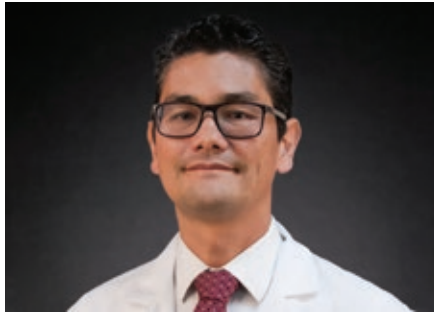
"Through the generosity and commitment of our event partners and attendees, we're advancing TGen's pivotal research in women's cancers, impacting patients locally and across the nation," said Massey. "The dollars raised have a transformative effect and we are very grateful to our Runway for Research co-chairs Beth McRae and Justine Hurry, their committee, Neiman Marcus, Scottsdale Fashion Square, and our sponsors and patrons for their commitment and energy toward making this year's event a great success."

The event raised more than \$320,000,

setting a Runway record. Nearly two dozen models graced the u-shaped catwalk, showcasing Neiman Marcus's high-fashion offerings.

Presenting sponsor, Betty McRae & The McRae Family, contributed to the success of this year's event along with the additional sponsors of the Jackson Family Foundation, Amazon, The Moreno Family Foundation, Trends Magazine, Martha and Wally Henkel, Priscilla Nicholas, Lisa Portigal, and Dee Dee Vecchione.

Planning for Runway for Research 2024 is already underway and we look forward to announcing that date in the coming months. To learn more about becoming a partner, please contact TGen Foundation at 602-343-8502.



ALAN H. BRYCE, M.D., JOINS TGEN AND CITY OF HOPE

City of Hope recently appointed Alan H. Bryce, M.D., chief clinical officer at City of Hope Cancer Center Phoenix and professor of molecular medicine at TGen. Bryce, a renowned prostate cancer expert, will lead clinical efforts across City of Hope locations in the Phoenix market. Board-certified in internal medicine and medical oncology, he focuses on individualized prostate cancer treatment, emphasizing genomics and developing new therapies.

As the region's senior clinical leader, Dr. Bryce will oversee care at the Goodyear cancer center and outpatient centers in Gilbert, North Phoenix, and Tatum Ridge. His goal is to establish a top-quality, coordinated cancer center for Arizona, integrating community and academic practices and improving access to breakthroughs.

"This move is motivated by my desire to build a top-quality, coordinated cancer center for the state of Arizona that includes both community and academic practices and enhances access to cancer breakthroughs," said Bryce. "This is no small task and one where others have tried before, but I am confident that we can succeed. More importantly, this is work that our community needs, and I am excited to meet the challenge."

At TGen, Dr. Bryce continues cancer research, therapeutic development, and immunotherapy approaches in prostate cancer. This collaboration with City of Hope Cancer Center Phoenix enhances the clinical setting for TGen's scientific discoveries. Dr. Bryce's extensive clinical trials portfolio in genitourinary cancers and melanoma, along with his focus on genomics for prognostic and predictive information in advanced cancers, contributes to advancing cancer care.

"I am delighted to welcome Dr. Bryce to City of Hope and TGen," said Jeffrey M. Trent, Ph.D., TGen president and research director. "I have had the privilege to work closely with him for over a decade, in efforts to use genomics to better individualize a patient's cancer treatment. His leadership role in national clinical trials for prostate cancer, and the broad range of cancer types for which he has clinical experience (including melanoma and early phase clinical trials), makes him an outstanding addition to City of Hope's advanced cancer care in Arizona and nationally."



DEDICATED AND DRIVEN TO SUCCEED

Participants laced-up their sneakers, embraced the rhythm of the pavement, and let their footsteps resonate with purpose at TGen's annual Step-N-Out 5K FUNdraiser, held on November 5 at Arizona Boardwalk. This was the 18th year of Step-N-Out which has raised more than \$2.1 million for pancreatic cancer research since its inception. Step-N-Out blended fun and purpose. Survivors, loved ones, caregivers, medical professionals, and supporters from across the nation converged in person and virtually to raise awareness and vital funds in support of the latest research and clinical advances for pancreatic cancer. In-person activities included a 5K run/walk, a 1-mile Fun Run, and a Kids' Dash.

"This event remains successful after nearly two decades due to the generosity of all who participate year after year," said Erin Massey, Chief Development Officer at TGen and Vice President of Philanthropy at City of Hope. "And it is extremely gratifying to know that commitment helps empower our TGen researchers to drive forward clinical trials that benefit pancreatic cancer patients."



STUDY LINKS INHERITED MUTATIONS TO OKUR-CHUNG NEURODEVELOPMENTAL SYNDROME

A recent study published in *Clinical Genetics* by TGen researchers identified CSNK2A1 gene mutations as the cause of Okur-Chung neurodevelopmental syndrome (OCNDS) in three families. The research improves genetic counseling and emphasizes the importance of genetic testing for accurate diagnosis and care.

"This study not only expands our knowledge of the syndrome's genetic basis but also underscores the importance of comprehensive genetic testing for accurate diagnosis and personalized management," said TGen's Sampath Rangasamy, Ph.D., one of the paper's senior authors. Supported by the CSNK2A1 Foundation, the study aims to help more families affected by OCNDS through advanced sequencing techniques.



HOW A TINY RNA MAY HOLD THE KEY TO TREATING CML

A recent study by researchers at City of Hope and TGen resulted in understanding a key aspect of Chronic Myeloid Leukemia (CML) and provides valuable insights into the evolution of CML from a manageable chronic phase to a more lethal version known as blast crisis (BC), potentially opening the door to improved treatments and the prospect of finding a cure.

Led by City of Hope researchers Guido Marcucci, M.D., and Bin Zhang, Ph.D., in collaboration with TGen's Patrick Pirrotte, Ph.D., the research, published in *Nature Communications*, sheds light on a hidden aspect of CML, offering a fresh perspective on its transformation into the more aggressive form.

To test their findings, the team created a synthetic version of miR-142 and tested it in mouse models with BP CML. They observed that miR-142 prevented CML transformation and even led to some mice being cured. Additionally, combining miR-142 with tyrosine kinase inhibitors, an approved therapy for CML, enhanced its anti-leukemic effects.

The researchers found lower amounts of a molecule called miR-142, an RNA molecule that regulates cell metabolism, in patients with the more severe stage of CML compared to those with the milder stage, suggesting it might be a factor in the development of the more fatal form of the disease.

"These key metabolic changes are at the heart of the transformation of CML into blast crisis, which, unfortunately, is associated with poor treatment options," said Pirrotte. "These new molecular findings provide interesting new avenues for therapies."

Leveraging TGen's unique molecular profiling platforms, this study also uncovered that the loss of miR-142 in CML causes major changes in the tumor metabolism. These changes trigger the transformation of CML into blast crisis, a phase characterized by limited treatment options.

"This study employed TGen's exciting new metabolomics platform, which promises to reveal novel therapeutic targets in CML and other cancers," said Khyati Pathak, Ph.D., a research assistant professor and TGen and study author.

The study was funded by The Robert & Lynda Carter Altman Family Foundation Research Fund.



A NIGHT TO CELEBRATE ARIZONA HISTORYMAKERS

On Saturday, October 14, a single cut of a turquoise ribbon opened the Historical League's display and celebration of the 2023 Arizona Historymakers ceremony.

An audience of 300 gathered at the Arizona Heritage Center to celebrate and honor this year's inductees, including TGen Drs. Jeffrey Trent and Daniel D. Von Hoff, who joined Frank Barrios, Dr. Michael Crow, Angel Delgadillo, Dolan Ellis, Terry Goddard, Denise Resnik, and Elizabeth White in the class of 2023.

Created in 1992, the award program recognizes Arizona individuals who have distinguished themselves with noted achievements and have maintained ties to Arizona. 90 Historymakers have been honored over the years at celebration events and included in the Historymakers Hall exhibit at the Arizona Heritage Center. Their videos, oral histories, and transcripts are uploaded to the League's website and preserved in the Library & Archives of Arizona Historical Society's Arizona Heritage Center.

Since 1979, the Historical League has contributed more than \$2 million dollars to the Arizona Heritage Center and League members have volunteered over 175,000 hours to the museum.



TGen's Matthew Huentelman, Ph.D., has expanded his online MindCrowd test by leveraging technology to revolutionize research recruitment through mobile laboratories.

"Our mobile brain imaging scanner will visit communities throughout Arizona, making it easier for people to participate without the hassle of a long commute," says Huentelman. "My hope is to encourage underserved and underrepresented populations, often unable to visit research laboratories, to become a part of the study."

The mobile lab enables Huentelman and his colleagues to conduct a range of functional tests and capture a non-invasive image of the brain, enhancing research capabilities across various scientific domains. Participants receive a \$20 gift card upon completion of the visit, as well as a 3D printed replica of their brain, generated from the mobile MRI data. To schedule a stop in your town, email mindcrowd-mobilelab@tgen.org for more details. Take the test at mindcrowd.org.



Translational Genomics Research Institute
445 North Fifth Street, Suite 600
Phoenix, Arizona 85004

Imagine a world with a cure for every patient

Each discovery we make and every new treatment we create gives people the opportunity for a longer, better, more fulfilled life.

Learn how a gift in your will makes this healthy future possible.

Visit myplanwithtgen.org/resources to download our free publication, *Imagine a World With a Cure for Every Patient: Your Gift for the Future*.

TGen Foundation
plannedgiving@tgen.org
866-370-8436

