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TGen Today

A PUBLICATION OF THE TRANSLATIONAL GENOMICS
RESEARCH INSTITUTE — AN AFFILIATE OF CITY OF HOPE



One in a Million

Dr. Matt Huentelman envisions
a future where successful aging
prevents age-related disease

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A Look Inside...



Dear Friends,

This edition of *TGen Today* explores the many ways TGen researchers, working with our colleagues at City of Hope, are at the frontier of scientific discovery.

Cancer, infectious diseases, lung disease — even the way we age — the increasingly positive impacts of TGen and City of Hope scientists on the health of people locally, nationally and throughout the world are all explored in these pages.

The voices of patients are heard, as well. Just like “Jeopardy!” host Alex Trebek, Sandra DeMey Forrest was diagnosed with Stage 4 pancreatic cancer. She was given only months to live. But thanks to new therapeutic combinations created by TGen, Sandra is still alive more than four years later.

Our cover story examines how TGen’s push for Precision Medicine — which has revolutionized the way we approach cancer by focusing on each individual patient — might now become the model for how we approach growing older through a process we call Precision Aging.

Each person is different, and the ways we help must be as equally unique.

To that end, a citizen-scientist project called *MyImmunity* — which joins TGen’s *MindCrowd* in enabling tens of thousands of people across the globe to be part of our scientific discoveries — is just beginning.

The future looks promising.

Join us!

With gratitude,



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



TGen, the Translational Genomics Research Institute, is an affiliate of City of Hope. We are 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.

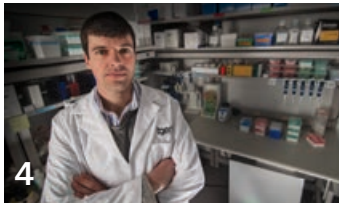


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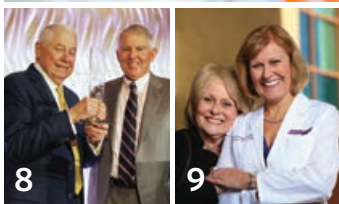
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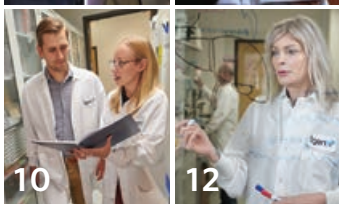
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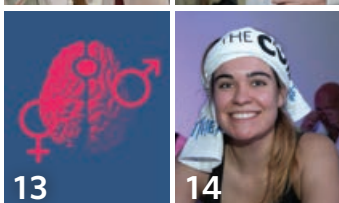
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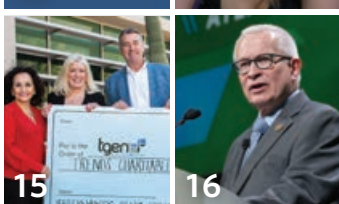
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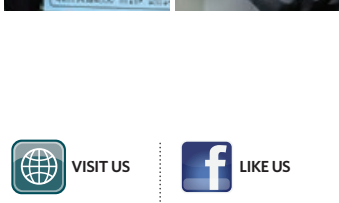
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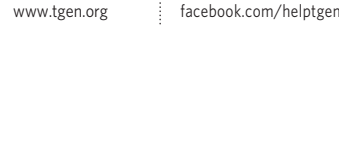
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IN PURSUIT OF PRECISION AGING

Dr. Matt Huentelman envisions a future where successful aging prevents age-related disease

Is it possible to prevent or significantly delay the onset of Alzheimer's, hearing loss, heart disease, cancer and other age-related conditions?

TGen's Dr. Matt Huentelman believes the answer is yes.

Early data from an ongoing project dubbed MindCrowd — a study on how the healthy brain works — convinces him that it's possible to apply the rigor that led to precision medicine in treating cancer to the aging process.

"'Precision Aging' is our term for a fully personalized assessment of an individual's risk and protective factors associated with how their cognitive — their brain's — performance may change with age," said Dr. Huentelman, Professor of TGen's Neurogenomics Division.

In many successful cancer treatments over the past decade, TGen's commitment to Precision Medicine has led to specific therapeutics given in the right dose, at the right time, to the right patient, based on precise genomic evaluations of cancer patients' DNA.

"We are excited to apply those same principles, for the first time ever, to the process of brain aging," said Dr. Huentelman, whose pursuit of MindCrowd could be one of the first steps in the development of a regimen for Precision Aging.

"Aging by itself is not a disease. But I think it is fair to say that all of us want to age as slowly, or put another way, as *successfully* as we possibly can," he adds.

"If we can achieve personal successful aging, there is ample evidence to show that alone could help us avoid many of the age-related diseases that are major concerns across the world; diseases like Alzheimer's, heart and blood vessel disease, cancer and many others."

Over the past six years, more than 115,000 people aged 18 to 95 — from every state and 150 nations across the globe — have completed the MindCrowd.org test.

Represented by these balls, TGen Professor of Neurogenomics Dr. Matt Huentelman (left) aims to gather 1 million diverse, individual participants in TGen's MindCrowd study.

Location: Ready, Set, Play! Paradise Valley Mall

Dr. Huentelman is always careful to point out that MindCrowd is not a diagnostic test. It will not tell you if you have Alzheimer's, or if you are at-risk for dementia. What it does give researchers is a set of data baselines about how normal, healthy brains perform at different ages; among men and women, among those with quick and slow physical responses, among those who smoke and those who don't, and among many other demographic, lifestyle and medical factors.

Establishing these baselines will help researchers in the future to more properly evaluate Alzheimer's patients and usher in a new era of precision aging. It also holds the promise of helping explain why some people do poorly on the test, and why some perform so well, even perfectly.

"MindCrowd has been immensely successful to date," said Dr. Huentelman. "During this 6th anniversary year for the study, we are looking deeply at the changes we want to make to the project."

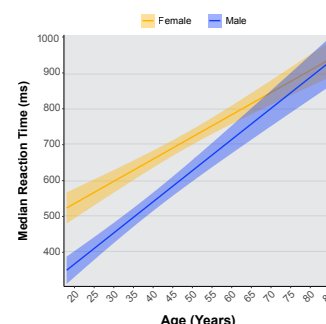
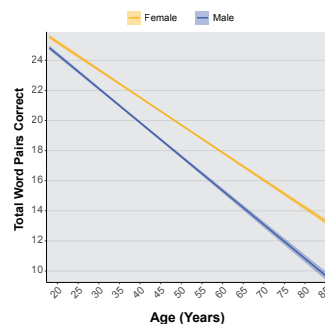
Those changes include improving the diversity of participants — differences in culture, education, socioeconomic levels — and incorporating yearly measurements of brain health, instead of just a single measurement.

"This way," he said, "we can begin to help people understand how their brain is changing across time, and expand the way we test each participant's brain to include brain games that examine other aspects of memory, thinking, emotion and intelligence."

MindCrowd to add Spanish and Chinese versions

One way to improve the study's accessibility — opening it to potentially 2 billion more participants — will be the launch of the site beyond English to include two additional languages: Spanish and Mandarin Chinese.

This should go a long way towards the study's goal of 1 million participants. The larger the number of samples, the more refined is the data. When MindCrowd.org started, the initial sample performances were all over the board. But after several tens of thousands of participants, trends and patterns began to clearly emerge.



For example, on the MindCrowd test, men generally have quicker physical response times than women. And women generally have better memory performance than men. Those general results hold true at every age level.

Dr. Huentelman now wants to incorporate the results of MindCrowd.org into a framework of Precision Aging measurements, joining with Dr. Nicholas Schork, Director of TGen's Quantitative Medicine and Systems Biology Division, and colleagues at the University of Arizona, to help create a Precision Aging Network.

"By using big data and artificial-intelligence analytical approaches, we aim to provide each individual with a personalized score that can be easily understood and explored more deeply," Dr. Huentelman said. "We can then help them ascertain their own unique risk, and protective factors, and thereby focus on exactly what we predict will benefit their aging brain the most."

"We think this is critically important. We believe strongly that the Precision Medicine approach has proven it's worth in oncology, and we are excited to now apply the same principles to help all of us age more successfully," Dr. Huentelman said. "There is a lot of advice out there about what to do to slow the aging process, but none of it is personalized — none of it is based on Precision Aging."

LEARN MORE: LISTEN TO OUR PODCAST



www.tgen.org/tgen-talks

EPISODE 15: MINDCROWD—A STUDY ON HOW THE HEALTHY BRAIN WORKS

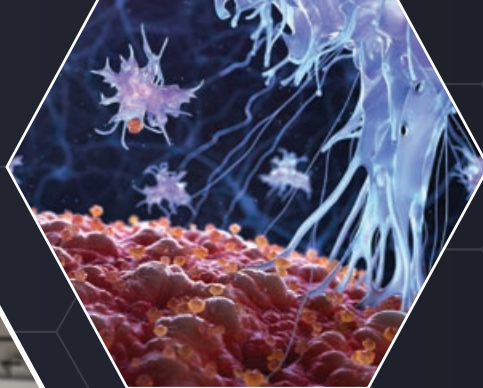
"There is a lot of advice out there about what to do to slow the aging process, but none of it is personalized — none of it is based on Precision Aging."

— Dr. Matt Huentelman,
Professor of TGen's Neurogenomics Division

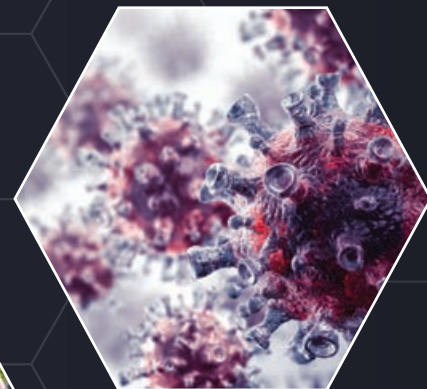
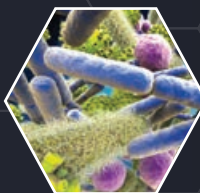
TAKE THE TEST



TGen needs citizen-scientists, like you, to take the MindCrowd.org test and help us measure how normal healthy brains perform at different ages. More than 115,000 people from all 50 states and more than 150 nations have taken the test. Please go to www.MindCrowd.org.



Dr. John Altin



Crowdsourcing Science

TGen's latest citizen-scientist project tackles viruses and immune response

There are more than 300 viruses that can trigger an immune response with defensive antibodies in humans. These viruses can be as deadly as HIV and Ebola, or as common as the cold. Many are not serious and produce no symptoms.

Still, depending on each individual's DNA, every person's response is unique, and what may not affect one person may cause another to become violently ill. On average, adults expose themselves to as many as 10 different viruses every year.

All of which led to a hypothesis by TGen North immunologist Dr. John Altin: What if there was a way to detect every virus we encounter, and record our immune system's response?

Inspired by MindCrowd (see Pages 2-3), Dr. Altin devised a different type of citizen-science project called *MyImmunity*, which will use large numbers of volunteers to create a global atlas of human immune responses.

"We now have the technology to look beyond one virus and one immune response at a time," said Dr. Altin, an Assistant Professor in TGen's Pathogen and Microbiome Division, TGen North, in Flagstaff,

Arizona. "*MyImmunity* will attempt to look across the entire universe of viruses and responses — all in one simple test. This will give us a holistic picture of how humans and virus co-exist."

Dr. Altin envisions *MyImmunity* as an app-based study that will look broadly at individuals' immune memory for exposure to a large set of pathogens. Individuals interested in participating in the study will download the study-related app, enroll, answer questions regarding their medical history, and then receive a blood collection kit.

The kit, part of a relatively new technology, records blood samples on special paper that doesn't require refrigeration. Participants submit a simple finger prick of blood — similar to the type of blood-sugar test used by many with diabetes — periodically taken over the course of several weeks or months, then mail the card back to TGen.

The genomic information contained within each sample traces how the immune system changes over time following exposure to numerous viruses. Each exposure is "seen" by the immune system and contributes to the body's "immune memory" by building an antibody response and resistance to each virus.

"This is about participants being able to better understand their own immune responses," Dr. Altin said. "Maybe an individual gets sick more than they think they should, and they want to know more about what might be causing their illness?"

"MyImmunity will attempt to look across the entire universe of viruses and responses — all in one simple test."

— Dr. John Altin, Assistant Professor, TGen North

The *MyImmunity* project could help researchers track disease outbreaks, explain how aging effects the immune system, and zero in on biomarkers that reveal how one individual's immune system differs from those of another. It also could lead to the development of vaccines against various diseases.

"We think there are some real possibilities for translational medicine. For example, viruses that normally cause few or no symptoms can become deadly after bone marrow transplantation. If we could track how the immune system recovers after transplantation, we may be able to provide personalized guidance that improves patient outcomes," Dr. Altin said.

While drawing inspiration from MindCrowd, Dr. Altin's project differs greatly in many ways. MindCrowd volunteers spend less than 10 minutes taking the on-line assessment. *MyImmunity* asks participants to collect data over weeks or months. MindCrowd data is instantly accessible. *MyImmunity* samples require laboratory analysis. MindCrowd seeks 1 million participants. Dr. Altin wants *MyImmunity* to eventually draw 10,000 volunteers.

"The early success of MindCrowd shows us crowdsourced science is possible," said Dr. Altin. "I look forward to seeing where this project takes us."

Creating a Tuberculosis Vaccine

In addition to *MyImmunity*, Dr. Altin's lab is involved in another critical pathogen investigation: tuberculosis, or TB.

Thanks to modern medicine, TB is virtually gone in the U.S., which records less than 10,000 cases a year, and very few deaths. But in the rest of the world, this potentially severe bacterial lung infection affects nearly 1-in-4 people, annually killing as many as 1.5 million.

"TB is the most deadly pathogen on the planet," Dr. Altin said. "It's a big problem that needs better solutions."

Currently, only one relatively effective vaccine against TB exists. Named after the French scientists who developed it, children in countries with high percentages of TB receive Bacillus Calmette-Guerin (BCG) to prevent TB-related meningitis and miliary TB. However, it's not considered a universal preventative.

"There also are a number of experimental vaccines, but nothing that has really taken off," Dr. Altin said. "Our hope is that we can better understand this disease; that we can identify individuals who have better immune responses to TB, and identify the biomarkers that show why some people are better protected than others."

Another factor in controlling TB is the speed at which it is evolving, developing drug resistance to current TB therapeutics. In a partnership with Tucson's Critical Path Institute, TGen is in the process of sequencing nearly 9,000 TB samples from around the world, searching for genetic vulnerabilities.

"If we can develop a successful biomarker," Dr. Altin said, "that would accelerate the process of creating a more effective TB vaccine."



Photo: Center for Disease Control and Prevention

TGen pursues global rollout of advanced TB test

In an important step toward the eventual global eradication of tuberculosis (TB), TGen has signed a licensing agreement with an international biomedical firm, Advanced Biological Laboratories (ABL), to market and distribute TGen's patented next generation sequencing based TB test technology — *DeepChek-TB*.

ABL is working toward distribution of the compact, portable and affordable diagnostic test that physicians worldwide could use to help determine the most appropriate treatment for each TB patient. Current tests can take 6-9 weeks to complete. *DeepChek-TB* can deliver results in just 2-3 days, and identify drug-resistant TB among mixed infections.

Because of modern medicine, TB in the U.S. continues to be a relatively minor threat. Globally, however, this lung-damaging communicable disease infects nearly one-fourth of the world's population and kills nearly 3 people every minute.

2-3 DAYS Current tests can take **6-9 weeks** to complete, *DeepChek-TB* can deliver results in just **2-3 days**.



Dr. Sunil Sharma

CREATING MONSTERS TO FIGHT CANCER

TGen partners with City of Hope to re-energize the body's own immune system against cancers

In Greek mythology, a Chimera is a hybrid creature composed of more than one animal, specifically a fire-breathing monster with the head of a lion, the body of a goat and a tail like a serpent. In developing new treatments that harness a patient's own immune system to fight cancer, Chimeric Antigen Receptor T cells, or CAR T cells, are among the promising new immunotherapies being developed by TGen and City of Hope. For tumors, CAR T cells might as well be fire-breathing monsters.

How it Works

Clinicians remove immune system T cells from the bloodstream of an individual cancer patient and re-engineer them in the laboratory using a hybrid of proteins. This process creates the CAR T cells. Treatment consists of reintroducing the CAR T cells into the patient's bloodstream, whereby they hunt down and destroy the targeted cancer.

CAR T cells, once they are injected back into the patient, propagate and persist, which is why CAR T therapy can provide both a rapid and long-term response, and the possibility of complete remission. At least, that's the way they have worked successfully in blood cancers, such as Leukemia.

Now, TGen and City of Hope researches are teaming up to see if they can get CAR T cells to work on solid tumors, including breast, pancreas and brain cancers.

More Ways to Harness Immune System

City of Hope and TGen investigators recently opened two clinical trials at City of Hope's Duarte, California, campus to test the effectiveness of combination immunotherapies to fight advanced liver, stomach, and esophageal cancers.

Both trials use an experimental immune system activation agent, IRX-2, produced by Brooklyn ImmunoTherapeutics. The trials combine IRX-2 with nivolumab for liver cancer patients, and IRX-2 with pembrolizumab for stomach and esophageal cancer patients. Both nivolumab and pembrolizumab are among a relatively new class of FDA-approved immunotherapies known as immune checkpoint antibodies.

"We're trying to turn potentially 'cold tumors' - those with strong fortresses nearly impenetrable to the immune system - into 'hot tumors' that have walls equipped with ladders for immune T cells so that more patients can derive benefit from treatment with immunotherapy," said Dr. Daneng Li, a co-principal investigator on the studies and an Assistant Clinical Professor in the Department of Medical Oncology and Therapeutics Research at City of Hope.

Dr. Sunil Sharma, Director of TGen's Applied Cancer Research and Drug Discovery Division, is also a co-principal investigator on the clinical trials. Dr. Sharma is supervising DNA, RNA and protein sequencing of tumor tissue to potentially identify biomarkers that can better target the treatments.

"After successful laboratory testing, we are excited to offer this new therapeutic approach for our patients," Sharma said. "We hope this unique immunologic approach will storm the walls surrounding these cancers and defeat these malignancies."

City of Hope Cancer Transplants

City of Hope has one of the nation's most celebrated bone-marrow transplant programs to fight blood cancers like leukemia and lymphoma. And while bone-marrow transplants themselves are not immunotherapies, the body's immune system plays a critical role in the success, or failure, of these treatments.

Dr. John Altin, an Assistant Professor in TGen's Pathogen and Microbiome Division, is working with City of Hope bone-marrow transplant expert, Dr. Ryo Nakamura, to fend off an often fatal post-transplant syndrome known as Graft Vs. Host Disease (GVHD), in which the life-saving bone marrow

transplanted from a healthy person goes rogue and sees the patient's body as an enemy to be attacked.

"One of the big problems in bone marrow transplantation is GVHD. We are developing an atlas of alloimmunity," explains Dr. Altin, "trying to predict who may develop this serious outcome."

It is not always possible to find a perfect donor match. There may be many potential donors available for a given patient.

"What we're aiming to do is develop an algorithm that helps select which donor is the best match; which has the least risk of an adverse outcome," said Dr. Altin, whose atlas will map all the possible compatibilities between donors and recipients. Adding detailed information from each new case to the atlas helps refine future compatibility match-ups.

Vaccine for blood cancer

Dr. Altin also is working with City of Hope's Dr. Larry Kwak on the development of a vaccine for B-cell lymphoma. Like a snowflake, the genetic make-up of each lymphoma tumor is unique. Researchers use this unique idotype as the basis of a vaccine made specifically for each patient.

"We've started working together on taking blood samples of those vaccinated, and testing to see if the vaccine has generated an effective immune response against the cancer," Dr. Altin said. "It has the potential to be very powerful, because it's targeted towards each individual's particular tumor."

TIL: Tumor Infiltrating Lymphocytes

Cancers often find ways to hide themselves from the body's immune system.

But sometimes, immune T cells find a way to burrow into the cancer before the cancer can seal itself off. Once inside the cancer, these immune system cells become exhausted, dysfunctional, having allowed the tumor in some way to turn them off.

"T cells represent the immune system's initial attempt to respond to the tumor," explains Dr. Altin, who is working with Dr. Sharma at Scottsdale's HonorHealth on this new way of re-training the immune system's T cells. "They live inside the tumor. We're trying to harness these cells as a way of treating cancer."

First, doctors remove the Tumor Infiltrating Lymphocytes (TIL) cells from inside the patient's tumor. Then — similar to CAR T cells — the TIL cells are manipulated in the

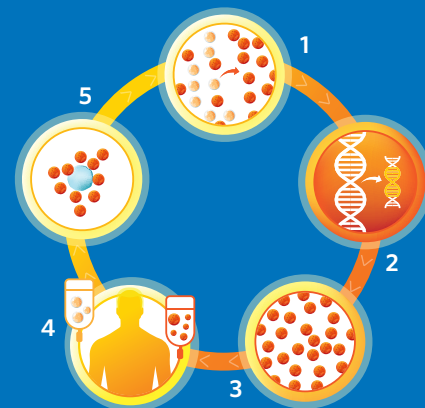
lab. Unlike CAR T cells, the TIL cells are incubated in the lab with specific peptides from the cancer.

"We are trying to re-energize them," Dr. Sharma said. "In the lab, we try to skew the errant T cells' repertoire, so they can again recognize the tumor and attack it."

With both TIL and CAR T cells, they are altered in the lab with the intent of re-igniting the power of the patient's own immune system.

The process for developing TIL cells, however, differs from CAR T cells in a significant way. CAR T cells start as T cells taken from the patient's bloodstream, while TIL cells come specifically from inside the patient's tumor, Dr. Altin said. "The TIL cells often already come with some sort of specificity, or targeting, against the tumor."

HOW DOES CAR T CELL THERAPY WORK?



STEP 1: ISOLATE

T cells are isolated from the patient by way of a specialized blood draw.

STEP 2: REPROGRAM

The T cells are then reprogrammed to produce special receptors on their surface called chimeric antigen receptors, or CARs. This enables the T cells to better recognize tumor cells.

STEP 3: EXPAND

The engineered CAR T cells are then grown in the laboratory until they number in the billions.

STEP 4: INFUSE

CAR T cells are infused back into the patient.

STEP 5: TARGET AND DESTROY

They multiply inside the patient's body and, with guidance from their engineered receptors, are able to recognize and then kill cancer cells.

McCain Endowment:

TGen Presents Richard C. Adkerson with John S. McCain Leadership Award



“It is an honor for TGen to recognize Richard Adkerson, who epitomizes the nature of the Award named for his close friend Senator McCain.”

— Erin Massey
TGen Chief Philanthropy Officer

Richard C. Adkerson of Freeport-McMoRan Inc., (left) with TGen President Dr. Jeffrey Trent was presented with TGen’s John S. McCain Leadership Award on May 9 at the annual TGen Founders Dinner.

In May 2018, TGen announced a fund to establish the John S. McCain III Endowed Chair in Brain Cancer Research. An endowed chair recognizes the holder’s accomplishments and often attracts the best and the brightest by offering a freedom to explore new ideas and opportunities.

A founding million-dollar gift by Richard C. Adkerson, the Vice Chairman, President and Chief Executive Officer of Phoenix-based Freeport-McMoRan Inc., launched the campaign that recently passed the \$2 million mark. To honor Mr. Adkerson’s and Freeport’s support, TGen presented Mr. Adkerson with the 2019 John S. McCain Leadership Award on May 9 at its 17th annual Founders Dinner. The award recognizes an individual or company whose leadership and dedication supports TGen’s mission of conducting groundbreaking research with life-changing results.

“It is an honor for TGen to recognize Richard Adkerson, who epitomizes the nature of the Award named for his close

friend Senator McCain,” said Erin Massey, TGen Chief Philanthropy Officer and Vice President of Development at City of Hope. “His outstanding leadership, longstanding support of TGen and the community, and his commitment to the McCain Chair all make him richly deserving of this annual award.”

TGen, working closely with the McCain family, announced the Chair shortly after the Senator passed from glioblastoma, an extremely aggressive brain cancer. (*More on glioblastoma; see page 13*)

The McCain Endowed Chair will recruit a nationally acclaimed physician-scientist who, much like the Senator, embodies a “maverick” spirit to drive unconventional, outside-the-box research and a willingness to actively promote excellence in training the next generation of leaders within the field. The individual will join a world-class translational brain cancer research program committed to pursuing game-changing approaches that set new standards of patient care for brain cancer.

BEATING PANCREATIC CANCER

Sandra DeMey-Forrest recently sent a note to long-time “Jeopardy!” host Alex Trebek, who was diagnosed in March with Stage 4 pancreatic cancer, meaning it had spread from the pancreas to other organs.

She got no response. But then, she really wasn’t expecting one.

“I just wanted him to know that there is hope,” said Sandra, who like Trebek battled Stage 4 pancreatic cancer. She was given only months to live. That was in January 2015.

More than four years later, Sandra is going strong, an inspiration to everyone who meets her, thanks to an experimental clinical trial designed by TGen and administered at HonorHealth Research Institute in Scottsdale.

The 72-year-old Peoria resident moved to the Phoenix area from San Diego over 11 years ago to be closer to her children and grandchildren.

In late 2014, after months of periodic pain in her abdomen, the pain became constant: “I knew I finally had to do something about it.”

Medical tests revealed late-stage cancer of the pancreas, an organ in the abdomen below the stomach that helps regulate digestion and blood sugar. Her doctors at the time gave her nothing but bad news. It was during surgery to remove the cancer that surgeons discovered the cancer had spread to her liver. They quickly ended the operation.

No options existed, her doctors said. Chemotherapy would diminish her quality of life. She was told to put her affairs in order; that she had only months to live.

Discouraged, Sandra went on the Internet and searched for Stage 4 pancreatic cancer and clinical trials. She stumbled onto the HonorHealth website, which described a new clinical trial designed by TGen. It featured a combination of two now-common anti-cancer drugs, gemcitabine and nab-paclitaxel — a combination for advanced pancreatic cancer approved by the FDA in 2013, following worldwide clinical trials supervised by TGen — plus a third drug, cisplatin, a combination called the TGen Triple.

In February 2015, Sandra became one of 25 volunteer patients enrolled in the yearlong trial. Within months, her tumor began to shrink. Soon after, doctors declared her cancer stable, meaning it was no longer growing and continued to shrink.

“I thought it was a miracle. I never got sick from the chemo,” said Sandra, who celebrated by popping a bottle of champagne with her husband, Jeff. “Even now, more than four years later, I feel good.”

In the time since, she has watched a granddaughter graduate from high school, and attended a grandson’s football games: “I’m not a bucket-list person. What matters most to me is just being able to grow old; to be here for my husband; to spend time with my family and enjoy the milestones. Now, I look forward to being a great-grandmother.”

While making regular follow-up visits to the hospital, she enjoys visiting with other patients and family members, lifting their spirits, giving them hope, and spending time with her doctors and nurses, whom she calls her expanded family.

“I think I’m happier now than I’ve ever been. You appreciate so much more,” said Sandra, who gives this advice to other patients: “You have to be your own advocate. You have to have faith and hope, and you have to never give up on yourself.”

“I think I’m happier now than I’ve ever been.”

— Pancreatic cancer patient
Sandra DeMey-Forrest



Pancreatic cancer patient Sandra DeMey Forrest (left) hugs Gayle Jameson, a nurse practitioner and clinical trials investigator at HonorHealth Research Institute.



“We must find new and better ways to help these patients.”

— Dr. Nicholas Banovich, TGen Assistant Professor



Breathing Life in to Scientific Research

Plight of a friend inspires TGen scientist to initiate groundbreaking research for lung disease

What began as an information gathering exercise to help a family friend soon evolved into a significant multi-million-dollar biomedical study that is shedding light on the possible causes of a deadly lung disease known as Idiopathic Pulmonary Fibrosis (IPF).

Dr. Nicholas Banovich, an Assistant Professor in TGen's Integrated Cancer Genomics Division, usually investigates the cause and potential new treatments for various types of cancer. But when his friend, Larry, asked for help navigating his illness following an IPF diagnosis, he soon added the pulmonary disease to his repertoire.

Having known Larry for nearly 14 years, Dr. Banovich recalls how he loved riding his motorcycle, crisscrossing states on long adventures to visit family and friends: "When I first met him, he was a very outgoing guy."

Then, nearly three years ago, Larry received the IPF diagnosis. A year and a half later, he started a precipitous decline. He had difficulty breathing, become easily fatigued, and eventually needed supplemental oxygen to survive.

"He followed the common trajectory of this disease," Dr. Banovich said. "Within five years of diagnosis, these patients typically need a lung transplant."

In December 2018, Larry — now in his 70s — received his lung transplant, a significant surgery with the potential for difficult complications. At one point, he required a medically induced coma to assist his recovery. Now, six months later, Larry is still in the hospital.

Collaborative research project

"When he first contacted me, I had never heard of the disease. I spent a good period of time looking through the literature available, and saw there were no medications that are particularly effective," said Dr. Banovich, who then committed himself to finding new treatments that could halt — maybe even reverse — the disease in patients before they required a transplant.

"My goal was to understand the biology of this disease that would lead us to new treatment options," he said. "I knew then that we must find new and better ways to help these patients."

Armed with federal grants from the National Institutes of Health and the U.S. Department of Defense, Dr. Banovich teamed up with colleagues at Vanderbilt University Medical Center, and at the Norton Thoracic Institute at Dignity Health St. Joseph's Hospital and Medical Center.

Using single-cell sequencing (a process that provides increased clarity of cell function and behavior), and after examining only 40 lung samples, Dr. Banovich and his colleagues discovered a potential biomarker that could lead to better treatment for IPF patients.

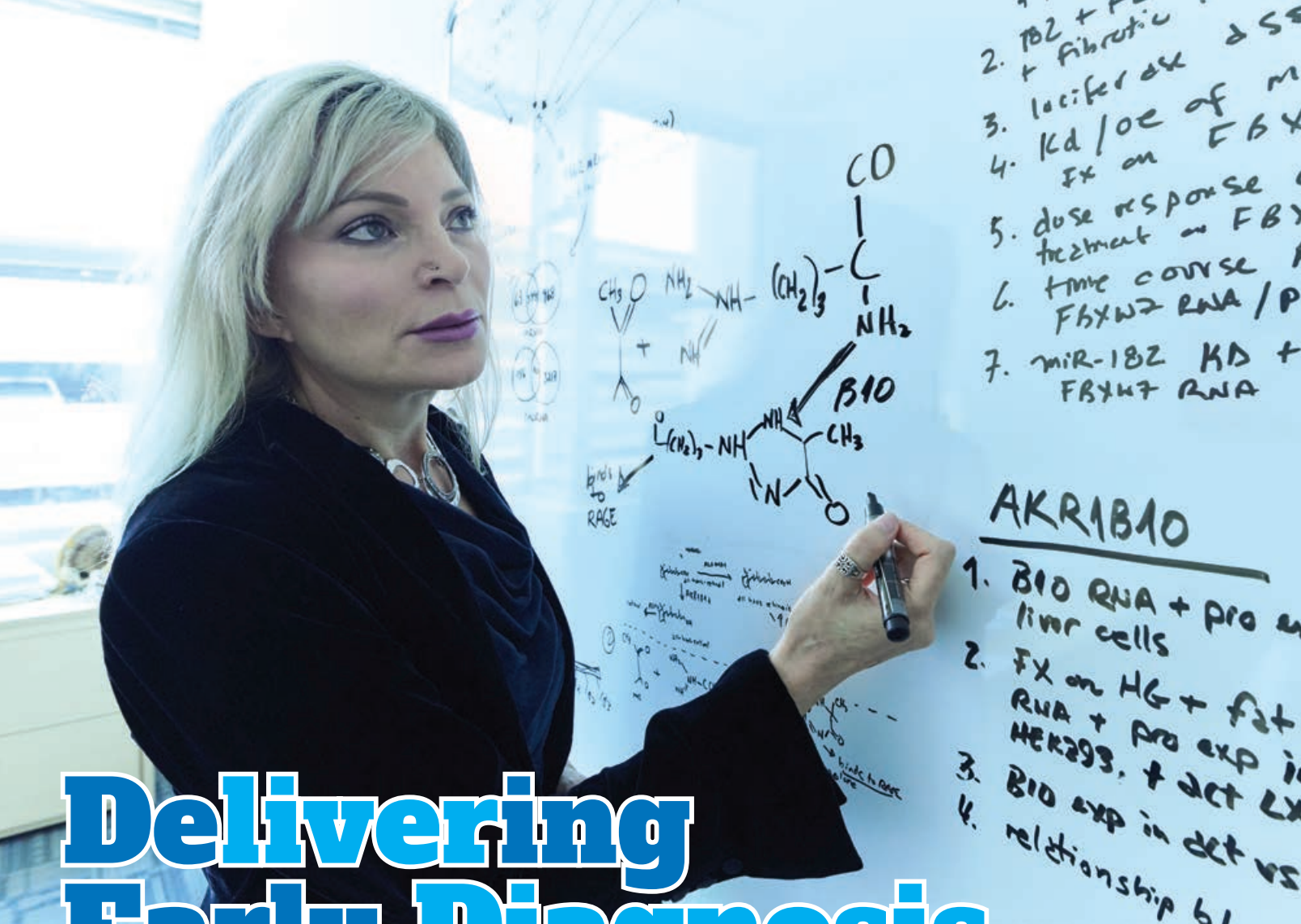
"With that small data set, we've already identified a novel, pro-fibrotic epithelial cell that exists only among patients with this disease," he said.

\$6.1 million in federal research grants

TGen received a \$3.5 million federal grant from NIH to study the cause of IPF and \$2.6 million from the Department of Defense to study a variety of other genomic factors associated with non-IPF forms of pulmonary fibrosis (PF).

"The goal is to generate the most comprehensive molecular characterization of healthy and IPF lungs to date. This study promises to answer fundamental questions about cell types, genetic variants, and gene expression changes driving the disease," said Dr. Banovich.

Prior to the advent of single-cell sequencing, researchers could not begin to decipher the molecular source of IPF, Dr. Banovich said. By closely examining individual cells, rather than a mash-up of many cells from a tissue sample, researchers are working to identify specific gene expression changes that cause IPF. This could produce earlier diagnosis and perhaps better treatments for this disease, which results in nearly 50,000 diagnoses in the U.S. each year.



Delivering Early Diagnosis

Dr. Johanna DiStefano

TGen links AKR1B10 gene to the most common liver cancer

The number of liver cancer diagnoses has nearly **doubled** since 2009

If the answer is hepatocellular carcinoma (HCC), the question might be: name the most common form of liver cancer today? A malignancy whose incidence has nearly doubled over the past decade, HCC is the fastest growing type of cancer in the U.S., and the third-leading cause of cancer-related death worldwide.

A review article by TGen researchers in the journal *Cancers* provides the first summary of the experimental evidence supporting the AKR1B10 enzyme as a promising therapeutic target for HCC, based on a review of more than 50 studies published since this gene was first identified and characterized in 1998.

“While the association between this gene and HCC is well recognized, in this review we see AKR1B10 emerging as not only a therapeutic target for this type of liver cancer, but also having potential use in early

diagnosis of this deadly disease,” said Dr. Johanna DiStefano, head of the Diabetes and Fibrotic Disease Unit at TGen.

Like many types of digestive cancers, HCC exhibits few early symptoms. Diagnosis often occurs in the late stages, when fewer treatment options exist and the chances of patient survival dim. People with diabetes have an increased risk of developing HCC.

In the U.S., the number of liver cancer diagnoses has nearly doubled since 2009 to an estimated 42,000 annually. Men are almost twice as likely to contract this disease as women.

This year, nearly 32,000 patients will die of liver cancer, making it the fifth leading cause of cancer related death in the U.S., according to the review paper: *Diagnostic and Prognostic Potential of AKR1B10 in Human Hepatocellular Carcinoma*.

Treatments for GLIOBLASTOMA should consider



*how sex makes
a difference*

TGen has helped identify why men die of glioblastoma brain cancer at nearly twice the rate of women. A study, published in the journal *Science Translational Medicine*, could help tailor drug treatments specifically designed for men and women based on their tumors' molecular subtypes.

"We have known for years that men contract and die from glioblastoma at a significantly higher rate than women," said Dr. Michael Berens, TGen Deputy Director, head of the TGen Brain Cancer Research Laboratory, and a contributing author of the study. "We now have a much clearer understanding of this phenomenon, and this study should help us in the future to improve survival for all glioblastoma patients."

Studying adults with glioblastoma, researchers found that standard treatment for glioblastoma is more effective in women than men. Researchers reviewed patient MRI scans, tumor genomic profiles, and survival data from a

cancer research database. They then calculated tumor growth velocity every two months for the duration of therapy in 63 glioblastoma patients — 40 males and 23 females.

While initial tumor growth velocities were similar between women and men, only females showed a steady and significant decline in tumor growth after treatment with temozolomide, the most common chemotherapy drug used to treat glioblastoma.

This study — *Clinically Important Sex differences in GBM biology revealed by analysis of male and female imaging, transcriptome and survival data* — was funded in part by the Scottsdale-based Ben & Catherine Ivy Foundation.



**See a video about Dr. Michael Berens
and his research in glioblastoma:
<https://bit.ly/314Bt1s>**



TGEN'S **FITNESS** FOR THE **CURE**

2019 *Fitness for the Cure* raises \$127,000 for TGen research

Nearly 200 people participated in this year's 9th annual *Fitness for the Cure*, raising more than \$127,000 in support of TGen cancer research.

Cancer treatment advocates, cancer survivors, their families and others hiked, cycled, ran, held yoga classes and participated in other activities in April at all four of the Phoenix area's Village Health Clubs and Spas.

The total amount raised over the past decade exceeds \$1.3 million.

Plans already are underway for the 10th anniversary *Fitness for the Cure* in spring 2020.

"We are so grateful to all the participants, volunteers, sponsors and instructors, as well as the Village Health Clubs and Spas for being our steadfast partner in Fitness for the Cure over the past decade," said Erin Massey, Chief Development Officer at TGen, and Vice President of Philanthropy at City of Hope. "We eagerly look forward to next year's event, knowing that it helps Arizona cancer patients first, and takes us ever closer to better treatments and someday cures."

For more information, contact TGen Foundation Vice President of Development Nadia Rivera at nrivera@tgen.org or 602-343-8470.

Trending for the Second Year

Trends Charitable Fund supports women's cancers and childhood disorders

For the second year in a row, *Trends Magazine* and the Trends Charitable Fund (TCF) has selected TGen as the beneficiary of its annual fall gala because of the biomedical research institute's innovative genomic technologies and its commitment toward discovery of new treatments and cures for women's cancers and childhood disorders.

"We are very happy to provide a second year of support to such a wonderful organization as TGen," said Susie Wesley, the 2019 TCF Board President.

The TCF *Evenings of Trends 2019, A Desert serenade*, will take place Friday, November 1, at the Omni Scottsdale Resort & Spa at Montelucia. For more information or to donate to the Trends Charitable Fund, visit: www.trendscharitablefund.org.

TCF's *Evening of Trends 2018* raised more than \$275,000 for TGen, specifically for Ovarian Cancer Research and also for TGen's Center for Rare Childhood Disorders, including funds for genetic

sequencing, which can help doctors treat TGen's pediatric patients.

"We are thrilled to once again receive the support of *Trends Magazine* and the Trends Charitable Fund," said Erin Massey, Chief Development Officer at TGen, and Vice President of Philanthropy at City of Hope. "These dollars contribute to the success of TGen by helping advance our research into diseases that directly impact women, children and their families."

Established in 1986, Trends Charitable Fund has granted more than \$5 million to charities benefiting Arizona women, children and families.

"The work of TGen is such a natural fit with the mission of Trends Charitable Fund, which supports programs that positively impact women, children and their families," said Vicki Vaughn, Co-Chair of *Evening of Trends 2019*.

To register for the *Evenings of Trends 2019, A Desert serenade*, visit tgen.org/events.

Trends Charitable Fund raised \$275,000 for TGen in 2018, and looks to do more in 2019



Event Chair Vicki Vaughn (right) and Vernon Vaughn



Trends Charitable Fund (TCF) presented TGen with a check for \$275,761, representing the proceeds from the 2018 Evening of Trends. Left to right are: Darlene Keller-Price, 2018 TCF Board President; Susie Wesley, 2019 TCF Board President; Bill Dougherty, Publisher of Trends Magazine; Keri Ramsey, Clinical Co-Director of TGen's Center for Rare Childhood Disorders; Erin Massey, TGen Chief Development Officer; Nadia Rivera, TGen Foundation Vice President; and Vicki Vaughn, Co-Chair of 2019 Evening of Trends.



The Trend's Charitable Fund's Evening of Trends honored Fabulous Phoenician Sue Glaw and Trends Magazine's Bold and Beautiful Trendsetters.



Julie Euber, TGen Manager of Education and Outreach, helps guide members of the TGen Women's Philanthropy Council extract DNA from strawberries during a tour of TGen's research facilities.



TGen Chief Operating Officer Tess Burlison (left) joins Arizona's U.S. Sen. Kyrsten Sinema and TGen President Dr. Jeffrey Trent during the senator's visit to TGen.



Dr. David Engelthaler, Co-Director of TGen North.

Women's Philanthropy Council off to a strong start

Since its launch in January, the TGen Women's Philanthropy Council (WPC) has recruited 34 members. The WPC is an empowering and engaging program, whereby members support great research and gain a personal understanding of precision medicine and how it influences health outcomes for themselves and their loved ones. ■ The WPC mission drives philanthropic investment in groundbreaking research and the acceleration of discoveries toward clinical care to improve patient outcomes. ■ In May, members attended a Genomics 101 seminar at TGen, where they learned the fundamentals of cell biology and function, gaining a better understanding of how TGen uses DNA to identify how disease starts, progresses, and how to beat it. ■ In September, WPC will host a living room social: SuperAgers. ■ For more information and to become a member of WPC, contact TGen Foundation Vice President of Development Nadia Rivera at nrivera@tgen.org or 602-343-8470.

Arizona's U.S. Senator Kyrsten Sinema includes TGen in tour of state businesses

U.S. Senator Kyrsten Sinema, D-Ariz., visited TGen on May 28 as part of her "Kyrsten Means Business" tour, an effort by the senator to listen to and meet job creators, care providers, and community leaders towards expanding Arizona's economic opportunities and supporting Arizona communities. ■ During each of her visits, Sen. Sinema spent time with leadership and employees to learn about challenges and identify ways to work together. ■ TGen had the pleasure of presenting our scientific breakthroughs and discussing our shared enthusiasm for research and development, disease prevention, and medical advances. Sen. Sinema heard presentations by: Drs. Jeffrey Trent, President and Research Director; Matt Huentelman, Professor of the Neurogenomics Division; Tim McDaniel, Senior Vice President for Emerging Opportunities; and Meredith Sanchez-Castillo, Clinical Research Coordinator for the TGen Center for Rare Childhood Disorders.

Flinn Foundation awards \$400,000 'Prevent HAARM' grant to C-Path and TGen

TGen North — the Pathogen and Microbiome Division of TGen in Flagstaff — and Tucson's Critical Path Institute (C-Path) have received a \$400,000 grant from the Flinn Foundation to develop a framework for Arizona's public health institutions to be more responsive to antimicrobial resistance. ■ TGen and C-Path are developing an integrated deployment plan for a statewide Healthcare Associated Antimicrobial Resistant Microbe genomic surveillance system, dubbed Prevent HAARM. ■ Potentially deadly antimicrobial resistant (AMR) infections — caused by microbial pathogens, including bacteria, viruses, fungi and parasites — constitute a growing threat that jeopardizes modern medicine and healthcare in Arizona and across the globe. ■ Prevent HAARM will monitor and track the emergence and transmission of antimicrobial resistant pathogens throughout Arizona, and provide rapid feedback to clinicians, hospitals, epidemiologists and public health professionals. ■ "We've been honored to work with great public health and clinical medicine partners across the state for over a decade. With this project, we have a chance to help make a real difference in the health of Arizonans," said Dr. David Engelthaler, Co-Director of TGen North. "TGen and C-Path have worked together on similar systems for tracking the spread of drug resistant tuberculosis in the developing world. Here is an opportunity for us to parlay that success into local benefit."

Von Hoff recognized by AACR with Distinguished Public Service Award

Dr. Daniel D. Von Hoff, TGen Distinguished Professor and Physician-In-Chief, received the 2019 Distinguished Public Service Award from the American Association for Cancer Research (AACR) at its 2019 Annual Meeting. ■ Dr. Margaret Foti, Chief Executive Officer of the AACR, said in a letter to Dr. Von Hoff that the award is “in recognition of your extraordinary clinical research career.” ■ Dr. Von Hoff has led or participated in more than 350 first-in-human investigational agent clinical trials. His career at TGen has brought new treatments into clinical practice, increasing the survival of patients with pancreas cancer and ushering in groundbreaking advances in other malignancies. He also holds significant positions at City of Hope, Mayo Clinic Scottsdale, US Oncology Research, McKesson Specialty Health, and HonorHealth.



Dr. Daniel D. Von Hoff, TGen Distinguished Professor and Physician-In-Chief, received the 2019 Distinguished Public Service Award from the American Association for Cancer Research (AACR) at its 2019 Annual Meeting.

Liang is one of Arizona's Outstanding Women in Business

The Phoenix Business Journal in April named Dr. Winnie Liang, TGen Director of Scientific Operations, as one of Arizona's 2019 Outstanding Women in Business.

■ Dr. Liang, an active member of the Arizona Alzheimer's Consortium, also serves as an Associate Professor in TGen's Integrated Cancer Genomics and Neurogenomics Divisions. ■ “I am incredibly flattered by this honor and to be recognized amongst other amazing women in Phoenix, but this is truly a testament to all the tremendous work being pursued here at TGen to benefit patients,” said Dr. Liang, who was selected as one of 25 Outstanding Women in Business from more than 280 nominations. ■ In 2010, Dr. Liang led the creation of TGen's Collaborative Sequencing Center, which acts as TGen's primary next-generation sequencing resource, using precision medicine to unlock the mysteries of the human genome and provide patients and their attending physicians with new insights into their diseases and conditions. ■ *The Phoenix Business Journal* previously recognized Tess Bursleson, TGen Chief Operating Officer, in their 2015 class of Outstanding Women in Business.



Dr. Winnie Liang, TGen Director of Scientific Operation was selected as one of 25 Outstanding Women in Business from more than 280 nominations.



Upcoming Events

www.tgen.org/events

July 28 — *Casa Nuova Italian Restaurant Customer Appreciation Day*, benefiting the Purple Pansies Organization and TGen pancreatic cancer research. (Alpharetta, Ga.)

September 6 — 13th annual *Terri Link Memorial Golf Tournament*, benefitting TGen adrenocortical carcinoma (ACC) research. The Georgia Club. (Athens, Ga.)

September 29 — 4th annual *Hope Through Hollis Tournament*, benefitting TGen DIPG research. Papago Golf Course. (Phoenix, Ariz.)

September 29 — 10th annual *Purple Pansies Gala and Wine Dinner*, benefitting TGen pancreatic cancer research. Freemanville Estate. (Milton, Ga.)

November 1 — *Evenings of Trends 2019, A Desert serenade*, sponsored by Trends Charitable Fund, benefitting TGen's Center for Rare Childhood Disorders and ovarian cancer research. Omni Scottsdale Resort & Spa at Montelucia. (Paradise Valley, Ariz.)

November 1-3 — 15th annual *Seena Magowitz Golf Classic*, benefitting TGen pancreatic cancer research. Arizona Biltmore Resort. (Phoenix, Ariz.)

November 3, 2019 — 14th annual *stepNout 5K FUNdraiser*, benefitting TGen pancreatic cancer research. Scottsdale Sports Complex. (Scottsdale, Ariz.)



The 15th Annual Seena Magowitz Golf Classic, benefitting TGen pancreatic cancer research will be held November 1-3 at the Arizona Biltmore Resort in Phoenix, Arizona.

For more information and if you'd like to participate, please contact Jenna Higgins, TGen Foundation Director of Development, at jhiggins@tgen.org or 602-343-8481.



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LOOKING FOR A WAY TO HELP TGEN AND SAVE ON YOUR 2019 TAXES?



Use a portion of your IRA Required Minimum Distribution (RMD) to make a gift to the TGen Foundation:

- Eligible for those age 70½ years or older.
- The distribution must be transferred directly from your IRA to TGen.
- Your transfer must be completed by Dec. 31, 2019, to qualify as a 2019 income tax deduction.

Benefits of gifting an IRA RMD to TGen:

- The portion of your RMD donated to TGen is not subject to income tax.
- Individuals may give up to \$100,000 annually (\$200,000 per couple).
- Your gift helps advance TGen's lifesaving research and patient care.

For more information, please visit
tgen.org/PlannedGiving and contact
TGen Director of Development
Jenna Higgins at jhiggins@tgen.org
or 866.370.8436

