

TGen Today

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A PUBLICATION OF THE TRANSLATIONAL GENOMICS RESEARCH INSTITUTE

A Non-Profit Biomedical Research Institute

A Life of Sharing

Maria Fundora continues her commitment to funding pancreatic cancer research at TGen



A Look Inside...



I hope you are safe and well.

It is hard to reflect on the past eleven months without wanting to share the burden of pain and suffering so many in the world have faced due to the COVID-19 pandemic.

For nearly two decades, TGen has responded when faced with unique health challenges; whether through innovative research or first-of-a-kind clinical trials. Our response to COVID, led by the internationally recognized pandemic experts in our Pathogen and Microbiome Division, came swiftly and with compassion. In this edition of TGen Today, we share how team TGen — collaboratively with public health and tribal health agencies, first responders, healthcare workers on the front lines, and others in need — worked tirelessly (and continue to do so) to test, track, and develop treatments for COVID-19.

Our cover story takes us to Alpharetta, Georgia, where we meet Maria Fundora, a one-woman powerhouse whose passion and commitment to ending pancreatic cancer took root on the island of Cuba and matured through a strong family bond and a life of caring.

Support from Maria and other donors with similar stories of commitment are what propels the work of TGen's Distinguished Professor Daniel D. Von Hoff, M.D., a physician-researcher considered the nation's foremost authority on pancreatic cancer. I have no doubt that Dr. Von Hoff will one day be the driving force behind a cure for pancreatic cancer.

Our work with colleagues at City of Hope resulted in a deeper understanding of how the trillions of bacteria, viruses and fungi living in our bodies — known collectively as the Microbiome — revealed information that benefits patients with metastatic kidney cancer and, for some, improves outcomes upon receiving FDA-approved immunotherapy treatments.

Whether through these or the other stories inside, I hope you will take pride in knowing we greatly value your partnership and support in all that we accomplish.

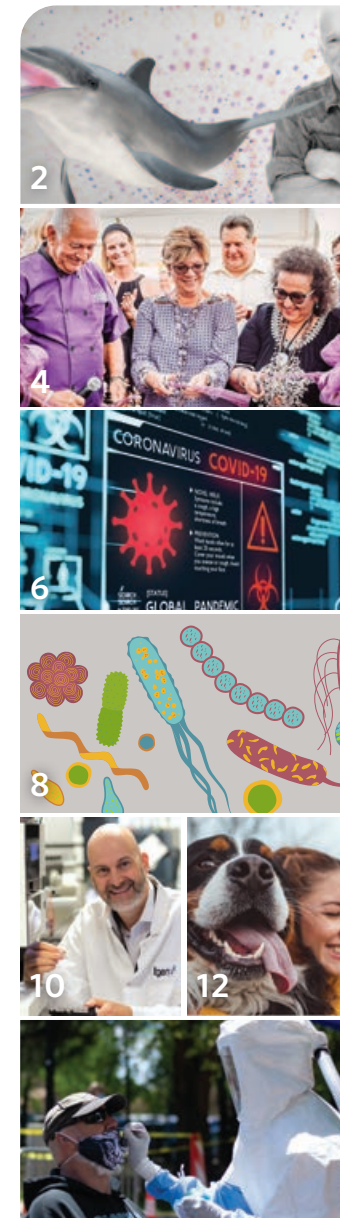
With gratitude,

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

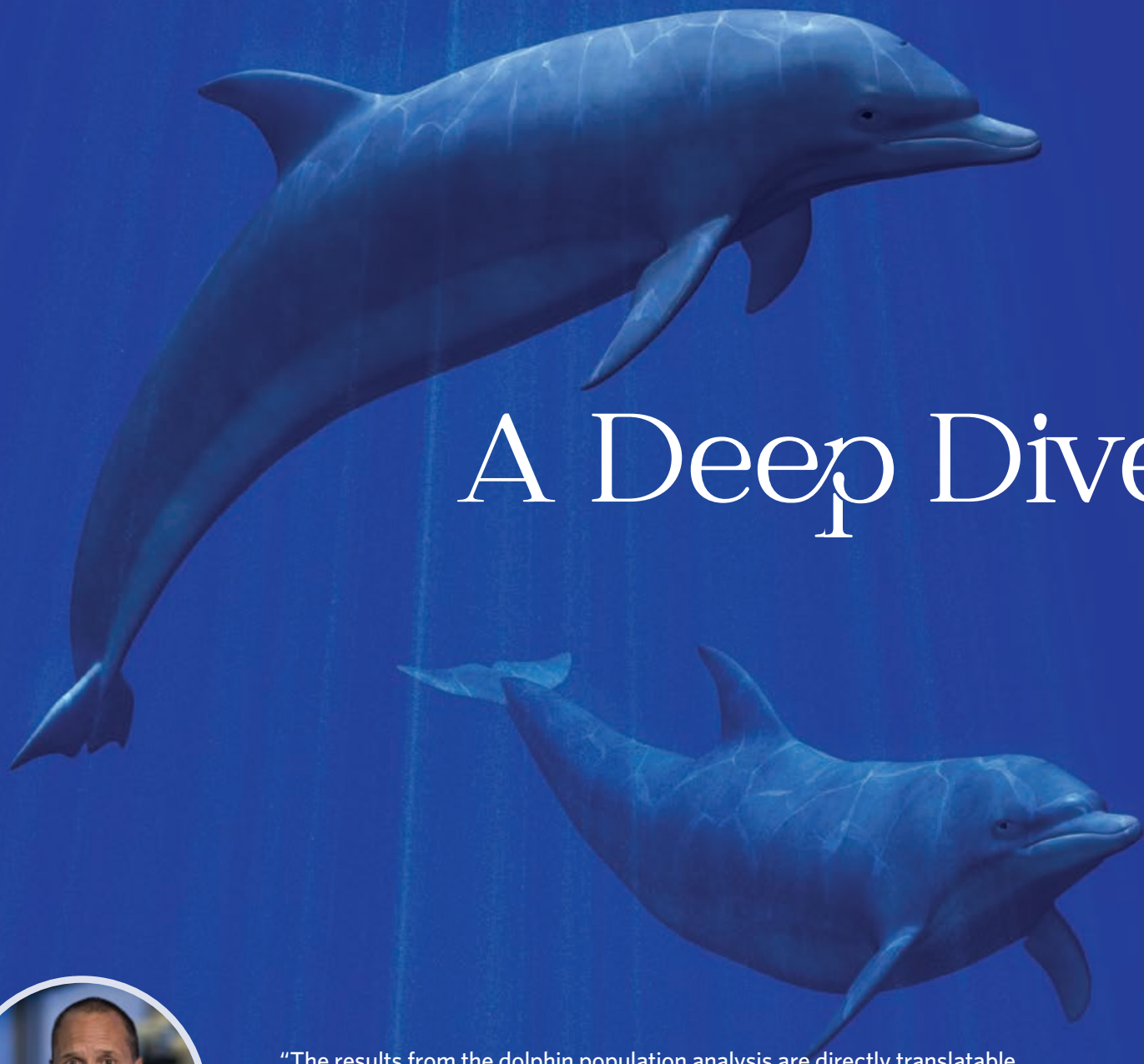
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TGen Talks is a monthly podcast that explores our latest science and discoveries. Find *TGen Talks* on the tgen.org homepage, through iTunes or on SoundCloud.



A Deep Dive into Aging



“The results from the dolphin population analysis are directly translatable into human biology and will now empower us to identify how aging rates vary in humans and — someday — let us all age gracefully.”

— TGen Distinguished Professor Dr. Nicholas Schork

POPULARIZED BY TELEVISION AND film, humans have long had an affinity toward dolphins. The sleek, intelligent mammals are fan favorites at water shows as they flip, tumble and pirouette their way to applause. Theatrics aside, TGen Distinguished Professor Dr. Nicholas Schork finds dolphins — in particular bottlenose dolphins — interesting for what they may offer scientifically toward understanding the biology of aging.

The results of a recent study by Dr. Schork, in collaboration with colleagues at Epitracker (a private research firm) and the United States Navy, lead to a publication in the *Proceedings of the National Academy of Sciences* that could help scientists develop a more in-depth knowledge of, and perhaps delay, the aging process and decrease chronic conditions associated with growing old.

Dolphins are one of the very few natural animal models for studying certain aspects of human physiology that cause or result from disease or injury. Dolphins can, for example, exhibit signs consistent with nonalcoholic fatty liver disease (which is present in as many as 25% of the population globally) and Alzheimer’s disease, the most common form of neurodegenerative disease in humans.

To reach their conclusions, the scientists pored over 25 years’ worth of data collected by the U.S. Navy on 144 dolphins — known as Navy dolphins — that received meticulous care throughout their lives; having undergone dozens of precision tests on a strict schedule to help ensure their health and wellbeing. These health data included 44 clinically relevant measurements on 5,889 biological

routine samples collected throughout the dolphins’ lifetimes.

“The results from the dolphin population analysis are directly translatable into human biology and will now empower us to identify how aging rates vary in humans and — someday — let us all age gracefully,” said Dr. Schork, who directs TGen’s Quantitative Medicine & Systems Biology Division and serves as Scientific Director for the National Institute on Aging’s Longevity Consortium.

It has long been believed that there are factors influencing why some humans and mammals age faster than others, and identifying those factors requires a data set that has been difficult to develop in species closely related to humans — one that is sufficiently large, robust, longitudinal in nature, and collected in a well-controlled population over lifetimes.

How data from Navy dolphins are filling the information gap

The nature of the Navy dolphins’ shared environment created a perfect setting to generate unparalleled longitudinal health data using easily measured biomarkers that identified slow and accelerated aging in dolphins.

“The study highlights how biological differences between dolphins, living in the same natural ocean environment and receiving routine medical examinations under the care of the U.S. Navy, may inform new approaches to slow processes associated with human aging,” said Dr. Schork.

The scientists theorized that because the Navy dolphins all share the same aquatic environment, food and healthcare, other factors must exist that explain why some Navy dolphins live longer than others. They found answers through biomarkers, biological beacons that serve

as an indicator of a certain disease state or some other physiological condition of an organism.

Navy dolphins, which on average live 50 percent longer than wild dolphins, consumed a controlled and well-maintained fish diet and received ongoing health monitoring and medical care.

Dr. Schork and colleagues tapped into this wealth of data, using dolphin biomarkers to identify trends that are likely to be very similar in people, in hopes of finding new ways to slow the degradative processes associated with aging.

The scientists identified four key biomarkers associated with accelerated aging. Some dolphins exhibited declines in these biomarkers as they aged, while others exhibited none. Two of these biomarkers, which already are used in assessing older people, decreased linearly

with age: hemoglobin, used to detect anemia; and lymphocytes, used to detect immunosenescence, or weakened immunity.

Importantly, while some dolphins had declines in these clinical biomarkers as they aged, including declines leading to clinical anemia and immunosenescence, others had no declines during the same aging timeframe.

“Amazingly, this work all started with the sole intent of continually improving the health and welfare of dolphins,” said Stephanie Venn-Watson, D.V.M., M.P.H., co-founder and CEO of Epitracker and Seraphina Therapeutics. “The fact that our work is resulting in groundbreaking approaches to delay aging and improve health for both dolphins and humans is a dream come true.”



MARIA FUNDORA

A LIFE of SHARING

WHEN MARIA FUNDORA SPEAKS ABOUT

supporting pancreatic cancer research and her hopes for improved treatments, you hear the passion in her voice; there's a resonance of belief and commitment to a purpose far beyond the dollars raised.

Her conscription in the fight began in 2008, when Fundora hosted a Mother's Day fundraiser at her restaurant, Casa Nuova, an Italian eatery beloved by the locals of Alpharetta, Georgia.

The event paid tribute to her mother, Iluminada, who Fundora had lost in late 2007 to pancreatic cancer. The inaugural gathering raised \$5,000 and launched what has become an enduring tribute to her mother and a voice for research and clinical trials that are charting a new course for pancreatic cancer patients.

That was the beginning.

And while Casa Nuova had always held weekly fundraisers in support of local schools and various charities, the Mother's Day event would give rise to Purple Pansies, an organization dedicated to

ending pancreatic cancer. In 2019, Fundora (through Purple Pansies) raised \$550,000 for research, the latest success in a life of challenges, perseverance, and charitable giving; a life that began in the Republic of Cuba.

Fundora, born in Havana, emigrated to the US in 1966. Her father had escaped the country four years earlier, having navigated the dangerous waters across the Straits of Florida in a small motorboat. She and her mother left Cuba on March 15 — the Ides of March coincidentally — aboard a Freedom Flight, the government sanctioned twice-daily flights between Cuba and Miami that ran from 1965 to 1973 and reunited nearly 270,000 refugees with their families. Once reunited, the family settled in Chicago.

"I grew up in a home where whatever we had, we shared. Whether it was food, extra clothing, or advice; we met with other refugees in our community and helped," Fundora said. "Those experiences formed the foundation for who I am today."

The family moved to Atlanta in 1984, following her mother's transfer during her time with Lucent Technologies. Her father, a restaurateur, who traveled and consulted with cities and corporations, was fatally stabbed in Santo Domingo in 1987. That same year she met her future husband, Antonio, on a blind date: he, too, a Cuban refugee. They wed two months and sixteen days later. As fate would have it, Antonio was also in the restaurant business, which Fundora recalls warmly with a laugh.

"When I was young I vowed never to marry a Cuban and having grown up in the profession, never work in the restaurant business."

Thirty-five years later, the Fundora's are still fixtures in a business that has shaped their lives and positively changed the lives of others through their charitable work.

When Maria and Antonio started their own family and opened Casa Nuova in 1998, Iluminada joined the team.

"She became kind of famous for her soups", Fundora said — garbanzo bean soup and cream of roasted garlic and red pepper especially."

Everything changed, however, on May 21, 2007; the day Iluminada received her pancreatic cancer diagnosis. She passed away that September.

"To our family, she was the rock of Gibraltar... I could not let go of her loss," Fundora explained. That deep-seated sense of wont ignited in Fundora a desire to once again offer what she could and make a difference. "That's my driving force, to honor my mother."

THE RISE OF PURPLE PANSIES

Following the success of her first event, Fundora heard from a number of patrons who expressed a desire to help further. Together with a friend, she set about developing a name under which to hold future events.

Both women knew that the color purple represented pancreatic cancer research, but it wasn't until her friend phoned one day to inform Fundora that she had a purple pansy growing in her flower garden — while the temperature hovered around 20 degrees — that it all clicked. Fundora

did a bit of quick research and learned that the pansy is known for its resilience and ability to flourish in tough conditions. From that call came Purple Pansies, a nonprofit dedicated to raising awareness and funds for pancreatic cancer research. Today, the charity hosts two yearly events; an open house in July and a gala in September.

In 2011, Fundora connected with TGen through Atlanta businessman and 19-year pancreatic cancer survivor Howard Young, who had turned to TGen's Physician-in-Chief, Daniel Von Hoff, M.D., to spearhead his life-saving treatments.

"TGen and I have a long history, a great history," she said, underscoring how energizing Dr. Von Hoff — a global leader in pancreatic cancer research and treatment — has been to her team.



Young introduced Fundora to TGen Chief Development Officer Erin Massey who shared with her the goals of the Institute and Dr. Von Hoff. Fundora was sold and in TGen she found more than an organization to support, she found a collaborator.

"Maria is most spirited when she is helping others, whether it's a customer in her restaurant, supporting a community project, or raising funds to tackle something as challenging as pancreatic cancer," said Massey. "She is a force for good and we are grateful she believes strongly in TGen. Our lives are enriched for knowing her."

Dr. Von Hoff is equally inspired by Fundora.

"As long ago as I can remember, I bought my mother a pot of pansies each Mother's Day. It was a guarantee for a loving smile back to me. It's amazing to me that many years later I meet Maria Fundora and learn of her efforts to honor her mother," Von Hoff said.

"The Purple Pansies funds enable us to build on our most promising results, whether in the lab or the clinic, and that is why at TGen, we try to honor Maria's efforts by doing our very best to wisely use the funds on the most impactful efforts."

In 2018, Purple Pansies raised \$250,000 solely through grassroots efforts. In 2019 American retail giant, Kroger, signed on as a sponsor. Kroger's Atlanta Division President, Tim Brown, has known Fundora for years and holds the distinction of having attended every Purple Pansies event since its inception. When he was named to head the Atlanta division in 2018, he came to Fundora and said he wanted to make a difference. With the Kroger name behind the event, the 2019 proceeds more than doubled.

You hear passion in her voice, commitment to a purpose far beyond the dollars raised.

"It makes the sleepless nights, the phone calls, the getting into people's personal space all worth it," Fundora said. "It marks your heart."

2020 looked to be a promising year. An anonymous donor had pledged a match of \$600,000 for this year's Purple Pansies Gala event. COVID-19 made reaching the goal a bit more difficult, but in true Maria Fundora fashion (perhaps channeling the inner strength of Iluminada) she didn't give up. The event was a success, raising more than \$1 million, bringing to more than \$2.5 million the total Purple Pansies has raised in support of TGen and Dr. Von Hoff.

In the meantime, Fundora and Casa Nuova continue their legacy of supporting their community by providing meals to healthcare and frontline workers.

"We are so blessed to open our eyes every day," Fundora said. "I'm simply living the lessons I learned as a child by doing what I'm able to keep people's hopes alive."

TGEN TAKES ON COVID-19

WITHIN DAYS OF THE FIRST REPORTS

of a potentially deadly new coronavirus coming out of China, TGen scientists began developing a genomic-based clinical test to determine whether a person had contracted the virus.

"David [Dr. David Engelthaler, Director of TGen's infectious disease division, TGen North] called and said, 'Jeff, this is going to be a monster. We need to join the groups developing FDA supported tests and we need to begin today,'" recalls TGen President and Research Director Dr. Jeffrey Trent.

Five weeks later — one day before the first reported death — the scientists at TGen North had developed and received FDA authorization for a PCR-based genetic test for the COVID-19 virus, while simultaneously receiving state certification for its new CLIA laboratory, a step necessary to return testing results to patients and their physicians.

The tools, technologies and approaches TGen is known for in cancer and infectious disease research were applied full force to the genome of the virus, which has since enabled the institute to develop serology (a blood plasma test that looks for antibodies in individuals who have been exposed to the virus) and saliva-based tests, track how the disease moves and mutates, and work toward developing treatments for COVID-19.

"This has been a devastating pandemic," said Dr. Engelthaler, citing the global toll, "certainly the most significant infectious-disease event in our lifetime. Yet, in a way, TGen North has been preparing for it for years."

Established in 2006, the faculty at TGen North apply their genomic expertise to pathogen diagnostics and microbial forensics. They are internationally known for their work identifying and tracing infectious disease outbreaks, large and small. Their investigative highlights include pinpointing the source of a cholera outbreak in earthquake-ravaged Haiti; identifying an extremely rare and highly fatal fungal infection infecting residents of Joplin, Missouri, in the wake of one of the most devastating tornados in American history; and helping CDC and FDA solve a medical product contamination case resulting in fungal meningitis outbreak that affected hundreds of patients and killed dozens of people in 20 states. COVID-19 is the latest.

To date, TGen has tested over 45,000 Arizonans and sequenced 5,000 SARS-CoV-2 genomes, providing a trove of genomic information to researchers racing to defeat COVID-19; a disease that has infected more than 226,000 Arizonans and claimed the lives of more than 5,700.

"It is important to understand that this pandemic is dynamic and will continue to shift genomically and geographically," said Dr. Engelthaler. "We will likely see additional waves as numbers continue to fluctuate in different locales, but hopefully not on the scale we saw throughout the spring and summer."

One thing that hasn't changed throughout the pandemic is that COVID-19 is first and foremost a deadly disease for those over 70, especially those with chronic lung or heart

conditions. Over two thirds of all deaths occur in this age group, even though it makes up less than 15 percent of total cases. Dr. Engelthaler cites one statistic when discussing who should be among the first to receive immunization.

"While the case fatality rate for most Arizonan's falls below 1 percent, it is currently 16 percent for the elderly. This age group is also experiencing the most adverse effects from social isolation, which can be just as devastating," he said, "these individuals, and their caregivers need the vaccine first."

In terms of a vaccine by year's end, Dr. Engelthaler remains optimistic. He notes there has been tremendous success in vaccine development and identifying good candidates that have been moving through the series of clinical trials that are necessary to ensure that they are safe and effective. It is likely that one or more of these vaccine candidates will conclude their clinical trials and be approved for use before the end of the year.

The Centers for Disease Control, World Health Organization and other health entities have worked on distribution plans for months, as have state and local health departments. Dr. Engelthaler points out that vaccines have been distributed in mass quantities for decades, whether for influenza, childhood immunizations, or other vaccine preventable diseases, so the infrastructure is in place and ready.

"Until then," said Dr. Engelthaler, "the best precaution is caution; we need to maintain vigilance, protect each other and stay resilient."



"A FEW DROPS

of blood could reveal insights into how antibodies could stop COVID-19," says Dr. John Altin, a TGen North Assistant Professor.

Through a research effort called The COVID

produces antibodies in response to a COVID-19 infection. One class of antibodies with the human body tackles the infection first, and then another comes in to finish the job. Knowing when these different

Therapy at City of Hope, one of Dr. Altin's collaborators.

Dr. Zaia leads a research project at City of Hope, in collaboration with Dr. Altin's lab, that will hopefully result in the development of a

COVID IMMUNITY STUDY

Immunity Study, Dr. Altin, his team, and colleagues at City of Hope are studying, in depth, the immune response to COVID-19. The results could eventually lead to new methods of diagnosing COVID-19, and help in the development of antibody therapies, and perhaps vaccines.

Ultimately, the study will help researchers learn more about how, when and why the body

immune responses occur, and how long they last, could help scientists understand why some patients gain a certain degree of immunity against reinfection while others seem to gain little benefit.

"Antibody testing will be critical very soon as we emerge from the COVID-19 pandemic, so this project is immensely important," says Dr. John Zaia, Director of the Center for Gene

COVID-19 virus antibody neutralization test.

The COVID Immunity Study collects blood spot samples that are remotely collected and sent to TGen by citizen scientists that have recovered from COVID-19. For more information, or to see if you qualify to participate, please visit covidimmunity.org/ or contact a TGen Clinical Research Coordinator at crc@tgen.org.

TRACKING COVID

IN EARLY APRIL, FACULTY AT TGEN, NORTHERN ARIZONA

University, the University of Arizona, and Arizona State University formed the Arizona COVID-19 Genomics Union (ACGU).

The goal was to sequence positive patient samples of SARS-CoV-2 with the express purpose of tracking the causative agent of COVID-19, SARS-CoV-2: how it evolves and how it spreads, within and outside of Arizona. The move may eventually prove to be the one of the most consequential long-term scientific responses to the global pandemic.

"Genomic sequencing and advanced analyses allows us to fully understand this disease at the molecular level and reveal the virus' inner workings," said TGen's Dr. David Engelthaler, Director of TGen North and Co-founder of the ACGU, who also coordinates the Union's genomic epidemiology efforts. The former State Epidemiologist and Biodefense Coordinator has

TREATMENT

IN LATE APRIL, TGen — in collaboration with HonorHealth — launched a clinical trial for patients with COVID-19. The trial features a combination of the drugs atovaquone and azithromycin. Predictive modeling suggests that atovaquone may be an active drug in the treatment of COVID-19 and its combination with azithromycin, studied in the rare infectious disease babesiosis, makes for an intriguing combination. "I'm excited to be working on this project and am hopeful that the translational aspects of this and other studies at TGen will open new avenues for diagnosis and treatment of COVID-19 in the future," said TGen's Sunil Sharma, M.D., a trial principal investigator who holds dual appointments at TGen and the HonorHealth Research Institute. The trial expects to enroll approximately 25 patients. Eligibility criteria can be found at clinicaltrials.gov.

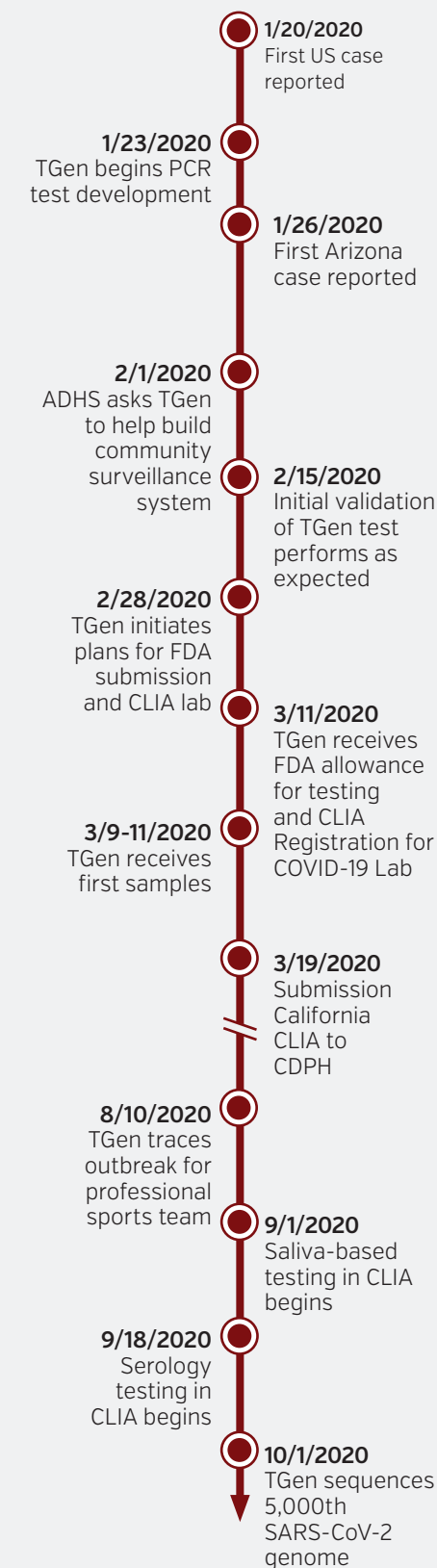
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FOR AN ORAL PERSPECTIVE,

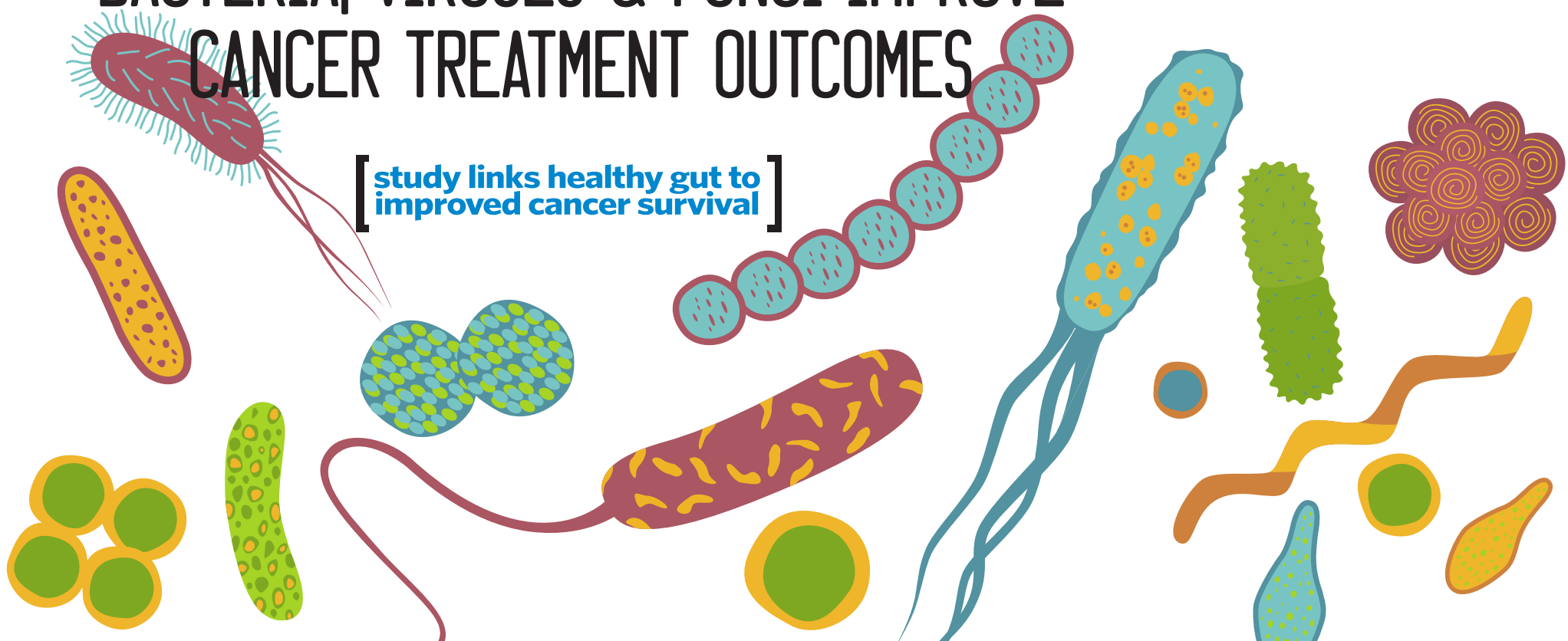
on TGen's efforts to combat COVID-19, check out our series of **TGen Talks** podcasts recorded at various points of the pandemic. Listen to these, and more, at tgen.org/tgentalks

COVID RELIEF Timeline



...continued on page 9

BACTERIA, VIRUSES & FUNGI IMPROVE CANCER TREATMENT OUTCOMES



[study links healthy gut to improved cancer survival]

THE HUMAN DIGESTIVE SYSTEM

it turns out is not all human.

It also depends on numerous types of friendly foreign bacteria to help break down the food we eat into microscopic fuel molecules that are absorbed into the walls of the small intestines. From there, they are whisked away into the bloodstream to wherever our bodies need them most.

Trillions of foreign microbes work within our bodies to help form the gut microbiome. Without them, we would starve. So, it only makes sense that a healthy gut microbiome plays a critical role in our overall health.

But what makes a healthy gut microbiome? And what effect does it have in cancer treatment?

Scientists and physicians at TGen and City of Hope recently found that, at least in patients with metastatic kidney cancer, a higher diversity of microbes in the gut is associated with better cancer treatment outcomes.

Their published findings, entitled — Stool Microbiome Profiling of Patients with Metastatic Renal Cell Carcinoma Receiving Anti-PD-1 Immune Checkpoint Inhibitors — appeared recently in the scientific

journal *European Urology*.

Studying samples collected from 31 individuals with metastatic kidney cancer (meaning the cancer had spread to other parts of the body), researchers for the first time sequenced microbes in the gut microbiome at three points in time: before therapy, and again four- and 12-weeks after the start of therapy.

All patients received an immunotherapy

"Our cumulative findings open the door to therapies directed at the microbiome."

— Sumanta Pal, MD, City of Hope

regimen to fight their cancer; some also received a probiotic supplement.

"The patients with the highest benefit from cancer treatment were those with more microbial diversity, but also those with a higher abundance of a specific bacterium known as *Akkermansia muciniphila*," said Sarah Highlander PhD, a research professor in TGen's Pathogen and Microbiome Division, and one

of the study's senior authors. "This organism has been associated with benefit in other immunotherapy studies."

Highlander said one potential takeaway from the study is that oncologists might encourage patients to pay attention to their gut microbiome by eating a high-fiber diet, including fruits and vegetables high in fructo-oligosaccharides (a small dietary fiber) such as bananas, dried fruit, onions, leeks, garlic, asparagus and artichokes, as well as grains with resistant starches such as barley or uncooked potato starch.

"We also reported the changes over time in the gut microbiome that occur during the course of therapy. The cumulative findings from our report open the door to therapies directed at the microbiome," said Sumanta Pal, MD, one of the study's senior authors and co-director of the Kidney Cancer Program at City of Hope.

It has only been in recent years that researchers have acknowledged the importance of the gut microbiome to general health, its role in disease states, and how microbes might interact with treatments. There still is so much more to be learned, including the role of the gut microbiome in fighting off infections.

Highlander suggested that next steps for researchers should include expanding their relatively small study to a much larger group of patients that are followed over a longer time period.

City of Hope researchers have embarked on a clinical trial to further explore the idea that modulating the gut microbiome during cancer therapy could have a positive impact on clinical outcomes.

Collaborations between investigators at TGen and clinicians at City of Hope have contributed to advancements in the understanding of not just the microbiome, but also in cancer biology and clinical outcomes at large.

"This current study is a further testament to the collaborative research structure we've developed between the affiliate institutions," said Dr. Pal, who is an internationally recognized leader in the area of genitourinary cancers. "Through these collaborations we can implement both a bench-to-bedside and bedside-to-bench research model that will lead to better patient care at City of Hope through access to clinical trials and precision medicine approaches."

TRACKING COVID...CONTINUED FROM PAGE 7

led investigations of local, national and international disease outbreaks for over 25 years.

Initial findings suggest that following Arizona's first reported case of COVID-19 in late January, the state experienced no cases that went undetected and was COVID-free until at least 11 distinct incursions occurred between mid-February and early April.

Similar to other groups across the globe, the ACGU mobilized quickly to openly share data and analysis with

COVID-19. This enables the Union to track both where and when the virus is moving through the state, helping public health officials identify hot spots where contact tracing efforts can be best applied.

NAU's Dr. Paul Keim, who serves as the ACGU director, credits much of the ACGU's abilities to the state's decades-long investment in fast, high capacity super-computers dedicated to probing the human genome.

"Our ability to advance the science here in Arizona in a way that informs public health, and helps us understand not only where we've been but where we're going with this disease is directly attributable to the state's investment in the latest technology and big data analysis, all of which helps us understand how the virus evolves and how it is transmitted through the general population," said Keim.

Dr. Keim, a world-renowned expert in pathogens such as bubonic plague and anthrax, holds the Cowden Endowed Chair in Microbiology and is Executive Director of The Pathogen and Microbiome Institute at NAU. He is also a distinguished professor at TGen and co-director of TGen's Pathogen and Microbiome Division.

Dr. Keim, a self-described optimist, notes that new discoveries are on the horizon; there are more than 100 vaccines using more than a dozen different technologies in development.

"When a safe and effective vaccine is eventually found, it's likely going to be based on amazing technological advances," said Keim, "and it will prepare us for future pandemics. This isn't the first, and it won't be the last, virus we have encountered. Ultimately, what we learn through our work with COVID-19 better prepares us for future outbreaks."

"Genomic sequencing and advanced analyses allows us to fully understand this disease at the molecular level and reveal the virus' inner workings."

— David Engelthaler, Ph.D.
Director, TGen North

epidemiologists and virologists critical to the scientific, medical and public health understanding of the pandemic.

The ACGU sequenced the SARS-CoV-2 genomes in as many virus-positive samples as possible, and working with Arizona's public health officials, applied the results toward statewide efforts to test and track patients, as well as provide guidance for Arizona public policy makers.

The published results, derived using molecular clock analysis, recently appeared in the scientific journal *mBio*. The molecular clock is a figurative term for a technique that uses biomolecular sequence data — DNA, RNA — to determine the development or mutation rate of a given organism, in this case



TGEN STUDIES ENGINEERED HEART TISSUE

ANALYSIS OF PROTEINS AND METABOLITES COULD PAVE THE WAY FOR FDA APPROVAL OF HUMAN CLINICAL TRIALS

MORE THAN 30 MILLION Americans have heart disease, resulting in over \$39 billion annually in medical treatment costs. Nearly 600,000 patients are newly diagnosed each year, and 650,000 Americans die annually, making it the nation's leading cause of death.

The condition is most often treated with drugs, but those efforts eventually fail. Heart transplants can help, but suitable donors are scarce, enabling fewer than 3,000 transplants each year. Mechanical hearts that run on battery packs also can help, but they are expensive; patients

someday might be applied to other failing organs.

To better understand how MyCardia works — at the infinitesimally small molecular level — Avery partnered with TGen, following an introduction made by the Flinn Foundation.

“Avery turned to TGen to understand which of their membranes are releasing molecules that produce therapeutic benefits,” said Dr. Patrick Pirrotte, Assistant Professor and Director of TGen’s Collaborative Center for Translational Mass Spectrometry. “Our collaboration will help them

could lead to human clinical trials. Up to now, Avery has studied the processes in laboratory and preclinical experiments.

“Avery’s technology is amazing,” Dr. Pirrotte said, noting that the MyCardia membranes actually beat like a heart. “Their idea is that, for a heart that is potentially weak, an inserted cardiac membrane could support regeneration of heart tissue.”

Avery licensed the technology for MyCardia from the University of Arizona, where Avery scientists had worked on developing engineered regenerative tissues to treat cardiovascular disease.

Key to the technology is the advancement in recent years of induced pluripotent stem cells (iPSCs), which can propagate indefinitely and theoretically give rise to every other cell type in the body. They represent a source of cells that could be used to replace those lost to damage or disease. Advancements in iPSC technology led to a Nobel Prize in 2012.

“It’s the concept of being able to take essentially any cell in the body and convert it into an embryonic-like cell, and then being able to make any cell. That’s how we are making our heart-muscle cells,” said Dr. Jordan Lancaster, Avery’s Chief Executive Officer.

Dr. Jen Koevary, Avery’s Chief Operating and Financial Officer, added: “We created the material based on the idea that you can use healthy cells to treat an unhealthy tissue and make it healthy again.”

HOW MYCARDIA WORKS

Through minimally invasive laparoscopic or robotic surgery, MyCardia is precisely grafted onto the surface of a damaged heart. It is loaded with a therapeutic cellular payload; a proprietary combination of cardiomyocytes (heart-muscle cells) and fibroblasts (general cells of the body).

Over time, the MyCardia membrane secretes proteins and metabolites, collectively called the secretome, which helps enable the heart to heal itself. The MyCardia eventually disappears. It’s the unique secretome that is being studied at TGen.

“We have lots of data, but we really don’t know what makes it tick,” Dr. Lancaster said.

There are hundreds of factors involved in the MyCardia process, explained Dr. Koevary: “Figuring out exactly how it works is very complex. It’s important for us to know how it’s working so we can, in the future, identify the best patients who would be candidates for treatment.”

MyCardia is a lab-grown cardiac membrane that can help repair the heart, either following a heart attack or as a result of progressive heart disease

are often left with limited mobility, poor quality of life and frequent hospital visits.

What if there were a better way?

Avery Therapeutics Inc. of Tucson has developed an engineered heart tissue, a lab-grown cardiac membrane that can help heal the heart, either following a heart attack or as a result of progressive heart disease.

The heart tissue, called MyCardia™, could revolutionize the treatment of cardiovascular disease, and

understand the mechanism of action on the molecular level, and the potential benefits to patients.”

TGEN EVALUATES MYCARDIA

TGen is conducting mass spectrometry analysis of the proteins and metabolites at work in MyCardia’s healing effect on heart-muscle tissue. This supporting data will be used in Avery’s submissions to the Food and Drug Administration (FDA) that

SUNIL SHARMA, M.D., M.B.A. APPOINTED PHYSICIAN-IN-CHIEF



ON OCTOBER 1, TGEN named Sunil Sharma, M.D., F.A.C.P., M.B.A., as Physician-in-Chief. Dr. Sharma succeeds Daniel D. Von Hoff, M.D., F.A.C.P., a leading expert in pancreatic cancer, who was instrumental in developing key clinical and research programs at TGen.

Dr. Von Hoff, who joined TGen in 2003, will continue as a Distinguished Professor and Executive Vice President, Molecular Medicine, to further his work in pancreatic cancer research and clinical trials.

“Dr. Von Hoff’s commitment to TGen and patients with pancreas cancer is second to none,” said TGen President and Research Director, Jeffrey Trent, Ph.D., F.A.C.M.G. “This transition provides him the opportunity to focus his energies solely on pancreas cancer research and treatment, a disease against which he’s made profound advances.”

Dr. Sharma joined TGen in 2017 as Deputy Director of Clinical Sciences, Professor, and Head of TGen’s Applied Cancer Research and Drug Discovery Division.

“Dr. Sharma’s appointment as Physician-in-Chief recognizes the important role he has played across TGen’s many biomedical disciplines since his arrival. He is a distinguished researcher and clinician and in addition to his leadership at TGen, he is rapidly bringing research in clinical efforts in immune treatments to the

forefront of patient benefit,” said Dr. Trent.

Dr. Sharma’s nearly three-decade career spans the areas of research, drug and clinical trial development. At TGen, he broadened his research and clinical portfolio beyond his specialty of gastrointestinal cancers (colon, pancreatic) to include drug development — immunotherapeutic treatments in particular — for COVID-19, Alzheimer’s disease, memory performance, and other cancers, including breast and ovarian cancer.

“I am grateful for the opportunity this new role provides, and humbled to follow in the footsteps of Dr. Von Hoff,” said Dr. Sharma. “I look forward to collaborating more broadly across the institute in search of new opportunities for patient benefit and am committed to keeping TGen at the forefront of precision medicine.”

Prior TGen, Dr. Sharma served as Deputy Director of Huntsman Cancer Institute, where he co-led the Experimental Therapeutics Program. He also built a phase I clinical trial program at the Nevada Cancer Institute, Las Vegas, and in the Division of Gastrointestinal Oncology at Memorial Sloan Kettering Cancer Center in New York. Dr. Sharma earned his medical degree at the University of Delhi in New Delhi, India, and his M.B.A. from the University of Massachusetts, Amherst.



TGen Bioscience Leadership Academy

July 24th marked the closing day of TGen's Bioscience Leadership Academy (TBLA), held virtually this year due to COVID-19.

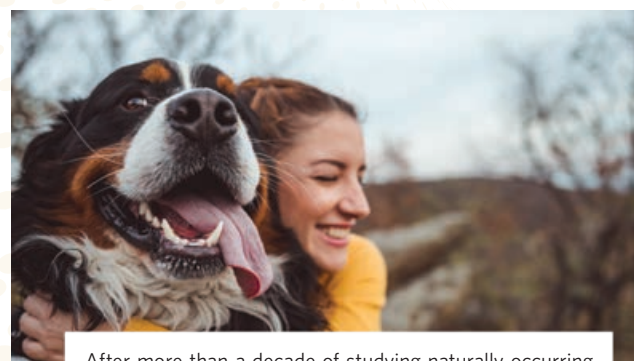
TBLA is TGen's two-week bioscience program serving 20 Arizona high school students annually. The intensive education and leadership program develops a greater understanding for the biosciences and precision medicine among participants. Though virtual, students and faculty interacted to the fullest.

"I wasn't sure what to expect, but the virtual environment didn't limit my ability to interact and establish solid relationships with my cohort and TGen mentors," said Pinnacle High's Kameron Cochrane.

The program exposed TBLA students to topics ranging from bioethics to marketing and everything in between, as well as break-out sessions and journal club.

TGen's Education team, led by Kristen Kaus, ensured that all participants gained the full experience of the program, which included virtual tours, guest speakers, and a platform for students to network and exchange ideas. 2021 applications open in December.

To learn more or become a sponsor of TGen's Bioscience Leadership Academy, please contact Kristen Kaus at kkaus@tgen.org



After more than a decade of studying naturally occurring cancer in pet dogs, TGen developed a company to provide genomic-based precision-medicine to veterinary oncologists and pet parents. **Vidium Animal Health** is built around the human-animal bond and offers the very best information, and hope, that science can offer. To increase a pet's chance of survival, Vidium created a test designed specifically to identify any of the nearly 120 known cancer-associated genetic mutations in dogs, and use the molecular profile of misbehaving genes to help guide diagnosis and treatment. Learn more at vidiumah.com

HOPE THROUGH HOLLIS

On September 27, in memory of 7-year-old Hollis Doherty, friends, family and supporters raised more than \$62,000 through the **5th annual Hope Through Hollis Golf Tournament** in support of the Hope Through Hollis Fund at TGen. The 2020 total helped push the fund past the \$1 million mark.

"Our brave and beloved Hollis is an example for us all; not just those with cancer, and not just other children with cancer, but for all of us — an example of living every moment to the fullest. He set a high bar for all of us and remains the inspiration for our #MostBestDays movement," said his father, Shane Doherty.

Hollis passed away in January 2017 of DIPG or Diffuse Intrinsic Pontine Glioma, an inoperable and aggressive brain tumor. His parents, Shane and Shawnee Doherty, remain tireless advocates for those families still fighting to find better treatments.

"Patient advocates and families, like Shane and Shawnee, are a continuous source of inspiration and motivation, driving ever-expanding research," said Dr. Michael Berens, Professor and Director of TGen's Cancer and Cell Biology Division, and head of TGen's Glioma Research Lab.

To support the Hope through Hollis Fund at TGen, please go to: www.tgen.org/hollis

It's not every day that a child's birthday is tied to a NASA launch, but that's exactly what happened when Alex Yiu, a young man whose rare neurological disorder TGen diagnosed in 2018, celebrated his 15th birthday.

Alex participated in NASA's *Send Your Name to Mars* program, which allowed space fans to register their names that NASA then etched on a microchip embedded on the latest Mars rover, fittingly called Perseverance. Participants are called Explorers, and if all goes according to plan, Alex the Explorer will arrive on the red planet in February, 2021.

Alex, a space enthusiast from a young age, couldn't be happier about it. To celebrate, his family hosted a virtual birthday and prelaunch party as a fundraiser for TGen's Center for Rare Childhood Disorders cold case reviews so that other families could receive another opportunity for a diagnosis.

At age 3, Alex displayed an unusual gait; his motor skills and coordination became awkward. By age 6, he could no longer walk. His speech slowed at age 7. Eating and drinking became challenging. A multitude of doctor consults ensued to no avail, including his first visit to TGen nearly a decade ago.

That changed in 2018 with the discovery of a mutation in a gene called IRF2BPL. Keri Ramsey, a nurse and Clinical Co-Director of TGen's Center came across Alex's file while searching for another patient and realized he carried the IRF2BPL mutation. After 12 years of relentlessly searching for answers to Alex's progressive neurodegenerative condition, Alex's family finally had a diagnosis: NEDAMSS (Neurodevelopmental disorder with regression, abnormal movements, loss of speech and seizures).

"What's amazing about Alex's mom is that she continues to fight for other families who still don't have a diagnosis. To her, it's still so important. She knows the value of having that diagnosis because for so many years they didn't have it," Ramsey said.

No treatment exists for NEDAMSS. Still, while Alex's family waits for a breakthrough, they raise funds so that other TGen patients and their families can receive a diagnosis.

"Our hearts ache knowing that there are other families struggling and feeling alone with no diagnosis," said Alex's mother, Caroline.



For many, the highlights of Barrett-Jackson collector car auctions are the exciting and often emotional moments when vehicles with a noble purpose cross the block.

One organization in particular has a special significance to Barrett-Jackson Chairman and CEO Craig Jackson: TGen. In 2010, Craig Jackson established the Barrett-Jackson Cancer Research Fund at TGen in memory of his father Russ (who died from prostate cancer) and his brother Brian (who died from colon cancer). Numerous charity cars have crossed the block since for this worthy cause, raising more than \$1.7 million to date.

"I'm proud we've kept alive the legacy of charitable giving my father Russ Jackson and his business partner Tom Barrett started nearly half a century ago," says Barrett-Jackson Chairman and CEO Craig Jackson.

Over the last decade, with the funds support, TGen has made a number of inroads into cancer research and therapeutic development.

Most recently, in an effort to find ways of identifying patients more likely to respond positively to immunotherapy, TGen and City of Hope colleagues applied a mathematical model developed by City of Hope's Dr. Andrea Bild and colleagues to analyze clinical trial data from patients with advanced colorectal or other gastrointestinal cancers from a trial led by TGen's Dr. Sunil Sharma.

"Our findings suggest, for the first time, an important predator-prey relationship between circulating immune cell dynamics and tumor response to immunotherapy. The concept could lead to the development of innovative clinical trials in the future," said Dr. Sharma, TGen Physician-in-Chief.

The results appeared in the *Proceedings of the National Academy of Sciences*.

Upcoming Events

November 1-7 — Step-N-Out 5K. Join your friends, neighbors or loved ones as they "come together" virtually to kick off Pancreatic Cancer Awareness month by walking, running or hiking in support of TGen's pancreatic cancer research. Register at tgen.org/step

December 1 — Giving Tuesday, a global generosity movement that kicks off the beginning of the holiday season. Proceeds support TGen's groundbreaking research with life-saving results.

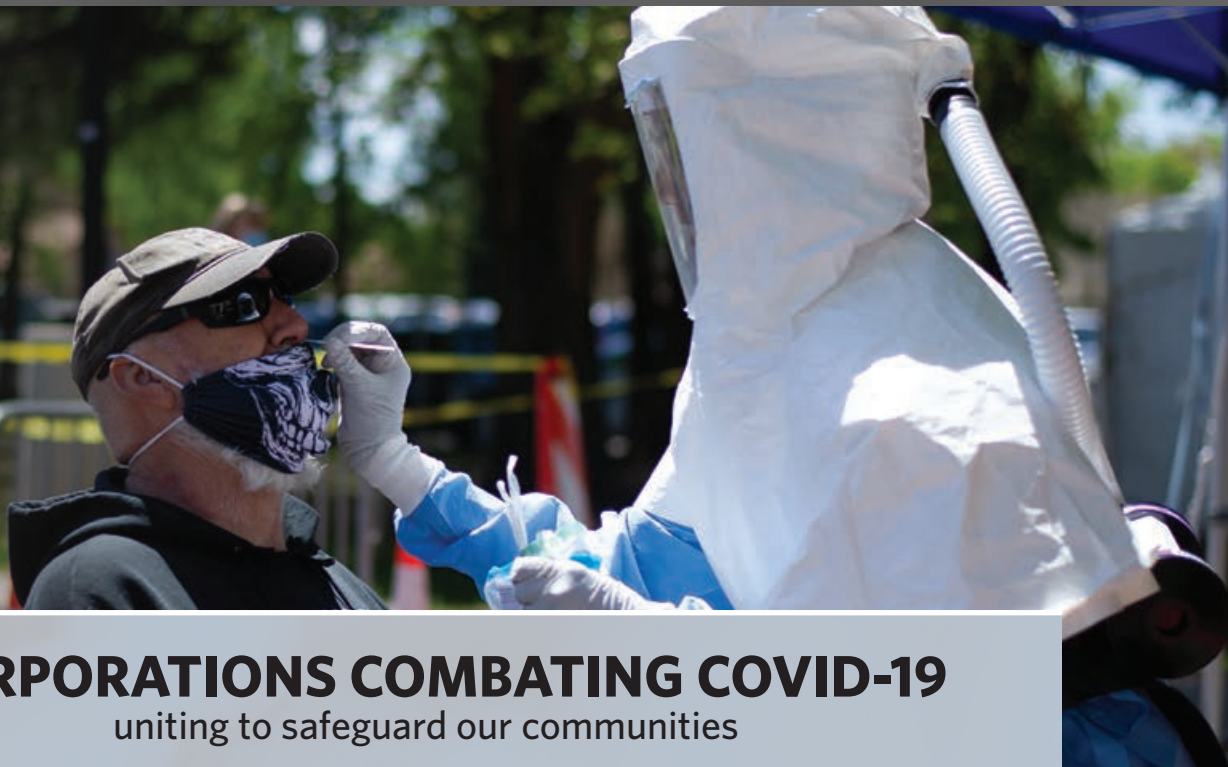
January 16-24, 2021 — Barrett-Jackson collector car auction, Westworld of Scottsdale.

To learn more about these and other upcoming events, please call the TGen Foundation at 602-343-8411 or visit: www.tgen.org/events





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CORPORATIONS COMBATING COVID-19

uniting to safeguard our communities

TGEN MAY CALL PHOENIX HOME, BUT ARIZONA IS OUR BACKYARD. When COVID-19 hit and our neighbors needed help, our biomedical experts became genomic first responders and acted quickly — from testing, to tracking, to tracing. Our work includes supporting tribal communities, long-term care and behavioral health facilities, groups who face barriers to testing, and workers at the front line.

But, we can't do it alone: we need your help. Invest in your community today by becoming a corporate partner.

To learn more, please call or email Jenna Higgins at 602-343-8481 or jhiggins@tgen.org