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TGen Today

A PUBLICATION OF THE TRANSLATIONAL GENOMICS RESEARCH INSTITUTE, AN AFFILIATE OF CITY OF HOPE
A Non-Profit Biomedical Research Institute

Looking *beyond* the pandemic

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A Look Inside...

Dear Friends,

If asked to sum up this edition of *TGen Today* in a single word, I'd lead with promise.

Starting with our cover story, where we recap the COVID pandemic and highlight the promise of a brighter tomorrow in terms of identifying and managing outbreaks of the future. The lessons learned have already bore fruit by our scientists at TGen North, whose bold approach and innate desire to apply the acquired knowledge quickly and passionately — often times in traditionally underserved populations — means a world of difference to those in need.

Perhaps no greater promise exists short term, however, than the work of the TGen scientists and clinicians engaged in developing a new cancer treatment and accompanying vaccine, work that also includes colleagues at City of Hope. If successful, these methods stand to dramatically redraw the treatment landscape for solid tumor cancers, such as lung, breast, colon or pancreatic and further TGen's mission of applying precision genomics for increased patient benefit.

Promise also flourishes at TGen in areas beyond the laboratory.

In step with a change occurring across many disciplines and many sectors of the workforce, TGen is furthering and redefining its approach to diversity, equity & inclusion (DEI) in the workplace. The establishment of a DEI council continues the Institute's commitment to equality and serving the underrepresented and underserved.

You'll meet TGen donor Diane Matsch, and *Helios Scholars at TGen* alumnus Sophie Wix.

Diane's is a story of commitment to TGen, and one that hopefully promises a more certain future for her children. A long-time supporter of TGen's research and clinical work in pancreatic cancer, Diane knows all too well the devastation wrought by cancer. Having lost her husband and multiple other family members and friends to pancreatic cancer — and knowing family history is a predictive factor — she gives with purpose and heart.

Sophie is a promising young medical student, whose passion for a career in science and medicine began at TGen. Hers is the arc of achievement we wish for every student who spends time in our laboratories alongside a committed mentor.

In closing, it is my hope that these and the other stories within this edition excite and inspire you as much as they drive all of TGen to achieve.

With gratitude,

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

TGen Today

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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The Long Road Out

Looking *Beyond* the Pandemic

DEPENDING ON ONE'S VIEWS, THE FINAL ACT of the COVID-19 pandemic — post vaccines — reverberates with either haunting refrain or sighs of relief. Thankfully, for many, vaccines are saturating the landscape. The Delta variant, however, remains a concern of the watchful.

In virology, a variant is a subtype, a microorganism spawned from its progenitor strain. Like most offspring, variants quickly develop a personality of their own; some more aggressive than others, though all on a singular mission to infect. SARS-CoV-2 spawned a great number of variants, prominent among them strains originating in the UK, South Africa, Brazil, and India — the origin to perhaps the worst of the lot, the highly-infectious Delta variant, which arrived nearly a year into the pandemic. By early summer, COVID-19, led by Delta, had once again strained healthcare systems around the globe, primarily in areas with low vaccination rates.

Globally, the pandemic continues to take a toll.

By mid-September, worldwide cases had reached 225 million with more than 4.6 million deaths. Friends, families and loved ones remain staggered but standing. The U.S. alone has seen nearly 42 million cases and almost 676,000 deaths.

When COVID arrived in January of 2020, the World Health Organization (WHO) announcement labelled it "a mysterious coronavirus-related pneumonia coming out of Wuhan, China." The WHO would elevate it to pandemic status two months later, but not before the onset of global air travel restrictions, cruise ship disasters and a CDC warning of how the U.S. — along with the rest of the world — seemed headed pell-mell toward a brewing health crisis. These developments and a rising death toll quickly embedded COVID-19 deep within humanities collective consciousness.

It's no wonder then that questions persist. When will it end? What have we learned? And ... Can it happen again?

According to David Engelthaler, Ph.D., director of TGen's Pathogen and Microbiome Division in Flagstaff, Arizona (more commonly known as TGen North) the answers are much like the virus itself, best delivered with nuance rather than a hard and fast yes or no.

"These past 20 months in many respects truly have felt like 20 years," says Dr. Engelthaler. "While there is no doubt that given the global devastation, COVID is a medical and virological phenomenon, the public health scientist in me finds relief in the knowledge we've acquired in terms of understanding the biology behind the virus and the epidemiology

behind the disease at a much deeper level than any previous disease outbreak. What's most heartening are the technological advances that drove much of the discovery and have led to our path out of the pandemic: vaccines."

"Short term, I can honestly say we are nearing the tail end of the pandemic; in the U.S. at least," adds Engelthaler. "It doesn't feel like it, with Delta spreading seemingly unabated, but the vaccines have absolutely changed the nature of the pandemic and are getting us to a point we can — and have to — live with. Globally, I don't see COVID going away as quickly."

Engelthaler attributes the continuing global pandemic to the lack of vaccine access in other countries and the mid-summer spike in the Delta variant. And while a COVID ending may not be a true ending — as in a complete eradication — he does believe any lingering aftereffects fall under the heading of endemic rather than pandemic.

"COVID is not going away, there is no 'COVID-Zero'. Our scientific understanding of COVID-19 suggests that the virus will stay with us, regardless of vaccination rates. We've seen first-hand how adept Delta is at finding the next susceptible person, even in communities with high vaccination rates. I expect that we all will be immunized within the next 6-12 months, either by vaccine or infection ... or both."

Downstream Benefits

Despite the Delta surges around the world, Engelthaler takes many positives away from the past 20 months.

The collective scientific and technological energy that went into the moon walk of 1969 netted numerous societal benefits, including fire proof material, solar panels and improved medical devices. Space shuttle technology gifted society the artificial heart, advanced prosthetics and improved cancer treatments. Engelthaler sees similar scientific and societal gains emerging post pandemic.

He says, "The whole idea of a moon shot stimulates and drives our intellectual capacity and resources focused on a singular goal. That happened in several distinct ways during this pandemic."

The most important involved vaccines. The speed at which teams developed the novel COVID vaccines had a great deal to do with the technical advances of the past decade or so and the vast amount of scientific data generated post Human Genome Project. The fact that the U.S. led the way in terms of funding and de-risking (this allowed for rapid and parallel vaccine production) also paved the way for expedited distribution across America.

"Overall, the vaccines work remarkably well. Yes, there are relatively rare breakthrough cases and we're monitoring the variants should mutations occur that render the vaccine less effective or ineffective, but to date they have significantly and essentially diminished the deadly part of the pandemic in the U.S. We will likely need a booster at some point in response to a new variant or to maintain a high level of personal immunity, similar to how we protect ourselves from influenza," says Engelthaler. "The FDA is already paving the way for boosters to get to those that need it most, but make no mistake – the vaccine is what turns this monster virus into a bad cold, at worst, for almost everybody going forward."

Digitizing the Natural World

Another major advance occurred with genomic sequencing – the digital decoding of the virus' genetic blueprint. Given the need to sequence as many samples as possible to track the virus and its variants, we are seeing a moonshot effect on the cost, speed and accuracy of viral genomic sequencing.

"Sequencing reveals the secrets of the virus – where it comes from, how it is changing and even if it will evade some treatments. It allows us to move beyond simply counting cases and generate actionable intelligence," says Engelthaler. "This in-depth information may one day allow hospitals and public health providers to jump ahead of outbreaks and treat patients based on the actual infection they have, not just on the type of infection they have, as we do now."

Today, the cost of sequencing a pathogen genome comes in at around $100. The goal is less than $25 per genome.

This, according to Engelthaler, would place it on par with many routine hospital tests and revolutionize the adoption of public health measures into the clinical care stream. Engelthaler refers to this as 'democratizing sequencing' and he hopes to make it the standard of care for response to all critical pathogens.

TGen's sequencing advances also gave rise to the Arizona COVID-19 Sequencing Dashboard, a web-based portal built by TGen for the state of Arizona.

"The portal provides a visual display of what's occurring in near real time across Arizona such as when did the first U.K. variant show up? How prevalent is the Delta variant in various regions?" says Engelthaler. "It helps health departments and health officials understand what variant exists and at what level (there are three levels: variants of interest, concern and high consequence) at any given point in time and provides insight into what communities are experiencing."

To date, TGen North faculty and staff have uploaded data from more than 36,000 genome sequences.

By generating such vast amounts of data — what Engelthaler calls 'pathogen intelligence' — scientists are digitizing the natural world, with variants tracked, data analyzed, risks carefully weighed and shared on a global scale. And not only for COVID. TGen North scientists are also busy applying this technology and approach on other viruses and bacteria that plague our world, particularly in healthcare settings, a direction Engelthaler views as a boon for advancing the state of both clinical medicine and public health.

Which begs the question, what's next?

"Undoubtedly, there will be a next," says Engelthaler. "COVID wasn't our first major outbreak and it won't be our last. We saw SARS-CoV-1 in 2003; Pandemic Swine Flu in 2009; MERS-CoV in 2012; and Ebola in 2014, and many others on a lesser scale that plague our communities and hospitals every day."

Engelthaler is quick to point out that Mother Nature is an inventor, and she is developing new strains, new variants and even new pathogens all the time. As we push into the world's natural habitats, we expose ourselves to new bugs that in turn give rise to new infectious diseases, which now can spread around the world at the speed of air travel.

Yogi Berra famously said, "It's tough to make predictions, especially about the future." And while it's doubtful Yogi had a pandemic in mind, the sentiment could easily apply to the next pathogen outbreak. The when, where and how remain anyone's guess, says Engelthaler, but he has no doubt that somewhere out there a new virus awaits a host.

"And that," he adds, "is why pathogen intelligence is critical. Understanding nature at the molecular level allows us to understand what is happing right now and hopefully prepare and be ready for the next one."

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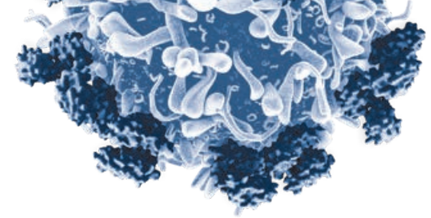
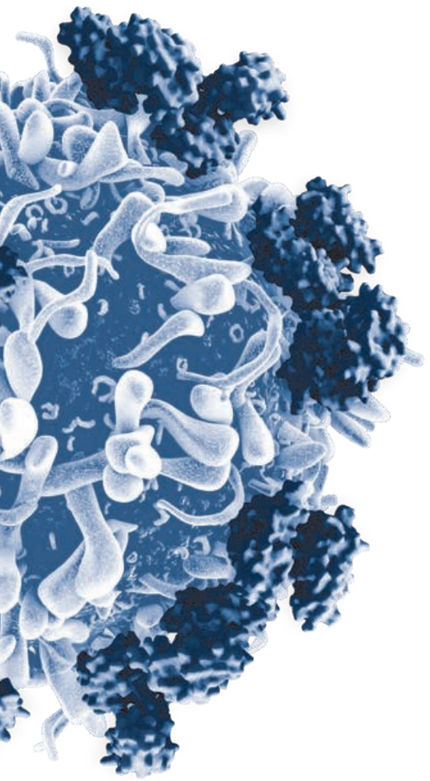
>
> *— David Engelthaler, Ph.D.*



INFUSED WITH HOPE

A NEW APPROACH TO CANCER TREATMENT



Like injured boxers, potentially life-saving elements of the human immune system lie buried within a cancerous tumor unable to land a knock-out blow.

The tumor may wall-off or incapacitate these key immune killer cells, called tumor infiltrating lymphocytes (TILs), effectively blocking their main function: the destruction of cancer cells.

But, what if it were possible to rehabilitate the TILs? What if scientists had a way to awaken them, put them back into the tumor and create a resurgent mass of cells capable of knocking out the cancer? And what if clinicians could then deliver a blueprint in the form of a vaccine that would trigger the patient's own immune system into creating even more anti-cancer cells that would not only help kill the tumor, but prevent the cancer from ever coming back?

While simple in theory, previous attempts to do so came up short. But now there are three punches that TGen investigators are throwing in a promising new effort that could theoretically disable virtually all cancers.

TGen's approach takes precision genomics, led by Jeffrey Trent, Ph.D., TGen's Research Director, and identifies the patient's genetic changes within their actual tumor cells. That is combined with precision immunotherapy, led by John Altin, Ph.D., a TGen Assistant Professor specializing in immune-therapy, identifying which among hundreds of genetic changes can be found on a patients cells. The final blow, led by Dr. Sunil Sharma, M.D., TGen's Physician-In-Chief, is "educating" and then returning the cells to the patient to recognize targets and have their own TILs search out and kill their tumor cells.

"Until recently, the field has lacked the molecular specificity required to re-educate the T cells," says Dr. Trent, whose lab is actively involved in the genomic underpinnings of the process. "Dr. Altin's work at TGen has developed an approach that identifies the exact tumor targets that the T cells need to see on the tumor. This allows Dr. Sharma's team — in concert with City of Hope's clinical cell processing team — to properly 're-educate' and expand the TILs so they can do their job and kill the tumor."

In the coming months, the TGen team will conduct a clinical trial on as many as 60 patients with varying types of cancer to determine the safety and effectiveness of this unique treatment method.

"We're attempting to fuse TIL technology with precision vaccines to achieve a positive treatment response," said Dr. Sharma, "This innovation, if successful, will take cancer care to an entirely new level."

Dr. Altin agrees, adding that laboratory experiments have already shown that the concepts should work in multiple cancer types: "The approach we are developing could be applied to almost any tumor in the human body."

Snap: the first treatment

The treatment method requires a four-step process.

First, through a biopsy, clinicians extract cells from a patient's tumor, including TILs. Scientists perform deep DNA and RNA sequencing to understand changes unique to the patients' cancer, and then sort these cells in the laboratory. Second, the TILs undergo rigorous genomic and proteomic analysis to identify those that have the greatest potential to be effective against the tumor. Third, the chosen TILs are isolated, multiplied and retrained to identify and attack specific antigen peptides (proteins) on the surface of a patient's cancer cells. The retrained TILs — composed primarily of immune system T cells — are known as specific neo-antigen peptide TILs, or snapTILs™. The fourth step involves introducing the snapTILs back to the patient through intravenous infusion.

"What's most fascinating is that we leverage each patient's genomic profile and a handful of the right T cells to drive the process," said Dr. Sharma. "Because we can replicate the most effective cells in the laboratory environment, we're capable of making millions to help each patient. It's a very genomic and immunologically precise way of aligning the cells against the tumor."

The process repeats itself with each patient, because each patient's cancer cells are different — even within the same type of cancer, and even that type of cancer within each patient. It's a penultimate example of precision medicine.

Dr. Altin calls this therapeutic a "living drug."

"Most drugs involve giving some chemical, something that is not alive, to the patient," he explained. "Whereas, in cellular therapy, you are actually taking living cells, re-training them, and putting them back into the patient."

Vaccine: the second treatment

Developing a vaccine to fight cancer is the Holy Grail of oncology. But is it possible?

Past attempts have simply lacked the precision needed to sufficiently activate the body's own innate immune system to identify and thwart tumor cells in the earliest stage of development, prior to their taking root.

As with the snapTIL treatment, TGen's vaccine relies on cells extracted from the tumor. Following identification and isolation of antigens on the surface of cancer cells they're infused in the patient where, once again, the body's immune system recognizes them and mounts a response. This stimulates the T cells already present in the patient, causing them to multiply and, like those created in a laboratory, incapacitate the tumors.

"The vaccine eliminates the need to replicate the effective cells in the laboratory by prompting the body's own immune system to provide the same function," said Dr. Altin.

Unlike the single-use snapTIL treatment, a patient could theoretically receive the vaccine multiple times in order to stimulate, or re-stimulate, the immune system against the cancer.

TGen will begin recruiting patients for the clinical trial phase in the near future. Ideally, said Dr. Sharma, they would like to have 60 patients representing a variety of tumor types: 30 to test the snapTILs treatment; and 30 to test the vaccine. Eventually, patients would receive both in tandem.

Different from CAR T therapy

Dr. Sharma is quick to point out that while similar in nature, both snapTIL and the vaccine differ from the more well-known CAR T therapy.

A drawback of CAR T therapy is that they've proven effective only in blood cancers such as lymphomas, multiple myeloma and certain types of leukemia. They have yet to show effectiveness against more genetically complex solid tumors, such as lung, breast, colon or pancreatic cancers.

"I believe an advantage our approach holds over CAR T is that we are training T cells for a specific function rather that attempting to engineer a cell to perform a certain task," explained Dr. Sharma.

Potential for mRNA in cancer treatment

The COVID-19 vaccines made by Pfizer and Moderna rely on a newly refined technology nearly three decades in the making called mRNA. Compared to previous vaccines, mRNA based vaccines are highly potent, safe to administer and rapidly developed at relatively low costs.

Dr. Altin said TGen researchers are not yet pursuing mRNA technology for cancer vaccines, but are considering it for future projects: "It's definitely got us thinking about whether we can use that mRNA platform."

Instead of a vaccine that gives patients versions of their own antigen peptides, they would receive mRNA, which is the genetic code that refers to those peptides.

"In the same way that the COVID vaccines work, those cancer peptides would be made by the body itself. The vaccine would provide the mRNA instructions to the body, which would then make the antigens," Dr. Altin said. "Using mRNA would elevate anti-cancer vaccines to a whole new level."

For now, though, snapTILs and vaccines are providing a sufficient enough challenge and one, that if successful, could potentially eliminate the need for additional therapies.

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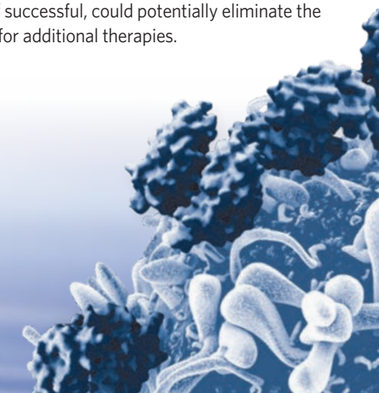
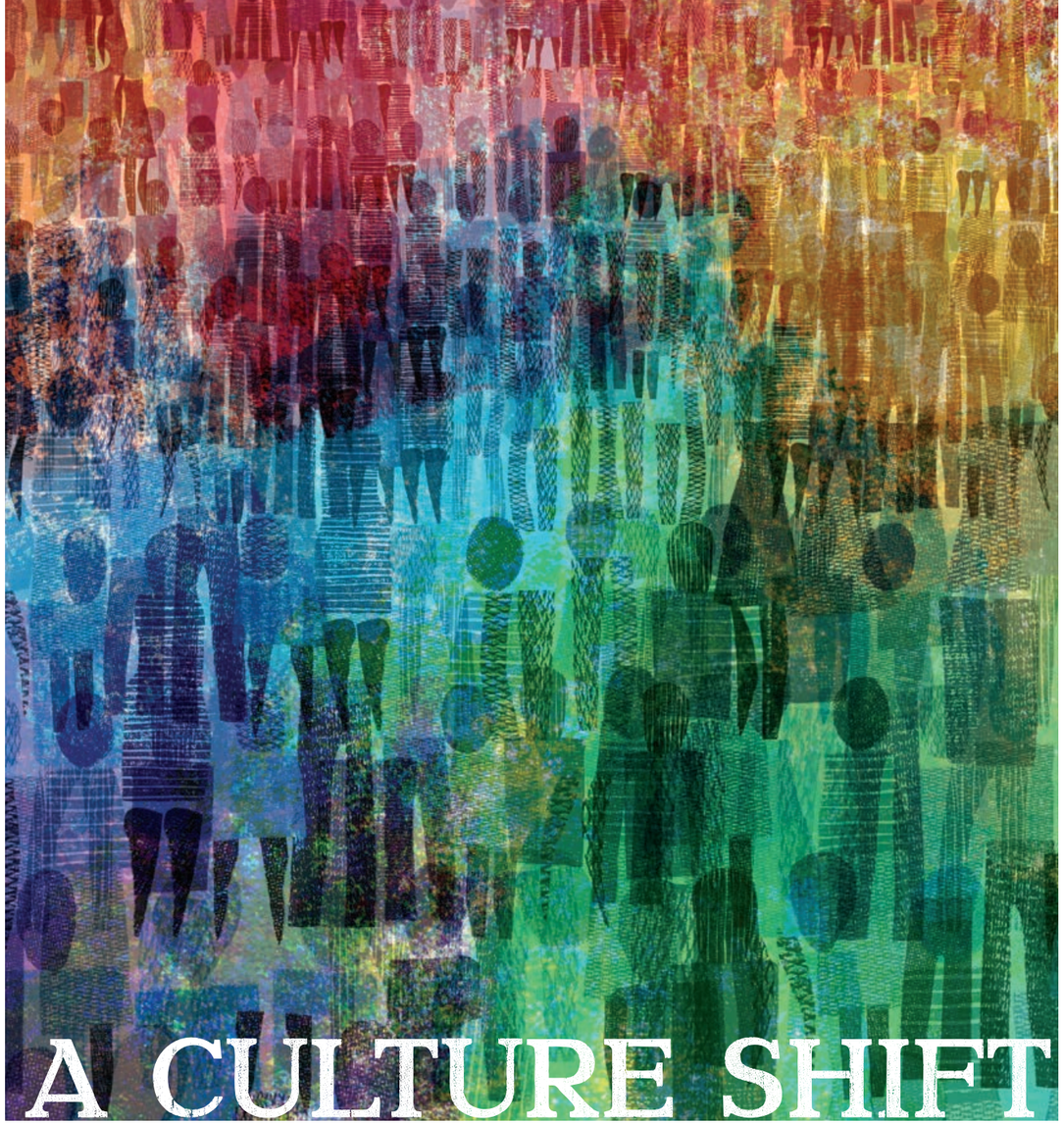
> *— Sunil Sharma, M.D.*





A CULTURE SHIFT WITHIN BIOMEDICAL RESEARCH

The pandemic may have dominated the headlines for the past two years, but news more cultural in nature spotlighted an increased desire for greater equity across broad swaths of society. Protests following the deaths of George Floyd, Breonna Taylor, and other Black Americans prompted essential dialogue on the topic of diversity, equity, and inclusion (DEI) in the United States.

The discussion around DEI has also made its way into the workplace.

"This isn't just a topic that affects one aspect of anyone's life, it really is quite pervasive. I often say it's personal *and* professional," says Dr. Joseph Mikhael, Professor of Applied Cancer Research and Drug Discovery at TGen and Chief Medical Officer of the International Myeloma Foundation. Dr. Mikhael is also the Chair of TGen's newly formed DEI Council. "The Council's goal is to inspire a more informed conversation about DEI at TGen to create avenues for organizational dialogue and learning," he adds. The eight-member Council — a diverse group representing nearly all aspects of TGen research and administration — shares a passion for ensuring that all employees have a voice and that TGen becomes an even better place to work.

Beyond the Initialism

Fully understanding and appreciating DEI's promise requires an understanding of the three components that form the whole. While most people understand the basic concept of *Diversity*, perhaps less familiar are the concepts of *Equity* (which is distinct from Equality) and *Inclusion*.

Diversity refers to the level of representation and conscious acceptance of identities and ideologies. These two dimensions may include gender, race, ethnicity, (dis)ability, sexual orientation, age, religious or political affiliation, and cultural background. A workforce or other community represented by many dimensions is diverse.

In their article *Social Equity: Its Legacy, Its Promise*, authors Mary Guy and Sean McCandless state that *Equity* recognizes that everyone has different advantages and disadvantages. Equity is thus a "flexible measure that allows for equivalency while not demanding sameness," whereas "equality can be converted into a mathematical measure by which equal parts are identical in size or number."

In short, equity is experienced by individuals or groups when opportunities are based on their individual advantages and disadvantages rather than on an established norm.

The third concept, *Inclusion*, aims to ensure that people feel they belong at their organization or within their community. Although essential to a thriving workplace, inclusion can be more nuanced than diversity or equity and thus more difficult to properly implement and track.

When Seema Plaisier, a TGen computational biologist and member of the DEI Council, speaks about DEI as it applies to science, technology, engineering and mathematics — more commonly known as STEM — she highlights the necessity of dedicated mentorship of students from underrepresented communities, an idea inspired by a talk given by Dr. Yeukai Mlambo from Arizona State University's Teachers College.

"[Underrepresented] students that had a mentor that took them in and talked to them about how things were going and if they had any problems … those were the ones that stuck. The ones that felt like they were an island where everybody was out for themselves … those are the ones that bailed," says Plaisier.

This intersectionality of diversity, equity, and inclusion highlights how a young scientist from a background uniquely dissimilar to many of their peers may bring different advantages and disadvantages to the table and could require more dedicated mentorship to gain a sense of belonging and acceptance.

Extending our Reach

DEI is a vital component of the Institute's organizational mindset in terms of supporting its employees, but it doesn't stop there. TGen researchers amplify this approach by incorporating a similar mindset when establishing a framework for their research objectives.

This commitment includes supporting populations historically and currently underrepresented in the biomedical field, including people of color, tribal citizens, and those housed in correctional facilities.

As Head of the Diabetes and Fibrotic Disease Unit at TGen, and a member of the DEI Council, Dr. Johanna DiStefano is passionate about including Latinos in her research on nonalcoholic fatty liver disease (NAFLD). While she cites that genetic factors may play a role in NAFLD prevalence in the Latino population, she says the problem is not only physiological.

"The reality is that healthy food is really expensive and many Latinos [relative to white citizens] in our country don't have the financial means to support a healthy diet," says Dr. DiStefano. "Because of this, Latino children have a much higher prevalence of NAFLD than white children. This is a systemic problem, not a consumer problem."

By better understanding how NAFLD affects Latinos and by connecting her findings to the issue of food deserts in the southwestern United States, Dr. DiStefano is working to holistically support Latino communities in Arizona.

"We often see the worst impacts of public health issues on areas that are underserved and unaccounted for, and in Arizona we see this issue most distinctly in our tribal communities," says Dr. David Engelthaler, Director of TGen North, TGen's Pathogen and Microbiome Division located in Flagstaff.

Engelthaler has worked for years with Arizona tribal communities to develop relationships rooted in the understanding that TGen North is a trusted and respectful partner.

"Because most of the state's population lives in urban centers," adds Engelthaler, "resources are allocated disproportionately, leaving many in rural areas without the necessities needed to truly thrive."

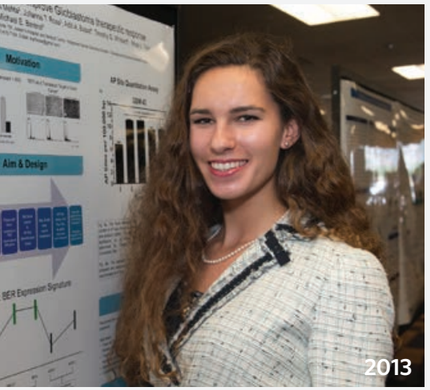
When COVID-19 hit the state, tribal communities were among the first partners on board for testing, and TGen North continues to support these populations through variant detection and whole-genome sequencing technologies. The TGen North team has undertaken similar efforts in correctional facilities throughout the state to curb outbreaks before they become unmanageable.

"Science should not preferentially serve one group to the detriment of another," says Engelthaler. "However, to make that ideal a reality, an openness and willingness to understand the often-hidden needs of our fellow humans is required."

Improving diversity, equity, and inclusion outcomes for both employees and the people that TGen's research serves is not without its challenges, but these efforts are essential for achieving TGen's vision of bridging genomic research with medical advancements that directly impact individuals, their families, and their communities.

By pursuing translational research in this manner, medicine will become more precise, more equitable, and more personal for everyone.

"This [DEI] isn't just a topic that affects one aspect of anyone's life, it really is quite pervasive. I often say it's personal and professional. It's about facilitating a more informed conversation about DEI at TGen in an effort to create avenues for organizational dialogue and learning." — *Dr. Joseph Mikhael*



A Helios Scholar Reflects on her Success

Sophie Wix is quick to say she owes her career trajectory to the lessons of science — and life — learned through the *Helios Scholars at TGen* program.

2021 marked the 15th year of TGen's flagship internship program from which Wix, and nearly 600 other alumni, gained often career-defining exposure to biomedical research and medicine by working alongside TGen faculty and staff.

"TGen was the launchpad for my career and Helios Scholars was the fuel," said Wix, who since her internship in the summer of 2013 has rocketed through her biomedical education: a bachelor's from the University of Southern California (USC), a coveted Fulbright Scholarship, and a master's from Cambridge University.

"Sophie's is the success story we want for every student in the program," said Kristen Kaus, Manager of TGen Education and Outreach, "and we hope it's one that our founding partners, Helios Education Foundation, regard as a point of pride and accomplishment."

Wix currently attends the combined Texas Christian University (TCU) and University of North Texas (UNT) Health Science Center School of Medicine where she's hard at work on her medical degree. While still undecided on her specialty as she enters her third year, she does have an over-arching goal in mind: help develop new diagnostics and therapeutics and provide greater access to patients from underserved populations.

"If there is anything I've learned in medical school it's that, beyond the world of academia, we have so much work to do. There are so many people who don't have access to very basic cancer treatment options," she said.

Even in this, Wix credits her Helios Scholars experience for sensitizing her to the needs of others, recalling a talk given by Paul Luna, President and CEO of Helios Education Foundation.

"He spoke of his personal history and his hopes that the program would provide underrepresented students exposure to world class science and greater opportunities in the biomedical sciences," she said. "That talk has stayed with me over the years and kept me focused on the fact that these disparities persist."

As founder and president of her school's chapter of the American Medical Women's Association, Wix also wants to overcome the challenges women face in a profession once dominated by men, including closing the pay gap and halting the micro-aggressions that persist to this day.

Where it all Began

A middle-school tour of TGen ignited Wix's passion for science and biology. Her acceptance following her junior year of high school as one of the 45 students selected annually for the *Helios Scholars at TGen* program set her on her way. Wix studied glioblastoma brain tumors under the mentorship of Dr. Michael Berens, a TGen Deputy Director who heads the institute's Glioma Research Lab.

"How other kids feel about Disneyland, that's how I felt about TGen. I was so enthralled with the technology, the people, the work," said Wix. "It was inspiring to be in a room with a dedicated group coming together to solve real-world problems and ask questions with potentially life-altering outcomes. I've held that experience close ever since."

Dr. Berens also was impressed, and still follows Sophie's career. "Sophie blended her intelligence and diligence with the focused research experience of the Helios Scholars program," he recalled. "She exemplifies the springboard lift that Helios Scholars offers."

Following a year of online classes due to COVID, Wix is glad to be back at her medical school's Fort Worth campus as the semester gets underway. She is a member of the school's inaugural class.

"Being part of a new medical school has given me an opportunity to shape my education for myself, and also for future generations," said Wix, who graduates with her medical degree in 2023, "And to think that it all began in my hometown because of an institute like TGen is pretty amazing."

For more information about Helios Scholars at TGen, please contact Kristen Kaus: kkaus@tgen.org, 602-343-8719, or visit **tgen.org/intern**

When the future is now

A DONOR'S STORY

When longtime TGen donor Diane Matsch first learned of her husband Lee's pancreatic cancer diagnosis, her sister told her: "Don't let anyone steal your hope."

Diane's sister spoke from experience. Her husband, Diane's brother-in-law, also was diagnosed with pancreatic cancer — as was Lee's mother, a cousin, and the sister-in-law of one of Lee's and Diane's daughters. All died of pancreatic cancer.

Now, with her own children — a son and two daughters — in their 50s and 60s, Diane worries about their future.

Family history is one of the major predictive factors of pancreatic cancer.

"My children are nearing the age where they could be affected by this cancer. That's why I support TGen and their pancreatic cancer research program," said Diane, whose husband survived for three years, but eventually succumbed to the disease in 2009.

Over the years, Diane has donated dozens of times to TGen; $200 a month almost every month since Lee's passing and as much as $1,000 annually in support of TGen's *Step-N-Out* 5K event supporting pancreatic cancer research.

Diane, now in her 80s, believes in helping others. Though she never worked outside the home, she has always given her time to worthy causes.

Today, she volunteers for Project C.U.R.E., the world's largest distributor of donated medical equipment, including several international trips visiting hospitals in Cuba, Panama and Tanzania.

An Expression of Gratitude

When Diane recounts her reasons for supporting TGen, chief among them is the professional and compassionate care received from Lee's physician, Dr. Daniel Von Hoff, who leads TGen's Molecular Medicine Division and is among the world's leading authorities on pancreatic cancer.

"We were fortunate that, through family and professional connections, we met a wonderful surgeon from Houston, and met with Dr. Von Hoff," Diane said. "Dr. Von Hoff was so helpful with Lee. His commitment to his patients was evident in the time he took with Lee. He never seemed in a hurry."

Today, 12 years removed from Lee's passing, Diane remains convinced that supporting TGen is important. And while 48,000 Americans will succumb to the disease this year, Diane has not lost hope.

One of Lee's last messages, urging on the fight against pancreatic cancer, remains vital today: "Together, with your support and many others, I am convinced we can make an urgently needed difference in this battle!"

Thanks to Diane and many others who join her in supporting TGen each year, Dr. Von Hoff and his team continue to make progress.

Last year, a team of TGen and Mayo Clinic researchers published the results of a study in the journal *Cancer Research*, identifying specific potential therapeutic targets for the most aggressive and lethal form of pancreatic cancer: adenosquamous cancer of the pancreas.

New treatments, early-detection diagnostics, and perhaps even a predictive genetic test, these can't come quick enough for Diane.

"My hope," she says, "is that there will come a day when pancreatic cancer is one hundred percent curable."

Until then, she keeps giving.

Support our research at **tgen.org/donate**

Education
TGen Bioscience Leadership Academy Caps a Successful 2021

"They may be young, but don't underestimate their potential," exclaims Dr. Michael Berens, TGen professor and Deputy Director of Institutional Initiatives, who delivered the closing address to the 2021 class of *TGen Bioscience Leadership Academy* (TBLA) on June 25. "I was deeply impressed with the caliber of students selected and the amount of information they absorbed during their 2-week immersion in TGen science."

TBLA annually offers 20 high school students the opportunity to explore topics and careers associated with biomedical research and precision medicine. By design, TBLA combines academic and instructional excellence to provide an overview of multiple disciplines rather than an in-depth examination of a specific topic or subject area.

"For many, TBLA represents the future of biomedical research," said TGen's Manager of Education and Outreach, Kristen Kaus. "We've demonstrated the value of connecting interested students with skilled academic and administrative mentors, and as importantly, created a pipeline that accounts for a diversity and inclusion that enriches the biomedical sciences."

The two-week program features more than 30 planned lectures or exercises where TGen faculty and staff share their knowledge and skills in areas that include bench work, clinical trials and bioethics. The program also offers a component focused on STEM professional skills and networking. Program graduates also receive a $1,000 scholarship.

The 2022 program takes place from June 13 through 24. Individuals or companies wishing to sponsor TBLA should contact Erin Massey (emassey@tgen.org) TGen Chief Development Officer, for additional information.

UPCOMING Events

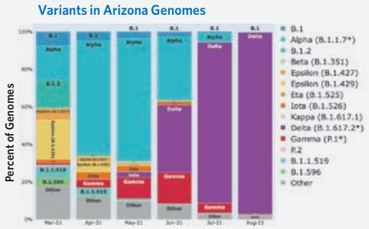
October 23 — An Evening of Trends. The Trends Charitable Fund, a longtime local nonprofit organization, will host its annual gala, "An Evening of Trends," at the Montelucia Resort in Paradise Valley, Arizona, with proceeds benefiting TGen. Learn more at: **trendscharitablefund.org**

November 6 — Casey's Cup on Wheels. Casey's story is one of miracles, survival, faith, modern medicine and simply believing. Adrenal Cortical Carcinoma affects only one or two people out of 1.7 million and it is often difficult to collect enough adrenal tumors to analyze, which is why TGen's work is so significant. With your support we can find new treatments for this devastating and rare form of adrenal cancer.

November 7 — Step-N-Out 5K. Kick off Pancreatic Cancer Awareness Month with a burst of energy. This year, we invite you to join us for a safe in-person event or virtually from anywhere you choose. 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.

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



Learn more at **pathogen.tgen.org**

Research
Grant Accelerates TGen's Monitoring of COVID-19

A grant from Taiwan Semiconductor Manufacturing Co. Ltd., one of the world's largest manufacturers of computer chips, advanced TGen's genomic sequencing of the COVID-19 virus. The grant rapidly pushes TGen toward its goal of providing a genomic sequence for every new COVID-19 infection in Arizona.

Sequencing provides a detailed molecular fingerprint of the virus that allows TGen to track — case-by-case — the variant(s) involved, identify those infections responsible for multi-person outbreaks, and identify mutations that may be associated with vaccine breakthrough events. Sequencing also allows comparison between mutations and strains identified in Arizona against those appearing around the globe.

Research
Blood-Based Clues of Parkinson's Disease

Published in *Nature Aging*, the results of a recent TGen-led study suggest that the immune system may play a key role in the early stages and progression of Parkinson's disease.

Working with collaborators at the Michael J. Fox Foundation for Parkinson's Research, University of Southern California and the National Institute on Aging, the team conducted

blood-based RNA sequencing analysis on 4,871 samples from more than 1,500 patients from the Parkinson's Progression Markers Initiative, one of the world's largest and best characterized Parkinson's studies. They conducted a second study comprised of samples from nearly 1,600 Parkinson's patients to validate their findings.

"There is a wealth of data for the research community to mine in this resource, especially when combined with the corresponding small RNA sequencing, genomic, and imaging data that are available," said the study's senior author, Kendall Van Keuren-Jensen, Ph.D., TGen Professor of Neurogenomics, and Director of TGen's Center for Noninvasive Diagnostics.

The team sought to create a comprehensive RNA transcriptomic resource from whole blood samples for use by the Parkinson's research community for biomarker development. The transcriptome is a collection of the readouts from DNA into RNA.

Philanthropy
Virginia G. Piper Charitable Trust Awards TGen $2 Million in Surprise Grant as Part of the Largest Single-Day Grant Initiative in Arizona History

"Humbled and honored," is how TGen President and Research Director, Dr. Jeffrey Trent, describes a surprise gift from the Virginia G. Piper Charitable Trust. Little did Dr. Trent and TGen Board Chair, William Post, know when they arrived at the Piper Trust on the morning of September 13, a Trustee awaited to present them a check for $2 million as part of the Trustee initiative *Now is the Moment Grants Commemoration*, which awarded surprise grants to 71 Arizona nonprofits totaling $123 million — the largest single-day grant initiative in Arizona's history.

Education
Space Tested

When 2021 *Helios Scholar at TGen* Kaitlyn Janssen learned that the project she worked on this summer made it to space, she was over the moon. The technology, an innovative way to collect and analyze saliva and blood, entered orbit courtesy of the astronauts aboard SpaceX Inspiration 4, which launched in mid-September.

Kaitlyn worked alongside Frederic Zenhausern, Ph.D., Director of the Center for Applied NanoBioscience and Medicine at the University of Arizona Collage of Medicine-Phoenix, where she helped create a system of collecting and analyzing saliva and blood in the microgravity of Earth's orbit.

Conventional methods of sampling body fluids rely on gravity to work. Kaitlyn helped develop, construct and test the vertical integrated flow assay system technology (VeriFAST), which uses saliva or blood deposited onto a device to perform rapid assessments of the physiological effects of space travel. VeriFAST provides precise measurements, including molecular diagnostics, of the effects of radiation exposure in space.

"I hope the technology becomes a reliable standard within diagnostics, and can assist in not only mid- and long-term space travel, but also as an accessible point-of-care device for individual patients," said Kaitlyn of Gilbert, Ariz., who is a senior at Arizona State University, majoring in Biomedical Engineering.

Research
Primed for Infection

An international study co-led by TGen Associate Professor, Nicholas Banovich, PhD, suggests that — like pouring water atop a wellhead before pumping — the airway cells of patients with chronic lung diseases are "primed" for infection by the COVID-19 virus.

Published in *Nature Communications*, the study — *Chronic lung diseases are associated with gene expression programs favoring SARS-CoV-2 entry and*

severity — findings depict the gene expression changes caused by chronic lung disease in the molecular makeup of a variety of cells, including the epithelial cells that line the lung and airways.

The researchers focused on changes within individual cells from over 600,000 samples representing both healthy and diseased lungs.

Single cell sequencing and analysis identified molecular characteristics that may account for the severity in some COVID-19 outcomes. Researchers specifically searched for changes in a particular lung epithelial cell type known as AT2, focusing on the actions that alter the cell and by doing so, that cell's function.

The data suggested that the immune microenvironment at both the molecular and cellular levels in lungs damaged by chronic diseases may promote severe COVID-19.

Dr. Jeffrey M. Trent and Mr. William J. Post

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