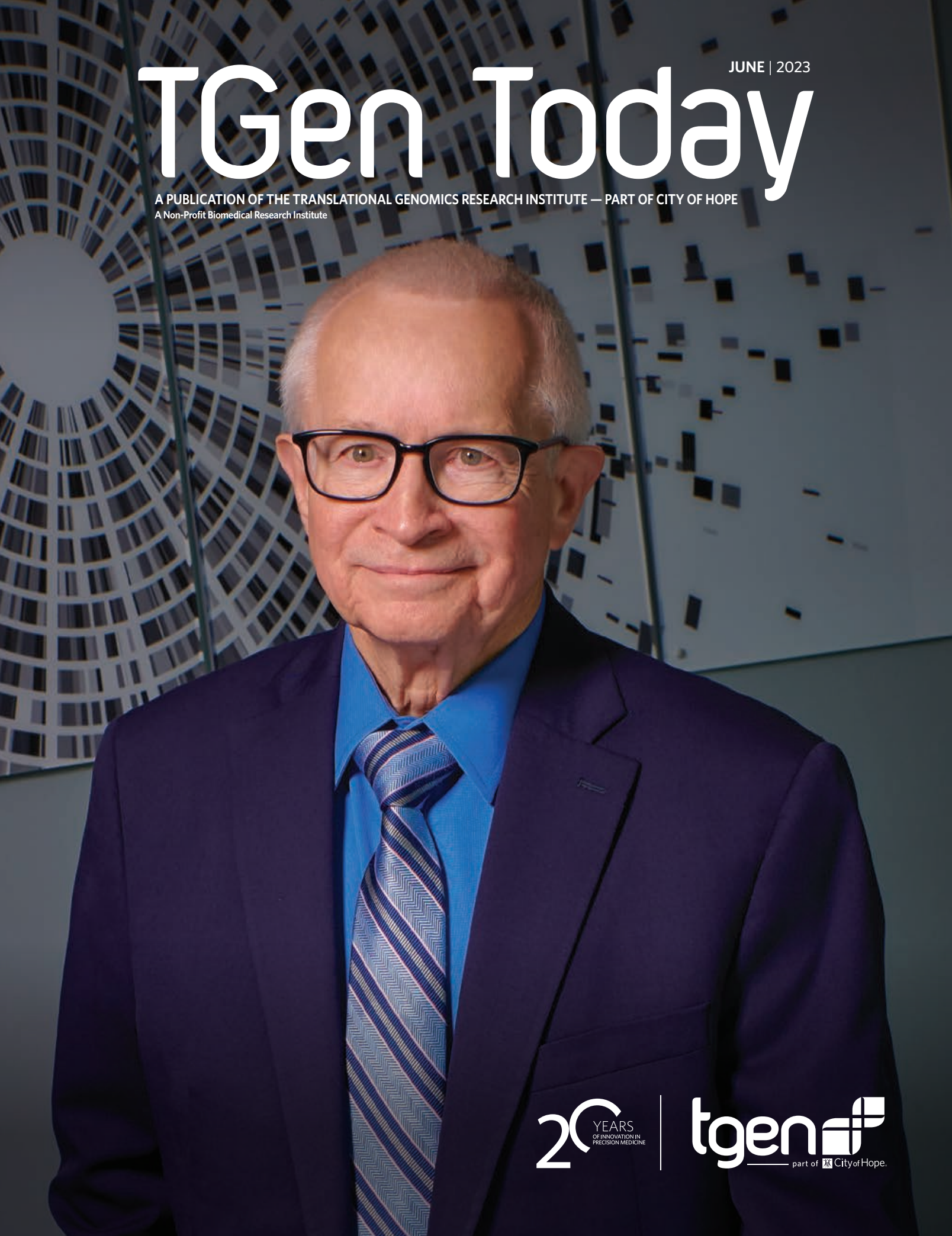
JUNE | 2023

TGen Today

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



A Look Inside...

Dear Friends,

June 26 marks the start of TGen's third decade of research and discovery.

The market president and publisher of the *Phoenix Business Journal* highlighted this date on February 16 during a breakfast event in celebration of TGen's 20th anniversary. The business gathering highlighted TGen's two decades of success in both biomedical science and economic impact. And, while celebrations are lovely, what matters most at TGen, however, is what's next.

Discovery, whether in pursuit of research breakthroughs, a new drug, or a new test, is the life-blood of biomedical research. If one were to look for a common thread that ties this narrative together, the answer is our faculty. Their thirst for knowledge forms the basis of every question they ask in pursuit of the next breakthrough.

A noted refrain from TGen's preeminent oncologist and researcher, Daniel D. Von Hoff, M.D., is that patients can't wait. We celebrate Dr. Von Hoff in this issue by announcing a named chair in his honor, and by highlighting a career that spans 5 decades of exploration and achievement in the areas of patient care, drug development, research and training. His ability to think outside the box to uncover new insights has led to the development of 15 new therapies for 11 different types of cancer, and one for multiple sclerosis. He has also trained and mentored more than four dozen physicians, many of whom have gone on to have remarkable and impactful careers themselves. And yet, as you work your way through his story, you'll come to understand his work is far from complete and that he has questions left to ask — and answer.

Dr. Von Hoff's story also reminds us that all careers have a beginning. For Crystal Hepp, Ph.D., an associate professor in the Pathogen and Microbiome Division at TGen North, those seeds took root in rural Montana. Today, examining a city's sewage for clues to COVID and developing collaborative relationships with county vector control agencies to collect and test mosquitoes in search of answers to combat West Nile virus is all in a day's work. Her limitless curiosity to explore the unknown, to question the untested, and to seek answers to the mysteries of the microbial world form the ethos of her work.

For Dr. Sampath Rangasamy, inspiration came in a small village in southern India, some 9,000 miles from Phoenix. Diagnosed at age 12 with diabetes, Rangasamy beat the odds to survive and today helps those with diabetes and children in a similar position who struggle with rare, undiagnosed disorders. His is a story of determination, perseverance and personal experience.

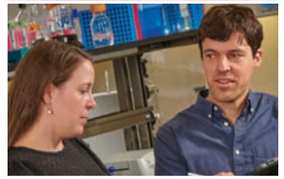
These and other features capture TGen scientists at their best, whether developing new approaches, asking bold new questions, or pushing for answers that hold the potential to save lives. Twenty years of achievement is rewarding, but so, too, will be the next twenty.

The future awaits.

Best,

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

TGen Today



VISIT US www.tgen.org
LIKE US facebook.com/helptgen
FOLLOW US twitter.com/tgen
SUBSCRIBE youtube.com/tgenvideo
DONATE tgen.org/donate

PODCAST

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.

2023 Runway for Research Co-chairs, Justine Hurry (left) and Beth McRae.

Fashion Forward for A Cause

Valley Society Leaders Help TGen Advance a Cure for Women's Cancer

THIS YEAR, THE TGEN FOUNDATION'S annual Runway for Research, a fashion show/fundraiser scheduled for October 13, is slated to combine big fun and high fashion with a serious mission—supporting women's cancer research at TGen.

TGen has partnered with Neiman Marcus and Scottsdale Fashion Square to raise critical funds, demystify science, and look fabulous. Runway for Research celebrates women's cancer survivors and supports TGen's pioneering DNA-based research, which uses the power of the human genome to provide hope and answers for cancer patients.

"We are trying to make the science more approachable," explains Beth McRae, owner of High Society Resale Boutique and Runway for Research committee co-chair. "The complexity of the work they (TGen) do can make it a little inaccessible, but if we can reduce those barriers through an event like this, we can help many more women becme aware of the options available to them."

"I was excited to learn that they could take a sample of your DNA and try to match a drug that will help you beat cancer," Justine Hurry, Runway for Research committee co-chair, elaborates, "I've had several family members that have had cancer. Several members have passed away. Learning that there are more humane treatments on the horizon was really, really exciting."

Justine attended the last two years and was honored to join Beth as co-chair for the 2023 event. "It's a fashion show. It's at Neiman Marcus and Fashion Square — how could you go wrong?" she enthused.

Beyond Justine's personal involvement as co-chair, this year brings a number of other firsts, starting with bringing back the signature pink as the color for the event.

"For years, pink has been associated with women's health issues, specifically breast cancer, which has made something of a branding challenge for our event," Beth, who also owns a PR agency, explains. "This year, we are reclaiming pink, which is significant from a branding perspective, but also a whole lot of fun!"

In addition to embracing the color and theme of the event, this year, Scottsdale Fashion Square has expanded the physical event into the mall area, which increases the potential number of attendees from 200 to 300 participants.

"We worked with Fashion Square and Neiman Marcus to make our runway longer and provide additional seating!" Justine expresses enthusiastically. "We set out to make it a bigger event this year and raise more awareness."

Last year, the event raised a record-setting amount of over $231,000, and the committee is looking to outdo itself yet again.

"Our initial goal for this year is $300,000," Justine says, "I am sure we will reach it."

Beth is direct about their strategy for getting there. "This year, we have been very proactive about our outreach to the philanthropic community," she notes. "We are recruiting some of the most powerful and influential women in the Valley."

A TGEN FAMILY

Beth's family has been supporters of TGen since its inception. In 2001-2002, early conversations in the Phoenix civic and business community centered around bringing the one-of-a-kind genomics research institute to Arizona. Her family was active in these foundational conversations. Alongside other community leaders, they funded a state-of-the-art lab, contributing to the launch of TGen at its very beginning.

"We are a TGen Family," Beth says proudly, "We have deep roots with the institution going back to its earliest days."

Today, Beth continues to honor these early investments through her philanthropic work. She is an active fundraiser and contributes personally. Beth's sister, Stephanie McRae, serves as General Counsel for TGen. Betty McRae, their mother, continues to donate and provide support, most recently as the Presenting Sponsor of the 2023 Runway for Research fashion show.

"It is especially exciting to know that your money is having such a powerful impact," Beth says of the funds she has helped raise for TGen. "We are helping advance the women's cancer research program —developing precision medicine— which provides treatment tailored to a patient's genetics."

Cancer is the second leading cause of death in the US. Nearly 307,000 American women are diagnosed with breast or ovarian cancer annually. The most common cancers among women in the U.S. are cervical and ovarian, breast, colorectal, lung, skin, and uterine.

Routine exams and early detection continue to be the keys to survival. TGen continues to provide new methods of early detection to diagnose and intervene at its earlier stages when treatment can be most effective, as well as targeted drug treatments with fewer side effects.

HOW TO GET INVOLVED

Runway for Research will be held on Friday, October 13, 2023 from 8:30 a.m. - 10:30 a.m. at the Luxury Wing, Scottsdale Fashion Square, 7014 E Camelback Rd, Scottsdale, AZ 85251.

Enjoy this season's latest fashions while advancing the science to beat women's cancers with TGen Foundation, Scottsdale Fashion Square, and Neiman Marcus.

For sponsorship or ticket information, please visit tgen.org/runway or contact Amiee Lay at 602-343-8502 or email alay@tgen.org.

> "IT IS ESPECIALLY EXCITING TO KNOW THAT YOUR MONEY IS HAVING SUCH A POWERFUL IMPACT. WE ARE HELPING ADVANCE THE WOMEN'S CANCER RESEARCH PROGRAM —DEVELOPING PRECISION MEDICINE — WHICH PROVIDES TREATMENT TAILORED TO A PATIENT'S GENETICS."
>
> — BETH MCRAE
> RUNWAY FOR RESEARCH CO-CHAIR

ANY POINT IN TIME

STUDY RESULTS OFFER GLIMPSE INTO THE FUTURE OF FORECASTING INFECTION AND IMMUNITY

WHEN TGEN ASSISTANT PROFESSOR, JOHN Altin, Ph.D., (pictured above at right) discusses PepSeq in terms of his latest study, you hear the excitement of discovery in his voice.

The PepSeq technology allows scientists to look across the universe of human-infecting viruses to determine precisely which infections someone has encountered and when, all from less than one microliter of blood plasma or serum. Overall, advancements like these have greatly expanded our ability to study diseases and viruses, providing the potential to lead to new breakthroughs that are changing how we interact with and interpret the world around us; foreshadowing the possibility of the day such technology enables surveillance of disease, much like a weather forecast.

A recent study led by Altin developed a new way of analyzing antibody signatures in repeat blood samples, enabling them to pinpoint the timing and cause of recent infections across the full suite of viruses that infected humans, simultaneously.

Using a powerful lab platform called PepSeq, Altin and a team of scientists used this new approach to detect epidemic waves of infection at the population level, as well as the rise and fall of antibody responses within individuals.

Published in *Nature Communications*, the findings suggest that PepSeq could one day allow for a far more complete picture of how infection and immunity move across a population in space and time.

"PepSeq allows us to look across the universe of human-infecting viruses to determine precisely which infections someone has encountered and when," said Altin. "The real power lies in the fact that we can get all this information from drop-size blood samples, tested over time."

Altin and Jason Ladner, Ph.D., a colleague at Northern Arizona University, designed PepSeq to do just that. PepSeq profiles viral antibodies by designing a "library" of peptides of interest—short strings of amino acids that are the building blocks of proteins. By linking each peptide to a unique DNA tag, the scientists are able to pinpoint specific peptides targeted by specific antibodies (or other proteins) in a given sample.

Traditional analyses of this type can only track the response of an antibody to one peptide target at a time. PepSeq allows researchers to track antibody response to thousands or hundreds of thousands of peptide targets at a time, making it ideal for examining the full range of viral infections within populations and individuals.

"Most previous work in this area used a single sample to map the whole history of viral exposures," said TGen North bioinformatician and the study's first author Erin Kelley (pictured at left), "but no information about when each virus was encountered."

By analyzing blood samples collected over time, the researchers were able to pinpoint when infections occurred and how antibody responses evolved.

To generate the data, the research team collaborated with researchers in Cape Town, South Africa. They looked at blood samples collected from three different groups, with individuals ranging in age from 12 to 60+ years old and totaling more than 100 person-years' worth of data.

One of the groups, the Adolescent Cohort Study (ACS), collected blood samples regularly for 18 months from tuberculosis-infected 12-18-year-olds in South Africa.

"We detected natural epidemic waves in the ACS data, including outbreaks of the respiratory viruses Influenza A and Enterovirus D, as well as the gastrointestinal Aichivirus A, in some cases showing that the viruses were widely circulating before being noted in the population," said Altin.

They also detected Rubella virus —German measles— within the ACS population, a disease not routinely targeted by childhood vaccination in South Africa. The study revealed that antibody signatures remained detectable more than five years after an initial infection in some people. In other cases, the researchers saw antibody responses rise and fall again in an individual within a week or two.

These findings suggest there may be opportunities to monitor someone's immunological health using these natural viral infections as a probe. This technology is very well adapted to screening across that kind of broad diversity, and PepSeq's rapid turnaround time and scalability make it an attractive tool for researchers in a variety of fields.

"The new approach could revolutionize the way in which we monitor disease outbreaks and help us better understand how infections and immunity spread across populations. By detecting epidemic waves of infection at the population level as well as the rise and fall of antibody responses within individuals, PepSeq offers a far more comprehensive view of infectious disease than ever before," said Altin.

Altin and his colleagues want to expand the PepSeq system to create even longer peptides for the libraries, including full-length proteins or domains, which could allow them to identify aspects of the response that are currently unseen.

> "WHILE PEPSEQ ALLOWS US TO LOOK ACROSS THE UNIVERSE OF HUMAN-INFECTING VIRUSES TO DETERMINE PRECISELY WHICH INFECTIONS SOMEONE HAS ENCOUNTERED AND WHEN, THE REAL POWER LIES IN THE FACT THAT WE CAN GET ALL THIS INFORMATION FROM DROP-SIZE BLOOD SAMPLES, TESTED OVER TIME."
>
> — JOHN ALTIN, PH.D.
> TGEN ASSISTANT PROFESSOR

TRACKING WEST NILE

> “THE FIRST THING WE WERE ABLE TO SHOW IS THAT WNV IS ACTUALLY ENDEMIC, AND SO IT ISN’T BEING IMPORTED INTO THE COUNTY EACH YEAR. IT ACTUALLY STAYS IN MARICOPA COUNTY, OVERWINTERING, AND REEMERGING WHEN CONDITIONS ARE RIPE FOR MOSQUITOES TO START BREEDING AGAIN.”
>
> — CRYSTAL HEPP, PH.D.., TGEN ASSOCIATE PROFESSOR

WEST NILE VIRUS (WNV) ARRIVES LIKE CLOCKWORK ANNUALLY during picnic season. As late spring and early summer bring sunshiny weather, mosquitoes awaken from their yearly slumber. WNV, the leading cause of mosquito-borne disease in the continental United States, often accompanies them. As of January 10, a total of 1,035 cases of the disease in people have been reported to the CDC.

At its worst, this virus can become neuroinvasive (meningitis or encephalitis), with 1 out of 150 infected people developing a serious, sometimes fatal, illness. Symptoms range from headache, high fever, neck stiffness, and muscle weakness to tremors, seizures, paralysis, and even death.

To date, there are no human vaccines to prevent the disease. Nor, at present, are there any medications to treat it. Crystal Hepp, Ph.D., a disease ecologist, trained evolutionary biologist, and genomics researcher with TGen North, TGen’s Pathogen and Microbiome Division, hopes to mitigate the impact of WNV by targeting endemic mosquito populations before they take off and grow.

Hepp’s lab focuses on using environmental surveillance and network analysis of pathogens, especially viruses, to understand their spread over time and space. “Through genomic analyses, we realized that the endemic variant circulating currently in Maricopa County entered in about 2010. The hope is that some sort of mitigation, like targeted insecticide applications at particular trap locations, can knock down the mosquito population before it results in high human caseloads.”

This is the goal: track the origins of the endemic population, target them at their home location, and intervene to save lives.

DISCOVERING A PASSION FOR VIRUS HUNTING BY NUMBER

Hepp grew up in a rural farming community. Her interest in science drove her toward a career in medicine. “Initially, I thought that I wanted to go to medical school,” she explains because, in her small-town community, most folks interested in science follow that path. Instead, she pursued a degree in Microbiology at Montana State and worked in a bioinformatics lab, funded by the Federal Work-Study program that provided assistance for students in need. The work focused specifically on RNA viruses—WNV is a single-stranded RNA virus that causes West Nile fever—but at the time, her work had a different orientation.

“From an academic perspective, we were trying to better understand the evolution of a variety of viruses, from rabies to HIV,” Hepp says of how the Lab influenced her trajectory, “That’s kind of how it started.”

She learned quickly that she had more of a passion for data analysis than she did the lab work, but she wasn’t clear on how all of these pursuits might converge. Dr. Sudhir Kumar, a pioneer in the intersection of evolutionary and computational biology, encouraged her to apply to Arizona State University (ASU) with the prescient advice, “You’re gonna find something that you really enjoy.”

She did.

In 2008, she started a unique grad program in molecular and cellular biology combined with a concentration in computational biology. She was the only student to take advantage of the coursework involved in the concentration program. From there, Hepp traded Phoenix for Flagstaff, graduating from ASU to do a postdoc with the Pathogen and Microbiome Institute at Northern Arizona University.

“We worked on a variety of pathogen investigations, primarily focusing on bacteria during my postdoc. Two years later, I got a faculty position at Northern Arizona University and transitioned back to viruses,” Hepp explains.

Per the advice of Maricopa County Environmental Services, Hepp focused the attention of her lab on WNV, searching for particular hot spots that genomics could help them identify. The virus was circulating in Arizona and throughout the Southwest.

It was an urgent concern, growing year after year.

FOLLOWING MUTATIONS ACROSS TIME & SPACE

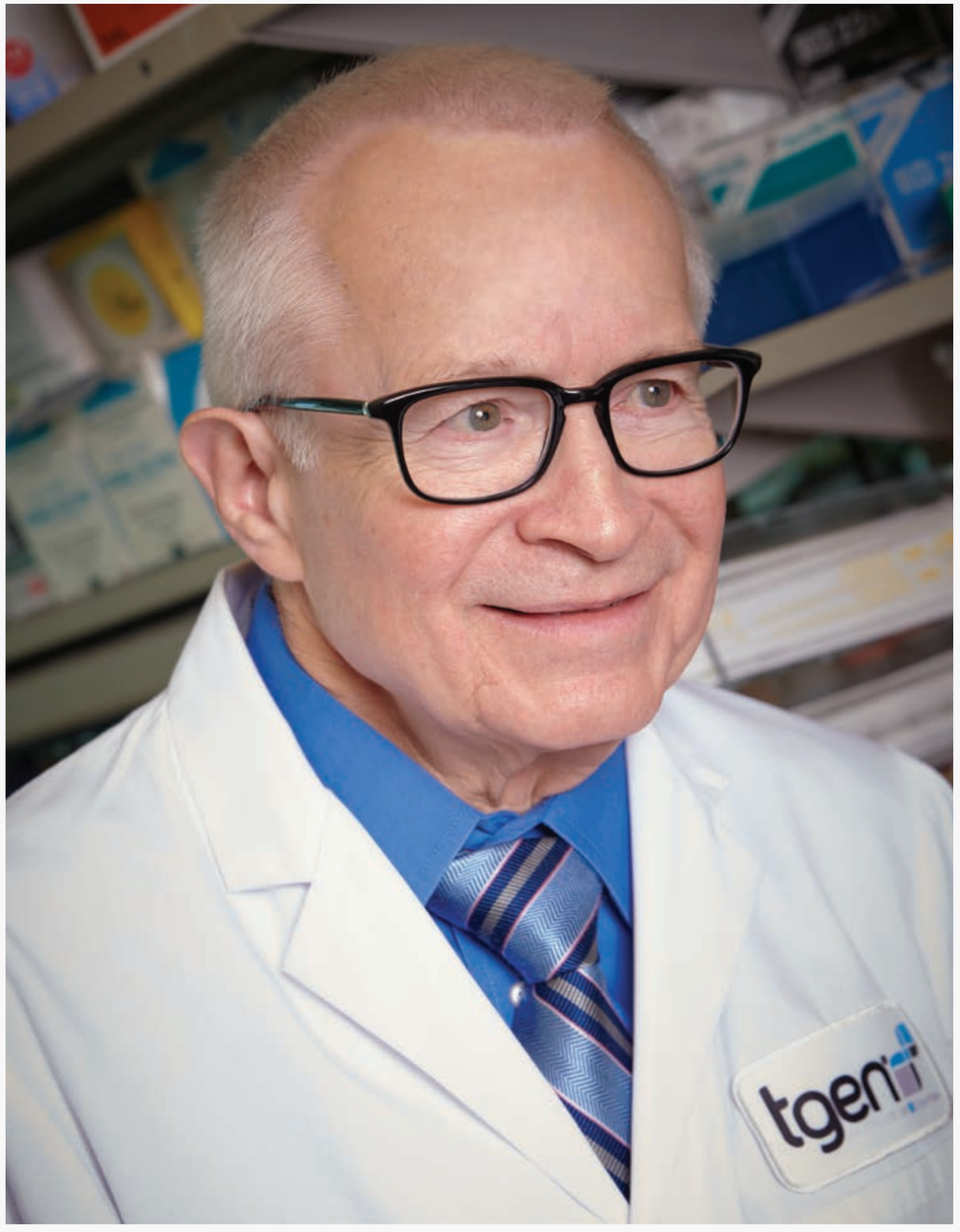
Viruses can be tracked using genomic sequencing data. Studying viral genomes provides insight into the evolution of mutations over time. Hepp’s lab has sequenced nearly 1000 different genomes of the WNV, which has led to identifying hot spots and tracking its origins.

“The first thing we were able to show is that WNV is actually endemic, and so it isn’t being imported into the county each year,” Hepp explains. “It actually stays in Maricopa County, overwintering, and reemerging when conditions are ripe for mosquitoes to start breeding again. At the same time, Culex mosquitoes start taking blood meals from birds, a major amplifier host for WNV, perpetuating a cycle which can drive up the environmental viral load.”

This means that as we understand WNV in Maricopa County, it isn’t a matter of if it is going to reemerge every year, it is a matter of when.

“Within the county, what we’re hoping is that in identifying highly connected locations that are important for maintaining the enzootic cycle, this research will lead to mitigation activities at those locations, and drive down not only the number of infected mosquitoes but also, the number of human cases.”

Hepp’s team is in the process of sharing these research protocols nationwide as part of her activities as a co-lead on the CDC funded Pacific Southwest Regional Center of Excellence in Vector-Borne Diseases.



RELENTLESS

HONORING A MAN AND HIS METHODS

DANIEL D. VON HOFF, M.D., IS CHARACTERIZED BY AN INDEFATIGABLE optimism, boundless creativity, and a relentless work ethic. He has been heralded a *Giant of Cancer Care*, an *Oncology Luminary*, a translational medicine pioneer, a visionary, an innovator, and a hero.

"He is, without question, the most innovative physician-scientist in the world – always pushing the envelope, being ahead of the curve in his thinking, and driving to accomplish more for the survival of his patients," states Margaret Foti, Ph.D., M.D., the long-time Chief Executive Officer for the American Association for Cancer Research (AACR). "Just think about how many peer-reviewed papers he has written – almost 800! Over 100 book chapters!"

Von Hoff's career is marked by advancing the field one game-changing transformation at a time and a commitment to finding a cure. He focuses on developing new anticancer agents—in the clinic and laboratory.

"He doesn't need much sleep," Dr. Foti adds.

More than 70 percent of patients with pancreatic cancer die within one year of diagnosis, and fewer than 12 percent survive more than five years. Despite these grim statistics, Von Hoff is hopeful. He points out that twenty years ago, patients diagnosed with pancreatic cancer had a 2% chance of surviving a year. Today patients now survive at least one year—while the survival rate for patients lasting two years climbed from zero to forty percent.

> "DR. VON HOFF IS, WITHOUT QUESTION, THE MOST INNOVATIVE PHYSICIAN-SCIENTIST IN THE WORLD – ALWAYS PUSHING THE ENVELOPE, BEING AHEAD OF THE CURVE IN HIS THINKING, AND DRIVING TO ACCOMPLISH MORE FOR THE SURVIVAL OF HIS PATIENTS."
>
> — MARGARET FOTI, PH.D., M.D., CHIEF EXECUTIVE OFFICER FOR THE AMERICAN ASSOCIATION FOR CANCER RESEARCH

Resistance to pancreatic cancer therapies results in poor survival. Von Hoff's current research involves developing precision therapies for pancreatic cancer patients by identifying the role of different pancreatic cancer cell populations in resistance to therapy. He has personally been involved in over 200 clinical trials, with his work leading to the first approved treatment for pancreatic cancer, the chemotherapy gemcitabine, and three of the four drugs approved by the FDA for the treatment of patients with advanced pancreatic cancer.

"Pancreatic cancer will be cured," Von Hoff says confidently, offering a warm, folksy smile. "Advancements are happening every day. Many other cancers have been cured. This one will be too."

TEACHER, MENTOR, HERO

In addition to his accomplishments in translational research, Von Hoff's most important contributions to science may be as a mentor and educator. Through his personal tutelage and professional guidance throughout his long career, he has attracted and trained countless clinical fellows and junior clinical faculty in how to apply their knowledge to solve challenges in the laboratory and at the patient bedside to save more lives from cancer.

"He is the hero of thousands of colleagues around the world who are stimulated by his love of science and inspired by his compassionate, caring spirit and desire to help patients!" effuses Foti.

Dr. David Bearrs, President, Chairman, and CEO of Halia Therapeutics, concurs. "He's been the greatest mentor to me not only professionally but personally."

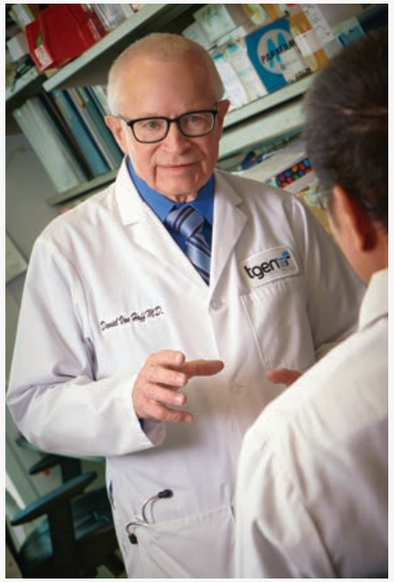
Bearrs joined Von Hoff as a post-doctoral fellow after defending his dissertation decades ago. He followed Von Hoff to Arizona for the chance to work in his lab. "It was an easy decision to make," he explains. "I still talk to him about once a week." This month, Dr. Bearrs was the 2023 recipient of the Utah Governor's Science Medal for Science and Technology: Industry.

"I got into research because of my family history, my grandpa died the year I was born. He was 50 and died of colon cancer. Then my mom dies of colon cancer. It made an imprint on my life," he explains. "That's the great thing about working with Dr. Von Hoff. You never lose track of why you are doing what you are doing. He reminds you each day that we're doing this for real people."

Similarly, Foti notes the depth of his humanity, the ability never to lose sight of the person behind the diagnosis, as a distinguishing characteristic. Von Hoff blends the personal and professional, "he always makes time for people when they need him," she explains. "In my case, when I called him about my sister's diagnosis of late-stage ovarian cancer, he was there to advise my family and give them hope," she explains. "It was an absolutely invaluable message of hope and caring that I have never forgotten."

David Kroin, Founder and Chief Investment Officer at Deep Track Capital, where Von Hoff has been an advisor for years, offers an even more succinct synopsis, "He's an incredible teacher with an incredible ability to understand the patient experience."

When Kroin's brother was diagnosed with rectal cancer three and a half years ago, he was told there was a 90% chance of having his whole colon removed. Kroin reached out to Von Hoff.



"There was no one else I would trust to advise on his cancer," he explains. "He made a huge difference to that one patient—my brother— who wasn't even his patient. Dan's advice gave me confidence in clinical trials. Ultimately my brother didn't have to have his colon removed."

At the AACR, where Von Hoff served as President and on the Board of Directors, he helped the organization, which embodies all the sciences from the laboratory to the clinic, recognize the role it could play in science-based clinical research.

"Through his work on our Annual Meeting Program Committee, on the Council of Scientific Advisors, and on myriad clinical and translational research committees, he stimulated new thinking about how we could make a difference in the clinic through high-quality research," Foti explains.

Beyond his institutional affiliations, Von Hoff leads educational workshops on methods in clinical cancer research. Since 1996, the Vail Workshop trains young investigators in clinical trial design. This extraordinary training opportunity has worked with 2,600 young clinical investigators in the U.S. and collectively more than 5,000 young clinical investigators around the world, delivering training from leading experts. This project alone has helped saved millions of lives from all types of cancer!

THE RELENTLESS PURSUIT INITIATIVE: HONORING THE MAN AND HIS METHODS

Honoring Von Hoff involves more than establishing a named position at TGen. It is about creating a sense of community and mutual respect for the physician's calling to heal. It is about creating a space where humanity is always the central aspect of the work. It is about fostering the researcher's intellectual curiosity and creativity.

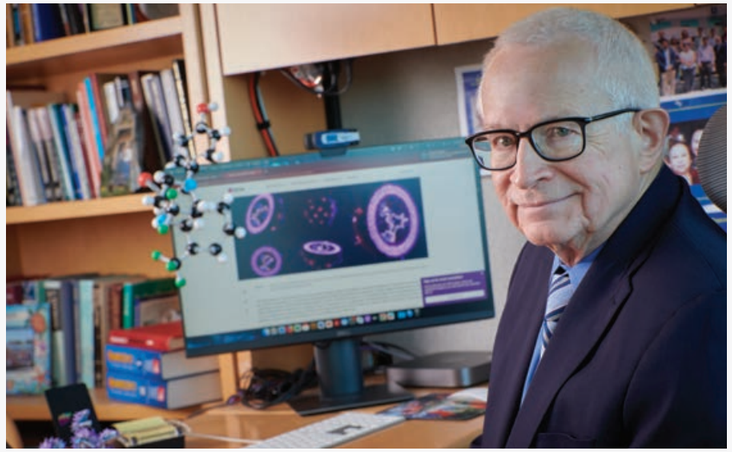
Reflecting on Von Hoff's mentorship, friendship, and guidance over the years, Bearrs explains, "At the end of my life, I don't really care how many scientific publications I've had or the many things we get measured by professionally…just knowing that you've helped save people's lives is what I care about."

We want to recognize, honor, and preserve that ability to center what is most important for future researchers. For this reason, the creation of *The Daniel D. Von Hoff, M.D. Endowed Chair in Cancer Research*, not only honors its namesake but sets the example for the next generation of physician-scientists to channel his compassion and relentless pursuit of cures for the most debilitating and life-threatening cancer diseases. The newly created endowed position will be an evolving representation of a life filled with faith, family, and friends. It is a recognition of a revered medical career and an exceptional human being.

Endowment, designed thoughtfully and intentionally, provides a perpetual source of funding to be used to support critically important institutional initiatives well into the future. At TGen, the goal is to eradicate disease with speed and precision. Our reality is that the more we learn about human disease, particularly in the context of cancer, the more complex it becomes. TGen's track record in moving new discoveries from our bench to the patients who need them has been swift—in the world of science—and stellar. And yet, this work continues to be time-consuming, resource intensive, and often too early or too risky for funding by traditional sources.

The Relentless Pursuit initiative creates *The Daniel D. Von Hoff, M.D. Endowed Chair in Cancer Research.* Creating an endowed chair position that honors Dr. Von Hoff's outstanding career with TGen and in the larger medical and research community ensures that research, with a focus on pancreatic cancer, remains at the forefront of TGen's commitment to early detection, smarter treatment and better outcomes for patients.

TGen honors Dr. Von Hoff with this named fund today with the understanding and expectation that his work will continue until pancreatic cancer is cured.



TO SUPPORT THE RELENTLESS PURSUIT INITIATIVE PLEASE VISIT THE TGEN FOUNDATION WEBSITE AT TGEN.ORG/RELENTLESS OR CONTACT A FOUNDATION MEMBER LISTED BELOW.

ERIN MASSEY
CHIEF DEVELOPMENT OFFICER
EMASSEY@TGEN.ORG
602-343-8411

STEPHANIE GRINAGE
VICE PRESIDENT, INDIVIDUAL GIVING
SGRINAGE@TGEN.ORG
602-343-8668

HOW BEST CAN I SERVE?

5 Questions for Daniel D. Von Hoff, M.D., F.A.C.P.

1. You have already contributed so much to cancer research and the development of promising therapies for patients. Is there a specific area of focus for you into the future?

I have been privileged to work on many new therapies which are now FDA approved. Therapies that include mitoxantrone for prostate cancer and leukemia, Taxol for treatment of breast, lung and multiple other cancers, gemcitabine for ovarian, pancreatic and lung cancer, irinotecan for colon and pancreas, capecitabine for colon and breast, and the list goes on. The great news is we are asked by many preclinical scientists to help develop their agents in the clinic. We will continue to pursue new agent development with enthusiasm and a sense of urgency.

2. What can we anticipate from your ongoing research and clinical trials toward finding a cure for pancreatic cancer?

There are finally some advances in terms of improving survival for patients with stage IV pancreatic cancer. We are proud of developing 3 of the 4 FDA approved regimens. But we haven't cured the disease yet and that is embarrassing. We have 2 efforts working toward the cure.

Our first plan is using the best possible science to continue to develop therapies to help patients who present with stage IV pancreatic cancer.

Our second plan is to develop a way for very early detection of the disease. This is a three-pronged approach called DEF (determine, enrich, find). This is done first by determining who is at highest risk at the population level. Our colleagues, Drs. Cristian Tomasetti and Nicholas Schork are doing just that. Enrichment is being done by Dr. Jeffrey Trent and his genetics team by defining who has a molecular risk. Finally, we have to apply their determination and enrichment to find individual patients to identify their cancer earlier.

3. What are you excited about right now resulting from the DEF approach?

Dr. Ajay Goel, Dr. Haiyong Han and I are working on a blood test for very early detection of pancreatic cancer. We recently published our early results and are excited to have just been awarded a major National Cancer Institute grant to perfect the test.

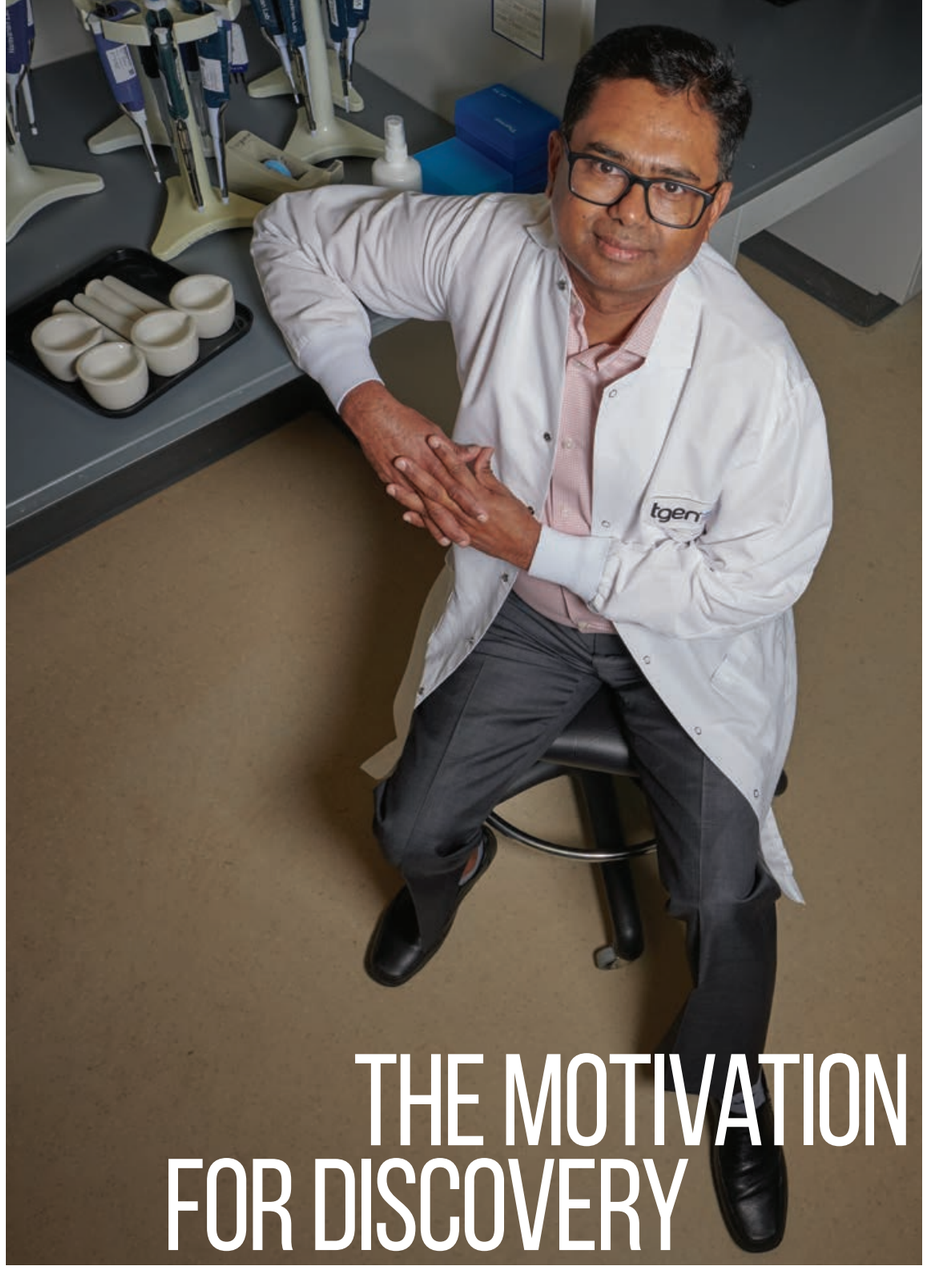
There is no doubt that like what happened for breast and so many other cancers, using therapies effective in stage IV cancer can cure patients with earlier stage I, II, or III diseases. We can do this! This will actually lead to a cure for pancreatic cancer.

4. As you continue your work into the future, where do you feel you can help the most?

The advances in medicine have been rather astounding—new antibiotics and antibodies and ways to treat cancers, neurological disorders, heart disease, that were once untreatable. In order to make more of these advances—in a compassionate, caring way—we must teach the next generation of physicians, nurses, and scientists. This is where I hope I can be most helpful. I am fortunate to work with TGen, City of Hope and HonorHealth Research Institute colleagues who are some of the very best creative caring people I have ever worked with. We are incredibly grateful and motivated by our funders, donors and supporters for giving us a special place to work against diseases that impact human health.

5. In June, TGen closes out its 20th Anniversary celebration. How are you approaching the next 20 years?

In Psalms 90:12 Moses prays, "so teach us to number our days that we may get a heart of wisdom." With the time that I have left I ask myself, "How can I best serve?"



THE MOTIVATION FOR DISCOVERY

GROWING UP IN OLAPALAYAM, AN ISOLATED AREA of southern India, a diagnosis of type-I diabetes at age 12 left Sampathkumar (Sampath) Rangasamy, Ph.D., with a deep desire to help those with rare diseases. Diabetes doesn't qualify as "rare" in the West, but in a remote farming village in India it does, and it instilled an empathy in Rangasamy that allows him to identify with the children his research at TGen's Center for Rare Childhood Disorders (C4RCD) seeks to benefit.

"Children with rare, undiagnosed disorders come to the clinic, after going from doctor to doctor without a diagnosis," Rangasamy explains of his work. "These families undergo tremendous stress."

Often referred to as a diagnostic odyssey, parents and child contend with the symptoms of a mysterious disorder that goes unidentified visit after visit, year after year. Now, genomic sequencing and other technologies have virtually eliminated this hardship by identifying the genetic cause of a disease so that many parents can have peace of mind in as little as 24 hours—after nearly a decade of struggle.

Rangasamy can relate.

For his family, the "diagnostic odyssey" was a literal journey. They traveled some 30 miles through the rugged backcountry, navigating unnamed streets and winding dirt paths, to secure a diagnosis. There was no refrigeration in Olapalayam, so his mother cleverly engineered a system of storage that kept the insulin in clay pots, one nested inside another, three deep, with the outer two in water to keep the center cool. "My Mom was innovative at the time," Rangasamy observes.

These experiences throughout his formative years have shaped much of his work at C4RCD and beyond. Trying to ease the pain for families facing challenges similar to his own.

HELPING FAMILIES MOVE FORWARD

Rangasamy received his Ph.D. in Biochemistry from the University of Madras, India. After, he traveled to the States for the first time, completing his post-doctoral training through the University of New Mexico and eventually settling in Arizona. Initially, he went to the Barrow Neurological Institute (BNI) before joining TGen's Neurogenomics Division at the Center for Rare Childhood Disorders (the Center).

At the Center, his work focuses on investigating cellular and molecular mechanisms underlying neurogenetic disorders. Rangasamy uses genetic sequencing to reach a diagnosis faster.

"My work can also play an important role after diagnosis," Rangasamy explains. "One aspect is gene therapy. Let's say they have a mutation in a single gene, and there is no therapeutic for them. We are developing this new technology where you put the correct gene into a virus, then the gene will enter the body and replace the gene's bad copy with the correct copy."

Fundamentally, gene therapy replaces a faulty gene or adds a new one in an effort to cure a disease or enhance the body's ability to fight the disease on its own.

Viruses deliver the therapy, as they are highly effective vehicles for introducing genetic material into cells. Scientists first remove the ability of the virus to cause infectious disease, then they equip it with a "payload" that includes the therapeutic genes.

Presently, Rangasamy is focusing on several areas to develop gene therapy for rare disorders.

APP GUIDED BY PERSONAL EXPERIENCE

Rangasamy has developed other health technologies as well.

Diabetes results when the body's ability to produce insulin on its own fails. Managing the disease requires insulin therapy to control the blood glucose level. Failure to maintain insulin balance can affect the bodies organs and lead to debilitating or life-threatening situations.

In order to maintain control, insulin pump technology replaced insulin injections to automate much of the process for those with both type 1 and type 2 diabetes. It operates like an externalized pancreas. The downside includes relocating the pump every 48 to 72 hours in a different area of the body. Usually, patients document these rotating positions in a small journal, but human error often leads to issues. People get busy and lose track of the details. A pump located in the same position on the body too many times in a row can lead to skin irritation, rashes, and other complications.

Rangasamy partnered with a friend, mathematician John Blanchard, to develop an app that guides users on where to place insulin pumps, insulin pens, and glucose monitors. It also keeps track of their position history to enable site rotation. Rangasamy has been using it personally for more than three years now.

The app, currently making its way through the patent process, could have utility for other diseases, including multiple sclerosis, cancer, or anything that needs biological injections.

MOVING FULL CIRCLE

For Rangasamy, his illness and the challenges it posed provided the inspiration for innovations that have driven his career. From using genomics in the C4RCD Lab to give families peace of mind, through faster diagnosis to helping develop treatments that enlist the body in the healing process, and now, the development of an app that helps make diabetes more manageable. The joys, the inspiration and the hardships that he and his family encountered have become the motivation for discovery.

TGEN HONORS LEADERS AT FOUNDERS DINNER

AWARDS RECOGNIZE SUSTAINED COMMITMENT TO FURTHERING RESEARCH AND PRECISION MEDICINE

From left to right: William J. Post, Jeffrey M. Trent, Ph.D., Erin Massey and Maria Fundora.

ON APRIL 20, TGEN HOSTED ITS ANNUAL EVENT, THE TGen Founders Dinner, where the organization showcased its latest scientific breakthroughs and paid tribute to two remarkable individuals.

Valley leader, William J. Post, received TGen's John S. McCain Leadership Award in recognition of his advocacy for TGen's and City of Hope's research and clinical advances in precision medicine. Named after the late U.S. Sen. John McCain of Arizona, the annual award recognizes individuals or organizations whose leadership and dedication have made a significant impact in the fight against disease and improving the quality of life for patients worldwide.

In presenting the award to Post, TGen President and Research Director Jeffrey M. Trent, Ph.D., said, "Bill is a great Arizona leader in the mold of Senator McCain and a great friend of TGen, without whom we never would have been able to reach the goals we continue to set for ourselves and help so many people. I cannot think of anyone who is more deserving of the award."

Post is a highly respected executive leader and public advocate in Arizona, renowned for his honesty, integrity, intellect, and sound judgment. He is currently the Chair of of the TGen Board of Directors and serves as a director on the boards of First Solar, Blue Cross Blue Shield of Arizona, City of Hope, ASU Foundation, and the Center for the Future of Arizona.

"What a tremendous honor," said Post. "When I think about the individual and the organization that this award represents, it truly is extraordinary accolade. To the extent that I could have a participatory role in all that TGen has accomplished is both gratifying and humbling."

Also honored at the event was Atlanta restaurateur and businesswoman, Maria Fundora, who received TGen's Collaborative Spirit Award. The award recognizes an individual or organization who supports TGen's research and clinical development efforts.

"It's a privilege to honor Maria and Purple Pansies. We're thankful Maria chose to share her story with TGen and City of Hope, and to come alongside our efforts and place trust in our ability to help patients in need," said Erin Massey, Chief Development Officer at TGen, and Vice President of Philanthropy at City of Hope.

Fundora's upbringing instilled a belief in giving back to her community and helping those in need. She founded Purple Pansies in 2009 following her mother's death from pancreatic cancer. Her goal is to honor her mother's memory and make a lasting difference in the lives of others through compassion and generosity.

"I'm grateful to accept this award on behalf of myself and all my colleagues at Purple Pansies," said Fundora. "We have one thing in common: we support each other, and we support TGen and City of Hope. They continue to make significant advances against pancreatic cancer with the patient at the heart of their work, and that is why I continue to fight alongside of them."

CHANGES IN BLOOD-BRAIN BARRIER RELATED TO ALZHEIMER'S

An international team of researchers, including TGen's Patrick Pirrotte, Ph.D., published a study that detailed how a grape-like structure in the brain called the choroid plexus becomes enlarged and shows increased accumulation of abnormal inflammatory molecular signaling in people with Alzheimer's disease.

The findings appear in Alzheimer's & Dementia: The Journal of the Alzheimer's Association.

One striking finding from the study was that "the larger the choroid plexus, the poorer the cognitive performance in those Alzheimer's patients," said Gorazd B. Stokin, M.D., Ph.D., principal investigator at the International Clinical Research Center of St. Ann's University Hospital Brno, Czech Republic, and senior author of the study.

The choroid plexus is a network of blood vessels and cells that produces cerebrospinal fluid (CSF) that helps maintain the brain's immune system activation and creates a barrier between CSF and blood circulating throughout the body.

The scientists compared the CSF choroid plexus in healthy individuals and people with Alzheimer's, as well as patients with other neurological diseases such as acute Lyme disease and amyotrophic lateral sclerosis or ALS. They found protein abnormalities and "an aberrant signaling of immune molecules" in the CSF and choroid plexus of people with Alzheimer's," said Pirrotte, a study author and Director of TGen's Integrated Mass Spectrometry Shared Resource.

While these biological changes appear in normal aging, he noted, they differ from those seen in other neurological disorders examined in the study.

The changes seen in aging and Alzheimer's patients were most pronounced in the 66-75 years old age group, the researchers found.

Dr. Pirrotte continues to work on potential external risk factors that might exacerbate these changes, "and could accelerate the development of Alzheimer's Disease," he said. Last year, for instance, he and his colleagues published a study on how the herbicide glyphosate can increase pro-inflammatory molecules in the brain that may be related to neurodegeneration.

BIOSCIENCE IMPACT BREAKFAST CHAMPIONS TGEN, ARIZONA

On February 16, the Phoenix Business Journal hosted a breakfast event marking TGen's 20th anniversary. The business gathering mixed biomedical science with economics, as TGen celebrated two decades of achievement in both areas.

Exact Sciences Chairman and CEO, Kevin Conroy, delivered the keynote address, where he touched upon the rise of Cologuard®, Exact's most recent launch of OncoExTra™ and their continued evolution as one of the strongest brands in the life sciences today, including an expanding footprint in Arizona. Exact Sciences is a leading provider of cancer screening and diagnostic tests, which help to prevent cancer, detect it earlier, and guide treatment for patients globally.

Conroy then joined a panel discussion on the state of bio in Arizona that also included Dr. Tammy McLeod, President and CEO of the Flinn Foundation; Pam Kehaly, President and CEO, Blue Cross Blue Shield of Arizona; and Dr. Jeffrey Trent, TGen President and Research Director.

The 90-minute event provided business leaders and community supporters from around the Valley the opportunity to hear from these industry and community leaders and learn how far the sector has progressed.

Reflecting the most substantial growth since its launch two decades ago, a recent report showed TGen's 2020 operational research activities alone provided a total annual economic impact on Arizona of $426 million. The study revealed that for every $1 invested by Arizona, TGen research operations returned $85.20 to the State.

The final analysis: the bioscience industry in Arizona is thriving and poised for continued growth.

GENOMIC TESTING BENEFITS DOGS WITH CANCER

An evaluation study published in the *Journal of the American Veterinary Medical Association* supports the use of tumor genomic testing for dogs with cancer, particularly those with ambiguous cancer diagnoses. The analysis evaluated the clinical utility of SearchLight DNA®, a canine cancer genetic test developed by TGen spinout Vidium Animal Health®.

Modeled after genomic-based successes in human oncology, SearchLight DNA identifies important mutations in 120 relevant cancer genes. The results provide treating veterinarians with diagnostic clarity, prognostic information, and therapeutic guidance that can lead to improved care for dogs with cancer.

Genomic testing was performed on 69 dogs with ambiguous cancer diagnoses. Overall, genomic testing with SearchLight DNA was clinically useful in 86% of cases.

"This study demonstrates the usefulness of genomic testing for the management of canine cancer, particularly those cases without specific diagnoses that are inherently harder to manage," said Esther Chon, DVM, DACVIM, head of veterinary affairs at Vidium Animal Health and a study author.

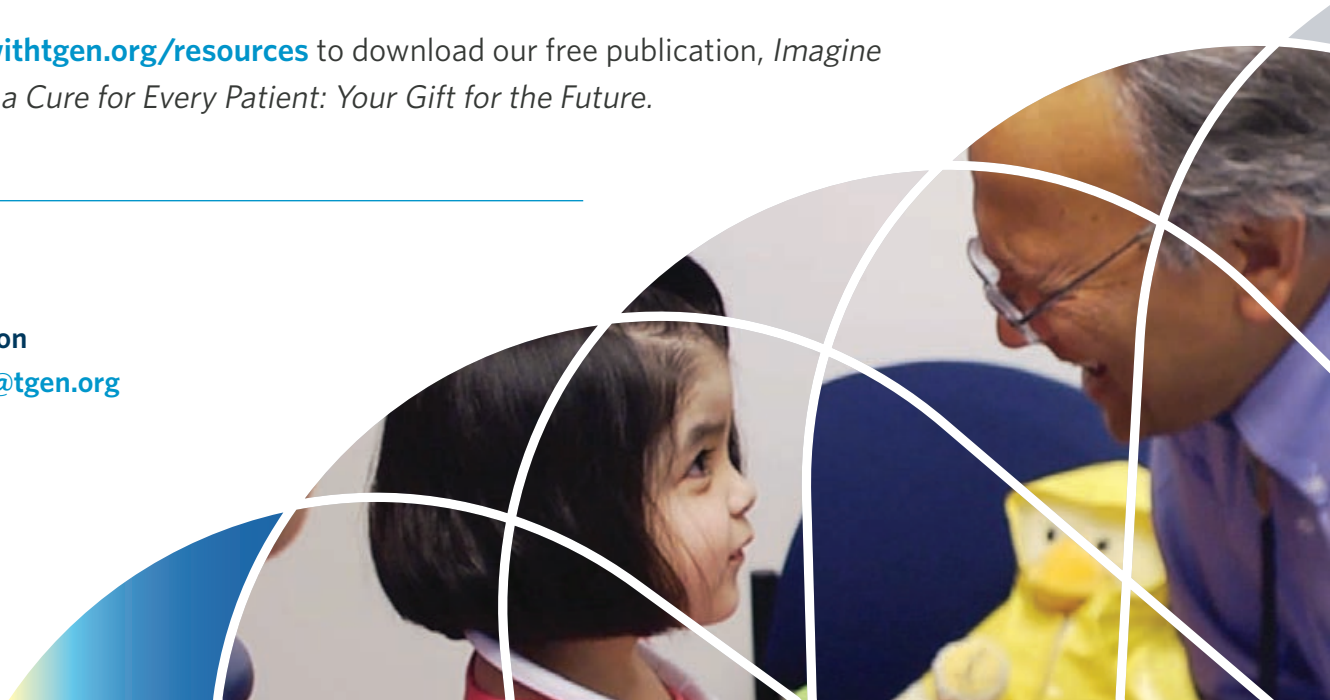
Translational Genomics Research Institute
445 North Fifth Street, Suite 600
Phoenix, Arizona 85004

Imagine a world with a cure for every patient

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

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

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



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