# SPARK

THE TULLIE AND RICKEY FAMILIES
SPARK AWARDS FOR
INNOVATIONS IN IMMUNOLOGY

# ANNUAL REPORT 2021

It really means a lot to us to see that people believe in us and enable us to keep going.

Thomas

Thank you to the people who donate to SPARK, because they are supporting young researchers like us with new ideas.

Abhijit

Thank you for believing in early career scientists

Cecilia

Science is all about collaboration, it is all about teamwork. If we want to get through these problems alone, we will barely survive, but together we will thrive.

- VIPUL

SPARK AWARDS IS A BOOST OF ENERGY AND REALLY MOTIVATES ME TO GIVE THE BEST OF MYSELF TO CONTINUE MY FIGHT AGAINST INFECTIOUS DISEASES.

SARA

SPARK

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Innovation doesn't come cheap. Without proof-of-concept to convince highly competitive granting agencies to fund a daring project, many bold ideas are never put into action. This is a particular challenge for younger scientists still establishing their career. La Jolla Institute's Tullie and Rickey Families SPARK Awards for Innovations in Immunology is designed to overcome these hurdles.

This philanthropically-financed program provides seed funding that allows researchers to act on their ideas and help make discoveries that could lead to answers for the important questions surrounding how we can better treat and prevent diseases that afflict us today. Each Tullie and Rickey Families SPARK Award is $25,000 and must be spent within one year. The goal is to enable scientists to generate enough preliminary data through their projects to attract additional funding to further their research and career.

In addition to funding cutting-edge research, the Tullie and Rickey Families SPARK program also trains and advances the careers of the next generation of researchers. Of course, SPARK Award winners ultimately gain experience in running an independent research project, an important career milestone. But equally as important, all SPARK finalists receive coaching in how to communicate their research to the public and how to present their ideas to funders. The value of this often overlooked skill set was never more evident than during the COVID-19 pandemic, which emphasized how critical it is for scientists to be able to clearly convey their work and the power of medical research to the public in a way they can understand and support. (We explore more ways that the pandemic impacted the SPARK program on the next page.)

Each year, LJI receives dozens of proposals from its postdoctoral scientists. A review panel (listed on page 31) narrows this pool down to the finalists who then have the opportunity to pitch their ideas to a donor panel with the hopes of securing funding to pursue their projects. Since 2017, more than 160 donors (listed on pg. 28) have generously funded 27 projects, all of which have the power to transform human health and launch the careers of promising researchers. We are incredibly grateful to all of the donors who are empowering young investigators to take risks that bridge the gap between imagination and ground-breaking discoveries.

It is our pleasure to present the 2021 Annual Report for The Tullie and Rickey Families SPARK Awards for Innovations in Immunology. This report features the results of the 2020 winners, provides progress updates from our 2021 winners, and offers a sneak peek of our 2022 finalists. We hope you also enjoy and are inspired by our SPARK Stars feature on pg. 22, where we highlight former winners who excelled in their careers or research projects this past year. Thank you again for your interest and support for The Tullie and Rickey Families SPARK Awards for Innovations in Immunology.

# PIVOTING DURING A PANDEMIC:

In January 2020, that year's newly minted Tullie and Rickey SPARK Awards winners were filled with excitement. They had just learned they would be receiving a $25,000 SPARK Award to embark on their independent research projects, an opportunity to explore their own scientific questions and build experience managing their own grants. But in just a few short months, our SPARK winners, like all of us, found themselves locked down at home as the SARS-CoV-2 virus spread rapidly around the globe. Quickly it became clear that what we all thought would be a two-week lockdown, was going to be much longer. What wasn't so clear for La Jolla Institute (LJI) scientists, including our SPARK winners, was what this meant for their research.

Eight labs at LJI quickly turned their research focus toward the new virus, aiming to provide critical information about the virus structure and immune system response that could inform vaccine and antibody therapeutic design. The LJI Coronavirus Task Force was established to enhance internal collaboration and help communicate fact-driven information with the public. Simultaneously, LJI leadership quickly came up with a plan for how to best keep the institute open and operating so that the labs working on critically time-sensitive SARS-CoV-2 research could safely continue their work. The result was that for several months, only researchers working on SARS-CoV-2 studies could have access to the building and their labs.

The challenges didn't stop there. In those LJI Coronavirus Task Force labs, scientists essentially dropped what they were working on to focus their efforts on research that could help the world tackle the pandemic. And for labs not working on COVID-19 projects? Well, they had to figure out how to keep making progress on their research without access to their equipment, samples and wet-lab experiments. Because hospital systems were overwhelmed as waves of critically sick people filled ICUs and non-emergency surgeries were delayed, many projects that relied on clinical collaborations with physicians for patient samples were stopped in their tracks. And while we were in the midst of all this, there was no way of knowing exactly how long things would remain this way.

But the thing about researchers is, they are remarkably resilient and perseverant. When we've asked our SPARK finalists over the past five years what the biggest obstacle to their career is, the most common answer is having to learn how to recommit to science after failed experiments or hypotheses, adjust quickly to new circumstances and environments and find a new approach to the problem. And that is exactly what the 2020 SPARK Award winners did.

As you will see in the final reports from this cohort over the next several pages, we asked each SPARK winner to share how they had to "pivot during the pandemic" to complete their project. For several of them, the biggest challenge was needing an extension due to the lack of access to the labs for several months. However, for others the impact was more substantial. **SARA LANDERAS BUENO, PH.D.** (pg. 16), a member of the Saphire Lab, had to put her Ebola-focused project on the back-burner as she helped contribute to her lab's efforts to untangle the structure of SARS-CoV-2.

**THOMAS RIFFELMACHER, PH.D.** (pg. 18), whose original project relied on getting tissue samples from patients who had surgery after a heart attack from his collaborator at Oxford University, essentially had to start over and find a different source for samples. Dr. Riffelmacher was able to leverage an existing collaboration to gain access to samples from sickle-cell patients, which still allowed him to study the same cell population involved in inflammation, albeit in a different disease context.

And unfortunately for **ALEX MARKI, PH.D.**, who was hoping to utilize samples from patients experiencing sepsis to better understand how to identify and treat the disease, his collaboration fell through completely because of the pandemic and he was unable to complete his project before moving onto a new position this fall. (Dr. Marki's SPARK Award funds were returned to the LJI Tullie and Rickey Families SPARK Award fund to be used for future awards).

LJI is very proud of how these scientists navigated this very difficult time to successfully complete their projects, and as a supporter of this program, we hope you are too.

We'd be remiss if we didn't acknowledge and thank all of the current and former SPARK winners who worked tirelessly over the past two years on SARS-CoV-2 studies, COVID-19 vaccines and therapuetics research and development, and even in Dr. Melanie McCauley's case, providing care to COVID-19 patients. These individuals were essential frontline workers, putting in incredibly long hours, spending time away from their loved ones, and taking risks to help us all get through this pandemic.

**Daniela Weiskopf, Ph.D.**
**'18 SPARK winner**

La Jolla Institute for Immunology
San Diego, CA

Along with her colleagues at LJI, Dr. Weiskopf has been a leader in this field, publishing several highly-cited papers and she received a $1.4M grant from the National Cancer Institute in 2020 to study COVID-19 in Latino Americans. Dr. Weiskopf has also been very dedicated to educating the public about COVID-19 research by participating in national and international media interviews and speaking at webinars.

**Melanie McCauley, M.D.**
**'18 SPARK winner**

Walter Reed Army Institute of Research (WRAIR), The Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF)
Bethesda, MD

Dr. McCauley is a research physician at the Emerging Infectious Disease Branch at WRAIR. Her team developed a SARS-CoV-2 vaccine based on nanoparticle technology and took the platform from animal models into clinical trials. Dr. McCauley herself worked as an associate investigator on the phase I trial, which is now concluding participant follow-ups. The team hopes to leverage this technology toward a pancoronavirus vaccine, effective against epidemic and pandemic-potential viruses like SARS1, MERS and SARS-CoV-2, and future coronavirus outbreaks. Additionally, Dr. McCauley spends a portion of her time caring for patients suffering from infectious diseases, like COVID-19, needing inpatient services at John Hopkins.

**Artem Romanov, Ph.D.**
**'21 SPARK winner**

La Jolla Institute for Immunology
San Diego, CA

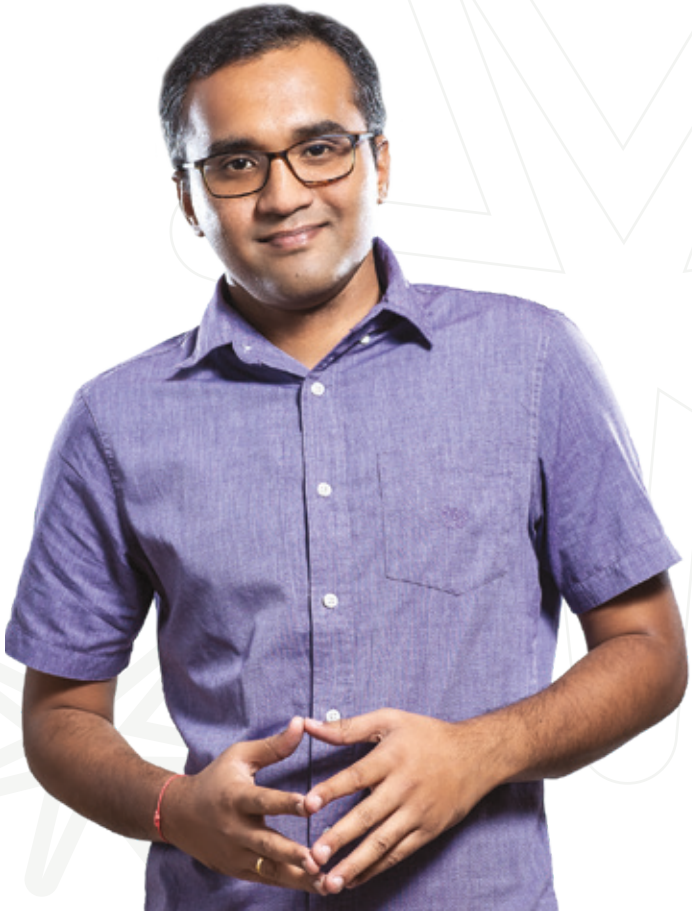
For his SPARK project, Dr. Romanov is seeking to understand why certain vulnerable patient populations, including cancer patients, patients with cardiovascular disease, type II diabetes or obesity, are prone to developing severe COVID-19 by measuring levels of immune-modulatory small molecule metabolites in the blood of several hundred patients in the greater Los Angeles and San Diego region.

**Sara Landeras Bueno, Ph.D.**
**'20 SPARK winner**

La Jolla Institute for Immunology
San Diego, CA

Dr. Landeras Bueno is working to solve the structure of the most abundant SARS-CoV-2 viral protein, whose function is essential to the viability of the virus. Understanding this structure will open avenues for the design of specific antiviral therapeutics that can cure patients already infected with the virus.

# Abhijit Chakraborty, Ph.D.



## Solving the Puzzle of a Shattered Chromosome

### What was the goal of your SPARK project?

Around 40 percent of cancer patients have tumors that show a "catastrophic" chromosomal rearrangement. This suggests that an understudied phenomenon called chromothripsis, a "shattering" of the chromosome, is a key factor in cancer progression.

For my SPARK project, I studied the role of chromothripsis in triggering acute lymphoblastic leukemia (ALL), which makes up 74% of childhood leukemia diagnoses, and is the most common childhood cancers. In 2021, there were more than 5,600 new cases of ALL diagnosed in the U.S. alone. I focused on genomic rearrangements involved in chromosome 21 (iAMP21), which are linked to the highest risk ALL cases. My goal was to shed light on the health consequences of genomic rearrangements at this site—and improve our general understanding of chromothripsis. I also aimed to devise new strategies for studying genomic rearrangements as a way to predict cancer growth and provide cancer patients with accurate prognoses.

### Pivoting during a pandemic:

Initially, the proposed genomic analysis of my SPARK project was supposed to be carried out using ependymoma and lung cancer samples, but due to the pandemic I was unable to acquire those samples. So I had to quickly find a new collaborator in 2020, which became Dr. Anusha Preethi Ganesan, at Rady Children's Hospital. With her help, I obtained ALL cancer samples to carry out a similar analysis and move chromothripsis research forward.

**FUNDED**

JANUARY 2020

**FUNDED BY**

The generosity of LJI Board Director François Ferré, Ph.D., and Magda Marquet, Ph.D., and various 2019 SPARK donors.

SPARK
IMPACT STATEMENT:

"I would consider receiving a SPARK Award as a pivotal moment in my career. The Tullie and Rickey Families SPARK Awards for Innovations in Immunology have given me the confidence as a scientist to independently carry out my experiments, and also offered me my first opportunity to secure significant funding for my own research."

## SPARK project results:

My first step was to establish a collaboration with iAMP21 and ALL expert Dr. Anusha Preethi Ganesan, an Assistant Adjunct Professor and a hematologist/oncologist at Rady Children's Hospital, San Diego. Working with Dr. Genesan led to important cancer insights and gave us access to pediatric cancer samples.

I then performed a differential gene expression analysis between samples from iAMP21 and non-iAMP21 patients. This work showed that 1,885 genes were significantly altered between these two groups. This was a fascinating finding, and led us to uncover potential clues as to how gene expression leads to rapid progression in pediatric blood cancer with rearrangements in iAMP21. Our analysis revealed that differential and highly expressed genes in iAMP21 are involved in biological processes linked to blood formation, immune system development, myeloid cell differentiation, and other relevant functions. I also investigated gene fusion in these samples, which gave us an estimate of the level of genomic stability in the tumors.

In the end, we also devised new methods to understand 3D maps of the human genome. This research is critical for understanding chromothripsis, a devastating phenomenon in cells where shattered chromosomes can lead to especially aggressive cancer.

## What's next for this project?

We know that genomic rearrangements at iAMP21 are devastating for patients. However this project has given me reason for hope for future patients. Because iAMP21 rearrangements come with certain tell-tale gene alterations, there may be a way to expose specific vulnerabilities of cancer cells in these patients and develop targeted therapies.

Going forward, we will perform whole genome sequencing to identify structural variants at the base-pair level resolution, Hi-C to understand the alterations in 3D organization, ATAC-seq to understand genome accessibility, and ChIP-seq to explore histone modifications in iAMP21 samples.

In 2021, I received a one-year $245,000 research grant from **The Conrad Prebys Foundation** to expand this line of investigation further. I'm working on this grant in collaboration with the Ay and Vijayanand Labs at LJI and Rady Children's Hospital and Children's Oncology Group. This additional funding has been made possible by the initial SPARK funds, which allowed us to explore this area of research. My hope is that this investment by The Conrad Prebys Foundation will allow us to collect sufficient data to compete for additional substantial multi-year research funds.

By the end of 2021, I expect to have sufficient data for an important proof-of-concept research paper, which will be the first of its kind in the studies of pediatric ALL cancers and specifically for iAMP21.

## What's next for Abhijit?

My aim is to become an independent scientist, and to do so, my goal is to secure a professorship and establish my own lab at a research institute or university in the next few years. My SPARK award proved to myself and others that I can independently carry out my experiments, analysis, properly handle my own grant budget, and succeed in securing follow-on grant funding. Gaining these critical experiences not only boost my confidence that I can achieve my goals, but will also help me stand out as a potential faculty candidate in the next stage of my career.

# Estefania Quesada-Masachs, M.D., Ph.D.

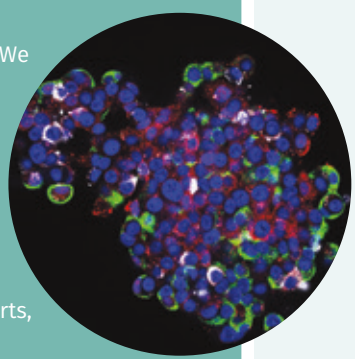
## Exploring Toxic Effects of T1D Patient Serum in Pancreatic Beta Cells

### What was the goal of your SPARK project?

Patients with type 1 diabetes (T1D) develop the disease when the immune system damages their insulin-producing beta cells, leading to loss of beta cell function and, ultimately, irreversible insulin deficiency. This autoimmune attack of insulin-producing beta cells is thought to be primarily mediated by autoreactive immune cells. Older studies have suggested that the blood serum of patients with T1D may directly harm beta cells, and scientists have hypothesized that autoantibodies and other unknown players in blood serum may be partly responsible for disease progression. For my SPARK project, we investigated whether serum derived from patients with T1D could alter the function of healthy islets and induce a different response than serum from non-diabetic patients.

### Pivoting in a Pandemic:

The pandemic did prove to be a challenge for my project. We had difficulties sourcing some essential reagents, and the organ donor program that provides human islets was temporarily halted for a few months. Despite the setbacks, we were able to use the extra time to perfect our experimental plan. Thankfully, we received all of the necessary materials with enough time to successfully complete the study. I was very proud to be able to finish all of the experiments without sacrificing any essential parts, and this allowed me to obtain meaningful data.



**FUNDED**

JANUARY 2020

**FUNDED BY**

The generosity of LJI Board Director Larry Spitcaufsky and Tiki Spitcaufsky.

SPARK
IMPACT STATEMENT:

"For me, SPARK started with a question I had about type 1 diabetes that I found biologically interesting, but that was so risky, it would have been difficult to attract traditional grant funding to pursue. Because of this award I was able to generate preliminary data that is helping piece together an answer to my question, and I hope it will lead us to a better understanding of type 1 diabetes."

## SPARK project results:

We found that islets incubated in serum from patients with T1D make more insulin in response to conditions of high and low glucose, compared to islets incubated in serum from non-diabetic patients. Furthermore, the increased insulin secretion observed in the islets cultured with serum from the T1D group was similar to that observed in islets incubated with proinflammatory molecules. This suggests that the serum of patients with T1D may be stressing these islets, leading them to secrete more insulin.

Despite using state-of-the-art microscopy techniques, we didn't observe differences in the presence of insulin, glucagon or inflammatory molecules, such as HLA-I, in the islets receiving the serum of T1D patients. To determine what may cause the altered islet insulin secretion, we next characterized the serum of the patients by measuring the levels of 97 different factors known to affect inflammation, immune-regulation, and cell growth. In our preliminary analysis, we found subtle differences in some of these molecules between the serum from T1D patients and the serum from non-diabetic patients, but not enough to justify the functional differences observed. Our more complex multivariate analysis is ongoing, which may yet uncover potential causes for these mysterious alterations in islet function.

## What's next for this project?

Prolonged durations of high levels of insulin secretion can lead to nonfunctional beta cells and/or insulin resistance. If the serum from patients with T1D can cause chronic elevated insulin secretion in islets, as we observed in our experiments, this could be a potential reason for dysfunction and eventual autoimmune recognition of beta cells, leading to diabetic symptoms in patients. In our preliminary characterization of the serum from T1D patients, we have not yet found the specific molecules that may cause this, but there may be other factors we have not studied that could impair islet function. Further studies will be required to determine the mechanism by which human serum from T1D patients dysregulates insulin secretion, and what specific factors are involved.

Given these preliminary findings, we plan to pursue a National Institutes of Health (NIH) R21 exploratory/developmental grant to further obtain proof-of-concept and to explore the mechanisms by which human serum from patients with T1D contribute to dysregulated insulin secretion in isolated islets (we hope to hear back by the end of 2021). With future funding, we will test more patients, and use different assays (e.g. cell death assays) to provide better readouts that will help us gain greater understanding of how the islets respond to serum treatment and which factors have the most influence. We hope this will provide greater insight into the potential factors responsible for the effects we observed on islet function.

## What's next for Estefania?

I've applied for a postdoctoral fellowship to the Juvenile Diabetes Research Foundation (JDRF). This fellowship would secure my position for the next few years, and serve as another important step in my career by demonstrating my ability to attract support for my research. I've also applied to the Sociedad Española de Reumatología (Spanish Society of Rheumatology) for a fellowship to support Spanish rheumatologists who are scientists pursuing research abroad.

My plans are to stay at LJI to continue to develop my research skills and mentor both technicians, graduate and undergraduate students. Also, this year I re-applied to the Tullie and Rickey Families SPARK Awards program with the hope of exploring a new question I have related to type 1 diabetes, and I'm honored to have been selected as a '22 SPARK finalist. I look forward to competing in the SPARK pitches again this fall, where I can build on my skills of communicating the importance of my research to the public and hopefully secure funding to pursue my new project.

# Vipul Shukla, Ph.D.

## Cracking the Folded Code in our DNA

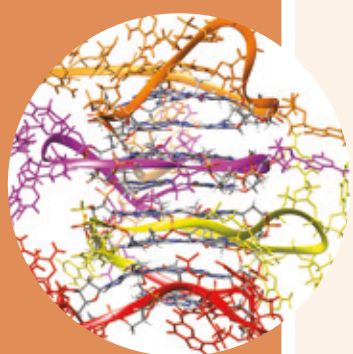
### What was the goal of your SPARK project?

My SPARK proposal was aimed at understanding the biological significance of unusual folded codes, known as G-folds in the genome. G-folds form in regions of DNA with a high abundance of "Gs", which is one of the four letters that make up DNA (A, T, G and C). For the last several decades, researchers have focused on understanding the mechanisms by which the linear sequence of letters in our DNA is read and interpreted within cells but we know very little about how cells, decipher the information encoded in unusual DNA structures, such as G-folds.

To answer this question with my SPARK project, I focused on two important objectives. The first objective was to develop new technologies to detect G-folds in normal cells, as well as their altered formation in cancer cells. My second objective was to identify precisely how our cells read and interpret information encoded in G-folds.

### Pivoting in a Pandemic:

During the pandemic, more than ever, our research relied on teamwork. While the past year presented unique challenges to normal work routines, and even prevented access to the lab for several weeks. Through the constant support from fellow colleagues and leadership at LJI, I was able to make the anticipated progress in accomplishing the objectives that I set out for my SPARK proposal.



**FUNDED**

JANUARY 2020

**FUNDED BY**

The generosity of LJI Board Director Tom Tullie and the Tullie Family.

SPARK
IMPACT STATEMENT:

"My SPARK award provided invaluable support to craft the quintessential framework needed to validate my ideas and open novel avenues for research, which will be instrumental in the long-term success of this project. My participation in the program also offered a unique opportunity to engage with the non-scientific community. I plan to leverage this experience to help promote community engagement for advancing biomedical research efforts in the future."

## SPARK project results:

We used a special chemical called NMM to detect G-folds in normal cells while also studying their perturbations during the development of cancer. We then used this newly developed NMM-based detection method to measure G-fold levels in normal cells and revealed a striking increase in the levels of G-fold structures in blood cancer cells that arise upon loss of certain DNA modifying proteins. Using unbiased genome-wide approaches, we also found that G-folds are a "fragility signature" in DNA and represent common sites in the genome where DNA frequently breaks. These DNA breaks are a hallmark of many different cancers.

Next, I set out to understand the mechanisms by which the information encoded in G-folds is relayed inside cells. I performed a mass-spectrometry screen to identify specific G-fold recognizing proteins. Since proteins are the key functional units in cells, this approach shed light on the biological functions of G-fold structures. We were able to identify several previously unknown G-fold interacting proteins. As we hypothesized, many of the G-fold recognizing proteins that we identified through our screen are known to be essential for controlling key functional genomic states, thereby further endorsing the notion that G-folds represent a critical and underappreciated code in the genome.

In summary, these findings have implications towards our fundamental understanding of genome biology and represent a crucial step towards elucidating the biological functions of these enigmatic DNA structures.

## What's next for this project?

In close alignment with the mission of the SPARK program, the research I performed under this project has opened up several new areas of investigation that I plan to pursue in my own independent laboratory. These studies highlighted G-folds as unique vulnerabilities that could be therapeutically targeted in cancer cells, and we intend to follow up on this in future studies. I'm also excited to share that this work has just been accepted for publication in a premier peer-reviewed journal, *Nature Immunology*, so it will be published very soon.

My collaborators and I are also working to further modify the chemical NMM to generate more reagents that we could apply to precisely map the location of G-folds across the entire genome. We are actively working on this aspect of the project and hope to develop a robust G-fold mapping method in the near future to chart G-fold structures in normal and cancer genomes.

## What's next for Vipul?

I recently accepted a faculty position at Northwestern University in Chicago, IL, where I plan to expand on this work. During the term of my SPARK award, I also received independent research funding in the form of the prestigious "K99/R00 pathway to independence award" from the National Cancer Institute, which will allow me to continue this research in my laboratory. I also plan to build on data generated from my SPARK project and apply for more independent funding from the National Institutes of Health and other organizations to carry this work forward.

# Cecilia Lindestam Arlehamn, Ph.D.

## The Fight against Mycobacteria

### What was the goal of your SPARK project?

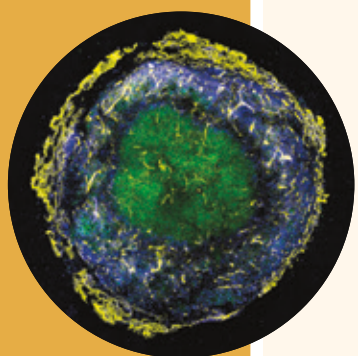
To control tuberculosis (TB), we need to understand the mechanisms of host resistance to the *Mycobacterium tuberculosis* bacterium (Mtb).

Non-tuberculous mycobacteria (NTM) are a group of over 140 mycobacterial species. For my SPARK project, I wanted to take a closer look at Mycobacterium avium complex (MAC), the NTM species that most frequently colonizes and infects humans. Some evidence suggests that MAC exposure varies in different geographic regions, which might explain the disparate outcomes of BCG vaccination (given where tuberculosis is common), as well as susceptibility to Mtb infection and TB. Despite their differences, MAC and Mtb are related and may have important structural similarities. These conserved "antigens" may induce similar T cell responses against MAC, TB and TB vaccines.

It has been traditionally hard to study these T cell responses due to a lack of reliable tools to measure MAC-specific immune responses in individuals. My initial goal was to identify reagents (T cell epitopes) to measure MAC-specific immune responses in the blood.

### Pivoting in a Pandemic:

I was fortunate to finish cell sorting and RNA sequencing right before lockdown began in March 2020, and thus I could focus on the analysis working remotely. I adjusted my approach to also involve a technician in the bioinformatic analysis, so that she could continue to be productive despite not being able to do lab work.



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JANUARY 2020

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The generosity of various 2019 SPARK donors.

SPARK
IMPACT STATEMENT:

"I have always found the opportunity as a scientist to solve problems and find answers to questions exciting. Oftentimes worthwhile questions remain unanswered due to lack of funding. This SPARK award allowed me to dive deeper into an exciting line of inquiry and discover results crucial for the project's long-term success."

## SPARK project results:

I found that MAC contains unique peptides and proteins not present in Mtb or other NTM, i.e. MAC-specific. However, T cell responses were low in all individuals with a history of MAC infection. Therefore, individuals with a history of MAC lung infection/disease do not respond with the same antigen-specific T cell responses seen in most patients with other infectious diseases. This finding suggests individuals with MAC disease may have other underlying immune deficiencies that predispose them to MAC infection.

Importantly, my results further indicated that individuals with MAC infection do not have a general defect in the other arms of their immune response, only in their MAC-specific T cell response. This is because they mounted T cell responses against Epstein-Barr and cytomegalovirus comparable to other patient cohorts.

I also found that individuals with MAC disease have lower frequencies of a specific T cell subset known to fight mycobacteria (including NTMs and Mtb), which was also reflected in their specific gene signature. This adds evidence for a T cell deficiency in individuals with MAC disease, which explains the lack of conventional antigen-specific T cell responses. In fact, this could explain why these individuals were infected with MAC in the first place. Further studies will pinpoint the reason for this lack of a specific T cell subset.

## What's next for this project?

I am, together with my collaborator, Professor Thomas Hawn at University of Washington, writing a manuscript on these findings and we aim to submit a five-year project grant (R01) application to the National Institutes of Health to take this area of research forward. This would be a gamechanger, allowing us to continue our collaboration and study these immune responses in more detail – not only T cells but also expanding to other cell subsets. Improved understanding of MAC disease could enhance and facilitate diagnoses, decrease invasive interventions in clinical care and decrease costs. It is also crucial to understand Mtb infections and vaccine efficacy against Mtb. We are currently drafting a manuscript including these results, as well as results generated at the University of Washington.

## What's next for Cecilia?

In January 2020, I was promoted to Research Assistant Professor, which means I now have my own lab and independence in working on research projects at my own discretion. Through this new position, I hope to continue to develop my research program studying T cell responses in mycobacterial infections, including both tuberculosis and other mycobacteria. I also have an interest and a research program close to my heart studying autoimmune T cell responses in neurodegenerative diseases including Parkinson's disease (which my dad is diagnosed with), Alzheimer's disease, and ALS. As part of both of these research programs I thoroughly enjoy working with and mentoring technicians, grad students and postdocs.

# Greet Verstichel, M.D, Ph.D.

## From Mouse to Man, Towards a Cure for Autoimmune Diseases

### What was the goal of your SPARK project?

More than 50 million Americans suffer from autoimmune diseases, and these numbers are rising at alarming rates. We know that patient immune cells damage healthy organs in autoimmune disease, but scientists don't understand exactly why these immune cells go off course. The thymus is where the body sorts helpful T cells from harmful T cells. T cells that recognize healthy tissue should be educated not to cause autoimmune disease, but in some cases this education is disturbed and harmful autoreactive T cells are the result. We've learned a lot about this process by studying mouse models, but we need more tools to see T cell receptor (TCR) selection in action. With my SPARK award, I worked to set up an organoid culture system for human T cells, starting from stem cells isolated from human thymus samples. My hope is to use this system to interfere during human T cell development and assess the functional profile and TCR repertoire of mature T cells.

### Pivoting in a Pandemic:

I had just started quality control of all my reagents to set up the organoids when the pandemic began and the Institute restricted access to scientists not working on COVID-19 research. So I had to freeze all the cell lines down again and wait until my access to the lab would be restored. Growing these cultures takes about 30 days, and the cells need my attention at least every three days, so it is a commitment to start a culture and access to it is critical. Because of this, I had to wait until the Institute had more clarity on the internal COVID-19 testing program that would allow employees to access the labs more regularly in order to run experiments. In addition, throughout the 2020-2021 school year, I had two elementary school-age children at home doing virtual school, which made planning harder since someone had to stay at home with them to supervise them while also trying to work from home. Once pandemic restrictions were relaxed enough for my children to attend summer camps and have full-time care in 2021, I could get started on long-term cultures, titrate my inhibitors and test which time points would be best for the actual experiment to generate the cells used for single cell sequencing. I'm grateful that the extensions granted to my cohort allowed me the opportunity to run these experiments and continue my project once our work-home routines normalized again.

SPARK
IMPACT STATEMENT:

"What I appreciate most about the SPARK program is how it pushes us as scientists to think about clinical relevance. It was a great experience towards independence to have the opportunity to be the leader on this project, from helping to raise the funds, to designing the experiments and performing them."

## SPARK project results:

We used an organoid culture system for human T cells, starting from stem cells, and tested if we could mimic the genetic models of mouse T cell generation by adding pharmaceutical compounds to the culture. We used single cell RNA sequencing to compare the nature of the generated T cells with those from normally-developed T cells. In addition, we wanted to get an idea of the ability of the cells to recognize a human body's own tissue and organs. For this purpose, we obtained the genetic sequences of the key structure of the T cell that recognizes its target.

We found that the use of a pharmaceutical compound (2-DG) during human T cell organoid culture mimics the genetic defect we observed in mouse models. This means that it is likely that similar mechanisms underlie the generation of functional T cells in humans and in mice. Identifying how we can manipulate these processes will significantly boost our knowledge of the pathways leading to autoimmunity and will aid in the design of effective new strategies to cure or even prevent autoimmunity.

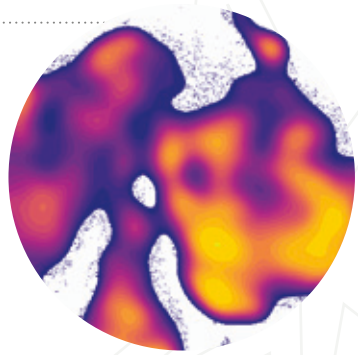
## What's next for this project?

I will build on these data and perform in-depth analyses of the TCR sequences we found. I will need to score the self-reactivity computationally and answer the question of whether inhibiting glycolysis during beta-selection alters the recognition of self-antigens. When I have this data, I will work with my Principal Investigator, Hilde Cheroutre, Ph.D., to add it to the paper I hope to prepare and submit to journals in 2022. Additionally, if the hypothesis proves right, this will be important preliminary data to submit an R01 grant to the National Institutes of Health on this project.

I'm also excited to share that Dr. Cheroutre and I will continue to build on this project together, thanks to a $400,000 grant from Praespero (a Canadian charity focused on funding autoimmune disease research) received in fall 2022.

## What's next for Greet?

For me personally, I really want to focus now on elaborating on the mechanism behind our findings in the mouse models. The more detail we can uncover, the better our options for publishing a paper or securing follow-on funding will be, and my options for my future career will depend on that. I must admit that when I joined LJI, my aspiration was to start my own lab one day and contribute to the scientific fields of T cell function and how they relate to autoimmunity and cancer. But with time, and especially having lived through the pandemic, I can see myself achieving professional goals in a company setting as well. Most importantly, I want to eventually transition to a leadership scientist position that will utilize my medical and scientific background to contribute to moving the health sciences forward.



**FUNDED**

JANUARY 2020

**FUNDED BY**

The generosity of Barbara Donnell, Bill Passey and Maria Silva, and various 2019 SPARK donors.

# Sara Landeras Bueno, Ph.D.

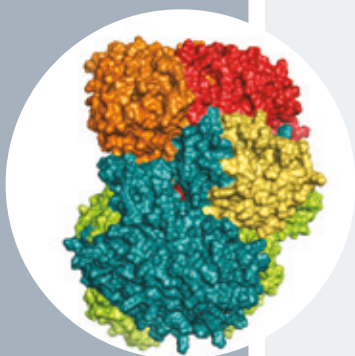
## Combating Emerging Ebola Virus Threats with Affordable Cures

### What was the goal of your SPARK project?

Ebola virus relies on a viral protein called the polymerase protein to infect cells. This protein makes copies of the viral genetic material needed to form new virus particles that go on to infect other cells or other people. Polymerase is also a potential target for antiviral drugs. To understand precisely where these drugs should attack the polymerase, scientists need to be able to see the protein structure at the atomic level. However, there are no atomic structures of polymerases, largely because these proteins are difficult to produce, purify, and image with techniques like cryo-electron microscopy (cryo-EM) or crystallography. I proposed purifying Ebola polymerase protein for use in structure work, and succeeding meant overcoming several major technical hurdles.

### Pivoting in a Pandemic:

The urgency generated by the COVID-19 pandemic in spring 2020 meant my lab had to quickly prioritize SARS-CoV-2 projects and I was asked by my Principal Investigator, Dr. Saphire, to support that critically sensitive work. However, thanks to the extensions granted to my SPARK cohort as a result of the pandemic, I was still able to work on my SPARK project and apply the tools I generated for my project with success.



**FUNDED**

JANUARY 2020

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The generosity of Rachel and Bob Perlmutter, Raydene and Peter St. Clair, and various 2019 SPARK donors.

SPARK
IMPACT STATEMENT:

"I think the COVID-19 pandemic highlighted the value of the SPARK program's vision to fund novel research. For example, my project, designed in 2019, was aimed at antiviral development to enable us to respond to future outbreaks of Ebola virus that could have pandemic potential. While this pandemic was caused by an emerging coronavirus, it underscored the importance of being proactive in identifying possible viral threats and discovering their weaknesses so that we can respond more quickly and effectively."

## SPARK project results:

I designed a platform that allows the rapid production and screening of variants of Ebola virus polymerase, that are engineered, to be more stable and produce more protein. I modified a battery of Ebola polymerases from different key pathogenic species of Ebola virus (Zaire and Sudan), the related Marburg virus, the original strain from bats (Mayinga), as well as the non-pathogenic Reston virus with a tag that allows more specific purification of the protein. Interestingly, I found that the expression levels of the various ebolavirus polymerases differed significantly among virus strains. Sudan and Mayinga ebola viruses expressed the highest amount of polymerase complex in human cells. I also stabilized the polymerase complex by co-producing it in cells with another viral protein called VP35. I rapidly upscaled the purification of the most promising engineered candidates using liters of insect cells. It was important to use insect cells for this step because they offer a high level of protein expression.

Preliminary purifications of the polmerase-VP35 complex had low protein yield, but by modifying our purification method, we increased the amount of protein we could get by 50%. From among the purification strategies, I selected those that showed both better yield and purity of the polymerase-VP35 complex. For the first time I can visualize the polymerase-VP35 complex clearly in a SDS-PAGE gel, but there are other lower abundant proteins in the mixture. We hypothesize that these proteins are contributing to the stability of the complex. In order to locate the polymerase-VP35 complex in the Electron Microscope grid we are labeling the complex with gold.

## What's next for this project?

I am now testing different sample preparation techniques to find conditions that will allow me to image this protein complex using cryo-EM, a high-resolution imaging technique that can shed light on atomic-level details of viral proteins.

I plan to further optimize the purification process and the stability of the Ebola virus polymerase-VP35 complex to pursue a high-resolution structure of the Ebola polymerase-VP35 complex. The interaction between the polymerase and VP35 is essential to fix the polymerase in one of its multiple functional states, but during this project, we learned that it is transient. Capturing this shifting interaction will affect the structural homogeneity required for getting high-resolution models by cryo-EM. We plan to increase the stability of the interaction through the binding with viral RNA and through a new artificial interface generated by self-complementing methods. We are also mapping the polymerase domains that serve as interaction partners for VP35. With this knowledge, we can engineer a construct that binds covalently both proteins and stabilizes their interaction. We are ready to start imaging the Ebola polymerase-VP35 complex using LJI's Titan Halo Electron Microscope. Once we get a low-resolution model of the complex, we will start the imaging of the Ebola polymerase-VP35 complex using LJI's Titan Krios Cryo-Electron Microscope. If conformational heterogeneity remains a problem, we will use computational methods to finely sort particles into class averages representing a single conformation. After processing the images, we aim to generate a three-dimensional model that will be further refined and validated.

## What's next for Sara?

I see myself eventually leading a team focused on medicines to cure diseases caused by highly pathogenic human viruses. The global pandemic reminded me why I am committed to virology and also the relevance of our research to society. Among the practical experiences SPARK provided in project management and execution, it also honed my communication skills and comfort in being more visible inside and outside the scientific community. I'm grateful to have developed these essential skills for my career, and to have experienced first-hand how private philanthropic support can be a critical bridge between having an idea and executing it.

# Thomas Riffelmacher, Ph.D.

## A New Cellular Target to Prevent Tissue Damage Following Heart Attack

### What was the goal of your SPARK project?

I was always fascinated with the question of how the lack of oxygen would impact immune functions on a cellular level. Of course, it didn't take a pandemic to teach us how quickly we are in trouble when we can´t breathe — but what does the lack of oxygen mean to our immune cells within tissue? During a heart attack, a stroke and in sickle cell disease, blood vessels become clogged, but we don't understand, on a cellular level, the impact this hypoxia has on the inflammatory response that follows. Using single cell RNA sequencing, I sought to explore the mechanistic changes within innate immune cells in this context, to see if it offers cues to novel druggable targets.

### Pivoting in a Pandemic:

The pandemic presented significant challenges to my project because my original plan relied on outpatient samples from patients who suffered heart attacks. Unfortunately, these samples were no longer collected during the pandemic. Also, since my original collaborator was in the U.K. and I was going to have to travel to retrieve the samples, that wasn't possible due to the travel bans between the U.S. and Europe. So I had to step back and think about what I could do, in the short time frame I had, to address this question with what is available more locally. Fortunately, thanks to a previous clinical study collaboration between LJI and the University of Wisconsin, I was able to get access to blood samples from sickle cell disease patients. This is a disease of chronic, recurring episodes of blood vessel occlusion, which causes inflammation of the lung. Simultaneously, I used a mouse model of sickle cell disease, harbouring the human disease-causing mutation in the haemoglobin gene, for mechanistic follow-up experiments. With these samples, I was still able to explore the impact of vaso-occlusion and resulting hypoxia on immune cells, albeit in a different disease context.

SPARK
IMPACT STATEMENT:

"This SPARK award really changed the dynamic of how I do research. Thanks to this award, I was able to experience what it is like to independently follow a line of inquiry that I was interested in, and truly take the lead in moving it forward. This award also allowed me to manage a budget and be accountable for following through and getting results. In short, this program has provided me with the perfect training ground for becoming an independent investigator."

## SPARK project results:

I initially set up a single cell sorting strategy to isolate the Natural Killer T ("NKT") cells and optimize the conditions using the phlebotomy core at LJI for sourcing blood (once it reopened). We requested and received IRB approval to get healthy African American volunteers to donate blood at LJI as appropriate controls for sickle cell patients. I then sorted the relevant immune cells from over 20 sickle cell disease patients and controls. Originally, I proposed to focus only on NKT cells, but we realized, thanks to the capabilities of LJI's sequencing and bioinformatics teams, that we could add four more relevant innate lymphocyte populations. I am now analyzing the data from a total of 10,841 lymphocytes to test if we find evidence for altered inflammatory signaling. The first results were promising, indicating that innate lymphocytes were noticeably depleted in the blood of patients but not in the controls, meaning they may have been recruited into the lung tissue to mediate inflammation. There were several thousand genes differentially expressed, including the pathways that produce inflammatory cytokines. Having the humanized mouse model allowed me to study this in more detail within lung tissue, which of course we cannot get from patients. Indeed, inside the lungs, the NKT cells dramatically increased in numbers and contributed to inflammation. They were also metabolically different. Due to the logistical challenges and need to really pivot my project, I have an extension to finish this through December 2021, so some of my results are still pending additional experiments and analysis.

## What's next for this project?

Thanks to the huge dataset I was able to obtain with the help of the SPARK award, I have a powerful tool that will help to understand the mechanism of how inflammation is mediated in response to the vaso-occlusive crisis. The data have already pointed us to relevant mediators of inflammation, which I am now following up on with mechanistic experiments. We would like to fully understand the mechanisms underlying this, and relate it to how it compares to inflammation following heart attacks – which we will be able to do using the patient sample data. While we may still be adding more data to this during the extension period, this represents a solid foundation that will facilitate future research into this area.

## What's next for Tom?

With the goal of becoming an independent investigator in mind, I have applied for a National Institutes of Health (NIH) K99 grant, which provides funding to promising young investigators to help them transition into faculty positions. I am also applying to similar grants in Germany, which is where I am originally from. So my hope is that I will be able to make this transition in the next couple of years in either the U.S. or Germany. Regardless of where I obtain a position, I remain interested in this line of immunology research and hope to continue this work in the future.

**FUNDED**

JANUARY 2020

**FUNDED BY**

The generosity of LJI Board Director Dave Rickey and the Rickey Family.

# 2021 SPARK AWARDS CELEBRATION

La Jolla Institute for Immunology welcomed guests to an outdoor reception on June 29, 2021, in celebration of the brilliant winners of the 2021 Tullie and Rickey Families SPARK Awards. The reception was a chance for LJI to recognize supporters of the Tullie and Rickey Families SPARK Awards program and honor the newest class of SPARK Award winners.

Over 50 people were in attendance, between donors and SPARK winners from 2018-2021. Guests had the opportunity to hear remarks from three former SPARK winners – Estefania Quesada-Masachs, Ph.D. ('20 SPARK winner), Marco Orecchioni, Ph.D. ('19 SPARK winner), and Daniela Weiskopf, Ph.D. ('18 SPARK winner) – on the impact the program has had on their careers and research.

SPARK donors Jackie, Tom and Judy Tullie (middle) with the '21 SPARK winners

SPARK donor and LJI Planned Giving Advisory Council Co-Chair John Kraemer (left) with Professor Klaus Ley, M.D.

SPARK donor Joani Nelson conversing with SPARK winners

From left to right: Sara MacArdle, Ph.D., '19 SPARK winner, Estefania Quesada-Masachs, M.D., Ph.D., '20 SPARK winner and Daniela Weiskopf, Ph.D., '18 SPARK winner

From left to right: Marco Orecchioni, Ph.D., '19 SPARK winner with '21 SPARK winners Nicolas Thiault, Ph.D., Artem Romonov, Ph.D. and Annie Elong Ngono, Ph.D.

Sharleen Wollach of the Jewish Community Foundation (left) with SPARK donor Sylvia Liwerant

LJI Chief Scientific Officer, Mitchell Kronenberg, Ph.D. (middle) with SPARK donors James Isaacs, Jr., J.D. (left) and Jeffrey Miller, Ph.D. (right)

## EIGHTH '21 SPARK WINNER FUNDED

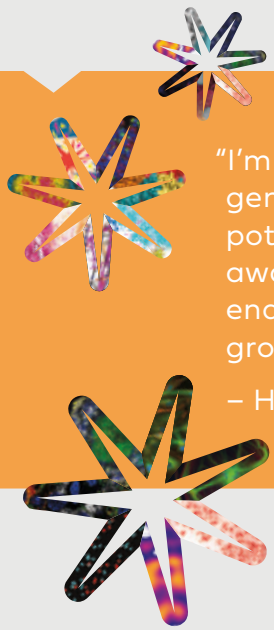
At the event, long-time LJI supporter, James Isaacs, Jr., J.D., (pictured on pg. 20 lower right) was discussing specific SPARK projects with Tom Tullie and LJI faculty, when he learned that one 2021 SPARK Awards finalist had not received funding. At that point he became interested in finding out more about the proposed project of Hui Zhi, Ph.D. After learning about the project from Dr. Zhi's lab leader, Chris Benedict, Ph.D., who was present at the event, Isaacs was inspired to invest his support.

Dr. Zhi's project will use state-of-the-art 'omics' techniques available at LJI to characterize the immune arsenal of ILC1 cells, critical players in controlling infection and cancer tumor growth.

"ILC1 cells have drawn very little attention, and in Hui's project I saw a block of scientific experiments and research with almost infinite potential upside," shares Isaacs. "These experiments would not have happened (at least for now) without me jumping in. In exchange for a relatively small investment, I saw a chance to expand the incredible work launched at LJI by the Tullie and Rickey families, and I grabbed it."

Viral infections are a huge health and economic threat to society, exemplified by the current COVID-19 pandemic. In turn, despite recent immunotherapy approaches to treating cancer, new strategies are still badly needed.

Dr. Zhi's study aims to establish a solid foundation for harnessing the power of ILC1 in humans for fighting against viral infection and cancer. Dr. Zhi was thrilled to learn his project had received funding and a progress report of his work thus far can be found on pg. 25. You can also read more about what makes ILC1 cells unique and learn more about Dr. Zhi's desire to pursue this new area of research at **lji.org/blog/hui**.



"I'm very grateful to Mr. Isaacs for his generosity and recognizing the significant potential of my work. Receiving this award is incredibly motivating and enabled me to get this project off the ground immediately."

– Hui Zhi, Ph.D.

## THANK YOU, REVIEWERS

We are extremely grateful for the time and support of the application and pitch reviewers in 2020, who helped select the '21 winners of The Tullie and Rickey Families SPARK Awards for Innovations in Immunology:

Amnon Altman, Ph.D.
Dick Bodman
Mark Bowles
Anthony Carr
Barbara Donnell
Gina Kirchweger, Ph.D.
Christopher A. Lee, MBA
Bob Mahley, Ph.D.
Linda Mahley
Margaret Ng Thow Hing, J.D.
Rachel Perlmutter
Brenda Rickey
Dave Rickey
Sage Shapery
Sandy Shapery, J.D.
Larry Spitcaufsky
Peter St. Clair
Raydene St. Clair
Ingrid Stuiver, Ph.D.
Anna Tullie
Jaqueline Tullie
Judy Tullie
Samantha Tullie
Tom Tullie
David Webb, Ph.D.
Stephen S. Wilson, Ph.D.
Eric Zwisler
Tori Zwisler

# PROGRESS REPORTS FROM THE '21 SPARK WINNERS

The ambitious and talented 2021 cohort is tackling problems as bold as improving outcomes for patients with cancer, COVID-19, autoimmune disease, diabetes and heart disease - and protecting us all from deadly infectious diseases. These energetic early-career scientists are marching right along with their projects. Here are the six-month progress reports for the 2021 Tullie and Rickey Families SPARK awardees:

## Mehdi Benkahla, Ph.D.

### WHAT IF VIRAL INFECTIONS COULD TRIGGER TYPE 1 DIABETES?

In people with type 1 diabetes (T1D), insulin-producing beta cells in the pancreas are destroyed—and scientists still don't know why. Yet there are clues suggesting that both environmental factors, such as viruses, and genetic susceptibility play important roles in triggering the disease. Several viruses, mainly from the enterovirus family, have been considered potential culprits for human T1D, but there is little solid evidence of this link. For my SPARK project, I investigated the impact of viral infections on human pancreatic tissue slices. We obtained these samples from non-diabetic donors provided by the Network for Pancreatic Organ Donors with Diabetes (nPOD). We infected, human pancreatic slices using a pathogen called coxsackievirus B3, which was genetically engineered to express a green fluorescent protein (GFP). After three days of infection, we could detect the GFP by high-resolution confocal microscopy in the insulin-producing beta cells. These infected beta cells also expressed HLA-I, a molecule that cells use to alert the immune system to a potential threat. HLA-I is also a hallmark of T1D. While it is too soon to conclude that a virus could trigger T1D, this study gives us a direction for further testing that link.

## Michael Norris, Ph.D.

### WHAT IF WE COULD ACT NOW TO PREVENT A FUTURE, EVEN DEADLIER PANDEMIC?

Paramyxoviruses include some of the most infectious and deadly viruses known to mankind—and we have no way to stop them. One of the most important pieces of these viruses is the matrix protein, also known as M. In an infected cell, the virus manufactures thousands of copies of M as it begins making copies of itself. If we could develop an antiviral drug that targets the M protein interaction with the membrane lipid, we could stop infections in their tracks.

For my SPARK project, I built on my previous success in solving the 3-D structure of a paramyxovirus M protein in complexes with a membrane lipid. This structure became my "blueprint" to find drugs that can inhibit the membrane binding process. I used a technique called virtual drug screening to evaluate millions of drugs for their potential to bind M. Through this process, I narrowed down the list of over 3.2 million drugs to a few thousand.

In the coming months I will begin the next phases in the virtual screening workflow by undertaking molecular docking of the compounds identified from shape screening and computationally determining if they can bond with the M protein.

## Nicolas Thiault, Ph.D.

### WHAT IF THERE IS A NEW IMMUNE CELL THAT COULD BE ENGINEERED TO SAFELY KILL TUMOR CELLS AND CURE CANCER?

Engineering chimeric antigen receptor (CAR) T cells represent one of the most promising immunotherapies against cancer. Unfortunately, CAR T cells are often associated with severe toxicity and a high failure rate in certain types of cancers. I'm aiming to apply the existing CAR T cell technology to new immune cells, discovered at La Jolla Institute for Immunology, called double negative T (DNT) cells. These cells harbor more effective killing capacity with lower toxic potential.

So far, I have focused on establishing methods to generate CAR DNT cells and their appropriate tumor targets. I also genetically modified tumor cells to allow their recognition by the engineered CAR DNT cells and provide the proof-of-concept for my hypothesis. These steps are essential for conducting upcoming in vitro and in vivo experiments. In fact, such characterization of the DNT cell biology has never been described in fundamental nor translational research and would be worth considering for future publications or grant submission.

I will now start the in vitro experiments to validate these protocols and address DNT efficiency against tumor cells. At the same time, I will confirm that our tumor model can grow in mice. Then I will address whether engineered DNT cells can safely kill tumors and cure cancer in vivo.

## Annie Elong Ngono, Ph.D.

### WHAT IF WE COULD HALT THE SPREAD OF DENGUE, THE MOST PREVALENT MOSQUITO-BORNE VIRUS, THROUGH IMPROVED VACCINE DEVELOPMENT?

By studying dengue and the related flaviviruses, Japanese Encephalitis (JEV) and Zika (ZIKV), we can develop safer and more effective vaccines and therapies. JEV and the four strains of DENV have very similar structures, and the immune system can target similar sites on these viruses. These similarities make it hard for researchers to detect specific antibody responses to only one flavivirus.

I plan to test two different techniques to determine the most specific and sensitive approach for detection of pre-exposure to JEV. I will test an in-house ELISA and an existing commercial JEV-IgG Kit from InBios. We will compare both approaches using samples collected in 2017.

We accomplished several major goals in the first six months of this project. First, it was critical that we develop procedures to safely manage research and collect samples in Nepal during the pandemic. We also launched new biohazard safety protocols and risk assessments needed to work on JEV in our Biosafety Level 3 facility at LJI.

The next six months will be critical for the project as we define the best approach to determine the JEV immune status of patients, including for patients samples collected in 2021.

## Payel Roy, Ph.D.

### WHAT IF WE COULD SCREEN FOR HEART DISEASE EARLIER AND IMPROVE PATIENT OUTCOMES?

It is becoming increasingly evident that heart disease progression is driven by immune cells, particularly T cells. My goal is to develop assays that can detect—and reveal—the biological identities of harmful T cells.

Normally, T cells respond only to foreign molecules, or "antigens," such as molecules on bacteria and viruses. But in case of heart disease, some rogue T cells recognize self-antigens, i.e., molecules that are present in our own bodies. Researchers studying mouse models have shown that the protein backbone of "bad" LDL cholesterol, called apolipoprotein B, is a major cause of heart-disease in subjects with these harmful immune responses. Therefore, I examined whether human T cells also respond to this self-antigen. For my initial analysis, I chose to study blood samples from young and middle-aged donors not diagnosed with heart disease.

The fact that my assays are able to detect heart-disease related inflammatory T cell responses in the general population signifies the tremendous potential of this workflow in evaluating early signs of the disease. My study also reveals that rogue T cells identify specific sites called "epitopes" in the human apolipoprotein B candidate antigenic protein. Identifying this epitope panel marks the first step towards the development of an immune-based diagnostic screening tool for disease-related T cell responses.

## Simon Brunel, Ph.D.

### WHAT IF WE HAD ONE THERAPY THAT COULD CURE ALL AUTOIMMUNE DISEASES?

It may be possible to generate therapeutic cells to treat many types of autoimmune diseases. For my SPARK project, I tested the techniques and technology we'll need to develop the best therapeutic cells. It shows that cells from bone marrow can differentiate into dendritic-like cells and migrate to the thymus, the organ where T cells develop. This discovery shows us that bone marrow cells can express the right molecular tools to let them migrate through the body—even after they are modified in the laboratory. Our follow-up research in a mouse model confirmed that cells expressing this protein, called CCR9, prefer to migrate to the thymus.

Thanks to this work, we now have the tools in place to analyze and track these modified cells. The next step is to confirm that the migration of those cells in the thymus can prevent or cure autoimmune disorders. The first model of autoimmune disorder will be the type I diabetes in mice. We hope this gives us a window into treating type 1 diabetes and the mystery of how that disease develops in the first place.

## Artem Romanov, Ph.D.

### WHAT IF WE COULD IMPROVE TREATMENT FOR SEVERE CASES OF COVID-19 TO SAVE LIVES?

I'm investigating the relationship between metabolites and COVID-19 pathogenesis to reveal new potential metabolic targets for treating severely affected COVID-19 patients. Thus far, I've collected, organized and annotated hundreds of plasma samples from the CS Cohort, including patients with COVID-19 (severe and non-severe disease) and relevant non-infected control patients. I've also categorized all the patient samples based on the clinical outcomes data and other relevant information(e.g. age, sex, ethnicity, BMI, etc.). After that, I extracted plasma metabolites from CS cohort patient samples, analyzed these extracted metabolites and pinpointed several metabolites specifically associated with severe COVID-19 or non-severe COVID-19.

I performed the first comprehensive analysis of metabolites in severe COVID-19 patients, and have shown for the first time that specific metabolites are present in the blood of patients with severe COVID-19. Metabolites associated with severe COVID-19 could be used as biomarkers to predict which patients should immediately receive special drugs (e.g remdesivir). Similarly, metabolites associated with non-severe COVID-19 could be developed and used as clinical therapeutics to lessen case severity.

We now plan to identify more metabolites associated with severe or non-severe COVID-19. We will also focus on identifying the structures of the metabolites we have found so far.

## Hui Zhi, Ph.D.

### WHAT IF THERE IS AN OVERLOOKED IMMUNE CELL THAT COULD BE KEY TO BOTH TREATING VIRAL INFECTIONS AND FIGHTING CANCER?

Type 1 innate lymphoid cells (ILC1) are among the first responders when a viral infection is trying to gain a foothold in the body. ILC1 cells reside in the tissues and run constant immunosurveillance to spot and eradicate any danger. My goal in this new study is to harness single-cell RNA sequencing techniques to identify the most powerful proteins ILC1 cells use to combat viruses.

Most likely, ILC1 cells don't use their full complement of "weapons" unless they encounter stressed cells, possibly due to the constant expression of CD200R on these cells (an anti-inflammatory receptor that controls the activation of ILC1 cells). Therefore, in my experiments thus far, I've stimulated these cells by treating mice with either pro-inflammatory reagent or antibodies that block CD200R signaling, which did in turn further activate ILC1 cells. After these stimulations, liver and salivary gland ILC1 cells were purified and sent for single-cell RNA sequencing for further analysis. My next steps will be to analyze the sequencing data and identify effector proteins of ILC1 cells uniquely expressed under stimulation. From these data, we plan to further test which of those proteins are most powerful for treating viral infection and cancers.

# SPARK STARS ARE LEADING CRITICAL RESEARCH ACROSS THE GLOBE.

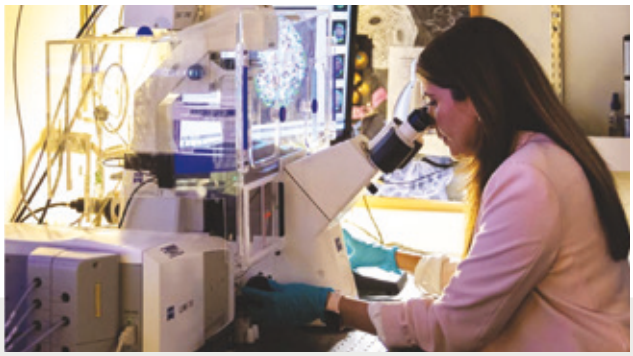
In addition to providing seed funding of innovative ideas, the Tullie and Rickey Families SPARK Awards program aims to train and support the most promising early-career scientists so they are equipped and encouraged to stay dedicated to medical research. Throughout 2021, we've shared some of the successes of our "SPARK Stars" who are demonstrating that donor investment in SPARK is helping to ignite discoveries and field the next generation of researchers. In case you missed them, here are a few of those updates and links to read more:

## DANIELA WEISKOPF, PH.D.

**'18 SPARK WINNER**

Dr. Weiskopf has been awarded the 2021 Junior Principal Investigator Award from the organization of Austrian Scientists & Scholars in North America (AsciNA). She received this honor due to her leadership on a groundbreaking study on T cell responses to SARS-CoV-2.

**READ HER Q&A ABOUT THIS HONOR AT:**
**lji.org/blog/daniela**



## ESTEFANIA QUESADA MASACHS, M.D. PH.D.

**'20 SPARK WINNER + '22 SPARK FINALIST**

Physician-scientist, Dr. Quesada Masachs was the featured Up & Coming Post-Doc in the Fall 2021 Issue of LJI's *Immune Matters* magazine. You can read about Dr. Quesada Masach's background and learn more about her paradigm-shifting research into type 1 diabetes that was supported by her Tullie and Rickey Families SPARK Award in 2020.

**FIND ESTEFANIA'S ARTICLE AT:**
**lji.org/immune-matters/estefania**

## IAN MATHEWS, PH.D.

**'18 SPARK WINNER**

The $25,000 grant from the donor-driven Tullie and Rickey Families SPARK Awards program led Dr. Mathews to receive a highly competitive NIH fellowship in 2019. Then in 2021, the National Cancer Institute also awarded $4.2 million in additional research funding for LJI-led follow-up studies, based on the data Dr. Mathews produced for his SPARK project. In fact, his mentor, LJI Associate Professor Sonia Sharma, Ph.D., has done the math. She found that the SPARK award led to about a 165-fold return on investment.

**READ MORE ABOUT IAN'S SUCCESS AT:**
**lji.org/blog/ian**

## MARCO ORECCHIONI, PH.D.

**'19 SPARK WINNER**

## ABHIJIT CHAKRABORTY, PH.D.

**'20 SPARK WINNER**

In March 2021, **The Conrad Prebys Foundation** awarded more than $450,000 in funding to support two early-career researchers at La Jolla Institute for Immunology (LJI). LJI Postdoctoral Fellow Dr. Orecchioni, is leading a project to uncover how human immune cells may trigger atherosclerosis, the cause of heart attacks and strokes. LJI Instructor Dr. Chakraborty, is using the funding to investigate how genomic instability can lead to childhood cancer.

**READ THE PRESS RELEASE AT:**
**lji.org/news/prebys21**

Scan the QR code to learn more about each researcher

## VIPUL SHUKLA, PH.D.

**'20 SPARK WINNER**

Dr. Shukla has recently accepted a faculty position at Northwestern University in Chicago, and will open his lab this winter. "The SPARK program provided an amazing platform to polish my highly ambitious research ideas. In 2020 I was also funded by the National Cancer Institute for a career transition award, which allowed me to accept a faculty position at Northwestern University. Following on the premise of our SPARK award, at Northwestern, our lab will continue to focus on studying the roles of alternative DNA codes in normal and cancer genomes."


## ANNIE ELONG NGONO, PH.D.

**'21 SPARK WINNER**

Have you ever wondered why our researchers dedicate their lives to pursuing *life without disease*? This fall, the LJI communications team captured Dr. Elong Ngono's story, where she shared how one of the hardest obstacles for young researchers is believing you will succeed. In the video, Annie remarks, "You have to be different to be a researcher. You need perseverance. You need to be able to stand up even after failure and never give up because that's the principle of research." An important aspect of the Tullie and Rickey SPARK Awards program is to give early-career researchers an opportunity to build on this confidence. We hope you will enjoy learning about Dr. Elong Ngono's journey to becoming a researcher, and that it helps you see how by supporting SPARK you've played a role in helping her and all of our SPARK winners realize they are,in Dr. Elong Ngono own words, "good enough" to succeed.

**WATCH THE VIDEO AT:**
**stories.lji.org/annie**

## MICHAEL NORRIS, PH.D.

**'21 SPARK WINNER**

Dr. Norris will be starting his own lab at University of Toronto in the spring of 2022. "The SPARK program gave me an indispensable glimpse into the responsibilities and day-to-day of running my own independently funded lab. There are no words for how crucial this learning experience has been for me as I transition to my new role as an Assistant Professor at the University of Toronto in Canada. My lab will now investigate the structure and molecular assembly of deadly RNA viruses like measles and Ebola. My work will not only provide the structural blueprints to accelerate drug discovery but will also generate new hypotheses to drive innovative biological discovery. I am forever grateful to the amazing donors and friends of LJI that have believed in my vision and jump started my career."

# DONOR HONOR ROLL

## PHILANTHROPY FUELS THE NEXT GENERATION OF RESEARCH

Thank you to all of the generous donors to the Tullie and Rickey Families SPARK Awards for Innovations in Immunology. The donor list below represents all donors to the Tullie and Rickey Families SPARK Awards for Innovations in Immunology since the beginning of the program in Fall 2017 through October 2021. Any donor with a SPARK icon after their name denotes they've given enough cumulatively to fund at least one whole SPARK Award.

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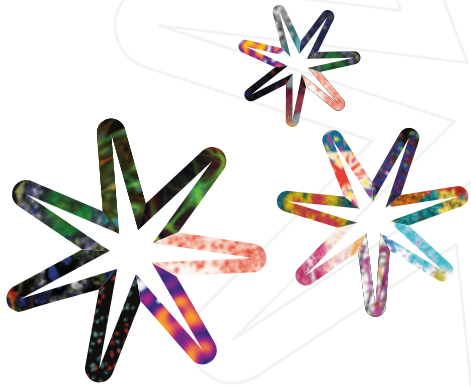

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*Deceased

# About the Tullie and Rickey Families

From left to right: Judy and Tom Tullie, Dave and Brenda Rickey

We'd like to thank and recognize the incredible support and generosity of LJI Board Director Tom Tullie and his wife Judy, as well as LJI Board Director Dave Rickey and his wife, Brenda, and their families. Their joint commitments to the SPARK program made in 2019 meant LJI has the assurance that this program will have funding in place for several awards a year for the next decade. That year, LJI honored their commitment by renaming the SPARK program to The Tullie and Rickey Families SPARK Awards for Innovations in Immunology.

Tom Tullie was one of the first SPARK pitch reviewers in 2018, and that was what drove him to get his family engaged in the program. "I've been an entrepreneur and involved in innovation my entire career, but this is the most exciting program I've seen because the ideas these young scientists have are not only fascinating, they have the potential to generate breakthrough discoveries that will someday save lives," says Tom. Since then, Tom and his wife Judy and their daughters Jaqueline, Anna and Samantha have all taken part in the pitch review process.

For the Rickeys, involvement in the SPARK program was spurred by an invitation from Tom and also by the couple's belief in the Institute's mission. "Brenda and I love the idea of 'life without disease' because so many of our friends and family have suffered or died from cancer, heart problems, dementia, and other ailments," Dave says. The Rickeys were attracted to the SPARK program largely due to its structure and opportunity to drive research forward. "In the philanthropy world, we like to give money where there will be a return. This program is really tangible and it's good to see."

The Tullie and Rickey families hope that by ensuring the program's longevity, other donors will be inspired to contribute to the program to fund additional awards and get as many of these ideas off the ground as possible. "I'd love to see people join us," shares Tom, "I guarantee you that it will be well worth our investment because these ideas are unbelievable and they need to get funded."

The Tullie and Rickey Families SPARK Awards program represents an opportunity for donors of all levels to have a profound impact on the future of early-career researchers and also help ignite the next big breakthroughs. You can donate online at donate.lji.org/SPARK or reach out to Kelsey Dale at kdale@lji.org or 858-752-6542 if you'd like to discuss other giving options.

We hope this annual report on **The Tullie and Rickey Families SPARK Awards for Innovations in Immunology** has emphasized the value of supporting this program. We are excited to announce this year's finalists who hope to win an award in January 2022. You can read more about their projects on our website at **lji.org/spark**. With a gift this year for the Tullie and Rickey Families SPARK Awards program, you can help bring these potential transformative discoveries to light.

## PREVIEW OF THE 2022 SPARK AWARDS FINALISTS

### Eduardo Olmedillas, Ph.D.

What if the sole survivor of a lethal disease holds the key to uncovering a lifesaving treatment?

### Estefania Quesada-Masachs, M.D., Ph.D.

**'20 SPARK winner**

What if a person's insulin-producing beta cells are orchestrating their own demise?

### Gurupreet Singh Sethi, Ph.D.

What if we could cure asthma by erasing the immune system's memory of allergens?

### Heather Callaway, Ph.D.

What if we could design longer-lasting vaccines?

### Maria Matias, Ph.D.

What if we could convert pro-tumor cells into tumor-fighting cells?

### Priyanka Saminathan, Ph.D.

What if we could uncover the biological mechanism that makes men more vulnerable to COVID-19?

### Shailendra Verma, Ph.D.

What if we could better understand how obesity influences the outcome of COVID-19 infection?

### Melissa Meyer, Ph.D.

What if we could target pro-tumoral immune cells while leaving infectious disease-fighting immune cells unharmed?

## THANK YOU TO OUR SPARK AWARDS APPLICATION REVIEWERS

We'd like to thank the Tullie and Rickey Families SPARK Awards application reviewers who helped identify the 2022 SPARK finalists from our pool of applicants this summer: Gina Kirchweger, Ph.D. (Chief Communications Officer, LJI), Christopher A. Lee, MBA (Chief Advancement Officer, LJI), Robert "Bob" Mahley, Ph.D. (Immunologist, SPARK Donor and Board Director, LJI), Samuel Myers, Ph.D. (Assistant Professor, LJI), Margaret Ng Thow Hing, J.D. (Senior Director, Technology Development, LJI), Dave Rickey (SPARK Donor and Board Director, LJI), Ingrid Stuiver, Ph.D., Tom Tullie (SPARK Donor and Board Director, LJI), David Webb, Ph.D. (Immunologist, SPARK Donor and Board Director, LJI), and Daniela Weiskopf, Ph.D. ('18 SPARK Winner, Research Assistant Professor, LJI).

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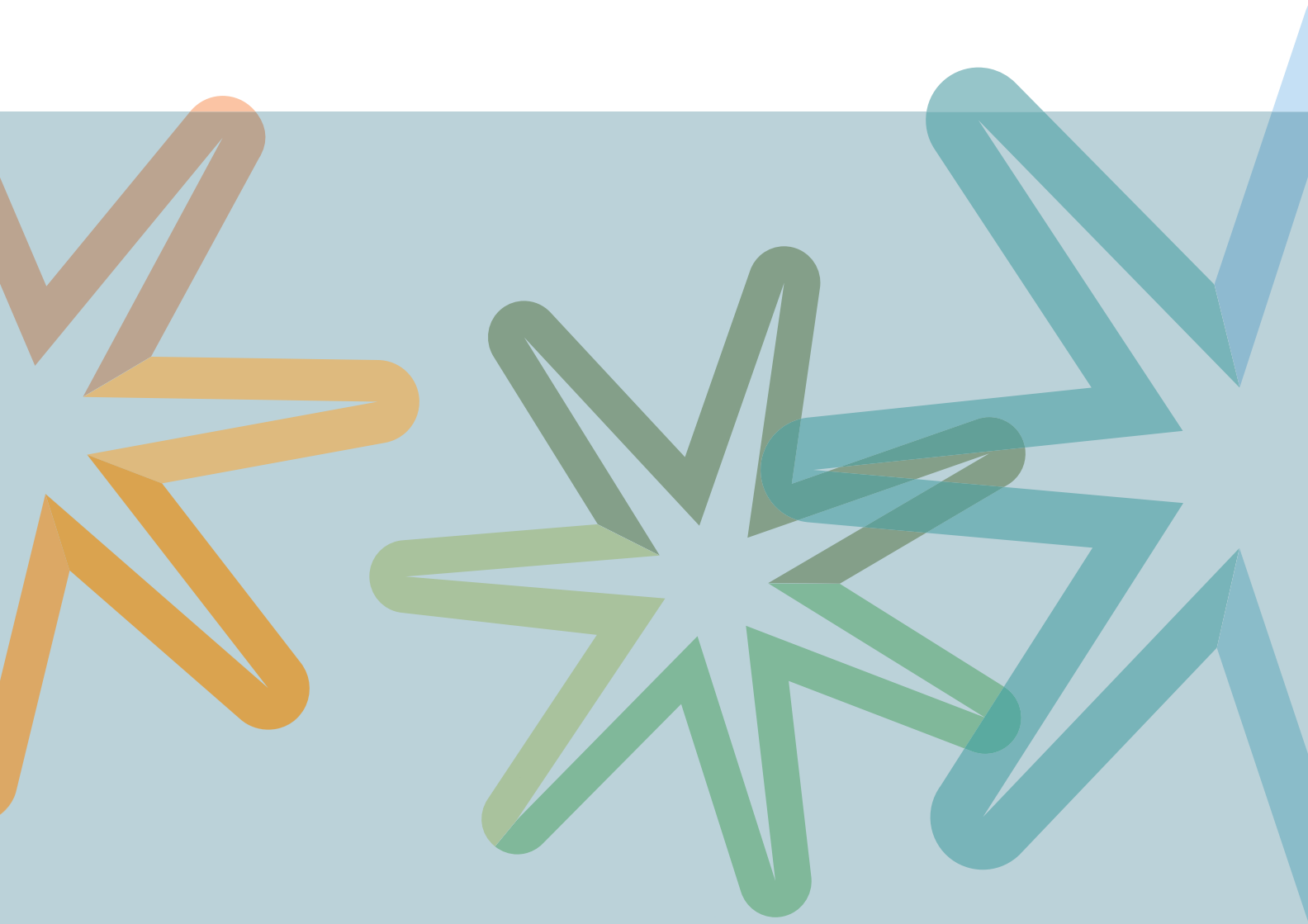

For more information about The Tullie and Rickey Families SPARK Awards for Innovations in Immunology, please reach out to:

**Kelsey Dale**
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