SPARK

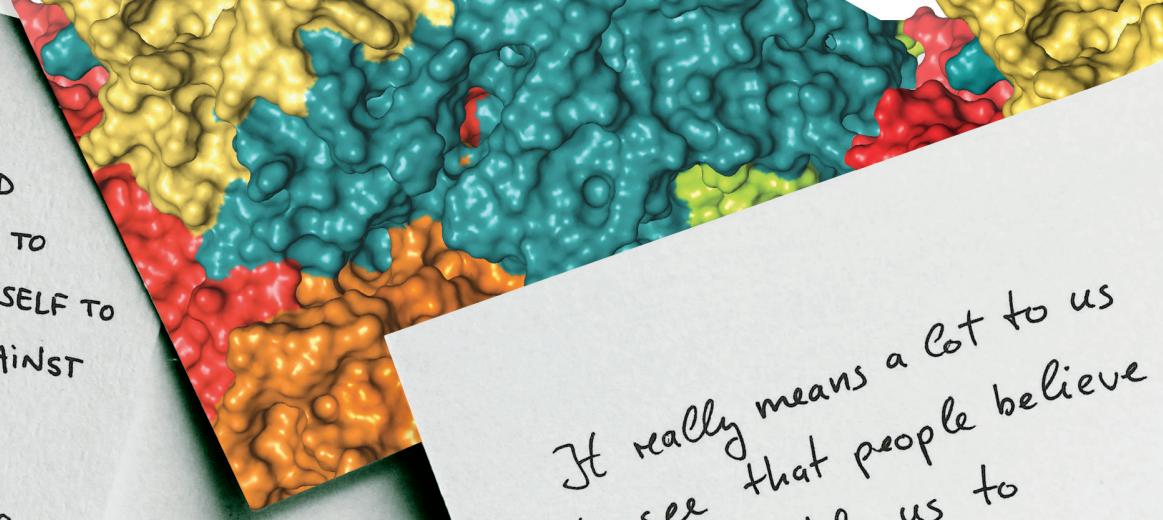
THE TULLIE AND RICKEY FAMILIES
SPARK AWARDS FOR
INNOVATIONS IN IMMUNOLOGY

2020 ANNUAL REPORT

LA JOLLA INSTITUTE FOR IMMUNOLOGY

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 LANDERAS BUENO



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

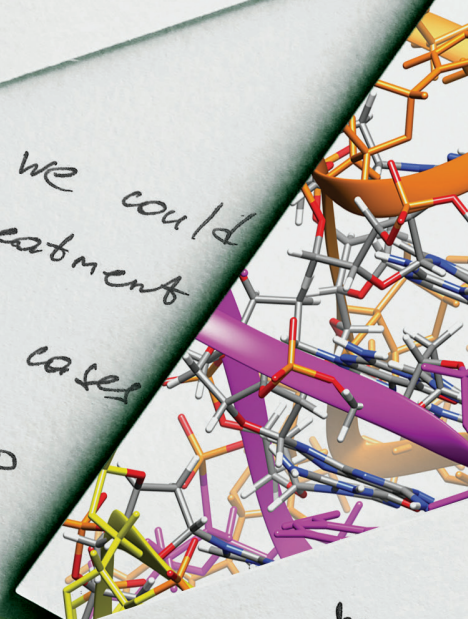
Thomas Riffelmacher

What if we could act now to prevent a future, even deadlier pandemic?

Michael Norris

What if we could improve treatment for severe cases of COVID-19 to save lives?

Artem Romanov



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

Abhijit

SPARK

THE TULLIE AND RICKEY FAMILIES
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Innovation doesn't come cheap. But 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 for bold new approaches to diagnoses, treatments, and possibly even cures for 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 to attract additional funding to further their research and career.

In addition to funding cutting-edge research that will help change how we prevent and treat disease, the Tullie and Rickey Families SPARK program also trains and advances the careers of the next generation of researchers. Finalists receive coaching in how to communicate their research to the public and how to present their ideas to funders. Award winners ultimately gain experience in running an independent research project, an important career milestone.

Each year, LJI receives dozens of proposals from its postdoctoral scientists. A review panel narrows this pool down to the finalists who then have the opportunity to pitch their ideas to the public with the hopes of securing funding to pursue their projects. Since 2017, more than 150 donors (see page 22) have generously funded 23 projects, all of which have the power to transform human health and launch the career of promising researchers. We are incredibly grateful to these donors who are empowering young investigators to take risks and fill the gaps between imagination and ground-breaking discoveries.

It is our pleasure to present the 2020 Annual Report for The Tullie and Rickey Families SPARK Awards for Innovations in Immunology. This report features the results of the 2019 Award winners, provides progress updates from our 2020 winners and offers a sneak peek of our 2021 finalists. We are also honored to share the story behind the Tullie and Rickey families' investment in the program and hope it inspires you to join them in supporting this transformative program.

"It's beyond expectations"

TOM TULLIE AND DAVE RICKEY ON SUPPORTING **SPARK**

Tom Tullie and Dave Rickey, both successful tech entrepreneurs, have a history of collaborating on new ventures. They first met in 1996 when Dave hired Tom at Applied Micro Circuits Corporation and they've been leading projects together ever since. As their careers grew, they looked for philanthropic opportunities that combined technology, entrepreneurship and a worthwhile mission.

This passion is what attracted them to La Jolla Institute for Immunology's SPARK program. The program, established by LJI in 2017, provides an opportunity for early career scientists at LJI to pitch their research ideas and win $25,000 to get the work off the ground. After serving as a reviewer forthe finalist pitches in 2018, Tom encouraged Dave to learn more about the program and consider partnering again, this time to invest in the innovative program's future. Together with their families, they made a joint commitment in 2019 that would ensure there would be funding for at least four projects for the next decade. Their hope was that by ensuring this program's longevity, other donors will be inspired to join them and help fund additional awards each year to get as many of these ideas off the ground as possible.

The program, now named The Tullie and Rickey Families SPARK Awards for Innovations in Immunology, is welcoming its fourth round of applicants this fall and Tom and Dave couldn't be prouder. Past winners have used their funding to investigate cancer genomics, explore the effects of type 1 diabetes, better address viral threats, and shed light on heart disease. Then with data in hand, many awardees have gone on to compete for larger follow-on grants, publish high-impact papers and share their research with the public. Notably several past winners are starting their own labs, where they will pursue independent research and mentor young scientists themselves (see page 16).

What will the awardees tackle next? That's what Tom and Dave are excited to see. By encouraging early career scientists to think like entrepreneurs, they've established a program where researchers have the freedom to explore new research directions. We took a moment to check in with the program's lead benefactors to hear their thoughts on the progress thus far and what's next.

"With the level that we're investing here, we want to fertilize something. With the SPARK program, our investment isn't going to be the tree, but it is going to be the first branches."

– Tom Tullie

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

Q: Do you have any major takeaways from what you've observed since becoming involved with the program?

Tom: I'm really happily impressed. I thought there would be good work, but the reality is that there's a higher level than what I was expecting. Not only have the research proposals all been good—they've been getting better. The ideas are inspiring. I'm a very cause-and-effect type guy, so I like seeing how the researchers lay out their goals and milestones. They pitch the projects, and then they see them through.

Dave: I love the concepts too. And the abstracts that I see are very relevant, very high-impact research – the applicants have picked great topics.

Q: Have the research proposals been different from what you initially expected to see?

Tom: Having seen what's presented, I'm surprised by the range of projects. For example, we've had winners taking on projects on the tech side—creating the tools of analysis instead of doing the analysis themselves. Then you've got projects on blood cancers and projects on autoimmune diseases. It's really different across the board. And I've noticed that they don't just do research in their lab specialty, but they tie in other specialties.

Q: How does it make you feel to see past Tullie and Rickey Families SPARK Awards recipients go on to start their own laboratories or publish significant research?

Dave: It's great. It's what we live for. 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.

Tom: That shows me we're on the right track. When I started out, I felt good about securing the program and getting Dave involved. Seeing how it's grown since then? It's really beyond expectations.

Q: How have you made the SPARK program a family cause?

Tom: My kids are between 18 and 22, so I've been bringing them into our foundation to make more decisions. This year, one of my kids is going to sit on the SPARK panel and listen to the pitches. I think this will make it more real for them to see the people actually asking for the money and explaining how they're going to spend it. I think it will give them a more lasting relationship with philanthropy.

Dave: My wife Brenda is a big supporter as well. She and I have both enjoyed getting more involved. Last year was our first opportunity to sit in and review the pitches and meet the finalists. And we got to celebrate with the winners and their families at the awards event, which was a nice way to connect.

Q: Going forward, what developments are you excited to see in biomedical research?

Dave: I would be interested in seeing even more SPARK projects related to autoimmune disease. This is an exciting field and it touches everything.

Tom: I'm excited to see more research into vaccines for blood cancer. It's interesting to see researchers look outside their field and come up with new strategies to treat cancer. I think that's one of the most exciting translational efforts to come out of the Institute, and it could be a game-changer.

Novel DNA blood test for early cancer diagnosis

Huy Dinh, Ph.D.

What was the goal of your SPARK project?

Doctors, patients and researchers desperately need ways to detect cancer earlier in the disease progression. One way to detect cancer may be to look for changes in neutrophils, the most abundant blood cell type. The goal of this project was to study if neutrophils and the cells they come from exhibit any special markers throughout cancer progression. To do so, we aimed to identify the molecular signatures of neutrophils in the blood of cancer patients. We hypothesized that neutrophils would change their molecular features after interacting with cancer cells, giving us a clue that the cancer was growing.

SPARK project results:

We compared protein and gene expression as well as DNA activity changes in neutrophils from healthy individuals and from patients with melanoma. Our preliminary data is promising and gives us insights into the next steps for figuring out why neutrophils are more abundant in the blood of cancer patients—and why they tend to suppress the immune system. The data plays an important part in our recent findings, published in the journal *Immunity* in August 2020, which brought us closer to determining important and cancer-related gene signatures and biological pathways in cancer patients. To the best of my knowledge, this is the first time this extent of data generation and analysis were done in the context of cancer and neutrophils in humans. I also believe that knowing how human neutrophils develop is especially relevant today because immature neutrophil levels are higher in both the blood and lungs of severe COVID-19 patients.

SPARK
IMPACT STATEMENT:

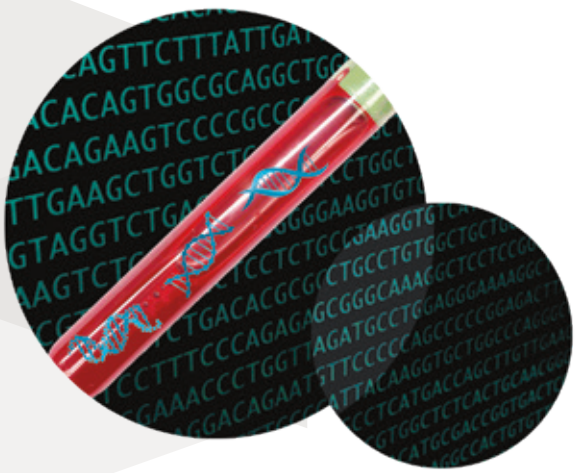
"As I interviewed for faculty positions, I was often asked about how I will differentiate myself from my postdoc mentors and succeed in leading my own lab. I found that my SPARK project came up as a perfect example of how I could lead independent research."

What's next for this project?

My next goal is to analyze these data for insights into the mechanism(s) that may control neutrophil levels and their role in promoting tumor growth. Understanding the underlying mechanism will help us design further experiments to identify if neutrophils can be new cancer drug targets or predictors of how patients will respond to cancer immunotherapy. I will also harness new technologies and insights from my neutrophil data to study whether neutrophils in cancer originate in the bone marrow—and how these cells may change when they interact with tumor cells. This will be a focus of mine in my newly established independent research lab at the University of Wisconsin-Madison. My start up package will fund these immediate next steps, and I plan to apply for a National Cancer Institute grant to secure more funding for this work in spring 2021.

What's next for Huy?

As mentioned above, in August 2020 I took a faculty position at UW-Madison where I hope to further study the roles of neutrophils as a blood biomarker for early detection of cancer. In addition, I am curious to look at the difference and similarity of neutrophils between cancer patients and COVID-19 patients to see how we can apply what we learned in cancer immunology to study this emerging disease. Currently, I am recruiting graduate students and postdocs to pursue these lines of research with me in Madison.



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The generosity of LJI Board Director Mark Bowles and Katie Bowles, Kathleen and Ira Robb, and various 2018 SPARK donors.

Immune crosstalk may improve the diagnosis of infectious diseases

Julie Burel, Ph.D.

What was the goal of your SPARK project?

There are many types of immune cells, and we're still figuring out how they work together. One interesting immune cell pairing is T cell: monocyte "doublets." For years, scientists have been seeing these conjoined cell pairs in patient samples, but many regarded doublets as an accidental artifact of the flow cytometry process, and it was common place to "dump" those conjoined cells before gathering data. We wondered—could doublets actually be a sign that the immune system is fighting off a disease? To answer this question, we needed to overcome the technological hurdles that make it difficult to detect doublets in patient samples. We also needed to isolate their genetic signatures to learn more about what they're doing in the body.

SPARK project results:

My project showed that combining several cell imaging techniques allows us to visualize, for the first time, immune cell doublets in human peripheral blood. We focused on a particular type of cell doublets, pairing one patrolling cell (myeloid lineage, monocyte) and one fighting cell (lymphocyte lineage, T cell). We looked at how common these doublets were and how they were functioning in healthy individuals, as well as, in the context of infection and vaccination. We found that doublet frequency fluctuates over time following tuberculosis treatment or Tdap vaccination. Doublet levels are also higher in patients with severe cases of dengue fever. With the publication of this research in *eLife* in June 2020, our group is now positioned as a major contributor in this completely novel field of research. At the same time, I addressed several technological challenges in the field. This work, published in the journal *Cytometry Part A* in May 2020, revealed that current single-cell technologies are not sensitive enough to reliably flag the presence of doublets within human cell suspensions such as human blood, which will "contaminate" single-cell studies and potentially lead to wrong interpretations, such as the discovery of novel immune cell types with mixed lineage features. To help address this technology gap, I identified robust data analysis and experimental strategies to help other researchers distinguish between doublets and singlets, and thus avoid data misinterpretation. Finally, I launched an experiment to use RNA sequencing to study which types of T cells and monocytes tend to be present in doublets. This work may open the door to understanding doublet biology.

SPARK
IMPACT STATEMENT:

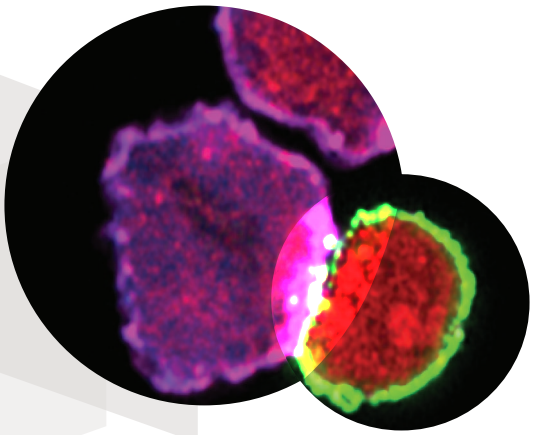
"This SPARK award was the first grant I've received as a principal investigator. It was a great introduction to research project management from designing experiments, data generation and interpretation, to budget management. It was also a fantastic opportunity to learn how to communicate my research to a non-scientific audience, and interact with our community of donors. All these skills are critical for growing as an independent scientist in academic research."

What's next for this project?

After seeing the results from the experiments funded by my SPARK award, my Principal Investigator, Bjoern Peters, Ph.D. committed some additional funding to further this study this past spring. This allowed me to perform single-cell RNA sequencing data in T cells and monocytes in doublets vs. singlets isolated from a small number of patients with active tuberculosis. My hope is that this small dataset will shed light on many outstanding questions about how doublets form, and which information they contain. Analysis of this pilot dataset showed that T cells pairing with a monocyte are enriched for antigen-specific signaling gene signatures, suggesting they might represent a critical cell population for better characterizing T cell immune responses in humans. I've used these results as preliminary data to apply for an R21 grant from the National Institutes of Health (NIH) this summer, which if I win, would provide $500,000 to continue this work over the next two years. I should hear back on my application this upcoming winter or spring. An important part of my work now is to share the existence and importance of doublets with the scientific community. Scientists need the resources and expertise to distinguish doublets from single cells. In this vein, I was invited to give an international webinar in April 2020 on the use of imaging flow cytometry to help detect doublets in "suspicious" dual-expressing cell populations.

What's next for Julie?

In January 2020, I was promoted to Instructor at LJI. In this new position, I'm aiming to gain more independence in my research by securing funding for projects I'd like to pursue, as I've had the opportunity to do so through the Tullie and Rickey Families SPARK Awards program. My hope is to return to Europe and start my own research group there in a few years, focusing on better understanding immunity to infectious diseases using systems biology approaches. A key question that fascinates me is how diverse the human population is in terms of immune responses, and how it shapes infection and vaccination outcomes globally.



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

We are what we eat... macrophages can smell this and drive heart disease

Marco Orecchioni, Ph.D.

What was the goal of your SPARK project?

One in four Americans will die from the consequences of atherosclerosis, the buildup of plaques of fat and cholesterol in the arteries. The development of atherosclerosis is strongly affected by what we eat. The bacteria in our intestine eat with us, and some of the metabolites they produce when we eat a western style diet are associated with atherosclerosis progression. Our lab has discovered hundreds of olfactory receptors expressed in specific immune cells called macrophages (big eaters) isolated from atherosclerotic aortas of mice fed with a diet similar in composition to western food. Macrophages are important immune cells because they serve as the first line of defense, protecting the body from bacteria, viruses and cancer cells. They are also the primary contributors to atherosclerosis, the cause of heart attacks and strokes. I investigated how these olfactory receptors might activate macrophages in response to diet-induced volatile compounds.

SPARK project results:

Thanks to SPARK support, I confirmed the importance of olfactory receptors, in mediating the function of macrophages in response to diet-induced volatile compounds. This finding was novel, and in fact, I've worked with LJI's Technology Development team to create an initial filing for intellectual property related to this discovery. The first screening of olfactory receptor function showed that seven olfactory receptors were able to induce inflammation. One particular receptor stood out: Olfr2, which acts as the receptor for octanal. Octanal, a diet-induced compound, can be detected in the blood of mice and humans—and can increase three times when the mice are set on a high-fat diet, similar to a typical western diet. Interestingly, we found that mice given high doses of octanal had a substantial increase in atherosclerosis plaque progression. I discovered that we could reduce inflammation and protect mice from atherosclerosis by blocking the receptor for octanal with a chemical inhibitor, or by modulating its expression with genomic editing techniques. These data give us a promising path for drug development to prevent and treat atherosclerosis-based cardiovascular diseases. This work also answered questions about the basic biology of olfactory receptors

SPARK
IMPACT STATEMENT:

"Being a Tullie and Rickey Families SPARK awardee was an amazing experience. My award gave me the freedom to test high risk ideas and we were rewarded with an important discovery that could lead to promising therapeutics for cardiovascular disease. No other program I'm aware of gives this freedom to post-doctoral researchers like myself. These awards truly have the power to boost high impact discoveries and careers."

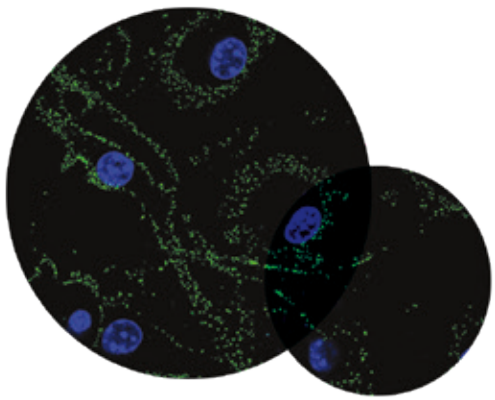
What's next for this project?

Thanks to additional funding from Kyowa Kirin Pharmaceutical Research to help us expand our screening to more receptors, I've been able to keep working on this project in 2020. I am now using new technology called Rhapsody to help retrieve important data as we interrogate hundreds of genes across tens of thousands of cells purified from the blood of healthy donors—before and after eating a western-style high fat breakfast. This approach should shed light on which Olfrs change during high-fat food consumption and how these Olfrs influence human immune cells. Going forward, I plan to use single cell technologies to connect Olfr expression with how these receptors function in cardiovascular disease progression. My aim is to figure out how Olfrs are activated and uncover pathways involved in the initiation of inflammation in atherosclerosis. I also hope to extend this study to patients with cardiovascular disease by securing additional support for this project, and am actively seeking funding for this.

What's next for Marco?

In October 2020, I applied to the NIH Pathway to Independence Award (K99) which is meant to help outstanding postdoctoral researchers transition in a timely manner to independent, tenure-track or equivalent faculty positions. In that application I was able to reference my work and experience from my SPARK project as an example of my ability to lead independent research. If successful, this grant would also help me continue my work on this project. My hope is that I will secure this K99 award or secure additional private funding to continue my research and ultimately help with my goal of transitioning to a faculty position in a couple years.

and the work in mice appears to be very relevant in humans. I discovered that the human octanal receptor, called OR6A2, functions similarly to the receptor in mice, inducing inflammation in response to octanal. Finally, some olfactory receptors, including the receptor for octanal, are expressed in certain white blood cells in humans. These cells can be incorporated in atherosclerotic plaques.



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Super-resolving cancer immunity

Sara McArdle, Ph.D.

What was the goal of your SPARK project?

Understanding how the immune system recognizes and responds to cancer is essential for developing treatments that augment our natural defenses. I aimed to develop a brand new technique that allows for single-molecule imaging of human tumor biopsies, which has never been done before. I believe that better imaging will lead to new insights into how immune cells interact with cancer cells and fuel the discovery of new therapeutic targets.

SPARK project results:

My Tullie and Rickey Families SPARK Award made it possible for me to explore a recently developed super-resolution microscopy technique called DNA-PAINT. With this technology, we are closer to developing a method for super-resolution imaging of human tissue sections. Super-resolution microscopy lets us image the interactions between cancer cells and immune cells with unprecedented detail, down to the single-molecule level. There are currently multiple techniques for super-resolution imaging but most require intricate sample preparation protocols which limits its applications. In contrast, DNA-PAINT is theoretically applicable to a wider range of samples, including tissue sections from patients' biopsies. I am adapting the existing published DNA-PAINT methods to perform multi-color imaging of clinical tissue biopsies. This will help scientists study the complex interactions between tumors and the immune system. I have also spent the last year working through the processes and pitfalls of DNA-PAINT imaging and taking on major technical challenges in image processing. By investigating these issues, I have gained far more knowledge of super-resolution imaging. I am now better prepared to help any researchers who comes to the LJI microscopy core to perform super-resolution imaging, whether through DNA-PAINT or a different technique.

SPARK
IMPACT STATEMENT:

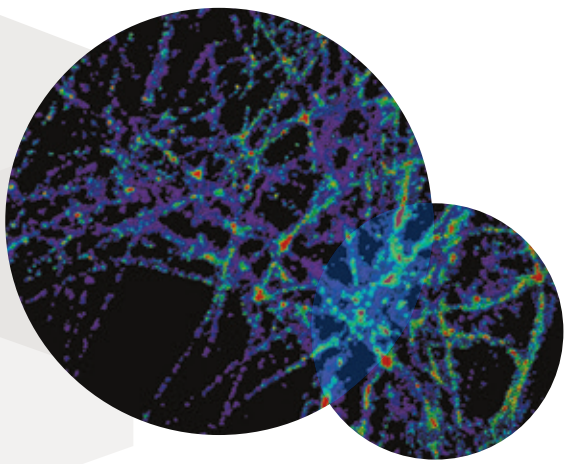
"The opportunity to take on a high-risk project was enormously valuable to my work in the microscopy core facility. We often encounter a dilemma where users would like to utilize a new method but are risk-averse about dedicating the time and resources to trying it. Because my SPARK Award gave me independent funding to explore this emerging technology, I will soon be able to help more researchers incorporate super-resolution microscopy in their projects, thereby amplifying the work of several labs at LJI focused on cancer, autoimmune diseases, and infectious diseases."

What's next for this project?

I plan to keep working towards the goal of super-resolution imaging of tissue sections to help improve cancer immunotherapy targets. The supplies, as well as most of the reagents and samples I purchased for this project, should be stable enough to last another year, so I actually have the resources I need to continue to work on this project. While COVID-19 and subsequent lab shutdowns have made predicting timelines more tricky, I hope that I will succeed in using DNA-PAINT for single molecule imaging of cultured cells within the next year. Once successful, I aim to publish my results to help advance the field of super-resolution imaging for a wider range of applications. This will also be immediately useful to ongoing research at LJI for cancer immunotherapy and other research areas. Furthermore, I used some of my SPARK funds to purchase clinical tumor biopsy samples, which are stable enough to last for years, even decades. After achieving DNA-PAINT imaging in cells and mouse tissues, I plan to use these blocks to perform super-resolution imaging on clinical samples to better understand the distribution of proteins of interest in cancerous tumors.

What's next for Sarah?

In March 2019, shortly after winning my Tullie and Rickey Families SPARK Award I also won an Imaging Scientist Award from the Chan Zuckerberg Initiative. This award provides multi-year funding for experts in core facilities who make novel or complex technologies more accessible to life scientists to help accelerate their research. This 5-year grant means I will stay at the LJI microscopy core, helping both LJI and external scientists perform microscopy studies, including super-resolution imaging through DNA-PAINT.



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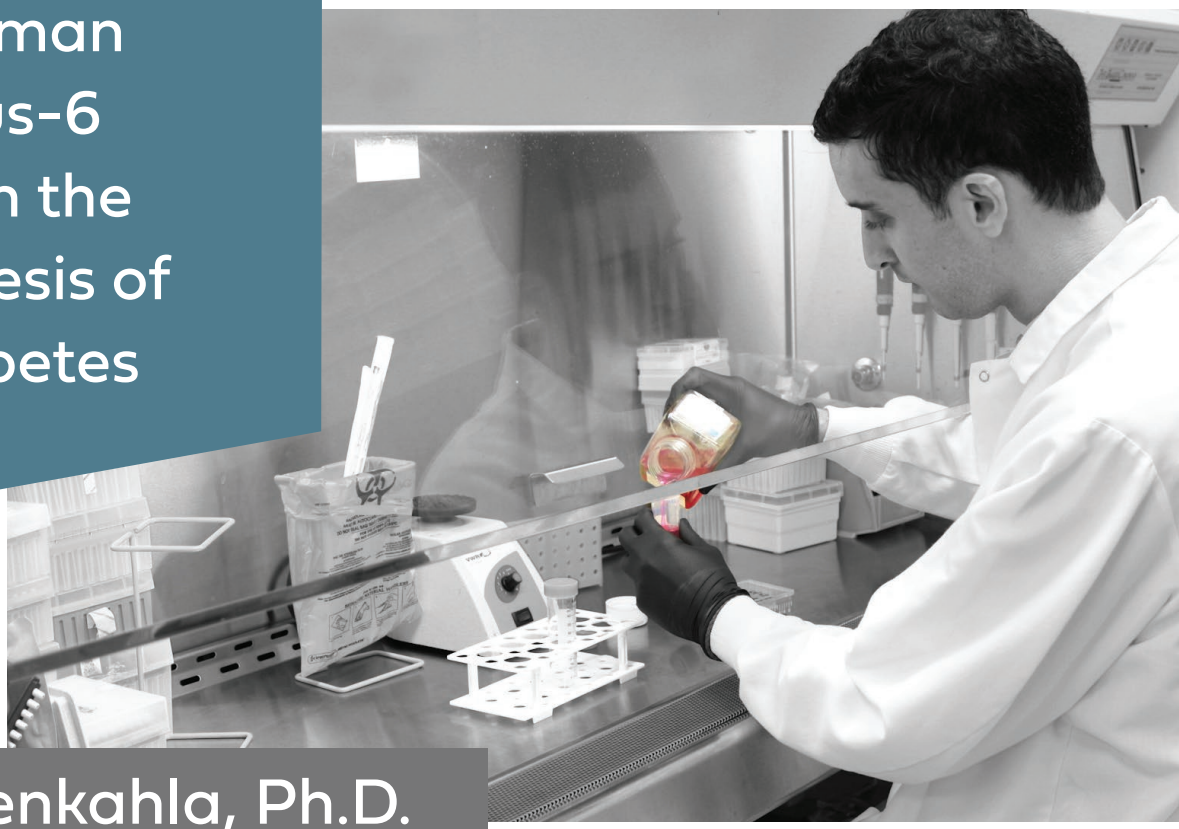
Role of human herpesvirus-6 infection in the pathogenesis of type 1 diabetes



Mehdi Benkahla, Ph.D.

What was the goal of your SPARK project?

Type 1 diabetes is an autoimmune disease where T cells destroy insulin-producing beta cells in the pancreatic islets. Scientists still don't understand the process that drives the immune system to target these cells. There are lines of evidence suggesting that both environmental factors such as viruses and genetic susceptibility play an important role in triggering the disease.

Several viruses, mainly from the enterovirus family, have been considered as potential causal agents for type 1 diabetes. However, little is known about the involvement of other viruses, such as herpesviruses. My project was focused on looking specifically at whether human herpesvirus-6 (HHV-6) could play a role in the development of type 1 diabetes.

SPARK project results:

I used high-resolution confocal microscopy to detect HHV-6 in pancreas samples from diabetic and non-diabetic organ donors. I specifically focused on the HHV-6 gB protein, a protein that plays a critical role during membrane fusion and viral entry, as a marker for the presence or absence of HHV-6 in individual pancreatic islets. Our data showed that patients with type 1 diabetes have a significantly higher level of viral gB protein in the pancreas, compared to donors without diabetes. We detected the gB protein in the islets of six out of seven type 1 diabetes donors, compared with only one out of four non-diabetic donors, and two out of five donors with auto-antibodies. We published the results of the study titled "Human herpesvirus-6 is present at higherlevels in the pancreatic tissues of donors with type 1 diabetes" in the *Journal of Autoimmunity* in November 2019. In summary, this novel research has shown that donors with type 1 diabetes are more likely to have been infected by a virus like HHV-6. This suggests a viral infection may be a potential cause of the disease through an indirect mechanism. For example, maybe pancreata of type 1 patients are in general more susceptible to infections, possibly due to alterations in cellular pathways that could make them more vulnerable to harmful viruses.

SPARK
IMPACT STATEMENT:

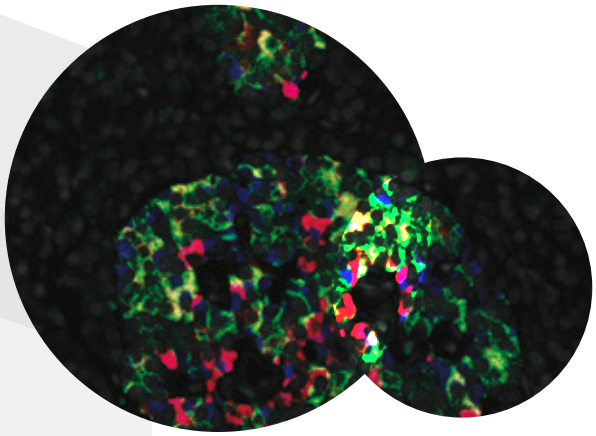
"I found great value in my participation in the Tullie and Rickey Families SPARK Awards program. It gave me a lot of first experiences like being able to talk to the public and private donors, having to pitch my idea in person, and being in charge of my own research grant. I hope to be able to build on this experience and my project as I seek supplemental funding to continue my work."

What's next for this project?

When studying the pancreatic sections and viral infections we faced many challenges since the organ was fixed. Upon completing my project, I submitted an application to the Network for Pancreatic Organ Donors with Diabetes (nPOD) with the hope of getting access to precious samples from patients. Our application was successful and in 2020 we were granted live human pancreatic slices to study viral infections. My next step is to secure additional grant dollars to continue this study using these rare samples. In that vein, I re-applied to the Tullie and Rickey Families SPARK Awards program this fall with the hopes of securing supplemental funding for this project. I'm honored to have been selected as a 2021 finalist, and to be the first Tullie and Rickey Families SPARK Awards alumnus to pitch for follow-on funding for my project. My hope is that if I'm successful in winning this award I will be able to tackle new research areas using this newly developed model of human pancreatic slices. I anticipate that with this additional preliminary data, we'll be able to apply for NIH funding to take this project further and help unravel the mystery of beta cell death in type 1 diabetes.

What's next for Mehdi?

In addition to competing for another Tullie and Rickey SPARK Award, I plan to apply for a postdoctoral fellowship to support my research while at LJI. This will help further my career and fund my current research projects with the hope of ultimately publishing my findings and advancing the type 1 diabetes field. Long term, I'd like to stay in the U.S. to continue studying type 1 diabetes whether in academia or industry.



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The generosity of Robert and Rachel Perlmutter and various 2018 SPARK donors.

SPARK Stars

are leading critical research across the globe.

Huy Dinh, Ph.D.
'19 SPARK winner

University of Wisconsin - Madison
Madison, WI

"Using data that was generated by my SPARK project, we recently published groundbreaking research on a rare but vital stem cell connected to tumor growth. These findings are a step toward developing rapid, blood-based diagnostic tests for cancer, and building on this research will be the focus of my new lab I've established at the The University of Wisconsin–Madison."

Daniela Weiskopf, Ph.D.
'18 SPARK winner

La Jolla Institute for Immunology
San Diego, CA

"In 2020 I've had to quickly shift gears from focusing on dengue to COVID-19. Our lab (Sette Lab) is at the forefront of understanding T-cell response to SARS-CoV-2, and most recently I've been awarded $1.4M from the National Cancer Institute to Study COVID-19 in Latino Americans, a population hit especially hard by the pandemic, in collaboration with the University of Puerto Rico."

Melanie McCauley, M.D.
'18 SPARK winner

The Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF)
Bethesda, MD

"At HJF I'm a civilian contractor for the Walter Reed Army Institute for Research. While I work on several Flavivirus projects, my main focus this year has been COVID-19. We have a COVID-19 vaccine candidate currently headed towards clinical trials and are also doing epidemiology studies among military recruits."

Cecilia Lindestam Arlehamn, Ph.D.
'20 SPARK winner

La Jolla Institute for Immunology
San Diego, CA

"While studying mycobacteria, the subject of my SPARK award, remains a focus of mine, we've just secured a $3.5 million award from Aligning Science Across Parkinson's (ASAP) to support a three-year study into how immune cells may contribute to Parkinson's disease. Recent studies from our lab (Sette lab) have shown that the immune system's T cells contribute to the onset of Parkinson's disease. This new funding will allow us to expand on this research by investigating T cells in people at risk of Parkinson's disease. I'll be spearheading this project in collaboration with Columbia University, California Institute of Technology and University of Alabama-Birmingham."

Rana Herro, Ph.D.
'18 SPARK winner

Cincinnati College of Medicine/Cincinnati Children's Hospital Medical Center
Cincinnati, OH

"My focus at Cincinnati Children's is developing effective therapeutics and novel prognostic biomarkers for fibrotic diseases. I'm particularly interested in tumor necrosis factor (TNF) superfamily members and their involvement in inflammation and fibrosis."

Holger Winkles, Ph.D.

'18 SPARK winner

University of Cologne Hospital, Cologne, Germany

"At the Heart Center of the University of Cologne Hospital I'm continuing my focus on the immune mechanisms of atherosclerosis and the potential for a vaccine-based therapy. Specifically I'm examining T cells with a special focus on children with an increased risk of heart disease, which should help to find the right time for a potential vaccination."

In addition to providing seed funding for innovative ideas, the Tullie and Rickey Families SPARK Awards program also aims to train and support the most promising early-career scientists so that they are equipped and encouraged to stay dedicated to medical research. We are excited to share some of the successes of our SPARK winners, who are demonstrating that donor investment in SPARK is helping to ignite discoveries *and* fuel the next generation or researchers.

Dan Giles, Ph.D. | '19 SPARK winner

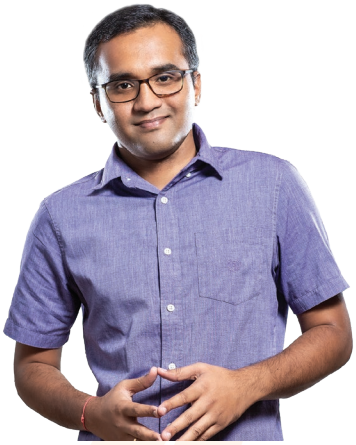
In the fall of 2019, Dan Giles, Ph.D. (2019 Tullie and Rickey Families SPARK awardee) was offered an opportunity to take a position as a scientist at Janssen Pharmaceutical Companies of Johnson & Johnson in San Diego working on the discovery of new therapies for inflammatory bowel disease (IBD) patients. Unfortunately, this meant that he was unable to complete his SPARK project which was focused on using artificial intelligence to better predict how IBD patients may respond to specific treatment options. While he wasn't able to complete his project, Dan still found great value in participating in the program. "Competing for a SPARK award gave me the chance to develop a high-risk and potentially high-reward project that would directly impact the quality of care patients receive," shares Dan. "This opportunity to work on a patient-focused project helped me to make a career transition into a scientist role at Janssen where I get to work on patient-focused projects everyday." Per the program guidelines, Dan's unused award funds were put back into the Tullie and Rickey Families SPARK Awards fund pool and were used to help fund an award in 2020.

Like all of us, the Tullie and Rickey Families SPARK Award winners of 2020 were faced with some unprecedented challenges caused by the COVID-19 pandemic this year. Just as they began their projects, many were not allowed into the Institute in an effort to protect the safety of Institute employees critically focused on SARS-CoV-2 research. And several projects that involved collaborations had to be modified or delayed. However, we are pleased to report that progress has resumed and these promising projects are moving forward. Here are the six-month progress reports for the 2020 Tullie and Rickey Families SPARK awardees:

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

EXPLORING TOXIC EFFECTS OF T1D PATIENT'S SERUM IN PANCREATIC BETA CELLS

I'm investigating the impact of serum of type 1 diabetes (T1D) patients on pancreatic beta cell function and survival. Using islets obtained through our collaboration with City of Hope hospital, I've begun determining the islet function through the glucose-stimulated insulin secretion test (GSIS). SPARK funds allowed me to purchase, and also upgrade the GSIS system with help from City of Hope, making it dynamic and more precise. The GSIS allows us to measure the response of the islets to different concentrations of glucose and other stimuli in real time, so we can measure variations in the islet insulin secretion by the minute. These variations tell us how functional the beta cells are at producing insulin and we can determine if they are unhealthy. Thus far, I've tested and identified some of the key antibodies for the project, including testing several antibodies to analyze beta cell death under different conditions. I've also calibrated the system to measure late cell death using the TUNEL staining. The high quality of this staining allows a precise quantification of the cells that are undergoing late cell death. My next steps are to identify early cell death markers, quantify the cytokines and other molecules in the human serum and further optimize the process of exposing the islets to human serum. Completing these steps will help determine if autoantibodies and sera from T1D patients have a direct deleterious effect on insulin-producing beta cells, which could help us understand T1D pathogenesis and completely re-write how we treat T1D patients.



Abhijit Chakraborty, Ph.D.

SOLVING THE PUZZLE OF A SHATTERED CHROMOSOME

My project investigates chromothripsis events in cancer. Chromothripsis is a complex genomic rearrangement defined as the shattering and reconfiguration of a chromosome, and is associated with worse clinical outcomes in cancer patients. This project aims to highlight the epigenetic impact of such events on cancer and improve prognoses for patients. Since receiving funding, I've been establishing collaborations and working on high-risk patient sample collections. We have established a collaboration with an oncologist at Rady Children's Hospital, San Diego, to study patients suffering from pediatric Acute Lymphoblastic Leukemia (ALL) involving amplification of chromosome 21 (iAMP21). We've recently received clearance from the Children's Oncology Group biospecimen bank to receive more iAMP21 and non-iAMP21 samples for this project. We are also in the process of selecting lung cancer biopsy samples from our colleague, Dr. Vijayanand Pandurangan's lab, to identify chromothripsis events. In parallel, we've purchased a breast and colon cancer cell line that has confirmed chromothripsis events and plan to use those to validate the novel computational algorithm we've developed to help advance this field. Once validated, we can confidently use our algorithm to analyze the patient samples, with the hope of finding new clues to molecular mechanisms underlying the aggressiveness of these cancers.

Katia Faliti, Ph.D.

SAFETY AND EFFICACY OF VACCINATIONS IN IMMUNOCOMPROMISED CHILDREN

My project faced challenges due to the COVID-19 restrictions and closures of medical centers where children are normally recruited and receive vaccinations, but we've made progress this summer. We received samples from Rady Children's Hospital from patients with confirmed or suspected cases of Common Variable Immune Deficiency (CVID) that received their pneumococcal or Tdap vaccines. From these samples we saw that in some patients the level of pertussis antibodies and B cells are reduced, which supports our hypothesis that immunodeficient children have less effective immune responses to vaccines. We also analyzed these samples for immune cell phenotype and are planning additional studies once more donor samples are collected to help determine if a particular type of cell is causing the deficient response. The second cohort for this project, composed of children affected by pediatric lupus, will be recruited soon and similar analyses will be performed. Also my lab recently purchased a powerful machine, called the Cytek Aurora, which analyzes up to 40 immunological related molecules and performs sophisticated immune cells phenotyping. This will greatly benefit my efforts to define the quality and quantity of the immune cells of these children, as this machine is incredibly precise even with our limited access to patient samples.

Greet Verstichel, M.D, Ph.D.

FROM MOUSE TO MAN, TOWARDS A CURE FOR AUTOIMMUNE DISEASES

I'm studying the disturbed development of T cells in autoimmune disease using human samples. In partnership with Rady Children's Hospital, I received thymus samples from patients undergoing heart surgery in which the surgeon needs to remove some of the thymus tissue. This was previously discarded but now with our collaboration and patient consent it can be used for research. So far I've processed and tested the viability of the samples when stored in liquid nitrogen, and also extracted stem cells from the total thymus pool that will be used for the cultures. For the second arm of the study, I've validated the growth of the bone marrow cell line that supports the development of human T cells and verified that the cell line expresses required ligands for the T cells to properly mature. Next I'll set up the organoids by mixing the stem cells and bone marrow cells and assess their ability to mature to functional T cells. I'll also experiment with interfering with the metabolism of the cells at certain stages of their development to see if that changes the ultimate profile and potential of the T cells. In particular, I'm testing if it predisposes the cells to recognize and attack self-antigens, which is what happens in autoimmune disease.

Cecilia Lindestam Arlehamn, Ph.D.

THE FIGHT AGAINST MYCOBACTERIA

To understand the immune response involved against infection with *M. avium* (MAC) and reveal differences between tuberculosis and MAC disease I have started an in-depth study of responses in individuals that were previously infected with MAC along uninfected controls. This includes determining the frequencies of major cell subsets in blood, measuring the immune response that is specific for mycobacteria and identifying the immune signatures that are triggered by the infection. Interestingly, I've found that MAC infected individuals have very low frequencies of a particular T cell subset as compared to uninfected controls. I've previously described this cell subset as being involved in immunity against mycobacteria and playing an important role in controlling the infection. The cell subset composition is also reflected in the specific gene signatures that I've observed when comparing the different patient cohorts. Lack of this specific T cell can help explain the differences in immune response between the cohorts. Currently, I am trying to find gene signatures that are specific for each cohort and stimulation. This will allow me to determine whether I can find immune markers and responses that further explain the differences between the cohorts and could lead to improved diagnosis.

Alex Marki, M.D.

ELONGATED NEUTROPHIL-DERIVED STRUCTURES (ENDS) IN SEPSIS

Prior to winning my SPARK Award, I discovered a new type of micro-particle, so called elongated neutrophil-derived structures (ENDS), which are significantly elevated in the blood of septic patients. The goal of my project is to collect blood samples from septic patients during their hospital stay that we can analyze to generate sufficient data to validate the predictive value of ENDS for sepsis. My hope is that this will help improve diagnosis and clinical outcomes for septic patients. My project was significantly impacted by the pandemic, as we experienced delays in getting approval to collect blood samples from UC San Diego's Human Research Protections Program and my clinical collaborator at UC San Diego Hillcrest ICU was overloaded with treating COVID-19 patients for much of this year. We are actively working through that approval process and hope to begin collecting patient samples soon so we can execute this project. We've also received an extension for this project from LJI to be able to complete this project by spring 2021. In the meantime, with funding from the laboratory of Klaus Lay, I've conducted additional preliminary experiments with mice which further corroborated our hypothesis for this project. I am eager to proceed with these experiments using human samples so that I can fulfill my project goal of identifying a better diagnostic option for sepsis.

Sara Laneras Bueno, Ph.D.

COMBATING EMERGING EBOLA VIRUS THREATS WITH AFFORDABLE CURES

The Ebola viruses cause hemorrhagic fever with up to 90% lethality and limited FDA-approved treatments against these viruses are available. High-resolution structures of key proteins involved in Ebola virus replication can accelerate identification and characterization of effective drugs to treat Ebola virus infections. The Ebola virus polymerase governs replication of viral genetic material and is a prime target for therapeutic interventions. I aim to generate the first near-atomic resolution structure of the Ebola virus polymerase to reveal conserved and essential atomic features that will guide design and improvement of antiviral drugs against Ebola virus. To produce this structure, I first explored techniques to stabilize this dynamic polymerase to facilitate imaging studies. I applied these techniques to express full-length polymerases of key pathogenic Ebola virus species (Zaire, Sudan, Reston, Mengla) and the related Marburg virus. The polymerase expression levels of the various ebolavirus polymerases differed significantly among virus strains. I identified the virus strain that expresses the most stable polymerase complex, which I am now successfully purifying on a larger scale to use in structural analyses with our state-of-the-art Titan Krios microscope at LJI. From these analyses, I will visualize structural details and vulnerabilities of Ebola virus polymerase.

Thomas Riffelmacher, Ph.D.

A NEW CELLULAR TARGET TO PREVENT TISSUE DAMAGE FOLLOWING HEART ATTACK

My proposed project relies on access to clinical samples from patients that experienced a hypoxic inflammatory disease, like atherosclerosis. I had a planned collaboration with a colleague at Oxford University to collect patient samples, however, due to the pandemic, this collaboration was no longer a viable option. In response, I shifted focus to sickle cell disease, because I have better access to patient samples, and it still allows us to answer essentially the same question: Does lack of oxygen in the blood vessel cause the activation of natural killer T (NKT) cells? Like in atherosclerosis, lack of oxygen may be causing the NKT cell activation in the sickle cell patients. Thus far, I've set up a collaboration with the University of Wisconsin to get these patients' blood samples. We've already received the first of these samples and I'm working with the flow cytometry core to characterize the patient NKT cells. Concurrently, we are awaiting IRB approval to recruit healthy blood donors to use as appropriate controls for sickle cell patients. While we wait, I've also set up an animal model of this disease which we can analyze in parallel to complement our findings. Once all samples are received, the analysis strategy remains the same: purify NKT cells from healthy patient samples and conduct single-cell sequencing to test if we find evidence for a contribution to inflammation by NKT cells. This will help us to understand how much NKT cells contribute to underlying mechanisms of inflammation.

What inspires me the most is the whole idea that my work can benefit other people and change lives. – Vipul

Vipul Shukla, Ph.D.

CRACKING THE FOLDED CODE IN OUR DNA

My SPARK project goal is to decipher the biological functions of unusual DNA structures known as G-folds. Addressing our intent to devise novel methods for efficient G-fold detection, we've developed G-fold specific agents that we're now testing in DNA sequencing applications to precisely map them across the entire genome. Using unbiased genome-wide approaches, I'm investigating the link between G-folds and accumulation of genomic instability, which is a common hallmark associated with development of many cancers. I've performed experiments geared towards exploring this relationship and we're now analyzing these datasets to identify correlations and draw specific conclusions. In parallel, to understand how information encoded in G-folds is relayed in cellular systems, I've performed a mass-spectrometry screen to identify specific G-fold recognizing proteins. Since proteins are the key functional units in cells, using this experimental approach, I've identified several novel G-fold interacting proteins as a step towards elucidating the biological functions of these enigmatic DNA structures. I'm now functionally validating and assessing the biological significance of the interactions between G-folds and the candidate proteins. Notably, many of these candidate proteins are known to be essential for regulating the functional landscape in the genome. Together, these studies endorse the notion that G-folds represent a critical code in the DNA that is often deregulated in cancers.

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*Deceased

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 2021. You can read more about their projects on our website at **lji.org/spark**. By renewing your support for the Tullie and Rickey Families SPARK Awards program you can help bring these potential transformative discoveries to light.

PREVIEW OF THE 2021 FINALISTS

Mehdi Benkahla, Ph.D.

'19 SPARK winner

Can a virus trigger type 1 diabetes?

Simon Brunel, Ph.D.

What if we had one therapy that could cure all autoimmune diseases?

Annie Elong Ngono, Ph.D.

How does prior exposure to closely-related viruses impact disease severity when subsequently infected by a related virus?

Michael Norris, Ph.D.

What if we could act now to prevent a future, even deadlier pandemic?

Artem Romanov, Ph.D.

Why are certain populations prone to developing severe cases of COVID-19?

Payel Roy, Ph.D.

What if we could screen for heart disease earlier and improve patient outcomes?

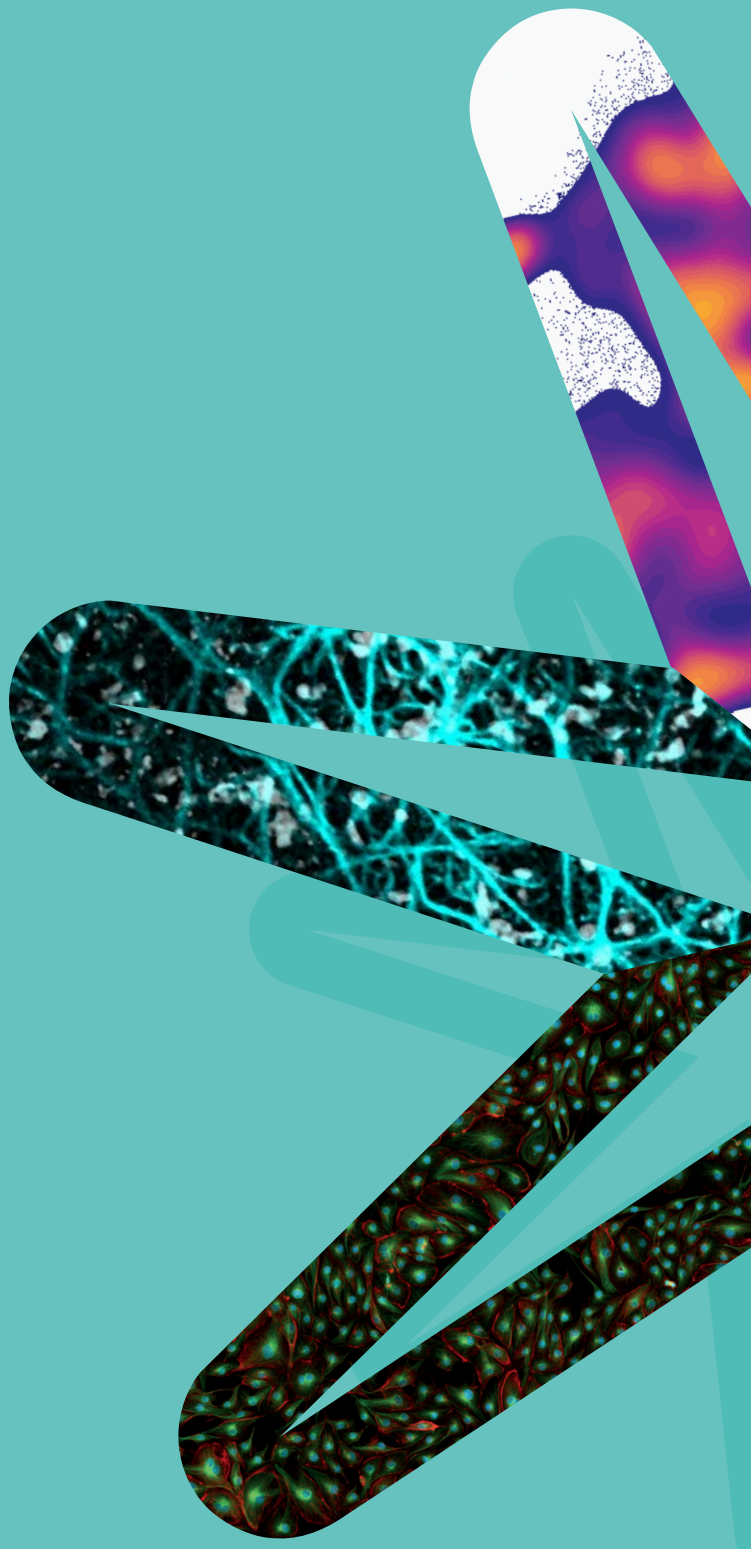
Nicolas Thiault, Ph.D.

What if there is a new immune cell that could be engineered to safely kill tumor cells and cure cancer?

Hui Zhi, Ph.D.

Can we harness the hidden powers of our own tissue-resident immune cells to quickly kill viruses and fight cancer?

We'd like to thank the 2021 Tullie and Rickey Families SPARK Awards application reviewers who helped identify these finalists from our pool of applicants: Ferhat Ay, Ph.D. (Assistant Professor, LJI), Gina Kirchweger, Ph.D. (Chief Communications Officer, LJI), Christopher Lee, MBA (Chief Advancement Officer, LJI), Margaret Ng Thow Hing, J.D. (Senior Director, Technology Development, LJI), Dave Rickey (Donor and Board Director, LJI), Ingrid Stuiver, Ph.D. (Senior Director, Translational Research), Tom Tullie (Donor and Board Director, LJI), and Stephen S. Wilson (EVP & Chief Operating Officer, LJI).



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Kelsey Dale
Deputy Director of Advancement
La Jolla Institute for Immunology

kdale@lji.org or 858-752-6542

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