message from the dean

We are in the midst of an enormous transformation in medicine and health care. The confluence of digital health technology, genomics, metabolomics, cell-free DNA detection, and much more is transforming the knowledge we have about the determinants of health and disease. We have within our grasp the opportunity to completely transform our approach to health by preventing diseases before they strike and curing them decisively if they do. This is the promise of Precision Health, an approach that is predictive, preventive, and proactive.

But there is too often a gap between discovery and delivery that can slow our progress towards this vision. Even when breakthrough science occurs at the bench, it doesn’t always translate to the bedside. That’s why the Stanford SPARK Program has been so transformative over the past decade to close this gap and make a seamless, fruitful relationship between basic science and clinical care possible. SPARK enables a cadence of discovery, clinical application, and iteration that our era of rapid technological progress and growing health care complexity requires. I am so proud of what the SPARK program has accomplished in the past decade, and I’m even more excited for the discoveries it will produce and the lives it will impact over the decades to come.

Lloyd B. Minor, MD
Carl and Elizabeth Naumann Dean
Stanford University School of Medicine
Professor of Otolaryngology / Head & Neck Surgery
Professor of Bioengineering and of Neurobiology, by courtesy
introduction

The Stanford SPARK program was established ten years ago, with the goal of advancing new biomedical research discoveries into promising new treatments for patients. Since its founding, SPARK has advanced scores of new diagnostics and drugs to the clinic and commercial sectors and educated hundreds of faculty, postdoctoral fellows, and students on the translational process. The majority of the SPARK projects address the neglected areas of child and maternal health, global health, and orphan diseases.

The booklet that you are holding provides a very brief summary of many of our projects from the past 10 years. The projects are color-coded to indicate the clinical indications (e.g., pink for child health and blue for cardiovascular disease; some projects fit more than one category). To help you find the SPARK scholars that are working in a particular area of interest, their name tags have the same color code. The SPARK scholars will be here the whole day—to meet with you and share their stories.

Before you start leafing through these projects, we must express our immense gratitude to the many people who made SPARK a success.

At the School of Medicine, we thank former Dean Philip Pizzo for his vision in allowing us to begin this endeavor and Dean Lloyd Minor for his tireless support of the Program. We also thank Marcia Cohen, Senior Associate Dean of Finance, who has been instrumental in the development of SPARK’s financial infrastructure and her advocacy for the program. In addition to the reliable funding of the program from the Dean’s office, we owe a big debt of gratitude to the Child Health Research Institute and the Lucile Packard Children’s Hospital for their generous support. Special thanks to LPCH CEO, Chris Dawes and his staff; former chair of the Department of Pediatrics, Dr. Hugh O’Brodovich; and Bonnie Whalen, Administrative Director of CHRI. We also thank Dr. Harry Greenberg, the Senior Associate Dean of Research and the PI of Stanford’s NIH CTSA grant; Dr. Rob Jackler, the Chair of the department of ENT; Dr. Michele Barry, the Senior Associate Dean for Global Health; the Weston Havens Foundation; and the Steve Sullivan Memorial Fund. SPARK would not be possible without your generous support.

We are very grateful to the SPARK faculty, postdoctoral fellows, and students (also known as SPARKees), who trusted us with their
inventions and believed in us to guide them through the next steps of translation. And to our department, Chemical and Systems Biology, that houses the program and supports us in our activities.

Over the years, SPARK has had talented staff members, including our past administrators, Shannon Shankle and Michelle Pualuan; the financial analysts, Adeline Shrewsbury, Xue Ma, and Dorey Clayton; past SPARK team members, Emily Egeler and Kanad Das; and the current team, Nancy Federspiel, Sun Young Kim, Mahima Agochiya and Kathy Johnson. We are also grateful to Dr. Juan Jaen who provided crucial support to Daria in laying the groundwork to establish SPARK.

But without a doubt—our biggest gratitude goes to our SPARK Advisors, who volunteer their time to help us fulfill the potential of Stanford’s inventions and help advance them to benefit patients and society. We are endowed with over 100 tenacious, experienced and highly talented industry executives and advisors, who regularly attend our SPARK meetings, some for ten years! They provide advice and share their wisdom with our SPARK teams, and they do it without any financial compensation, all the while keeping the discussion confidential. You can identify the advisors by the gold name tag—they are our treasures and that is why we do not provide their names. Thank you SPARK advisors—we owe it all to you!

We hope that you will enjoy the booklet and the event,

Daria Mochly-Rosen, PhD
founder and co-director / SPARK Translational Research Program
The George D Smith Professor in Translational Medicine
Professor, Chemical and Systems Biology

Kevin Grimes, MD, MBA
co-director / SPARK Translational Research Program
Associate Professor, Chemical and Systems Biology
about SPARK

what is SPARK?
SPARK is a unique partnership between the university and industry. Our purpose is to provide the education and mentorship necessary to advance research discoveries from the bench to the bedside. SPARK provides access to specialized knowledge and technical expertise regarding drug and diagnostic development, dedicated core laboratory facilities, and sources of funding to support translational efforts.

why SPARK?
Bridging the gap between bench and bedside is a challenging endeavor. There is an inherent risk that early-stage programs will fail during development, no matter how promising is the science. Such nascent programs are unlikely to attract interest from industry until they have reached significant milestones, and very little funding is available from the NIH, foundations, or private enterprise for this critical transition.

Chemical and Systems Biology Professor Daria Mochly-Rosen founded the SPARK program in 2006 to provide a cost-effective model to generate proof of concept using industry standards. Building upon Stanford’s tradition of technological innovation and entrepreneurship, SPARK emphasizes new ways of thinking about bridging the gap between bench and bedside.

how SPARK works
SPARK at Stanford includes graduate level courses about the drug development process as well as a program for “SPARK Scholars”, which provides funding for product development and mentoring for participants. Mentoring is provided by advisors with expertise in product development, clinical care, and business, preparing participants for careers that link fundamental research to important new therapies. Proposals are reviewed annually by an expert panel of faculty and industry advisors. The panel reviews new, unlicensed disclosures made to the University Office of Technology Licensing as well as proposals submitted from across the university. SPARK Scholars (aka “SPARKees”) are funded for an average of two years and participate in weekly seminars with industry and academic experts.

who participates?
SPARK at Stanford is open to professors, clinicians, postdoctoral scholars, and graduate students. Our industry partners, who have all signed a confidentiality agreement, play a vital role in the program through their mentorship and advising. We invite you to learn more about how industry contributes to SPARK at Stanford. Other academic institutions have successfully replicated the Stanford SPARK model and we are committed to supporting their work.
SPARKing everywhere

Strength in numbers: SPARK programs have been established or are under development in a dozen academic institutions throughout the world, increasing the likelihood that new treatments will be developed from research across the globe. With SPARK Global, we also created a network of like-minded scientists in academia that can be recruited quickly to address global health challenges when they arise.
SPARK by indications

SPARK projects are developed for any clinical area where there are patients in need, regardless of financial return.

Focal areas (118 total projects)

- Oncology (cancer)
- Infectious disease
- Neuropsychiatry
- Other
- Metabolic disease
- Immunology
- Cardiovascular
- Hematology
- Gastroenterology
- Dermatology
- Otolaryngology
- Platform
- Pulmonary
In keeping with Stanford’s not-for-profit mission, many of SPARK’s projects focus on areas that are not prioritized by the commercial biopharmaceutical industry, including child and maternal health, global health, and very rare orphan diseases.

65% child/maternal health, orphan diseases, global health

35% other areas

65% out of 113 projects

73 out of 113 projects

14 for child/maternal health

19 for orphan diseases

16 for global health

9 at the intersection of child/maternal health and global health

2 at the intersection of orphan diseases and global health

1 at the intersection of child/maternal health and orphan diseases
developing a SPARK program

The SPARK model for translational research has proven to be a successful model which can be replicated at other academic institutions as a cost-effective way to facilitate development of research discoveries into novel therapeutics or diagnostics.

A number of academic institutions have successfully developed their own SPARK programs based upon the SPARK at Stanford model. SPARK at Stanford actively supports our US and international partners in the development of their programs with visits, guest lectures, and more.

SPARK co-directors Daria Mochly-Rosen and Kevin Grimes have published a book, SPARK: A Practical Guide to Drug Development in Academia, to help other academic institutions develop their own SPARK Programs.

key requirements for SPARK success

- Strong foundation in basic and clinical research
- Local resource of highly-skilled industry advisors
- Seed money to fund drug development projects

other critical components

- Multiple voices—don’t rely on a single expert
- On campus—bring industry experts and academics together in a single room
- Open exchange—with no hierarchy
- Ongoing—so that learning accumulates and response to challenges is immediate
- Sharing failure—so that others will learn and avoid it

outcomes (74 graduated projects)

- commercial / in clinic (21)
- commercial / not in clinic (15)
- in clinic / not commercial (10)
- other / failed POC or unlicensed (28)
Projects are color-coded to indicate the clinical indications (e.g., amber for infectious diseases and blue for cardiovascular disease). The majority of projects address the neglected areas of child and maternal health, global health, and orphan diseases, also color-coded.
PROJECT

DRUG TO INDUCE BETA CELL REGENERATION FOR TREATMENT OF TYPE 2 DIABETES

Our goal is to develop a first-in-class regenerative therapy for diabetes that works by expanding the number of insulin secreting cells (beta cells) of affected individuals. Using high-content small molecule screening, we identified “hit” compounds that promote human beta-cell proliferation. Through SPARK support, we performed structure-activity relationship studies to optimize our lead compound. This effort uncovered a new lead compound with 1000-fold greater potency. For the first time, we have in hand a molecule that is amenable for further development, which we are pursuing.

We are grateful for SPARK’s translational vision, early and continued support of this project, and strategic guidance.

Justin Annes, MD, PhD
ASSISTANT PROFESSOR OF MEDICINE (ENDOCRINOLOGY)

A major research goal of Dr. Annes’ team is to uncover therapeutic strategies to stymie the ensuing diabetes epidemic. The team has developed a variety of innovative experimental approaches to uncover novel ways of curing diabetes.
PROJECT

GENE CORRECTED AUTOLOGOUS HEMATOPOIETIC STEM CELLS FOR THE TREATMENT OF IPEX SYNDROME

IPEX (Immune dysregulation Polyendocrinopathy Enteropathy-X linked) Syndrome is an often fatal genetic autoimmune disease due to mutations of FOXP3, a transcription factor which is highly regulated and preferentially expressed in a small subset of T cells, named T regulatory cells. SPARK supported the use of an advanced technology we have available at Stanford (CRISPR/Cas9 genome editing), to precisely correct and replace the mutated FOXP3 gene in its physiological genomic site. This could be performed in the hematopoietic stem cells of the IPEX patients and be curative. We are now testing the feasibility of the approach in vitro and in vivo, in a humanized-mice model of the disease, to demonstrate that the gene-edited cells will reconstitute a “normal” immune system. Results from this work will constitute the preclinical studies required for a gene therapy clinical trial to cure IPEX patients.

Rosa Bacchetta, MD
ASSOCIATE PROFESSOR (RESEARCH) OF PEDIATRICS (STEM CELL TRANSPLANTATION)

The main goal of the lab is to challenge the limits of “inexplicable” and “untreatable” diseases, to elucidate the mechanisms of impaired cellular immune function underlying the clinical manifestations and to develop curative treatments. The group implements robust functional studies to understand consequences of gene mutations in single case/family first, validate the molecular and cellular defects in other patients with similar phenotypes, and develop complementary cellular and gene therapy strategies.

SPARK value

SPARK gave me the possibility to examine the importance of working on advanced gene-based therapeutics to cure genetic diseases that otherwise have no alternative definitive treatment and are worldwide under-diagnosed. SPARK’s recognition and support made me confident that translating scientific findings into cure is feasible.
Paul Bollyky, MD, PhD
ASSISTANT PROFESSOR OF MEDICINE (INFECTIOUS DISEASES) AND OF MICROBIOLOGY AND IMMUNOLOGY

Paul Bollyky’s group studies how immune responses are regulated within injured and infected tissues. They work at the intersection of immunology, structural biology, and microbiology to develop novel therapeutics to promote wound healing and immune tolerance.

PROJECT

REPURPOSED SMALL MOLECULE TO PREVENT PROGRESSION OF AUTOIMMUNE DISEASE

Stanford SPARK and Kevin and Daria in particular have been vital supporters of our research program on preventing autoimmune diseases like type 1 diabetes (T1D) and primary sclerosing cholangitis (PSC). With their help, we’ve repurposed a drug, originally developed for a different therapeutic indication, which may be able to prevent these diseases. We currently have a clinical trial in place to evaluate this therapy in patients at Stanford hospital. We’re very excited to see if it works. None of this would have happened without Kevin and Daria’s vision and support.

SPARK has provided far more than dollars to my research program. The team of SPARK chemists, regulatory experts, and business minds have been critical to the development of our project and to my education. I’ve learned a ton from these collaborative and interesting folks. Further, I feel that we’ve worked on these projects as a team and that has made this process far more fun and satisfying. Thank you Daria and Kevin and Happy Birthday SPARK!
PROJECT

MULTIPLEXED DIAGNOSTIC TO PREDICT AND DETECT PRE-ECLAMPSIA

Given preliminary ideas and findings funded by the March of Dimes, we proposed to design a novel diagnostic for pre-eclampsia, developed from publicly-available molecular data. This diagnostic would help obstetricians and pregnant women, as pre-eclampsia is still a major source of mortality during pregnancy.

Using SPARK funds and advice, we validated the diagnostic tool and created a startup company, Carmenta Biosciences. Carmenta has since been acquired by Progenity, a diagnostic company in San Diego.

Atul Butte, MD, PhD
PROFESSOR, UCSF SCHOOL OF MEDICINE, PEDIATRICS

In 2015, Dr. Butte was recruited from Stanford to be the Director of the Institute for Computational Health Sciences at UCSF. He is a pediatrician and a leading expert in biomedical informatics. His research focuses on building and applying computational tools to convert molecular, clinical, and epidemiological data collected by researchers worldwide into new diagnostics, therapeutics, and insights into both rare and common diseases.
Daniel Beswick, MD

RESIDENT IN ENT/HEAD AND NECK SURGERY

Dr. Beswick worked for 2 years for EPIC Systems, leading aspects of enterprise electronic health record implementations. Currently he is conducting translational research with Dr. Capasso to address unmet medical needs in head and neck surgery patients.

Robson Capasso, MD

CLINICAL ASSISTANT PROFESSOR, OTOLARYNGOLOGY (HEAD AND NECK SURGERY)

Dr. Capasso’s clinical focus includes sleep surgery and medicine, Otolaryngology, and Biodesign. His research focuses on clinical use of smartphone applications and consumer-based devices for sleep disordered breathing, biomarkers for obstructive sleep apnea, pre-surgical evaluation and upper airway changes after surgery in obstructive sleep apnea sufferers.

PROJECT

A HUMAN GROWTH FACTOR AS PREVENTION FOR POST TONSILLECTOMY HEMORRHAGE

Over one million tonsillectomies are performed annually in the United States and Europe. A significant number of patients experience post-tonsillectomy bleeding, which is a significant burden to the health care system in terms of emergency department revisits, inpatient readmissions, reoperation and even death. It can be an extremely frightening experience to patients and relatives. The reasons why it happens and ways of preventing it are not known. Our project is targeting these questions. Our study has initially developed an animal model for tonsillectomy wounds based on a tongue wound murine model, as most animals lack or have really negligible tonsillar tissue. We have then studied the histology effects of a human growth factor on wound healing in a serial fashion, and tested the proof of concept of how it may positively affect healing and decrease the incidence of post-tonsillectomy bleeding.

SPARK has been instrumental in providing funding and mentoring for the next challenging step in our project: to develop a drug delivery method for the growth factor in the tonsillar wound. It has been really invaluable to interact with the whole SPARK community, and we have gained great insights about our project and drug development in general by our discussions with the SPARK affiliated experts and broad community.
Gene therapy is a promising approach to correct defective genes in patients with inherited conditions such as hemophilia. In our SPARK project, we will harness a fundamental discovery on how viruses penetrate our tissues to make current gene therapy approaches more efficient. We are focusing on improving gene therapy approaches for genetic diseases of the blood including severe combined immunodeficiency and hemophilia. We are currently testing the approach in primary cells and in in vivo models of these diseases.

Dr. Carette’s research team focuses on the identification of host genes that play critical roles in the pathogenesis of infectious agents including viruses. They use haploid genetic screens in human cells as an efficient approach to perform loss-of-function studies. Besides obtaining fundamental insights on how viruses hijack cellular processes and on host defense mechanisms, it might also facilitate the development of new therapeutic strategies.

The SPARK program encouraged us to take a fundamental discovery in virus biology and translate it into a product that has the potential to drastically improve current gene therapy approaches. Even more important than the financial support and the invaluable advice and feedback of excellent industry advisors, the SPARK program provides a mindset where academic research can make an impact on patients’ lives.
The current research focus of the lab is in trying to understand how cells repair DNA damage induced by UV or ionizing radiation. Dr. Chu's lab is also collaboratively developing a point-of-care device to measure blood ammonia from a single drop. The device will facilitate diagnosis and management of elevated blood ammonia, benefiting children with inborn errors in the urea cycle, patients with liver disease, and cancer patients with chemobrain due to elevated ammonia.

**PROJECT**

**DIAGNOSIS OF CAPECITABINE-INDUCED ENCEPHALOPATHY AND RAPID SMALL VOLUME DETECTION OF BLOOD AMMONIA**

(with Matthew Kanan, PhD, Assistant Professor of Chemistry)

The goal of our project was to determine how often elevations in blood ammonia are associated with brain dysfunction in patients treated with the anti-cancer drug, capecitabine. Diagnosis will facilitate personalized medicine by alerting the oncologist to decrease the dose of capecitabine, or substitute a different chemotherapy. The project showed that elevations in blood ammonia may occur in 5% of capecitabine-treated patients, and revealed the importance of finding a new method for measuring blood ammonia. Subsequently, we developed an inexpensive device that measures ammonia in a drop of blood, thus eliminating the need for intravenous access. The device will help prevent brain damage in newborns and children with any one of 44 different inherited diseases, cancer patients with “chemobrain” from capecitabine, and patients with liver failure. We are now seeking funding to conduct a small clinical trial of the device in children and adults.

Thank you again for your faith, support, and invaluable advice, especially Daria’s encouragement, to find a collaborator (Matt Kanan), who could help develop a device for measuring blood ammonia.

**SPARK value**
PROJECT

NOVEL TARGET FOR INDUCTION OF BROWN FAT TO TREAT OBESITY

My SPARK project is focused on identifying a novel small molecular therapeutic for the treatment of obesity and diabetes. It will be beneficial for people for whom life style changes are not enough to become healthy. We have completed the first two initial high-throughput screens and are assessing the ‘hits’ from our assays in our laboratory that alter the fate of critical cells in the context of these two diseases.

SPARK has been a career-changing program for me. It enabled me to envision translating our basic science discoveries to benefit patients. SPARK provides both training in the nuts-and-bolts of translational research and an active support system that connects SPARK scholars with scientific collaborators and interested industry partners. Without this program, it is hard to imagine how an academic scientist could stay involved in fostering an idea over all of the challenges to become a product that helps patients.
Reduced cognitive function is a hallmark for children with Down syndrome (DS), impairing learning and memory function as well as the development of language skills. Currently, there are no effective treatments. While I was at Stanford, our SPARK project was designed to evaluate whether previously approved GABA_A receptor antagonists could safely be administered, resulting in a normalization of cognitive function. Our studies revealed that pentylenetetrazole (PTZ) had an excellent therapeutic window of efficacy, normalizing cognitive function by improving the consolidation of memories during sleep.

With the help of the Stanford SPARK team and advisors, we obtained a patent and were introduced to Lyndon Lien, who co-founded Balance Therapeutics Inc with us. Balance performed all preclinical studies and recently completed a Phase Ib trial, demonstrating not only that PTZ can be safely administered to young adults with DS, but also that it improved their cognitive function. My positive experience inspired me to found SPARK Berlin, after my move to Germany.
We identified a patient who had a large lymph vessels overgrowth (lymphangioma) who improved when given sildenafil (Viagra®) for her pulmonary hypertension. SPARK supported a study of 7 children with lymphangiomas, which led to an approved FDA IND #113112 and a $1,592,842 NIH grant to treat 60 children with lymphangiomas with sildenafil. That study is currently active enrolling subjects at several centers across the USA.

Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a severe, painful, and lethal blistering disease of infants missing collagen type (C7) that holds the outer layer of skin to the inner layer of skin. These children develop blisters and wounds that never heal. SPARK supported an initial study developing microneedles that can deliver C7 into the skin and heal the wounds of these children. That study is now moving forward with a corporate partner and financial support from the Epidermolysis Bullosa Research Partnership and the Epidermolysis Bullosa Medical Research Foundation.
PROJECT

REPURPOSED SMALL MOLECULE TO TREAT CHRONIC IMMUNE THROMBOCYTOPENIA IN JUVENILES

My SPARK project is evaluating an oral antioxidant, N-acetylcysteine, in the treatment of pediatric chronic immune thrombocytopenia. Children with this chronic autoimmune disorder would potentially benefit from this treatment, as it is an attractive alternative to conventional therapy (which includes splenectomy, immunosuppression, or thrombopoietin mimetics). The clinical study is currently open at Stanford.
PROJECT

TOPICAL BENZAMIL FOR PSORIASIS

This is a study which examines a new class of agents to treat psoriasis on a novel target that does not cause immunosuppression. These agents, of which benzamil is a prototype, target ion channels in the outer layer of the skin called the epidermis. We have a mouse model of psoriasis in our lab in which we tested topical benzamil, and we found that it reversed the skin disease.

M. Peter Marinkovich, MD
ASSOCIATE PROFESSOR OF DERMATOLOGY

Dr. Marinkovich is a faculty member in the Program in Epithelial Biology and the Stanford Cancer Biology Program. He has an interest in inflammatory skin disease and is Director of the Stanford Bullous Disease and Psoriasis Clinics as well as an attending dermatologist at the VA Palo Alto Medical Center. Dr. Marinkovich's research focuses on pathogenesis and therapy of epidermolysis bullosa, psoriasis, hair disorders and skin cancers.
PROJECT

PROJECT 1
MONOCLONAL ANTIBODY THERAPY TO PREVENT ACUTE GRAFT-VERSUS-HOST DISEASE FOLLOWING HEMATOPOIETIC CELL TRANSPLANTATION

This SPARK project is to develop two monoclonal blocking antibodies to prevent graft-versus-host disease following bone marrow transplantation and for other immune disorders. The patent has been licensed to a start-up company to commercialize the invention.

PROJECT 2
ANTIBODY-GUIDED CELLULAR THERAPY TO TREAT ACUTE GASTROINTESTINAL GRAFT VERSUS HOST DISEASE

Our second SPARK project is to develop a novel cellular therapy approach using genetically modified regulatory T cells to prevent graft-versus-host disease but also to facilitate immune tolerance to tissue grafts such as the insulin-producing pancreatic islets. This project has resulted in significant follow-on foundational funding and now is the centerpiece of an active collaboration of four laboratories here at Stanford, with efforts to form collaborations with partners in industry underway.

The two projects have the potential to significantly improve outcomes for patients in need of hematopoietic stem cell transplantation and other transplants, or who need new therapeutic options for some autoimmune diseases.

I am very fortunate to have SPARK support. SPARK has been an incredible resource. The education and project-based review are outstanding and provide a much needed perspective. My projects would not have gone nearly as far without the help of SPARK -- they have given me the sea legs to help captain the critical voyage across “the turbulent ocean of death” from academia to approval and to get new therapies to patients.

Everett Meyer, MD, PhD
ASSISTANT PROFESSOR OF MEDICINE (BLOOD AND MARROW TRANSPLANTATION) AT THE STANFORD UNIVERSITY MEDICAL CENTER

Dr. Meyer’s team focuses on research in T cell immunotherapy and T cell immune monitoring using high-throughput sequencing and genomic approaches, with an emphasis on hematopoietic stem cell transplantation, the treatment of graft-versus-host disease and immune tolerance induction.
Dr. Purzner’s focus is the study of brain tumors which are the number one cause of cancer-related deaths in children. She has been combining novel techniques in mass spectrometry with developmental neurobiology to discover new drug targets in pediatric brain tumors. This approach has led to the identification of a potential new drug for the disease.

**PROJECT**

**SMALL MOLECULE FOR TREATMENT OF HEDGEHOG-DRIVEN MEDULLOBLASTOMA**

I have been combining novel techniques in mass spectrometry with developmental neurobiology to discover new drug targets in pediatric brain tumors. In particular, I am focusing on medulloblastoma, which is the most common pediatric brain tumor. This approach has led to the identification of a potential new drug that we are hoping to bring to children in a Phase I clinical trial next summer. SPARK has been a tremendous influence on the success of my project.
PROJECT

NOVEL SMALL MOLECULES TO PREVENT OTOTOXICITY

We are developing a new class of aminoglycoside antibiotics in order to alleviate the major side effect of hearing loss that occurs in 20-40% of aminoglycoside users after a single dose and up to 80% with repeated treatments. As these are the most widely used antibiotics worldwide, our new drugs will enable many people, particularly newborn babies, to use these drugs without putting their hearing health at risk. At present we are in a third round of compound synthesis, having received R01 grant support from NIH.

Anthony Ricci, PhD
PROFESSOR OF OTOLARYNGOLOGY, EDWARD C. AND AMY H. SEWALL PROFESSOR IN THE SCHOOL OF MEDICINE AND PROFESSOR, BY COURTESY, OF MOLECULAR AND CELLULAR PHYSIOLOGY

Dr. Ricci’s group uses advanced electrophysiologic, imaging, molecular and pharmacologic techniques to probe mechanisms of mechanotransduction and synaptic transmission at the auditory periphery. A major goal of the laboratory is to delineate the functional relevance of mechanotransduction and to identify proteins and their function in this process.

Without the support and guidance of the SPARK program, our idea about how to modify these antibiotics would never have become a reality. Their financial support was important, but the broad range of expertise and availability of SPARK mentors for getting advice, and the specific guidance by one of the medicinal chemists, Bob Greenhouse, was and remains critically important for our project.

SPARK value

Without the support and guidance of the SPARK program, our idea about how to modify these antibiotics would never have become a reality. Their financial support was important, but the broad range of expertise and availability of SPARK mentors for getting advice, and the specific guidance by one of the medicinal chemists, Bob Greenhouse, was and remains critically important for our project.
Of more than 900 naturally occurring amino acids in nature, only 22 have been selected by evolution for inclusion within proteins. Azetidine-2-carboxylic acid (Aze), an amino acid found in members of the beet family, has been found to replace proline in dozens of proteins, changing their size, shape, antigenicity, and function. One third of the world’s sugar supply comes from sugar beets. Sucrose can be readily extracted by a distillation process and the Aze-rich byproduct is fed to dairy cattle. Our research has found Aze in milk from sugar beet-fed cows. We are studying the possible role of dietary Aze in triggering multiple sclerosis and type 1 diabetes mellitus, two diseases that closely track sugar beet agriculture geographically. Our hope is that this research will one day help prevent diseases such as multiple sclerosis and diabetes mellitus.
Sarah Adler, PsyD
CLINICAL ASSISTANT PROFESSOR, PSYCHIATRY AND BEHAVIORAL SCIENCES
Dr. Sadler’s research focuses on disordered eating behaviors and obesity, and the development and treatment of problematic eating patterns in patients following bariatric surgery.

Debra Safer, MD
ASSOCIATE PROFESSOR OF PSYCHIATRY AND BEHAVIORAL SCIENCES
Primary research interests of Dr. Safer’s lab include the nature and treatment of eating disorders (particularly bulimia nervosa and binge eating disorder), the development and treatment of obesity, and the development and treatment of problematic eating patterns in patients following bariatric surgery.

PROJECT

REPURPOSED SMALL MOLECULE TO TREAT BULIMIA NERVOSA AND BINGE EATING DISORDER

We are conducting a study to test whether Qsymia (phen-termineline - topiramate), a drug originally FDA approved for obesity, can be repurposed to improve eating disorder symptoms in patients with bulimia nervosa and binge eating disorder. There is a need for improved treatment options for patients with bulimia nervosa and binge eating disorder. Not all patients respond to currently available treatments. Also, psychotherapy, the treatment of choice, requires commitments of time and can be costly. Current medication options tend to have high side effect profiles. If medications like Qsymia are well-tolerated and effective, they will offer an important benefit for currently suffering patients. We have currently randomized 22 patients out of our goal of 30 as part of our randomized double blind crossover trial. We hope to complete the trial in about 1 year. We are so grateful to have received help from SPARK for additional funding so that we can meet our goals.

SPARK value

We are HUGELY indebted to SPARK for so many reasons. Even more than providing financial support for our study, SPARK’s advisors and amazing team gave us invaluable advice on our study design. This advice has greatly improved our study. We feel so supported and encouraged by the amazing SPARK team, headed by Kevin and Daria. SPARK is an amazing program whose impact is highly significant and meaningful! We feel so appreciative and fortunate to be a part of it!
The transcription factor CREB is overexpressed in most patients with acute myeloid leukemia (AML) and CREB overexpression is associated with a worse prognosis. The project supported by SPARK focuses on identifying small molecules and peptides that inhibit CREB function to provide more effective and less toxic therapy for AML patients. We are currently working with medicinal chemists and other scientists at Stanford to develop a drug that inhibits CREB binding to its coactivator, CBP (CREB Binding Protein).
My SPARK project at Stanford was to translate a non-surgical treatment to regenerate the ear drum after a hole had formed in it. This condition affects up to 200 million children and adults with its largest impact in the third world but also a significant population in first world countries. Even in those who have access to surgery, it still involves an admission to hospital, general anesthetic and cut behind the ear. We’re hoping to remove all of these factors with an injectable gel through the ear canal. I had spent eight years understanding the wound healing of the ear drum with many ideas of how this may translate into a real world solution. We are currently partnering with a pharmaceutical company and testing some further models before moving into manufacturing for a clinical trial.

For this I cannot thank Daria, Kevin and the whole SPARK community enough! And now I founded SPARK in Perth, Australia!
Minnie Sarwal, MD, PhD
PROFESSOR, UCSF SCHOOL OF MEDICINE, DEPARTMENT OF SURGERY

Dr. Sarwal held the Professor of Surgery/Immunology/Peds and the Medical Director position in the Peds Kidney Transplant Program at Stanford University. She now heads a personalized medicine initiative for Sutter Health and is currently Professor of Surgery at UCSF. As a PI for industry and NIH multicenter clinical trials, she leads trial design, execution, and human subject safety policies. As an entrepreneur, she has founded and sold a diagnostic company and is experienced in legal, fiscal, regulatory and reimbursement requirements for product development and commercialization.

PROJECT

GENE ARRAY TO PREDICT TRANSPLANT TOLERANCE AND THE LIKELIHOOD OF REJECTION

Our project was funded in the very first batch of SPARK projects to be selected! We focused on identifying the changes in the level of certain biomarkers in urine that would signal that the body is beginning to reject a new kidney. What makes this discovery important is that a transplant recipient now often doesn’t find out that a kidney is being rejected until it is too late to prevent damage to the organ. We spun out Organ-I after the original support from SPARK. Since then I worked on the company for 2 yrs after leaving Stanford and then sold it to Immucor in 2014. The assay is available as a commercial product for patients today!

So many thanks to you for believing in me and the technology.

PROSPERITY
With our SPARK funding, we were able to design formulations of a metalloporphyrin, zinc protoporphyrin (ZnPP), using spray-drying and emulsion encapsulation techniques to incorporate ZnPP into microparticles. These formulations were designed to allow oral bioavailability and enhance gastric passage and intestinal absorption of ZnPP for the potential treatment of newborn infants with hyperbilirubinemia, particularly due to a hemolytic cause. Among the formulations created and tested, we found that the lipid-only-based preparation (ZnPP-Lipid), prepared using FDA-approved biodegradable endogenous phospholipids (DPPC and DSPC), was the most promising. The results of our evaluation have culminated in two publications [(Acta Paediatrica (103:474-9, 2014, doi: 10.1111/apa.12554. PMID: 24417721 and Pediatric Research (79:251-7, 2016, doi: 10.1038/pr.2015.207. PMID: 2648855)], and in addition, led to patent applications in the US and abroad as well as a technology transfer agreement with La Jolla Pharmaceuticals.
Through the help of the SPARK program, we have developed a number of molecular diagnostic markers and a potential therapeutic target to assist in the prevention and treatment of the newborn disease Necrotizing Enterocolitis (NEC). NEC is a leading cause of premature newborn death and disability, yet there are currently no effective prevention strategies and, once diagnosed, current treatment is largely supportive.
While I was at Stanford, SPARK supported extended biological studies on an interventional trial of high-dose oral N-acetyl cysteine (NAC) for patients with cystic fibrosis, at the phase 1b stage. This allowed us to gain important mechanistic insights that were in turn instrumental in pushing the candidate drug through phase 2. SPARK support paved the way for funding from the Cystic Fibrosis Foundation ($653,000) to conduct a successful 4-yr, 12-center RCT (https://clinicaltrials.gov/ct2/show/NCT00809094). This randomized controlled clinical trial showed significant clinical benefit of the drug over placebo, as published in a recent paper (Conrad et al., J Cyst Fibros 2015).
A NOVEL THERAPEUTIC TARGET IN PEDIATRIC AND ADULT SARCOMAS

In this project, we plan to develop a new therapy for several pediatric and adult malignancies by targeting a cell surface protein, a novel kinase receptor. Patients with Wilm’s tumor (a pediatric kidney malignancy) have high levels of expression of this receptor on the tumor cells. In addition, 30% of patients with leiomyosarcoma and GIST and 20% of patients with breast cancer express this protein on their tumor. We are developing antibodies that inhibit the function of this receptor and will determine whether these antibodies inhibit tumor growth. In parallel, we will examine whether these same antibodies can be used to direct the body’s immune system towards killing the tumor cells. Currently we have shown that expression of this protein receptor is associated with increased tumor size and with poor patient outcome. We already have raised several monoclonal antibodies that in preliminary experiments appear to inhibit tumor growth.
Our SPARK funding supported my group to perform a screen to identify small molecules that blocked the function of a virulence factor from the pathogenic bacteria, Clostridium difficile. Using this funding, we identified a number of lead molecules including one that is currently in human clinical trials for other indications. This compound was able to protect mice from C. diff-associated pathology and we are currently working to move this molecule into clinical trials for treatment of Clostridium Difficile infection (CDI). CDI results in nearly a quarter million hospitalizations each year and places a $4.8 billion burden on the US healthcare system. Our findings could help to treat those with CDI and prevent disease symptoms that lead to significant pathology and even death.
The goal of this project is to develop small molecules that inhibit the host cell enzymes AAK1 and GAK as broad-spectrum antivirals, both via repurposing already approved anticancer drugs and discovering novel, chemically distinct, more selective inhibitors. This strategy has already shown great promise in murine models of dengue and Ebola virus disease as well as against multiple other emerging viral infections in tissue culture models. We are currently advancing this antiviral strategy into the clinic. Such a “multiple threats-one drug” approach is intended to fill a large gap in our public health capabilities and will position us to meet future challenges posed by newly emerging pathogens.

SPARK has shared its expertise in medicinal chemistry for the synthesis of novel, more selective compounds and provided critical guidance with the choice of disease models to focus on, the design of in vivo efficacy studies, preparation of drug formulations, investigation of the mechanism of action, etc. SPARK has also been playing a fundamental role in advancing this program into the clinic for combating Ebola virus disease (through to an FDA-approved protocol for future outbreaks) as well as dengue.
PROJECT

ANTIVIRAL THERAPEUTICS

Our first SPARK project was in the field of hepatitis drug development. After critically helpful discussions with SPARK advisors, this was eventually followed by the outlicensing of the IP to Eiger BioPharmaceuticals, Inc, a company I founded. The company, now public (NASDAQ: EIGR), is performing multiple phase II studies around the world. Another SPARK project targeted host cell lipid kinases as a novel antiviral therapy predicted to be broad spectrum with a high barrier to the development of resistance. This led to an NIH Center for Excellence in Translational Research award of $28 million (ViRx@Stanford: http://med.stanford.edu/virx.html.html), and several novel molecules are currently moving towards the clinic. A third project was in the field of targeting RNA secondary structure as a novel class of antiviral agents that completely prevents influenza mortality in mice.

Jeffrey Glenn, MD, PhD
ASSOCIATE PROFESSOR OF MEDICINE (GASTROENTEROLOGY AND HEPATOLOGY) AND OF MICROBIOLOGY AND IMMUNOLOGY

Dr. Glenn’s primary interest is in molecular virology, with a strong emphasis on translating this knowledge into novel antiviral therapies. Other interests include exploitation of hepatic stem cells, development of a small animal model for HCV, and engineered human liver tissues.
Athelas Therapeutics is developing a novel class of medicines to treat lethal, invasive fungal infections (IFIs). Despite current medicines, IFIs are responsible for over two million deaths throughout the world every year. Thus new and better drugs address a critical unmet clinical need that could save thousands of lives. Athelas Therapeutics was incorporated in early 2016 and the company is presently located in the Boston, Massachusetts area.

**Or Gozani, MD, PhD**

**Professor of Biology**

The group studies the molecular mechanisms by which chromatin-signaling networks affect nuclear and epigenetic programs, and how dysregulation of these pathways leads to disease. Their work centers on the biology of lysine methylation, a principal chromatin-regulatory mechanism that directs epigenetic processes.

**PROJECT**

**REPURPOSED SMALL MOLECULES TO TREAT FUNGAL INFECTIONS**

Athelas Therapeutics is developing a novel class of medicines to treat lethal, invasive fungal infections (IFIs). Despite current medicines, IFIs are responsible for over two million deaths throughout the world every year. Thus new and better drugs address a critical unmet clinical need that could save thousands of lives. Athelas Therapeutics was incorporated in early 2016 and the company is presently located in the Boston, Massachusetts area.

**SPARK provided me with crucial funding to do some early pilot experiments. More importantly, SPARK connected me with numerous people working in all areas relevant to a biotech start-up, which was essential for me to learn how to launch a new drug discovery company. It is a wonderful program - thanks so much.**
PROJECT

TOWARD A NOVEL INHIBITOR OF EBOLA VIRUS

The Zaire strain responsible for the deadly 2014 West Africa Ebola outbreak is one of four strains of Ebola filoviruses that can infect humans. Our project focuses on developing broad-spectrum inhibitors that will target all filoviruses. Currently, we are optimizing our lead candidate, which has demonstrated exceptional stability and high affinity binding in vitro.

SPARK has enabled us to explore beyond the traditional paradigms and create novel agents that are potential therapeutics.

Peter Kim, PhD
VIRGINIA AND D. K. LUDWIG PROFESSOR OF BIOCHEMISTRY

Dr. Kim, who was the president of Merck Research Laboratories, Merck & Co., Inc. (2003 - 2013), joined Stanford as a professor in Biochemistry in 2014. His group is studying the mechanism of viral membrane fusion and its inhibition by drugs and antibodies. They use the HIV envelope protein (gp120/gp41) as a model system and some of their studies are aimed at creating an HIV vaccine. They are also interested in protein surfaces that are referred to as “non-druggable”.

GLOBAL HEALTH

Infectious Diseases
PROJECT

REPURPOSED SMALL MOLECULES TO TREAT OR PREVENT DENGUE FEVER

We develop novel machine learning approaches to predict which existing drugs could be used for therapies in infectious disease. Our first applications of this technology have been to Chagas Disease and Dengue Fever, and we are continuing to look at related diseases such as African Sleeping Sickness, Ebola, and Zika. These repurposed drugs could help the world broadly, as these diseases are becoming worldwide threats.

Currently, the Dengue work has been spun out into a company for clinical trials and the other diseases are undergoing pre-clinical studies at Stanford.
PROJECT

PEPTIDE THERAPEUTIC AGAINST A PATHOGEN-SPECIFIC TARGET IN Leishmania sp.

Leishmaniasis is a parasitic infectious disease that afflicts millions of people annually, mainly in rural areas. Strikingly, it is the most common neglected disease after malaria, with a global death rate of ~30,000 per year. Nearly 70% of all deaths occur in children. Current anti-parasitic drugs are expensive, toxic and induce drug resistance. We developed novel and selective peptides and peptoids (modified peptides), based on rational design models, that specifically inhibit critical protein-protein interactions unique to Leishmania. Furthermore, we demonstrated that these peptide-based drugs are efficacious in parasite culture-based systems. Preliminary animal toxicology studies show that the peptides are not toxic. Collaborations with international investigators are planned to continue development of these molecules towards clinical testing.

The SPARK program supported this successful development, and also provided excellent and professional mentorship by key opinion leaders in the space of drug discovery and transitional research. Thank you for all the support you gave me and all the wonderful academic discussions.

Nir Qvit, PhD
POSTDOCTORAL SCHOLAR, STANFORD UNIVERSITY
Dr. Qvit is developing novel peptide therapeutics aimed at inhibiting pivotal protein-protein interactions in neglected parasitic diseases.
The goal of the Singh lab SPARK project is to help identify new drugs for a parasitic infection that has significant global impact, but for which very limited treatment options exist. Amebic dysentery, caused by the pathogen Entamoeba, is largely endemic in resource-poor countries, and is thus of low priority to pharmaceutical companies. The parasite Entamoeba affects >500 million people worldwide with 50 million people getting invasive disease annually; children, malnourished individuals and pregnant women get more severe infections and outcomes. Through the SPARK project, we screened >4,000 compounds to identify new drugs that may target the parasite. We are currently testing select compounds in further assays.

The SPARK program has literally “sparked” our interest in drug development. My lab has always been highly focused on basic science and molecular biology of Entamoeba but we had not previously ventured into the arena of drug development. The outstanding SPARK support (advisors, weekly meetings, and mentoring etc) has ensured that our work progresses in a streamlined, focused manner. I’m confident that we would not have progressed as rapidly to this extent without the framework of support provided by SPARK.
PROJECT

PROJECT 1
INFLUENZA PROJECT

We are developing a stabilized influenza vaccine that would confer broadly protective immunity against both common and pandemic strains of influenza, thereby requiring just a few injections at a young age rather than yearly vaccination. This would effectively benefit the entire world population by providing an influenza vaccine and dosing schedule with increased effectiveness, reduced costs, and increased access.

PROJECT 2
ZIKA PROJECT

Through the SPARK Global effort, we are working with the Universidade de São Paulo in Brazil to develop a Zika vaccine using our stabilized virus-like particle platform to present antigens from the Zika virus in an ordered and repetitive manner. The recent Zika outbreaks in French Polynesia and Brazil have demonstrated a causative association between the Zika virus and serious medical conditions known as microcephaly and Guillain-Barré syndrome. Current infection prevention methods rely strongly on regular patient compliance, and an effective vaccine, which we are developing, would go a long way toward stopping the transmission of Zika virus. We hope to begin testing our vaccine candidates in relevant animal models soon.
Malaria caused by *Plasmodium* spp parasites creates an enormous disease burden that disproportionately affects the young and poor in the developing world. Progress in disease control is threatened by resistance to all available anti-malarial drugs. Using an innovative screen, we identified 2 inhibitors that target a unique plastid organelle in *Plasmodium* parasites and are identifying the drug targets. Both compounds can serve as starting points for antimalarial drug development.

**PROJECT**

**SMALL MOLECULE INHIBITOR OF AN ESSENTIAL PATHWAY IN THE MALARIA PARASITE *Plasmodium falciparum***

Malaria caused by *Plasmodium* spp parasites creates an enormous disease burden that disproportionately affects the young and poor in the developing world. Progress in disease control is threatened by resistance to all available anti-malarial drugs. Using an innovative screen, we identified 2 inhibitors that target a unique plastid organelle in *Plasmodium* parasites and are identifying the drug targets. Both compounds can serve as starting points for antimalarial drug development.
PROJECT

NOVEL POLYMER-IMPRINTED DIAGNOSTIC TO RAPIDLY DETECT MYCOBACTERIUM TUBERCULOSIS FROM SPUTUM USING TRADITIONAL STAINING METHODS

Under SPARK support, my research group developed a cheap, robust diagnostic procedure for the detection of tuberculosis mycobacterium in the sputum of potential TB carriers. This was accomplished by creating artificial antibodies by imprinting a polymer film with the targeted mycobacteria. The capture selectivity was shown to involve not only the sizes and shapes of the impressions on the polymer film surface but, more importantly, to be based on chemical recognition of the target through the reorganization of the oligomer units by contact with the surface of the bacterium, which were locked into place by the polymerization of the film.

I am deeply grateful to SPARK who were willing to support this project when we had only the most preliminary results to suggest feasibility of this approach to making a new diagnostic device. In these times when research needs to be almost completed before it can be funded, SPARK’s support was key in allowing us to explore the advantages and drawbacks of the cell imprinting of polymer films.

Dick Zare, PhD
PROFESSOR OF CHEMISTRY, MARGUERITE BLAKE WILBUR PROFESSOR IN NATURAL SCIENCE AND PROFESSOR, BY COURTESY, OF PHYSICS

Dr. Zare’s group is exploring a variety of topics that range from the basic understanding of chemical reaction dynamics to the nature of the chemical contents of single cells. Analytical efforts involve the use of capillary zone electrophoresis, two-step laser desorption multiphoton ionization mass spectrometry, cavity ring-down spectroscopy, and Hadamard transform time-of-flight mass spectrometry. The group believes that these methods can revolutionize trace analysis, particularly of biomolecules in cells.

global health
infectious diseases
A major area of investigation in our lab is the study of mechanisms that selectively enable transcription through expanded nucleotide repeat (NR) regions in human genes. Our SPARK project is focused on identifying and developing drugs that may be effective in treating Huntington’s Disease and other horrific and fatal inherited neurodegenerative diseases caused by expansion of segments of nucleotide repeats in certain genes. Our team has identified small molecules that inhibit this pathological expansion, and we are in the process of forming a startup company around these discoveries.
Neurodegenerative disorders, such as Alzheimer’s disease (AD), Parkinson’s disease (PD) and amyotrophic lateral sclerosis (ALS), remain poorly understood and with limited treatment options. Inflammation in the brain is likely a major contributing factor to these diseases, and we have identified a specific defect that drives neuroinflammation. Moreover, we have discovered a promising new orally deliverable drug candidate that crosses the blood-brain barrier, reverses this defect and ameliorates these diseases in experimental AD, PD and ALS in mice. This drug candidate is ready for clinical development.

Edgar Engleman, MD
PROFESSOR OF PATHOLOGY AND OF MEDICINE (IMMUNOLOGY AND RHEUMATOLOGY)

Dr. Engleman is a founding member of Vivo Capital, (formerly BioAsia Investments) and co-founded a number of biopharmaceutical companies including Cetus Immune, Genelabs, and Dendreon. At Stanford, his group studies the biology of immune cells and their roles in the pathogenesis of cancers and other life-threatening diseases. They have been particularly interested in the biology and functions of dendritic cells (DC), which are potent antigen presenting cells that can either induce or suppress immunity.
We performed a screen to search for drugs that might have a beneficial effect on the aging process. To find these drugs, we performed a bioinformatics screen in which we compared the genome-wide transcriptional changes that occur during the normal aging process of the kidney (kidney aging transcriptome) to the transcriptional changes in response to a drug (drug transcriptome). The drug transcriptome data were accessed from the Connectivity Map database, which contains the genome-wide transcriptional response for several thousand drugs. We found three drugs that caused an anti-aging transcriptional response; i.e. addition of the drug caused transcriptional changes that were the opposite of those caused by normal kidney aging. Kidney diseases such as chronic kidney disease and end stage renal disease are relatively common among the elderly. Our SPARK study may benefit people with age-related kidney disease by partially alleviating some of the symptoms of renal aging.
We sought to develop a unique, scalable subcutaneous formulation of the glucagon-like peptide-1 receptor antagonist, exendin (9-39), for treatment of post-bariatric hypoglycemia (PBH), which affects 1-6% of Roux-en-Y gastric bypass patients. PBH is characterized by frequent episodes of severe hypoglycemia with neurologic symptoms including loss of consciousness and seizures, marked disability, and possibly death. There is no approved treatment for this condition. Our prior research suggested that the gut-derived hormone, glucagon-like peptide-1, played a pivotal role in mediating PBH, and with SPARK support we successfully piloted a first-in-human Phase 1 trial with subcutaneous Exendin 9-39, and subsequently licensed our invention to Eiger BioPharmaceuticals, a small biopharmaceutical company that specializes in developing therapeutics for rare diseases. Eiger is currently conducting a phase 2 multi-ascending dose trial in patients with PBH and is actively moving this technology forward.

We are especially thankful for the regulatory, trial design, and PK advice by SPARK advisors Carol Karp, Todd Lorenz, Werner Rubas, Yeping Zhao, and David Lechuga, who selflessly devoted time and expertise as our project evolved.

Dr. McLaughlin conducts a number of clinical research studies related to obesity, insulin resistance, diabetes, and cardiovascular disease. Current studies include: 1) the impact of macronutrient composition on weight loss and cardiovascular risk (diabetic and nondiabetic patients); 2) comparison of weight loss and cardiovascular risk reduction in diabetic patients treated with different classes of antihyperglycemic drugs; 3) the role of the adipocyte in modulating insulin resistance.
Pulmonary arterial hypertension (PAH) is a disease that primarily affects young to middle-aged women. As a frequently lethal disease without cure, current FDA-approved therapies have focused on vasodilation to open up blood vessels. Our group has focused on how autoimmune injury induced by a molecule called leukotriene B4 (LTB4) may be responsible for the disease. SPARK helped us with funding to transition our basic science into a new therapeutic.

Mark Nicolls, MD
PROFESSOR OF MEDICINE (PULMONARY AND CRITICAL CARE)

Dr. Nicolls’ lab focuses primarily on the contribution of the immune response to lung disease. They are specifically examining the contribution of inflammation to the development of pulmonary hypertension. The group also focuses on studying how airway remodeling occurs in transplantation specifically with respect to the microvascular circulation and to the initiation of fibroproliferation.

PROJECT

NOVEL REPURPOSED SMALL MOLECULE FOR TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (PAH) is a disease that primarily affects young to middle-aged women. As a frequently lethal disease without cure, current FDA-approved therapies have focused on vasodilation to open up blood vessels. Our group has focused on how autoimmune injury induced by a molecule called leukotriene B4 (LTB4) may be responsible for the disease. SPARK helped us with funding to transition our basic science into a new therapeutic.

Through SPARK we met advisors, made contacts with the biotech community, developed a business strategy, became paired with a CEO, formed a company, and gained venture funding. The company was folded into another company, went public on NASDAQ in 2016, received an FDA IND, and commenced a Phase II trial (“LIBERTY”) which has enlisted 45 sites in the U.S. and Canada. The first PAH trial patient was dosed with drug a few weeks ago.
Pulmonary arterial hypertension (PAH), a devastating rare disease that affects children and adults alike, is characterized by the narrowing of the pulmonary vessels resulting in right heart failure. In a high throughput screen of FDA approved drugs, we identified the immunosuppressive drug FK506 (Tacrolimus) as the best activator of a signaling pathway, BMPR2, which is downregulated in PAH. We showed that FK506 reversed PAH in experimental PAH. With SPARK support and that of the Wall Center for Pulmonary Vascular Disease at Stanford, we used FK506 on a compassionate basis in end-stage PAH patients awaiting lung transplantation and initiated and completed a clinical phase IIa trial. Our patent was licensed by Selten Pharma Inc, which is devoted to develop the product further and secure funding for a phase IIb/III efficacy trial. Furthermore, we received the orphan drug designation for FK506, which facilitates further commercial development.
PROJECT

REPURPOSING A DRUG FOR INTERSTITIAL CYSTITIS

Our investigation tests a novel, inexpensive treatment for interstitial cystitis, a disease causing long-term bladder pain with no known cause, cure, or reliable treatment options. Interstitial cystitis symptoms are present in up to 5 million Americans, all of whom will potentially benefit from a new treatment option. We are completing preliminary experiments in animal models and analyzing data now with hopes to reach out to national investigators for human trials in the coming months.

Craig Comiter, MD, PhD
Professor of Urology and, by courtesy, of Obstetrics and Gynecology

Dr. Comiter’s team is investigating how intervening with pharmacotherapy, neuromodulation, and other novel therapies may help to reverse the adverse changes in the bladder due to the obstruction.

Amandeep Mahal, MD
Fellow, Department of Urology

Dr. Amandeep Mahal specializes in obstetrics/gynecology and is investigating novel treatments for interstitial cystitis.

The SPARK program allowed us to have an incredible combination of funding for the initial project set up as well as access to some amazing scientists, regulators and innovators. These both were vital to our success and I fear this investigation would have fallen flat without both!
oncology projects listed in other sections:

- Gilbert Chu
  DIAGNOSIS OF CAPECITABINE-INDUCED ENCEPHALOPATHY
- Teresa Purzner
  TREATMENT OF HEDGEHOG-DRIVEN MEDULLOBLASTOMA
- Kathleen Sakamoto
  TREATMENT OF ACUTE MYELOID LEUKEMIA
- Matt van de Rijn
  TREATMENT OF PEDIATRIC AND ADULT SARCOMAS
PROJECT

ROLE OF VASCULOGENESIS IN RESISTANCE OF TUMORS TO IRRADIATION

We proposed a novel hypothesis that recurrence of solid tumors after irradiation is the result of regrowth of the tumor vasculature from circulating cells (a process known as “vasculogenesis”). We had preliminary evidence from mouse tumors implanted in the brain that this might be the case. The SPARK funding allowed us to greatly expand this work using autochthonous brain tumors in rats. We were able to show that inhibiting the interaction of SDF-1 with its receptor CXCR4 on CD11b+ monocytes was highly effective in prolonging or preventing recurrence of these tumors in rats.

Initially my lab was the benefactor as the SPARK data enabled us to get an R01 grant that led us to understand the process further. We hope that cancer patients will benefit. The SPARK funding and subsequent R01 has led to a clinical trial to show safety and proof of concept in patients with brain cancer. This has been ongoing at Stanford for almost 2 years and the initial data look very promising.

Martin Brown, PhD
PROFESSOR OF RADIATION ONCOLOGY, EMERITUS

Dr. Brown's group seeks to understand the mechanisms responsible for the resistance of solid tumors to cancer therapies and to develop strategies to overcome these resistances.
Millions of people who receive chemotherapy for cancer report numbness, tingling, and pain in their hands and feet following treatment. This chemotherapy-induced peripheral neuropathy (CIPN) dramatically reduces patient quality of life and limits cancer treatment. Its cause is not known and there are no FDA-approved treatments. Currently, this project is on-hold, pending resolution of an unexpected technical barrier. We hope to restart the work in the future.

In our SPARK-funded project, which was inspired by conversations with my mother-in-law, my team developed a novel in vivo model of CIPN and sought to identify existing experimental drugs that could be re-purposed to prevent or alleviate CIPN.
Our SPARK project aims to develop small molecule inhibitors to specific members of the enzyme class called acetyltransferases, which are critical for not only tumor growth, but are also important for the tumor’s ability to evade the immune system. By concurrently reactivating anti-tumor immunity and blocking tumor growth, we limit the tumor’s ability to develop resistance to a single therapy. We are designing molecules to provide therapeutic benefit to patients with a specific molecular profile in several major cancers. Following a large scale screen for inhibitors of these enzymes, we are currently in the process of optimizing our inhibitors to improve their efficacy and pharmacological properties.

Participation in the SPARK program has provided critical funding for our drug development and put us in regular contact with experts in several areas of drug development. Drug development requires a broad set of chemical and biological tools, and SPARK is a central part of Stanford’s ability to enable and use these tools.
PROJECT

REPURPOSED ORAL SMALL MOLECULE AS A TREATMENT/RADIATION SENSitizer FOR PROSTATE CANCER

We are conducting a Phase I trial of sodium selenite in combination with palliative radiation therapy in patients with metastatic prostate cancer. This is an investigator-initiated study based on work demonstrating that sodium selenite has activity as a single agent and as a radiosensitizer in prostate cancer models. The primary objectives of this study are to determine the maximum tolerated dose of sodium selenite when given with palliative radiation therapy based on safety and tolerability. Secondary objectives include assessment of pharmacokinetics and evaluation of anti-tumor activity. This is an ongoing trial. To date there has been no significant toxicity attributable to the study drug and PK results have confirmed the optimal time for selenite administration relative to delivery of the radiation therapy treatments. We hypothesize that this combination treatment will be safe and tolerable, and will improve response rates in patients with metastatic prostate cancer.

This trial would not be possible without the support of the SPARK program and the broad and deep expertise of the SPARK advisors. In addition to funding the clinical trial, SPARK provided critical advice regarding drug supply, regulatory issues, study design and drug development.

Susan Knox, MD, PhD
ASSOCIATE PROFESSOR OF RADIATION ONCOLOGY

A primary area of research in Dr. Knox's laboratory is the study of novel therapies (targeted therapies, radiosensitizers, radioprotectors, and biological response modifiers) for the treatment of solid tumors, with a particular focus on prostate cancer, breast cancer and melanoma, using small animal tumor models.
TOPICAL SMALL MOLECULE FROM PLANT EXTRACT TO PREVENT RADIATION DERMATITIS DURING CANCER TREATMENT

We are developing a topical treatment for reducing the severity of dermatitis caused by radiation therapy. Currently 95% of cancer patients undergoing radiation therapy experience dermatitis, which can cause pain, discomfort, itching, hyperpigmentation, and in some cases temporary discontinuation of radiation therapy. Using a screen of small molecules, we identified a compound that has substantial safety data in humans. We have demonstrated proof-of-concept in a mouse dermatitis model and are planning to move to a guinea pig model.
Our project has focused on developing a therapeutic monoclonal antibody (mAb) directed against CD81 to treat cancer and prevent metastatic disease. We are currently carrying out in vivo testing of class-switched mouse and chimeric anti-CD81 mAbs in immunocompromised mice and are testing for possible toxicity of the mAbs in a humanized immunocompetent mouse model. We ultimately seek to develop a humanized antibody that is both safe and effective for treating cancer patients.
PROJECT

NOVEL PATHWAY FOR TREATING ADENOCARCINOMAS

Our SPARK sponsored project focused on developing an AGR2-targeted therapy for cancer. The approach is novel because it disrupts cell signaling by inhibiting delivery of the EGF receptor (EGFR) to the cell surface. We expect the therapy to be effective in all EGFR-dependent cancers, which includes pancreatic and non-small cell lung cancers. The project was successfully transferred to a new startup this year and is currently progressing very well. This was my second SPARK-sponsored project. The first was a diagnostic assay for chronic pancreatitis that was successfully transferred to InBios International in Seattle, Washington.

Anson Lowe, MD
ASSOCIATE PROFESSOR OF MEDICINE (GASTROENTEROLOGY AND HEPATOLOGY)

Dr. Lowe’s laboratory is focused on human cancers that are dependent on EGFR cell signaling. In particular, the team recently established that the AGR2 protein serves an essential role in EGFR presentation to the cell surface, and represents a novel mechanism of regulating cell signaling. Active projects are focused on cancer pathogenesis, tissue regeneration, development of diagnostic assays, and drug development.

As a physician-scientist, SPARK has been invaluable in my development in translational science. Before SPARK, I knew nothing about how to translate a discovery from my laboratory to people, which should be the endgame for our efforts. The feedback I have received from my fellow SPARKees has always been well-intentioned and constructive, and often more useful than reviews for manuscripts or NIH applications. Programs like SPARK fill a tremendous void in the education of students and faculty, and I hope their continued growth will benefit many more in the future.
**PROJECT**

Our project aims to develop small molecule inhibitors to treat hedgehog dependent cancers like basal cell carcinoma and medulloblastoma. In our studies we have found new therapeutic pathways that allow the tumors to become resistant to clinically available Smoothened inhibitors. We have encouraging preclinical proof of concept data in mice, but needed help in maturing the small molecule from a good idea into a more mature therapeutic that could be commercialized. We have identified the compound and now are addressing formulation issues with the help of SPARK advisors.

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**Anthony Oro, MD, PhD**

**PROFESSOR OF DERMATOLOGY**

Dr. Oro’s lab studies skin stem cells to understand mechanisms of tissue regeneration and carcinogenesis. They have a longstanding interest in the mechanisms of Sonic hedgehog signaling in the hair follicle and the pathogenesis of the most common human tumor, basal cell carcinoma of the skin.

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**Ramon Whitson, PhD**

**POSTDOCTORAL RESEARCH FELLOW, PROGRAM IN EPITHELIAL BIOLOGY**

Dr. Whitson is working with Dr. Oro’s group to determine the molecular basis for secondary resistance in basal cell carcinoma.

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**SPARK value**

What SPARK has provided is seed funding and advice on pathways to mature our clinical therapeutic, organized experts in our area to help us with answers to basic questions in therapeutic development, and brought in speakers to provide additional information. Overall, SPARK represents a key resource to mature early phase therapeutics for skin cancer.
The goal of our SPARK funded project is to repurpose an FDA-approved anti-parasitic drug as a novel treatment for liver cancer, which is a highly fatal disease affecting close to one million patients worldwide. These patients have limited treatment options and typically very poor prognosis. Currently, we are designing new formulations to improve the systemic absorption and efficacy of this drug in mouse models of liver cancer.

Through SPARK, we have been connected to advisors in specialized fields who have provided invaluable and concrete advice on how to move our drug towards a clinical trial for liver cancer patients. This will potentially have a huge impact on the clinical management of liver cancer patients.
Jean Y. Tang, MD, PhD
ASSOCIATE PROFESSOR OF DERMATOLOGY

Dr. Tang’s lab uses mouse models of skin cancer, epidemiology, clinical trials and next gen sequencing methods to identify and test new therapeutics especially for orphan diseases such as Basal Cell Nevus Syndrome (where patients have hundreds of BCC tumors) and patients with Epidermolysis Bullosa who have no treatment.

Jean Y. Tang, MD, PhD

PROJECT

REPURPOSED SMALL MOLECULE TO TREAT BASAL CELL CARCINOMA

SPARK helped the team develop a topical anti-skin cancer therapeutic with a repurposed anti-fungal drug to use in high risk patients. Patients with many skin cancers will benefit from its use to avoid multiple, complicated and sometimes disfiguring surgeries. With SPARK’s help, I learned how to use CROs, to file IP, to file an IND, to pitch, and to find funding to help launch our startup, PellePharm Inc., which now holds the license to topical itraconazole. We are in clinical trials testing topical itraconazole on skin tumors and this trial will be completed by this year.

SPARK taught me the essential differences between a research project and a drug product and de-mystified the steps in between. The SPARK team helped me cross the valley of death between pre-clinical results and human clinical trial testing. SPARK has a treasure trove of industry advisors that bring expertise and resources that are out of the normal scope of academia. I didn’t need to spend a lot of time to network with 50 plus people to find consultants to answer key questions—I just needed to tap into SPARK.
The goal of our project is to further develop and bring to clinical trial a second generation vaccine for the treatment of glioblastoma. This vaccine would benefit these brain tumor patients, and its more robust activity could potentially enhance the survival of patients whose tumor carries the target antigen. We are currently engaging in pre-IND work and plan to initiate clinical trials within a year.

SPARK has been instrumental in obtaining the funds to move this work forward as well as advising on the best direction to take with our work to enhance its commercial potential.
neuropsychiatric projects listed in other sections:

- Craig Garner
  Repurposed small molecule antagonist to improve cognition in Down’s syndrome

- Debra Safer
  Repurposed small molecule to treat Bulimia Nervosa and Binge Eating Disorder

- Stanley Cohen
  Inhibitors of a novel pathway to treat Huntington’s disease and other poly-Q diseases

- Edgar Engleman
  Novel small molecule to treat microglia dysfunction in neurodegenerative diseases
Triggering receptor expressed on myeloid cells-1 (TREM1) is a unique inflammatory membrane receptor that serves as a potent amplifier of severe pro-inflammatory responses. Extensive data in peripheral models of inflammation links TREM1 signaling pathway to increased morbidity and mortality in models of autoimmune disease, infection, and cancer. Our studies indicate that TREM1 also plays a prominent role in pathogenesis in neurological disease models characterized by a significant inflammatory response, including stroke and Alzheimer’s disease. We are interested in developing (i) an inhibitor to TREM1 to block the deleterious effects of runaway brain inflammation and (ii) a TREM1 PET tracer as a companion diagnostic to enable staging of neuroinflammation in models of neurological disease. We have validated TREM1 as a therapeutic target in models of post-stroke inflammation, are working towards validation of TREM1 as an effective target in models of Alzheimer’s disease, and are developing a cell-based assay to use for high-throughput screening for antagonists to TREM1.
Opioid agonists are the most effective drugs for the treatment of both acute and chronic pain; however, the abuse of opioid agonists has become a world-wide epidemic resulting in the deaths of over 15,000 in the United States alone in 2014. The goal of this project is to develop safe, non-addictive opioid analgesics that lack the property of respiratory suppression, the major cause of death from opioid agonists. Using the crystal structure of the mu-opioid receptor as a docking target for in silico screening, we identified a novel opioid agonist (PZM21). PZM21 is an effective agonist in a mouse model of pain, but does not suppress respiration.

Having recently published our initial discovery campaign and positive preclinical results with our first lead molecule, we are currently optimizing the PZM21 scaffold to identify molecules with improved in vivo properties.

The SPARK program enabled us to get valuable feedback from industry experts and provided a framework for the key next steps that would help us translate this discovery. More broadly, SPARK provides a unique educational forum to help academic scientists understand various aspects of the current biotech industry.

Brian Kobilka, MD
HELENE IRWIN FAGAN CHAIR IN CARDIOLOGY; PROFESSOR OF MOLECULAR AND CELLULAR PHYSIOLOGY; PROFESSOR, BY COURTESY, OF CHEMICAL AND SYSTEMS BIOLOGY

Brian Kobilka, Nobel laureate in chemistry, is a biochemist who has devoted most of his career to studying the structure and workings of G-protein-coupled receptors, or GPCRs.

Aashish Manglik, MD, PhD
STANFORD DISTINGUISHED FELLOW AT STANFORD SCHOOL OF MEDICINE; INSTRUCTOR, MOLECULAR AND CELLULAR PHYSIOLOGY

The group’s research is focused on decoding the molecular basis of transmembrane signaling and transport, using a broad range of methods in structural biology, protein biophysics, pharmacology, and protein engineering.
PROJECT

REPURPOSED SMALL MOLECULE TO TREAT POSTOPERATIVE PAIN

We received SPARK funding for a clinical pilot study that tested whether pre-treatment with an IL-1 inhibitor prior to surgery would reduce incisional pain, narcotic drug use, and other outcomes in patients undergoing hip replacement. This treatment was discovered through analysis of a mouse genetic model of incisional wound responses (Anesthesia and Analgesia 111:1525, 2010 and 111:1534, 2010). This study represents an attempt to develop new therapeutic approaches to reduce pain that do not require treatment with narcotic drugs. The initial results indicated that treatment with the IL-1 inhibitor did reduce the production of several cytokines in incisional wound. Further testing is needed to confirm and extend this finding.

Gary Peltz, MD, PhD
PROFESSOR OF ANESTHESIOLOGY, PERIOPERATIVE AND PAIN MEDICINE

Dr. Peltz started his research career at Syntex Inc and then worked for 11 years at Roche Palo Alto, where he was the Head of Genetics and Genomics for 8 years. In 2008 he joined the Anesthesia Department at Stanford, where his laboratory develops and uses state of the art genomic methods to identify genetic factors affecting disease susceptibility, and to translate these findings into new treatments.
Lithium is one of the most effective medications for the treatment of bipolar disorder, but its use is limited by side effects including irreversible kidney damage. Naturally occurring lithium is composed of two isotopes: lithium-7 (about 93%) and lithium-6 (about 7%). In our SPARK project, we are testing whether lithium-7 and lithium-6 differentially contribute to the effectiveness or side effects of lithium. Identifying differential effects from the isotopes would dramatically influence the utility of this medication in those suffering from mental illness.
PROJECT

REPURPOSED AND NOVEL SMALL MOLECULES TO IMPROVE MEMORY IN ALZHEIMER’S DISEASE

Initially, our SPARK project demonstrated the effectiveness of a repurposed drug, a beta1-adrenergic receptor partial agonist, as a therapeutic agent for Alzheimer’s disease. As of July 2014, our program and the intellectual property (IP) related to it were licensed out to Cortice Biosciences, which is aiming to start a phase IIA proof of concept human trial.

Based on the initial repurposed drug, a second funding award from SPARK was used to develop a new small molecule that can pass the blood brain barrier, minimizing cardiovascular side effects and thus effectively providing symptom relief and disease-modifying effects for Alzheimer’s disease. If successful, our project will lead to the generation of a novel class of drug candidates for Alzheimer’s disease and thus benefit millions of people affected by the disease.
cardiovascular SPARK
The goal of this project is to develop a therapeutic molecule for the treatment of heart failure that will act on a novel receptor pathway that controls appetite and sleep. There are over five million people in the US with heart failure that could benefit from this novel type of treatment. We are currently designing and evaluating small molecules that act on this pathway.

Although the funding from SPARK allowed our project to progress, it really has been the guidance we received from our SPARK mentors that pointed us in the right direction. The feedback from the entire SPARK community has been generous and very concretely helped guide our path.

Marco Perez, MD
ASSISTANT PROFESSOR OF MEDICINE (CARDIOVASCULAR MEDICINE)

Dr. Marco Perez's research goal is to better understand the fundamental causes of cardiovascular disease through the study of genetics and epidemiology. He has led the studies of atrial fibrillation in the Women's Health Initiative, one of the largest nation-wide population-based cohorts.

Euan A. Ashley, MB, ChB, DPhil
ASSOCIATE PROFESSOR OF MEDICINE (CARDIOVASCULAR), OF GENETICS AND, BY COURTESY, OF PATHOLOGY

Dr. Ashley's research is focused on precision medicine, and he led the team that carried out the first clinical interpretation of a human genome. He is co-founder of Personalis Inc, a genome scale genetic diagnostics company.

SPARK VALUE

Although the funding from SPARK allowed our project to progress, it really has been the guidance we received from our SPARK mentors that pointed us in the right direction. The feedback from the entire SPARK community has been generous and very concretely helped guide our path.
metabolic
SPARK
metabolic projects listed in other sections:

Justin Annes
DRUG TO INDUCE BETA CELL REGENERATION FOR TREATMENT OF TYPE 2 DIABETES

David Stevenson
NEONATAL HYPERBILIRUBINEMIA

Tracey McLaughlin
REFORMULATED BIOLOGIC TO TREAT HYPOGLYCEMIA AFTER RNY GASTRIC BYPASS
PROJECT

SMALL MOLECULE ACTIVATORS OF TARGET ENZYME TO PREVENT OXIDATIVE STRESS INJURY AND ACCELERATE DETOXIFICATION OF ALDEHYDES

My SPARK project focuses on the development of a new drug category to enhance a cell's ability to detoxify many toxic aldehydes that cause human diseases. Buildup of toxic aldehydes has been associated with many neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease and orphan diseases such as Fanconi anemia and Sjögren-Larsson syndrome, and currently there is no cure for these diseases. I identified a novel small molecule activator of a key enzyme in the process and SPARK provided much needed medicinal chemistry and clinical advice, helped choose the first clinical indication, and provided guidance on the preparation of the preclinical package.

Through the assistance of SPARK, we successfully launched a new biotech company, completed the FDA filing and a phase I trial. Currently, we are securing additional funding to initiate a new program targeting additional diseases. The SPARK program has helped me tremendously in learning and understanding the complexity of new drug development. The advisors provided insight that comes from years of experience, without which the project would not have progressed this far.

Che-Hong Chen, PhD
SENIOR RESEARCH SCIENTIST

Dr. Chen has been working with Prof. Daria Mochly-Rosen’s laboratory at Stanford University for the past 21 years. His current focus is to study the function of the Aldehyde Dehydrogenase (ALDH) multi-gene family and its association with human diseases.
PROJECT

NOVEL SMALL MOLECULE SELECTIVE CHLORIDE CHANNEL INHIBITORS TO TREAT HYponATREMIA

Chloride “ion channels” form pathways (literally nano-scale “channels”) that allow movement of chloride ions across cell membranes in the body. Chloride ion channels specific to the kidney play crucial roles in the balance of salt and water in the body, which in turn is crucial to cardiovascular health. In this project, we developed small molecules that specifically modulate the function of kidney chloride channels. These novel molecules are excellent candidates for treating certain cardiovascular diseases more safely and effectively than current therapies. To test these newly developed candidate molecules, we performed pilot studies in rats and determined that the molecules have good bioavailability. Currently, we are seeking funding to test efficacy of the molecules in animal models whose kidneys are more closely related to those of humans.

metabolic

Merritt Maduke, PhD
ASSOCIATE PROFESSOR OF MOLECULAR AND CELLULAR PHYSIOLOGY

Dr. Maduke’s group studies the molecular mechanisms of ion channels and transporters, and the proteins that catalyze this transport. Their major research focus is on the chloride-selective CLC family, which contains both types of ion-transport protein. The team uses a combination of biophysical methods to investigate membrane-protein structure and dynamics together with electrophysiological analyses to directly measure function.

SPARK v a l u e

SPARK uniquely enabled us—three Stanford faculty members with complementary expertise in chemistry, biophysics, and renal physiology—to successfully develop this project and to gain invaluable guidance from SPARK advisors with broad expertise in cost-effective translation of academic discoveries into drugs. We are excited and grateful to have launched this project and to continue towards developing novel therapies.
PROJECT

DEVELOPMENT OF DESETHYLHYDROXYCHLOROQUINE (DHCQ) TO TREAT NON-ALCOHOLIC STEATOHEPATITIS (NASH) AND OTHER INFLAMMATORY DISEASES

Our SPARK project is to develop desethylhydroxychloroquine (DHCQ) for non-alcoholic steatohepatitis (NASH), also known as fatty liver disease. NASH affects 2-5% of the U.S. population, yet there are no disease-slowing therapies. We demonstrated that DHCQ prevents and treats NASH in mouse models, and that its activity is due to blocking Toll-like receptor (TLR)-mediated activation of macrophages. We are now working to take DHCQ forward into human clinical trials. We have benefited tremendously from the SPARK program in multiple dimensions.

SPARK value

SPARK provided education on the drug development process and invaluable guidance/technical input on our project. For example, despite selecting a well-known CRO, SPARK’s chemistry experts realized that the CRO had not synthesized the correct molecule. They then guided the CRO to perform the necessary analytical assays and to modify their synthesis approach to ultimately produce the correct molecule. As we are medical and biologic investigators without expertise in chemistry, SPARK advisors were critical to the success of our project.
gastroenterology projects listed in other sections:

Karl Sylvester
DIAGNOSTIC FOR NECROTIZING ENTEROCOLITIS AND PREDICTOR OF FEEDING INTOLERANCE IN PREMATURE BABIES
PROJECT

CHINESE BOTANICAL FOR TREATMENT OF INFLAMMATORY BOWEL DISEASE

We are developing a botanical drug for ulcerative colitis. We hope that this treatment will accelerate the induction and maintenance of remission and thereby prevent disease extension and other complications, reduce second-line therapy use and the number of colectomies, and improve quality of life in ulcerative colitis patients. SPARK advisors guided us through the completion of the preclinical plan, designing the trial, filing the IND and finding the clinical team to execute it. We currently have an open Investigational New Drug Application and are conducting a Phase1b clinical trial at Stanford with the first patient enrolled a few weeks ago.

Julie Saiki, MS
GRADUATE STUDENT IN CHEMICAL AND SYSTEMS BIOLOGY

Julie Saiki completed the masters of medicine program at Stanford Medical School and joined the Mochly-Rosen lab in 2014 as a graduate student.

Berkeley Limketkai, MD
CLINICAL ASSISTANT PROFESSOR, MEDICINE (GASTROENTEROLOGY AND HEPATOLOGY)

Dr. Limketkai’s clinical and research interests lie at the nexus of inflammatory bowel disease (IBD), intestinal failure, and nutrition. Their multi-disciplinary team specializes in the treatment of patients with simple to complex IBD, intestinal failure, and/or nutrition-related disorders. They often combine targeted nutritional and medical treatment strategies to optimize clinical outcomes.

SPARK value

Julie started the project while still a PhD student in music! The SPARK advisors patiently guided her through the complicated process of translating an observation from a patient’s experience to a proper clinical trial. None of that was possible without hours and hours of experts’ advice and encouragement. SPARK also transformed Julie’s career; she is working now towards a PhD in Chemical and Systems Biology to pursue a career in the biopharmaceutical field.
hematology projects listed in other sections:

- Clara Lo
  REPURPOSED SMALL MOLECULE TO TREAT CHRONIC IMMUNE THROMBOCYTOPENIA IN JUVENILES

- Everett Meyer
  MONOCLONAL ANTIBODY THERAPY TO PREVENT ACUTE GRAFT-VERSUS-HOST DISEASE FOLLOWING HEMATOPOIETIC CELL TRANSPLANTATION
New oral anticoagulants are in use for preventing pathological blood clots without an antagonist available to reverse their effects in the event of bleeding. We developed a modified form of thrombin that blocks the activity of one of the new anticoagulants, dabigatran, whose mode of action is to inhibit thrombin. Development has been halted because we were scooped; other potential antagonists have been discovered that can block all of the novel anticoagulants.

The funding from SPARK allowed us to prove the concept that a modified thrombin could reverse the effects of dabigatran and to identify a development candidate.
for more information

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