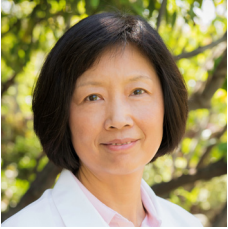


# 2019 TRANSLATIONAL RESEARCH GRANT

Awarded by the Pancreatic Cancer Action Network



## YUAN CHEN, PhD

Dr. Chen is currently the dean of transdisciplinary research and professor in the department of molecular medicine at the Beckman Research Institute of the City of Hope. She obtained her PhD in structural biology and biochemistry from Rutgers University. She then conducted postdoctoral studies at the Scripps Research Institute before joining Beckman Research Institute of the City of Hope as faculty in 1994.

Her current research interests center on the role of ubiquitin-like modifications in major oncogenesis pathways and anti-tumor immunity, and on the development of therapies to target novel mechanisms to treat recalcitrant cancers like pancreatic cancer.



### PROJECT TITLE

Activating Anti-Tumor Immunity by Targeting a Ubl Modification



### INSTITUTION

Beckman Research Institute of the City of Hope



### AMOUNT

\$500,000

## PROJECT OVERVIEW

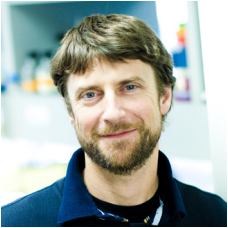
Immunotherapies, using the patient's immune system to fight off their cancer, have greatly improved treatment of several solid tumors, extending patient survival and reducing side effects compared to traditional chemotherapy. However, patients with pancreatic cancer have not benefited from this approach, largely because the immune cells present in the tumor are not the ones that respond to immunotherapy. In fact, the cells act to suppress the immune response by blocking other anti-cancer immune cells from entering the tumor. The goal of Dr. Chen's proposed study is to characterize a new target and mechanism that her research team expects will remove the immune privilege of pancreatic cancers so that an anti-tumor immune response could be achieved to improve patient outcomes.

The proposed study aims to enhance the role of immune cells that confer long-term memory against cancer, known as T-cells. Two types of T-cells play key roles in fighting pancreatic and other cancers: effector T-cells that kill cancer cells and regulatory T-cells that inhibit the activity of effector T-cells. Emerging research and Dr. Chen's preliminary data indicate that blocking the signaling pathways controlled by a mechanism known as SUMOylation (small ubiquitin-like modifications) reduces regulatory T-cell numbers and function, while enhancing the ability of effector T-cells to infiltrate and kill cancer cells. The proposed studies will further investigate these effects and help Dr. Chen and colleagues understand the mechanism using mouse models and novel drugs to inhibit this pathway.

Dr. Chen has gathered a transdisciplinary team of doctors and scientists who are leaders in cell signaling and immunity, pancreatic cancer and surgical oncology. This innovative research leverages City of Hope's outstanding research infrastructure, which focuses on rapidly translating new discoveries into more effective therapies for patients. They believe these studies have the potential to transform pancreatic cancer therapy.

# 2019 TRANSLATIONAL RESEARCH GRANT

Awarded by the Pancreatic Cancer Action Network



## NICHOLAS COSFORD, PhD

Dr. Cosford received his BSc and PhD degrees in chemistry from the University of Bath and pursued postdoctoral studies at Emory University. He has 20 years' experience leading small-molecule drug discovery projects in biotech and big pharma, and more recently in the non-profit sector at Sanford Burnham Prebys Medical Discovery Institute.

Dr. Cosford's research is broadly structured around the chemical biology of diseases and involves the investigation of small molecule interactions with therapeutically important proteins and cellular signaling pathways. One aspect of his research is focused on studying cellular pathways that regulate tumor cell metabolism, apoptosis and autophagy.

Therapeutically, he is interested in the discovery and optimization of compounds that have the potential to treat cancer, central nervous system diseases and infectious diseases. He is also interested in the application of microfluidic technology to chemical and biological problems.



### PROJECT TITLE

Preclinical  
Development of a  
ULK1/2 Inhibitor for  
Pancreatic Cancer



### INSTITUTION

Sanford Burnham  
Prebys Medical  
Discovery Institute



### AMOUNT

\$500,000

## PROJECT OVERVIEW

Cancer cells undergoing rapid division rely on a cellular recycling process called autophagy, which removes damaged cellular components and supplies required nutrients for growth. Pancreatic cancer has been shown to be particularly reliant on autophagy and is sensitive to its disruption. Dr. Cosford and his research team's efforts are directed toward the development of selective compounds that can interfere with autophagy and the advancement of these compounds into clinical trials.

The investigators have identified a series of compounds that inhibit a key activator of the autophagy pathway, a protein called ULK1. Their lead ULK1 inhibitor drug kills pancreatic tumor cells grown in a dish, reduces pancreatic tumor size in animal models, is orally available and is well tolerated in mice.

To prepare their candidate drug for trials in pancreatic cancer patients, Dr. Cosford and colleagues propose to conduct a series of preclinical studies. They will produce large quantities of their drug for animal testing and optimize how the drug is prepared in order to meet the exacting standards required by the Food and Drug Administration (FDA) for human trials. They will then assess the effectiveness of the lead drug and whether it has the expected effect using genetic models of pancreatic cancer as well as mouse models derived from patient tumors. They will also examine the drug-like properties of their compound using established criteria for safety and potency. Performing these studies will allow the team to obtain the critical data required to move this new therapeutic into the clinic.

AWARD PERIOD

JULY 1, 2019

JUNE 30, 2021

# 2019 SKIP VIRAGH CAREER DEVELOPMENT AWARD

Awarded by the Pancreatic Cancer Action Network



## DANNIELLE ENGLE, PhD

Dr. Engle is currently an assistant professor at the Salk Institute for Biological Studies. She earned her PhD from the University of California, San Diego, in 2011. While completing her doctoral studies, her father passed away from pancreatic cancer.

In 2012, Dr. Engle joined the lab of Pancreatic Cancer Action Network grantee David Tuveson, MD, PhD, as a postdoctoral fellow. As a postdoc, Dr. Engle focused on developing new models of pancreatic cancer to facilitate the discovery of early detection strategies and new treatment approaches.

Dr. Engle is the recipient of a National Institutes of Health/National Cancer Institute Career Transition Award and a Theodore T. Puck Award, among other honors.



### PROJECT TITLE

CA 19-9 Promotes  
Pancreatitis and  
Pancreatic Cancer



### INSTITUTION

Salk Institute for  
Biological Studies



### AMOUNT

\$200,000

## PROJECT OVERVIEW

Pancreatitis is a type of pancreatic inflammation that results in more than 275,000 hospital admissions each year in the United States and is lethal in 10 percent of cases. Pancreatitis is a major risk factor for developing pancreatic cancer. More research into pancreatitis, and how it contributes to tumor formation, may uncover treatment targets.

CA19-9 is a biomarker that is often elevated in both pancreatitis and pancreatic cancer patients. In her previous work, Dr. Engle discovered that CA19-9 elevation causes pancreatitis in pancreatic cancer mouse models. And in the mouse models, blocking CA19-9 dramatically reduced the severity of pancreatitis.

Building on her past work, Dr. Engle's study will further investigate ways through which CA19-9 elevation promotes pancreatitis and pancreatic tumor formation. The study will serve as the basis for future pre-clinical and clinical intervention trials using agents that target CA19-9 and the proteins and pathways it activates.

AWARD PERIOD

JULY 1, 2019



JUNE 30, 2021

# 2019 JULIA STAGLIANO CATALYST GRANT

Awarded by the Pancreatic Cancer Action Network



## INGUNN STROMNES, PhD

Dr. Stromnes is currently an assistant professor in the department of microbiology and immunology at the University of Minnesota. She received her PhD from the University of Washington in 2007. As a postdoctoral scientist at the Fred Hutchinson Cancer Research Center, she developed a novel and promising immunotherapy by genetically engineering T-cells to invade and attack pancreatic cancer without the toxic side effects of chemotherapy. Her postdoctoral studies were conducted under the mentorship of Pancreatic Cancer Action Network (PanCAN) research grant recipients Drs. Philip Greenberg and Sunil Hingorani.

In 2017, Dr. Stromnes established her laboratory at the University of Minnesota. Also in 2017, Dr. Stromnes received the Skip Viragh Career Development Award from PanCAN. Dr. Stromnes' current research interests focus on integrating basic cancer immunology research with clinical translation of new cellular immunotherapies for pancreatic cancer patient treatment.



### PROJECT TITLE

Overcoming  
Immunotherapy  
Resistance in  
Pancreas Cancer



### INSTITUTION

University of  
Minnesota



### AMOUNT

\$500,000

## PROJECT OVERVIEW

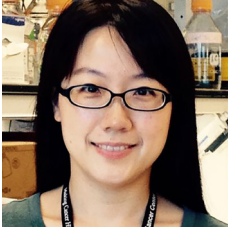
Immunotherapy, treatment that helps a person's immune system fight diseases, is producing remarkable results in many advanced cancers. However, immunotherapy has not been effective for the treatment of pancreatic cancer, because of the suppressive microenvironment (area around the tumor) that shields tumor cells from immune system detection. It is also likely that pancreatic cancer expresses only a few proteins different from proteins expressed in normal tissues, which also limits detection by the immune system.

To overcome these obstacles, Dr. Stromnes and colleagues have developed and studied genetically engineered immune cells, called T-cells, designed to specifically target and kill tumor cells. While the study results were promising, they also showed that the engineered T-cells lessened in quality and quantity over time.

Dr. Stromnes and colleagues hypothesize that the tumor and microenvironment use a cloaking mechanism, through production of TGF $\beta$ , to evade and suppress T-cells. In this proposed study, Dr. Stromnes and colleagues will test the effectiveness of T-cells that are genetically modified to both attack cancer cells and interfere with TGF $\beta$ . Their goal is to identify a T-cell therapy that will provide safe and durable clinical responses in pancreatic cancer patients.

# 2019 TRANSLATIONAL RESEARCH GRANT

Awarded by the Pancreatic Cancer Action Network



## WANTONG YAO, MD, PhD

Dr. Yao is an assistant professor at University of Texas MD Anderson Cancer Center. Dr. Yao obtained her PhD degree from Fudan University, China, where she focused her research on understanding the molecular mechanisms for pancreatic cancer (pancreatic ductal adenocarcinoma) development and progression, specifically on the regulation and function of cytoskeleton remodeling.

The clinical challenges she faced during her clinical training specialized in pancreatic cancer surgery in Shanghai Cancer Center further motivated her to pursue further postdoctoral training in Dr. Giulio Draetta's lab in MD Anderson Cancer Center with the goal of discovering new mechanisms, biomarkers and vulnerabilities as drug targets for pancreatic cancer. Her research work during this period led to the discovery of syndecan-1 (SDC1), a cell surface proteoglycan linked to cytoskeleton, as an important functional protein activated by mutant KRAS. This work was funded by the Pancreatic Cancer Action Network Pathway to Leadership Grant in memory of Carina Rogerson. Following the establishment of her independent lab in 2018, Dr. Yao continues to explore the therapeutic potential of SDC1 and explore additional key targetable nodes for the treatment of pancreatic cancer.



### PROJECT TITLE

Targeting Syndecan1  
in Pancreatic Cancer



### INSTITUTION

MD Anderson  
Cancer Center



### AMOUNT

\$500,000

## PROJECT OVERVIEW

The most common type of pancreatic cancer, pancreatic ductal adenocarcinoma, is almost universally driven by genetic mutations in KRAS, designating it an ideal therapeutic target. However, no effective drugs directly inhibiting mutant KRAS have reached the clinic.

Dr. Yao and her colleagues' recent work has established that the protein syndecan-1 (SDC1) plays a critical role in helping pancreatic cancer cells survive and grow. Furthermore, they have shown that SDC1 is tightly regulated by mutant KRAS, and this relationship is required for pancreatic cancer progression and maintenance. The team's studies to determine why the mutant KRAS-SDC1 relationship is needed for pancreatic cancer uncovered that SDC1 is crucial for a process called macropinocytosis, by which pancreatic and other tumors scavenge "food" to fuel their growth.

It stands to reason that blocking the food supply of pancreatic cancer cells by inhibiting SDC1-triggered macropinocytosis may result in cell death. Thus, in Dr. Yao's effort to target this SDC1 driven cancer mechanism, she and her team developed therapeutic antibodies to target SDC1. Building on this substantial work, the overarching objective of this proposed research is to further characterize the role of SDC1 in the metabolic reprogramming of pancreatic cancer cells and to explore the potential of SDC1 as a therapeutic target with its antibody. These studies will provide important new data regarding the potential of SDC1 to serve as a therapeutic target for pancreatic cancer in the clinic.

AWARD PERIOD

JULY 1, 2019

JUNE 30, 2021

# 2019 TRANSLATIONAL RESEARCH GRANT

Awarded by the Pancreatic Cancer Action Network



## XIAOCHUN YU, MD, PhD

Dr. Yu received his MD from Beijing Medical University in China and PhD from Kurume University in Japan. He did research fellowship training at Mayo Clinic from 2002 to 2006. Dr. Yu established his laboratory at University of Michigan Medical School in 2006. From 2006 to 2015, Dr. Yu was promoted from assistant professor to full professor. In 2015, Dr. Yu moved to City of Hope.

The research interests from Dr. Yu's laboratory focus on DNA damage repair and its role in tumor suppression. His group not only examines the underlying molecular mechanism but also translates the basic research findings into clinical cancer treatment. Dr. Yu has received several awards such as American Cancer Society Research Scholar, Department of Defense Era of Hope Scholar and Leukemia and Lymphoma Society Research Scholar.



### PROJECT TITLE

Targeting  
dePARylation for  
Pancreatic Cancer  
Treatment



### INSTITUTION

Beckman Research  
Institute of the City  
of Hope



### AMOUNT

\$500,000

## PROJECT OVERVIEW

Normal cells in the body, including ductal cells and acinar cells of the pancreas, encounter DNA damage on a daily basis. However, healthy cells have precise mechanisms to repair damage to DNA. Genetic mutations can stop DNA damage repair (DDR), which causes genomic instability and can lead to tumor formation. Thus, a subset of pancreatic cancer is defective in DDR.

Recently, accumulated evidence shows that drugs called PARP inhibitors, which block a process called poly(ADP-ribosyl)ation, selectively kill tumor cells with DDR defects, such as mutations in BRCA 1 or 2 or similar-acting proteins. Several PARP inhibitors have been approved by the FDA for the treatment of advanced breast cancer and ovarian cancer with BRCA mutations.

However, the efficacy of PARP inhibitors in pancreatic cancer treatment remains elusive. One of the reasons is that currently available PARP inhibitors may not be able to fully shut down poly(ADP-ribosyl)ation-mediated DDR in pancreatic cancer cells. However, based on Dr. Yu and his team's preliminary studies, they find dePARylation is a key event during DDR. Thus, in this application, they plan to characterize the role of dePARylation in DDR and develop a novel chemotherapeutic approach to target dePARylation for pancreatic cancer treatment.

AWARD PERIOD

JULY 1, 2019



JUNE 30, 2021