Research Publications from the Hirshberg Translation Laboratory in 2024

The Ronald S. Hirshberg Translational Pancreatic Cancer Research Laboratory is a pillar of our UCLA research program. It is the first lab exclusively dedicated to investigating the biology of pancreatic cancer. Under Dr. Guido Eibl's leadership, the lab is consistently funded by the National Institutes of Health (NIH) and continues to advance our understanding of how diet, obesity, and inflammation contribute to tumor development.

We celebrate Dr. Eibl and his team's ongoing contributions and look forward to sharing more groundbreaking discoveries from their research.

Publications from the Translational Laboratory in 2024

Upregulated Matrisomal Proteins and Extracellular Matrix Mechanosignaling underly Obesity-associated Promotion of Pancreatic Ductal Adenocarcinoma. **Cancers** 2024;16(8):1593 (PMCID: PMC11048773)
R.Waldron, A.Lugea, H.-H.Chang, H.-Y.Su, C.Quiros, M.Lewis, M.Che, V.K.Ramanujan, E.Rozengurt, G.Eibl, S.Pandol.

This study is a comprehensive proteomic analysis of the pancreas of KC mice fed either a control or high-fat diet. Our results clearly demonstrate that multiple changes in pancreatic protein and phosphoprotein expression occur during the development of pancreatic cancer in obese KC mice. This study also utilized spatial proteomics to locate the expression patterns in certain

regions and cell populations of the pancreas.

Stress and obesity signaling converge on CREB phosphorylation to promote pancreatic cancer. **Molecular Cancer Research** 2024, Dec 6, Online ahead of print
X.Sun*, Y.Teper*, J.Sinnett-Smith, M.Markarian, O.J.Hines, G.Li, G.Eibl#, E.Rozengurt#. (* dual first authorship, # dual senior authorship)

This is the first report of the combinatorial effect of social isolation and diet-induced obesity in any preclinical cancer model. We found that social isolation accelerates pancreatic cancer development in obese KC mice, with a stronger impact in female mice. Mechanistically, our data suggest that the effect of social isolation and diet-induced obesity is mediated by activating signaling pathways that converge on CREB. Detailed cell culture experiments dissected the signaling pathways involved. Our study also suggests a beneficial effect of beta blockers in this disease.

New grants awarded in 2024

"Impact of dietary lipids on pancreas cancer initiation and progression"
MPI: Christofk/Eibl/Plath
This project will define the effects of high-fat diets, mostly lard or coconut oil, on the pancreatic microenvironment and pancreatic tumorigenesis using an innovative mouse model and transcriptomic and metabolic analyses.

Presentations in 2024

American Pancreatic Association
Maui, HI, December 9-12, 2024
"Chronic social isolation stress in combination with diet-

induced obesity accelerates pancreatic cancer development in KC mice.”
Y.Teper, X.Sun, R.T.Waldron, A.Lugea, J.Sinnett-Smith, O.J.Hines, G.Li, D.W.Dawson, S.J.Pandol, E.Rozengurt, G.Eibl. 55th Annual Meeting of the American Pancreatic Association

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Seed Grant Awardee Advances Groundbreaking Research on Pancreatic Cancer and Pain Management

Since 2005, our Seed Grant Program has fostered an environment for research to bloom. As we mark 20 years since our first cohort of grantees, it is more exciting than ever to look back and see all that is being accomplished.

We’re delighted to share an exciting update on Jami Saloman, PhD, a distinguished recipient of a 2016 Seed Grant Award, whose pioneering research on pancreatic cancer and pain regulation has gained national recognition and funding from major organizations. The Seed Grant initially awarded to Dr. Saloman has been instrumental in her journey, enabling the collection of critical data that has now culminated in a prestigious R01 grant from the National Cancer Institute (NCI) for her project titled “Peripheral Nerve Regulation of Pancreas Cancer Progression.” The Research Project (R01) is NIH’s most commonly used grant program for independent research projects. It is awarded to support mature, hypothesis-driven research projects with strong

preliminary data. The grant funds a discrete, specified, circumscribed project in an area representing the researcher's specific interest and competencies.

Dr. Saloman's interest lies in understanding how the nervous system, particularly sensory nerves, interacts with pancreatic cancer. In her postdoctoral work, she was the first to demonstrate that ablation of sensory nerves could significantly inhibit pancreatic ductal adenocarcinoma (PDAC) progression, showing that nerves in the pancreas might create a "safe harbor" environment for tumor development. Thanks to the Hirshberg Foundation Seed Grant, Dr. Saloman showed an increased anti-tumor immune response in the absence of nerves—a finding with vast implications for immunotherapy and cancer treatment strategies.

One of her significant achievements with the Seed Grant was refining methods for isolating individual neurons connected to the pancreas and performing transcriptomic analysis. This breakthrough revealed that these sensory neurons express immune-regulating genes, including certain "inhibitory checkpoints." Such insights laid the groundwork for her Career Development Award from the Pancreatic Cancer Action Network. As a junior faculty member, Dr. Saloman explored the role of neuronally expressed PDL1 and NRP1 in the regulation of both PDAC-related immune responses and cancer pain.

This momentum led Dr. Saloman to secure an R01 grant from the NCI, where she will continue her work to understand the neural influence on the tumor microenvironment and lymphatic spread, focusing on PDAC-related pain and potential interventions. Additionally, she recently received funding from the National Institute of Neurological Disorders and Stroke (NINDS) to investigate inhibitors of the NRP1 protein, potentially offering new therapeutic avenues for PDAC pain management.

Dr. Saloman's work exemplifies the impact that the Hirshberg Foundation's Seed Grant Program has on accelerating critical research that reshapes our understanding of pancreatic cancer and advances innovative treatment solutions. We are honored to support researchers like Dr. Saloman, whose dedication to discovery holds promise for transformative therapies for cancer progression and cancer-related pain.

Thanks to your support, we've been planting seeds of hope through our Seed Grant Program for 20 years. It's a delight to watch research grow from the lab to the clinic and bloom into clinical trials and new treatment options.

Help us continue to sow seeds of hope for a cancer-free future, donate today.

Exciting Updates from our Scientific Advisory Board Member & past Seed Grant Awardee

Since 2005, our Seed Grant Program has fostered an environment for research to bloom. As we mark 20 years since our first cohort of grantees, it is more exciting than ever to look back and see all that is being accomplished.

Marina Pasca di Magliano, PhD is one of the world's leading pancreatic cancer researchers. As a 2015 Seed Grant Awardee, her project deepened the understanding of mutant P53 in

pancreatic cancer progression and metastasis. The resulting research, published in 2018 by Dr. Pasca di Magliano and her lab, found that p53 mutation is required for the formation and maintenance of KRAS-induced pancreatic cancer precursor lesions. Her lab photo shows a large and diverse group of researchers that she fostered to help publish this insight.

For the past 15 years, Dr. Pasca di Magliano has run a lab at the Rogel Cancer Center at the University of Michigan. Now, thanks to a $50 million gift, she will co-lead and help create the Rogel and Blondy Center for Pancreatic Cancer. The center will be co-led by Dr. Pasca di Magliano, Costas Lyssiotis, Ph.D., and Timothy Frankel, M.D., a 2014 Seed Grant Awardee. This new Center embodies a key tenet that the Hirshberg Foundation has long heralded: collaboration is key.

Dr. Pasca di Magliano told Michigan Medicine that one key to their success is that "many of us have labs next to each other…It allows for an exchange of ideas, joint mentoring of trainees, and a lot of collaboration." She shares that having clinicians involved in research is another key that "helps us keep in perspective that everything we do is about patients, about preventing, detecting, and treating pancreatic cancer."

When asked about the future of pancreatic cancer research, Dr. Pasca di Magliano said, "research is moving toward a more personalized oncology approach… We have to respond to each patient's disease, not just initially but throughout treatment." Another area of potential is "to get an immune response to the tumor. I strongly believe that's the only way we will get long-term control over the disease."

In 2023, it was an honor to have Dr. Pasca di Magliano join our Scientific Advisory Board to help shape the future of our Seed Grant Program and foster collaboration across and among

universities. We celebrate and admire the work that Dr. Pasca di Magliano is leading at the Rogel and Blondy Center for Pancreatic Cancer.

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American Cancer Society Shares Latest Pancreatic Cancer Statistics

The American Cancer Society (ACS) has officially published their Annual Cancer Facts & Figures Report, a reputable record for national cancer statistics. The latest data shows the 5-year pancreatic cancer survival rate holding steady at 13%. Pancreatic cancer remains the third-leading cause of cancer-related deaths in the United States after lung and colon cancers. **This report also shares that individuals diagnosed with local stages of the disease have a survival rate of 44%, a number that has increased in survival by 5% since 2021, emphasizing the importance of early detection.** It's important to remember that these are statistics, but they are not the driving force behind the Hirshberg Foundation's commitment to fight this disease – patients and families are!

The journey of pancreatic cancer remains unique for each individual, and survivors should have support and care that fits their needs. **Dr. Timonthy Donahue, Director of the AH Center for Pancreatic Diseases at UCLA shared at the Foundation's Symposium, "We are not only giving state of the art care, we are redefining state-of-the-art care."** Additionally, scientists are vigorously investigating pancreatic cancer as part of the Foundation's Seed Grant Program with the newest cohort of scientists focusing on therapies and treatments, early diagnosis, and prevention. Advancing research to improve patient care, pioneering new therapies, and ultimately boosting pancreatic cancer survival rates is a fundamental part of the Foundation's mission. Pancreatic cancer will continue to be relentlessly fought on all fronts.

Foundation news, educational videos, and research updates shared in the last few months include: the new cohort of Seed Grant recipients for 2024/2025, improving patient care through the Canopy Cancer Collective, and Targeting KRAS to Treat Pancreatic Cancer. Executive Director Lisa Manheim shares, "**Our dedication to improving outcomes for patients has never been more resolute.** A dedicated community of skilled scientists and doctors is advancing pancreatic cancer research worldwide. Each year, we make significant strides fueled by progress, exploration, and partnership. Our commitment to offering patients the hope of improved outcomes has never been stronger."

This analysis in this report demonstrates a continued need to address modifiable risk factors, consider genetic testing, and explore avenues for early detection. Modifiable risk factors like smoking put individuals at twice the risk of diagnosis. **These risk factors are being investigated by Hirshberg Foundation scientists in our labs at UCLA and across the country; the research is in the areas of type 2 diabetes, obesity, and pancreatitis.** The UCLA based Sahin-Toth Laboratory

focuses on major risk factor for pancreatic cancer, hereditary chronic pancreatitis; this lab is led by our Scientific Advisory Board Chair, Dr. Miklos Sahin-Toth. The Hirshberg Translational Laboratory is solely dedicated to investigating the intricate ways that diet, obesity and inflammation can accelerate tumor development. The Hirshberg Foundation looks forward to sharing more advances in 2025!

The Hirshberg Foundation continues to lead the fight for a cure and share our mantra: *Never Give Up*. Survivors, caregivers, and families remain the most powerful champions and heartfelt supporters in this fight. Join us by making a donation, attending a Hirshberg event, or elevating awareness in your community, so together we can continue this momentum towards a cure.

The 19th Annual Symposium on Pancreatic Cancer will be held in-person at UCLA on April 5th, with videos made available to watch online. This is a pivotal event for our community with Founder, Agi Hirshberg sharing last year, “If you’re here for the first time, you will meet friends that have enjoyed cancer free life for 5, 10, 15 and 22 years!” Patients, caregivers, long-term survivors, and family members are invited to sign up for this free event when registration opens in February.

Read more on the ACS report →

Resources for Patients, Preventions, and Education

One-on-One Support
Patient & Family Webinars
Genetic Testing
Clinical Trials

Summary of the Hirshberg Symposium at the 2024 American Pancreatic Association

Each year, the APA gathers a global community of researchers to explore the latest advancements and opportunities in clinical and basic science research focused on pancreatic diseases, with an emphasis on pancreatic cancer. As part of this collaboration, the Hirshberg Foundation hosts the annual Hirshberg Symposium, spotlighting cutting-edge topics. This year's symposium, *Targeting KRAS to Treat Pancreatic Cancer,* delved into the evolving therapeutic landscape of KRAS inhibitors and shared fresh perspectives on the biology and treatment strategies for pancreatic cancer.

Field and Historical Timelines

Channing Der, PhD
University of North Carolina, Chapel Hill

Dr. Der reviewed the seminal findings in the field of KRAS starting with the identification of this signaling protein and the central role it plays in cellular physiology. Dr. Der is an expert in KRAS, made many of the initial discoveries about KRAS and continues this research. Nearly all pancreatic cancers have a mutation in KRAS, and it is thought that this is an initiating factor in pancreatic carcinogenesis. KRAS may have the same impact on as many as 20% of all cancer types.

Current Therapeutic Landscape of KRAS Inhibitors

Gabriela Chiorean, MD
Fred Hutchinson Cancer Center

Dr. Chiorean reviewed many of the clinical trials that have used KRAS inhibitors to treat cancer. Very recently, advances in the understanding of the structure and function of KRAS has allowed the ability to develop drugs that target this protein. Early trials with KRAS inhibitors like sotorasib (the first KRAS inhibitor approved by the FDA which targets the G12C mutation) and others indicate these drugs can have equal benefit to traditional chemotherapy in delaying cancer progression in patients with advanced disease. Now there is interest in combining KRAS inhibitors with other modalities like tumor vaccines and chemotherapy.

New Insights Into the Biology and Therapy Strategies for Pancreatic Cancer

Raghu Kalluri, MD, PhD
University of Texas MD Anderson Cancer Center

Dr. Kalluri reviewed the biology of KRAS inhibitors and how cancers can have variable KRAS mutations in tumor development. Importantly, it is possible to reverse the impact of KRAS on early changes in the pancreatic cancer development before the cancer is formed with KRAS inhibition in models. This demonstrates the importance of KRAS and how targeting this abnormally active protein is potentially very valuable for patient treatment.

Mechanisms of Resistance to KRAS Inhibitors

Andrew Aquirre MD, PhD
Dana-Farber Cancer Institute, Broad Institute at Harvard and MIT

Dr. Aquirre discussed the current status of KRAS drugs and relayed that there are as many as 100 new KRAS inhibitors in development to treat cancer. Each drug has a different mechanism of action and because pancreatic cancers can have variable expression of mutant KRAS throughout the tumor and over time, it will be important to understand the mechanisms of resistance to these new drugs so treatment can be revised for the patient as the tumor evolves.

The 2024 Hirshberg Symposium provided a comprehensive exploration of the latest advancements in KRAS research, emphasizing its critical role in pancreatic cancer development and treatment. From historical milestones and groundbreaking therapeutic strategies to insights into resistance mechanisms and evolving clinical approaches, the panelists illuminated the promising future of targeting KRAS to improve patient outcomes.

As research continues to unlock new possibilities, collaboration and innovation are key to driving progress towards a cure for pancreatic cancer. The Hirshberg Foundation remains committed to supporting transformative research and sharing these critical updates with the community.

Watch the full recording of the Hirshberg Symposium from the APA →

What is Pancreatitis?

Pancreatitis is an inflammatory condition of the pancreas, with both acute (short-lived) and chronic forms, and a known risk factor for developing pancreatic cancer, especially in cases of long-term chronic inflammation.

Inflammation is an important part of the body's response to infection or physical injury; it's the signal that brings in the immune cells to fight the infection or to start the healing process. Usually, when the infection or injury is resolved, inflammation stops, but sometimes, this does not happen. This is called chronic inflammation and can damage cells and tissues. While pancreatitis is rare, it is a risk factor for developing pancreatic cancer.

Acute vs Chronic Pancreatitis

- **Acute Pancreatitis**: This is a sudden inflammation often caused by gallstones that physically block the vessels of the pancreas or with heavy alcohol consumption. The main symptom is severe abdominal pain. While it usually affects just the pancreas, it can sometimes be more widespread and life-threatening.
- **Chronic Pancreatitis**: This type involves long-term inflammation that damages the pancreas tissue over time and can decrease the ability of the pancreas to function. A mixture of risk factors includes chronic alcohol use, tobacco use, and inherited genetic mutations. As the pancreas gets damaged, it can lead to issues like weight loss, malnutrition, and diabetes, and it raises the risk of pancreatic cancer.

Pancreatitis is generally considered acute (short-lived) or

chronic, but there is a spectrum of disease between these two designations. Patients can have one acute case over the course of their lives or multiple episodes, and acute pancreatitis, when not treated, can lead to chronic pancreatitis.

Chronic Pancreatitis & Substance Abuse

Alcohol abuse can cause chronic pancreatitis and increase the risk of developing pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer. The risk is further increased in those patients who also smoke. As the body breaks down alcohol, it generates byproducts that can be toxic to cells. If there is a buildup of these toxic byproducts, an increase in digestive enzymes can occur. An overproduction of these enzymes, meant to break down protein in our foods, can disrupt the cells of the pancreas and lead to further health problems.

While genetics and inherited conditions are beyond our control, we can limit inflammation and reduce risk factors. Ongoing research aims to find better treatments and improve outcomes for pancreatitis patients. If you or a loved one has pancreatitis and needs help, please contact Patient Support.