

Research Publications from the Hirshberg Translation Laboratory in 2023

The [Ronald S. Hirshberg Translational Pancreatic Cancer Research Laboratory](#) is a cornerstone of our research program, the first at UCLA to be solely dedicated to investigating the driving forces and biology of pancreatic cancer. Dr. Guido Eibl's research program is consistently funded by the National Institutes of Health (NIH) and continues to deepen our understanding of the intricate ways that diet, obesity and inflammation can accelerate tumor development.

We applaud Dr. Eibl and his lab and look forward to sharing more of the progress being made through their projects.

Publications from the Translational Laboratory in 2023

[Low dose combination treatment with metformin and simvastatin inhibits obesity-promoted pancreatic cancer development in male *KrasG12D* mice.](#) Scientific Reports 2023;13(1):16144 (PMCID: PMC10522691) (* dual first authorship)

Y.Teper*, L.Ye*, R.T.Waldron, A.Lugea, X.Sun, J.Sinnett-Smith, O.J.Hines, S.J.Pandol, E.Rozengurt, G.Eibl.

This original research paper reported that a combination of low dose simvastatin and low dose metformin inhibited pancreatic cancer development in a mouse model. This effect was only seen in male mice. Our results may be of translational importance for future clinical trials testing the efficacy of metformin and simvastatin in preventing pancreatic cancer progression in

humans. The Scientific Reports is an open-access journal publishing original research from all areas of life sciences. It is part of the prestigious Nature Research journal family.

Presentations in 2023

American Pancreatic Association

San Diego, CA, November 15-18, 2023

“Linking pancreatitis, oxidative stress, and lipid metabolism in pancreatic cancer progression: a new avenue to early intervention.”

L.Antonucci, A.Duran, I.Cobo, K.Watari, C.Nicoletti, S.Nandi, L.Caputo, **G.Eibl**, A.M.Lowy, G.Hatzivassiliou, P.Tamayo, Y.Wu, R.Sears, C.Glass, D.Scott, L.Alexandrov, P.Puri, D.Dawson, Y.Hu, M.Diaz-Meco, J.Moscat, M.Karin

“Low dosage combination treatment with metformin and simvastatin inhibits obesity promoted pancreatic cancer development in male KrasG12D mice.”

Y.Teper, L.Ye, R.Waldron, A.Lugea, X.Sun, J.Sinnett-Smith, J.Hines, S.Pandol, E.Rozengurt, **G.Eibl**

“Combined Simvastatin and Metformin Treatment Targets Growth and Fibroinflammatory Responses in Pancreatic Stellate Cells.”

R.Waldron, L.Huo, E.Rozengurt, **G.Eibl**, S.Pandol, A.Lugea

Seed Grant Research Update:

Biomarkers for Early Detection

The Hirshberg Foundation's [Seed Grant Program](#) remains instrumental in funding pancreatic cancer research worldwide, spanning many critical areas. Although pancreatic cancer is difficult to detect early, the Foundation is committed to changing these outcomes through scientific advancement. With this goal in mind, in 2017, Nelson Yee, MD, PhD, RPh was awarded a Seed Grant to fund a project for early detection: [Extracellular Vesicles as Biomarkers for Early Detection of Recurrent Pancreatic Ductal Adenocarcinoma](#). The aim of Dr. Yee's study is to determine whether Nanoscale extracellular vesicles cargo proteins and nucleic acids can sensitively detect early recurrence of pancreatic cancer. Early detection is a critical step to fighting pancreatic cancer. As he continues to make strides forward, we look forward to sharing more updates.

In 2022, Dr. Yee shared that ten (evaluable) enrolled patients had undergone surgical resection of pancreatic carcinoma. Each patient was followed up with surveillance and their blood specimens were to be collected and stored as described in the protocol. Dr. Yee and his team have been analyzing (using the proposed methodology and novel methodology) the blood specimens for extracellular vesicles and genetic mutations along with the clinicopathological data.

2023 Project Abstract:

The mortality rate of pancreatic cancer is among the highest among all human malignancies, and treatment is mostly palliative except for patients with localized tumor that can be resected with a curable intent. Even following surgical resection, the rate of tumor recurrence either locally or as distant metastasis is frequently high. Molecular biomarkers for early detection of

tumor recurrence following surgical resection will facilitate prompt treatment and improve patient survival. However, there is no sensitive and specific method or biomarkers for detecting tumor recurrence.

Nanoscale extracellular vesicles (nEVs), molecules in bodily fluids, contain proteins and nucleic acids, which can reflect disease status. Hence, we hypothesize nEV cargo proteins and nucleic acids could sensitively detect early recurrence of pancreatic cancer. In our previous study, we developed a lipid nanoprobe (LNP) system for rapid and efficient nEV isolation and performed subsequent nEV cargo analyses. The LNP system overcomes low throughput, low purity and other common shortcomings in nEV isolation, showing great potential for clinical use. This proposed research aims to use the LNP system to analyze several key proteins and genetic mutations, and to evaluate these molecules as biomarkers of pancreatic cancer recurrence.

The validation of this hypothesis will demonstrate the potential of nEV cargo as a promising tool to track evolution of pancreatic carcinoma and monitor tumor dynamics with the goal of improving survival of patients. We have completed collection of the blood specimens and molecular data as well as the clinicopathological data of the enrolled subjects. We have been analyzing the biospecimens along with the clinicopathological data, and we expect to report the study results in the year 2024.

To date, the Hirshberg Foundation has provided funding for more than 120 research projects in the following areas: treatment/therapy, patient care, early diagnosis, detection, cancer biology, basic science, prevention/metabolism and research core facilities. [Make a donation today in support of early detection research](#) and cutting-edge science funded by the

The 2023 APA Meeting highlights the impact of AI in pancreatic cancer research

The partnership between The Hirshberg Foundation and the [American Pancreatic Association](#) (APA) continues to unite brilliant minds, showcases significant topics and keynote speakers, and highlights the contributions of researchers through an annual award. The APA meeting typically assembles a global community of scientists and clinicians each year who present and delve into the latest research findings on pancreatic diseases. This year, the Foundation sponsored a groundbreaking [symposium on Artificial Intelligence in Pancreatic Cancer](#) and presented two remarkable scientists with an award for the Best Abstract in Pancreatic Cancer.

Moderated by our Scientific Advisory Board [Chair, Miklos Sahin-Toth MD, PhD](#), individual presentations were led by researchers from Mayo Clinic, Cedars Sinai, and MD Anderson Cancer Center, each discussing innovation in the AI space as it relates to early detection and diagnostics. The topics included:

- Harnessing Next Generation Imaging for Redefining Early Pancreas Cancer Detection, presented by Ajit Goenka MD, FSAR.
- PDAC Risk Prediction Using Artificial Intelligence Analysis of Pre-Diagnostic Abdominal CT Scans, presented

by Debiao Li PhD.

- Integrating Radiomics, AI, and Biomarkers into Early Detection Strategies, presented by Eugene Koay.

We invite you to [watch a recording of these presentations](#) and learn more about the impact of AI in pancreatic cancer research. The Foundation is dedicated to empowering an ever-growing research community by promoting the exploration of new and innovative approaches to combat this disease.

Join us in also celebrating the winners of the [2023 Best Abstract in Pancreatic Cancer Award](#). Michael Pfluger MD at Johns Hopkins University was presented with the award based on his work on Ductal Cancerization at the Pancreatic Neck Margin – Prevalence and Clinical Implications. In addition, Xiuhui Shi MD at the University of Oklahoma Health Sciences Center received the award for their work based on ZIP4 Promotes Anorexia and Cachexia Through Activating Tumor-Associated Macrophage Infiltration and GDF15 Secretion in Pancreatic Cancer Research.

Updates from our UCLA Seed Grant Recipients

In early October, we hosted a gathering of scientists and researchers working on pancreatic cancer at UCLA, highlighting some of our recent Seed Grant awardees. With the goal to share innovative work happening across disciplines, connect researchers, and foster collaboration, it was an inspiring afternoon.

We're excited to share some updates from past Seed Grant

researchers that came from this gathering. We look forward to sharing more from these great minds as the afternoon sparked connections and potential future collaborations.

In 2019, [Thuc Le, PhD](#), was awarded a Seed Grant for his project *Mapping and Targeting Nucleotide Biosynthetic Plasticity in Mutant KRAS Driven Pancreatic Cancer*. This research focuses on tackling mutant KRAS in pancreatic cancer and understanding its effects on cell signals and metabolism to influence the immune response. One important discovery that has been made to date is that blocking KRAS leads to higher levels of adenosine released by tumor cells, which can make the immune system less effective. Combining therapies that target both KRAS and adenosine shows promise in achieving stronger anti-cancer effects in this difficult-to-treat cancer.

Some pancreatic adenocarcinoma (PDAC) patients survive exceptionally long despite metastatic disease; these patients are able to generate effective, systemic immune responses against their tumors. [Jason Link, PhD](#), a 2022 awardee, looked at the anti-tumor immune response that takes place in tertiary lymph structures to understand if these structures can be therapeutically ignited as a treatment avenue. Patients with poor outcomes fail to generate these immune responses due to ineffective signals between the tumor and immune cells, but these signals are therapeutically targetable.

KRAS mutations are the most common drivers of pancreatic ductal adenocarcinoma (PDAC). Recent clinical translation of mutant KRAS-specific inhibitors has reinvigorated hope for direct targeting; however, research has shown they need to be administered as combination therapies. Research from [Evan Abt, PhD](#), a 2022 Seed Grant Awardee, uncovered new mechanisms that restrain anti-tumor immunity in pancreatic cancer. The suppression of the immune response is partly due to unexpected

crosstalk between metabolic and immune networks. These insights provide a rationale for new therapeutic interventions to unleash immune responses targeting pancreatic cancer.

2022 Seed Grant researcher, [Alexandra Demcsak, MD, PhD](#), looked into hereditary pancreatitis, an early-onset form of chronic pancreatitis caused by mutations in the digestive proteases (enzymes that break down proteins). Her research investigated the effects of carboxypeptidase A1 (*CPA1*) gene mutations on pancreatic ductal adenocarcinoma development. Based on the results, the p.N256K mutation of the *CPA1* gene accelerates the development of precancerous lesions in the pancreas of *KrasG12D* \times *p48-Cre* models. These findings provide support for the concept that misfolding *CPA1* mutants are risk factors for pancreatic ductal adenocarcinoma, deepening our understanding of how chronic inflammation promotes tumor growth in the pancreas.

An innovative 2021 Seed Grant project by [Keisuke Iwamoto, PhD](#) used weak magnetic fields to enhance treatment sensitivity of pancreatic cancer cells.

The projects presented at the UCLA gathering helped spark inspiration, collaboration, and connection across disciplines. We look forward to sharing future progress reports from these researchers as they continue their important work. It is because of your support that we can fund these crucial projects and help move science towards better diagnostic and treatment options, and ultimately, a cure.

UCLA Joins the Pancreatic Cancer Early Detection (PRECEDE) Consortium to Transform Early Detection and Survival Rates

Dr. Timothy Donahue, Director of the UCLA Agi Hirshberg Center for Pancreatic Diseases and Garry Shandling Chair in Pancreatic Surgery at David Geffen School of Medicine at UCLA, has joined the Pancreatic Cancer Early Detection (PRECEDE) Consortium as a Principal Investigator. This Consortium brings together an international, multi-institutional collaborative group of experts with the aim to increase the 5-year survival rate from 10% to 50% in the next 10 years. With Dr. Donahue as a Principal Investigator, UCLA patients with a family history of pancreatic cancer or individuals who carry pathogenic genes will be able to enroll in the PRECEDE study for longitudinal follow up.

The PRECEDE Study is an observational long-term study of people with an increased risk for pancreatic cancer due to family history, a history of chronic pancreatitis or pancreatic cysts, or the presence of specific gene mutations linked to the disease. Study participants have blood work every 6 to 12 months with additional imaging collected for those in defined high-risk groups. This data-driven model integrates basic, translational and clinical research to greatly enhance our understanding of this disease and to drive early detection and prevention methods. The consortium aims to identify high-risk individuals, create an effective early detection test for pancreatic cancer, understand the risk factors, including susceptible genes, and

develop a strategic pancreatic cancer prevention plan. As Dr. Donahue told us, “It is critical for high-risk individuals to join this important study in order to maximize identification and advance early detection of pancreatic cancer. Early detection would drastically change the trajectory of the disease and ultimately save thousands of lives.”

The Agi Hirshberg Center for Pancreatic Diseases and UCLA’s involvement in this study will expand the population of high-risk individuals involved and allow family members of patients to participate in deepening our knowledge of pancreatic cancer risk factors. We are hopeful that this collaborative, multi-institution project will make early detection and prevention for pancreatic cancer accessible for all so that we may see a marked increase in survival rates.

An Overview of the Updates to the NCCN Guidelines for Pancreatic Cancer

The National Comprehensive Cancer Network (NCCN) works to improve cancer care through their vast collection of Guidelines for Patients. The latest version of the [Guidelines for Patients: Pancreatic Cancer](#), sponsored by the Hirshberg Foundation, provides information to help patients and their families navigate a pancreatic cancer diagnosis in an empowered and informed way.

The extensive guidelines include care options, treatment

protocols, quotes from patients, advice for how to discuss treatment with doctors, and much more. The Guidelines for Patients are based on the recommendations in the NCCN Clinical Practice Guidelines in Oncology available to [physicians](#). One of the most recent updates included for patients is the addition of a new first-line therapeutic option, liposomal irinotecan + 5-FU + leucovorin + oxaliplatin (known as NALIRIFOX). This new drug regime has shown promise in early-stage trials conducted by [Dr. Zev Wainberg](#), a member of the UCLA Agi Hirshberg Center for Pancreatic Diseases, Professor of Medicine at UCLA and co-director of the UCLA GI Oncology Program.

Another highlight of the updated version is the recommendation that all individuals diagnosed with pancreatic cancer have genetic testing for a range of inherited mutations. The advice is to screen beyond just *BRCA1* and *BRCA2* to look at an array of mutations that can assist with treatment planning. There is also an expanded section on biomarker profiling for advanced and metastatic pancreatic cancer which can provide a molecular profile of small yet important features of the cancer. Biomarkers detect abnormal changes in cancer cells' genes that occurred during your lifetime and may also help with treatment planning.

An update that we are excited to focus on is the whole-body approach to treatment that is emphasized in the latest Patient Guidelines. The Hirshberg Foundation has long advocated for a holistic method of treatment that takes into consideration the [mind-body connection](#). The newest updates include details on [supportive care](#) that is recommended from the point of diagnosis. Treatment options have also taken on the best-practice of a more individualized approach based on individual and cancer specific characteristics.

The Hirshberg Foundation is proud to support this great work to

ensure that all patients and caregivers receive the most up-to-date information to assist them through their cancer journey. The NCCN Guidelines for Patients booklet is available for [digital download](#) or to purchase through [Amazon](#).