School of Nursing Grant Focused on Emotional Wellness

A new study, funded through the Hirshberg Foundation's Seed Grant program, will focus on the emotional wellbeing of patients and their caregivers as they face pancreatic cancer.
Through a new partnership with the clinical teams at the UCLA Agi Hirshberg Center for Pancreatic Diseases and the psychosocial clinicians at the Simms/Mann-UCLA Center for Integrative Oncology, Dr. Eden Brauer, Dr. Denice Economou, and Barbara Demman have developed a study to identify the optimal way to provide a mindfulness-based intervention to patients and caregivers facing pancreatic cancer. The team has devised an intervention plan to provide four pre-recorded, self-paced modules that will focus on four aspects of the cancer journey and ways to be mindful. These include: 1. Introduction to Mindfulness, 2. Cultivating Self-Compassion, 3. Making the Most of the Moment, and 4. Life Review and Legacy Envisioning.

These modules, recorded by a nursing faculty member who is a mindfulness certified facilitator, will be available online through a study website so participants can engage with them in a flexible way. This will allow study participants to access the four modules when it is convenient for them and as often as they need over a six-week period. The team's primary objective will be to determine the best way to provide a web-based mindfulness practice and set of tools for those facing pancreatic cancer. Another objective of the study is to collect data on other aspects of the patient and caregiver emotional well-being throughout the cancer journey. This mindfulness intervention aims to track and improve self-reported symptoms of depression, anxiety, spiritual wellbeing, sleep, and quality of life for both the patients and caregivers.

The Hirshberg Foundation is honored and excited to partner with the UCLA School of Nursing to work towards understanding the ways to support and improve both patient and caregiver emotional well-being throughout the cancer journey. This research is made possible thanks to our community.

Mindfulness Study

Patients are not required to have been treated for cancer at UCLA. However, they do need to have a caregiver who will also enroll. This can be anyone, from a family member to a friend to a loved one who has supported them in their cancer journey.
Learn more and enroll today

Research Publications from the Sahin-Toth Laboratory in 2023

The Sahin-Toth Laboratory remains an important part of the Hirshberg Foundation's research program and is central to our efforts on UCLA's campus. Led by our Scientific Advisory Board Chair, Dr. Miklos Sahin-Toth, his lab is focused on hereditary chronic pancreatitis, a major risk factor for pancreatic cancer. Dr. Sahin-Toth's work is in partnership with Dr. Guido Eibl in our Translational Laboratory. Their two teams are committed to better understanding genetics, obesity, diet, and inflammation and how they contribute to pancreatic cancer acceleration.

Dr. Sahin-Toth and his team continue to contribute to prestigious journals, participate in conferences across the globe, and secure funding from the NIH. We eagerly await more updates from Dr. Sahin-Toth and his research group in the future.

Publications from the Sahin-Toth Laboratory in 2023

1. Modelling chronic pancreatitis as a complex genetic disease in mice. **Gut** 2023, 72:409-410. PMC9666703.

Jancsó Z, Demcsák A, Sahin-Tóth M.

The final published form of a remarkable paper from 2022. Chronic pancreatitis is a complex genetic disease, and patients often carry multiple genetic variants. Here we crossed mouse strains with different pancreatitis-associated gene variants to study their combined effect. Mice with single genetic changes showed no pancreas disease; however, mice with both gene

variants developed severe chronic pancreatitis. Gut is a preeminent journal in gastroenterological sciences.

2. Trypsin activity in secretagogue-induced murine pancreatitis is solely elicited by cathepsin B and does not mediate key pathologic responses. **Gastroenterology** 2023, 164:684-687. PMC10441611.

Geisz A, Tran T, Orekhova A, Sahin-Tóth M.

Our flagship paper of 2023! Here we demonstrated that trypsin activity generated by cathepsin B during the early phase of pancreatitis is a marker rather than a driver of the disease. One important implication is that cathepsin B should not be considered as a therapeutic target in pancreatitis. Gastroenterology is the official journal of the American Gastroenterological Association (AGA), and the most prominent US publication in the gastroenterological sciences.

3. No evidence for the benefit of PPIs in the treatment of acute pancreatitis: a systematic review and meta-analysis. **Scientific Reports** 2023, 13:2791. PMC9935541.

Horváth IL, Bunduc S, Hankó B, Kleiner D, Demcsák A, Szabó B, Hegyi P, Csupor D.

Alexandra Demcsak (2022 Seed Grant recipient) contributed to this clinical paper showing that acid-reducer PPIs have no therapeutic benefit in acute pancreatitis. 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.

4. Mouse model of PRSS1 p.R122H-related hereditary pancreatitis highlights context-dependent effect of autolysis-site mutation. **Pancreatology** 2023, 23:131-142. PMC10492521.

Jancsó Z, Morales Granda NC, Demcsák A, Sahin-Tóth M.

Modeling the pathogenic effect of the p.R122H cationic trypsinogen mutation in mice has been a challenge since its discovery in 1996. Here we clarify why this mutation causes pancreatitis in humans but not in mice. Pancreatology is the official journal of the International Association of Pancreatology and the European Pancreatic Club.

5. Substrate specificity of human chymotrypsin-like protease (CTRL) characterized by phage display-selected small-protein inhibitors. **Pancreatology** 2023, 23:742-749. PMC10528761.

Németh BZ, Nagy ZA, Kiss B, Gellén G, Schlosser G, Demcsák A, Geisz A, Hegyi E, Sahin-Tóth M*, Pál G*. *contributed equally.

The most recent chapter of our long-running collaborative work with the Pál laboratory aimed at the characterization of the substrate specificity of human pancreatic chymotrypsins and elastases. It is hard to believe, but we published the first joint paper on this problem in 2011. Pancreatology is the official journal of the International Association of Pancreatology and the European Pancreatic Club.

6. Risk of chronic pancreatitis in carriers of the c.180C>T (p.Gly60=) CTRC variant: case-control studies and meta-analysis. **Pancreatology** 2023, 23:481-490. PMC10586708.

Berke G*, Beer S*, Gede N, Takáts A, Szentesi A, Hegyi P, Rosendahl J, Sahin-Tóth M*, Németh BC*, Hegyi E*. *contributed equally.

This important addition to the literature on pancreatitis genetics provides a quantitative assessment of the effect of a common chymotrypsin C (CTRC) variant on the risk of chronic pancreatitis. Pancreatology is the official journal of the

International Association of Pancreatology and the European Pancreatic Club.

7. CFTR p.F508del mutation carrier status is not associated with biliary acute pancreatitis. **Pancreas** 2023, 52:e256-e257.

Martonosi ÁR, Németh BC, Párniczky A, Vincze Á, Szentesi A, Erőss B, Sahin-Tóth M, Hegyi P, Hegyi E.

An intriguing hypothesis that turned out to be wrong. The risk of biliary pancreatitis is not increased by CFTR mutations. Pancreas is the official journal of the American Pancreatic Association.

8. Functional predictors of pathogenicity of missense CPA1 variants in chronic pancreatitis. **Gut** 2023

Sándor M, Sahin-Tóth M.

Another highlight of our 2023 publications! After functionally characterizing 50 carboxypeptidase A1 (CPA1) mutations, we found, to our surprise, that very few cause chronic pancreatitis and despite measurable functional defects, most CPA1 mutations are benign. Gut is a preeminent journal in the gastroenterological sciences.

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 Hirshberg Foundation.

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 x 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.