National Cancer Prevention Month: Taking a Proactive Approach to Your Health

In recognition of National Cancer Prevention Month the Hirshberg Foundation is sharing important educational resources and steps you can take to live a healthier life. The goals of prevention are to help you and your loved ones remain cancer-free and to empower our community with the resources to keep you healthy. This month we will provide resources including a prevention worksheet, share the facts about risk factors, genetics, and the role of nutrition and exercise in your prevention plan. Pancreatic cancer prevention and awareness, especially for high-risk individuals, should be a priority for every family impacted by this disease. ***February 4th is also World Cancer Day, a reminder for all of us to raise awareness in our community, make an appointment for a cancer screening or genetic testing, and start a new healthy living plan.***

Your cancer prevention plan can become a year-round effort, however, as you start to check off your new year resolutions, this is the perfect time for a health check-in. Although pancreatic cancer remains the 3rd leading cause of cancer deaths in the U.S., taking steps to improve your health today can reduce your risk of being diagnosed. The key components to pancreatic cancer prevention include:

Know the inherited risk factors
Specific communities are disproportionately at higher risk for pancreatic cancer, learn whether you are in one of these groups.

Avoid the modifiable risk factors (obesity and smoking)

Choosing a nutritious diet, reducing stress and quitting habits including smoking and excessive drinking can extend your life.

Learn about pancreatic cancer testing and surveillance
Testing or surveillance may also be clinically recommended in instances such as a new diagnosis of a pancreas cyst or lesion.

Seek genetic counseling
Meeting with a genetic counselor can help you determine your level of risk and how to tackle challenges.

In addition to personal pre-emptive steps you can take in your everyday life, the Foundation's Seed Grant Program continues to fund critical research and with the aim of pancreatic cancer prevention as well as therapeutics, diagnosis, immunology, and cancer biology. Thanks to these research projects, we are making strides forward everyday. Recently, the the 5-year survival rate for pancreatic cancer has increased to 12% putting it on an upward trajectory for the second year in a row. This news from the ACS (American Cancer Society) Cancer Facts & Figures Report gives survivors and families some additional hope as they navigate a diagnosis. We are headed in the right direction, but it is just as important that individual remain pro-active in our day-to-day lives.

Learn more about how to support our efforts and raise funds for cancer prevention.

[MAKE A DONATION]

Research Publications from the Sahin-Toth Laboratory in 2022

The most recent addition to our laboratories at UCLA, the Sahin-Toth Laboratory focuses on hereditary chronic pancreatitis, a major risk factor for pancreatic cancer. Dr. Miklos Sahin-Toth joined UCLA to work in partnership with Dr. Guido Eibl in our Translational Laboratory to better understand how genetics, obesity, diet, and inflammation contribute to pancreatic cancer acceleration.

Dr. Sahin-Toth and his researchers continue to publish extensively in renowned journals, present at conferences around the world and receive NIH funding. With additional publications forthcoming and grant proposals under consideration, we look forward to sharing updates from Dr. Sahin-Toth and his lab in the near future.

Publications from the Sahin-Toth Laboratory in 2022

1. *Chronic progression of cerulein-induced acute pancreatitis in trypsinogen mutant mice.* ***Pancreatology*** 2022, 22:248-257. PMC8941852
Jancsó Z, Sahin-Tóth M.

This is an important follow-up study on our high-impact 2020 Gastroenterology paper that described increased severity of acute pancreatitis in mice carrying a trypsinogen mutation. Here we demonstrated that this trypsinogen mutation also sensitizes mice to chronic pancreatitis. Pancreatology is the official journal of the International Association of Pancreatology and the European Pancreatic Club.

2. *Misfolding-induced chronic pancreatitis in CPA1 N256K mutant*

mice is unaffected by global deletion of Ddit3/Chop. ***Scientific Reports*** 2022, 12:6357. PMC9012826
Németh BC, Demcsák A, Geisz A, Sahin-Tóth M.

In our seminal 2019 Gut paper, we found high levels of the signaling molecule CHOP in mice with chronic pancreatitis due to a mutation in the digestive enzyme carboxypeptidase A1 (CPA1). In this follow-up study, we demonstrated that CHOP plays no role in disease initiation or progression. In other words, CHOP is a marker rather than a driver of chronic 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.

3. *Modelling chronic pancreatitis as a complex genetic disease in mice.* ***Gut*** 2022 May 16. Epub ahead of print. PMC9666703
Jancsó Z, Demcsák A, Sahin-Tóth M.

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. This remarkable study showed that 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 the gastroenterological sciences, published in Europe by BMJ.

4. *Variants in the pancreatic CUB and zona pellucida-like domains 1 (CUZD1) gene in early-onset chronic pancreatitis – A possible new susceptibility gene*. ***Pancreatology*** 2022, 22:564-571. PMC9250292

Rygiel AM, Unger LS, Sörgel FL, Masson E, Matsumoto R, Ewers M, Chen JM, Bugert P, Buscail L, Gambin T, Oracz G, Winiewska-Szajewska M, Mianowska A, Poznanski J, Kosińska J, Stawinski P, Płoski R, Koziel D, Gluszek S, Laumen H, Lindgren F, Löhr JM,

Orekhova A, Rebours V, Rosendahl J, Párniczky A, Hegyi P, Sasaki A, Kataoka F, Tanaka Y, Hamada S, Sahin-Tóth M, Hegyi E, Férec C, Masamune A, Witt H.

Discovery of new gene variants that increase risk for chronic pancreatitis is an ongoing collaborative effort. In this paper, we contributed biochemical experiments to demonstrate that mutations in the CUZD1 gene may act as risk factors for chronic pancreatitis. CUZD1 is an abundant protein in the pancreas with unclear function. Pancreatology is the official journal of the International Association of Pancreatology and the European Pancreatic Club.

5. *Risk of chronic pancreatitis in carriers of loss-of-function CTRC variants: A meta-analysis.* ***PLoS One*** 2022, 17:e0268859. PMC9122191
Takáts A, Berke G, Gede N, Németh BC, Witt H, Głuszek S, Rygiel AM, Hegyi P, Sahin-Tóth M, Hegyi E.

Meta-analysis of published studies is an important tool to define the extent of risk associated with various genetic variants in chronic pancreatitis. In this collaborative paper, we analyzed variants in the chymotrypsin C (CTRC) gene, which encodes a pancreatic digestive protease that protects the pancreas against harmful trypsin activity and pancreatitis. The journal PLoS One is published by the Public Library of Science as a peer-reviewed, open-access forum for a broad spectrum of scientific results.

6. *Rate of autoactivation determines pancreatitis phenotype in trypsinogen mutant mice.* ***Gastroenterology*** 2022, 163:761-763. PMC9398983
Demcsák A, Sahin-Tóth M.

Our flagship paper for the year! Here we demonstrated that the propensity of mutant trypsinogen to become active determines the

severity of pancreatitis in mice, and by extension, in humans. Gastroenterology is the official journal of the American Gastroenterological Association (AGA), and the most prominent US publication in the gastroenterological sciences.

7. *Loss-of-function variant in chymotrypsin like elastase 3B (CELA3B) is associated with non-alcoholic chronic pancreatitis.* ***Pancreatology*** 2022, 22:713-718. PMC9474678

Tóth A, Demcsák A, Zankl F, Oracz G, Unger LS, Bugert P, Laumen H, Párniczky A, Hegyi P, Rosendahl J, Gambin T, Płoski R, Koziel D, Gluszek S, Lindgren F, Löhr JM, Sahin-Tóth M, Witt H, Rygiel AM, Ewers M, Hegyi E.

Discovery of new gene variants that increase risk for chronic pancreatitis is an ongoing collaborative effort. In this paper, we contributed biochemical experiments to demonstrate that a mutation in the CELA3B gene acts as a risk factor for chronic pancreatitis. The CELA3B gene encodes a pancreatic digestive protease called elastase 3B. Pancreatology is the official journal of the International Association of Pancreatology and the European Pancreatic Club.

8. *Hereditary pancreatitis-25 years of an evolving paradigm: Frank Brooks Memorial Lecture 2021.* ***Pancreas*** 2022, 51:297-301. PMC9348779
Sahin-Tóth M.

On November 4, 2021, Dr. Sahin-Tóth had the special honor of delivering the Frank Brooks Memorial Lecture at the Annual Meeting of the American Pancreatic Association. This article summarizes key points of the lecture, and the milestones of the past 25 years spent on researching hereditary pancreatitis. Pancreas is the official journal of the American Pancreatic Association (APA).

9. *Arg236 in human chymotrypsin B2 (CTRB2) is a key determinant of high enzyme activity, trypsinogen degradation capacity, and protection against pancreatitis*. ***Biochimica et Biophysica Acta – Proteins and Proteomics*** 2022, 1870:140831. PMC9426946.

Németh BZ, Demcsák A, Micsonai A, Kiss B, Schlosser G, Geisz A, Hegyi E, Sahin-Tóth M, Pál G.

As part of a large international collaboration, previously we identified a common genetic change in the chymotrypsin B1-B2 genes (CTRB1-CTRB2) that protects against chronic pancreatitis (Gut 2018). In this elegant follow-up study, we collaborated with Dr. Gabor Pal's group to provide biochemical data that further clarified the mechanism by which chymotrypsins protect against pancreatitis. Biochimica et Biophysica Acta is one of the oldest scientific journals in the field of biochemistry, published by Elsevier.

10. *Preclinical testing of dabigatran in trypsin-dependent pancreatitis*. ***Journal of Clinical Investigation Insight*** 2022, 7:e161145. PMC9675574
Pesei ZG, Jancsó Z, Demcsák A, Németh BC, Vajda S, Sahin-Tóth M.

A compelling story offering hope for the development of a drug treatment for chronic pancreatitis! Here we used mice with a trypsinogen mutation to demonstrate that the anticoagulant drug dabigatran etexilate (brand name Pradaxa) had good therapeutic efficacy in pancreatitis. JCI Insight is the open-access sister journal of the distinguished Journal of Clinical Investigation (JCI), which publishes high-quality studies that provide meaningful contributions to the understanding of the biology and treatment of disease.

11. *Bicarbonate defective CFTR variants increase risk for chronic pancreatitis: A meta-analysis*. ***PLoS One*** 2022, 17:e0276397. PMC9584382.

Berke G, Gede N, Szadai L, Ocskay K, Hegyi P, Sahin-Tóth M, Hegyi E.

Meta-analysis of published studies is an important tool to define the extent of risk associated with various genetic variants in chronic pancreatitis. In this collaborative study, we analyzed the association of variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and chronic pancreatitis. The journal PLoS One is published by the Public Library of Science as a peer-reviewed, open-access forum for a broad spectrum of scientific results.

12. *Novel p.G250A mutation associated with chronic pancreatitis highlights misfolding-prone region in carboxypeptidase A1 (CPA1).* ***International Journal of Molecular Sciences*** 2022, 23:15463. PMC9779553

Sándor M, Thiel FG, Schmid M, Demcsák A, Morales Granda NC, Németh BC, Vajda S, Hoerning A, Sahin-Tóth M.

Characterization of novel gene mutations found in patients with chronic pancreatitis is an ongoing project in our laboratory. Here we described functional properties of a newly identified gene variant in the digestive enzyme carboxypeptidase A1 (CPA1). Mutations in this enzyme have been known to cause hereditary pancreatitis in humans. The International Journal of Molecular Sciences is an open-access journal providing an advanced forum for a large variety of research projects, including biochemistry.

Research Publications from the Hirshberg Translation Laboratory in 2022

This February marks 25 years since the creation of the Ronald S. Hirshberg Translational Pancreatic Cancer Research Laboratory. A cornerstone of our research program, this lab was 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 2022

1. *Statins inhibit inflammatory cytokine production by macrophages and acinar to ductal metaplasia of pancreatic cells.* ***Gastro Hep Advances*** 2022; 1:640-651 (PMCID: PMC9615480)
S. Ako*, Y. Teper*, L. Ye, J. Sinnett-Smith, O.J. Hines, E. Rozengurt, G. Eibl. (* dual first authorship)

This original research paper reported that statins, FDA-approved drugs to treat hypercholesteremia, inhibited early pancreatic cancer development in cell culture and animal models. At least some of the effects were mediated by inhibiting macrophages, important inflammatory cells in the pancreatic microenvironment. This study supports the notion that statins may be beneficial in reducing the risk of pancreatic cancer.

2. *Opposite effects of Src family kinases on YAP and ERK activation in pancreatic cancer cells: Implications for targeted therapy.* ***Molecular Cancer Therapeutics*** 2022;21(11):1652-1662 (PMCID: PMC9630827)
J. Sinnett-Smith, T. Anwar, E.F. Reed, Y. Teper, G.Eibl, E. Rozengurt.

This paper described a novel signaling crosstalk in pancreatic cancer cells. In addition, the combination of SRC inhibitor and MEK inhibitor, FDA-approved drugs to treat certain types of human cancers, very strongly inhibited pancreatic cancer growth in mice. This novel finding indicates a potential role of these drugs for a combination therapy in pancreatic cancer.

3. *Body Mass Index Trajectories Across the Adult Life Course and Pancreatic Cancer Risk.* ***Journal of the National Cancer Institute: Cancer Spectrum*** 2022;6(6) (PMCID: PMC9651977)

S. Arjani, P.F. Saint-Maurice , S. Julián-Serrano, G. Eibl, R. Stolzenberg-Solomon.

In collaboration with an epidemiology group at the NCI, this manuscript described the risk of developing pancreatic cancer in humans with various body mass index (BMI) trajectories across their adult life. It unequivocally shows that subjects that were overweight and/or obese as young adults and stayed in the overweight/obese category later in life carry the greatest risk of developing pancreatic cancer. The risk was greater in males than in females.

Symposium Speaker Spotlight: Shelby Yaceczko to present Dietary Management Post-Diagnosis

The Hirshberg Foundation is happy to share that Shelby Yaceczko, MS, RDN-AP, CNSC will be joining us at the 17th Annual Symposium on Pancreatic Cancer to discuss nutrition management post-diagnosis.

This interactive discussion will explore nutrition principles after a diagnosis of pancreatic cancer and what both patients and caregivers should know. We will review the importance of diet and wellness at every phase of the pancreatic cancer journey including meal planning and symptom management as it relates to food.

Shelby Yaceczko works with the Integrated Practice Unit (IPU) at UCLA leading the *Nutrition for Safer Surgeries Program*, funded through the Hirshberg Foundation. This program aims to provide early nutrition assessment and intervention for any patient with a new or existing gastrointestinal cancer diagnosis, with a special focus on pancreatic cancer. Shelby provides medical nutrition therapy services covering a range of areas such as preventing or correcting nutritional deficiencies, enhancing quality of life during cancer treatment, minimizing side effects from cancer treatments, and providing personalized nutrition prescriptions and goals to both patients and caregivers. She knows how important nutrition is before, during, and after cancer treatment and its related surgeries, and this new program aims to support patients and their caregivers throughout the process.

Shelby Yaceczko is one of few advanced practice registered dietitian nutritionists in California. She holds a master's degree in Exercise Physiology and is currently finishing her Doctor of Clinical Nutrition studies. Additionally, she is board certified in sport nutrition, transplant nutrition, and nutrition support. Shelby focuses her efforts on providing personalized nutrition therapy in the treatment of complex disease states at UCLA Health including nutrition for cancer, gastrointestinal surgeries, and improving the general wellness of patients through diet and lifestyle changes. She understands that good nutrition is a catalyst to help you thrive and reach life potential. Shelby is described as passionate and innovative, while firmly believing in the mind-body connection. Throughout her career, she has worked to empower people of all ages to better understand the power of nutrition and its impact on overall well-being and disease management.

Nutrition plays an important role at all stages of treatment and it is one of the most requested topics at our annual Symposiums. We look forward to hearing Shelby Yaceczko's, MS, RDN-AP, CNSC presentation on **Dietary Management Post-Diagnosis.**

Symposium Speaker Spotlight: Dr. Sandra Sacks to present Palliative Care – It's Not

Hospice!

The Hirshberg Foundation is pleased to welcome Sandra H. Sacks, MD, MEd to the 17th Annual Symposium on Pancreatic Cancer to discuss Palliative Care – It's Not Hospice!

There is clear evidence that patients living with serious illnesses can benefit greatly from early palliative care. Palliative care is not hospice care. It does not replace any cancer-directed treatment. Instead, palliative care teams work together with oncology teams to decrease pain, relieve symptom burden, and improve the quality of life in patients living with serious illnesses and their families.

Dr. Sacks is a triple board-certified physician in Anesthesiology, Palliative Medicine, and Pain Medicine. She serves as the current Chair of the Committee on Palliative Medicine for the American Society of Anesthesia (ASA). She is a cancer pain specialist at UCLA, and is committed to delivering compassionate and quality palliative care to patients and their families. Her clinical focus is on managing oncologic pain through multimodal medical management and minimally-invasive interventions.

We are thrilled to have Dr. Sacks present on this ever-important topic **Palliative Care – It's Not Hospice**!

Symposium Speaker Spotlight:

Dr. Randall Brand to evaluate clinical trial participation

The Hirshberg Foundation is delighted to announce that Randall Brand, MD will be joining the 17th Annual Symposium on Pancreatic Cancer to present Should I Participate in a Clinical Trial?

Dr. Brand will describe the importance of clinical trials for pancreatic cancer early detection and treatment. He will also discuss how to get involved in a clinical trial and review how to determine if participating in a particular clinical trial is the right step for a treatment plan.

Randall Brand, MD, is a gastroenterologist and Professor of Medicine at the University of Pittsburgh School of Medicine. He is the academic director for the GI Division at UPMC Shadyside Hospital. Dr. Brand also directs the University of Pittsburgh Medical Center's GI Malignancy Early Detection, Diagnosis and Prevention Program and leads UPMC's Hereditary GI Tumor Clinic.

Dr. Brand's clinical interests include the early detection of pancreatic cancer, evaluating and caring for family members from pancreatic cancer-prone families, hereditary GI cancers, and evaluation of pancreatic cystic lesions. He participates in multiple NCI-, NIH- and DoD-funded research projects focused on the early diagnosis of pancreatic cancer.

We are excited to welcome back Dr. Brand to our Symposium to present **Should I Participate in a Clinical Trial?**