New Research Shows Chronic Stress and Obesity Accelerate Pancreatic Cancer Growth

A new study led by Hirshberg-funded investigators at UCLA sheds light on how chronic stress and an unhealthy diet may work together to accelerate the early development of pancreatic cancer. These findings provide critical insight into how lifestyle factors contribute to this disease and reinforce the urgent need for prevention and early intervention strategies.

Researchers identified a key molecular mechanism by which stress and obesity trigger changes in pancreatic cells that may lead to cancer. Specifically, stress-related neurotransmitters and obesity-related hormones activate a protein called CREB, which is linked to cancer cell growth. While stress hormones stimulate the β-adrenergic receptor/PKA pathway, obesity-related signals primarily use the PKD pathway. These findings suggest that both stress and obesity fuel pancreatic cancer growth through similar mechanisms, providing a new understanding of how lifestyle factors contribute to disease progression.

In preclinical models, mice fed a high-fat diet developed precancerous pancreatic lesions. However, when combined with social isolation stress, these mice developed even more advanced lesions, demonstrating the compounding effects of chronic stress and obesity on cancer risk. Notably, social isolation stress had a more pronounced impact on female mice than males. Researchers hypothesize that biological differences, including estrogen levels and increased β-adrenergic receptor activity in females, may contribute to this heightened susceptibility.

These findings underscore the urgent need for a multifaceted

approach to pancreatic cancer prevention, addressing both biological and lifestyle-related risk factors. Encouragingly, researchers suggest that existing medications could potentially mitigate these risks. Since β-adrenergic receptors play a crucial role in stress-related cancer growth, beta-blockers, commonly prescribed for high blood pressure, are being explored as a possible strategy to counteract these effects.

The study's first authors are Yaroslav Teper, a 2021 Seed Grant awardee and project scientist at the David Geffen School of Medicine at UCLA and Xiaoying Sun, a postdoctoral researcher at UCLA. The senior authors are Dr. Guido Eibl, director of the Hirshberg Translational Pancreatic Cancer Research Laboratory at UCLA and Dr. Enrique Rozengurt, distinguished professor of medicine and chief of research in the division of digestive diseases at UCLA and Ronald S. Hirshberg Chair in Translational Pancreatic Cancer Research.

It is thanks to our Seed Grant funding of Drs. Eibl and Teper, and our investments in our UCLA labs that this research has deepened our understanding of how lifestyle factors contribute to pancreatic cancer development. In today's uncertain funding landscape, we remain steadfast in our mission to advance breakthrough pancreatic cancer research that changes and saves lives.

For nearly three decades, the Hirshberg Foundation has nurtured nearly every major advance in pancreatic cancer research, to ensure that pioneering ideas receive the support they need to grow into life-saving discoveries.

Learn more about Dr. Guido Eibl's research →

Read more about this study from UCLA →

Research Publications from the Sahin-Toth Laboratory in 2024

The Sahin-Toth Laboratory continues to be vital to the Hirshberg Foundation's research program, driving groundbreaking discoveries at UCLA. Led by our Scientific Advisory Board Chair, Dr. Miklos Sahin-Toth, the lab is dedicated to unraveling the genetic factors behind hereditary chronic pancreatitis, one of the most significant risk factors for pancreatic cancer. Working closely with Dr. Guido Eibl and the Hirshberg Translational Laboratory, their combined efforts explore the connections between genetics, obesity, diet, and inflammation in pancreatic disease progression.

Dr. Sahin-Toth's team remains at the forefront of scientific research. The lab contributes to high-impact journals, presents at leading conferences worldwide, and secures ongoing funding from the NIH, which is critical to improving the lives of patients facing pancreatic cancer. We look forward to sharing the latest advancements from his lab and their impact on pancreatic disease research.

Publications from the Sahin-Toth Laboratory in 2024

1. Functional predictors of pathogenicity of missense *CPA1* variants in chronic pancreatitis. **Gut** 2024, 73:1589-1590. PMC11031613.

Sándor M, Sahin-Tóth M.

This seminal study reported the functional characterization of 50 carboxypeptidase A1 (CPA1) variants from patients with chronic pancreatitis and healthy subjects. Unexpectedly, we found that despite measurable functional defects, very few CPA1 variants caused chronic pancreatitis, and most variants reported in the literature were benign. Gut is a preeminent journal in the gastroenterological sciences.

2. Secretagogue-induced pancreatitis in mice devoid of chymotrypsin. **American Journal of Physiology-Gastrointestinal and Liver Physiology** 2024, 327:G333-G344. PMC11427105. *contributed equally

Demcsák A*, Shariatzadeh S*, Sahin-Tóth M.

An important follow-up study which cemented our contention that the digestive enzyme chymotrypsin protects the pancreas against pancreatitis by reducing harmful intrapancreatic trypsin activity. The American Journal of Physiology – Gastrointestinal and Liver Physiology is an official journal of the American Physiological Society.

3. Novel chymotrypsin C (*CTRC*) variants from real-world genetic testing of pediatric chronic pancreatitis cases. **Pancreatology** 2024, 24:690-697. PMC11529566

Stefanovics R, Sándor M, Demcsák A, Berke G, Németh BC, Zhang W, Abu-El-Haija M, Sahin-Tóth M.

This collaborative study analyzed the functional impact of novel chymotrypsin C (*CTRC*) gene variants identified during real-world genetic testing in a pediatric pancreatitis center. We demonstrated that functional analysis is necessary to distinguish pathogenic risk variants from innocuous genetic variations. Pancreatology is the official journal of the International Association of Pancreatology and the European

Pancreatic Club.

4. Heterozygous *Spink1* deficiency promotes trypsin-dependent chronic pancreatitis in mice. **Cellular and Molecular Gastroenterology and Hepatology** 2024, 18:101361. PMC11292374

Demcsák A, Sahin-Tóth M.

This important animal study provided direct evidence that heterozygous loss-of-function mutations in the SPINK1 gene can promote pancreatitis elicited by high intrapancreatic trypsin levels. SPINK1 is a trypsin inhibitor that protects the pancreas by inactivating unwanted trypsin. Cellular and Molecular Gastroenterology and Hepatology is the official research journal of the AGA Institute and it covers a broad spectrum of themes in gastroenterology and pancreatology.

5. Intron-mediated enhancement of SPINK1 expression for pancreatitis therapy. **Gut** 2024, 74:e9. PMC11631692

Berke G, Sahin-Tóth M.

This is the surprise finding of the year! While studying the expression of the trypsin inhibitor SPINK1 in cell culture, we found that introducing a short intron into the coding DNA could boost mRNA and protein expression by at least 10-fold. This method can inform the design of novel viral vectors for gene therapy against pancreatitis. Gut is a preeminent journal in the gastroenterological sciences.

6. Carboxyl ester lipase hybrid 1 (*CEL-HYB1*) haplotypes confer varying risk for chronic pancreatitis. **Scientific Reports** 2024, 14:30965.

Berke G, Sándor M, Xiao XK, Lowe ME, Ewers M, Erőss B, Masson E, Németh BC, Vincze Á, Czakó L, Rygiel AM, Rosendahl J, Chen JM, Witt H, Hegyi P, Sahin-Tóth M*, Hegyi E*. *contributed equally

This collaborative study analyzed the occurrence of a genetic variant of the carboxyl ester lipase gene (called *CEL-HYB1*) in European populations. We found that *CEL-HYB1* existed in two forms; these variants were geographically restricted and had different effects on pancreatitis risk. 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.

7. AlphaMissense versus laboratory-based pathogenicity prediction of 13 novel missense *CPA1* variants from pancreatitis cases. **Gut** 2024 Sep 10. E-publication ahead of print

Sándor M, Scheers I, Masamune A, Witt H, LaRusch J, Chen JM, Németh BC, Geisz A, Uc A, Sahin-Tóth M.

Building on our previous study published earlier in the year (see above, first citation), we investigated whether newly found CPA1 variants in pancreatitis cases were pathogenic. Surprisingly, most variants turned out to be benign. The AI-based program AlphaMissense did not perform well in predicting pathogenicity, indicating that laboratory-based functional analysis is necessary for the correct classification of CPA1 variants detected during genetic testing. Gut is a preeminent journal in the gastroenterological sciences.

8. The high-affinity chymotrypsin Inhibitor Eglin C poorly inhibits human chymotrypsin-like protease: Gln192 and Lys218 are key determinants. **Proteins** 2024 Sep 20. E-publication ahead of print

Németh BZ, Kiss B, Sahin-Tóth M, Magyar C, Pál G.

This collaborative study investigated the biochemistry of a digestive enzyme, the human chymotrypsin-like protease. It elucidated the reasons for its unique resistance to the leech-

derived chymotrypsin inhibitor eglin C. We contributed purified enzymes to the study. The journal "PROTEINS: Structure, Function, and Bioinformatics" publishes original reports in all areas of protein research.

9. Misfolding *PRSS1* variant p.Ala61Val in a case of suspected intrauterine pancreatitis. **Pancreatology** 2024 Dec 24. E-publication ahead of print

Sándor M, Vitale DS, Nagy ZA, Ibrahim SY, Abu-El-Haija M, Lazou M, Vajda S, Sahin-Tóth M.

This collaborative study described and characterized a novel genetic variant in human cationic trypsinogen (PRSS1), which was identified in an infant who suffered pancreatitis while in the womb. Pancreatology is the official journal of the International Association of Pancreatology and the European Pancreatic Club.

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

Nineteenth Annual Symposium on Pancreatic Cancer

In-Person registration is now closed. Join us virtually via webinar.

Webinar Registration »

Held in collaboration with the UCLA Agi Hirshberg Center for Pancreatic Diseases at the Luskin Conference Center
April 5, 2025
8:30 am – 3:00 pm

Schedule

8:30 am – 9:00 am	Check-in
9:00 am – 9:15 am	Welcome and Opening Re
	Lisa Manheim, Executive
	Hirshberg Foundation for Pancreati
	Agi Hirshberg, Founder
	Hirshberg Foundation for Pancreati
	Tim Donahue, MD
	University of California, L
9:15 am – 9:45 am	Navigating Your Pancreatic Cancer Treatm
	Emily Martin, MD

	University of California, L
9:45 am – 9:55 am	Q & A
9:55 am – 10:25 am	Pancreatic Cancer Progress
	Tim Donahue, MD
	University of California, L
10:25 am – 10:35 am	Q & A
10:35 am – 10:50 am	Break
10:50 am – 11:15 am	Surgical Treatment of Pancreatic Can
	Jon King, MD
	University of California, L
11:15 am – 11:25 am	Q & A
11:25 am – 11:50 am	Staying Strong Through Pancreatic Cancer Treatmen
	Shelby D. Yaceczko, DCN, RD
	University of California, L
11:50 am – 12:00 pm	Q & A
12:00 pm – 12:10 pm	Survivor Photo
12:00 pm – 1:00 pm	Lunch
1:00 pm – 1:20 pm	Empowering Pancreatic Cancer Patien
	Barbara Demman, MSN, RN,
	University of California, L

1:20 pm – 1:50 pm	Cannabis and Oncology: What Pancrea Should Know
	Ziva Cooper, PhD
	University of California, L
1:50 pm – 2:00 pm	Q & A
2:00 pm – 3:00 pm	Panel Discussion: Perspectives from Su
	Moderator: Annette Stant
	University of California, L

Symposium Speaker Spotlight: Emily Martin, MD, to discuss Navigating Your Pancreatic Cancer Treatment Right From The Start

The Hirshberg Foundation is happy to announce Emily Martin, MD, will be joining us at the 19th Annual Symposium on Pancreatic Cancer to share ways to navigate your pancreatic cancer treatment once diagnosed.

In this presentation, Dr. Martin will introduce a framework for patient-centered pancreatic cancer care and provide practical tools and resources to assist patients in navigating their treatments. She will address common challenges patients face and highlight the importance of a multidisciplinary, team-based

approach to treatment starting at diagnosis.

Dr. Emily Martin is a Palliative Medicine physician, physician informaticist, and health services researcher at UCLA. She serves as the Director of Palliative Care and is co-leading UCLA’s efforts to advance the delivery of comprehensive, interdisciplinary, person-centered pancreatic cancer care across the trajectory of illness.

An important topic for our pancreatic cancer community, we are so happy to have Dr. Martin present **Navigating Your Pancreatic Cancer Treatment Right From The Start** at the 19th Annual Symposium.

Symposium Speaker Spotlight: Tim Donahue, MD to share Pancreatic Cancer Progress Report 2025

The Hirshberg Foundation is pleased to announce that Dr. Tim Donahue will attend the 19th Annual Symposium on Pancreatic Cancer to share a 2025 progress report on pancreatic cancer.

Dr. Donahue will provide an update on promising new treatment developments for pancreatic cancer. These include advancements in earlier diagnosis strategies, surgical interventions, targeted therapies, and immunotherapies, which are beginning to show potential for this challenging disease. He will also review state-of-the-art approaches to medical and comprehensive patient

care offered at the Agi Hirshberg Center for Pancreatic Diseases.

Dr. Timothy Donahue serves as Chief of the Division of Surgical Oncology and Professor of Surgery at the David Geffen School of Medicine at UCLA. He also holds a joint appointment in the Department of Molecular and Medical Pharmacology, which supports his robust research program. As the Medical Director for Cancer Services, Dr. Donahue oversees all cancer-related care across the UCLA Health System. In his role as Director of the UCLA Agi Hirshberg Center for Pancreatic Diseases, Dr. Donahue is a highly skilled pancreatic surgeon, performing three to four pancreatic surgeries per week. He and his team tackle some of the most complex cases, achieving outcomes that rank among the best in the world. Dr. Donahue is deeply committed to providing patients with pancreatic cancer state-of-the-art care and personalized treatment. Beyond his clinical expertise, Dr. Donahue leads a National Institutes of Health-funded research laboratory as Principal Investigator. His research focuses on developing innovative drugs and improving treatment strategies for pancreatic cancer. He collaborates extensively with researchers across UCLA to advance the scientific understanding and management of this challenging disease.

An important presentation for our pancreatic cancer community, we are so happy to have Dr. Donahue present **Pancreatic Cancer Progress Report 2025** at the 19th Annual Symposium.