Research Publications from the Sahin-Toth Laboratory in 2020

In 2019 the Hirshberg Foundation supported UCLA in the recruitment of Miklos Sahin-Toth, MD, PhD, a leading pancreatic disease researcher and a specialist in chronic pancreatitis. The Sahin-Toth Laboratory is located next door and works closely with the The Ronald S. Hirshberg Translational Pancreatic Cancer Research Laboratory, headed by long-standing director Guido Eibl, MD, Professor, Department of Surgery.

The two labs formed a strategic alliance to better understand how diet, obesity, genetics & inflammation contribute to pancreatic cancer acceleration. Dr. Eibl's lab remains at the forefront of cutting-edge investigations into treatment, cancer biology, and potential preventive measures. Dr. Sahin-Toth's lab focuses on hereditary chronic pancreatitis, a major risk factor for pancreatic cancer. Drs. Eibl and Sahin-Toth are committed to illuminating the role of pancreatic inflammation in cancer development and exploring potential interventions that could thereby reduce cancer risk. The two labs were awarded a collaborative research grant in 2020 to continue their important coordinated efforts.

In 2020, Dr. Sahin-Toth's lab published the results of their research in various medical journals. Publishing this research adds to the understanding and body of knowledge on pancreatic cancer, helping researchers around the globe. As we heard from all labs, 2020 brought the added study of COVID-19 research to all disciplines, including Dr. Sahin-Toth's. We are very proud of the accomplishments of both teams and look forward to continued progress.

Publications from the Sahin-Toth Laboratory in 2020

1) Mutation that promotes activation of trypsinogen increases severity of secretagogue-induced pancreatitis in mice.

Gastroenterology 2020, 158:1083-1094. Jancsó Z, Sahin-Tóth M.

This seminal study demonstrates that a mutation in the main digestive enzyme, trypsinogen, makes mice more susceptible to pancreatitis. The genetic mutation investigated in this study was described in patients with hereditary pancreatitis. A major goal of our laboratory is to model human disease in mice and use the mouse models to test new therapeutics.

Gastroenterology is the leading US journal in the gastroenterological sciences.

2) Alcohol-dependent effect of *PRSS1-PRSS2* haplotype in chronic pancreatitis.

Gut 2020, 69:1-2. Hegyi E, Tóth AZ, Vincze Á, Szentesi A, Hegyi P, Sahin-Tóth M.

This paper describes the observation that a commonly found genetic risk factor that predisposes to pancreatitis has a larger effect in the context of chronic alcohol abuse. The findings confirm that genetic and environmental risks factors interact and amplify each other's effect on disease development.

Gut *is considered the top journal in the gastroenterological sciences.*

3) Measuring digestive protease activation in the mouse pancreas.

Pancreatology 2020, 20:288-292. Mosztbacher D, Demcsák A, Sahin-Tóth M.

This is an important methodological paper that describes how to measure the activity of digestive enzymes trypsin and chymotrypsin in the pancreas of mice. These digestive enzymes play important roles in the development of pancreatitis and routine and reliable measurement of their levels is a key experimental technique.

Pancreatology *is the official journal of the International Association of Pancreatology and the European Pancreatic Club.*

4) LIFEStyle, Prevention and Risk of Acute PaNcreatitis (LIFESPAN): protocol of a multicentre and multinational observational case-control study.

BMJ Open 2020, 10:e029660. Koncz B, Darvasi E, Erdősi D, Szentesi A, Márta K, Erőss B, Pécsi D, Gyöngyi Z, Girán J, Farkas N, Papp M, Fehér E, Vitális Z, Janka T, Vincze Á, Izbéki F, Dunás-Varga V, Gajdán L, Török I, Károly S, Antal J, Zádori N, Lerch MM, Neoptolemos J, Sahin-Tóth M, Petersen OH, Hegyi P.

This clinical study protocol originated from Peter Hegyi, Phd, Professor of Medicine, University of Pécs, Hungary. This publication lays out the parameters for LIFESPAN, an observational, multicenter, multinational case-control study to examine associations between socioeconomic factors, dietary habits, physical activity, chronic stress, sleep quality and acute pancreatitis. The Sahin-Toth lab was invited to

contribute as part of an international board of advisers.

BMJ Open *is an open access journal, dedicated to publishing medical research from all disciplines.*

5) Ethanol feeding accelerates pancreatitis progression in CPA1 N256K mutant mice.

American Journal of Physiology-Gastrointestinal and Liver Physiology 2020, 318:G694-G704. Orekhova A, Geisz A, Sahin-Tóth M.

Here, we investigated the interaction of genetic predisposition and environmental injury on the development of pancreatitis. In this study, a mouse model carrying a mutant digestive enzyme was fed an alcohol diet, which facilitated the progression of pancreas damage.

The ***American Journal of Physiology-Gastrointestinal and Liver Physiology*** *publishes papers on the physiology and mechanism that affect the liver and gastrointestinal system.*

6) Inactivation of mesotrypsin by chymotrypsin C prevents trypsin inhibitor degradation.

Journal of Biological Chemistry 2020, 295:3447-3455. Toldi V, Szabó A, Sahin-Tóth M.

This biochemical study examined how one digestive enzyme (chymotrypsin C) regulates another (mesotrypsin) and how this impacts the development of pancreatitis. Our laboratory has a long track record in digestive enzyme biochemistry, and experiments like these formed the basis of our successful mouse model program.

*The **Journal of Biological Chemistry** is a preeminent biochemical journal.*

7) Channelopathy of the pancreas causes chronic pancreatitis.

Gastroenterology 2020, 158:1538-1540. Sahin-Tóth M.

This is an editorial on the recent discovery of TRPV6 mutations in patients with chronic pancreatitis. TRPV6 is a calcium channel found in the excretory ducts of the pancreas. Identification of new genetic risk factors is always exciting as these represent novel targets for therapeutic intervention.

***Gastroenterology** is the leading US journal in the gastroenterological sciences.*

8) International Consensus Guidelines for Risk Factors in Chronic Pancreatitis.

Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club.

Pancreatology 2020, 20:579-585 Hegyi P, Párniczky A, Lerch MM, Sheel ARG, Rebours V, Forsmark CE, Del Chiaro M, Rosendahl J, de-Madaria E, Szücs Á, Takaori K, Yadav D, Gheorghe C, Rakonczay Z Jr, Molero X, Inui K, Masamune A, Fernandez-Del Castillo C, Shimosegawa T, Neoptolemos JP, Whitcomb DC, Sahin-Tóth M; Working Group for the International (IAP – APA – JPS – EPC) Consensus Guidelines for Chronic Pancreatitis.

Consensus guidelines are important documents that guide clinical management and decision-making. Opinion leaders and experts in

the field contributed to this paper that discusses risk factors for chronic pancreatitis.

Pancreatology *is the official journal of the International Association of Pancreatology and the European Pancreatic Club.*

9) Loss of chymotrypsin-like protease (CTRL) alters intrapancreatic protease activation but not pancreatitis severity in mice.

Scientific Reports 2020, 10:11731. Mosztbacher D, Jancsó Z, Sahin-Tóth M.

This study tested the role of a digestive enzyme (chymotrypsin-like protease) in pancreatitis using a novel mouse model deficient in this enzyme. The observations indicated that chymotrypsin-like protease does not play a significant role in the disease. Although this is considered a "negative study," the findings are still important as they add to our growing knowledge on digestive enzyme function in health and disease.

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.*

10) Lipotoxicity and cytokine storm in severe acute pancreatitis and COVID-19.

Gastroenterology 2020, 159:824-827. Hegyi P, Szakács Z, Sahin-Tóth M.

This paper is our contribution to understanding the science behind COVID-19. In this editorial, which also contains original data, we highlight similarities between severe COVID-19 and

severe acute pancreatitis. Remarkably, the same toxic substances and immunological factors determine progression of both diseases.

Gastroenterology *is the leading US journal in the gastroenterological sciences.*

Don’t Give Up the Fight

This article originally appeared in U Magazine, a publication of UCLA Health, David Geffen School of Medicine. The Centennial Campaign for UCLA Issue 2020’s theme was “Giving Matters – Visionary philanthropy shapes a new future for UCLA Health.” We are proud that our founder, Agi, is featured in a story about the Foundation’s commitment to never give up and the slow but steady progress towards a cure.

By Shari Roan • Illustration by Jenny Kroik
Originally published in UCLA Health’s U Magazine

In the competitive wholesale apparel business, Agi and Ronald Hirshberg would implement a new business idea and give it 18 months to bear fruit. If it wasn’t successful, they would pull the plug and move on. After Ronald died of pancreatic cancer in 1997 at age 54, Hirshberg focused that same determination on the effort to find a cure for the ravaging illness that took her husband’s life. “I had that business mentality,” Hirshberg recalls. “You begin, build inventory and sell it. I figured I’d give a little donation, and 18 months later there would be a cure for pancreatic cancer.”

However, the world of medical research is vastly different than

that of apparel, and the time it takes to reach a breakthrough is measured in years, not months. Patience and resolve are necessary to sustain the effort. More than two decades later, a cure for pancreatic cancer is closer but still not in hand.

Hirshberg never thought of abandoning the fight. Her philanthropy established the UCLA Agi Hirshberg Center for Pancreatic Diseases, one of the nation's leading centers focused on the disease, and she has funded scores of research projects through the Hirshberg Foundation for Pancreatic Cancer Research. "I am pleased and happy we've helped so many patients, but I don't have the satisfaction of finishing the job just yet," she says. "With my business mindset, I can't take credit until the job is done. But I do feel that, within the next five years, we'll have an early detection test for pancreatic cancer."

Pancreatic cancer is among the most devastating cancer diagnoses. About 57,000 Americans are diagnosed with the disease – often at a late stage – each year. The five-year survival rate is only nine percent, although the survival outlook for people diagnosed today is improving.

Agi and Ronald Hirshberg were in the small town of Portsmouth, N.H., when he became ill and was diagnosed with the disease. The couple returned to their home in Los Angeles and sought care at UCLA. Ronald had an inoperable tumor and, despite the best efforts of his physicians, he survived just eight months.

"My relationship with the doctors who took care of him was perfection," Hirshberg says. "Their kindness, their caring was unforgettable. I felt UCLA really treated him so beautifully. After he passed, I called UCLA and said I wanted to support the pancreatic cancer program. They said they didn't have a pancreatic cancer program. I said you have one now."

Hirshberg's efforts have helped fuel tangible progress in

improving the care of patients with pancreatic cancer. She was an early advocate of seed grants, money to fund high-risk, high-reward research projects needed to find new and creative ways to crack the mysteries surrounding the disease. That research has resulted in a much better understanding of the molecular processes that steer the disease, promising work on early detection and improved surgical and chemotherapeutic treatments.

In choosing to direct her philanthropy to UCLA, Hirshberg says she "picked the right partner." The UCLA Agi Hirshberg Center for Pancreatic Diseases has set the highest bar for contemporary pancreatic cancer care. The center is home to an integrative-practice unit, a groundbreaking program that allows patients to receive an extensive evaluation and personalized treatment plan in one visit. "My determination never wavered," she says. "What sustained me is that we kept going and improving. There were so many baby steps. I felt if we could not find an early detection test right this second, my next concern was the patient experience. Today, UCLA is one of the few integrative-practice units that provide the kind of services patients need, including the psychosocial portion that helps not only patients, but also caregivers."

She says she is especially heartened by the efforts of top pancreatic cancer clinicians and researchers at UCLA and elsewhere who are collaborating to accelerate the pace of progress. And when it feels like things are still moving too slowly, she thinks about the annual LA Cancer Challenge, a run/walk held on the UCLA campus that benefits the Hirshberg Foundation for Pancreatic Cancer Research. The event reinvigorates her, Hirshberg says. "On that day, with all those people gathered who have the same wish as I do, I know our loved ones are up there watching," she says. "Ronald and I were partners in life. We had pancreatic cancer together. We were fighting it together. Although he is gone, it has never occurred

to me that I could stop.”

Our 2020 Year in Review

As this unprecedented year of change and uncertainty winds to a close, it is more important than ever to look back and celebrate our accomplishments. Thanks to your continued support and a “Never Give Up” attitude we have been able to accomplish the unimaginable in a year of upheaval. We’ve held fast to our promise to fund innovative research, to connect and educate patients & families, to unite the pancreatic cancer community to make a difference. We have shown our resilience, and as we optimistically look toward to the new year, we want to make time to celebrate.

Our Seed Grants Continue to Lead to Big Research Results

When the world shutdown in March, unfortunately so did labs conducting research. As we adapted to our new normal, so have our Seed Grant recipients. As Dr. Gina Razidlo, of the Mayo Clinic, shared, “*Pancreatic cancer doesn’t stop for a pandemic, and neither do we.*” This spirit has been adopted across the board as our researchers continue to work towards a cure for pancreatic cancer while also contributing to COVID-19 research.

We are happy to share that Seed Grant awardee, Dr. David Wong of UCLA, has received funding to develop a saliva test for COVID-19 and its antibodies. His EFIRM technology, funded through our

Seed Grant program, is currently in various clinical trials for early cancer detection.

Earlier this year we received the amazing news that our UCLA research team was awarded $5.75 million from the NIH to work on three collaborative projects to study the role of obesity & inflammation in pancreatic cancer. Our early funding is bearing fruitful results and this great accomplishment is just another stepping-stone towards a cure.

A key word of 2020 was pivot, which aptly applies to our Seed Grant program. This year we funded a first-of-its-kind collaborative Seed Grant to investigate how inflammation from chronic pancreatitis promotes tumor growth. We are optimistic that the future holds great strides for advancing early detection, prevention, and treatment options for pancreatic cancer!

Delivering Crucial Patient & Family Support, In Brand New Ways

When the pandemic began, we knew our top priority was to our patients & families. While we could not gather in person for our Annual Symposium, we, like most, took to Zoom to bring the doctors and resources to your homes. Our Patient & Family Webinars provided a space for pancreatic cancer patients & caregivers to learn, share their stories and connect with one another. So far, we have 12 amazing webinars in our resource library. We look forward to adding more in the coming year.

Being Apart Did Not Stop Us from Fundraising!

Despite not being able to gather for our fundraising events, our community rallied to continue fundraising & shining a light on pancreatic cancer. In March, our 35 Hirshberg Training Team members raised a record $143,000! If you've ever considered running a marathon, the Los Angeles Marathon will be on May 23, 2021 so there's plenty of time to join our team and start training.

Our Tour de Pier held not one but two great events. As a thanks to our South Bay community, we hosted the Fight & Flight Flyover show on what would have been the 8th Annual Tour de Pier, May 17th. Our hope was to be able to ride together in September but in this year of surprises, we pivoted to a virtual event. We created the Virtual Tour de Pier ride, an outstanding 50-minute workout that captures the spirit of the event. It's now available for all, delivering the essence of the TDP to the comfort of your home.

The LA Cancer Challenge was our true success story of the year. Despite not being able to hold our 5K at UCLA, our community persevered and brought the LACC home. From Anchorage, Alaska to Woodbridge, Virginia, sunny Honolulu to snowy Salt Lake City, you made the LACC a family priority and a day to remember. We indeed colored the map purple for pancreatic cancer with participants in 44 states raising over $385,000!

We rolled right into November to shine a bright light on this disease for Pancreatic Cancer Awareness Month. Our Celebrate, Participate & Dedicate campaign continued to empower, educate and inspire our community. We celebrated with partnerships with small businesses that give back, participated in virtual events

near and far, and shared dedications to loved ones lost and survivors. Our month was full and renews our commitment to making a difference for all those touched by this disease!

This year was not without setbacks. The loss of Justice Ruth Bader Ginsburg, Rep John Lewis and Jeopardy host Alex Trebek to pancreatic cancer shook the nation. Each one inspired us before they were diagnosed then became motivators to pancreatic cancer fighters everywhere as they battled this disease. Their loss is a reminder that despite the odds, we must never give up.

This year of being apart yet together has highlighted the resilience, determination and passion of our community – we thank you for sticking with us through the ups and downs of this rocky year.

Through December 31st, the spirit of generosity continues with a matching gift! Thanks to Birdie & Bob Feldman and Agron, Inc., all donations up to $100,000 will be matched dollar for dollar. Now is the time to **double your year-end donation** *while* helping to lower your tax bill. The CARES Act states that *all donors* can claim up to $300 per taxpayer or $600 for jointly filing married couples on charitable gifts made in 2020, whether you itemize or take a standard deduction. Help *drive research towards a cure while supporting the families facing this disease today.* If you are able, please give today, so that we may continue in our efforts and end 2020 on a high note, worthy of celebration.

Thank you again for making all these 2020 accomplishments possible. Warmest holiday wishes from the Hirshberg Foundation & all those we support.

Scientific Update: How the Pandemic has Reshaped Research

A few of our 2019 Seed Grant recipients share how they have adapted their work in the face of COVID-19

Collaborative Seed Grant Award Focuses on Understanding Pancreatitis-Promoted Pancreatic Cancer

The Hirshberg Foundation is pleased to announce a multi-researcher project will be funded for the 2020 Seed Grant. Expanding on current research underway at the Hirshberg Laboratory for Pancreatic Cancer Research at UCLA, this project will look at the influence of hereditary pancreatitis on pancreatic cancer development.

While there is no one cause for developing pancreatic cancer, it is known that environmental factors such as smoking and diet can increase one's risk. Chronic pancreatitis, an inflammatory condition, is also a known risk factor. It is well established that Kras mutations play a necessary role in initiating pancreatic cancer and subsequent growth but the environmental risk factors that promote tumor development are far less understood. These risk factors offer a potential for interceptive strategies to prevent the development of pancreatic

cancer.

Zsanett Jancso, PhD, will work with Dr. Guido Eibl, Director of the Hirshberg Laboratory on a project titled, *Preclinical Model of Hereditary Pancreatitis-Promoted Pancreatic Cancer*, thanks to 2020 Seed Grant funding. UCLA's Translation Research Lab is focused on identifying and understanding the causes and risk factors of pancreatic cancer. Dr. Jancso's research aims to investigate whether hereditary pancreatitis accelerates pancreatic cancer development and tumor growth. Through studying early-onset pancreatitis, they aim to gain a deeper understanding of how inflammation impacts and promotes tumor growth.

While our Seed Grant program has historically focused on early research projects, the need for collaborative research and partnership has become apparent. In order to make the strides we need to combat this disease, we must focus on projects that will bring science from the bench to the bedside. For our 2020 Seed Grant program, we are honored to be funding a first-of-its-kind, collaborative research grant. Dr. Jancso's research will offer critical insight into how hereditary-pancreatitis associated pancreatic cancer develops and how chronic inflammation promotes tumor growth in the pancreas. The hope is that these findings will then be translatable into preventative strategies against pancreatic cancer.

Thanks to continued support throughout this difficult year, the Hirshberg Foundation has been able to maintain our promise to fund novel pancreatic cancer research. Despite the set-backs of the COVID-19 pandemic, we are unwavering in our quest towards a cure for this disease. Thank you for staying the course with us and making this research possible.

Read the Project Abstract »

A2A Designs Gives Back Throughout November While Helping You Raise Awareness

Friends Alli, age 11, and Avery, age 12, started A2A Designs during the COVID-19 pandemic as a way to give back to their community. They began creating mask chains for friends and family as a fun and stylish way to keep their masks handy while running errands and walking the dog. With an emphasis on supporting essential workers, each month they chose a different non-profit organization and donate a portion of their sales. For November, A2A Designs has partnered with the Hirshberg Foundation to help raise pancreatic cancer awareness with a collection of special purple mask chains.

We are excited to partner with these young entrepreneurs to help raise pancreatic cancer awareness in style! As November community partner for A2A Designs, Alli & Avery will be donating half of their monthly profits to the Hirshberg Foundation for Pancreatic Cancer Research. In addition, they have specially designed two purple chains, the Never Give Up and Purple Power, that will continue to give back towards research & patient support services.

Order your mask chains online »

We are excited to have Alli & Avery join us at our Flower Truck Pop Up for World Pancreatic Cancer Day on November 19th. Plus, each mask chain purchased that day will come with a free Never Give Up mask. Learn more and add it to your calendar »