The 2022 UCLA Activity Summary Report

The UCLA Agi Hirshberg Center for Pancreatic Diseases continues to be one of the nation's leading institutions for pancreatic cancer research, diagnosis, and treatment thanks to funding from the Hirshberg Foundation and our supporters. As we celebrated our 25 years of progress, we were elated to see the five-year survival rate for pancreatic cancer jump to 12 percent, a huge increase from the five-percent five-year survival rate of 1997, when we began. It is thanks to our fundraising events and our donors that we have been able to advance research, improve patient outcomes, and take these crucial steps towards a cancer-free future.

Each year, UCLA provides the Hirshberg Foundation with a detailed report of the progress that is possible thanks to our partnership. Below are updates on the important work taking place at UCLA.

UCLA Agi Hirshberg Center for Pancreatic Diseases

The Hirshberg Center is moving to a brand-new space on the top floor of 100 Medical Plaza on the UCLA campus. With state-of-the-art accommodations for patients and their loved ones, this larger space will be optimized to provide the uncompromising care the center is known for. Overseeing the development of this incredible space as the new Director of the UCLA Agi Hirshberg Center for Pancreatic Diseases, Dr. Timothy Donahue. The new space will unite the Integrated Practice Unit's (IPU) team of specialists under one roof for enhanced collaboration among

different departments and care areas. Currently all IPU pancreatic cancer patients undergo genetic testing, allowing the team to tailor treatment with new drugs that can target identified genetic alterations. Input from multiple disciplines on each patient's case allows clinicians to deliver exceptional comprehensive care that is disease- and patient-specific. This new location will provide a beautiful healing space for patients to receive world-class care.

Nutrition for Safer Surgeries

Nutrition for Safer Surgeries is a new program at UCLA funded by the Hirshberg Foundation. Developed by Shelby Yaceczko, MS, RDN-AP, CNSC, CSSD, an advanced practice dietician at UCLA and speaker at our 17th Annual Hirshberg Symposium on Pancreatic Cancer, the program provides early nutrition assessment and intervention for any patient with a new or existing gastrointestinal cancer diagnosis, with a special focus on pancreatic cancer. Medical nutrition therapy services can prevent or correct nutritional deficiencies, enhance quality of life during cancer treatment, and minimize treatment's side effects. Research has shown that perioperative nutrition evaluation and optimization are essential to the success of pancreatic cancer surgery and result in decreased morbidities and mortalities. A member of the IPU, Yaceczko consults with patients before surgery to improve surgical outcomes.

Robotic Surgery at UCLA

A 2016 Seed Grant recipient, Mark Girgis, MD, continues to advance robotic surgery at UCLA. Dr. Girgis, Director of Robotic Surgery and Assistant Professor of Surgery, David Geffen School of Medicine at UCLA, has helped robotic surgery gain momentum in the treatment of pancreatic disease. The minimally invasive

technique improves long-term recovery prospects due to decreased healing time which allows patients to begin post-surgery chemotherapy sooner. The robotic surgery expertise of Dr. Girgis and his team enables them to expand patient populations eligible for surgery, regardless of complications and disease stage. The popularity of robotic surgery is on the rise with both patients and surgeons, and we are optimistic that this treatment option will improve patient care.

Clinical Trials for Treatment

Clinical trials are a crucial step in the development of effective therapies for pancreatic cancer. Many patients also benefit from participation in a clinical trial as part of the treatment. Patients seen through the Hirshberg Center's IPU have access to an array of treatment options including the 19 clinical trials currently in progress at UCLA. Plus, the UC Pancreatic Cancer Consortium is currently running over 46 clinical trials focused on pancreatic cancer. These clinical trials not only help advance understanding of this disease, but they also offer patients and their families hope for better treatment options. The Hirshberg Center's vast offerings of clinical trials for promising treatments put it at the forefront of pioneering translational research.

The Hirshberg Foundation's partnership with UCLA has created a premiere pancreatic cancer center with cutting-edge research and world-class care that draws patients from across the country. Together we are making progress toward improved treatments, outcomes, and quality of life for patients with pancreatic cancer. We are hopeful that we can watch research progress accelerate towards a cancer-free future.

Read the full summary here →

Exciting Changes to the Hirshberg Center for Pancreatic Diseases

We are seeing the seeds we planted 25 years ago with the creation of the Foundation come to full bloom. A pillar of our Foundation mission was "*to create premier Pancreatic Cancer Center where all needs of pancreatic cancer patients can be met in one location with the most advanced treatment options.*" That dream is now the UCLA Agi Hirshberg Center for Pancreatic Diseases and it is moving to a beautiful new space. We've had a celebratory sneak peek and look forward to sharing more when the Center opens this summer. This gorgeous new space will offer patients and loved ones world-class integrative care in one convenient location.

As we prepare for the new space, we are honored to welcome Dr. Timothy Donahue as the new Director of the UCLA Agi Hirshberg Center for Pancreatic Diseases. Dr. Donahue is the Garry Shandling Chair of Pancreatic Cancer Surgery, Chief of the Division of Surgical Oncology, and Program Director of the General Surgery Residency at UCLA. He is an expert in the treatment of pancreatic disease and oversees a NIH funded research program focused on pancreatic cancer. With Dr. Donahue as the Director and Dr. Joe Hines as Chair and Executive Medical Director of the Department of Surgery, our pancreatic cancer program at UCLA is in the most capable hands so that all patients can receive best in class care.

Taking the helm of our Scientific Advisory Board will be

esteemed researcher, Dr. Miklos Sahin-Toth. Dr. Sahin-Toth has lead his namesake lab at UCLA since 2019. A world-renowned expert in the area of the pancreas disorders with a focus on genetic risk factors in chronic pancreatitis, Dr. Sahin-Toth brings a fresh perspective and talent as Chair of the board, particularly as we look towards the future. For the past 25 years we have invested in progress. Now, we look toward the next 25 years filled with hope for all that is to come.

These exciting changes are possible thanks to those equally invested in our motto, "Never Give Up: Finding a Cure is Worth Fighting For."

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.

The Hirshberg Laboratories at UCLA

As we commemorate 25 years of progress in the field of pancreatic cancer research, we take a moment to reflect on where we started. When the Hirshberg Foundation was established in 1997, it was organized around five mission pillars. To date, we have accomplished 4 of those 5 goals, with “a cure” being the final piece.

One mission pillar is

To create a premier Pancreatic Cancer Center where all needs of pancreatic cancer patients can be met in one location with the most advanced treatment options.

The work of our UCLA Labs is bringing that goal to life. Learn more about the collaboration and progress happening at our UCLA laboratories.

Watch Our UCLA Labs Video →

Just a few months after Ronnie passed away from pancreatic

cancer, Agi connected with the doctors who had treated him to establish a research program at UCLA. In February 1998, the Ronald S. Hirshberg Translational Pancreatic Cancer Research Laboratory was opened, the first lab dedicated solely to pancreatic cancer research. Shortly thereafter, the Basic Research chair was created and Dr. Enrique Rozengurt was appointed to this distinguished position. In 2019, with the recruitment of Dr. Miklos Sahin-Toth, the Hirshberg research centers at UCLA grew to encompass three laboratories.

These three laboratories are located in the same building, with two of the labs side-by-side to generate new ideas and foster collaboration. The research being done at these labs is also shared and directly applicable to patients being treated through the UCLA Agi Hirshberg Center for Pancreatic Cancer Diseases. This deeply collaborative, integrated approach to holistic patient care was a dream in 1997. Thanks to the tireless efforts of researchers, donors, physicians, families, supporters and entire extended network of Hirshberg Foundation family, this dream is now a world-renowned reality.

The mission pillar of a “premier pancreatic cancer center” has guided our work. The progress that has been made through research at the UCLA Labs has influenced pancreas-focused institutions across the globe, and has driven research towards a cure. After 25 years of milestones, we are more committed than ever to our motto “Never Give Up: Finding a Cure is Worth Fighting For.”

Pivotal research on RNA splicing may hold key to treatment

As we celebrate summer and all that is blooming, we look back at seeds planted through our Seed Grant Program, and are optimistic about the progress being made in pancreatic cancer research. Our 2019 Seed Grant cohort faced a difficult year for conducting research, establishing their labs and providing updates. We are catching up with these great scientists to share their progress and advances in pancreatic cancer research.

When Luisa F Escobar-Hoyos, MSc, PhD, applied for a Seed Grant in 2019, she was a Senior Post-Doc at Memorial Sloan Kettering Cancer Center. Shortly after receiving her award, in February 2020, she became an Assistant Professor of Therapeutic Radiology and Molecular Biophysics and Biochemistry at Yale. Despite the pandemic severely impacting the establishment of her lab, she and her team continued to publish and their discoveries led to a new therapeutic modality for pancreatic cancer. Dr. Escobar-Hoyos is making great strides to cure pancreatic cancer, most notably through the discovery that pancreatic cancers are highly susceptible to a range of therapies directed at RNA splicing.

A majority of pancreatic ductal adenocarcinoma (PDAC) tumors are driven by mutations in the KRAS gene that increase the activity of KRAS driving cell growth and survival. A large subset of these tumors (70%) also have mutations in the TP53 gene but efforts to inhibit or drug these mutant proteins have largely failed. More recently, it has been shown that a specific group of mutations in TP53, called hotspot mutations, combined with high expression of genes involved in RNA splicing are markers of

aggressive PDAC. RNA splicing is a process where one gene can produce many different forms of a protein and involves a number of RNA splicing proteins. Dr. Escobar-Hoyos's recent work, published in Cancer Cell, aimed to investigate if and how mutant TP53 and RNA splicing co-operate in pancreatic tumor cells. They found that mutant p53 hijacks RNA splicing to favor the production of proteins that stimulate KRAS to promote tumor growth and metastasis. Based on these findings, Dr. Escobar-Hoyos's lab developed and patented a new therapy for pancreatic cancers that harbor mutant KRAS and mutant p53, which corrects the RNA splicing errors, selectively killing pancreatic cancer cells in animal models.

This remarkable discovery, that oncogenic KRAS is susceptible to inactivation through the inhibition of RNA splicing, led Dr. Escobar-Hoyos to submit a patent for this type of therapy. The patent relates to a method for treatment administering an anti-sense oligonucleotides (a small piece of modified RNA) that block the splicing of cancer-related genes, thereby treating the cancer. This novel therapy, Splicing-Hit Oligonucleotide Therapy (SHOT), is currently being tested in Dr. Escobar-Hoyos's lab. As pancreatic tumors often don't respond to treatment, the hope that SHOT will be effective in tumors that are resistant to current therapies. Dr. Escobar-Hoyos is currently working with the Yale Cancer Center on a clinical trial to test this novel form of therapy for pancreatic cancers.

We applaud the work of Dr. Escobar-Hoyos and her lab and are hopeful that her discovery helps pave the way to a cure. As Dr. Escobar-Hoyos writes, "thank you for your support and I hope that [the Foundation] funds other pancreatic cancer scientists!" We are honored to fund Seed Grants and, thanks to your support, look forward to continuing our progress.