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DIVISION OF GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

Inside This Edition

Message from the Chief

First they came for the socialists, and I did not speak out — because I was not a socialist.
Then they came for the trade unionists, and I did not speak out — because I was not a trade unionist.
Then they came for the Jews, and I did not speak out — because I was not a Jew.
Then they came for me — and there was no one left to speak for me.
Pastor Martin Niemöller, after WWII

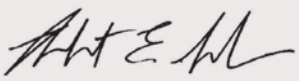
Saturday, October 27, 2018, forever changed Pittsburgh. The Tree of Life Synagogue, where the massacre of 11 innocent, Jewish parishioners took place, is only four blocks from where I live. The Squirrel Hill community, where the tragedy unfolded, is only three miles from the main UPMC hospital complex. Victims were treated in our emergency room. It could not have hit any closer to home.

The Bible repeatedly instructs us to treat the "stranger" as a native and love him as yourself. Although worthy morally, protecting the stranger is actually in our own self-interest. Every time we defend the oppressed, guard the scapegoat against discrimination, or stand up for the other, we are preserving and protecting our own freedom. Ignoring hate because it isn't directed at yourself or your people is a losing proposition. Eventually, you too may become a target. As the above quote from Pastor Niemöller implies, once you retreat from the obligation to speak out against what is wrong, you are embracing isolation and ensuring defeat.

In an extraordinary display of devotion to duty, as the killer arrived at the Allegheny General Hospital emergency department shouting "I want to kill all the Jews," he was greeted and attended to by strangers including Jewish doctors, nurses, and staff. Medicine is the great equalizer. All of our bodies have the same anatomy and physiology, and are prone to the same emotional spectrum of happiness, grief, loneliness, and anger. We are all equal in the face of the human condition. In a hospital and in the practice of medicine, we are extraordinarily lucky to be surrounded by an enormous diversity of culture, ethnicity, race, and spirit. We are proud and thankful for the first responders who bravely and courageously acted on our behalf, and of our community who have attended vigils and supported the affected. We are thankful to all of you who have contacted us to inquire about our safety, have prayed on our behalf, and have empathized with our collective tragedy. We can only hope this sad circumstance will spur closer collaboration, greater appreciation, and more recognition of the beauty that each of us brings to this world.

In this issue, we highlight our faculty's research efforts in pancreatic disease, both pancreatic cancer, led by **Randall Brand, MD**, and inflammatory disease of the pancreas and its complications, by **Georgios Papachristou, MD, PhD**, and **Anna Evans Phillips, MD, MS**. **Ramon Bataller, MD, PhD**, our section chief of Hepatology, discusses new horizons in the management and understanding of alcoholic hepatitis. We also share a synopsis of recent, high-profile, impact publications that aptly illustrate how our Division is making an impact.

To good health,



Robert E. Schoen, MD, MPH
Professor of Medicine and Epidemiology
Chief, Division of Gastroenterology, Hepatology and Nutrition
University of Pittsburgh School of Medicine

Pancreatic Cancer:
Collaborative Efforts to Promote Early Detection

How do you improve survival rates for pancreatic cancer? Better early detection methods? More accurate risk assessments and profiles? A better understanding of the genetic variants, both inherited and acquired? The answer is yes to all three. However, there's a unifying force working behind all of these paths. That force is collaboration — locally, nationally, and internationally. Without it, we likely won't be successful, or won't be nearly as successful or timely as we could be to improve survivability.

"Much of my work, and that of collaborators here at UPMC and the University of Pittsburgh and beyond, is dedicated to making early detection a real possibility."

Randall Brand, MD

Randall Brand, MD, is a professor of medicine with an extensive background in pancreatic diseases and an interest in familial pancreatic cancer. His work as a physician-scientist is focused on the early diagnosis of pancreatic cancer and cystic lesions of the pancreas. Dr. Brand's research interests involve familial pancreatic cancer and other hereditary GI disorders. He was recruited to the University of Pittsburgh more than 10 years ago to pursue ground-breaking pancreatic cancer research and, since his arrival, has been the leader of the University of Pittsburgh Pancreatic Adenocarcinoma Gene-Environment Registry (PAGER) study. The pancreatic cancer biospecimen repository developed through the PAGER study is a nationally recognized resource for multiple NIH/NCI-funded projects, along with national and international collaborations. At present, the biorepository contains data and samples from more than 7,000 individuals. It has become an immensely powerful, shared tool for advancing the research of pancreatic cancer in the United States.

Dr. Brand is a key contributor to the National Cancer Institute's Early Detection Research Network (EDRN), especially for research related to pancreatic cancer and cystic neoplasms. He is currently funded as an EDRN principal investigator leading both a multicenter Pancreatic Cancer Clinical Validation Center and a Biomarker Developmental Laboratory.

Dr. Brand's clinical practice focuses on the management of pancreatic cancer, cystic lesions of the pancreas, and patients with other gastrointestinal (GI) cancers. As director of the Hereditary GI Tumor Program, Dr. Brand specializes in the management of individuals at high risk for the development of colon cancer, pancreatic cancer, and other GI malignancies.

"I am privileged to be part of this dedicated field and to work with so many exemplary and accomplished collaborators within our Division, through the EDRN, and in our collaborative, multicenter NIH studies. The difficulties associated with pancreatic cancer — its relative rarity and its generally late presentation at an advanced stage — make it such a deadly disease. These challenges will only be overcome through shared investigations, as we use combined resources to fight for the support of more studies across the United States and internationally," says Dr. Brand.

Pancreatic cancer is the third-leading cause of cancer death in the United States.[1] The vast majority of pancreatic cancer cases present at a late stage with metastasis to distant sites, making successful treatment extremely difficult. Five-year survival rates remain dismally low. If treatments for late-stage disease are unable to improve outcomes, the only alternative may be to find the disease early when it is amenable to surgery or other treatment modalities. The same can be said for many types of cancer.

"It continues to be true that treatments for late-stage disease remain suboptimal. In most cases, we are unable to effectively treat late-stage pancreatic cancer. However, advances in late-stage disease management are being made. We see much better survival with cases of early-stage disease when the tumor is localized to just the pancreas (resectable) and the burden is much less.

If you look at the advances that have been made with colon cancer in recent years, five-year survival rates now approach 80 to 85 percent because of the surgical and adjuvant treatments available, along with our ability to detect the disease early. Similarly, finding pancreatic tumors when they are resectable, and aggressively treating systemic disease, may be our best approach. We must do a better job of finding pancreatic cancer at an early stage. Much of my work, and that of my collaborators here at UPMC and the University of Pittsburgh and beyond, is dedicated to making early detection a real possibility," says Dr. Brand.

Pancreatic Cancer Research: Early Detection Through Cyst Fluid, Biomarkers, and Germline Research

Early detection of pancreatic cancer on a molecular level may be the ultimate method of early detection. A number of avenues of research are under active investigation by Dr. Brand and his colleagues at the University of Pittsburgh and the EDRN member sites.

Pancreatic Cysts and Fluid Research

Pancreatic cyst fluid may be the most viable way to identify potential cancer at an early stage. Work along these lines is progressing with Aatur Singhi, MD, PhD, from the UPMC Department of Pathology. Dr. Singhi's efforts were preceded by the research of Asif Khalid, MD, associate professor of medicine and chief of GI services at the VA Pittsburgh Healthcare System, along with Kevin McGrath, MD, and other members of the Division. Dr. Khalid led the PANDA study on pancreatic cyst fluid analysis that was published in 2006.

Funding from the Pancreatic Cyst Biomarker Alliance (PCBA), a collaborative funded by the EDRN, and six member sites, including the University of Pittsburgh, Johns Hopkins University, Stanford University, University of California San Francisco, Washington University in St. Louis, and the Van Andel Research Institute in Grand Rapids, Mich., has enabled research teams to attempt the validation of promising biomarkers from cystic fluid.

"Our goal with this line of research is to better understand which pancreatic cysts need to be watched, which ones need to be resected, and which ones are benign with little risk of a cancerous future. This unique project, which to the best of our knowledge has never been done with cyst fluid, allows for the testing of multiple potential biomarkers on a common set of samples. The tests determine how these markers can be combined to develop a panel of markers to improve the management of patients with pancreatic cysts through identification of those cysts that have a high and low risk for progressing to a malignant state," says Dr. Brand.

Blood-Based Biomarkers for Early Detection

One of Dr. Brand's current studies is now in its third year of funding and is quite promising. He is leading an EDRN-funded clinical validation center (CVC) along with Surinder Batra, MD, at the University of Nebraska to evaluate the ability of the biomarkers MUC5AC and MUC4 to distinguish pancreatic adenocarcinoma among healthy individuals and diseased control patients, including patients with a benign biliary obstruction or chronic pancreatitis.

"Certain mucins have been shown to be overexpressed in pancreatic cancer in EDRN studies thereby, presenting as a hallmark of the disease. MUC5AC and MUC4 are two forms of mucin that have been shown to be promising biomarkers of disease. This study evaluates these two markers using samples from our PAGER biorepository to see if we can validate them with respect to their ability to distinguish between cancers and healthy and diseased controls. In a separate study aim, promising mucin markers are being developed to determine if they can be used to predict those cysts that are at high risk for progressing to pancreatic cancer. There is much excitement in our collective groups about the promise of these studies, and in a few years, we will likely have some answers," says Dr. Brand.

Along and with EDRN partners, a number of open investigations are aimed at finding biomarkers that can point to the presence of pancreatic cancer at its most early stage. Brian Haab, PhD, from his laboratory at Van Andel, and Dr. Brand at the University of Pittsburgh have been involved in glyco-biology research concerning pancreatic cancer as part of their EDRN-funded Biomarker Developmental Laboratory. Dr. Brand and his colleagues also have been working with industry as part of a large, multicenter trial to test various biomarkers and a novel panel for early detection of pancreatic cancer in high-risk individuals with a genetic predisposition.

"We are fortunate to learn from, work with, and, when possible, assist our colleagues in their efforts as part of our shared objectives of making pancreatic cancer a more treatable illness," says Dr. Brand.

Collaboration Is the Key

"For certain, our success will be proportionate with the diverse shared samples and complementary acumen found in our collaborative efforts. I am both grateful and honored that our national and international pancreatic cancer research groups are so robust. So much of what we do is shared within the field, but we also benefit greatly from internal UPMC partnerships, as well as collaborations with like-minded institutions and industry colleagues," says Dr. Brand.

Specifically, at the University of Pittsburgh and UPMC, Dr. Brand notes numerous pancreatic research collaborators. In addition to Dr. Singhi, Dr. McGrath, and Dr. Khalid, who were discussed earlier in this article, Kenneth Fasanella, MD, and Jennifer Chennat, MD, are working on related and independent lines of investigation in pancreatic cancer.

"Dr. Fasanella has a sharp focus on surveillance of cystic pancreatic lesions, and Dr. McGrath is working along similar lines. Dr. Khalid's work with pancreatic tumors and cysts continues to advance the field. Together with Dr. Singhi, and our surgical collaborators, most notably Amer Zureikat, MD, chief of Gastrointestinal Surgical Oncology and co-director of the UPMC Pancreatic Cancer Center, and

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New Research in Alcoholic Hepatitis and Liver Disease

Section Chief of Hepatology, **Ramon Bataller, MD, PhD**, studies the epidemiological, clinical, and molecular aspects of alcoholic fatty liver disease and alcoholic hepatitis. As a member of the American Association for the Study of Liver Diseases (AASLD), Dr. Bataller sits on the Alcoholic Liver Disease Special Interest Group (ALD SIG). Dr. Bataller is a co-editor of *The Journal of Hepatology,* and in 2018 he was named as a permanent member to the Hepatobiliary Pathophysiology Study Section at the National Institutes of Health (NIH).

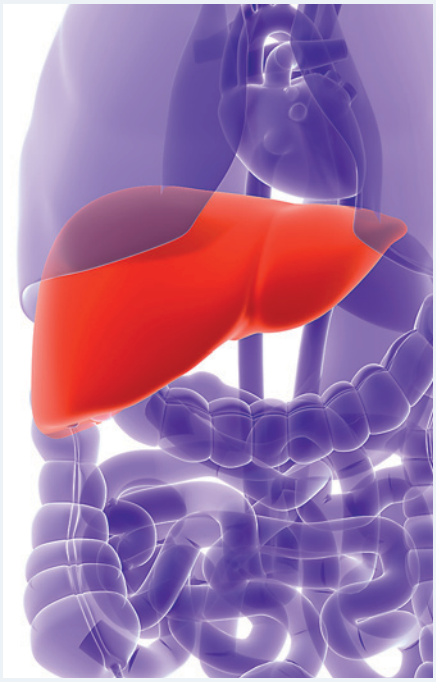
"Incidence of alcoholic hepatitis is increasing, and we still have few effective treatments outside of prevention. Once it manifests, decompensation can be rapid and irreversible."

Ramon Bataller, MD, PhD

Dr. Bataller is a primary investigator in one of four NIH-funded consortia seeking to identify the molecular targets responsible for disease pathogenesis and novel treatments for alcoholic hepatitis — the most severe form of alcoholic liver disease (ALD).

Dr. Bataller's research has identified that a systemic inflammatory response as part of the alcoholic hepatitis disease course is likely driving the induction of renal failure and other complications. Identifying which molecular signatures emanate from the liver and cause the inflammatory response may lead to more effective, targeted therapies. Further research by Dr. Bataller seeks to better understand the regenerative mechanisms of the liver in relation to alcoholic hepatitis — when, how, and why the regeneration process fails, leading to acute and dramatic decompensation and liver failure. Previous work also has shown that a decrease in persistent alcohol intake is the primary determinant of long-term survival in patients with alcoholic hepatitis.

"Alcoholic liver diseases and associated patient morbidity and mortality have been steadily increasing over the last two decades, particularly in the United States, with troubling increases in younger patients and also in females who in the past have had a lower incidence of disease. The recent large epidemiological studies highlight these trends and the new challenges we are facing with preventable liver disease. Layer into these findings the rising rates of obesity in the general population, and the rampaging national opioid abuse problem, and it should come as little surprise that liver disease associated with alcohol consumption is affecting more and younger people," says Dr. Bataller.



Severe Consequences — Alcoholic Hepatitis

The most severe form of alcoholic liver disease is alcoholic hepatitis (AH). It is a condition Dr. Bataller has spent many years studying, and one he sees all too frequently in the clinic. "Incidence of the condition is increasing, and we still have few effective treatments outside of prevention. Once it manifests, decompensation can be rapid and irreversible. There is a 30 percent chance of death within three months. We see AH in younger and younger patients. Of course, not everyone who abuses or uses alcohol excessively ends up with AH, and this conundrum is the focus of one of our recently received grants," says Dr. Bataller.

Dr. Bataller has three current, active research grants funded by the NIH to investigate various aspects of alcoholic hepatitis. One study examines the potential genetic factors that may predispose an individual to the condition. This study is a collaborative effort with Dr. Laura Nagy at the Cleveland Clinic, the NIH, and other institutions to pinpoint genetic determinants predisposing individuals to AH.

A second project, an NIH-funded U01 grant, is a basic science study designed to further Dr. Bataller's research into why hepatocytes in the liver fail during alcoholic hepatitis. This research will explore the main transcription factors that regulate gene expression in hepatocytes.

"From previous studies, we determined that in alcoholic hepatitis the hepatocytes that regenerate revert to a fetal-like state. New hepatocytes form in response to the liver injury. They grow, sometimes with massive hepatomegaly, but they do not function properly. As a consequence of this improper functioning, the liver fails. These hepatocytes grow massively in a dedifferentiated fashion but cannot synthesize albumin or clotting factors. There are many of these new hepatocytes, but they are metaplastic and dysfunctional. We hope, with our new research over the next five to six years, to identify a way to modulate or inactivate this fetal transcription factor," says Dr. Bataller.

Lastly, Dr. Bataller is leading a multicenter, multiarmed clinical trial with the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and nine centers across the United States to examine new and promising therapeutics to combat alcohol-caused liver disease and damage. One of the first trials in this new effort will compare the use and effectiveness of the growth factor known as granulocyte colony-stimulating factor (G-CSF) versus the use of anakinra, an interleukin-1 antagonist. Both agents are being compared against the current standard-of-care treatment — prednisone — in cases of alcoholic hepatitis.

"G-CSF is a colony growth factor that can mobilize the glomerular cells to repopulate the liver and regenerate it. Anakinra, also known as Kineret®, is a biologic agent that works to decrease inflammation and is currently used in the treatment of rheumatoid arthritis and other inflammatory conditions. We are completing the study design and IRB reviews for this trial now. This is but one of a number of new clinical investigations to examine new and novel therapeutic targets for treating AH. We are tremendously excited to see where the science leads us," says Dr. Bataller.

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UPMC Physician Resources

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Selected CME Course Offerings in Gastroenterology, Hepatology and Nutrition Include:

Frailty, Sarcopenia, and Liver Transplantation
Presented by Michael A. Dunn, MD

Management of Patients with Alcoholic Liver Disease
Presented by Ramon Bataller, MD, PhD

Live Donor Liver Transplant at UPMC: Changing the Paradigm
Presented by Abhinav Humar, MD

Psycho-Behavioral Approaches to GI Disease
Presented by Eva M. Szigethy, MD, PhD

Endoscopic Management of GI Bleeding
Presented by Adam Slivka, MD

ERCP Indications and Complications
Presented by Jennifer S. Chennat, MD

Nonalcoholic Steatohepatitis: Evaluation and Management
Presented by Jaideep Behari, MD, PhD

Diagnosis and Treatment of Esophageal Motility Disorders
Presented by David Levinthal, MD, PhD

Screening for GI Malignancy
Presented by Robert E. Schoen, MD, MPH

Inflammatory Bowel Disease: Evaluation and Management
Presented by Marc B. Schwartz, MD

Unraveling the Mysteries of Pain in Chronic Pancreatitis

Anna Evans Phillips, MD, MS, is a clinician-researcher in the Division of Gastroenterology, Hepatology and Nutrition. Dr. Phillips attended the University of Pittsburgh School of Medicine after graduating from Harvard University. Her medical training included a residency at Yale New Haven Hospital, followed by gastroenterology training at New York Presbyterian/Columbia Hospital and the University of Pittsburgh School of Medicine. She is currently completing a medical pancreatology fellowship at the University of Pittsburgh School of Medicine under the mentorship of Dhiraj Yadav, MD, MPH, and David C. Whitcomb MD, PhD. In 2018, Dr. Phillips received an American Pancreatic Association Young Investigator Career Development Award to continue her explorations of the nature and role of pain in chronic pancreatitis.

"Abdominal pain affects more than 90 percent of chronic pancreatitis patients. Chronic, daily pain significantly impacts patients' quality-of-life and functioning."

Anna Evans Phillips, MD, MS

In addition to the study of pain in chronic pancreatitis, Dr. Phillips' research interests include understanding the underlying mechanisms in acute and chronic pancreatitis, fatty acid and lipotoxicity in severe acute pancreatitis, and nutrition and nutritional support in patients with pancreatitis.

Origins of Pain in Chronic Pancreatitis

Chronic pancreatitis (CP) is often the result of repeated episodes of acute pancreatitis (AP). Some patients experience recurrent episodes of acute pancreatitis that eventually result in a scarred, fibrotic pancreas. These patients develop diabetes from an inability to make enough insulin and may have difficulty absorbing nutrients since their pancreas can no longer supply adequate digestive juices. Furthermore, they may have pain from damage to their pancreatic nerves, and if the pain has gone on extensively, then they may have remodeling of peripheral nerves that results in more systemic symptoms.

"Abdominal pain affects more than 90 percent of chronic pancreatitis patients. Chronic, daily pain significantly impacts patients' quality-of-life and functioning, as was seen in the North American Pancreatitis Study 2 (NAPS2) led by the University of Pittsburgh," says Dr. Phillips.

One of Dr. Phillips' ongoing research investigations seeks to create a protocol that will phenotype patients with chronic pain from chronic pancreatitis. "The underlying purpose of this research is to identify specific patterns of pain that may predict the potential for responses to available therapy."

In the current understanding of CP, scarring to the organ often occurs early in the central, or main, pancreatic duct. It is theorized that this leads to an elevated level of pressure — either from the scarring or blockage or, perhaps, from the formation of calcified stones that cause a blockage.

"Current invasive therapy often involves endotherapy, where we insert a stent in the pancreatic duct to alleviate a blockage or stricture, or we try and remove stones from the pancreatic duct to relieve resultant elevated pressures. Invasive surgical therapies are targeted to remove diseased portions of the gland, or in extreme cases the whole gland. In some cases, neither endotherapy nor surgery is appropriate, and we focus efforts on using medications to dull or decrease the neural response to stimulation from the pancreatic nerves. We currently rely on extensive clinical expertise to make the decision about which therapy to recommend. We do not know, however, which patients will respond to therapy. It would greatly strengthen our decision-making to have a tool that would allow us to predict how likely a patient is to experience pain reduction as part of their response. This would allow us to forego unnecessary or high-risk procedures for those patients in favor of conservative measures that could have a more long-lasting impact," says Dr. Phillips.

Of particular interest in CP is the understanding that a patient's pain does not correlate with imaging findings of disease. This finding was part of the NAPS2 cohort study and was published several years ago by colleagues from the Division.

"Similar studies have confirmed these original findings. For example, some patients who have evidence of parenchymal calcifications, dilated ducts, or large pancreatic duct stones on CT or MRI

may have no pain; in the opposite manner, someone else could experience chronic daily debilitating pain and have a pancreas that looks very mildly affected. Pain does not correlate with disease activity, at least related to the physical appearance of the pancreas on cross-sectional imaging. This tells us, frankly, that pain associated with CP is a highly complex and heterogeneous process," says Dr. Phillips.

Quantitative Sensory Testing (QST) and Patient Phenotyping

Previous animal model studies have shown that patients with chronic pain undergo remodeling of their central nervous system, which can change their perception of pain over time. This process may alter patients' sensitivity to pain on a systemic level. Early work in CP has suggested that this phenomenon may similarly be present in these patients.

To study this phenomenon and to phenotype patients, Dr. Phillips is using a process called quantitative sensory testing (QST). Researchers at the Aalborg University in Denmark have pioneered the methodology, and Dr. Phillips is collaborating with this institution as she investigates a modified QST protocol for patient testing.

"Our colleagues in Denmark created a simplified QST protocol based on their past work, which is what we are currently using for testing in our subjects. The QST protocol captures a series of surface stimulations on the body from which we elicit a measured response. Subjective and objective measures are collected. We hypothesize that pain phenotypes identified by QST will correlate with specific patient and disease-related characteristics," says Dr. Phillips.

The basic idea behind QST is that it can map a pain system in the body. The neural pathways can be explored using a standardized stimulation followed by recording the patient's response. QST has been shown to be able to differentiate pancreatic sensitization from a more central pain sensitization. Dr. Phillips' research, if successful, may allow for patients to be phenotyped based on QST findings to allow clinicians to better understand and treat pain syndromes occurring in cases of CP, and it may also allow for the prediction of response or pain resolution from endoscopic or surgical interventions.

Burnout Theory and CP

Another aspect of Dr. Phillips' investigations into pain in CP deals with the phenomenon known as burnout theory. Approximately 15 percent of chronic pancreatitis patients experience a peak in their pancreatitis-related pain at some point relatively early in their disease course. These individuals then enter a stage where they no longer have pain from their chronic pancreatitis.

"The theory is that chronic inflammation has burned out the neural response in the pancreas. Burnout theory affects a minority of patients. However, it will be intriguing to compare those patients to patients who have a similar clinical history but still experience severe pain," says Dr. Phillips.

References and Further Reading

Past research by Dr. Phillips has examined a number of aspects of pancreatitis in various settings. Below is a sample of published papers for further reading.

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Pancreatic Cancer *Continued from Page 3*

Nathan Bahary, MD, PhD, medical director of the UPMC Pancreatic Cancer Program, we continue to build a world-class pancreatic cancer research program," says Dr. Brand.

In the long term, finding biomarkers to identify traces of the earliest stages of disease at the molecular level is the proverbial "Holy Grail" of pancreatology. Of course, we will also need to understand how to intervene at the molecular level to suppress or eliminate the growing malignancy.

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Acute Pancreatitis Research and the Role of CAPER — An Interview With Georgios Papachristou

The Pancreas and Biliary Center in the Division of Gastroenterology, Hepatology and Nutrition, home to some of the foremost pancreas researchers and clinicians in the world, specializes in the treatment and research of the full spectrum of pancreaticobiliary diseases. In this issue, the research work of one of its key members, **Georgios Papachristou, MD, PhD**, will be highlighted.

"Acute pancreatitis is the third most common cause of GI-related admissions in the United States. This translates to about 300,000 admissions per year."

Georgios Papachristou, MD, PhD

Dr. Papachristou, a professor of medicine in the Division, specializes in pancreaticobiliary diseases, particularly the study of acute pancreatitis and the practice of state-of-the-art endoscopic retrograde cholangio-pancreatography (ERCP), and endoscopic ultrasound (EUS). Dr. Papachristou's research over the last 15 years has focused on acute pancreatitis. He leads a number of clinical trials investigating different aspects of acute pancreatitis. Dr. Papachristou also has been involved in the Collaborative Alliance for Pancreas Education and Research (CAPER) initiative. He recently concluded a two-year term as president and continues to serve on the CAPER board of directors.

You have a number of ongoing observational studies and clinical trials with respect to acute pancreatitis, one of which is the Pancreatitis-associated Risk of Organ Failure or PROOF Study. Can you give an overview of its aims and outcomes measures, and the possible clinical significance of the study in relation to treatment approaches?

"PROOF is an observational trial with several goals, the first of which is to assess the risk factors for severe acute pancreatitis. We also aim for the clinical data we are collecting to help validate risk factors and predictive scoring systems for severe disease states. In addition, the study has a translational aspect, which involves the collection of bio-samples for analysis of important acute pancreatitis markers, such as cytokines, free fatty acid levels, and the assessment of genetic predisposition for severe disease. PROOF has been an extremely successful study resulting in more than 25 original publications to date. The study has opened many doors for collaborative work with other groups around the country, which is vitally important to further advance the field."

You also are currently running the APPRENTICE study, the Acute Pancreatitis Patient Registry To Examine Novel Therapies In Clinical Experiences. How does this study relate to PROOF, and what is its significance?

"About two and a half years ago, we realized that the creation of an international prospective registry of acute pancreatitis patients was needed. This international observational study has so far enrolled more than 1,700 patients from 22 centers in four continents. The goal is to use APPRENTICE in the near future as a platform for randomized trials. In 2018, we presented a few abstracts on early-phase clinical data, and we were invited to present our work at the American Pancreatic Association annual meeting in November 2018."

For individuals who have acute pancreatitis, there can be significant and lasting long-term consequences. How are you approaching this from a research perspective in the Division?

"Acute pancreatitis can certainly have lasting effects. We know some of them, and others are still being investigated. We proposed a study in 2017 to follow patients for up to 12 months after discharge for a case of acute pancreatitis. This study, called Post-acute Pancreatitis Pancreatic Exocrine Insufficiency, will follow patients long-term to better understand what happens months after the injury, with a special emphasis on quality-of-life measures and development of exocrine insufficiency. This is an investigator-initiated with support from a biopharmaceutical company. We have recently expanded to a multicenter trial with Ohio State University, and Johns Hopkins University is joining the study as well."

Acute pancreatitis is a worrisome issue. Can you encapsulate the problem and its consequences, which likely speak to why so much of your research is directed at acute pancreatitis?

"Acute pancreatitis is the third most common cause of GI-related hospital admissions in the United States. This translates to about 300,000 admissions per year. It's a major health care burden, and its incidence is growing. We spend about $2 billion dealing with it every year in this country. That's the big picture. For patients, it's an acute illness, which puts them in great distress because of the associated abdominal pain. For a subgroup of patients, this disease can become extremely complicated with prolonged hospitalization and high rates of morbidity and mortality. Acute pancreatitis is a potentially lethal acute inflammatory disease and, unfortunately, we have no disease-specific medications to treat it, so we can only focus on adequate intravenous hydration and support of the patient rather than treating the disease itself. And, of course, it's a disease that can persist in a subclinical manner with recurrences, which lead to a vicious circle of slow decline."

A deeper understanding of acute pancreatitis really necessitates that you approach the condition from multiple directions. How else are you trying to combat the disease from a research perspective?

"We have one randomized trial open right now that is looking at the use of indomethacin suppositories to prevent severe acute pancreatitis. This is a pilot trial in which we are testing the use of this anti-inflammatory medication in cases of acute pancreatitis to see if we can control the disease better and to see if the medication can prevent complications and reduce the severity of the disease. Past work by others to prevent acute pancreatitis in patients undergoing a procedure called ERCP with indomethacin appears to not only prevent the development or the incidence of post-acute pancreatitis, but also to prevent severe pancreatitis. Therefore, we decided to expand the use of indomethacin in all patients with acute pancreatitis, not just patients undergoing ERCP. The advantage of indomethacin is that it can be administered rectally in those patients with nausea and vomiting. Importantly, it's a very safe and tolerable medication for most people."

The field likely won't continue to advance without the infusion and training of new clinicians and researchers who dedicate their careers to understanding acute pancreatitis and the other myriad conditions on the gastroenterology spectrum. Can you highlight some of the educational and training programs in which you are currently involved?

"I am very much committed, and so is our entire Division and leadership, to cultivating an academic center that mentors young scientists in pancreatitis and other research. This commitment to teaching and training extends to my involvement with CAPER, whose mission is very closely aligned with my focus on mentoring young scientists. CAPER helps to facilitate collaboration among pancreas researchers, and it supports scientifically rigorous multicenter investigations in pancreatic diseases. For example, our own APPRENTICE study was launched and initially supported through CAPER. CAPER also functions to educate and train health care providers in pancreatic diseases to foster a greater public health awareness of acute pancreatitis, while at the same time supporting providers through educational and training programs.

References and Further Reading

Below are references to clinical trials that are currently in progress, for which Dr. Papachristou serves as principal investigator and which are discussed in this article.

A Randomized Controlled Pilot Trial of Indomethacin in Acute Pancreatitis. ClinicalTrials.gov Identifier: NCT02692391.

Post-ERCP Pancreatitis Severity Indication (PEPSI) Study. ClinicalTrials.gov Identifier: NCT03075592.

Acute Pancreatitis Patient Registry To Examine Novel Therapies in Clinical Experiences 2. ClinicalTrials.gov Identifier: NCT03075618.

Acute Pancreatitis Patient Registry To Examine Novel Therapies in Clinical Experiences (APPRENTICE). ClinicalTrials.gov Identifier: NCT03075618.

Post-Acute Pancreatitis Pancreatic Exocrine Insufficiency. ClinicalTrials.gov Identifier: NCT03063398.

PROOF: Pancreatitis-Associated Risk of Organ Failure. ClinicalTrials.gov Identifier: NCT03075605.

Stent vs. Indomethacin for Preventing Post ERCP Pancreatitis. ClinicalTrials.gov Identifier: NCT02476279.

Adenomatous Polyps and Long-term Risk of Colorectal Cancer

New research[1] published in *JAMA* in May 2018 by **Robert E. Schoen, MD, MPH**, and collaborators from the National Cancer Institute using participants in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer trial of colorectal cancer screening, provide new insights on adenoma findings during colonoscopy and their long-term association with incidence of colorectal cancer (CRC).

Robert E. Schoen, MD, MPH

Current guidelines in the United States recommend that people with one or two nonadvanced tubular adenomas return for repeat surveillance colonoscopy in five to 10 years. However, there is no guidance about who should return at five, seven, or 10 years, and there has never been a long-term study evaluating the relationship between non-advanced adenomas and colorectal cancer.

Dr. Schoen explains, "Bringing everyone back at five years is incurring a lot of testing that may not be preventing much cancer, because only a small fraction of polyps will ever turn into cancer. Millions of people are receiving follow-up colonoscopy exams for non-advanced polyps. We need to find out what is necessary. Potentially, this is an area where we could reduce testing and costs."

To determine the risk of developing colorectal cancer after finding polyps, the study looked at data from 15,900 participants who underwent a colonoscopy as a result of their participation in the PLCO trial. At baseline, the researchers found that 2,882 (18.1 percent) of patients had an advanced polyp; 5,068 (31.8 percent) had nonadvanced adenomas; and 7,985 (50.1 percent) had no adenomas. Patients were followed for up to 15 years.

Subjects with advanced adenoma polyps had a 2.7-fold increased long-term risk of colorectal cancer compared to those with no adenomas. In contrast, subjects with nonadvanced adenomas had a colorectal cancer risk that is similar to people in whom no polyps were found.

"This finding concerning nonadvanced adenomas is significant and of interest, because it tells us that we may not have to surveil or follow these patients with repeated colonoscopy as aggressively as we have in the past. This has obvious implications for patients and providers — fewer procedures, less worry, and reduced costs," says Dr. Schoen.

As a follow-up to this study, Dr. Schoen and colleagues have drafted a proposed randomized trial with NRG Oncology to study nonadvanced adenoma patients over five- and 10-year periods, assessing outcomes and the incidence of cancer. "We have approvals but have not yet secured funding for such an initiative. It would be a large-scale endeavor, and NCI is still considering it, but we are hopeful we will have the opportunity to explore the long-term implications of clinical practice updates more thoroughly."

References

[1] Click B, Pinsky PF, Hickey T, Doroudi M, Schoen RE. Association of Colonoscopy Adenoma Findings With Long-Term Colorectal Cancer Incidence. *JAMA*. 2018; 319(19): 2021-2031.

A Blood Test for Early Detection of Cancer

Robert E. Schoen, MD, MPH, and **Randall Brand, MD**, were collaborators in a multicenter investigation led by researchers from Johns Hopkins University that evaluated the efficacy, sensitivity, and specificity of measuring circulating tumor DNA (ctDNA) and proteins in the blood for detection of cancer.

"There is a lot of research that attempts to find blood-based markers for early-stage cancer before a tumor has had the chance to grow into advanced disease. The reasons are clear. The earlier you find cancer, the better chance you have at defeating it," says Dr. Schoen.

The study utilized a test panel called CancerSEEK. The panel is based on the concept that even the tiniest tumors are undergoing apoptosis and spilling DNA into the circulation. DNA mutations in tumors are unique, and using digital genomic techniques can be detected with exquisite sensitivity and specificity. Protein biomarkers were added to detect tumors that do not shed detectable quantities of circulating tumor DNA.

CancerSEEK was tested in a cohort of just over 1,000 patients with eight different nonmetastatic cancers — ovary, breast, lung, stomach, pancreas, esophagus, liver, and colorectum — and compared them to control subjects without cancer.

"This study showed a detection rate of about 70 percent with a range of sensitivity from 69 to 98 percent, with greater than 99 percent specificity. Using machine learning, one could predict the location of the primary tumor to one or two sites nearly 83 percent of the time," explains Dr. Schoen.

Should this technology advance to clinical utility, we would have a blood test that could detect multiple frequently occurring cancers, many for which we currently have no screening tests, including ovarian, stomach, pancreatic, liver, and esophageal cancers.

"Our Division has a number of similar investigations with respect to biomarkers and early detection," reports Dr. Brand. For example, our pancreatic group is looking at pancreatic cyst fluid for early detection of pancreatic cancer. "This work will undoubtedly continue as the creative and dedicated efforts of our faculty in the field make steady progress," says Dr. Schoen.

References and Further Reading

Cohen JD, Li L, Wang Y, et al. Detection and Localization of Surgically Resectable Cancers With a Multi-Analyte Blood Test. *Science*. 2018; 10.1126/science.aar3247. Epub ahead of print.

Save the Date: PancreasFest 2019

The Division of Gastroenterology, Hepatology and Nutrition will again host the annual PancreasFest conference, **July 24–26, 2019**, in Pittsburgh, Pennsylvania. Please mark your calendar for this premier event, which brings together the world's foremost clinicians and researchers committed to learning and collaborating on translational studies of pancreatic diseases.

PancreasFest 2019 is the annual pancreas research and clinical conference designed for gastroenterologists, surgeons, oncologists, researchers, and interested medical professionals. Lectures and discussion groups will mix with investigative research meetings to further the multidisciplinary understanding and treatment of pancreatic diseases.

PancreasFest 2019 will feature discussions on pancreatic cancer, pancreatic diabetes, and acute pancreatitis.

Course Directors

Randall Brand, MD
Walter Park, MD
Aliye Uc, MD
David Whitcomb, MD, PhD
Amer Zureikat, MD

Multicenter Investigator Meetings

- **CAPER** (**C**ollaborative **A**lliance for **P**ancreatic **E**ducation and **R**esearch)
- **INSPPIRE** (**IN**ternational **S**tudy Group of **P**ediatric **P**ancreatitis **I**n Search of a Cu**RE**)
- **APPRENTICE** (**A**cute **P**ancreatitis **P**atient **R**egistry to **E**xamine **N**ovel **T**herapies **I**n **C**linical **E**xperience)
- **PRIMO** (**P**rospective **R**esearch in **I**PMN **M**anagement and **O**utcomes)

For more information, or to register for the conference, please visit **PancreasFest.com**.

Division News

Dr. Szigethy to Lead PCORI Grant

Eva Szigethy, MD, PhD, will be the principle investigator for a $6.3 million PCORI (Patient-Centered Outcomes Research Institute) grant, "Specialty Medical Homes to Improve Outcomes for Patients with Inflammatory Bowel Disease (IBD) and Behavioral Health Conditions." Dr. Szigethy submitted this grant in collaboration with the UPMC Center for High-Value Health Care. Dr. Szigethy is a professor of psychiatry, pediatrics, and medicine, and is a faculty member with the Division of Gastroenterology, Hepatology and Nutrition. She also co-leads the UPMC Total-Care IBD program, a medical home treatment plan for patients with IBD, and is the founder of the Division's Visceral Inflammation and Pain (VIP) Center. Dr. Szigethy also directs UPMC Behavioral Health through UPMC's Chief Medical and Scientific Office.

Dr. Arteel Chairs NIH Study Section

Gavin Arteel, PhD, will chair the Hepatobiliary Pathophysiology (HBPP) Study Section for the National Institutes of Health (NIH) for a two-year term. As part of this appointment, Dr. Arteel will lead the review of NIH applications involving the understanding and treatment of hepatobiliary diseases. Dr. Arteel is a professor of medicine with the Division of Gastroenterology, Hepatology and Nutrition, where he also serves as the associate chief for Basic Science and the pilot and feasibility core director for the Pittsburgh Liver Research Center.

2019 Pittsburgh Gut Club

The Pittsburgh Gut Club is a gastroenterology education and networking series designed to bring novel and relevant subspecialty advancements to the greater Pittsburgh region. Gastroenterologists, physicians, and allied health professionals are encouraged to attend. All Gut Club dinner lectures will be held from 6 p.m. to 8:15 p.m. at the University Club, 123 University Place, Pittsburgh, Pennsylvania.

Sponsored by:
Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine, UPMC Center for Continuing Education in the Health Sciences

Course Director:
Robert E. Schoen, MD, MPH
Professor of Medicine and Epidemiology
Chief, Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine

Thursday — March 28, 2019

Endoscopic Treatments of Obesity

Reem Sharaiha, MD, MSc
Associate Professor of Medicine
Advanced Endoscopy and Metabolic Endoscopy
Weill Cornell Medicine
New York, New York

Thursday — May 2, 2019

The Changing Epidemiology of Liver Cancer

Fasiha Kanwal, MD, MSHS
Professor of Medicine
Chief, Gastroenterology and Hepatology
Baylor College of Medicine
Houston Veterans Affairs
HSR&D Center of Excellence
Michael E. DeBakey VA Medical Center
Houston, Texas

Monday — September 23, 2019

Are Newer Biologics Better Than Our Old Ones?

Maria T. Abreu, MD
Director, Crohn's & Colitis Center
Vice Chair of Research, Department of Medicine
Martin Kalser Chair in Gastroenterology
Professor of Medicine, Microbiology and Immunology
University of Miami, Miami, Florida

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ABOUT THE UPMC DIVISION OF GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

The Division of Gastroenterology, Hepatology and Nutrition is one of the leading centers for gastrointestinal clinical care and research in the country.

The UPMC Digestive Disorders Center is a comprehensive care program for patients that covers the full range of digestive health conditions, including:

— Inflammatory Bowel Diseases
— Cancer Prevention and Treatment
— Functional Bowel Disorders
— Hepatic Disorders and Diseases
— Pancreatic and Biliary Diseases
— Nutrition Support

The Division also includes eight Centers of Excellence that provide specialized care for complex cases and conduct research on numerous fronts to better understand, and develop treatments for, disorders and diseases of the gastrointestinal and related systems.

Centers of Excellence

— Pancreas and Biliary Center
— Center for Liver Diseases
— Center for Intestinal Health and Nutrition Support
— Center for Women's Digestive Health
— IBD Center and UPMC Total Care-IBD
— GI Cancer Prevention and Treatment Center
— Neurogastroenterology and Motility Center
— Visceral Inflammation and Pain Center

To learn more about the UPMC Division of Gastroenterology, Hepatology and Nutrition, please visit **UPMCPhysicianResources.com/GI.**

UPMC PHYSICIAN RESOURCES

UPMC Division of Gastroenterology, Hepatology and Nutrition

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For consults and referrals, please call UPMC's 24-hour physician OnDemand service at **1-866-884-8579.**

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