PANCREAS CANCER RESEARCH GROUP LEADERS

Laura Attardi, PhD
Professor of Radiation Oncology and of Genetics
Co-Director, Stanford Cancer Biology Graduate Program

George Fisher, MD, PhD
Colleen G. Haas Professor of Medicine (Oncology Division)

Seung Kim, MD, PhD
Professor of Developmental Biology and
(by courtesy) of Medicine (Oncology Division)
Director, Stanford Diabetes Research Center

For a complete listing of members visit pcrg.stanford.edu.

DIRECTOR, STANFORD CANCER INSTITUTE

Steven Artandi, MD, PhD
Jerome and Daisy Low Gilbert Professor of
Medicine and Biochemistry

Photomicrograph of pancreatic ductal adenocarcinoma, the most common type of pancreatic cancer.

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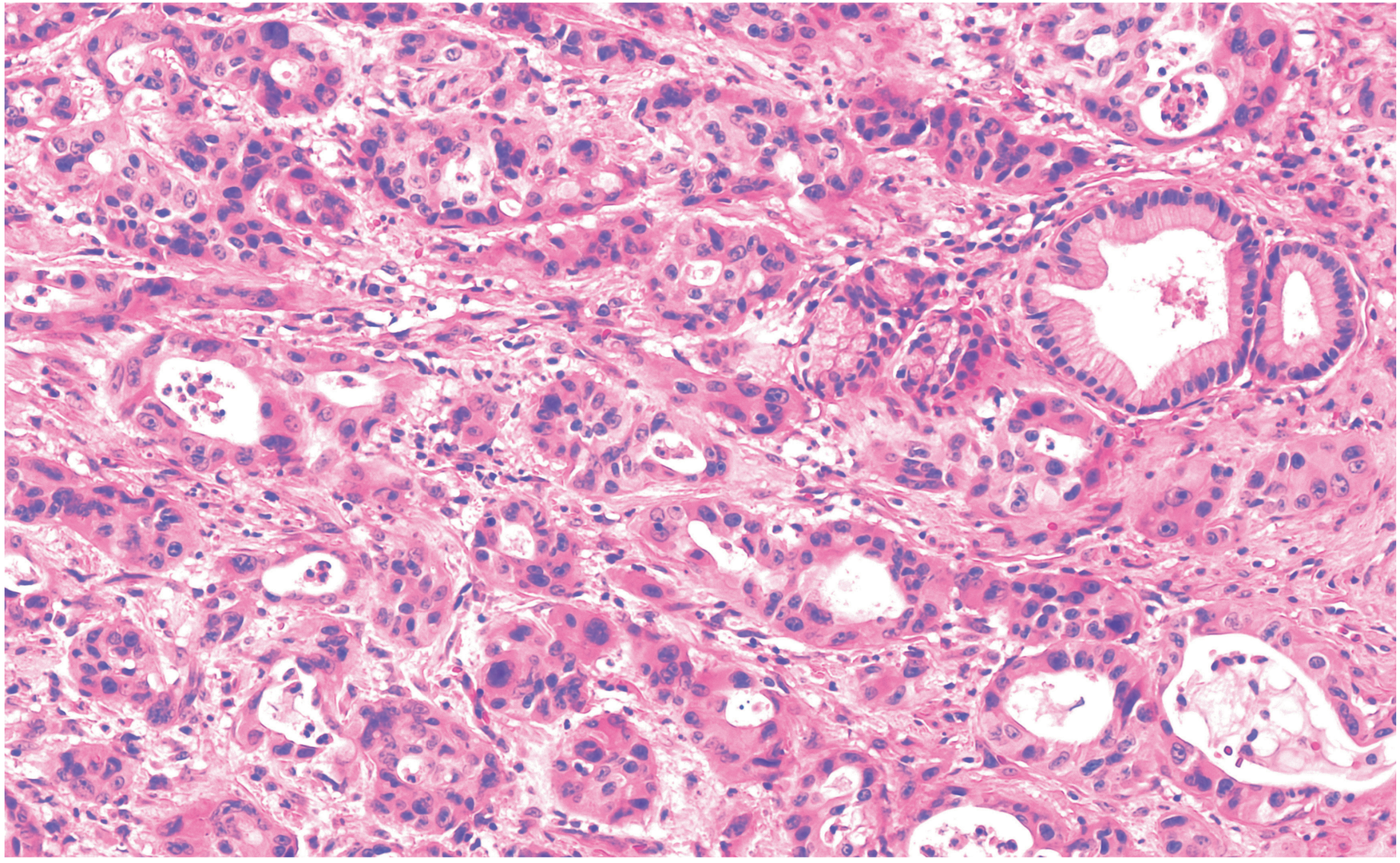

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Pancreatic Cancer Pipeline

A MULTIDISCIPLINARY EFFORT TO TRANSLATE DISCOVERIES INTO PERSONALIZED INTERVENTIONS

Pancreatic cancer is one of medicine's toughest challenges. Growing deep in the abdomen, it is notoriously difficult to detect and treat. According to the American Cancer Society, less than 20% of these cancers are detected before they have spread to other parts of the body. When symptoms do appear, they are often vague and attributed to other causes. In addition to being difficult to detect, pancreatic cancers are challenging to remove surgically and can become resistant to other forms of treatment. These factors contribute to its having the highest mortality rates of all major cancers.

We must discover how and why pancreatic cancers develop and translate that knowledge into effective interventions. It is estimated that nearly 56,000 Americans will receive a pancreatic cancer diagnosis in 2018, and that number is expected to increase as the population ages. However, there are currently no proven early detection methods and no cures other than surgery, which is an option only in a minority of cases. We know that if we catch pancreatic cancer earlier, the odds of successful treatment and management of this disease increase greatly. And we've uncovered important clues about the genetic and molecular mechanisms behind these cancers. There is much to be hopeful about, and we are committed to finding long-term solutions for patients through a dedicated and coordinated effort that spans fundamental research to clinical trials.

Leveraging Stanford University's top-ranked programs in medicine, biology, chemistry, computer science, and engineering, Stanford's Pancreas Cancer Research Group brings together the multidisciplinary expertise it will take to transform outcomes, not just for those diagnosed with pancreatic cancers, but for all who are at risk of developing them. Many of the world's foremost experts in developmental biology, immunology, bioinformatics, stem cell science, imaging, genomics, pathology, and more are steps away from each other on Stanford's single campus, providing unmatched opportunities for synergy and collaboration. This diverse cohort, empowered by our outstanding clinical enterprise and our designation as a Comprehensive Cancer Center by the National Cancer Institute (NCI), is working to develop precise, personalized approaches to diagnosis, treatment, and prevention.

Stanford Medicine's position in the heart of Silicon Valley offers further advantages. Not only does our location give us the connections with top pharmaceutical and biotech companies to quickly advance innovations to clinical trials, it contributes to one of our most valuable assets—our culture. Stanford drives and reflects the creative, entrepreneurial, risk-taking approach that has made Silicon Valley a global engine of change. From our first-year graduate students to our seven Nobel laureates, scientists here are encouraged to take intellectual risks and ignore traditional academic boundaries. The result is an ecosystem where bold endeavors like this can thrive like nowhere else.

Our goal is to predict, prevent, and cure pancreatic cancers. The members of Stanford's Pancreas Cancer Research Group, many of whom have had family and friends affected by this disease, are striving to discover and implement solutions for people who have pancreatic cancer or are at risk of developing it. With your philanthropic partnership, we look forward to transforming this deadly diagnosis into a manageable—and even preventable—condition.

Pancreatic Cancer Pipeline

From determining causes and risk, to untangling biological mechanisms, to developing novel biomarkers and interventions and testing them both in the lab and in the clinic, we're driving progress at all phases of the translational pipeline simultaneously. Here are examples of the innovative and promising pancreatic cancer research taking place at Stanford:

1 Causes and Risk

Determining why some people get pancreatic cancers while others don't.

Hereditary Genetic Mutations – Jim Ford, MD, and Uri Laudabaum, MD, are studying people with a strong family history of pancreatic cancer or genetic mutations known to increase their risk. They plan to collect samples from these individuals over time to help them develop predictive biomarkers.

Chronic Pancreatitis – Aida Habtezion, MD, MSc, and her team have found and are investigating a link between how immune cells respond to injured and dying pancreatic cells and how smoking promotes disease progression in both pancreatitis and pancreatic cancers.

New Onset (Type 3c) Diabetes – This newly recognized type of diabetes arises during mid-life and often precedes pancreatic cancer. A group of Stanford researchers including Seung Kim, MD, PhD, Walter Park, MD, MS, and Aida Habtezion are investigating the mechanisms that link these conditions both independently and as part of a multi-institutional consortium organized by the NCI.

2 Biological Mechanisms

What are the genetic and molecular mechanisms that drive the initiation and progression of pancreatic cancers?

Tumor-supressing gene p53 – This gene regulates cell proliferation, triggering abberant cells to self-destruct. Mutated or missing in more than half of all human tumors, p53 acts as an critical brake on cancer. Laura Attardi, PhD, and her team have found a mutation of p53 that amplifies its tumor-suppressing capabilities. They are now working to untangle the genetic and molecular mechanisms behind it to find new diagnostic and treatment approaches.

Telomere dysfunction – Telomeres are tails of on the ends of chromosomes that protect genes from damage during replication. They also act as timers, growing shorter with each replication until cells can no longer divide. Steve Artandi, MD, PhD, and his team have found that certain pancreatic cells overexpress telomerase, an enzyme that stimulates telomeres to grow longer when they shouldn't. This can lead to cell immortality and cancer. Artandi and his team are working to understand the mechanisms behind telomere dysfunction and define the roles they play in the early development of pancreatic cancer.

3 Biomarkers/Early Detection

Identifying pancreatic cancer at early stages—or before it starts—is critical to changing the outcome for patients.

Liquid biopsies – CAPP-seq, a method that can detect and precisely measure tiny amounts of tumor DNA in a blood sample, has been developed in the labs of Ash Alizadeh, MD, PhD, and Maximilian Deihn, MD. This extremely sensitive and specific technique has been successfully tested in early-stage lung cancer patients and applications for pancreatic cancer are currently under investigation.

Radiomics – The extraction of large amounts of quantitative features from medical images using algorithms holds great promise for early diagnosis and assessment. Bhavik Patel, MD, and his team are using this approach to visualize features of pancreatic cancers that have been invisible to the naked eye until now.

Cyst-based biomarkers – It's thought that up to 15% of pancreatic cancers originate from pancreatic cysts, yet not all of these cysts become cancer. As part of a multi-institutional effort under the auspices of the NCI, Walter Park, MD, MS, and his team are building a biobank of pancreatic cysts and creating a pancreatic cyst fluid database. Their goal is to find biomarkers in this fluid that will help physicians determine whether a patient's cyst is benign or at risk of becoming cancerous.

4 Pre-Clinical Development

Success in taking discoveries from the lab to clinical application requires testing in animal, organoid, and other models that predict efficacy in people as accurately as possible.

Organoids – Calvin Kuo, MD, PhD, and his team are reprogramming skin cells to create pancreatic organoids, tiny 3-D clusters of cells that share the genetic makeup and cellular architecture of a patient's pancreas. They can also create cancerous versions of these miniature organs to test new treatments or customize therapy for individual patients. Likewise, Seung Kim, MD, PhD, and his group have used CRISPR gene-editing technology to generate early-stage pancreatic cancer lesions from normal human pancreatic cells. The ability to produce pancreatic cancer and conduct clinical trials "in a dish" is helping to bridge the gap between lab research and successful application in humans.

Dendritic cells and macrophages – Dendritic cells act as messengers that "teach" T-cells to recognize and attack intruders. Edgar Engleman, MD, and his team have discovered how to arm, activate, and stimulate these cells, resulting in an extremely potent immune response that can eradicate solid tumors. His team has also discovered a way to reprogram macrophages to achieve a similar effect. They have shown both methods to be successful against pancreatic cancer in mouse models.

5 Clinical Trials

Stanford is currently conducting a variety pancreatic cancer clinical trials. For a complete listing, visit clinicaltrials.stanford.edu.

Immunotherapy – George Fisher, MD, PhD, recently collaborated on a clinical trial that resulted in FDA approval of the immunotherapy drug Keytruda (pembrolizumab) to treat pancreatic tumors that have a specific genetic mutation called a mismatch repair defect. Ron Levy, MD and Idit Sagiv-Barfi, PhD, are investigating an approach that involves injecting tiny amounts of immune-stimulating agents directly into solid tumors. Currently being tested in a trial for lymphoma, these "in-situ vaccines" could soon be tested for pancreatic and other cancers.

Intraoperative molecular imaging – George Poultsides, MD, and his team have completed the first in-human trial using molecular imaging in the operating room to ensure that surgeons don't leave any cancerous tissue behind when removing malignant pancreatic tumors.

Advanced chemotherapy approaches – Daniel Chang, MD, and his team are conducting a trial to determine the effectiveness of a newer chemotherapy regimen in combination with stereotactic body radiotherapy (SBRT) in patients with locally advanced disease. George Fisher and his team are currently enrolling patients in a trial that combines chemotherapy with immunotherapy agents.