Pancreatic Cancer
This work is dedicated to our wives Linda, Gwen, Marie, and Hedi and to our patients and their relatives.
For those of us immersed in cancer research, the last decade has been a fruitful one, with many significant achievements and real clinical advances. One needs to look only at the declining mortality rates in many malignancies such as breast and prostate cancer to appreciate that new discoveries have a positive impact on our patients. In some arenas, the advances have been transforming. For example, imatinib mesylate and successor drugs that target an enzyme called BCR/ABL in chronic myelogenous leukemia have turned this previously uniformly fatal disease into an easily manageable condition. Similarly, the work of the legendary Judah Folkman on the importance of the angiogenesis in malignancy spawned a number of agents that can interfere with the angiogenic pathway either by neutralizing ligands or inhibiting receptors. As a result, patients with breast, colon, kidney, lung, and other cancers are living longer and feeling better. Agents that target EGFR and HER2, among others, have also strengthened our therapeutic arsenal.

However, in reflecting on pancreatic cancers, especially pancreatic ductal adenocarcinoma, one is immediately struck by how little progress we have made. Incidence rates continue to rise because of an aging population, and patients still present primarily with locally advanced or metastatic disease because cost-effective early detection tools are not available. Our treatments, while clearly improved, have not yet had a major impact on the overall mortality rate.

Have we done anything to turn this warhead around? Most certainly! It has been almost ten years since we published Pancreatic Cancer: An Agenda for Action, a Report of the Pancreatic Cancer Progress Review Group sponsored by the US National Cancer Institute (NCI). In that document, we identified the gaps in our knowledge, laid out a scientific toolkit, and encouraged the NCI to support more research in this area, and to help train young investigators. Since then, new transgenic animal models that faithfully recapitulate human diseases have been developed, and we have a better understanding of the aberrant signaling networks in malignant pancreatic epithelium moving us closer to finding the critical nodes that comprise the Achilles heel for this tumor. An increased emphasis on understanding stromal biology is beginning to yield clues about potential new therapeutic targets, such as activated hedgehog signaling, and is allowing us to unravel the role of stroma on invasion and progression in this disease, which is characterized by its profound desmoplastic component. In the clinical arena, we now have more insight into inherited patterns of disease and have identified more genetic syndromes. Thanks to work within the NCI Cancer Cohort Consortium, genomic material from patients enrolled in large epidemiologic studies is now being shared and probed for further clues about genetic susceptibility. Screening, although not yet practical on a population-wide basis, is proving to be extremely useful for patients at high risk because of their family histories. Therapy is improving. Surgery is safe and the benefit of adjuvant therapy is now clearly apparent, supported by the highest level of medical evidence. Research activity aimed at identifying new drugs and new drug combinations has been robust, but unfortunately has yielded very few approved drugs. As a result, the NCI convened a state-of-the-science
meeting last year which resulted in consensus on standardization in trial design and harmonization of eligibility criteria in an effort to minimize unintended bias in clinical trial conduct. Most assuredly, we have learned that large global adjuvant trials are feasible and that many patients are also willing to participate in large randomized trials in locally advanced and metastatic disease. Thus, the infrastructure is in place to do much more.

So how do we get to the next level? As we probe further into the biology of this disease, it is becoming increasingly clear that there is more diversity than we appreciated. Thus, there will be more need for an individualized management in this cancer as is now clearly appreciated in many other malignancies. Understanding the host genotype, gene–gene and gene–environment interactions, and the biological consequences of the many mutations that occur in pancreatic ductal adenocarcinoma will allow us to risk-adapt our management from surveillance and screening to the identification and selection of effective therapy. Developing large biorepositories of pancreatic cancer tissue and related specimens with exquisite clinical and molecular annotation will be one of the highest priorities. And investigators will need access to an appropriate context in order to advance knowledge.

This textbook, *Pancreatic Cancer*, is a carefully composed compendium of the state-of-the-science in all aspects of research in both pancreatic ductal adenocarcinoma and pancreatic neuroendocrine tumors. The experts who were selected to provide contributions are the best in their fields. The content is contemporary and comprehensive. This text will be a necessary reference for anyone already doing research in pancreatic cancer.

Although research funding for pancreatic cancer research has improved, the level of funding lags far behind other cancers, including much less lethal ones. In addition, the army of capable investigators is still too small. This text will also serve as a vehicle for change since its content will whet the appetite of highly competent investigators entrenched in other fields and encourage them to change direction. The book will also serve as a tremendous guide for young investigators to help them understand the landscape and plan their research strategy.

I am truly grateful to my colleagues around the world who have worked so hard and so tirelessly to create this reference. Disseminating what we know now will accelerate our progress, and there is no doubt in my mind that the scientific breakthroughs that will transform the lives of our patients are just round the corner.

Margaret A. Tempero, M.D.
University of California, San Francisco
Trying to advance the agenda for pancreatic cancer has always been a huge challenge but we are living in exciting times for cancer research as a whole. Although the numerous hurdles hindering the understanding, diagnosis and treatment of pancreatic cancer seem as daunting as ever, one by one these are now being dismantled. This has only been possible by bringing together large multi-disciplinary teams of world class scientists and clinicians in comprehensive cancer centres and specific centres of pancreas cancer excellence.

DNA sequencing has shown that pancreatic cancer has just over 1,000 somatic mutations involving 12 critical pathways: apoptosis, DNA damage control, regulation of the G1/S transition, Hedgehog signalling, homophilic cell adhesion, integrin signalling, c-Jun N-terminal kinase signalling, KRAS signalling, other small GTPase-dependent signalling, regulation of invasion, TGFβ signalling and Wnt/Notch signalling. What is interesting is that there are a similar number of genetic mutations in breast cancer involving the identical number of pathways. Or at least that is how the vast amount of accumulated molecular data is perceived. How can two human cancers appear so similar at the genetic level yet behave so differently in the clinic? A few percent of patients with pancreatic cancer make it to five years and most are dead well within the year. What shocks so much in pancreatic cancer is the unerring predictability of the time of death.

Yet there is now some real hope emerging. Even a few years ago it seemed unthinkable that we could detect early pre-invasive pancreatic cancer. Yet now, pancreas units all over the world are resecting an increasing proportion of intraductal papillary mucinous neoplasms, often with the welcome ‘no invasion seen’ in the histopathology report. Pancreas cancer resection was once infrequently performed partly because of the technical difficulty and partly because there was a fearsome post-operative mortality rate (30–40%). Today, pancreas resection can be performed in 20% or so of pancreas cancer patients with localized disease with a very low mortality rate and producing a five year survival rate that readily exceeds 20% with adjuvant therapy. There is some evidence that we can also improve survival even in advanced pancreatic cancer. Moreover there is increasing optimism for successful novel therapies with over 200 therapeutic clinical trials underway, many using agents based on the concepts of the new biology.

Emulating the successes made in breast cancer over the past 30 years may still seem a long way off except it is important to recall that mortality then for breast cancer exceeded 50% at five years compared to an 80% ten year survival today. The clues as to why there is the gap between pancreas cancer and other tumour types are contained within these pages.

The contributors have been put together as much for their style of thinking as well as representing the best there is in their own areas of expertise. The outcome of this collective endeavour is that it has met and exceeded expectations and - much more importantly - with added value throughout.

This kind of labour becomes dated as soon as the keyboards are hit but by its very nature and quality is invaluable for all those involved in any aspect of pancreatic cancer.

John P. Neoptolemos
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The Editors would like to dedicate their work to all the pancreatic cancer patients and their families.

The Editors wish to acknowledge Sarah Cottle in the office of Professor Neoptolemos (Liverpool, UK). Ms. Cottle provided incalculable time and effort overseeing the accuracy and timeliness of this publication.

We also acknowledge the significant support offered by our individual editorial assistants, who provided the day-to-day contacts, oversights, and management of manuscripts that were submitted in each international office. We specifically wish to thank the assistance of Professor Jens Werner and Irmgard Alffermann in the office of Professor Büchler (Heidelberg, Germany), Anne LeBourgeois in the office of Professor James Abbruzzese (MD Anderson Cancer Center, USA), and to Dr. Martin Fernandez-Zapico and Dr. Gwen Lomberk in the office of Professor Raul Urrutia (Mayo Clinic, USA).

All of these people provided an invaluable service that is appreciated highly by the Editors and allowed Springer to publish in a timely and organized fashion.

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He studied Natural Sciences and then Philosophy at Cambridge before completing his clinical undergraduate training at Guys Hospital. He completed his academic and clinical training in Leicester under Professor Sir Peter Bell and was awarded a Doctorate in Medicine for his research thesis. In 1981, he became a Fellow of the Royal College of Surgeons in England. He also trained in San Diego, Paris, and Ulm before being appointed senior lecturer at the University of Birmingham in 1987. He became a Full Professor of Surgery in 1994 and then moved to the University of Liverpool and Royal Liverpool University Hospital in 1996 as the Head of the Department of Surgery, followed by the Head of the Division of Surgery and Oncology in 2004.

In 2005, Professor Neoptolemos was appointed as the Head of the School of Cancer Studies and in 2009 became the Chairman of the Cancer Research UK Cancer Centre. He is also Director of the Cancer Research UK Liverpool Cancer Trials Unit, Co-Director of the Liverpool Experimental Cancer Medicine Centre, and Scientific Director of the National Institute for Health Research Liverpool Pancreas Biomedical Research Unit.

He has been the President of the Pancreatic Society of Great Britain and Ireland; Secretary and then President of the European Pancreatic Club; and President of the International Association of Pancreatology.

Professor Neoptolemos is the Chairman of the Pancreatic Cancer Sub-Group, National Cancer Research Institute (UK) Committee on Upper GI Cancer; Chairman of the European Study Group for Pancreatic Cancer (ESPAC); and member of the Cancer Research UK Science Strategy Advisory Group. In 2007, he was elected as a Fellow of the Academy of Medical Sciences (UK).
Raul Urrutia, M.D., is the Professor and Chair of the GI Unit and Director of the Epigenetics and Chromatin Dynamics Laboratory at the Mayo Clinic. Over the years at Mayo, he has served as the Director of the Ph.D. Program in Tumor Biology, Associate Director for Genomics at the Mayo Clinic General Clinical Research Center (GCRC), and Director of the GI Cancer Research Program at the Mayo Cancer Center.

Born in Mendoza, Argentina, Dr. Urrutia graduated Magna Cum Laude in 1987 from the University of Cordoba Medical School in Cordoba, Argentina, as a surgeon. During medical school, he did research at the Cell Biology Institute of the University where he studied pancreatic cancer. Immediately following graduation, he traveled to the United States where he was a visiting fellow at the Laboratory of Molecular Otology at the NIDCD-National Institutes of Health in Bethesda, MD. He worked at the National Institutes of Health for three years in various titles including guest researcher, visiting fellow, and visiting associate. In 1993, Dr. Urrutia joined the faculty at the Mayo Clinic for Basic Research in Digestive Diseases. He is married and has two children, twins.

Dr. Urrutia has published over 300 publications among peer-reviewed articles, chapters, and reviews. He has prided himself on a commitment to scientific mentorship, with over 30 researchers ranging from graduate students to postdoctoral students, as well as junior faculty members. Currently, he is the Director of the Mayo Clinic GI Unit, which accommodates the research of 10 independent faculty members, all of whom have space adjacent to the Epigenetics and Chromatin Dynamics Laboratory on the tenth floor of the Guggenheim research building. In addition, he is the PI for an Institutional Research Grant for the Mayo Clinic Cancer Center awarded by the American Cancer Society, which administers funds for career development of young investigators. Dr. Urrutia has participated in multiple teaching activities since 1993 at the Mayo Graduate School. His current teaching capacity includes the course on Transcription, Chromatin, and Epigenetics.

He is currently the Editor-in-Chief of three journals, including Pancreatology, Case Reports in Gastroenterology, and Journal of Gastrointestinal Cancer, and member of several other editorial boards including past service for the Journal of Biological Chemistry and Pancreas.


Dr. Urrutia has served on various national and international society governments. He is the past chair for Pancreatic Diseases Section of the American Gastroenterological Association, the past president of the American Pancreatic Association (2007), and member of the International Association of Pancreatologists board.

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He is a Deputy Editor of *Clinical Cancer Research*, and a member of several other editorial boards including the past service for the *Journal of Clinical Oncology*. His scholarly interests center on clinical and translational research for pancreatic cancer.
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He is member of the Editorial Boards of many journals in general and gastrointestinal surgery, translational and molecular research in pancreatology, and other gastrointestinal diseases.

He has been the President of the European Pancreatic Club (EPC) in 2002 and President of the International Hepato–Pancreato–Biliary Association (IHPBA) in 2006–2008 and is the elected President of the German Surgical Association.
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