EDITORIAL



# Advancing on pancreatic cancer

Pancreatic cancer is a notoriously lethal condition characterised by aggressive malignancy and dismal outcomes. However, translational advances are showing us that hope is on the horizon.

> “There is encouraging progress towards improving the lives of patients and families affected by PDAC”

The global burden of pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer, has doubled in the last quarter century and is projected to be the second leading cause of cancer deaths in the USA in the next 20–30 years[1]. Outcomes in PDAC make for grim reading: 5-year survival has only just reached double digits in some regions[2]; current chemotherapeutics lead to survival in the range of months; and ~50% of new diagnoses are the metastatic form of PDAC, with an average survival of less than a year[1]. Such bleak statistics are driven by a disease that often has non-specific symptoms until it is too late; most diagnoses are made once the opportunity for surgical intervention has passed.

Despite this situation, there are reasons to be hopeful. Research investment in pancreatic cancer in the USA has increased more than any other cancer site, driving cutting-edge translational research that aims to enhance strategies towards PDAC detection and treatment[3]. In this Focus Issue of *Nature Reviews Gastroenterology & Hepatology*, we provide an overview of some of these advances in a series of Reviews and commentaries, which are also available online in a Collection. Each of these articles features a different aspect of PDAC that highlights the inherent challenges of the disease, but each also reveals how advancements are paving the way for improved patient care.

A key feature of the PDAC microenvironment is its dense, hypoxic and immunosuppressive stroma that limits infiltration by immune cells and therapeutics. Adding to our understanding of the mechanisms underlying the stroma, Encarnación-Rosado and Kimmelman explain how it mediates a reprogramming of PDAC metabolism to facilitate tumour survival. By understanding how metabolism is rewired in PDAC and by identifying the metabolic dependencies, new strategies for targeted therapeutic interventions could be revealed.

PDAC is one of the most aggressive and chemoresistant forms of cancer, largely due to the diversity of genetic mutations that give rise to a highly heterogenic disease. Hayashi, Hong and Iacobuzio-Donahue examine the PDAC genome and discuss how our understanding has advanced beyond the common driver genes and major hereditary components. By examining genomic PDAC studies in the context of its cellular origins and evolutionary growth dynamics, they show how distinct genomic events are associated with phenotypes that indicate therapeutic vulnerabilities.

The low prevalence of PDAC in the general population presents further challenges towards a feasible, cost-effective solution to population screening. In their Review, Klein summarises the epidemiology of pancreatic cancer, including modifiable risk factors as well as those that could help identify high-risk individuals and focus screening procedures. Other efforts aiming to improve detection of the disease early in its natural history are detailed by Singhi and Wood. They discuss the precursor lesions of pancreatic cancer and approaches and challenges to their early detection using DNA-based molecular techniques, which demonstrate the promise of technology for overcoming the fundamental problem of late presentation in PDAC.

Another technological advancement, single-cell RNA sequencing, forms the basis of a Comment by Han, DePinho and Maitra. The authors explore how in-depth cellular profiling in PDAC has furthered our understanding of the molecular underpinnings of the disease but also the potential mechanisms responsible for therapeutic resistance. A final reason to be hopeful comes in the form of immunotherapy. Although this field seems poised to revolutionise cancer treatment, PDAC is known to be resistant to many current approaches. However, as discussed in a Comment by Rojas and Balachandran, promising strategies to unlock the potential of immunotherapy in PDAC are underway.

There is encouraging progress towards improving the lives of patients and families affected by PDAC. However, more investment in both data repositories such as biobanks and high-visibility research is urgently needed, particularly in Europe where pancreatic cancer is relatively neglected[4] despite the increasing burden. Improved awareness of the early signs and risk factors of PDAC will be crucial to increase early diagnosis, as will coordinated cooperation between academia, patient organisations, scientific societies and advocacy groups. Leveraging these stakeholders will be critical in maintaining the momentum needed to translate these hopeful advances to the clinic, where their benefits can be seen.

1. Mizrahi, J. D. et al. Pancreatic cancer. *Lancet* **395**, 2008–2020 (2020).
2. Siegel, A. et al. Cancer Statistics, 2021. *CA: a cancer journal for clinicians* **71**, 7–33 (2021).
3. Abudu, R. Trends in International Cancer Research Investment 2006-2018. *JCO Glob. Oncol.* **7**, 602–610 (2021).
4. Prades, J. et al. Bratislava Statement: consensus recommendations for improving pancreatic cancer care. *ESMO Open* **5**, e001051 (2020).