The Pancare Foundation Research Framework for Pancreatic Ductal Adenocarcinoma (PDAC)

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Reviewed

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Acknowledgements

In 2014 the American National Cancer Institute (NCI) and the National Institute for Health (NIH) developed a scientific framework for PDAC aimed at improving the outlook for Americans with pancreatic ductal adenocarcinoma (PDAC) and for those at high risk of developing PDAC.

This Pancare document has reproduced much of the NCI/NIH scientific framework, with some Australian additions and has not repeated the literature research undertaken to produce the American scientific framework.

Pancare acknowledges the expertise of the NCI and NIH in developing the scientific framework for PDAC, without which the Pancare Research Framework for PDAC would not have been possible.

Pancare would also like to acknowledge the work of the Avner Nahmani Pancreatic Cancer Foundation, the Australasian Pancreatic Club and the Australasian Gastrointestinal Trials Group for their support of improving outcomes for people with PDAC, some of which is captured in this document.

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1 Aim

The aim of this document is to develop a research framework for the Pancare Foundation that will be used to inform decisions regarding the funding of national pancreatic research initiatives to achieve significant increases in survival rates for pancreatic cancer.

2 Background

Pancreatic cancers are a group of heterogeneous diseases of both the endocrine and exocrine pancreas. Pancreatic ductal adenocarcinoma (PDAC), an exocrine tumor, represents over 90% of all pancreatic malignancies[1].

The Australian Institute of Health and Welfare estimated the number of new cases of pancreatic cancer diagnosed in 2016 in Australia to be 3123 and the chance of surviving five years 7%[2].

Approximately 10% of PDACs occur in families with a history of PDAC[3]; some occur in association with other cancers or diseases, but most do not occur in association with a defined syndrome[4]. The overwhelming majority of PDAC cases are sporadic; that is, occurring without a history of the disease in first degree relatives.

Significant scientific progress has been made in the last decade in understanding the biology and natural history of pancreatic ductal adenocarcinoma (PDAC); major clinical advances, compared to some other common cancer types, however, have not occurred. Although PDAC shares some of the characteristics of other solid malignancies, such as mutations affecting common signaling pathways, tumor heterogeneity, development of invasive malignancy from precursor lesions, inherited forms of the disease, and common environmental risk factors, there are unique obstacles that have made progress against PDAC difficult. These include:

- diagnosis at a late stage in the disease because of a lack of specific symptoms or biomarkers to facilitate early diagnosis, and the anatomical location of the pancreas;
- metastatic spread when the primary tumor is too small to detect by current methods;
- the small percentage of patients for whom surgery is a feasible option, due to locally advanced or metastatic disease;
- dynamic interaction of the tumor with stromal cells creating dense fibrous tissue around the tumor that contributes to therapeutic resistance.

Although much is known about the evolution of PDAC from its earliest non-malignant precursor lesions, PDAC cases are most often diagnosed at late stages: about 30% of patients have locally advanced disease and over 50% have metastases at distant sites when the disease is first diagnosed. Early detection has been problematic because of the absence of specific symptoms, the insufficiency of serological biomarkers with appropriate sensitivity and specificity, the lack of a clinically practical diagnostic

examination for the disease, and the retroperitoneal position of the pancreas. Unlike many other malignant diseases, the metastatic spread of PDAC is thought to begin when the primary tumor is approximately 10 mm in size, when results of routine non-invasive imaging are often equivocal or negative[5].

Currently pancreatic surgery, which varies according to the location of the malignancy (pancreaticoduodenectomy, subtotal, total or distal pancreatectomy) provides the only possible curative therapy for PDAC, but less than 20% of patients are suitable candidates for this difficult procedure because the disease has already spread or become locally advanced. Overall, surgery produces long-term, disease-free survival in only 3-4% of all individuals presenting with this disease—generally in patients with "early" PDAC (i.e., tumors < 20 mm) and without tumor involvement in the surgical resection margins.

Resistance to therapy is a characteristic feature of PDAC, and the extent of resistance is greater than in many other human tumors. This could be due to inefficient drug delivery, intrinsic and acquired resistance of the tumor, tumor hypoxia, or the insensitivity of cancer stem-like cells to currently used agents. It is thought that the dense desmoplasia produced by the dynamic interaction of stromal cells with the tumor, and which constitutes 90% of the tumor volume, creates a barrier to systemic drug delivery and penetration.

Evidence comparing stage of disease with outcome following surgery suggests that death rates for PDAC would be reduced if the disease could be diagnosed at an earlier stage[5,6]. Since genomic sequencing data from primary and metastatic PDACs indicate that it takes approximately 17 years for PDAC to progress from the tumor-initiating cell to the development of metastatic disease[7], it would appear that there is ample time to diagnose and intervene, if diagnostic barriers to earlier detection could be overcome.

Avner Nahmani Pancreatic Cancer Foundation Workshop.

The Avner Nahmani Pancreatic Cancer Foundation brought together a group of leading researchers, clinicians, data experts and research funders from inside and outside the pancreatic cancer field in December 2013 to see if coordinated, strategic action was possible to maximise Australia's investment in improving outcomes for people with pancreatic cancer and perhaps generate new ideas.

Workshop participants identified the following challenges in pancreatic cancer:

- Rapid disease progression making tissue collection and clinical trial participation for patients difficult
- Huge heterogeneity and complexity of the disease – one size fits all approach does not work
- Interrupted, intermittent funding making it hard to sustain success
- Few avenues exist for early detection
- Large disparity in outcomes for patients with unacceptable variations in care depending on where a patient lives, their socioeconomic status and where they first present for care go for treatment.
- Restricted access to clinical, laboratory and outcome data

- The numbers of patients being treated for pancreatic cancer relative to some other cancers are low and therefore the aim should be to 'capture' every patient and provide treatment along the lines of integrated high quality clinical and research based pathways
- In general, the best outcomes are from hospitals and surgeons with volume and experience

Participants also identified the following opportunities

- Development of therapies that target the surrounding tissue of the tumour – the stroma – which appears to be a key player in making pancreas cancer spread early and so hard to treat
- Minimising unacceptable variation in clinical care so that every patient has access to the outcomes achieved by the best units
- Capitalising on Australia's lead in pancreatic cancer genotyping
- Implementing familial screening of patients to identify biomarkers in high risk groups

The Australasian Gastro Intestinal Trials Group (AGITG).

The AGITG recently published a consensus statement to define when a patient is clearly operable, borderline and locally advanced inoperable.[8] They are also developing recommendations regarding when to consider neo-adjuvant treatment.

3 Summary of the Literature and Recent Advances Biology and Genetics

PDACs arise from a ductal cell lineage or from acinar cells that undergo acinar-to-ductal metaplasia[9]. Pancreatic intraepithelial neoplasms (PanINs) are the most common precursors to PDAC, and are often found associated with areas of focal pancreatic inflammation. Certain cystic lesions of the pancreas are also premalignant: pancreatic intraductal papillary mucinous neoplasms (IPMNs) are found equally in men or women in their 60s and communicate directly with the main pancreatic duct; mucinous cystic neoplasms (MCNs), which are overwhelmingly found in women in their late 40s[10], are often solitary cystic lesions in the body or tail of the pancreas. Virtually all PanINs, even the earliest type, PanIN-1, harbor KRAS mutations. Mutant KRAS alleles show increased expression as PanIN-1 evolves to intermediate PanIN-2, and then to the carcinoma *in situ* lesion (PanIN-3)[11,12].

The few precursor lesions that do not contain mutant KRAS often have mutations in other genes in the KRAS signaling pathway, such as those in BRAF[13]. Loss of CDKN2A, a tumor suppressor, is also found in some early PanINs. It is now thought that a KRAS mutation is necessary, but not sufficient, to drive PanINs to PDAC[12,14]. Recent studies, however, have shown that in mutant KRAS-driven PDACs, KRAS is required at all states

of pancreatic carcinogenesis and for subsequent tumor maintenance[15,16].

KRAS is mutated in approximately 95% of all PDACs— the highest percentage of all solid malignancies[1]. Besides mutated KRAS and the loss of CDKN2A, genetic alterations have been found in tumor suppressor genes SMAD4 (also termed DPC4) and TP53. A more detailed genomic analysis of a large number of PDACs has uncovered an average of 63 genetic alterations, mostly point mutations, which affect up to 12 different signaling pathways or processes.

Based on research arising from the Australian Pancreatic Genome initiative (APGI), genomic analysis of several hundred pancreatic cancer specimens has identified 32 recurrently mutated genes that can be aggregated into 10 Pathways : KRAS, TGF-β, WNT, NOTCH, ROBO/SLIT signalling, G1/S transition, SWI-SNF, chromatin modification, DNA repair and RNA processing.[17] Expression analysis defined 4 subtypes: (1) squamous; (2) pancreatic progenitor; (3) immunogenic; and (4) aberrantly differentiated endocrine exocrine (ADEX) that correlate with histopathological characteristics. These data suggested that there identification of particular subtypes may provide opportunities for therapeutic development.

Various responses correlating with specific tumour characteristics have been documented in several studies, [18] including gemcitabine responsive (human equilibrative nucleoside transporter-1, hENT1 expressing), oxaliplatin responsive (BRACA2/PlaB2), nab-paclitaxel responsive (SPARC expression), anti-EFGR responsive (KRAS wild type), irinotecan responsive (Topoisomerase 1 expressing), and fluoropyrimidine responsive (unknown biomarker).

3.1 Risk Assessment and Screening

Risk assessment studies have been performed associating germline susceptibility genes with the development of PDAC. Many of these case-control studies were performed using registries of families with a strong history of pancreatic cancer. Individuals with three first degree relatives affected by pancreatic cancer for example have a 32-fold increase in risk of developing pancreatic cancer. Mutations in the following germline genes appear to have a role in susceptibility to PDAC although most do not have a high penetrance: BRCA2, STK11, PALB2, ATM, and CDKN2A[19-21]. In addition, mutations in PRSS1 and SPINK are associated with susceptibility for hereditary pancreatitis, which greatly increases the risk of PDAC. Other hereditary diseases and syndromes have also been shown to increase risk of PDAC; individuals with these syndromes often harbor mutations in the genes that confer risk for PDAC. Studies of the gene alterations in high risk individuals could also be important in informing studies of sporadic PDAC and lead to a better understanding of the etiology of the disease.

Among the known non-genetic risk factors are: tobacco use; age; obesity; chronic pancreatitis; and diabetes, both long-term type 2 diabetes and especially new-onset diabetes, which may be an early consequence of PDAC itself.

Early detection of small resectable lesions, particularly pre-neoplastic lesions such as PanINs (2 and 3) and IPMNs or MCNs is the best hope for increasing overall survival, since locally advanced and metastatic PDACs are relatively insensitive to chemotherapy or radiation therapy, and surgical resection is often followed by relapses. So far, no serum or tumor-based biomarkers or biomarker panels have been discovered that are both sensitive and specific enough for accurate early detection. CA19.9 is the most commonly used tumor biomarker for monitoring therapeutic progress in PDAC, but the lack of specificity of the assay is a concern, and CA19.9 therefore cannot be used for early detection. Progress in this area will have to come from new diagnostic discoveries—perhaps employing circulating tumor cells, tumor-derived DNA, autoantibodies, miRNA profiles, cytokines and chemokines, and from specific genetic, epigenetic, or proteomic signatures. Advances in non-invasive imaging technology that can detect tumors or pre-cancerous pancreatic lesions as small as 0.5 mm will also be needed. Invasive imaging such as endoscopic ultrasound can detect most pancreatic cysts[22,23] and targeted imaging agents have been shown to detect PanIN-3 lesions[24]. These methods of detection are expensive and cannot be used for routine screening, but could be employed in high risk individuals.

One approach is to focus screening efforts on the groups of asymptomatic individuals who have been shown to have a higher risk of PDAC than the general population: those with hereditary risk factors, environmental risk factors, or other diseases that increase the odds of developing PDAC. The risk relationship between long-standing type 2 diabetes and PDAC, based on epidemiological evidence, is well-known as is the increased risk of PDAC in patients with newly-diagnosed diabetes[25]. Evidence suggests that screening for PDAC in patients with specific subtypes of diabetes, such as those newly diagnosed, and particularly in association with other risk factors (such as genetic predisposition or tobacco use), should be considered in early detection protocols [24,26,27].

There is consensus that the discovery of biomarkers that can identify early lesions (PanINs 2 and 3, and high risk mucinous pancreatic cysts) and perhaps serve as therapeutic targets is a critical goal in advancing progress in PDAC since diagnosis of pre-invasive or even small cancers can improve respectability, prognosis after resection, and survival. To date, there are no biomarkers or panels of biomarkers that are sensitive and specific enough for diagnosis of PDAC in its early stages. Cysts can be detected by current imaging techniques, but many cysts are benign and wholesale surgery is not recommended because of morbidity and cost considerations.

3.2 Therapy and Resistance

For over a decade, gemcitabine alone was the standard of care for advanced PDAC[28]. In 2011, FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and 5-FU) was shown to provide a modest increase in overall survival, although the toxicity was greater[29]. More

recently the combination of gemcitabine and nab-paclitaxel has also shown modest increases in overall survival, with somewhat less toxicity than FOLRINOX, but greater than gemcitabine alone. The addition of molecularly targeted therapies has been evaluated; to date, only erlotinib, targeting the EGF receptor, has demonstrated a modest, albeit statistically significant, response rate in combination with gemcitabine[30,31]. The recent elucidation of alterations in the various signaling pathways in PDAC and in pancreatic cancer stem-like cells may lead to the testing of new agents and combinations in the future, and to defining the patient populations that might benefit from targeted systemic therapy.

4 Research Initiatives Proposed

Seven general areas of PDAC research are recommended based on the 2014 National Cancer Institute Framework and the work done in 2013 by the Avner Foundation for a national strategy for pancreatic cancer outcomes, listed below (not in any order of importance);

1. ***Understanding the biological relationship between PDAC and diabetes mellitus***
2. ***Improving early detection of PDAC through identification of biomarkers and investigating and evaluating screening protocols for early detection of PDAC and its precursors***
3. ***Studying new therapeutic strategies in immunotherapy***
4. ***RAS/KRAS dependent signaling pathways***
5. ***Targeting the surrounding tissue of the tumour – the stroma***
6. ***Development of personalized medicine strategies***
7. ***Developing strategies to reduce variations in pancreatic cancer care***

4.1 Relationships between PDAC and diabetes mellitus (DM)

Clinical and genetic epidemiological studies have identified an association between DM of recent diagnosis and a subsequent diagnosis of pancreatic cancer[24]. About half of all PDAC patients have DM at the time of diagnosis, and half of those have experienced the onset of DM within the prior 3 years. Yet, only 1% of recent-onset DM patients will develop PDAC within 3 years[24].

Progress in the early detection of PDAC will be aided by a more detailed understanding of the clinical and biological characteristics of the population of patients who subsequently develop or have undiagnosed PDAC in the setting of newly diagnosed diabetes. It will be essential to define specific risk factors to make screening efforts cost-effective by focusing on these individuals. It also will be important to understand whether other risk factors for the development of PDAC (such as exposure to tobacco smoke) interact with diabetes to increase the risk of PDAC. This is especially true for individuals

with type 3c diabetes (diabetes secondary to pancreatic diseases) with coexisting chronic pancreatitis, in whom the risk of PDAC is increased 30-fold. Research efforts should determine whether risk factors of sufficient specificity can be defined to justify a coordinated early detection program in certain patient groups.

4.2 Improving early detection of PDAC through identification of biomarkers and investigating and evaluating screening protocols for early detection of PDAC and its precursors

The goal of early detection strategies is to identify patients with the earliest-stage pancreatic cancers, who have the best chance of cure, and those individuals who are at highest risk; i.e., individuals who have precursor lesions that are likely to evolve into PDAC. Two groups of patients with precursor lesions, defined by pathologic or radiologic criteria, are those with type 3 highly dysplastic PanINs or cystic neoplasms of the pancreas-either IPMN or MCN. These patient populations overlap with the population of individuals who have germline mutations in specific genes that predispose to PDAC (such as *BRCA2, LKB1,* etc.) as well as families with multiple first-degree relatives who have developed PDAC. Genetically defined patient populations also frequently harbor high-grade PanINs or small mucinous cysts that serve as pathologic precursors to invasive pancreatic cancer[32]. However, estimating the true extent of these lesions in the entire population has proven difficult; thus, the major diagnostic challenge is to develop more accurate and sensitive methods of imaging and more accurate and sensitive methods to identify the molecular alterations that characterize these lesions to improve early detection.

For further progress in the development of early detection biomarkers, it will be essential to optimise screening protocols, to improve enrollment of high risk populations in screening studies, and to demonstrate that screening can improve the patient outcomes.

4.3 Immunotherapy approaches

The intrinsic cellular heterogeneity and genetic instability[33] of PDACs as well as the lack of understanding of the complex interrelationships among tumor cells, stromal cells, and immune cells characteristic of this malignancy have contributed in the past to the slow progress in developing effective systemic therapies for this disease[34]. In addition, the dense desmoplastic reaction itself, with its extensive deposition of extracellular matrix, is thought to act as a physical barrier and a great challenge to therapeutic success. It has recently been shown in a PDAC GEMM that mutational activation of KRAS triggers the production, by PDAC precursor lesions, of the growth factor GM-CSF, which promotes the expansion of Gr-1+ CD11B+ myeloid cells as part of the inflammatory reaction[35,36]. These immature myeloid cells (also known as myeloid suppressor cells) suppress CD8+ T cell antitumor immunity. Breakthroughs in targeting stromal cells, in reversing immunosuppression, and in the use of immune checkpoint blockade agents, vaccines, and T cell-based immunotherapies, alone or in combination, have created opportunities for progress against PDAC. Progress in pancreatic cancer immunotherapy will be aided by include the discovery and validation of new immunotherapy targets, the rational

combination of immune modifiers in preclinical and clinical studies, and the production of immune-modulatory molecules to facilitate the initiation of early phase PDAC trials in the area of immunotherapy.

4.4 RAS-specific therapeutics

Advanced PDAC is resistant to treatment with cytotoxic agents as well as the molecularly targeted drugs that have been tested to date. One of the reasons for this is the high frequency of an activating mutation in KRAS—the oncogenic driver of PDAC—which has been notoriously difficult to target with drugs. After more than 30 years of research into RAS and its role in pancreatic (and other) cancers, it has become evident that targeting this oncogene requires new approaches. These should include efforts to develop new treatments employing recently discovered techniques in chemical biology supporting the discovery of molecules that interfere with RAS-oncogene-dependent signaling pathways. Since *KRAS* mutations are common in PDAC and many other malignancies, endeavors to target KRAS provide an opportunity to make inroads into establishing new therapies that might be widely applicable to the treatment of PDAC as well as other cancers.[17,37-39]

4.5 Targeting the surrounding tissue of the tumour – the stroma

A pronounced desmoplastic and hypovascular microenvironment is a histological hallmark feature in pancreatic cancer. Tumour-stromal interactions also play an important role in the growth and spread of PDAC. The stromal component of PDAC forms the major part of the tumour tissue and is composed of a dynamic milieu with several different cell types including pancreatic stellate cells, endothelial cells, nerve cells, immune cells, and the extracellular matrix. The stroma may contribute to the treatment resistance noted in PDAC by acting as a physical and pathophysiological barrier to cancer drug delivery. The interactions that occur within the stroma are, however, much more complex than simply a barrier function. Stromal depletion or modification therapies should be investigated carefully since tumour-suppressive and promoting functions of the stroma have been described[40]. The prognostic role of stroma density and activated pancreatic stellate cells in patients with PDAC should be revisited as results are highly controversial to date.

4.6 Development of personalized medicine strategies

Preliminary research through AGITIG and APGI was undertaken to determine from biopsy specimens the genomic characteristics of pancreatic cancer that could be used to guide chemotherapy regimens in small trial titled: Individualized Molecular Pancreatic Cancer Therapy (IMPaCT). [37] Cancers were screened for three molecular targets: HER2 amplification; KRAS wild-type; and mutations in DNA damage repair pathways (BRCA1, BRCA2, PALB2, ATM). These findings could allow patients to be treated in a more precise manner, utilising chemotherapy regimens that are not routinely used. The study was a pilot study and did show promise, but highlighted that rapid screening of biospecimens for actionalble molecular markers is required for large clinical trials. The

recent classification of pancreatic cancer into four types: (1) squamous; (2) pancreatic progenitor; (3) immunogenic; and (4) aberrantly differentiated endocrine exocrine (ADEX) that correlate with histopathological characteristics,[17] could further aid in personalizing treatments. Further research into personalized approach based on tumour profiling and development of platforms for rapid chemotherapy screening of specimens (eg. using pancreatic organoid cultures) is required.

4.7 Research that supports a reduction in the variations in pancreatic cancer care

Australian data shows that many patients do not receive optimal care, and this is particularly true for patients living in outer regional or remote areas.[41] While discrete studies of patterns of care have been undertaken, the development of registries to enable ongoing assessment of care will assist all patients with PDAC to receive the best evidenced-based standard of care regardless of geographic location. Research that systematically assesses variations in treatment and the relationship to patient outcomes including health-related quality of life will facilitate improvements in patient care.

5 Conclusion

Seven priority areas for research have been identified for funding by the Pancare Foundation. These are based on the considerable work and expertise of the American NCI and NIH who developed a scientific framework for PDAC in 2014 and the challenges identified which reflect the Australian context.

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