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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (14): Pancreatic cancer

Personalising pancreas cancer treatment: When tissue is the issue

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Abstract

The treatment of advanced pancreatic cancer has not moved much beyond single agent gemcitabine until recently when protocols such as FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin) and nab-paclitaxel-gemcitabine have demonstrated some improved outcomes. Advances in technology especially in massively parallel genome sequencing has progressed our understanding of the biology of pancreatic cancer especially the candidate signalling pathways that are involved in tumorigenesis and disease course. This has allowed identification of potentially actionable mutations that may be targeted by new biological agents. The heterogeneity of pancreatic cancer makes tumour tissue collection important with the aim of being able to personalise therapies for the individual as opposed to a one size fits all approach to treatment of the condition. This paper reviews the developments in this area of translational research and the ongoing clinical studies that will attempt to move this into the everyday oncology practice.

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Key words: Pancreatic neoplasms; Molecular targeted therapy; Genomics; Tissue banks; Chemotherapy

Core tip: State of art review of genomic developments in pancreatic cancer that will hopefully lead to a new treatment paradigm of recognising that pancreatic cancer is a heterogenous disease. Adequate tissue col-

lection is important to allow biomarker testing and molecular sequencing to allow determination of actionable mutations so that personalised therapies can be used in a rational manner.

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INTRODUCTION

Until recently, progress in understanding of pancreas cancer has been frustratingly slow. Prognosis remains exceedingly poor, with the majority of patients presenting with rapidly lethal advanced disease^[1,2]. Distinct phenotypes, while clinically recognised, have been difficult to capture using common diagnostic tests. In addition, the value of doing so for directing therapy has been minimal, with limited treatment options and a lack of alternatives to gemcitabine which has remained the standard of care for advanced disease until recently.

Advances in technology have recently accelerated our understanding of the biology of pancreatic cancer and tumour-host interactions. Recent initiatives such as Australian Pancreatic Cancer Genome Initiative (APGI, <http://www.pancreaticcancer.net.au/apgi>) and International Cancer Genome Consortium (ICGC, <http://icgc.org>) have seen major progress in the acquisition of high quality biospecimens for molecular studies in comprehensive cancer cohorts. Whole genome sequencing has facilitated identification of potentially actionable mutations with greater sensitivity and specificity. As tissue requirements and costs for genome sequencing decrease, the potential to select treatments in a “personalised” manner based on tumour biology moves closer to the clinic^[3].

The move towards “personalised” treatment of pancreatic cancer is not without challenges. The anatomical location of the pancreas and clinical presentation of the majority of cancers in advanced stages present particular barriers to diagnostic and exploratory tissue sampling. The relative inaccessibility of the pancreas, compared to many other tumour types, limits the ability to collect adequate μ -tissue (for example core biopsies) from primary lesions. Recent trials have demonstrated that core biopsies are currently feasible in some settings; the Liberal Education and America's Promise (LEAP) trial required core biopsy for trial participation and were able to do this prior to enrolment in 367 participants with metastatic disease^[4]. Patients presenting *de novo* with advanced disease can rapidly deteriorate and any additional diagnostic tests need to demonstrate therapeutic value and provide useful information with minimal delay to be useful in routine practice.

Tumour and patient profiling are critical in understanding the disease, developing new treatments, and better selecting patients for existing treatments. The timely, accurate and appropriate collection of tissue and blood samples are fundamental to driving future research and evolving patient care in the era of personalised and precision medicine. Future strategies, including profiling of circulating tumour DNA^[5], may minimise the invasiveness of testing but at present access to tumour tissue remains important in developing new treatment strategies and understanding their failures.

This review highlights recent advances in understanding of pancreas cancer at a molecular level including key signalling pathways and markers of treatment sensitivity. The current evidence base for a personalised approach is summarised, together with relevant ongoing trials.

RECENT ADVANCES IN SYSTEMIC THERAPY FOR ADVANCED PANCREATIC CANCER

Very little progress has been made in the systemic treatment of advanced pancreatic cancer until recent years. Gemcitabine a nucleoside analogue became established as the standard therapy following the demonstration of improved survival and clinical benefit (pain, performance status and weight) against 5-fluorouracil^[6]. This led to the subsequent focus on combining other drugs with gemcitabine to test doublets against gemcitabine monotherapy. For a time no doublet was clearly superior to monotherapy. A number of meta-analysis of gemcitabine combination studies have been carried out^[7-9]. These have shown an improvement in survival with platinum based combinations as well as fluorouracil based combinations^[10]. There was a suggestion of more benefit from combination therapy in good performance status patients and a worse prognosis in poor performance patients with combination therapy^[8]. The most recent meta-analysis of 26 studies with a total of 8808 patients has found that the relative risk of 1 year survival was lower for monotherapy when compared to combinations with platinum, fluoropyrimidine and targeted agents respectively but no statistical differences were found^[9]. When median progression free survival and overall survival were assessed only fluoropyrimidine was statistically superior. The combination therapies were associated with more toxicity.

A non-gemcitabine based intensive chemotherapy schedule FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin) in good performance status patients under 76 years of age has shown clear superiority to gemcitabine monotherapy (response rate 31.6% *vs* 9.4% ($P < 0.001$), median survival 11.1 mo *vs* 6.8 mo ($P < 0.01$) and one year survival 48.4% *vs* 20.6% at a cost of increased toxicity^[11]. Quality of life was assessed in the study and it was found that the FOLFIRINOX arm improved global health status and the time until definitive

deterioration was significantly longer than gemcitabine^[12].

A recently reported phase III trial demonstrated for the first time an overall survival benefit with gemcitabine based doublet therapy. The MPACT trial randomised gemcitabine *vs* gemcitabine plus nab-paclitaxel (Abraxane) found an improvement in median survival from 6.7 to 8.5 mo with 1 year survivals of 22% and 35% respectively ($P < 0.001$)^[13]. The response rate also increased in the combination arm (7% *vs* 23%, $P > 0.001$), although this was at the expense of higher rates of myelosuppression and peripheral neuropathy with the doublet.

The role of biological agents has been studied in pancreatic cancer. They have generally been tested in combination with the traditional chemotherapy backbone of gemcitabine. One positive trial was the combination of gemcitabine with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib *vs* gemcitabine alone^[14]. This NCIC phase III study found no difference in response rates or quality of life between the arms but did find an improvement of median overall survival from 5.91 to 6.24 mo ($P = 0.038$) with the addition of erlotinib and the one year survival improved from 17% to 23% ($P = 0.023$)^[14]. The very modest benefit in median survival (2 wk) raises the question as to whether this is clinically relevant although there is a tail of increased survivors at one year. Tumour tissue was collected in this study from 184 patients out of 569 patients with only 162 with sufficient tumour for immunohistochemistry, limiting the power to detect whether EGFR expression had any effect on outcome. Although a positive relationship between the development of rash and survival was observed in this study suggesting that this may be a identify a favourable prognostic subgroup, a subsequent study that explored dose escalation of erlotinib until development of rash found no added benefit to standard fixed dose erlotinib when combined with gemcitabine^[15]. Also of note, a subsequent SWOG phase III trial using the monoclonal antibody cetuximab as an anti-EGFR strategy in advanced pancreatic cancer found no additional benefit when added to gemcitabine^[16].

Antiangiogenics have been tested in a number of phase III trials in combination with gemcitabine. These include the anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibodies bevacizumab^[17,18] and aflibercept^[19] as well as the oral small molecule tyrosine kinase inhibitor axitinib^[20,21]. These trials have been uniformly negative and suggest that targeting VEGF is an ineffective strategy in pancreatic cancer. Similarly, trials of the matrix metalloproteinase inhibitors marimastat^[22] and BAY 12-9566^[23] have also been negative. A phase III trial of the multikinase inhibitor sorafenib in combination with gemcitabine was also negative^[24], as was a study of enzastaurin a PKCbeta and PI3K/AKT signalling inhibitor^[25].

These trials have all taken a “one size fits all” approach to treatment of advanced pancreatic cancer in enrolling unselected patients. With the recognition that pancreatic cancer is a biologically heterogenous disease, a person-

alised approach would mean selecting out patients into enriched groups with biomarker or genomic profiles of activated pathways that are more likely to respond to targeted agents being tested therapeutically^[26]. This approach has been taken with the randomised phase II RECAP trial (NCT01423604) of capecitabine in combination with placebo or ruxolitinib a JAK1 and JAK2 inhibitor in which patients with recurrent or treatment refractory pancreatic cancer has analysed a prespecified subgroup of patients identified prospectively as likely to benefit from JAK inhibition. Within this subgroup which is half of the randomized population the hazard ratio for survival was 0.47 with ruzolitinib with 6 mo survival being 42% and 11% for placebo^[27]. This trial is yet to be formally reported but a phase III study is expected to be launched soon.

Current understanding of core signalling pathways in pancreatic cancer

Detailed molecular analysis of pancreatic cancer began at the beginning of the 21st century, with *CDKN2A*, *SMAD4*, *TP53* and *KRAS* the first candidate genes identified^[28-32]. In late 2008 Jones *et al*^[33] published a seminal paper in *Science* detailing global genomic analysis of 24 pancreatic cancers. In this paper, the authors made the case for 12 core signalling pathways that are genetically altered in the majority of pancreas cancers.

One pathway they highlighted was Wnt/Notch and Hedgehog signalling. Four years later, thanks to the international genome sequencing efforts described above, Biankin *et al*^[34] published genomic data from 142 early stage pancreatic cancers. Although substantial heterogeneity was identified, 16 genes were significantly mutated. Reassuringly, some of these were common to those identified by Jones *et al*^[33] but additional novel mutated genes were identified. Of these, the strongest signal was obtained from the SLIT/ROBO pathway of axon guidance that was identified previously in 2003^[35,36]. Further work on this pathway to establish its role in tumorigenesis of pancreatic cancer is ongoing. Clearly the ongoing challenge for biologists in this field is to determine drivers of pancreas cancer, understanding that there may be different drivers in different cases. Using this method of separating pancreatic cancers into subgroups by driver has led us to test targeted, personalised treatment in animal models and also in human subjects.

Potential “actionable mutations” based on molecular profiling of pancreatic cancers

Several actionable changes have been identified in pancreas cancer; those with greatest potential clinical significance are summarised in Table 1.

Some of these were able to be verified with accredited, confirmatory genomic tests that are available commercially, such as *KRAS* mutation testing, *BRCAl* and *BRCAl2* mutation testing and *ATM* mutation testing. It is envisaged that the future will see targeted sequencing panels for pancreas cancer being commercially available, accredited and clinically applicable with short timelines

Table 1 Potentially 'actionable' phenotypes and supporting evidence

Actionable phenotype	Therapeutic	Rationale	Molecular characterization
Gemcitabine responsive	Gemcitabine	In PC, Phase III trials showed benefit in adjuvant (DFS 13.4 mo <i>vs</i> 6.9 mo) and palliative setting (MS 5.65 <i>vs</i> 4.41) ^[6,87]	High hENT1, hCNT1, hCNT3 Phase III data suggested that hENT1 correlated with response to Gemcitabine in adjuvant setting in PC ^[65,88] , however this was not shown in the metastatic population ^[89]
Anti-EGFR responsive	Erlotinib, Cetuximab	A Phase III trial showed that Erlotinib plus Gemcitabine had an overall survival benefit (HR = 0.82) compared with Gemcitabine alone in PC ^[14] Phase III data did not show a difference in OS when Cetuximab was added to Gemcitabine in an unselected population with PC ^[16]	Classical subtype PC cell lines with a "classical" subtype were shown to be more sensitive to Erlotinib ^[90] EGFR expression did not correlate with response to Cetuximab in patients with PC ^[16]
Taxane responsive	<i>nab</i> -Paclitaxel	Phase III data showed that the addition of <i>nab</i> -Paclitaxel to Gemcitabine increased PFS (HR = 0.69) and OS (HR = 0.72) in the metastatic PC population ^[13]	SPARC expression (stromal) A phase I / II study showed that SPARC expression in the stroma correlated with survival ^[71]
5-FU responsive	5-Fluorouracil	Small phase III trials showed activity of 5-FU containing regimens in the metastatic population in PC ^[91,92] 5-FU was shown to prolong survival when used in the adjuvant setting in PC (HR = 0.7) ^[93]	Thymidylate Synthase High intra-tumoural expression was shown to correlate with an increased benefit from 5-FU based chemotherapy in pre-clinical ^[94] and retrospective patient populations ^[95]
Irinotecan responsive	Irinotecan	In PC, a small effect as monotherapy has been shown in the second-line setting ^[96] , and a significant effect on OS was shown when used as part of FOLFIRINOX (HR = 0.57) ^[11]	Topoisomerase 1 expression High topo 1 expression was associated with a larger benefit from Irinotecan containing regimens in metastatic colorectal cancer ^[97]
HER2 amplified	Trastuzumab	Has shown activity in HER-2 overexpressing breast and gastric cancers ^[39,98,99] Phase II trials do not show a benefit of adding Trastuzumab to Gemcitabine in PC (OS = 7 mo), however, no standardised approach to FISH testing was used ^[41,70]	<i>HER2</i> amplification Pre-clinical studies suggested that <i>HER2</i> overexpression predicts a response to Trastuzumab in PC ^[100]
m-TOR responsive	Everolimus, Temozolomide	A phase III trial of Everolimus in renal cell cancer shows prolongation in PFS (PFS 4 mo <i>vs</i> 1.9 mo) ^[101] Phase II data showed minimal activity (OS = 4.5 mo) of Everolimus for second line treatment in an unselected population of patients with metastatic PC ^[102] A case study in a patient with PC and Peutz-Jeghers syndrome (SK11 deficient) responds to Everolimus ^[103]	P-TEN Deficient, High p-mTOR/p70S6, AKT amplified, STK11/LKB1 deficiency, PI3K mutation Pre clinical studies showed that p-TEN deficient cell lines are sensitive to m-TOR inhibitors ^[104] Retrospective studies suggested that SK11, p-MTOR, p-70S6, PI3K and AKT can select tumours that will respond to m-TOR inhibitors ^[103,104-110]
VEGF inhibitor responsive	Sunitinib, Bevacizumab	Phase III trial showed no benefit with adding Bevacizumab to Gemcitabine in an unselected population of patients with PC ^[127] Phase II data showed that maintenance Sunitinib after primary chemotherapy improved 2 yr OS (22.9% <i>vs</i> 7%) in the metastatic PC population ^[109]	CSF1R up-regulation, High HIF- α expression <i>In vitro</i> studies showed CSF-1R up-regulation was associated with response to Sunitinib in AML ^[110] High HIF- α predicted response to Sunitinib in a retrospective cohort in renal cell cancer ^[111]
DNA damage repair deficient	Platinum; MMC; PARP inhibitor	<i>In vitro</i> work showed that cells with defects in BRCA2 are preferentially sensitive to PARP inhibitors ^[112] Case reports of PC patients with BRCA2 deficient tumours respond to PARP ^[113,114] Multiple clinical trials are on-going assessing the effects of PARP inhibition	DDR signature; mutation of DDR genes, <i>BRCA/ATM/PALB2</i> Loss of BRCA1 was associated with sensitivity to DNA damaging agents ^[115] BRCA2 mutations were associated with improved response to platinum agents ^[116] <i>In vivo</i> studies showed PALB2 inactivation was a determinant of response to DNA damaging agents in PC ^[114]
SMO inhibitor responsive	Saridegib, Vismodegib	A phase II trial found that Saridegib plus Gemcitabine was no better than Gemcitabine alone in an unselected population of metastatic PC patients (data not published) ^[117] <i>In vivo</i> studies show SMO inhibitors block metastasis formation in pancreatic cancer ^[118]	Gli1 and PTCH1 transcript levels GLI1 mRNA may predict response to SMO inhibitors in pancreatic cancer <i>in vivo</i> ^[119] High Gli1/PTCH1 transcript levels were correlated with response to SMO inhibitors in CLL ^[120]

PC: Pancreatic cancers; EGFR: Epidermal growth factor receptor; VEGF: Vascular endothelial growth factor; DFS: Disease-free survival; OS: Overall survival.

and low cost. Others, such as Her2 upregulation, can be tested for using immunohistochemistry and *in situ* hybridisation.

Her2 as an example of an "actionable" mutation

The *HER2* (human epidermal growth factor receptor)/*neu/ERBB2* gene is a member of a family of genes that

play a role in regulating cell growth. *HER2* signalling promotes cell proliferation through the RAS-MAPK pathway and inhibits cell death through the phosphatidylinositol 3'-kinase-AKT-mammalian target of rapamycin (mTOR) pathway. Although *HER2* overexpression has been described in a variety of human malignant conditions, gene amplification is uncommon except in breast and gastric cancer^[37]. Anti-*HER2* therapy is clinically indicated and effective for both *HER2* amplified breast^[38] and gastric^[39] cancers. There is growing evidence that *HER2* is an important biomarker and key driver of tumorigenesis in pancreatic cancer.

Recent evidence suggests *HER2* amplification occurs in 2% of pancreatic ductal adenocarcinoma, and may potentially respond to anti-*HER2* therapy^[37], similar to *HER2*-amplified breast cancer. On a molecular level, *HER2*-amplified pancreatic cancers demonstrated a mRNA expression profile which clustered with the *HER2*-amplified intrinsic subtype of breast cancer using the PAM50 classifier. Clinically, *HER2*-amplified pancreatic cancers showed an atypical metastatic pattern characterized by spread to the lungs and brain with avoidance of the liver, not unlike the pattern of spread seen in *HER2*-amplified breast cancer. These findings suggest that *HER2* is likely to be the main driver of tumorigenesis in this subgroup of pancreatic cancer, analogous to *HER2*-amplified breast cancer and may respond to anti-*HER2* therapy.

Three clinical trials have assessed anti-Her2 therapy in pancreatic cancer. All 3 were single arm phase II trials utilising anti-Her2 agents active in other cancers in conjunction with traditional cytotoxics. Only 2 of the trials selected patients based on Her2 status, and utilised immunohistochemistry alone to detect *HER2* overexpression^[40-42].

In Safran's first study patients with *HER2* overexpressing metastatic pancreatic cancers were recruited and showed a response rate of only 6% which was considered as not significantly different from historical controls of gemcitabine alone^[40]. The majority of the patients recruited however had *HER2* 2+ tumors. In Safran's second study lapatinib (a dual *HER1* and *HER2* inhibitor) and gemcitabine were given to an unselected population of patients with metastatic pancreatic cancer^[42]. The study was terminated after 6 mo due to poor response rate. Harder *et al*^[41] recruited 17 patients with *HER2* expressing metastatic pancreatic cancer for trastuzumab and capecitabine, and this study closed prematurely due to lower than expected prevalence of *HER2* 3+ tumours and therefore slow accrual.

The selection of patients was based on *HER2* expression using immunohistochemistry alone and these were not standardized assays performed in reference laboratories. As a result it is possible that the use of non-standardised assays performed outside accredited reference laboratories overestimated *HER2* positivity. The likely overestimation of *HER2* positivity underpowered the trials and makes a negative result difficult to interpret.

Identifying *HER2* overexpressing pancreatic cancers

(PC) by genomic profiling has the potential to identify a cohort more likely to benefit from anti-*HER2* therapy. This enrichment strategy is being utilised in the recently opened IMPaCT (Individualised Molecular Pancreatic Cancer Therapy) trial (Table 2) of which several authors are investigators.

Preclinical trials of repurposed drugs in patient-derived xenografts

In order to maximize benefit to patients clinical trials should be conducted in populations based on molecular characteristics^[43]. This highlights the importance of biomarker driven therapeutic development. Such trials are expensive, labour intensive and pose significant logistical difficulties which in PC, are compounded by the rapidity of clinical deterioration and the small percentage of patients who are well enough to receive more than one line of chemotherapy. Using patient derived xenografts presents an attractive option to test potential biomarkers and partnered therapeutic interventions.

Xenograft models derived from established tumour cell lines may not fully recapitulate the complexities of human disease and therefore may not be the ideal medium with which to test novel therapeutics^[44-46]. In addition the vast majority of cell lines that have been used in the past do not have associated germline sequence data. As a consequence, the accuracy of genomic aberrations identified by comparing to a reference sequence is not sufficient for subsequent testing of genotype-guided treatment strategies. Genetically engineered mouse models (GEMM) will develop PC predictably and can be used to study pancreatic carcinogenesis^[47]. However, Singh *et al*^[48] showed that the PDAC *Pdx1-Cre LSL-Kras^{G12D} p16/p19^{fl/fl}* GEMM had a greater response to gemcitabine than typically observed in the patient population, suggesting these models too lack the heterogeneity and complexity of the human condition.

Primary xenografts are generated directly from engraftment of individual human tumour tissue into severely immunocompromised mice [nonobese diabetic /severe combined immunodeficiencies IL2rg -/- (NSG) mice] allowing efficient engraftment of the tumour^[49,50]. These have been shown to faithfully represent the histopathological, biological and genomic characteristics of the primary tumour^[51,52]. These models may represent valuable tools for testing novel therapies. Primary xenograft models have been used to test novel therapies in childhood leukaemia^[53-55] and neuroblastoma^[56,57]. More recently in PC, primary xenografts have been used to test the efficacy of sorafenib and everolimus alone and in combination^[58].

The generation of primary xenografts provides a renewable and valuable resource with which multiple treatments may be studied. Large pre-clinical trials may be designed where a specific tumour of interest may be examined for its sensitivity to numerous different therapies or efficacy of a single novel therapy may be examined in a range of tumours with different molecular profiles. The

Table 2 Ongoing biomarker directed therapy trials in pancreatic carcinoma

Trial Identifier ¹	Name of study	Phase	Sponsor	Arms	Primary outcome	Biomarker
ACTRN1261200077897	The IMPACT trial: Individualised Molecular Pancreatic Cancer Therapy A randomised open label phase II study of standard first line treatment or personalised treatment in patients with recurrent or metastatic pancreatic cancer	II	The Australasian Gastro-Intestinal Trials Group Collaborating groups: Australian Pancreatic Cancer Genome Initiative Sydney Catalyst; the Translational Cancer Research Centre of Central Sydney and Regional NSW	Patients with actionable phenotypes randomised 1:1 to Standard -gemcitabine alone OR Personalised Treatment -allocated based on molecular phenotype: - gemcitabine HER2 positive sub-group - gemcitabine plus trastuzumab Homologous recombinant defects sub-group: 5FU plus MMC antiEGFR responsive sub-group: gemcitabine plus erlotinib Gemcitabine and cisplatin	Progression free survival (initial pilot phase will assess feasibility of personalised approach)	Identification of actionable phenotypes based on molecular phenotype in tumour tissue in one of 3 subgroups: HER2 positive (HER2/neu amplification) subgroup Homologous recombination defects (BRCA1, BRCA2 or PALB2 mutation) AntiEGFR phenotype subgroup (KRAS wildtype or KRAS codon 13 mutation)
NCT01188109	Gemcitabine/cisplatin for resected pancreas cancer: Establishing the role of ERCC1 in treatment decision	II	Emory University	Gemcitabine + Nab-paclitaxel induction FOLFIRINOX consolidative Metformin + targeted agent selected by biomarkers for maintenance	Progression free survival and overall survival Complete response rate	Immunohistochemistry, rt-PCR, and single nucleotide polymorphism assessment to determine status of ERCC1 expression and gene IHC Analysis will be performed on a fresh tissue biopsy of the tumor after chemotherapy has been administered. A targeted-based regimen will be determined from the results of the IHC analysis for the next therapy given to the patient in the maintenance phase of the study Low expression of ERCC1 protein and mRNA
NCT01488552	A Phase II study of induction consolidation and maintenance approach for patients with advanced pancreatic cancer	I / II	Pancreatic Cancer Research Team	Gemcitabine+oxaliplatin	6 mo overall survival	
NCT01524575	Gemcitabine and oxaliplatin in the management of metastatic pancreatic cancers with low expression of ERCC1	Phase II	University of Hawaii	Gemcitabine + oxaliplatin	Timing of biopsy and treatment Number of days from study entry to biopsy to molecular results to first dose	Selection of doublet treatment on basis of molecular analysis of tumour
NCT01888978	A Pilot Study of Molecularly Tailored Therapy for Patients With Metastatic Pancreatic Cancer	Phase II	Georgetown University	Gemcitabine + 5FU Gemcitabine + docetaxel FOLFOX6 Oxaliplatin + docetaxel FOLFIRI Docetaxel-irinotecan Cisplatin+gemcitabine +/-veliparib	Optimal dose of veliparib Response rate	BRCA1 or BRCA2 mutation carrier
NCT01585805	Gemcitabine Hydrochloride and Cisplatin With or Without Veliparib or Veliparib Alone in Patients With Locally Advanced or Metastatic Pancreatic Cancer	Randomised phase II	National Cancer Institute	FOLFOX Gemcitabine	PFS between arms in hENT1 high and hENT1 low patients	hENT1
NCT01586611	Study of Gemcitabine vs FOLFOX in the First Line Setting for Metastatic Pancreatic Cancer Patients Using Human Equilibrative Nucleoside Transporter 1 (hENT1) Biomarker Testing	Phase III	AHS Cancer Control Alberta			

NCT01454180	Study of Individualized Selection of Chemotherapy in Patients With Advanced Pancreatic Carcinoma According to Therapeutic Targets	Phase II	Centro Nacional de Investigaciones Oncológicas CARLOS III	Arm A: Physician discretion Arm B: Therapeutic target guided	Overall survival	Therapeutic targets expressed in tumour tissue
NCT01726582	Molecular Profiling to Guide Neoadjuvant Therapy for Resectable and Borderline Resectable Adenocarcinoma of the Pancreas	Phase II	Medical College of Wisconsin	Gemcitabine Gemcitabine + capecitabine Gemcitabine + erlotinib FOLFOXIRI FOLFOX FOLFIRI Targeted chemotherapy prior to surgery Standard FOLFIRINOX chemotherapy prior to surgery Gemcitabine after surgery No additional therapy after surgery Targeted chemotherapy after surgery Chemoradiotherapy (Targeted chemotherapy include the following schedules: FOLFIRINOX, FOLFIRI, gemcitabine+irinotecan, gemcitabine + oxaliplatin, gemcitabine + cisplatin, gemcitabine+nab-paclitaxel, capecitabine + nab-paclitaxel, gemcitabine, capecitabine, 5FU)	Resectability rate	Molecular profile of tumour will point to particular chemotherapy treatment

¹Trial number prefixes correspond to location of registry/portal. ANZCTR/N: Australian New Zealand Clinical Trials Registry; 5FU: 5-fluorouracil; FOLFIRINOX: Fluorouracil, leucovorin, irinotecan and oxaliplatin; MMC: Mitomycin C; IHC: Immunohistochemistry; ERCC1: Excision repair cross complementation gene-1.

impact of this is two-fold, with the opportunity for a patient's tumour to undergo pre-clinical testing to determine the clinician's choice of therapy having obvious advantages to patient outcomes but also, that tumours bearing particular biomarkers of interest may be tested extensively against existing and novel therapies to guide the design of molecularly driven human clinical trials.

PREDICTING RESPONSE TO TREATMENT/IMPROVING TREATMENT DELIVERY

Another important facet of personalising therapy for pancreatic cancer is identifying patients who will derive net clinical benefit from existing treatments. Biomarkers of potential benefit or toxicity from existing systemic therapies as well as radiation therapy have been identified.

Identifying biomarkers for patients likely to benefit from radiotherapy treatment

Autopsy studies^[59,60] have shown that more than 80% of patients with pancreatic cancer develop distant metastases even in those who have undergone curative resection, suggesting the presence of occult metastases at time of surgery. Therefore, patients who would benefit from local radiotherapy treatment are those less likely to develop systemic disease. Futures areas of research should not only focus on identifying those patients with locally aggressive disease but also those with radiosensitive tumours more likely to respond from radiotherapy treatment.

An autopsy study^[61] found that positive staining for the intracellular protein DPC4 (or SMAD4) might indicate a patient that was more likely to harbour locally aggressive disease. Only twenty-two percent of patients with no metastatic disease at autopsy showed loss of expression of DPC4. Conversely, 73% of patients with extensive metastatic disease demonstrated loss of expression of this protein.

Identification of a biomarker of radiosensitivity has been explored in other tumour sites. The XRCC1 (X-ray repair cross-complementing group 1) protein is involved in base excision repair. A single nucleotide polymorphism known as Arg399Gln has been shown to affect radiosensitivity. The ECOG 1201 Phase II trial analysed patients to determine whether the presence of this allele affected complete response rates after neoadjuvant cisplatin based chemoradiotherapy in oesophageal adenocarcinoma^[62]. Fifty-two percent of patients had the Arg399Gln allele and only 6% of those had a complete response at time of surgery 5 wk after completion of their neoadjuvant treatment. The odds ratio for failing to undergo a complete pathological response in the presence of this allele was 5.37 ($P = 0.062$). This did not translate to a reduction in disease free or overall survival though it does suggest there are certain patients who are more likely to respond to radiotherapy.

Optimising drug delivery with predictive biomarkers

The co-development of novel chemotherapeutic and therapeutic strategy with companion diagnostics is the paradigm of modern clinical oncology. Outcomes from these efforts have been somewhat mixed to date, and the reasons are many and complex. For the purpose of this review, the authors will only concentrate on two drugs that have been approved for use in pancreatic cancer.

Gemcitabine: The putative biomarkers of gemcitabine responsiveness include nucleoside transporters such as hENT1, hCNT1/3 and kinases involved in gemcitabine metabolism such as deoxycytidine kinase^[63,64]. The most studied biomarker of therapeutic responsiveness to date in PC is hENT1, a membranous equilibrative nucleoside transporter encoded by the *SLC29A1* gene. There is promising evidence to support the role of hENT1 in gemcitabine responsiveness in PC cells both *in vitro* and *In vivo*, but its precise role as a predictive biomarker in the clinic has not been well established, with conflicting results reported. Small cohort studies and retrospective analysis of large Phase III randomised-controlled trials (RCT), such as RTOG 9704 and ESPAC 1/3 have supported its role as a predictive biomarker of adjuvant gemcitabine responsiveness, where patients with hENT1 positive tumour had significant survival benefit from adjuvant gemcitabine as compared to patients with low hENT1 tumours^[65,66]. However, a recent Phase II RCT stratified by hENT1 expression (LEAP: Low hENT1 and Adenocarcinoma of the Pancreas) comparing gemcitabine *vs* CO-101 (lipophilic gemcitabine) in metastatic PC failed to demonstrate this in metastatic disease^[4]. Though the reasons for this are still unclear, the discrepancy may be due to the use of different hENT1 antibodies for immunohistochemistry, and/or perhaps the significance of hENT1 as a predictive biomarker is different in the metastatic as compared to the adjuvant setting. LEAP was the first purposely designed biomarker stratified trial in PC with prospec-

tive tissue acquisition, further analysis of the available tissue samples may offer more insight into gemcitabine responsiveness biomarkers.

nab-Paclitaxel (Abraxane®): Secreted Protein Acid and Rich in Cysteine (SPARC, also known as osteonectin) regulates extracellular matrix modeling and deposition and may act as a tumour suppressor or an oncogenic driver depending on its differential expression in epithelial and stromal compartments in different cancer types^[67]. High stromal and low epithelial expression of SPARC has been shown to be a poor prognostic biomarker in PC^[68,69] and based on its hypothesised function as an albumin “sticker”, it was developed as a therapeutic target for nab-paclitaxel to enable “stromal depletion” and in turn, to improve drug delivery. A positive phase I / II study of gemcitabine plus nab-paclitaxel demonstrated in a biological sub-study that SPARC expression in the stroma, but not in the epithelium, co-segregated with improved survival in PC, and hence a candidate predictive biomarker for nab-paclitaxel responsiveness^[70]. This led to the recently reported Phase III MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) RCT comparing gemcitabine *vs* gemcitabine plus nab-paclitaxel which demonstrated the significant addition survival benefit of nab-paclitaxel in patients with metastatic PC^[71]. However, data concerning SPARC as a predictive biomarker of nab-paclitaxel responsiveness are not currently available. Although the relationship between SPARC expression and nab-paclitaxel responsiveness is still evolving, these proof-of-concept data suggest it warrants further exploration.

Improving treatment delivery: Targeting stroma

There is mounting evidence that stromal factors may be crucially important not only in determining the development and behaviour of carcinoma, but in influencing treatment response and, ultimately, prognosis. Stromal and epithelial cells may interact through direct cell-cell contact, or *via* paracrine signaling, and various non-cellular components in the stroma may influence either or both cell types. Many of these factors may contribute to cancer progression and metastasis through altered cell adhesion, epithelial-mesenchymal transition (EMT), matrix remodeling (facilitating tumour cell migration), and neovascularisation. These concepts have been examined in more detail elsewhere^[72].

Individual differences in gene expression have been demonstrated within the stromal component of breast tumours, and these different phenotypes correlated with clinical outcome^[73,74]. Differential expression of some of these same genes at the protein level appears to correlate with tumour regression in irradiated rectal carcinoma (Hemmings, unpublished data). One such protein is SPARC (Secreted Protein Acidic and Rich in Cysteine), a matricellular protein which modulates cell-cell and cell-matrix interactions, as described previously. Treatment with SPARC can block fibroblast activation and may

serve to inhibit angiogenesis^[75]. There is some evidence that SPARC may act as a chemosensitiser by potentiating apoptosis^[76]. SPARC may be upregulated in pancreatic cancer, and suppressing its expression may inhibit cancer cell migration, offering a potential therapeutic target^[77]. Modulation of other matricellular proteins has also been shown (at least in a murine model) to alter chemotherapy response, without directly altering drug delivery^[78], and the addition of agents which modify the tumour stroma may enhance chemotherapy response in clinical cases of operable pancreatic cancer^[79].

Another important stromal variable is the host immune response to invading tumour cells. Whilst generally thought to be part of the host's armamentarium against cancer, it has become clear that inflammatory cells may promote the formation and progression of some tumours, and the balance of pro- and anti-tumour effects varies between individuals as well as between different tumour types. In pancreatic cancer, tumour-infiltrating TH17 (lymphoid) cells may act on stroma to induce angiogenesis, as well as activating other tumour-promoting transcription factors^[80]. In one model, tumours which were resistant to VEGF inhibitors were rendered sensitive by inhibition of TH17 effector function, suggesting that immunomodulation may improve the efficacy of antiangiogenic treatments^[81]. Similarly, tumour-associated macrophages (TAMs) may produce various growth factors as well as proteases which degrade the extracellular matrix, facilitating tumour invasion and angiogenesis^[73], and may promote EMT in pancreatic cancer cells^[82]. Transition of normal macrophages to tumour-promoting TAMs may be induced by IL-4 produced by pancreatic carcinoma cells^[83], again offering a possible therapeutic target, and other inflammatory mediators may serve as biomarkers of prognosis in patients with advanced pancreatic carcinoma^[84].

DEVELOPING THE EVIDENCE BASE FOR A "PERSONALISED APPROACH"

Many challenges exist in developing the evidence base for a "personalised approach" to PC treatment. These include: appropriate design of clinical trials; development, interpretation and accreditation of standardised tests; matching appropriate patients to suitable trials; and minimising turn around time of new molecular based diagnostic tests required for trial eligibility and ultimately treatment selection^[26,85,86]. A number of clinical trials examining different aspects of personalised treatment for pancreatic cancer are ongoing (Table 2). Biobanking of tissue samples linked to clinical outcomes data is possible within clinical trials and community cohorts. Such resources hold significant potential for true translational research.

Molecular profiling of tumours and the role of biobanks

Next generation sequencing is providing unprecedented opportunities to uncover the underlying genetic pathways driving cancer and is accelerating the drive towards per-

sonalized medicine. Human specimens that are analyzed using these technology platforms are a critical resource for basic and translational research in cancer because they are a direct source of molecular data from which targets for therapy, detection, and prevention are identified. The recent Federal Drug Administration approval of next generation sequencing platforms for diagnostic use (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm375742.htm>) and the rapidly falling costs of whole genome sequencing will bring this technology into the clinic in the near future.

Biobanking has the potential to be a powerful platform for health innovation and knowledge generation, as biospecimens represent essential materials that fuel the advance of technology, scientific and medical research. This has stimulated a growing demand for appropriately qualified, well annotated biospecimens world-wide.

However, establishing a biobank of value, presents unique ethical, logistical, scientific, informational, and financial challenges in tissue acquisition and resource development. To be of maximum value tissue samples and analytical methods must be "fit for purpose" and reproducible.

Controlling pre-analytical variables is critical to ensure that the results of multidimensional high-throughput profiling are accurate and reproducible. The Australian Pancreatic Cancer Genome Initiative, an Australian led, international effort to characterise the genome of pancreatic cancer, has led international efforts to harmonise and standardize biospecimen collection, processing and downstream application. Factors critical to the success of this initiative include using best practice to guide processes, collection of multiple aliquots of specimens, ensuring all samples have a reference germline sample and expanding the repertoire to include the development of patient derived xenografts and cell lines. It is crucial to set appropriate standards from the projects initiation, and the human aspects of this complex enterprise cannot be underestimated to ensure quality samples that accurately represent the spectrum of cancer.

Meeting the challenges of biospecimen quality and interoperability requires a more modern approach to biobanking. Modern biobanking sees a new type of biospecimen emerge: where biospecimens are collected at distinct time points, and in a pre-specified clinical context. These samples are comprehensively annotated with clinico-pathological and treatment data, and linked to genomic and molecular data sets. Procurement of these types of samples requires a new organisational structure that includes specific clinical disciplines such as interventional radiology and molecular pathology.

CONCLUSION

Recent advances in the treatment of pancreatic cancer have evolved through greater understanding of clinical tumour biology. None of this would be possible without access to tumour tissues. Biospecimen collection for

future research is becoming an integral part of trials and increasingly part of practice. Appropriate methods for collection, analysis and annotation of specimens are critical for maximising benefit from this valuable resource and ensuring reliability and reproducibility of results.

There is still much progress to be made in improving outcomes for patients with pancreatic cancer. Oncologists are increasingly recognising the importance of bio-specimen collection to facilitate precision medicine. To make this a reality in practice, engagement of patients and other related clinicians (gastroenterologists, radiologists and pathologists) is vital. Acceptability to patients in routine practice is a crucial step in moving not just from bench to bedside but from trial to clinic.

The contribution of patients in allowing their specimens to be accessed for research cannot be undervalued. At both global and individual levels, for contribution to research and for personalisation of treatment, tissue is -and will continue to be- an important issue.

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