colitis induced by dextran sulfate sodium (DSS) in rats. *Int. J. Food Microbiol*. 2007; **114**: 267–74.
12 Torok VA, Ophel-Keller K, Loo M, Hughes RJ. Application of methods for identifying broiler chicken gut bacterial species linked with increased energy metabolism. *Appl. Environ. Microbiol*. 2008; **74**: 783–91.
13 Kamil R, Geier MS, Butler RN, Howarth GS. *Lactobacillus rhamnosus* GG exacerbates intestinal ulceration in a model of indomethacin-induced enteropathy. *Dig. Dis. Sci*. 2007; **52**: 1247–52.
14 Guarner F. Prebiotics in inflammatory bowel diseases. *Br. J. Nutr.* 2007; **98** (Suppl. 1): S85–9.
15 Geier MS, Butler RN, Giffard PM, Howarth GS. Prebiotic and synbiotic fructooligosaccharide administration fails to reduce the severity of experimental colitis in rats. *Dis Colon Rectum* 2007; **50**: 1061–9.
16 Rachmilewitz D, Karmeli F, Takabayashi K *et al*. Immunostimulatory DNA ameliorates experimental and spontaneous murine colitis. *Gastroenterology* 2002; **122**: 1428–41.

Individualizing therapy for pancreatic cancer

Emily K Colvin,* David K Chang,*,† Neil D Merrett,*,† James G Kench*,‡ and Andrew V Biankin*,†

*Cancer Research Program, Garvan Institute of Medical Research, †Upper Gastrointestinal Surgery Unit, Bankstown Hospital, and ‡Department of Anatomical Pathology, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia

See article in *J. Gastroenterol. Hepatol.* 2008; 23: 1852–1859

The study by Jiang and colleagues in this issue of the *Journal of Gastroenterology and Hepatology* reports the relationship of neural growth factor (NGF), tyrosine kinase receptor A (TrkA), and perineural invasion in pancreatic cancer (PC). They hypothesize that these molecules may play a key role in perineural invasion, and hence, tumor progression and metastases. As a consequence, they may be clinically useful markers (biomarkers) of poor prognosis and potential targets for the development of novel therapeutic strategies.

The rationale that underpins 'biomarker' studies is that cancer therapeutic agents commonly benefit only a subset of treated patients. The delineation of cancer phenotypes based on molecular markers (biomarkers) of therapeutic responsiveness and overall outcome can enable stratification of patients to appropriate individualized therapeutic regimens, so that optimal treatment is given without delay and unnecessary adverse side-effects are minimized. In addition, the ongoing investigation of resistant subgroups facilitates the identification of novel, more effective therapies. Finally, the identification of prognostic markers provides the ability to inform patients of the likely outcome of their disease and their likely response to a given therapy. All of these gains improve patient management and potentially reduce morbidity and mortality.

This path of advancement is best illustrated in breast cancer, where hypotheses that led to the discovery and application of effective endocrine therapies that target the estrogen receptor (e.g. tamoxifen) were generated from clinical and experimental observations of the sensitivity of breast cancer to estrogen. Subsequent identification of HER2/*neu* amplification as a marker of poor prognosis facilitated the development of the anti-erbB2 monoclonal antibody trastuzumab (Herceptin; Genentech, San Francisco, CA, USA). More recently, gene expression profiling has identified at least five breast cancer subtypes that overlap with previously defined phenotypes: luminal A and B (both estrogen receptor [ER] positive), normal-like, erbB2, and basal (ER negative).[1] These subsets differ in their prognosis and response to specific treatments and identify potential targets for the development of novel therapeutic strategies to treat resistant subtypes.

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or a response to a therapeutic intervention. A molecular biomarker may either itself play a significant role in the development of a specific phenotype or simply be a surrogate marker of underlying molecular mechanisms. In the example of breast cancer, ER and HER2 are both biomarkers with specific functional contributions, and so molecular therapies that target these molecules are effective.

Stratification of therapy using biomarkers can potentially be applied in two major ways. They can either be used to refine existing staging and grading classifications or supplant existing classifications.[2] The variability of outcomes between individuals with similar cancer types and stages may be better defined through an understanding of the underlying molecular mechanisms. Such mechanisms may be represented by biomarkers that discriminate these different prognostic groups, and as a result have significant clinical utility. Biomarkers of therapeutic responsiveness may also be independent of stage and grade. Thus, c-kit expression is predictive of the response to imatinib (Glivec; Novartis Pharmaceuticals, Basel, Switzerland) therapy, where c-kit status is potentially more clinically relevant than stage or grade. In addition, different biomarkers may be important at different clinical decision points.

While biomarkers have been used with success in predicting response to therapies targeting a known molecular aberration, such as ER and HER2 in breast cancer, and c-kit for gastrointestinal stromal tumor, the ability of biomarkers to predict the response to established therapies targeting more generic mechanisms, such as cytotoxic chemotherapy, has not been as successful.[3] The advent of modern technologies allow a high-throughput assessment of multiple molecular aberrations, and thus the definition of gene 'signatures' may potentially provide a more accurate and more clinically relevant phenotypic classification of morphologically similar cancers. Although such methodologies have been successful in instances such as breast cancer, molecular phenotyping in other cancers is less advanced for several reasons. These include feasibility and priority. This is particularly pertinent in the case of PC, where work to date has predominantly examined individual

Accepted for publication 8 September 2008.

Correspondence
Associate Professor Andrew V Biankin, Pancreatic Cancer Research Group, Cancer Research Program, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, NSW 2010, Australia.
Email: a.biankin@garvan.org.au

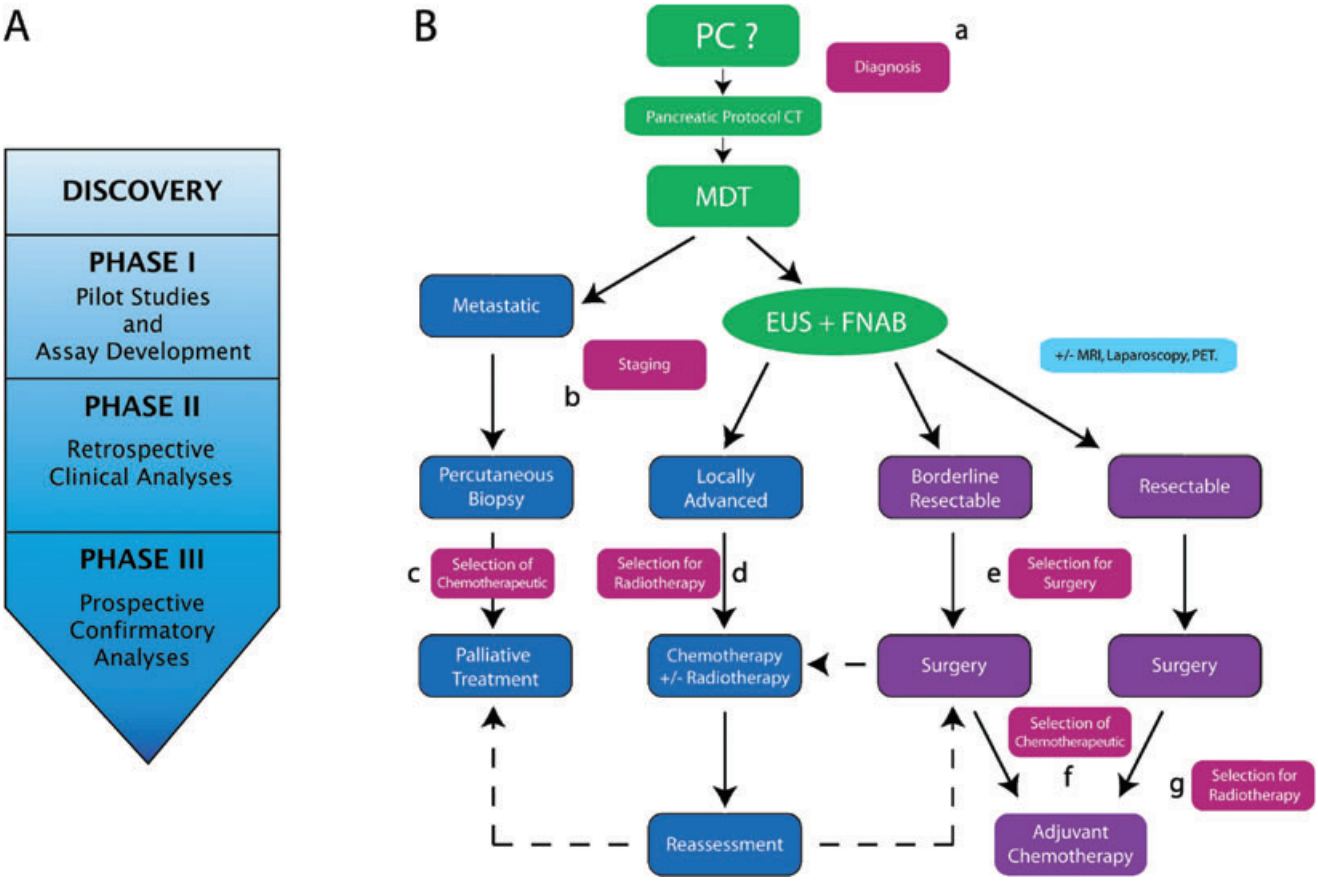

Figure 1 (a) National Cancer Institute USA strategy for biomarker discovery and development. Discovery phase is underpinned by analyses of large datasets of global analyses of molecular genetic aberrations. Phase I involves the development of assays for priority-listed targets, which are assessed for their relevance to pancreatic cancer (PC) and potential utility as biomarkers in retrospective cohorts of patients with archival tissue (training sets). Phase II takes promising biomarkers from phase I through assessments in larger independent cohorts which may be from cohort studies and randomized controlled trials. Phase III takes candidate biomarkers further into prospective analyses using appropriate clinical trials. (b) Generic approach to the management of pancreatic cancer showing the points at which biomarkers could significantly improve current treatment and better individualize therapy (i–vii). CT, computed tomography; EUS, endoscopic ultrasound; FNAB, fine needle aspiration biopsy; MDT, multidisciplinary team; MRI, magnetic resonance imaging; PET, positron emission tomography.

candidate genes as potential biomarkers of clinical utility. The National Cancer Institute USA has defined a strategy for the discovery and development of biomarkers for translation in the clinic (Fig. 1a). Initial observations in a single retrospective cohort require validation in an independent cohort, preferably from a clinical trial, before they progress to prospective assessment. While some biomarkers have progressed through these steps, the most recent being KRas mutation status and response to anti-epidermal growth factor receptor (EGFR) monoclonal antibody Cetuximab (Bristol–Myers Squibb, New York City, NY, USA) in colorectal cancer,[4] no biomarkers of potential clinical utility identified in PC have yet been independently validated.[5]

PC is the fourth leading cause of cancer death in Western societies, and the 5-year survival rate is less than 5%.[6,7] Advances in neoadjuvant and adjuvant regimens have resulted in some improvement in outcomes, but pancreatectomy remains the single most important treatment modality for PC, and offers the only potential for cure. Decisions concerning the appropriateness of pancreatectomy are currently based purely on imaging criteria. Because of this, major prognostic factors are not determined until after the resected specimen has been examined microscopically. Further, despite microscopically clear resection margins (R0), up to 80% of patients still die of their disease, with a significant proportion succumbing within 12 months of resection. This observation indicates that occult metastatic disease was present at the time of surgery.[8–15] In addition, a high proportion of deaths from PC after attempted curative resection occur due to disease relapse in the form of metastases rather than local recurrence.[16]

Significant gains could be made in the short term through refining current therapeutic approaches for PC.[7] First, morbidity and mortality for those who would not benefit from pancreatectomy could be avoided, and conversely, more aggressive approaches may be justified if the ability to forecast individual tumor behavior and response to surgery preoperatively could be improved. Second, the ability to predict which patients would respond to specific chemotherapeutics (5-fluorouracil, gemcitabine,

capecitabine, and erlotinib), or radiotherapy would also provide significant benefits. Third, deciding if stent placement or surgical bypass for palliation of biliary obstruction is more appropriate for an individual would be greatly facilitated with the ability to forecast the prognosis for an individual patient. Points at which biomarkers could significantly improve overall outcomes for PC in the short term are outlined in Figure 1b. These include: (i) diagnosis, which may be either through improved accuracy, screening, or early detection; (ii) staging, through better detection of occult metastatic disease to discriminate metastatic from loco-regional disease, thus determining the potential utility of surgery and radiotherapy; (iii) predicting and monitoring the response to systemic therapies; (iv) detection of disease relapse or recurrence; and (v) prognostication. At this time, only serum carbohydrate antigen 19-9 (CA19-9) has a limited role in the clinical management of PC. However, there are several new candidate markers currently being assessed. Some of the more promising are outlined below.

Diagnosis

While many molecular markers are under investigation in serum and pancreatic juice and show promise as markers for the early detection of PC, many require validation using optimal laboratory methods and appropriate patient populations before they can be considered for use in clinical settings.[17] Serum CA19-9 has been the most studied, and has at best a limited role in diagnosis;[17] however, reliable markers that are superior to or enhance the diagnostic accuracy of CA19-9 are yet to be defined. Efforts to better characterize the molecular pathology of precursor lesions of PC, including pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms may better define candidates for early detection strategies.[18]

Staging

Current staging methods for PC are inadequate and significantly hamper progress towards stratification of therapy directed at loco-regional disease. As a consequence, studies that assess treatment directed at loco-regional disease, such as radiotherapy, in the treatment of locally advanced disease or as adjuvant therapy are substantially underpowered. Promising biomarkers that predict the response to surgical resection or radiotherapy include serum markers (CA19-9,[19] C-reactive protein [CRP][20]), and tumor markers, such as HOXB2 and cyclin E1.[21–24] Recent data suggest that preoperative serum CA19-9 and the change in CA19-9 after resection predict survival.[19] Similarly the serum CRP also cosegregates with survival after pancreatectomy.[20]

Predicting and monitoring response to systemic therapies

The ability to discriminate responders and non-responders prior to or early during therapy improves overall outcomes by directing the individual to the therapy that is most likely to be effective. Again, there are few markers currently being used in clinical practice. The most promising are decreasing serum CA19-9 levels during chemotherapy and nucleoside transporters, such as human equilibrative nucleoside transporter 1, in predicting the efficacy of gemcitabine.[25]

Detection of disease relapse/recurrence and prognostication

Although serum CA19-9 levels are sometimes used, the lack of specificity restricts their interpretation. Many molecular markers have been assessed with respect to prognostication as mentioned earlier; serum levels of CA19-9 and CRP have some utility, but again, no markers detected in tumor samples have been independently validated.[5]

In summary, the individualization of therapy for PC lags behind many other cancers. Identification of a biomarker with clinical utility would significantly improve outcomes with current therapy through individualizing treatments; however, promising candidates are yet to be validated and adopted in routine clinical practice. Candidate biomarkers selected for assessment based on an understanding of the molecular mechanism of PC development and progression (such as NGF and TrkA reported by Jiang *et al*. in this issue of the *Journal of Gastroenterology and Hepatology*) may guide management decisions in the future, but require further assessment prior to their implementation.

References

1 Brenton JD, Carey LA, Ahmed AA *et al*. Molecular classification and molecular forecasting of breast cancer: ready for clinical application? *J. Clin. Oncol*. 2005; **23**: 7350–60.
2 Ludwig JA, Weinstein JN. Biomarkers in cancer staging, prognosis and treatment selection. *Nat. Rev. Cancer* 2005; **5**: 845–56.
3 Lost in validation (Editorial). *Nat. Biotechnol*. 2006; **24**: 869.
4 Lievre A, Bachet JB, Boige V *et al*. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J. Clin. Oncol*. 2008; **26**: 374–9.
5 Garcea G, Neal CP, Pattenden CJ *et al*. Molecular prognostic markers in pancreatic cancer: a systematic review. *Eur. J. Cancer* 2005; **41**: 2213–36.
6 Michalski CW, Weitz J, Buchler MW. Surgery insight: surgical management of pancreatic cancer. *Nat. Clin. Pract. Oncol*. 2007; **4**: 526–35.
7 Chang DK, Merrett ND, Biankin AV. Improving outcomes for operable pancreatic cancer: is access to safer surgery the problem? *J. Gastroenterol. Hepatol*. 2008; **23**: 1036–45.
8 Nitecki SS, Sarr MG, Colby TV *et al*. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? *Ann. Surg*. 1995; **221**: 59–66.
9 Sperti C, Pasquali C, Piccoli A *et al*. Survival after resection for ductal adenocarcinoma of the pancreas. *Br. J. Surg*. 1996; **83**: 625–31.
10 Millikan KW, Deziel DJ, Silverstein JC *et al*. Prognostic factors associated with resectable adenocarcinoma of the head of the pancreas. *Am. Surg*. 1999; **65**: 618–23; Discussion 623–4.
11 Benassai G, Mastrorilli M, Quarto G *et al*. Factors influencing survival after resection for ductal adenocarcinoma of the head of the pancreas. *J. Surg. Oncol*. 2000; **73**: 212–8.
12 Sohn TA, Yeo CJ, Cameron JL *et al*. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J. Gastrointest. Surg*. 2000; **4**: 567–79.
13 Neoptolemos JP, Dunn JA, Stocken DD *et al*. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet* 2001; **358**: 1576–85.

14 Brennan MF, Kattan MW, Klimstra D *et al*. Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas. *Ann. Surg*. 2004; **240**: 293–8.
15 Raut CP, Tseng JF, Sun CC *et al*. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Ann. Surg*. 2007; **246**: 52–60.
16 Barugola G, Falconi M, Bettini R *et al*. The determinant factors of recurrence following resection for ductal pancreatic cancer. *JOP* 2007; **8**: 132–40.
17 Goggins M. Identifying molecular markers for the early detection of pancreatic neoplasia. *Semin. Oncol*. 2007; **34**: 303–10.
18 Hruban RH, Takaori K, Klimstra DS *et al*. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am. J. Surg. Pathol*. 2004; **28**: 977–87.
19 Ferrone CR, Finkelstein DM, Thayer SP *et al*. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. *J. Clin. Oncol*. 2006; **24**: 2897–902.
20 Jamieson NB, Glen P, McMillan DC *et al*. Systemic inflammatory response predicts outcome in patients undergoing resection for ductal adenocarcinoma head of pancreas. *Br. J. Cancer* 2005; **92**: 21–3.
21 Biankin AV, Morey AL, Lee C-S *et al*. *DPC4*/Smad4 expression and outcome in pancreatic ductal adenocarcinoma. *J. Clin. Oncol*. 2002; **20**: 4531–42.
22 Murphy NM, Scarlett CJ, Kench JG *et al*. LMO4 expression and outcome in pancreatic ductal adenocarcinoma. *Br. J. Cancer* 2008; **98**: 537–41.
23 Segara D, Biankin AV, Kench JG *et al*. Expression of HOXB2, a retinoic acid signaling target in pancreatic cancer and pancreatic intraepithelial neoplasia. *Clin Cancer Res* 2005; **11**: 3587–96.
24 Skalicky DA, Kench JG, Segara D *et al*. Cyclin E expression and outcome in pancreatic ductal adenocarcinoma. *Cancer Epidemiol. Biomarkers Prev*. 2006; **15**: 1941–7.
25 Denlinger CS, Cohen SJ. Progress in the development of prognostic and predictive markers for gastrointestinal malignancies. *Curr. Treat. Options Oncol*. 2007; **8**: 339–51.

Newly acquired hepatitis C—many hurdles from diagnosis until treatment initiation

Johannes Wiegand

University of Leipzig—Medical Clinic and Policlinic II, Leipzig, Germany

See article in *J. Gastroenterol. Hepatol.* 2008; 23: 1891–1894

Hepatitis C virus (HCV) infection is a global health care burden which can lead to liver cirrhosis and hepatocellular carcinoma. Many Western countries have established surveillance systems to acquire comprehensive data on epidemiological trends of the disease, to define certain risk groups and to calculate the number of individuals who are potential candidates for antiviral therapy.[1–3] However, serosurveys detecting anti-HCV antibodies by enzyme immunoassays (EIA) and confirmatory recombinant immunoblot assays (RIBA) are unable to differentiate between acute, recent, chronic or resolved HCV infection. Identification of patients with acute or newly acquired hepatitis C is important, because it allows calculation of the incidence of the infection, may identify infectious clusters and offers important insights into relevant modes of transmission. Moreover, in contrast to chronic hepatitis C, treatment in the acute phase of the disease offers high sustained virological response (SVR) rates and prevents chronicity, with its potential deleterious consequences, in 71%–98% of cases.[4]

The Australian Trial in Acute Hepatitis C (ATAHC) is investigating the natural course and treatment efficacy in predominantly injecting drug use (IDU)-acquired early diagnosed hepatitis C.[5] In the HCV surveillance article of this issue of the Journal, Walsh *et al*. describe the enhanced surveillance system of the Australian Department of Human Services to identify patients with newly acquired HCV infection and the efforts to recruit eligible individuals in the ongoing ATAHC trial.[6]

Unfortunately, several clinical, viral, social and legal characteristics prevent easy detection of patients with acute HCV infection:

Clinically, many patients develop unspecific symptoms, such as 'flu-like' discomfort, myalgia and nausea. Acute jaundice leading to further investigation is present in 20–30% of cases only.[7] Virologically, acute HCV infection presents with a 'window-period' for up to 12 weeks, in which only HCV-RNA, but not anti-HCV can be detected in serum. Thus, asymptomatic disease and anti-HCV antibody based screening approaches lead to underreporting.

Socially, modes of infection have substantially changed since the identification of the hepatitis C virus. Transmission via infected blood products is effectively prevented in Western countries, especially in countries where routine testing with nucleic acid techniques (NAT) has been initiated. Instead, IDU has become the most important risk factor. Recent data describe incidence rates per 100 person years of 0.0028 for blood donors, 15.4–33.1 for US-[8] and 12.9 for British intravenous drug addicts.[9] However, cohort-studies with serial samples in high risk individuals can be limited by patient compliance and the length of time required for follow-up.

Legally, serological surveillance results are often only linked to basic personal details, such as sex and age, without reporting additional laboratory test results, clinical information and exposure history which could help to distinguish between acute and chronic HCV infections.[2] Further, even if these important details can theoretically be provided, only 40% of case reports are completely documented.[1]

How can these various hurdles be overcome?

Asymptomatic acute HCV infection can only be detected by surveillance programs with periodic HCV-RNA analysis by polymerase chain reaction (PCR), especially in defined risk populations. Medical personnel are at risk after invasive injuries, although the HCV seroconversion rate after needle stick exposure

Accepted for publication 16 September 2008.

Correspondence
Dr Johannes Wiegand, University of Leipzig—Medical Clinic and Policlinic II, Philipp-Rosenthal-Str. 27 Leipzig 04103, Germany. Email: johannes.wiegand@medizin.uni-leipzig.de

