Changing the Way We Do Business: Recommendations to Accelerate Biomarker Development in Pancreatic Cancer

Margaret A. Tempero1, David Klimstra2, Jordan Berlin4, Tony Hollingsworth7, Paula Kim5, Nipun Merchant6, Malcolm Moore8, Doug Pleskow9, Andrea Wang-Gillam10, and Andrew M. Lowy2

Abstract

Pancreatic ductal adenocarcinoma is the most aggressive of all epithelial malignancies. In contrast to the favorable trends seen in most other common malignancies, the five-year survival of patients with this disease remains only 6%, a statistic that has changed minimally for decades. Only two drugs have been approved by the U.S. Food and Drug Administration (FDA) for use in pancreatic cancer in the last 15 years, and there are no established strategies for early detection. Clin Cancer Res; 19(3); 538–40. ©2012 AACR.

At a recent meeting sponsored by the National Cancer Institute (NCI) on pancreatic cancer treatment, investigators concluded that one major barrier has been lack of access to clinically annotated biospecimens, which can be used to define useful biomarkers (1). Most patients present with locally advanced or metastatic disease, and diagnosis is made by a fine-needle aspirate, often yielding only scant epithelial tissue. While 10% to 20% of patients will undergo resection, a minority of cases are conducted in a setting where tissue is routinely banked for research purposes. Even then, special handling is required to prevent autolysis that can result from pancreatic enzymes in the resection specimen. Further complicating research efforts is the fact that pancreatic cancer is characterized by a profound desmoplastic reaction with a scant epithelial compartment frequently insufficient for some analyses, such as deep gene sequencing. Institutions with specialized banking programs often also have a robust research in pancreatic cancer and may be reluctant to share specimens with outside investigators. Finally, restricting correlative studies to resection specimens focuses molecular correlative studies on a subset of the patient population that may have biologically different pancreatic carcinomas from the group who present with metastases and cannot undergo resection (2).

Many large clinical trials in pancreatic cancer in the United States are conducted within the NCI cooperative group system. These groups are strategically positioned to serve as an important infrastructure for the collection of clinically annotated biospecimens. For this reason, the Intergroup Pancreatic Cancer Task Force appointed a Tissue Acquisition Working Group to make strategic recommendations to address this problem. The Working Group acknowledged that existing efforts to obtain material for correlative studies has been marginally successful. Indeed, this was exemplified by the experience of investigators conducting RTOG 9704: phase III randomized study of adjuvant fluorouracil-based chemoradiotherapy preceded and followed by fluorouracil versus gemcitabine in patients with resected adenocarcinoma of the pancreas (3). In this trial, a concerted effort was made to obtain archival blocks from resection specimens. Ultimately, only 225 samples (from 451 patients) were available for construction of a tissue microarray to be used for subsequent correlative studies. It is important to note that in the current conduct of adjuvant trials, candidates for study are not identified until after surgery, and thus only archival material is usually available.

To better understand the challenges associated in obtaining archival material acquisition, the Tissue Acquisition Working Group conducted a survey of gastrointestinal pathologists at both academic and community-based institutions in the United States and abroad. The survey was sent to 130 institutions and we received 45 responses (28 academic, 11 private, and 6 international sites). The survey is summarized in Table 1. Of the 28 academic institutions, only 2 would release blocks without conditions and 22 would release blocks with specific restrictions, such as requirement of an Institutional Review Board (IRB)-approved protocol (13) and/or inclusion of a pathology department member on the protocol (5). Seven required the block to be returned by a specified date. Twelve institutions would release a block only when more than 1 block exists, and 11 require demonstration that unstained sections would not suffice to conduct the specific studies being...
proposed. The reluctance of departments to release blocks was primarily related to the need to maintain custody of the block. Only 18 departments (5 with special conditions) were willing to allow cores to be punched for tissue microarrays. On the positive side, all institutions were willing to prospectively collect an extra block of tissue, if protocol specified, but this option would only exist for patients undergoing resection of a sizeable primary tumor or multiple biopsies of metastatic/unresectable disease. Seventeen of 28 institutions required additional funding to do this. Similar responses were obtained from both private and international sites.

The prospective collection of tissue for research purposes in patients with pancreatic cancer is difficult for many reasons. In addition to the safety concerns of additional invasive procedures, there are many operational hurdles, such as the lack of acceptance by patients for any delay in therapy, rapid clinical deterioration because of delay in therapy, and the cost of additional procedures outside of usual patient care.

A further complication is the current status of biorepositories within the existing cooperative groups. All cooperative groups currently maintain their own tissue banks, and standard operating procedures for procuring and processing specimens, or for quality control, have not been completely standardized across the groups. A recent revision of the NCI biospecimen repository guidelines (4) may be useful if widely used, but the provisions are daunting for many small tissue procurement efforts. Furthermore, support for and management of the banks is variable and the process of accessing specimens for research is cumbersome for investigators. No mechanisms exist to prevent duplication of effort or to establish research priorities for use of tissue across the groups.

The Working Group agreed that robust biorepositories are critical to the discovery of predictive and prognostic biomarkers that can guide the care of patients with pancreatic cancer. Thus, the development of such biorepositories should be of high priority in all cooperative group studies. To do this, appropriate specimens [including but not limited to prospectively collected specimens such as blood and serum as well as an additional formalin-fixed paraffin-embedded (FFPE) blocks from resected specimens, archived specimens such as cytology slides, cell blocks, and core biopsies] should be collected whenever possible. Obviously, the process of distribution of biospecimens and any associated clinical or molecular annotation should be prioritized according to the quality and impact of the scientific question, and should be equitable, transparent, and efficient.

The following recommendations were endorsed by the working group:

1. Change workflow. The cooperative groups should require central submission of a mandatory research block or material derived from a block (when sufficient material is surgically procured) for all adjuvant trials. Implementing this will require a new approach to patient enrollment for adjuvant trials. Patients will need to be identified and consented during the preoperative setting, allowing for the prospective procurement of a research block of the resected specimen. In addition to increasing the opportunity for tissue acquisition, this recommendation will ensure that the “eligible universe” of patients is studied. Currently, adjuvant trials focus on the “athletes” who survive surgery, recover in a timely fashion, and do not have rapid recurrence of disease. Encompassing the “real world” of patients with pancreatic ductal adenocarcinoma will allow for unbiased interpretation of molecular data.

2. Incorporate biomarker development in randomized phase III trials. Prospective collection of blood, serum, and plasma should be mandatory in all phase III trials. These samples can be interrogated for candidate pharmacogenetics biomarkers or for shed biomarkers in serum and/or plasma. In the event that candidate markers are not prospectively identified, samples can at least be banked until sufficient markers are proposed. Recognizing the limitations and barriers in collecting archival material, there may be circumstances in which candidate biomarkers can be assessed in multiple tissue sources: primary resection specimens, core or excisional biopsies, and fine-needle aspirates. In these cases, there should be a mandatory requirement to collect archival material (providing there is sufficient sample to share for research purposes) as a routine procedure in the conduct of phase III trials.

3. Leverage resources and harmonize. Centralization of the banks could provide some shared economy and would more easily permit implementation of standardized operating procedures across groups. Existing tools such as digitized imaging and tissue-tracking systems can be readily deployed across the groups to assist the research community. Similarly, all studies conducted using banked tissue can be entered into a common and publicly accessible database such as the University of California at Santa Cruz (UCSC; Santa Cruz, CA) Genome Browser (5).

4. Invest in technology. The NCI should prioritize investigation and collaborations aimed at technologic improvements, which allow for the expanded use of archived fine-needle aspirates specimens (the most common diagnostic specimen) and prospectively collected circulating tumor cells (CTC). In addition, studies that focus on germline DNA in blood or serum-based biomarkers may be particularly useful. Such studies can be supported via cooperative group mechanisms and/or via other grant mechanisms.
In summary, it is clear that a remedy for this complicated situation will require some investment and change in policy. However, the U.S. cooperative group infrastructure is well situated to serve as a "framework for change." A commitment to develop an improved national process for collecting and sharing pancreatic cancer tissues will bring a welcome transformation to our national research agenda in this disease. Accelerating research in the most common causes of cancer-related death have resulted in a declining incidence and/or declining mortality rate for lung, breast, prostate, and colorectal cancers. With concerted effort, this can surely be achieved in pancreatic cancer as well.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors' Contributions
Conception and design: M.A. Tempero, D. Klimstra, J. Berlin, N. Merchant, M. Moore, D. Pleskow, A.M. Lowy
Development of methodology: D. Klimstra, N. Merchant, M. Moore
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Klimstra, M. Moore
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.A. Tempero, D. Klimstra, N. Merchant, M. Moore
Writing, review, and/or revision of the manuscript: M.A. Tempero, D. Klimstra, J. Berlin, T. Hollingsworth, P. Kim, N. Merchant, M. Moore, D. Pleskow, A. Wang-Gillam, A.M. Lowy
Study supervision: M.A. Tempero, J. Berlin, A.M. Lowy

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References

Table 1. Survey results

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<th>Policies on release and use of blocks</th>
<th>Academic</th>
<th>Community</th>
<th>International</th>
</tr>
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<tr>
<td>Blocks always released</td>
<td>2 (7%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Blocks never released</td>
<td>4 (14%)</td>
<td>0</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Only if another exists</td>
<td>12 (43%)</td>
<td>3 (27%)</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Only if unstained slides will not suffice</td>
<td>11 (39%)</td>
<td>4 (36%)</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Punch for core allowed</td>
<td>18 (64%)</td>
<td>6 (55%)</td>
<td>5 (83%)</td>
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<th>Reasons for reluctance to release blocks</th>
<th>Academic</th>
<th>Community</th>
<th>International</th>
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<tbody>
<tr>
<td>Requirements to maintain custody</td>
<td>15 (54%)</td>
<td>3 (27%)</td>
<td>2 (33%)</td>
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<tr>
<td>Cost of retrieval</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Both of above</td>
<td>8 (29%)</td>
<td>4 (36%)</td>
<td>2 (33%)</td>
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</table>

<table>
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<tr>
<th>Willingness to procure &quot;extra blocks&quot; for research</th>
<th>Academic</th>
<th>Community</th>
<th>International</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes without restrictions</td>
<td>8 (29%)</td>
<td>4 (36%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Only if funds available</td>
<td>17 (61%)</td>
<td>3 (27%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>No or possibly</td>
<td>5 (18%)</td>
<td>4 (36%)</td>
<td>3 (50%)</td>
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</table>
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