Pancreatic ductal adenocarcinoma (PDA) has recently become the fourth leading cause of cancer-related death in the United States, with an annual incidence and mortality approaching 40,000 cases. Invariably diagnosed at late stages when curative resection is not possible and resistant to all tested chemical and radiation therapies, PDA has the worst prognosis among major epithelial malignancies, with an overall 5-year survival of less than 3%. Infusional gemcitabine, a deoxycytidine analog and the current standard of care for advanced disease improves survival modestly at best and provides palliation for a minority of patients. The need for new therapies is undisputed. This article describes new therapeutic strategies currently under investigation and discusses possible reasons that others have failed. New potential targets in the treatment of this formidable disease are suggested based on recent findings. (JNCCN 2007;5:1042–1053)

Thus, the disease has thwarted the best attempts at containment and eradication, and new strategies are clearly needed. This article discusses some of the more promising possibilities. This discussion is intended to be illustrative rather than exhaustive, and presents an overview of the current investigational landscape (Figure 1; Table 1).

**Cell Autonomous Targets**

Concerted efforts over the past 2 decades have elucidated the genetic alterations in human PDA. Mutations in the KRAS protooncogene occur early in disease progression and are found in nearly 95% of invasive PDA. Cardinal tumor suppressor pathways have also been implicated in PDA progression. The CDKN2A/INK4A locus is frequently methylated or deleted in PDA. Inactivation of TP53 and SMAD4/DPC4 tends to occur late in disease progression and is ultimately found in approximately 75% and 50% of invasive PDAs, respectively. These genetic events provide a starting point for understanding mechanisms of pathogenesis and suggest potential pathways and targets for therapy.

**KRAS**

The oncogenic potential of KRAS is activated by single point mutations at codons 12, 13, 59, 61, or 63. Mutations in KRAS are found in greater than 90% of PDAs, with most occurring in codon 12. Oncogenic KRAS mutations result in constitutive activation of downstream signaling cascades, thereby conferring a growth advantage. Targeting endogenous expression to the murine pancreas initiates precursor ductal lesions, termed pancreatic intraepithelial neoplasias (PanINs), recapitulating morphologic and molecular aspects of the human disease. As the mice age, these lesions spontaneously progress to invasive and metastatic PDA, with near-complete penetrance (unpublished observations). Activation of oncogenic KRAS seems to represent the rate-limiting
step for the development of PanIN and PDA. The observed progression of murine preinvasive lesions has helped validate the PanIN progression model suggested for human pancreatic cancer.

Although these studies establish that oncogenic KRAS expressed in tissue progenitor cells can initiate PDA, whether mutant Ras is required for maintaining the transformed state in vivo remains to be established. Nevertheless, activated KRAS represents the most attractive target for definitive therapy. Among the many challenges in targeting Ras is to selectively inhibit the mutant and not the wild-type form, which is necessary for normal cell survival. Several strategies designed to target Ras or its effectors have been recently reviewed. Ras functions as a molecular switch, active in its guanosine triphosphate (GTP)-bound state and inactive when bound to guanosine diphosphate. Perhaps the most concerted effort exploring the potential efficacy of Ras inhibition has involved perturbing the posttranslational modifications necessary to target this small GTP-binding protein to the plasma membrane, its presumptive site of activity.

Farnesylation of KRAS by farnesyl transferase is required to direct the protein to the cell membrane. Inhibition of KRAS by farnesyl transferase inhibitors (FTIs) has been readily achieved in vitro and in vivo.

Figure 1 The complex interplay between epithelial and stromal elements in pancreatic ductal adenocarcinoma provides a number of potential cell-autonomous and non-cell-autonomous targets for therapy, including growth factors, cell surface receptors, intracellular effectors, cytokines, and immune cells.

Abbreviations: COX-2, cyclooxygenase-2; EGFR, epidermal growth factor receptor; IGFR, insulin-like growth factor receptor; IL, interleukin; MDSC, myeloid-derived suppressor cell; MMPs, matrix metalloproteinases; PaSCs, pancreatic stellate cells; Shh, Sonic Hedgehog; TAM, tumor-associated macrophage; TGF, transforming growth factor; VEGFR, vascular endothelial growth factor receptor.
in defined contexts. However, in the clinical setting, FTIs have been disappointingly ineffective when administered either as monotherapy or in combination with gemcitabine. None of these compounds specifically inhibits mutant KRAS.

The failure of FTIs in the treatment of pancreatic cancers can be ascribed to several factors. First, in the presence of FTIs, KRAS can undergo alternative iso-prenylation by geranylgeranyltransferase I, bypassing the requirement for farnesylation. Second, multiple downstream effector pathways may need to be targeted simultaneously to inhibit or reverse Ras-induced transformation. Despite an extraordinary amount of research into the mechanisms and effects of Ras signaling over the past 25 years, new findings continue to challenge some of the most basic principles of Ras activity. For example, Mor and Philips showed that oncogenic Ras can engage downstream effectors from endomembrane compartments, raising the intriguing possibility that mutant Ras signaling may support different biologic activities from distinct cellular and subcellular localizations. Thus, although no clinical trial has shown significant antitumor activity using agents that target KRAS or its downstream effectors, one can argue that the therapeutic potential of targeting oncogenic KRAS has not yet been convincingly tested. The authors believe that it remains the most attractive, albeit frustratingly elusive, target.

**Tumor Suppressor Genes**

In principle, tumor suppressor gene mutations also represent potential avenues for intervention. In practice, however, the approach generally requires reconstitution of a lost function, which is a decidedly more difficult proposition than inhibiting a newly acquired one. The major hurdles of gene therapy remain to be surmounted, including effective delivery of the agent to tissues or cells of interest, maintained expression of the therapeutic gene, and ensuring adequate safety of the delivery mechanisms. Thus, although some preliminary work involving TP53 and CDKN2A/INK4A, for example, suggest promise, until the aforementioned obstacles are surmounted, this approach remains speculative.

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**Table 1 Clinical Trials With Targeted Agents for Invasive Pancreatic Ductal Carcinoma**

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Category</th>
<th>Preclinical Data</th>
<th>Clinical Data</th>
<th>Phase of Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>Bevacizumab</td>
<td>Monoclonal antibody against VEGF</td>
<td>Decreased metastatic burden and increased survival in xenograft models</td>
<td>No survival benefit in combination with gemcitabine</td>
<td>Phase II and III</td>
</tr>
<tr>
<td>COX-2</td>
<td>Rofecoxib</td>
<td>Inhibitor of COX-2</td>
<td>Inhibited xenograft growth</td>
<td>No significant therapeutic benefit in combination with gemcitabine</td>
<td>Phase II</td>
</tr>
<tr>
<td>EGFR</td>
<td>Cetuximab</td>
<td>Monoclonal antibody against EGFR</td>
<td>Inhibited xenograft growth</td>
<td>Improved 1-year survival in combination with gemcitabine (32%) vs. gemcitabine alone (12%)</td>
<td>Phase II</td>
</tr>
<tr>
<td>EGFR</td>
<td>Erlotinib</td>
<td>Small molecule inhibitor of EGFR tyrosine kinase</td>
<td>Marginal improved median and 1-year survival in combination vs. gemcitabine alone</td>
<td></td>
<td>Phase III</td>
</tr>
<tr>
<td>HER-2/Neu</td>
<td>Trastuzumab</td>
<td>Humanized anti-Her-2 antibody</td>
<td>Inhibited xenograft growth</td>
<td>Similar to gemcitabine alone</td>
<td>Phase I</td>
</tr>
<tr>
<td>Kras</td>
<td>Tipifarnib</td>
<td>FTIs</td>
<td>Inhibited xenograft growth</td>
<td>No benefit in combination with gemcitabine</td>
<td>Phase II and III</td>
</tr>
</tbody>
</table>

Abbreviations: COX-2, cyclooxygenase-2; EGFR, epidermal growth factor; FTIs, farnesyltransferase inhibitors; VEGF, vascular endothelial growth factor.
Epidermal Growth Factor Superfamily

The mammalian family of epidermal growth factors, (EGFs) small polypeptides that regulate cell proliferation and differentiation, includes EGF, transforming growth factor α (TGF-α), heparin-binding EGF-like growth factor (HB-EGF), amphiregulin, epieregulin, and neuregulins. These ligands activate 4 closely related receptor tyrosine kinases: EGFR (ErbB1, HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). Ligand binding to the receptor activates the intracellular tyrosine kinase activity and a subsequent array of downstream signaling pathways. The main signaling routes include the Ras-Raf-mitogen activated protein kinase pathway, phosphatidylinositol 3-kinase/Akt pathway, and Vav1. Each of these proteins may represent an important therapeutic target. Several mechanisms can lead to aberrant activation of EGFR, including receptor or ligand overexpression, mutation, and other methods of ligand-independent activation. EGFR is overexpressed in human pancreatic cancer and has been linked to a more aggressive phenotype and poor prognosis.

Two broad classes of therapeutic approaches targeting EGF and its receptor have been attempted in the treatment of pancreatic cancer: 1) monoclonal antibodies that block ligand binding, and 2) small molecule inhibitors of the receptor tyrosine kinase activity. Cetuximab (Erbitux), a chimeric mouse monoclonal antibody targeting EGFR, binds competitively and prevents stimulation of the receptor by endogenous ligands, resulting in inhibition of cell proliferation and enhanced apoptosis in vitro and reduced angiogenesis and tumor invasiveness in xenograft studies. The combination of cetuximab and gemcitabine caused regression of human pancreatic carcinoma cells grown orthotopically in nude mice. Cetuximab and gemcitabine also showed promising results in a phase II trial of advanced pancreatic cancer and immunohistochemically showed expression of EGFR. The results of a recent phase III trial evaluating this combination in the setting of advanced disease were therefore particularly disappointing, as they failed to show any significant benefit.

An alternative strategy has used small molecule inhibition of EGFR. Gefitinib (Iressa) and Erlotinib (Tarceva, OSI-774) are tyrosine kinase inhibitors that compete with adenosine triphosphate for binding to the kinase domain and have generated considerable excitement over their activity in a subset of patients with lung cancer, particularly those with specific point mutations in EGFR. Tarceva was recently approved by the U.S. Food and Drug Administration (FDA) in combination with gemcitabine for treating advanced pancreatic cancer based on a phase III trial showing modest improvement in median (6.4 vs. 5.9 months) and 1-year survival (24% vs. 17%). Interestingly, however, erlotinib combined with gemcitabine failed to significantly improve quality of life parameters compared with gemcitabine and placebo. Although the reasons for the different results using cetuximab and erlotinib to target EGFR signaling are not immediately apparent, they may suggest potential additional effects of erlotinib on other targets. Notably, although several components of the EGF signaling pathway are overexpressed in PDA, point mutations have not been described. Thus, the modest efficacy in PDA is perhaps not surprising. Moreover, a detailed characterization of EGF expression in a highly faithful murine model of the disease showed patchy expression in primary PDA and essentially no detectable expression in metastases, consistent with the observed minimal impact of receptor kinase inhibition in the clinical trials.

Other members of the EGFR or ErbB family of receptors have also been targeted in pancreatic cancer. Herceptin, a humanized anti-HER2 antibody, similarly reduced tumor growth in nude mice but showed no significant benefit in patients with advanced pancreatic cancer. Several potential explanations and perhaps lessons emerge from these studies. First, overexpression alone may not be the most reliable predictor of the value of target inhibition. Second, targeting multiple pathways simultaneously may be required for significant therapeutic benefit. For example, lapatinib, a dual ErbB1/ErbB2 kinase inhibitor, has recently shown significant activity in combination with capecitabine, an oral fluorouracil, in heavily pretreated metastatic breast cancer. Testing this agent in PDA would also be of interest. Finally, these studies underscore the fundamental discordance between results from current preclinical models and trials in patients (see later discussion).

Targeting Developmental Pathways

Specific signaling pathways are required for normal specification of cell fate in both the endocrine and exocrine lineages of the pancreas. Although these signaling pathways are mostly repressed in the adult pancreas, several recent studies have shown aberrant reexpression in preinvasive and invasive disease. For
example, analyses of human and murine pancreatic sections showed increased levels of Sonic Hedgehog (Shh) in PanIN lesions and invasive adenocarcinoma. Efforts to target showed that RON promoter induced PanIN-like complex ductal structures, which developed spontaneous mutations in KRAS, and inhibition of Hh ligand activity with cyclopamine reduced the growth of pancreatic cancer xenografts. Notch, another developmental signaling pathway normally quiescent in the mature pancreas, is also aberrantly activated in both human and murine PDA. Thus, the recapitulation of ontogeny by oncogeny provides several potential pathways that can be exploited therapeutically, provided they do not also prove to be essential for maintaining the viability of tissue progenitor cells and repair of tissue injury.

Other Notable Possibilities
The RON receptor tyrosine kinase interacts with hepatocyte growth factor (HGF)–like protein and stimulates cell growth. Transgenic mouse models overexpressing RON in the lung or mammary gland develop adenocarcinomas and metastases, respectively. Recently, Thomas et al. showed that RON protein is highly expressed in late-stage PanINs, primary tumors, and metastases in both the human and murine disease. Mutations in RON have not yet been described, however. Nevertheless, inhibition of RON sensitized pancreas tumor cells to gemcitabine-induced apoptosis, suggesting that RON may represent a potential therapeutic target in pancreas cancer. Additional potential targets known to be overexpressed in pancreatic cancer and believed to contribute to its malignant phenotype include mesothelin and insulin-like growth factor receptor (IGFR). Efforts to target each of these proteins is currently in various stages of testing, using for example, MORAb-009, a monoclonal antibody directed against a cell surface epitope of mesothelin, and IMC-A12, a monoclonal inhibitor of IGFR. The role of mesothelin in the development of a tumor vaccine is also being explored.

MicroRNA
MicroRNAs (miRNAs) are small noncoding RNA transcripts that negatively regulate gene expression. Changes in expression of certain miRNAs in disease-specific patterns suggest the currently hypothetical possibility of potential oncogenic or tumor suppressor functions in disease pathogenesis. Changes in miRNA levels have been described in many human tumors. Recent studies identified a miRNA signature that differentiates PDA from normal pancreas and chronic pancreatitis. This signature includes miRNAs previously reported as deregulated in other human cancers (miR-155, -21, -222, and -221) and those not previously reported in cancer (miR-376a and miR-301). miRNAs encoded by the let-7 family down-regulate Ras expression in human cells, suggesting that targeting KRAS by overexpressing let-7 family members could be used to treat pancreatic cancer. Of course, this option is limited by the same obstacles to effective gene delivery noted earlier. No effective nucleic acid delivery system specific for pancreas tissue has yet been developed.

Non–Cell-Autonomous Targets
PDAs are characterized by the elaboration of an intense desmoplastic reaction, a remarkable infiltration of fibroblasts, inflammatory cells, and endothelial cells, all within an altered extracellular matrix. The tumor microenvironment provides a rich and complex stew of soluble and insoluble factors that promote the growth, progression, invasion, and metastasis of tumor cells. Intriguingly, the proportion of malignant epithelial cells in some invasive PDAs represents less than 10% of the bulk tumor mass. Nevertheless, the desmoplastic reaction in PDA has received comparatively little attention. Several factors involved in the dynamic interplay between tumor and stromal cells represent potential targets for cancer therapy, several of which are discussed later. Perhaps worth remembering, however, is that although specific targeting of stromal elements may affect primary tumors still dependent on these elements for continued survival, metastatic cells may have decreased, or circumvented altogether, these dependencies.

Angiogenesis
Angiogenesis seems to be an essential process for tumor growth and metastasis. The notion of an angiogenic switch has been illuminated in an elegant series of studies. The theory expounds that for a tumor to grow beyond a limited size and thereby threaten the host, an additional dedicated vascular network must be elaborated. Thus, inhibition of angiogenesis represents an attractive concept for tumor therapy, and several antiangiogenic agents are being explored for treating PDA.
Vascular endothelial growth factor (VEGF) is a homodimeric heparin-binding glycoprotein that binds to a family of kinase receptors, including VEGF receptor-1 (VEGFR-1) and VEGFR-2. VEGF potently induces angiogenesis, and increased VEGF expression correlates with progression of PDA, enhanced metastatic spread, and poor outcome. Bevacizumab, a recombinant humanized monoclonal antibody to VEGF, has significantly improved survival of patients with metastatic colorectal cancer. The combination of gemcitabine and bevacizumab decreased metastatic burden and improved survival of nude mice with pancreatic tumor xenografts and has shown promise in a phase II trials. However, in a phase III trial conducted by the Cancer and Leukemia Group B in which 602 patients with advanced pancreatic cancer were randomized to receive gemcitabine with or without bevacizumab, no differences in overall survival were seen between the treatment arms (http://www.calgb.org/index.php?action=fullnews&id=28; accessed October 8, 2007). Thus, despite notably impacting the management of colorectal carcinoma, inhibition of angiogenesis to date has not improved the management of patients with pancreatic cancer.

A detailed description of angiogenic processes in pancreas cancers is currently lacking. The possibility exists that VEGF is not the dominant angiogenic factor in PDA, or that pancreatic cancers are not as dependent on extensive neovascularization. Imaging studies have shown PDAs to be hypovascular, and studies of CD34 expression have revealed heterogeneous microvessel density with both hypo- and hypervascular areas noted within each tumor. Thus, the precise nature of the vascular network and the factors driving its formation remain unclear.

Cyclooxygenase-2
Cyclooxygenase-2 (COX-2) catalyses the synthesis of prostaglandins. Overexpression of COX-2 has been described in human PanINs and invasive carcinoma, and in murine correlates of the disease. COX-2 expression also seems to increase during progression from low- to high-grade PanINs. In orthotopic studies in immunodeficient animals, celecoxib, a selective COX-2 inhibitor, induced cell-cycle arrest genes and reduced tumor growth. In another study using similar strategies, celecoxib inhibited VEGF expression and reduced angiogenesis and metastasis of xenografted human pancreatic cells. Dramatically elevated levels of COX-2 in murine PanIN lesions suggested both the potential and means to test the therapeutic benefit of inhibiting COX-2 activity. The hypothesis was recently examined and a slowing of preinvasive disease progression was seen in these genetically engineered animals when nimesulide was added to their diet. Thus, although clinical trials using COX-2 inhibitors in combination with conventional therapy have shown no significant therapeutic benefit in advanced disease, their greatest efficacy may lie in chemoprevention.

Matrix-Metalloproteinase Inhibitors
Matrix metalloproteinases (MMPs) are proteolytic enzymes that degrade the extracellular matrix, permitting invasion and metastasis of epithelial cells to distant organs. MMPs are up-regulated in human cancers. These properties marked MMPs as prime candidates for preclinical studies. Sadly, results from phase III trials using MMP inhibitors (MMPIs) in patients with advanced pancreatic cancer have been disappointing. The reasons for these failures may be instructive, however. In preclinical studies, MMPIs reduced tumor development and metastasis of human...
colon cancer cell lines implanted in nude mice. Similar observations were seen in a transgenic mouse model of islet carcinogenesis. In both studies, MMPIs were administered beginning at the early stages of disease. In contrast, in the clinical settings, MMPIs were used in patients with advanced disease, an inevitable limitation of the understandable constraints imposed on phase I trials. In addition, it is now appreciated that individual MMPIs are involved in distinct stages of tumor progression and angiogenesis through regulating the activities of several nonmatrix substrates, including growth factors, adhesion molecules, and chemokines. For each of these reasons, MMPIs may be misplaced in regimens to treat advanced tumors. MMPIs should perhaps even be conceptualized as chemopreventive agents in patients at high-risk for pancreatic cancer.

**Matriptase**

Matriptase is a transmembrane serine protease commonly overexpressed in epithelial cancers. Matriptase activates HGF, which regulates the proliferation and migration of epithelial cells. A direct oncogenic role for matriptase in pancreatic cancer is still lacking, although in a recent study in transgenic mice overexpressing matriptase in the epidermis, the spontaneous development of squamous cell carcinoma and potentiation of carcinogen-induced tumor formation was observed. A small molecule inhibitor of matriptase (CVS-3983) has also shown efficacy in prostate cancer xenografts. Given its potential role in tumor initiation, inhibiting matriptase could potentially benefit patients with a genetic predisposition for pancreatic cancer.

**Stellate Cells**

Pancreatic stellate cells (PaSCs) are myofibroblast-like cells residing in the exocrine pancreas. Human PDAs exhibit abundant PaSCs in the stroma, along with increased expression of collagen and α-smooth muscle actin, indicating that the PaSCs are activated. Conditioned media from pancreatic cancer cell lines activate PaSCs in vitro, inducing them to produce extracellular matrix proteins and MMP-2. PaSCs also promote the growth and invasion of xenografts. Several molecules involved in the proliferation and activation of PaSCs, including platelet-derived growth factor, TGF-β, and angiotensin II, lend themselves to inhibitory strategies. A better understanding of the role of PaSCs in the pathogenesis of PDA may help reveal new points of vulnerability in the disease.

**Immune Reaction**

Leukocytic infiltration is observed in all solid cancers, although the precise complement of leukocyte populations and their respective roles have yet to be elucidated for any epithelial malignancy. The composition and kinetics of infiltration by specific leukocyte sub-populations has been elucidated in a genetically engineered murine model of PDA during the entire course of disease progression from the earliest precursors to invasion and metastasis. These analyses have shown that several mechanisms of immune suppression, including tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSC), and regulatory T cells, occur surprisingly early during pancreatic tumorigenesis and even at the preinvasive stage. The role of TAMs in tumor proliferation, survival, invasion, and metastasis has been supported by several studies. Infiltration by TAMs correlates significantly with VEGF expression and microvessel density in ductal carcinoma of the breast and facilitates the growth of renal cell carcinoma. Indeed, TAMs express several proangiogenic factors, including interleukin (IL)-1, VEGF, IL-8, basic fibroblast growth factor, TNF-α, and MMP-9. Areas of hypoxia within tumors seem to attract TAMs, which also cause up-regulation of transcription factors such as hypoxia-inducible factors 1 and 2. In light of these findings, the poor prognosis associated with high numbers of TAMs in several cancers is not surprising. Conversely, antiangiogenic agents, such as linsamide, pentoxifylline, and genistein, reduced TAM numbers, blood vessel density, and epithelial cell growth in a rat prostate cancer model.

Strategies have also been elaborated to take advantage of some of the unique properties of TAMs. Because TAMs infiltrate hypoxic areas of tumors, these cells have been used as vehicles for genes or angiostatic compounds to target tumors. In a recent study, human macrophages were transfected with a hypoxia-regulated cytochrome P450, which converts cyclophosphamide into its active metabolite. Infiltration of breast tumor spheroids by these transduced macrophages enhanced killing of cancer cells in the presence of cyclophosphamide. Studies in true in situ models of epithelial malignancies are required to validate this innovative form of gene delivery strategy.
MDSC also infiltrate murine PanINs early in disease progression. MDSC encompass a heterogeneous population of cells, including macrophages, granulocytes, and myeloid cells of varying but incomplete stages of maturation. In the mouse, these cells express both CD11b and Gr-1 surface markers and seem to play critical roles in tumor progression and tumor escape through suppressing immune function. They have been found in the peripheral blood of patients with advanced solid tumors and MDSC found infiltrating tumors or in draining lymph nodes are capable of suppressing T-cell function and inducing apoptosis of CD8+ T cells. Several strategies have been tested to overcome the immunosuppressive activity of MDSC. In tumor-bearing mice, depletion of MDSC with a monoclonal antibody against Gr-1 enhanced the cytotoxicity of CD8+ T cells and eradicated the tumor. The immunosuppressive properties of MDSC can also be abrogated by inducing them to differentiate into mature antigen-presenting cells.

Finally, another major component of the immunosuppressive network is the CD4+CD25+ T<sub>Reg</sub> cell, attracted to neoplastic lesions and well-known to suppress the functions of cytotoxic T cells. Recruitment of T<sub>Reg</sub> cells is associated with diminished effector T-cell function, increased tumor growth, and a poor outcome in patients with ovarian cancer. In this study, macrophages from the tumor microenvironment were found to produce CCL2, a chemokine that induced T<sub>Reg</sub> migration to the primary tumor site. A fusion protein, denileukin diftitox, has been genetically engineered to couple full-length IL-2, which binds CD25, to the enzymatically active domains of diphtheria toxin. CD25+ cells internalize this fusion complex through endocytosis. The active domain of diphtheria toxin is then cleaved in the endosome and translocated into the cytosol, where it inhibits protein synthesis and induces apoptosis. This drug has been FDA-approved for the treatment of CD4+CD25+ cutaneous T-cell leukemia. Thus, depletion of immunosuppressive cells or inhibition of their trafficking may constitute promising tools to boost antitumor efficacy.

**Immunotherapies**

The long-standing observations of antitumor immune cells surrounding malignant lesions have inspired Herculean efforts to mobilize the immune response to combat cancer. Effective immunotherapy requires the presence of sufficient numbers of lymphocytes with vigorous tumor-antigen recognition that are capable of infiltrating tumors and killing tumor cells. Immunotherapies for cancer have used 2 broad approaches to help achieve these goals: vaccine therapy and adoptive T-cell therapy. Cancer vaccines are used to generate in vivo lymphocytes after immunization. Adoptive T-cell therapy involves ex vivo activation and expansion of autologous lymphocytes, followed by reinfusion into the host, or infusion into a new host (i.e., allogeneic transfusion).

The potential of cancer vaccines was shown in patients with melanoma who received Melacine, a vaccine generated from the subcutaneous nodules of 2 patients. Vaccination induced a specific expansion of CD8+ lymphocytes population and produced a significant survival benefit. Jaffee et al. developed an allogeneic vaccine using pancreatic cancer cell lines genetically modified to produce granulocyte macrophage colony-stimulating factor, a potent cytokine known to induce antitumor immunity. Phase I studies proved the vaccine to be safe and well-tolerated, and long-term survival has been reported for 3 of 14 patients treated to date.

A second modality of immunotherapy involves the priming and ex vivo expansion of autologous lymphocytes with the ability to infiltrate, recognize, and destroy tumor cells. The advantages of this strategy include the possibility to infuse a large number of antitumor-specific cells prepared ex vivo. Rosenberg first described this technique. The authors injected IL-2 with tumor-specific lymphocytes isolated from patients and expanded ex vivo. This strategy showed significant success in the treatment of patients with metastatic melanoma. Future studies should focus on understanding the complex interactions between the immune cells and tumors to better modulate the immune system to fight against cancer.

**Conclusions**

PDA represents among the most daunting of challenges for clinicians, scientists, and patients. Nowhere is the potential promise of molecular medicine more acutely needed or more noticeably absent. How, then, to break the seemingly endless cycles of futility in identifying promising preclinical approaches only to watch them fail dishearteningly in the clinic? A recurring theme in the aforementioned studies is the almost invariant use of in vitro culture and xenograft experiments as the primary means to both identify
potential targets and test or establish their therapeutic efficacy. These systems have not been particularly successful in predicting clinical efficacy in patients. Using model systems that more faithfully reproduce not only the cell autonomous factors but also the rich and complex panoply of non–cell-autonomous factors that engage, suppress, shape, and define an emerging cancer should improve the predictive power of preclinical studies.\textsuperscript{103,125} Identifying targets in rigorously characterized genetically engineered murine models of the disease and then establishing efficacy in these systems may prove more reliable in bringing effective strategies to the clinic.

Faithful animal models also permit investigations and interventions at defined stages of tumor progression from preinvasive to invasive to metastatic disease. One can also determine whether the presumptive target was inhibited, explore the possibility that primary and metastatic lesions may have different therapeutic vulnerabilities and therefore require distinct treatment strategies, and answer many similar questions that are difficult, if not impossible, to address in patients. What is required is a reassessment of the preclinical paradigm used to develop and substantiate detection and treatment methodologies. Through raising the bar for preclinical data to require demonstrated efficacy in rigorously defined animal models, the use of the patient can potentially be mitigated as the first true in vivo test of a drug, and precious time, resources, and patient-years can be saved by preventing approaches destined to fail from getting to the clinic. Minimizing the failures should also afford a greater opportunity to nourish success. The combination of an increasingly sophisticated armamentarium in genomics, proteomics, and bioinformatics coupled with a new generation of animal models inspires tenable hope of finally tilting the balance in this war on pancreas cancer in our favor. It is time to bring the promise and power of these technologies to bear on this formidable disease.

References

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