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*TOPIC HIGHLIGHT*

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# Novel strategies for managing pancreatic cancer

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## Abstract

With the incidence reports of pancreatic cancer increasing every year, research over the last several decades has been focused on the means to achieve early diagnosis in patients that are at a high risk of developing the malignancy. This review covers current strategies for managing pancreatic cancer and further discusses efforts in understanding the role of early onset symptoms leading to tumor progression. Recent investigations in this discussion include type 3c diabetes, selected biomarkers and pathways related to pancreatic intraepithelial neoplasia lesions, drug resistance, and advances in nanomedicine which may provide significant solutions for improving early detection and treatments in future medicine.

**Core tip:** Pancreatic cancer is currently one of the most aggressive cancers without standard treatment for improving chances of long-term survival. This paper highlights significant research in translational nanomedicine and the challenges in treating pancreatic cancer.

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## INTRODUCTION

Pancreatic cancer is responsible for over 40000 deaths every year in the United States, representing about 3% of the newly diagnosed cancer cases. However, pancreatic cancer is the fourth most common cause of cancer related death in the United States, predominantly affecting patients ages 60-80 years[1-4]. Pancreatic ductal adenocarcinoma (PDAC) constitutes up to 95% of pancreatic malignancies[4]. Due to poor prognosis and delayed treatment, survival rate during the first year of diagnosis is as low as 20% and decreases to 6% by the fifth year[2]. Reasons for this poor prognosis are related in part to the chemoresistance of PDAC and inability of chemothera-

peutic agents to penetrate the dense fibrotic microenvironment associated with this malignancy. Early detection may improve the outcome and is occasionally possible when small tumors in the head of the pancreas cause obstructive jaundice. However, only 10%-15% of patients are diagnosed in the early stages when surgical resection can be offered[5,6]. Over 90% of subjects are diagnosed with PDAC in the advanced stages[4].

In the past decade, many efforts have been made in translational cancer research, particularly nanomedical avenues, to create novel approaches to drug delivery and understand the early developmental stages of pancreatic cancer. Such advances suggest that stem cell signaling pathways can be used as targets for drug delivery. To date methods of prevention, standard diagnosis, and treatment for pancreatic cancer remain ineffective in improving the survival rate of diagnosed patients. This review covers recent investigations on type 3c diabetes, selected genetic markers, and advances in nanomedicine for early diagnosis of pancreatic cancer.

## HISTOPATHOLOGY OF PANCREATIC CANCER

Tumors are classified as invasive ductal carcinoma, intraductal papillary mucinous neoplasm, neuroendrocrine tumors, or islet cell tumors[7]. Invasive ductal carcinoma is referred to as PDAC. Pancreatic cells undergo (1) endoderm formation; (2) pancreatic morphogenesis; and (3) beta cell differentiation to endocrine and exocrine cells[8]. Pancreatic intraepithelial neoplasia (PanIN) lesions are believed to be one of the precursors of PDAC that coincides with multiple successions of genetic mutations[9]. These mutations are possibly provoked by inflammatory stimulus from alcohol abuse or metabolic syndrome[10]. Based on the grade of dysplasia, PanIN lesions can be categorized as type 1A, 1B, 2, or 3, from minimum to severe expansion of immature cells at the ductal epithelium (Figure 1). Genetic defects that follow PanIN-2 and PanIN-3, involve the dysfunction of one or more tumor suppressor genes that result in aberrant signaling pathways driving pancreatic cancer[1,9,11,12].

## SYMPTOMS ASSOCIATED WITH PDAC

PDAC can be asymptomatic in the early stages for months or years. Unfortunately, symptoms of pancreatic cancer typically do not manifest until the disease is in an advanced stage[13]. Patients experience a range of symptoms that are not pathognomonic features to pancreatic cancer. Traditional diagnoses highlight notable symptoms, including obstructive jaundice, abdominal and back pain, weight loss, anorexia, dyspepsia, gallbladder enlargement, migratory thrombosis (Trousseaux syndrome), subcutaneous fat necrosis (panniculitis), and hyperglycemia[14,15].

Carcinoma of the head of the pancreas is often detected when small tumors compress the bile duct, resulting in obstructive jaundice in about 75% of subjects[14].

Nausea, vomiting, lethargy and weight loss may also result from change of appetite, bowel habits, and cancer cachexia. While PDAC can cause abdominal and back pain, it is not uncommon for pancreatic cancer patients to have "painless" jaundice where symptoms are not immediately intrusive[15]. On occasions, tumors of the pancreas invade the superior mesenteric vessels or splenic vein resulting in hemorrhage from varices.

Collective evidence supports the claim that type 3c diabetes is pancreatogenic diabetes and can be caused by chronic pancreatitis due to loss of functioning pancreatic islet cells or may occur as the result of a paraneoplastic phenomenon caused by pancreatic cancer. While further studies are needed to distinguish cancer-induced diabetes from diabetes caused by other exocrine pancreatic diseases, they are classified as two different types of diabetes mellitus by the American Diabetes Association[16,17]. This paraneoplastic syndrome precedes most cancer-specific symptoms by several months or years before tumors become radiologically detectable[17]. New-onset diabetes may also increase the likelihood of pancreatic cancer by 5 to 8 times, with approximately 1% of patients developing the cancer within three years. Progressive and unintentional weight reduction is associated with type 3c diabetes[18]. Unlike type 2 diabetes that is associated with weight gain and obesity, patients with type 3c continue to lose weight as glycemic control worsens in parallel with cancer advancement (Figure 2A). Weight loss is an early event of type 3c that is attributed to either cachexia or loss of adipose tissue[17]. Cachexia is a chronic physical wasting and malnutrition disease that results in more than 10% body weight loss in late cancer stages. When cachexia is absent or has yet to occur, patients rapidly lose weight by adipose tissue inflammation from interactions with pancreatic cancer (Figure 2B). Inflammation in adipose tissue can contribute to peripheral insulin resistance by altering adipocyte secretion and propagate pathogenic processes similar to type 2 diabetes. About 90% of the hormonal secretion from adipose tissue macrophages is comprised of inflammatory cytokines[17,19]. The accumulation of inflammatory cytokines triggers abnormal adipocyte secretion and reduced hepatic insulin sensitivity. This reaction leads to an increase of leptin levels (related to the loss of appetite) and decrease in adiponectin. Leptin and adiponectin are primary precursors to insulin resistance in type 2 diabetes[20-22], which can be regulated by limiting glucose intake and weight gain. Diet changes, such as reduction in carbohydrate intake, have minimal effect on pancreatic cancer-induced diabetes. Weight loss symptoms and diabetes will persist until the tumors are resected. One potential mediator of the cancer-associated diabetes is the over-expression of a pluripotent hormone adrenomedullin that mediates insulin resistance through the interaction of adrenomedullin receptors on β-cells[17]. An increase in endogenous expression of adrenomedullin results in β-cell dysfunction which inhibits insulin secretion in the plasma and tumors.
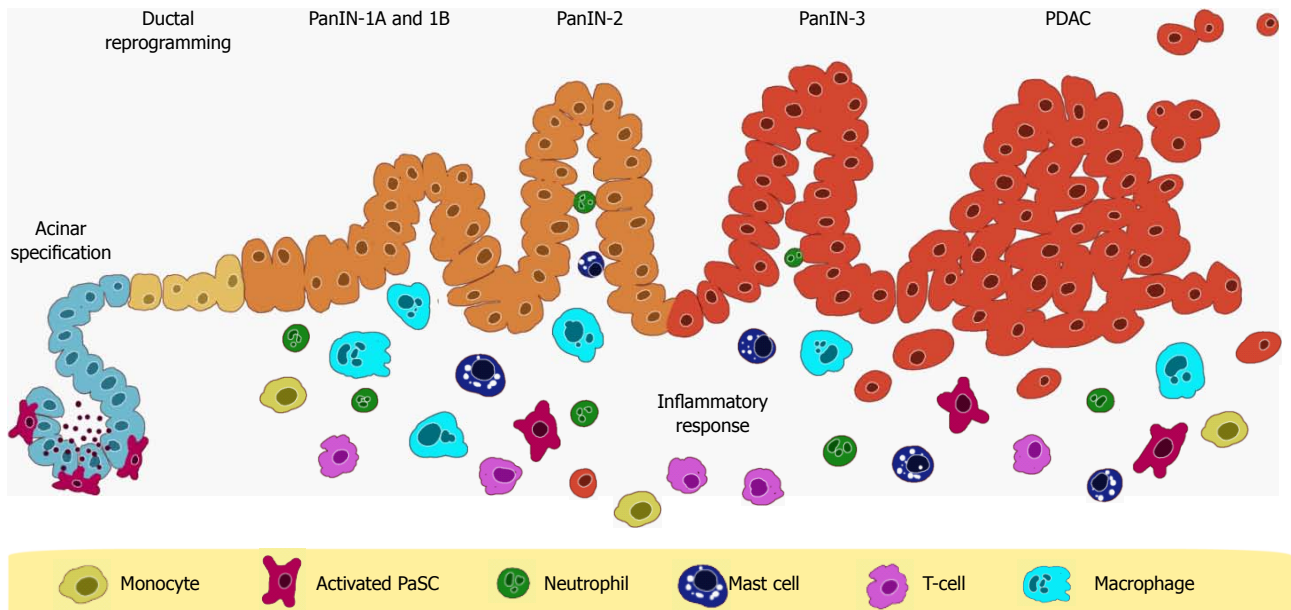
**Figure 1  Example of pancreatic intraepithelial neoplasia lesion development to pancreatic ductal adenocarcinoma.** Inflammatory stimuli trigger the activation of pancreatic stellate cells (PaSC) surrounding acinus cells.  Inflammatory cells (monocytes, T-cells, neutrophils, mast cells, and macrophages) gather in response and release ligands (interleukin-6) that activate *STAT3* gene to promote pancreatic intraepithelial neoplasia (PanIN) development in susceptible tissue with oncogenic mutations such as the Kras. PDAC: Pancreatic ductal adenocarcinoma. Figure redrawn with permissions from Elsevier: [10] and Macmillan Publishers Ltd: [12].

The relationship between diabetes and pancreatic cancer has been studied since the early 1830s, but the biological significance of type 3c diabetes in relation to pancreatic cancer had not been acknowledged until recently[23]. Early diagnosis of type 3c could potentially lead to early diagnosis and treatment of patients with pancreatic cancer months to years before the tumor appears radiologically. Early distinction between type 2 and type 3c diabetes requires a high level of awareness and expertise, and may lead to the earlier diagnosis of pancreatic cancer. Severe weight loss is also intimately associated with a variety of cancers and occasionally occurs several months prior to death[24]. Thus, understanding the collective effects of type 3c is substantial in distinguishing pancreatic cancer from the diverse array of malignancies.

## DIAGNOSTIC TESTS AND BIOMARKERS

Currently there are no adequate diagnostic tests for early detection of pancreatic cancer, and routine radiographic tests or endoscopic ultrasound screening is only recommended for those individuals with a family history of pancreatic cancer, chronic pancreatitis, precancerous lesions, or new-onset diabetes. Serological markers such carbohydrate antigen (CA)19-9, MIC-1, carcinoembryonic antigen, human chorionic gonadotropin β, and CA72-4 have also been of interest but lack sufficient sensitivity and specificity for effective early cancer detection[25-28].

However, research continues to make progress on uncovering genetic markers that are responsible for notable pancreatic cancer cell phenotypes. Recently, the role of mucin-1 (MUC-1) in malignant cells was first reported to upregulate multi-drug resistance genes such

as *ABCC1*, *ABCC3*, *ABCC5* and *ABCB1*[29]. MUC-1 is a transmembrane glycoprotein that lines the apical surface of epithelial cells, normally present to protect the body from infectious pathogens. Overexpression of MUC-1 is found in patients with common cancers that include pancreatic[30], breast[31], ovarian[32] and thyroid[33] cancers. MUC1 overexpression may be and enabled by the phosphatidylinositol 3'-kinase/Akt signaling pathway, a pathway associated with chemotherapeutic drug resistance in other cancers[34].

## GENETIC MUTATIONS ASSOCIATED WITH PANCREATIC CANCER

While there are at least 25 altered genes related to cancer pathways (*i.e.,* cell adhesion, apoptosis, and replication), only a handful have been identified in pancreatic cancer studies[35,36]. BCRA2 mutations are found in up to 10% of those with PDAC. A germline variant of the cholecystokinin-B gene has been identified in over 35% of patients with PDAC and predicts both risk and survival[28]. Activated Kirsten-Ras (Kras*)* oncogene is harbored in > 95% of pancreatic cancer tumors and is critical in cell proliferation and apoptotic resistance to hostile microenvironments (in the presence of anti-cancer agents)[1]. Activation of the Kras oncogene releases Ras proteins that initiate mitogen-activated protein (MAPK) cascades[37-39]. MAPK participates in many critical cellular events, including cell division, response to surroundings, movement, and cell death. Mutated Kras is accepted as a "Driver" gene for pancreatic cancer that propagates a series of ongoing cellular signal transduction processes that cause uncontrollable proliferation and architectural
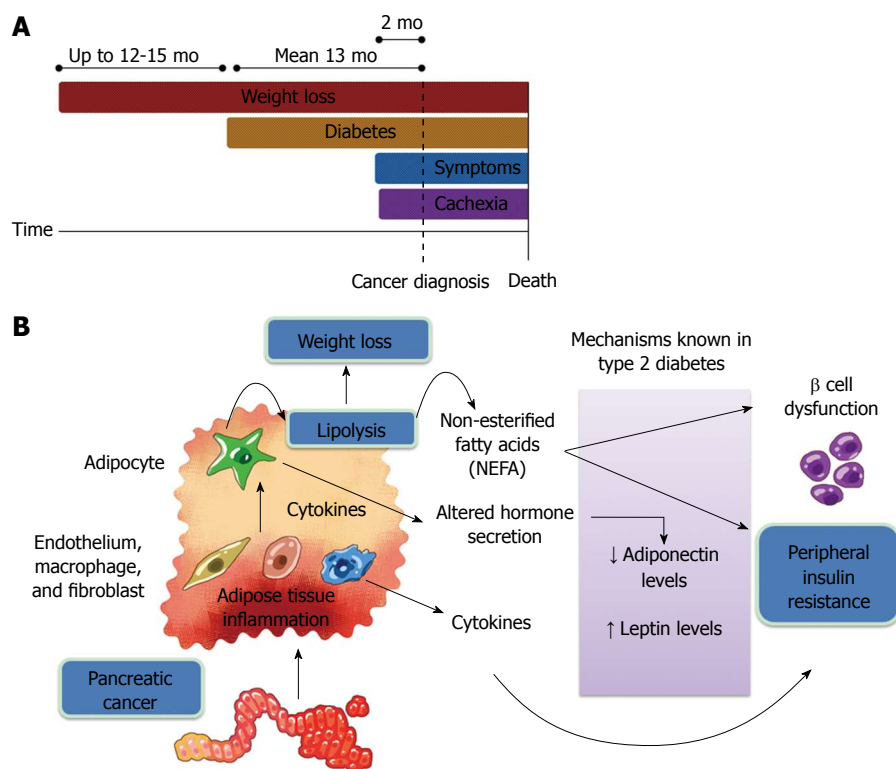
**Figure 2  Symptoms of paraneoplastic type 3c diabetes preceding pancreatic cancer.** A: A comparison of weight-loss timeline to cancer-specific symptoms; B: Schematic representation of the cause for progressive weight reduction and insulin resistance. Adipose tissue inflammation triggers an alteration of adipocyte secretion and propagates pathogenic processes similar to type 2 diabetes, eventually leading to cachexia. Figures redrawn with permission from Macmillan Publishers Ltd: [17].

abnormalities where acinar tissue is replaced with ductal lesions.

Kras mutations are also capable of reducing tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) sensitivity[40]. Abnormalities are likely to occur at codon 12 (G12D), involving a point mutation of one glycine to aspartic acid (G12D), or glycine to valine (G12V). TRAIL is a transmembrane protein that can be proteolytically cleaved from the cell surface to mediate apoptosis and anti-tumor activities[40]. Inhibitors that directly target oncogenic Kras have not yet been developed, but remain an active area of investigation. However, Kras mutations can trigger an enrichment of a cytokine receptor, osteoprotegerin (OPG), which directly inhibits TRAIL solubility and potentially induces apoptosis[40,41]. Interestingly, increased OPG and TRAIL levels are also found in subjects with type 2 diabetes mellitus[42], but connections to type 3c diabetes have not been implicated.

## SIGNALING PATHWAYS ACTIVATED IN PANCREATIC CANCER

Oncogenes depend on various signaling pathways to initiate tumor formation. Since most attempts to directly inhibit oncogenes like Kras have failed, attention has shifted to other critical signaling pathways for targeted cancer therapy[43]. The Notch pathway, for instance, exerts its biological influence by maintaining homeostasis

during embryonic development in multicellular organisms[44] and is important in development of the pancreas. The loss of Notch signaling in the pancreas results in premature differentiation of endocrine and exocrine cells. Therefore, this pathway is essential for determining the fate of functioning pancreatic cells in epithelial and non-epithelial tissues. However, controversy exists in literature as to whether the Notch pathway serves as a promoter for tumor progression or an inhibitor[45,46]. Lateral inhibition mechanisms of the Notch pathway involve a group of receptors (Notch1, Notch2, Notch3, and Notch4), target, and ligand key components that contribute uniquely to PanIN progression[46]. For example, deletion of the Notch1 receptor generally accelerates PanIN lesion development and lowers median survival in Pdx1-Cre[ERT2]; LSL-Kras[G12D], Pdx1-Cre;Kras[G12D], and Ptf1a-Cre; Kras[G12D] mouse models[46-49]. The loss of the Notch2 receptor in Ptf1a-mouse models, however, halts lesion progression and increases chances of survival[49]. Tumor inhibition was also reported in several studies where the up-regulation of Hes1 from activated Notch pathway suppresses the expression of p57, which prevents progenitors from undergoing premature differentiation and uncontrollable proliferation[50]. Without harming healthy adult cells, tumor suppression was achieved in zebrafish by forcing exocrine pancreatic precursors through Notch signaling to inhibit acinar cell differentiation[45]. Ongoing investigations on type 2 diabetes also imply that the Notch pathway is responsible for insulin-resistance in pancreatic cells

**Table 1  Desired characteristics for a nanoparticle drug-delivery platform**

| Desired characteristic | Comments |
|---|---|
| Inherently non-toxic materials and degradation products | The initial material selection should be based on non-toxic materials especially with an aim toward human health care |
| Small size (10–200 nm) | There is not a particular size that seems most efficacious, particularly based on *in vivo* studies. This is the range of particle diameters that have proven most effective for a wide variety of delivery systems. Also of note is the debate around the influence of particle shape[83] |
| Encapsulation of active agent | To be effective, the active agent must be encapsulated within the nanoparticle vehicle. Surface decoration (*i.e.*, adsorption) will often be effective *in vitro* but falls short for *in vivo* studies because of the reticulum endoplasmic systems *in vivo* |
| Colloidally stable in physiological conditions | The nanoparticle vehicle and surface functionalization must resist agglomeration for the solution pH values, ionic strength, macromolecular interactions, and temperature encountered in the physiological environment |
| Clearance mechanism | The nanoparticle vehicle must have a ready clearance mechanism to avoid the cumulative and/or systemic effects of the drug-laden particles |
| Long clearance times | Resistance to agglomeration and other effects that remove the nanoparticle-encapsulated drug from the patient must be avoided to promote long circulation times in the circulatory system for as many of the nanoparticles to find and sequester in the cancer cells as possible |
| Biologically or extrinsically controlled release of therapeutic agents | There should be a trigger mechanism such as the acidic pH within the tumor or during endosome maturation designed into the nanoparticle platform to ensure the release of the encapsulated drug into the targeted tissue |
| Can be targeted to cell/tissue of choice | The nanoparticle platform should be capable of surface bioconjugation to target molecules for the specific cancer to provide the greatest uptake with the lesions and fewest least side effects with healthy tissue |

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(from the expression or inactivation of *Hes1* gene, Rbp-Jk protein ligand, and *Ngn3* gene)[51]. The function of the Notch pathway during PDAC development is dependent on the targeted receptor and the genes expressed. Clearly, Notch signaling pathway targeted therapy serves as a potential target for treating pancreatic cancer. Such therapies must be exercised with caution since a wide variety of cells rely on ligand-dependent pathways for growth and survival.

Another important pathway activated by GTP-protein coupled receptors (GPCRs) is the PI3 kinase signaling pathway that phosphorylates Akt and activates downstream mTOR and subsequent proliferation. In a large GWAS study, GPCRs were found to be the most frequent signaling pathways involved in PDAC[52]. One GPCR, the cholecystokinin (CCK) receptor is over-expressed and ubiquitous in PDAC[53]. Stimulation of the CCK receptor accelerates PanIN development in the Kras transgenic mouse model[54]. Targeting the CCK receptor has become important in new therapeutics for PDAC and indeed if this receptor is down-regulated growth is inhibited and downstream signaling through PI3 kinase is blocked[55].

## TREATMENT

Treatment options for PDAC patients that present in the late stages are limited to chemotherapy and radiation. Conventional chemotherapeutic agents are ineffective against PDAC for several reasons among which include the microenvironment. PDAC tumors are highly fibrous and poorly vascularized[13] prohibiting adequate penetration of the tumor by chemotherapeutic agents. The heterogeneous nature of cancer cells and tissue hypoxia is associated with drug resistance, often requiring higher drug dosages during treatment and increased toxicity such as peripheral neuropathy, bone marrow

toxicity, and cardiotoxicity. Gemcitabine is the gold standard for advanced PDAC, but only affords survival up to six months[56,57]. Survival with gemicitabine is, however, improved when administered with other agents[58]. Capecitabine and 5-fluorouracil[59,60] are also common antimetabolites administered in clinical trials as a standard single-drug treatment[61]. These agents have been used in conjunction with platinum-based agents and other cancer drugs such as leucovorin, exactecan, and irinotecan[5]. Radiation therapy is recommended in conjunction as an adjuvant and a chemosensitizer[62,63]. Clinical trials that administer combined drug therapy such as FOLFIRINOX (5-fluorouracil with leucovorin, irinotecan, and oxaliplatin) have shown greater efficacy for metastatic cancer, but with profound limitations due to systemic toxicity and neurotoxicity[64-67]. Recently, survival of PDAC patients has been marginally improved by using a combination of nab-Paclitaxel plus gemcitabine[58].

Patients may be offered surgery in absence of metastatic spread as determined by positron emission tomography, magnetic resonance imaging, and triphasic computed tomography scans. The Whipple operation is performed on pancreatic cancer involving the head of the pancreas if the superior mesenteric vessels are not affected[6,68]. Pylorus preserving Whipple operation involves removing the first section of the duodenum while others may undergo the standard Whipple operations which involve the removal of a part of the stomach. Adjuvant chemotherapy and radiation therapy usually follow the resection in an attempt to decrease relapse rates. Preoperative chemotherapy and radiation therapy can sometimes restage tumors and make them amenable to surgical resection, but patients with locally advanced pancreatic cancer from the body and tail of the pancreas are often not qualified for surgery due to metastatic spread to the celiac artery. Evidently, surgery assures the longest survival, but

**Table 2 The selection criteria for nanomaterial drug delivery systems**

| Nano particulate material | Size (nm) | Therapeutic agent(s) carried | Advantages | Limitations |
|---|---|---|---|---|
| Biodegradable polymers | 10-100 | Plasmid DNA, proteins, peptides, low molecular-weight (MW) organic compounds | Sustained localized drug delivery for weeks | Exocytosis of undissolved nanoparticles. Fixed functionality after synthesis may require new synthetic pathways for alternate surface functionalities |
| Ceramic | < 100 | Proteins, DNA, chemotherapeutic agents, high MW organic compounds | Easily prepared, water dispersible, stable in biological environments | Toxicity of materials, exocytosis of undissolved nanoparticles, time consuming synthesis, surface decoration instead of encapsulation |
| Metals | < 50 | Proteins, DNA, chemotherapeutic agents | Small particles present a large surface area for surface decoration delivery | Toxicity of materials, exocytosis of undissolved nanoparticles, time consuming synthesis, surface decoration instead of encapsulation |
| Polymeric micelles | < 100 | Proteins, DNA, chemotherapeutic agents | Suitable for water-insoluble drugs due to hydrophobic core | Toxicity of materials, fixed functionality after synthesis |
| Dendrimers | < 10 | Chemotherapeutic agents, anti-bacterial, anti-viral agents, DNA, high MW organic compounds | Suitable for hydrophobic or hydrophilic drugs | May use toxic materials, time consuming synthesis, fixed functionality after synthesis may require new synthetic pathways for alternate surface functionalities |
| Liposomes | 50-100 | Chemotherapeutic agents, proteins, DNA | Reduced systemic toxicity, increased circulation time | Fixed functionality after synthesis, some leakage of encapsulated agent, lack of colloidal stability |
| 3D printing | 20-2000 | Chemotherapeutic agents, proteins, DNA, imaging agents | Precise control over size, shape, and surface functionalization. 3D printing can be used with an array of processing techniques to create porous scaffolds[85] and lab-on-chip devices[86] for personalized medicine[87] | Toxicity of materials depending on material |
| Calcium phosphosilicate | 20-60 | Chemotherapeutic agents, RNA, high and low MW organic compounds, imaging agents | Simple preparation, suitable for hydrophilic or hydrophobic drugs, colloidal stability in physiological environments, pH-dependent dissolution results in intracellular delivery of drugs, composed of bio-resorbable material | Encapsulated materials limited to solubility in water or organic solvent |

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promise for full recovery from advanced PDAC is not yet feasible[69,70].

# FUTURE DIRECTIONS BASED ON NANOMEDICINE

Novel approaches for pancreatic cancer therapy are desperately needed. The trinity offered by nanomedical approaches to simultaneously seek, treat, and track human cancer is slowly emerging from the basic nanoscience toward clinical deployment to treat pancreatic cancer. Adair *et al*[71] reviewed the selection criteria for drug delivery strategies based on several nanomaterial platforms. The selection criteria for nanomaterial drug delivery systems are summarized in Tables 1 and 2. Novel strategies using nanotechnology research may lead to advantages in early detection via bioimaging, specific targeting of cancer cell receptors and effective treatment with lower side effects and drug degradation. There is a great demand to improve current drug delivery procedures to overcome drug resistance without causing serious off target toxicity. Targeting proteins involved with signal transduction is one strategy that is currently under investigation. Studies in growth factor inhibitors (opioid growth factors)[72,73] for biotherapy and biocompatible nanomaterials for drug carrier systems, introduce promising directions towards effective cancer management despite limitations. Novel

biomarkers like Plectin-1 (Plec1)[74] have been found to be useful in the early detection of small pre-invasive PanIN III lesions and metastases. Such biomarkers provide an advantage in early detection when they are over-expressed in specific organs. It was shown that Plec1 can also be used to safely distinguish PDAC from benign conditions and thus this method is more effective than cross-sectional abdominal and invasive endoscopic imaging techniques. Although a cure for PDAC is not feasible with currently available treatment, research in the next decade will develop better prevention and prognosis modalities to diagnose PDAC and improve chances of survival.

One of the most promising nanomedical approaches reported in recent years is based on a novel material system, calcium phosphosilicate hydrate nanoparticles (CPSNPs), in which encapsulated imaging agents and/or drugs, can be delivered in a targeted manner to a variety of cancers including pancreatic cancer[71,75-80]. For example, Barth *et al*[81] have demonstrated that a FDA-approved near infra-red fluorophore, indocyanine green (ICG), also known as Cardio-Green™, when encapsulated in the CPSNPs, can be used as a theranostic (*i.e.*, a combined diagnostic and therapeutic) agent for a variety of cancers based on a new cancer diagnosis and treatment strategy designated as photo-immuno nanotherapy (PINT). PINT results resurrection of the immune response of the host animal, permitting the immune system to fight the cancer

directly. In an earlier report, Barth *et al*[82] also demonstrated that gastrin-10 can be used for targeted delivery of ICG-encapsulated CPSNPs *in vivo* based on an orthotopic graft of a human pancreatic cancer in the athymic murine model. The trigger to release the chemotherapeutic agent is inherent dissolution of the CPSNPs in either the acidic local pH in the fluid surrounding many solid tumor types or, after endosomal uptake of the drug-laden CPSNPs into cancer cells, the decreased pH associated with maturation of endosome to endo-lysosomes. Targeting permits the PINT to be used for efficacious uptake in solid tumors and, in an unprecedented fashion, for non-solid tumor cells such as chronic myeloid leukemia[78,81,82]. Thus, the combination of early detection with more efficacious delivery and more effective treatment promised by nanomedical approaches is emerging as a viable alternative for pancreatic cancer diagnosis and treatment.

## ACKNOWLEDGMENTS

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