SPARC: A Potential Prognostic and Therapeutic Target in Pancreatic Cancer

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Abstract: Pancreatic cancer is a complex and heterogeneous disease that often lacks disease-specific symptoms in early stages. The malignancy is currently the fourth leading cause of cancer-related death in Western countries. In advanced stages, the overall 5-year survival is less than 1% to 2%. Most available treatments lack convincing cost-efficiency determinations and are generally not associated with relevant success rates. Targeting stromal components and stromal depletion is currently becoming an area of extensive research in pancreatic cancer. In this context, a glycoprotein, SPARC (secreted protein acidic and rich in cysteine) appears to play a central role. Still, the role of SPARC in carcinogenesis is controversial because conflicting results have been reported, and the pathways involved in SPARC signaling are not well established. Nonetheless, SPARC is highly expressed in the tumor stroma, primarily in peritumoral fibroblasts, and the overexpression of SPARC in this compartment is associated with poorer prognosis. Interestingly, it has been suggested that SPARC present in the tumor stroma could sequester albumin-bound paclitaxel, enhancing the delivery of paclitaxel into the tumor microenvironment. In the present review, we summarize the known associations between SPARC and pancreatic cancer. Moreover, present and future therapies comprising SPARC-targeting are discussed.

Key Words: albumin-bound paclitaxel, pancreatic cancer, pathophysiological mechanisms, SPARC, stromal depletion

Pancreatic cancer is a devastating disease. Worldwide, more than 200,000 people are diagnosed every year, and rising incidence numbers have been reported. The malignancy is currently the fourth leading cause of cancer-related death in Western countries, but it may become the second leading cause of cancer-related death in the United States within this decade if no substantial breakthroughs are made in the management of this disease.

Pancreatic ductal adenocarcinoma (PDAC) is by far the most common form of pancreatic cancer. Pancreatic ductal adenocarcinoma is a complex and heterogeneous disease that often lacks disease-specific symptoms in early stages. Several novel biomarkers have been proposed, but none of them meets the requirements needed for clinical use. Raised concentrations of the serum carbohydrate antigen 19-9 (CA 19-9) are reported in about 80% of patients. However, CA 19-9 is not a primary screening test because of its poor specificity in early disease. Consequently, PDAC is habitually diagnosed in late stages. Once detected, the disease is almost unavoidably lethal within 5 to 6 months. In advanced stages, the overall 5-year survival is less than 1% to 2%. Furthermore, resectable tumors are present in only 10% to 15% of patients. Unfortunately, long-term complete remission is unusual, and the median survival observed after surgery and concomitant adjuvant chemotherapy is about 20 months.

Palliative chemotherapy is thus the only treatment justifiable in most cases. Unfortunately, the existing treatments have had minimal impact on the natural course of PDAC. Gemcitabine increases the quality of life, but only prolongs the mean survival by 30 days. FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) further prolongs the mean survival by 4 months compared with gemcitabine monotherapy. Yet, FOLFIRINOX is suitable only for patients with a good performance status. Thus, gemcitabine still represents the criterion standard for most patients. As the drug is well tolerated and inexpensive compared with alternative treatments, most research has focused on finding ideal “drug chaperons” that facilitate and/or potentiate the effect of gemcitabine. Several cytotoxic agents have been tried in combination with gemcitabine. For instance, the combination gemcitabine and erlotinib (Tarceva) has been approved in metastatic PDAC. In recent years, several agents targeting both tumor cells and the tumor stroma have been developed. Indeed, SHH (sonic hedgehog) inhibitors, CD40 agonists, platelet-derived growth factor receptor inhibitors, and hyaluronidase have been proposed as novel potential treatments in PDAC. Therefore, targeting stromal components and stromal depletion is currently becoming an area of extensive research in PDAC. In this context, a glycoprotein, SPARC (secreted protein acidic and rich in cysteine), appears to play a central role.

In addition, the role of SPARC in PDAC may not be limited to its linkage to the tumor stroma, as SPARC is related to several pathophysiological mechanisms in numerous cancer forms.

We aim to summarize known and hypothetical associations between SPARC and PDAC. In addition, present and future therapeutic strategies comprising SPARC are reviewed.

TUMOR STROMA AND SPARC

The causes of PDAC are mainly unknown. Pancreatic intraepithelial neoplasia (PanIN) is considered the primordial precursor of PDAC. Several mutations have been reported, but the activation of the KRAS oncogene together with CDKN2A/p16 loss and the inactivation of TP53 and SMAD4/DPC4 seem to be characteristic in PDAC. For instance, aberrantly activated KRAS and inactivated CDKN2A genes are found in 90% and 95% of PDAC tumors, respectively.

Another hallmark of PDAC is its tumor stroma, which comprises 80% to 90% of the tumor volume. The stroma contains dense fibrotic tissue composed of extracellular matrix (ECM) proteins, pancreatic stellate cells (PSCs), immune-inflammatory cells, adipocytes, and blood and lymphatic vessels. The resulting microenvironment supports tumor initiation, progression, invasion, and metastasis. Moreover, stromal cells express multiple proteins and growth factors associated with treatment resistance, restrained
antitumor immunity, and poor prognosis.\textsuperscript{15} Pancreatic stellate cells are activated myofibroblasts responsible for stromal development and turnover. These cells contribute to the poor vascularization that is characteristic of PDAC.\textsuperscript{17} Moreover, PSCs produce soluble factors that stimulate signaling pathways related to proliferation and survival of PDAC cell lines.\textsuperscript{18} Cells of the innate and the adaptive immune system, such as T cells and macrophages, are able to create an immunosuppressive tumor microenvironment in PDAC.\textsuperscript{19}

SPARC, also known as osteonectin and/or BM-40 (basement membrane 40), is a 32- to 35-kd multifunctional calcium-binding glycoprotein belonging to a group of matricellular proteins. SPARC is transiently secreted to the ECM and does not become a part of the ECM mesh.\textsuperscript{20} The \textit{SPARC} gene is located on human chromosome 5q31.3–q32, and the transcription consists of a single polypeptide (285 amino acids) that can be divided into 3 different structural domains. The N-terminal is highly acidic, binds calcium ions with low affinity, and interacts with hydroxyapatite. The follastatin-like domain is a cysteine-rich structure. Finally, the C-terminal constitutes the extracellular calcium ion–binding domain.\textsuperscript{13}

SPARC is involved in many biologic processes, including development, wound repair, tissue remodeling, angiogenesis, matrix cell adhesion, cell differentiation, proliferation, and migration.\textsuperscript{21–24} The functions of SPARC might be in part mediated by interactions with matrix metalloproteinases (MMPs) and several growth factors, such as transforming growth factor β (TGF-β) and fibroblast growth factor.\textsuperscript{22} Interestingly, there are no known SPARC receptors, and the protein part is rapidly the subject of proteolysis by several proteases.\textsuperscript{23} In the adult, the expression of SPARC is restricted to tissues with high ECM turnover, such as bone and the gut epithelium.\textsuperscript{25}

SPARC expression and secretion in tumor tissue emerge as an important clinical factor in several malignancies (briefly reviewed in Table 1). SPARC is involved in numerous mechanisms in cancer, comprising proliferation, cell cycle progression, angiogenesis, apoptosis, cell adhesion, migration, and metastasis (shown in Fig. 1).\textsuperscript{13} Still, the role of SPARC in carcinogenesis is controversial because conflicting results have been reported, and the pathways involved in SPARC signaling are not well established. Nevertheless, the overexpression of SPARC in stromal cells in

| Tumor Type   | Endogenous SPARC: mRNA Expression and/or Protein Level | Prognosis          | Reference |
|--------------|--------------------------------------------------------|--------------------|-----------|
| Ampulla of Vater | High/low (SCs)                                           | Poorer: high SPARC in SCs | 26        |
| Bladder      | High/low (TT)                                             | Poorer: high SPARC in TT | 27        |
| Breast       | High/low (CCs)                                            | Poorer: high SPARC in CCs | 28        |
| Colon        | High (SCs)                                                | Better: high SPARC in SCs | 29        |
| Colon        | Low (CCs)                                                 | Poorer: low SPARC in SCs | 30        |
| DLBCL        | High/low (CCs)                                            | Better: high SPARC in CCs/SCs | 31        |
| Endometrial  | Low (TT)                                                  | Unknown             | 32        |
| Gastric      | Low (CCs)                                                 | Poorer: high SPARC in SCs | 33        |
| Glioma       | High (CCs)                                                | Poorer: high SPARC in VT | 34        |
| Head and neck| Low (CCs)                                                 | Poorer: high SPARC in SCs | 35        |
| Leukemia     | Low (CCs)                                                 | Poorer: high SPARC | 36        |
| Hepatocellular| Low (CCs)                                                 | Poorer: high SPARC in SCs | 37        |
| Lung         | Low (CCs)                                                 | Poorer: high SPARC in CCs | 38        |
| Melanoma     | High/low (CCs)                                            | Poorer: high SPARC in CCs | 39        |
| Neuroblastoma| Low (CCs)                                                 | Poorer: high SPARC in CCs | 40        |
| Esophagus    | High (CCs)                                                | Unknown             | 41        |
| Osteosarcoma | High/low (TT)                                             | Poorer: high SPARC in TT | 42        |
| Ovarian      | Low (CCs)                                                 | Unknown             | 43        |
| Pancreatic   | Low (CCs)                                                 | Poorer: high SPARC in SCs | 44        |
| Prostate     | Low (CCs)                                                 | Poorer: high SPARC in CCs | 45        |
| Thyroid      | High/low (CCs)                                            | Poorer: high SPARC in CCs | 46–48     |

CCs indicates cancer cells; DLBCL, diffuse large B-cell lymphoma; SCs, stromal cells; SSCs, stromal Schwann cells; TT, tumor tissue; VT, vascular tissue.

TABLE 1. The Role of SPARC in Human Cancer
Cancer seems to be strongly related to increased invasive capacity and poorer prognosis.12

**SPARC GENE SILENCING IN PDAC**

Epigenetic alterations are identified to contribute to the development of PDAC. Histone modifications, microRNAs, and DNA methylation are well-known epigenetic mechanisms. Hence, the intervention of these mechanisms has been subject of intense research in PDAC.54 It has been shown that DNA methylation is associated with the inactivation of tumor suppressor genes in cancer.55

SPARC gene expression is present in normal pancreatic duct epithelial cells and in immortalized nonneoplastic pancreatic epithelial cells (HPDE).56 Intriguingly, the abnormal methylation of the SPARC gene CpG islands is found in 28% of resected PanIN tissue.57 Early recognition of PanINs would dramatically change the prognosis of PDAC because most patients could be cured through a surgical resection before they develop metastatic disease. Unfortunately, PanINs are microscopic lesions that are usually less than 5 mm and undetectable for available imaging methods as of today.58 In contrast to PanINs, intraductal papillary mucinous neoplasms (IPMNs) are precursors of PDAC that can be detected by imaging.59 In IPMNs, the expression of SPARC is lost in 50% of low-grade and moderate dysplasia. In high-grade dysplasia, the expression of SPARC is lost in 80% of the IPMNs.60 Thus, augmenting SPARC loss in IPMNs appears to be related to tumor development. Intraductal papillary mucinous neoplasms and PDACs have similar pathophysiological genomic alterations, but significant molecular dissimilarities between PDA and IPMNs have been reported.61 Besides, the differentiation between IPMNs and other pancreatic cysts and neoplasms is often challenging. These results are still promising and suggest that loss of SPARC expression is a characteristic feature of premalignant pancreatic lesions. Possibly, the implementation of methylation panels including SPARC and other common hypermethylated genes (such as Reprimo) could be used for early detection of PanINs and IPMNs by the analysis of pancreatic juice and/or cystic fluid.62,63 It has recently been reported that the SPARC CpG islands are hypermethylated in 58% of fine-needle aspirates from PDAC patients (sensitivity 68%, specificity 100%).64

![Figure 1. The diverging role of SPARC in carcinogenesis. A brief selection of the reported associations is shown.](13,52,53)
SPARC gene CpG islands are also aberrantly methylated in PDAC cell lines and tumor xenografts. While all CpG sites were completely unmethylated in HPDE and primary fibroblasts from PDAC, most cell lines were completely or partially methylated. Altogether, the SPARC gene was aberrantly methylated in 94% (16/17) of the examined PDAC cell lines and in 88% (21/24) of the tumor xenografts established from primary PDAC. Importantly, this methylation pattern was absent in normal epithelium samples. Predictably, the hypermethylation of SPARC resulted in loss of mRNA expression of SPARC in 94% of PDAC cell lines. The administration of a demethylating agent (5Aza-2'-deoxycytidine) reestablished the mRNA expression of SPARC in 88% of the challenged cells.56

The methylation of the SPARC gene transcriptional regulation region is more prominent in CpG region 1 (CpG sites 1-7) and CpG region 2 (CpG sites 8-12) in PDAC. Importantly, the methylation at both regions is also present in pancreatic tissue, chronic pancreatitis (CP), and nonneoplastic tissue adjacent to the tumors. The frequency of methylated regions increases gradually from normal tissue to pathological tissue. CpG region 2 methylation was more sensitive in pancreatic carcinogenesis. Moreover, the percentage of methylation at the CpG region 2 was associated with larger tumor size and exposure to tobacco smoke and alcohol consumption. Besides, increased tumor size, tobacco smoking, and alcohol consumption were independent contributors to the percentage of CpG region 2 methylation.65 The authors concluded that the aberrant methylation of CpG region 2 could be useful as a marker for early PDAC diagnosis, but their results need to be verified in larger studies, because the conclusions were based on 40 PDAC cases alone.

Nevertheless, the correlation between SPARC methylation and tobacco smoke is of particular concern because the latter is a major risk factor for PDAC. At least 20% of the tumors have been reportedly caused by cigarette smoking.5 Tobacco smoke can induce KRAS gene mutation in PDAC, and the associations between tobacco smoke and the hypermethylation of tumor suppressor genes are currently being elucidated.66,67 Heavy alcohol intake can lead to CP and liver cirrhosis, which have been related to an increased risk of PDAC.68 A family history is also a well-defined risk factor for PDAC, present in 5% to 10% of cases.5 SPARC is hypermethylated in ≈92% of familiar PDAC, which indicates that both sporadic and familiar PDACs share pathophysiological mechanisms that involve SPARC.69

In a dose-dependent manner, gemcitabine altered the SPARC expression in a PDAC cell line.70 The mechanisms behind this effect are mainly unknown, but it has been reported that gemcitabine can

**TABLE 2.** SPARC Gene Silencing and mRNA Expression in PDAC Cell Lines

| Cell Line | Derivation | Metastasis | Differentiation | Silenced SPARC Gene | SPARC mRNA Expression | Reference |
|-----------|------------|------------|----------------|---------------------|----------------------|-----------|
| A818-4    | Pancreas   | No         | Moderate to poor| Undetermined        | Absent               | 75        |
| A8 (R)    | Ascites    | Yes        | Moderate       | Undetermined        | Present              | 75        |
| AsML (R)  | Pancreas   | Yes        | Moderate to poor| Undetermined        | Present              | 75        |
| AsPC-1*   | Ascites    | Yes        | Poor           | Hypermethylation    | Mostly absent        | 56,75–77  |
| BxPC-3*   | Pancreas   | No         | Moderate to poor| Mostly hypermethylated| Absent               | 56,75–77  |
| Capan-1*  | Liver      | Yes        | Well           | Hypermethylation    | Mostly absent        | 56,75–77  |
| Capan-2*  | Pancreas   | No         | Well           | Hypermethylation    | Absent               | 56        |
| CFPAC-1*  | Liver      | Yes        | Well           | Hypermethylation    | Absent/present       | 56,75     |
| Colo357   | Lymph node | Yes        | Moderate       | Hypermethylation    | Absent/moderate to low| 56,75,76  |
| DAN-G     | Pancreas   | No         | Moderate       | Undetermined        | High                 | 75        |
| HPAC*     | Pancreas   | No         | Undetermined   | Present             | 75                   |
| HPAF-II*  | Ascites    | Yes        | Well           | Undetermined        | Low                  | 75        |
| HS766T*   | Lymph node | Yes        | Not described  | Hypermethylation    | Absent               | 56        |
| MiaPaCa-2*| Pancreas   | Yes        | Poor           | Hypermethylation    | Absent/moderate to low| 56,75–77  |
| Panc-1*   | Pancreas   | Yes        | Poor           | Partially hypermethylated | High                | 56,75–77  |
| Pan02 (M) | Pancreas   | Yes        | Poor           | Undetermined        | Present              | 79        |
| Patu 390  | Pancreas   | No         | Moderate       | Undetermined        | Absent               | 75        |
| Patu 8988 | Pancreas   | No         | Moderate to poor| Hypermethylated      | Undetermined         | 65        |
| PK8       | Liver      | Yes        | Moderate       | Undetermined        | Present              | 80        |
| PK45H     | Pancreas   | No         | Moderate       | Undetermined        | Present              | 80        |
| PK59      | Pancreas   | No         | Moderate       | Undetermined        | Present              | 80        |
| PL-1, 3, 6, 10-13 | Pancreas | No | Moderate | Hypermethylated | Absent | 56 |
| PL-9      | Pancreas   | No         | Moderate       | Mostly hypermethylated | Present | 56 |
| PL45      | Pancreas   | Yes        | Poor           | Undetermined        | Low                  | 78        |
| PSN-1     | Pancreas   | Yes        | Poor           | Undetermined        | Absent               | 46        |
| Suit2-007 | Liver      | Yes        | Moderate to poor| Undetermined        | Present              | 75        |
| Suit2-013 | Liver      | Yes        | Moderate to poor| Undetermined        | Absent               | 75        |
| SU86.86*  | Liver      | Yes        | Moderate to poor| Undetermined        | High                 | 76        |
| T3M4      | Lymph node | Yes        | Poor           | Undetermined        | Absent/moderate to low| 75–77     |
| YPK-1     | Ascites    | Yes        | Moderate to poor| Undetermined        | Absent               | 70        |

*Most referred PDAC cell lines in the literature.81
(M) indicates murine PDAC cell line; (R), rat PDAC cell line.
function as a DNA methyltransferase inhibitor in other solid tumors. Moreover, SPARC overexpression seems to enhance the chemosensitive of PDAC cells to gemcitabine. Likewise, curcumin analogs seem to be DNA-methylating agents that increase SPARC expression in PDAC cell lines and in tumor xenografts.

In summary, the hypermethylation of SPARC gene CpG islands in premalignant lesions and PDAC cell lines and tissue strongly indicates that the protein is involved in the development and progression of PDAC. Similar associations have been reported in other gastrointestinal malignancies. Other mechanisms responsible for SPARC gene silencing in PDAC could be loss of heterozygosity. Loss of heterozygosity at 5q is found in up to 20% of PDAC tumors.

SPARC EXPRESSION AND EFFECT IN PDAC

Conflicting results have been reported concerning the mRNA expression of SPARC in PDAC cell lines. As described above, almost all cells (94%) showing aberrant methylation patterns lack SPARC expression, and conditioned media from several cell lines show undetectable SPARC levels. However, several PDAC cell lines appear to express SPARC, and even cell lines initially reported as lacking SPARC expression in PDAC have shown conflicting results. The different PDAC cell lines, their reported methylation pattern, and supposed mRNA expression of SPARC are presented in Table 2. Here, we found that the mRNA expression of SPARC is absent or low in about 64% of the 11 most referred cell lines in PDAC. PanC-1 and MiaPaCa-2 are important exceptions showing high to moderate SPARC expression. Possibly, the patients’ ethnicity, the derivation tissue, or the grades of differentiation of the cells cause the differing expression of SPARC among these cell lines. Importantly, SPARC is expressed in murine and rat PDAC cell lines.

In vitro experiments have shown that the inhibition of endogenous SPARC enhances cell growth in PDAC. Moreover, treatment with exogenous SPARC significantly suppressed the growth

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**FIGURE 2.** The role of SPARC in the pathophysiology of PDAC. A suggested model.

- **Initiation**
  - Longstanding diabetes
  - Chronic pancreatitis
  - Family history
  - Obesity
  - Recruitment and activation of fibroblasts/PSCs

- **Progression**
  - SPARC is overexpressed due to factors present in the increasing stroma and interactions with abnormal epithelial cells and other cell populations

- **Invasion**
  - SPARC expression lost in PDAC cells
  - Soluble factors secreted by CAFs/PSCs inhibit cell growth by inducing SPARC expression in PDAC cells
  - Soluble factor secreted by PDAC cells decrease SPARC expression in CAFs/PSCs.
  - Still, CAFs/PSCs are able to overexpress SPARC due to autocrine or paracrine stimulation.
  - CAFs/PSCs-secreted SPARC increases the invasive capacity of PDAC cells, resulting in poorer prognosis due to augmented metastasis

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of PDAC cell lines, independently of their endogenous expression and without inducing apoptosis.\textsuperscript{76,75,76} Furthermore, exogenous SPARC caused transient $G_1/S$ phase accumulation in Colo357 and MiaPaCa-2 cells (moderate to low endogenous SPARC levels).\textsuperscript{76,82} SPARC increased the invasive capacity of Colo357 cells. In addition, down-regulation of vascular endothelial growth factor (VEGF) and increased expression of MM2 and $p21$ were observed. Inversely, SPARC down-regulation in Panc-1 (high endogenous SPARC levels) led to increased cell growth and VEGF expression, decreased MMP-2 and $p21$ expression, and reduced the invasive capacity of the.\textsuperscript{76,82} Furthermore, the down-regulation of SPARC in MiaPaCa-2 cells decreases their invasive capacity.\textsuperscript{73}

Matrix metalloproteinases and their blockage have been subject of intensive research. The overexpression of MMP-2 is associated with tumor progression, invasion, and metastasis in PDAC.\textsuperscript{84,85} Interestingly, SPARC expression in PDAC cell lines was positively associated with MMP-2 expression.\textsuperscript{75} SPARC seems to stimulate MMP-2 expression in cancer cells, augmenting their metastatic potential. Moreover, SPARC undergoes proteolysis via MMPs, and the degradation products may have different biological activities.\textsuperscript{86,87} A peptide of SPARC seems to modulate and enhance apoptosis in MiaPaCa-2 cells.\textsuperscript{88}

The cyclin-dependent kinase inhibitor $p21$ promotes cell cycle arrest in response to several stimuli.\textsuperscript{89} Pancreatic ductal adenocarcinoma cells challenged with the controversial drug Ukrain (also called celandine) showed up-regulation of SPARC expression. In addition, the drug inhibited cell proliferation and cell cycle $G_2/M$ arrest.\textsuperscript{75} Thus, cell cycle modulation may be 1 of the mechanisms behind the antiproliferative properties of SPARC in PDAC. Supposedly, $p21$ up-regulation could be a key factor in this context. However, $p21$ has also shown a tumor-promoting function because it is also an inhibitor of apoptosis in cancer.\textsuperscript{89,90} Moreover, it has recently been suggested that SPARC induces $G_1/S$ cell cycle arrest by the up-regulation of $p53$, $p23$\textsuperscript{91} and down-regulation of phosphorylation $pRB$.\textsuperscript{82}

SPARC may act as an angiogenesis inhibitor by regulating the activity of VEGF and platelet-derived growth factor.\textsuperscript{90} The SPARC-dependent down-regulation of VEGF in PDAC cells is a puzzling phenomenon also seen in colon cancer.\textsuperscript{30} Hypothetically, SPARC may in part be responsible for the deregulation of angiogenesis in PDAC, resulting in decreased tumor growth (due to hypoxia), poor vascularization, and changes in the deposition and organization of the tumor microenvironment.

The overexpression of TGF-$\beta_1$ has been associated with pancreatic cancer.\textsuperscript{51} Transforming growth factor $\beta_1$ signaling is important in pancreatic carcinogenesis and can be either tumor suppressive or tumor promoting.\textsuperscript{52} Moreover, high levels of TGF-$\beta_1$ are correlated with metastasis, angiogenesis, and a poor prognosis in cancer.\textsuperscript{81} Exogenous SPARC stimulates the expression of TGF-$\beta_1$ in PDAC cells, whereas TGF-$\beta_1$ expression decreases the expression of SPARC in tumor cells.\textsuperscript{76} The consequences of this observed feedback loop in PDAC carcinogenesis are unknown.

As shown previously, cancer-associated fibroblasts (CAFs) isolated from PDAC tissue lack the abnormal pattern of methylation found in several cancer cell lines.\textsuperscript{56} Consequently, SPARC is highly expressed in these cells, including PSCs.\textsuperscript{70,86} Interestingly, fibroblasts derived from CP or noncancerous tissue from a PDAC patient show a weaker SPARC expression as compared with CAFs.\textsuperscript{56} When cocultured, cancer cells significantly increase the expression of SPARC in fibroblasts from noncancerous tissue.\textsuperscript{56} Unusually, conditioned medium from cancer cells reduced the endogenous expression of SPARC in PSCs. Furthermore, conditioned medium from PSCs has no effect on the endogenous expression of SPARC in cancer cells.\textsuperscript{77} Altogether, it seems that PDAC cells modulate the expression of SPARC in stromal fibroblasts. It is unclear why PDAC cells have opposite effects in naive fibroblasts and PSCs. Remarkably, in vitro experiments exploring the associations between SPARC and PSCs/CAFs in PDAC are very limited. Still, CAFs/PSCs are main protagonists in PDAC tissue, as described above. Based on reported data from PDAC and other malignancies, we propose a model for the role of SPARC in PDAC cells (Fig. 2). This suggestion should be interpreted with caution, because the associations between SPARC and fibroblasts in PDAC are largely unknown.

In PDAC tissue samples, SPARC expression is found both in tumor and stromal cells.\textsuperscript{70,86} In normal pancreas, SPARC is weakly expressed. In normal ductal cells, SPARC is reported as mainly absent or weakly expressed.\textsuperscript{46,76} Compared with normal pancreas, a 31-fold increase in SPARC expression in PDAC has been reported. Likewise, a 16-fold increase was observed in CP when compared with normal.\textsuperscript{76} These results correlate well with $SPARC$ gene methylation patterns found in other experiments.\textsuperscript{56} However, the grade of SPARC overexpression in the different PDAC compartments is debated, as immunohistochemical methods have shown conflicting results (reviewed in Fig. 3). SPARC levels in serum do not appear to be suitable for general screening.\textsuperscript{56,76} Nonetheless, SPARC is highly expressed in the tumor stroma, principally in peritumoral fibroblasts, and the overexpression of SPARC in this compartment is associated with a less favorable prognosis (results presented in Table 3).\textsuperscript{46,70,82,94}

FIGURE 3. Immunohistochemical staining of SPARC in normal pancreas and PDAC. SPARC is found in most tissue samples from PDAC patients. SPARC is highly expressed in stromal fibroblasts. The anatomical image adapted from Don Bliss. The original image was released into the public domain by its author, who has granted anyone the right to use this work for any purpose, without any conditions, unless law requires such conditions. The original image is work of the National Cancer Institute, www.cancer.gov. As a work of the U.S. Federal Government, the image is in the public domain. August 2014.
### TABLE 3. SPARC as a Prognostic Factor in PDAC

| Samples | Survival | SPARC Expression | Survival | SPARC Expression | Prognostic Factor | Reference |
|---------|----------|------------------|----------|------------------|-------------------|-----------|
|         |          |                  | High/Positive SPARC | Low/Negative SPARC |                   |           |
| 29      | 5 y: 20% | Negative: 68.7%  | 5 y: 31.7% | 20%              | SPARC-negative cases had significantly poorer prognosis than SPARC-positive cases | 82        |
|         |          | Positive: 31.3%  |          |                  |                   |           |
| 299     | MOS: 17 mo | Expression most clearly seen in peritumoral fibroblasts | MOS: 15 mo | MOS: 30 mo | UA: stromal SPARC expression in peritumoral fibroblast was correlated with poor prognosis. HR, 2.36 (95% CI, 1.67–3.34) | 47        |
|         |          | Tumor negative/stroma negative: 17% |          |                  | SPARC expression in PDAC cells was not associated with prognosis |           |
|         |          | Tumor positive/stroma negative: 17% |          |                  |                   |           |
|         |          | Tumor negative/stroma positive: 52% |          |                  |                   |           |
|         |          | Tumor positive/stroma positive: 15% |          |                  |                   |           |
| 49      | MOS: 10 mo | Expressed predominantly in the peritumoral and distal stroma | MOS: 7.6 mo | MOS: 10.2 mo | High SPARC expression in peritumoral stroma was not a prognostic factor | 46        |
|         |          |                  | 10-mo survival: 29% | 10-mo survival: 52% | MA: high SPARC expression in distal stroma was a strong prognostic factor for survival in patients treated with CRT. HR, 2.23 (95% CI, 1.31–2.74) | 49        |
|         |          |                  | 15-mo survival: 12% | 15-mo survival: 35% | No statistical significance reached | 93        |
| 31      | MOS: 14 mo | Low: 64.5% | 10 mo (95% CI, 6–14 mo) | 27 mo (95% CI, 7–47 mo) | High SPARC expression in peritumoral stroma was not a prognostic factor | 46        |
| (Range, 2–60) |          |                  |          |                  |                   |           |
| 104     | High: 35.5% | Low: 90.4% | 5 y: 0.0% | 5 y: 22.48% | UA: high SPARC expression was positively correlated with poor prognosis | 49        |
| (Range, 2–60) |          |                  |          |                  |                   |           |
| 160     | MOS: 21.5 | Low stromal: 41.9% | MDFS | MDFS | MA: high SPARC expression was an independent prognostic factor for poor survival. HR, 1.29 (95% CI, 1.63–5.50) | 48        |
| (Range, 9.2–13.3) | High stromal: 58.1% | Stromal: 9.0 mo (95% CI, 5.4–12.5 mo) | Stromal: 12.6 mo (95% CI, 9–16 mo) | MA: SPARC expression was independently predictive of patient outcome. HR, 1.47 (95% CI, 1.02–2.14) |           |
| MOS: 7.4 | Low cytoplasmic: 40.6% | Cytoplasmic: 10.7 mo (95% CI, 7.6–14.0 mo) | Cytoplasmic: 11.8 mo (95% CI, 9.1–14.5 mo) |            |           |
| (Range, 17.6–25.4) | High cytoplasmic: 59.4% | Stromal: 19.5 mo (95% CI, 14–25.7 mo) | Stromal: 26.6 mo (95% CI, 17.2–36.1 mo) | MA: SPARC expression was independently predictive of patient outcome. HR, 1.47 (95% CI, 1.02–2.14) |           |
| (Range, 9.2–13.3) |                  | Cytoplasmic: 20.4 mo (95% CI, 16.5–24.3 mo) | Cytoplasmic: 26.2 mo (95% CI, 18.6–34.7 mo) |

CI indicates confidence interval; CRT, chemoradiation; HR, hazard ratio; MA, multivariate analysis; MDFS, median disease-free survival; MOS, median OS; UA, univariate analysis.
SPARC in Murine PDAC

Pan02 is a murine PDAC cell line with the capacity to cause aggressive tumors in orthotopic models.95 This cell line has been used in several important experiments. In murine PDAC, SPARC is involved in several mechanisms comprising tumor growth, apoptosis, invasive capacity, angiogenesis, ECM composition, and immune response.39,79,96–100 Interestingly, Pan02 is capable of producing SPARC both in vitro and in vivo, a finding that strongly differs from data reported in human PDAC cell lines.56,79 Apparently, SPARC has mainly tumor suppressor functions in murine disease. Nevertheless, murine PDAC models have resulted in invaluable data for the elucidation of the role of SPARC in human PDAC. The associations found in murine PDAC are summarized in Table 4.

In essence, in vitro studies indicate that SPARC has both oncogenic and tumor suppressor properties. Seemingly paradoxical, the influence of SPARC in PDAC may be explained by pole-opposite effects that the protein has in different cell populations in the tumor microenvironment. Interestingly, SPARC is found not only in primary tumors, but also in metastases. This indicates that SPARC is associated with PDAC, independently of differentiation grade or site of metastasis. As in murine disease, SPARC seems to be a tumor suppressor in PDAC cells, but as SPARC overexpression is related to a poor prognosis, it can be assumed that the oncogenic functions in stromal cells are prevailing in PDAC. However, SPARC seems to interact with albumin-bound paclitaxel (nab-paclitaxel, Abraxane, ABI-007), opening a new window of opportunity in PDAC.

### TABLE 4. The Role of SPARC in Murine PDAC

| Reported Association | Reference |
|----------------------|-----------|
| SPARC is expressed in Pan02 cells and in tumors | 79 |
| SPARC is produced by Pan02 cells in vitro and in vivo | 79 |
| SPARC enhances the migration potential in Pan02 cells | 98 |
| Exogenous SPARC does not affect the proliferation rate in Pan02 cells | 79 |
| Increase in pericyte recruitment by diminishing TGF-β1 activity | 100 |
| Lack of host endogenous SPARC causes Enhanced tumor growth | 79,96,97 |
| Reduced apoptosis in tumor cells | 79 |
| Alteration in the disposition of ECM constituents within the tumor | 79 |
| Decrease in collagen fibrillogenesis at the tumor borders | 99 |
| Increased macrophage recruitment/activation | 99 |
| Polarization of the macrophages within tumor toward an M2 phenotype | 99 |
| Altered distribution of macrophages within the tumor | 79 |
| Increased recruitment and mobilization of regulatory T cells | 98 |
| Decreased microvessel density | 99 |
| Increased perfusion and vascular permeability | 99 |
| Reduced density of the vascular basement membrane | 99 |
| Discontinuous endothelial cell layer | 99 |
| Decreased hypoxia in tumors | 99 |
| Reduced periocyte recruitment | 99 |
| A decrease in the percentage of blood vessels that maintain pericyte support | 79 |
| Increased invasion and metastasis | 97–99 |
| Less differentiated tumors | 96 |
| Reduced survival | 96,99 |
| Increased TGF-β1 activity | 98 |

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TARGETING SPARC IN PDAC

Paclitaxel is a microtubule-stabilizing agent that inhibits the depolymerization of microtubules, inducing mitotic arrest in G2 and M phases of the cell cycle, resulting in cell death.101–103 Consequently, paclitaxel shows selectivity for proliferating cells over quiescent cells. Paclitaxel is considered a cornerstone of therapy in breast, ovarian, and non–small-cell lung cancer.104 Solvent-based (ab-) paclitaxel and docetaxel (a semisynthetic analog) have shown encouraging results in several clinical trials and are approved treatment components in different cancer types.105 However, these compounds are associated with less predictable pharmacologic profiles, hypersensitivity reaction, and toxicity.106 Thus, the promising effect of paclitaxel was self-limited by the occurrence of serious adverse events (AEs), and novel formulations were highly demanded.

Albumin is the most abundant protein in blood plasma, constituting more than 50% of total proteins. Albumin, noncovalently and reversibly, binds molecules in the bloodstream. Moreover, the protein has a long lifetime (about 21 days) and does not elicit an immune response. These characteristics make albumin an attractive candidate for selective drug delivery.107,108 Nab-paclitaxel is formulated with human serum albumin with a concentration similar to the concentration of albumin seen under physiological conditions.109 The drug is obtained by high-pressure homogenization in which particles measuring 130 nm in diameter are created. Importantly, albumin and paclitaxel are not covalently bound after the process, but rather linked through hydrophobic interactions.110 Upon injection, the particles dissolve into soluble albumin-paclitaxel complexes measuring 10 nm. Because of its combination with albumin, nab-paclitaxel can be reconstituted with simple saline solution.106 Thus, nab-paclitaxel can be administered without solvent-related risks and steroid or antihistamine prophylaxis. Moreover, nab-paclitaxel can be administered at higher doses when compared with sb-paclitaxel and docetaxel, and it has a more predictable pharmacokinetic profile.106,111

The mechanisms of delivery of nab-paclitaxel are closely associated with the biological properties of albumin. Two major mechanisms have been described: transcytosis and the enhanced permeability and retention effect. Both mechanisms have recently been summarized by others and are described in Figure 4.104,106 Importantly, it has been shown that injected albumin-conjugated molecules accumulate in proximity of tumors.112,113 SPARC has high affinity for albumin.56 It has been suggested that SPARC present in the tumor stroma could sequester nab-paclitaxel, enhancing the delivery of paclitaxel into the tumor microenvironment. The resulting “stromal collapse” effect is defined as stromal depletion that brings tumor cells closer to each other and to blood vessels.114 Still, it has been debated if SPARC is related to nab-paclitaxel efficacy, because SPARC deficiency did not affect the intratumoral nab-paclitaxel concentration, stromal deposition, and the immediate therapeutic response in genetically engineered mice.115 Results from murine models suggest that nab-paclitaxel reduces the levels of cytidine deaminase, an enzyme responsible for the primary metabolism of gemcitabine.116

Several clinical trials evaluating the effect of nab-paclitaxel in metastatic PDAC have been completed with encouraging results (Table 5). In a phase I/II clinical trial, the nab-paclitaxel maximum tolerated dose (MTD) has been established at 125 mg/m² on days 1, 8, and 15 every 28 days in combination with fixed doses of gemcitabine (1000 mg/m² on days 1, 8, and 15 every 28 days).118
Dose-limiting toxicities (DLTs) were neutropenia and sepsis. At the MTD, a median overall survival (OS) of 12.2 months was registered. The response rate was 48%. The OS was correlated with stromal SPARC, decreased CA 19-9 levels, and complete metabolic response analyzed by 18F-fluorodeoxyglucose positron emission tomography. Interestingly, patients with complete metabolic response had significantly longer survival (20.1 months) than those without complete response (10.3 months). The expression of SPARC was evaluated in 36 patients. Those with high SPARC expression had a significant increase in OS compared with patients with low SPARC expression (17.8 vs 8.1 months). Concordantly with previous results (Table 3), stromal SPARC levels (but not SPARC in tumor cells) were a significant predictor for OS in multivariate analysis. Thus, nab-paclitaxel appears to interact with stromal SPARC. Interestingly, stromal SPARC, a confirmed factor for poorer prognosis in PDAC, has become good news upon nab-paclitaxel treatment, as SPARC overexpression seems to be associated with better treatment response rates and increased OS.

Preclinical studies coupled to this study showed that in mice with human PDAC xenografts nab-paclitaxel, alone or combined with gemcitabine, caused stromal depletion. Tumor regression was observed in 64% of the animals. Likewise, nab-paclitaxel treatment increased 2.8-fold the intratumoral concentration of gemcitabine when compared with gemcitabine monotherapy. Altogether, these results support previous theories about the association between SPARC, nab-paclitaxel, and stromal depletion.

In another phase I/II trial, the combination of nab-paclitaxel and gemcitabine was evaluated in Chinese patients. Nab-paclitaxel at 120 mg/m² on days 1 and 8 every 21 days in combination with fixed doses of gemcitabine (1000 mg/m² on days 1 and 8 every 28 days) was administered. The regimen was well tolerated. Moreover, the MTD was not met, but similar results concerning DLTs and median OS were observed. Interestingly, this regimen resulted in lower response rates and progression-free survival (PFS) as compared with previous results. This may in part be caused by the lower dose of nab-paclitaxel administered.
### TABLE 5. Clinical Trials Evaluating the Effect of Nab-Paclitaxel (Abraxane) in PDAC

| Phase | Tumor Stage | Combination | No. of Patients | Arms/Groups | Efficacy Results | Safety Results |
|-------|-------------|-------------|----------------|-------------|-----------------|---------------|
| I     | Metastatic  | Gemcitabine (750 or 1000 mg/m² on day 4 every 14 d) Capcitabine (750 mg/m² BID days 1–7 every 14 d) | 15 | Abraxane 100 mg/m² + gemcitabine 750 mg/m² on day 4 + capcitabine 750 mg/m² BID days 1–7 (dose level 0) Abraxane 100 mg/m² + gemcitabine 1000 mg/m² on day 4 + capcitabine 750 mg/m² BID days 1–7 (dose level 1) | MTD: dose level 0 Median PFS (n = 14): 4.5 mo Median OS (n = 14): 7.5 mo Partial response, dose level 0: 14.3% | DLTs: anemia, neutropenia and nausea/vomiting Treatment-related AEs (most common): anemia (80%), fatigue (80%), maculopapular rash (66.7%), alopecia (60%), anorexia/weight loss (60%), nausea/vomiting (53%), pruritus (53%), and hand-foot syndrome (46.7%) Most common grade ≥3 AEs: elevated LFTs (13.3%), nausea/vomiting (13.3%), anemia (6.7%), and neutropenia (6.7%). Ten patients (66.7%) experienced at least 1 grade 3–4 AE |
|      |             |             |                |             |                 |               |
| I/II | Metastatic  | Gemcitabine (1000 mg/m² on days 1, 8, and 15 every 21 d) | 67 | Abraxane 100 mg/m² + gemcitabine (dose level 1) Abraxane 125 mg/m² + gemcitabine (dose level 2) Abraxane 150 mg/m² + gemcitabine (dose level 3) | MTD: dose level 2 (n = 44) Median PFS: 7.9 mo (95% CI, 5.8–11.0 mo) Median OS: 12.2 mo (95% CI, 8.9–17.9 mo) 1-y Survival: 48% For all 67 patients: Median PFS: 7.1 mo (95% CI, 5.7–8.0 mo) Median OS: 10.3 mo (95% CI, 8.4–13.6 mo) | DLTs: sepsis and neutropenia Treatment-related AEs: anemia (98%), leukopenia (91%), neutropenia (89%), thrombocytopenia (83%), fatigue (76%), alopecia (76%), sensory neuropathy (63%), and nausea (48%) Most common grade ≥3 AEs: neutropenia (67%), leukopenia (44%), thrombocytopenia (23%), fatigue (21%), and sensory neuropathy (15%) |
|      |             |             |                |             |                 |               |
| I/II | Metastatic  | Gemcitabine (1000 mg/m² on days 1 and 8 every 21 d) | 21 | Abraxane 80 mg/m² + gemcitabine (dose level 1) Abraxane 100 mg/m² + gemcitabine (dose level 2) Abraxane 120 mg/m² + gemcitabine (dose level 3) | MTD: was not met; dose level 3: Median PFS: 5.23 mo (95% CI, 3.42–7.04 mo) Median OS: 12.17 mo (95% CI, 4.09–20.14 mo) For all 21 patients: Median PFS: 4.43 mo (95% CI, 4.01–4.83 mo) Median OS: 12.17 mo (95% CI, 9.49–14.84 mo) | ORR dose level 2: 48% ODCR dose level 2: 68% DLTs: elevated ALT and febrile neutropenia Treatment-related AEs: nausea/vomiting (61.90%), neutropenia (57.14%), alopecia (42.86%), anemia (33.33%), fatigue (38.10%), thrombocytopenia (19.05%), sensory neuropathy (9.52%), elevated ALT/AST (9.52%), diarrhea (4.76%), and rash (4.76%) Most common grade ≥3 AEs: neutropenia (9.52%), febrile neutropenia (4.76%), thrombocytopenia (4.76%), and sensory neuropathy (4.76%) |

(Continued on next page)
| Phase | Tumor Stage | Combination | No. of Patients | Arms/Groups | Efficacy Results | Safety Results | Reference |
|-------|-------------|-------------|----------------|-------------|-----------------|---------------|-----------|
| II    | Advanced    | None        | 19             | Abraxane 100 mg/m² on days 1, 8, and 15 every 28 d | Median PFS: 1.7 mo (95% CI, 1.5–3.5 mo) | Treatment-related AEs (most common): nausea (63%), anorexia (47%), hypocalcaemia (37%), and vomiting (26%) | 96 |
|       |             |             |                |             | Median OS: 7.3 mo (95% CI, 2.8–15.8 mo) | Most common grade ≥3 AEs: neutropenia (32%), febrile neutropenia (11%), and anemia (11%) |          |
|       |             |             |                |             | 6-mo OS: 58% (95% CI, 33%–76%) |                |          |
|       |             |             |                |             | 1 Patient had confirmed partial response |                |          |
|       |             |             |                |             | 6 Patients (32%) had stable disease as their best response |                |          |
|       |             |             |                |             | Median PFS: 1.7 mo (95% CI, 1.5–3.5 mo) |                |          |
|       |             |             |                |             | Median OS: 7.3 mo (95% CI, 2.8–15.8 mo) |                |          |
|       |             |             |                |             | 6-mo OS: 58% (95% CI, 33%–76%) |                |          |
|       |             |             |                |             | 1 Patient had confirmed partial response |                |          |
|       |             |             |                |             | 6 Patients (32%) had stable disease as their best response |                |          |
| III   | Metastatic  | Gemcitabine (1000 mg/m² on days 1, 8, and 15 every 28 d) | 861           | Albumin-bound paclitaxel 125 mg/m² + gemcitabine (N + G) | Median PFS (N + G): 5.5 mo (95% CI, 4.5–5.9 mo); median PFS (G): 3.7 mo (95% CI, 3.6–4.0 mo); HR, 0.69 (95% CI, 0.58–0.82) | Treatment-related AEs (N + B): fatigue (54%), alopecia (50%), and nausea (49%) | 12 |
|       |             | Gemcitabine 1000 mg/m² weekly for 7 of 8 wk (cycle 1) and then on days 1, 8, and 15 every 28 d (cycle 2 and subsequent cycles) (G) | | | | Most common grade ≥3 AEs: neutropenia (32%), febrile neutropenia (11%), and anemia (11%) |          |
|       |             |             |                |             | Median OS (N + G): 8.5 mo (95% CI, 7.9–9.5 mo); median OS (G): 6.7 mo (95% CI, 6.0–7.2 mo); HR, 0.72 (95% CI, 0.62–0.83) | |          |
|       |             |             |                |             | 1-y Survival (N + G): 35% (95% CI, 30%–39%); 1-y survival (G): 22% (95% CI, 18%–27%) | |          |
|       |             |             |                |             | 2-y Survival (N + G): 9% (95% CI, 6%–13%); 2-y survival (G): 4% (95% CI, 2%–7%) | |          |
|       |             |             |                |             | ORR (N + G): 23% (95% CI, 19%–27%); ORR (G): 7% (95% CI, 1%–5%) | |          |

ALT indicates alanine transaminase; AST, aspartate aminotransferase; HR, hazard ratio; LTFs, liver function tests; ODCR, overall disease control rate; ORR, overall response ratio.
As nab-paclitaxel alone results in stromal depletion and tumor regression in tumor xenografts, a small phase II trial with the drug as monotherapy was carried out in patients with advanced disease as second-line therapy following gemcitabine-based therapy. At 100 mg/m² on days 1, 8, and 15 every 28 days, nab-paclitaxel administration resulted in a median PFS of 1.7 months, an OS of 7.3 months, and a 6-month survival of 58%. Unexpectedly, only 2 of 15 patients had positive SPARC expression in examined tissues, and these patients did not respond to treatment. Even if this report supports results from experiment in mice that disprove the role of SPARC in the nab-paclitaxel effect, it should be noted that the origin of the biopsies in this clinical trial was not specified. This is of significance because the pattern of SPARC expression may differ between primary tumors and metastases.

Other drugs have been tested in combination with nab-paclitaxel. For instance, nab-paclitaxel combined with gemcitabine and increasing doses of vandetanib (Caprelsa) was tried in a phase I trial in different solid tumors, including metastatic PDAC. Vandetanib is a kinase inhibitor commonly used in medullary thyroid cancer. The combination showed acceptable tolerance levels and a partial response rate of 14.3%. However, AEs of grade 3 or greater were experienced by more than 66% of patients. Nab-paclitaxel, combined with 5-fluorouracil, leucovorin, oxaliplatin, and bevacizumab, has shown a surprisingly high response rate (50%) in a phase II trial. According to clinicaltrials.gov, there are 39 clinical trials registered (4 active not recruiting and 35 recruiting) for the evaluation of nab-paclitaxel, alone or in combination with other agents, in different PDAC stages (search results for “nab-paclitaxel” AND “pancreatic cancer,” “Abraxane” AND “pancreatic cancer”; accessed August 2014).

The promising results of phase I/II trials led to a very important phase III clinical trial comprising 861 PDAC patients (MPACT: Metastatic Pancreatic Adenocarcinoma Clinical Trial). The previous regimen of nab-paclitaxel at 125 mg/m² on days 1, 8, and 15 every 28 days in combination with fixed doses of gemcitabine (1000 mg/m² on days 1, 8, and every 28 days) was compared with gemcitabine monotherapy (1000 mg/m² weekly for 7 of 8 weeks and then on days 1, 8, and 15 every 28 days). The results are summarized in Table 5. Briefly, the combination increased the PFS (5.5 vs 3.7 months) and the median OS (8.5 vs 6.7 months). Importantly, nab-paclitaxel combined with gemcitabine showed superior response rates (23% vs 7%), 1-year survival (35% vs 22%), and 2-year survival (9% vs 4%), as compared with gemcitabine alone. Even if grade 3 or higher AEs were observed (especially sensory neuropathy), these were reversible and disappeared or improved to grade 1 in less than 30 days. Based on these solid data, the Us Food and Drug Administration approved nab-paclitaxel combined with gemcitabine for first-line treatment in metastatic PDAC in September 2013.

Like FOLFIRINOX, nab-paclitaxel combined with gemcitabine has become a new option among therapeutic agents used against PDAC. The next quest is to find combinations that take advantage of the stromal depletion induced by nab-paclitaxel. Similarly to FOLFIRINOX, the implementation of the new regimen may not be limited to metastatic disease and could be implemented as neoadjuvant therapy in less malignant PDAC stages. Retrospective studies have shown promising results in resectable, locally advanced, and borderline/unresectable PDAC. Interestingly, sequential neoadjuvant administration of nab-paclitaxel plus gemcitabine and FOLFIRINOX seems to induce complete remission in locally advanced and unresectable PDAC. Thus, nab-paclitaxel has emerged as a central therapeutic agent in PDAC, and it may become part of novel therapeutic regimens in the future.

**CONCLUSIONS**

Despite conflicting results, most data indicate that SPARC plays an important role in the pathophysiology of PDAC. The fact that the SPARC gene is already hypermethylated in premalignant lesions indicates that the protein is important in tumor initiation and progression. Even if SPARC acts as a tumor suppressor in PDAC tumor cells, the overexpression of SPARC in peritumoral fibroblast has devastating effects leading to an even worse prognosis. Apparently, PDAC cells and components of the tumor microenvironment induce SPARC overexpression in stromal cells. However, the mechanisms behind this effect are completely unknown. While serum SPARC levels do not seem to be useful as a tumor marker, increased SPARC levels in serum, pancreatic juice, or ascites could be used in the prediction of response rates to nab-paclitaxel–containing regimens. Likewise, methylation panels comprising SPARC may be suitable for early detection. The associations between nab-paclitaxel and SPARC are controversial. Preclinical results suggest that stromal depletion achieved upon nab-paclitaxel treatment is associated with SPARC. However, murine studies suggest the opposite. The combination of nab-paclitaxel and gemcitabine has shown promising results, but it should be remembered that the median survival is prolonged only by 1.8 months when compared with gemcitabine alone. Thus, despite the improvements accomplished during the past years, PDAC still has a dismal prognosis. Perhaps, more efforts should be put on the development of novel compounds that takes advantage of the high affinity of SPARC for albumin. Nab technology could be combined with other chemotherapeutic agents.

The use of nanoparticles for drug delivery in cancer is a reality, and it is only a matter of time before novel and more effective compounds targeting SPARC in PDAC are discovered. To reach this goal, further research and elucidation of involved mechanisms between SPARC and PDAC are warranted.

**REFERENCES**

References are available online at: http://links.lww.com/MPA/A450.