Pancreatic cancer remains one of the most intractable cancers, with a dismal prognosis reflected by a 5-year survival of ~6%. Since early disease symptoms are undefined and specific biomarkers are lacking, about 80% of patients present with advanced, inoperable tumors that represent a daunting challenge. Despite many clinical trials, no single chemotherapy agent has been reliably associated with objective response rates above 10% or median survival longer than 5 to 7 months. Although combination chemotherapy regimens have in recent years provided some improvement, overall survival (8-11 months) remains very poor. There is therefore a critical need for novel therapies that can improve outcomes for pancreatic cancer patients. Here, we present a summary of the current therapies used in the management of advanced pancreatic cancer and review novel therapeutic strategies that target tumor biomarkers. We also describe our recent research using phosphatidylserine-targeted saposin C–coupled dioleoylphosphatidylserine nanovesicles for imaging and therapy of pancreatic cancer.

Introduction
Although it ranks as the 12th most frequent cancer worldwide, pancreatic cancer is the 4th leading cause of cancer-related deaths and carries the highest mortality rate (~94% at 5 years) of all major cancers [1,2]. In the United States, where currently about 127 people are diagnosed with pancreatic cancer and 108 die of the disease each day, a recent analysis predicts that pancreatic cancer will become the second leading cause of cancer deaths by 2030 [3,4]. Its most prevalent form at diagnosis, pancreatic ductal adenocarcinoma (PDAC), is usually asymptomatic in its early stages but progresses rapidly. Thus, the majority of the pancreatic cancer cases are detected when the tumor has already metastasized and about 70% of these patients die of the disease in less than 1 year. A minority of patients, around 15% to 20%, are eligible for potentially curative resection, and yet, in spite of adjuvant, post-resection chemotherapy or chemoradiation, the 5-year survival for these patients is only 20%, with death resulting from metastatic disease and/or locoregional recurrences [5,6].

Etiology and Pathogenesis of Pancreatic Cancer
The etiology of pancreatic cancer remains largely unknown. It is believed that PDAC arises not from ductal cells but through a process known as acinar to ductal metaplasia, in which mature acinar cells transdifferentiate into ductal-like cells [7]. The risk increases with age (>50 years), obesity, and type 2 diabetes. Smoking is the most common risk factor, responsible for ~25% of PDAC cases [8,9]. Genetic predisposition, involved in 5% to 10% of cases, has been
associated with several germline mutations in the BRCA2, STK11/ LKB1, p16/CDKN2A, and PRSS1 genes [10]. Inflammation, associated with chronic pancreatitis (commonly triggered by heavy alcohol consumption), also increases the risk of pancreatic cancer [11,12].

A signature molecular profile has emerged from genetic studies, identifying activating mutations in the oncogene KRAS and inactivating mutations in the tumor suppressors CDKN2A, TP53, and SMAD4/DPC4, as the main drivers of pancreatic carcinogenesis [13,14]. Analysis of early-, middle-, and late-stage disease samples revealed that mutations in these genes arise sequentially and contribute to increased malignancy [15]. Propelling the search for novel therapies, further insights highlighting the complexity of PDAC have come from genetic studies showing that advanced pancreatic cancers contain an average of 63 genetic alterations, defining 12 core signaling pathways represented in two thirds of all tumors analyzed [13]. Another significant step forward was provided by a recent analysis of clinical data sets and human pancreatic cancer cell lines, which allowed the molecular characterization of three subtypes of PDAC, namely, classic, quasimesenchymal, and exocrine-like, with distinct progression rates and differential therapeutic responses [16].

**Current Treatment Strategies**

**Early-Stage Resectable PDAC**

Complete surgical resection with negative surgical margins (R0 resection) is the only treatment that can potentially result in long-term survival for some patients with early-stage pancreatic cancer (5-year survival around 20%). However, only 15% to 20% of patients are eligible for surgical resection, and many of these patients develop recurrent and metastatic disease soon after resection. Several studies have shown negative surgical margin and nodal status as important prognostic factors. In fact, some studies have demonstrated similar survival of early-stage PDAC patients who had positive surgical margins and locally advanced unresectable PDAC patients treated with chemoradiotherapy or chemotherapy only [17]. Adjuvant chemotherapy improves the outcomes for these patients, as shown in the European Charité Onkologie CONKO-001 trial where 368 patients were randomly assigned to gemcitabine versus observation after surgical resection. This study showed significant and persistent improvement in overall survival with 6 months of gemcitabine therapy (21% vs 10%, 5-year survival and 12.2% vs 7.7%, 10-year survival) [18].

Neoadjuvant chemotherapy or chemoradiotherapy is gaining popularity in an attempt to achieve R0 resection in more patients. Phase I/II studies have demonstrated that neoadjuvant chemoradiotherapy can be safely delivered to patients with localized pancreatic cancer; however due to the lack of a surgery-alone arm, it is not clear if this approach improves resectability or survival, and benefits are not inferior to adjuvant therapy. Advancements in imaging and surgical techniques have made the distinction between resectable and unresectable locally advanced tumors somewhat blurry, and more patients are classified as borderline resectable. Neoadjuvant therapy may be especially useful in these patients, and clinical trial participation is strongly encouraged in this group of patients to determine the most appropriate preoperative therapy.

**Unresectable Locally Advanced PDAC**

For almost 40% of PDAC patients with unresectable non-metastatic disease, there is no known best treatment strategy, and options include radiotherapy, chemotherapy, or chemoradiotherapy [19]. Most patients undergo chemotherapy initially, with single agent gemcitabine still considered standard treatment in this setting [20,21]. Many centers however are using FOLFIRINOX, a combination of 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin, for patients with excellent performance status and normal liver function or gemcitabine with nab-paclitaxel, citing higher response rates for these combination chemotherapy regimens in the metastatic setting (10% with gemcitabine alone, 23% with gemcitabine plus nab-paclitaxel [albumin-bound paclitaxel] i.e. GEM/NAB-P, and 32% with FOLFIRINOX), making it more likely to convert these patients into resectable disease [22,23]. However, evidence from prospective trials in favor of this theory is still lacking, and no randomized trials have been conducted comparing neoadjuvant versus adjuvant therapy. Most patients will also undergo chemoradiotherapy if no progression is noted on interval staging. Best concomitant chemotherapy with external beam radiotherapy is also not well established and could include infusional 5-FU, capecitabine, or gemcitabine. Many centers are also evaluating stereotactic body radiation as an alternative to conventional external beam radiotherapy. Unfortunately, even with all these therapies, the prognosis, rate of resection, and long-term survival remain dismal for patients who initially have categorically unresectable tumors at diagnosis.

**Metastatic PDAC**

Pancreatic cancer is strikingly unresponsive to most conventional chemotherapies [24]. The nucleoside analog gemcitabine (2′,2′-difluorodeoxycytidine), adopted in the mid-1990s as first-line chemotherapy, provides only modest survival benefits (<6 months) to pancreatic cancer patients [25] and has been combined with many other drugs, including cisplatin, [26,27] oxaliplatin [28,29], irinotecan [21,30], exatecan [31], 5-FU [32], and pemetrexed [33], in phase III trials without significant improvements [2]. Although gemcitabine in combination with erlotinib (an inhibitor of the epidermal growth factor receptor type 1) demonstrated a statistically significant improvement in overall survival (6.2 vs 5.9 months) in a phase III study, the difference was not clinically meaningful [34]. In 2011, FOLFIRINOX showed significant survival benefit (11.1 vs 6.8 months) compared with gemcitabine alone in a phase III study of metastatic PDAC [22]. This trial also demonstrated a significant increase in toxicity, limiting the use of FOLFIRINOX to patients with good performance status [35]. Another phase III study evaluated GEM/NAB-P versus gemcitabine alone in patients with untreated metastatic pancreatic cancer after early studies showed promising activity of this combination [23]. The combined chemotherapy yielded a modest but significant survival benefit (8.5 vs 6.7 months), and due to its milder toxicity, it may be a better option for older patients with poorer performance status [36]. A recent network meta-analysis of chemotherapy regimens for advanced pancreatic cancer provided a comprehensive assessment of the efficacy and tolerability of combined therapies versus gemcitabine alone [37].

**Molecular Targets for Pancreatic Cancer Therapy**

On the basis of our increasing knowledge of the genetic and molecular alterations in pancreatic cancer, numerous trials combining gemcitabine and one or more tumor-targeted agents are currently under way [38]. These efforts are largely driven by preclinical data generated in animal models, including heterotopic and orthotopic human pancreatic cancer xenografts as well as genetically engineered mouse models that closely resemble the molecular alterations encountered in the clinic [39,40]. Among the latter, the most enticing target is the...
KRAS, a critical driver of tumorigenesis that is mutated in ~95% of pancreatic cancers [41–43]. Thirty years after this realization, however, attempts to target activating, mutant KRAS proteins have been largely unsuccessful [20,44]. New approaches have focused instead on targeting RAS effector pathways such as RAF→mitogen-activated protein kinase kinase→extracellular signal-regulated kinase and phosphatidylinositol 3-kinase→AKT, with synergistic antitumor effects observed upon simultaneous inhibition of these pathways in human cell lines and pancreatic cancer mouse models [45]. Recent studies also advanced potential therapies that target gene transcription mediated by the proto-oncogene c-Myc [46] and mitochondrial respiration in stem cells resistant to KRas ablation [47].

**Tumor Stroma**

Advanced pancreatic tumors have a dense, fibrotic, hypovascular stroma with low cellularity and pro-inflammatory infiltrating cells (i.e., desmoplastic reaction) that contributes to tumor progression and reduces therapeutic success by hampering the penetration of drugs [48,49]. In recent years, several studies sought to target the cellular components (pancreatic stellate cells, fibroblasts, and immune cells) of the desmoplastic matrix and their tumor-promoting molecular mediators, such as cytokines, growth factors, and metalloproteases (MMPs) [50]. Two animal model studies in particular shed light on the importance of the PDAC stroma in the resistance to antitumor therapies. The first, conducted in a genetically engineered mouse model, showed that inhibition of the Hedgehog signaling pathway, involved in tumor-stromal crosstalk, depleted the tumor stroma, restored vascularity, enhanced delivery of gemcitabine, and produced a modest extension in survival, although the stromal reaction ultimately returned [51]. Unfortunately, a clinical trial prompted by this research was stopped before conclusion due to better responses in the control arm. The second preclinical study tested gemcitabine with enzymatic therapy to degrade hyaluronic acid, a main determinant of the barrier properties of PDAC stroma; this treatment normalized interstitial pressure and vascularization and doubled survival in mice [52]. MMPs play a fundamental role in tumor stroma remodeling and promotion of tumor growth [53,54]. Building on promising preclinical data, anti-MMP therapies using marismat and BAY-12-9566 were tested in clinical trials without positive results [48]. Likewise, attempts to block angiogenesis, a critical mechanism facilitating the expansion of most solid tumors, also yielded disappointing results in clinical trials [55–57]. However, animal studies suggest that novel antiangiogenic therapies targeting the C-X-C chemokine receptor type 2 may prove beneficial [58].

**Tumor Immunity and Inflammation**

Inflammation and immunosuppression collaborate to create a permissive environment for tumor growth [50,59]. Highlighting the role of immunosuppression in pancreatic cancer, preclinical studies showed that ablation of KRAS-driven granulocyte-macrophage...
colony-stimulating factor production reduced myeloid cell infiltration, unleashing T cell (CD8+)–dependent immune responses and causing tumor growth arrest [60,61]. Further efforts to evoke intrinsic antitumor responses are exemplified by the development of an α-enolase DNA vaccine, which halted tumor progression by activating humoral and cellular responses [62], and vaccination with *Listeria* monocytes engineered to express Kras(G12D) after depletion of regulatory T cells, which triggered T cell–dependent cytotoxicity and blocked tumor progression at early stages [63].

Tumor-associated macrophages are another relevant therapeutic target, since they contribute to gemcitabine resistance by upregulating cytidine deaminase, the enzyme that metabolizes gemcitabine, rendering it inactive [64]. In a small study of patients with inoperable PDAC, administration of an agonist CD40 antibody in combination with gemcitabine caused tumor regression in some patients [65]. Modeling this study in mice showed that pancreatic tumor-associated macrophages became activated on CD40 antibody ligation and elicited T cell–independent antitumor actions leading to a tumor regression rate (~ 30%) that reproduced that in human patients [66]. Other appealing therapeutic targets are the signaling hubs represented by the Stat3 and nuclear factor kappa-light-chain-enhancer of activated B cells pathways, which determine the release of proinflammatory cytokines such as tumor necrosis factor alpha and interleukins 6 and 1 [50].

**Phosphatidylserine-Targeted Imaging and Therapy of Pancreatic Cancer with SapC-DOPS Nanovesicles**

Phosphatidylserine (PS) is an anionic phospholipid with important structural and signaling properties [67]. In animal cell membranes, it localizes in the internal aspect of the cell membrane, but it is externalized on induction of apoptosis and at sites of injury, where it stimulates hemostasis and activates the complement cascade [68,69]. Notably, viable cancer cells and tumor-associated vascular cells usually present elevated levels of PS on the surface of their membranes [70,71]. It is not clear whether this is advantageous for tumor cells, although evidence seems to indicate that tumor immunity and metastatic potential may be counteracted and favored, respectively, by increased surface PS levels [72]. In the last decade, our group and others have worked to exploit this distinctive feature of cancer cells to develop PS-targeted therapies. What follows is a summary of our work using PS-binding lipid-protein nanovesicles for imaging and treatment of pancreatic cancer.

Saposin C (SapC) is a small, thermostable lysosomal protein that binds to PS and acts as a co-factor in the activation of acid β-glucosidase, acid sphingomyelinase, and acid β-galactosylceramidase [73,74]; the catalytic action of these enzymes results in the formation of ceramide, a well-established pro-apoptotic mediator [75]. Given the strong affinity of SapC toward PS, and its role

![Figure 2](image-url)
in lysosomal hydrolase activation, we hypothesized that SapC-containing nanovesicles may be useful agents to selectively target and kill tumor cells. To this end, we combined recombinant human SapC and dioleoylphosphatidylserine (DOPS) to generate stably assembled proteoliposomal nanovesicles (SapC-DOPS) [76] and tested their targeting and antitumor capabilities against pancreatic cancer cells [77]. We first examined the correlation between PS levels and the antitumor efficacy of SapC-DOPS in a panel of eight human pancreatic cancer cell lines. As shown for glioblastoma [78] and lung cancer cells [79], a higher killing capacity (i.e., lower half maximal inhibitory concentration; IC50) was observed for high PS-expressing cells (Figure 1). To evaluate the tumor-targeting potential of SapC-DOPS, we attached a far-red, lipophilic, fluorescent dye (CellVue Maroon, CVM) and analyzed the biodistribution of SapC-DOPS-CVM in subcutaneous and orthotopic xenografts of human pancreatic cancer cells in nude mice. As shown in Figure 2, specific tumor fluorescence was observed in both models after intravenous injection of SapC-DOPS-CVM. The PS selectivity of SapC-DOPS was confirmed by showing that blocking surface PS residues in cancer cells before subcutaneous implantation abolished targeting by CVM-labeled nanovesicles [77]. The antitumor actions of SapC-DOPS were evaluated in mouse models of pancreatic cancer (Figure 3, A–C). These experiments showed that SapC-DOPS treatment significantly suppressed subcutaneous tumor growth and eradicated orthotopic tumors in four of six mice with pancreatic xenografts. Molecular studies suggested that caspase-mediated apoptosis is involved in SapC-DOPS cytotoxicity against pancreatic cancer cells (Figure 3D) [77].

Other investigators have also exploited the ubiquitous expression of PS in tumor cells and tumor vasculature to design and test the tumor-targeting and therapeutic efficacy of anti-PS antibodies. For instance, a recent study used liposomes functionalized with a PS-targeted human monoclonal antibody that contained both a near-infrared dye and superparamagnetic iron oxide nanoparticles to perform selective, bimodal (magnetic resonance and optical) imaging of breast cancer xenografts [80]. Interestingly, another study has shown that anti-PS antibodies can elicit immune antitumor responses by converting myeloid-derived suppressive cells into tumoricidal M1 macrophages or dendritic cells capable of engaging cytotoxic T cell–dependent cytotoxicity [81]. Preclinical studies showed good targeting efficacy of PS-directed antibodies in several tumor models [82–86]. In orthotopic mouse models of pancreatic cancer, Beck et al. showed that gemcitabine plus the PS-targeting antibody 3G4 had additive antitumor activity and significantly reduced metastases [87]. PS-targeted antibodies have shown, so far, modest therapeutic efficacy in clinical trials [88, 89]. A randomized, open-label phase II trial evaluated an anti-PS antibody, bavituximab, plus gemcitabine versus gemcitabine alone in patients with advanced PDAC. The combined regimen was well tolerated and showed moderate activity with 28% tumor response rate versus 13% in the gemcitabine arm. Median
survival was 5.6 months versus 5.2 months for the control arm (hazard ratio = 0.75) [90].

Conclusions

Pancreatic cancer is a devastating disease for which there are no effective therapies. While concerted efforts to reduce risk factors such as obesity and tobacco and alcohol abuse are clearly paramount to prevent pancreatic cancer, its incidence is only expected to increase with a larger aging population sustained by constant medical advances. Two factors contribute to the high mortality of pancreatic cancer: the difficulty in early detection, due to unspecific symptomatology and a lack of robust biomarkers, and the resistance of advanced tumors to conventional chemotherapeutic agents and radiation therapy. Targeted therapies are poised to revolutionize cancer treatment by providing increasing efficacy while avoiding or reducing the adverse side effects characteristic of conventional cancer treatments. A formidable challenge, however, is presented by the complex nature of most tumors, in which multiple redundant and compensatory mechanisms virtually guarantee that tumor eradication cannot be achieved by silencing any individual molecule or signaling pathway. Rather, strategies that target broadly expressed tumor-specific antigens, while concurrently triggering tumor autolysis, may provide a breakthrough in the treatment of pancreatic and other cancers.

Our recent work has shown that PS targeting and tumor toxicity can be effectively achieved in mouse models of pancreatic cancer with PS-targeted nanovesicles [77]. Preclinical studies from our laboratory have also shown the potential of PS-targeted SapC-DOPS nanovesicles as imaging and therapeutic agents in a number of primary and metastatic tumors [76,78,91–95]. Importantly, the affinity of SapC for PS is greatly enhanced at acidic pH [96,97], a condition encountered in the majority of solid tumors that is known to stimulate drug resistance and create a propitious environment for tumor stem cells [78,79,98]. This evidence, along with the favorable safety profile of SapC-DOPS [76], strongly supports testing its applicability as a diagnostic and therapeutic agent for pancreatic cancer patients in clinical studies [99].

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