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## Embryonic stem cell factors and pancreatic cancer

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## Abstract

Pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic tumor, is a highly aggressive human cancer with the lowest five-year survival rate of any human malignancy primarily due to its early-metastasis and lack of response to chemotherapy and radiation. Recent research suggests that PDAC cells comprise a hierarchy of tumor cells that develop around a population of cancer stem cells (CSCs), a small and distinct population of cancer cells that mediates tumorigenesis, metastasis and resistance to standard treatments. Thus, CSCs could be a target for more effective

treatment options. Interestingly, pancreatic CSCs are subject to regulation by some of key embryonic stem cell (ESC) transcription factors aberrantly expressed in PDAC, such as SOX2, OCT4 and NANOG. ESC transcription factors are important DNA-binding proteins present in both embryonic and adult somatic cells. The critical role of these factors in reprogramming processes makes them essential not only for embryonic development but also tumorigenesis. Here we provide an overview of stem cell transcription factors, particularly SOX2, OCT4, and NANOG, on their expression and function in pancreatic cancer. In contrast to embryonic stem cells, in which OCT4 and SOX2 are tightly regulated and physically interact to regulate a wide spectrum of target genes, *de novo* SOX2 expression alone in pancreatic cancer cells is sufficient to promote self-renewal, de-differentiation and imparting stemness characteristics *via* impacting specific cell cycle regulatory genes and epithelial-mesenchymal transition driver genes. Thus, targeting ESC factors, particularly SOX2, could be a worthy strategy for pancreatic cancer therapy.

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**Key words:** Embryonic stem cells; NANOG; SOX2; OCT4; Pluripotency; Pancreatic cancer; Cancer stem cells

**Core tip:** Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal human cancer due to its early metastasis and lack of response to chemoradiotherapy. Pancreatic cancer stem cells (CSCs) are implicated in tumorigenesis and metastasis as well as therapy resistance, therefore represent a potential target for effective therapeutic options. Recent publications including our own research demonstrate that key embryonic stem cell (ESC) factors, such as OCT4, NANOG and SOX2, are aberrantly expressed in PDAC and contribute to pancreatic CSC-like characteristics, such as self-renewal and de-differentiation. This review aims to summarize our current knowledge on the role of ESC

factors particularly SOX2 in regulating pancreatic CSC-like feature and implication for therapy.

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## INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death in men and women in the United States. In 2012 alone, an estimated 43920 adults in the United States were diagnosed with pancreatic cancer and 37390 deaths from this disease occurred<sup>[1]</sup>. About 280000 new cases of pancreatic cancer were recorded in 2008 worldwide. Pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer, is also the most lethal among the human solid tumors with a 5-year survival rate of less than 5 percent<sup>[2]</sup>. The main reasons for this outcome include lack of early detection, invasive behavior and intrinsic resistance to most chemo-/radio- and immuno-therapy strategies<sup>[3,4]</sup>. Recently, several studies have identified PDAC cancer stem cells (CSCs), which are highly tumorigenic and have the capacity to not only self-renew, but also generate differentiated progeny<sup>[3,5-7]</sup>. Pancreatic CSCs are also resistant to chemotherapies commonly used to treat patients with PDAC<sup>[8-10]</sup>. Thus, studies identifying key determinants in pancreatic cancer and pancreatic CSCs can provide both biomarkers of PDAC aggressiveness and potentially optimal targets to overcome chemoresistance (Table 1). Here we review how embryonic stem factors contributes to the aggressiveness of this disease and the potential for targeted therapy.

## STEM CELL DEFINITION AND TYPES

Stem cells (SCs) are traditionally defined as cells that can both self-renew and generate a progeny that are capable of following more than a single differentiation pathway<sup>[11]</sup>. Currently, four types of SCs have been described<sup>[12]</sup>. The first two are physiologically present at different stages of life, namely, the embryonic stem cells (ESCs) and the somatic or adult stem cells (ASCs). The ESCs are the best studied SCs and knowledge derived from ESCs research has guided the investigations of other types of SCs. ASCs are postnatal derivatives of ESCs located throughout the body. ASCs have been shown to retain co-expression of at least three of the core transcription factors characteristic of ESCs (OCT4, KLF4, and SOX2). Similar to ESCs, the presence of a balanced network of core stem markers, rather than the overt expression of a single factor, contributes to maintenance of ASC characteristics. The third SC type is induced

pluripotent stem cells (iPSCs), which are artificially engineered from a non-pluripotent cell, such as *via* somatic cell nuclear transfer or reprogramming with gene transfer. The generation of iPSCs represents a milestone achievement in SC research, which not only breaks the dogma that somatic cell differentiation is an irreversible process, but also makes possible a new approach for regenerative medicine without controversial use of embryos. The fourth SC type is CSCs, also referred to as cancer initiating cells (CICs), which are defined as those cells within a tumor that can self-renew, produce differentiated progeny, and drive tumorigenesis. The ability of cancer cells to form nonadherent spheroids *in vitro* culture is frequently used as a surrogate of stemness. Unlike ESCs, CSCs are highly heterogeneous with great variation among the markers for each tumor type.

## ESCs AND ESC TRANSCRIPTION FACTORS

ESCs are derived from the inner cell mass (ICM) of the preimplantation mammalian embryo and can be maintained indefinitely in culture<sup>[13]</sup>. By definition, ESCs are pluripotent. They are able to give rise to all somatic and the three germ cell lineages of the developing embryo. Pluripotency is maintained through self-renewal, which allows ESCs to duplicate themselves without losing the ability to differentiate. This can be achieved *via* both symmetric and asymmetric cell divisions<sup>[14]</sup>.

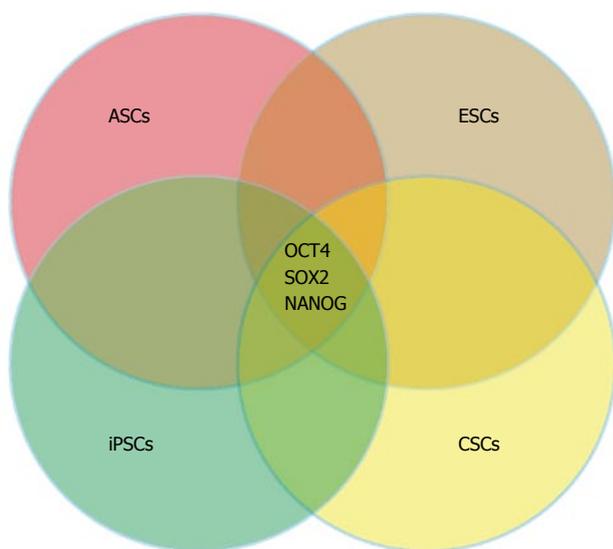
Over the last decade, there has been accumulating evidence indicating that the maintenance of pluripotency in ESCs is governed by core genetic and epigenetic regulators, which allow self-renewal and prevents specific differentiation pathways. Recent progress on the molecular mechanism(s) governing stem cells pluripotency has provided critical insights into the role of nine core transcription factors OCT4 (POU5F1), NANOG, SOX2, Dppa4, Dppa5, Sall4, Utl1, Rex2, and Rif1 in maintaining mouse cells in the undifferentiated stage<sup>[15-18]</sup>. Among these genes, OCT4, NANOG, and SOX2, referred to as pluripotency genes, are highly expressed in the ICM. The perfect balance of these proteins maintains pluripotency and self-renew in ESC during the first days of embryonic development<sup>[18]</sup>. Broadly, the pluripotency genes have been shown to be common to all SC types (Figure 1). In contrast to OCT4, NANOG and SOX2, *c-MYC*, an important oncogene as well as a reprogramming factor for pluripotency<sup>[17]</sup>, is highly heterogeneous in cells from the ICM. However, it is not always considered a pluripotency gene in ESCs. The activity of these three core pluripotency genes regulates and coordinates the expression of a second set of core genes, which include transcription factors, cell surface markers, ABC transporters, and enzymes. Together, these proteins orchestrate the specific stem cells properties<sup>[19]</sup>.

SOX2 and OCT4 form a protein complex in the nucleus of ESCs. This complex is auto-regulated in a loop

**Table 1 Biological role and clinical implications for embryonic stem cell factors in pancreatic cancer**

Gene	Biological role/behaviour	PDAC implications	Ref.
OCT4	Overexpressed in 69% of PDAC. Pro-oncogenic role	Correlation with N1/M1 status and indicative of worse prognosis	Polvani <i>et al</i> <sup>[47]</sup> , 2013
	Overexpressed in 48.8% of PDAC. Induces cell proliferation, migration and invasion	Contribution to metastasis and drug resistance	Lu <i>et al</i> <sup>[50]</sup> , 2013
	Overexpressed in human cell lines	Multidrug resistance and metastasis	Wang <i>et al</i> <sup>[52]</sup> , 2013
	Induction of tumorigenic capacity	Chemo-resistance	Wang <i>et al</i> <sup>[53]</sup> , 2013
SOX2	Overexpressed in 79.2% metaplastic ducts	Early carcinogenesis and worse prognosis	Wen <i>et al</i> <sup>[49]</sup> , 2010
	Overexpressed in poorly differentiated human tumors	Correlation to aggressiveness	Sanada <i>et al</i> <sup>[54]</sup> , 2006
	Ectopic expression in 19.3% of PDAC. Promotes cancer cell proliferation/dedifferentiation	Rapid tumor progression and poor differentiation	Herrerros-Villanueva <i>et al</i> <sup>[58]</sup> , 2013
NANOG	Induction of tumorigenic capacity	Chemo-resistance	Wang <i>et al</i> <sup>[53]</sup> , 2013
	Overexpressed in 53.5% of PDAC. Induces proliferation, migration and invasion	Associated with early stage carcinogenesis and worse overall survival	Lu <i>et al</i> <sup>[50]</sup> , 2013
	Overexpressed in cells capable of initiating spheres	Resistance to 5-FU treatment	Lonardo <i>et al</i> <sup>[68]</sup> , 2013
	Overexpressed in pancreatic tumors	Contribution to carcinogenesis and correlates to worse prognosis	Wen <i>et al</i> <sup>[49]</sup> , 2010

PDAC: Pancreatic ductal adenocarcinoma.



**Figure 1** Overlapping expression of SOX2, NANOG, and OCT4 in all four types of stem cells: embryonic stem cells, adult stem cells, induced pluripotent stem cells, and cancer stem cells. ASCs: Adult stem cells; ESCs: Embryonic stem cells; iPSCs: Induced pluripotent stem cells; CSCs: Cancer stem cells.

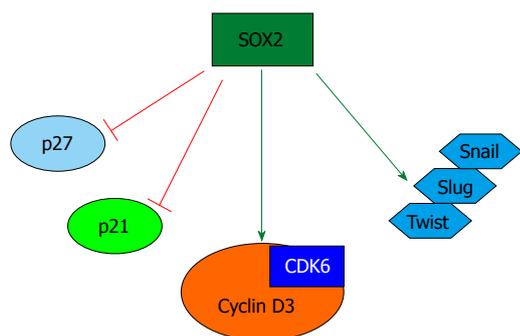
that, transcriptionally, also induces the expression of pluripotency genes (most importantly NANOG), cell cycle, apoptosis, DNA repair, chromatin structure genes, and genes regulating endoderm, mesoderm, and ectoderm differentiation. Thus, tight control of all these genes may allow ICM cells to exit from their inherent developmental program, as they acquire the ability to self-renew, while retaining pluripotency as ESCs<sup>[20]</sup>. Finally, when the expression of these pluripotency genes decreases in a properly regulated way, an induction in the expression of early differentiation markers occurs. These markers include ectoderm markers (*Pax6*, *Otx1*, *Neurod1*, *Nes*, *Lhx5*, and *Hoxb1*), mesoderm markers (*Tbx2*, *T*, *Nkx2-5*, *Myo1*, *Myf5*, *Mesdc1*, *Mesdc2*, *Kdr*, *Isl1*, *Hand1* and *Eomes*), endoderm markers (*Onecut1*, *Gata4*, *Gata5*, and *Gata6*),

and extraembryonic markers (*Cdx2* and *Tp53*).

## KEY ESC FACTORS IN iPSCs

iPSCs were first derived by the transduction of mouse and human fibroblasts through integrating viruses carrying four transcription factors: OCT4, SOX2, MYC and Kruppel-like factor 4 (KLF4)<sup>[21]</sup>, also referred as the Yamanaka factors. Takahashi and Yamanaka<sup>[21]</sup> broke a dogma in developmental biology by showing that mammalian somatic cell differentiation is a reversible process<sup>[17,21]</sup>. By transfecting human somatic cells with the four Yamanaka factors, they were able to revert the differentiated cells to an embryonic-like state. Because these newly generated cells showed the morphology, pluripotency, and capacity to form teratomas similar to ESCs, they named these cells iPSCs. Later, Yu *et al*<sup>[22]</sup> further demonstrated that the combination of OCT4, NANOG, SOX2 and Lin28, also called Thomson Factors, was able to produce iPSCs. Both, Yamanaka and Thomson Factors are Reprogramming Factors as Reprogramming is the process that converts differentiated cells back to pluripotent cells, namely the reversal of differentiation.

Recently, new methods have been developed to reprogram human somatic cells with or without MYC<sup>[22,23]</sup> and to combine only some of the reprogramming transcription factors with chemical inhibitors<sup>[24-26]</sup>. However, the fact remains that OCT4, SOX2, MYC, and KLF4 reside at the heart of the reprogramming process. Given that the transcription factors in this network not only associate with one another, but also associate with many of the same proteins in the network, there is a high degree of interdependence between these transcription factors. Thus, it is not surprising that the levels of SOX2 and OCT4 need to be controlled carefully for optimal production of iPSC, or that small changes in the levels of these master regulators can lead to dramatically altered cell fates. However, it remains to be determined how



**Figure 2** Diagram depicting the molecular mechanism underlying SOX2 expression-induced self-renewal and pluripotency in pancreatic cancer stem cells.

their levels affect the molecular efficiency of reprogramming. Given the strict requirement for SOX2 and OCT4 during development, their key roles in ESC differentiation, and the pronounced differences in reprogramming when their levels are not optimized, additional efforts should be made to determine why small changes in the levels of these two master regulators alters the behavior of pluripotent stem cells.

## ESC FACTORS AND CSCs

Although initially discovered in hematopoietic malignancies, such as acute myelogenous leukemia and chronic myelogenous leukemia<sup>[27,28]</sup>, CSCs were later described in various solid tumors, including glioblastoma<sup>[29]</sup>, melanoma<sup>[30]</sup>, prostate<sup>[31]</sup>, colon<sup>[32]</sup> head and neck squamous cell carcinoma<sup>[33]</sup>, breast<sup>[34]</sup>, ovarian<sup>[35]</sup>, bladder<sup>[36]</sup>, lung<sup>[37]</sup> and pancreatic cancer<sup>[6,7,38,39]</sup>. In these malignancies, a small population of CSCs can self-renew and differentiate into all of the other cell types forming the bulk tumoral population. However, the bulk of tumor cells lack the ability to differentiate into other subpopulations of cancer cells and thus possess limited self-renewal capacity. In addition, it has been shown that CSCs have tumor initiation capacity, forming xenograph tumors in mice and are radio- and chemo-resistant, contributing to lack of therapeutic response in patients<sup>[39]</sup>.

Although several proteins have been proposed as CSC markers, there is great variation between tumor types<sup>[40,41]</sup>. This variation might be the result of the lack of standardized techniques to obtain and analyze CSCs, as well as the intrinsic plasticity of these cells<sup>[40]</sup>. Since CSCs express many genes in common with early ESCs, primarily OCT4, NANOG, and SOX2, the picture that emerged was that these transcription factors could also work together as part of a highly integrated network to regulate pluripotency and self-renewal in tumors. Nevertheless, the heterogeneity of tumors and the plasticity that characterize CSCs render the expression pattern of these transcription factors highly heterogeneous in different tumors and even within the same tumor.

Several publications show that overexpression of OCT4, SOX2 and NANOG, together or separately, led

to tumor transformation, tumorigenicity, tumor metastasis, and even distant recurrence after chemoradiotherapy<sup>[42]</sup>. It is well known that these transcription factors are more frequently overexpressed in poorly differentiated tumors (compared to well differentiated tumors) and, in theory, that the expression level of the pluripotent transcription factors should decrease with the differentiation of cells<sup>[43]</sup>. In this regard, how these genes contribute to specific CSC properties has not been fully elucidated. Based on data obtained from iPSCs, several mechanisms have been proposed to explain the properties that these transcription factors could be imparting on CSCs. For example, once these transcription factors are overexpressed, they might activate several genes whose promoters are accessible to them. These “first responders” must then engage the epigenetic machinery to remodel the chromatin through histone modification and DNA methylation. In this process, genes critical for pluripotency must be switched on, while genes responsible for differentiation must be turned off and kept off<sup>[44]</sup>. From this data, it is clear that OCT4, NANOG and SOX2 are master regulators, which together drive the transition from a somatic cell to either a CSC or iPSC (Figure 2).

## ESC FACTORS AND PANCREATIC CANCER

As mentioned above, CSCs have also been described in PDAC (Table 1). Originally Li *et al.*<sup>[6]</sup> identified human pancreatic CSCs as CD44<sup>+</sup>/CD24<sup>+</sup>/ESA<sup>+</sup>. A few months later, Hermann *et al.*<sup>[7]</sup> showed that CD133 and CXCR4 are also expressed in cells with CSC properties. In addition, some other markers such as c-Met<sup>[5]</sup> and aldehyde dehydrogenase 1 activity (ALDH1)<sup>[45]</sup> have been demonstrated in pancreatic CSCs. Recently, some reports describe the presence of a side population (SP) of cells in pancreatic cancer, a chemoresistant population of cells that could be enriched in CSCs. Additionally, this data indicates that SP cells express pancreatic CSC markers (*CXCR4*, *CD133*) and multidrug resistance genes (*ABCB1*), associating these cells with candidate therapeutic targets and potential prognostic value<sup>[46]</sup>.

The regulation and characterization of CSCs in various types of human cancer, in which SOX2, OCT4 and NANOG are important players, is currently a hot topic. However, the number of specific publications analyzing their role in pancreatic cancer is very limited. In particular, a literature search on PUBMED database using the terms “OCT4”, “NANOG” and “SOX2” together with “pancreatic cancer”, showed 24, 27, and 20 published articles, respectively. Furthermore, only a few of these articles discuss these factors in the context of CSCs (Table 1). Polvani *et al.*<sup>[47]</sup> found that OCT4 is expressed in 69% of PDAC and that this expression correlates with N1/M1 status and clinical stage, being an independent prognostic factor for worst outcomes. In agreement with several breast cancer publications<sup>[48]</sup>, patients with OCT4<sup>+</sup> PDAC a shorter survival, suggesting this ESC factor

as a marker of poor prognosis. Importantly, high levels of OCT4 and NANOG in human pancreatic cancer tissues were found to be associated with early stages of carcinogenesis<sup>[49]</sup> and correlate with worse prognosis<sup>[50]</sup>. Additionally OCT4 seems to contribute to multidrug-resistance and metastasis<sup>[51,52]</sup>. Wang *et al.*<sup>[53]</sup> recently demonstrated that SP cells positive for NANOG, OCT4 and SOX2 possessed aggressive growth, invasion, migration and drug-resistance properties.

To date, very little is known regarding how OCT4 and NANOG contribute to pancreatic CSC properties at the molecular level. Interestingly, recent studies suggest that SOX2 is aberrantly expressed in a significant fraction of pancreatic tumors. Initially, Sanada *et al.*<sup>[54]</sup> analyzed 14 cases of human PDAC immunohistochemically, and observed weak expression of SOX2 in pancreatic intraepithelial neoplasia (PanIN-3) lesions. They also observed relatively high and frequent expression in invasive and poorly differentiated PDAC. Later, it was shown that at the mRNA level, SOX2 expression driven by hedgehog-EGFR signaling is necessary for tumor-initiating pancreatic cancer cells<sup>[55]</sup>. Very recently, the molecular mechanism underlying SOX2 regulation of pancreatic cancer stemness has been elucidated. Using primary human cancer tissues and cell lines (L3.6, Bxpc3, CFPAC-1, Panc1 and Panc04.03), our group demonstrated a critical role for SOX2 in promoting cell proliferation, dedifferentiation and impartment of stem cell-like features to pancreatic cancer cells<sup>[38]</sup>. In particular, SOX2 gene suppression arrested cells at the G<sub>1</sub> phase and its overexpression alone was sufficient to drive cell proliferation by facilitating G<sub>1</sub>/S transition. Mechanistically, G<sub>1</sub> arrest in SOX2 knockdown cells is associated with a marked induction of p21<sup>Cip1</sup> and p27<sup>Kip1</sup>, two key cyclin/CDK inhibitors, whereas SOX2 overexpression induces G<sub>1</sub>/S-specific cyclin D3 expression. All of three cell cycle regulators were identified as *bona fide* SOX2 regulatory targets. SOX2 also confers pancreatic cancer cell stemness and its overexpression alone is sufficient to drive sphere-formation and expression of CSC markers<sup>[7,38,45,56]</sup>, as well as induce EMT drivers such as Snail, Slug and Twist (Figure 2). Consistently, loss of *miR-145* elevates SOX2 and impairs differentiation in pancreatic tumors<sup>[57]</sup>.

It is now evident that the core stem cell factors OCT4<sup>[16]</sup>, SOX2<sup>[58]</sup>, and NANOG<sup>[59]</sup> play essential roles in the maintenance of pluripotency and self-renewal of ESCs, ASCs, iPSCs and CSCs. These stem cell factors promote self-renewal by interacting with other transcription factors (Stat3, Hesx1, Zic3), critical cell signaling molecules (Hedgehog, TCF3, FGF2, LEFTY2)<sup>[60]</sup>, and have been found aberrantly expressed in several types of human tumors including pancreatic cancer<sup>[61-63]</sup>. Although ESCs and CSCs share the property of self-renewal, they also reveal distinct features in that ESCs favor differentiation, whereas CSCs are more biased toward proliferation and inhibition of apoptosis. In particular, SOX2 has demonstrated OCT4 and/or NANOG independent activity in pancreatic cancer cells in promoting cell pro-

liferation, survival, and/or de-differentiation<sup>[38]</sup>. Recent work by Polvani *et al.*<sup>[47]</sup> further supports this statement demonstrating that OCT4 silencing reduces OCT4 and increases NANOG, but does not alter SOX2 expression.

## CSCs AS TARGET FOR CANCER THERAPY

SOX2 immunoreactivity has been demonstrated in PanIN lesions, as well as moderately and poorly differentiated tumors, which is consistent with previous reports showing an enrichment of SOX2 in pancreatic CSCs<sup>[64]</sup>, as well as a decreased expression after anti-ESCs therapies<sup>[55,65]</sup>. Since SOX2 appears to be a key factor aberrantly expressed in PDAC and confers CSCs-like properties<sup>[38]</sup>, targeting SOX2 or its upstream regulator(s) may be exploited for therapeutic purposes. Recent reports demonstrate that using poly (lactide-co-glucolide) to knockdown DCLK1 results in an increase in miR-145 associated with decreased pluripotency factors including SOX2, and consequently, tumor growth arrest in xenografts<sup>[57,66]</sup>. Lastly, data from Sobrevals *et al.*<sup>[67]</sup> elucidates the relevance of uPAR-controlled oncolytic adenoviruses in the elimination of pancreatic CSCs. Along these lines, C-Met inhibitors have been demonstrated to overcome gemcitabine resistance and stem cell signaling through downregulation of CSC markers including SOX2<sup>[65]</sup>. Strategies to target CSCs for cancer therapy have been proposed and are under investigation. For instance, metformin directed against pancreatic CSC has been shown to reduce tumor burden and prevent disease progression<sup>[68]</sup>. Disulfiram, an ALDH inhibitor, was tested *in vitro* and *in vivo* demonstrated a capacity to suppress pancreatic CSCs<sup>[69]</sup>. Promising results suggest that HAb18G/CD47 or Phospho-valproic acid (MDC-1112) could also be a promising target in pancreatic cancer surrogating anti-STAT3 therapies<sup>[70,71]</sup>. More recently, HAb18G/CD147 has been identified as another promising therapeutic target for highly aggressive pancreatic cancer and a surrogate marker in the STAT3-targeted molecular therapies, such as by phospho-valproic acid (MDC-1112), a novel valproic acid derivative. Since targeting CSCs has been demonstrated to be a viable therapeutic strategy against pancreatic cancer, a better understanding of OCT4, NANOG and particularly SOX2 on their expression and regulatory circuitry in PDAC will facilitate the design of individualized therapies for PDAC patients.

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