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**Unveiling FKBP7 as an Early Endoplasmic Reticulum Sentinel in Pancreatic Stellate Cell Activation,  
Collagen Remodelling and Tumor Progression**

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## Abstract

In pancreatic ductal adenocarcinoma (PDAC), fibroblast activation leads to excessive secretion of extracellular matrix (ECM) and soluble factors that regulate tumor progression, prompting investigation into endoplasmic reticulum (ER)-resident proteins that may support this activation. We identified FKBP7, a peptidyl-prolyl isomerase in the ER, as overexpressed in PDAC stroma compared to cancer cells, and in patients with favorable prognosis. Analysis of single-cell RNA sequencing databases revealed FKBP7 expression in pancreatic stellate cells (PSCs) and cancer-associated fibroblasts (CAFs). When analyzed by immunohistochemistry on PDAC patient tissues, FKBP7 emerged as an early activation marker in the preneoplastic stroma, preceding  $\alpha$ SMA expression, and responding to FAK- and TGF $\beta$ -induced stiffening and pro-fibrotic programs in PSC. Functional analyses revealed that FKBP7 knockdown in PSCs enhanced contractility, Rho/ FAK signaling, and secretion of pro-inflammatory cytokines as well as remodeling of type I collagen, promoting an activated phenotype and accelerating tumor growth *in vivo*. Conversely, FKBP7 expression supported a tumor-restraining (i.e. encapsulating) ECM characterized by type IV collagen. Mechanistically, FKBP7 interacts with BiP, and blocking this interaction instead leads to increased PSC secretion of type I collagen. Thus, FKBP7 serves as a novel PSC marker and ER regulator in a complex with BiP of the secretion of specific collagen subtypes, highlighting its potential to mediate ECM normalization and constrain PDAC tumorigenesis.

## Keywords

Pancreatic cancer, Pancreatic Stellate Cells, Cancer-associated fibroblasts, Endoplasmic reticulum, Collagen, Extracellular matrix, BiP

## Highlights

- FKBP7, an endoplasmic reticulum protein, is an early marker of pancreatic stellate cell (PSC) activation in the stroma of pancreatic cancer (PDAC)
- FKBP7 in PSCs is upregulated by early tumorigenesis signals (TGF $\beta$  and matrix stiffness)
- FKBP7 limits PSC from adopting CAF contractile traits, acting as a tumor-suppressor
- FKBP7-BiP interaction reduces type I collagen remodeling, creating a tumor-restraining environment
- High FKBP7 levels link to less aggressive stroma, better PDAC survival, and therapy potential

## Introduction

Pancreatic ductal adenocarcinoma (PDAC) is among the deadliest cancers, with a near 100% mortality-to-incidence ratio and an increasing incidence that will likely make it the second leading cause of cancer-related deaths by 2030. Its high mortality stems from an often silent onset but rapid metastatic spread, limiting curative surgical options for most patients [1]. Despite aggressive poly-chemotherapy, patient survival gains remain limited, and immunotherapy has largely failed in PDAC [2-4].

Recent advances highlight the central role of the tumor microenvironment in PDAC aggressiveness and therapy resistance, suggesting that effective treatment will require multi-drug approaches targeting both cancer cells and their chemoprotective, immunosuppressive microenvironment [3, 5]. PDAC is characterized by an extensive fibrotic stroma that can comprise up to 80% of tumor volume and profoundly influences tumor biology. For instance, excessive extracellular matrix (ECM) deposition compresses blood vessels, making PDAC highly hypoxic and nutrient-poor, which drives metabolic reprogramming in both cancer and stromal cells that favors tumor progression [6-8]. The ECM in PDAC can also be spatially and structurally heterogeneous, forming thick collagen bundles that facilitate tumor cell invasion and metastasis [9]. Cancer-associated fibroblasts (CAFs), which in PDAC largely derive from pancreatic stellate cells (PSCs) activation, are the primary contributors to ECM deposition and stiffening [10]. PSCs are activated by tumor-derived factors like PDGF, SHH, and TGF $\beta$  early in tumorigenesis, initiating a pro-fibrogenic, pro-contractile reprogramming that promotes ECM remodeling [11-13]. This ECM remodeling provides structural tracks that cancer cells exploit for invasion [14, 15]. Reprogrammed CAFs also secrete a variety of pro-tumorigenic factors, including growth factors and cytokines that support tumor growth, invasion, and chemoresistance [10]. This prolonged reprogramming is driven by epigenetic changes in CAFs [16]. CAF's high protein production and secretion capacity in PDAC require high protein synthesis, facilitated by increased mTOR-dependent mRNA translation [17].

Targeting this CAF reprogramming—particularly its protein secretion machinery—could reveal potential therapeutic vulnerabilities. Targeting the stroma is now seen as essential to improve PDAC

treatment outcomes [18]. Instead of eradicating CAFs, “normalizing” the stroma may be more effective, as shown in preclinical models using SHH pathway inhibitors or ECM-modifying enzymes. Yet, these approaches failed in clinical trials, underscoring the need for a deeper understanding of PDAC stroma biology [19-24]. Increased protein secretion in CAFs implies adaptive mechanisms in the endoplasmic reticulum (ER), as most membrane-bound and secreted proteins are synthesized on ER-associated ribosomes. These proteins enter the ER in an unfolded state, where chaperones assist in protein folding and stabilization. The ER maintains protein homeostasis through the unfolded protein response (UPR), adjusting folding capacity based on cellular needs. ER stress occurs when folding demands exceed capacity, triggering sensors that activate the UPR to restore balance [25, 26].

In this study, we explored ER adaptations supporting the increased protein synthesis in PSCs as they reprogram into CAFs. We identified FKBP7, an ER-resident peptidyl prolyl isomerase (PPI), as a key protein overexpressed in the stroma compared to epithelial tissues in both pancreatitis and PDAC samples from human and murine models. FKBP7 has been described as a regulator of BiP, a major heat shock protein (Hsp) 70 chaperone in the ER, where it negatively affects BiP’s ATPase activity and contributes to protein synthesis regulation [27, 28]. Here, we investigated how FKBP7 expression is regulated and its function in PDAC.

Our findings show that FKBP7 expression in PSCs increases in response to TGF $\beta$  and stiffness signals, both early events in pancreatic tumorigenesis. FKBP7 acts as a negative feedback regulator that limits PSCs from fully adopting the contractile and pro-inflammatory traits typical of the CAF pro-tumor phenotype. By restraining these characteristics, FKBP7 may counteract some of the pro-tumorigenic functions attributed to CAFs, highlighting its potential as a therapeutic target in PDAC stroma management. Mechanistically, we provide evidence that distinct collagen types are produced by PSCs dependently on the expression of FKBP7 and interaction with BiP. This novel understanding of FKBP7’s role in PSC activation provides insights into how ER chaperones might influence stromal reprogramming and CAF functions in PDAC, offering new avenues for stromal-targeted interventions in this aggressive cancer.

## Materials and Methods

### Cell isolation, genetic modifications, culture and treatments

CAFs and PSCs: they were isolated from human pancreatic tumor or adjacent tissues, respectively, using the outgrowth method described by Bachem *et al* [29]. Briefly, cells were isolated using explant techniques from histologically fibrotic areas of surgically resected PDA. Small tissue blocks were cut (0.5–1 mm<sup>3</sup>) using razor blade and seeded in 10-cm<sup>2</sup> uncoated culture wells in Dulbecco's modified Eagle's medium F12 (DMEM/F12, Sigma-Aldrich) containing L-Glutamine (LGIln) and supplemented with 10% fetal calf serum (FCS) (Eurobio), penicillin and streptomycin (P/S). Human pancreatic tumor tissues were obtained from the Pathology Department of Limoges Hospital, France, from patients undergoing pancreatic resections for pancreatic adenocarcinoma (Convention CRB/MAD-CC-2013-002). Tissue blocks were cultured at 37°C in a 5% CO<sub>2</sub>-air humidified atmosphere. Eighteen hours after seeding, culture medium was changed. CAFs grew out from the tissue blocks 1–3 days later. CAF primary cultures were immortalized *via* retrovirus-mediated expression of human telomerase reverse transcriptase (hTERT). An authorization for collecting and conserving this collection was given by the Comité de protection des personnes Sud-Ouest et Outre-Mer II (Déclaration de conservation et préparation de collections DC-2016-2654). This study was approved by the ethic committee of the Institution.

MEFs: MEFs were isolated from E8.5 embryo explant culture, and were expanded and maintained on dishes pre-coated with 0.1% gelatin (Sigma-Aldrich) in DMEM/F12 10% FCS plus P/S and LGln. After expansion and limited passage, primary MEFs were immortalized via retrovirus-mediated expression of human telomerase reverse transcriptase (hTERT) followed by puromycin selection, or spontaneously immortalized.

Stable cell lines knocked-down for FKBP7 or overexpressing wild-type or mutant FKBP7: To decrease FKBP7 expression in a stable-dependent manner, four distinct shRNAs targeting FKBP7 (sh399, sh000, sh001 and sh002) were engineered and packaged using the lentivirus delivery system from the

following FKBP7 shRNA plasmids (sh399 TRCN00005399, and sh000 TRCN000054000) and from the shRNA control (CTR) pLKO.1-puro non-mammalian plasmid (SHC002) (Sigma-Aldrich). PSCs and CAFs were then transduced with either lentivirus shFKBP7 #399, #000, or shCTR, using protamine sulfate at 10 µg/mL in Opti-MEM I Reduced Serum Medium. After 12 hours of transduction, the transduction medium was replaced by puromycin-selecting medium at 1 µg/mL. To overexpress FKBP7 in cells, the lentivector ploc FKBP7 (OHS5897, Discovery Horizon), or control vector ploc CTR lacking the FKBP7 sequence, were transduced in PSCs and CAFs as described above except that a blasticidin-selecting medium was used at 3 µg/ml. FKBP7 mutants were engineered using different G-blocks (Integrated DNA Technologies), to delete the FKBP7 PPI (peptidyl prolyl isomerase) domain or the FKBP7 C-terminal domain (G-block PPI domain: TAA ACT TAA GCT TGG TAC CGA GCT CGG ATC CAC TAG TCC AGT GTG GTG GAA TTC TGC AGA TAT CAC AAG TTT GTA CAA AAA AGC AGG CTC CAC CAT GCC AAA AAC CAT GCA TTT CTT ATT CAG ATT CAT TGT TTT CTT TTA TCT GTG GGG CCT TTT TAC TGC TCA GAG ACA AAA GAA AGA GGA GAG CAC CGA AGA AGT GAA AAT AGA AGT TTT GCA TCG TCC AGA AAA CTG CTC TAA GAC AAG CAA GAA GGG AGA CCT ACT AAA TGC CCA TTA TGA CGG CTA CCT GGC TAA AGA CGG CTC GAA ATT CTA CTG CAG CCG GAC ACA AAA TGA AGG CCA CCC CAA ATG GTT TGT TCT TGG TGT TGG GCA AGT CAT AAA AGG CCT AGA CAT TGC TAT GAC AGA TAT GTG CCC TGG AGA AAA GCG AAA AGT AGT TAT ACC CCC TTC ATT TGC ATA CGG AAA GGA AGG CTA TGC AGA AGG CAA GAT TCC ACC GGA TGC TAC ATT GAT TTT TGA GAT TGA ACT TTA TGC TGT GAC CTA CCC ATA CGA TGT TCC AGA TTA CGC TCA CGA TGA ACT ATG AAT CCA CCC AGC TTT CTT GTA CAA AGT GGT TGC TAG CTA ATG AAC CGG GCG CGC CCC GCC CC); (G-block C-terminal domain: TAA ACT TAA GCT TGG TAC CGA GCT CGG ATC CAC TAG TCC AGT GTG GTG GAA TTC TGC AGA TAT CAC AAG TTT GTA CAA AAA AGC AGG CTC CAC CAT GCC AAA AAC CAT GCA TTT CTT ATT CAG ATT CAT TGT TTT CTT TTA TCT GTG GGG CCT TTT TAC TGC TCA GAG ACA AAA GAA AGA GGA GAG CAC CGA AGA AGT GAA AAT AGA AGT TTT GCA TCG TCC AGA AAA CTG CTC TAA GAC AAG CAA GAA GAC CAA AGG ACC ACG GAG CAT TGA GAC ATT TAA ACA AAT AGA CAT GGA CAA TGA CAG GCA GCT CTC TAA AGC CGA GAT AAA CCT CTA CTT GCA AAG GGA ATT TGA AAA AGA TGA GAA GCC ACG TGA CAA GTC ATA TCA GGA TGC AGT TTT AGA AGA TAT TTT TAA GAA GAA TGA CCA TGA



TGG TGA TGG CTT CAT TTC TCC CAA GGA ATA CAA TGT ATA CCA ATA CCC ATA CGA TGT TCC AGA TTA  
CGC TCA CGA TGA ACT ATG AAT CCA CCC AGC TTT CTT GTA CAA AGT GGT TGC TAG CTA ATG AAC CGG  
GCG CGC CCC GCC CC). G-block recombination with the ploc CTR plasmid generated two plasmids  
containing either a FKBP7 mutant lacking the PPI domain ( $\Delta$ PPI), or a FKBP7 mutant lacking the C-  
terminal domain ( $\Delta$ C-ter), from which lentivirus were produced and transduced in PSCs, as described  
above.

Cell treatments: FAK inhibitor (PF-562271, Selleckchem, #S2890) was added at  $1\mu\text{M}$  on cells pre-  
starved in DMEM/F12 0.5% FCF overnight. Thapsigargin ( $3\mu\text{M}$ ), tunicamycin ( $8\mu\text{g/mL}$ ), Brefeldin A  
( $0.5\mu\text{g/mL}$ ), or TGF $\beta$  ( $8\text{ng/ml}$ ) were added on adherent cells cultivated in complete medium (10% FCS)  
for a timing described in the figure legends.

### **Western blot**

Cell lysis was performed in lysis buffer (20 mmol/L Tris, pH 7.5, 150 mmol/L NaCl, 1 mmol/L EDTA, 1%  
NP40, 1 mmol/L sodium orthovanadate, 1 mmol/L NaF, and a cocktail of protease inhibitors (Roche)).  
The protein extract concentration was measured using the Protein Assay reagent (Bio-Rad). Equal  
amounts of proteins were resolved by sodium dodecyl sulfate–polyacrylamide gel electrophoresis and  
electroblotted onto nitrocellulose membranes. Membranes were blocked (5% powdered milk in Tris-  
buffered saline with 0.1% Tween 20) followed by incubation with primary antibodies (see Table S1)],  
and; z. Membranes were incubated with horseradish-peroxidase–coupled secondary antibody and  
treated with Pierce ECL Western Blotting Substrate before detection with the PXi imaging system  
(Syngene).

### **SUnSET assay**

SUnSET assay, a nonradioactive equivalent of  $^{35}\text{S}$ -Met assay based on puromycin incorporation into nascent polypeptides [30], was used to monitor the rate of protein synthesis using an anti-puromycin antibody. Briefly, 10 min prior cell harvesting, puromycin was added to culture medium at 1  $\mu\text{g}/\text{mL}$ . CAFs, PSCs or tumor cells extracts were then processed for Western blotting using anti-puromycin antibody (see Table S1).

### **Co-immunoprecipitation**

Cell lysis was performed in lysis buffer (20 mmol/L Tris, pH 7.5, 150 mmol/L NaCl, 1 mmol/L EDTA, 0.5% NP40, 1 mmol/L sodium orthovanadate, 1 mmol/L NaF, and a cocktail of protease inhibitors; Roche). 200  $\mu\text{g}$  of cellular extracts were incubated overnight with Protein G sepharose beads (Ge Healthcare # 170618-01) and anti-FKBP7 antibody or irrelevant antibody as immunoprecipitation control (anti-FLAG antibody, CST 14793S). After four bead-wash with lysis buffer, immunoprecipitated proteins were analyzed by SDS-PAGE.

### **Subcellular fractionation**

To isolate cytosolic fraction, cell pellets were resuspended with cytosolic extraction buffer containing (NaCl 150mM, Hepes 50mM pH 7.4, EGTA 0.1mM, DTT 1mM, a cocktail of protease inhibitors and digitonine at 100  $\mu\text{g}/\text{mL}$ ). After 10 minutes on ice, cell suspensions were centrifugated at 2000 rpm during 10 minutes and cytosolic fractions which correspond to supernatant were collected. Then, after two washes with the cytosolic extraction buffer, cell pellets were resuspended with membrane extraction buffer containing (NaCl 150mM, Hepes 50mM pH 7.4, EGTA 0.1mM, DTT 1mM, a cocktail of protease inhibitors and NP40 0.5 %). After 30 minutes on ice, cell lysates were centrifugated at 7000 rpm during 5 minutes. Cell supernatants corresponding to the membrane fractions (plasma membrane+organelles) were collected. Both cytosolic and membrane fractions were analyzed by SDS-PAGE.

## **Immunofluorescence**

Human CAFs or PSCs cultured on glass coverslips were fixed (10 min, 10% formalin) and permeabilized (10 min, 0.05% Triton X-100). After blocking with 3% BSA for 1 h, they were incubated with primary antibodies (see Table S1) in PBS-3% BSA overnight at 4°C. Cells were PBS washed and incubated with the appropriate Alexa Fluor secondary antibodies, plus TRITC-phalloidin (1:1000, Sigma) for 1 h at room temperature (RT). After PBS washes, nuclei were stained with DAPI (1:1000, Sigma-Aldrich) for 10 minutes. After PBS washes, coverslips were mounted in Fluorescent mounting medium (Dako). Images were acquired using a confocal Zeiss LSM 780 microscope. For quantification, fields were chosen arbitrarily and the mean fluorescence intensity (MFI) was quantified on regions of interest (ROI) using Zen 2.3 lite software (Zeiss).

For immunofluorescence staining of deposited collagens, confluent PSCs cultured on glass coverslips were treated with alkaline detergent extraction buffer (0.5% Triton X-100, 20mM NH<sub>4</sub>OH in PBS). After 2 min, coverslips were washed with PBS and DNase treated (10µg/mL) for 30 min at 37°C, then washed with PBS. Immunofluorescence staining was then performed to detect collagen I or collagen IV as described above. Corresponding MFI were quantified on fields chosen arbitrarily using Zen 2.3 lite software (Zeiss). Collagen fiber alignment was determined using the Directionality plugin in ImageJ.

## **Histological analysis: colorations, immunohistochemistry and immunohistofluorescence**

Paraffin-embedded tissue sections were incubated 30 min at 60°C before being deparaffinized and rehydrated. For hematoxylin-eosin (H&E) staining, slides were then incubated 3 min in hematoxylin, washed 5 min in water, incubated 3 min in eosin and dehydrated in 100% ethanol before being cleared in xylene for 5 min and mounted using Eukitt. For picrosirius red staining, deparaffinized and rehydrated sections were incubated with picrosirius red solution (Abcam) for 1h, rinsed quickly in 0.5% acetic acid, dehydrated, cleared and mounted in Eukitt. Sections were analyzed using Cell Observer

widefield microscope (Zeiss) with polarizer D, 90° rotatable for Axio Observer (Zeiss). Areas of yellow-orange birefringent fibers corresponding to thick fibers and green birefringent fibers corresponding to thin fibers were quantified using ImageJ software.

For immunohistochemical (IHC) and immunohistofluorescence (IHF) stainings, after rehydration, sections were processed for antigen retrieval (10 mM Tris-EDTA pH9 and autoclaved at 120°C for 12 min) and quenched or not (IHF) for peroxidase activity (10 min with 0.3% hydrogen peroxide at RT) before being washed 5 min in PBS. After treatment with blocking buffer (45 min, RT), sections were incubated with primary antibodies (see Table S1) overnight at 4°C. Sections were PBS-washed and incubated (1h, RT) with ImmPRESS secondary antibodies (IHC) or appropriate Alexa Fluor-conjugated secondary antibodies (IHF). For IHC, after PBS washes, antibody binding was visualized with AEC (3-Amino-9-ethylcarbazole) chromogen substrate and counterstained with haematoxylin (2 min). Slides were washed with water, mounted using Glycergel and imaged with a Panasonic 250 scanner (Imag'IN core, Institut Universitaire du Cancer Toulouse, France). For IHF after PBS washes, nuclei were stained with DAPI (1:1000, 10 min, RT) and slides were mounted with fluorescent mounting medium. Images were acquired using a confocal Zeiss LSM 780 microscope.

### **Electron microscopy**

For scanning electron microscopy (SEM) analysis, cells were grown on glass coverslips, fixed in glutaraldehyde 2.5% in cacocylate buffer (0.1M, pH 7.4) (Electron Microscopy Sciences) for 1h and then washed with distilled water. After dehydration, samples were mounted on microscope stubs followed by platinum sputtering. Specimens were examined on a FEI Quanta 250 FEG scanning electron microscope at an accelerating voltage 10 kV at the CMEAB (Toulouse).

### **High content screen (HCS)**

PSCs overexpressing FKBP7 or not were plated (5000 cells/well) in culture medium in 96-well plate with optically clear bottom (PerkinElmer). After 48h, cells were fixed for 30 min at RT with paraformaldehyde 4%, 3-times washed with PBS and permeabilized with PBS/0.2% Triton-X-100 for 20 min at RT. After 3 PBS-washes, non-specific antibody binding was reduced by a blocking step with 3% BSA in PBS for 1 hour at RT. Antibodies targeting FKBP7 and  $\alpha$ SMA (see Table S1) were added in 3% BSA in PBS, overnight at 4°C. After 3 PBS-washes, cells were incubated with the secondary antibodies (Alexa Fluor-546 for FKBP7, and Alexa Fluor-647 for  $\alpha$ SMA) for 1h. Antibodies were removed by 3 PBS-washes and nuclei were stained with DAPI (1:1000, 10 min). After an additional PBS-wash, 96-well plates were sealed and images were acquired with an Operetta CLS High Content Imaging system from Perkin Elmer at 20x air objective and processed using Harmony software (version 4.9). Nuclei,  $\alpha$ SMA and FKBP7 images were acquired in the DAPI (blue), Alexa 546 (Red) and Alexa 647 (Far red) channels, respectively. After data acquisition, subsequent analyses were performed with Columbus software (version 2.8.2). Image analysis was performed using a custom made image analysis protocol [31], with quantification of total number of cells, of number of activated cells based on per cell  $\alpha$ SMA MFI, and of per cell  $\alpha$ SMA fiber length.

#### **MTT assay**

Tumor cells were seeded in 96-well plates (5000 cells/well for PSCs or CAFs, and 7500 cells/well for tumor cells) and treated if needed. At time described in the figure, MTT, (4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium (Life Technologies) was added to each well at 0.5 mg/mL for 2 hours. Hundred  $\mu$ L of dimethylsulfoxide 4 were added for 1 h to each well. Viability was estimated by measuring absorbance at 570 nm on MRX plate reader (Dynex Technologies).

#### **Collagen gel contraction assay**

Collagen lattices were prepared using type I collagen (Corning, #354249) according to the manufacturer's instructions. FKBP7 knock-down or overexpressing PSCs and CAFs were trypsinized, counted for dilution at  $2 \times 10^5$  cells/mL, suspended in collagen (1 mg/mL of collagen final concentration) and plated into 24-well plates (500  $\mu$ l/well). Collagen lattices were kept for 2 h at RT for polymerization. To initiate collagen gel contraction, polymerized gels were gently released from the underlying culture dish and DMEM/F12 10% FCS medium was immediately added. The degree of collagen gel contraction was analyzed during 4 days. Gel surface was measured using ImageJ software. Gel contraction =  $100 \times (\text{well surface} - \text{gel surface}) / \text{well surface}$ .

### **Cytokine membrane antibody arrays**

Cytokine assays were performed using the Proteome Profiler Human XL Cytokine Array kit (ARY022B; R&D Systems) according to the manufacturer's instructions. Membrane chemoluminescence was captured with the PXi imaging system (Syngene). Data acquisition and quantification were performed using Quick Spots Tool software (Western Vision Software).

### **Pancreatic cancer cells and PSCs orthotopic co-xenografting**

Pancreatic cancer cells and PSCs were trypsinized, washed and resuspended in sterile PBS. A 1:3 mix of pancreatic cancer cells ( $10^6$  MiaPaCa-2 cells) and PSCs shCTR or shFKBP7 ( $3 \times 10^6$ ) were co-injected in 50  $\mu$ l of PBS, into the pancreas of anesthetized (Isoflurane, Isovet from Piramal Health) 8 week-old female Swiss Nude mice (Charles River, France). Tumor volumes were measured by ultrasound using the 3-dimensional reconstruction tool (Vevo 2100; VisualSonics), or using the following formula: tumor area \* tumor diameter \* (2/3) (Aixplorer; Supersonic imagine). Thirty-three days after injection, mice were euthanized and pancreata were removed and paraffin-embedded before being sliced and stained.

Mice were kept under specific pathogen-free conditions. All experiments were in accordance with institutional guidelines and European animal protection law and approved by the responsible government agency (Facility agreement number A31555010; Project number: AP AFIS#2|117-2019061900061441).

### **Bioinformatical and statistical analyses**

PDX transcriptome analyses were obtained from processed dataset of the PaCaOmics clinical trial (NCT01692873) [32]. Laser microdissected stromal and epithelial compartments of RNAseq analyses from 65 PDA patients were obtained from the gene omnibus database (GSE93326) [33]. Raw counts from RNA-Seq were normalized using the upper quartile normalization, after excluding genes in the Y chromosome locus, genes with fewer than 5 reads in 50% of samples and genes with null variance in the dataset. Differentially expressed genes between the stromal and the epithelium compartments were significant if their adjusted p-value is below than 0.05. Gene annotation was performed using the function *enrichGO* from the R package *clusterProfiler*. Single cell datasets were obtained from Peng *et al.* [34]. Raw counts were log-normalized using the *Seurat* R package after exclusion of low-quality cells (<200 genes/cell and >4% mitochondrial genes). To identify cell type clusters, PCA was performed using the most variable genes. Significant principle components were determined using JackStraw analysis on PCs 1 to 50. PCs 1 to 25 were used for graph-based clustering at  $res = 0.4$ . These groups were projected onto t-SNE analysis run using previously computed principle components 1 to 25. Fibroblastic populations were subtracted with the use of *ACTA2*, *POSTN*, *PDPN*, *PDGFRA* and *FAP* gene expressions, for further analyses. Pathway enrichment analyses for each cell were assessed using *GSVA* (gene set variation analysis) R package [35]. Pearson correlations between FKBP7 expression and *GSVA* results were computed.

All statistical analyses were performed using GraphPad Prism 9 software (GraphPad Software Inc., San Diego, USA). Number of animals and replicate *in vitro* experiments are specified in each figure legend. Results are presented as the mean  $\pm$  SEM. Normal distribution of variables was computed using

D'Agostino-Pearson normality test. Comparison of a continuous variable in two or more than two groups with normal distribution was performed using parametric test, *i.e.*, t-test or ANOVA, respectively, with a Bonferroni post-test for multi-parametric analyses. If the variable was not normally distributed, a non-parametric test, *i.e.*, Mann-Whitney or Kruskal-Wallis, was applied for comparison in two or more than two groups, respectively, with a Dunns post-test for multi-parametric analyses. All p-values were two-sided, and  $P < 0.05$  was considered statistically significant.



## Results

### Identification of FKBP7 as an ER-resident protein specifically overexpressed in human PSCs and CAFs as compared to tumor cells

To compare protein synthesis on cytosolic versus ER-bound ribosomes, a SUnSET assay [30] was performed on fractionated protein extracts from two pancreatic tumor cell lines (MiaPaCa-2, Panc-1) and from immortalized PSCs and CAFs. In PSCs and CAFs, puromycin incorporation was consistently higher in the membranous (organelles) fraction than in the cytosolic fraction, which are enriched in ER-resident PERK and cytosolic eIF4E-BP1 proteins, respectively (Fig. 1A, S1A). In contrast, tumor cell lines showed the opposite pattern. The elevated protein synthesis at ER-bound ribosomes in PSC and CAF also correlated with higher basal ER stress, as indicated by increased ATF4 expression and a higher p-eIF2 $\alpha$ /total eIF2 $\alpha$  ratio in untreated (UT) cells, compared to tumor cells (Fig. 1A-B).

While PSCs and CAFs displayed similar ER stress responses to thapsigargin—a non-competitive inhibitor of ER Ca<sup>2+</sup> ATPase that depletes ER calcium stores—compared to tumor cells, the outcomes were different. Under induced ER stress, PSC and CAF showed reduced apoptotic cell death and increased survival, measured by PARP cleavage and MTT assays, respectively (Fig. 1B-C, S1B). This suggests an optimized ER stress response in PSC and CAF, likely to support their high protein folding demand.

To identify stroma-specific ER proteins contributing to this resilience, we screened for ER-related genes in two PDAC RNAseq databases: patient-derived xenografts [32], and tissue microdissected lesions [33], where stromal and tumor epithelial gene expression are separately quantified. We found 7 and 4 upregulated genes (Log<sub>2</sub>FC>1) among chaperones and co-chaperones in the stromal compartment *versus* the tumor epithelium, respectively of [32] (Table 1) or of [33] (Table 2), with FKBP7 mRNA showing the highest expression among stromal-enriched genes (Fig. 1D).

Immunohistochemistry on PDX tumors confirmed high FKBP7 protein levels in stromal areas negative for CK19 (tumor epithelial marker) (Fig. 1E). Western blots further showed high FKBP7 levels in PSC

and CAF cultures expressing fibroblast markers (e.g.,  $\alpha$ SMA, FAP $\alpha$ , collagen type I, periostin), but not in cancer cells (Fig. 1F) [36]. Single-cell RNAseq analysis from Peng *et al.* [34] supported these findings, indicating FKBP7 is predominantly expressed in fibroblast populations (Fig. 1G-H), where cluster numbers 4, 5, 11 and 12 co-express at least one of the previously described fibroblast markers (LUM, DCN, COL1A1, ACTA2, FAP, POSTN, PDPN, PDGFRA, ISLR, and LRRC15) (Fig. S1C); similarly as those markers, the percentage of fibroblasts expressing FKBP7, and expression level, are higher in the tumor compared to normal adjacent tissue (Fig. S1D). Additionally, murine PDAC tissue (KPC tumors, *Pdx-1-Cre ; LSL-Kras<sup>G12D/+</sup> ; LSL-Trp53<sup>R172H/+</sup>* [37]) showed FKBP7 expression in the stroma but not in adjacent CK19-positive tumor glands (Fig. S1E).

Given the heterogeneity of FKBP7 expression across PSC and CAF cell lines (Fig. 1F) and within single-cell data (Fig. 1H, S1C-D), we examined whether stromal FKBP7 expression correlates with clinical outcomes in PDAC patients. In a tissue microarray of 27 PDAC tumors, high FKBP7 expression in the stroma, as assessed by immunohistochemistry (Fig. 1I), was significantly associated with improved overall survival (Fig. 1J) and nearly with progression-free survival (Fig. S1F).

Collectively, these results establish that FKBP7 is primarily expressed in PSC and CAF and that its elevated stromal expression correlates with a better prognosis in PDAC patients.

### **FKBP7 expression is upregulated by stiffness- and TGF $\beta$ -triggered signals**

We examined FKBP7 expression by immunohistochemistry in patient and murine pancreatic lesions. In patients, FKBP7 is expressed in the stroma around early acinar-to-ductal metaplasia (ADM) and PanIN lesions, found at a distance from PDAC tissue, but not in healthy exocrine tissue (Fig. 2A, S2A). Unlike FKBP7,  $\alpha$ SMA, an early TGF $\beta$ -induced marker of activated PSCs, does not appear in tumor-distant stroma adjacent to ADM lesions;  $\alpha$ SMA is only weakly expressed in a thin stromal layer near PanIN lesions and in vascular smooth muscle in healthy tissue (Fig. 2A). In mice, FKBP7 is absent in healthy pancreas, where  $\alpha$ SMA stains only blood vessels (Fig. S2B). However, in pancreatitis lesions

(induced by caerulein injection), both FKBP7 and  $\alpha$ SMA are present in the stroma, accompanied by abundant CD45-positive inflammatory cells (Fig. S2B).

To explore FKBP7 expression regulation, we tested signals that occur early during pancreatic tumorigenesis, i.e. tissue stiffening and TGF $\beta$  secretion and activation. We cultured immortalized PSCs with or without TGF $\beta$  for up to 48 hours. FKBP7 showed basal expression in two PSC lines, which increased slightly over time alongside collagen-1 expression and FAK phosphorylation (Fig. 2B, S2C). On high-stiffness plastic, TGF $\beta$  did not alter FKBP7 levels but significantly increased Smad2 and FAK phosphorylation, as well as  $\alpha$ SMA, collagen-1, and CTGF expression, as expected (Fig. 2B, S2C).

Since plastic culture mimics high-stiffness conditions, we tested if FKBP7 is responsive to mechanical stimulus by culturing PSC on low- (0.5 kPa) and high- (32 kPa) stiffness dishes, with or without TGF $\beta$ . FKBP7,  $\alpha$ SMA, collagen-1, and FAK phosphorylation were elevated on high-stiffness or plastic compared to low-stiffness conditions; FAK inhibition reduced these levels. On low-stiffness, TGF $\beta$  increased FKBP7 expression, as well as Smad2 phosphorylation,  $\alpha$ SMA, and collagen-1 (Fig. 2C). A similar TGF $\beta$ -induced gene expression pattern, including FKBP7, was observed in MEFs on low-stiffness dishes (Fig. 2D).

Overall, these findings suggest FKBP7 is an early marker of PSC activation in pancreatitis or pancreatic cancer. Its expression aligns with pro-fibrogenic signals from matrix stiffening or TGF $\beta$  treatment and depends on FAK activity.

### **FKBP7 inhibits PSC contractility**

Given FKBP7's association with better PDAC prognosis, we tested its role in PSCs by altering FKBP7 expression through lentiviral knockdown (shRNA FKBP7, FKBP7<sup>KD</sup>) or overexpression (ploc FKBP7, FKBP7<sup>OE</sup>) in three PSC lines with varying basal FKBP7 levels (Fig. 1F). Scanning electron microscopy showed that control PSCs (shCTR cells, expressing FKBP7) spread out with a crisscrossed cytoskeletal network, likely actin fibers. In contrast, FKBP7<sup>KD</sup> PSC were stretched, displaying well-aligned fibers

along the cell axis (Fig. S3A). Confocal imaging, using actin stain phalloidin, p-FAK and  $\alpha$ SMA antibodies, revealed that both shCTR and FKBP7<sup>KD</sup> PSC contain  $\alpha$ SMA but with different actin organization. ShCTR PSCs displayed transverse and dorsal fibers, while FKBP7<sup>KD</sup> PSC had long ventral stress fibers that branch at each end with large p-FAK-positive focal adhesions rich in p-MLC2 (Fig. 3A, S3B).

FKBP7<sup>OE</sup> PSCs showed fewer  $\alpha$ SMA stress fibers associated with p-FAK-positive focal adhesions, than mock PSCs (ploc CTR) (Fig. 3B). This was confirmed by fluorescence signal quantification (Fig. S3C-D, left panels): higher FKBP7 expression in FKBP7<sup>OE</sup> PSCs reduced per-cell  $\alpha$ SMA fluorescence, indicating fewer  $\alpha$ SMA-activated PSCs in FKBP7<sup>OE</sup> compared to mock PSCs (Fig. S3C-D). High-content screening further showed that mock PSC had larger and longer  $\alpha$ SMA fibers, indicative of contractile fibers, compared to FKBP7<sup>OE</sup> cells (Fig. S3C-D). Consistently, lower FKBP7 expression, with more stress actin fibers in PSCs FKBP7<sup>KD</sup> and mock PSCs compared to shCTR and FKBP7<sup>OE</sup> PSCs, respectively, correlated with increased cell contractility in a collagen gel contraction assay (Fig. 3C).

Moreover, FKBP7<sup>OE</sup> PSCs showed reduced stiffness-induced activation, evidenced by lower, compared to mock PSCs, FAK phosphorylation and  $\alpha$ SMA expression on stiff matrices (32 kPa or plastic), though TGF $\beta$  treatment on soft matrix (0.5 kPa) had the same outcomes in FKBP7<sup>OE</sup> and mock PSCs (Fig. 3D). These results suggest FKBP7 in PSCs inhibits the acquisition of a contractile fibroblast-activated phenotype, specifically when triggered by matrix stiffening and FAK-dependent stress fiber formation.

### **FKBP7 modulates PSC secretome and restrains *in vivo* pancreatic tumor growth**

To investigate FKBP7's role in preventing a pro-tumoral activated fibroblastic phenotype, we analyzed the secretome of control PSC (shCTR) and two FKBP7<sup>KD</sup> PSC lines (shFKBP7- shRNA1 and shFKBP7- shRNA2) using cytokine arrays (Fig. S4A). FKBP7 knockdown led to 52 downregulated and 30 upregulated proteins, with 26 common downregulated and 20 common upregulated across both FKBP7<sup>KD</sup> lines (Fig. 4A, S4A). Notably, FKBP7 knockdown induced a switch to an inflammatory state, increasing secretion of cytokines like IL-6, IL-23, LIF, IL-8, and LCN2, which are linked to a STAT3-centered network (Fig. 4A, S4B, String interactome prediction). Conversely, proteins like

thrombospondin-1 (TSP1) were downregulated (Fig. 4A). We confirmed TSP1 downregulation and IL-6 upregulation in FKBP7<sup>KD</sup> PSC protein lysates and conditioned media, with FKBP7 rescue (FKBP7<sup>OE</sup>, overexpressing FKBP7 in FKBP7<sup>KD</sup> cells) reversing these changes (Fig. 4B-E). STAT3 phosphorylation, which increased in FKBP7<sup>KD</sup> cells, decreased upon FKBP7 rescue (Fig. 4B, 4D), aligning with the prediction that FKBP7 knockdown upregulates STAT3-activating cytokines (Fig. S4A). Further bioinformatics analysis of Peng *et al.* pancreatic single-cell RNAseq data [34] revealed a negative correlation between FKBP7 expression and both the “activated inflammatory stroma” signature of Puleo *et al.* [38], and the “CAF IL6/LIF” signature of Dominguez *et al.* [39] (Fig. S4C), consistent with the inflammatory profile, IL-6 secretion, and STAT3 activation seen in FKBP7<sup>KD</sup> PSC (Fig. 4A-C).

To evaluate the impact of FKBP7 on pro-tumor functions in PSCs, we xenografted MiaPaCa-2 pancreatic cancer cells with either control PSCs (shCTR) or FKBP7<sup>KD</sup> PSCs (two FKBP7-targeting shRNA lines) into the pancreas of nude mice, monitoring tumor growth (Fig. 4F). By day 33, co-xenografts with FKBP7<sup>KD</sup> PSCs produced larger tumors compared to those with FKBP7-expressing control PSCs (shCTR) (Fig. 4F). This result indicates that the activated PSC phenotype observed *in vitro* following FKBP7 knockdown promotes tumor progression *in vivo*.

Overall, these findings demonstrate that FKBP7 expression in PSC supports a tumor-inhibitory phenotype, consistent with FKBP7's *in vitro* effects on reducing PSC contractility and inflammatory secretion, thereby limiting tumor growth.

### **Restraining effect of PSC expressing FKBP7 on tumor growth correlates with the formation of an encapsulating fibrous shell**

Microscopic analysis of Sirius red-stained sections from MiaPaCa-2 and PSC co-xenografts under polarized light showed that tumors with FKBP7-expressing control PSCs (shCTR) displayed both thick (yellow-orange) and thin (green) fibrillary collagens, which decreased significantly when FKBP7 was knocked down in PSC<sup>KD</sup> (Fig. 5A-B) despite larger tumor size (Fig. 4F, S5A).

Immunohistochemical revealed that FKBP7-expressing PSC tumors were encapsulated in a shell rich in fibronectin and collagens III and IV (but low in collagen I), effectively separating tumor cells (identifiable by high mutant p53 expression) from the surrounding acinar compartment. In contrast, FKBP7<sup>KD</sup> PSC tumors showed no such separation, and the extracellular matrix (ECM) was remodeled with high collagen I but low collagens III and IV, alongside increased MMP-9 expression, enabling tumor cell invasion (Fig. 5C).

*In vitro* FKBP7 knockdown in PSC FKBP7<sup>KD</sup> increased collagen I but reduced collagen IV expression, while FKBP7 overexpression in PSC FKBP7<sup>OE</sup> had the opposite effect (Fig. 5D-E, S5B-D). Collagen I fibers in FKBP7<sup>KD</sup> PSCs were aligned, contrasting with the dispersed fibers seen in FKBP7-expressing shCTR PSCs (Fig. 5F). These findings indicate that *in vivo* control FKBP7-expressing PSCs promote the formation of a collagen III/IV and fibronectin-rich shell, which inhibits tumor growth and invasion, while FKBP7 loss within PSCs leads to the secretion of a collagen I-dense, invasive ECM, fostering tumor progression.

### **Mechanism for FKBP7 effect in PSCs**

Our study shows FKBP7 is more abundant in the membranous fraction compared to the cytosolic fraction in PSCs (Fig. 6A). As reported in another cell type [27], we confirmed FKBP7 complexes with BiP in PSCs, as BiP co-immunoprecipitated with an anti-FKBP7 antibody, though this interaction appears unstable as FKBP7 was not found in the BiP co-immunoprecipitate (Fig. 6B). Unlike in prostate cancer cells, eIF4G did not co-immunoprecipitate with FKBP7 in PSCs, suggesting a cell-specific role for FKBP7 in mRNA translation [28].

Despite BiP's role in ER stress regulation, altering FKBP7 expression in PSCs FKBP7<sup>KD</sup>, whether treated with UPR-activating drugs (thapsigargin), did not affect UPR markers (PERK and eIF2 $\alpha$  phosphorylation, ATF4, IRE1 $\alpha$ , BiP, spliced XBP1 expression) or cell survival, with similar outcomes in shCTR and FKBP7<sup>KD</sup> cells (Fig. S6A-C).

We further explored FKBP7's domains to determine their role in the PSC phenotype (Fig. 3-5) by creating HA-tagged mutants lacking either the PPI (peptidyl-prolyl isomerase) (FKBP7 $\Delta$ PPI) or C-terminal (EF-hand) (FKBP7 $\Delta$ cter) domain [27, 39] (Fig. S6D). While FKBP7 $\Delta$ PPI binds BiP, FKBP7 $\Delta$ cter does not (Fig. 6C-D). Overexpression of FKBP7 WT or FKBP7 $\Delta$ PPI reduced collagen gel contraction, FAK and MLC2 phosphorylation, whereas FKBP7 $\Delta$ cter increased both, mimicking FKBP7 knockdown effects (Fig. 6E-F, S6E-F). FKBP7 $\Delta$ cter also enhanced collagen I production (Fig. 6G-H), suggesting that FKBP7 suppresses PSC activation through its BiP interaction, thereby reducing collagen I production and CAF contractility.

## Discussion

To identify ER-resident proteins that may support increased synthesis of membranous and secreted proteins during PSC activation into myofibroblasts, we examined FKBP7, an ER-resident peptidyl prolyl isomerase. Our analysis revealed that FKBP7 is overexpressed in the tumor stroma compared to the epithelium, and is specifically present in fibroblastic populations within PDAC tissue also expressing other reported CAF markers (ACTA2, FAP, POSTN, PDPN, PDGFRA) [8, 40]. FKBP7 was detected at varying levels in PSCs and CAFs isolated from PDAC stromal tissue, though it was absent in tumor cells. Given FKBP7's known interaction with the major ER chaperone BiP —where it negatively regulates BiP's ATPase activity [27] —, and its role in protein synthesis regulation [28], we initially hypothesized that FKBP7 might regulate ER stress and protein synthesis in PSCs and CAFs. PSCs and CAFs produce and secrete more proteins and display greater resistance to ER stress-induced apoptosis than tumor cells. ER stress can induce fibroblast differentiation into myofibroblasts in fibrotic conditions, promoting both ER expansion and expression of  $\alpha$ SMA, which supports ECM protein secretion and fibroblast contractility [41]. However, when we knocked down FKBP7 in PSCs, our results showed that FKBP7 does not influence ER stress, disproving our hypothesis.

Interestingly, FKBP7 expression was observed in the stroma surrounding preneoplastic lesions such as acinar-to-ductal metaplasia (ADM) and PanIN, as well as around PDAC lesions, but not in pericytes or smooth muscle cells. This expression pattern in the stroma, particularly around ADM where  $\alpha$ SMA is absent, suggests that FKBP7 may act as an earlier marker of PSC activation than  $\alpha$ SMA. Our experiments also demonstrated that FKBP7 expression in PSCs is increased by TGF $\beta$  and matrix stiffness, which are early triggers of PSC activation during pancreatic tumorigenesis, suggesting that FKBP7 may regulate these PSC activation programs.

Our findings show that altering FKBP7 expression in PSCs produced opposite effects on cell phenotype. Low FKBP7-expressing PSCs (knockdown cells) exhibited larger contractile stress fibers, more adhesion sites, and increased FAK and Rho (p-MLC2) signaling. These cells were more contractile, secreted more



pro-inflammatory cytokines (like LIF and IL6), and displayed higher STAT3 signaling—all features associated with a pro-tumorigenic, contractile phenotype with increased collagen I production and deposition. When co-grafted with human pancreatic cancer cells in mice, these FKBP7 knockdown PSCs accelerated tumor progression and induced high levels of ECM remodeling (marked by MMP9 and type I collagen). In contrast, control PSCs in the tumors generated an encapsulating layer rich in type III and IV collagens and fibronectin, suggesting a more tumor-restraining environment. This aligns with our bioinformatics analysis showing that FKBP7 mRNA expression inversely correlates with “activated stroma” or “inflammatory CAF” signatures [38, 42], and indicates that high FKBP7 levels in the stroma predict better survival outcomes for PDAC patients.

Our findings support a role for FKBP7 as a restraining factor in pancreatic tumorigenesis, similar to other tumor-suppressive fibroblasts such as those lacking meflin or CD105 [43, 44]. This contrasts with the typical binary view of CAF subtypes, which are traditionally categorized as either inflammatory (iCAF) or myofibroblastic (myCAF), linked to JAK-STAT or TGF $\beta$ -SMAD pathway activation, respectively [45]. Notably, FKBP7 knockdown in PSCs led to both secretory inflammatory and contractile phenotypes, demonstrating PSCs' phenotypic plasticity. This shift between CAF phenotypes may involve epigenetic regulation, sustaining JAK1/STAT3 signaling and ECM remodeling, as reported in other cancers [16].

To explore how FKBP7 affects PSC contractility, we tested whether its interaction with BiP (involving FKBP7's C-terminal domain) [39] plays a role. Interestingly, BiP was described to modulate type I collagen lysyl hydroxylation, through the regulation of the formation of a complex comprising the lysyl hydroxylase 2 (LH2) and the two other chaperones HSP47 and FKBP10 [46]. Our results demonstrate that disruption in PSCs of the FKBP7 interaction with BiP via a FKBP7 mutant lacking the BiP-binding domain (FKBP7 $\Delta$ Cter), increased contractility, FAK and Rho signaling, and collagen I production, mirroring the effects of FKBP7 knockdown. Notably, FKBP7-expressing PSCs instead produce type IV collagen, which typically comprises the basal membrane in normal tissue and was abundant in the fibrous encapsulation seen in tumors with FKBP7-expressing PSCs. This suggests that FKBP7, through

BiP interaction, might limit type I collagen maturation and promote a “normalized” ECM structure, potentially inhibiting tumor spread. Further evidence shows that FKBP7’s PPI activity, which is weak [47], is not required for its regulatory effect, as seen with the FKBP7 $\Delta$ PPI mutant, which preserved PSC phenotype. Together, our work suggests that FKBP7 and possibly other FKBP family proteins specifically regulate ER maturation of distinct collagen types, with FKBP7 associated with type IV collagen and FKBP10 with type I collagen (such as in clear cell renal cell carcinoma) [46, 48].

This study identifies FKBP7 as an early marker of PSC activation, associated with improved prognosis for PDAC patients, and describes its role in restraining PSC-mediated pancreatic tumorigenesis by modulating the myofibroblastic contractile phenotype through BiP interaction. Understanding how ER chaperones like FKBP7 and BiP modulate myofibroblast activation and ECM composition by controlling the maturation of specific pro-tumor collagens could offer novel approaches to targeting the PDAC stroma.

## Figure Legends

### Figure 1. PSC and CAF are resistant to ER stress as compared to tumor cells, and overexpress the ER co-chaperone FKBP7

**A-** Representative Western blots showing SunSET assay after subcellular fractionation (cyto: cytoplasm; mem: membranes) of tumor cells, PSC1 and CAF3, with PERK, eIF4E-BP1,  $\alpha$ SMA and puromycin antibody. Red ponceau staining serves as loading control. N=3 experiments. **B-** Representative Western blots of tumor cells (MiaPaCa-2 and Panc-1), CAF3 and PSC2 treated or not (UT) with thapsigargin (3  $\mu$ M) for the indicated times, with PERK, eIF2 $\alpha$ -p, eIF2 $\alpha$ , quantified ratio of eIF2 $\alpha$ -p/ total eIF2 $\alpha$ , ATF4, IRE1 $\alpha$ , XBP1s, BIP, PARP and Cleaved (Cl) PARP antibody. GAPDH antibody serves as a loading control. N=3 experiments. **C-** Viability of tumor cells (MiaPaCa-2 and Panc-1), CAF3 and PSC2 treated or not (UT) for 48h with thapsigargin (3  $\mu$ M) was assessed by MTT. Results (mean, SEM) are presented for each cell type. (N=3) ANOVA was used to generate p values, \*\*\*p < 0.001, ns. non significant. **D-** Differential expression of (co)-chaperone mRNAs (expressed as Log2FC) in stromal *versus* tumor epithelial compartments of the Nicolle et al. (patient-derived xenografts) [32] and Maurer et al. (patient tumors) [33] cohorts. **E-** Representative immunohistochemistry (IHC) of CK19 and FKBP7 in sections of human patient-derived xenografts [30], n=5 PDX. **F-** Representative Western blots of tumor cells (MiaPaCa-2, Panc-1), two different CAF and three PSC with Coll, Periostin, FAP,  $\alpha$ SMA and FKBP7 antibodies. GAPDH antibody serves as a loading control. N=3 experiments. **G-** Plot of the different cell types onto the t-SNE map from single cell RNA sequencing [34]). Fibroblasts are highlighted in green. **H-** Plot of expression levels of FKBP7 in each analyzed cell (all cell types, Peng *et al*) onto the t-SNE map or as a heatmap. Color key from light to dark red indicates relative expression levels from low to high. **I-** Representative immunohistochemistry images of two patient PDAC tissues extracted from a 27-patient tissue-microarray analysis using an anti-FKBP7 antibody, and showing low or high FKBP7 expression. **J-** Kaplan-Meier plot showing Overall Survival of 27 PDAC patients (each patient IHC is performed in sextuplicate), and split based on the median expression of FKBP7

quantified by immunohistochemistry using an anti-FKBP7 antibody and a tissue-microarray comprising 6 spots for each patient tumor. A Log-rank (Mantel-Cox) test was used to generate p-value.

**Figure 2. FKBP7 expression is increased during PSC activation *in vivo* and *in vitro***

**A-** Representative immunohistochemistry of FKBP7 and  $\alpha$ SMA on acinar-to-ductal metaplasia (ADM) and PanIN, observed at distance from PDAC lesions (N=5 samples); N= nerve; V= vessel. **B-D-** Representative Western blots of human PSC3 cells treated or not (UT) with TGF $\beta$  (8 ng/mL) for 6h, 24h and 48h (B), or of human PSC3 plated for 7 days on soft (0.5kPa) or stiff matrix (32 kPa), and treated or not (UT) with TGF $\beta$  (8 ng/mL) or with the FAK inhibitor (1  $\mu$ M) for 24h (C), or of Mouse Embryonic Fibroblasts (MEF) treated or not (UT) with TGF $\beta$  (8 ng/mL) for 6h, 24h and 48h (D); blotting was performed with the phospho-smad2, smad2, phospho-FAK, FAK,  $\alpha$ SMA, Coll, CTGF or FKBP7 antibody, GAPDH antibody serves as a loading control. N=3 experiments.

**Figure 3: FKBP7 expression impacts PSC morphology and restrains their activation.**

**A-** Representative immunofluorescence staining (from left to right) of phalloidin/phospho-FAK,  $\alpha$ SMA, phospho-FAK and the merge of all stainings, performed in shCTR (upper panel) and shFKBP7 (shRNA-1, lower panel) PSC2. N=3 experiments. **B-** Representative immunofluorescence staining (from top to bottom) of  $\alpha$ SMA, phospho-FAK and the merged of both stainings, performed in control PSC3 (CTR) in left panels, or PSC3 overexpressing FKBP7 (FKBP7) in right panels. N=3 experiments. **C-** Quantification of collagen I gel contraction induced for 3 days by shCTR vs. shFKBP7 (shRNA-1, left panels) PSC2, or by CTR vs. FKBP7 (right panels) PSC3. Values (mean, SEM) are from three independent experiments of triplicates, student t-test was used to generate p values, \*p < 0.05. Representative images of collagen gels contracted by the respective PSCs. **D-** Representative Western blot of CTR PSC3 and FKBP7 - transduced PSC3 grown on 0.5 or 32 kPa matrix, or on plastic, and treated when indicated with TGF $\beta$

(8 ng/mL) or the FAK inhibitor (1  $\mu$ M) for 24h; Are presented blots with phospho-FAK, FAK, and quantified ratio of p-FAK/ total FAK, phospho-smad2, smad2,  $\alpha$ SMA, CTGF and FKBP7 antibody,  $\beta$  actin antibody serves as a loading control. N=3 experiments.

**Figure 4: FKBP7 inhibits FAK signaling pathway in PSC, altered their secretome and is involved in PSC antitumoral properties *in vivo***

**A-** Table representing the list of proteins down-regulated or up-regulated in the conditioned media of PSC2 fibroblasts shFKBP7 compared to shCTR, as measured using a membrane antibody array assay; Values are mean fold changes of the two shFKBP7 compared to shCTR. **B-** Western blot performed on protein cell lysates (upper panels) or conditioned medium (lower panels) of PSC2 shCTR or shFKBP7 (shRNA-1 or shRNA-2) with the TSP1 or FKBP7 or phospho-STAT3 and STAT3 antibody ;  $\beta$  actin or Red ponceau serve as a loading control for cell lysates or conditioned media, respectively. **C-** ELISA for IL-6 on conditioned media (from 5B). ANOVA was used to generate p values, \*p < 0.05 \*\*p < 0.01. N=3 experiments. **D-** Western blot performed on protein cell lysates (upper panels) or conditioned medium (lower panels) of PSC1 shCTR or shFKBP7 (shRNA-1) rescued for FKBP7 (ploc FKBP7), with the FKBP7, phospho-STAT3, STAT3, or TSP1 antibody; GAPDH or Ponceau red serve as a loading control for cell lysates or conditioned medium, respectively. **E-** ELISA for IL-6 on conditioned media (from 5D). ANOVA was used to generate p values, \*\*\*p < 0.001. N=3 experiments. **F-** MiaPaCa-2 cells were injected in the pancreas of nude mice, with PSC shCTR (n=7 mice), or with PSC shFKBP7 (shRNA-1, n=6 mice; shRNA-2, n=6 mice). Tumor weight at the day of sacrifice was measured. Man-Whitney test was used to generate p values, \*p < 0.05 ,\*\*p < 0.01, ,\*\*\*p < 0.001; ns, non significant.

**Figure 5: Loss of FKBP7 expression in PSC leads to a remodeling of the extracellular matrix both *in vivo* and *in vitro*.**

**A-B-** Representative images of Sirius red coloration of tumors from mice grafted with MiaPaCa2 tumor cells + shCTR PSCs, or MiaPaCa2 tumor cells + shFKBP7 (shRNA-1 or shRNA-2) PSCs (from Fig. 5E), and analysis under polarized light microscopy with quantification of the yellow-orange and green collagen fibers in 6 tumors for each condition. ANOVA was used to generate p values, \*p < 0.05. **C-** Representative immunohistofluorescence co-stainings (merged images) of (from left to right): fibronectin/collagen IV/p53/DAPI, fibronectin/collagen I/p53/DAPI, fibronectin/collagen III/p53/DAPI, vimentin (human specific)/MMP9/p53/DAPI, performed on primary tumors (MiaPaCa2 + shCTR PSC2 (upper panel), and MiaPaCa2 + shFKB7 (shRNA-1) PSC2 (lower panel)). **D-E-** MFI quantification of collagen I or IV performed in 5-12 ROI from immunofluorescence images obtained on shCTR or shFKBP7 (shRNA-1) PSC2 (Fig. S5C), and PSC3 transduced with FKBP7 (ploc FKBP7) or not (ploc CTR) (Fig. S5D), using antibodies for collagen I or IV, respectively. Student t-test was used to generate p values, \*p<0.05. N=3 experiments. **F-** Immunofluorescence performed on shCTR or shFKBP7 (shRNA-1) PSC2, using antibodies for collagen I or phalloidin, and representative analysis of collagen I fiber orientation, histograms indicating the amount of fibers in various directions (angle from -90° to 90°), and the corresponding analyzed images.

**Figure 6: Mechanism for FKBP7 effect in PSC.**

**A-** Representative Western blot after subcellular fractionation of PSC1 (cytoplasm and membranes) with PERK, eIF4E-BP1, and FKBP7 antibody.  $\beta$ actin antibody serves as loading control. N=3 experiments. **B-** Representative Western blots after co-immunoprecipitation in CAF1 of FKBP7, or BIP (negative control). BIP, FKBP7 and eIF4G1 antibodies were used. Input represents 10% of total immunoprecipitation. Irrelevant IP anti Flag serves as negative control. N=3 experiments. **C-** Representative Western blots of PSC1 overexpressing FKBP7WT,  $\Delta$ PPI or  $\Delta$ Cter mutant, performed using protein extracts after subcellular fractionation (cyto: cytosol; mem: membranes), and showing expression of PERK, 4E-BP1, FKBP7 (blotted with an antibody specific to the Nter part of the protein),

GAPDH and the HA-tagged FKBP7 mutants. 4E-BP1 and GAPDH serve as loading controls for the cytosolic fraction, and PERK for the membrane fractions. N=3 experiments. **D-** Representative Western blots after co-immunoprecipitation with the anti-HA antibody (IP HA) using protein extracts from PSC1 transduced or not (UT) with HA-tagged FKBP7 mutants ( $\Delta$ PPI or  $\Delta$ Cter); Immunoprecipitation with the anti-BiP or irrelevant anti-Flag antibody was used as negative control. BiP and HA antibodies were used for blotting. Input represents 10% of total immunoprecipitation. N=3 experiments. **E-** Quantification of collagen I gel contraction induced for 3 days by PSC1 transduced with empty vector (mock), or FKBP7WT, or FKBP7 $\Delta$ PPI or FKBP7 $\Delta$ Cter mutant. Values (mean, SEM) are from three independent experiments of triplicates. ANOVA was used to generate p values, \*p < 0.05, \*\*\*\*p < 0.0001. Representative images of collagen gels contracted by the respective PSC (upper panels). **F-** Representative Western blot of PSC1 transduced with empty vector (mock), or FKBP7WT, or FKBP7 $\Delta$ PPI or FKBP7 $\Delta$ Cter mutant; Are presented blots with phospho-FAK, FAK, and quantified ratio of p-FAK/ total FAK, FKBP7 and HA antibody.  $\beta$ -actin antibody serves as a loading control. N=3 experiments. **G-H-** Immunofluorescence on PSC1 transduced with empty vector (mock), or FKBP7WT, or FKBP7 $\Delta$ PPI or FKBP7 $\Delta$ Cter mutant, using antibodies for collagen I and phalloidin, and merged images (G), and associated MFI quantification of collagen I in 5 ROI (H). ANOVA test was used to generate p values, \*p<0.05. N=3 experiments.

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## **Author Contributions**

C.Q, C.J., M.F, Y.M., S.P. and C.B. conceived the study and/or designed experiments. C.J., Y.M., M.F. and C.B. supervised the study and provided funding. C.Q. performed experiments throughout the entire study. E.D. and M.J. participated in immunofluorescence, immunohistochemistry and image analyses. R.N. and J.R. analyzed RNAseq data and performed computational biology. C.J., A.B. and I.B. participated in orthotopic xenografting. A.P. and M.M. provided primary cultures of cancer-associated fibroblasts. N.D provided PDX slices. J.C. provided patient PDAC tissues. Y.M. provided expertise on SunSET mRNA translation analyses. H.A., Y.M. and G.L. provided expertise and participated in experiments on molecular cloning, mutagenesis and co-immunoprecipitation experiments. C.Q., M.F. and C.B. drafted the manuscript. C.J., Y.M., M.F. and C.B. edited the manuscript.

## **Declaration of Interest Statement**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



## Declaration of generative AI and AI-assisted technologies in the writing process

Statement: During the preparation of this work the author(s) used ChatGPT in order to improve the readability and language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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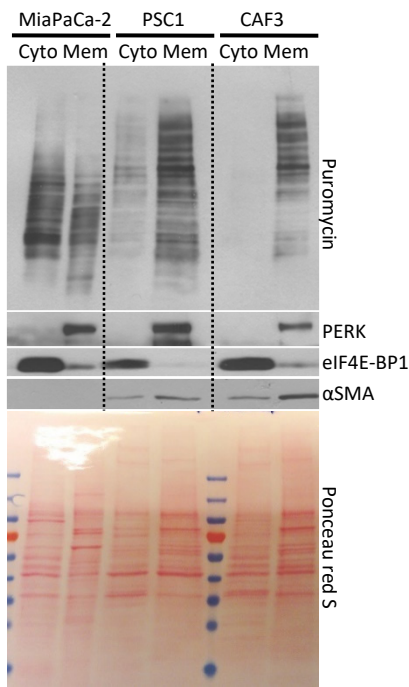
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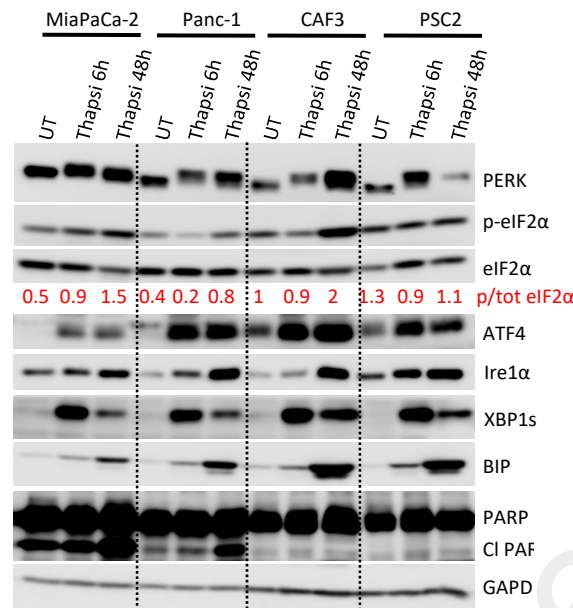
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# Figure 1

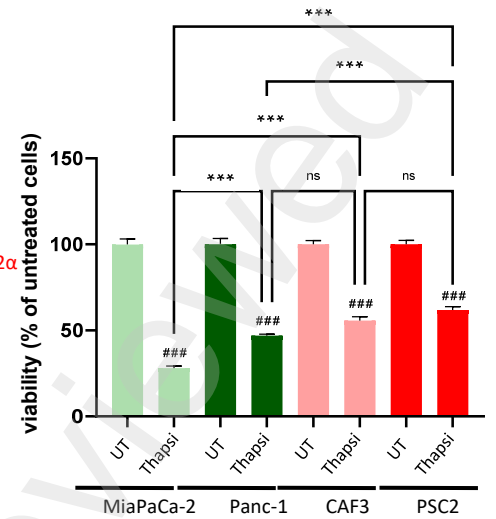
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1B



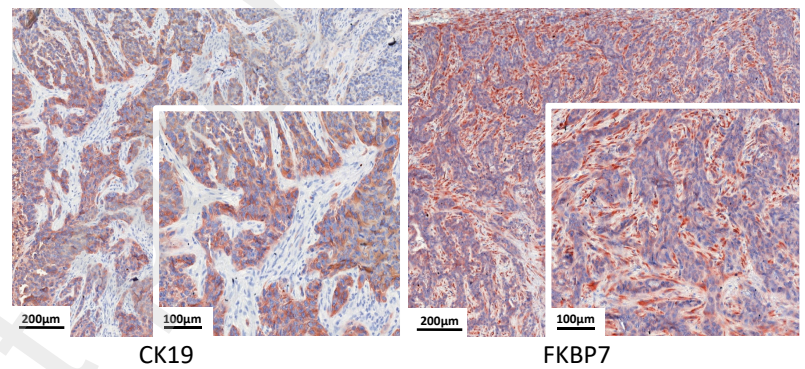
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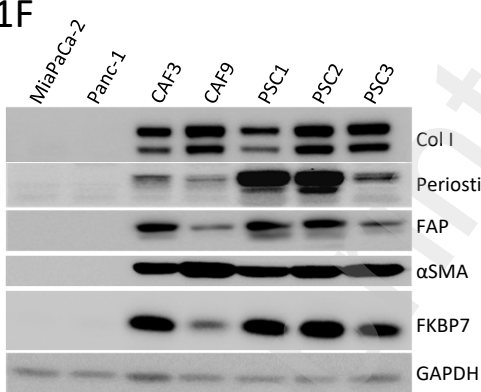
1D

Nicolle et al.	gene	Log2FC	FDR
	CALR3	5.925	3.57E-31
	FKBP7	4.105	5.58E-31
	TOR2A	1.727	2.17E-30
	TMX3	1.444	8.91E-29
	FKBP14	1.410	8.80E-28
	FKBP9	1.294	6.89E-29
	TOR3A	1.090	6.54E-24
Maurer et al.	gene	Log2FC	FDR
	BAG2	3.642	3.93E-14
	FKBP7	3.402	8.89E-18
	FKBP14	2.530	1.04E-14
	TMX3	1.271	1.48E-09

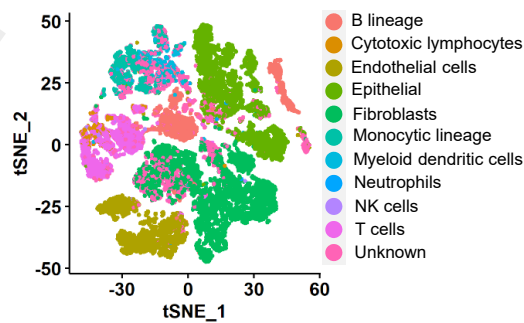
1E



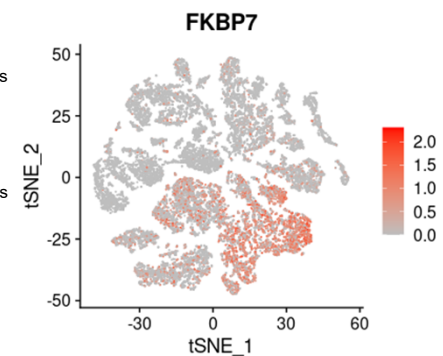
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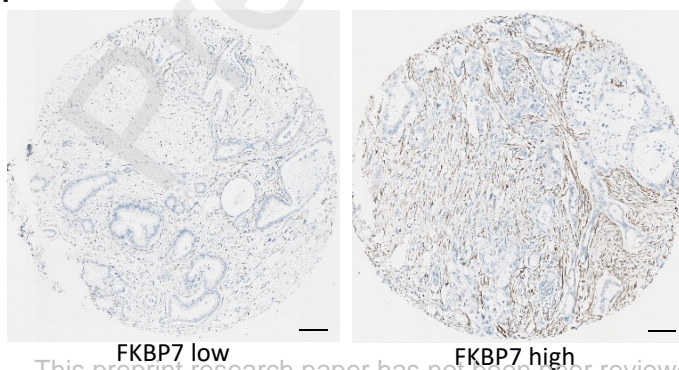
1G



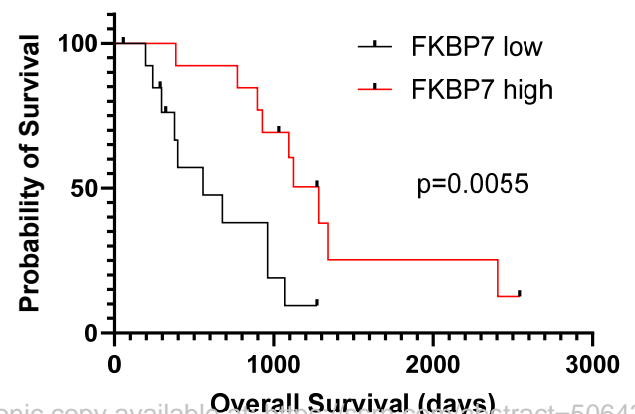
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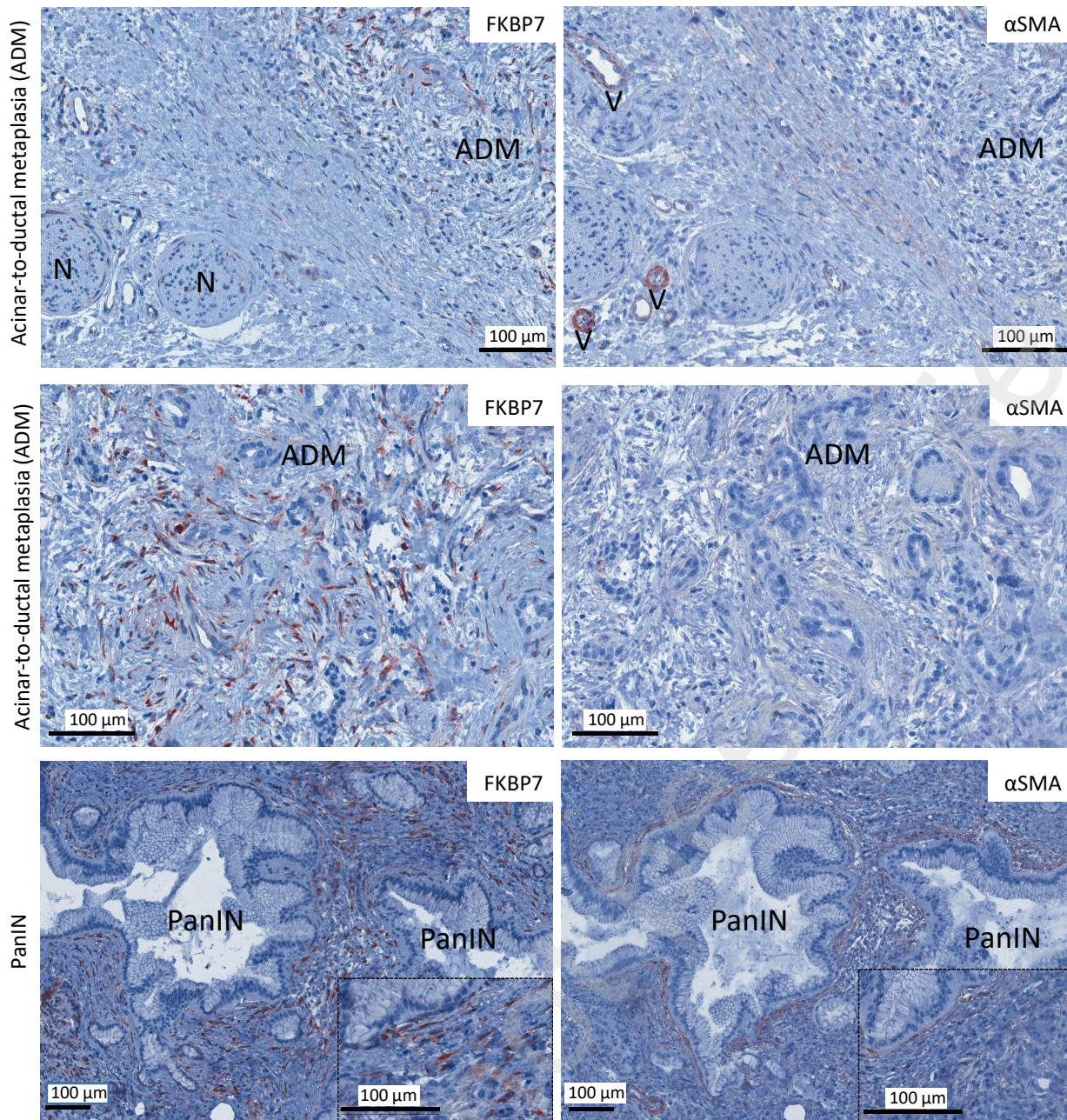


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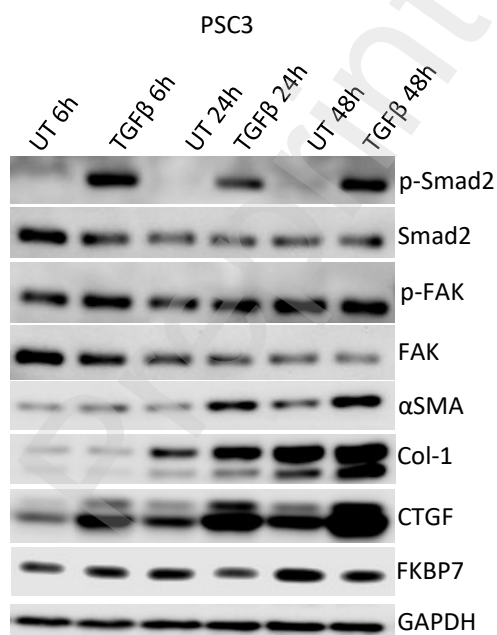


# Figure 2

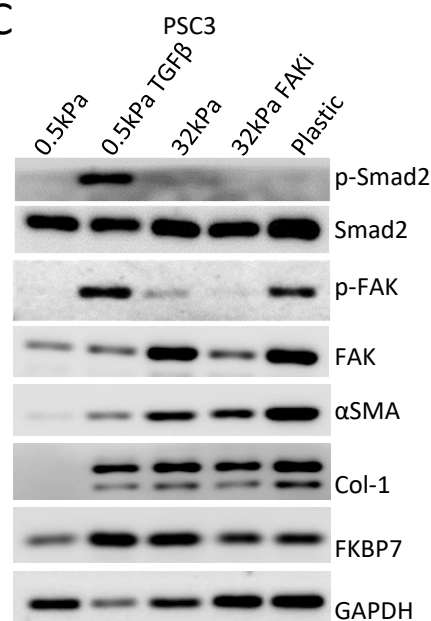
## 2A



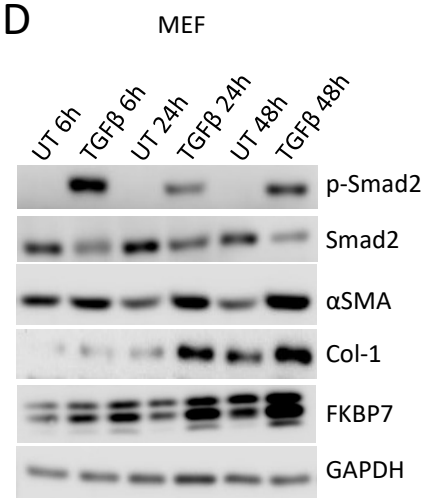
## 2B



## 2C

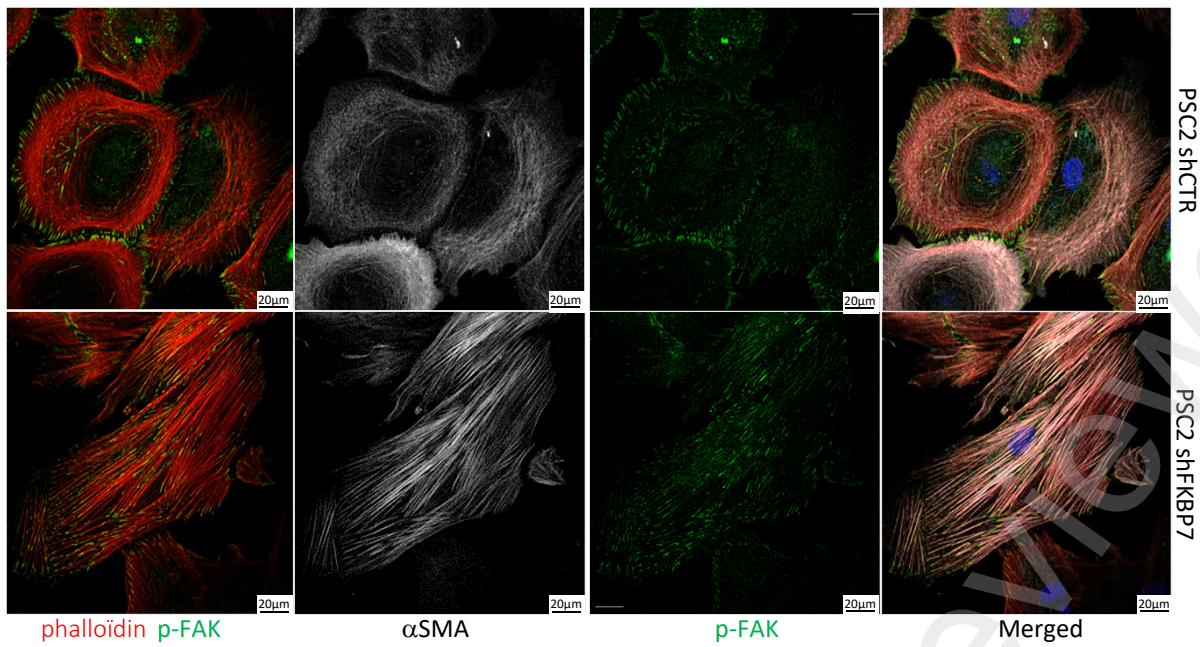


## 2D

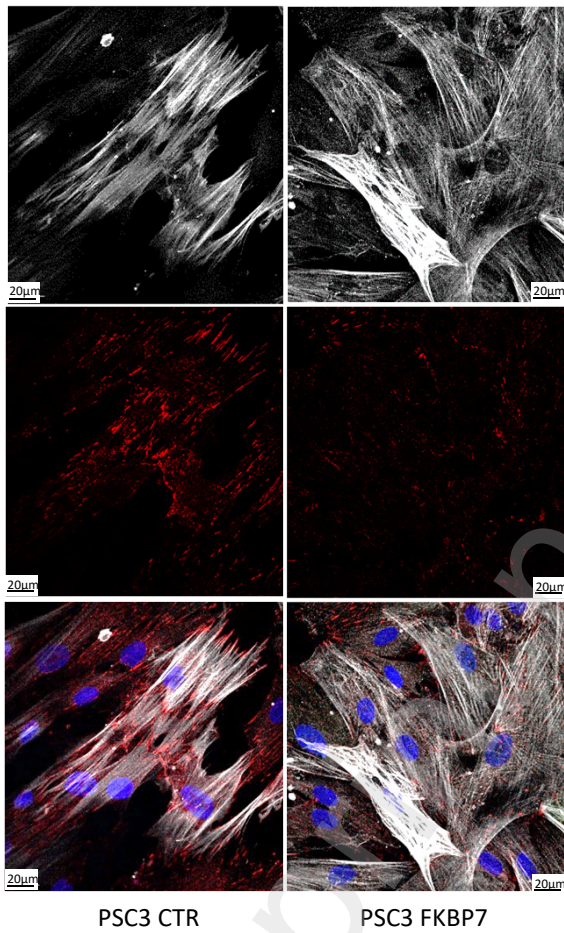


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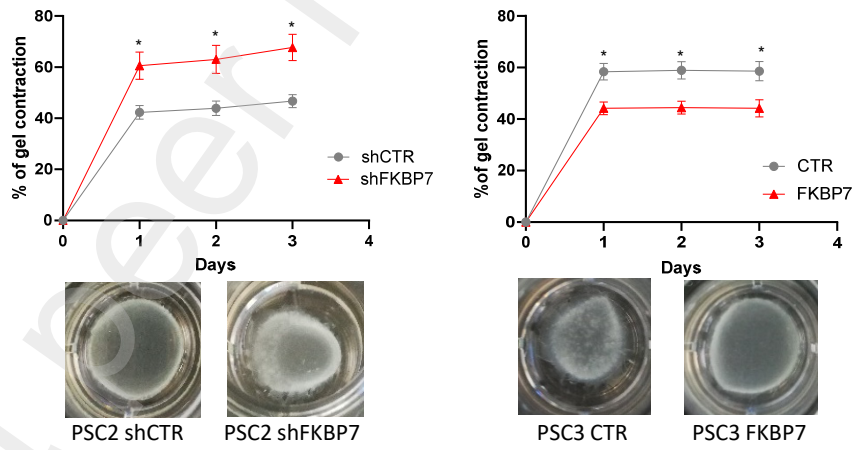
## 3A



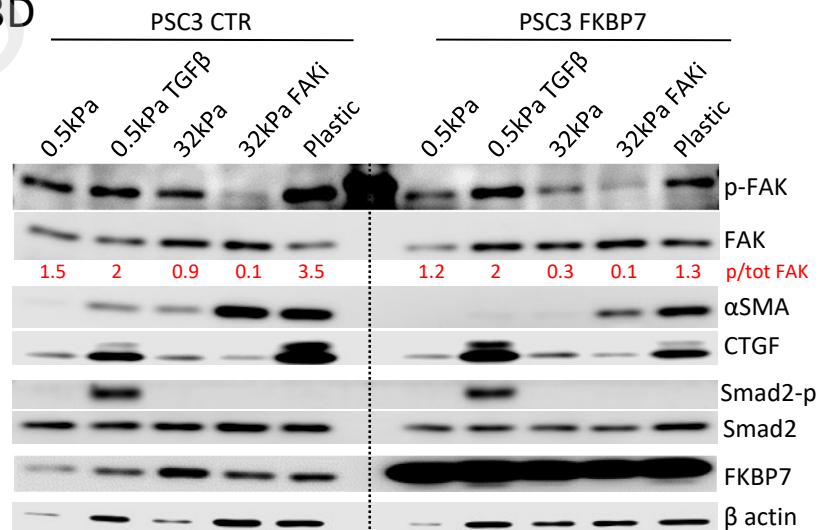
## 3B



## 3C



## 3D

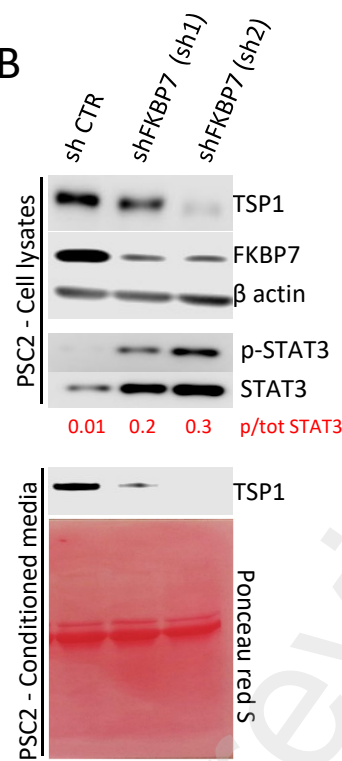


# Figure 4

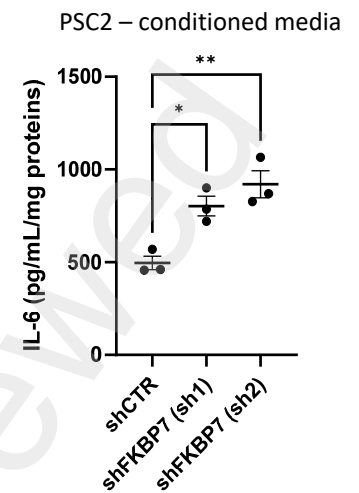
## 4A

Down-regulated	% of shCTR	Up-regulated	% of shCTR
RANTES (CCL5)	42.77589464	IL-31	126.7257846
IGFBP-2 (IBP2)	43.27767255	IL-17A	129.0385171
CD14	43.77020152	IL-27 (C19orf10)	134.5645195
<b>Thrombospondin-1</b>	46.2380644	PF4	135.5914093
IL-5	53.01147325	IL-10	137.6217985
Complement C5	54.74303878	MCP-3 (CCL7)	142.2485162
Cripto-1 (TDGF1)	56.01885516	IL-22	142.3308513
BDNF	57.60138763	DPPIV	147.753166
IL-12 p70 (IL12B)	58.88764206	IL-24	151.2087706
BAFF (TNFS13B)	60.066537	MIF	155.56108
CD30 (TNFRSF8)	60.40218539	IL-8 (CXCL8)	155.9988803
Fas Ligand	61.33343006	Pentraxin-3	158.9926087
IGFBP-3 (IBP3)	63.54925113	PDGF-AA	160.5827165
GDF-15	64.57041565	PDGF-AB/BB	166.260657
CD40 ligand	65.88723568	Lipocalin-2 (LCN2)	172.6354283
IL-1alpha	66.5528146	LIF	188.8068965
Chitinase 3-like 1 (CHI3L1)	66.93576591	VCAM-1	194.1291661
Vitamin D BP (GC)	68.48216983	TFF3	204.3061181
Cystatin C	69.51821986	<b>IL-6</b>	249.1087779
IL-33 (IL1F11)	72.6926122	IL-23 (IL23A)	250.1341827
IL-1ra (IL1RN)	74.33277662		
MIG (CXCL9)	74.39300043		
IL-2	76.76876333		
MIP-3alpha (CCL20)	79.4195825		

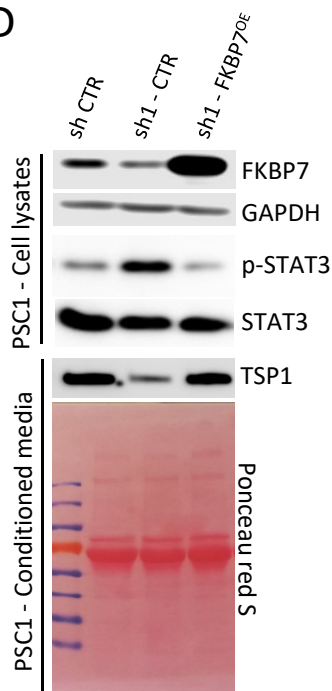
## 4B



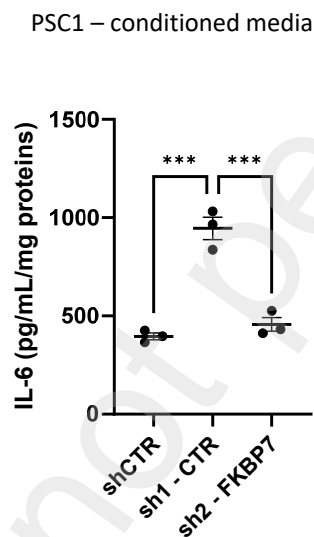
## 4C



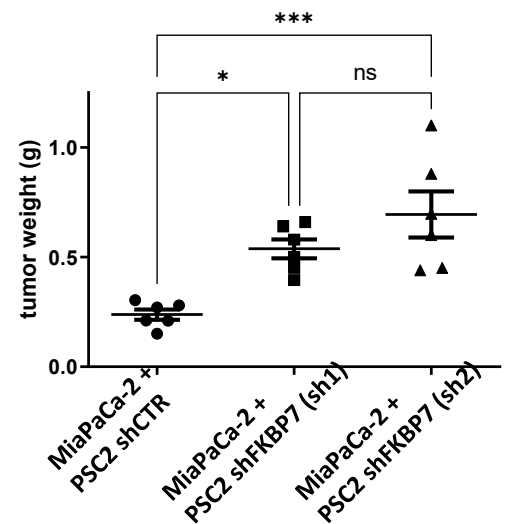
## 4D



## 4E

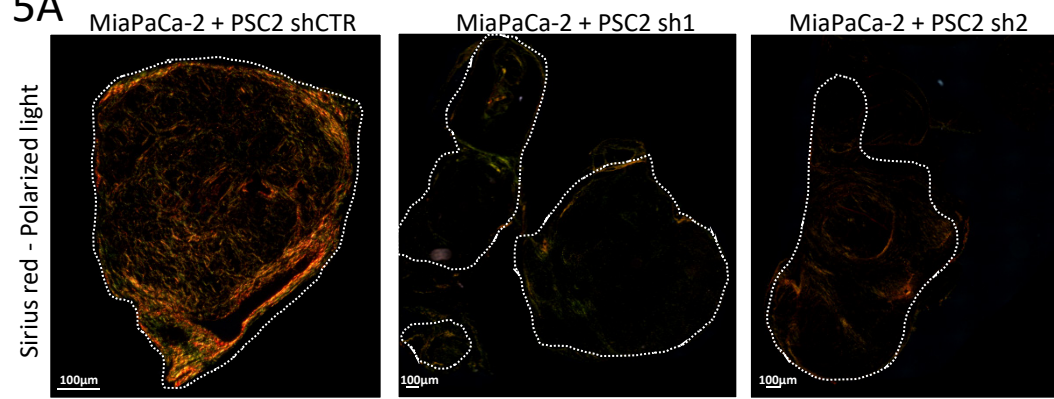


## 4F

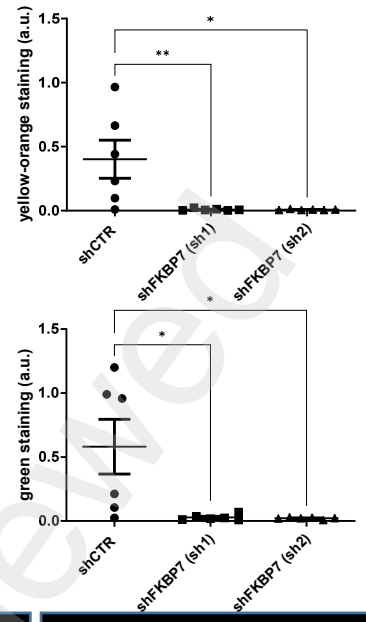


# Figure 5

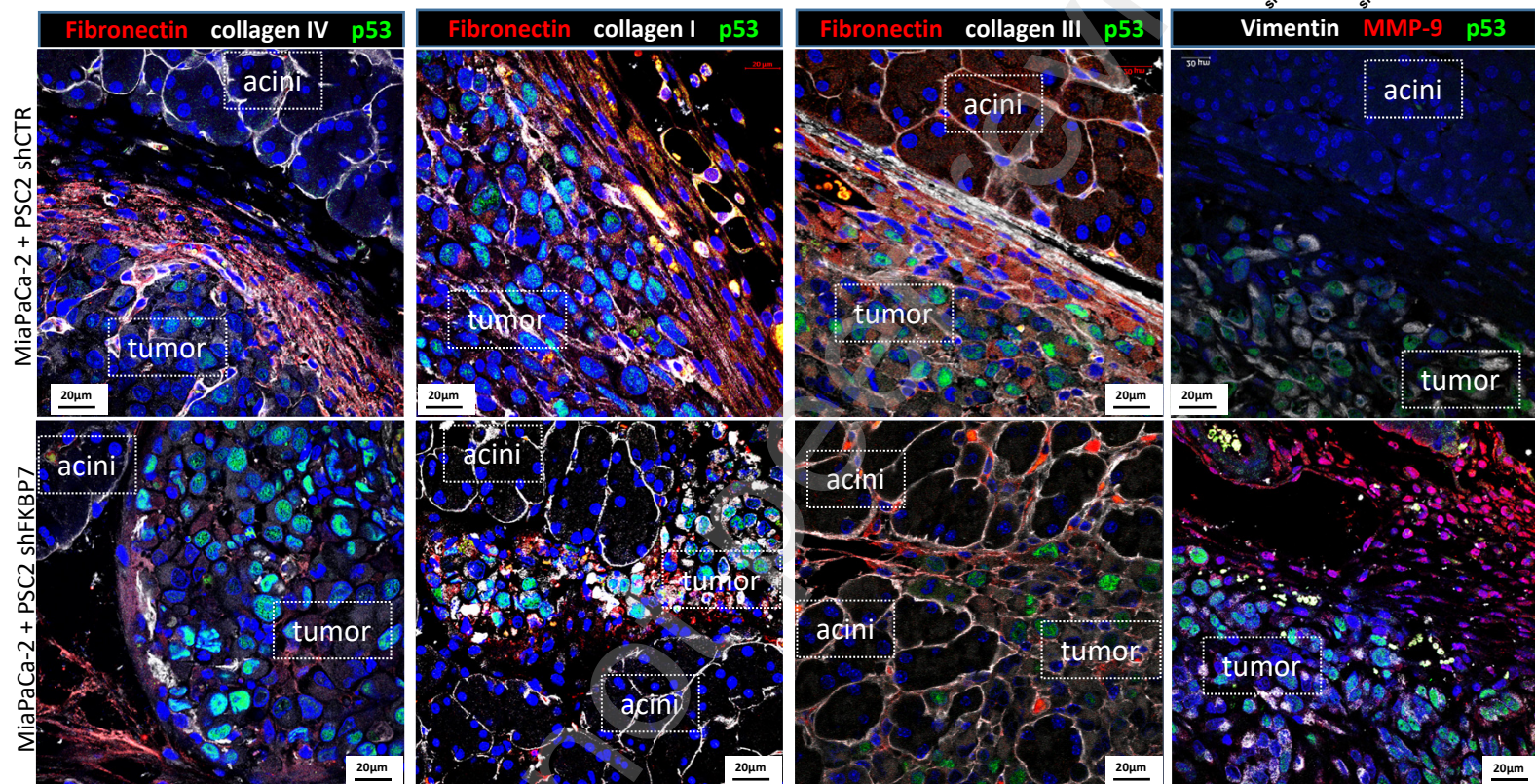
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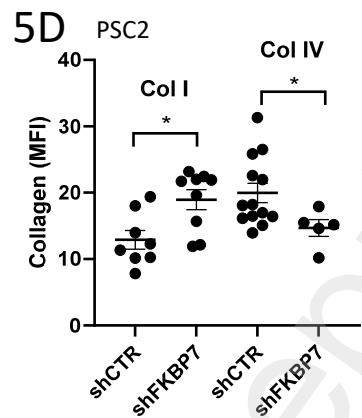
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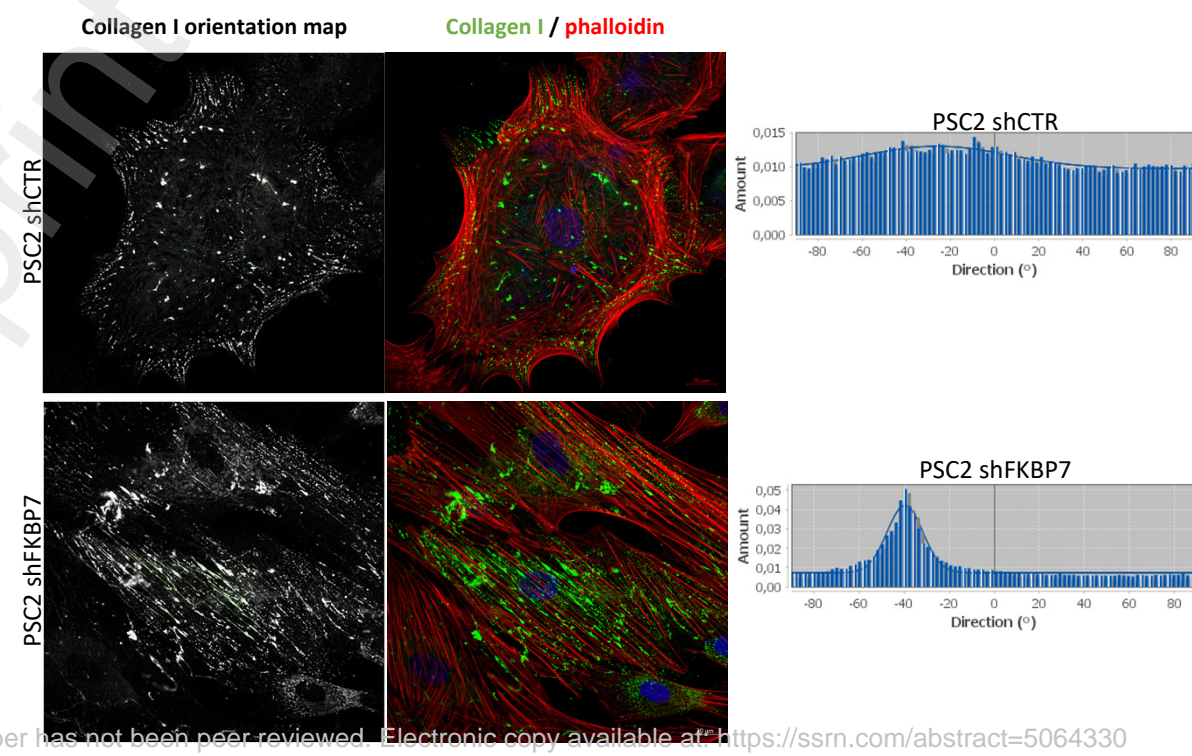
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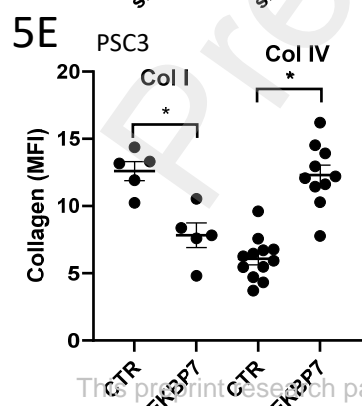
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5F



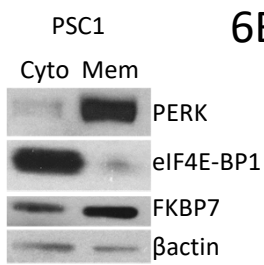
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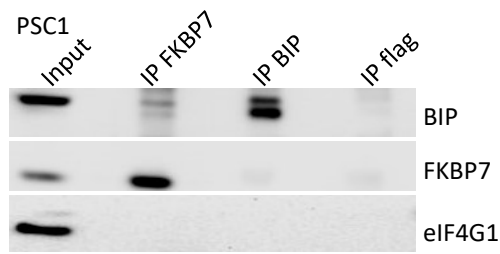


# Figure 6

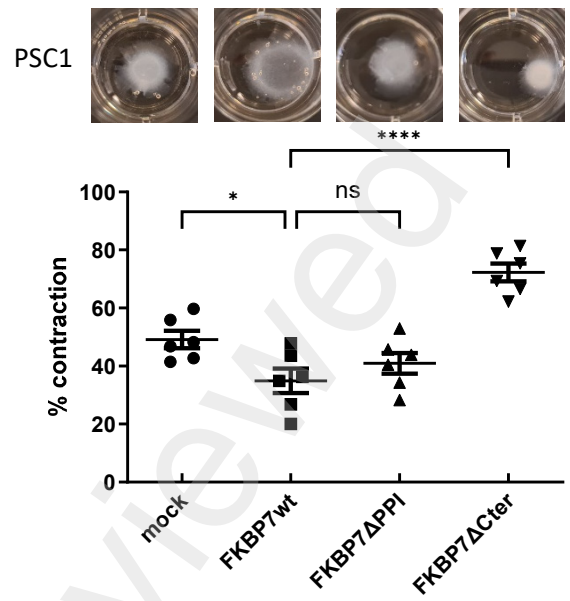
6A



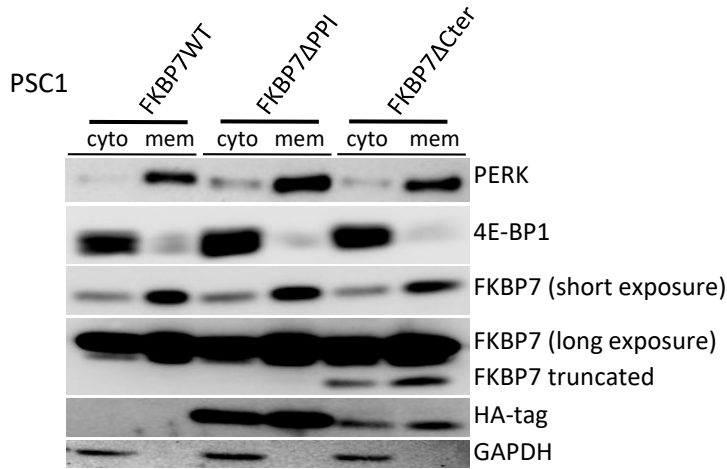
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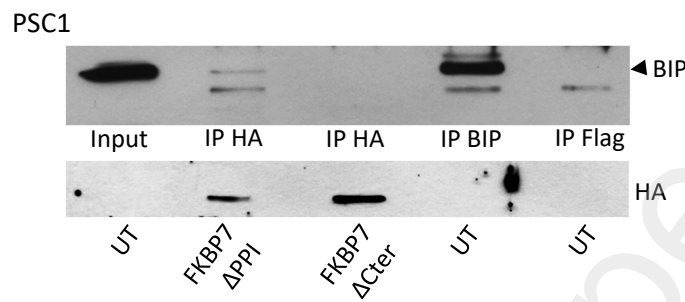
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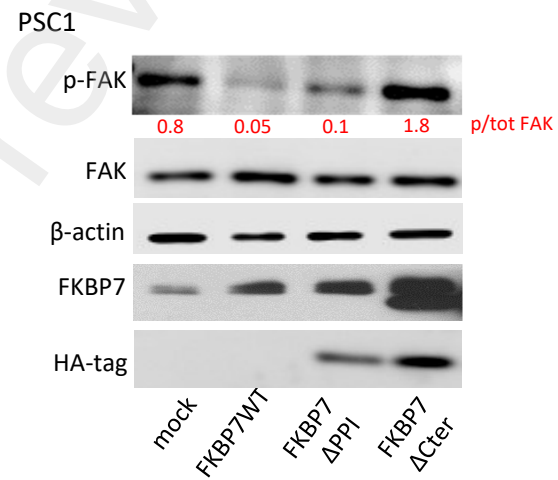
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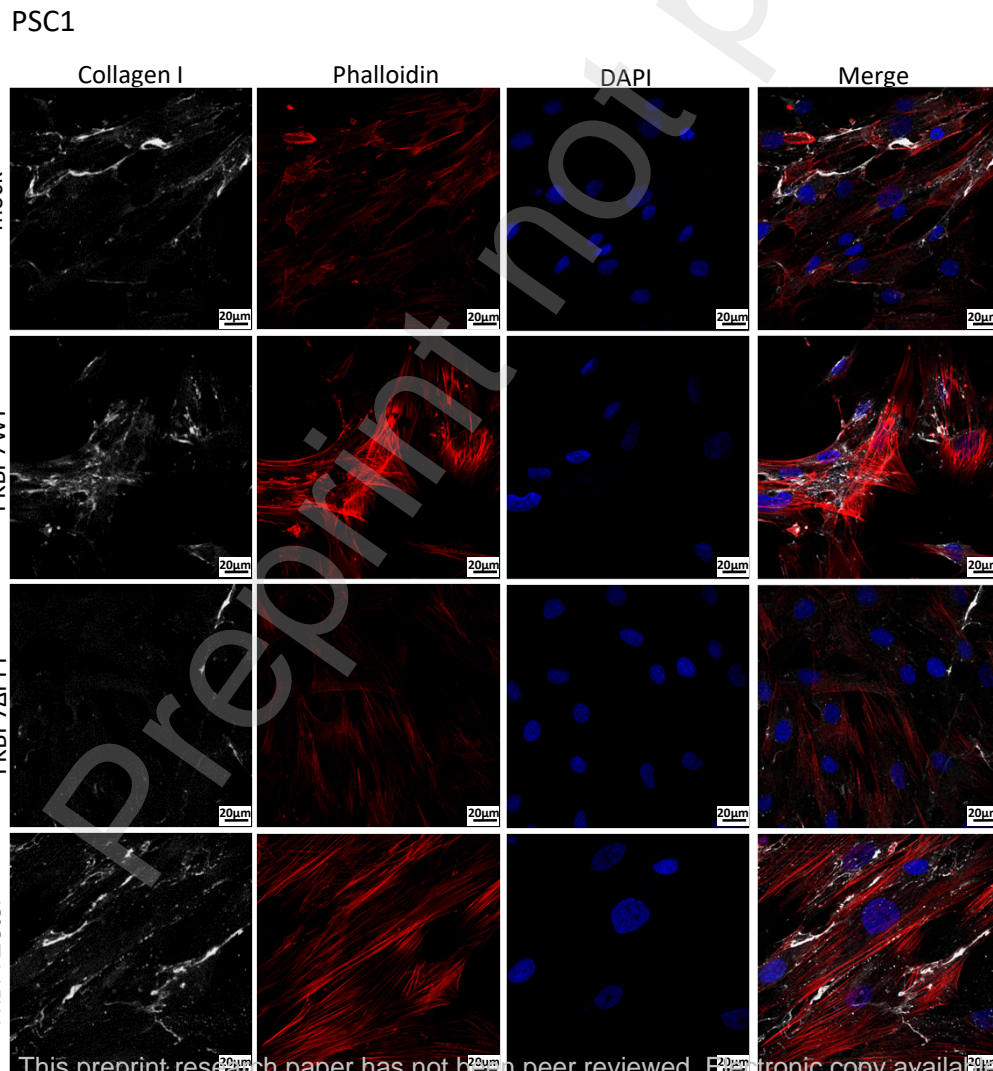
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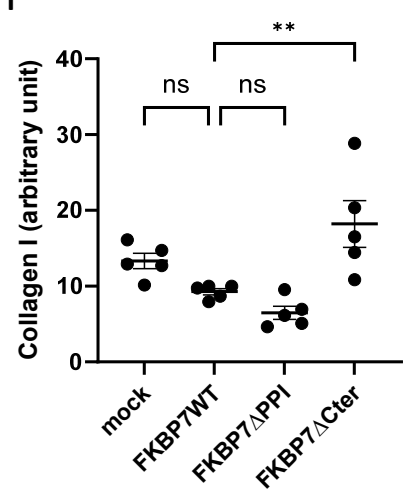
6F



6G



6H



**Table 1: Comparison of expression of ER-related genes in PDX tumor epithelium versus stroma**

gene	Log2FC	FDR
PENK	-13.806	6.72E-32
FCGR2B	-13.527	1.11E-31
ADAMTS5	-12.535	4.15E-32
IGF1	-11.623	3.68E-31
TRDN	-11.426	5.12E-19
COL11A1	-11.243	1.32E-31
COL10A1	-10.804	6.04E-30
PRSS57	-10.787	4.71E-32
COL15A1	-10.622	4.88E-31
APOE	-10.452	4.89E-31
COL3A1	-10.140	4.89E-31
HK3	-9.884	4.51E-31
F13A1	-9.707	1.73E-31
COL26A1	-9.621	2.40E-27
DCSTAMP	-9.374	9.88E-34
SPARC	-9.331	4.89E-31
CCR5	-9.246	3.68E-31
COL14A1	-9.073	5.05E-31
COL1A2	-8.940	4.89E-31
COL23A1	-8.883	4.78E-31
FBN1	-8.861	4.89E-31
COL8A1	-8.802	5.30E-31
SPARCL1	-8.771	4.89E-31
HGF	-8.116	8.32E-32
IL27	-8.111	1.47E-32
COL5A1	-8.087	4.70E-31
COL5A2	-8.063	4.89E-31
PRTN3	-7.913	2.03E-32
DOCK2	-7.877	3.79E-31
SYT6	-7.844	2.87E-29
ARG1	-7.819	8.06E-31
ISLR	-7.811	2.06E-31
COL6A3	-7.797	4.89E-31
THBS4	-7.761	5.05E-31
MMP8	-7.694	2.05E-31
COL1A1	-7.468	4.89E-31
CACNA1G	-7.450	5.05E-31
HLA-DQA1	-7.445	1.24E-30
IGFBP5	-7.443	7.71E-31
ARHGAP9	-7.439	4.89E-31
COL4A1	-7.307	4.89E-31
FGR	-7.293	4.88E-31

<b>MAN1C1</b>	-7.201	4.89E-31
<b>CASQ1</b>	-7.075	5.40E-31
<b>CFP</b>	-7.009	4.89E-31
<b>COL5A3</b>	-7.007	4.89E-31
<b>WNT5A</b>	-6.993	5.61E-31
<b>CASQ2</b>	-6.895	4.50E-30
<b>TIMP3</b>	-6.757	5.57E-31
<b>COL8A2</b>	-6.471	1.72E-30
<b>COL12A1</b>	-6.430	5.78E-31
<b>SPP1</b>	-6.273	7.35E-31
<b>TGFB3</b>	-6.195	5.05E-31
<b>FMO1</b>	-6.162	9.55E-30
<b>DMP1</b>	-6.135	2.92E-31
<b>EBI3</b>	-6.105	4.51E-31
<b>SERPING1</b>	-6.070	4.89E-31
<b>TNC</b>	-6.061	8.90E-31
<b>CALR3</b>	-5.926	3.57E-31
<b>CLEC3B</b>	-5.792	1.15E-28
<b>VWF</b>	-5.714	6.82E-31
<b>COL4A2</b>	-5.709	4.89E-31
<b>CTSG</b>	-5.678	3.76E-27
<b>IGFBP7</b>	-5.655	5.05E-31
<b>COL6A2</b>	-5.654	4.88E-31
<b>HLA-DQB1</b>	-5.566	2.25E-30
<b>FASLG</b>	-5.469	1.41E-25
<b>ACTN2</b>	-5.369	2.04E-12
<b>BIN2</b>	-5.298	4.89E-31
<b>CTSW</b>	-5.260	3.81E-30
<b>SYT3</b>	-5.241	9.71E-31
<b>F2RL3</b>	-5.204	5.27E-30
<b>FN1</b>	-5.186	5.30E-30
<b>ARSI</b>	-5.169	1.28E-30
<b>PTX3</b>	-5.125	1.21E-29
<b>RARRES2</b>	-5.116	7.79E-31
<b>NKD2</b>	-5.115	1.42E-30
<b>COL20A1</b>	-4.999	1.09E-30
<b>ABCA1</b>	-4.996	4.89E-31
<b>P4HA3</b>	-4.957	8.33E-31
<b>DLC1</b>	-4.957	4.88E-31
<b>F7</b>	-4.926	7.55E-29
<b>FSTL1</b>	-4.701	1.02E-30
<b>SDC2</b>	-4.694	3.82E-29
<b>CRYAB</b>	-4.690	5.47E-30
<b>ADAMTSL1</b>	-4.665	7.81E-30
<b>SPON1</b>	-4.649	1.02E-29

<b>GRIA1</b>	-4.615	1.94E-19
<b>MMRN1</b>	-4.598	4.20E-18
<b>PGLYRP1</b>	-4.561	4.89E-31
<b>ARSB</b>	-4.443	4.89E-31
<b>PF4</b>	-4.440	5.12E-30
<b>GPX7</b>	-4.427	6.88E-31
<b>BCL2</b>	-4.383	5.05E-31
<b>THBS1</b>	-4.319	7.35E-30
<b>CRISPLD2</b>	-4.246	1.46E-30
<b>CHRD1</b>	-4.236	1.26E-28
<b>IL12B</b>	-4.171	1.52E-28
<b>FKBP7</b>	-4.106	5.59E-31
<b>COL24A1</b>	-4.100	3.17E-29
<b>ADAMTS7</b>	-4.000	6.17E-31
<b>ELANE</b>	-3.950	6.76E-12
<b>KDELC1</b>	-3.935	4.89E-31
<b>IGFBP4</b>	-3.925	5.23E-31
<b>KNG1</b>	-3.920	3.30E-28
<b>CSF1</b>	-3.870	7.11E-30
<b>GRP</b>	-3.866	3.60E-14
<b>OTOR</b>	-3.830	6.13E-16
<b>CFD</b>	-3.824	0.02477241
<b>SERPINH1</b>	-3.719	4.89E-31
<b>GAS6</b>	-3.702	5.23E-31
<b>LGALS1</b>	-3.660	1.12E-29
<b>SYT4</b>	-3.645	6.30E-29
<b>SYT15</b>	-3.606	2.25E-30
<b>VEGFC</b>	-3.587	1.61E-27
<b>GMFG</b>	-3.559	2.33E-27
<b>F2R</b>	-3.513	8.94E-30
<b>SERPINE1</b>	-3.478	4.99E-28
<b>DPYSL3</b>	-3.430	2.04E-30
<b>COL6A1</b>	-3.426	1.09E-29
<b>FABP5</b>	-3.390	2.09E-29
<b>GPC3</b>	-3.317	4.83E-28
<b>PCSK2</b>	-3.304	4.9279E-05
<b>CD74</b>	-3.240	1.17E-26
<b>DOC2B</b>	-3.205	9.57E-28
<b>ASGR2</b>	-3.172	3.02E-28
<b>MPO</b>	-3.032	3.34E-21
<b>SLC37A2</b>	-3.014	1.99E-27
<b>MAN2B1</b>	-3.008	4.89E-31
<b>BACE1</b>	-3.008	1.42E-30
<b>NPC2</b>	-2.976	3.34E-30
<b>RYR1</b>	-2.965	4.32E-08

<b>F10</b>	-2.962	1.71E-25
<b>MFGE8</b>	-2.925	1.73E-30
<b>COL18A1</b>	-2.903	9.86E-30
<b>HPSE</b>	-2.876	1.16E-30
<b>COL19A1</b>	-2.858	0.00187238
<b>TF</b>	-2.770	9.55E-30
<b>PROS1</b>	-2.692	5.59E-31
<b>KCTD17</b>	-2.691	5.78E-31
<b>PDGFD</b>	-2.663	8.96E-28
<b>LRRK2</b>	-2.640	1.52E-27
<b>COL25A1</b>	-2.620	1.68E-22
<b>COPG2</b>	-2.616	4.89E-31
<b>TXNDC16</b>	-2.604	6.17E-31
<b>ITPR1</b>	-2.586	2.11E-28
<b>GM2A</b>	-2.560	1.20E-29
<b>C3</b>	-2.557	2.48E-23
<b>CYR61</b>	-2.554	2.56E-28
<b>HLA-DRB5</b>	-2.545	7.47E-18
<b>MAN1A1</b>	-2.535	1.05E-29
<b>CTSD</b>	-2.500	8.63E-29
<b>TIMP2</b>	-2.445	2.84E-30
<b>IGFBP3</b>	-2.377	5.50E-25
<b>LIN28A</b>	-2.377	1.64E-07
<b>FAM20C</b>	-2.359	2.10E-26
<b>RAB3A</b>	-2.336	2.53E-29
<b>COL16A1</b>	-2.309	2.56E-27
<b>HIST1H4A</b>	-2.306	2.47E-15
<b>POMC</b>	-2.305	1.11E-29
<b>APOOL</b>	-2.279	4.89E-31
<b>PKD2</b>	-2.275	1.12E-29
<b>MXRA8</b>	-2.269	3.00E-28
<b>COL13A1</b>	-2.249	1.21E-21
<b>ARSK</b>	-2.201	2.66E-30
<b>CALU</b>	-2.198	5.23E-31
<b>GUSB</b>	-2.168	5.78E-31
<b>TGFB1</b>	-2.149	1.33E-30
<b>CTSA</b>	-2.124	1.37E-30
<b>HIST2H3A</b>	-2.110	0.00030948
<b>GPX8</b>	-2.110	5.48E-28
<b>PRSS23</b>	-2.105	3.52E-28
<b>SERPINC1</b>	-2.053	7.45E-26
<b>FERMT3</b>	-2.048	1.26E-24
<b>COL11A2</b>	-2.041	1.46E-27
<b>HIST1H3A</b>	-1.996	2.30E-14
<b>RPH3A</b>	-1.954	1.60E-15

<b>HEXB</b>	-1.923	1.98E-28
<b>S100A8</b>	-1.908	1.57E-26
<b>SYT11</b>	-1.893	1.06E-22
<b>GRN</b>	-1.879	5.40E-31
<b>OSTF1</b>	-1.861	4.89E-31
<b>FBXO6</b>	-1.836	1.23E-28
<b>HLA-G</b>	-1.788	2.22E-21
<b>APOA2</b>	-1.756	2.44E-17
<b>TOR2A</b>	-1.727	2.18E-30
<b>VAT1</b>	-1.718	8.91E-29
<b>CST3</b>	-1.717	2.48E-28
<b>RTN1</b>	-1.708	9.04E-21
<b>STX5</b>	-1.661	1.20E-30
<b>CAMP</b>	-1.645	2.89E-11
<b>CTSZ</b>	-1.625	9.82E-29
<b>ANAPC1</b>	-1.593	4.89E-31
<b>CACNA1H</b>	-1.580	2.71E-17
<b>PTPN6</b>	-1.566	9.21E-29
<b>LAMB1</b>	-1.545	6.31E-27
<b>CTSC</b>	-1.539	2.03E-24
<b>CKAP4</b>	-1.533	4.39E-29
<b>EPHA5</b>	-1.523	1.0828E-05
<b>SPPL2A</b>	-1.507	2.84E-30
<b>CREB3L2</b>	-1.501	4.25E-28
<b>LMAN1L</b>	-1.493	2.06E-11
<b>FTL</b>	-1.491	1.52E-25
<b>EHMT2</b>	-1.484	4.89E-31
<b>SERPINA3</b>	-1.461	1.62E-17
<b>GNS</b>	-1.452	1.77E-29
<b>TMX3</b>	-1.445	8.91E-29
<b>CREB3L3</b>	-1.431	2.68E-18
<b>ARSA</b>	-1.427	2.49E-30
<b>SGPL1</b>	-1.417	7.12E-29
<b>FKBP14</b>	-1.411	8.80E-28
<b>GOSR2</b>	-1.391	5.05E-31
<b>SCG3</b>	-1.345	3.74E-18
<b>RAP1GDS1</b>	-1.342	5.59E-31
<b>AMPD3</b>	-1.338	3.81E-23
<b>PRKCD</b>	-1.334	3.53E-26
<b>GALNS</b>	-1.320	2.91E-28
<b>KCNB1</b>	-1.308	7.95E-19
<b>SCAMP5</b>	-1.305	1.51E-21
<b>FKBP9</b>	-1.295	6.89E-29
<b>GLA</b>	-1.284	6.77E-22
<b>TUSC3</b>	-1.270	3.92E-14

ITIH3	-1.269	2.05E-19
MAPK7	-1.269	3.30E-28
ATF3	-1.257	1.30E-14
HFE	-1.252	1.76E-27
PDGFC	-1.249	1.46E-19
HIST1H2BB	-1.246	0.00238364
FUCA1	-1.241	1.37E-26
FITM1	-1.240	0.0020121
FAM129A	-1.239	7.58E-21
MZB1	-1.233	0.00017533
LYZ	-1.231	1.43E-17
REEP2	-1.230	6.02E-25
COTL1	-1.227	3.76E-24
HLA-A	-1.225	5.09E-20
TBC1D20	-1.217	5.05E-31
LAMC1	-1.216	5.67E-25
ANAPC2	-1.214	4.89E-31
EXT1	-1.205	1.80E-26
CREG1	-1.204	3.10E-22
SSR3	-1.190	3.00E-28
PDGFB	-1.177	3.54E-19
EVA1A	-1.150	4.99E-17
TRAM2	-1.133	5.18E-24
XXYL1	-1.129	1.02E-25
ELOVL4	-1.128	6.40E-11
HGFAC	-1.114	1.49E-15
POGLUT1	-1.103	5.66E-30
PTPN1	-1.102	8.01E-28
GYG1	-1.091	3.17E-16
TOR3A	-1.091	6.54E-24
CDKN2B	-1.068	3.74E-10
CLN8	-1.048	2.10E-21
FKBP10	-1.035	6.30E-13
SLC35B4	-1.032	2.37E-26
CPPED1	-1.026	2.62E-21
CDKN2D	-1.023	1.30E-22
TMEM132A	-1.021	2.21E-15
PADI2	-1.017	8.62E-13
SAMD8	-1.014	1.42E-24
NUCB1	-1.008	5.15E-28
PLG	-1.002	1.95E-06
LRAT	1.006	0.03611232
GOLGB1	1.011	3.84E-27
PDCD6	1.022	7.36E-27
CREB3L1	1.034	1.0748E-05

<b>GHDC</b>	1.039	5.49E-24
<b>UFM1</b>	1.041	1.99E-25
<b>CEBPB</b>	1.060	2.89E-14
<b>FOS</b>	1.065	1.36E-15
<b>ANAPC7</b>	1.068	6.70E-26
<b>PARK7</b>	1.075	9.98E-25
<b>INSIG1</b>	1.083	6.91E-15
<b>TMBIM6</b>	1.092	4.39E-28
<b>DAB2IP</b>	1.102	1.01E-19
<b>TMCO1</b>	1.105	1.69E-26
<b>SRP14</b>	1.106	3.28E-27
<b>CSTB</b>	1.108	6.76E-15
<b>FOXRED2</b>	1.127	7.77E-14
<b>EIF2B5</b>	1.133	5.40E-31
<b>TFG</b>	1.143	5.05E-31
<b>ZC3H12A</b>	1.147	6.62E-21
<b>NPLOC4</b>	1.149	3.74E-29
<b>VEGFB</b>	1.151	1.34E-20
<b>CA4</b>	1.168	8.99E-14
<b>APLP2</b>	1.174	1.45E-22
<b>FRK</b>	1.174	4.54E-18
<b>CEP290</b>	1.179	3.88E-22
<b>TMED4</b>	1.181	4.89E-31
<b>PDXK</b>	1.181	4.45E-20
<b>MAP3K5</b>	1.182	5.64E-19
<b>PA2G4</b>	1.212	1.05E-29
<b>DAG1</b>	1.215	9.45E-22
<b>TRAM1</b>	1.233	8.54E-26
<b>ATL2</b>	1.260	3.52E-28
<b>PCYOX1L</b>	1.262	3.94E-12
<b>CAV2</b>	1.263	6.14E-12
<b>H2AFX</b>	1.273	9.19E-22
<b>PPIE</b>	1.296	6.71E-27
<b>MPPE1</b>	1.321	1.51E-24
<b>DBI</b>	1.326	2.48E-27
<b>UBAC2</b>	1.342	5.68E-29
<b>EDEM3</b>	1.344	1.39E-15
<b>DERA</b>	1.349	2.33E-27
<b>ADAMTSL4</b>	1.360	2.7914E-05
<b>BCAP31</b>	1.374	8.94E-30
<b>ARL6IP1</b>	1.388	1.19E-28
<b>OLA1</b>	1.396	4.89E-31
<b>SYT14</b>	1.404	0.00049219
<b>NIT2</b>	1.445	6.82E-31
<b>CASP4</b>	1.456	5.47E-30



<b>IMPDH2</b>	1.457	3.62E-25
<b>DERL3</b>	1.464	8.42E-11
<b>QPCT</b>	1.472	0.00165744
<b>DGAT2</b>	1.477	4.32E-16
<b>GPAA1</b>	1.478	5.33E-29
<b>THADA</b>	1.506	5.05E-31
<b>CES1</b>	1.546	0.00024184
<b>MBOAT4</b>	1.548	5.25E-08
<b>ANXA2</b>	1.553	3.81E-30
<b>FAM3C</b>	1.557	1.52E-23
<b>SYTL3</b>	1.582	9.07E-15
<b>MARCH6</b>	1.597	1.83E-29
<b>ACTN4</b>	1.599	1.24E-29
<b>TUBB4B</b>	1.606	1.46E-30
<b>DHCR7</b>	1.623	1.24E-27
<b>ANAPC16</b>	1.629	1.12E-30
<b>GET4</b>	1.643	9.24E-30
<b>SGMS2</b>	1.664	2.38E-25
<b>PNPLA2</b>	1.673	1.64E-26
<b>PCSK1</b>	1.678	1.66E-12
<b>AHSG</b>	1.690	4.11E-12
<b>TMED2</b>	1.706	4.89E-31
<b>STX1A</b>	1.709	5.03E-25
<b>LBR</b>	1.716	1.19E-28
<b>RAB37</b>	1.731	7.6455E-05
<b>PPP1R15A</b>	1.734	2.11E-28
<b>ANKLE2</b>	1.761	1.12E-30
<b>MVP</b>	1.767	8.90E-31
<b>CHIT1</b>	1.768	7.6998E-05
<b>CACNA1I</b>	1.769	0.00080609
<b>RAB27A</b>	1.786	5.68E-23
<b>CAPN2</b>	1.794	5.97E-31
<b>CATSPER2</b>	1.836	5.18E-24
<b>GCC2</b>	1.847	5.68E-29
<b>TMEM97</b>	1.855	7.28E-28
<b>EIF2AK1</b>	1.876	4.89E-31
<b>SCCPDH</b>	1.879	3.00E-28
<b>LEFTY2</b>	1.881	3.9228E-05
<b>BGLAP</b>	1.888	1.41E-22
<b>SORL1</b>	1.892	3.60E-20
<b>DSN1</b>	1.911	4.89E-31
<b>ILF2</b>	1.927	4.89E-31
<b>SPPL2B</b>	1.944	1.12E-29
<b>LIPC</b>	2.004	0.00443379
<b>F2</b>	2.014	2.03E-06

<b>TRIB3</b>	2.050	1.61E-18
<b>HIST1H2AB</b>	2.071	2.25E-10
<b>HLA-E</b>	2.077	7.28E-28
<b>GHRL</b>	2.104	2.75E-25
<b>PTGES2</b>	2.116	3.34E-30
<b>RNF103</b>	2.127	5.15E-28
<b>TRIM13</b>	2.148	4.89E-31
<b>ASPH</b>	2.168	2.11E-30
<b>QSOX1</b>	2.171	1.06E-25
<b>DNAJB1</b>	2.175	5.05E-31
<b>NHLRC2</b>	2.184	7.05E-31
<b>ARSJ</b>	2.196	6.27E-21
<b>GOLM1</b>	2.205	8.80E-26
<b>COL9A3</b>	2.207	5.7239E-05
<b>HSPH1</b>	2.209	1.02E-30
<b>HIST1H2BL</b>	2.231	2.63E-19
<b>VEGFA</b>	2.232	2.45E-26
<b>SLC37A4</b>	2.241	5.23E-31
<b>NOL3</b>	2.246	8.94E-30
<b>CAPN1</b>	2.253	4.89E-31
<b>MATN3</b>	2.265	1.08E-15
<b>ALDOC</b>	2.268	1.56E-24
<b>GBA2</b>	2.309	4.89E-31
<b>ITIH4</b>	2.316	1.25E-22
<b>ALOX5</b>	2.368	8.62E-13
<b>CLU</b>	2.385	0.01791219
<b>OSBPL3</b>	2.501	1.79E-30
<b>GCA</b>	2.574	5.30E-30
<b>TMEM117</b>	2.579	1.99E-27
<b>OSCAR</b>	2.587	1.15E-09
<b>OSBPL7</b>	2.592	1.87E-27
<b>RYR3</b>	2.596	1.93E-27
<b>ARV1</b>	2.642	4.89E-31
<b>SYTL4</b>	2.735	1.28E-27
<b>TM6SF2</b>	2.751	4.60E-07
<b>SVIP</b>	2.760	5.97E-31
<b>ABCB9</b>	2.780	4.89E-31
<b>PIGG</b>	2.797	4.89E-31
<b>SUMF2</b>	2.814	4.89E-31
<b>PYGB</b>	2.829	6.38E-31
<b>HIST1H2BC</b>	2.867	1.85E-20
<b>SYTL2</b>	2.947	2.21E-23
<b>DBH</b>	2.973	1.80E-07
<b>HSP90AA1</b>	3.065	4.89E-31
<b>DNAJB2</b>	3.097	4.89E-31

DHRS9	3.108	6.19E-07
SYT17	3.111	3.30E-28
SYT13	3.204	5.48E-21
CD55	3.226	8.53E-28
UNC13D	3.235	1.05E-29
ELOVL6	3.277	7.29E-31
YOD1	3.280	4.89E-31
UBC	3.313	4.89E-31
COL4A3	3.325	0.00215237
HIST3H2BB	3.371	5.71E-24
HEBP2	3.382	4.89E-31
PDIA2	3.407	2.57E-19
GSTP1	3.424	5.05E-31
SERPINB1	3.466	2.74E-30
HIST1H2AD	3.577	6.84E-19
HIST1H2BO	3.608	3.06E-24
RNASET2	3.626	1.86E-28
DYNLT1	3.639	4.89E-31
SYT16	3.653	3.83E-11
SYT7	3.655	9.60E-17
TTC23L	3.719	1.04E-27
JUP	3.723	9.55E-30
SRP9	3.812	4.89E-31
IGF2	3.856	0.00025444
HSPA1L	3.939	1.41E-29
F8	3.944	1.08E-10
SERPINF2	3.960	1.90E-26
SLC37A1	3.967	3.94E-30
TMEM30B	3.988	1.49E-28
TMEM170A	4.010	4.89E-31
XRCC6	4.046	4.89E-31
COL4A4	4.056	4.97E-16
MAPK10	4.074	3.25E-12
SLPI	4.084	1.17E-26
F5	4.100	5.89E-22
BRSK2	4.128	8.71E-28
LRRC7	4.164	3.51E-30
BMP4	4.237	1.02E-25
ITIH2	4.288	1.42E-15
AREG	4.318	4.88E-27
SYT2	4.357	5.28E-31
CDA	4.366	8.46E-22
SEC31B	4.482	4.89E-31
COL4A6	4.536	0.0205178
A1BG	4.548	7.97E-28

<b>COL9A2</b>	4.631	4.25E-28
<b>COL9A1</b>	4.712	8.83E-16
<b>FGA</b>	4.719	1.61E-08
<b>ATG10</b>	4.771	4.89E-31
<b>TH</b>	4.777	3.37E-18
<b>RYR2</b>	4.780	4.50E-18
<b>BPI</b>	4.796	0.00014809
<b>SERPINA1</b>	4.834	1.56E-24
<b>FOLR1</b>	4.938	2.03E-14
<b>COL22A1</b>	4.945	5.99E-17
<b>SRP54</b>	4.960	4.89E-31
<b>CDK6</b>	4.989	1.42E-30
<b>TRPV6</b>	5.009	1.92E-18
<b>WNT7B</b>	5.203	8.80E-28
<b>XRCC5</b>	5.214	4.89E-31
<b>ADAMTS13</b>	5.216	4.83E-31
<b>HLA-F</b>	5.314	4.80E-30
<b>SYT1</b>	5.334	1.60E-12
<b>TMED6</b>	5.580	7.01E-32
<b>SYTL1</b>	5.625	7.83E-27
<b>TGFA</b>	5.787	5.40E-31
<b>TC2N</b>	5.815	3.99E-29
<b>FBXO2</b>	5.831	1.41E-26
<b>FGG</b>	5.873	3.8073E-05
<b>PCSK9</b>	5.931	4.50E-29
<b>APOA1</b>	5.965	6.64E-17
<b>SLC27A5</b>	6.033	4.86E-31
<b>C2CD4A</b>	6.039	2.13E-26
<b>LCN2</b>	6.181	2.12E-27
<b>SYT8</b>	6.255	1.02E-29
<b>IL23A</b>	6.284	3.46E-31
<b>ELOVL7</b>	6.320	1.37E-30
<b>C2CD4D</b>	6.320	7.97E-33
<b>TMEM27</b>	6.433	1.88E-28
<b>LAMP5</b>	6.489	1.02E-21
<b>CNIH3</b>	6.498	3.39E-32
<b>PROM1</b>	6.664	8.08E-27
<b>SYTL5</b>	6.787	2.58E-28
<b>HIST1H2BN</b>	6.820	6.21E-32
<b>WNT3</b>	7.072	6.00E-32
<b>APOB</b>	7.598	4.06E-11
<b>F12</b>	7.799	2.18E-31
<b>ALB</b>	7.821	9.52E-14
<b>RBX1</b>	7.854	4.89E-31
<b>PTGDS</b>	7.937	7.36E-23

<b>GJB2</b>	7.974	6.81E-31
<b>SHH</b>	8.208	6.25E-31
<b>SGPP2</b>	8.230	8.61E-31
<b>MSLN</b>	8.424	2.64E-29
<b>CD59</b>	8.534	4.89E-31
<b>HIST1H2BD</b>	8.597	1.92E-31
<b>SLC27A2</b>	8.608	1.58E-30
<b>MIA</b>	8.961	3.60E-30
<b>OLFM4</b>	9.108	3.35E-18
<b>WNT7A</b>	9.625	1.18E-26
<b>IGFBP1</b>	10.243	6.86E-30
<b>HIST1H2BK</b>	10.405	2.18E-31
<b>AOC1</b>	10.520	3.32E-30
<b>UBA52</b>	11.119	4.86E-31
<b>AGR2</b>	15.964	1.55E-31

**Table 2: Comparison of expression of ER-related genes in PDA microdissected lesions of the tumor epithelium vs. stroma**

Gene	log2FC	FDR
IGF1	-6.854	5.60E-19
MATN3	-6.476	2.74E-19
COL8A1	-6.428	3.30E-20
COL14A1	-6.423	1.15E-19
COL11A1	-6.267	2.21E-19
ISLR	-6.086	3.30E-20
TIMP3	-5.994	3.30E-20
COL15A1	-5.753	3.37E-20
HGF	-5.568	9.24E-19
FBN1	-5.555	3.30E-20
COL8A2	-5.506	6.80E-18
COL5A1	-5.482	3.30E-20
COL3A1	-5.420	3.30E-20
COL1A1	-5.309	3.30E-20
MXRA8	-5.296	3.33E-20
F13A1	-5.292	5.49E-18
COL6A3	-5.254	3.30E-20
COL10A1	-5.201	3.37E-20
SPON1	-5.187	3.28E-18
COL1A2	-5.128	3.30E-20
SPARC	-5.114	3.30E-20
PTGDS	-5.088	4.83E-15
IGFBP5	-5.075	6.34E-20
DOCK2	-5.039	9.94E-18
THBS4	-5.012	1.94E-14
COL5A2	-5.011	3.91E-20
COL24A1	-4.990	9.94E-18
CYR61	-4.984	3.93E-19
VWF	-4.903	4.93E-16
SPARCL1	-4.898	9.41E-20
FN1	-4.879	6.25E-20
CRISPLD2	-4.800	1.08E-19
COL4A1	-4.797	3.92E-20
DLC1	-4.784	6.68E-19
THBS1	-4.782	3.33E-20
MAN1C1	-4.772	5.08E-17
COL6A2	-4.727	7.74E-20
COL16A1	-4.710	3.92E-20
RARRES2	-4.702	4.07E-18
CRYAB	-4.682	2.63E-17
COL4A2	-4.662	4.49E-20

<b>CHRD1</b>	-4.622	1.61E-13
<b>TGFB3</b>	-4.608	3.85E-17
<b>IGFBP7</b>	-4.606	3.30E-20
<b>ADAMTSL1</b>	-4.544	4.75E-17
<b>SDC2</b>	-4.544	3.30E-20
<b>ADAMTS5</b>	-4.529	7.98E-16
<b>DPYSL3</b>	-4.506	1.91E-19
<b>WNT5A</b>	-4.413	4.63E-19
<b>LGALS1</b>	-4.380	5.40E-19
<b>RASGRF2</b>	-4.349	1.59E-15
<b>COL12A1</b>	-4.327	3.37E-20
<b>BCL2</b>	-4.292	5.39E-16
<b>SERPINE1</b>	-4.280	2.36E-17
<b>F2R</b>	-4.222	1.83E-19
<b>VEGFC</b>	-4.147	5.60E-17
<b>LRRK2</b>	-4.121	9.28E-16
<b>COL6A1</b>	-4.114	4.41E-18
<b>FSTL1</b>	-4.045	3.30E-20
<b>VCAN</b>	-4.025	6.74E-20
<b>A2M</b>	-3.937	1.77E-19
<b>FCGR2B</b>	-3.832	3.08E-16
<b>APOE</b>	-3.827	1.06E-14
<b>CDKN2B</b>	-3.820	8.52E-14
<b>IGFBP3</b>	-3.805	2.51E-18
<b>MAPK10</b>	-3.780	1.30E-13
<b>GPX7</b>	-3.769	6.80E-13
<b>SYT11</b>	-3.766	5.45E-15
<b>FKBP10</b>	-3.666	3.86E-16
<b>BAG2</b>	-3.643	3.93E-14
<b>GMFG</b>	-3.579	1.24E-11
<b>PDGFC</b>	-3.572	3.32E-18
<b>CCR5</b>	-3.525	8.01E-12
<b>OSBPL6</b>	-3.426	8.16E-13
<b>PRSS23</b>	-3.425	4.72E-19
<b>KDELC1</b>	-3.403	1.44E-12
<b>FKBP7</b>	-3.403	8.89E-18
<b>LTBP1</b>	-3.394	6.25E-20
<b>FMO1</b>	-3.384	2.72E-10
<b>PDGFD</b>	-3.379	2.65E-11
<b>GPC3</b>	-3.334	8.13E-11
<b>P4HA3</b>	-3.333	3.06E-13
<b>HLA-DQA1</b>	-3.323	6.67E-11
<b>SERPING1</b>	-3.315	2.50E-17
<b>ARSB</b>	-3.214	2.29E-15
<b>MFGE8</b>	-3.196	1.05E-15

<b>ABCA1</b>	-3.188	1.87E-19
<b>STC2</b>	-3.183	5.46E-11
<b>CACNA1H</b>	-3.141	1.71E-10
<b>BIN2</b>	-3.130	4.55E-13
<b>CDH2</b>	-3.088	1.56E-08
<b>GPX8</b>	-3.071	3.50E-18
<b>COL4A5</b>	-3.009	1.06E-10
<b>SERPINH1</b>	-2.909	2.30E-18
<b>C3</b>	-2.876	1.97E-09
<b>CSF1</b>	-2.843	4.91E-10
<b>TRAM2</b>	-2.831	5.90E-18
<b>ARHGAP9</b>	-2.830	9.73E-11
<b>COL5A3</b>	-2.776	5.93E-10
<b>GAS6</b>	-2.735	7.52E-12
<b>ELOVL4</b>	-2.719	7.71E-12
<b>PKD2</b>	-2.705	9.90E-18
<b>LAMB1</b>	-2.684	1.70E-19
<b>TIMP2</b>	-2.674	2.61E-18
<b>SCG2</b>	-2.605	2.78E-07
<b>IGFBP4</b>	-2.570	1.81E-17
<b>F2RL3</b>	-2.551	5.38E-11
<b>CES1</b>	-2.535	3.64E-09
<b>FKBP14</b>	-2.530	1.04E-14
<b>SYTL4</b>	-2.513	7.45E-13
<b>BACE1</b>	-2.486	2.46E-16
<b>RYR2</b>	-2.463	1.89E-06
<b>ADAMTS7</b>	-2.442	2.42E-07
<b>S100A8</b>	-2.435	2.17E-08
<b>HLA-DQB1</b>	-2.421	1.77E-06
<b>FAM20C</b>	-2.401	4.89E-10
<b>FAM129A</b>	-2.394	9.60E-11
<b>RTN1</b>	-2.379	5.27E-08
<b>HLA-DRA</b>	-2.280	2.12E-09
<b>MAN1A1</b>	-2.249	1.25E-14
<b>TIMP1</b>	-2.229	8.19E-16
<b>ITPR1</b>	-2.221	1.55E-11
<b>TGFB1</b>	-2.154	7.15E-10
<b>VEGFB</b>	-2.110	1.03E-09
<b>FGR</b>	-2.105	9.78E-07
<b>COL4A4</b>	-2.097	2.84E-05
<b>GALNS</b>	-2.088	1.75E-07
<b>CRTAP</b>	-2.085	1.50E-16
<b>SYT1</b>	-2.023	0.00020496
<b>COL18A1</b>	-1.959	1.10E-07
<b>ARSG</b>	-1.934	2.09E-07



<b>CNIH3</b>	-1.915	0.00018154
<b>LAMB2</b>	-1.910	5.07E-13
<b>SLC37A2</b>	-1.858	1.87E-05
<b>TUSC3</b>	-1.839	0.00041831
<b>PYGL</b>	-1.814	0.00030538
<b>KDELC2</b>	-1.807	8.09E-13
<b>MMRN1</b>	-1.804	9.13E-05
<b>CD74</b>	-1.748	1.43E-08
<b>HLA-DRB5</b>	-1.689	0.00023998
<b>SEC23A</b>	-1.678	8.70E-14
<b>LAMC1</b>	-1.636	5.01E-16
<b>PADI2</b>	-1.622	0.00133335
<b>CALU</b>	-1.604	3.93E-17
<b>ADAMTSL4</b>	-1.597	0.00186842
<b>ATL1</b>	-1.567	5.57E-06
<b>VAT1</b>	-1.545	3.28E-10
<b>PROS1</b>	-1.475	0.0001385
<b>FTL</b>	-1.436	1.46E-10
<b>FSTL3</b>	-1.414	0.00603576
<b>FERMT3</b>	-1.403	0.00277423
<b>SPP1</b>	-1.383	0.00238724
<b>GJB2</b>	-1.371	9.08E-05
<b>ARSK</b>	-1.364	0.00095114
<b>SLC35B4</b>	-1.357	1.34E-06
<b>CREB3L2</b>	-1.353	7.84E-13
<b>MAGED2</b>	-1.342	2.96E-08
<b>GM2A</b>	-1.325	2.22E-07
<b>CKAP4</b>	-1.323	6.80E-10
<b>HERPUD1</b>	-1.308	2.27E-07
<b>CNN2</b>	-1.291	2.27E-08
<b>TMX3</b>	-1.271	1.48E-09
<b>CFD</b>	-1.267	0.00349052
<b>PIK3R1</b>	-1.265	1.00E-08
<b>RPS6KA2</b>	-1.252	8.62E-06
<b>SEC24D</b>	-1.229	2.55E-11
<b>MAN2B1</b>	-1.224	1.47E-05
<b>ACTN1</b>	-1.212	2.91E-12
<b>TNC</b>	-1.205	0.02913793
<b>TGFB2</b>	-1.201	0.01814096
<b>ELOVL5</b>	-1.185	2.29E-06
<b>RGMB</b>	-1.171	8.32E-05
<b>COL7A1</b>	-1.152	0.01652916
<b>TP53</b>	-1.127	0.04164063
<b>F8</b>	-1.112	0.00151011
<b>FOXRED2</b>	-1.101	0.01004867

NEU1	-1.100	0.05194287
TMTC3	-1.099	9.73E-08
RCN1	-1.093	7.10E-07
GSN	-1.076	2.72E-06
NUCB1	-1.076	0.00025704
CPPED1	-1.070	0.02217519
FKBP11	-1.068	0.004347
CEBPB	-1.036	0.00018513
TMCO1	1.003	7.45E-07
ELOVL1	1.012	0.0002326
TBL2	1.020	0.00063544
SRP9	1.040	1.99E-06
PIGG	1.040	0.00668933
SEC16B	1.054	0.01269919
APRT	1.055	0.00313812
BLOC1S3	1.075	0.00849932
LBR	1.075	3.29E-07
ARV1	1.082	0.00014765
ANXA2	1.093	2.49E-10
AIFM1	1.095	0.00162357
ACAA1	1.103	0.00269328
CSTB	1.108	1.07E-08
FUCA1	1.132	1.05E-05
HEBP2	1.133	6.95E-06
TMEM33	1.133	9.09E-10
SLC35B1	1.133	8.24E-05
OLA1	1.135	1.25E-09
TEX264	1.149	0.00428873
HSP90AA1	1.149	1.07E-13
CCDC115	1.151	0.00089106
H2AFZ	1.162	2.01E-07
UBQLN4	1.162	0.00100115
PSMA5	1.166	2.12E-05
PTGS2	1.169	0.00111025
EIF2AK1	1.170	1.19E-10
ARFGAP2	1.171	0.00551118
ATL2	1.176	1.20E-08
H2AFX	1.182	0.0041568
GSDMD	1.189	0.01408204
SORL1	1.203	2.14E-05
VWA1	1.208	0.00100718
TRAF2	1.216	0.00103768
SEC23B	1.220	3.70E-10
QSOX1	1.224	7.98E-08
UNC13D	1.232	0.00596797

<b>DNAJB2</b>	1.239	0.00124739
<b>TMED4</b>	1.251	5.21E-05
<b>GCA</b>	1.255	3.10E-06
<b>ASPH</b>	1.256	1.81E-09
<b>PSMD14</b>	1.258	9.92E-07
<b>DAB2IP</b>	1.265	0.00018841
<b>APLP2</b>	1.270	3.93E-11
<b>CAPN1</b>	1.272	1.15E-07
<b>VPS33B</b>	1.281	0.00207547
<b>PMM2</b>	1.283	0.00015424
<b>GAK</b>	1.305	0.00011593
<b>YOD1</b>	1.311	2.66E-07
<b>LMAN2L</b>	1.315	0.00423172
<b>TMEM170A</b>	1.342	0.0001837
<b>ZC3H12A</b>	1.343	0.00412738
<b>SCCPDH</b>	1.349	1.71E-07
<b>RNF103</b>	1.354	3.33E-08
<b>RPS6KA1</b>	1.402	0.00090909
<b>DNASE1L1</b>	1.426	0.00042631
<b>LYZ</b>	1.442	5.17E-05
<b>TECR</b>	1.447	5.97E-08
<b>GET4</b>	1.459	0.00136111
<b>BAK1</b>	1.463	0.00016382
<b>RNASET2</b>	1.498	1.52E-06
<b>CLN6</b>	1.537	0.00016884
<b>CTAGE5</b>	1.550	1.39E-14
<b>PIGU</b>	1.554	2.67E-05
<b>DSN1</b>	1.596	0.00023102
<b>GSTP1</b>	1.601	1.41E-11
<b>GOLM1</b>	1.652	1.40E-12
<b>PTGES2</b>	1.658	1.86E-05
<b>ZFYVE27</b>	1.669	0.00020239
<b>OSBPL3</b>	1.674	3.19E-11
<b>HPSE</b>	1.677	4.20E-05
<b>ARL6IP1</b>	1.681	3.34E-13
<b>PDCD6</b>	1.692	2.96E-08
<b>HSPBP1</b>	1.695	1.78E-05
<b>BCAP31</b>	1.702	9.32E-11
<b>PNPLA2</b>	1.720	4.21E-07
<b>CDA</b>	1.726	0.00053269
<b>HIST1H2BK</b>	1.757	9.35E-10
<b>BAG1</b>	1.762	2.64E-09
<b>IDH1</b>	1.763	2.34E-13
<b>NOL3</b>	1.789	3.52E-06
<b>SERPINB1</b>	1.798	4.08E-10

<b>DOLPP1</b>	1.834	3.57E-06
<b>CANT1</b>	1.849	1.03E-08
<b>PRKCD</b>	2.004	4.21E-07
<b>JUP</b>	2.070	4.61E-14
<b>SVIP</b>	2.091	1.26E-09
<b>REEP1</b>	2.209	2.78E-05
<b>OSBPL7</b>	2.213	3.19E-07
<b>PNP</b>	2.287	7.67E-07
<b>HIST1H2BD</b>	2.342	3.90E-12
<b>PYGB</b>	2.410	5.88E-14
<b>ELOVL6</b>	2.418	1.46E-09
<b>UBE2C</b>	2.496	1.33E-07
<b>SLC37A4</b>	2.651	1.75E-09
<b>SERPINA1</b>	2.666	8.65E-11
<b>RAB3D</b>	2.714	9.55E-10
<b>TMEM30B</b>	2.726	1.09E-15
<b>DHRS9</b>	2.764	5.01E-05
<b>SLC37A1</b>	2.815	3.61E-12
<b>CCNA2</b>	2.877	1.77E-10
<b>SERPINA3</b>	2.909	7.68E-07
<b>SYT17</b>	2.973	6.37E-10
<b>FRK</b>	3.098	8.76E-16
<b>F5</b>	3.196	1.73E-11
<b>PLAC8</b>	3.199	7.44E-10
<b>DHCR7</b>	3.249	2.41E-12
<b>TC2N</b>	3.753	3.44E-19
<b>TMEM97</b>	3.772	9.64E-16
<b>TGFA</b>	3.791	3.54E-15
<b>CP</b>	3.926	8.89E-09
<b>ELOVL7</b>	4.252	2.68E-15
<b>SGPP2</b>	4.538	2.24E-16
<b>SLPI</b>	4.555	1.23E-16
<b>LCN2</b>	4.798	3.79E-14
<b>MSLN</b>	4.868	5.54E-15
<b>SYT13</b>	5.009	8.44E-14
<b>OLFM4</b>	5.669	1.89E-11
<b>PROM1</b>	5.817	1.02E-17
<b>AGR2</b>	5.986	2.14E-19