**Supplemental table 1A** List of miRNAs, miRBase accession number and mature sequence of 46 selected-miRNAs used to build the Firefly 46plex circulating custom panel. There miRNAs have previously been linked to pancreatic cancer or to *KRAS*.

**Supplemental table 1B** List of PDX pancreatic samples. Information regarding *KRAS*-mutation and gemcitabine resistance profile. S for sensitive, R for Resistant.

**Supplemental Figure 1. A)** Left panel: Visualization of the miRNA profile of normal pancreas samples (n=3 control). Right panel: Visualization of the miRNA profile of PDAC PDX tumor samples (n=27 cases). Relative expression is shown as mean of fluorescence (MFI). miRNAs profiling was done through Firefly Circulating miRNA Assay and normalized using two miRNAs that are not significantly deregulated between all samples miR-22-3p and miR-30b-5p defined by the geNorm-like algorithm. **B)** Visualization of miRNA profiles of PDAC cell lines (n=4), PDAC 3D-model (n=2) and Patient-derived-organoid (PDO 286 and PDO 281) compared to normal pancreatic cell and organoid (n=2 control). miRNAs profiling was done via Firefly Circulating miRNA Assay and normalized using miR-181b-5p, miR-103-3p, miR-30b-5p defined by the geNorm-like algorithm. Normalized miRNA signal intensities are presented as fold-change (log10 of the ratio between a probe value to the average of all the other samples for that probe). Green represents highly expressed miRNAs and red represents lowly expressed miRNAs.

**Supplemental Figure 2. A)** Relative expression Left panel: Mean of fluorescence and right panel: qPCR validation of miR-21-5p expression level in the set of cell lines, 3D-models and organoid compared to normal controls. **B)** qPCR analysis of PDCD4 and PTEN expression levels in the PANC1 stable cell lines (Lenti-21) inhibiting miR-21 activity (pLenti-III-miR-off). **C)** qRT-PCR of miR-21-5p expression after lipofectamine transfection of PANC1, BxPC3 and PL-45 cells with anti-miR-21 inhibitor (mirVana ®) at the dose of 50nM after 48h. For qPCR each miRNA sample was normalized on the basis of it’s 18s content and on the basis of GAPDH for mRNAs.

**Supplemental Figure 3. A)** iRGD-TAMRA (red) binding after 15 min at 4 degree in normal cells (Low integrins-NRP1) and in human and mice PDAC cells (High integrins-NRP1). Scale bars 200μm **B)** qRT-PCR of miR-21-5p expression after treatment of PANC1, BxPC3 and PL-45 cells with TPN-21 at the dose of 100nM after 48h. **C)** Representation of 3D-model treatment course with TPN-21. For qPCR each miRNA sample was normalized on the basis of its 18s content. Error bars, mean ± s.d \**P* = 0.01–0.05; \*\**P* = 0.001–0.01; \*\*\**P* < 0.001; \*\*\*\**P* < 0.0001 N.S., not significant, two-tailed *t*-test; *n* = 3 biological replicates.

**Supplemental Figure 4. A)** qPCR analysis of miR-21-5p expression level after 4 treatments with TPN-21 in PDO 286. **B)** Relative tumor burden after (4 I.V injection of PBS (n=6) TPN-control n=6 or TPN-21 n=5 (5mg/kg). For qPCR each miRNA sample was normalized on the basis of its 18s content.

**Supplemental Figure 5. A)** Representatives PDO 286 images and metabolic activity measured from MTT assay after repeated TPN-21 or gemcitabine treatments (100nM) or both treatments. Scale bars 1000μm. **B)** Quantification of organoid size after treatments. Organoids size was measure through ImageJ software on a total of ⩾ 35 spheroids and are presented in arbitrary units (UA). Error bars, mean ± s.d \**P* = 0.01–0.05; \*\**P* = 0.001–0.01; \*\*\**P* < 0.001; \*\*\*\**P* < 0.0001 N.S., not significant, two-tailed *t*-test; *n* = 3 biological replicates.