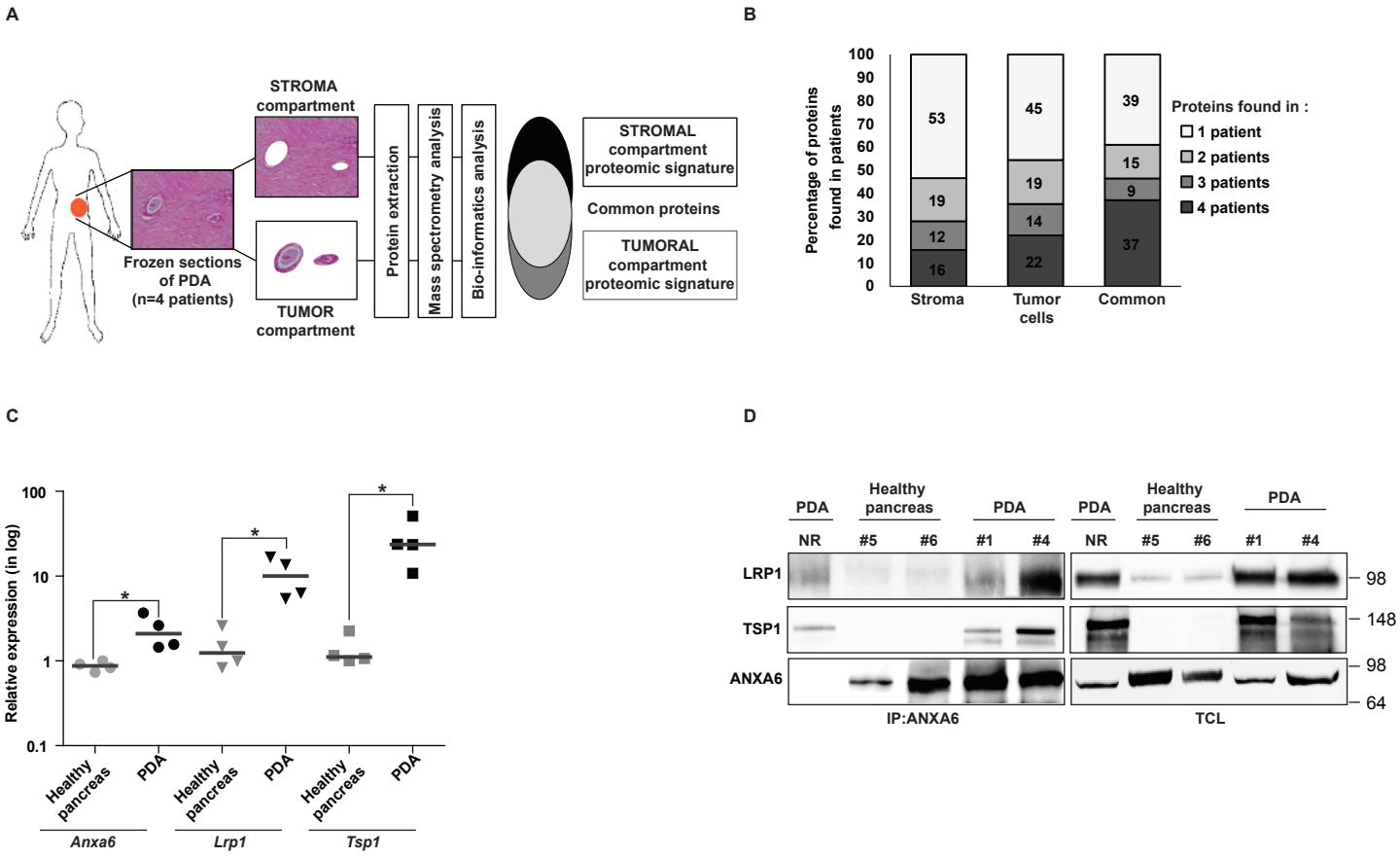
## SUPPLEMENTAL DATA

| STROMAL COMPARTMENT | | | | |
|---|---|---|---|---|
| **GO** | **Term** | **Count** | **Fold Enrich.** | **Benjamini** |
| GO:0005578 | Proteinaceous extracellular matrix | 43 | 1.71 | 6.03E-04 |
| GO:0031012 | Extracellular matrix | 49 | 1.69 | 2.31E-04 |
| GO:0044421 | Extracellular region part | 118 | 1.58 | 1.75E-09 |
| GO:0005615 | Extracellular space | 82 | 1.54 | 2.89E-05 |
| GO:0005576 | Extracellular region | 200 | 1.53 | 4.87E-16 |
| **TUMORAL COMPARTMENT** | | | | |
| **GO** | **Term** | **Count** | **Fold Enrich.** | **Benjamini** |
| GO:0070013 | Intracellular organelle lumen | 216 | 1.14 | 9.74E-04 |
| GO:0005829 | Cytosol | 270 | 1.13 | 1.18E-04 |

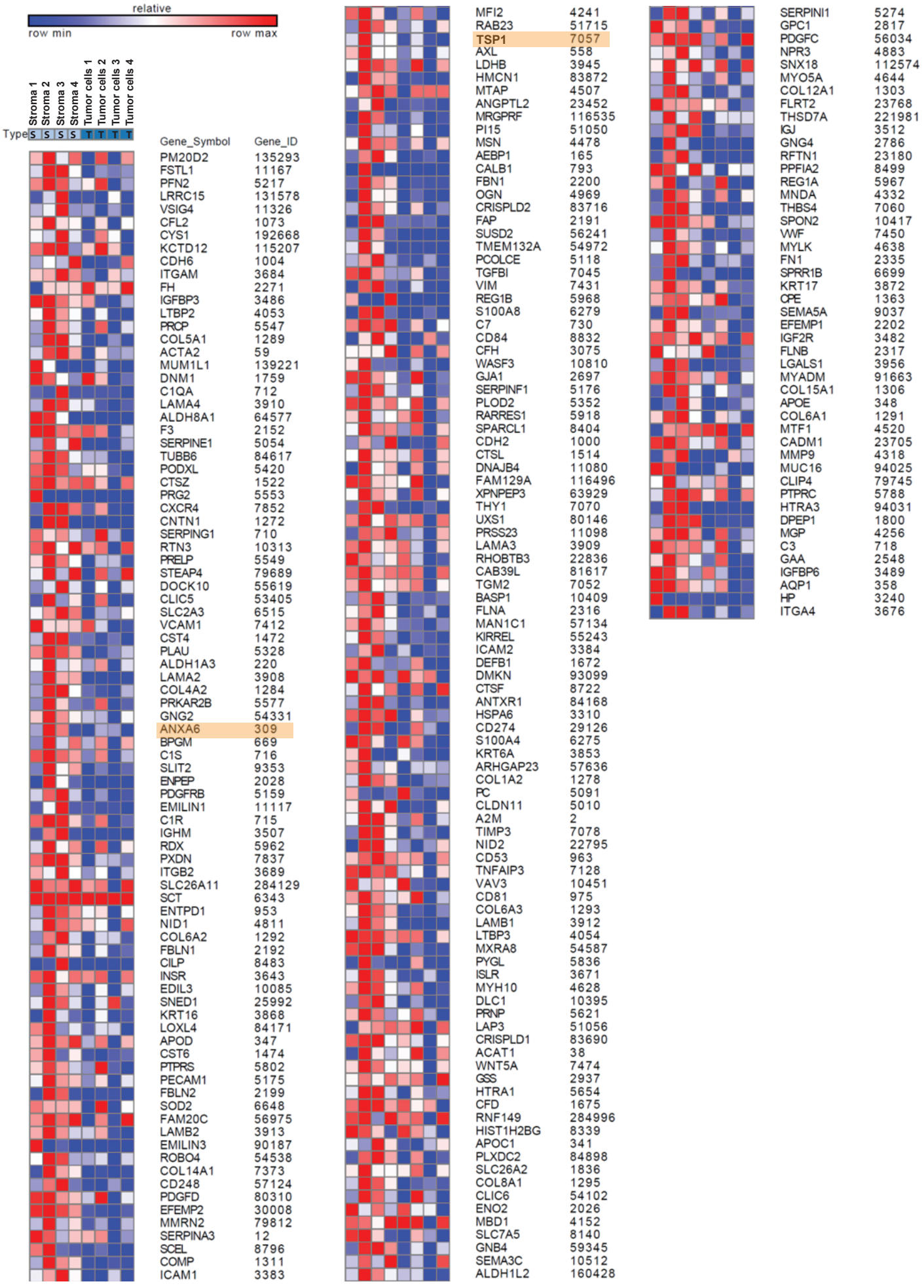
**Supplementary Table 1. Cellular location within stromal or tumoral compartment.** Table giving GO, term, proteins number, fold enrichment and *P* value (corrected using Benjamini and Hochberg method), depending cellular compartment using DAVID database.

| GO | Term | Count | Fold Enrich. | Benjamini |
|---|---|---|---|---|
| GO:0030141 | Secretory granule | 24 | 8.14 | 1.03E-04 |
| GO:0016023 | Cytoplasmic membrane-bounded vesicle | 51 | 6.07 | 2.16E-06 |
| GO:0005912 | Adherens junction | 21 | 4.00 | 1.34E-03 |
| GO:0031988 | Membrane-bounded vesicle | 53 | 3.73 | 1.41E-06 |
| GO:0043292 | Contractile fiber | 25 | 3.55 | 2.80E-05 |
| GO:0070161 | Anchoring junction | 24 | 3.35 | 3.76E-05 |
| GO:0005576 | Extracellular region | 153 | 3.15 | 1.45E-10 |
| GO:0042995 | Cell projection | 60 | 2.66 | 1.49E-06 |
| GO:0009986 | Cell surface | 35 | 2.6 | 8.99E-06 |
| GO:0032994 | Protein-lipid complex | 9 | 2.37 | 6.61E-03 |
| GO:0005856 | Cytoskeleton | 141 | 2.08 | 2.80E-10 |
| GO:0043228 | Non-membrane-bounded organelle | 182 | 1.95 | 1.32E-13 |
| GO:0031012 | Extracellular matrix | 40 | 1.94 | 4.93E-06 |
| GO:0005577 | Fibrinogen complex | 5 | 1.82 | 9.82E-03 |
| GO:0060205 | Cytoplasmic membrane-bounded vesicle lumen | 15 | 1.97 | 4.12E-03 |
| GO:0031983 | Vesicle lumen | 15 | 1.6 | 3.98E-03 |

**Supplementary Table 2. Associated terms within stromal compartment.** Table giving GO, term, proteins number, fold enrichment and *P* value corrected using Benjamini test for each family.

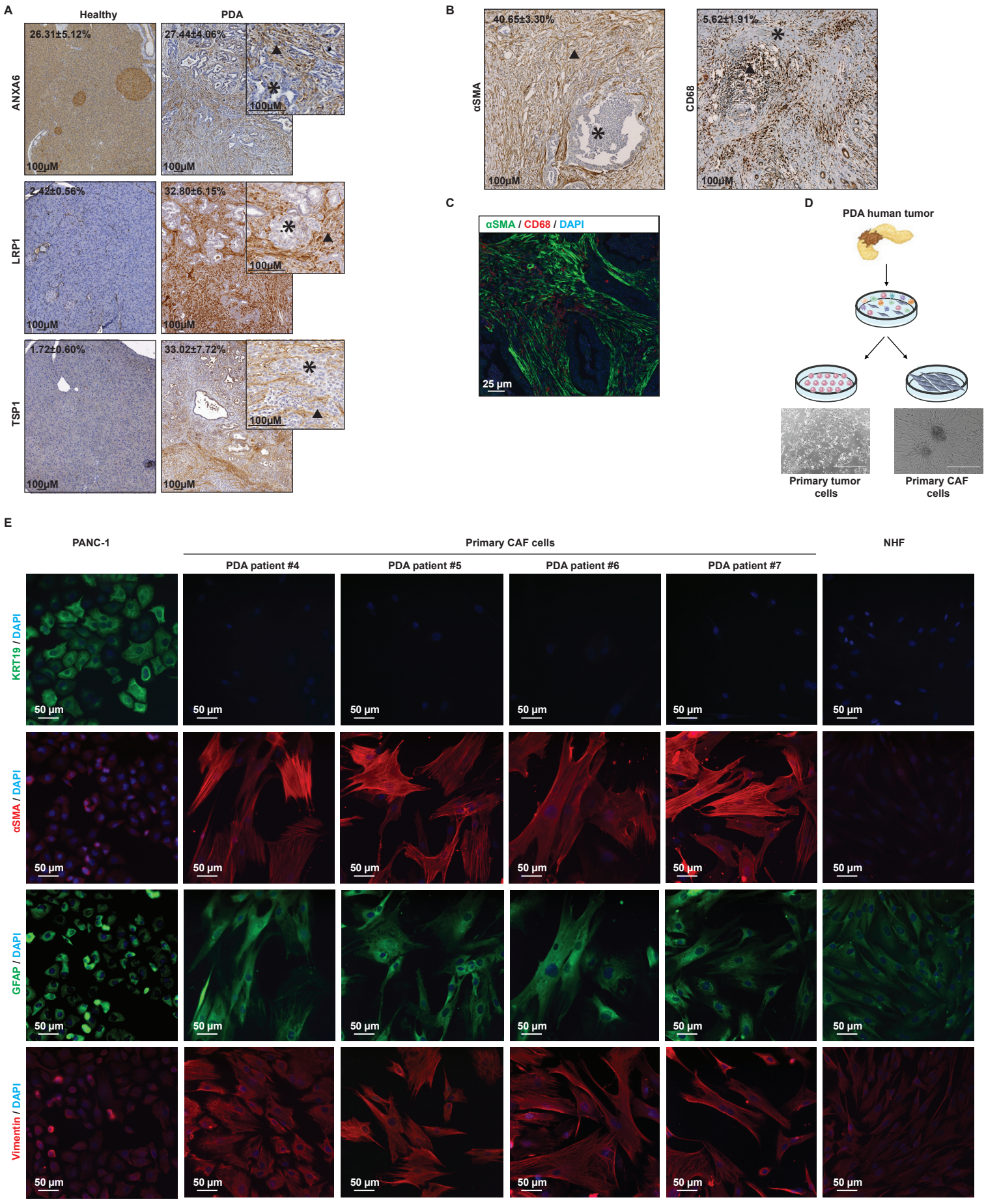



**Supplemental Figure 1. Human PDA microdissection followed by mass Spectrometry coupled to bio-informatics analyses identified a new complex in stroma PDA.** (**A**) Graphical representation of technical procedure used to obtain proteomic signature of each compartment (n=4). (**B**) Percentage of proteins, in both compartments, present in 1, 2, 3 or 4 patients. (**C**) Relative expression of Anxa6, Lrp1 and Tsp1 mRNA in mice healthy pancreas (n=4, #7 – # 10) and PDA (n=4, #5 – # 8). Data are expressed as fold increase compared with one healthy pancreas. 36B4 mRNA level is used for normalization. Data represent median ± interquartile range from three independent experiments. NS: Non Significant, **P* < 0.05, Mann–Whitney U-test. (**D**) Co-immunoprecipitation of ANXA6 with LRP1 and TSP1 in protein extracts from mouse healthy pancreas and PDA . Total cell lysate and non-relevant (NR) antibody were used as loading and negative control respectively. Data are representative of three independent experiments.

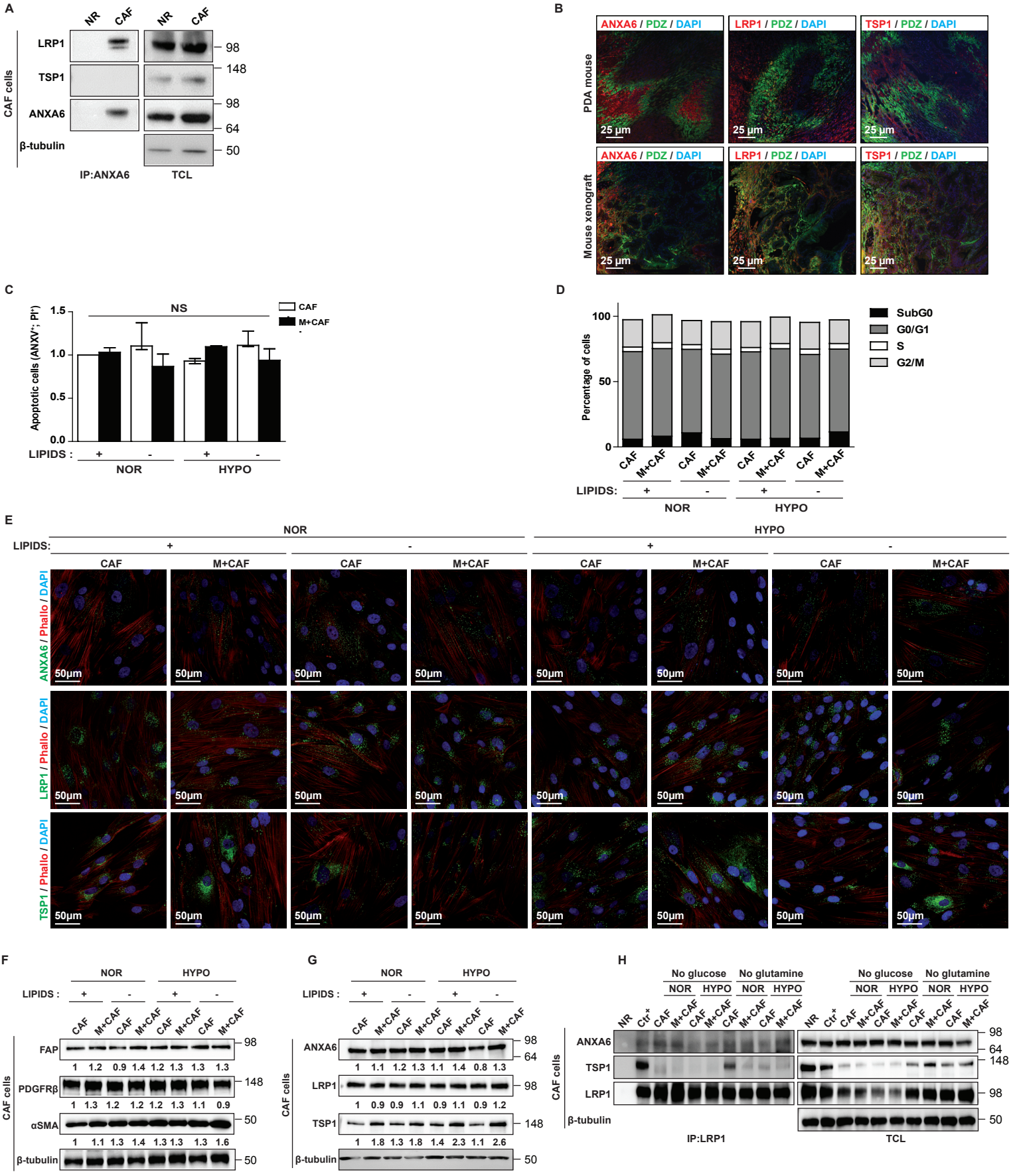



**Supplemental Figure 2. Determination of stromal transcriptomic signature and characterization of the extracellular vesicles exosome family.** These data are obtained from previous study (12), after laser microdissection from human PDA and transcriptomic analysis. Heat map highlighting transcripts marked as "Extracellular vesicular exosome" found to be significantly over-expressed in stromal compared to tumor tissue using gene ontology (GO) enrichment. It was measured by a hypergeometric distribution and Bonferroni-corrected (*P*=2.34*10-16). Each column is related to a single Affymetrix chip hybridized using the cDNA synthesized from individual stroma (S) or tumor (T). Red color represents higher gene expression values and blue represents lower expression. Anxa6 and Tsp1 are highlighted in orange.

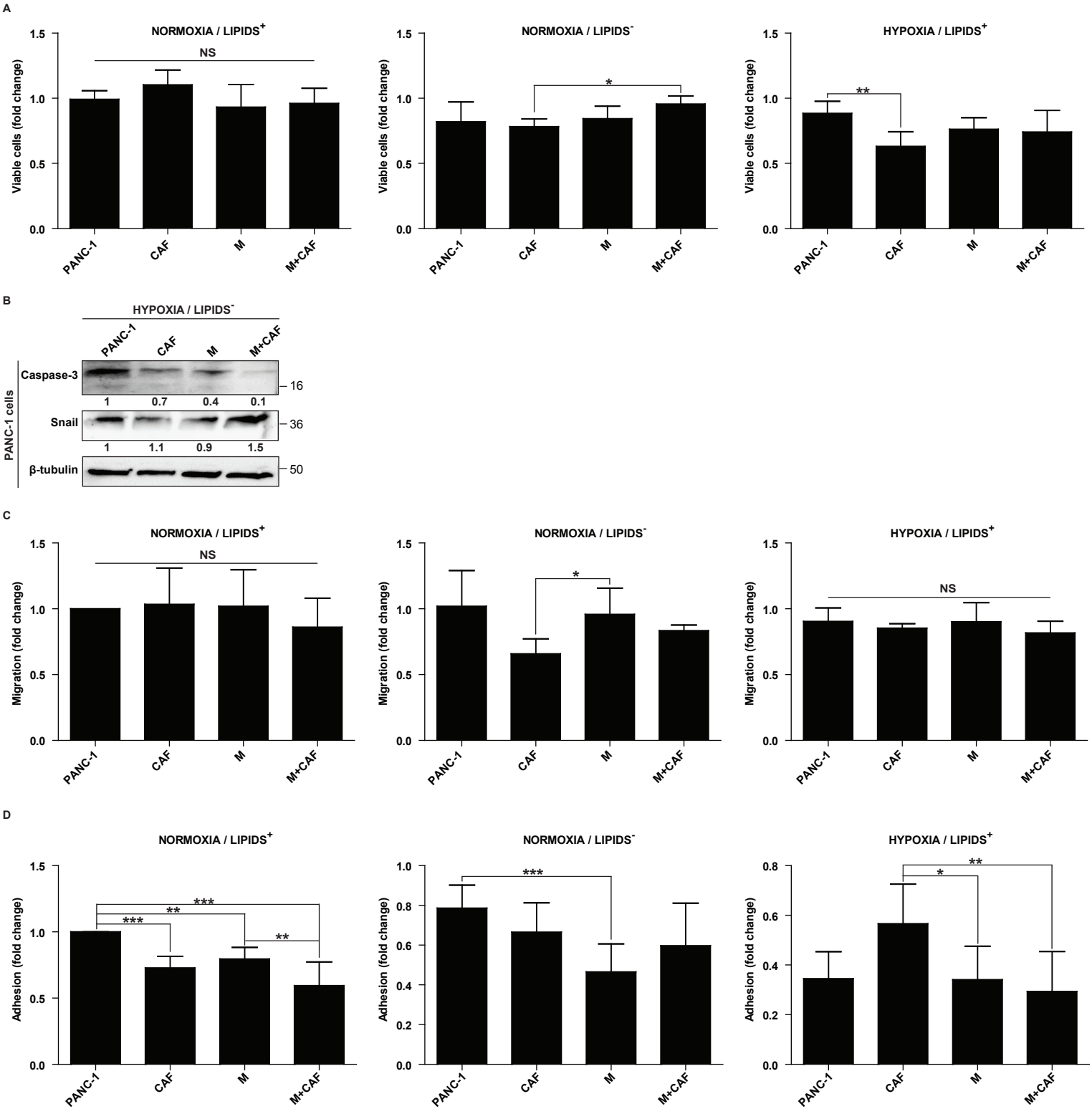
Figure S2



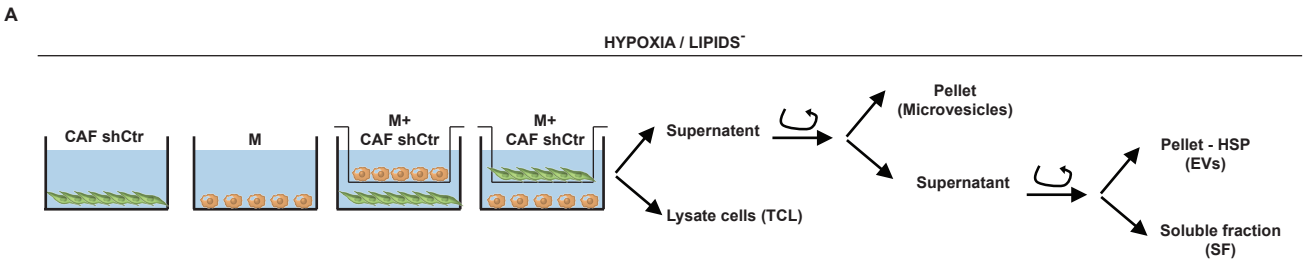

**Supplemental Figure 3. Microenvironment cells, and mainly CAFs, drive ANXA6, LRP1 and TSP1 expression in PDA**. (**A**) Representative micrographs (scale bars : 100µm) and quantifications of ANXA6, LRP1 or TSP1 staining in mouse healthy pancreas or PDA (median value ± interquartile range, n=3). (**B**) Representative micrographs (scale bars : 100µm) and quantifications of αSMA and CD68 staining in human PDA (median value ± interquartile range, n=3). (**C**) Representative micrograph (scale bars : 25µm) of dual-immunofluorescence using αSMA staining with CD68 in human PDA, n=3. (**D**) Graphical representation of primary tumor cells or primary CAF cells preparation from freshly resected human PDA samples. (**E**) Representative micrographs (scale bars : 50µm) of immunofluorescence using KRT19, αSMA, GFAP and vimentin staining in PANC-1, Primary CAFs cells (n=4) and NHF. Data are repesentative of three independent experiments.

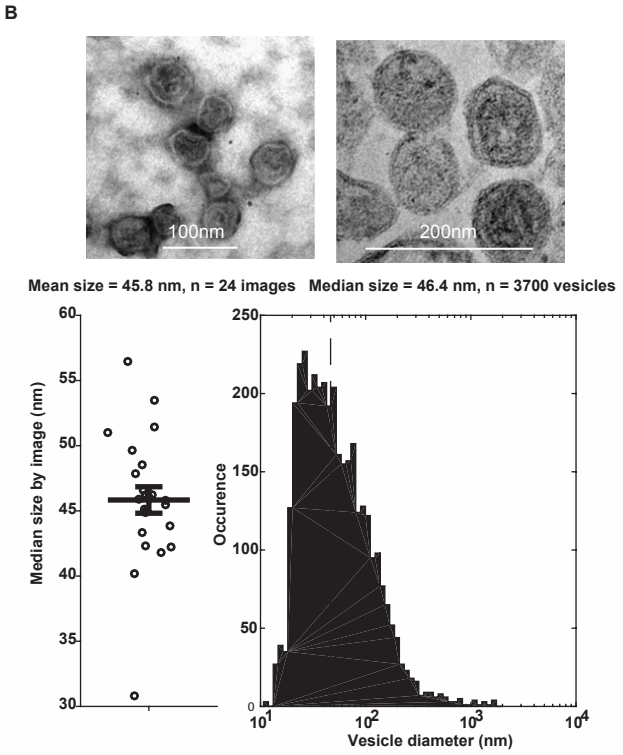


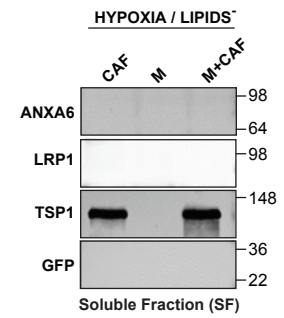

**Supplemental Figure 4. CAFs drive ANXA6, LRP1 and TSP1 complex in vitro.** (**A**) Western blot of the indicated proteins following endogenous co-immunoprecipitation with anti-ANXA6 antibody in CAFs lysates. Total cell lysate and non-relevant (NR) antibody were used as loading and negative control respectively. Data are representative of three independent experiments. (**B**) Representative micrographs (scale bars : 25µm) of dual-immunofluorescence using ANXA6, LRP1 or TSP1 staining with pimonidazol (PDZ; hypoxic marker) in mouse PDA or mouse xenograft. (**C**) Cell apoptosis measurement of CAF. Data are expressed as fold increase compared with CAF in normoxia and lipids presence (median ± interquartile range, n=3). NS : non significant, two-way ANOVA. (**D**) Cell cycle measurement of CAF (median ± interquartile range, n=3). (**E**) Representative micrographs (scale bars : 50µm) of dual-immunofluorescence using ANXA6, LRP1 or TSP1 staining with phalloïdine. (**F** and **G**) Western blot of the indicated proteins in lysates established from CAFs cultured under various conditions. Quantifications are expressed as fold increase compared with CAFs cultured under normoxia in presence of lipids. (**H**) Western blot of the indicated proteins following endogenous co-immunoprecipitation with non-relevant antibody (NR) as negative control or anti-LRP1 antibody in protein lysates from CAFs cultured under various conditions. (TCL : Total cell lysates). Ctr+ represents CAF in physiopathologic cultures. Data are representative of three independent experiments.

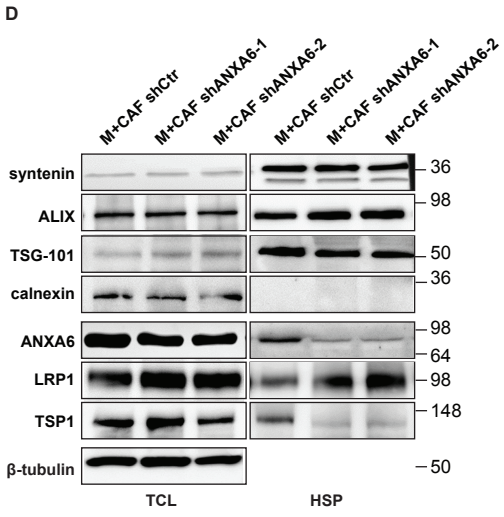



**Supplemental Figure 5. Impact of stromal cell cultures on tumor cell abilities.** (**A**) PANC-1 cells viability measurement (median ± interquartile range, n=3). NS : Non significant, * $P < 0.05$, ** $P < 0.005$, Two-way ANOVA. (**B**) Western blot analysis of Caspase-3 and Snail in PANC-1 from co-culture with CAF in physiopathologic conditions. Quantifications are expressed as fold increase compared with PANC-1 alone. Data are representative of three independent experiments. (**C**) PANC-1 migration ability measurement (median ± interquartile range, n=3). NS : Non significant, * $P < 0.05$, Two-way ANOVA. (**D**) PANC-1 adhesion ability measurement (median ± interquartile range, n=3). * $P < 0.05$, ** $P < 0.005$, *** $P < 0.001$, Two-way ANOVA. **A**, **C** and **D**, data are expressed as fold increase compared with PANC-1 alone in Normoxia/Lipids+.

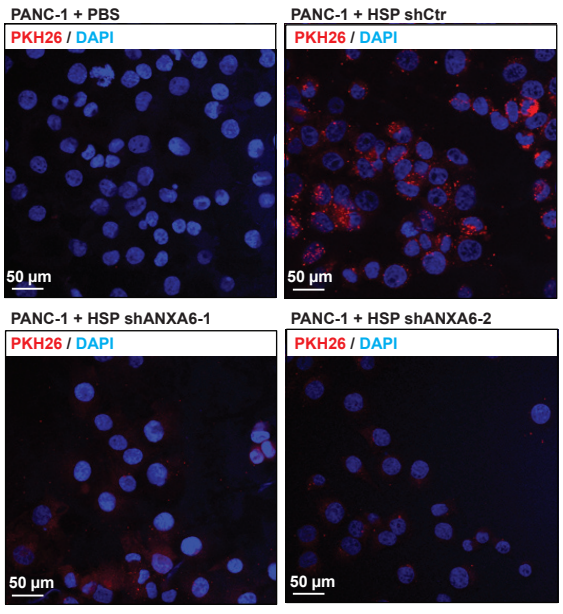


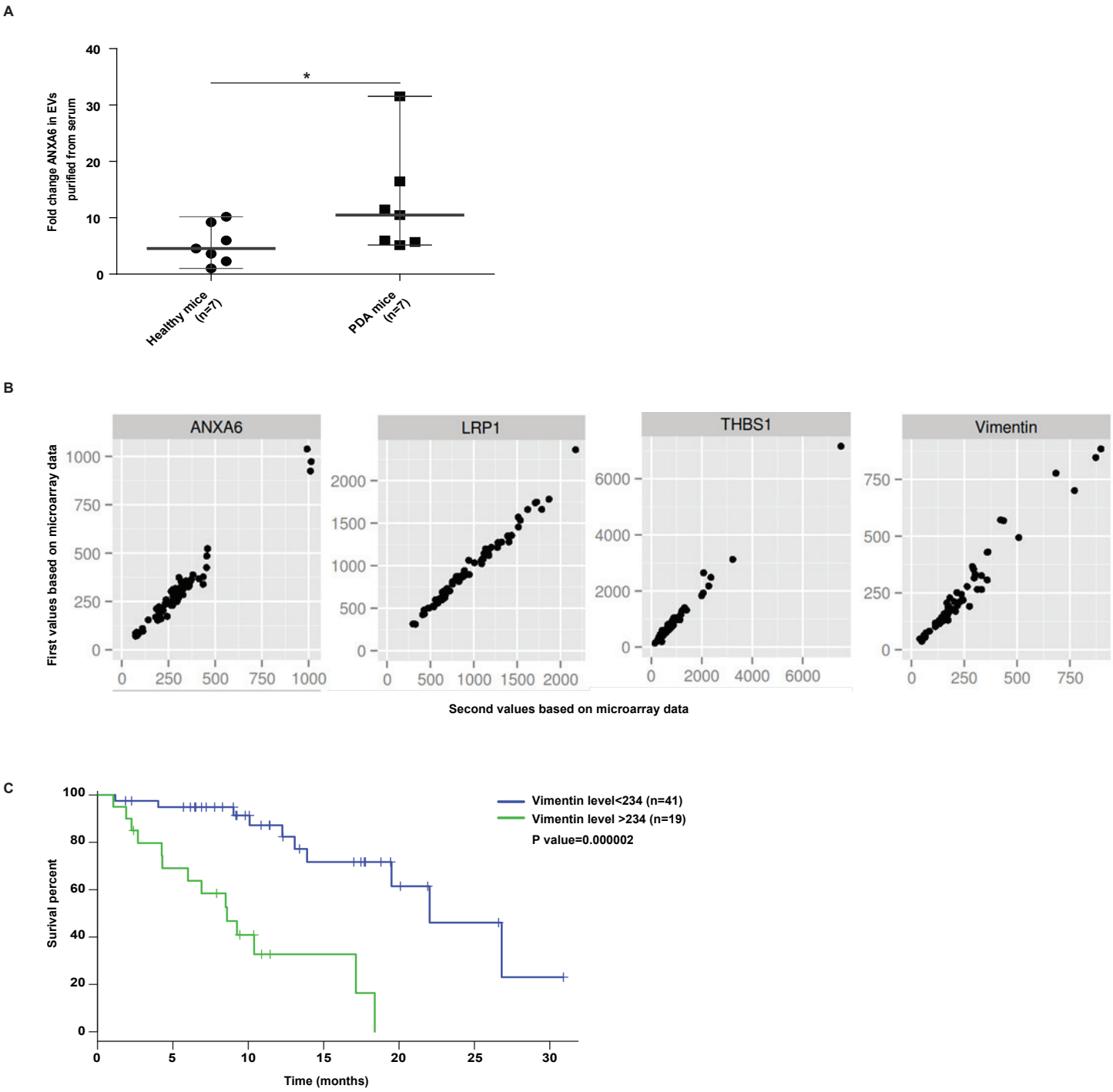








**Supplemental Figure 6. EVs quantification and uptake by tumor cells.** (**A**) Graphical representation of culture protocol to obtain HSP containing EVs or soluble fraction (SF). CAF are infected with GFP-containing shRNA. (**B**) Microscopy electronic pictures and EVs distribution obtained from cells supernatant. Left picture represents EVs after negative staining (scale bars : 100nm) and right picture represents EVs after morphologic protocol (scale bars : 200 nm). The mean or median diameter was assessed from 3700 vesicles, measured over 24 images.(**C**) Western blot of the indicated proteins in soluble fraction. Data are representative of three independent experiments. (**D**) Western blot of the indicated proteins in total cell lysate (TCL, left panel) or HSP extractions (right panel) established from CAFs infected with shCtr or shANXA6s cultured under physiopathologic conditions. β-tubulin served as loading control. Data are representative of three independent experiments. (**E**) Silver-stained protein bands coloration in polyacrylamide gels of HSP. Data are representative of three independent experiments. (**F**) Representative micrographs (scale bars : 50µm) of immunofluorescence using PKH26 staining in PANC-1. Data are representative of three independent experiments.

Figure S6

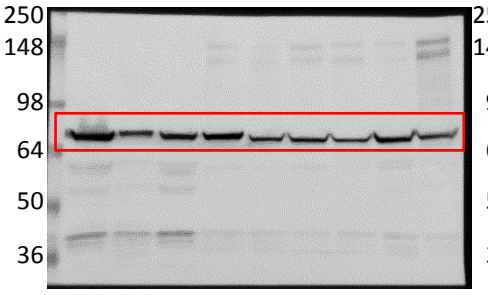



**Supplemental Figure 7.** (**A**) Quantification of ANXA6$^{+}$-EVs purified from healthy mice (n=7) or PDA bearing mice (n=7) sera (median ± interquartile range). * $P < 0.05$, Mann–Whitney U-test. (**B**) Reproducibility of two chips using for transcriptomic analysis on patients derived xenografts, for Anxa6, Lrp1, Thbs1 and Vimentin. (**C**) Kaplan–Meier survival curve using transcriptomic analysis on patients derived xenografts, divided into high-(>234) and low-(<234) Vimentin expression groups based on the log-rank statistic test (n = 41 and n = 19, respectively). $P$=0.000002.

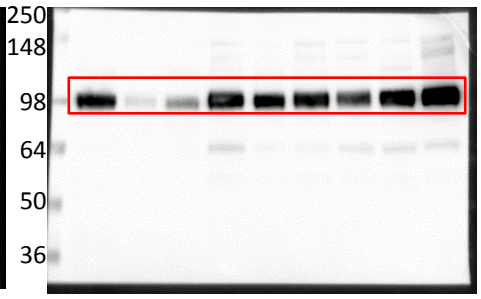
Figure S7

## Full unedited gel for Figure 1D

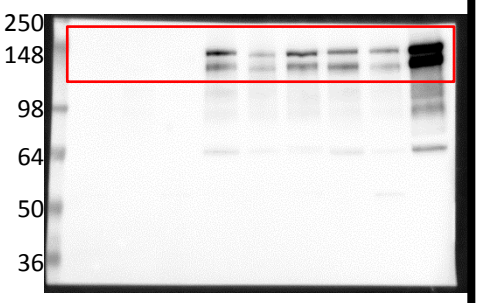
ANXA6




LRP1

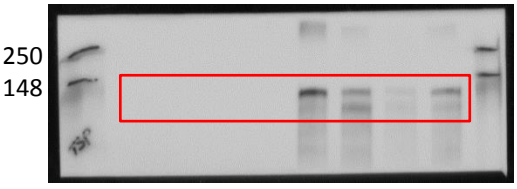



TSP1

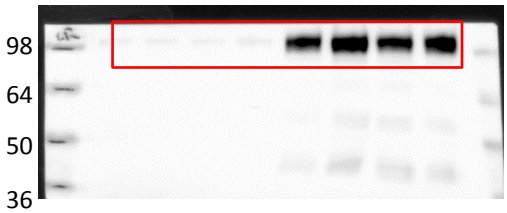



## Full unedited gel for Figure 1E

TSP1

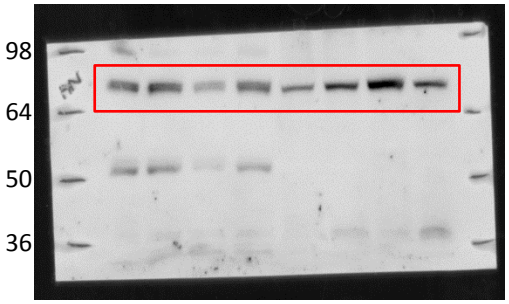



LRP1



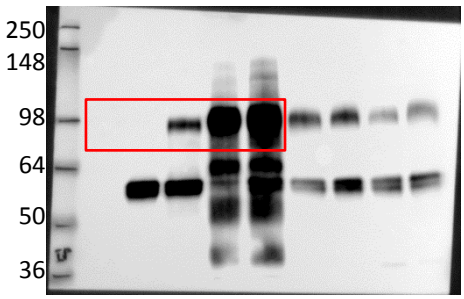

Membrane cut at 98kDa – shared with LRP1 and ANXA6

ANXA6

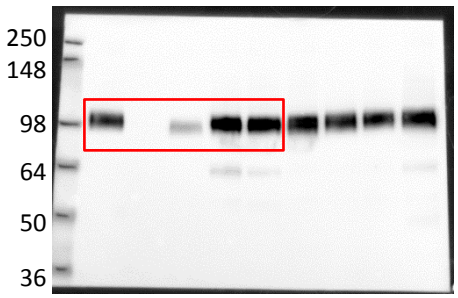



## Full unedited gel for Figure 1F

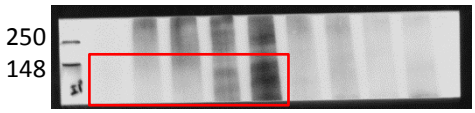
IP - LRP1, WB LRP1



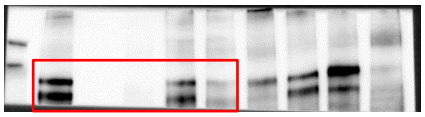

TCL - LRP1




IP - LRP1, WB TSP1

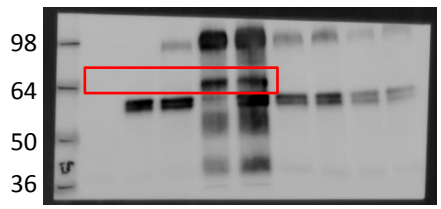



TCL – TSP1

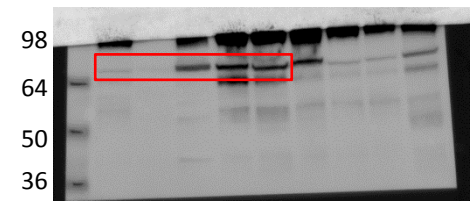



Membrane cut at 98kDa – shared with ANXA6

IP - LRP1, WB ANXA6




TCL – ANXA6



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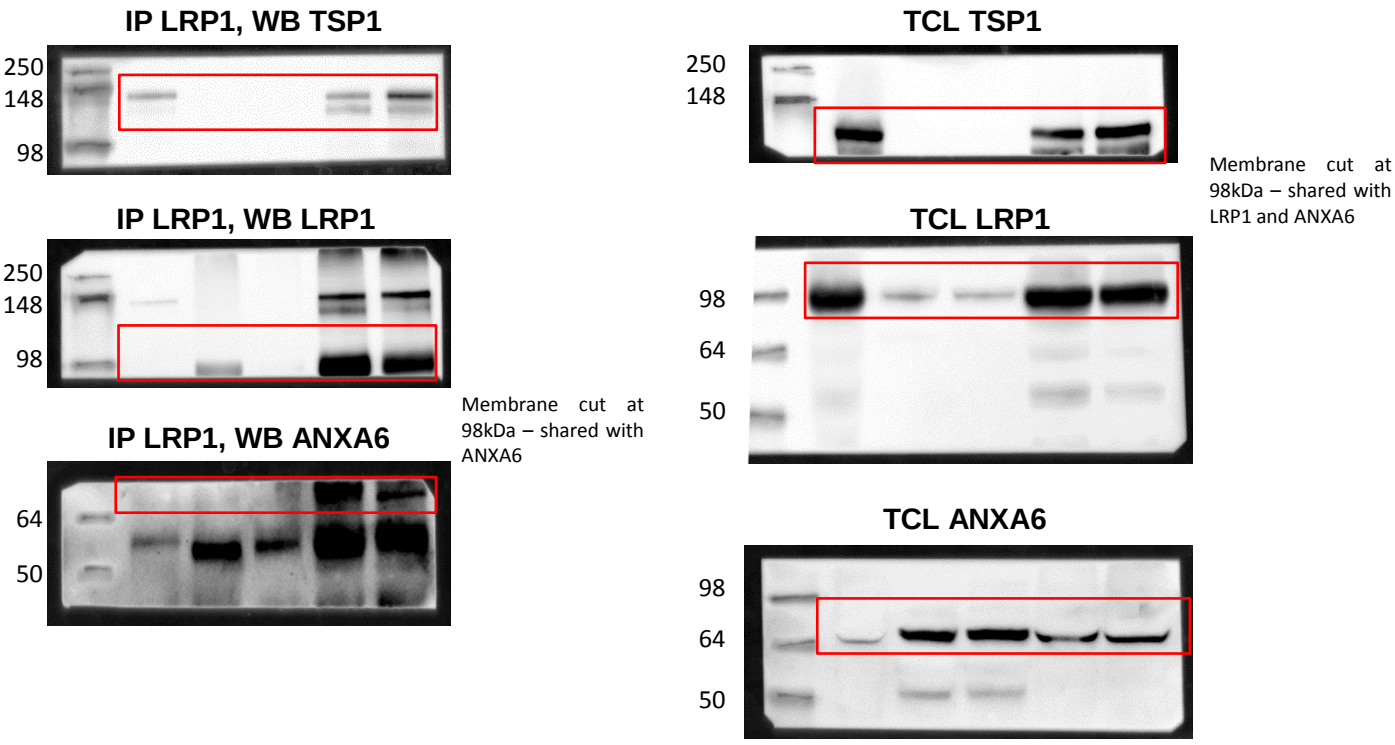


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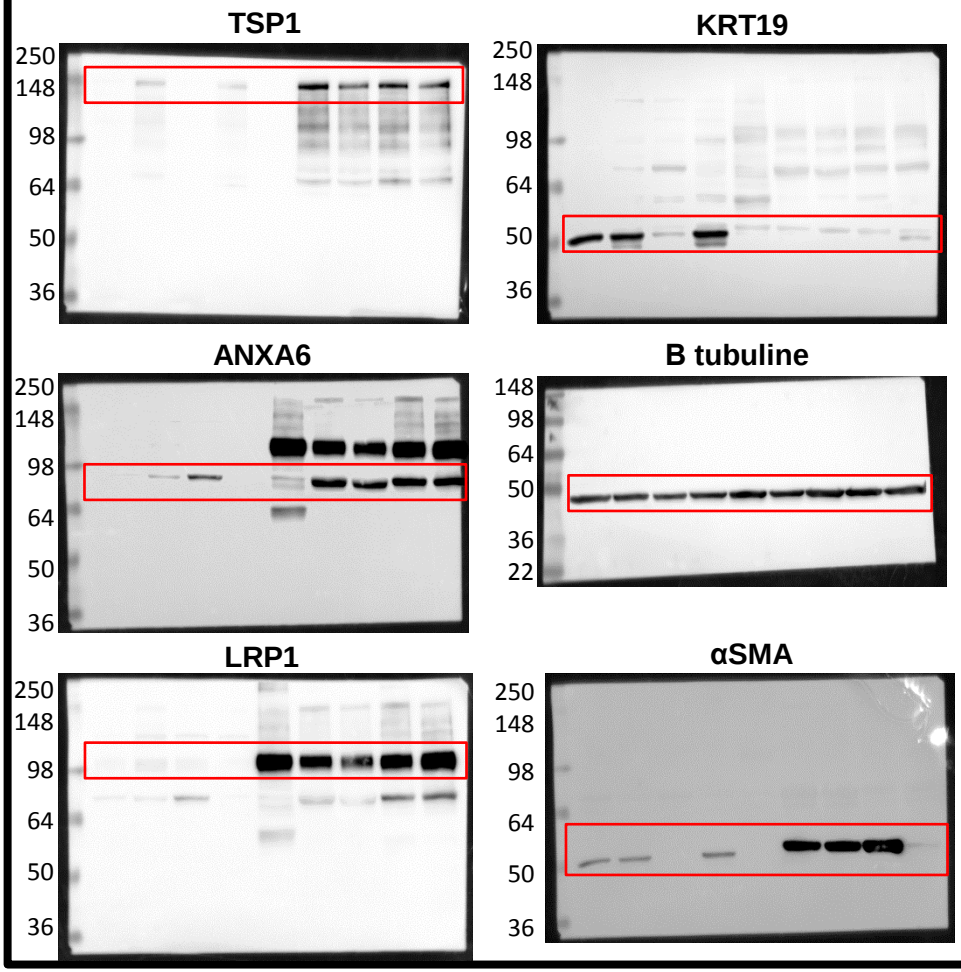
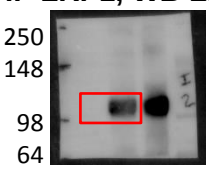
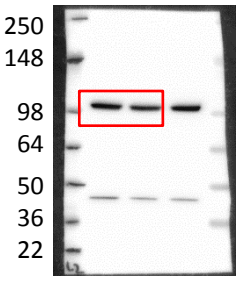


## Full unedited gel for Figure 2F

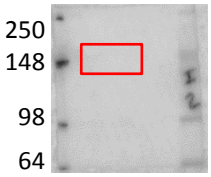
IP LRP1, WB LRP1



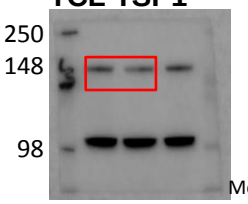

TCL LRP1




IP LRP1, WB TSP1

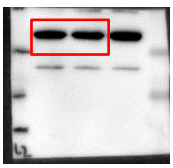



TCL TSP1

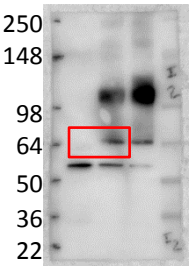



Membrane cut at 64kDa – shared with βtubulin

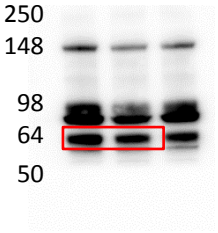
TCL B-tubuline




IP LRP1, WB ANXA6

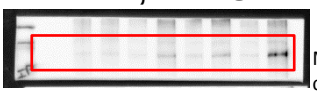



TCL ANXA6




## Full unedited gel for Figure 2H

IP LRP1, WB TSP1



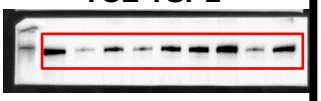

Membrane cut at 98kDa – shared with LRP1

IP LRP1, WB LRP1


Membrane cut at 64kDa – shared with LRP1

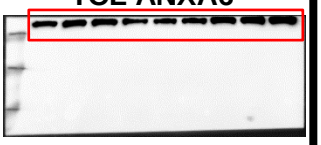
IP LRP1, WB ANXA6


TCL TSP1




TCL LRP1


TCL ANXA6

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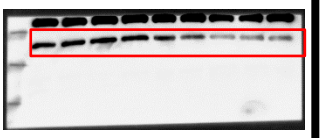
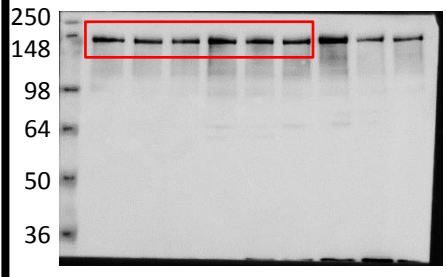
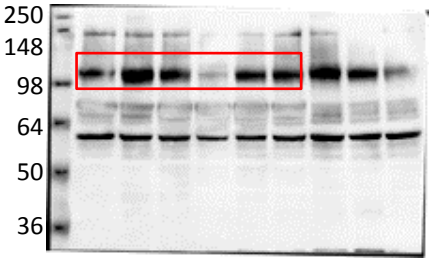



## Full unedited gel for Figure 3D

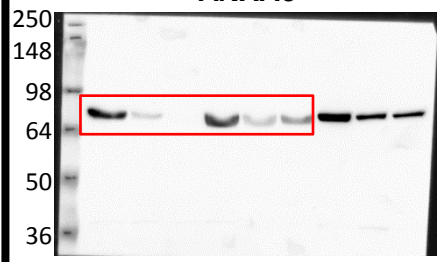
TSP1



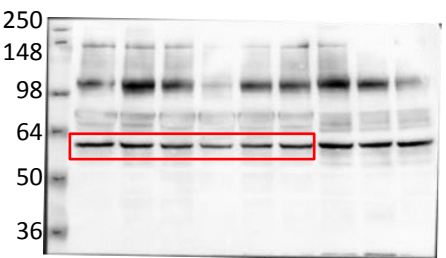

LRP1



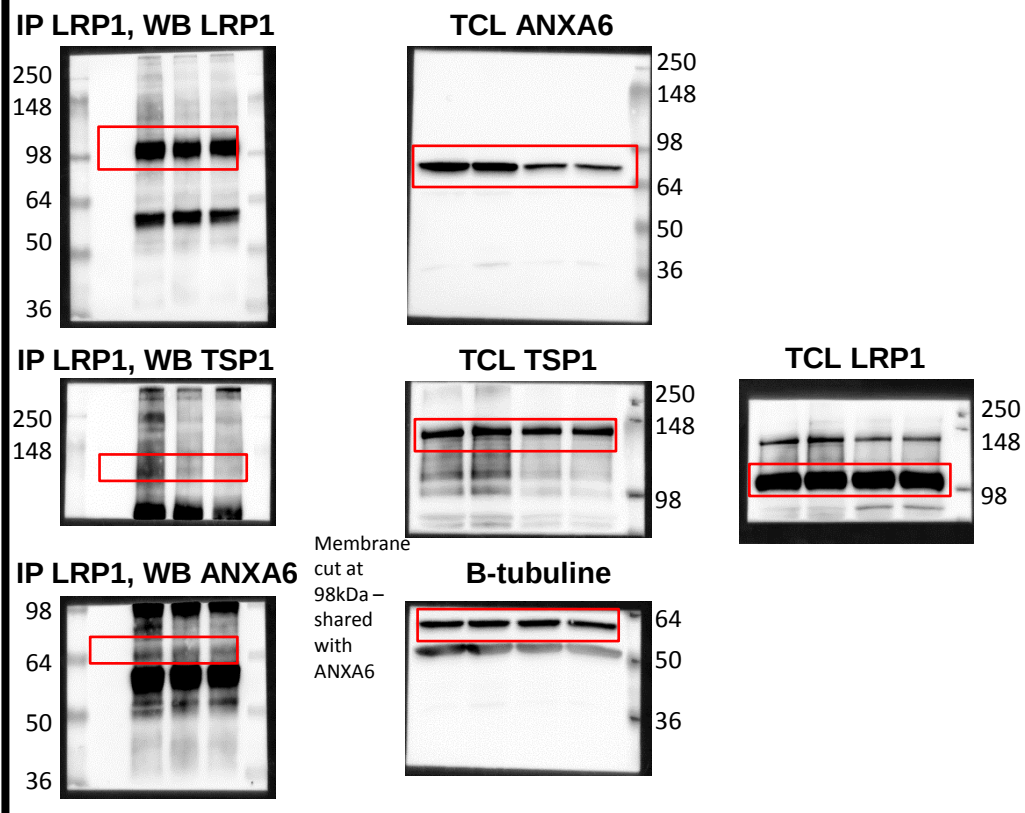

ANXA6



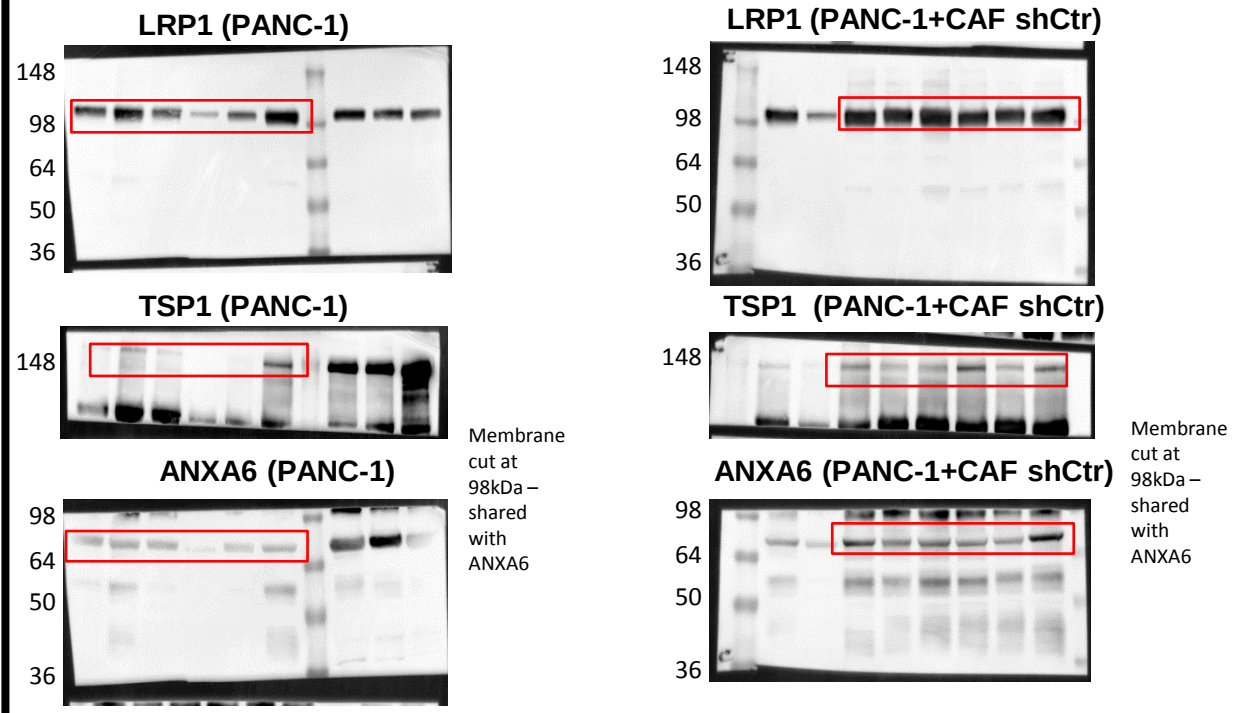

B-tubuline



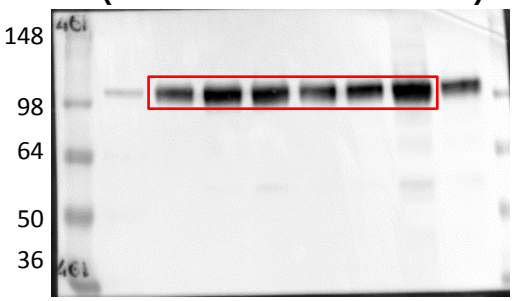
## Full unedited gel for Figure 3E



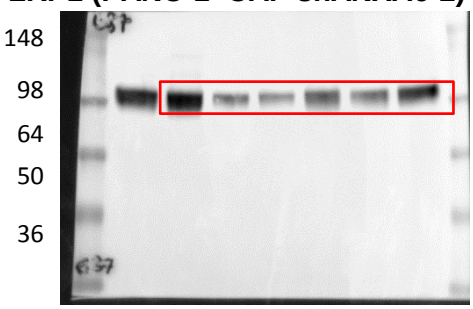

## Full unedited gel for Figure 4C



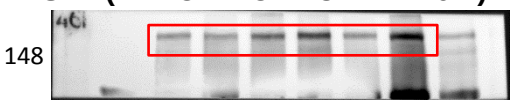
LRP1 (PANC-1+ CAF shANXA6-1)




LRP1 (PANC-1+CAF shANXA6-2)

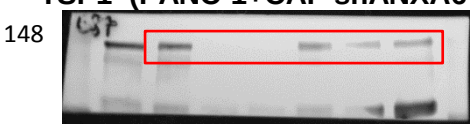



TSP1 (PANC-1+ CAF shANXA6-1)



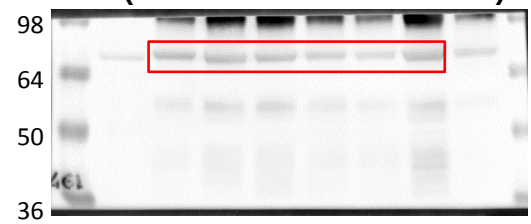

Membrane cut at 98kDa – shared with ANXA6

TSP1 (PANC-1+CAF shANXA6-2)

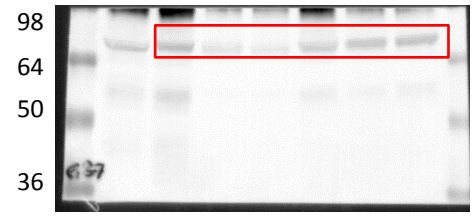



Membrane cut at 98kDa – shared with ANXA6

ANXA6 (PANC-1+ CAF shANXA6-1)

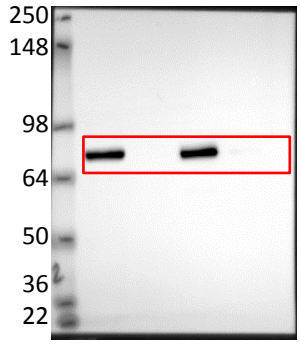



ANXA6 (PANC-1+CAF shANXA6-2)

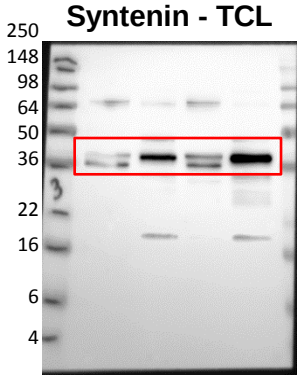



## Full unedited gel for Figure 5A

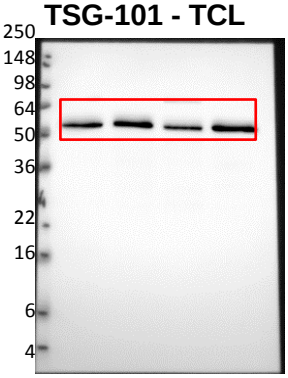
ANXA6 - TCL



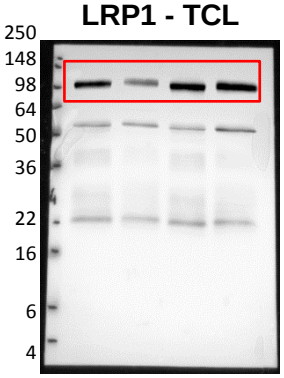

Syntenin - TCL



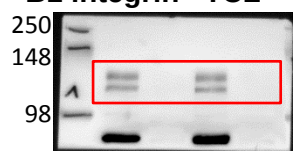

TSG-101 - TCL




LRP1 - TCL

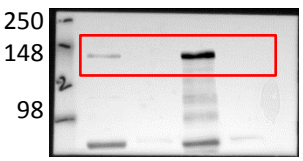



B1 integrin - TCL



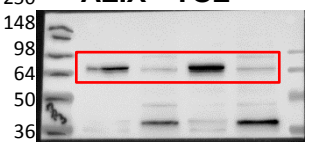

Membrane cut at 98kDa – shared with VDAC1

TSP1 - TCL

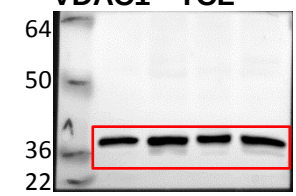



Membrane cut at 98kDa – shared with calnexin

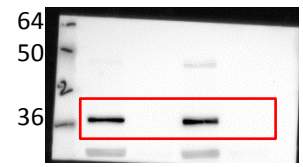
ALIX - TCL



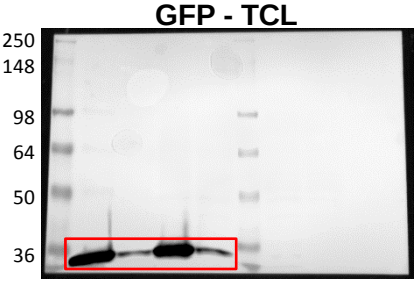

VDAC1 - TCL



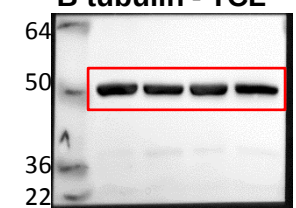

calnexin - TCL



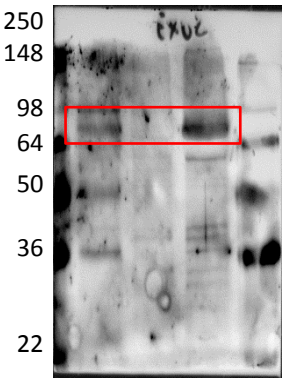

GFP - TCL



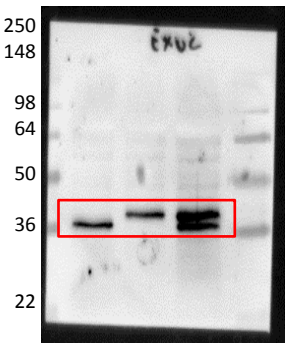

B tubulin - TCL



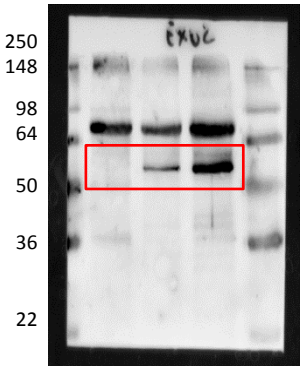
ANXA6 - HSP



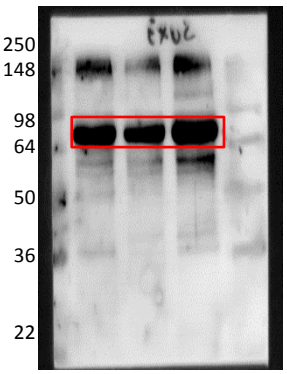

Syntenin - HSP



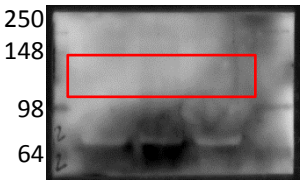

TSG-101 - HSP



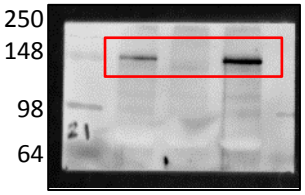

LRP1 - HSP




B1 integrin - HSP

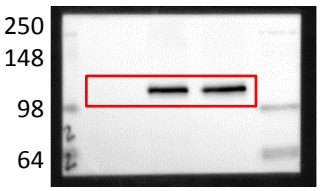



TSP1 - HSP



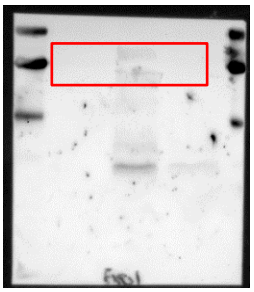

Membrane cut at 64kDa – shared with VDAC1

ALIX - HSP

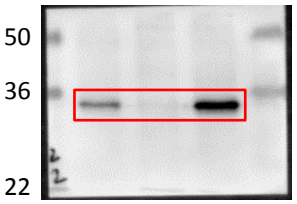



Membrane cut at 64kDa – shared with GFP

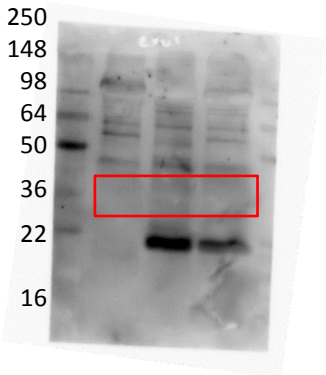
VDAC1 - HSP




GFP - HSP




Calnexin - HSP

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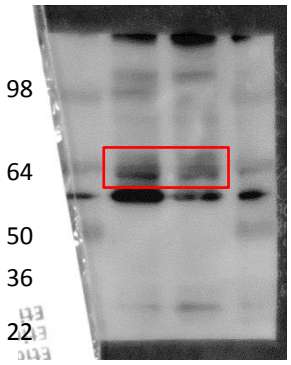
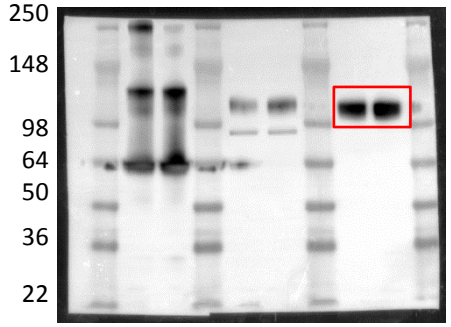
## Full unedited gel for Figure 5B

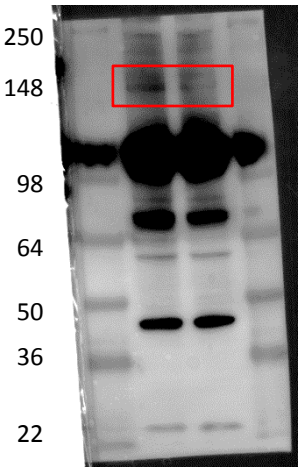
IP LRP1, WB ANXA6



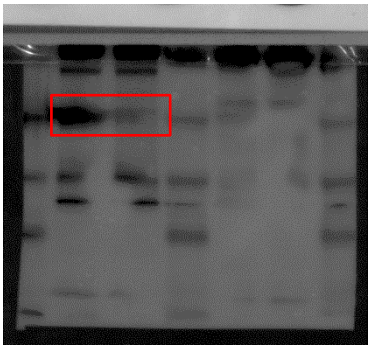

IP LRP1, WB LRP1



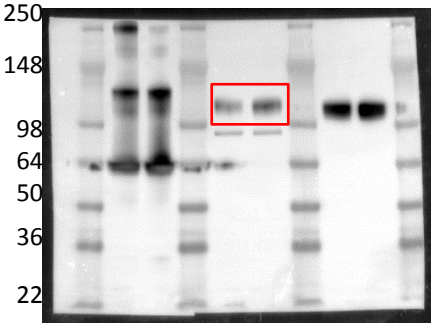

IP LRP1, WB TSP1



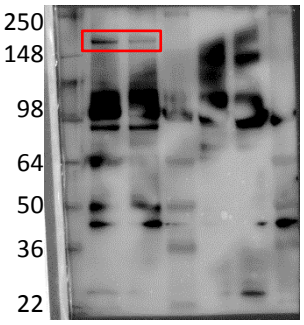
HSP, WB ANXA6



HSP, WB LRP1



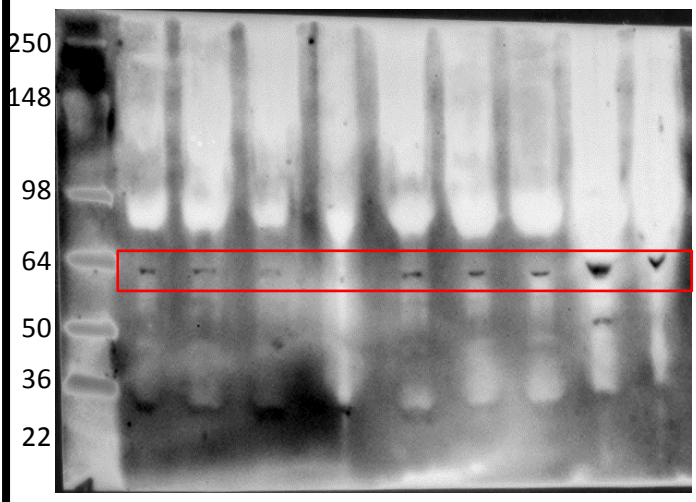

HSP, WB TSP1



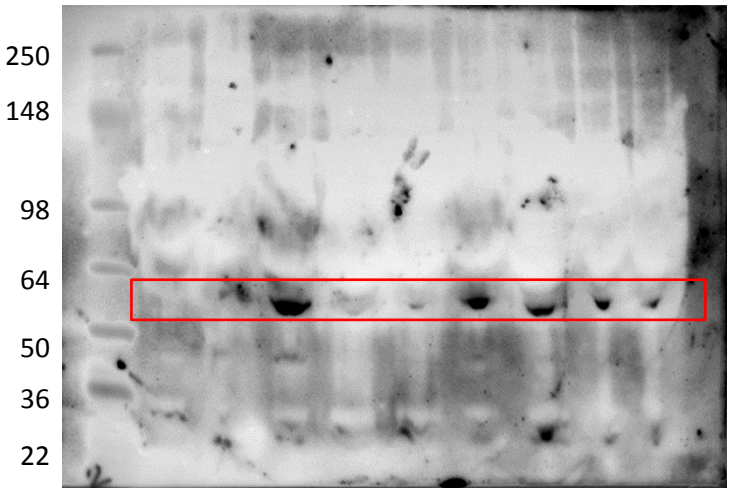

## Full unedited gel for Figure 6A

ANXA6

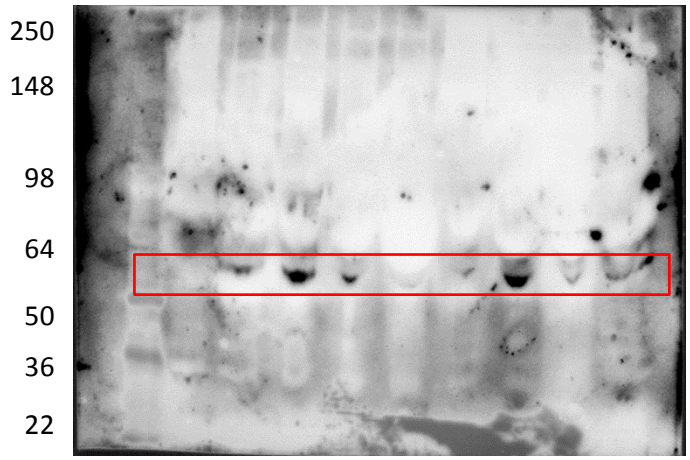
Healthy (n=7) | PDA (n=2)



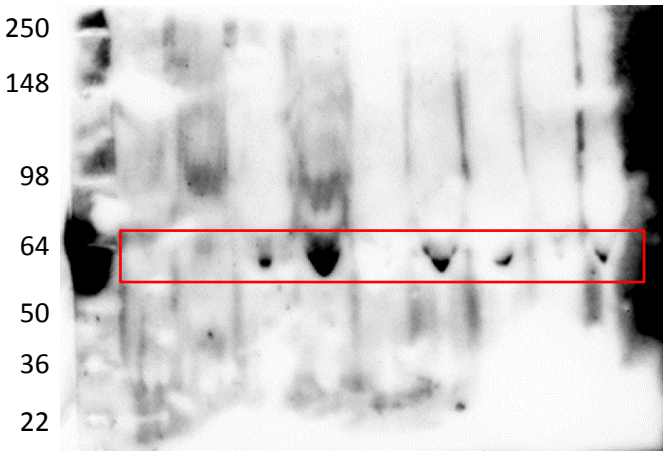

Healthy (Ctr-) | PDA (n=8)



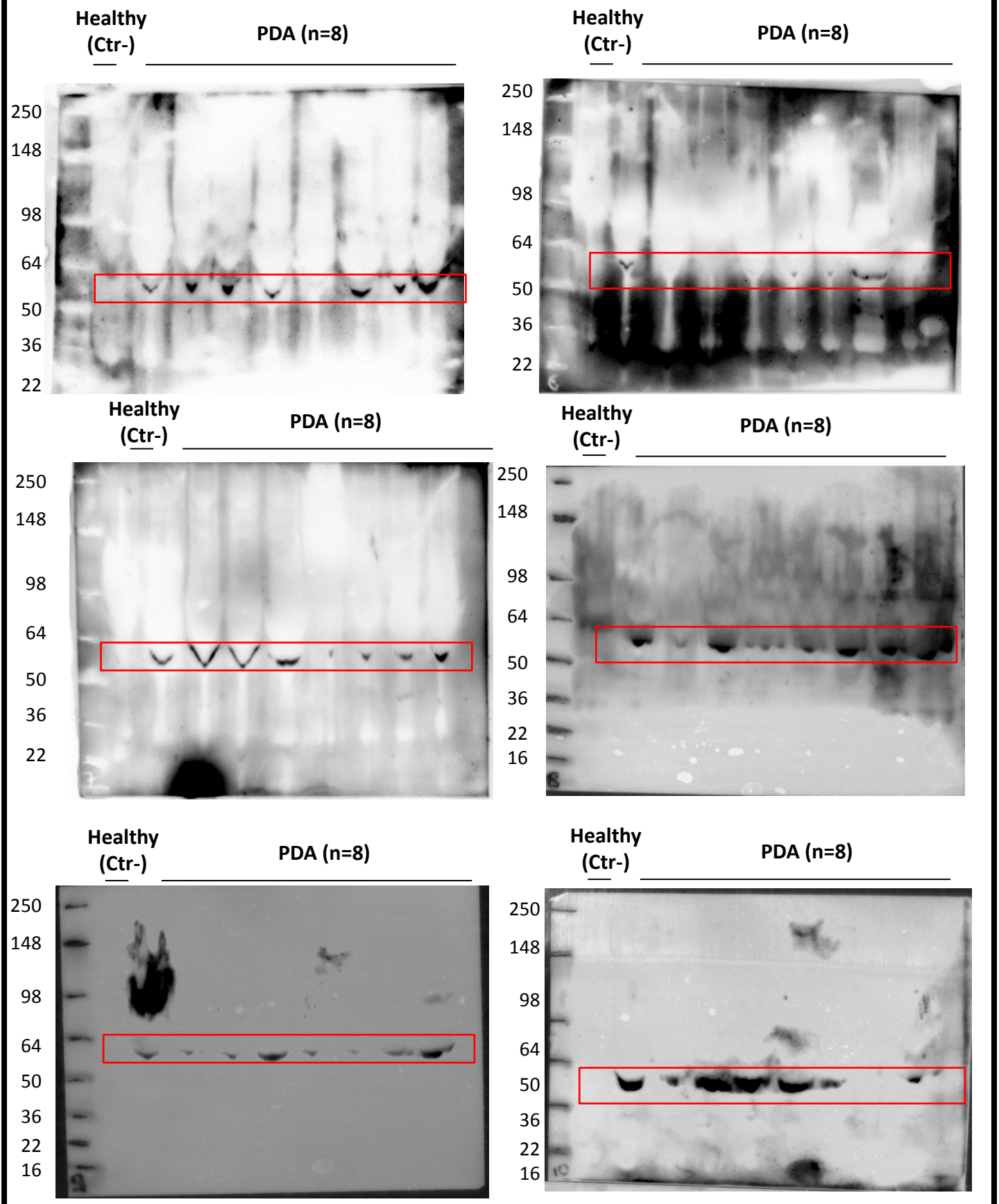

Healthy (Ctr-) | PDA (n=8)



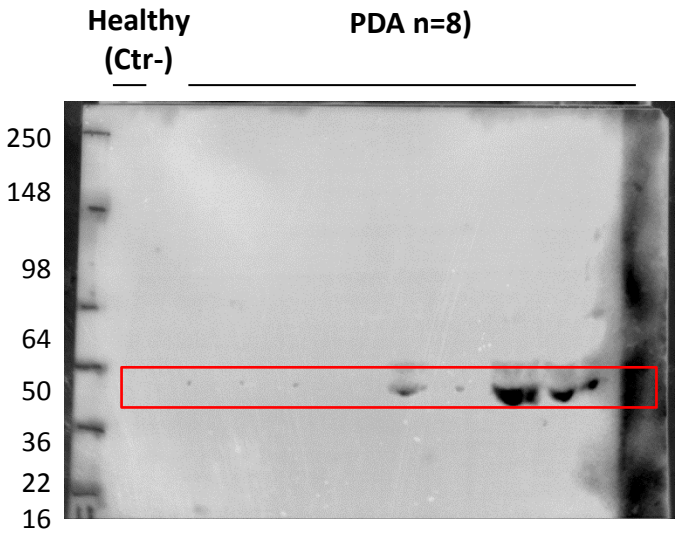

Healthy (Ctr-) | PDA (n=8)

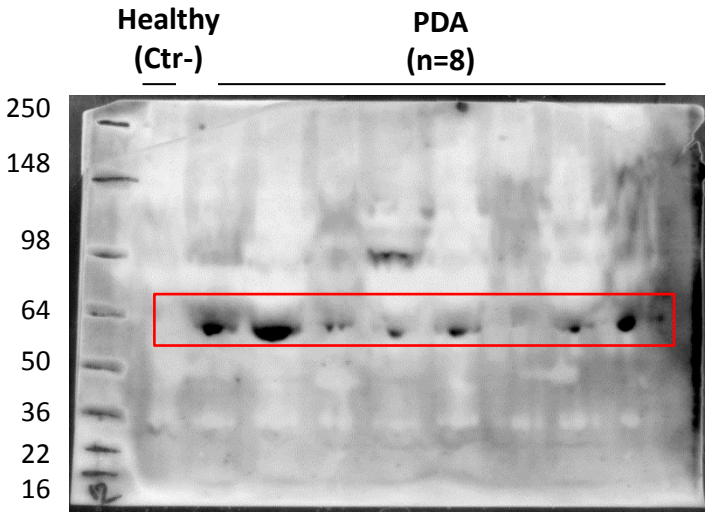


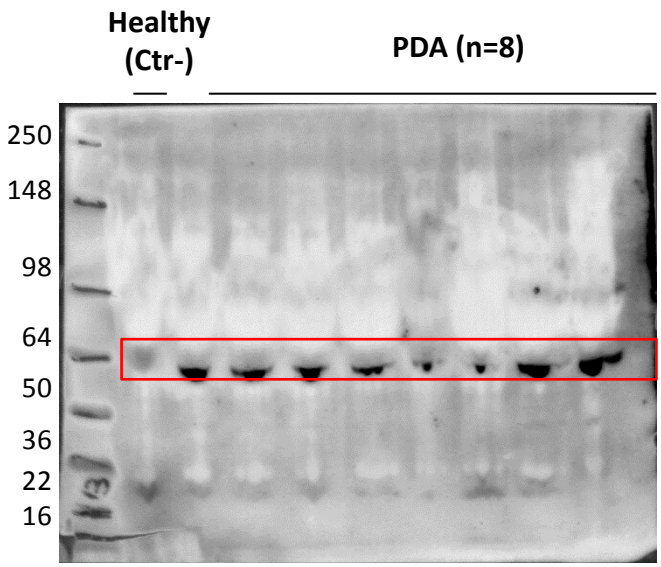
ANXA6

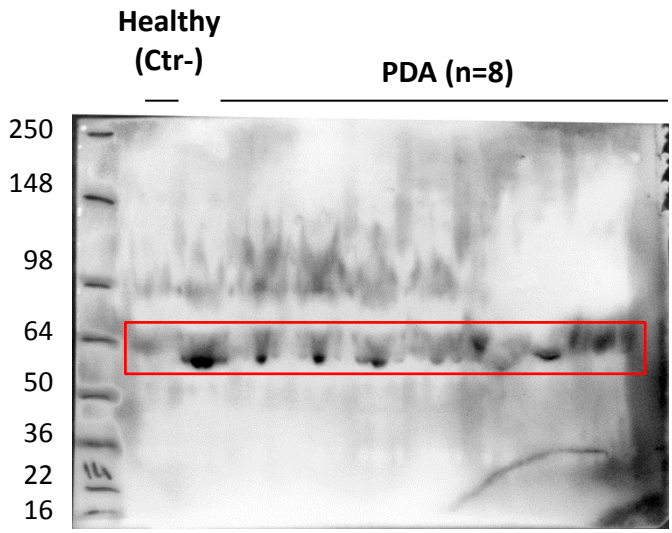

Healthy (Ctr-)
PDA (n=8)
250
148
98
64
50
36
22
Healthy (Ctr-)
PDA (n=8)
250
148
98
64
50
36
22
Healthy (Ctr-)
PDA (n=8)
250
148
98
64
50
36
22
Healthy (Ctr-)
PDA (n=8)
250
148
98
64
50
36
22
16
Healthy (Ctr-)
PDA (n=8)
250
148
98
64
50
36
22
16
Healthy (Ctr-)
PDA (n=8)
250
148
98
64
50
36
22
16

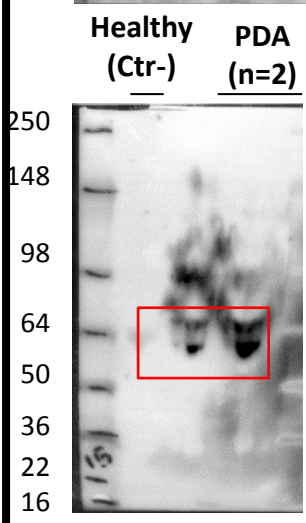
ANXA6

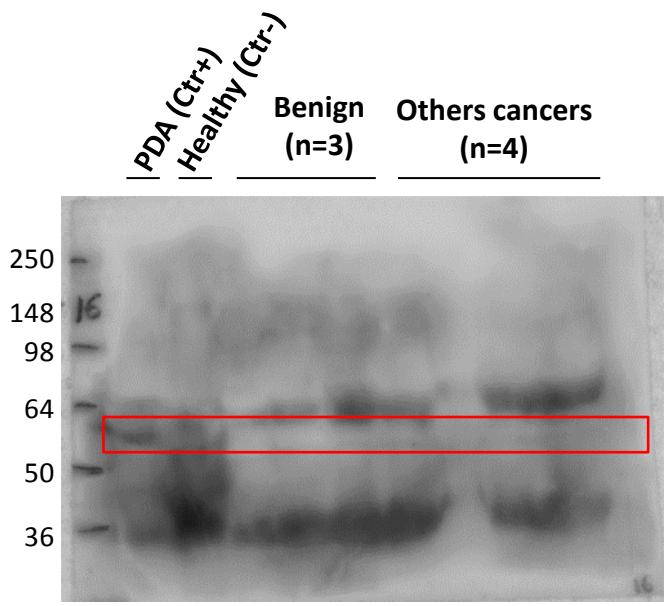

Healthy (Ctr-)
PDA n=8)
250
148
98
64
50
36
22
16


Healthy (Ctr-)
PDA (n=8)
250
148
98
64
50
36
22
16

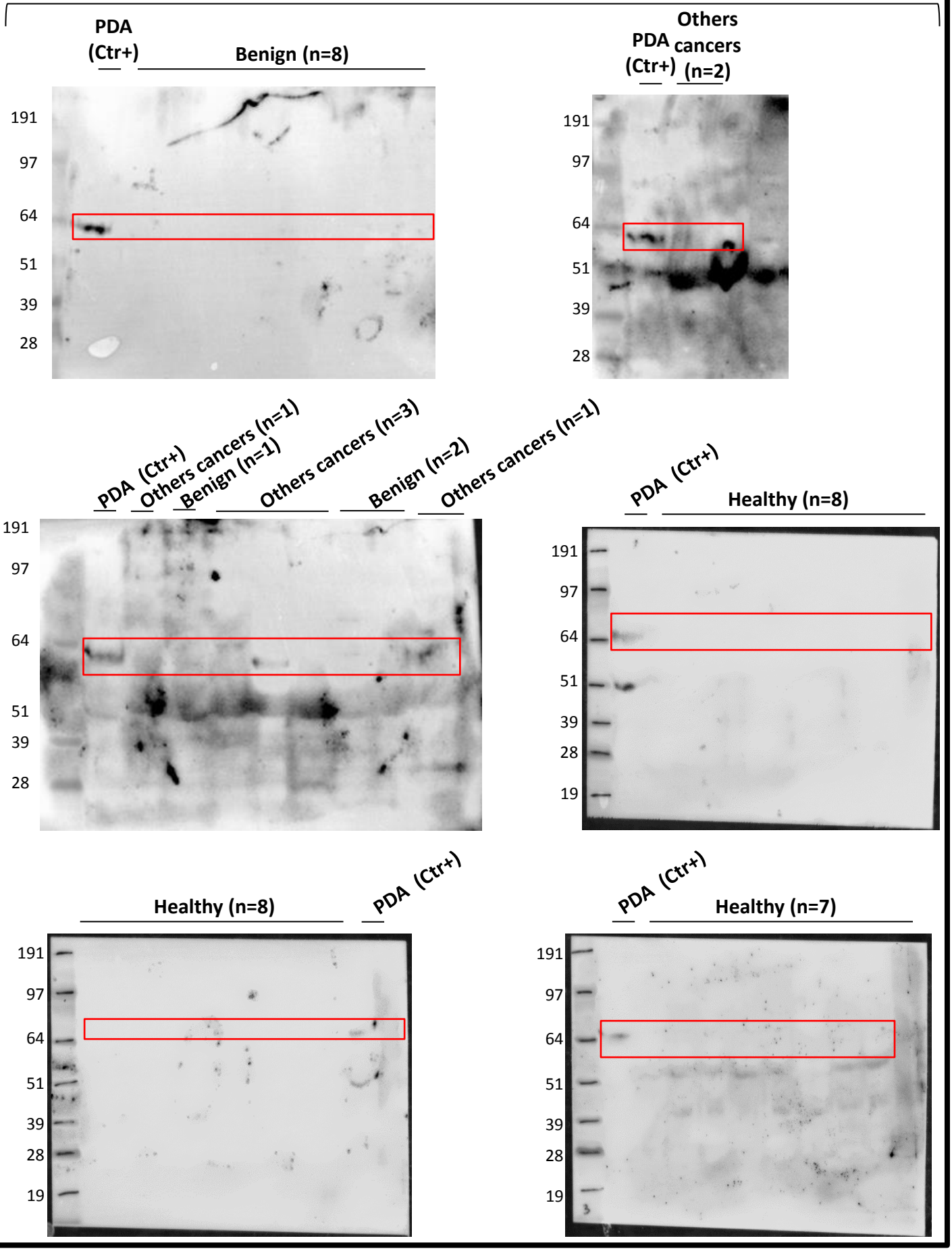

Healthy (Ctr-)
PDA (n=8)
250
148
98
64
50
36
22
16


Healthy (Ctr-)
PDA (n=8)
250
148
98
64
50
36
22
16


Healthy (Ctr-)
PDA (n=2)
250
148
98
64
50
36
22
16


PDA (Ctr+)
Healthy (Ctr-)
Benign (n=3)
Others cancers (n=4)
250
148
98
64
50
36

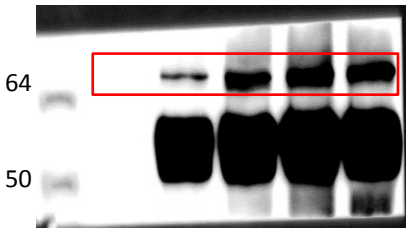
ANXA6


PDA (Ctr+)
Benign (n=8)
191
97
64
51
39
28
PDA (Ctr+)
Others cancers (n=2)
191
97
64
51
39
28
PDA (Ctr+)
Others cancers (n=1)
Benign (n=1)
Others cancers (n=3)
Benign (n=2)
Others cancers (n=1)
191
97
64
51
39
28
PDA (Ctr+)
Healthy (n=8)
191
97
64
51
39
28
19
Healthy (n=8)
PDA (Ctr+)
191
97
64
51
39
28
19
PDA (Ctr+)
Healthy (n=7)
191
97
64
51
39
28
19

# Full unedited gel for Supplemental Figure S1 D

### IP ANXA6, WB TSP1

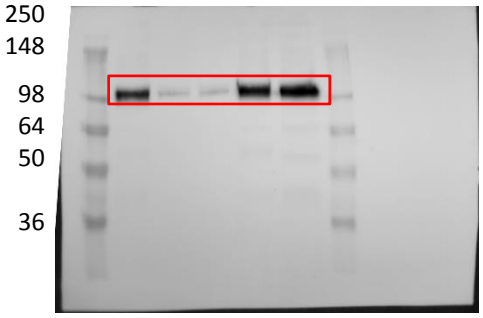

### IP ANXA6, WB ANXA6



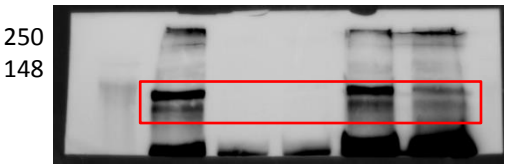

Membrane cut at 98kDa – shared with ANXA6

### IP ANXA6, WB LRP1


### TCL - WB LRP1

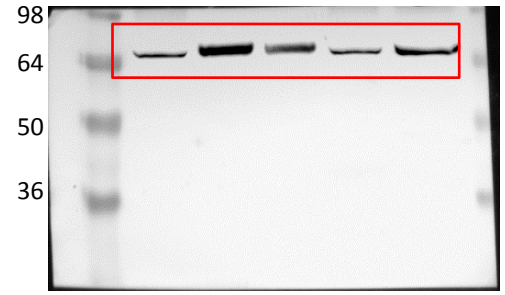



### TCL - WB TSP1



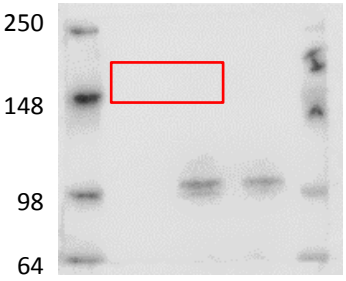

Membrane cut at 148kDa – shared with ANXA6

### TCL - WB ANXA6

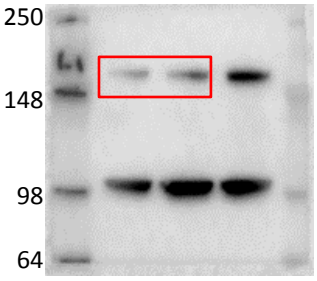


## Full unedited gel for Supplemental Figure S4A

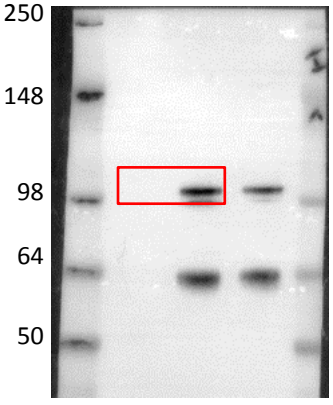
IP ANXA6, WB TSP1



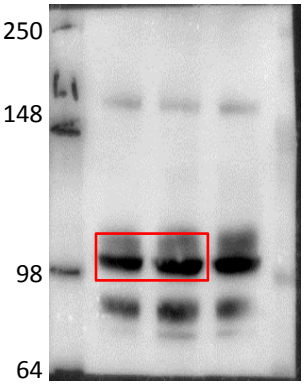

TCL- WB TSP1



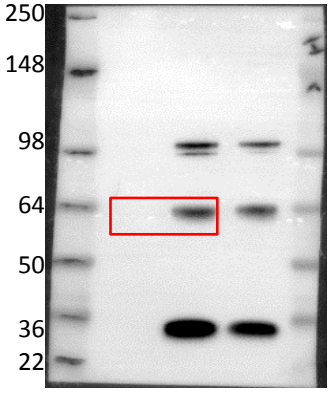

IP ANXA6, WB LRP1



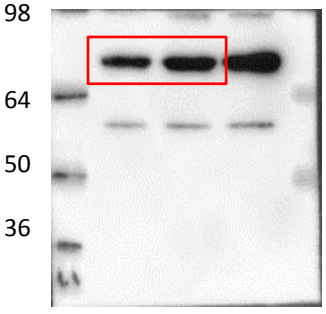

TCL- WB LRP1



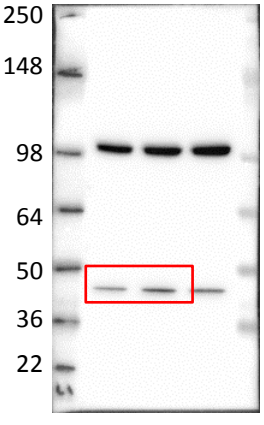

IP ANXA6, WB ANXA6




TCL – WB ANXA6

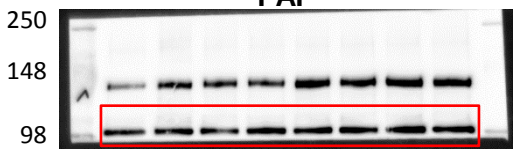



TCL – B-tubulin

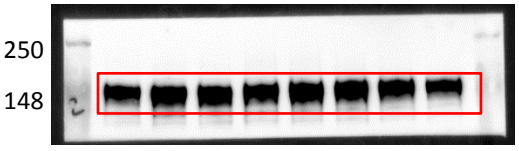



## Full unedited gel for Supplemental Figure S4F

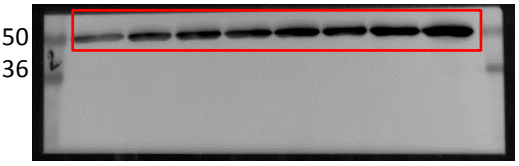
FAP



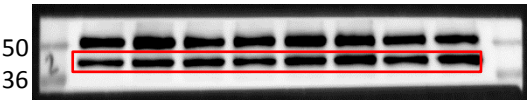

PDGFRB




aSMA

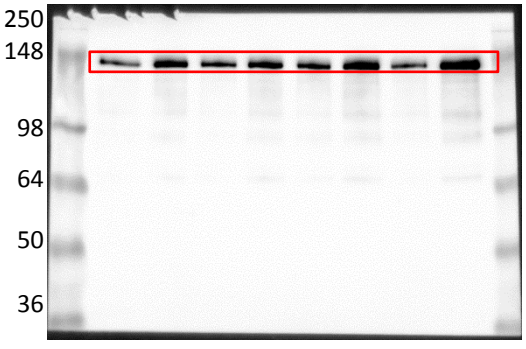



B-tubulin

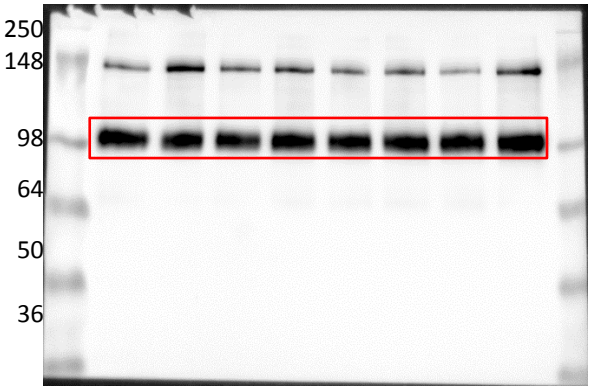



## Full unedited gel for Supplemental Figure S4G

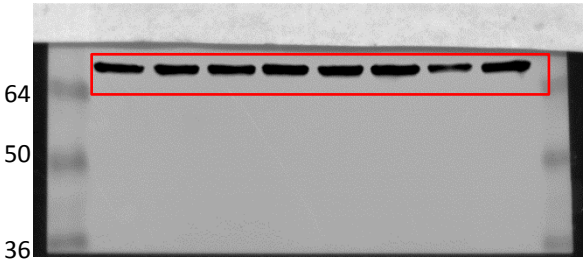
TSP1



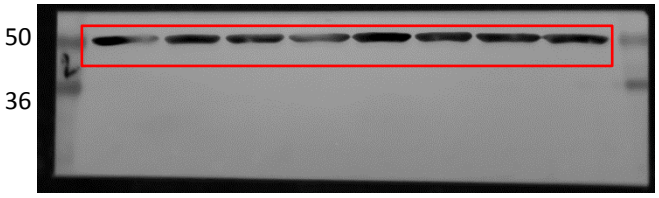

LRP1



ANXA6




B-tubulin

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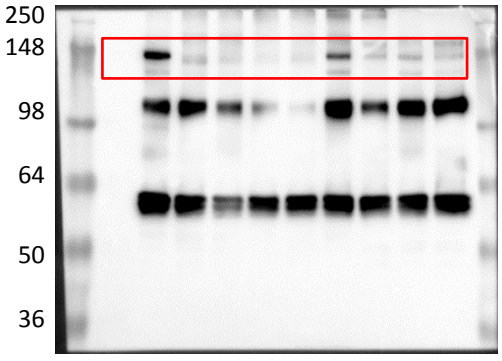
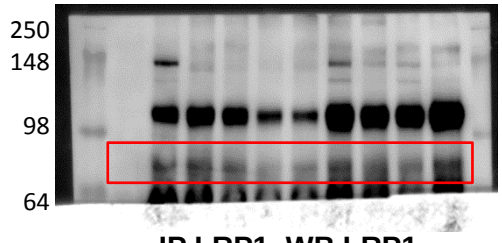
## Full unedited gel for Supplemental Figure S4H

IP LRP1, WB TSP1

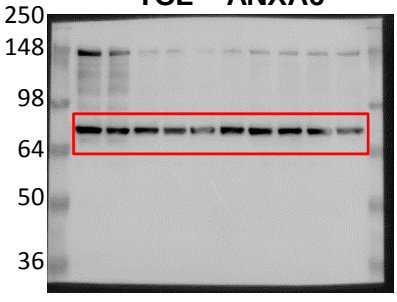



TCL – TSP1

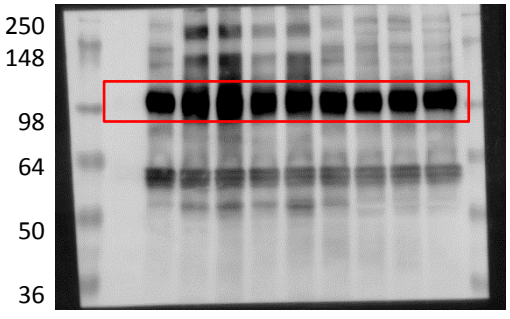

IP LRP1, WB ANXA6



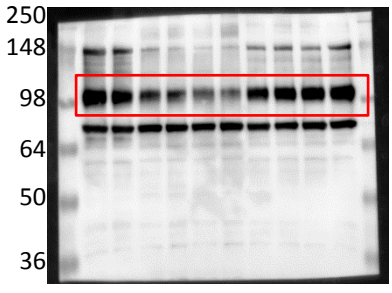

TCL – ANXA6



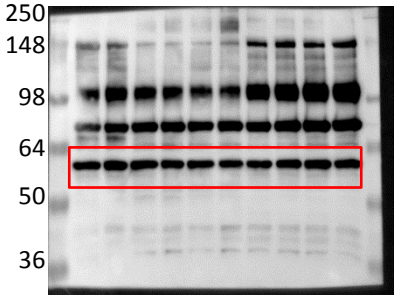

IP LRP1, WB LRP1



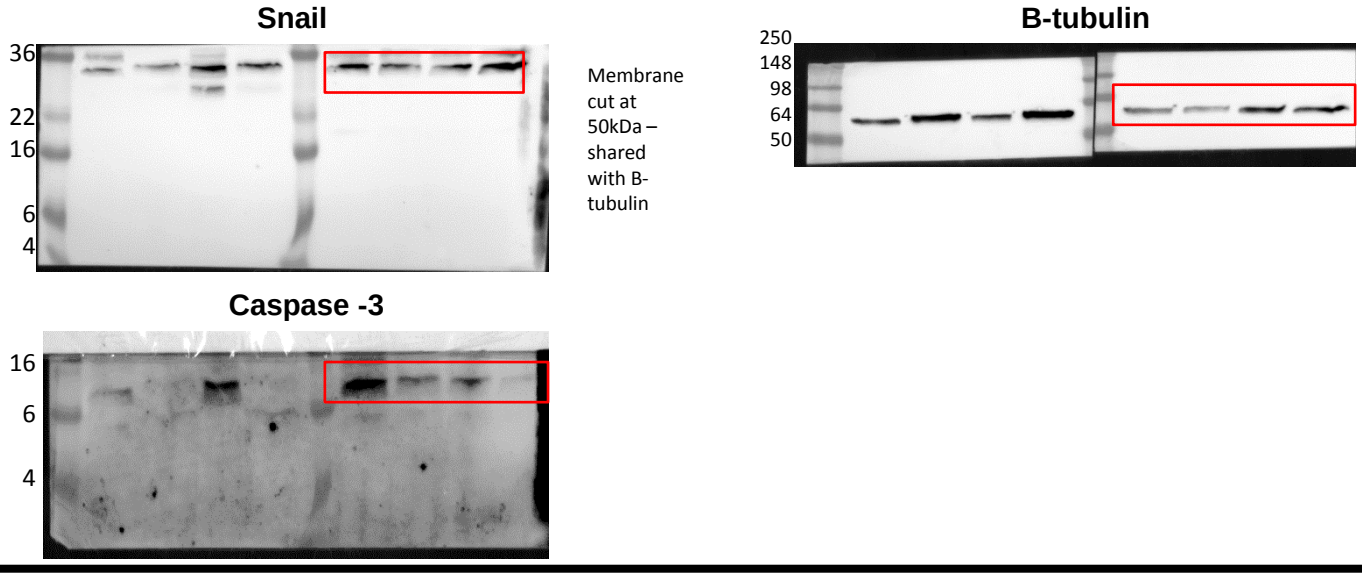

TCL – LRP1



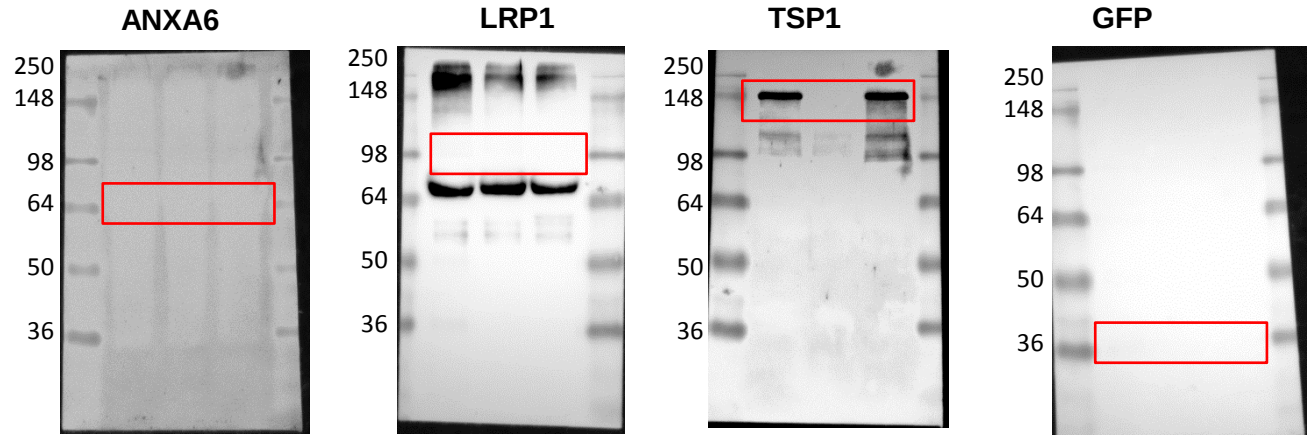

TCL – B-tubulin



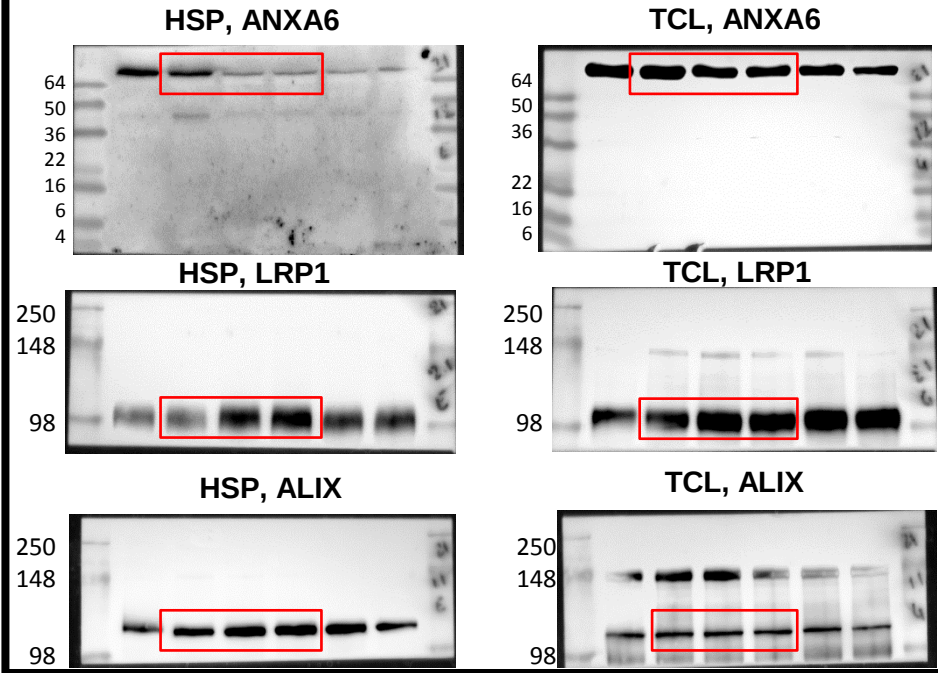
## Full unedited gel for Supplemental Figure S5B



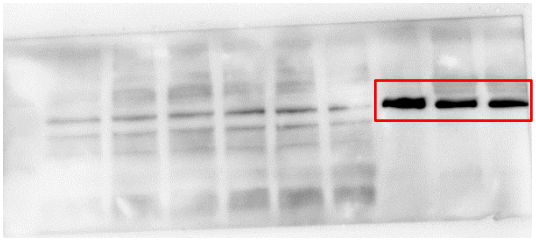

## Full unedited gel for Supplemental Figure S6C



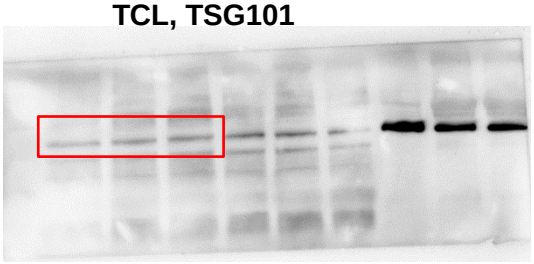

## Full unedited gel for Supplemental Figure S6D



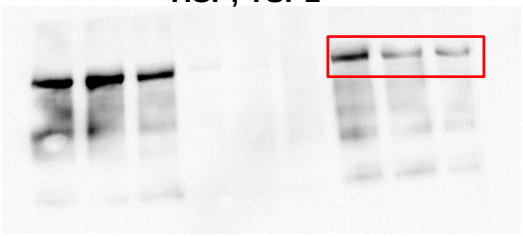
HSP, TSG101



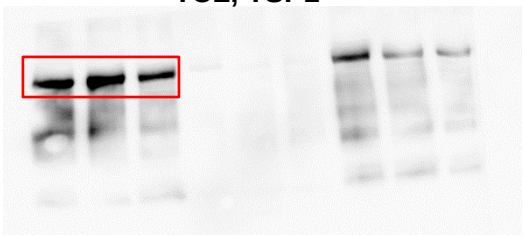
TCL, TSG101



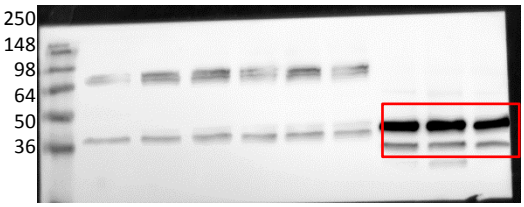
HSP, TSP1



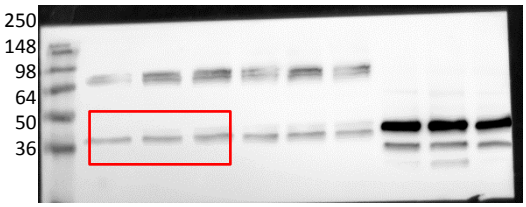
TCL, TSP1



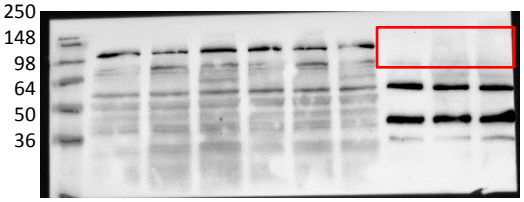
HSP, syntenin



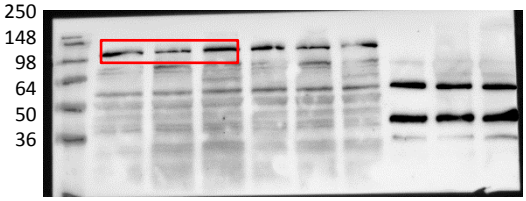

TCL, syntenin



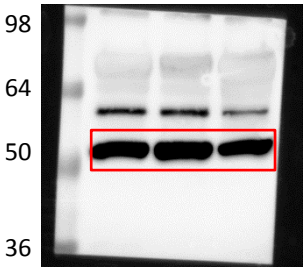

HSP, calnexin




TCL, calnexin




TCL, B tubulin



**Full unedited gel for Supplemental Figure S7A**