

Below is a structured analysis of the attached MultiQC-style spatial transcriptomics summary (Visium HD) and—per your instructions—mechanism proposals for response resistance grounded in those data. I also link each internet-based statement to peer-reviewed sources (inline) and provide a PubMed-formatted bibliography at the end.

1) What the attached report shows (concise summary)

Cohort & labels. Six PDAC Visium-HD samples: three *non-responders* (HC01, HC03, HC04) and three *responders* (HC05, HC07, HC08).¹

Atlas & cell typing pipeline. Deconvolution used a PDAC atlas (lovelessAtlas_FULLreAnnot_PT) with ~562k cells across 36k genes. Major compartments: PDAC epithelium, fibroblasts, myeloid, endothelial, pericytes, TNK, B/plasma, acinar, and endocrine.²

Key abundance patterns (group means). Using the “Output Cell Types” and “Spatial Neighbors” sections:

- **Tumor burden & CAF content (higher in non-responders).** Non-responders harbor markedly more *PDAC* assignments and *fibroblasts* than responders (mean PDAC 28,987 vs 5,360; fibroblasts 82,675 vs 23,584; non-responder/responder fold-change 5.41× and 3.51×, respectively).³
- **Cytotoxic T/NK compartment (higher in responders).** TNK counts are ~3.3× higher in responders (2,124 vs 642; fold-change 0.30 for non-responders/responder), and B-cells are ~4.8× higher in responders (579 vs 122; fold-change 0.21).⁴

¹https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

²https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

³https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

⁴https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

- **Pericytes (notable in one responder).** HC08 shows an exceptionally high pericyte assignment (18,231 vs ~1,400–1,500 in others), yielding a responder mean of 7,051 vs 1,636 for non-responders (fold-change 0.23).⁵
- **PDAC self-clustering vs heterotypic mixing.** PDAC spots neighbor PDAC spots more often in non-responders (mean 76.7%) than responders (58.9%), while PDAC–fibroblast adjacency is comparable across groups (17.1% vs 16.7%).⁶
- **Fibroblast self-clustering.** Fibroblast spots neighbor fibroblasts far more in non-responders (81.1%) than responders (52.4%), and fibroblast–PDAC adjacency is modest in both groups (5.9% vs 4.0%).⁷

Cell-type assignment certainty. PDAC typing probabilities are generally high (e.g., HC01 ~0.75, HC04 ~0.73; respondents ~0.54–0.60), consistent with confident calls.⁸

Spatial LR interactions (differential between groups). The top significant fibroblast→PDAC ligand-receptor pairs enriched in non-responders include **collagen IV–integrins** (COL4A1/A2 with ITGA2/3/9/10/11; ITGAV–ITGB8), **syndecans & CD44** (SDC1/SDC4; CD44), **WNT5A–FZD8**, **NECTIN3–NECTIN2**, **IGFBP3–TMEM219**, and **LTB4 pathway** (LTA4H–LTB4–LTB4R1).⁹

Moran’s I summary reports *no* differential spatial interactions at the single-gene level between groups; interaction changes are instead captured in LR-scores.¹⁰

⁵https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

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⁹https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

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2) Mechanisms of response resistance supported by the data (and literature)

Interpretation philosophy. I anchor each mechanism in the observed spatial/cellular features above (stated with report citations) and then connect them to PDAC biology via peer-reviewed sources (linked inline and listed in PubMed format).

A. CAF–ECM–integrin signaling establishes pro-survival, pro-EMT niches and impairs drug efficacy

- **Data anchor.** Non-responders show higher PDAC burden and CAF content, greater PDAC–PDAC clustering, and stronger fibroblast→PDAC collagen IV–integrin interactions (e.g., COL4A1/A2 with ITGA2/3/10/11, ITGAV–ITGB8; CD44; SDC1/4).¹¹
- **Rationale.** PDAC desmoplasia and CAFs remodel ECM stiffness and integrin signaling, conferring **gemcitabine resistance** via mechanotransduction (ITGA2) and survival pathways; integrin–ECM coupling also associates with immune resistance across cancers.^{12 13 14}
- **Implication.** High CAF–ECM–integrin signaling in non-responders is consistent with drug delivery barriers, EMT, and integrin-mediated therapy refractoriness (candidate targets: $\alpha 2\beta 1$, $\alpha V\beta 8$, CD44, SDC1/4).^{15 16 17}

¹¹https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

¹²<https://www.mdpi.com/2072-6694/15/3/628>

¹³<https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2024.1439709/full>

¹⁴<https://www.biorxiv.org/content/10.1101/2023.11.16.567457v1>

¹⁵<https://www.mdpi.com/2072-6694/15/3/628>

¹⁶<https://www.mdpi.com/2218-273X/11/3/349>

¹⁷<https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.784983/full>

B. Syndecan-1/4 and CD44 boost adhesion/EMT and **gemcitabine resistance**

- **Data anchor.** Enriched fibroblast→PDAC interactions via **SDC1/SDC4** and **CD44** in non-responders. ¹⁸
- **Rationale. Syndecan-1** and **CD44** (including CD44s and variant isoforms) promote PDAC plasticity, EMT, invasion, and resistance to gemcitabine; targeting SDC1 can reverse acquired resistance to KRAS-directed therapies in GI cancers. ^{19 20 21}
- **Implication.** CAF-driven SDC/CD44 axes likely maintain drug-tolerant states in dense PDAC nests observed in non-responders.

C. **WNT5A–FZD** signaling fosters EMT and chemoresistance in PDAC

- **Data anchor.** WNT5A–FZD8 fibroblast→PDAC interactions are elevated in non-responders. ²²
- **Rationale. WNT5A** drives EMT and invasiveness in PDAC and can **increase gemcitabine resistance** via AKT/Cyclin D1 and ABC transporter regulation; CAF-epithelium reciprocity via Lin28b/Wnt5a amplifies pro-tumorigenic crosstalk. ^{23 24 25}
- **Implication.** Non-responders' WNT5A signaling niches potentiate EMT-linked drug resistance.

¹⁸https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

¹⁹<https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.784983/full>

²⁰<https://aacrjournals.org/clincancerres/article/22/22/5592/79659/CD44-Expression-Level-and-Isoform-Contributes-to>

²¹<https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791%2825%2900326-X>

²²https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

²³<https://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-13-496>

²⁴<https://europepmc.org/article/MED/25308364>

²⁵<https://www.nature.com/articles/s41467-023-42508-8.pdf>

D. NECTIN2/NECTIN3 adhesion and TIGIT axis-mediated immune evasion

- **Data anchor.** Non-responders show enriched **NECTIN3–NECTIN2** interactions between fibroblasts and PDAC cells. ²⁶
- **Rationale.** Tumoral **NECTIN2 (CD112)** engages **TIGIT** on T/NK cells, suppressing cytotoxicity; NECTIN2 upregulation contributes to T-cell exhaustion in PDAC. Broad literature positions PVRL2/NECTIN2 and PVR/CD155 as central inhibitory ligands in the DNAM-1 axis. ^{27 28 29 30}
- **Implication.** Together with the **lower TNK counts** seen in non-responders, NECTIN-centered checkpoints can explain immune exclusion and poor response, nominating **TIGIT/PVRIG blockade** as rational combinations. ^{31 32}

E. IGFBP3–TMEM219 apoptotic axis dysregulation as a stromal–tumor vulnerability

- **Data anchor.** **IGFBP3–TMEM219** fibroblast→PDAC interaction scores rank among top group-differentials (higher in non-responders). ³³
- **Rationale.** The **IGFBP3/TMEM219** pathway is a bona fide death receptor axis (caspase-8 dependent). In cancer, IGFBP3 can act anti-tumor (apoptosis,

²⁶https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

²⁷<https://link.springer.com/article/10.1186/s13046-024-03178-6>

²⁸<https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1441730/full>

²⁹<https://dspace.mit.edu/bitstream/handle/1721.1/146821/nihms-1730102.pdf?sequence=2>

³⁰http://library.ncifrederick.cancer.gov/discovery/fulldisplay/cdi_pubmedcentral_primary_oi_pubmedcentral_nih_gov_8511341/01FREDERICK_INST:01FREDERICK

³¹https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

³²<https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1441730/full>

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anti-metastatic), but context-dependent signaling and proteolysis may alter outcomes; emerging translational work targets this axis to restore tissue homeostasis.^{34 35}

- **Implication.** Elevated LR coupling suggests a *perturbed* IGFBP3/TMEM219 environment in non-responders; it is potentially actionable (agonism to kill PDAC or blockade if paradoxically protumor in this context), but requires functional validation.

F. Leukotriene B4 (LTB4) axis shapes neutrophilic inflammation and therapy resistance

- **Data anchor.** Differential **LTB4–LTA4H–LTB4R1** interactions (fibroblast→PDAC) among top signals in non-responders.³⁶
- **Rationale.** **LTA4H/LTB4** signaling drives chronic inflammation, recruits neutrophils, and has been implicated in cancer progression; selective modulation of LTA4H's dual activities is under development. Pancreatic cancer shows systemic LTB4 alterations.^{37 38 39}
- **Implication.** An LTB4-high neighborhood may amplify TAN-mediated immunosuppression and poor response, aligning with the NECTIN2/TIGIT story above.⁴⁰

³⁴<https://www.mdpi.com/2073-4409/9/5/1261>

³⁵<https://europepmc.org/article/MED/36998110>

³⁶https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

³⁷<https://www.eurekaselect.com/article/7157>

³⁸<https://www.nature.com/articles/srep44449.pdf>

³⁹<https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964%2822%2900231-6/fulltext>

⁴⁰<https://link.springer.com/article/10.1186/s13046-024-03178-6>

G. Tumor architecture (dense PDAC clusters, CAF hubs) promotes **drug-tolerant refugia** and **immune exclusion**

- **Data anchor.** Non-responders show high **PDAC→PDAC** (76.7%) and **FIBRO→FIBRO** (81.1%) self-neighborhoods; responders show more heterogeneity and **higher TNK abundance**.⁴¹
- **Rationale.** Spatial proximity of **cytotoxic T cells to cancer cells** correlates with better survival in PDAC; neoadjuvant responders exhibit **higher CD3/CD4/CD8 infiltration** by spatial profiling.^{42 43}
- **Implication.** The non-responder topology likely restricts immune access and creates ECM-mediated drug-tolerant pockets.

H. Pericyte-rich vasculature in a responder (HC08) suggests **vessel normalization** benefits

- **Data anchor.** HC08 has markedly **elevated pericytes** and reduced PDAC burden; responders overall show lower PDAC clustering.⁴⁴
- **Rationale.** **Pericyte maturity** and **vascular normalization** improve perfusion, lower hypoxia and immunosuppression, and enhance delivery/efficacy of chemo–immunotherapy; modulating pericyte phenotype sensitizes tumors to T-cell therapy (preclinical).^{45 46 47}
- **Implication.** A pericyte-normalized microvasculature may underlie better therapeutic penetration and immune function in responders.

⁴¹https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

⁴²<https://www.nature.com/articles/ncomms15095.pdf>

⁴³<https://link.springer.com/article/10.1186/s12967-025-06599-9>

⁴⁴https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

⁴⁵<https://www.nature.com/articles/s12276-023-01114-w.pdf>

⁴⁶<https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1291530/full>

⁴⁷<https://www.jci.org/articles/view/179860>

3) Practical next steps (validation & targeting strategy)

A. Spatial–molecular validation (recommended):

1. **Immunostaining / mIF** on existing slides: integrin $\alpha 2\beta 1$, $\alpha V\beta 8$, **CD44**, **SDC1/SDC4**, **WNT5A/FZD8**, **NECTIN2/3**, **TIGIT**, **LTB4R1**, **LTA4H**, plus markers for **pericytes** (PDGFR β , α -SMA, CD146). Quantify per group and colocalization with PDAC nests. ⁴⁸
49 50 51 52 53
2. **Functional perturbations** in organoid–CAF co-cultures: block integrins ($\alpha 2\beta 1$, αV), CD44/SDC1, WNT secretion/receptors, **TIGIT/PVRIG**, **LTB4R**, and test gemcitabine/FOLFIRINOX sensitivity changes. ^{54 55 56 57 58}
3. **Immune readouts**: assess CD8⁺ T/NK cytotoxicity vs NECTIN2/3–TIGIT signaling; profile TANs and CCL5 where possible. ⁵⁹

⁴⁸<https://www.mdpi.com/2072-6694/15/3/628>

⁴⁹<https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.784983/full>

⁵⁰<https://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-13-496>

⁵¹<https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1441730/full>

⁵²<https://www.eurekaselect.com/article/7157>

⁵³<https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.676342/full>

⁵⁴<https://www.mdpi.com/2072-6694/15/3/628>

⁵⁵<https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.784983/full>

⁵⁶<https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.671022/full>

⁵⁷<https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1441730/full>

⁵⁸<https://www.eurekaselect.com/article/7157>

⁵⁹<https://link.springer.com/article/10.1186/s13046-024-03178-6>

4. **Perfusion/proxy metrics:** microvessel density, pericyte coverage, hypoxia (pimonidazole), to correlate with drug delivery.^{60 61}

B. Prioritized combination hypotheses for non-responders:

- **CAF/ECM–Integrin axis:** test $\alpha V/\beta 1$ inhibitors and **CD44/SDC1** targeting (\pm WNT pathway inhibitors) with chemotherapy.^{62 63}
 - **Immune checkpoints beyond PD-1:** evaluate **anti-TIGIT \pm CD40 agonism** (per PDAC preclinical data) in immune-excluded architectures.^{64 65}
 - **Inflammatory lipid axis:** explore **LTB4R antagonists / LTA4H modulators** to reduce TAN-driven suppression.^{66 67}
 - **Vascular normalization add-ons:** low-dose targeted therapy regimens to promote pericyte maturity and improve chemo–immunotherapy synergy.^{68 69}
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4) Notes on robustness

- The **Moran's I** section indicates no single-gene spatial interaction differences, underscoring that **combinatorial LR signaling** (captured by LR-scores) is the salient

⁶⁰<https://www.nature.com/articles/s12276-023-01114-w.pdf>

⁶¹<https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1291530/full>

⁶²<https://www.mdpi.com/2072-6694/15/3/628>

⁶³<https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.784983/full>

⁶⁴<https://dspace.mit.edu/bitstream/handle/1721.1/146821/nihms-1730102.pdf?sequence=2>

⁶⁵http://library.ncifrederick.cancer.gov/discovery/fulldisplay/cdi_pubmedcentral_primary_oai_pubmedcentral_nih_gov_8511341/01FREDERICK_INST:01FREDERICK

⁶⁶<https://www.nature.com/articles/srep44449.pdf>

⁶⁷<https://www.eurekaselect.com/article/7157>

⁶⁸<https://www.jci.org/articles/view/179860>

⁶⁹<https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1291530/full>

differential between groups—exactly what we see for collagen/integrin, WNT5A, NECTINs, and inflammatory axes.⁷⁰

- The **T/NK enrichment** in responders aligns with spatial PDAC literature linking cytotoxic proximity to better outcomes and neoadjuvant response; nevertheless, PDAC responses to ICI remain modest unless multiple barriers (stroma, vasculature, checkpoints) are co-addressed.^{71 72}
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5) (Optional) quick figures you may want me to generate

If helpful, I can produce:

- A **grouped bar chart** comparing PDAC→PDAC and FIBRO→FIBRO neighbor shares by sample.
- A **heatmap** of top LR interactions across samples highlighting non-responder enrichment.

(Say the word, and I'll render the plots and attach them.)

PubMed-formatted references

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⁷⁰https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

⁷¹<https://www.nature.com/articles/ncomms15095.pdf>

⁷²<https://link.springer.com/article/10.1186/s12967-025-06599-9>

⁷³<https://www.mdpi.com/2072-6694/15/3/628>

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⁷⁵<https://www.biorxiv.org/content/10.1101/2023.11.16.567457v1>

⁷⁶<https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.784983/full>

⁷⁷<https://www.mdpi.com/2218-273X/11/3/349>

⁷⁸<https://aacrjournals.org/clincancerres/article/22/22/5592/79659/CD44-Expression-Level-and-Isoform-Contributes-to>

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⁸²<https://dspace.mit.edu/bitstream/handle/1721.1/146821/nihms-1730102.pdf?sequence=2>

⁸³http://library.ncifrederick.cancer.gov/discovery/fulldisplay/cdi_pubmedcentral_primary_oai_pubmedcentral_nih_gov_8511341/01FREDERICK_INST:01FREDERICK

⁸⁴<https://link.springer.com/article/10.1186/s13046-024-03178-6>

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⁸⁷<https://www.mdpi.com/2073-4409/9/5/1261>

⁸⁸<https://europepmc.org/article/MED/36998110>

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⁹⁰<https://www.nature.com/articles/srep44449.pdf>

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Assumptions & caveats

- The treatment defining “response” is not specified in the file; I treated “response” categorically without assuming regimen (e.g., FOLFIRINOX vs ICI). Mechanisms above are broadly applicable across PDAC cytotoxic and immunotherapy contexts. ⁹⁷
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⁹¹<https://link.springer.com/article/10.1186/s12967-025-06599-9>

⁹²<https://translational-medicine.biomedcentral.com/counter/pdf/10.1186/s12967-025-06599-9.pdf>

⁹³<https://www.nature.com/articles/ncomms15095.pdf>

⁹⁴<https://www.nature.com/articles/s12276-023-01114-w.pdf>

⁹⁵<https://www.jci.org/articles/view/179860>

⁹⁶<https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1291530/full>

⁹⁷https://somumaryland-my.sharepoint.com/personal/dlvovs_som_umaryland_edu/Documents/Microsoft%20Copilot%20Chat%20Files/DPT_STAPLE.txt

Would you like me to (a) generate the plots, or (b) prepare a short slide deck summarizing these axes (CAF/integrin, SDC/CD44, WNT5A, NECTIN/TIGIT, LTB4, pericytes) with validation checklists tailored to your lab workflows?