Selective targeting of integrins αVß8 and αVß1 within the dynamic ecosystem of pancreatic cancer to improve overall anti-tumor response

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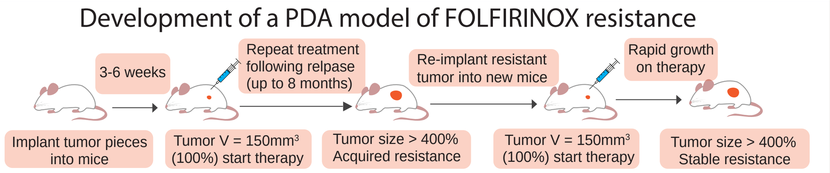
Background

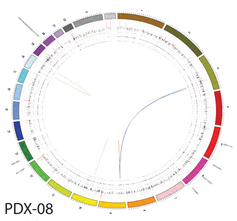
- Pancreatic ductal adenocarcinoma (PDA) has a 5-year survival of less than 10% and remains the 3rd leading cause of cancer-related death in Western societies. New treatment options are urgently needed.
- We previously characterized molecular subsets of PDA, including fibrotic elements of the disease, associated with pre-clinical and clinical response to select tailored treatment strategies[1-4].
- TGF-β promotes stromal cell reprogramming, immunosuppression, and fibrinogenesis in cancers, including PDA[5,6]. Integrins αVβ8 and αVβ1 are important activators of TGF-β signaling. Selective integrin blockade has recently emerged as a promising therapeutic approach to address TGFβ-mediated immunotherapy resistance, and improve anti-tumor response across cancer models[7-9].
- PLN-101095, a selective small molecule inhibitor of αVβ8 and αVβ1, is in early Phase I trials. Here, we assessed the preclinical efficacy and potential of PLN-101095 for the treatment of PDA.

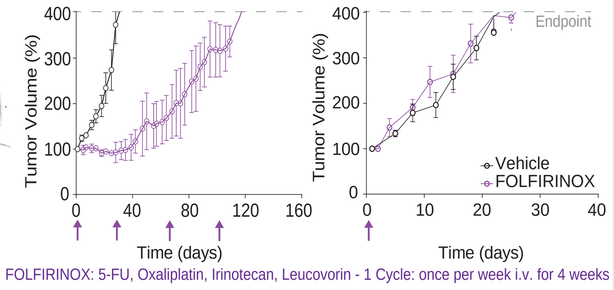
Results

PLN-101095 mediated targeting of αVβ8/ αVβ1 improves chemoresponse in a FOLFIRINOX resistant patient-derived PDA setting

Development of a PDA model of FOLFIRINOX resistance

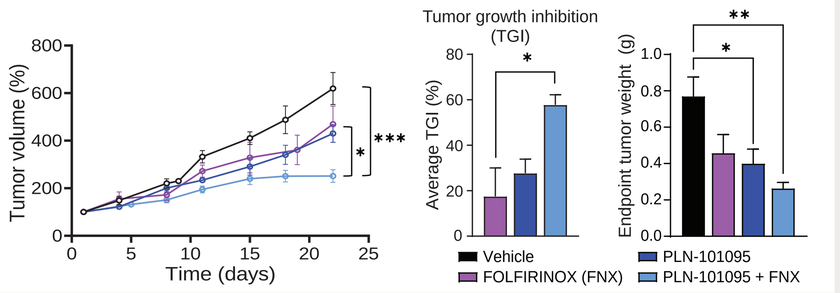




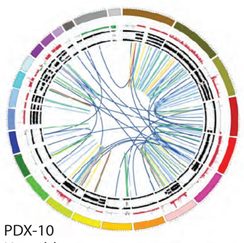


FOLFIRINOX: 5-FU, Oxaliplatin, Irinotecan, Leucovorin - 1 Cycle: once per week i.v. for 4 weeks

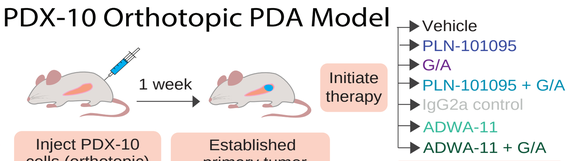
- PLN-101095 + FOLFIRINOX combination delayed disease progression and significantly reduced in vivo tumor growth in a PDA model of FOLFIRINOX resistance (*p<0.05; **p<0.01; ***p<0.001).



PLN-101095 decreases primary tumor growth, improves chemosensitivity in metastatic PDA

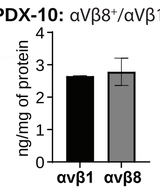


PDX-10 Orthotopic PDA Model

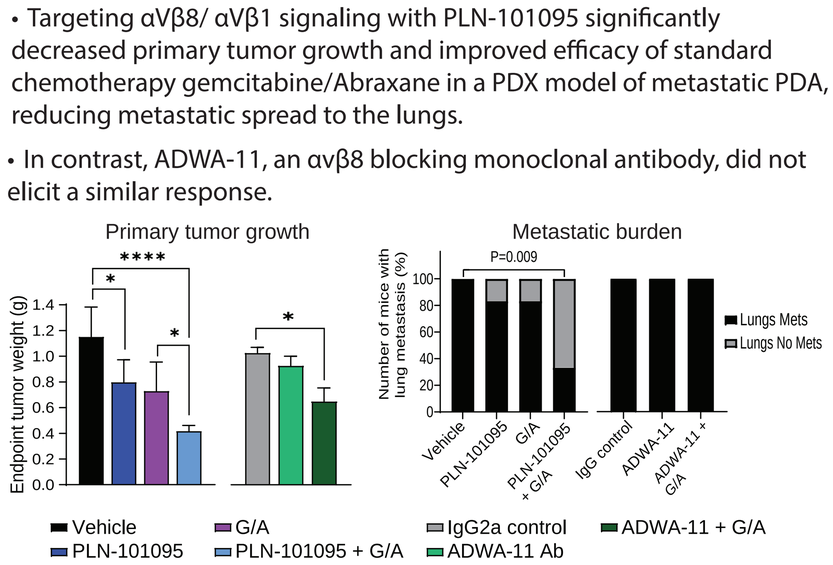


GEMCITABINE/ABRAXANE(G/A): once per week i.p. for 4 weeks

PDX-10: αVβ8⁺/αVβ1⁺



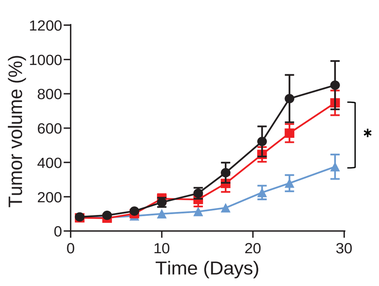
- Targeting αVβ8/ αVβ1 signaling with PLN-101095 significantly decreased primary tumor growth and improved efficacy of standard chemotherapy gemcitabine/Abraxane in a PDX model of metastatic PDA, reducing metastatic spread to the lungs.
- In contrast, ADWA-11, an αvβ8 blocking monoclonal antibody, did not elicit a similar response.



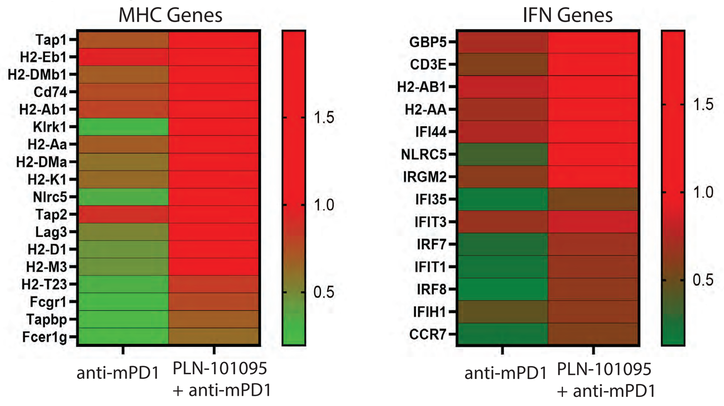
PLN-101095 treatment reduces primary tumor growth and improves anti-PD1 response in a range of 'immune-cold' models of advanced PDA

Pan02 syngeneic PDA Model

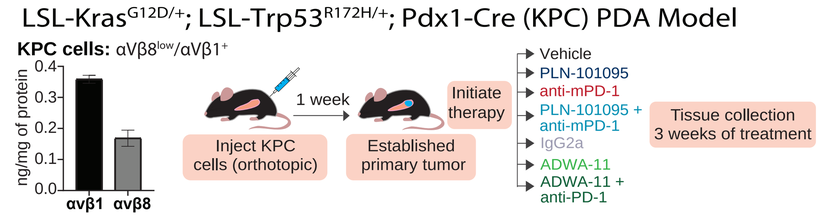
- PLN-101095 improves response to immune checkpoint blockade (ICB) and improves intra-tumoral CD8+ lymphocyte infiltration.



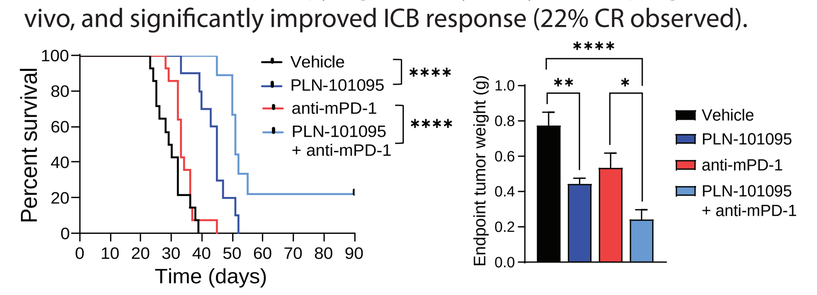
- PLN-101095 combined with ICB induces expression of MHC and IFN IFN response genes in PDA tumors.



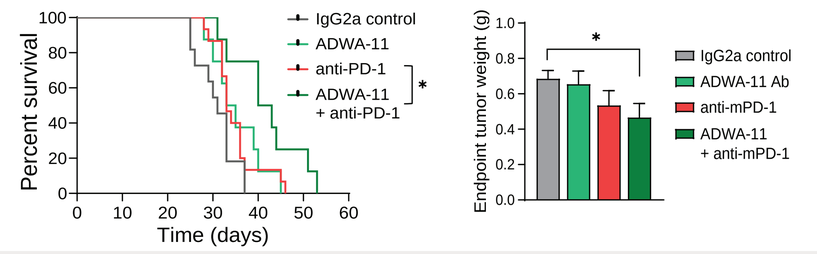
LSL-Kras$^{G12D/+}$; LSL-Trp53$^{R172H/+}$; Pdx1-Cre (KPC) PDA Model



- PLN-101095 monotherapy significantly delayed PDA progression in vivo, and significantly improved ICB response (22% CR observed).

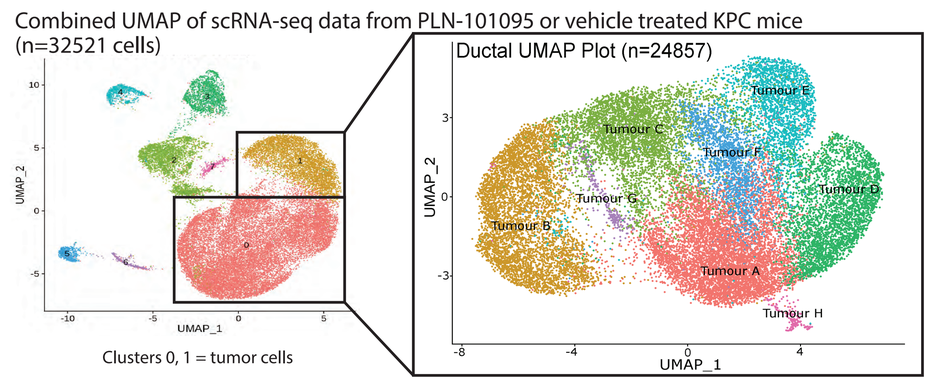


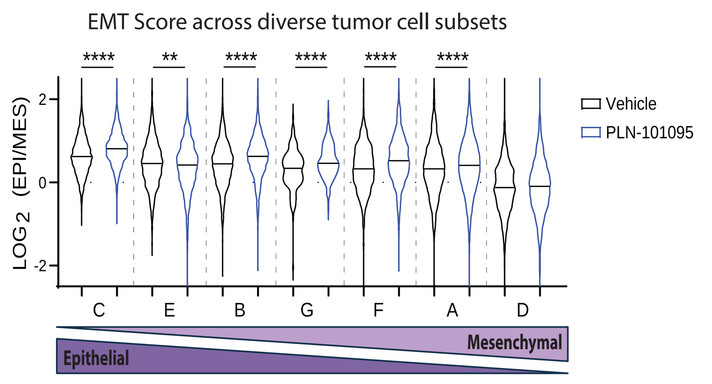
- In comparison, blocking αvβ8 with ADWA-11 Ab elicited a modest response when combined with ICB in the KPC orthotopic PDA model.



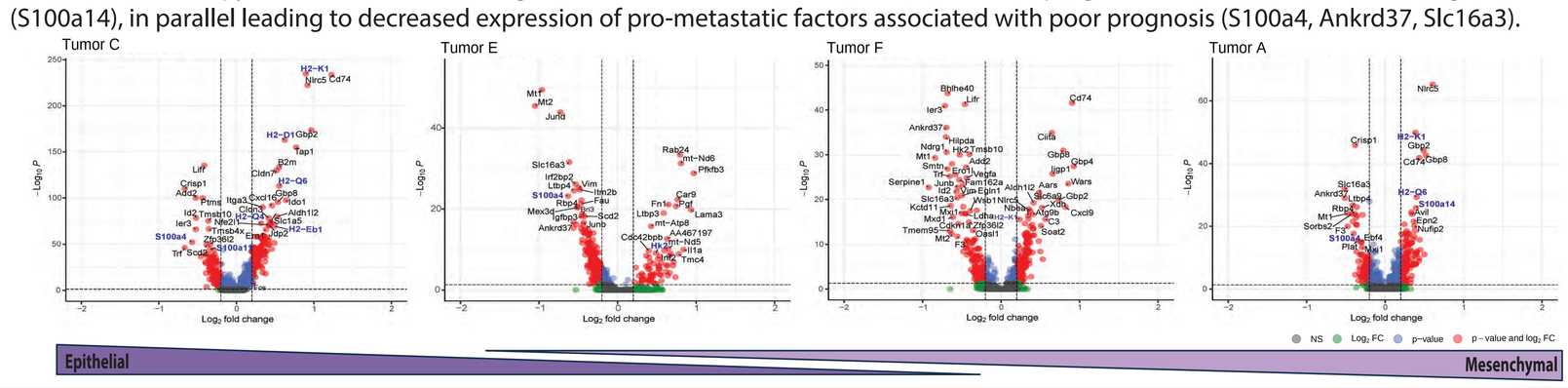
Charting the complex tumor landscape in the KPC model of PDA post-PLN-101095 therapy

- Dual targeting of αVß1/αVß8 induced a shift towards a more epithelial-like phenotype across diverse cancer cell subsets in murine PDA (KPC) tumors ('Thierry signature' Tan TZ et al EMBO Mol Med 2014), previously associated with improved prognosis in PDA.



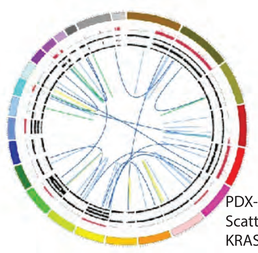


- PLN-101095 therapy induced MHCI class antigens and their transactivators (Nlrc5, H2-k1, H2-q6), genes associated with low tumor grade (S100a14), in parallel leading to decreased expression of pro-metastatic factors associated with poor prognosis (S100a4, Ankrd37, Slc16a3).

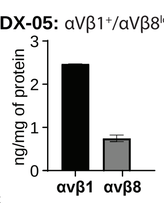


Selective targeting of αVβ8 and αVβ1 (PLN-101095) or αVβ1 signaling (PLN-76104) potently inhibit primary tumor growth, spread and improve chemotherapy response in models of PDA

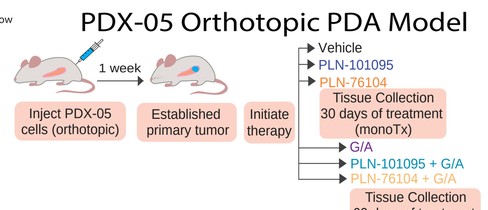
- Promising therapeutic efficacy of PLN-101095 and PLN-76104 in a αVß1⁺ PDX model of metastatic pancreatic cancer: robust inhibition of tumor growth and metastasis (liver and lungs), suggesting blocking αVß1 integrin alone may elicit a significant therapeutic response in PDA.

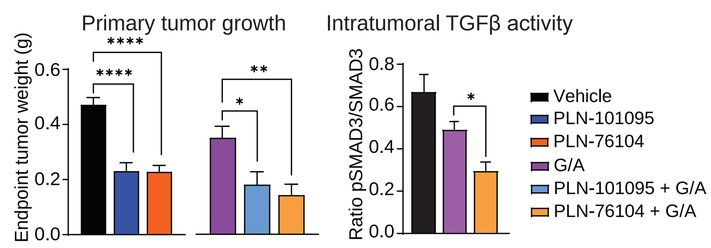


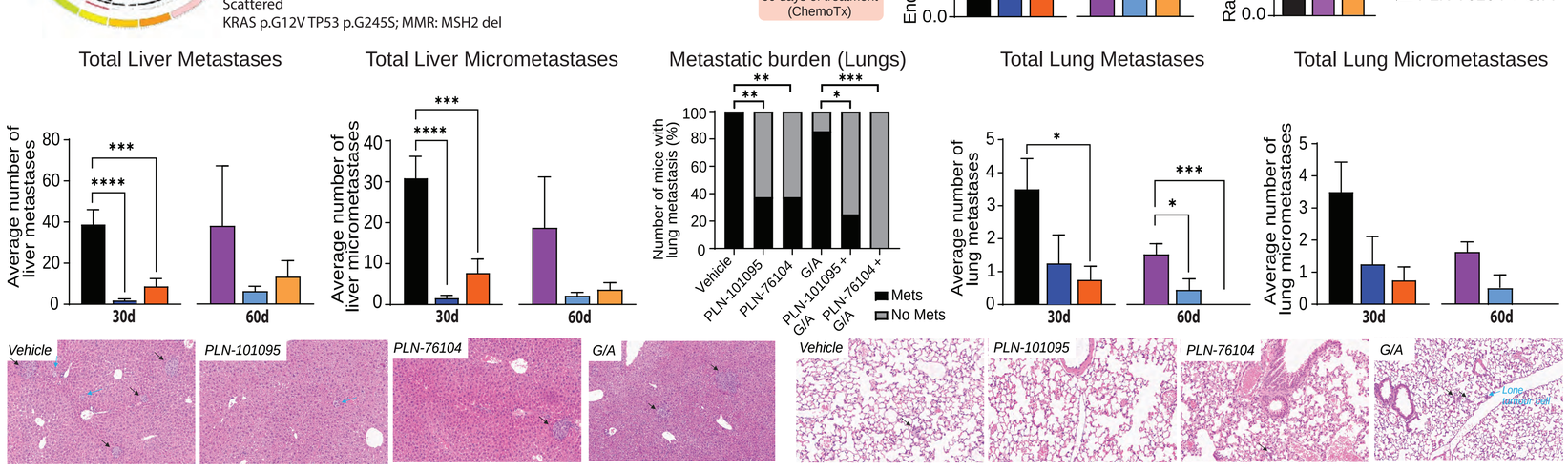
PDX-05: αVβ1⁺/αVβ8^{low}



PDX-05 Orthotopic PDA Model







Conclusions

Dual targeting of αVβ8/αVβ1 signaling by PLN-101095 significantly enhanced response to immunotherapy or contemporary chemotherapies in models of advanced PDA. Promising signal of in vivo activity was also observed for PLN-76104, selective inhibitor of αVβ1 integrin. Mechanistic studies revealed PLN-101095-induced positive reprogramming of malignant PDA cells towards an epithelial expression state and gene expression changes associated with favorable immune response and improved prognosis. These data provide scientific rationale for the design of future PLN-101095 and SoC chemotherapy as well as immunotherapy combinations in pancreatic cancer, with Phase I first-in-human oncology studies with PLN-101095 plus ICB aleady underway.

References

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