

Characterizing the Epigenetic Landscape Identifies Putative Therapeutic Targets in the Pancreatic Cancer Chimera

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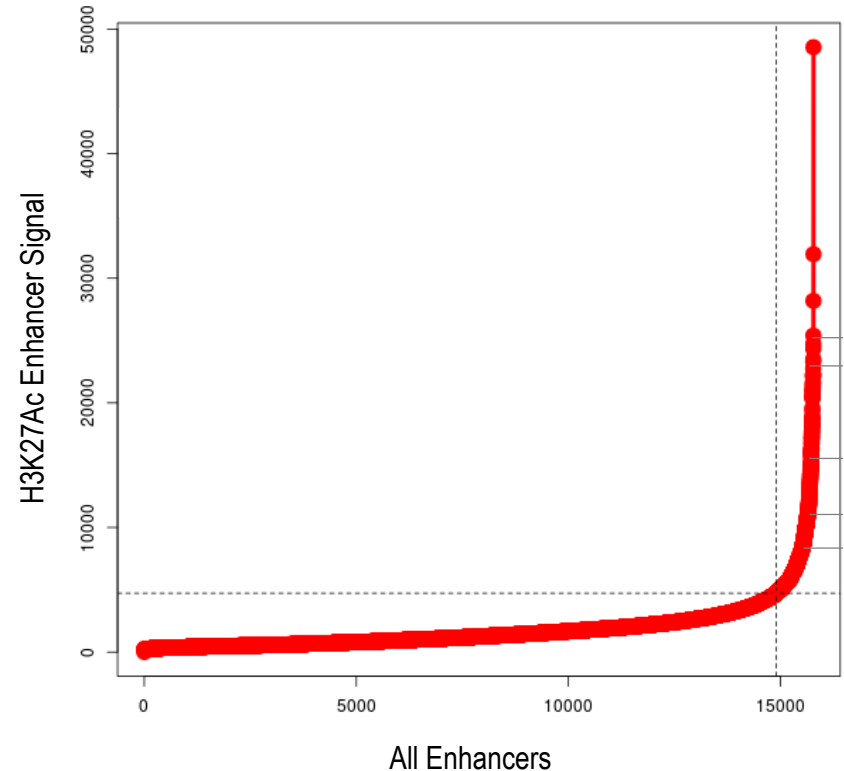
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Disclosures

Kathryn Austgen PhD, Chris Fiore PhD, David Orlando PhD, Brian Johnston MS, Sofija Miljovska MS, Cindy Collins MS, and Tracey Lodie PhD are current or former employees of Syros Pharmaceuticals, Inc. and may have an equity interest in the company.

Super-enhancers

- Large non-coding regions made up of clusters of transcription regulators
 - Rich acetylation of Histone H3 lysine 27 (H3K27ac) indicates high levels of super enhancer activity
- Drive expression of genes that
 - define cell type differentiation
 - affect immune cell functional states
- Play a role in regulation of tumor promoting or inhibiting genes



Pancreatic Cancer

- Highly lethal
 - Currently the 3rd leading cause of cancer-related deaths in US (surpassed breast cancer in 2016)
 - Expected to surpass colon cancer to become the 2nd leading cause this decade
- Limited therapeutic options
 - Most present metastatic (no surgical options)
 - Nucleoside analogs (gemcitabine, 5-FU)
- Characterized by immunosuppressive microenvironment
 - Tumor-promoting macrophages
 - Lack of cytotoxic T cells

Hypotheses

Super-enhancer analysis can be used to:

- identify key drivers of oncogenesis in the epithelial, stromal, and immune cell populations within pancreatic cancer
- compare and select appropriate pre-clinical models of pancreatic cancer

Methods

Normal pancreas, primary PDAC, PDX tumors, PDX-derived organoids, PDAC cell lines



Dissociated and sorted into whole tumor, and epithelial, stromal, and immune populations



ChIPSeq to identify SE regions (rich in H3K27ac)

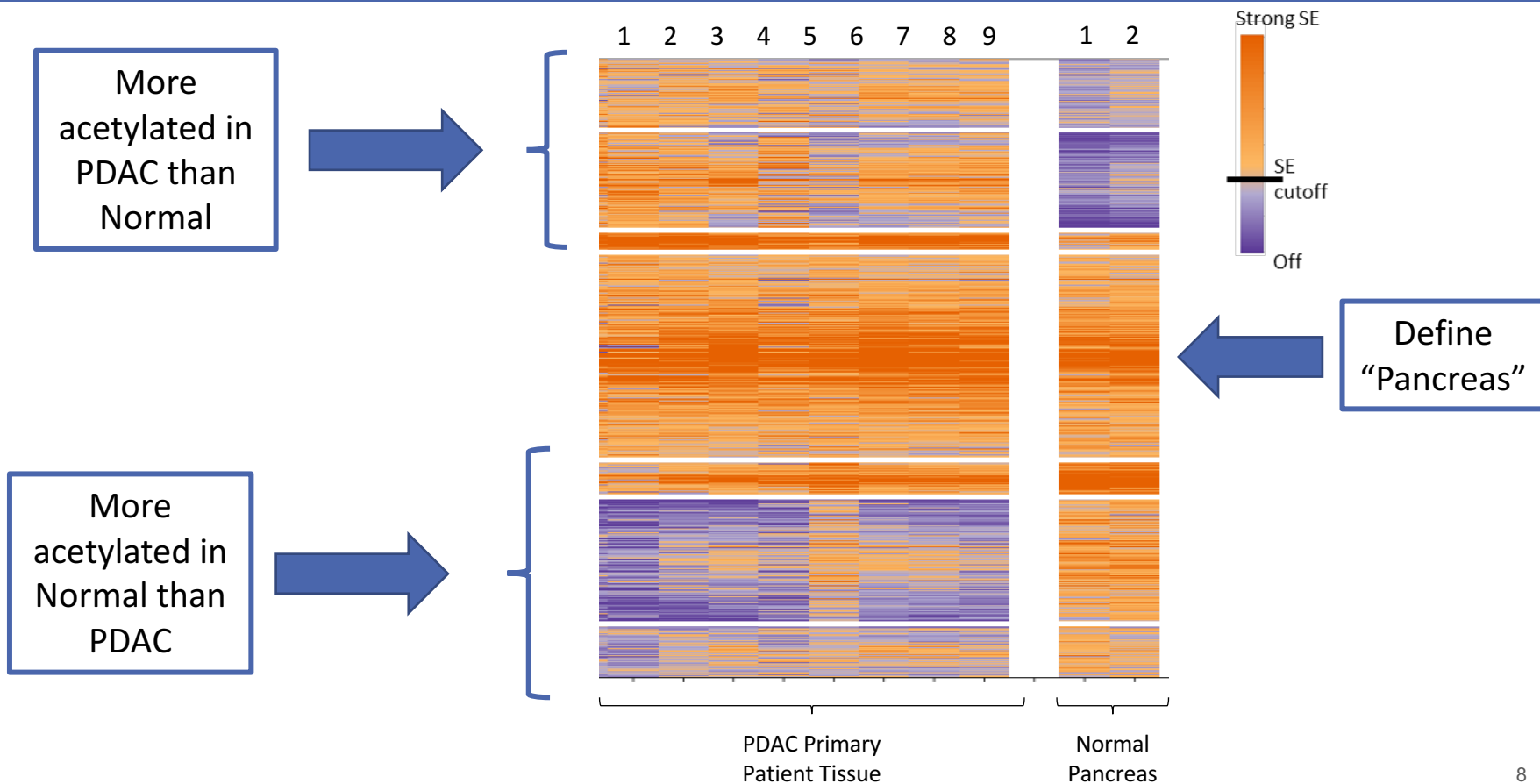


SE regions linked to specific genes

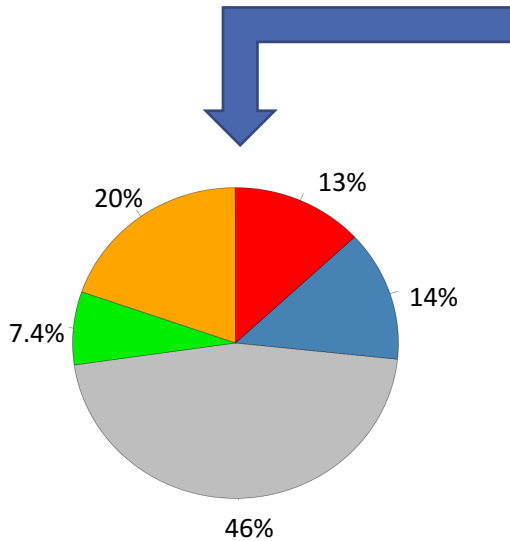


Genes linked to signaling pathways with Ingenuity Pathway Analysis

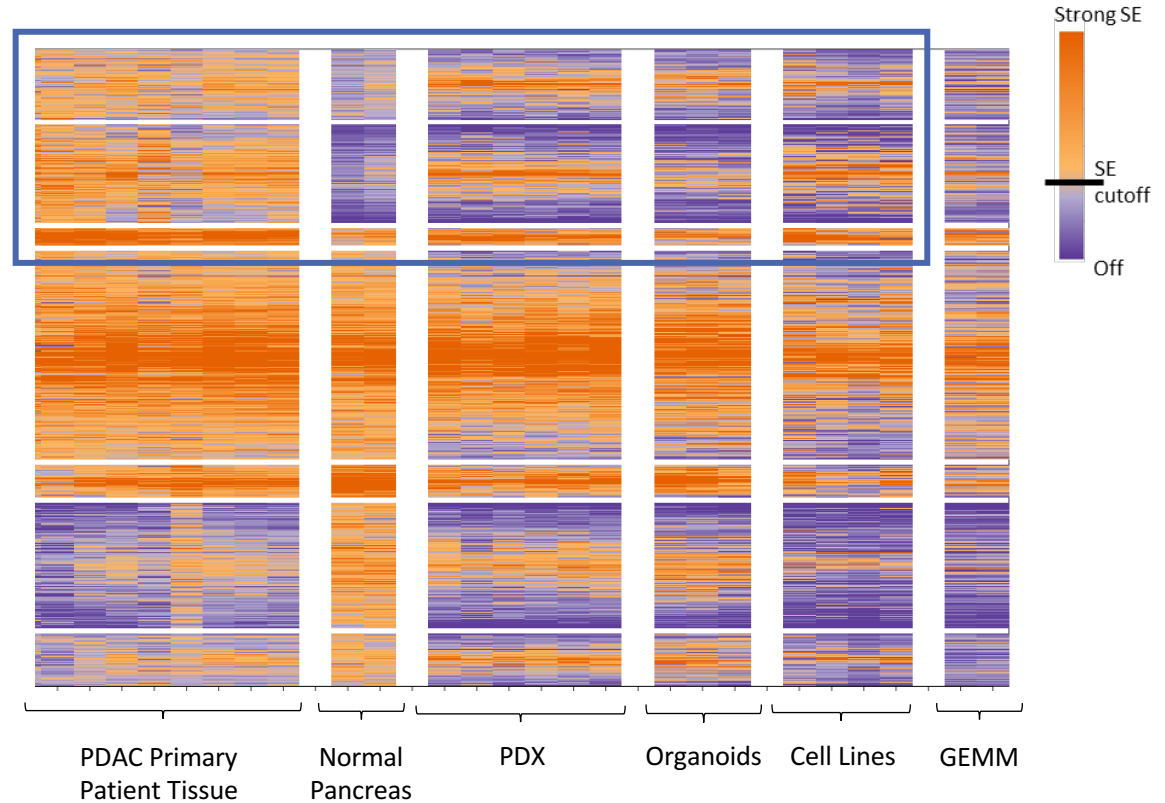
Primary PDAC samples have unique epigenetic landscapes compared to Normal Pancreas



There is variable maintenance of the epigenetic landscape across PDAC models

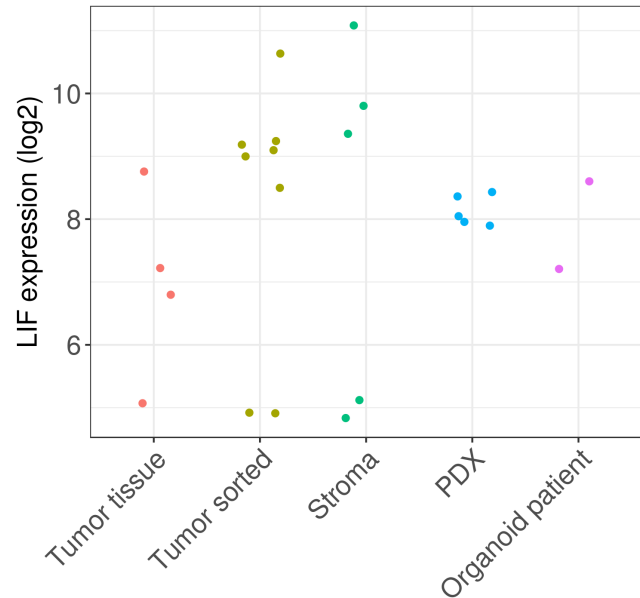
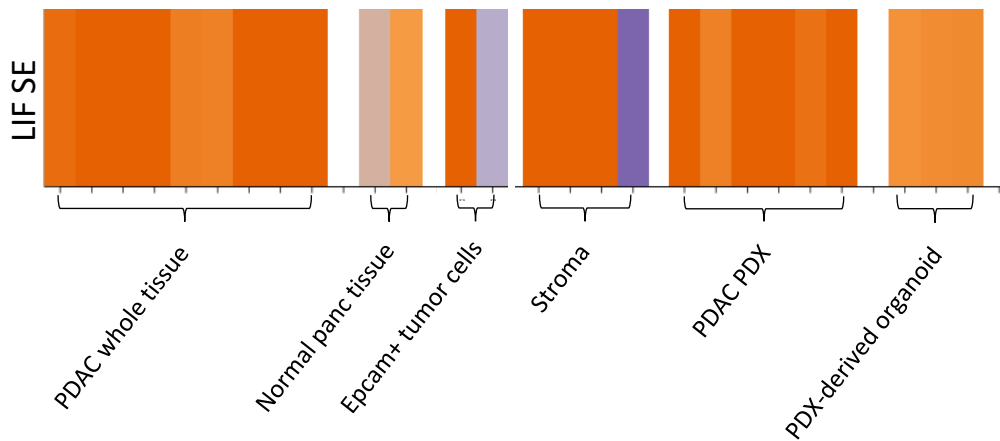


- Tagged in all 3 models
- Tagged in PDX + 1 other
- Tagged in only PDX
- Tagged in at least one non-PDX model
- Not SE tagged in any model

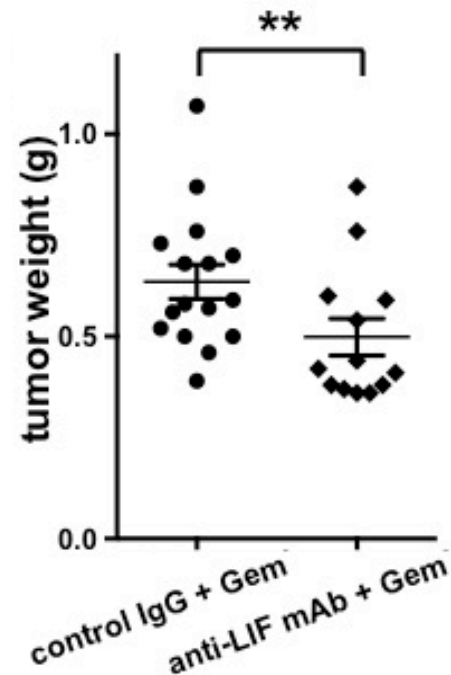
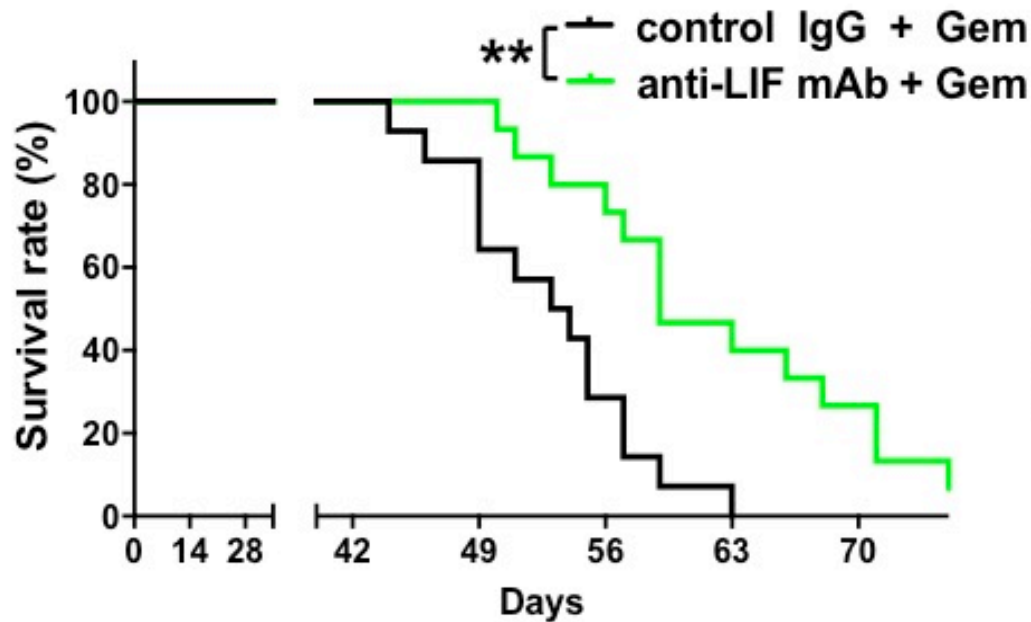


LIF1 is the most highly acetylated locus in PDAC versus normal and is maintained in model systems

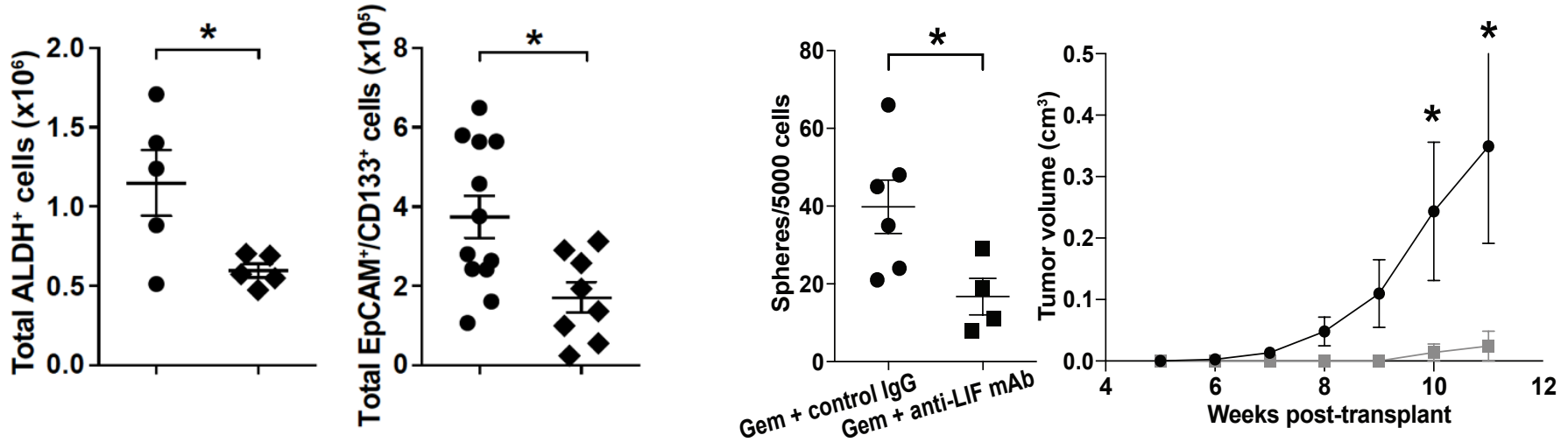
- Leukemia Inhibitory Factor (LIF)
- Interleukin cytokine involved in cell differentiation and cell growth
- JAK/STAT, MAPK, PI3K pathways



LIF blockade by neutralizing antibody enhances the chemotherapy efficacy and prolongs survival of KPC mice



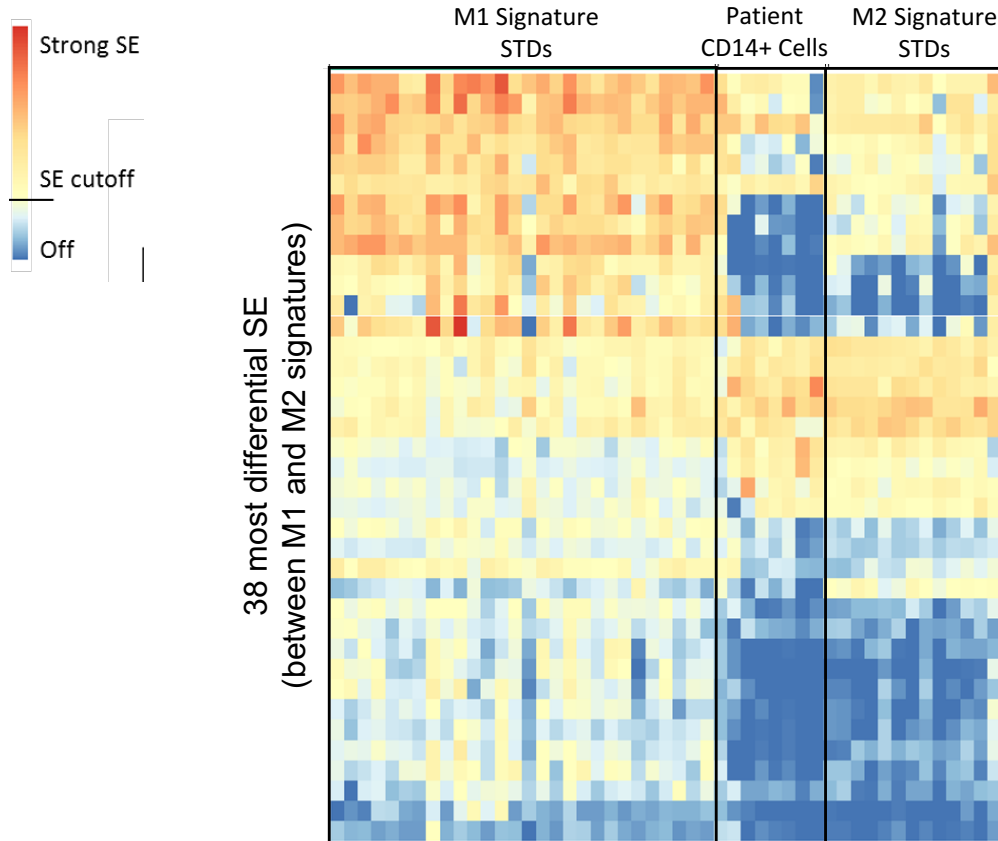
LIF blockade targets the cancer stem cell population and inhibits tumor growth



Analysis confirms the significance of the immune system in PDAC

- Many of the genes with the highest differential SE status in PDAC vs Normal are associated with immune signaling pathways
- Majority of genes with SE status in primary PDAC that are lost in PDX, organoid & cell line models are associated with immune signaling pathways
 - i.e. Th1/2 activation, antigen presentation, IL10 signaling, macrophage activation
 - Consistent with the known lack of immune component in the models (only epithelial cells)
 - Many of these immune-related genes are maintained in the GEMM syngeneic model which represents a validation path for the role of these genes in immune-driven oncogenesis.

SE signatures of M1 and M2 macrophages give insight into the functional state of CD14+ cells from patient samples



Conclusions

- SE analysis can define key genes in the epithelial, stromal, and immune populations that may drive pancreatic cancer oncogenesis
- There is variable maintenance of super-enhancer status of these genes across preclinical models of pancreatic cancer
- Epigenetic understanding of macrophage functional state provides insight into the heterogeneity of myeloid component in the tumor microenvironment

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