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HIGH CXCR4 EXPRESSION IN PANCREATIC DUCTAL ADENOCARCINOMA IS CHARACTERIZED BY AN INFLAMMATORY TUMOR PHENOTYPE WITH POTENTIAL IMPLICATIONS FOR AN IMMUNOTHERAPEUTIC APPROACH

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Background / Aim of the project

- Single agent immune checkpoint inhibitors largely ineffective in pancreatic ductal adenocarcinoma (PDAC) (1).
- C-X-C motif chemokine receptor 4 (CXCR4)-CXCL12 axis modulates the immune tumor microenvironment (TME) in preclinical models (2)
- BL-8040 (motixafortide) is a small synthetic peptide that binds CXCR4

  → blockade of which promotes T cell infiltration; is synergistic with anti-PD1 therapy in mouse models (3)

  → COMBAT trial/KEYNOTE202: BL-8040 + pembrolizumab +/- chemotherapy (4)

  - Cohort 1: 31 chemo-resistant pts treated, with BL8040+pembro: DCR=34.5%
  - Cohort 2: 22 pts treated with BL8040+pembro+chemo: DCR=77% and mDoR=7.8m

Aim of the project: Describing the molecular and immunological landscape of CXCR4 PDAC

(1) Brahmer JR et al, N Engl J Med 2012; (2) Seo YD et al, Clin Cancer Res 2019; (3) Gaur P et al, J Clin Oncol 2018; Bockorny B et al, Nat Med 2020

Patients and Methods

- 3,647 PDACs were analyzed using whole-exome sequencing, whole-transcriptome sequencing and immunohistochemistry (at Caris Life Sciences, Phoenix, AZ, USA).
- Pathway gene enrichment analyses were done using GSEA.
- Immune cell fraction was calculated by QuantiSeq.
- Survival was extracted from insurance claims data and calculated from time of tissue collection to last contact using Kaplan-Meier estimate.
- Cell-type specific CXCR4 expression was analyzed using the Human Protein Atlas.

(1) Subramanian et al., Proc Natl Acad Sci U S A. 2005; (2) Finotello et al., Genome Med. 2019

Patients characteristics & TPM distributions

Quantiles		
100.0%	maximum	792.955
99.5%		279.76264
97.5%		176.5853
90.0%		102.022
75.0%	quartile	59.3156
50.0%	median	32.021
25.0%	quartile	17.0308
10.0%		8.953114
2.5%		4.397366
0.5%		2.0988304
0.0%	minimum	0.451832

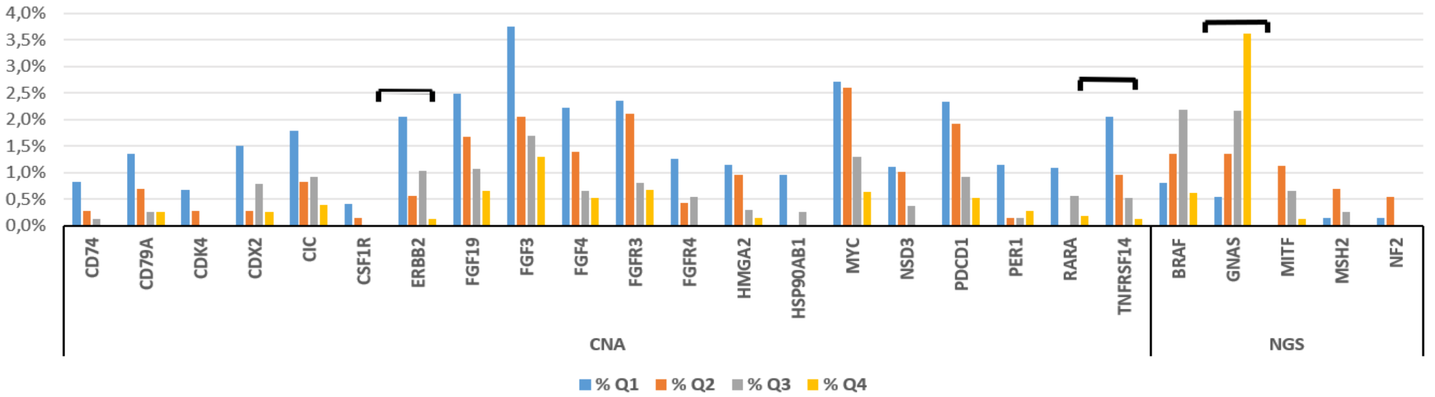
Summary Statistics	
Mean	47.106357
Std Dev	49.461024
Std Err Mean	0.8190213
Upper 95% Mean	48.712143
Lower 95% Mean	45.500572
N	3647

Percentile	Quartile	Value
25th	1	17.05505
50th	2	32.021
75th	3	59.3091
Max	4	792.955

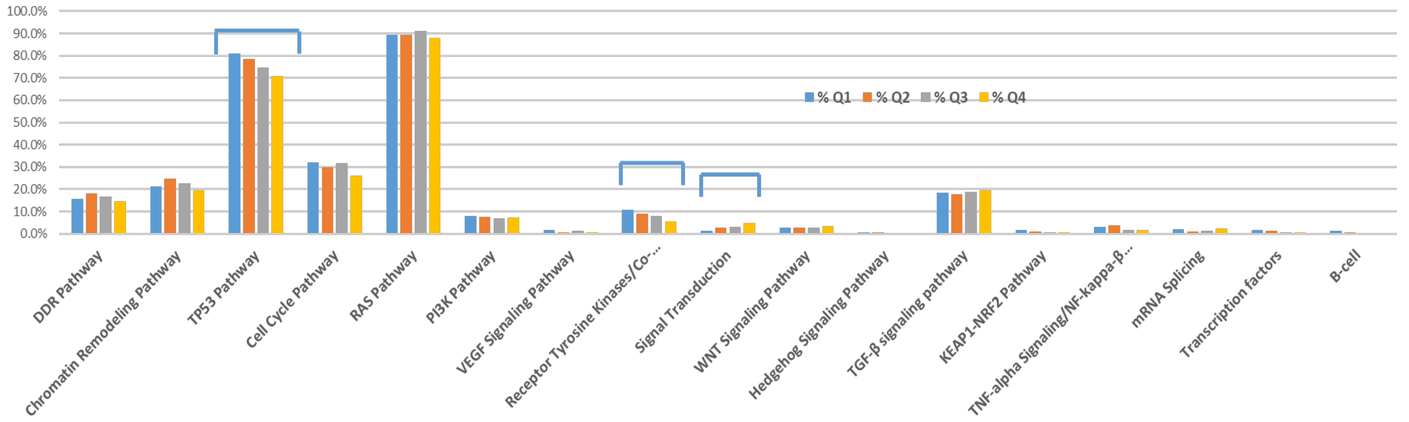
	Quartile 1		Quartile 2		Quartile 3		Quartile 4		
Gender	N	Average Age	N	Average Age	N	Average Age	N	Average Age	Total
Female	416	67.2	408	65.8	425	66.6	438	65.4	1687
Male	496	64.5	504	64.1	486	64.8	474	65.7	1960
Total	912		912		911		912		3647

Genetic analyses reveal a distinct molecular profile

Differences in CXCR4 gene expression were linked to other gene alterations, such as ERBB2 and TNFRSF14. Further, GNAS mutation was much more frequently detected in CXCR4 high tumors compared to CXCR4 low expressors.



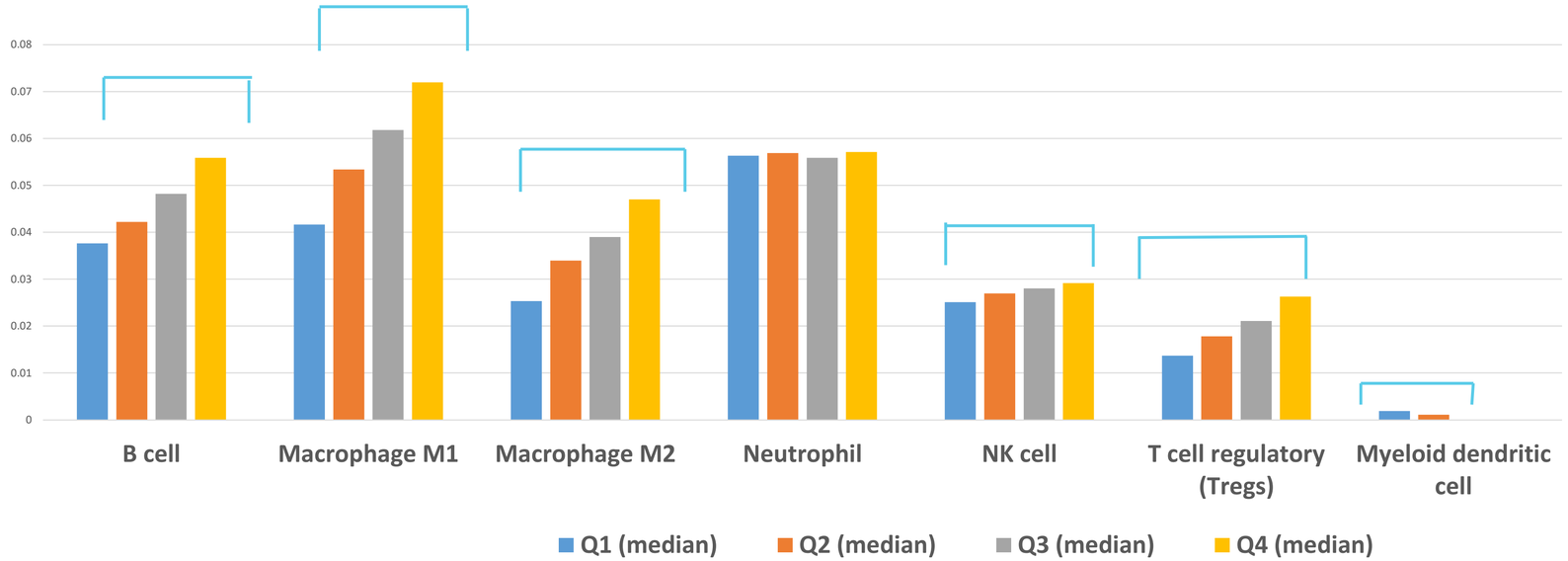
Gene sets of signal transduction pathways (FBXW7, GNA13, GNAQ, GNAS, GNA11) showed a significantly higher frequency of genomic alterations (mutations and copy number amplifications) in CXCR4 high tumors. Inversely, TP53 pathway genes and RTK pathway genes had lower alteration rates in CXCR4 high tumors.



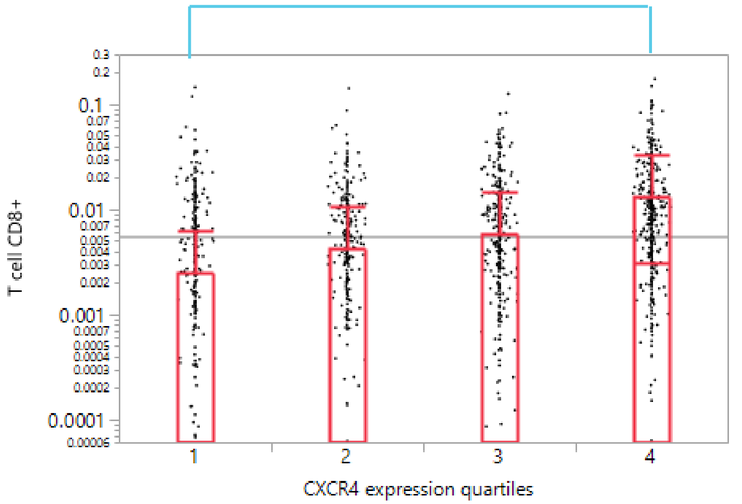
Connective lines: statistically significant after correction for multiple comparison

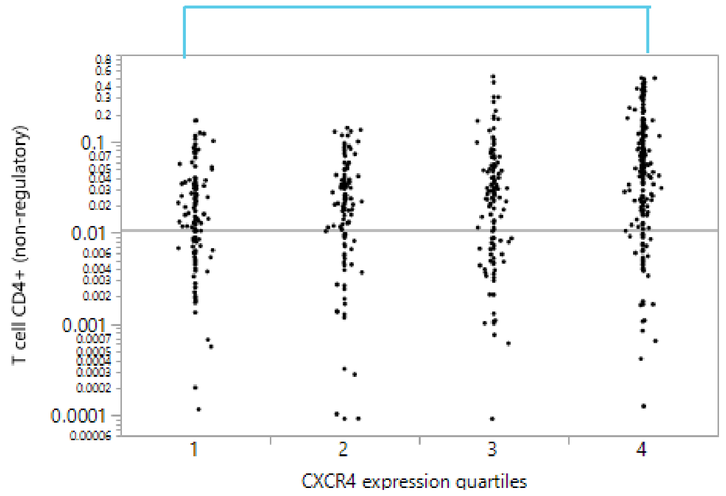
Tumor microenvironment in CXCR4 subpopulations

Using the QuantiSeq method, infiltration of immune cells was calculated and revealed a higher prevalence of B-Cells, M1 and M2 macrophages, NK-cells and Tregs in CXCR4 high compared to CXCR4 low expressing tumors.



*bars indicate significantly different

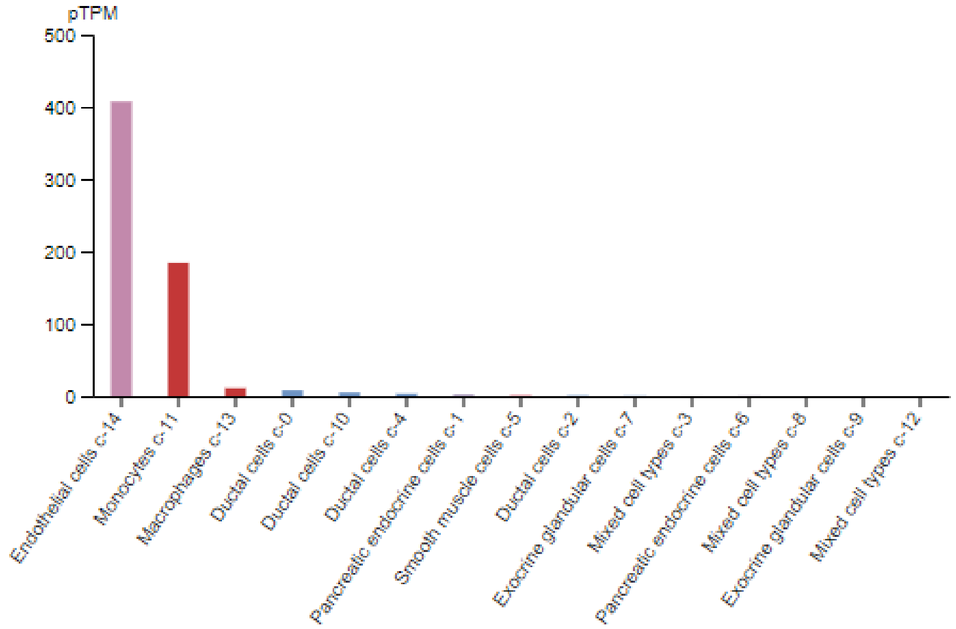


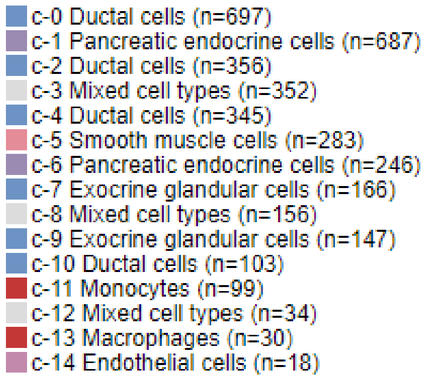


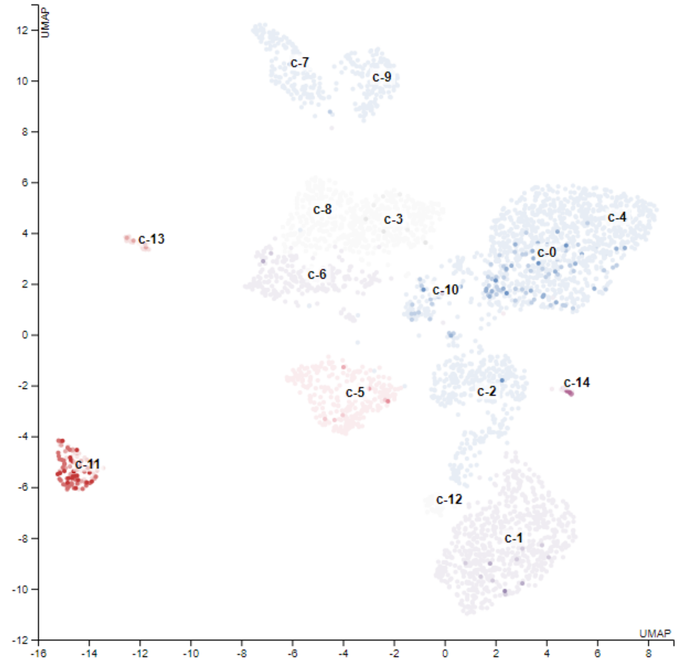
Presented By: **Andreas Seeber, MD PhD**

CXCR4 expression & survival

Human Protein Atlas-based analyses revealed, that CXCR4 is predominantly expressed in endothelial cells and monocytes. Left: relative CXCR4 RNA expression status according to cell types. Right: Scatter plot illustrating cell clusters.







The Human Protein Atlas: www.proteinatlas.org

Conclusion

- **This is the first study deciphering the immunlogical/genetic landscape of CXCR4 in PDAC.**
- **CXCR4 expression is associated with a pro-inflammatory immune cell signature in PDAC.**
- **CXCR4 high expressors might be a potential candidates for immunotherapy.**