Identifying combination therapy targets for neoantigen vaccines in pancreatic ductal adenocarcinoma

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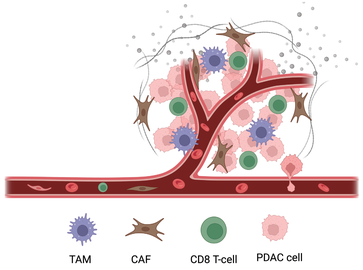
BACKGROUND

- Pancreatic ductal adenocarcinoma (PDAC) has a 5-year survival rate of ~13% and novel therapies are **urgently needed**
- Neoantigen vaccines are personalized immunotherapies that drive **tumor-specific T-cell responses**
- Despite showing clinical promise, many patients treated with neoantigen vaccines show **disease recurrence**
- In order to make neoantigen vaccines clinically successful, we must enhance their therapeutic efficacy by developing **rational combination therapies**
- Our project aims to systematically to neoantigen vaccines **define the mechanisms of response and resistance** to neoantigen vaccines in PDAC by integrating advanced preclinical models, single-cell omics technologies, and clinical trial biopsies



METHODS

Clinical Trials: NCT03122106 and NCT03956056 were Phase I clinical trials testing neoantigen vaccination in patients with resected PDAC

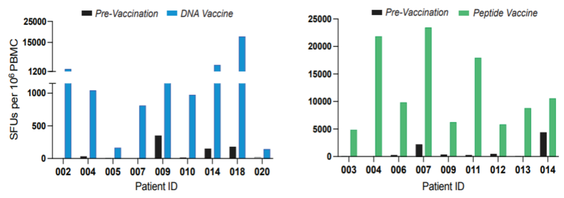
Mouse modeling: C57BL/6 mice implanted with 300,000 KP2-E cells on Day 0 prior to being vaccinated on Days 5, 8, 11 with neoantigen vaccine or polyIC alone (n=10 mice/group)

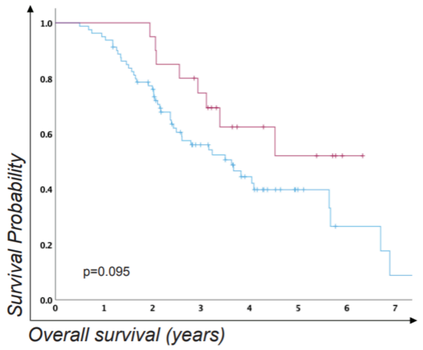
pSMartCODE library generation: A degenerate oligonucleotide was cloned into pBA439 before lentiviral transduction into KP2-E to generate KP2-ESC for combined single-cell lineage tracing and transcriptomics

NGS: PCR of the barcode locus was performed on gDNA extracted from KP2-ESC and sequenced with paired-end Illumina sequencing for ~400M reads

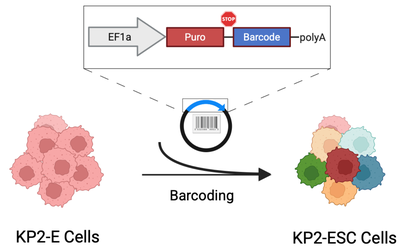
RESULTS

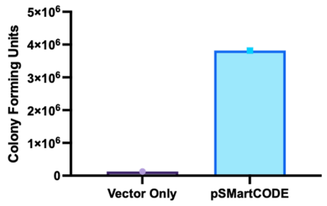
Neoantigen vaccines are immunogenic and may improve OS in PDAC



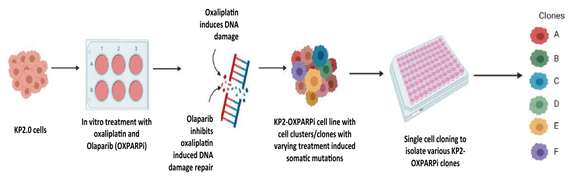


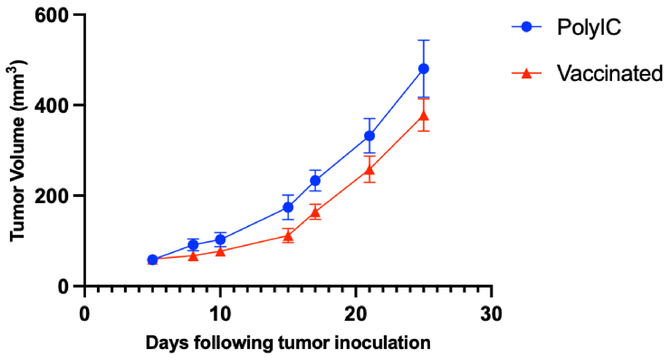
pSMartCODE will enable combined single-cell lineage tracing and transcriptomics



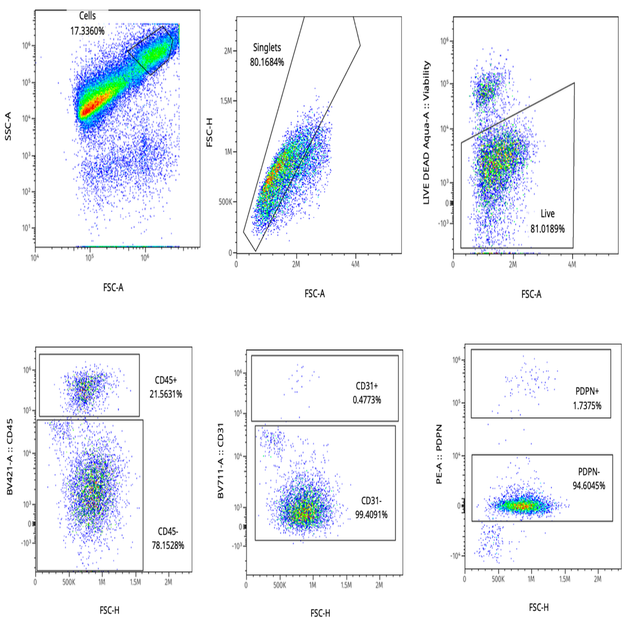


KP2-E mimics response to neoantigen vaccines in patients

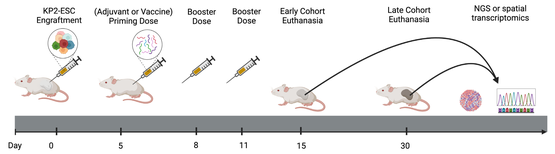


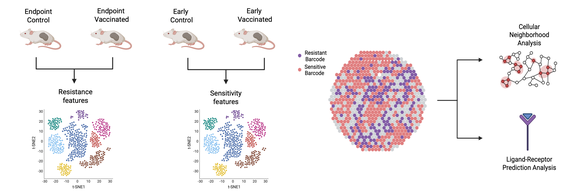


Digestion of KP2-ESC tumors recapitulates the PDAC TME



Identifying tumor-intrinsic and extrinsic regulators of neoantigen vaccine response





CONCLUSIONS

- Neoantigen vaccines are immunogenic, safe, and show clinical promise in PDAC patients
- The KP2-E mimics partial response to neoantigen vaccines seen in PDAC patients
- Illumina paired-end sequencing confirmed successful integration of pSMartCODE into KP2-E with ~400 unique lineages
- scRNAseq and spatial transcriptomics will decode tumor-intrinsic and extrinsic drivers of vaccine response and resistance

REFERENCES

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