TARGETING STROMAL CANCER ASSOCIATED FIBROBALSTS AS AN ADJUVANT TO IMMUNOTHERAPY FOR PANCREATIC CANCER

RESEARCH PROPOSAL

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STATE OF THE ART

- The 5-year overall survival rate of Pancreatic ductal adenocarcinoma (PDAC) patients is 5-10%. Standard treatment is systemic chemotherapy.
- Immunotherapy is a promising treatment for PDAC. However, only ~1% respond to it.
- Immunosuppressive tumor microenvironment (TME) is the most significant barrier.
- Inflammatory cancer associated fibroblasts (iCAFs) are located more distal to the tumor edge and express high levels of IL6 by STAT3 hyperactivation.
- Combined treatment with EGFR and STAT3 inhibitors overcomes resistance and shows a synergistic antitumor effect both *in vitro* and *in vivo*.

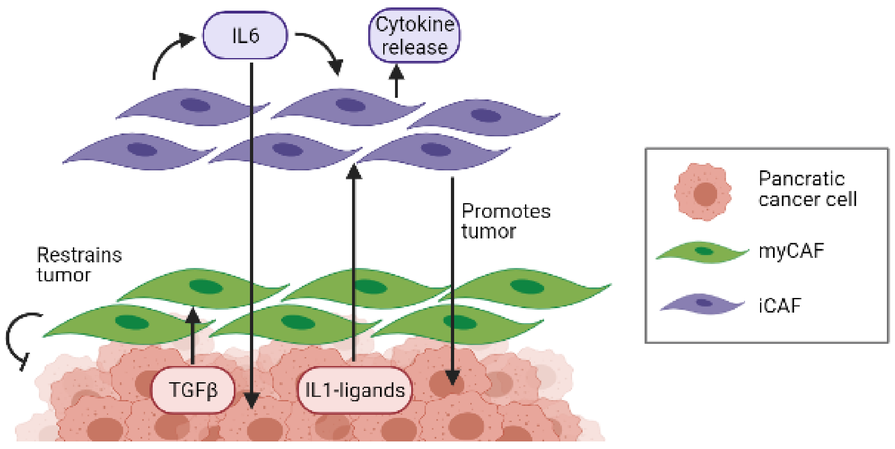


Figure 1. Intratumoral fibroblast heterogeneity in PDAC. Protumor iCAFs and myCAFs are produced when receive IL1-ligands paracrine signaling and TGFβ juxtacrine signaling respectively within the TME.

HYPOTHESIS AND OBJECTIVES

STAT3 and EGFR inhibition in stromal iCAFs of PDAC is a sensitization therapy to immune checkpoint inhibitors by inhibiting expression and secretion of IL6.

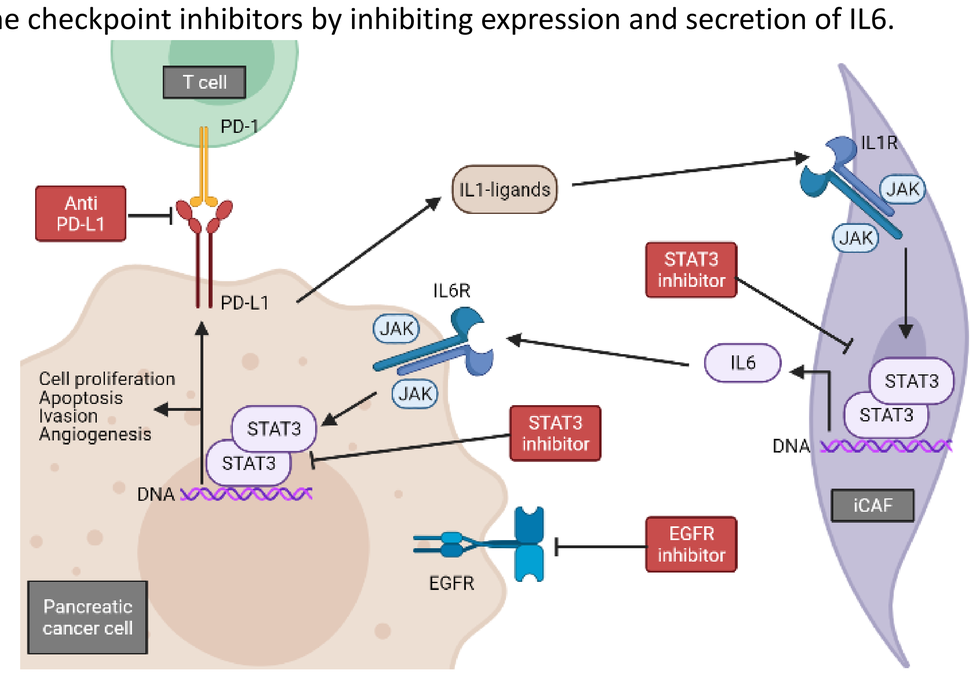
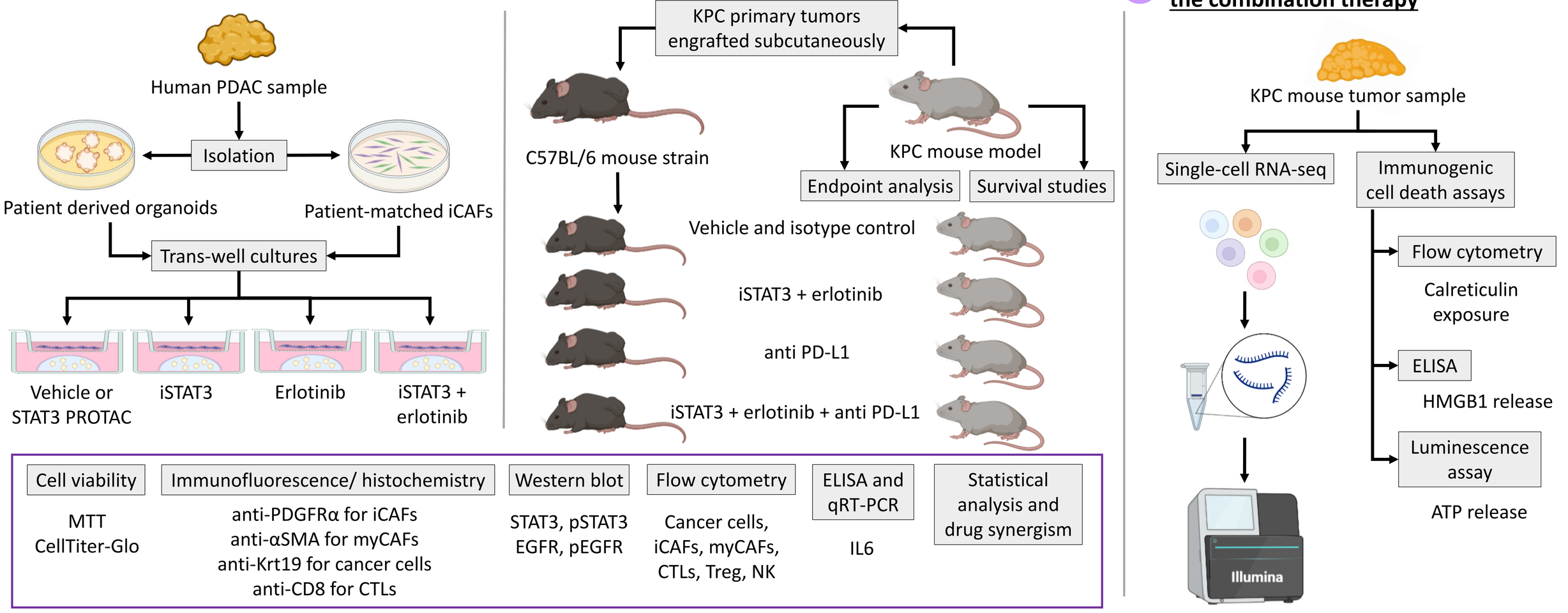


Figure 2. Combinatorial treatment of STAT3 and EGFR inhibitors as a sensitization therapy to anti PD-L1 immunotherapy through a decrease in IL6 signaling, which is secreted by stromal iCAFs.

1. To assess IL6 secretion by iCAFs treated with a STAT3 inhibitor (iSTAT3) and an EGFR inhibitor (erlotinib) *in vitro*.
2. To determine in an *in vivo* model whether there is a higher suppression of tumor growth when iSTAT3 and erlotinib treatment is combined with anti PD-L1, compared to immunotherapy alone.
3. To determine the mechanism that causes sensitization to immunotherapy.

METHODOLOGY AND WORKPLAN



EXPECTED RESULTS

Scientific impact → new approach to improve immunotherapy efficacy for PDAC

- Proof-of-concept for the described STAT3-dependent IL6 secretive phenotype of iCAFs.
- Pharmacological proof *in vivo* for STAT3 and EGFR inhibition as an adjuvant to anti PD-L1 immunotherapy for PDAC.
- Understanding of the molecular mechanism of the sensitization therapy.
- Role of stromal iCAFs in immunosuppressive TME maintenance.

Social repercussion → contribution to societal health

- Development of a new therapeutic strategy for such a poorly immunotherapeutic-responsive cancer.
- Leading to further preclinical and clinical studies to improve pancreatic cancer patient's life length and quality.

DIFFUSION PLAN

- Scientific community
  - Open access publications in high impact journals → Cancer Research, Clinical Cancer Research
  - Presentation in scientific meetings → AACR Annual Meeting, ASEICA International Congress
- Non-specialist public
  - Dissemination in social networks and press releases
  - Participation in science divulgation events → Science week

RELEVANT REFERENCES

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