A novel immuno-oncology preclinical pipeline to study *FGFR2* fusion-driven cholangiocarcinoma

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BACKGROUND

FGFR2 fusions represent the most frequent genetic alteration in intrahepatic cholangiocarcinoma (iCCA). However, FGFR inhibitors have proven to be suboptimal, illustrating the need for more effective treatment options. A major hurdle to these goals is that current preclinical models do not mimic the immunobiology of the human disease. We have developed and characterized an autochthonous and immunocompetent *FGFR2* fusion-driven mouse model of iCCA.

METHODS

- Using the hydrodynamic tail-vein injection method, we generated a mouse model harboring the *FGFR2-PPPHLN1* fusion and activated *YAP1*. Additionally, the resistance mutation V565F was introduced.
- *We* characterized resulting tumors *by* flow cytometry and bulk RNA-sequencing.
- From the murine tumors, we established 2D cell lines and 3D organoids.
- FGFR inhibitors were used for *in vitro* and *in vivo* treatment.

RESULTS

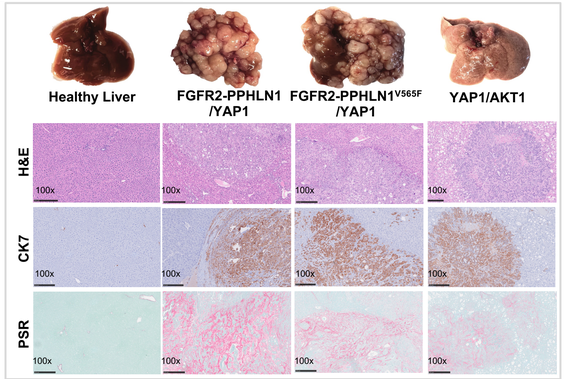

Figure 1: Representative images of healthy liver and *FGFR2*-driven tumors (FGFR2-PPHLN1$^{+/-V565F}$/YAP1) compared to previously characterized YAP1/AKT1 tumors.

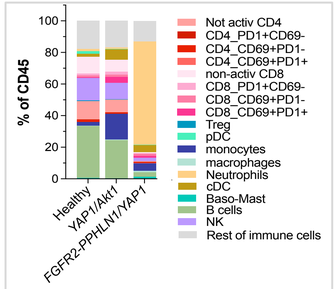

Figure 2: Comparison of lineage proportions between healthy livers, YAP1/AKT1, and FGFR2-PPHLN1/YAP1 (flow cytometry). FGFR2-PPHLN1/YAP1 derived tumors show selective accumulation of tumor-associated neutrophils (TANs).

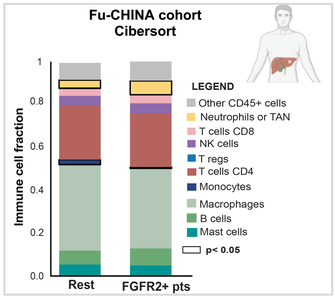

Figure 3: Intra-tumor immune deconstruction of *FGFR2* fusion-driven iCCA and rest of patients via CibersortX in the Fu-CHINA cohort. Human data corresponds to murine model with an increased population of tumor-associated neutrophils (TANs) in FGFR2+ patients.

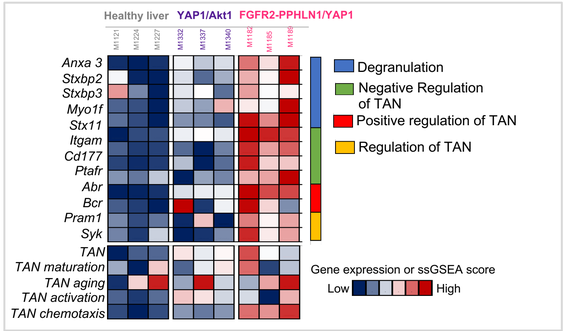

Figure 4: Heatmap of the expression levels of gene association with TAN degranulation and regulation (top). Bottom: heatmap representation of the ssGSEA enrichment score for previously reported TAN signatures.

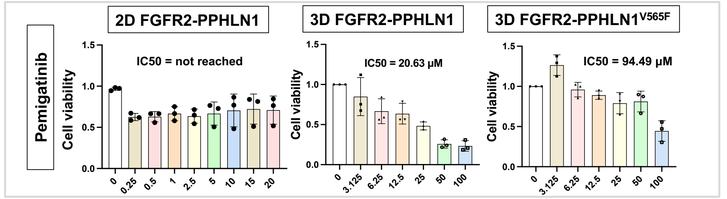

Figure 5: Viability assay of 2D cell lines and 3D organoids derived from murine tumors responding to increasing concentrations of FGFR inhibitor pemigatinib.

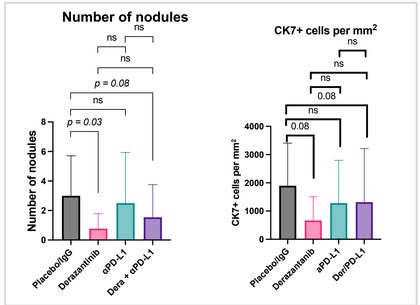

Figure 6: Accumulated tumor nodules and quantified CK7+ cells for HTVI FGFR2-PPHLN1/YAP mice treated with placebo/IgG, FGFR inhibitor derazantinib, immune checkpoint inhibitor anti-PD-L1 monoclonal antibody or the combination. Bar graphs illustrate mean +- STDEV, along with corresponding p values.

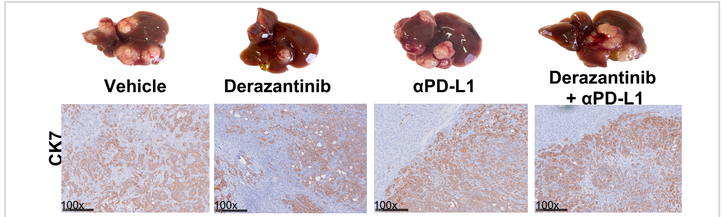

Figure 7: Representative CK-7-stained images of liver of mice treated with vehicle (placebo/IgG), derazantinib, anti-PD-L1 or combination.

CONCLUSION AND FUTURE DIRECTIONS

This study develops a mouse model of *FGFR2*-driven iCCA that recapitulates the immunobiology and therapeutic sensitivities of the human disease. Inter-species and cross-species analyses suggest a critical role of *FGFR2* fusions in shaping a *cold* microenvironment with TAN accumulation in humans and mice. Poor sensitivity to ICI suggests the need for novel therapeutic strategies harnessing the immunosuppressive nature of these tumors.

Novel *FGFR2* fusion mouse model for iCCA

Background: A significant number of iCCA patients have *FGFR2* fusions, however their treatment continues to show suboptimal results. Preclinical models also do not accurately depict the human disease.

Methods: Injection of mutant DNA through mouse tail vein.

Results: Tumors in our mouse model were molecularly and immunologically similar to human iCCA patients carrying *FGFR2* alterations, with an accumulation of tumor associated neutrophils (TANs) and reduced T cell infiltration. Our mouse model reproduced clinical responses to FGFR inhibitors, whereas PD-L1 blockade *in vivo* failed to provide benefit, alone or in combination.

Conclusions: Our team has developed a mouse model of *FGFR2*-driven iCCA that mimics the human disease, providing a useful tool for future preclinical therapeutic options for this pathology.

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