TUMOR-ASSOCIATED SIRPαEXPRESSION EVALUATION IN MELANOMA PDX MODELS VIA IHC FOR POTENTIALICI-PREDICTIVE APPLICATIONS

1Xiaolong Tu*, 1Wenjuan Zhou, 1Likun Zhang, 1Hongjiang Yu, 1Cheng Jiang, 2Henry Li, 1Annie An. 1Crown Bioscience Inc., San Diego, CA, USA; 2Hanx Pharmaceutical Inc., Oceanside, CA, USA

Background Immune checkpoint inhibition (ICI) has become one of the most successful approaches in cancer therapy, as exemplified by the success of PD-1/PD-L1 blockade in clinical trials.1 However, the objective response rate is only ~26% across all cancer types, thus it’s crucial to identify key biomarkers to identify patients that will benefit from ICI.2 SIRPα is an emerging immune regulatory target which has been implicated in immune escape by interacting with the ligand CD47 in tumor cells, so called ‘don’t eat me’ signaling.3 Recently, deep transcriptomic and proteomic analyses across multiple clinical cohorts under ICI treatment found intrinsic SIRPα in enhancing antitumor immunity in melanoma4 Given that SIRPα has been confirmed as highly expressed in treatment responsive patient melanoma cells and the expression levels are positively correlated with survival rate, tumor-specific SIRPα could become a potential predictive biomarker of treatment or be developed as a companion diagnostic (CDx).

We explored a tumor-associated SIRPα IHC assay that can potentially be used for developing clinical testing by using pre-clinical FFPE samples established from patient-derived xenograft models (PDXs), recapitulating the main clinical and pathological features of the tumor of origin.

Methods Hundreds of melanoma PDXs of Western patient origins have been comprehensively annotated, including RNAseq and histopathology data (HuBase™ https://hubase.crownbio.com). IHC staining of melanoma PDX models on FFPE slides was performed in the Bond RX Automated IHC/ISH Staining System (Leica Biosystems) using a commercial SIRPα antibody (Abcam, ab191419), followed by whole slide imaging using the NanoZoomer NDP2.0-HT Digital Slide System (Hamamatsu) and quantified by HALO™ image analysis software (Indica labs). SIRPα IHC scores were also compared to the RNA expression determined by whole transcriptome sequencing.

Results A total of 226 melanoma PDXs were comprehensively evaluated. Pathology analysis indicated that the majority were malignant melanoma with skin or lymph node origin. Human origin tumor RNASeq transcriptome analysis from the melanoma PDX displayed SIRPα gene overexpression (Log2 (FPKM)>3 in 233/248 models) in >90% of models, consistent with TCGA data of melanoma. IHC data also revealed high tumor SIRPα expression, with IHC scores largely correlated with the RNA data.

Conclusions Here we have shown the successful validation of SIRPα IHC staining workflow in a large melanoma PDX cohort that has potential application for the evaluation of tumor-associated SIRPα as a predictive biomarker for ICI response.

REFERENCES

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