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QUANTITATIVE ASSESSMENT OF CAR-T CELL THERAPY TARGETS USING COMPUTATIONAL PATHOLOGY

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Background CAR-T cell-based therapies have improved the treatment of some advanced lymphomas and leukemias. While loss of CAR-T target expression is an established resistance mechanism, a large fraction of target-negative patients responded well to CAR-T cell therapy in early phase clinical trials revealing the urgent need for precise quantification of cell therapy targets as biomarkers. Typically, biomarkers are assessed by standard pathologist scoring of immunohistochemically stained tissue. However, this process is subjective, semi-quantitative and does not assess expression heterogeneity.

Methods To tackle this challenge, we used an automatic image analysis approach for Quantitative Continuous Scoring (QCS) of GPC3 and TGF- β expression in Hepatocellular carcinoma (HCC) patient-derived xenograft (PDX) samples. Our approach is based on supervised Deep Learning (DL) to precisely quantify GPC3 membrane expression and TGF- β membrane and cytoplasmic expression in tumor epithelium on digitized IHC whole slide images (WSI).¹ QCS consists of two supervised DL models which (1) identify epithelium versus non-epithelium regions and (2) segment tumor cells into cell nucleus, cytoplasm, and membrane compartments (figure 1). Based on this segmentation, GPC3 and TGF- β expression is computed as the mean optical density (OD) as a measure of brown staining intensity for each subcellular compartment. All WSIs used in this study have been scored by pathologists for validation.

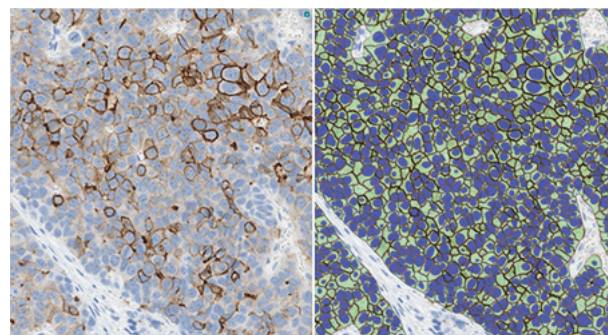
Results We validated our approach on a set of 23 WSIs by correlating the automatically computed mean GPC3 expression on membranes with pathologist's H-scores (Pearson correlation 0.93, 95% CI [0.85, 0.97]), as well as the computed TGF- β percentage positive cells (based on mean OD on membrane and cytoplasm, OD threshold=25) with the pathologist scoring of TGF- β percentage positive cells (Pearson correlation 0.95, 95% CI [0.89, 0.98]). Our automatic scoring provides continuous measurements of expression levels which allows us to reproduce the pathologist scoring, and provides additional resolution and enables analysis of expression heterogeneity.

Conclusions We adjusted QCS to precisely quantify GPC3 and TGF- β expression in HCC PDX samples and validated our approach based on pathologist's scoring and our automatic GPC3 scoring enables detailed and precise studies of CAR-T cell targets.

REFERENCE

1. Sade H, Kapil A, Wortmann P, Spitzmueller A, Triltsch N, Meinecke L, Haneder S, Shumilov A, Lesniak J, Bertani V, Tan TH, Hidalgo-Sastre A, Christ S, Storti A, Alleze R, Medrikova D, Chan J, Lanzmich S, Schick M, Schmidt G, Barrett JC. Quantitative assessment of IHC using computational pathology allows superior patient selection for biomarker-informed patients. *Cancer Res.* 2022;**82**: 468.

Ethics Approval All study protocols, amendments, and documents were approved by the appropriate institutional review boards.



Abstract 339 Figure 1 Example of segmentation result for GPC3 stained HCC sample

Left: raw image, right: overlay of automatic segmentation into cellular compartments nucleus (blue), cytoplasm (green), and membrane (red) after detection of epithelial regions.

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