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Defining transcriptional phenotypes and heterogeneity across biliary tract cancers and matched PDX models

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Background and Objectives: Biliary tract cancers (BTC) are an aggressive family of malignancies characterized by significant heterogeneity and poor patient outcomes. While numerous efforts have characterized BTCs genomically, few studies have focused on the RNA classification of primary BTCs at single-cell resolution. We will present our work to 1) identify conserved malignant cell RNA expression states, 2) define the role of non-malignant cells in supporting tumor growth and, 3) benchmark PDX model systems against their primary patient counterparts.

Methods: We performed probe-based single-cell RNA sequencing (scRNA-seq; 10X Genomics Flex) on a cohort of BTC resection specimens including intra- and extra-hepatic cholangiocarcinoma and gall bladder carcinoma. A subset of these samples had matched PDX models that were also analyzed with scRNA-seq.

Results: We successfully captured a total of 232,631 patient cells across both malignant and non-malignant compartments. Using non-negative matrix factorization (NMF), we identified multiple conserved malignant cell RNA expression states, some of which were unique to specific disease subtypes (e.g., intra- versus extra-hepatic cholangiocarcinoma). Cross-correlation analysis comparing these single-cell programs to literature-curated gene sets demonstrated overlaps with major states described in prior bulk RNA-seq datasets but also revealed several new gene expression programs. We

benchmarked PDX model systems against their corresponding patient tumors and observed variable preservation of clinical states in models.

Conclusions: We are continuing to interrogate this dataset to identify transcriptional programs associated with specific BTC genotypes. In future efforts, we plan to relate our dissociative scRNA-seq findings to spatial transcriptomic measurements across clinical BTC tissue microarrays. We anticipate that these high-resolution maps of BTC tumors and paired patient models will provide a blueprint for understanding how BTC transcriptional states shape malignant cell behaviors and will uncover new approaches to therapeutically target this challenging set of cancers.