Cancer research highlights:
Resolve cancer with single cell and spatial multiomics

Introduction

Whether deciphering the tumor microenvironment, decoding tumor heterogeneity, or investigating tumor-immune interactions, researchers need methodological approaches that offer the scale and resolution required to address their questions of interest. Now, cancer researchers are applying single cell and spatial tools from 10x Genomics to fundamentally alter our understanding of cancer and accelerate novel translational applications in diagnosis, prognosis, therapeutic development, and treatment.

Browse the collection of publications below to see how researchers are using 10x Genomics technology to decode the complexities of cancer. What will you *resolve*?

Featured publication	Experiment snapshot	Research highlights
Single-Cell Analyses Reverse Increased Intratumoral Heterogeneity After the Onset of Therapy Resistance in Small-Cell Lung Cancer CA Stewart et al., *Nat. Cancer.* (2020).	**Research area:** Tumor Contexture **10x Genomics product:** Chromium Single Cell Gene Expression Solution **Sample type:** Human small cell lung cancer (SCLC) circulating tumor cell-derived xenograft models	• Applied single cell RNA-seq (scRNA-seq) to investigate the contribution of heterogeneity to therapeutic resistance in circulating tumor cell-derived murine xenografts. • Results suggest that treatment resistance in SCLC is characterized by coexisting subpopulations of cells with heterogeneous gene expression of therapeutic targets and potential resistance pathways, leading to multiple, concurrent resistance mechanisms.
CRISPR-Engineered T Cells in Patients with Refractory Cancer EA Stadtmauer et al., *Science.* (2020).	**Research area:** Biomarkers and Therapeutic Development **10x Genomics product:** Chromium Single Immune Profiling Solution **Sample type:** Human CRISPR-Cas9 engineered T cells from blood of a patient with evidence of tumor regression	• Leveraged scRNA-seq and T-cell receptor (TCR) sequencing to analyze the transcriptomic phenotype and evolution of engineered T cells 10 days and 4 months after infusion. • PCR amplification of target sequences in 5' scRNA-seq libraries allowed non-invasive monitoring of the gene-edited T cell stability and abundance in circulation. • Stable frequency of gene-edited T cells demonstrated the feasibility of CRISPR-Cas9 gene editing for cancer immunotherapy. After 4 months, 40% of peripheral blood circulating T cells were mutated at any one of the targeted genes.

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Integrating Microarray-Based Spatial Transcriptomics and Single-Cell RNA-seq Reveals Tissue Architecture in Pancreatic Ductal Adenocarcinomas R Moncada et al., *Nat. Biotechnol.* (2020).	**Research area:** Immune and Tumor Microenvironment Contexture **10x Genomics product:** Spatial Transcriptomics (now available as Visium Spatial Gene Expression Solution) **Sample type:** Primary human pancreatic ductal adenocarcinomas	• Integrated scRNA-seq with spatial gene expression profiling to characterize cell types and subpopulations within pancreatic tumors, and annotated spatially restricted enrichments and other distinct coenrichments. • Identified colocalization of cancer cells expressing a stress-response gene module and inflammatory fibroblasts that produce IL-6. This cytokine participates in signaling cascades with factors encoded by the same stress-response genes identified in local cancer cells, suggesting a link between the stress-response cancer cell state and inflammatory cell types in the microenvironment.
Massively Parallel Single-Cell Chromatin Landscapes of Human Immune Cell Development and Intratumoral T Cell Exhaustion A Satpathy et al., *Nat. Biotechnol.* (2019).	**Research area:** Immune and Tumor Microenvironment Contexture **10x Genomics product:** Chromium Single Cell ATAC Solution **Sample type:** Human blood and basal cell carcinoma	• Obtained chromatin profiles of more than 200,000 single cells in human blood and basal cell carcinoma. • Analyzed serial tumor biopsies before and after PD-1 blockade, revealing chromatin regulators of therapy-responsive T-cell subsets. • Identified a shared regulatory program that governs intratumoral CD8^{+} T-cell exhaustion and CD4^{+} T follicular helper cell development.
Clonal Replacement of Tumor-Specific T Cells Following PD-1 Blockade K Yost et al., *Nat. Med.* (2019).	**Research area:** Immune and Tumor Microenvironment Contexture **10x Genomics product:** Chromium Single Cell Immune Profiling Solution **Sample type:** Primary tumors from patients with advanced basal cell carcinoma	• Performed scRNA-seq and TCR sequencing on 79,046 cells from site-matched tumors from patients with basal or squamous cell carcinoma, before and after anti-PD-1 therapy. • Observed preferential clonal replacement in exhausted CD8^{+} T cells after checkpoint blockade, but found that expanded clones did not derive from reinvigorating exhausted tumor-infiltrating T lymphocytes and may have been recruited from outside the tumor microenvironment.

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c-Jun Overexpression in CAR T Cells Induces Exhaustion Resistance R Lynn et al., *Nature*. (2019).	**Research area:** Biomarkers and Therapeutic Development **10x Genomics product:** Chromium Single Cell Gene Expression Solution **Sample type:** Human HA-28z CAR T cells; in vitro and in vivo (NSG mice bearing 143B osteosarcoma tumors)	• Performed multiomic analysis on human HA-28z CAR T cells, discovering that over-expression of the transcription factor c-Jun prevents T-cell exhaustion by decreasing and/or displacing AP-1–IRF complexes from chromatin. • Leveraged scRNA-seq to profile osteosarcoma tumors in mice treated with JUN CAR T cells, observing downregulation of numerous exhaustion-associated genes and a memory-like population of T cells capable of self-renewal.
Differences in Tumor Microenvironment Dictate T Helper Lineage Polarization and Response to Immune Checkpoint Therapy S Jiao et al., *Cell.* (2019).	**Research area:** Immune and Tumor Microenvironment Contexture **10x Genomics product:** Chromium Single Cell Immune Profiling Solution **Sample type:** Mouse T cells from castration-resistant prostate cancer metastatic sites in bone and soft tissue	• Used cytokine profiling and mass cytometry to profile the bone microenvironment in a murine model of metastatic pancreatic cancer, observing that high levels of TGF-β restrain the Th1 lineage and hinder immune checkpoint therapy. • Performed scRNA-seq and TCR sequencing on FACS-sorted intratumoral T cells to characterize the clonal response to combination therapy with TGF-β blockade, finding dramatic clonal enrichment of intra-tumoral CD8$^+$ T cells compared to TGF-β blockade or ICT alone.
Macrophage-Tumor Cell Interaction Promotes ATRT Progression and Chemoresistance V Melcher et al., *Acta Neuropathol.* (2019).	**Research area:** Tumor Contexture **10x Genomics product:** Chromium Single Cell Gene Expression Solution **Sample type:** Atypical teratoid/rhabdoid tumors (ATRT) from a genetically engineered mouse model	• Characterized the immune cell infiltrate of human and mouse ATRT samples via immunofluorescence staining and scRNA-seq, identifying a prominent population of CD68$^+$ macrophages. • Performed scRNA-seq on a xenograft mouse model of ATRT, observing genetic exchange between CD68$^+$ macrophages from the mouse host and grafted human tumor cells that led to a gene expression signature associated with chemo-resistance, tumor recurrence, and metastasis.
Spatial Maps of Prostate Cancer Transcriptomes Reveal an Unexplored Landscape of Heterogeneity E Berglund et al., *Nat. Commun.* (2018).	**Research area:** Tumor Contexture **10x Genomics product:** Spatial Transcriptomics (now available as Visium Spatial Gene Expression Solution) **Sample type:** Snap-frozen whole human prostate sections	• Investigated tissue-wide gene expression heterogeneity throughout a multifocal prostate cancer using spatial transcriptomics technology. • Identified region-specific gene markers for normal, cancerous, and prostatic intraepithelial neoplasia (PIN) tissue that enabled deconvolution of heterogeneity within histologically annotated cancer areas, and pointed to Wnt signaling as a driver in the initiation and progression of PIN.

Additional Publications

Biomarkers and Therapeutic Development

1. B Fairfax et al., Peripheral CD8+ T Cell Characteristics Associated with Durable Responses to Immune Checkpoint Blockade in Patients with Metastatic Melanoma. *Nat. Med.* 26, 2. (2020). [Single Cell Immune Profiling]

2. B Maayan et al., A Population of Stress-Like Cancer Cells in Melanoma Promotes Tumorigenesis and Confers Drug Resistance. *bioRxiv.* 2020. [Spatial Gene Expression Profiling]

3. R Zemek et al., Sensitization to Immune Checkpoint Blockade Through Activation of a STAT1/NK Axis in the Tumor Microenvironment. *Sci. Trans. Med.* 11, 501. (2019). [Single Cell Gene Expression]

Immune and Tumor Microenvironment Contexture

4. MJ Halaby et al., GCN2 Drives Macrophage and MDSC Function and Immunosuppression in the Tumor Microenvironment. *Sci. Immunol.* 4, 42. (2019). [Single Cell Gene Expression]

5. N Baryawno et al., A Cellular Taxonomy of the Bone Marrow Stroma in Homeostasis and Leukemia. *Cell.* 177, 7. (2019). [Single Cell Gene Expression]

Tumor Contexture

6. K Ganesh et al., L1CAM Defines the Regenerative Origin of Metastasis-Initiating Cells in Colorectal Cancer. *Nat. Cancer.* 1, 1. (2020). [Single Cell Gene Expression]

7. J Granja et al., Single-Cell Multiomic Analysis Identifies Regulatory Programs in Mixed-Phenotype Acute Leukemia. *Nat. Biotechnol.* 37, 12. (2019). [Single Cell Gene Expression, Single Cell ATAC]

8. C Neftel et al., An Integrative Model of Cellular States, Plasticity, and Genetics for Glioblastoma. *Cell.* 178, 4. (2019). [Single Cell Gene Expression]

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