AACR – Debbie's Dream Foundation Scholar-in-Training Award

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Abstract 7475 will be presented in a **Poster Session** titled **Identification of New Cancer Vulnerabilities Through Convergence Science** on **Wednesday, April 30, 2025, 9:00 a.m.–12:00 p.m.**

A comprehensive single-cell atlas of gastric cancer reveals malignant cell state dynamics and plasticity in tumor progression and metastasis

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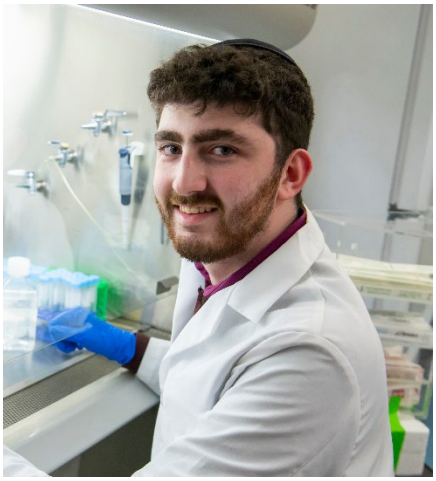
Background: Gastric cancer exhibits diverse malignant cell states that contribute to intratumor heterogeneity (ITH), a fundamental factor that drive tumor progression, metastasis, and treatment resistance. While previous single-cell RNA sequencing (scRNA-seq) studies have provided novel insights into ITH in gastric cancer, they are often constrained by small sample sizes and limited transcriptional coverage. Methods: In this study, we curated, annotated, and integrated scRNA-seq datasets from 21 studies, comprising 626 samples from 316 individuals, including healthy donors and patients with precancerous lesions and gastric cancer. Within the epithelial compartment, malignant and non-malignant cells were distinguished using three complementary computational methods. To refine malignant cell subclustering, we developed a novel approach that incorporates patient-specific copy number variations, minimizing the impact of inter-patient heterogeneity on clustering analysis. Results: Following rigorous quality control and data integration, unsupervised clustering analysis classified 2,088,266 high-quality cells into six major cell types or compartments: B cells, T cells, innate lymphoid cells, myeloid cells, stromal cells, and epithelial cells. Within the epithelial cell compartment, we identified 12 distinct malignant cell states characterized by unique expression profiles and phenotypic characteristics, such as cell proliferation capacity and lineage-specific plasticity. These cancer cell states exhibited substantial variation in the activity of hallmark cancer signaling pathways, with their presence and composition closely linked to tumor aggressiveness and clinical outcomes. Proliferative cancer cells and translationally active cancer cells predominated in intermediate tumor stages, dormant cells were prevalent in advanced stages, and epithelial-mesenchymal transition (EMT) states were enriched in metastatic tumors. Additionally, we

identified a malignant cell population with high expression of intestinal lineage markers in patients with signet ring cell carcinoma, and these findings were validated using spatial transcriptomic. Conclusions: This study presents a comprehensive single-cell transcriptomic atlas of gastric cancer epithelial cells, providing valuable insights into transcriptional ITH. Our findings define distinct malignant cell states, elucidate their dynamics, and highlight their clinical significance, establishing a framework for understanding how these states contribute to disease progression and metastasis.

Personal Statement: I am Enyu Dai, a postdoctoral fellow at The University of Texas MD Anderson Cancer Center. My research focuses on single-cell and spatial transcriptomic analysis in gastric cancer. Specifically, I investigate the cellular and molecular dynamics driving gastric cancer progression and metastasis, emphasizing how tumor heterogeneity and microenvironment interactions influence cancer development and therapeutic responses. Through advanced single-cell RNA sequencing and spatial transcriptomics, I aim to identify novel biomarkers and actionable targets to improve patient outcomes. Attending AACR 2025 offers a unique opportunity to engage with leading scientists in cancer research. This conference will allow me to share findings, gain expert feedback, and explore the latest advancements in single-cell technologies and cancer biology. The sessions and workshops align with my research, providing insights into translating basic discoveries into clinical applications. My long-term goal is to become an independent investigator leading impactful research bridging sequencing technologies and translational oncology. I aim to contribute to precision medicine approaches that improve cancer diagnostics and therapies. By attending AACR 2025, I hope to build collaborations, broaden my perspective, and advance toward this vision.

Reflection on Annual Meeting:
"I am deeply honored to receive the Scholar-in-Training Award. This recognition is an encouragement and affirmation of my work, providing invaluable support for my research and professional development. Attending the AACR Annual Meeting offered me tremendous insights and inspiration, enabling me to engage deeply with groundbreaking research and to connect with leading experts in the field. It also provided opportunities to foster new collaborations and enhance my scientific perspective."



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Abstract 2374 will be presented in a **Poster Session** titled **Biomarkers and Molecular Targets for Prevention** on **Monday, April 28, 2025, 9:00 a.m.–12:00 p.m.**

Identifying ZNF469 as a biomarker in cancer of the colon and stomach

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Introduction: Zinc Finger Protein 469 (ZNF469) is a protein involved in the formation of the extracellular matrix. While the non-coding RNA linc-ZNF469-3 has previously been identified to be overexpressed in certain cancers and promote metastasis, there have yet to be any studies attempting to establish a link between the protein ZNF469 and cancer formation or growth. In this study, we attempt to determine whether ZNF469 may act as a biomarker in colon and stomach cancers.
Methods: A systems biology approach was used to explore the impact of varying ZNF469 expression and mutations. Patient data was retrieved from the TCGA database. TIMER2.0 software was utilized for statistical analysis along with visualization.
Results: The expression of ZNF469 was found to increase in cancer compared to non-tumor control in the colon ($p = 2.4e-11$) and stomach ($p = 2.2e-17$). Furthermore, Kaplan-Meier plots indicate that higher expression of ZNF469 resulted in worse probability of survival in colon (HR = 1.70, CI = 1.35-2.15) and stomach (HR =1.68, CI = 1.34-2.10). We also found an association between immune infiltration and ZNF469. In colon cancer, ZNF469 expression moderately correlated with the immune infiltration of macrophages (partial correlation = 0.50, $p = 6.2e-27$), neutrophils (partial correlation = 0.57, $p = 3.9e-35$), and dendritic cells (partial correlation = 0.56, $p = 3.9e-34$). In stomach cancer, these correlations were present but weaker in macrophages (partial correlation = 0.23, $p = 6.5e-6$), neutrophils (partial correlation = 0.25, $p = 8.5e-7$), and dendritic cells (partial correlation = 0.29, $p = 1.6e-8$). In the colon, arm level gain mutations of ZNF469 were found to correlate with altered immune infiltration in CD8+ T cells ($p < 0.001$), neutrophils ($p < 0.001$), and dendritic cells ($p < 0.01$) with a few additional mutations found to be significant as well. Conversely, in the stomach, arm level deletions were found to correlate with altered immune infiltration in B cells ($p < 0.01$), CD8+ T cells ($p < 0.001$), neutrophils ($p < 0.05$), and dendritic cells ($p < 0.001$) with additional mutations found to be significant.
Conclusion: The increased expression of ZNF469 in stomach and colon cancer suggests that it may facilitate in oncogenesis and may be induced by rapid tumor growth. The expression correlating with worse outcomes further supports ZNF469 as a pro-oncogenic protein in these cancers. High ZNF469 levels were also correlated with higher immune infiltration, especially in colon cancer, and arm level gain or arm level deletion mutations were associated with altered immune

infiltration. Overall, the findings suggest that ZNF469 can serve as a biomarker in colon and stomach cancers. ZNF469 is upregulated in these cancers, and the increase of ZNF469 correlates with both worse outcomes as well as increased immune infiltration. This data suggests that further research into ZNF469 may be beneficial in stomach and colon cancers.

Personal Statement: I am a medical and public health student passionate about all forms of cancer research. My passion stems from the profound complexity of cancer and its impact on human lives. Throughout my academics and research, I’ve sought to contribute to both the molecular and cellular understanding of cancer and the improvement of care for patients and their families. I've explored treatments for colorectal cancer with KRAS mutations, focusing on autophagy regulation and its potential to enhance therapies. This work led to co-authoring several publications and presenting at the AACR while an undergraduate. The experience showed me the value of collaboration in advancing cancer care and the potential research has to save lives of those who need it. More recently, my focus broadened to public health and psychosocial aspects of cancer. I investigate barriers to cervical cancer screening, aiming to improve accessibility for underserved populations. In psychosocial oncology, I study the psychological challenges faced by cancer caregivers, working to inform better support systems. I currently have 2 papers undergoing peer-review on these topics. My experiences have shaped my goal of integrating research and medicine to make a meaningful impact on others. By combining a deep understanding of cancer biology with a commitment to patient-centered care, I aim to develop treatments and interventions that are both effective and compassionate.


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