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Decoding Resistance to Trastuzumab Deruxtecan in Metastatic Breast Cancer: S100 Signaling and Immune-Niche Barriers

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Background

- Trastuzumab deruxtecan (T-DXd) serves as 2nd-line standard of care for HER2+/low metastatic solid cancers.
- ~50-60% response rate,[1] with *few treatment alternatives for non-responder patients.*
- T-DXd response does not solely depend on HER2 score.[1] Discovery of response biomarkers is key for treatment planning.

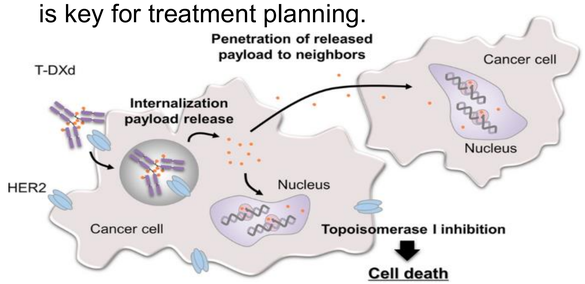


Figure 1: T-DXd mechanism of action. "Discovery and development of trastuzumab deruxtecan and safety management for patients with HER2-positive gastric cancer," Shitara et al. (2021).

Purpose and Hypothesis

Purpose: Investigate markers of resistance to T-DXd in metastatic breast cancer (mBC).

Hypothesis: Spatial multiomics can uncover novel T-DXd resistance pathways.

Methods

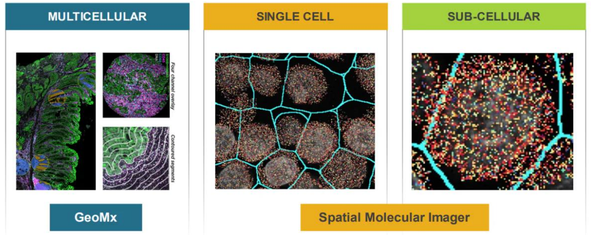
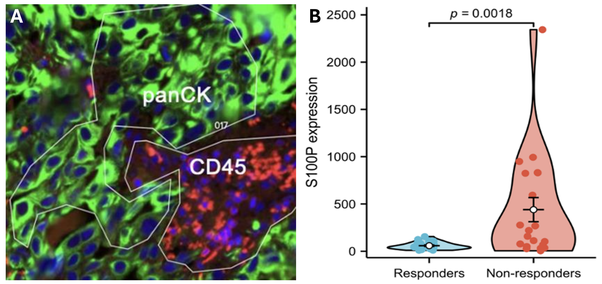


Figure 2: Overview of Bruker GeoMX Digital Spatial Profiling and CosMX Spatial Molecular Imager platforms.

S100P in Bone and Brain Metastases



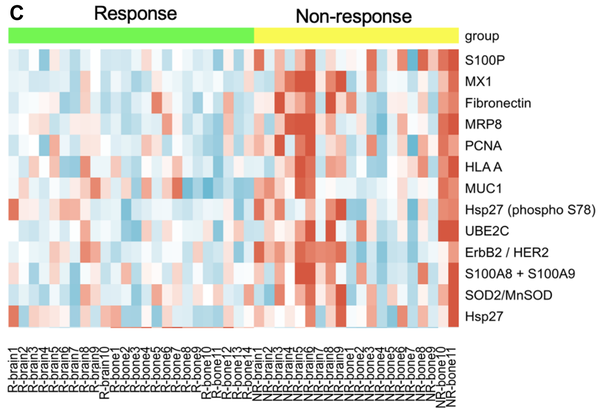


Figure 3: GeoMX spatial proteomics. (A) Region of interest (ROI) selection with segmentation for cancer (PanCK) and immune (CD45) cells. (B) S100P is upregulated in T-DXd non-responder PanCK ROIs. (C) Per-ROI proteomics top upregulated proteins in non-responders.

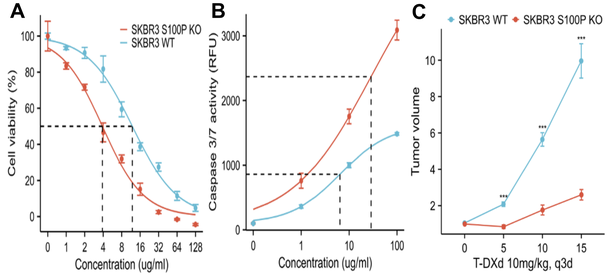


Figure 4: S100P KO improves T-DXd sensitivity. (A) Cell viability in WT vs S100P KO SKBR3 (HER2 3+) cells. (B) Caspase activity in WT vs S100P KO SKBR3 cells. (C) Volume of tumors formed in mice by injected WT vs S100P KO SKBR3 cells.

S100A in Brain Metastases

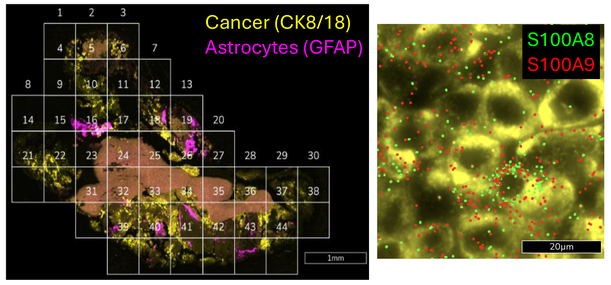


Figure 5: CosMX platform for spatial transcriptomics analysis of patient samples. (A) Fields of view. (B) Transcript locations for S100A8 (green) and A9 (red).

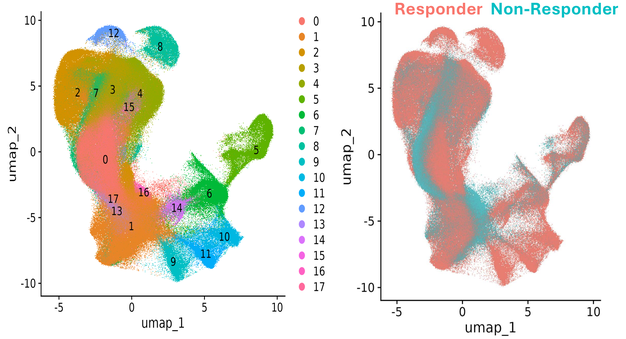


Figure 6: UMAP representations of single cell profiling for responder vs. non-responder brain metastases.

Seurat Cluster	Cell Type	Cluster Proportion	Top Marker Genes
0	Luminal A Cancer	0.14	**S100A1**, GABARAP, NR4A1
3	Luminal A Cancer	0.10	**S100A9**, **S100A8**, BST2
14	Monocyte (S100A9-high)	0.29	**S100A8**, **S100A9**, SRGN
14	Monocyte (FCGR3A+)	0.18	**S100A8**, **S100A9**, NAMPT
16	Luminal A Cancer	0.14	**S100A1**, GABARAP, ARF5

Table 1: Cell types and S100A genes overrepresented in non-responder brain metastases.

Discussion

- S100P most highly upregulated among non-responder bone and brain mets; S100A8/9 also ↑ in brain mets.
- S100P KO improves HER2 3+ response to T-DXd *in vitro* and *in vivo*.
- S100A1, A8, and A9 ↑ non-responder brain mets among luminal A cells.
- S100 proteins have been previously implicated in poor breast cancer prognosis by driving tumor proliferation and invasiveness.[2]
- More S100A8/A9+ monocytes in non-responder brain mets—immune-microenvironment remodeling to support resistance.

Future Actions

- Validate S100P and S100A8/A9 as response biomarkers in a larger patient cohort.
- Investigate if S100 proteins directly impair T-DXd activity or activate broader survival pathways.
- Evaluate S100/RAGE pathway inhibitors as T-DXd sensitizers for clinical translation

Acknowledgments

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References

1. Mosele F, Deluche E, Lusque A, et al. Trastuzumab deruxtecan in metastatic breast cancer with variable HER2 expression: the phase 2 DAISY trial. *Nat Med.* 2023;29(8):2110-2120. doi:10.1038/s41591-023-02478-2
2. Cancemi P, Buttacavoli M, Di Cara G, et al. A multiomics analysis of S100 protein family in breast cancer. *Oncotarget.* 2018;9(49):29064-29081. Published 2018 Jun 26. doi:10.18632/oncotarget.25561