SLC39A7 (ZIP7) as a Tumor-Specific Antigen Enabling Precision Immunotherapy in Breast and Prostate Cancers

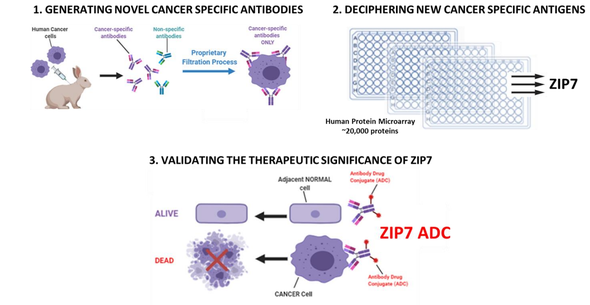
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Background

- Antibody-based therapies—including ADCs—require tumor-specific surface antigens to achieve targeted cytotoxicity with minimal off-target effects. However, widely used targets like PSMA are also expressed in normal tissues (e.g., salivary glands, kidneys), leading to significant toxicities. These limitations underscore the need for safer, more selective antigen targets.
- ZIP7 (SLC39A7), a zinc transporter normally restricted to the ER/Golgi in healthy cells, was found to be aberrantly expressed on the surface of malignant cells, making it accessible for antibody-based targeting. It was identified using the Oncotope™ Platform—a proprietary system developed by Cancer Antibodies Inc. (Mor *et al.*, 2022; Manavalan *et al.*, AACR 2024).
- Our data show that ZIP7 is a tumor-specific, surface-accessible antigen selectively expressed in breast and prostate cancers, including castration-resistant subtypes, with no detectable expression in key normal tissues (kidney, brain, spleen). ZIP7-targeted antibody–drug conjugates induced strong and selective cytotoxicity, supporting its potential as a therapeutic target for precision immunotherapy.

Graphical Abstract



Oncotope™-Driven Discovery and Targeted Killing of ZIP7-Expressing Cancer Cells via Antibody–Drug Conjugates"

Methods and Materials

Tissue Samples & Histology: FFPE sections (4 µm) from prostate cancer and TNBC patients were analyzed alongside matched benign tissues. TNBC status was pathologist-confirmed (ER–/PR–/HER2–). H&E staining and digital pathology guided tumor vs. benign annotation.
Immunofluorescence & Imaging: Sections were stained with anti-ZIP7 and anti-TROP2 antibodies, visualized with Alexa Fluor dyes, and imaged using confocal microscopy. ZIP7 localization was further assessed in live, non-permeabilized LNCaP cells.
Surface & Spatial Validation: ZIP7 surface expression was confirmed by biotinylation and co-localization with PSMA in LNCaP cells. CyTOF was used to map ZIP7 within prostate tumor microenvironments alongside immune infiltrates.
In Vivo & Normal Tissue Analysis: ZIP7 was evaluated by IHC in xenografted PC3/LNCaP tumors and in normal mouse organs (kidney, spleen, brain). Tumors stained positive; normal tissues were ZIP7-negative.
Cytotoxicity Assay: LNCaP cells were treated with a ZIP7-targeted ADC-like construct. Real-time impedance monitoring (RTCA) showed selective tumor cell killing.

Results

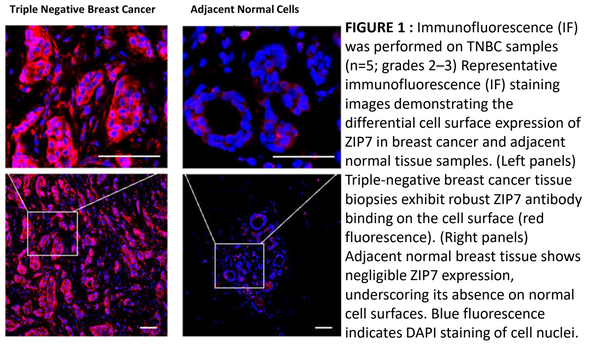


FIGURE 1 : Immunofluorescence (IF) was performed on TNBC samples (n=5; grades 2–3) Representative immunofluorescence (IF) staining images demonstrating the differential cell surface expression of ZIP7 in breast cancer and adjacent normal tissue samples. (Left panels) Triple-negative breast cancer tissue biopsies exhibit robust ZIP7 antibody binding on the cell surface (red fluorescence). (Right panels) Adjacent normal breast tissue shows negligible ZIP7 expression, underscoring its absence on normal cell surfaces. Blue fluorescence indicates DAPI staining of cell nuclei.

Results

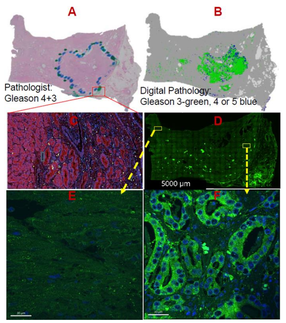


FIGURE 2: Immunofluorescence (IF) was performed prostate cancer samples (n=6; Gleason 3+4, 4+3, including CRPC): Representative prostate cancer biopsy cores from a patient with Gleason score 4+3 showing IF staining with anti-ZIP7 polyclonal antibodies confirmed ZIP7 expression localized to the surface of malignant glands but not detected in adjacent normal prostate tissue

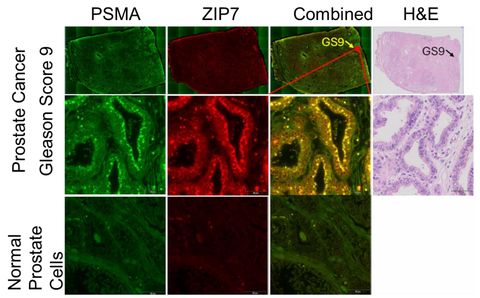


FIGURE 3: Immunofluorescence staining shows that ZIP7 (red) is co-expressed with PSMA (green, Prostate-Specific Membrane Antigen) on malignant prostate glands, correlating with higher Gleason scores, while both markers are absent in adjacent normal prostate tissue, underscoring ZIP7's potential as a tumor-selective diagnostic marker comparable to PSMA

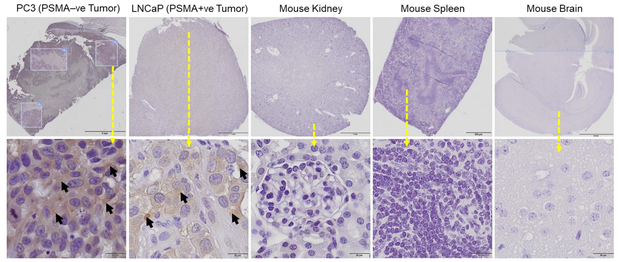


FIGURE 4 : ZIP7 expression is tumor-specific in prostate cancer xenografts. Representative immunohistochemistry (IHC)–DAB staining using anti-ZIP7 polyclonal antibodies on formalin-fixed, paraffin-embedded tissue sections from PSMA-negative PC3 and PSMA-positive LNCaP human prostate tumor xenografts, and normal mouse tissues (kidney, spleen, and brain). Strong membranous and cytoplasmic ZIP7 staining (brown, black arrows) was observed in both PC3 and LNCaP tumor xenografts, confirming ZIP7 expression in prostate tumor cells regardless of PSMA status. In contrast, no detectable ZIP7 signal was found in normal mouse kidney, spleen, or brain tissues, indicating tumor-specific expression of ZIP7. Nuclei were counterstained with hematoxylin (blue). Scale bars: 2 mm (upper panels), 20 µm (lower panels).

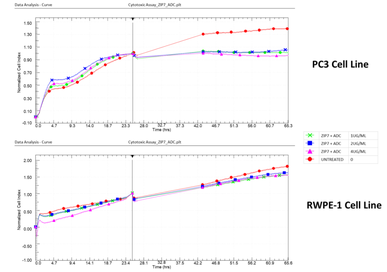


FIGURE 5: Real-time cell analysis (RTCA) was used to monitor viability of PC3 cancer cells and RWPE1 normal prostate cells over 65 hours. After 24 hours of stabilization, cells were treated with anti-ZIP7 antibody followed by a cytotoxic anti-rabbit IgG secondary (ADC-like, 4 µg/mL). ZIP7-targeted treatment caused a rapid decline in Cell Index beginning ~18–20 hours post-treatment, indicating loss of adhesion and viability. Control cells showed continuous growth. Data represent mean ± SEM.

Conclusions

Our findings identify ZIP7 as a tumor-specific, surface-accessible antigen in breast and prostate cancers, including castration-resistant and PSMA-negative subtypes, with no expression in key normal tissues. ZIP7-targeted antibody–drug conjugates induced potent, selective cytotoxicity, highlighting ZIP7's therapeutic potential. These results position ZIP7 as a next-generation immunotherapy target, with future work focused on humanized ADC and CAR-T development and in vivo validation to advance ZIP7-directed strategies for precision oncology.

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References

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2. Manavalan, J. S., Mor, D., Davis, J., Saini, S., Pal, I., Feith, D., Hikichi, Y., & Davis, E. (2024, April). Discovery of a novel cancer-specific antigen for therapeutic targeting using the Oncotope platform. AACR Annual Meeting 2024, Session PO.IM01.08, Abstract 4109/20.

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