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Mechanisms of resistance of STP938 in ovarian cancer

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OBJECTIVES/GOALS: Ovarian cancer is the most lethal gynecologic cancer with emergence of recurrent and resistant disease being frequent. We sought to identify novel ways to effectively kill chemotherapy-resistant forms of ovarian cancer and to prevent recurrence following curative intent with surgical and adjuvant regimens. METHODS/STUDY POPULATION: Our group identified CTPS1 as a novel dependency in triple negative breast cancer (TNBC) and ovarian cancer. We found CTPS1 was highly expressed in breast and ovarian tumor tissues and therapy-resistant models. We demonstrated siRNA knockdown of CTPS1 reduced proliferation in sensitive and resistant cell lines. In collaboration with Step Pharma, who developed the first CTPS1 inhibitor (STP938), we performed genome-wide CRISPR KO screens on STP938-sensitive and -resistant cells. Top synthetic lethal hits identified included TSC1, TSC2, and PPP2R2A. Synergy assays were conducted with STP938 in combination with mTOR inhibitors (Everolimus, Sirolimus, and Temsirolimus) and the PPP2R2A inhibitor LB-100 to evaluate the therapeutic benefit of combination therapies. RESULTS/ANTICIPATED RESULTS: We identified CTPS1 as a novel vulnerability in many ovarian cancer cell line models, including models of chemotherapy and/or PARP inhibitor resistance. The first-in-class CTPS1 inhibitor (STP938) was shown to be a highly effective anticancer agent in sensitive and resistant forms of ovarian cancer, both *in vitro* and *in vivo*. Genome-wide CRISPR KO screens identified central components of the mTOR pathway (TSC1 and TSC2), as well as PPP2R2A, as synthetic lethal targets in the setting of STP938 exposure. We anticipate that combinatorial treatment of mTOR inhibitors and PP2R2A inhibitors with STP938 will further enhance efficacy and reduce the risk of recurrence when used in the adjuvant treatment of ovarian cancer patients. DISCUSSION/SIGNIFICANCE OF IMPACT: This study will validate synthetic lethal interactions from our CRISPR screen, reveal genes that could be mutated in ovarian cancer patients that may be driving resistance to STP938, and uncover combination therapies that can be used to increase efficacy in ovarian cancer patients treated with STP938.

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A bone to pick: morphometric characterization of black bone MRI toward clinical implementation*

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OBJECTIVES/GOALS: Conventional magnetic resonance imaging (MRI) methods are unable to visualize bone comparable to computed tomography (CT). Radiation therapy can result in post-treatment complications, such as osteoradionecrosis (ORN). We aim to integrate black bone (BB) MRI into routine follow-up MRI scans as an alternative to CT to monitor the development of ORN. METHODS/STUDY POPULATION: We assess the CT, T2-weighted (T2W), and BB MRI scans of 21 head and neck cancer patients without active ORN. All images are acquired within 4 weeks of each other to minimize anatomical variability. The mandibles are manually segmented on each image, and the MR images are registered to the CT to map the CT contour onto the MR images for comparison. Image segmentation evaluation metrics, including dice similarity coefficient (DSC), mean distance to agreement (MDA), and Hausdorff distance (HD), assess for spatial differences between each MRI sequence, using CT as reference standard. DSC measures contour volume, while MDA and HD assess the differences in contour boundaries, with HD sensitive to outliers. We employ a Wilcoxon signed-rank test using a significance value of $p \leq 0.05$ to assess for statistical significance. RESULTS/ANTICIPATED RESULTS: Using metrics widely accepted in biomedical research, we assess the performance of BB to visualize mandible against its conventional T2W MRI counterpart when compared to CT. Black bone has a significantly different DSC (median=0.878, IQR=0.0397) than T2W (median=0.806, IQR=0.0876; $p<0.0001$), indicating high volumetric overlap between contours on BB and CT. Black bone has a significantly different MDA (median=0.0731mm, IQR=0.0227mm) than T2W (median=0.119mm, IQR=0.0697; $p<0.0001$), indicating high agreement between contour boundaries on BB and CT. Black bone has a significantly different HD (median=0.649mm, IQR=0.211mm) than T2W (median=1.80, IQR=0.933; $p<0.0001$), indicating a submillimeter difference between contour boundaries, including outliers, on BB and CT. DISCUSSION/SIGNIFICANCE OF IMPACT: Our results exhibit BB as a promising non-ionizing alternative to CT for bony visualization compared to conventional MRI. BB has potential to detect early anatomical changes in bone, providing a standardized assessment of ORN. This can improve our dose–response understanding of post-treatment toxicities, refining radiation treatment planning.

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NEK9 modulates triple negative breast cancer cell biology.

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https://doi.org/10.1017/cts.2026.10552 Published online by Cambridge University Press