

Targeting Siglec-engaging immunosuppressive sialoglycans to suppress prostate cancer bone metastasis

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Abstract

Background: New treatments for metastatic castration resistant prostate cancer (mCRPC) are urgently needed, especially for tumours that have spread to bone. Sugar molecules (glycans) attached to the surface of prostate cancer cells have crucial roles in bone metastasis. Sialylated glycans (sialoglycans) are overexpressed by tumour cells and promote immune evasion by engaging Siglec receptors on immune cells. Targeting aberrant sialylation holds substantial potential for the development of new therapeutics but is relatively unexplored in the context of prostate cancer.

Methods: Here, using high-affinity Siglec-based sialoglycan-binding reagents (HYDRA) immunohistochemistry, we quantify tumour sialoglycans in tissues representing the full clinical heterogeneity of prostate cancer. Using immunofluorescence, we profile Siglec receptors in prostate tumours, and using syngeneic mouse models we evaluate an engineered dual-action sialidase (E-612) as a treatment for prostate cancer bone metastasis.

Results: We find that sialoglycans that can engage Siglec-3 (CD33), Siglec-7, and Siglec-9 are upregulated in bone metastatic prostate cancers and show that sialoglycan ligands for Siglec-7 and -9 correlate with and poorer patient prognosis. Furthermore, we reveal Siglec receptors and Siglec ligands are co-expressed by immune cells in prostate-derived tumours growing in bone. Indicating the Siglec-sialoglycan axis is clinically actionable in prostate cancer, we show systemic therapy with E-612 can suppress the growth of tumours, increase immune cell infiltration, and prolong survival times of mice with bone metastasis.

Conclusions: Our findings identify a novel mechanism involving Siglec-engaging sialoglycans in driving the growth of prostate cancer bone metastasis and demonstrate that targeting this axis using an engineered sialidase can impede lethal prostate cancer progression. While this study provides evidence that desialylation is a promising therapeutic strategy, the drug used was not targeted to prostate cancer. Excitingly, Palleon Pharmaceuticals have developed a novel targeted way to remove sialic acid from cancer cells. E-688 is a sialidase enzyme targeted to B7-H3, a protein that is highly expressed on both primary and bone metastatic prostate cancer. This pioneering therapy is currently in a clinical trial for ovarian cancer but has not yet been tested for prostate cancer. Future work funded by a 2026 Prostate Cancer Foundation Young Investigator Award will address this gap and generate the prerequisite data for a clinical trial in mCRPC.

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