Nanoparticle therapeutic restores function of tumor suppressor in prostate cancer

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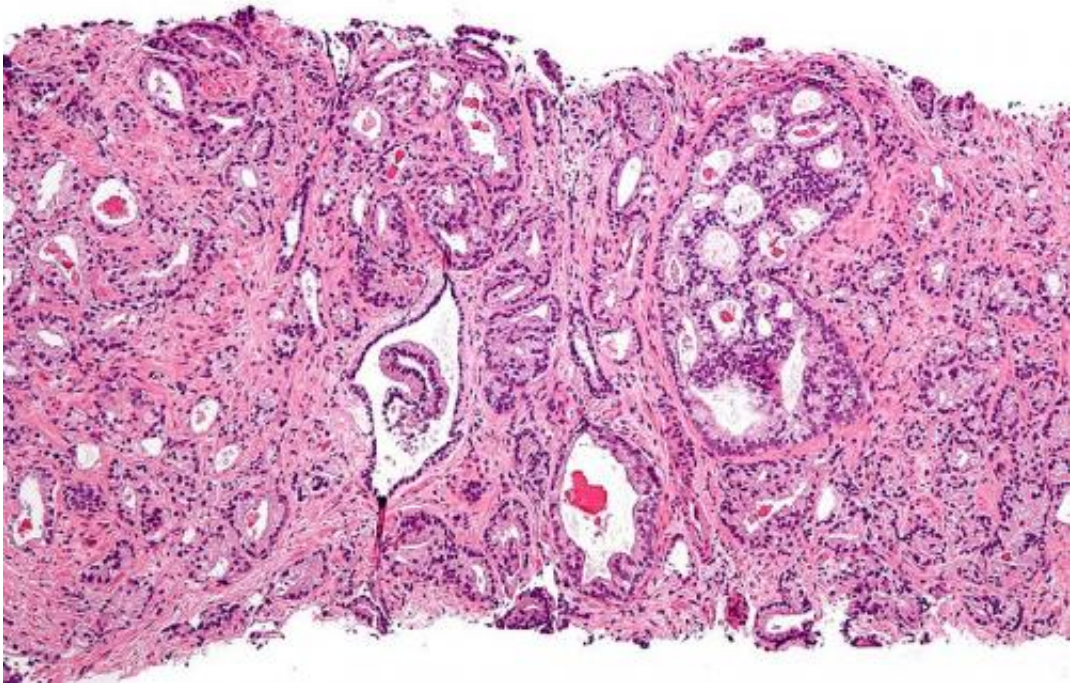

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

Think of it as a cancer therapy zag instead of a zig. While many groups are developing cancer therapies to target proteins and pathways that are highly active in cancer cells, a team of investigators from Brigham and Women's Hospital and Boston Children's Hospital, with collaborators at Memorial Sloan Kettering Cancer Center, is taking a new approach that allows them to go after what is not there. Loss of tumor

suppressors—genes such as PTEN and p53—help cancer grow unchecked. But targeting proteins that have been lost rather than gained in cancer has been challenging. The Boston-based collaborative team has leveraged advances in nanotechnology and the unique properties of mRNA to inhibit tumor growth in preclinical models of prostate cancer by targeting PTEN. The results of the team's efforts are published this week in *Nature Biomedical Engineering*.

"Our approach represents the convergence of nanotechnology and biology," said co-corresponding author Jinjun Shi, Ph.D., faculty of the Center for Nanomedicine and Associate Professor of Anesthesia at BWH. "Loss or mutation of PTEN has been observed in about half of metastatic castration-resistant prostate cancers and in many other human cancers, yet the reconstitution of functional PTEN has proven difficult. The potential impact of this mRNA-based nanotherapeutic is that it offers a new strategy for cancer treatment and can complement currently available therapies such as target inhibitors."

The team's goal is to reintroduce functional copies of PTEN into cancer cells to turn back on the body's natural tumor suppressing mechanisms. To do so, investigators have developed mRNA nanoparticles—super-small-scale delivery vehicles that can get messages of genetic information into cells. The team tested the effects of the hybrid nanoparticles on prostate cancer cells in the lab, finding that the nanoparticles could efficiently infiltrate the cells, protect mRNA from degradation and restore tumor suppressor function, killing cancer cells. The team also reported significant suppression of tumor growth and progression in mouse models of prostate cancer, including a prostate cancer bone model (the most common site to which prostate cancer can spread). Using imaging analysis, the team visually confirmed these results, finding that the PTEN mRNA delivered via the nanoparticles was responsible for the increase in cancer cell destruction. In addition, the team reported evidence of the safety of this therapeutic strategy as

the mice showed no significant changes in body weight and no organ toxicity.

"Most cancer therapies block something, such as an oncogene, that makes a tumor cell abnormal. In this approach, we have added back a protein that makes the tumor cell more like a normal cell, less likely to grow out of control," said co-corresponding author Bruce R. Zetter, Ph.D., Charles Nowiszewski Professor from the Program in Vascular Biology at Boston Children's Hospital.

"Comprehensive genomic sequencing of clinical specimens has revealed that the progressive loss/inactivation of distinct tumor suppressors including PTEN is correlated with the development and metastasis of prostate cancer. There is enormous need for restoration of tumor-suppressing pathways, highlighting the clinical relevance of this work," said Philip Kantoff, MD, chairman of Department of Medicine at Memorial Sloan Kettering Cancer Center and a co-author in this paper.

"These are exciting times for the field of nucleic acid therapeutics, with the recent regulatory approval of the first siRNA therapeutics and numerous mRNA therapeutics under clinical investigation. This work is the first proof-of-concept of using nanotechnology for systemic delivery of mRNA to restore tumor-growth suppression in vivo, including in the metastatic setting where the tumor burden is widely distributed. Our approach may prove useful in treatment of a myriad of malignancies and for other unmet medical needs," said co-corresponding author Omid Farokhzad, MD, director of Center for Nanomedicine and Professor of Anesthesia at BWH.

The authors noted that this work is a proof-of-concept study that demonstrates the potential impact of this approach but will need further testing and validation before use in humans. The team will continue testing the approach and plans to explore its applications for other tumor

suppressors, such as p53, and the ability to combine this strategy with other therapies.

More information: Restoration of tumour-growth suppression in vivo via systemic nanoparticle-mediated delivery of PTEN mRNA, *Nature Biomedical Engineering* (2018). DOI: 10.1038/s41551-018-0284-0 , www.nature.com/articles/s41551-018-0284-0

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