Androgen receptor-regulated long non-coding RNA 1 is a novel prostate cancer oncogene and therapeutic target

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Background
Long non-coding RNAs (lncRNAs) outnumber protein-coding genes, and are emerging as important players in many diseases, including prostate cancer (PCa). Our group recently cataloged the human lncRNA transcriptome by applying *ab initio* bioinformatic analysis to 7,256 RNA seq libraries derived from normal and tumor tissue. This effort identified over 58,000 lncRNA species, comprising 68% of coding elements in the human genome. Non-parametric analysis of transcripts differentially expressed between samples allowed detection of disease-specific lncRNAs. While this method positively identified known PCa-associated lncRNAs PCA3 and SChLAP1, the species most strongly correlated with PCa was a novel lncRNA termed androgen receptor-regulated long non-coding RNA 1(ARlnc1) (also called PRCAT47). ARlnc1 levels are several-fold higher in PCa primary tumors and metastases vs normal prostate tissue. In turn, immunohistochemistry demonstrates robust ARlnc1 staining in patient PCa samples, with near absence in benign prostate tissue. Given these data, we hypothesized ARlnc1 is a novel PCa oncogene critical for tumorigenesis and disease progression.

Methods and Results
We first knocked down ARlnc1 in in LNCaP and MDA_PCa_2b cells, and found this maneuver inhibited both *in vitro* proliferation and *in vivo* xenograft growth. We then aimed to determine whether ARlnc1 represented a viable therapeutic target. Antisense oligonucleotides (ASOs) are an emerging drug class that inhibit nucleic acid species through complimentary binding. In collaboration with Ionis Pharmaceuticals we identified and tested ARlnc1-specifc ASOs. ASOs yielded effective ARlnc1 knockdown *in vitro*, and inhibited proliferation of ARlnc1-expressing PCa cells. To assess therapeutic effectiveness *in vivo*, we systemically delivered ARlnc1-specific ASOs to animals bearing cell line or patient tumor–derived xenografts. This therapy markedly inhibited *in vivo* tumor growth.

Conclusion
ARlnc1 is novel lncRNA PCa oncogene, associated with advanced disease and amenable to therapeutic inhibition with complimentary antisense oligonucleotides.

Conflict of Interest Statement
No potential conflicts of interest were closed

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