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Priority Report

Cancer Research

A Pyrrole-Imidazole Polyamide Is Active against Enzalutamide-Resistant Prostate Cancer

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Abstract

The LREX' prostate cancer model is resistant to the antiandrogen enzalutamide via activation of an alternative nuclear hormone receptor, glucocorticoid receptor (GR), which has similar DNA-binding specificity to the androgen receptor (AR). Small molecules that target DNA to interfere with protein–DNA interactions may retain activity against enzalutamide-resistant prostate cancers where ligand-binding domain antagonists are ineffective. We reported previously that a pyrrole-imidazole (Py-Im) polyamide designed to bind the consensus androgen response element half-site has antitumor activity against hormone-sensitive prostate cancer. In enzalutamide-resistant LREX' cells, Py-Im polyamide interfered with both AR- and GR-driven gene expression, whereas enzalutamide interfered with only that of AR. Genomic analyses indicated immediate interference with the AR transcriptional pathway. Long-term treatment with Py-Im polyamide demonstrated a global decrease in RNA levels consistent with inhibition of transcription. The polyamide was active against two enzalutamide-resistant xenografts with minimal toxicity. Overall, our results identify Py-Im polyamide as a promising therapeutic strategy in enzalutamide-resistant prostate cancer. *Cancer Res; 77(9); 1–6. ©2017 AACR.*

Introduction

Prostate cancer is the second leading cause of cancer-related death in American men with 26,000 deaths annually (1), the majority from metastatic, castrate-resistant prostate cancer (mCRPC), in which androgen deprivation therapy (ADT), which suppresses androgen receptor (AR) signaling, is ineffective. Enzalutamide, a potent AR ligand-binding domain (LBD) antagonist, is effective against mCRPC and is a current standard of care (2). Unfortunately, *de novo* or acquired resistance to enzalutamide is common (3); overcoming this is an unmet need.

Mechanisms of enzalutamide resistance include restoration of AR signaling through LBD mutations or expression of transcriptionally active splice variants lacking the LBD (4), bypass of AR signaling through alternative nuclear hormone receptors (NHR; ref. 5), or development of complete independence from AR signaling (6). Glucocorticoid receptor (GR) is an NHR with a sequence preference similar to AR (7). After enzalutamide treatment, the LREX' cell line highly expresses GR, which drives enzalutamide resistance by regulating gene expression significantly overlapping that of AR, suggesting prostate cancers coopt GR to progress through AR antagonism (5). Furthermore, GR expression in mCRPC associates with poor response to enzalutamide (5). Therefore, interference with the NHR–DNA interface may overcome enzalutamide resistance.

A pyrrole-imidazole (Py-Im) polyamide (ARE-1) is effective against hormone-sensitive LNCaP xenografts with minimal host toxicity (8). Py-Im polyamides are minor groove DNA-binding small molecules with modular sequence specificity and high affinity (9). Polyamide–DNA binding induces widening of the minor groove and compression of the opposing major groove (10), interfering with transcription factor–DNA interactions and the transcriptional machinery (11, 12). A polyamide targeted to the ARE might prevent AR and GR signaling, and transcription.

We hypothesized that ARE-1 may be effective against enzalutamide-resistant prostate cancer. We report ARE-1 efficacy against enzalutamide-resistant VCaP and LREX' prostate cancer models in cell culture and xenografts. Mechanistic studies reveal immediate interference with androgen-induced gene expression and reduced transcription after long-term treatment.

Materials and Methods

Cell culture conditions and cytotoxicity assays

The LREX' and LNCaP/AR cell lines were gifts from Charles Sawyers (Memorial Sloan Kettering Cancer Center, New York, NY) and were received in 2014 and 2007, respectively. The VCaP cell line was a gift from Kenneth Pienta (University of Michigan Medical School, Ann Arbor, MI) and was received in 2012. Cells were maintained as described previously (5, 8, 11–13) and were used within 10 passages from thawing. Cells were validated to parental cell lines by STR profile at IDEXXX Bioresearch following experimentation and confirmed to be mycoplasma free. WST-1 assay (Roche) was used to measure cytotoxicity. Long-term toxicity in VCaP cells was assayed by cell counting.

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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Confocal imaging

Imaging was as described in ref. 8. Briefly, 2 μmol/L of **ARE-1-FITC** was added for 16 hours, washed with PBS, and imaged on a Zeiss LSM 5 Exciter.

Gene expression analysis

LNCaP/AR and LREX' cells were cultured for 72 hours after plating in phenol-red free RPMI1640 (10% CT-FBS) in 6-well plates at 4×10^4 and 5×10^4 cells/mL, respectively. LNCaP/AR cells were treated with 10 μmol/L ARE-1, bicalutamide, or enzalutamide (Aurum Pharmatech) for an additional 48, 2, and 2 hours, respectively, prior to treatment with 1 nmol/L DHT or ethanol for 16 hours. LREX' cells were treated with 10 μmol/L ARE-1 for 16 hours prior to induction with 1 nmol/L DHT or 100 nmol/L dexamethasone for 8 hours. RNA extraction (RNeasy columns, Qiagen), cDNA generation (Transcriptor First Strand cDNA Kit, Roche), and qRT-PCR (SYBR Green Master Mix, Applied Biosystems, ABI7300 instrument) were as described in refs. 8, 11, 12. Expression was normalized to β-glucuronidase.

RNA sequencing analysis

LREX' cells were plated at 5×10^4 cells/mL in 10-cm^2 dishes, treated with or without 10 μmol/L of ARE-1 in fresh media, incubated 16 hours, and induced with 1 nmol/L DHT for 8 hours. Tumor samples were homogenized mechanically. Total RNA was TRIzol extracted, sequenced (Illumina HiSeq2000), and mapped against the human genome (hg19) with Tophat2 using Ensembl GRCh37 gene annotations. Human and mouse reads from tumor samples were parsed with BBSplit and unique reads were mapped. Htseq-count was used for exon alignment and DESeq2 for differential expression. Gene set enrichment analysis (GSEA) was performed on genes with $P_{adj} < 0.05$ and fold change ≥ 1.6 for cell samples and $P_{adj} < 0.05$ for tumor samples (SRP102746).

Nascent RNA measurement

LREX' cells were plated at 1×10^5 cells/mL in 96-well plates in RPMI1640 (20% FBS and 1 μmol/L enzalutamide), adhered for 24 hours, dosed with ARE-1, and incubated for 48 hours. The Click-iT RNA Alexa Fluor 488 HCS Kit was used for dye conjugation, and incorporation of 5-ethynyl uridine (5-EU) was measured on a FlexStation 3 plate reader.

Flow cytometry

LREX' cells were plated at 1×10^5 cells/mL in 175-cm^2 flasks, adhered 24 hours, incubated with 10 μmol/L ARE-1 24, 48, and 72 hours, and then with 300 μmol/L 5-EU in fresh media. Cells were detached by Accumax or Accutase, and Alexa Fluor 488 azide dye was conjugated. Cells were passed through 35-μm mesh prior to flow, sorted on a FACSCalibur instrument (Becton Dickinson), and analyzed using FlowJo.

Animal experiments

Animal experiments were performed at Caltech (Pasadena, CA) under IACUC approval. VCaP and LREX' cells were engrafted as 1:1 mixtures of 3×10^6 cells in Matrigel (BD Biosciences) into the flanks of intact and castrated male SCID mice (Charles River Laboratories), respectively. LREX' engrafted mice received 10 mg/kg enzalutamide (oral gavage) daily. Once tumors were 100 mm^3 (0.5*l*w*w), ARE-1 was administered subcutaneously to opposing flanks in 20% DMSO:saline. For circulation studies, 4 C57BL6/J animals were injected subcutaneously with ARE-1 at 30 mg/kg and blood collected retro-orbitally. Plasma concentrations of ARE-1 were analyzed by HPLC, AUC approximated by the linear trapezoidal method, as described previously (8).

IHC

Tumors were fixed in neutral-buffered formalin, paraffinized, sectioned, and stained as described previously (12). Quantification of five random fields per slice was performed by ImmunoRatio.

Statistical analysis

Cell culture experiments represent ≥ 3 independent biological replicates. Sequencing analyses were duplicates for cell culture and quadruplicates for tumor samples. For xenografts, animals were randomly assigned to groups. For circulation experiments, concentrations of ARE-1 were duplicate measurements. Measurements in cell culture, animal, and IHC experiments were assessed by Student *t* test.

Results

ARE-1 is more potent than enzalutamide against prostate cancer cell growth and is not rescued by GR activation

ARE-1 (Fig. 1A) targets the sequence 5′-WGWWCW-3′ (W=A or T), similar to the consensus half-site recognized by either AR or GR. Nuclear uptake in LNCaP/AR, LREX', and VCAP cells was evaluated using fluorescent analogue ARE-1-FITC (Supplementary Fig. S1). The LNCaP/AR cell line overexpresses full-length AR, modeling castration resistance (14). ARE-1 reduced proliferation of LNCaP/AR cells more than bicalutamide (Fig. 1B). The VCaP cell line overexpresses AR with modest GR expression, the activation of which reduces the antiproliferative effects of enzalutamide (5). ARE-1 reduced proliferation of both VCaP and LREX' cells regardless of induction of AR signaling by 1 nmol/L DHT, induction of GR signaling by 100 nmol/L dexamethasone, or both (Fig. 1C and D). Long-term cell viability studies in VCaP cells show 10 μM ARE-1 is more potent than enzalutamide and insensitive to GR activation (Fig. 1D).

Py-Im polyamide attenuates androgen- and glucocorticoid-driven gene expression

In androgen-depleted conditions, bicalutamide activates AR in the LNCaP/AR cell line (14). Enzalutamide and ARE-1 demonstrate no agonist activity; ARE-1 reduced baseline expression of *KLK3* (Fig. 2A). In LREX' cells, ARE-1 represses *KLK3* and *HOMER2* expression, which are coregulated by AR and GR (Fig. 2B). Whereas enzalutamide was more potent than ARE-1 in reducing DHT-induced transcription, the opposite was observed with dexamethasone induction. Furthermore, coadministration of enzalutamide and ARE-1 was additive, suggesting ARE-1 may potentiate enzalutamide's activity.

Global transcriptomic effects of Py-Im polyamides

We performed RNA sequencing analysis on three treatment conditions in LREX' cells: vehicle, DHT treatment, and cotreatment with ARE-1 and DHT, and two conditions in parental LNCaP cells: vehicle and ARE-1 treatment. GSEA of affected genes in LREX' cells using the hallmark pathways in the Molecular Signatures Database revealed DHT treatment enriched for the AR signaling pathway as expected (Fig. 2C, Supplementary Fig. S2;

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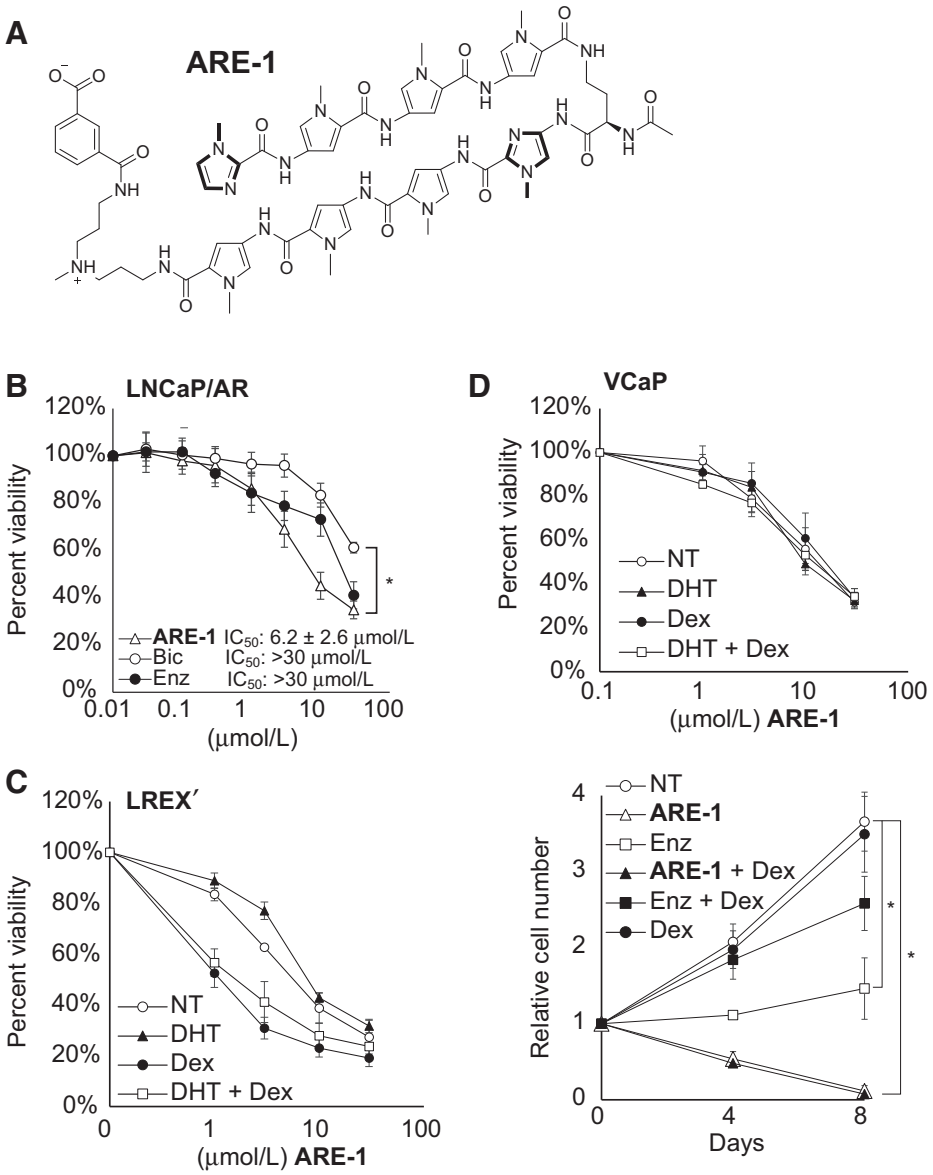

Figure 1.

A, Structure of ARE-1. **B,** Cytotoxicity of ARE-1, bicalutamide (Bic), and enzalutamide (Enz) in LNCaP/AR cells over 72 hours. **C,** Cytotoxicity of ARE-1 in LREX′ cells is not attenuated by AR or GR activation. **D,** Top, cytotoxicity of ARE-1 in VCaP cells is not affected by dexamethasone (Dex); bottom, long-term incubation of ARE-1 or enzalutamide in VCaP cells. Error bars, SEM. *, $P < 0.05$.

Supplementary Table S1). DHT-induced LREX' cells treated with ARE-1 negatively enriched for the AR signaling pathway (NES, −3.875; Fig. 2C, Supplementary Table S1), consistent with interference in AR-driven gene expression by ARE-1. In addition, ARE-1 treatment negatively enriched for the UV DNA damage response pathway down (NES, −4.310; Fig. 2C). Similarly, ARE-1 treatment in LNCaP cells negatively enriched for the AR signaling pathway (NES, −2.778) and the UV DNA damage response pathway down (NES, −2.240 Fig. 2D; Supplementary Table S1). UV radiation induces DNA helical distortions through formation of pyrimidine dimers and 6-4 photoproducts, which arrest RNA polymerase II (RNAP2) during elongation, triggering degradation of RPB1. ARE-1 reduced nascent RNA in LREX' cells as measured by 5-EU incorporation (Fig. 3), and we have previously observed RPB1 degradation after long-term treatment with ARE-1 and related polyamides (8, 12). This suggests that long-term treatment with ARE-1 reduces global transcription in LREX' cells.

Suppression of enzalutamide-resistant, CRPC *in vivo*

We further tested the efficacy of ARE-1 in VCaP xenografts, which exhibit modest response to 10 mg/kg enzalutamide treatment, and in mice engrafted with enzalutamide-resistant LREX' cells (5, 13). In VCaP xenografts, ARE-1 dose dependently reduced tumor growth by 70% at 5 mg/kg compared with vehicle (Fig. 4A) without significant toxicity (Supplementary Fig. S3A). In castrated mice bearing LREX' tumors, ARE-1 and enzalutamide cotreatment reduced growth by 80% compared with enzalutamide alone (Fig. 4B) without significant toxicity (Supplementary Fig. S3B). Enzalutamide was administered daily postengraftment at 10 mg/kg to maintain GR expression, which was confirmed by IHC. LNCaP tumors, which do not express GR, were used as controls (Fig. 4C). Furthermore, LREX' tumors treated with ARE-1 and enzalutamide showed reduced *KLK3* expression (Supplementary Fig. S3C), elevated TUNEL, and reduced Ki67 staining compared with enzalutamide alone (Supplementary Fig. S3D). GSEA of tumor expression profiles

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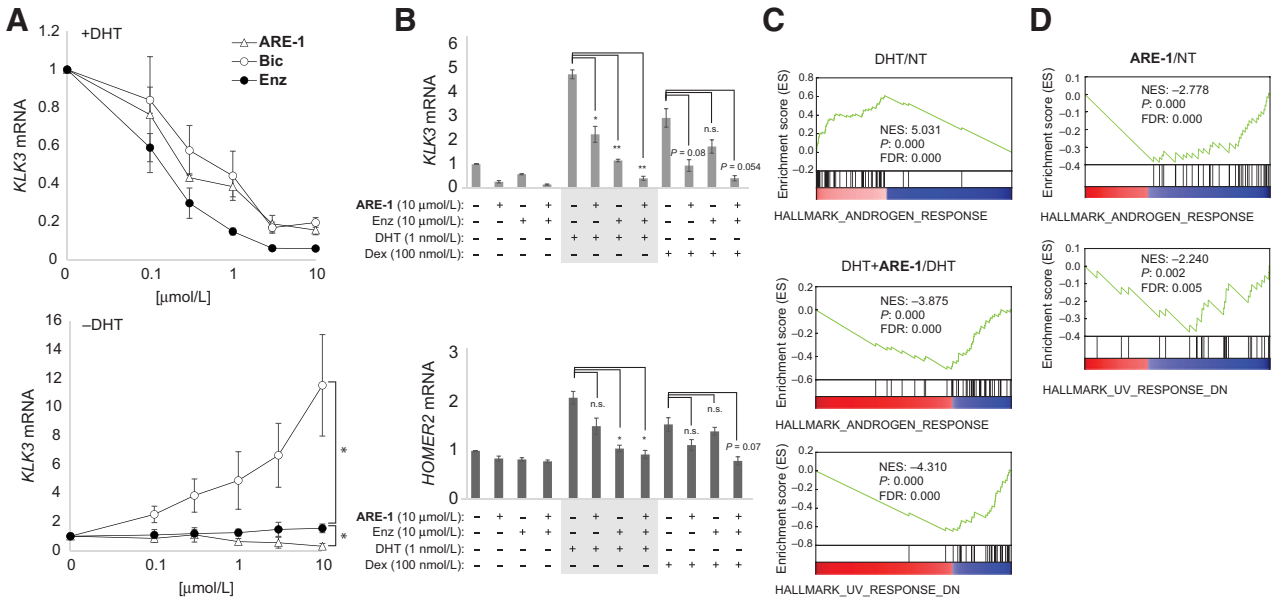

Figure 2.

A, Effects of ARE-1, bicalutamide (Bic), and enzalutamide (Enz) on DHT-induced *KLK3* mRNA in LNCaP/AR cells (top), and baseline (charcoal-stripped media; bottom). **B,** Effects of ARE-1 and enzalutamide against select genes coregulated by AR and GR in LREX′ cells. **C,** GSEA analysis in LREX′ cells. n.s., not significant. Top, DHT enriches for the androgen response. Bottom, ARE-1 with DHT negatively enriches for androgen response and the UV response down. **D,** ARE-1 treatment of LNCaP cells negatively enriches for androgen response and the UV response down. *, $P < 0.05$.

shows ARE-1 treatment elicits similar UV response signatures as seen in cell culture and represses ontologies associated with DNA binding–dependent transcription (Supplementary Tables S2 and S3). Plasma concentration of ARE-1 from terminal blood samples from LREX'-engrafted animals was compared with the plasma concentration in C57BL6/J animals treated with 30 mg/kg ARE-1; AUC was 25.9 and 189.9 μg*h/mL, respectively (Supplementary Fig. S4). At 30 mg/kg ARE-1, mice experienced a 6% weight loss but recovered within 5 days without visible signs of distress (not shown).

Discussion

AR LBD mutations, expression of transcriptionally active splice variants lacking the LBD, cooption of NHRs with similar DNA-binding specificities, or loss of reliance on AR may drive enzalutamide resistance (3). Furthermore, different metastatic foci within a patient may resist enzalutamide through different mechanisms (15), suggesting a successful treatment strategy might use multiple therapeutics that overcome different resistance mechanisms, or alternatively, a single therapeutic

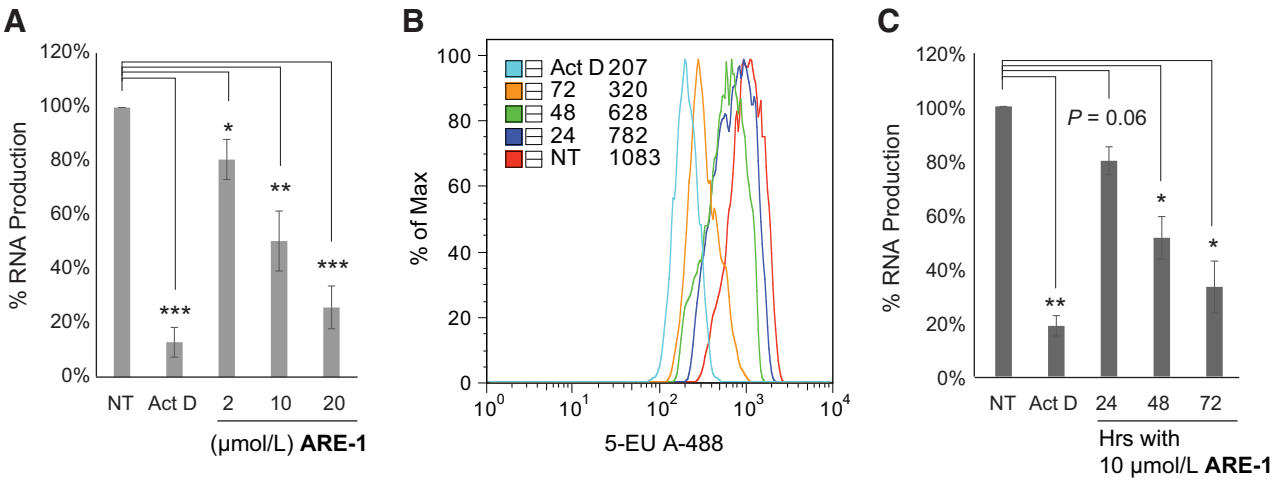

Figure 3.

A, Nascent RNA in LREX′ cells treated with ARE-1 for 48 hours. Actinomycin D (Act D), positive control. **B,** Nascent RNA in LREX′ cells by flow cytometry after treatment with 10 μmol/L ARE-1 for 24, 48, 72 hours. **C,** Composite of flow cytometry results. Error bars, SEM. *, $P < 0.05$; **, $P < 0.005$; ***, $P < 0.0005$.

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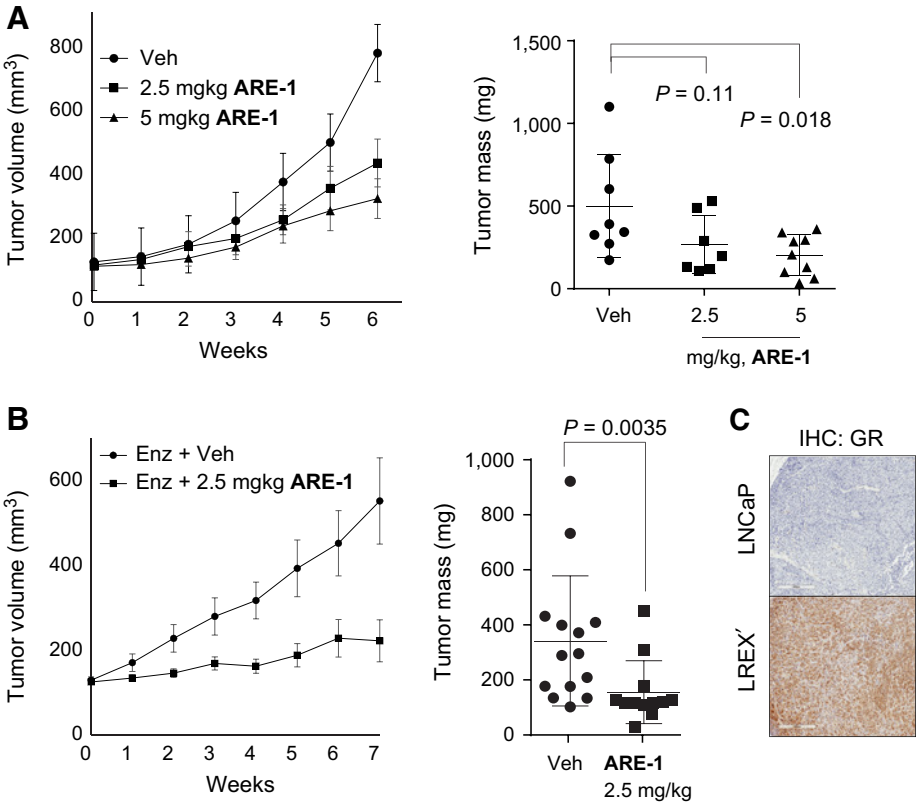

Figure 4.

Mice were treated three times per week with ARE-1 subcutaneously to flanks opposite engrafted tumor. **A,** Tumor volumes (left) and final tumor masses (right) of VCaP xenografts treated with vehicle (Veh; $n = 8$), 2.5 mg/kg ($n = 7$), and 5 mg/kg ($n = 8$) ARE-1. **B,** Tumor volumes (left) and final tumor masses (right) of LREX′ xenografts in castrated animals treated daily with 10 mg/kg enzalutamide (Enz) and vehicle ($n = 14$) or enzalutamide and 2.5 mg/kg ARE-1 ($n = 12$). **C,** GR staining of LREX′ and LNCaP tumors. All LREX′ tumors stained for GR. Error bars for tumor volumes are SEM. Whisker plots represent means, SDs.

capable of overcoming multiple mechanisms. Therapeutic targeting of the NHR–DNA interface may overcome most known enzalutamide resistance mechanisms.

The GR antagonist mifepristone added to ADT was previously tested in mCRPC patients and was not effective (16). Trials for mCRPC patients combining enzalutamide with mifepristone are underway. Other NHRs may also be active in refractory prostate cancer (3). Notably, progesterone receptor inhibitors have entered clinical trials for mCRPC. Therapeutics targeting the N-terminal domain (NTD) of AR, or that mediate degradation of AR, may overcome treatment resistance due to AR splice variants. The NTD inhibitor EPI-506 has entered clinical trials (17). However, this approach may not overcome resistance due to cooption of alternate NHRs. Others have reported small molecules that interfere with the AR DNA-binding domain (18). The clinical utility of this approach is unknown.

We report a Py-Im polyamide with activity against enzalutamide-resistant prostate cancer in cell and animal models. Polyamide ARE-1, targeted to the sequence 5′-WGWWCW-3′, which is similar to the ARE and GRE half-site, attenuates ligand-induced AR and GR transcriptional activity, is more potent than enzalutamide and bicalutamide in cell culture, and is active against enzalutamide-resistant xenografts. Long-term treatment of LREX' cells with ARE-1 also decreases nascent RNA synthesis. In biophysical experiments, polyamides can halt RNAP2 elongation directly upstream of a polyamide-binding site (19). We hypothesize this stalling of RNAP2 promotes ubiquitination and degradation of RPB1, ultimately interfering with RNA synthesis, which may contribute to efficacy against treatment-refractory prostate cancer. Other molecules that interfere with RNA synthesis are proposed as potential drug candidates for prostate cancer (13, 20).

Disclosure of Potential Conflicts of Interest

F. Yang is the vice president (research) at and has ownership interest (including patents) in Gene Sciences, Inc. N.G. Nickols has ownership interest (including patents) in Gene Sciences, Inc. P.B. Dervan is the founder of, has ownership interest (including patents) in, and is a consultant/advisory board member for Gene Sciences, Inc. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: A.A. Kurmis, F. Yang, N.G. Nickols, P.B. Dervan
Development of methodology: A.A. Kurmis, F. Yang, T.R. Welch
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.A. Kurmis, F. Yang, T.R. Welch, N.G. Nickols
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.A. Kurmis, F. Yang, N.G. Nickols, P.B. Dervan
Writing, review, and/or revision of the manuscript: A.A. Kurmis, F. Yang, N.G. Nickols, P.B. Dervan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N.G. Nickols
Study supervision: P.B. Dervan

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References

1. American Cancer Society. Cancer Facts & Figures 2016. Atlanta, GA: American Cancer Society; 2016.
2. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33.
3. Watson PA, Arora VK, Sawyers CL. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nat Rev Cancer 2015;15:701–11.
4. Ware KE, Garcia-Blanco MA, Armstrong AJ, Dehm SM. Biologic and clinical significance of androgen receptor variants in castration resistant prostate cancer. Endocr Relat Cancer 2014;21:T87–103.
5. Arora VK, Schenkein E, Murali R, Subudhi SK, Wongvipat J, Balbas MD, et al. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. Cell 2013;155:1309–22.
6. Beltran H, Prandi D, Mosquera JM, Benelli M, Puca L, Cyrta J, et al. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. Nat Med 2016;22:298–305.
7. Meijsing SH, Pufall MA, So AY, Bates DL, Chen L, Yamamoto KR. DNA binding site sequence directs glucocorticoid receptor structure and activity. Science 2009;324:407–10.
8. Yang F, Nickols NG, Li BC, Szablowski JO, Hamilton SR, Meier JL, et al. Animal toxicity of hairpin pyrrole-imidazole polyamides varies with the turn unit. J Med Chem 2013;56:7449–57.
9. Dervan PB, Edelson BS. Recognition of the DNA minor groove by pyrrole-imidazole polyamides. Curr Opin Struct Biol 2003;13:284–99.
10. Chenoweth DM, Dervan PB. Allosteric modulation of DNA by small molecules. Proc Natl Acad Sci U S A 2009;106:13175–9.
11. Nickols NG, Dervan PB. Suppression of androgen receptor-mediated gene expression by a sequence-specific DNA-binding polyamide. Proc Natl Acad Sci U S A 2007;104:10418–23.
12. Yang F, Nickols NG, Li BC, Marinov GK, Said JW, Dervan PB. Antitumor activity of a pyrrole-imidazole polyamide. Proc Natl Acad Sci U S A 2013;110:1863–8.
13. Asangani IA, Dommeti VL, Wang X, Malik R, Cieslik M, Yang R, et al. Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer. Nature 2014;510:278–82.
14. Chen CD, Welsbie DS, Tran C, Baek SH, Chen R, Vessella R, et al. Molecular determinants of resistance to antiandrogen therapy. Nat Med 2004;10:33–9.
15. Gundem G, Van Loo P, Kremeyer B, Alexandrov LB, Tubio JMC, Papaemmanuil E, et al. The evolutionary history of lethal metastatic prostate cancer. Nature 2015;520:353–7.
16. Taplin M-E, Manola J, Oh WK, Kantoff PW, Bubley GJ, Smith M, et al. A phase II study of mifepristone (RU-486) in castration-resistant prostate cancer, with a correlative assessment of androgen-related hormones. BJU Int 2008;101:1084–9.
17. Myung J-K, Banuelos CA, Fernandez JG, Mawji NR, Wang J, Tien AH, et al. An androgen receptor N-terminal domain antagonist for treating prostate cancer. J Clin Invest 2013;123:2948–60.
18. Dalal K, Roshan-Moniri M, Sharma A, Li H, Ban F, Hassona MD, et al. Selectively targeting the DNA-binding domain of the androgen receptor as a prospective therapy for prostate cancer. J Biol Chem 2014;289:26417–29.
19. Xu L, Wang W, Gotte D, Yang F, Hare AA, Welch TR, et al. RNA polymerase II senses obstruction in the DNA minor groove via a conserved sensor motif. Proc Natl Acad Sci U S A 2016;113:12426–31.
20. Peltonen K, Colis L, Liu H, Jäämaa S, Zhang Z, Af Hällström T, et al. Small molecule BMH-compounds that inhibit RNA polymerase I and cause nucleolar stress. Mol Cancer Ther 2014;13:2537–46.

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