Cancer Therapy: Preclinical

Galeterone Prevents Androgen Receptor Binding to Chromatin and Enhances Degradation of Mutant Androgen Receptor

Ziyang Yu, Changmeng Cai, Shuai Gao, Nicholas I. Simon, Howard C. Shen, and Steven P. Balk

Abstract

**Purpose:** Galeterone inhibits the enzyme CYP17A1 and is currently in phase II clinical trials for castration-resistant prostate cancer (CRPC). Galeterone is also a direct androgen receptor (AR) antagonist and may enhance AR degradation. This study was undertaken to determine the molecular basis for AR effects and their therapeutic potential.

**Experimental Design:** Effects of galeterone on AR expression and activities were examined in prostate cancer cell lines.

**Results:** Similar to the AR antagonist enzalutamide, but in contrast to bicalutamide, galeterone did not induce binding of a constitutively active VP16-AR fusion protein to reporter genes and did not induce AR recruitment to endogenous androgen-regulated genes based on chromatin immunoprecipitation. Galeterone at low micromolar concentrations that did not induce cellular stress responses enhanced AR protein degradation in LNCaP and C4-2 cells, which express a T878A mutant AR, but not in prostate cancer cells expressing wild-type AR. Further transfection studies using stable LNCaP and PC3 cell lines ectopically expressing wild-type or T878A-mutant ARs confirmed that galeterone selectively enhances degradation of the T878A-mutant AR.

**Conclusions:** Similar to enzalutamide, galeterone may be effective as a direct AR antagonist in CRPC. It may be particularly effective against prostate cancer cells with the T878A AR mutation but may also enhance degradation of wild-type AR in vivo through a combination of direct and indirect mechanisms. Finally, these findings show that conformational changes in AR can markedly enhance its degradation and thereby support efforts to develop further antagonists that enhance AR degradation.

Clin Cancer Res; 1–11. ©2014 AACR.

Introduction

Prostate cancer is the second leading cause of cancer-related death in the United States. The androgen receptor (AR) plays a central role in prostate cancer, and the standard treatment for metastatic prostate cancer is androgen deprivation therapy by medical or surgical castration. Although most patients initially respond, they invariably relapse despite castrate androgen levels (castration-resistant prostate cancer, CRPC). Previous studies have identified increased intratumoral androgen synthesis from precursor steroids generated by the adrenal glands or possibly de novo androgen synthesis from cholesterol, as a mechanism of castration resistance (1–6). CYP17A1 is the critical enzyme required for the conversion of C21 steroids to C19 steroids such as dehydroepiandrosterone (DHEA) that can be further reduced to the potent androgens testosterone and dihydrotestosterone (DHT). CYP17A1 inhibitors can thereby further markedly decrease the levels of residual androgens and precursor steroids that remain after castration, and the CYP17A1 inhibitor abiraterone is now approved by the FDA for treatment of CRPC (7, 8).

The direct AR antagonist enzalutamide has also recently been approved for treatment of CRPC (9, 10). Previous AR antagonists used for prostate cancer (flutamide, nilutamide, and bicalutamide) do not effectively prevent AR binding to chromatin and may thereby have weak agonist properties that limit their efficacy in CRPC (11–13). In contrast, the enzalutamide-liganded AR does not bind to chromatin, making this drug a purer AR antagonist with improved efficacy in CRPC (10). However, the survival advantages for abiraterone and enzalutamide therapy in CRPC post-chemotherapy are only about 4 months (7, 9), and mechanisms of intrinsic or acquired resistance to these agents remain to be established (14).

Authors’ Affiliation: Hematology-Oncology Division, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts

Corresponding Author: Steven P. Balk, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215. Phone: 817-735-2065; Fax: 817-735-2050; E-mail: sbalk@bidmc.harvard.edu

doi: 10.1158/1078-0432.CCR-14-0292

©2014 American Association for Cancer Research.
Galetone (previously known as VN/124-1 or TOK-001) was developed as a CYP17A1 inhibitor, but similar to related compounds, it has AR antagonist activity and was also found to promote AR degradation (15–17). However, its effects on AR binding to chromatin have not been examined. Moreover, further studies indicated that galetone at high concentrations could induce an endoplasmic reticulum (ER) stress response (18) and may decrease AR translation through direct or indirect effects on mTOR (19), suggesting that some of its effects on AR expression may be indirect. Galetone is currently in phase II clinical trials for CRPC, and responses in these trials may be related to both its activities toward CYP17A1 and its direct effects on AR. Therefore, this study was undertaken to determine the molecular basis for galetone actions as a direct AR antagonist and for its effects on AR protein expression.

**Materials and Methods**

**Cell culture and immunoblot analyses**

LNCaP, VCaP, LAPC4, CWR22RV1, PC3, and HEK293T cells were purchased from ATCC. LAPC4-CR and C4-2 cells were derived from castration resistant xenografts of LAPC4 and LnCaP, respectively. Cells were cultured in RPMI-1640 or DMEM supplemented with 10% FBS. Androgen deprivation was conducted by culturing cells in RPMI-1640 or DMEM supplemented with 5% CSS for at least 48 hours. Whole-cell lysates (WCL) were prepared using lysis buffer containing 2% SDS and subjected to immunoblotting. Nuclear and cytoplasmic fractions of the cell were prepared using the NE-PER nuclear and cytoplasmic extraction kit (Thermo Scientific) following manufacturer’s instructions. The antibody against human AR (N20) and lamin A/C was obtained from Santa Cruz Biotechnology. The antibody against V5 epitope tag was from Invitrogen. Antibodies against β-actin (AC-15) and β-tubulin were from Millipore. Antibody against PSA was from Meridian Life Science. Antibodies against eIF2α and phospho-eIF2α were from Cell Signaling. The results from a minimum of 2 experiments were subjected to densitometry and normalized to β-actin or β-tubulin loading control and the mean values relative to vehicle control (set to 1.0) given.

**Recombinant DNA and stable cell lines**

The AR-WT, T878A, and W742C cDNA were subcloned from previously described constructs (20, 21) to pCMV-3xFLAG vector and to pDONR223 entry vector. For AR-F877L mutant, site-directed mutagenesis using pDONR223-AR-WT as template was performed. The primer sets used were: sense 5’-cagagagctgcaatgtattcttttggcgtc-3’, antisense 5’-tagcaggtcaaaagttagctgcatcaccttcttg-3’.

**Reporter gene assays and quantitative RT-PCR**

COS-7 cells were transfected with a luciferase reporter gene construct driven by 4 androgen-responsive elements (ARE), Renilla luciferase gene construct, and pCMV-FLAG-AR or pCMV-VP16-AR in RPMI-1640 with 5% CSS. Forty-eight hours later, transfected cells were treated with DHT or vehicle (ethanol) in the presence of galetone (Tokai Pharmaceuticals), abiraterone, bicalutamide, or enzalutamide. Transfection was done in triplicates. Luciferase and Renilla luciferase activity was measured using the Dual-luciferase Reporter Assay (Promega). For quantitative RT-PCR (qRT-PCR), RNA was isolated using RNeasy Mini Kit (Invitrogen). The TaqMan primer probe sets for PSA were: Forward, 5’-gtgataaaaggctgtggc-3’, reverse, 5’-ccctaca-cagctactccacgc-3’, probe, 5’-FAM-caggaacaaaagcgtgatcttg-cctcg-3’. The primer probe sets for FKBP5 and GAPDH were from Life Technologies. The qRT-PCR was performed in an ABI7900 thermal cycler.

**Chromatin immunoprecipitation**

For anti-AR chromatin immunoprecipitation (ChIP), androgen-deprived VCaP cells were treated with DHT or antagonists for 4 hours. DNA–protein crosslinking was induced by formaldehyde treatment and the cell lysates were subjected to sonication. Immunoprecipitation was done with anti-AR antibody or control IgG (Santa Cruz). The bound DNA was quantified by qRT-PCR using the following primer sets: PSA enhancer: Forward, 5’-tcagttttgctctggcttac-3’, reverse, 5’-tcttctgtctctgtctgtctgt-3’; KLK2 enhancer: Forward, 5’-gtcttctgcagagac-3’.
Galeterone functions directly as an AR antagonist

We first examined the effects of galeterone on AR signaling in prostate cancer cells. Androgen-deprived LNCaP and VCaP cells were stimulated with DHT at 0.1, 1, or 10 nmol/L in the presence of 1 or 10 μmol/L galeterone or vehicle control (DMSO). Twenty-four hours later, samples were immunoblotted for PSA protein expression. β-Tubulin was probed as control for loading. G...
Galeterone impairs AR binding to chromatin

An important distinction between bicalutamide and enzalutamide is that the bicalutamide-ligated AR can associate with chromatin, which may contribute to weak partial agonist activity (10, 12). To test whether galeterone stimulates AR binding to DNA, we used a plasmid encoding the full-length AR fused to the VP16 transactivation domain (VP16-AR), which can stimulate transcription independently of coactivator recruitment by AR. COS-7 cells were transfected with this plasmid and with the ARE4-LUC reporter construct and then stimulated with a series of ligands (Fig. 2A). As a positive control, DHT treatment led to substantial increases in nuclear AR. VP16-AR similarly could be stimulated by bicalutamide, enzalutamide, or galeterone. Expression of FKBP5 mRNA was tested as an indicator of AR transcription activity. Galetorene and enzalutamide both potently blocked FKBP5 mRNA expression induced by up to 10 nmol/L DHT, whereas this inhibitory effect was partially reversed by the treatment with 100 nmol/L DHT. Overall, these results confirm that galeterone can function as a direct AR antagonist.

Galeterone does not directly enhance degradation of wild-type AR

The unliganded AR is degraded by a proteasome-dependent pathway, and its stability is increased by androgen binding (22–24). Galetorene has been shown previously to decrease AR protein expression in prostate cancer cell lines (LNCaP and LAPC4) and in LAPC4 xenografts (16, 17). However, these decreases in AR protein and increases in AR degradation may, in part, be due to competitive displacement of androgen from the AR ligand domain by galeterone. Moreover, galeterone at higher concentrations (generally over 10 μmol/L) has been reported to activate cellular stress pathways that may indirectly decrease AR protein expression (18, 19). Therefore, to determine whether galeterone binding to the AR could directly enhance AR degradation, we assessed the effects of galeterone at up to 10 μmol/L in androgen-deprived cells. Importantly, on the basis of the results in Fig. 1, we anticipate that most of the AR would be liganded to galeterone at 10 μmol/L, so that effects at higher concentration would be indirect and mediated by off-target mechanisms.

In one set of experiments, we used LAPC4 cells and its subline LAPC4-CR cells, which both express wild-type (WT) AR. The LAPC4-CR line was established from a relapsed castration-resistant LAPC4 xenograft. The cells were cultured in androgen-depleted medium for 48 hours and then treated with galeterone at 0.5 to 10 μmol/L for 24 hours. In LAPC4 cells, galeterone at concentrations of 0.5 to 5 μmol/L did not lead to decreased AR expression but did lead to a 48% decrease at 10 μmol/L (Fig. 3A). To more directly assess AR protein stability, we then treated the androgen-deprived and vehicle or galeterone-stimulated LAPC4 cells with cycloheximide to block new protein synthesis. Significantly, the rate at which AR protein decayed in these cells was not altered by the treatment with galeterone compared with vehicle control (Fig. 3B). In LAPC4-CR cells, galeterone had no clear effect on overall AR protein levels or stability (Fig. 3C and D).

We next similarly examined VCaP cells, which express an amplified WT AR. In androgen-deprived VCaP cells,
Galeterone led to a moderate decrease of AR protein levels (Fig. 3E). However, as there is substantial de novo androgen synthesis in VCaP cells (2), any decrease in AR protein may reflect decreased intracellular androgen levels due to the inhibition of CYP17A1 by galeterone. To clarify whether any decrease in AR expression is a direct effect of galeterone on AR rather than an indirect effect via its CYP17A1 activity, we treated VCaP cells with abiraterone at up to 5 \( \mu \text{mol/L} \), which effectively blocks CYP17A1 activity in these cells (2). Abiraterone treatment alone did not have a clear effect on AR protein, but addition of galeterone to the abiraterone did modestly decrease AR protein, suggesting a direct effect of galeterone on AR (Fig. 3F). The addition of galeterone at 10 \( \mu \text{mol/L} \) to the abiraterone similarly decreased AR protein in VCS2 cells, which were derived from a castration-resistant VCaP xenograft (2). However, when we next used cycloheximide treatment to directly assess for effects of galeterone on AR stability in VCaP cells, we found that galeterone...
at 10 μmol/L did not increase the rate of AR degradation (Fig. 3G). On the basis of these results, we conclude that galeterone at concentrations up to 10 μmol/L does not substantially enhance AR degradation in VCaP cells but may decrease AR protein by indirect mechanisms at higher concentrations or in combination with other agents.

Similar results were obtained when we examined CWR22Rv1 cells. The AR in the parental CWR22 cells has
a mutation in codon 875 that broadens its ligand specificity, and the CWR22Rv1 cells have in addition a duplication of exon 3 encoding the DNA-binding domain (25). These cells also express an alternatively spliced AR isoform that deletes the ligand-binding domain (26). As observed in VCaP cells, AR protein was slightly decreased at 10\(\mu\text{mol/L}\) galeterone, whereas bicalutamide, enzalutamide, or abiraterone treatment did not change AR levels (Fig. 3H). As expected, the full-length AR protein was slightly increased by DHT, with no clear effect on the AR splice variant (AR-V). Overall, these results indicate that galeterone does not have marked direct effects on AR protein stability but may decrease AR protein by indirect mechanisms at concentrations at or above 10 \(\mu\text{mol/L}\).

Galeterone markedly enhances AR protein degradation in LNCaP and C4-2 cells

In contrast to the results above, galeterone at concentrations well below 10 \(\mu\text{mol/L}\) in androgen-deprived C4-2 cells markedly decreased AR protein (Fig. 4A). This decrease was from 36% to 87% at 0.5 to 10 \(\mu\text{mol/L}\), whereas there was no decrease in AR protein with abiraterone at 2.5 or 5 \(\mu\text{mol/L}\) (Fig. 4A). Using cycloheximide to block new protein synthesis, we found that galeterone decreased the half-life of endogenous AR in androgen-deprived C4-2 cells from about 6 to 2 hours (Fig. 4B). The parental line of C4-2, LNCaP, was also tested. Galeterone at 5 or 10 \(\mu\text{mol/L}\) similarly dramatically decreased AR protein expression in androgen-deprived LNCaP cells (Fig. 4C), and treatment...
with cycloheximide showed that galeterone was increasing AR degradation in these cells (Fig. 4D).

To confirm that the decrease in AR protein was through proteasome-mediated degradation, we used a proteasome inhibitor, MG132. Treatment of LNCaP cells with MG132 prevented the decrease in AR protein expression caused by galeterone (Fig. 4E). To determine whether the effects of galeterone were direct and mediated by AR binding, we also assessed whether DHT could prevent the decline in AR protein. As shown in Fig. 4F, DHT could partially block the galeterone-mediated decrease in AR protein.

Finally, as galeterone has been reported to induce an ER stress response that may indirectly affect AR expression (18), we addressed whether galeterone treatment in these cells was inducing an ER stress response. The ER stress response was assessed on the basis of phosphorylation of eukaryotic initiation factor 2α (eIF2α). Consistent with a previous report (18), an ER stress response could be induced by galeterone, which we observed at 20 μmol/L (Fig. 4G). However, galeterone at 10 μmol/L, which still markedly reduced AR protein, did not induce this stress response. These results together indicate that galeterone is directly enhancing AR protein degradation in LNCaP and C4-2 cells.

**Galeterone enhances degradation of the T878A-mutant AR**

The marked effects of galeterone on AR protein expression in the C4-2 and LNCaP cells could reflect their T878A-mutant AR or other distinct features of these cell lines such as their PTEN deficiency. To initially address the role of the T878A mutation, LNCaP cells were transfected with a construct coding for FLAG-tagged WT AR and genetin resistance, and short-term genetin-resistant cells were selected. These cells were then androgen-deprived for 48 hours and treated with galeterone for 24 hours at increasing doses. Expression of ectopic WT AR was probed using anti-FLAG antibody. No decrease in the expression of ectopic WT AR was observed at up to 10 μmol/L galeterone, whereas the endogenous T878A AR protein in the parental LNCaP cells was decreased (Fig. 5A).

To rule out the possible confounding effect of the ectopic expression vector versus the endogenous AR, we established PC3 stable cells using lentiviral vectors expressing AR WT or

---

**Figure 5.** Galeterone enhances degradation of AR T878A mutant. A, LNCaP cells were transiently transfected with pCMV-3xFLAG-AR vector and selected for ectopic AR expression. The resulting LNCaP-FLAG-AR cells were treated with galeterone (Gale, 1–20 μmol/L) or vehicle alongside the parental LNCaP cells in hormone-depleted medium. Twenty-four hours later, cell lysates were subjected to immunoblotting. The endogenous AR T878A mutant in LNCaP cells was probed for with anti-AR antibody, and the ectopic AR (WT) in LNCaP-FLAG-AR cells was detected with anti-FLAG antibody. AR expression was quantified and normalized to β-actin. B and C, PC3 and LNCaP stably expressing AR-WT or T878A were treated with galeterone (10 μmol/L) or vehicle for 24 hours in hormone-depleted medium and cell lysates were prepared. Anti-AR antibody was used to detect ectopic AR in PC3 cells and anti-V5-epitope antibody was used for ectopic AR in LNCaP cells. The expression of AR was quantified and normalized to that of β-tubulin. Data are representative of 2 independent experiments. D, PC3 cells were transfected with constructs expressing AR-WT, F877L, or T878A and allowed to grow for 30 hours in medium containing 5% CSS. Cells were then treated with galeterone (10 μmol/L) or vehicle for 24 hours, and lysates were subjected to immunoblotting for AR and β-tubulin (as control). Data are representative of 2 independent experiments. E, LNCaP cells were transfected with pCMV-3xFLAG-AR-W742C and selected with genetin. These AR-W742C-expressing LNCaP cells were androgen-starved and treated with galeterone (10 μmol/L) or vehicle alongside the LNCaP-FLAG-AR-WT cells as described in A. Twenty-four hours later, cell lysates were subjected to immunoblotting for ectopic AR using FLAG antibody. β-Tubulin expression was used as loading control. Data are representative of 2 independent experiments.
AR T878A. Treatment of these stable PC3 cells with galeterone led to about 30% decrease in AR WT, but the decrease in AR T878A was substantially greater (~70%; Fig. 5B). To further validate this result, LNCaP stable cells expressing epitope-tagged AR WT or T878A were also established. Similar to the PC3 stable cells, galeterone substantially decreased AR T878A expression, with minimal effect on AR WT levels (Fig. 5C).

The T878A AR can be strongly stimulated by the AR antagonists hydroxylflutamide and nilutamide. Therefore, we also tested whether galeterone enhances degradation of AR with other known mutations that can mediate resistance to AR antagonists such as enzalutamide or bicalutamide. Recent reports have found that enzalutamide can activate an F877L-mutant AR (27–29). However, in contrast to the transfected T878A AR, galeterone did not decrease expression of the F877L-mutant AR (Fig. 5D). Similarly, we found that expression of the W742C-mutant AR, which is stimulated by bicalutamide, was not decreased by galeterone (Fig. 5E). Taken together, these results show that galeterone markedly and directly enhances degradation of the T878A-mutant AR while having only modest effects on expression of WT AR that may be cell line–dependent and through direct or indirect mechanisms.

Discussion

Galeterone suppresses AR activity both by functioning as a CYP17A1 inhibitor and by binding directly to AR (15, 16). It has clear activity against AR-dependent prostate cancer cells in vitro and in xenograft models, and its efficacy in patients is currently being assessed in phase II clinical trials. However, the molecular basis for its direct effects on AR remains to be fully established. In this study, we confirmed that galeterone functions as a direct AR competitive antagonist. Moreover, we found that galeterone, in contrast to bicalutamide but similar to enzalutamide, does not stimulate AR binding to chromatin. Previous studies have shown that bicalutamide functions as an AR antagonist because it does not effectively recruit coactivator proteins and may instead recruit corepressors (12, 30). However, this antagonist activity may be circumvented in CRPC through several mechanisms, such as increased AR or alterations in transcriptional coactivator or corepressor proteins, which may enhance the weak partial agonist activity of bicalutamide (14). In contrast, enzalutamide has a distinct mechanism of action as it does not stimulate AR binding to chromatin, which makes it a purer antagonist and likely contributes to its efficacy in CRPC (10). Therefore, our findings suggest that galeterone will function similar to enzalutamide in CRPC as a relatively pure direct AR antagonist, which in conjunction with its activity as a CYP17A1 inhibitor may enhance the ability of galeterone to suppress AR function in CRPC.

Previous studies have also shown that galeterone treatment can decrease AR protein levels and may increase AR protein degradation (16). However, it has not been clear whether this is due to direct effects on AR, as galeterone at higher concentrations (~20 μmol/L) has been found to induce an ER stress response (18) and to decrease phosphorylation of 4EBP1, possibly reflecting decreased TORC1 activity (19). Using galeterone at lower concentrations (up to 10 μmol/L) that could effectively suppress DHT-stimulated AR activity, but did not stimulate a stress response, we found that galeterone did not substantially enhance degradation of WT AR in androgen-starved LAPC4 or VCaP prostate cancer cells. In contrast, degradation of the T878A-mutant AR, which is expressed by LNCaP and C4-2 cells, was markedly increased by a proteasome-dependent mechanism in response to galeterone binding.

These findings are consistent with previous data showing that galeterone at 5 to 10 μmol/L could decrease AR protein expression in LNCaP cells in vitro (16). While galeterone has also been found previously to decrease AR protein in LAPC4 cells in vitro, this effect was observed at higher galeterone concentrations (15–20 μmol/L) that may have decreased AR expression by indirect mechanisms (16). Significantly, in vivo studies using LAPC4 xenografts have shown marked decreases in AR protein in response to galeterone (16, 17). Our in vitro data certainly do not rule out the possibility that galeterone binding may directly enhance AR degradation in vivo due to displacement of an endogenous ligand and/or subtle differences in mechanisms regulating AR degradation in vivo versus in vitro. Alternatively, the decreased AR protein in vivo may be mediated by indirect mechanisms or possibly synergy between direct and indirect mechanisms. Finally, a recent study found that galeterone and related compounds could enhance degradation of the full-length AR and truncated AR (ligand-binding domain deleted) in CWR22Rv1 cells, further establishing that galeterone has a mechanism of action that is independent of binding to the AR ligand-binding domain (31).

Structural studies have shown that T878 in helix 9 of the AR ligand-binding domain sits in the steroid-binding pocket and that the T878A mutation provides more room in this pocket (32, 33). As a result, binding of the AR antagonist hydroxylflutamide to the T878A-mutant AR does not distort the ligand-binding pocket and this drug thereby functions as a potent agonist of the T878A AR (34). Galeterone is a steroidal compound modified with a bulky benzimidazole group at the C17 position, which in DHT has a hydroxyl group that contacts T878. However, as galeterone is still an antagonist for the T878A AR, it is apparent that the benzimidazole group must still distort the ligand-binding pocket. Nonetheless, we propose that the T878A mutation alters the positioning of helix 9 in the galeterone-liganded AR and may thereby enhance the ubiquitylation of one or more helix 9 lysines by an E3 ubiquitin ligase that normally mediates degradation of the unliganded AR or that mediates turnover of the agonist-liganded AR. Alternatively, the galeterone-liganded T878A-mutant AR may be degraded through a distinct mechanism that does not normally mediate AR degradation. In either case, these findings demonstrate that certain conformations of AR can markedly enhance its degradation and support efforts to identify novel mechanisms of AR antagonism.
antagonists that can similarly alter the structure of WT AR and thereby enhance its degradation.

Disclosure of Potential Conflicts of Interest
S.P. Balk reports receiving a commercial research grant from TOKAI. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions
Conception and design: Z. Yu, C. Cai, S. Gao, S.P. Balk
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Z. Yu, N.I. Simon, H.C. Shen, S.P. Balk
Analysis and interpretation of data (e.g., statistical analysis, bioinformatics, computational analysis): Z. Yu, C. Cai, S. Gao, S.P. Balk
Writing, review, and/or revision of the manuscript: Z. Yu, C. Cai, S. Gao, S.P. Balk
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Z. Yu, S.P. Balk

Study supervision: S.P. Balk

References

Acknowledgments
The authors thank Tokai Pharmaceuticals for providing galeterone and Douglas Jacoby (Tokai Pharmaceuticals) for helpful suggestions.

Grant Support
This study was supported by a Department of Defense Prostate Cancer Research Program Postdoctoral Training Award (W81XWH-12-PCRP-P2A to Z. Yu) and Idea Development Awards (W81XWH-11-1-0295, W81XWH-09-1-0414, and W81XWH-07-1-0443 to S. Balk). DF/HCC-Prostate Cancer SPORE P50 CA09381, and NIH K9 award CA166507 (C. Cai), NIH P01 CA163227-01A1 (S. Balk), a Prostate Cancer Foundation Challenge Award, and by a sponsored research grant from Tokai. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received February 3, 2014; revised April 24, 2014; accepted May 18, 2014; published OnlineFirst May 29, 2014.


Galeterone Prevents Androgen Receptor Binding to Chromatin and Enhances Degradation of Mutant Androgen Receptor

Ziyang Yu, Changmeng Cai, Shuai Gao, et al.

Clin Cancer Res  Published OnlineFirst May 29, 2014.