Cancer Cell, Volume 35

Supplemental Information

ARv7 Represses Tumor-Suppressor Genes

in Castration-Resistant Prostate Cancer

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Figure S1 (related to Figure 1). Efficiency of ARv7 and ARfI knockdown in LNCaP95 and 22Rv1 cells and its effect on 22Rv1 cell growth

A. Western blot of nuclear lysates of LNCaP95 shGFP, shARv7 and shARfl cells induced with dox for 3 days and treatment with vehicle (-) or 10 nM DHT (+) for 4 hr. AR levels were detected (and specificity of the respective antibodies confirmed) using antibodies against the AR N-terminus (ARN; which recognized both ARfl and ARv7) or antibodies specific for ARfl or ARv7. Equal protein loading was confirmed with Lamin B1. **B.** Representative scanning electron microscope images of LNCaP95 cell lines grown in 3D/PEGda cryogels and in the presence of dox (as in Figure 1 C). Images were acquired after 7 days of growth. Scale bar = 20 μ m. **C.** Western blot of nuclear lysates from 22Rv1 cells with dox-inducible sh constructs against GFP (shGFP), ARv7 (shARv7) or ARfl (shARfl). Cells were hormone starved and treated with dox and vehicle (ETOH) for 6-days. Proteins were detected as described in A, using the ARN and ARv7 antibodies. **D.** Cell growth assay of 22Rv1 cells, as in C, grown over a 6 day period in the presence of dox and vehicle (ETOH). Data is the mean of 3 independent experiments ± SD. p values were calculated using standard t test; **: p ≤ 0.01; ****: p ≤ 0.0001.



Figure S2 (related to Figure 2). DHT dose-dependent responses in shARv7 or shARfl LNCaP95 cells

A, **B**. Lineplots of differentially-expressed genes in the shARv7 (A) or shARfl (B) LNCaP95 cell lines, compared to the shGFP control. Cells were grown in the presence of dox for 3 days, with different doses of DHT (0.1, 1, and 10 nM) or with vehicle (ETOH) for 24 hr. Genes significantly dysregulated relative to the control (shGFP) for all DHT concentrations are drawn in blue. Genes with missing values are drawn in orange. The opacity of the lines is proportional to their variance over the four concentrations: i.e. higher standard deviation equals higher opacity. The numbers indicate the number of points with a positive (top) or negative log2 fold change (log2FC) (bottom) for a given DHT concentration.

Table S1 (related to Figure 2). Hallmark Gene Set Enrichment Analysis of ARfI- and ARv7-regulated genes

NAME	NES	NOM p val	CELL LINE
E2F TARGETS	1.875	0.0000	LN95 shARv7 ETOH
G2M CHECKPOINT	1.862	0.0000	LN95 shARv7 ETOH
ESTROGEN RESPONSE EARLY	1.752	0.0000	LN95 shARv7 ETOH
ESTROGEN RESPONSE LATE	1.720	0.0000	LN95 shARv7 ETOH
IL2 STAT5 SIGNALING	1.695	0.0000	LN95 shARv7 ETOH
MITOTIC SPINDLE	1.605	0.0000	LN95 shARv7 ETOH
EMT	1.488	0.0000	LN95 shARv7 ETOH
ADIPOGENESIS	1.519	0.0015	LN95 shARv7 ETOH
NOTCH SIGNALING	1.651	0.0018	LN95 shARv7 ETOH
UV RESPONSE UP	1.446	0.0030	LN95 shARv7 ETOH
UV RESPONSE DN	1.498	0.0032	LN95 shARv7 ETOH
INFLAMMATORY RESPONSE	1.507	0.0046	LN95 shARv7 ETOH
APICAL JUNCTION	1.416	0.0046	LN95 shARv7 ETOH
APICAL SURFACE	1.757	0.0054	LN95 shARv7 ETOH
IL6 JAK STAT3 SIGNALING	1.656	0.0086	LN95 shARv7 ETOH
PEROXISOME	1.453	0.0100	LN95 shARv7 ETOH
OXIDATIVE PHOSPHORYLATION	1.359	0.0119	LN95 shARv7 ETOH
ANGIOGENESIS	1.570	0.0124	LN95 shARv7 ETOH
FATTY ACID METABOLISM	1.370	0.0216	LN95 shARv7 ETOH
HEDGEHOG SIGNALING	1.536	0.0295	LN95 shARv7 ETOH
BILE ACID METABOLISM	1.373	0.0356	LN95 shARv7 ETOH
WNT BETA CATENIN SIGNALING	1.443	0.0359	LN95 shARv7 ETOH
CHOLESTEROL HOMEOSTASIS	1.385	0.0403	LN95 shARv7 ETOH
MTORC1 SIGNALING	1.286	0.0425	LN95 shARv7 ETOH
DNA REPAIR	-1.336	0.0258	LN95 shARv7 ETOH
MYC TARGETS V1	2.112	0.0000	LN95 shARfl ETOH
E2F TARGETS	1.970	0.0000	LN95 shARfl ETOH
G2M CHECKPOINT	1.941	0.0000	LN95 shARfl ETOH
TGF BETA SIGNALING	1.677	0.0000	LN95 shARfl ETOH
OXIDATIVE PHOSPHORYLATION	1.661	0.0000	LN95 shARfl ETOH
MYC TARGETS V2	1.777	0.0023	LN95 shARfl ETOH
MITOTIC SPINDLE	1.278	0.0305	LN95 shARfl ETOH
FATTY ACID METABOLISM	1.325	0.0355	LN95 shARfl ETOH
ANDROGEN RESPONSE	-1.934	0.0000	LN95 shARfl ETOH
UNFOLDED PROTEIN RESPONSE	-1.666	0.0000	LN95 shARfl ETOH
INFLAMMATORY RESPONSE	-1.594	0.0000	LN95 shARfl ETOH
HEME METABOLISM	-1.478	0.0016	LN95 shARfl ETOH
EMT	-1.565	0.0017	LN95 shARfl ETOH
CHOLESTEROL HOMEOSTASIS	-1.677	0.0017	LN95 shARfl ETOH
TNFA SIGNALING VIA NFKB	-1.416	0.0051	LN95 shARfl ETOH
PROTEIN SECRETION	-1.563	0.0053	LN95 shARfl ETOH
MTORC1 SIGNALING	-1.377	0.0081	LN95 shARfl ETOH
COAGULATION	-1.497	0.0085	LN95 shARfl ETOH

ESTROGEN RESPONSE EARLY	-1.327	0.0237	LN95 shARfl ETOH
KRAS SIGNALING UP	-1.332	0.0244	LN95 shARfl ETOH
BILE ACID METABOLISM	-1.391	0.0389	LN95 shARfl ETOH

NES: (Normalized Enrichment Scores) the degree to which a given gene set is overrepresented compared to all analyzed gene sets. NOM p value: (Nominal p values) the statistical significance of the enrichment score. Pathways highlighted in blue are shared between the shARv7 and shARfl cell lines.

Table S2 (related to Figure 2C). Detailed statistics of the DHT dose-dependent transcriptional responses in shARv7 or shARfI LNCaP95 cells

	Set A		Set B		tHSD		Data	
Transf.	DHT conc.	mean log2FC	Transf.	DHT conc.	mean log2FC	p adj	sign.	subsets
shARv7	ETOH	0.101015802	shARv7	0.1 nM	0.065699762	0.058050204	n.s.	All
shARv7	ETOH	0.101015802	shARv7	1 nM	0.059176828	0.008472829	**	All
shARv7	ETOH	0.101015802	shARv7	10 nM	0.052469159	0.001722733	**	All
shARv7	ETOH	0.101015802	shARfl	ETOH	-0.024528024	6.57E-14	****	All
shARv7	ETOH	0.101015802	shARfl	0.1 nM	-0.050549201	0	****	All
shARv7	ETOH	0.101015802	shARfl	1 nM	-0.018436402	9.19E-14	****	All
shARv7	ETOH	0.101015802	shARfl	10 nM	-0.06131223	0	****	All
shARv7	0.1 nM	0.065699762	shARv7	1 nM	0.059176828	0.998646135	n.s.	All
shARv7	0.1 nM	0.065699762	shARv7	10 nM	0.052469159	0.933327401	n.s.	All
shARv7	0.1 nM	0.065699762	shARfl	ETOH	-0.024528024	9.46E-14	****	All
shARv7	0.1 nM	0.065699762	shARfl	0.1 nM	-0.050549201	5.96E-14	****	All
shARv7	0.1 nM	0.065699762	shARfl	1 nM	-0.018436402	1.43E-12	****	All
shARv7	0.1 nM	0.065699762	shARfl	10 nM	-0.06131223	8.20E-14	****	All
shARv7	1 nM	0.059176828	shARv7	10 nM	0.052469159	0.99869698	n.s.	All
shARv7	1 nM	0.059176828	shARfl	ETOH	-0.024528024	2.77E-13	****	All
shARv7	1 nM	0.059176828	shARfl	0.1 nM	-0.050549201	9.47E-14	****	All
shARv7	1 nM	0.059176828	shARfl	1 nM	-0.018436402	5.16E-11	****	All
shARv7	1 nM	0.059176828	shARfl	10 nM	-0.06131223	6.21E-14	****	All
shARv7	10 nM	0.052469159	shARfl	ETOH	-0.024528024	2.52E-10	****	All
shARv7	10 nM	0.052469159	shARfl	0.1 nM	-0.050549201	9.00E-14	****	All
shARv7	10 nM	0.052469159	shARfl	1 nM	-0.018436402	2.03E-08	****	All
shARv7	10 nM	0.052469159	shARfl	10 nM	-0.06131223	1.01E-13	****	All
shARfl	ETOH	-0.024528024	shARfl	0.1 nM	-0.050549201	0.405401058	n.s.	All
shARfl	ETOH	-0.024528024	shARfl	1 nM	-0.018436402	0.999476191	n.s.	All
shARfl	ETOH	-0.024528024	shARfl	10 nM	-0.06131223	0.059440793	n.s.	All
shARfl	0.1 nM	-0.050549201	shARfl	1 nM	-0.018436402	0.168211728	n.s.	All
shARfl	0.1 nM	-0.050549201	shARfl	10 nM	-0.06131223	0.993058836	n.s.	All
shARfl	1 nM	-0.018436402	shARfl	10 nM	-0.06131223	0.015163179	*	All

shARv7	ETOH	0.412119564	shARv7	0.1 nM	0.450191355	2.05737E-05	****	Up
shARv7	ETOH	0.412119564	shARv7	1 nM	0.409918282	0.999991801	n.s.	Up
shARv7	ETOH	0.412119564	shARv7	10 nM	0.393006619	0.237353559	n.s.	Up
shARv7	ETOH	0.412119564	shARfl	ETOH	0.363676569	5.71E-08	****	Up
shARv7	ETOH	0.412119564	shARfl	0.1 nM	0.490935854	8.82608E-09	****	Up
shARv7	ETOH	0.412119564	shARfl	1 nM	0.459979097	1.95E-07	****	Up
shARv7	ETOH	0.412119564	shARfl	10 nM	0.645198704	8.82601E-09	****	Up
shARv7	0.1 nM	0.450191355	shARv7	1 nM	0.409918282	4.57594E-07	****	Up
shARv7	0.1 nM	0.450191355	shARv7	10 nM	0.393006619	8.82664E-09	****	Up
shARv7	0.1 nM	0.450191355	shARfl	ETOH	0.363676569	8.83E-09	****	Up
shARv7	0.1 nM	0.450191355	shARfl	0.1 nM	0.490935854	5.96E-05	****	Up
shARv7	0.1 nM	0.450191355	shARfl	1 nM	0.459979097	9.15E-01	n.s.	Up
shARv7	0.1 nM	0.450191355	shARfl	10 nM	0.645198704	8.83E-09	****	Up
shARv7	1 nM	0.409918282	shARv7	10 nM	0.393006619	0.300080308	n.s.	Up
shARv7	1 nM	0.409918282	shARfl	ETOH	0.363676569	2.90E-08	****	Up
shARv7	1 nM	0.409918282	shARfl	0.1 nM	0.490935854	8.83E-09	****	Up
shARv7	1 nM	0.409918282	shARfl	1 nM	0.459979097	1.15E-08	****	Up
shARv7	1 nM	0.409918282	shARfl	10 nM	0.645198704	8.83E-09	****	Up
shARv7	10 nM	0.393006619	shARfl	ETOH	0.363676569	4.48E-03	**	Up
shARv7	10 nM	0.393006619	shARfl	0.1 nM	0.490935854	8.83E-09	****	Up
shARv7	10 nM	0.393006619	shARfl	1 nM	0.459979097	8.83E-09	****	Up
shARv7	10 nM	0.393006619	shARfl	10 nM	0.645198704	8.83E-09	****	Up
shARfl	ETOH	0.363676569	shARfl	0.1 nM	0.490935854	8.82601E-09	****	Up
shARfl	ETOH	0.363676569	shARfl	1 nM	0.459979097	8.82601E-09	****	Up
shARfl	ETOH	0.363676569	shARfl	10 nM	0.645198704	8.82601E-09	****	Up
shARfl	0.1 nM	0.490935854	shARfl	1 nM	0.459979097	0.015520346	*	Up
shARfl	0.1 nM	0.490935854	shARfl	10 nM	0.645198704	8.82601E-09	****	Up
shARfl	1 nM	0.459979097	shARfl	10 nM	0.645198704	8.82601E-09	****	Up
shARv7	ETOH	-0.391452534	shARv7	0.1 nM	-0.382616663	0.972680671	n.s.	Down
shARv7	ETOH	-0.391452534	shARv7	1 nM	-0.338362766	2.36307E-08	****	Down
shARv7	ETOH	-0.391452534	shARv7	10 nM	-0.335184282	1.1808E-08	****	Down
shARv7	ETOH	-0.391452534	shARfl	ETOH	-0.387748216	1.00E+00	n.s.	Down
shARv7	ETOH	-0.391452534	shARfl	0.1 nM	-0.499942533	3.82667E-09	****	Down
shARv7	ETOH	-0.391452534	shARfl	1 nM	-0.445998655	1.82E-08	****	Down
shARv7	ETOH	-0.391452534	shARfl	10 nM	-0.648881929	3.82667E-09	****	Down
shARv7	0.1 nM	-0.382616663	shARv7	1 nM	-0.338362766	4.78492E-08	****	Down
shARv7	0.1 nM	-0.382616663	shARv7	10 nM	-0.335184282	2.33885E-08	****	Down
shARv7	0.1 nM	-0.382616663	shARfl	ETOH	-0.387748216	9.97E-01	n.s.	Down
shARv7	0.1 nM	-0.382616663	shARfl	0.1 nM	-0.499942533	3.83E-09	****	Down
shARv7	0.1 nM	-0.382616663	shARfl	1 nM	-0.445998655	3.83E-09	****	Down
shARv7	0.1 nM	-0.382616663	shARfl	10 nM	-0.648881929	3.83E-09	****	Down
shARv7	1 nM	-0.338362766	shARv7	10 nM	-0.335184282	0.999894208	n.s.	Down
shARv7	1 nM	-0.338362766	shARfl	ETOH	-0.387748216	4.15E-09	****	Down
shARv7	1 nM	-0.338362766	shARfl	0.1 nM	-0.499942533	3.83E-09	****	Down
shARv7	1 nM	-0.338362766	shARfl	1 nM	-0.445998655	3.83E-09	****	Down
shARv7	1 nM	-0.338362766	shARfl	10 nM	-0.648881929	3.83E-09	****	Down
shARv7	10 nM	-0.335184282	shARfl	ETOH	-0.387748216	4.00E-09	****	Down
shARv7	10 nM	-0.335184282	shARfl	0.1 nM	-0.499942533	3.83E-09	****	Down

shARv7	10 nM	-0.335184282	shARfl	1 nM	-0.445998655	3.83E-09	****	Down
shARv7	10 nM	-0.335184282	shARfl	10 nM	-0.648881929	3.83E-09	****	Down
shARfl	ETOH	-0.387748216	shARfl	0.1 nM	-0.499942533	3.82667E-09	****	Down
shARfl	ETOH	-0.387748216	shARfl	1 nM	-0.445998655	3.82692E-09	****	Down
shARfl	ETOH	-0.387748216	shARfl	10 nM	-0.648881929	3.82667E-09	****	Down
shARfl	0.1 nM	-0.499942533	shARfl	1 nM	-0.445998655	4.53458E-09	****	Down
shARfl	0.1 nM	-0.499942533	shARfl	10 nM	-0.648881929	3.82667E-09	****	Down
shARfl	1 nM	-0.445998655	shARfl	10 nM	-0.648881929	3.82667E-09	****	Down

Set A and Set B: Values used for ANOVA. tHSD: Tukey's honest significance test. Transf.: Transfection of the cell line. DHT conc.: DHT concentration in which the cells were grown. Mean log2FC: Averages of logarithm to the base 2 of the fold changes for the cell lines relative to control (shGFP). P adj: adjusted p values for the tHSD. Sign: Significance of the adjusted p values. Data subsets: Indication which data points were used in the analyses. All: Using all differentially expressed genes (adj p < 0.05). Up: Using up regulated differentially expressed genes (log2FC > 0, adj p < 0.05). Down: Using down regulated differentially expressed genes (log2FC < 0, adj p < 0.05).



Figure S3 (related to Figure 3). ARv7 and ARfI ChIP-seq in LNCaP95 and 22Rv1 and AR isoformspecific fluorescence recovery after photobleaching (FRAP) microscopy

A. Western blot of nuclear lysates of LNCaP95 cells treated with vehicle (-) or 10 nM DHT (+) for 4 h. AR levels were detected (and specificity of the antibody confirmed) using ARN, ARfl or ARv7 antibodies. Equal protein loading was confirmed by probing with Lamin B1. B. Western blot of AR N-terminus (ARN) or ARv7 co-IPs, using formaldehyde cross-linked and sonicated lysates from LNCaP95 cells, in the absence of hormone. Blots were probed (IB) with either ARN or ARv7 antibodies, as indicated. C. Heatmap of ARv7 or ARN ChIP-seq signals centered at ARv7 peaks in LNCaP95 parental or shARv7 cell lines, as indicated. Each ChIP-seq dataset was normalized separately. ARv7 peak signals are hierarchically clustered by Euclidian distance and ward functions in R. 523 ARv7 peaks clustered separately. These peaks were defined as "ARv7 rejected peaks" and were removed from further downstream analyses, because they did not show signals in an additional N-terminal AR-specific cistrome, and did not show a reduction of signal with shARv7. D. Comparison of DNA binding motifs of ARfl-only (n=4737) and ARv7-ARfl-shared ChIP-seq peaks (n=2629) peaks, as defined in Figure 3B. Peaks were randomly subsampled for this analysis to 1000 each. The height of the bars represents the Zscore from SeqPos which is proportional to the p value of the motif, as well as its position within the peaks. The numbers indicate the number of times the motif was found within the 1000 peaks; multiple hits per peak are possible. E. Expression of significantly dysregulated genes (adj. p < 0.05) associated with ChIP-seq peaks as defined in D (50 kb interval around the transcription start site). The boxplots show mRNA fold changes (FC) after knock-down of either ARfl (shARfl) or ARv7 (shARv7) relative to control (shGFP). P values between groups were calculated using the Kruskal-Wallis H test. Boxplots show the median, the 1st and 3rd quartile. Whiskers extend to 1.5 the interquartile range and data beyond that is shown as individual points. F. ARfI-ARv7 ChIP-re-ChIP for select binding sites (as indicated) in LNCaP95 cells in the absence of DHT. Cells were first ChIPed with an ARfI-specific antibody (AR C19) and then re-ChIPed with either IgG (control) or an ARv7 antibody. Results are normalized to the negative control locus (Neg) and expressed as a fold change (FC) of the ARv7 re-ChIP over the IgG re-ChIP. P values were calculated relative to control (Neg) using standard t-test; *: $p \le 0.05$ G. Heatmap of ARfI and ARv7 ChIP-seq in indicated 22Rv1 cell lines treated for 4 hr with 10 nM DHT (DHT) or vehicle (ETOH). The heatmap shows the signal intensities of the 10000 most variable peaks of the ETOH-treated ChIP-seq experiments, which were then clustered on the ARfl signals using Pearson correlation. H. ChIP-seg signal profiles for the peaks in cluster I from G. P values were calculated using standard t-test; **: $p \le 0.01$; ****: $p \le 0.0001$. I. Comparison of DNA binding motifs of peaks defined in G. Peaks were randomly subsampled to 1000 each. The height of the bars represents the Zscore from SeqPos, which is proportional to the p value of the motif as well as its position within the peaks.

Table S3 (related to Figure 3) Gene Ontology Hallmark gene sets associated with ARfl only and ARfl/ARv7 shared peaks.

Examined gene set (%) Gene Set Numon (%) In Gene (%) Overlap (%) FDR q (%) FDR q (%) FDR q (%) FDR q (%) RR1 only (4737 peaks) RESPONSE Genes defining response to androgens. 32 0.3168 3.39E-18 1.69E-16 AR1 only (4737 peaks) RESPONSE 101 androgens. 32 0.3168 3.39E-18 1.69E-16 AR1 only (4737 peaks) MLIMARK 200 senoblicits. 40 0.2 1.10E-14 1.83E-13 AR1 only (4737 peaks) SIGNALING VIA 200 response to IL2 simulation. 40 0.2 1.10E-14 1.83E-13 AR1 only (4737 peaks) SIGNALING VIA Genes troubled in the G2/W -118E 1.31E-12 1.63E-11 AR1 only (4737 peaks) HALLMARK FATTY (4737 peaks) Genes defining early response to 142 30 0.165 4.81E-10 2.73E-9 AR1 only (4737 peaks) HALLMARK FATTY (4737 peaks) Genes defining early response to 147 33 0.165 4.81E-10 2.73E-9 AR1 only (4737 peaks) ACID METABOLISM Genes defining early response to introuolp			# Genes		# Genes in			
gene set Gene Set Name Set (K) Description (k) K/K p value value ARI only ANDROGEN Genes defining response to 2 0.3168 3.39E-18 1.89E-16 RRI only XENOBIOTIC in processing of drugs and other 41 0.205 2.10E-15 5.25E-14 RRI only METABOLISM Cenes up-regulated by STAT5 in 41 0.205 2.10E-15 5.25E-14 RRI only HALLMARK Cenes up-regulated by STAT5 in 41 0.205 2.10E-15 5.25E-14 (4737 peaks) FKIS Cenes up-regulated by NF-KB in 0.185 1.31E-12 1.63E-11 (4737 peaks) NFKB Constraint of through the call division cycle. 35 0.175 2.68E-11	Examined		in Gene		Overlap			FDR q
HALLMARK (4737 peaks) HALLMARK RESPONSE Genes defining response to androgene. 32 0.3168 3.39E-18 1.69E-16 ARI only (4737 peaks) RESPONSE 101 androgene. 32 0.3168 3.39E-18 1.69E-16 ARI only (4737 peaks) METABOLISM 200 Genes encoding proteins involved in processing of drugs and other vanobiotics. 41 0.205 2.10E-14 1.83E-13 ARI only (4737 peaks) STATS SIGNALING 200 response to TNF [GeneID]_7124] 37 0.185 1.31E-12 1.63E-11 ARI only (4737 peaks) NFKB Constraints in progression 35 0.175 2.68E-11 7.18E-10 ARI only (4737 peaks) NFKB Genes involved in the GZM chroaph the call division cycle. 30 0.189 8.61E-11 7.18E-10 ARI only (4737 peaks) NEETABOLISM 158 in metabolism of latity acks. 30 0.165 4.81E-10 2.73E-99 ARI only (4737 peaks) HALLMARK TORCI Genes devine on TORCI complex. 30 0.165 4.81E-10 2.73E-99 ARI only (4737 peaks) HALLM	gene set	Gene Set Name	Set (K)	Description	(k)	k/K	p value	value
ARII only AND ROGEN Genes defining response to androgene. 32 0.3168 3.39E-18 1.69E-16 (4737 peaks) HALLMARK Genes encoding proteins involved in processing of drugs and other 41 0.205 2.10E-15 5.25E-14 ARI only METABOLISM Constraints Constraints 41 0.205 2.10E-14 1.83E-13 ARI only METABOLISM Constraints Constraints 0.155 1.31E-12 1.63E-11 (4737 peaks) STATS SIGNALING Constraints Constraints 0.165 1.31E-12 1.63E-11 ARI only HALLMARK TITFA Genes sequelted by KF-KB 0.175 2.68E-11		HALLMARK						
(4737 peaks) RESPONSE 101 androgens. 32 0.3168 3.39E-18 1.69E-16 ARI only METABOLISM 200 Encessing of drugs and other (4737 peaks) AETABOLISM 200 1.69E-16 5.25E-14 ARI only METABOLISM 200 response to IL2 stimulation. 40 0.2 1.10E-14 1.83E-13 ARI only HALLMARK TNFA Genes regulated by STATS in OLS in Microbiol in the G2M 0.185 1.31E-12 1.63E-11 (4737 peaks) NFKB Checkpoint, as in progression 35 0.175 2.68E-10 2.68E-11 7.18E-10 ARI only HALLMARK C2M Checkpoint, as in progression 35 0.175 2.68E-11 7.18E-10 ARI only HALLMARK MTORC1 Genes defining early response to 0.1899 8.61E-11 7.18E-10 ARI only HALLMARK MTORC1 Genes involve in metabolism of 0.165 4.81E-10 2.73E-09 ARI only HALLMARK UV Genes encoding components of 0.165 4.81E-10 2.73E-09 ARI only	ARfl only	ANDROGEN		Genes defining response to				
HALLMARK ARII only (H737 peaks) HALLMARK III2 METABOLISM Genes encoding proteins involved in processing of drugs and other vanobiotics. 41 0.205 2.10E-15 5.25E-14 ARII only (H737 peaks) STATS SIGNALING 200 response to II.2 stimulation. 40 0.21 1.10E-14 1.33E-13 ARII only (H737 peaks) SIGNALING VIA Genes regulated by NF-KB in response to TNF [GeneID-7124] 37 0.185 1.31E-12 1.63E-11 ARII only (H737 peaks) HALLMARK KO2M Genes involved in the G2/M 0.185 1.31E-12 1.63E-11 ARII only (H737 peaks) HALLMARK KO2M Genes encoding proteins involved (H737 peaks) 0.165 4.81E-10 2.73E-09 ARII only (H737 peaks) Genes defining early response to (H737 peaks) 0.165 4.81E-10 2.73E-09 ARII only (H737 peaks) Genes involve in metabolism of activation of mTORC1 complex. 3 0.165 4.81E-10 2.73E-09 ARII only (H737 peaks) HALLMARK NUV Genes involve in metabolism of activation of mTORC1 complex. 3 0.165 4.81E-10 2.76E-09 ARII only (H737 peaks) HALLMARK NUV Genes incodu	(4737 peaks)	RESPONSE	101	androgens.	32	0.3168	3.39E-18	1.69E-16
ARI only XENOBIOTIC in processing of drugs and other (4737 peaks) METABOLISM 200 41 0.205 2.10E-15 5.25E-14 ARI only MALLMARK IL2 Genes up-regulated by STATS in other seponse to IL2 stimulation. 40 0.2 1.10E-14 1.83E-13 ARI only HALLMARK TNFA Genes regulated by NF-KB in character of the cell division cycle. 30 0.155 2.68E-11 7.18E-10 7.78E-03 ARI only HALLMARK ADUSM Genes encoding proteins involved 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MOTOCI Genes defining early response to 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MDICCI Genes up-regulated frough 30 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MDICCI Genes encoding components of 30 0.165 4.91E-10 2.73E-09 (4737 peaks) GONALING 200		HALLMARK		Genes encoding proteins involved				
(4137 peaks) METABOLISM 200 xenobiotics. 41 0.205 2.10E-15 5.25E-14 ARR only STATS SIGNALING 200 response to IL 2 stimulation. 40 0.2 1.10E-14 1.33E-13 ARI only SIGNALING VIA Genes regulated by NF-KB in 0.2 1.10E-14 1.33E-13 ARI only SIGNALING VIA Genes regulated by NF-KB in 0.185 1.31E-12 1.63E-11 ARI only HALLMARK K32M Genes involved in the G2/M 0.185 1.31E-12 1.63E-11 ARI only HALLMARK K32M Genes involved in the G2/M 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MTORCI Genes uncoding proteins involved 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MTORCI Genes involve in metabolism of 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MTORCI Genes involve in metabolism of 0.165 4.81E-10 2.73E-09 ARI only HALLMARK VU Genes involve in metabolism of 24 0.2143 4.91E-10 2.7	ARfl only	XENOBIOTIC		in processing of drugs and other				
ARI only (4737 peaks) HALLMARK IL2 STATS SIGNALING SIGNALING VIA (4737 peaks) Genes up-regulated by STATS in response to IL2 simulation. 40 0.2 1.10E-14 1.83E-13 ARI only (4737 peaks) NFKB 200 response to IL2 simulation. 40 0.2 1.10E-14 1.83E-13 ARI only (4737 peaks) NFKB 200 response to INF [GeneID-7124]. 37 0.185 1.31E-12 1.63E-11 ARI only (4737 peaks) CHECKPOINT 200 response to INF [GeneID-7124]. 37 0.185 2.68E-10 2.68E-11 2.68E-11 2.68E-11 2.68E-11 2.68E-11 2.68E-11 7.18E-10 2.73E-09 ARI only HALLMARK KATTY Genes subcomp regulated through 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MTORC1 Genes subvolve in metabolism of HALLMARK KBLE Genes dom-regulated in response to Utraviolet (UV) 1.2 1.10E-14 1.38E-10 2.73E-09 ARI only HALLMARK KUV Genes dom-regulated in response to Utraviolet (UV) 1.3 0.165 4.81E-10 2.73E-09 ARI only HALLMARK KUV resp	(4737 peaks)	METABOLISM	200	xenobiotics.	41	0.205	2.10E-15	5.25E-14
(4737 peaks) STATS SIGNALING 200 response to IL2 simulation. 40 0.2 1.10E-14 1.83E-13 ARI only SIGNALING VIA Genes regulated by NF-KB in (737 peaks) NFKB 200 response to TNF [GeneID=7124]. 37 0.185 1.31E-12 1.63E-11 ARI only HALLMARK G2M CheckOrolin, as in progression 0.175 2.68E-11 2.68E-10 ARI only HALLMARK FATTY Genes concoding proteins involved 0.1899 8.61E-11 7.18E-10 (4737 peaks) CHECKPOINT 200 etrocoding proteins involved 0.1899 8.61E-11 7.18E-10 (4737 peaks) SIGNALING 200 etrocoding proteins involved 0.1899 8.61E-11 2.73E-09 ARI only HALLMARK MTORC1 Genes defining early response to 33 0.165 4.81E-10 2.73E-09 ARI only HALLMARK BILE Genes sinvolve in metabolism of 4.737 peaks) SIGNALING 200 earles down-regulated in 20 0.1875 9.91E-10 2.73E-09 ARI only HALLMARK BILE </td <td>ARfl only</td> <td>HALLMARK IL2</td> <td></td> <td>Genes up-regulated by STAT5 in</td> <td></td> <td></td> <td></td> <td></td>	ARfl only	HALLMARK IL2		Genes up-regulated by STAT5 in				
HALLMARK TWFA Genes regulated by NF-KB in response to TNF [GeneID=7124]. 37 0.185 1.31E-12 1.63E-11 (4737 peaks) NFKB 200 response to TNF [GeneID=7124]. 37 0.185 1.31E-12 1.63E-11 ARI only HALLMARK G2M checkpoint. as in progression (4737 peaks) 0.1165 2.68E-110 2.68E-110 2.68E-111 7.18E-10 2.73E-09 ARI only HALLMARK FATTY Genes encoding proteins involved (4737 peaks) 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MTORC1 Genes involve in metabolism of 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MTORC1 Genes involve in metabolism of 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MTORC1 Genes involve in metabolism of 0.165 4.81E-10 2.73E-09 ARI only HALLMARK WU Genes involve in metabolism of 0.1187 9.91E-10 4.95E-09 ARI only HALLMARK UV response to ultraviolet (UV) 0 1.1875 9.91E-10 4.95E-09 ARI only </td <td>(4737 peaks)</td> <td>STAT5 SIGNALING</td> <td>200</td> <td>response to IL2 stimulation.</td> <td>40</td> <td>0.2</td> <td>1.10E-14</td> <td>1.83E-13</td>	(4737 peaks)	STAT5 SIGNALING	200	response to IL2 stimulation.	40	0.2	1.10E-14	1.83E-13
ARR only SIGNALING VIA (4737 peaks) Genes regulated by NF-RB in (4737 peaks) O.185 1.31E-12 1.83E-11 ARR only HALLMARK G2M Genes involved in the G2/M (checkpoint, as in progression 0.175 2.68E-11 2.68E-10 ARR only CHECKPOINT 200 through the cell division cycle. 35 0.175 2.68E-11 2.68E-10 ARR only HALLMARK FATTY Genes cencoding proteins involved 0.1899 8.61E-11 7.18E-10 (4737 peaks) ACID METABOLISM 158 in metabolism of fatty acids. 30 0.165 4.81E-10 2.73E-09 ARR only HALLMARK MTORC1 Genes up-regulated through 33 0.165 4.81E-10 2.73E-09 ARR only HALLMARK BILE Genes sinvolve in metabolism of 4737 peaks) 2.61E-10 2.73E-09 ARR only HALLMARK UV response to ultraviolet (UV) 1.4357 9.91E-10 2.73E-09 ARR only HALLMARK UV response to ultraviolet (UV) 1.43E-10 2.73E-09 ARR only HALLMARK Up-regulated in platelets. 2		HALLMARK TNFA						
(4737 peaks) NFKB 200 response to TNF [GenelD=7124] 37 0.185 1.31E-12 1.63E-11 ARR only HALLMARK G2M Cenes involved in the G2M 35 0.175 2.68E-11 2.68E-11 ARR only HALLMARK FATTY Cenes encoding proteins involved 30 0.189 8.61E-11 7.18E-10 ARR only HALLMARK MTORC1 Genes defining early response to 30 0.165 4.81E-10 2.73E-09 ARR only HALLMARK MTORC1 Genes involve in metabolism of fatty acids. 30 0.165 4.81E-10 2.73E-09 ARR only HALLMARK MTORC1 Genes involve in metabolism of 30 0.165 4.81E-10 2.73E-09 ARR only HALLMARK BUE Genes defining components of 30 0.165 4.91E-10 2.73E-09 ARR only HALLMARK UV response to ultraviolet (UV) 27 0.1875 9.91E-10 4.95E-09 ARR only HALLMARK Genes encoding components of 100 0.1875 9.91E-10 4.95E-09 ARR only HALL	ARfl only	SIGNALING VIA		Genes regulated by NF-kB in				
ARI only (4737 peaks) HALLMARK G2M CHECKPOINT Genes involved through the cell division cycle. 35 0.175 2.68E-10 2.68E-10 ARI only (4737 peaks) HALLMARK FATTY Cenes encoding proteins involved HALLMARK 30 0.1899 8.61E-11 7.18E-10 ARI only (4737 peaks) ESTROGEN RESPONSE EARLY 200 estrogen. 33 0.165 4.81E-10 2.73E-09 ARI only (4737 peaks) HALLMARK MTORC1 (4737 peaks) Genes up-regulated through activation of mTORC1 complex. 33 0.165 4.81E-10 2.73E-09 ARI only (4737 peaks) HALLMARK BUE Genes down-regulated in response to Ultraviolet (UV) 27 0.1875 9.91E-10 2.73E-09 ARI only (4737 peaks) HALLMARK BUE Genes down-regulated in response to Ultraviolet (UV) 27 0.1875 9.91E-10 4.95E-09 ARI only (4737 peaks) HALLMARK Up-regulated in platelets. 26 0.1884 1.80E-09 7.42E-09 ARI only (4737 peaks) HALLMARK Genes defining late response to estrogen. 2 0.16 1.39E-09 7.42E-09 ARI only (4737 peaks) HALLMARK	(4737 peaks)	NFKB	200	response to TNF [GeneID=7124].	37	0.185	1.31E-12	1.63E-11
ARI only HALLMARK G2M checkpoint, as in progression (4737 peaks) CHECKPOINT 200 through the cell division cycle. 35 0.175 2.68E-10 2.68E-11 7.18E-10 ARI only HALLMARK FATTY Genes encoding proteins involved 33 0.169 8.61E-11 7.18E-10 ARI only HALLMARK Genes defining early response to 33 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MTORC1 Genes up-regulated through 33 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MTORC1 Genes involve in metabolism of 33 0.165 4.81E-10 2.73E-09 ARI only HALLMARK UV response to ultraviole (UV) 7 0.213 4.91E-10 2.73E-09 ARI only HALLMARK UV response to ultraviole (UV) 7 0.1875 9.91E-10 4.95E-09 CARI only HALLMARK UV response to ultraviole (UV) 7 0.1875 9.91E-10 4.95E-09 ARI only HALLMARK Uv resencoding components of 7 <				Genes involved in the G2/M				
(4737 peaks) CHECKPOINT 200 through the cell division cycle. 35 0.175 2.68E-11 2.67E	ARfl only	HALLMARK G2M		checkpoint, as in progression				
ARR only HALLMARK FATTY Genes encoding proteins involved in metabolism of faty acids. 30 0.1899 8.61E-11 7.18E-10 ARI only HALLMARK Genes defining early response to estrogen. 33 0.165 4.81E-10 2.73E-09. ARI only HALLMARK MTORC1 Genes up-regulated through (4737 peaks) 33 0.165 4.81E-10 2.73E-09. ARI only HALLMARK MTORC1 Genes involve in metabolism of (4737 peaks) 0.165 4.81E-10 2.73E-09. ARI only HALLMARK BILE Genes involve in metabolism of (4737 peaks) 0.165 4.81E-10 2.73E-09. ARI only HALLMARK VU response to ultraviolet (UV) 7 0.1875 9.91E-10 4.95E-09. ARI only HALLMARK blood coagulation system; also (4737 peaks) 0.161 1.93E-09 7.42E-09. ARI only ESTROGEN Genes defining late response to (4737 peaks) 1.93E-09 7.42E-09 2.016 1.93E-09 7.42E-09. ARI only HALLMARK Genes encoding components of (4737 peaks) 1.0155 7.47E-09 2.67E-08. ARI only </td <td>(4737 peaks)</td> <td>CHECKPOINT</td> <td>200</td> <td>through the cell division cycle.</td> <td>35</td> <td>0.175</td> <td>2.68E-11</td> <td>2.68E-10</td>	(4737 peaks)	CHECKPOINT	200	through the cell division cycle.	35	0.175	2.68E-11	2.68E-10
Identify Action Merk Solution	ARfl only	HALLMARK FATTY		Genes encoding proteins involved				
HALLMARK Genes defining early response to (473 peaks) RESPONSE EARLY 200 estrogen. 33 0.165 4.81E-10 2.73E-09 ARII only HALLMARK MTORC1 Genes up-regulated through 33 0.165 4.81E-10 2.73E-09 ARII only HALLMARK BILE Genes involve in metabolism of 0.2143 4.91E-10 2.73E-09 ARII only HALLMARK VU Genes down-regulated in Compose to ultraviolet (UV) 1.80E-09 2.73E-09 ARII only HALLMARK UV response to ultraviolet (UV) 1.80E-09 7.42E-09 ARII only HALLMARK Genes defining late response to 26 0.1884 1.80E-09 7.42E-09 ARII only HALLMARK Genes defining late response to 32 0.16 1.93E-09 7.42E-09 ARII only ESSPONSE LATE 200 else sencoding components of 32 0.16 1.93E-09 7.42E-09 ARII only HALLMARK Genes up-regulated in response 32 0.16 1.93E-09 7.42E-09 ARII only	(4737 peaks)	ACID METABOLISM	158	in metabolism of fatty acids.	30	0.1899	8.61E-11	7.18E-10
ARI only ESTROGEN Genes defining early response to 33 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MTORC1 Genes up-regulated through 33 0.165 4.81E-10 2.73E-09 ARI only HALLMARK BILE Genes involve in metabolism of 33 0.165 4.81E-10 2.73E-09 ARI only HALLMARK BILE Genes down-regulated in 7 2.73E-09 ARI only HALLMARK UV response to ultraviolet (UV) 7472 peaks) 2.73E-09 ARI only HALLMARK UV response to ultraviolet (UV) 7.74E-09 7.42E-09 ARI only HALLMARK blood coagulation system; also 2.6 0.1884 1.80E-09 7.42E-09 ARI only ESTROGEN Genes defining late response to 2.0 1.93E-09 7.42E-09 ARI only ESTROGEN Genes up-regulated in response 2.0 1.93E-09 7.42E-09 ARI only HALLMARK HYPOXIA 200 and networks. 31 0.155 7.42E-09 ARI only HALLMARK HYPOXIA 2		HALLMARK		•				
(4737 peaks) RESPONSE EARLY 200 estrogen. 33 0.165 4.81E-10 2.73E-09 ARI only HALLMARK MTORC1 Genes up-regulated through (4737 peaks) 33 0.165 4.81E-10 2.73E-09 ARI only HALLMARK BILE Genes up-regulated in regense down-regulated in Genes encoding components of (4737 peaks) 24 0.2143 4.91E-10 2.73E-09 ARI only HALLMARK UV regense down-regulated in regense down-regulated in radiation. 27 0.1875 9.91E-10 4.95E-09 ARI only HALLMARK UV response to Utraviolet (UV) 27 0.1875 9.91E-10 4.95E-09 ARI only HALLMARK blood coagulation system; also 26 0.1884 1.80E-09 7.42E-09 ARI only HALLMARK blood coagulation system; also 26 0.16 1.93E-09 7.42E-09 ARI only HALLMARK Genes encoding components of 4737 peaks) 1.93E-09 7.42E-09 ARI only HALLMARK HYPOXIA Genes encoding components of 4737 peaks) 1.93E-09 7.42E-09 ARI only </td <td>ARfl only</td> <td>ESTROGEN</td> <td></td> <td>Genes defining early response to</td> <td></td> <td></td> <td></td> <td></td>	ARfl only	ESTROGEN		Genes defining early response to				
ARI only HALLMARK MTORC1 (4737 peaks) Genes up-regulated through activation of mTORC1 complex. 33 0.165 4.81E-10 2.73E-09 ARI only HALLMARK BILE Genes involve in metabolism of deres down-regulated in 24 0.2143 4.91E-10 2.73E-09 ARI only HALLMARK BILE Genes down-regulated in 24 0.2143 4.91E-10 2.73E-09 ARI only HALLMARK UV response to ultraviolet (UV) 4.91E-10 2.73E-09 ARI only HALLMARK Genes down-regulated in 27 0.1875 9.91E-10 4.95E-09 ARI only HALLMARK Genes down-regulated in plateletis. 26 0.1884 1.80E-09 7.42E-09 ARI only ESTROGEN Genes up-regulated in response to estrogen. 32 0.16 1.93E-09 7.42E-09 ARI only HALLMARK Genes up-regulated in response to estrogen. 32 0.16 1.93E-09 7.42E-09 ARI only HALLMARK HYPOXIA 200 ot low oxygen levels (hypoxia). 32 0.16 1.93E-09 7.42E-09 ARI only <td>(4737 peaks)</td> <td>RESPONSE EARLY</td> <td>200</td> <td>estrogen.</td> <td>33</td> <td>0.165</td> <td>4.81E-10</td> <td>2.73E-09</td>	(4737 peaks)	RESPONSE EARLY	200	estrogen.	33	0.165	4.81E-10	2.73E-09
(4737 peaks) SIGNALING 200 activation of mTORC1 complex. 33 0.165 4.81E-10 2.73E-09 ARIt only HALLMARK BILE Genes involve in metabolism of 0.165 4.91E-10 2.73E-09 ARIt only HALLMARK BULE Genes involve in metabolism of 0.2143 4.91E-10 2.73E-09 ARIt only HALLMARK UV response to Ultraviolet (UV) 7 0.1875 9.91E-10 4.95E-09 ARIt only HALLMARK Uradiation. 27 0.1875 9.91E-10 4.95E-09 ARIt only HALLMARK Diood coagulation system; also 26 0.1884 1.80E-09 7.42E-09 ARIt only HALLMARK Diood coagulation system; also 20 1.93E-09 7.42E-09 ARIt only RESPONSE LATE 200 estrogen. 32 0.16 1.93E-09 7.42E-09 ARIt only HALLMARK HYPOXI Genes encoding components of 1.93E-09 7.42E-09 ARIt only HALLMARK HYPOXI Genes encoding components of 1.97E-08 5.96E-08	ARfl only	HALLMARK MTORC1		Genes up-regulated through				
ARIT only HALLMARK BILE Genes involve in metabolism of 24 0.2143 4.91E-10 2.73E-09 Genes down-regulated in response to ultraviolet (UV) response to ultraviolet (UV) 7 0.1875 9.91E-10 4.95E-09 ARII only HALLMARK UV response to ultraviolet (UV) 7 0.1875 9.91E-10 4.95E-09 ARII only HALLMARK Genes encoding components of 0.1884 1.80E-09 7.42E-09 ARII only HALLMARK Genes defining late response to 20.16 1.93E-09 7.42E-09 ARII only ESTROCEN Genes up-regulated in response 20.16 1.93E-09 7.42E-09 ARII only HALLMARK Genes up-regulated in response 20.16 1.93E-09 7.42E-09 ARII only HALLMARK P53 Genes up-regulated in p53 pathways 31 0.155 7.42E-09 ARII only HALLMARK P53 Genes encoding components of 21 0.2019 1.79E-08 5.96E-08 ARII only HALLMARK Genes encoding components of 21 0.2019 1.79E-08 5.96E-08 ARII only HALLMARK Gen	(4737 peaks)	SIGNALING	200	activation of mTORC1 complex.	33	0.165	4.81E-10	2.73E-09
[4737 péaks] ACID METABOLISM 112 bile acids and salts. 24 0.2143 4.91E-10 2.73E-09 ARfl only HALLMARK UV Genes down-regulated in response to ultraviolet (UV) 27 0.1875 9.91E-10 4.95E-09 ARfl only HALLMARK CoAGULATION 138 up-regulated in platelets. 26 0.1884 1.80E-09 7.42E-09 ARfl only HALLMARK Bile acids and salts. 26 0.1884 1.80E-09 7.42E-09 ARfl only HALLMARK Bile acids and salts. 26 0.1884 1.80E-09 7.42E-09 ARfl only HALLMARK Genes defining late response to estrogen. 32 0.16 1.93E-09 7.42E-09 ARfl only HALLMARK HYPOXIA 200 to low oxygen levels (hypoxia). 32 0.16 1.93E-09 7.42E-09 ARfl only HALLMARK HYPOXIA 200 and networks. 31 0.155 7.47E-09 2.67E-08 ARfl only HALLMARK Genes encoding components of 1.97E-08 5.96E-08 (4	ARfl only	HALLMARK BILE		Genes involve in metabolism of				
ARfl only HALLMARK UV Genes down-regulated in response to ultraviolet (UV) (4737 peaks) RESPONSE DN 144 response to ultraviolet (UV) ARfl only HALLMARK Genes encoding components of 0.1875 9.91E-10 4.95E-09 ARfl only HALLMARK blood cosquilation system; also 0.1884 1.80E-09 7.42E-09 ARfl only ESTROGEN Genes defining late response to estrogen. 32 0.16 1.93E-09 7.42E-09 ARfl only ESTROGEN Genes up-regulated in response to estrogen. 32 0.16 1.93E-09 7.42E-09 ARfl only HALLMARK HYPOXIA 200 to low oxygen levels (hypoxia). 32 0.16 1.93E-09 7.42E-09 ARfl only HALLMARK PS3 Genes encoding components of peroxisome. 21 0.2019 1.79E-08 5.96E-08 ARfl only HALLMARK Genes encoding proteins involved in glycolysis and glycolysis and glycolysis and glycolysis and glycolycolysis and glycolycolysis and glycolycel differentiation 2.79E-08 8.20E-08 ARfl only HALLMARK Genes up-regulated during adipocyte differentiation 2.0 0.15 2.79E-08 8.20E-08	(4737 peaks)	ACID METABOLISM	112	bile acids and salts.	24	0.2143	4.91E-10	2.73E-09
ARI only HALLMARK UV response to ultraviolet (UV) (4737 peaks) RESPONSE DN 144 radiation. 27 0.1875 9.91E-10 4.95E-09 ARI only HALLMARK blood coagulation system; also 0 0.1884 1.80E-09 7.42E-09 (4737 peaks) COAGULATION 138 up-regulated in platelets. 26 0.1884 1.80E-09 7.42E-09 ARI only ESTROGEN Genes defining late response to 2 0.16 1.93E-09 7.42E-09 ARI only ESTROGEN Genes up-regulated in response 32 0.16 1.93E-09 7.42E-09 ARI only HALLMARK HYPOXIA 200 to low oxygen levels (hypoxia). 31 0.155 7.47E-09 2.67E-08 ARI only HALLMARK Genes encoding components of 0 1.93E-09 7.42E-09 (4737 peaks) PEROXISOME 104 peroxisome. 21 0.2019 1.79E-08 5.96E-08 ARI only HALLMARK Genes encoding proteins involved in glycolysis and 0 0.15 2.79E-08 8.20E-08 ARI only HALLMARK				Genes down-regulated in				
(4737 peaks) RESPONSE DN 144 radiation 27 0.1875 9.91E-10 4.95E-09 AR1 only HALLMARK Genes encoding components of blood coagulation system; also 0 7.42E-09 7.42E-09 AR1 only HALLMARK up-regulated in platelets. 26 0.1884 1.80E-09 7.42E-09 AR1 only ESTROGEN Genes defining late response to estrogen. 32 0.16 1.93E-09 7.42E-09 AR1 only HALLMARK Genes up-regulated in response 32 0.16 1.93E-09 7.42E-09 AR1 only HALLMARK Genes involved in p53 pathways 31 0.155 7.47E-09 2.67E-08 AR1 only HALLMARK Genes encoding proteins involved in p153 pathways 31 0.155 7.47E-09 2.67E-08 AR1 only HALLMARK Genes encoding proteins involved in glycolysis and 6.17E-08 8.20E-08 AR1 only HALLMARK Genes up-regulated during adipcycte differentiation 4.73F peaks) 30 0.15 2.79E-08 8.20E-08 AR1 only HALLMA	ARfl only	HALLMARK UV		response to ultraviolet (UV)				
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ARfl and ARv7 ANDROGEN Genes defining response to (2629 peaks) RESPONSE 101 androgens. 25 0.2475 2.11E-17 1.06E-15 HALLMARK TNFA HALLMARK TNFA Genes regulated by NF-kB in 200 response to TNF [GeneID=7124]. 28 0.14 1.23E-12 3.07E-11 ARfl and ARv7 HALLMARK G2M Genes involved in the G2/M checkpoint, as in progression 200 0.145 0.1		HALLMARK	200			0.100		c. 2 00
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ARfl and ARv7 HALLMARK G2M OUTED FOR THE CONTRACT OF THE CONTRACT. THE CONTRACT OF THE CONTRAC	(2629 neaks)	NEKB	200	response to TNF [GeneID-712/]	28	0 14	1 23E-12	3 07E-11
ARfl and ARv7 HALLMARK G2M checkpoint, as in progression	(2020 pouro)		200	Genes involved in the G2/M	20	0.17		5.07 E 11
	ARfl and $\Delta Rv7$	HALLMARK G2M		checkpoint as in progression				
(2629 peaks) CHECKPOINI 200 through the cell division cvcle. 23 0.115 6.16F-09 1.03F-07	(2629 peaks)	CHECKPOINT	200	through the cell division cvcle.	23	0.115	6.16E-09	1.03E-07

ARfl and ARv7	HALLMARK MITOTIC		Genes important for mitotic				
(2629 peaks)	SPINDLE	200	spindle assembly.	22	0.11	2.95E-08	2.95E-07
· · · ·	HALLMARK		Genes encoding proteins involved				
ARfl and ARv7	XENOBIOTIC		in processing of drugs and other				
(2629 peaks)	METABOLISM	200	xenobiotics.	22	0.11	2.95E-08	2.95E-07
			Genes up-regulated during				
ARfl and ARv7	HALLMARK		adipocyte differentiation				
(2629 peaks)	ADIPOGENESIS	200	(adipogenesis).	21	0.105	1.34E-07	9.60E-07
ARfl and ARv7	HALLMARK KRAS		Genes up-regulated by KRAS				
(2629 peaks)	SIGNALING UP	200	activation.	21	0.105	1.34E-07	9.60E-07
ARfl and ARv7	HALLMARK IL2		Genes up-regulated by STAT5 in				
(2629 peaks)	STAT5 SIGNALING	200	response to IL 2 stimulation.	20	0.1	5.82E-07	3.64E-06
(2020 pound)			Genes involved in metabolism of		••••	0.022 0.	0.0.12.00
			heme (a cofactor consisting of				
ARfl and ARv7	HALLMARK HEME		iron and porphyrin) and				
(2629 neaks)	METABOLISM	200	erythroblast differentiation	19	0 095	2 39E-06	1 33E-05
(2020 peaks)		200	Genes up-regulated during	10	0.000	2.001 00	1.002 00
A Pfl and A Pv7	HALLMARK		production of male gametes				
(2620 neaks)	SPERMATOGENESIS	135	(sperm) as in spermatogenesis	15	0 1 1 1 1	1 00E-06	2 00E-05
(2023 реакз)	HALLMARK	100	(sperin), as in sperinatogenesis.	10	0.1111	4.00L-00	2.00L-00
A Bfl and A Dv7			Conoc defining inflammatory				
(2620 poaks)		200		19	0.00	0.265.06	4 21 E 05
(2029 peaks)		200	Tesponse.	10	0.09	9.202-00	4.21E-03
A Dfl and A Dv7			Conce involved in chalasteral				
(2620 pooko)		74	benes involved in cholesterol	10	0 1 2 5 1	2 045 05	1 21 5 04
(2029 peaks)	TIONEOSTASIS	/4	Conce un regulated in reanance	10	0.1351	2.946-05	1.216-04
(2620 packs)		200	Genes up-regulated in response	17	0.005		1 21 5 04
(2029 peaks)		200	to low oxygen levels (hypoxia).	17	0.065	3.39E-05	1.21E-04
			Canad an adding protoing involved				
ARII and ARV/		200	Genes encoding proteins involved	47	0.005		
(2629 peaks)	PHOSPHORYLATION	200	In oxidative phosphorylation.	17	0.085	3.39E-05	1.21E-04
ARTI and ARV/	HALLMARK APICAL	000	Genes encoding components of	4.0	0.00	4 475 04	0.045.04
(2629 peaks)	JUNCTION	200	apical junction complex.	16	0.08	1.17E-04	3.24E-04
			Genes encoding cell cycle related				
ARfl and ARV/	HALLMARK E2F		targets of E2F transcription	4.0			
(2629 peaks)	TARGETS	200	factors.	16	0.08	1.17E-04	3.24E-04
			Genes encoding proteins involved				
ARfl and ARv7	HALLMARK		in glycolysis and				
(2629 peaks)	GLYCOLYSIS	200	gluconeogenesis.	16	0.08	1.17E-04	3.24E-04
ARfl and ARv7	HALLMARK MTORC1		Genes up-regulated through				
(2629 peaks)	SIGNALING	200	activation of mTORC1 complex.	16	0.08	1.17E-04	3.24E-04
ARfl and ARv7	HALLMARK FATTY		Genes encoding proteins involved				
(2629 peaks)	ACID METABOLISM	158	in metabolism of fatty acids.	13	0.0823	3.77E-04	8.99E-04
	HALLMARK		Genes defining epithelial-				
	EPITHELIAL		mesenchymal transition, as in				
ARfl and ARv7	MESENCHYMAL		wound healing, fibrosis and				
(2620 noaks)	TRANSITION	200	metastasis.	15	0.075	3.77E-04	8.99E-04

Pathways highlighted in blue are with the top 20 enriched pathways for both the genes associated with the ARfl only and the ARfl and ARv7 peaks.



Figure S4 (related to Figure 4). ARv7 and ARfI coregulator interaction assays

A. Line plots (*left*) and representative images (*right*) of FRAP microscopy of wild-type ARfl or ARv7 and their respective DNA-binding mutants (R585K). Results are the mean of 33-47 cells ± SEM and are shown in arbitrary units (AU). Image scale bar is 10 µm. B. MARCoNI peptide binding array of cell lysates from shGFP (dotted green), shARv7 (solid blue) and shARfl cells (solid red) grown in the presence of dox for 3 days and induced with 10 nM DHT for 30 min. Peptide binding for AR was assessed with a pan-AR antibody, and mean binding (± SEM), displayed as arbitrary binding units (AU) of triplicate experiments, is shown. Statistically significant interactions with classical corepressors are highlighted in bold. C. Representative example of the co-immunoprecipitation (co-IP) of ARv7 with selected co-repressors (NCOR1 and NCOR2) using nuclear lysates of shGFP, shARv7 and shARfl LNCaP95 cells grown in the absence of hormone (used in Figure 4B). D. Representative example of Input samples (1/25th of the IP samples) for co-IPs from B. before IP with IgG or ARv7. E. Quantification of all Input samples in arbitrary units (AU). F, G. Volcano plots for the experiments depicted in Figure 4C. Expression fold changes (FC) and adjusted p values (adj. p) after siRNA-mediated knock-down of NCOR1 (siNCOR1, F) and siNCOR2 (siNCOR2, G) relative to a si control (siCtrl) are shown in LNCaP95 cells with additional depletion of either ARv7 (shARv7), ARfl (shARfl) or a control (shGFP). H. Heatmap of genes significantly (adj.p < 0.05) dysregulated upon siRNA-mediated silencing of NRIP1 (siNRIP1) in LNCaP95 cell lines with an additional knock down of either ARv7 (shARv7), ARfl (shARfl) or a control (shGFP). The analysis was performed together with the one in Figure 4C. The heatmap shows the log₂ fold changes of the dysregulated genes for the indicated siRNA-treatments relative to a si control in each row.



Figure S5 (related to Figure 5). Clustering of ChIP-seq peaks and FOXA1 protein levels in ARfl and ARv7 knockdown cells

A. Hierarchical clustering of the normalized read-counts from H3K27ac ChIP-seq, for the ARv7 and ARfl peaks defined in Figure 3B. The clustering is used in Figures 5A-5F. **B.** *Left*: Western blot of nuclear lysates of dox-inducible shGFP, shARv7 and shARfl cells, grown with dox for 3 days. Proteins were detected with indicated antibodies. Lamin B1 serves as a loading control. *Right*: Quantification of Western Blot signals. Signals of the ARfl-, ARv7- and FOXA1 antibodies were normalized to their Lamin B1 values and expressed as a fold change (FC) relative to shGFP **C.** ARfl, H3K27ac and FOXA1 ChIP-seq signals in indicated LNCaP95 cell lines (shGFP, shARfl and shARv7) at ARfl only (n=4737) and at ARfl/ARv7 shared peaks (n=2629), as defined in Figure 3B. The difference in the medians between ARfl/ARv7 shared and ARfl only peaks is indicated. Boxplots show the median, the 1st and 3rd quartile. Whiskers extend to 1.5 the interquartile range. P values were calculated using standard t-test; ****: p ≤ 0.0001.



Figure S6 (related to Figure 6). IHC controls for the ARv7-specific antibody and expression levels of ARv7-repressed target genes that inhibit CRPC growth

A-C. Representative staining and scores (average nuclear optical density multiplied with the fraction of positive nuclei) from PCa spots on TMA 55, stained with an ARv7-specific antibody. A. low ARv7, score: 4; B. medium ARv7, score: 14; C. high ARv7, score: 24. **D.** Heatmap of leading edge gene expression levels in patient samples, as determined by GSEA (see Figure 6B). Patients were selected according to the lowest (low ARv7 expression) and highest quartiles (high ARv7 expression) of ARv7 IHC scores. E. Expression of B4GALT1, HIF1A, SLC30A7 and SNX14 in patients with known AR (left) and PTEN (right) copy number variations (CNV). Patients were grouped by cbioportal (Cerami et al., 2012) into deep deletions potentially missing both copies (Deep Del), shallow deletion potentially missing one copy (Sh. Del.), diploid having two copies (Dipl.) gain indicating a low level amplification (Gain) and amplification indicating a high level amplification (Amp.). Samples with AR (red), PTEN (green), B4GALT1 (azure) or SNX14 mutations (blue) are color-coded. No mutations were detected for SLC30A7 or HIF1A. Boxplots show the median, the 1st and 3rd guartile. Whiskers extend to 1.5 the interquartile range. P values were calculated using Wilcoxon test; n.s.; not significant p > 0.05; *: $p \le$ 0.05; **: $p \le 0.01$; ****: $p \le 0.0001$. **F.** Hierarchical clustering of the 4 ARv7-regulated, positively-selected target genes from Figure 6D, and gene expression data from patient samples (Taylor et al., 2010). Three clusters, low (blue), mixed (orange) and high (red), based on the average expression of the 4 genes, are shown. G, H. Kaplan-Meier graphs of PSA recurrence-free survival (BCR Free Survival) for the three patient clusters defined in F. Data for either primary or metastatic samples (G), or primary samples only are shown (H). P values were determined using the log rank test; ns: not significant; *: p < 0.05; **: p < 0.01. I. Heatmap of gene expression levels of the ARv7-repressed target genes B4GALT1, SLC30A7, HIF1A, and SNX14 in primary compared to metastatic PCa in the Taylor dataset (Taylor et al., 2010).