

Cheminformatics driven development of novel therapies for drug resistant prostate cancer

Artem Cherkasov PhD, DSc



a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA



VANCOUVER
PROSTATE CENTRE
A UBC & VGH Centre of Excellence



Conflicts

La Hoffman-Roche collaborator, licensor
LeadGen Ltd consultant, Aranda contractor

ANDRONEX Pharmaceuticals

ABT Therapeutics

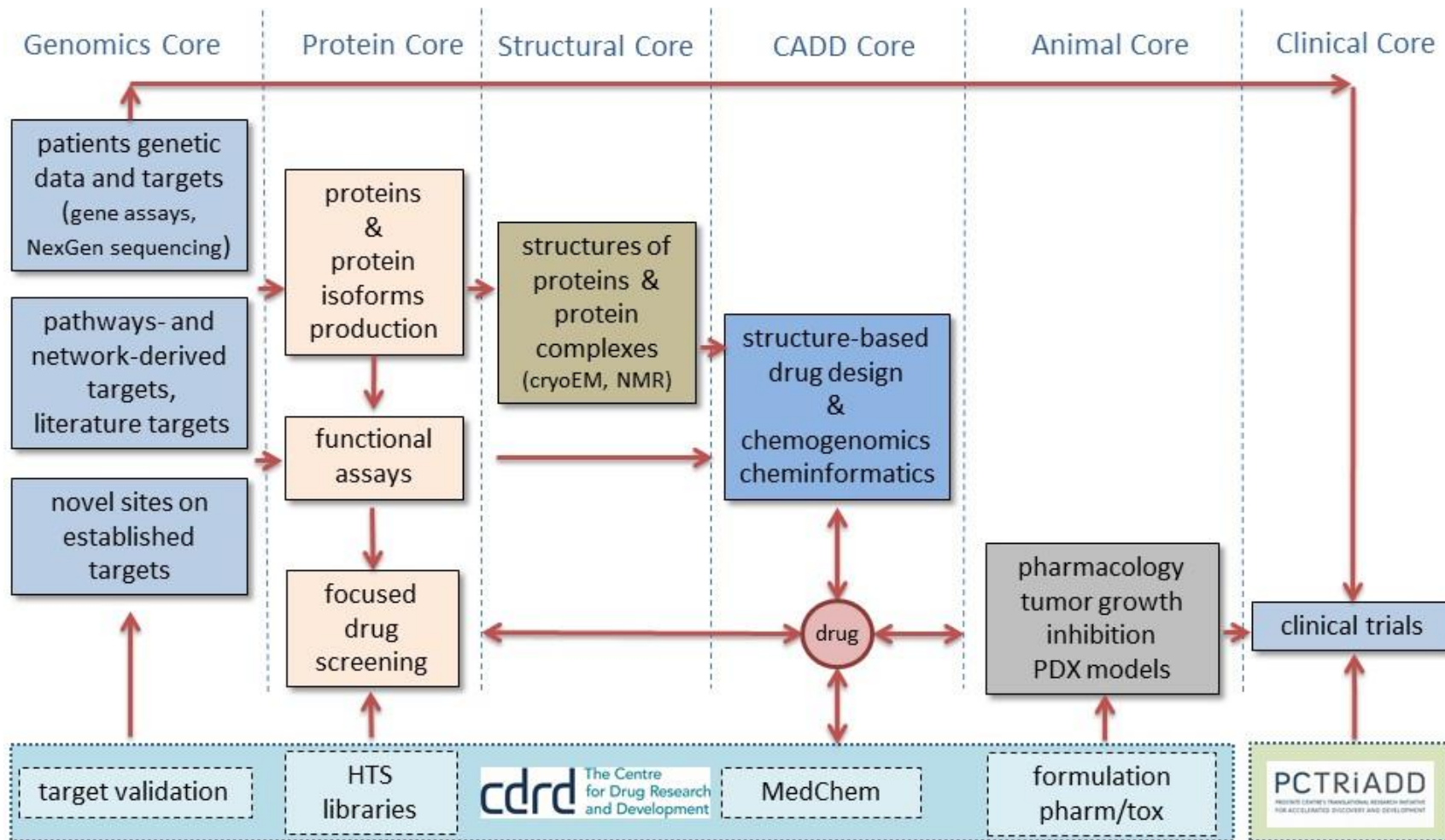
LAST Innovation

APT Therapeutics

INDEL Therapeutics

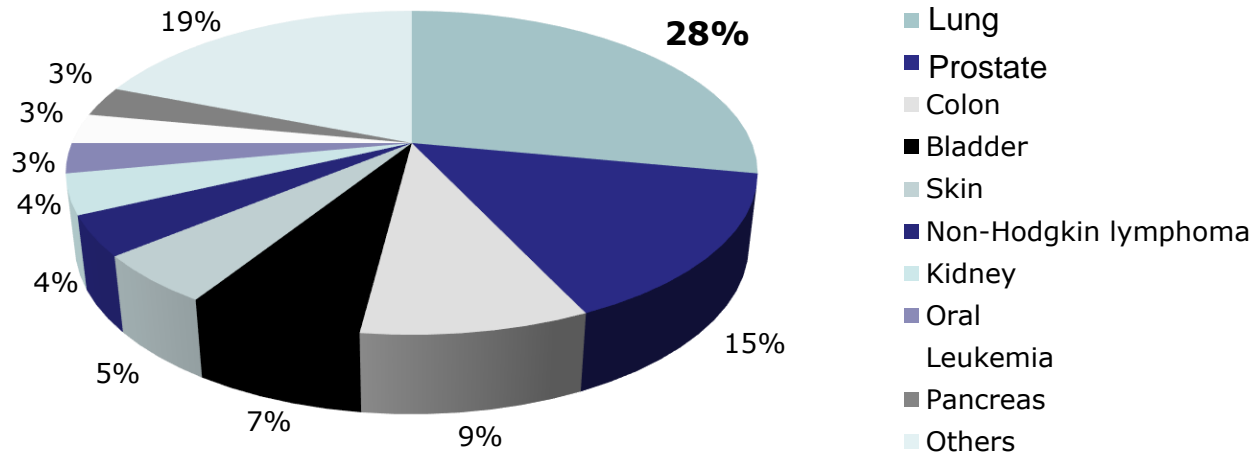
founder and shareholder

Lab Organization & Structure



Prostate Cancer

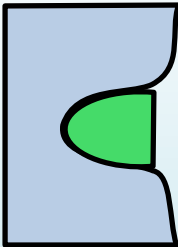
- Estimated new cancer cases in males



AR Mechanism of Action

Prostate Cell

Androgen Receptor



Androgen (DHT)

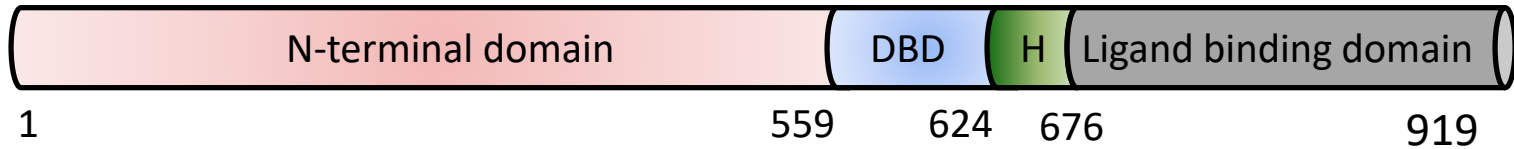
Nucleus



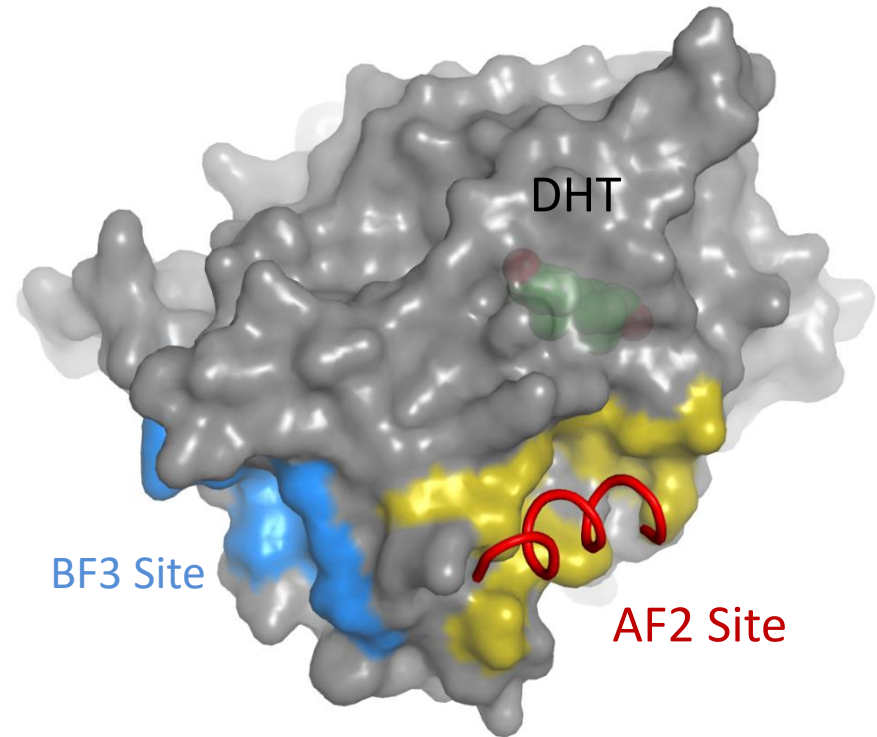
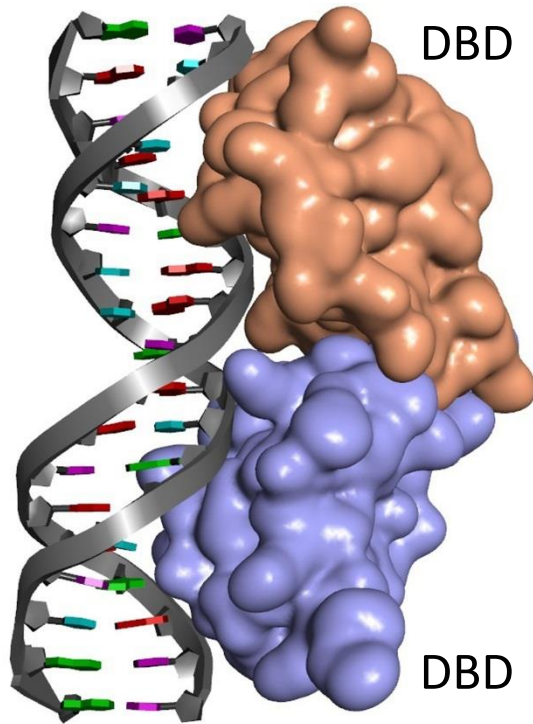
Transactivation of AR regulated genes

AR Conventional (LBD) Targeting

Structural Domains of AR



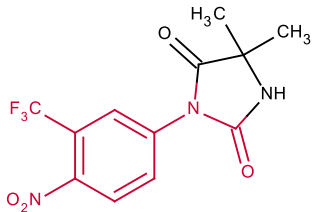
?
NTD



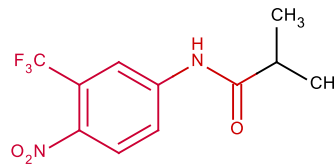
AR Inhibitors as Prostate Cancer Drugs

- AR inhibitors are used as androgen deprivation therapy
- They all exhibit similar mode of action (target DHT site)
- They share similar chemical scaffold

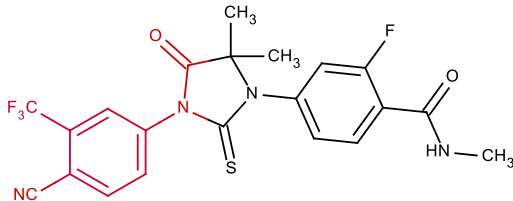
Nilutamide



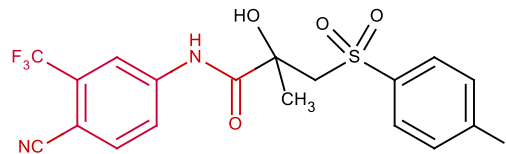
Flutamide



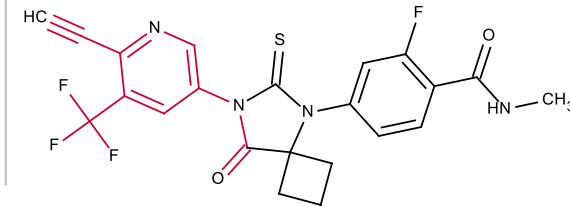
Enzalutamide



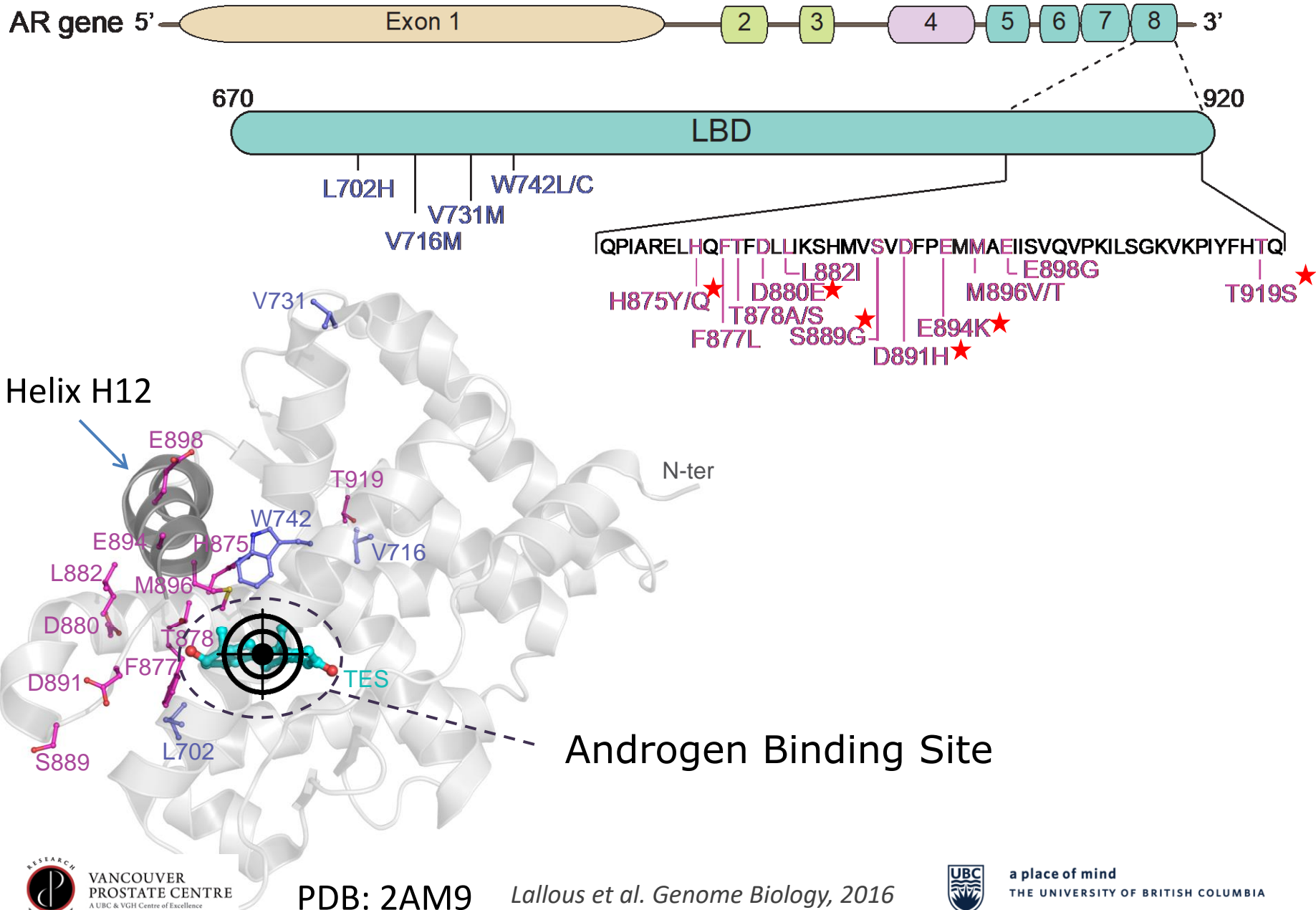
Bicalutamide



ARN-509



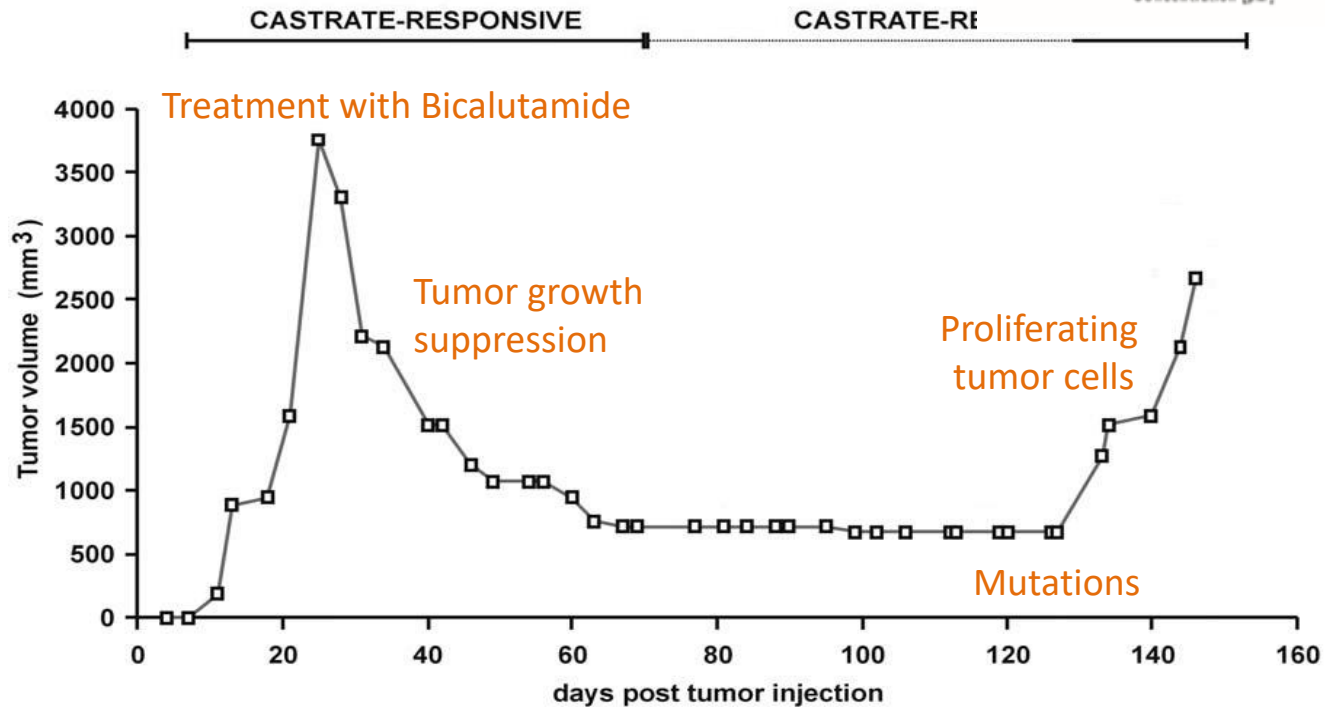
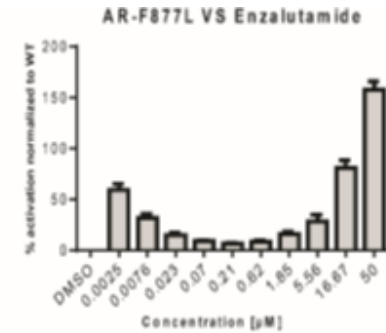
Identification of AR mutants using liquid biopsy



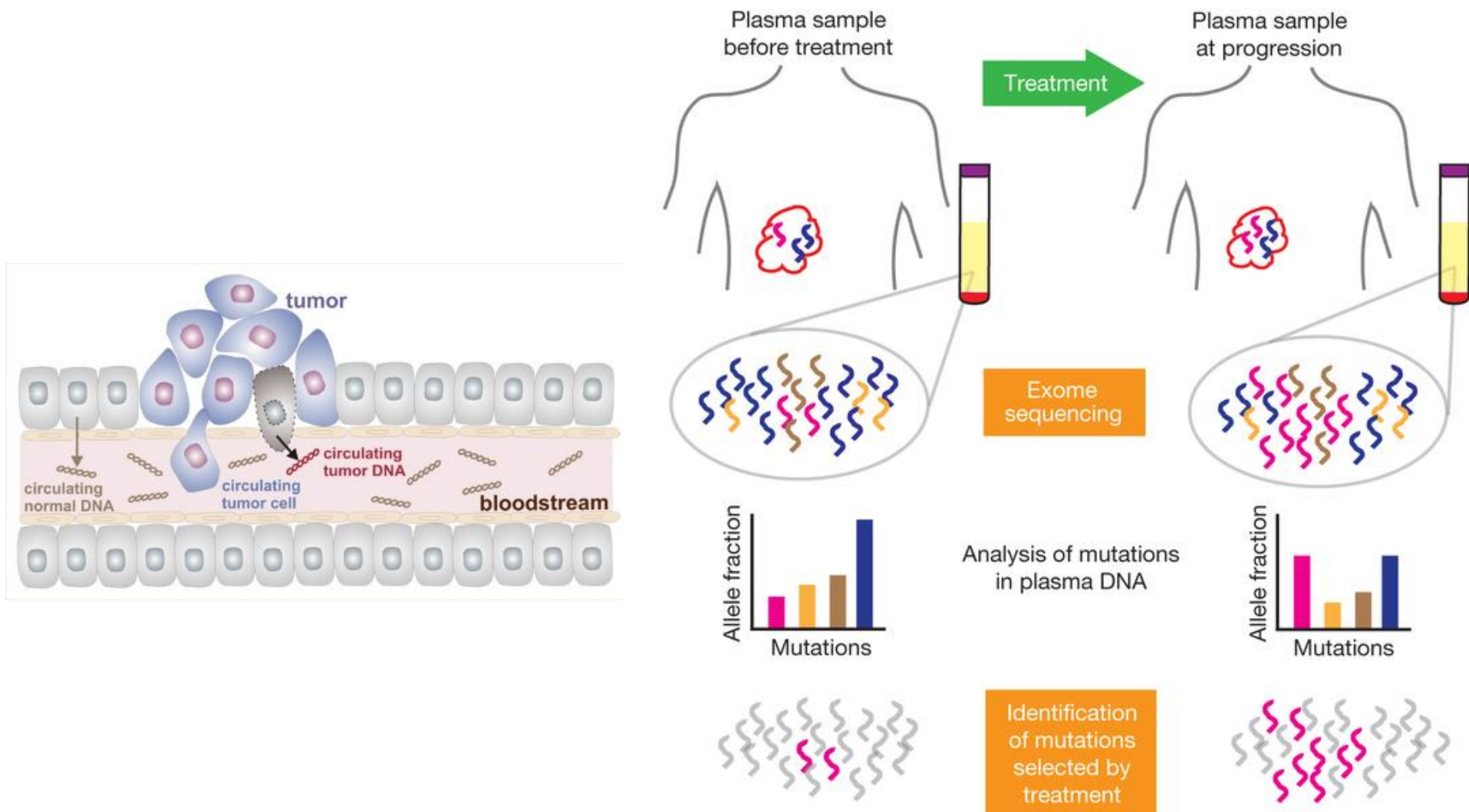
Factors that Causes Resistance to Anti-AR Drugs

Mutations in the DHT site hampers the efficacy of known anti-androgens

- **W741C** : Bicalutamide
- **T877A** : Flutamide
- **F876L** : Enzalutamide

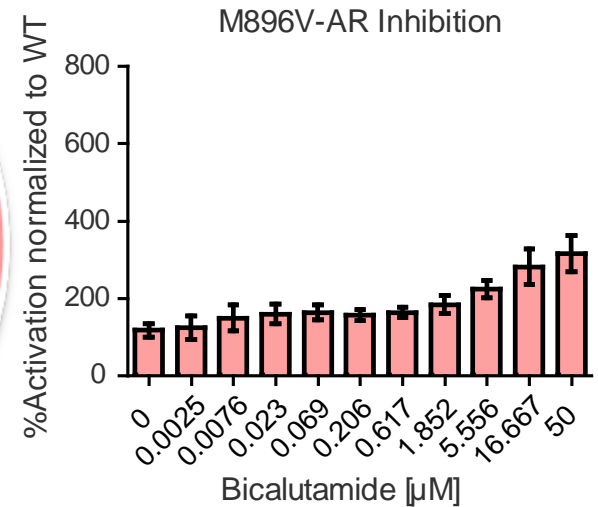
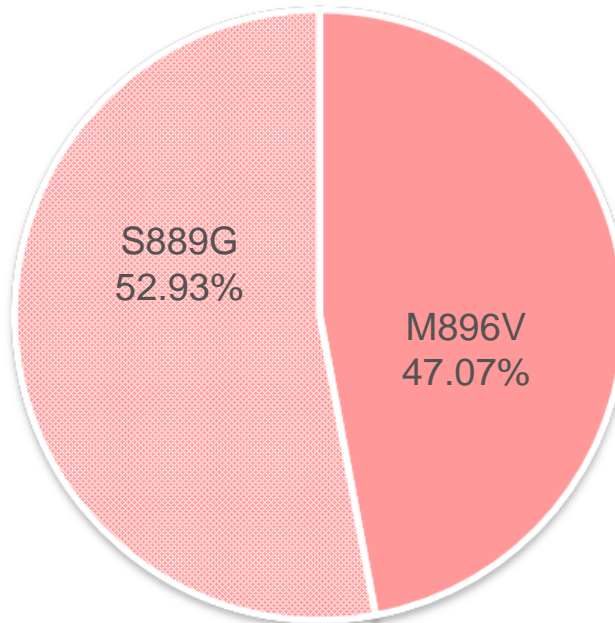
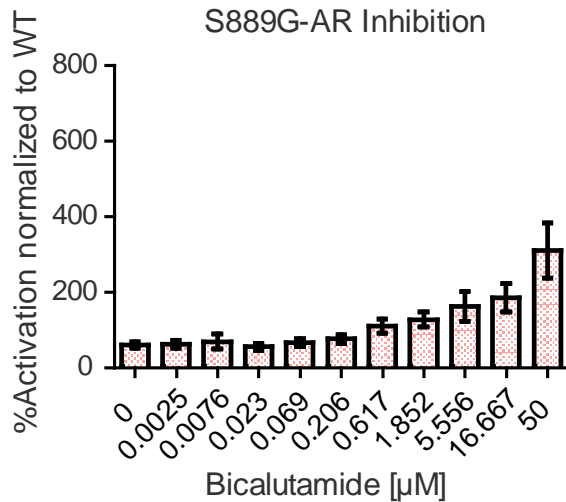


Circulating Cell Free DNA



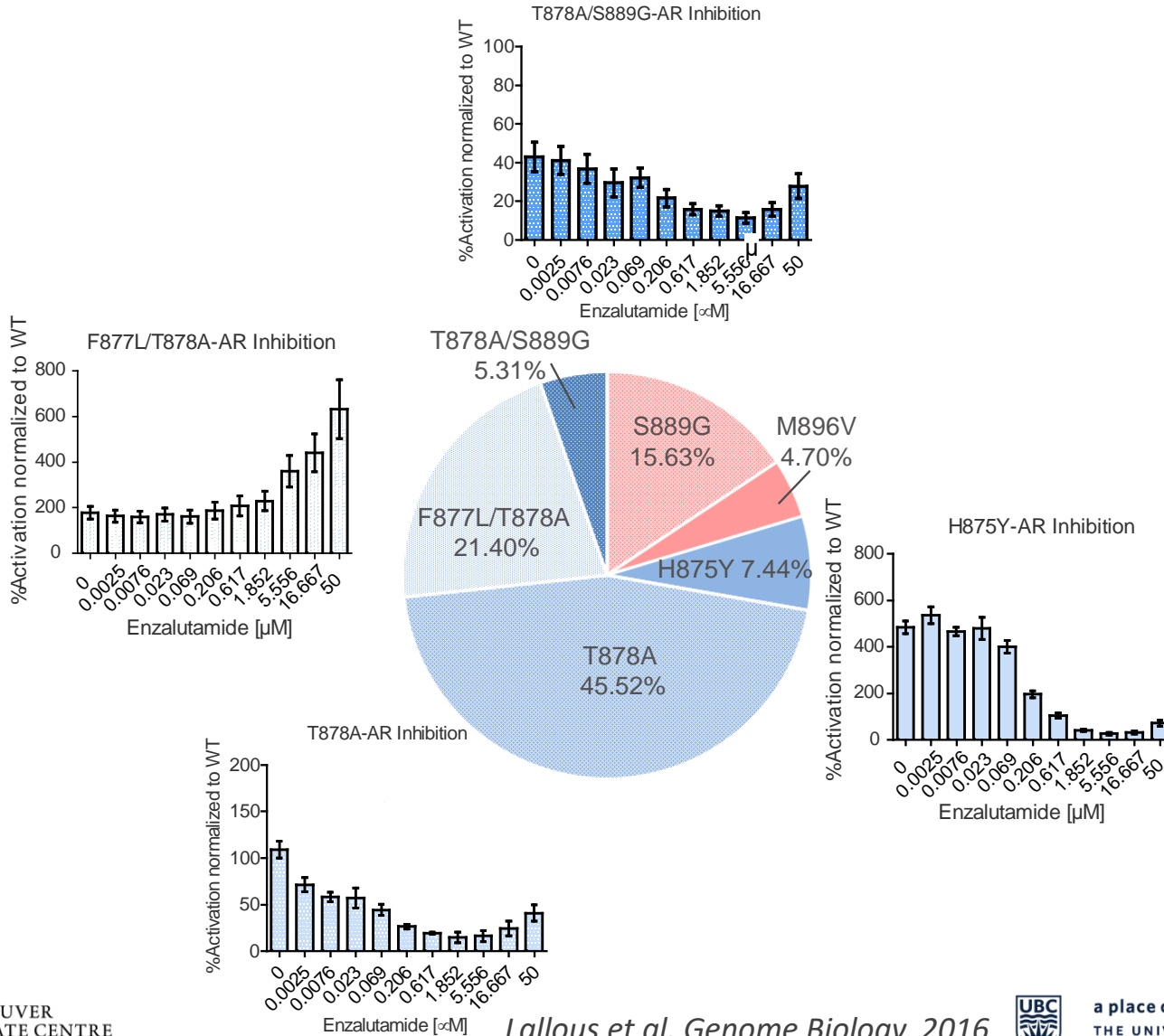
Specific Case: Patient VC-012

VC-012 progressing on bicalutamide



Specific Case: Patient VC-012

VC-012 progressing on enzalutamide

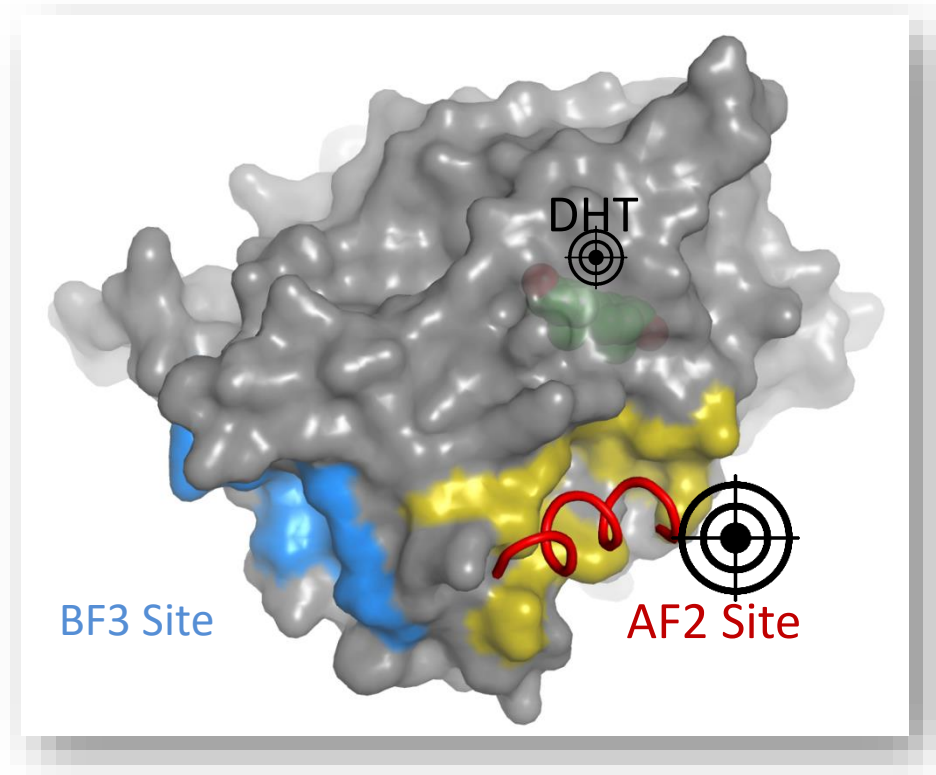
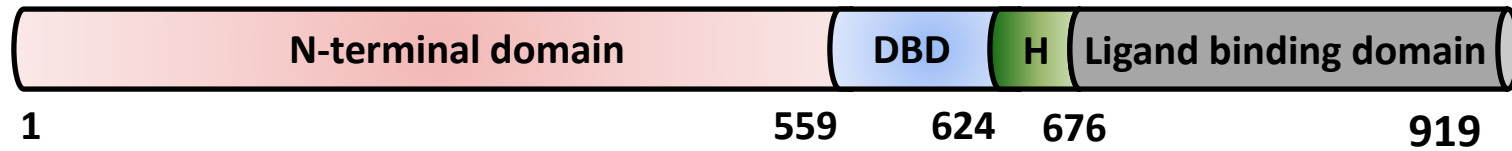


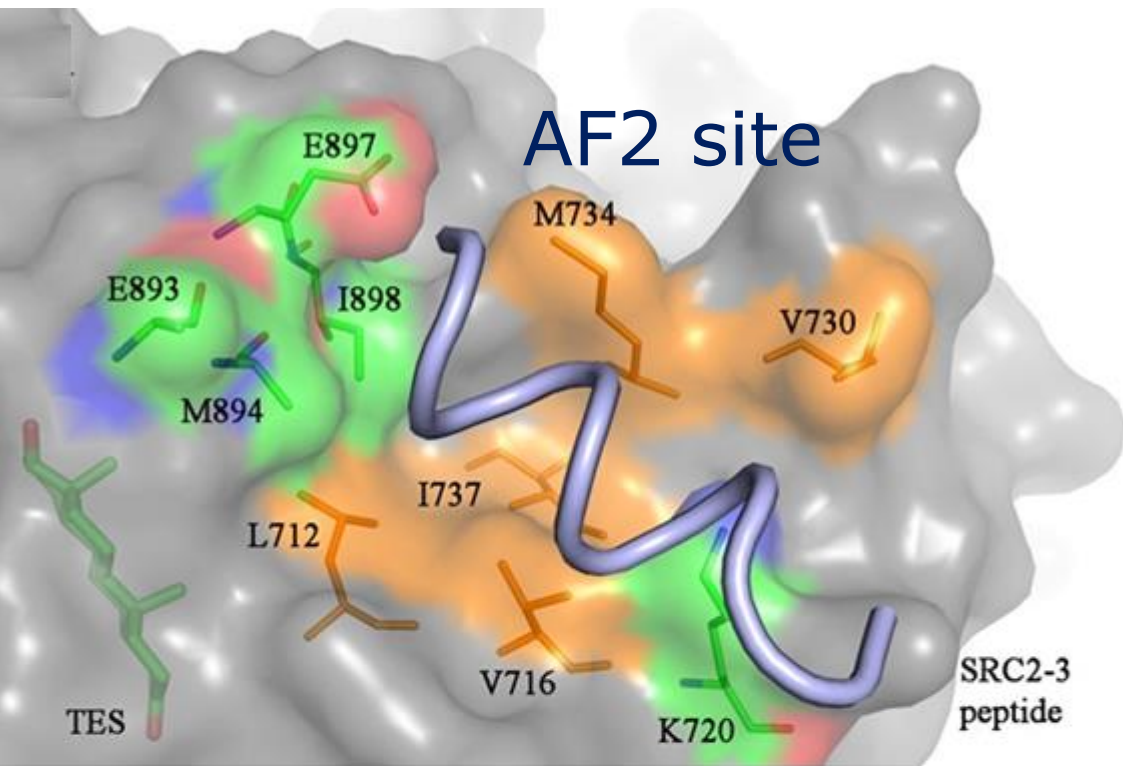
Agonist effect of anti-androgens on AR mutants

Patient	Sample ID	H875	F877	T878	D880	L882	S889	D891	E894	M896	E898	T919	Agonistic response	
VC-001	VC-001_JC_01Aug13			A										
		Y												
		Y		A									Ongoing	
	VC-001_JC_28Nov13	Y			A									
		Y			A									Ongoing
					A				H					
VC-005	VC-005_JWR_29Aug13							H	K					
VC-012	VC-012_LW_13Aug13									V				
	VC-012_LW_13Aug13						G							
	VC-012_LW_05Dec13										V			
		Y												
					A									
			L		A									
			A				G							
VC-014	VC-014_PW_29Aug13										G			
VC-015	VC-015_GNP_05Sep13			A										
VC-017	VC-017_EWP_12Sep13			A										
VC-018	VC-018_DWH_23Oct13	Y												
VC-021	VC-021_JHK_19Sep13	Q												
VC-022	VC-022_GST_10Oct13				E							S		
VC-040	VC-040_JNO_31Oct13	Y												
VC-041	VC-041_LJO_14Nov13	Y												
	VC-041_LJO_24Feb14	Y												
VC-053	VC-053_JPS_12Dec13	Y												
VC-063	VC-063_MDW_13Feb14	Y												
VC-064	VC-064_PSS_27Feb14					I								

AR AF2 Targeting

Structural Domains of AR



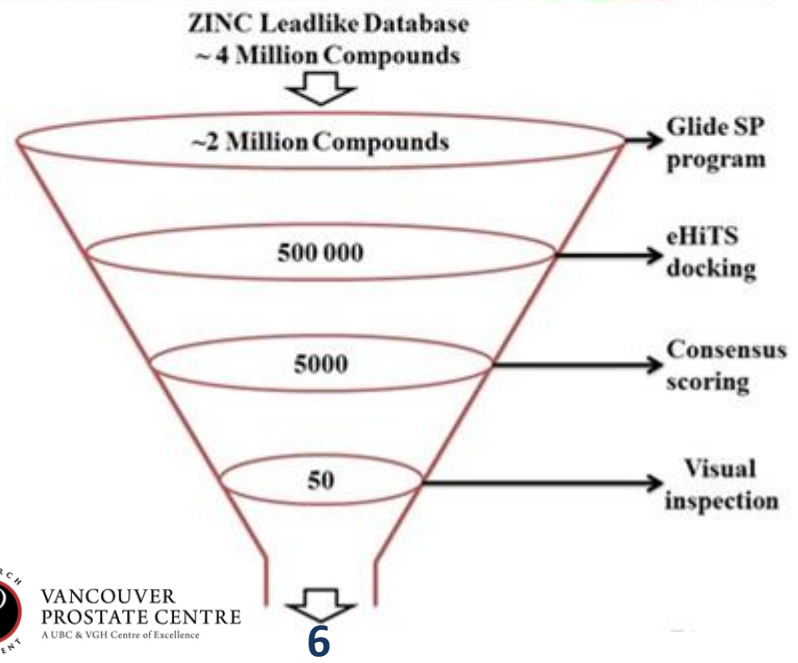


```

CTGGCTTTTCAGCTGGTGCCCAAAGTGACAAATGTATCTGCAATGACAAAGGTAC
TTAACTCTGTGGATTGATTTGCCCGGTTGTACATTCTGAGCAGCCACAACCTA
GGAATTCCTTGGGAGTCTAACTTGGAGATTTTGTCTTCTGCTTTGCTCCTG
GGTATGTCCCCCTCAGTGATGGTTTCTGTTGGCTTCC CAGGGTGAGGATGACT
CCTCTGGGTAAAGGAAATCCTGGGAAACACACTGTTTT CATGCATCCTCTGGAA
TCTTGAGGATCCATGNTCTGTGAAGGAATCCAAGCTCTCATTTGCACTACCT
TACAGTTACTGTGGACTTCCAGTTTGTGTCTTAGTATTCCATTGTAGCTC
GACAGTAGAAGGGTGTTCAGAATGTCTGCTGTGCCCTCATGGAGGAAGAGNGCT
CAGGCACGACAGAGTGGAGACGGCGCTGCTGGCTCTCA GGGGAATGGGCATGGA
TGGTCTCCTGCATGCCAGAGGTACCAGCCATCTTTTT TCCTAAACTTGATGAC
GATCATCCCTATCCCTGGGGTGTGGCTTCTGTGTCAC AGTCAGCTTCTAGTTC
CACGCATCAGCAGCTGGGCCAGGGAGTTGCCCACTGAGCACTGCGGGCTGAC
AAGGGTGCAGTTGGGTCCCTGCGAGAAAATGTCTCAGT TGTGGCAACTGATTGG
CTGATGGCTCGGTGATGCCAGGGTGAAGGAAGACTTGA TTTTGGGAGGGGAGT
GTGTGTCTGAGCTGTGTGGGAGCGGGAAGCGCTCA GTGGGCGGAGGGAGCG
TTCGGAGCGTGGGGACCCTTGGGTGAGCTGCCACATGA AGCAGCCCAAGACCT
CCAGTGCCTTACCCGAGGAGCTACTGGCCAGTGGGGG AGGCATTGAGGTGGGC
CCTTCCCTCAGGTCCAGGCTCCTGCGTGAAGTGATGC TCCTCTTGCCTTACT
CGAGAATCCACCTGGAGATTCTGGGCCACTTTGGTTC CCCATGAGCCAAGACG
AATGACAAAGGTACCTTGAAGGGCTCGCCCTCGCGGA ATTTTCAGTTCATGCA
CGAGCCACAACCTACTGCATCCCATGAGAAGTGGAAV TGACCTGATTTTTTTC
TGCCTTTGCTCCTGGGGCTTAATCACTTCTGTGCCTC TGGTTATCTGTGGCAC
GGGTGAGGATGACTCATGACCACTTGCAAGTGGTTTTT GTGTCTGGGGTTATG
TGCATCCTCTGGAAGATGAGGCGCTGAAGTTACCAGGGT CTCTGTTTGTCTGATGC
TTTTGCACACTCACCTTGGCCCTGGCTCTGTCTCCAGG ACCTCTCTACTACAAAA
TTCCATTGAGCTCTTGGGTATTTTTCCCATCCACCCCA AGATCCAGCTGAAAA
GGAGGAAGAGNGCTCAGTGTACATGCTCTGGGTGAGTA GGTGCCCTTGGAGCCA
GGAATGGGCATGGAGTGGGTAGGAGATCCACCTAAGGA GGCTGGCTGGCTGGAC
CTAAACTTGATGACCTAGGGCTAGGGGCATGTTGAATC TCAGCTCGCCCACTG
TCAGCTTCTAGTTCTGTAGCCCAAGCTGCTCCTGCGGT GGAGGGAGCTACACG
CATCGCGGCTGACCTGCTCCCAACCAAGGAGATGGAG CTCCCCCTTGATGCTG
TGGCAACTGATTTGGTGACCTGGGGGGCGTTTTCTGAG CC CACAGTGCTGGCATCA
TTTTGGGAGGGGAGTTCTCTGTAATGACACTGAGGATG CCTCAAGTTGGGCTT
GGGCGGAGGGAGCGGGAAGCGCTCAGTGGGCGGAGTA TTTGAGAACATTTTAC
GTTGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGG AGGAGACTCATGAGGCCG
TTCCTTGGCTTCTAGCCATGCTCCCTCCCTCCCTCCCT CCCTCCCTCCCTCCCTCC
CGTGAAGTGATGCTCCTCTTTGCCTTACTCCTAGCCAT GGAGCTCCCATTGGTG
GTTTGGTGGTTCATGAGCTGCTGCTGCTGCTGCTGCTG CTAAATTTGCAATCCCTACC
GTTCCCTTGGGCTTTTGGGATTTTCAGTGTGGTGTGGT GATTTCCACATCTGTCC
GTAGAAGTGGAAAGTGACCTGATTTTTTCTGCTTTTT CAAGGCTGTATGTTTACA
ACTTCTGTGCCTCTGGTTATCTGTGGCACATTTGTATT TGTGATTAGTCAACCG
GCAAGTGGTTTTTGTGTCTGGGGTTATGATCACACAG TCATACACGTTCTAAC
AAGTTACCAGGGTCTCTGTTTGTCTGATGCTGATGATCC ACATTTTCTAGGCCAC
CTGTCTCCAGGACCTTCTACTACAAAATCCTAAAGC TCTGGGAGCTGGGTGT
CCCATCCACCCCAAGATCCAGCTGGAATCAGTGAACA CACTTGATGGGAGTTT
CTCTGGGTGAGTGGTGGCTTGGAGCCAGCTTTGGGA GCAATGTTGGATGAGT
ATCCACCTAAGGAGGCTGGTGGTGGTGGTGGTGGTGG GCCCCTTCCAAGGGTG
GGCATGTTGAA

```

6 compounds identified with AF2
 $K_i = 5 - 25\mu\text{M}$



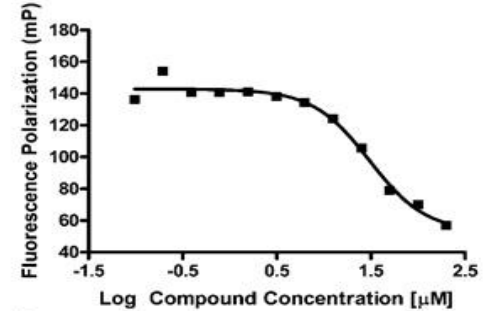
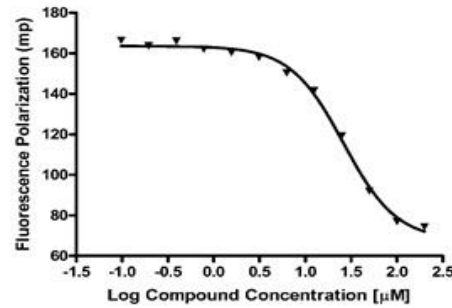
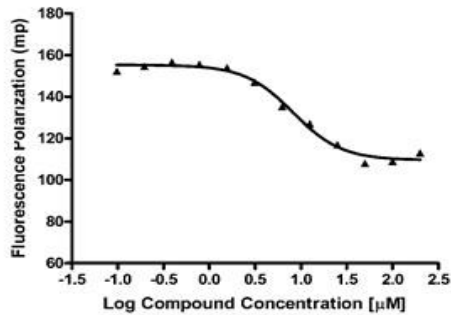
Inhibition of AF2 coactivator binding, AR transcriptional activity and SPR

VPC-4107

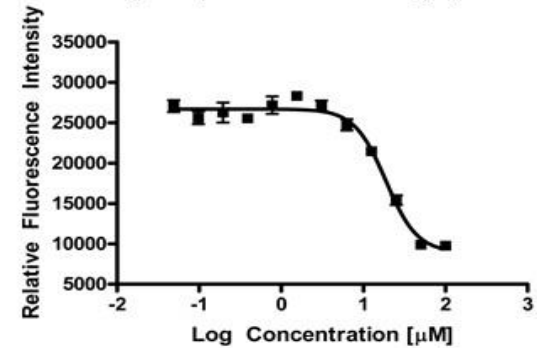
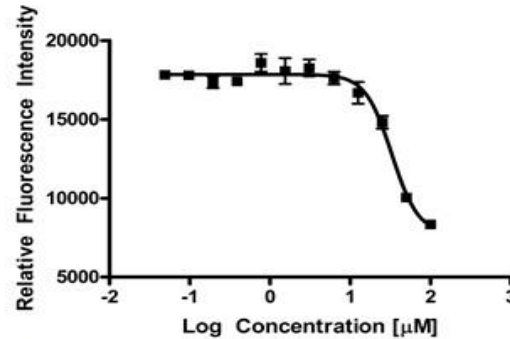
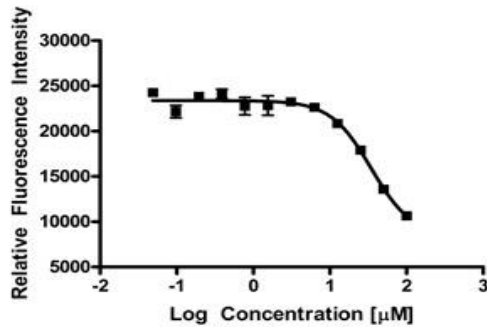
VPC-0100

VPC-0061

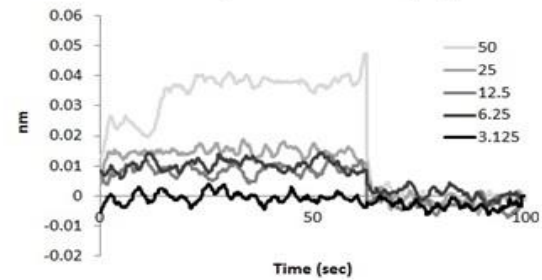
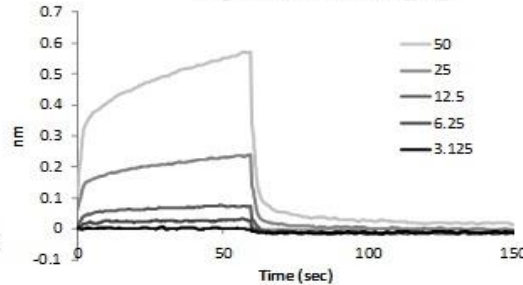
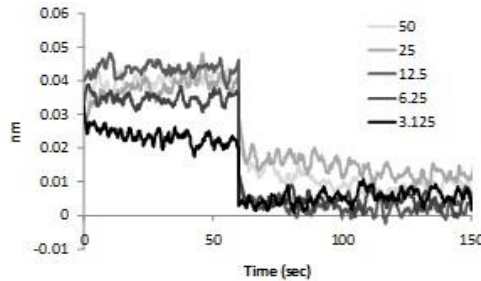
1



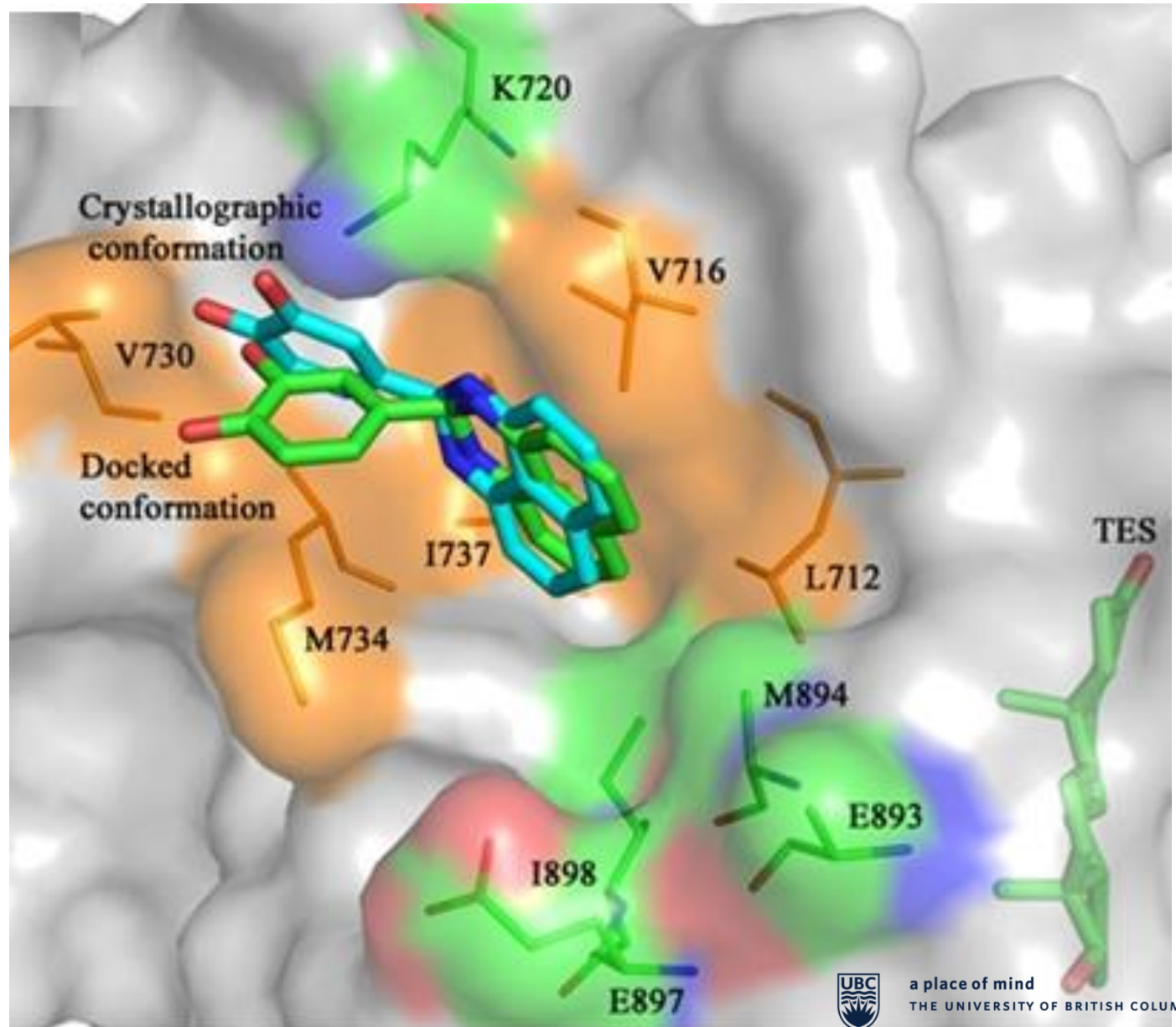
2



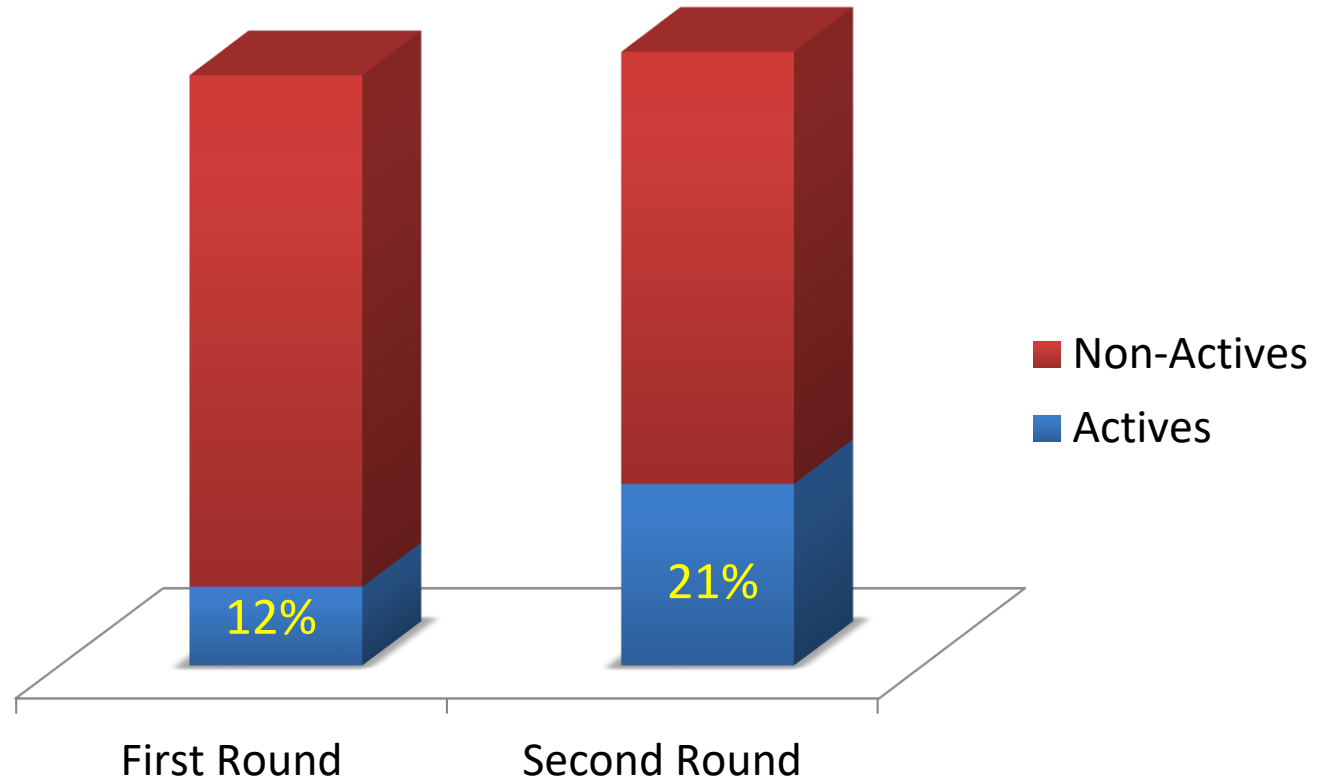
3



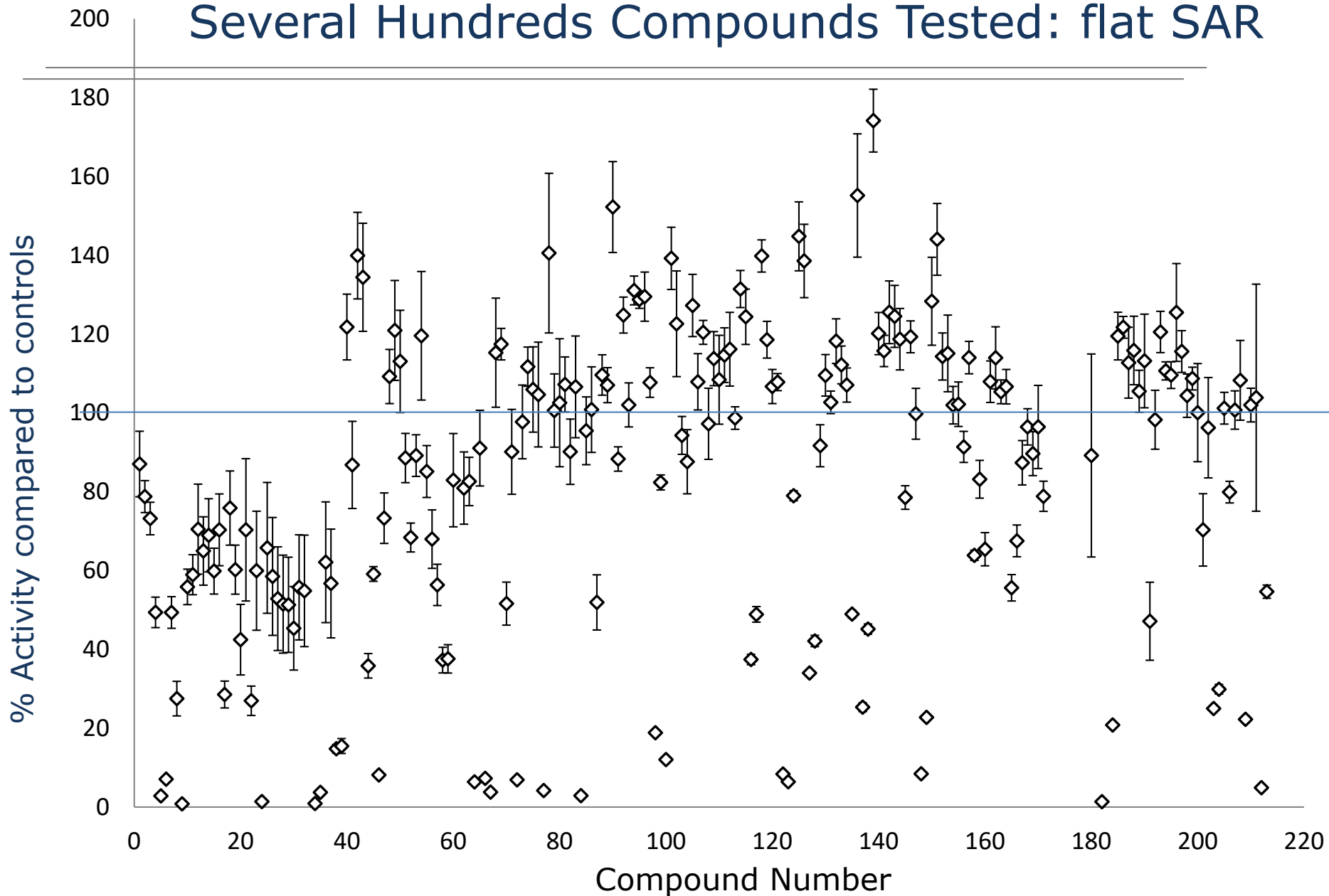
The comparison between docked and experimental orientation of CMPD61 inside the AF2 site



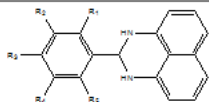
Rounds of Virtual Screening



Several Hundreds Compounds Tested: flat SAR



Several Hundreds Compounds Tested: flat SAR



number	EC50 (uM) (FP)	IC50 eGFP (uM)	R1	R2	R3	R4	R5
1	>200	2.5					
3	>200	Inactive	OH	Cl	H	Cl	H
4	>200	4.7	H	Br	H	H	H
5	Inactive	2.5	OH	H	NEt2	H	H
6	Inactive	0.19	CF3	H	H	H	H
7	14.7	51.48	H	Br	OH	OMe	H
8	Inactive	1.5					
9	>200	1.5	H	F	H	H	H
10	Inactive	0.1	H	H	CN	H	H
11	Inactive	1.3	F	H	H	Br	H
13	Inactive	7.0	H	NO2	H	H	H
16	Inactive	Inactive	H	OMe	OMe	OMe	H
17	30.7	3.9	H	H	OH	H	H
18	Inactive	Inactive	Cl	H	H	NO2	H
19	Inactive	1.682	Cl	H	H	H	F
20	Inactive	9.939	H	OCH2Ph	H	H	H
21	Inactive	5.895	H	H	OC2H5	H	H
22	167	6.7	H	H	H	H	H
23	Inactive	1.311	OH	H	H	H	H
24	Inactive	Inactive	H	OMe	H	H	H
25	Inactive	Inactive	H	H	NEt2	H	H
26	Inactive	Inactive	H	OMe	OEt	H	H
27	Inactive	Inactive	H	H	CH3	H	H
28	Inactive	Inactive	H	NO2	Cl	H	H
29	Inactive	Inactive	OMe	H	OMe	OMe	H
30	Inactive	Inactive	Cl	H	H	H	Cl
31	Inactive	Inactive	H	Br	H	H	H
32	Inactive	Inactive	H	H	Br	H	H
33	Inactive	Inactive	Cl	H	Cl	H	H
34	Inactive	Inactive	OMe	H	H	H	H
35	Inactive	Inactive	H	H	F	H	H
36	Inactive	Inactive	H	H	OMe	H	H
38	27.62	6					
39	Inactive	Inactive	OMe	H	H	Br	H
40	Inactive	Inactive	NO2	H	H	H	H
41	>200	Inactive	H	H	Cl	H	H
42	62.23	Inactive	H	Cl	H	H	H
43	Inactive	Inactive	H	H	NO2	H	H
44	Inactive	Inactive	H	H	C2H5	H	H
45	Inactive	Inactive	H	H	OMe	H	H
46	Inactive	Inactive	H	H	NMe2	H	H
47	Inactive	Inactive	Cl	Cl	H	H	H
48	Inactive	Inactive	H	H	SMe	H	H
49	Inactive	Inactive	H	H	H	H	H

49	89.42	Inactive	H	OMe	OH	H	H
51	28.68	2.5	H	Cl	Cl	H	H
52	Inactive	Inactive	H	Br	OMe	H	H
53	>200	Inactive	OH	OMe	H	H	H
54	Inactive	Inactive	H	H	OEt	H	H
55	Inactive	Inactive	OMe	H	H	OMe	H
56	33.47	6.9	H	OEt	OH	H	H
57	Inactive	Inactive	Cl	H	H	H	H
58	Inactive	Inactive	H	OMe	OC(O)Me	H	H
59	Inactive	Inactive	H	OMe	OC(O)Me	OMe	H
60	Inactive	Inactive	H	H	Cl	H	H
61	Inactive	Inactive	H	tBu	OH	tBu	H
62	Inactive	Inactive	OH	H	H	Br	H
63	Inactive	Inactive					
64	Inactive	Inactive	H	H	iPr	H	H
65	17.1	26.65	H	H	COO-	H	H
66	Inactive	Inactive	OH	Br	H	Br	H
67	Inactive	Inactive	OMe	OMe	H	H	H
68	Inactive	Inactive	H	H	C(O)OMe	H	H
69	Inactive	Inactive	OMe	OMe	OMe	H	H
70	Inactive	Inactive	H	H	F	H	H
71	>200	Inactive	OH	H	OH	H	H
72	Inactive	Inactive	F	H	H	H	H
73	Inactive	Inactive	H	OMe	H	H	H
74	30.5	23.2	H	OH	OH	H	H
75	8.2	14	H	OH	OMe	H	H
76	100	5	H	Br	OH	H	H
77	Inactive	6	H	Cl	OH	H	H
78	Inactive	32					
79	Inactive	16					
80	Inactive	Inactive					
81	Inactive	4					
82	Inactive	Inactive	H	COO-	H	H	H
83	Inactive	13	H	Cl	OH	OMe	H
84	Inactive	11	H	H	CH2OH	H	H
85	Inactive	Inactive	H	OH	COO-	H	H

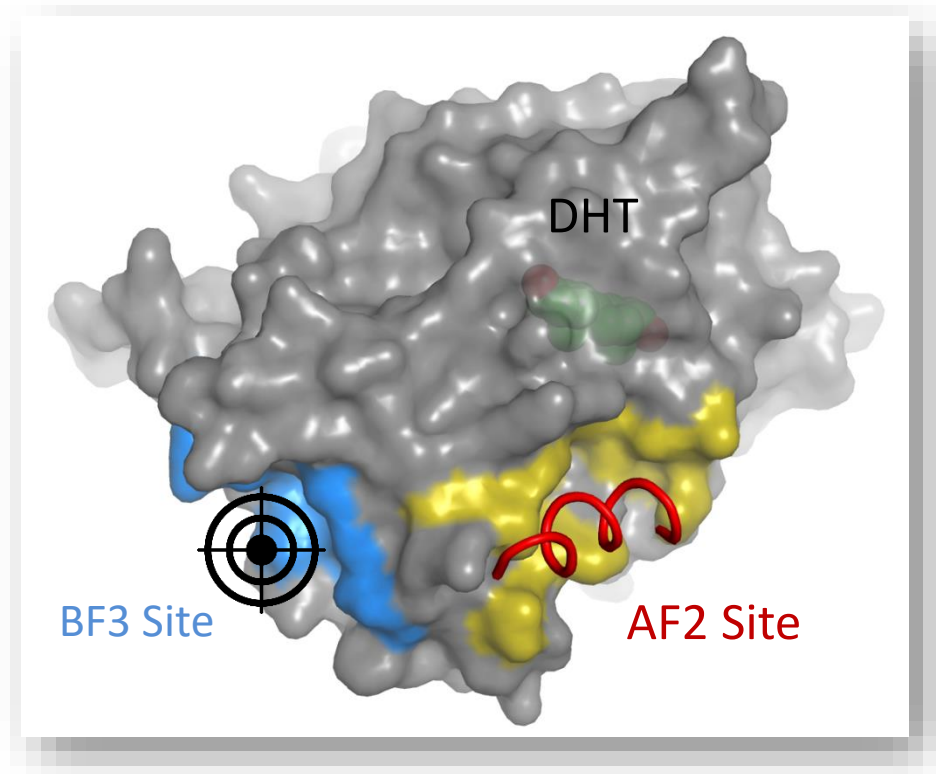
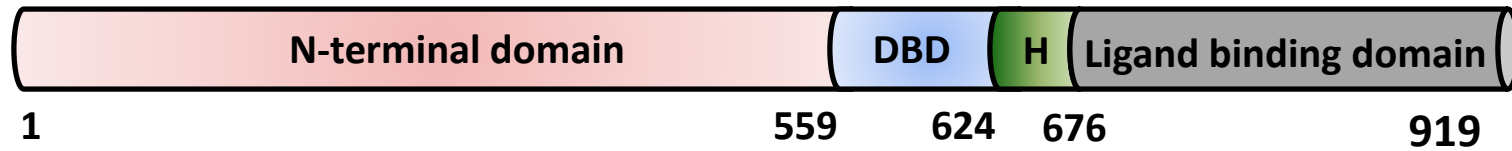
VPC-0061
IC50=30.6 uM



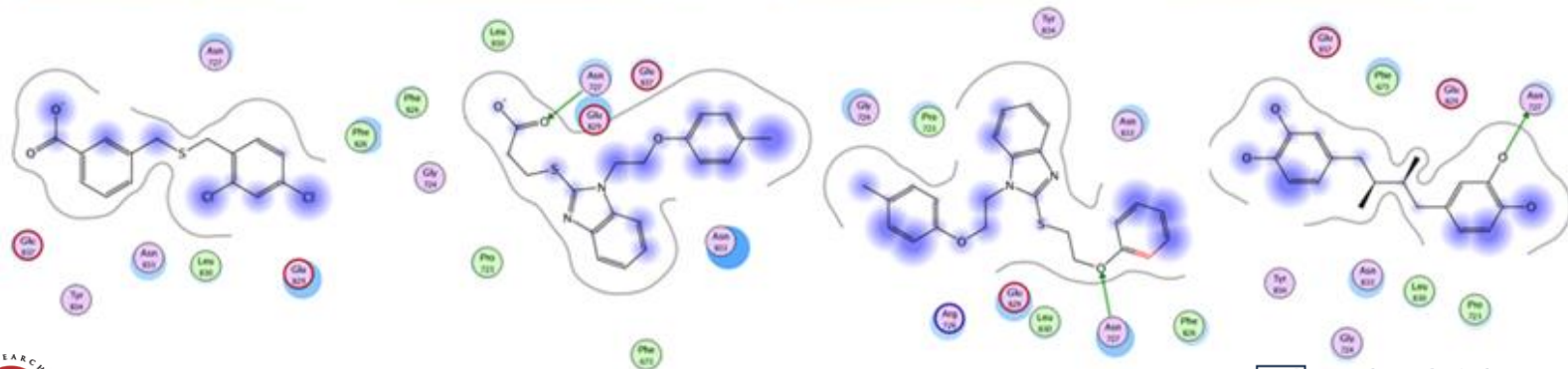
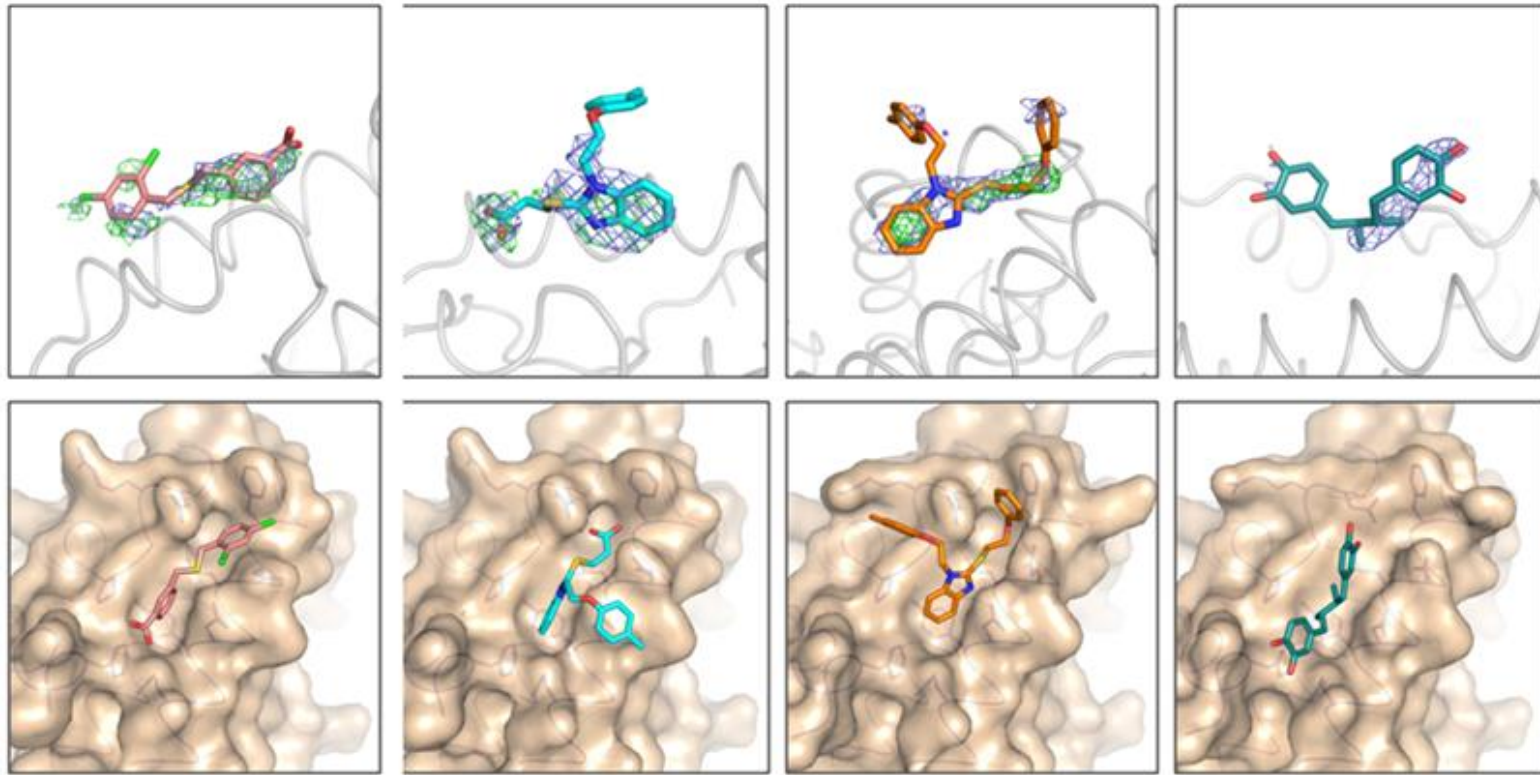
VPC-7051
IC50=2.5 uM

AR BF3 Targeting

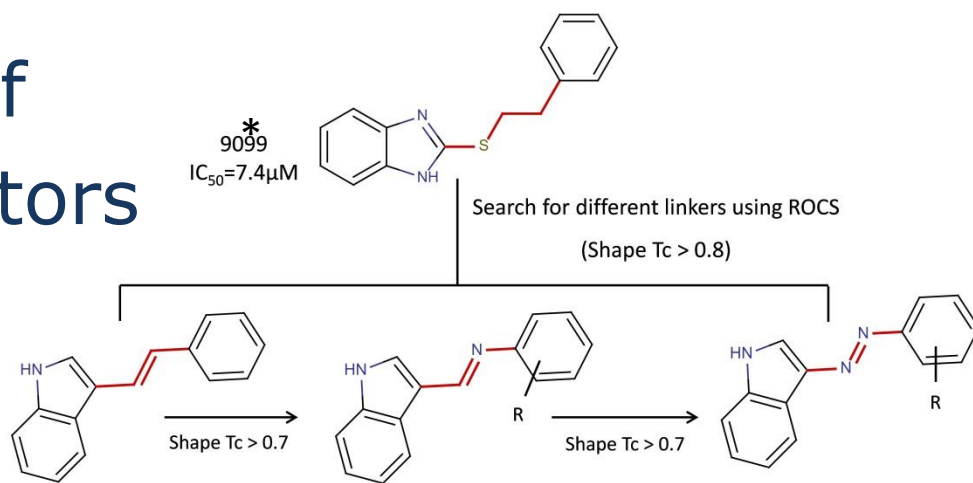
Structural Domains of AR



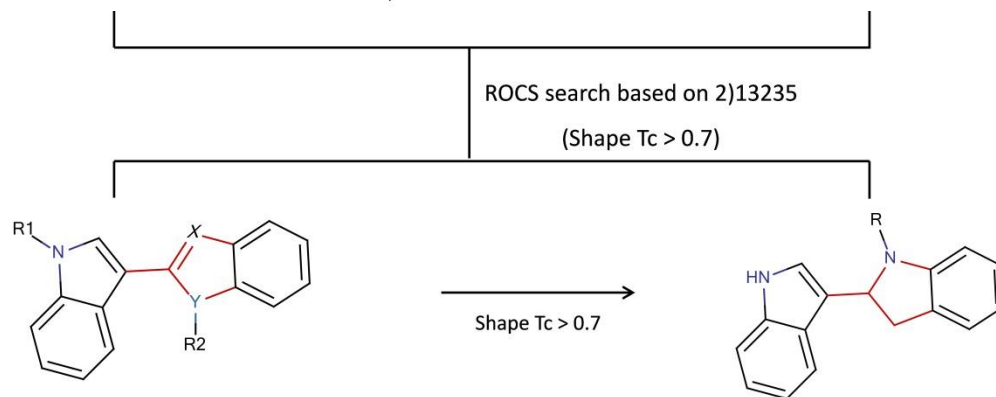
Four BF3 crystallographically confirmed hits



Identification of Potent BF3 Inhibitors using ROCS



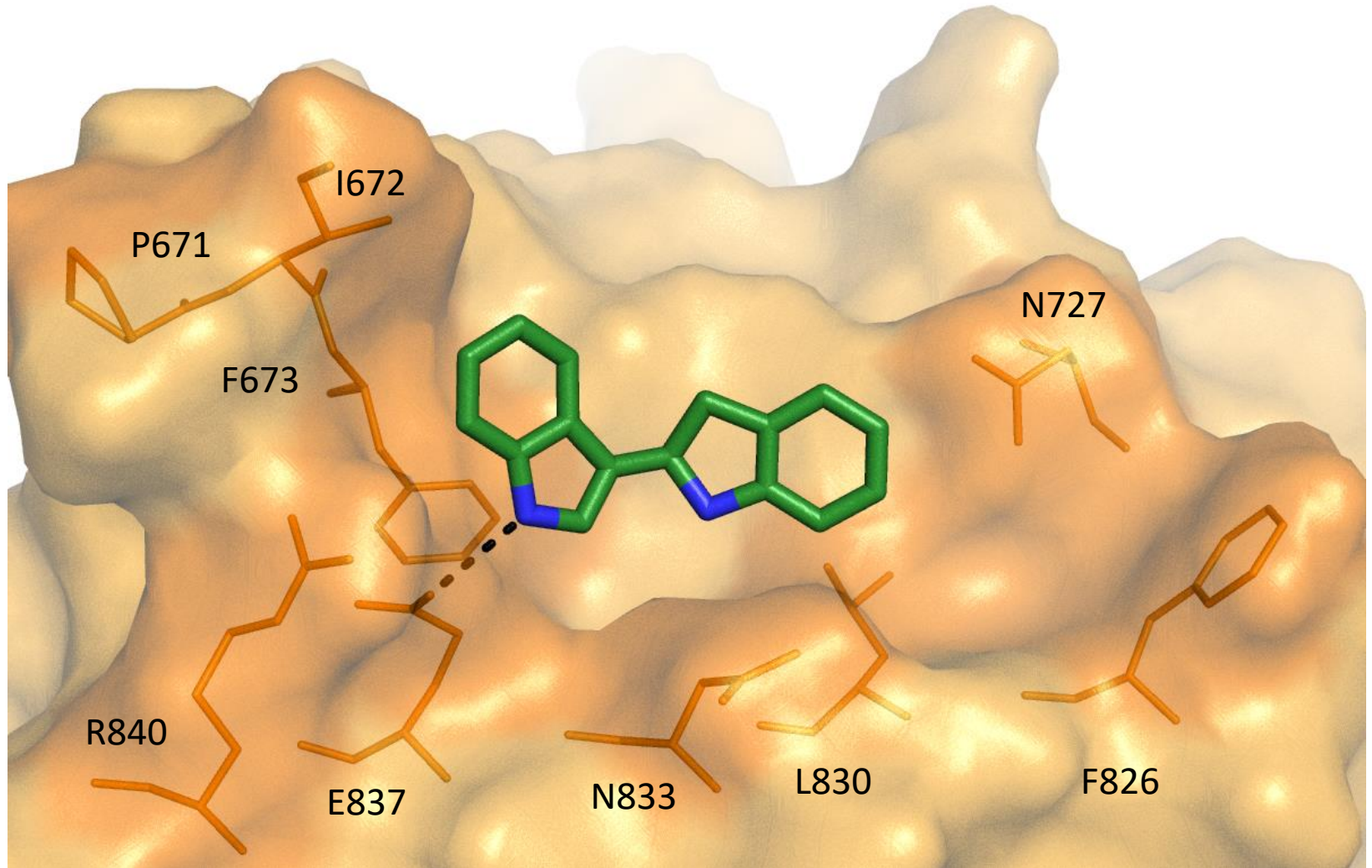
ID	IC ₅₀ (μM)	ID	R	IC ₅₀ (μM)	ID	R	IC ₅₀ (μM)
13235	2.21	13303	2-CF3	4.46	13259	1-CF3	0.31
		13304	2,4-Cl	7.27	13256	-	0.38
		13299	3-Me	8.16	13255	1-Cl	0.52
		13300	3-OMe	9.33	13225	1,3-Me	0.70
		13310	2,3-Me	10.31	13254	3-Cl	1.20
		13345	1,6-Cl	13.89	13257	3-Me	4.18
		13320	2-OMe	25.23	13258	1-Ph	6.78
		13321	2,3-Cl	25.78			
		13309	1,3-Br	27.21			



ID	Group	IC ₅₀ (μM)
13127	X=C, Y=N	0.60
13166	X=C, Y=N, R ₁ R ₂ =Me	1.69
13167	X=N, Y=C, R ₂ =NO	1.91
13221	X=N, Y=N	>25

ID	R	IC ₅₀ (μM)
13163	-	0.31
13164	Me	0.43

Binding Pose of VPC-13163

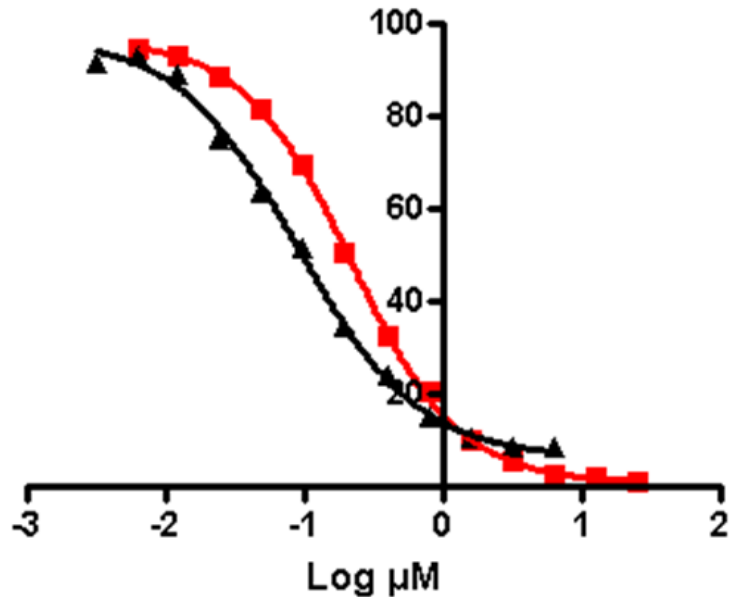


Effect of 13163 on MDV-resistant cell line

LNCaP

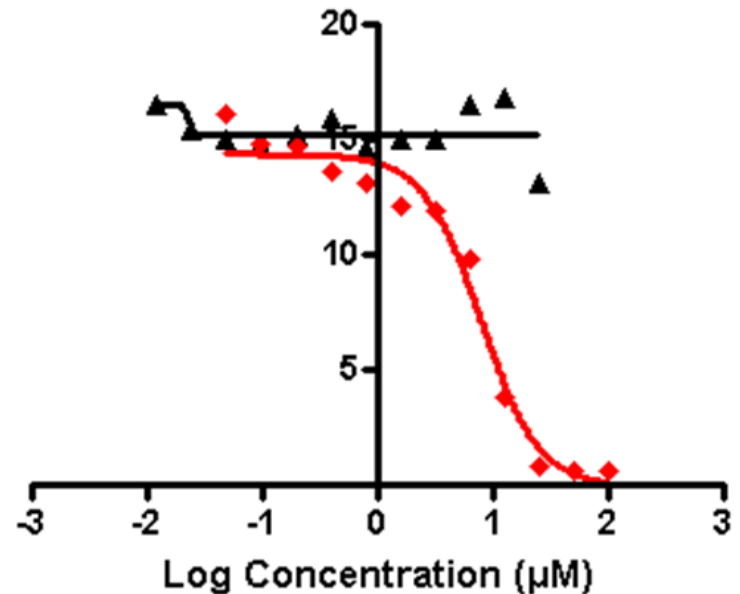
MR49F cell line

% of control
(R1881 0.1 nM)



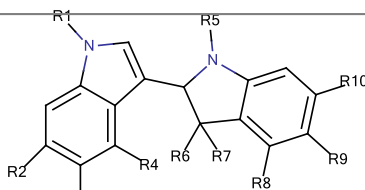
13163: 0.216 μM
MDV3100: 0.090 μM

PSA units



13163: 7.031 μM
MDV3100: Inactive

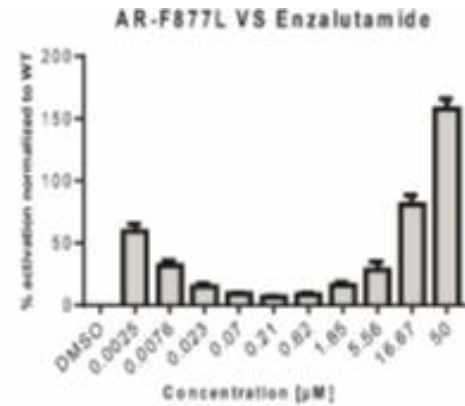
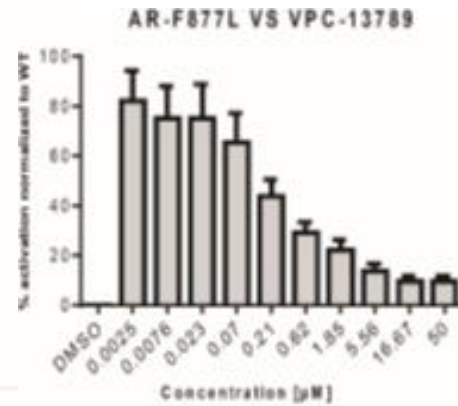
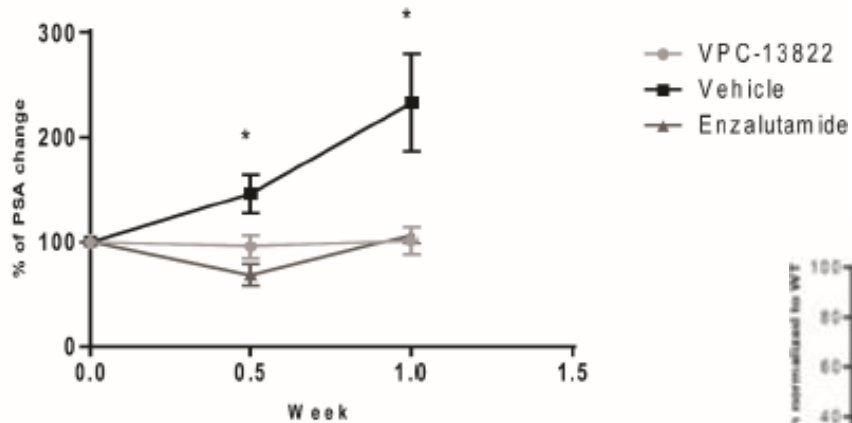
Med Chem Derivatives of 13163



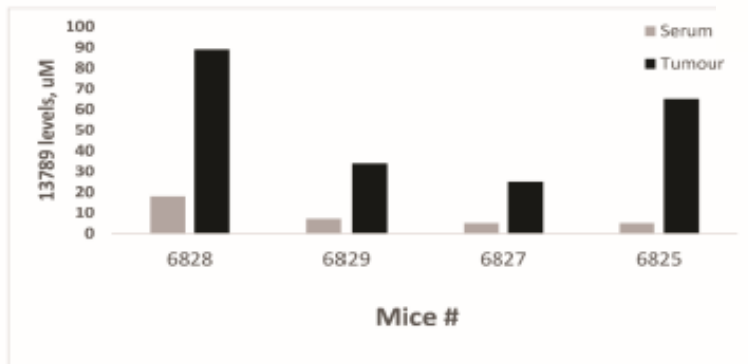
ID	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈	R ₉	R ₁₀	PSA IC ₅₀	eGFP IC ₅₀	Date
13530			NO ₂			Me	Me				4.7	1.60	Mar'13
13531			F			Me	Me				0.39	0.31	Mar'13
13532					CH ₂ COO Et	Me	Me				2.84	3.10	Mar'13
13521		Cl				Me	Me				0.4	0.26	Feb'13
13506						Me	Me				0.18	0.20	Jan'13
13504				Br				Br			1.69	2.01	Aug'12
13502		Br								Br	3.80	4.14	Aug'12
13503			Br						Br		4.21	4.54	Aug'12
13508	C ₂ H 4OH					Me	Me				2.70	4.81	Aug'12
13510			Br			Me	Me					>25	Dec'12
13511						Me	Me		Br			>25	Dec'12
13512			Br			Me	Me		Br			>25	Dec'12
13516	Me					Me	Me					>25	Dec'12

In vivo effect of VPC-13822

A)



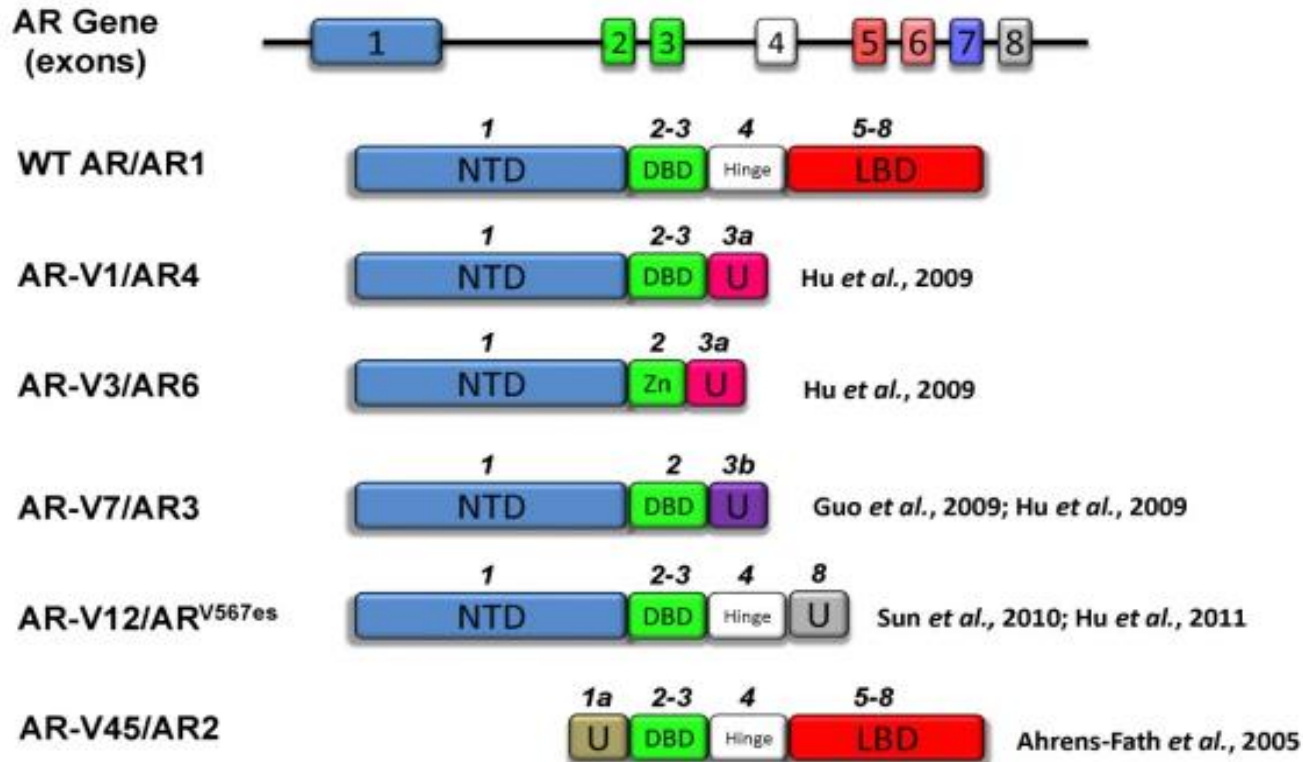
B)



AR DBD Targeting

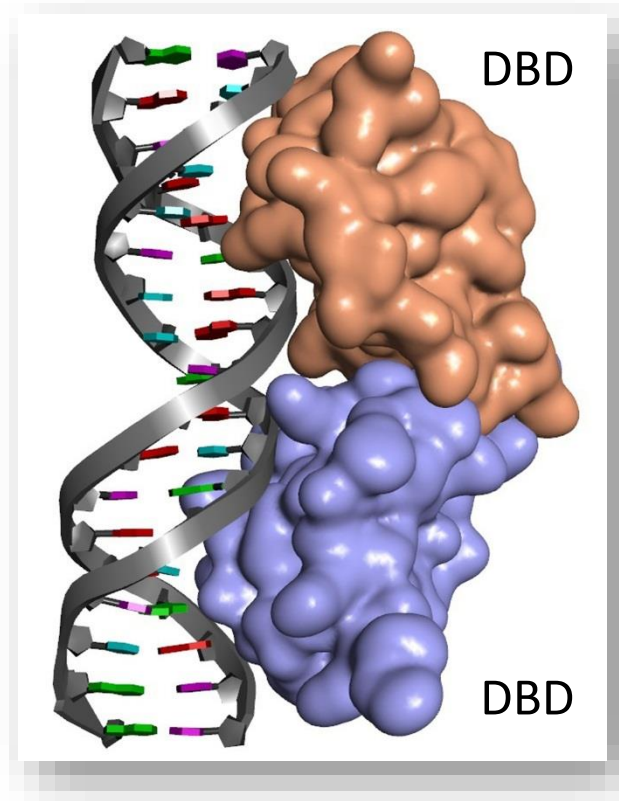
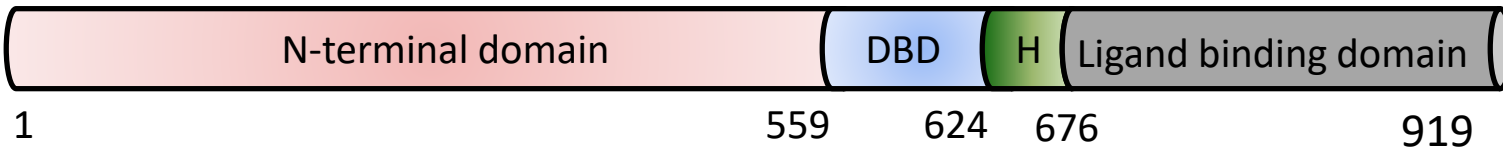
CRPC Resistance Driven by AR Splice Variants

Lallous et al. *Int J Biol Sci* 2011; 7(6) 815-822

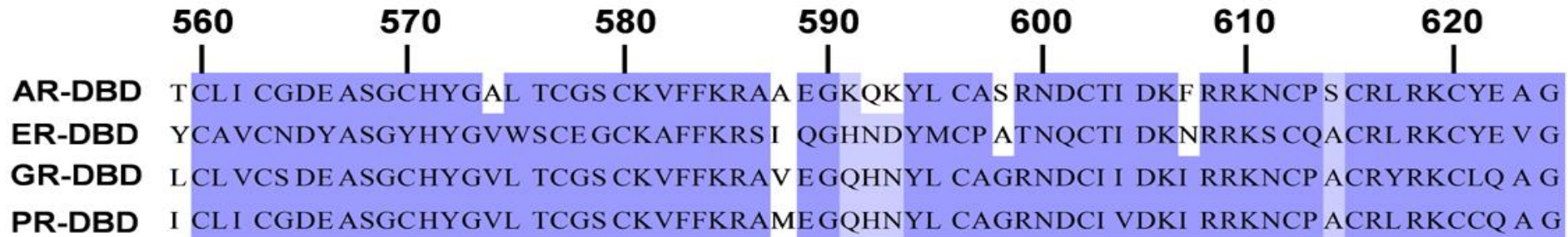


- NEED FOR DRUGS WITH NOVEL MOA, targeting both full length and splice variants of AR

Structural Domains of AR

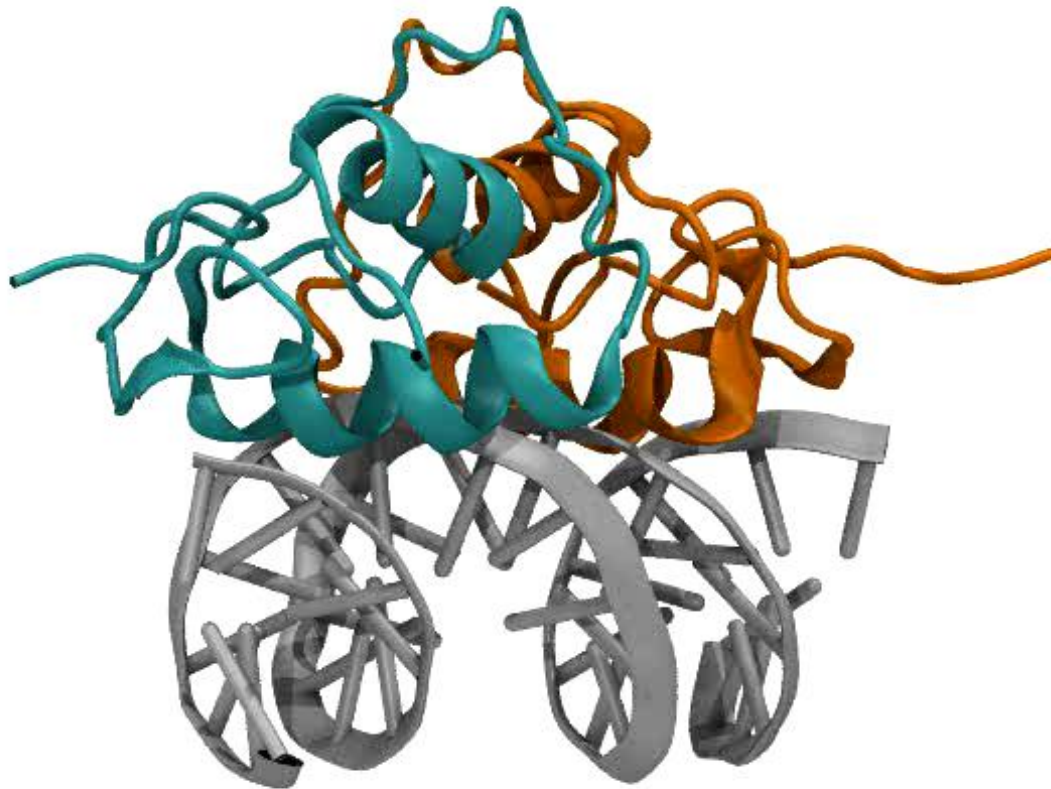


DBD is the Most Conserved Area of all NRs

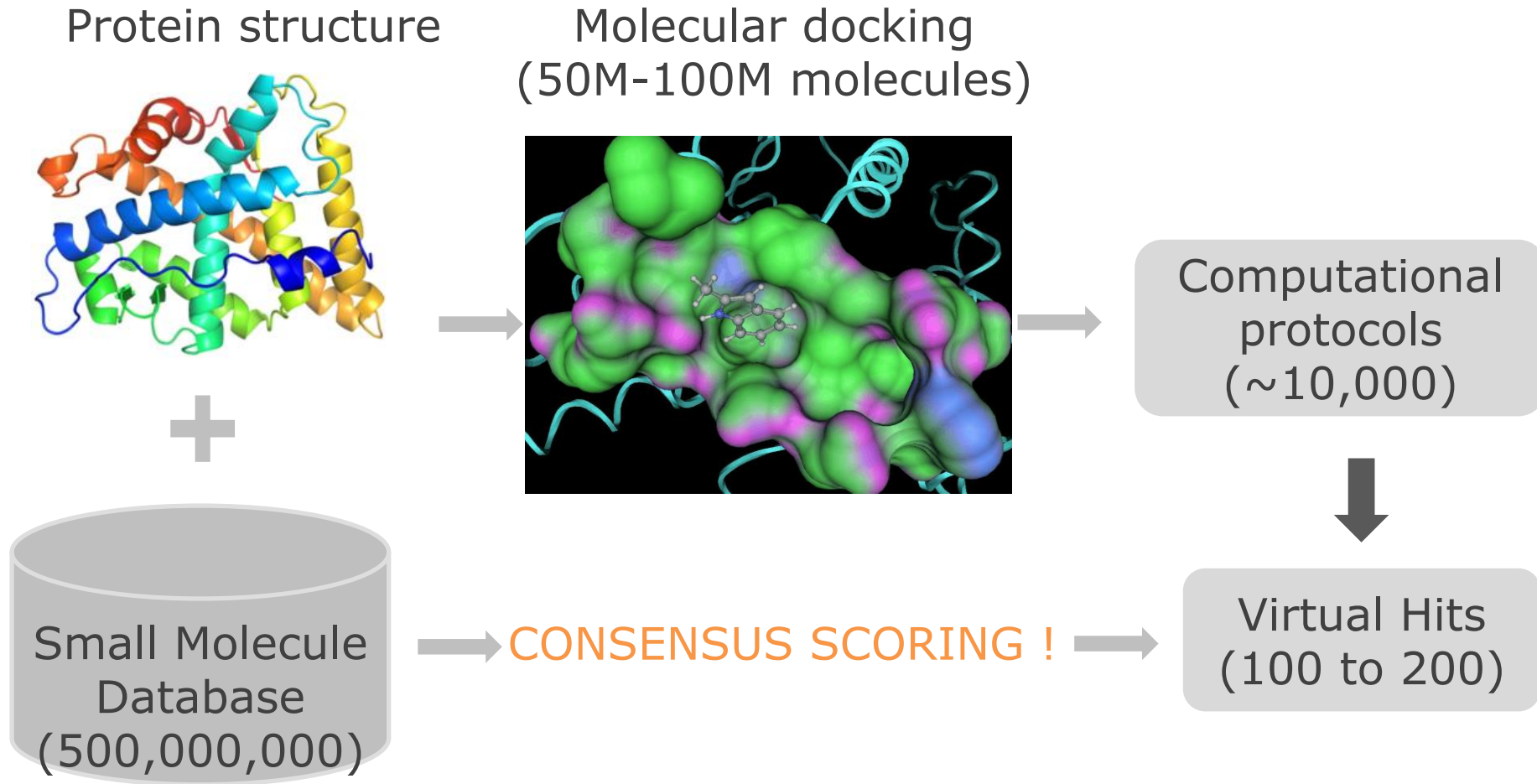


Novel Strategy to Target AR

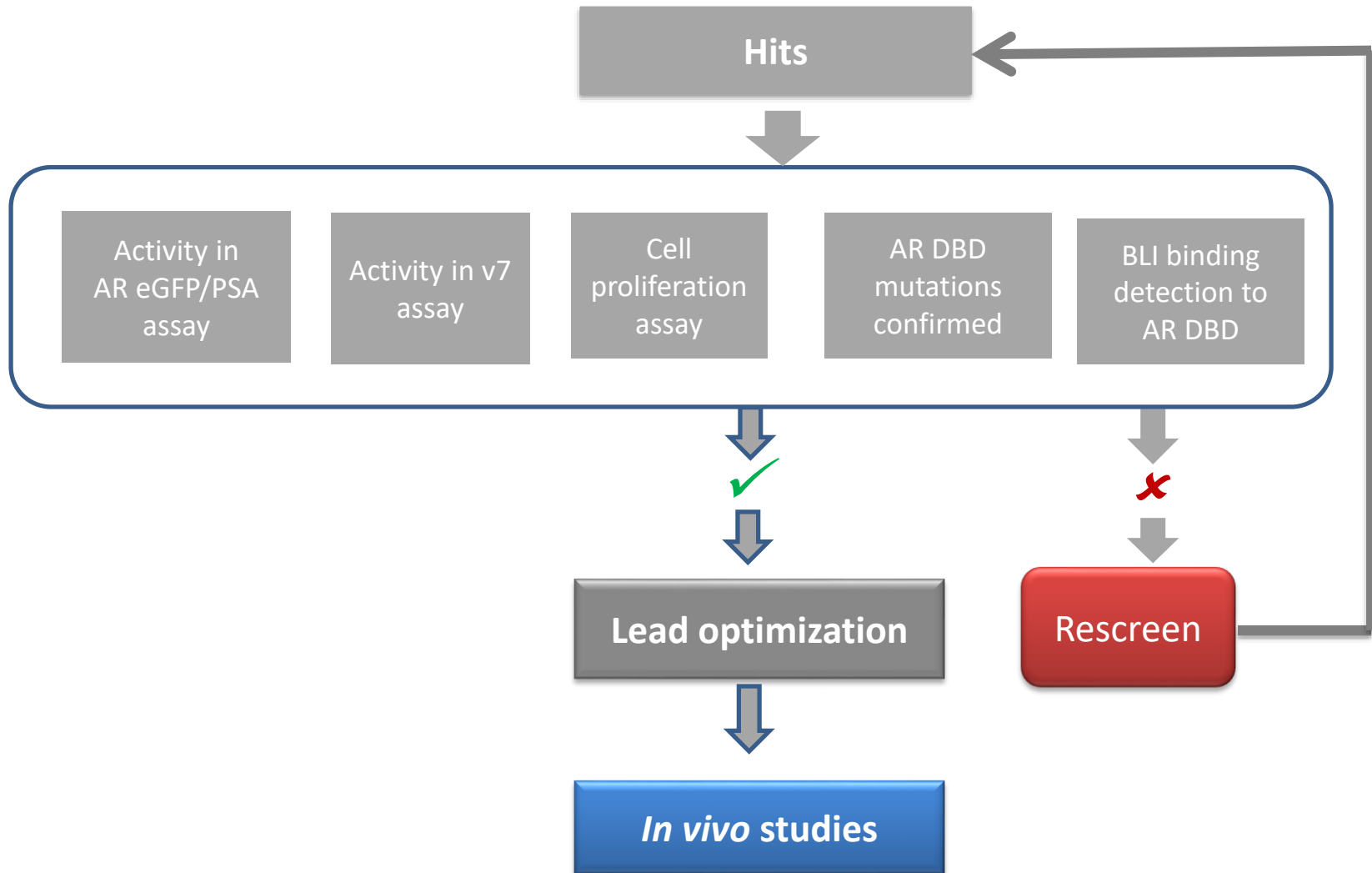
Hypothesis: Targeting alternative functional sites on AR should provide a promising strategy for treatment of PCa including its resistant forms where known mutations and splice variants hamper efficacy of the current drugs



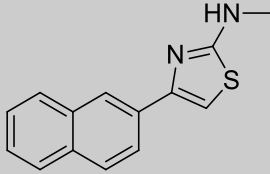
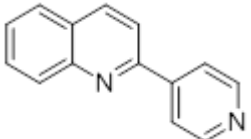
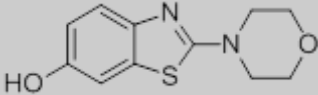
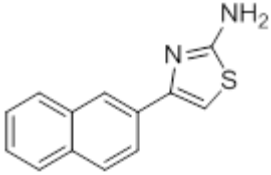
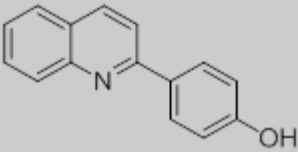
In Silico Screening Workflow



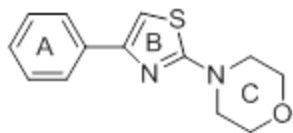
Experimental Screening Workflow



Initial in silico hits

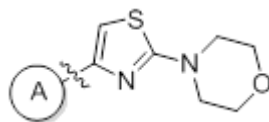
VPC-ID	Structure	eGFP IC50 (μM)	PSA IC50(μM)
14203		3.17 ± 0.3	3.91
14320		4.20 ± 0.6	2.26
14378		7.41 ± 0.4	8.08
14204		9.16 ± 0.5	10.6
14410		9.84 ± 3	N/A

MedChem analogues, 1st round



VPC-ID	A ring	B ring	C ring	eGFP IC50 (μM)	PSA IC50 (μM)
14228				0.33 ± 0.12	0.28
14103				0.52 ± 0.03	0.51
14385				0.62 ± 0.06	N/A
14292				0.61 ± 0.02	0.58
14293				0.62 ± 0.06	0.52
14255				0.65 ± 0.06	0.41

MedChem analogues, 2nd round

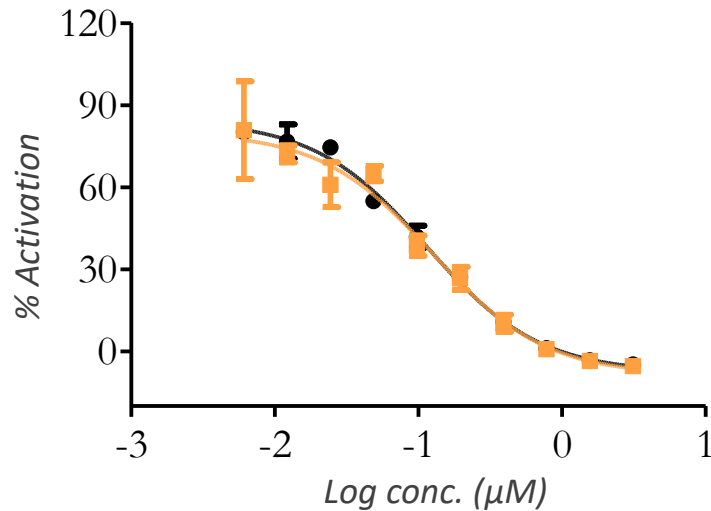


ID	Ring A	eGFP IC50 (μM)	PSA IC50(μM)
14449		0.10 \pm 0.05	0.17
14370		0.18 \pm 0.01	0.25
14408		0.25 \pm 0.05	0.43
14404		0.26 \pm 0.02	0.22
14365		0.27 \pm 0.04	0.15
14367		0.30 \pm 0.02	0.23
14450		0.33 \pm 0.01	0.44
14402		0.68 \pm 0.01	0.57

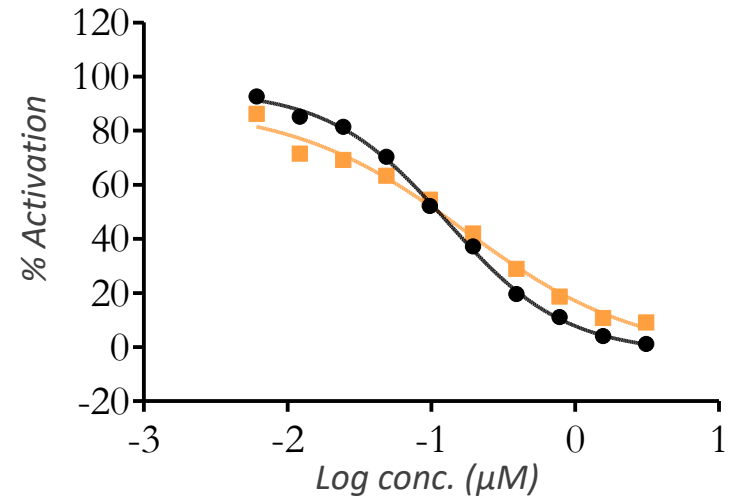
Activity Profile of the Lead VPC-14449

■ 14449 ● Enzalutamide

Inhibition of AR transcription



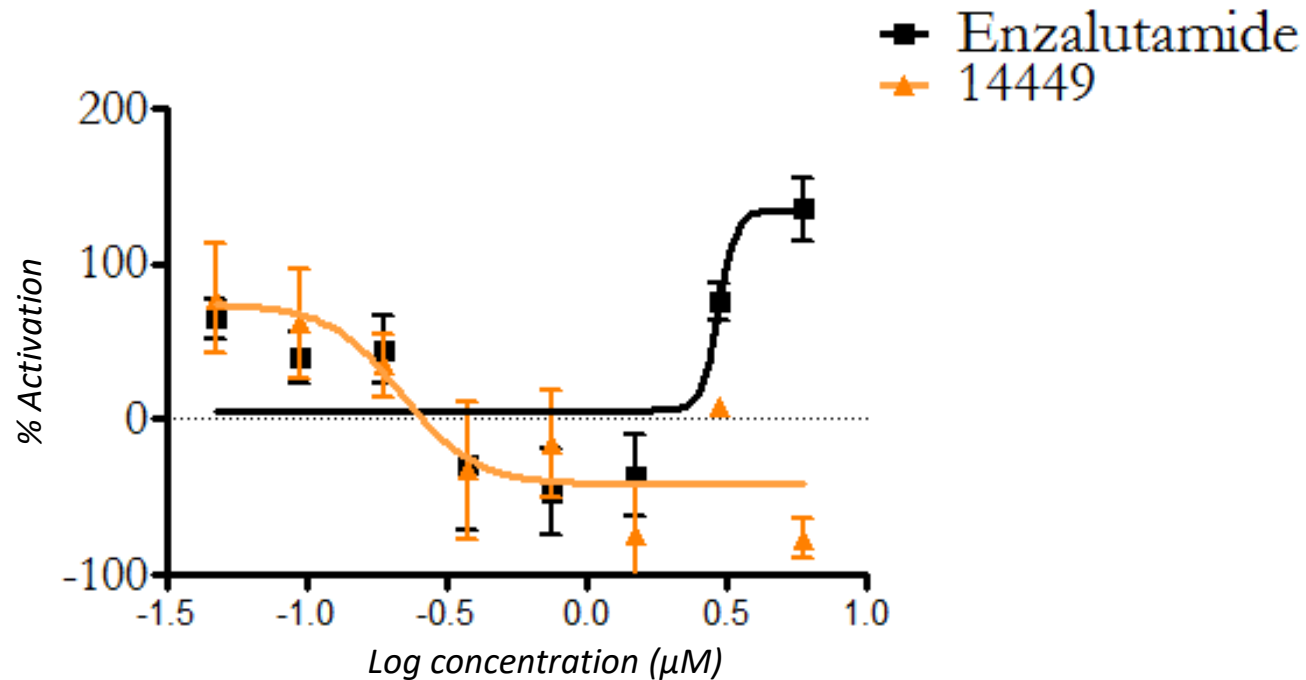
Inhibition of PSA



(Left) Dose-response curve of the inhibiting effect of 14449 ($IC_{50} = 0.10\mu M$) Enza ($IC_{50} = 0.08\mu M$) on the AR transcriptional activity in LNCaP cells

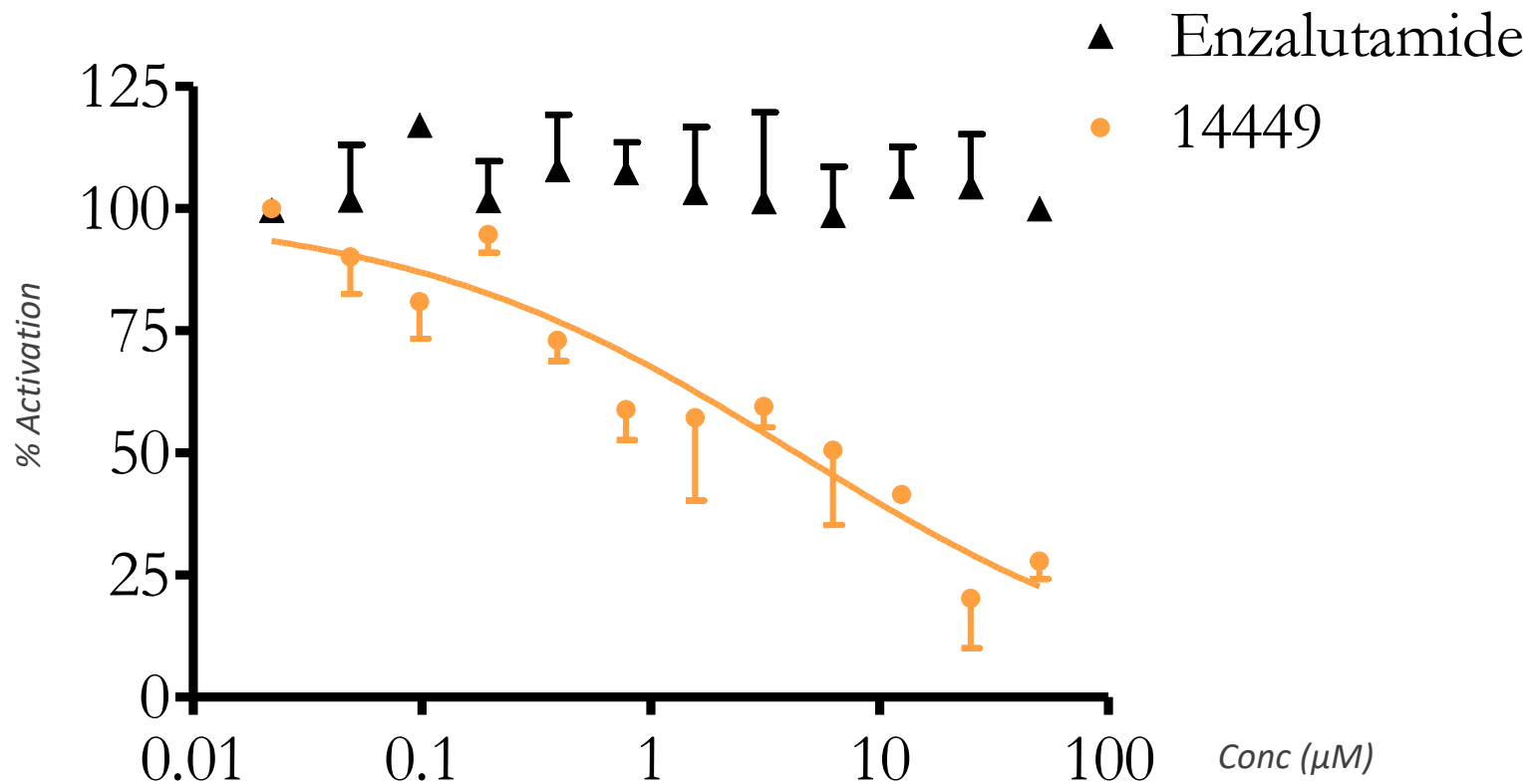
(Right) IC_{50} curve illustrating the inhibiting effect of 14449 ($IC_{50} = 0.17\mu M$) and Enzalutamide ($IC_{50} = 0.08\mu M$) on the PSA levels in LNCaP cells

14449 Effect on MR49F(Enza Resistant) Cell Line



The effect of 14449 on cell viability in an Enzalutamide resistant cell line (MR49F) where the compound demonstrated IC_{50} of $0.21\mu\text{M}$

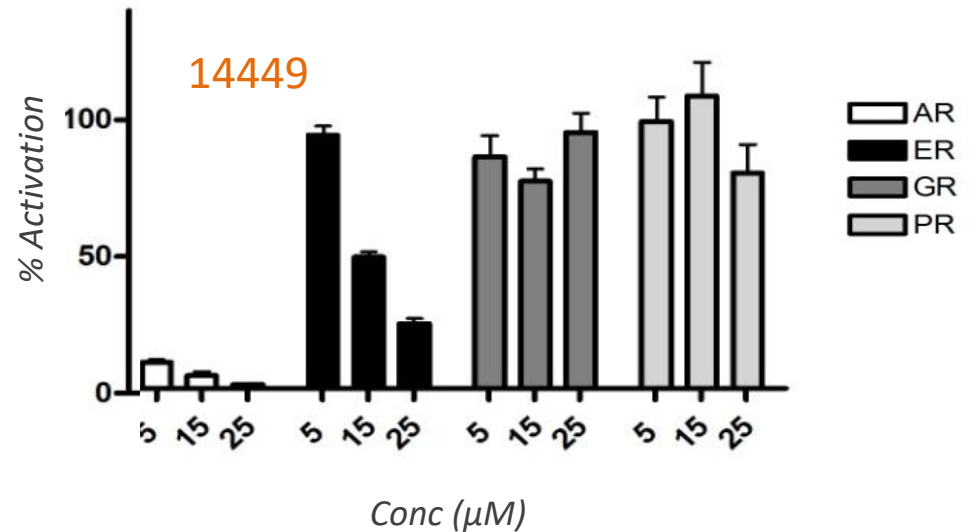
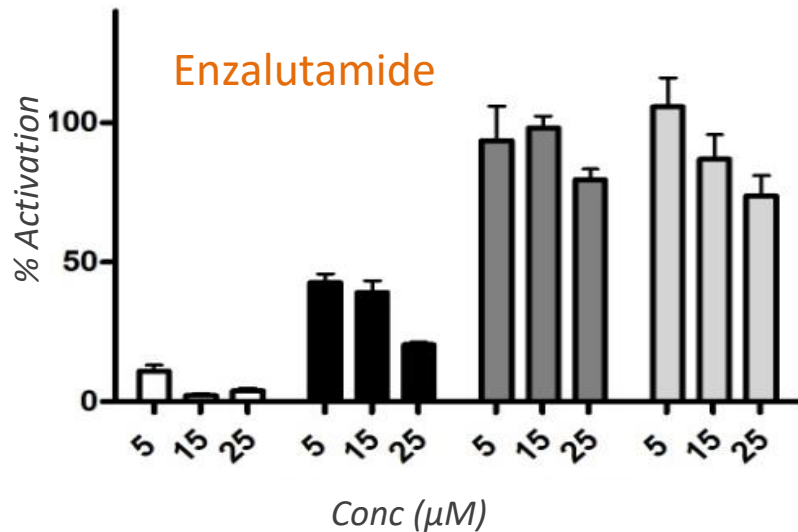
14449 Inhibits AR Splice Variant V7



14449 inhibits the transcriptional activity of wild type AR splice variant, V7 assay. Enzalutamide has no effect on V7.

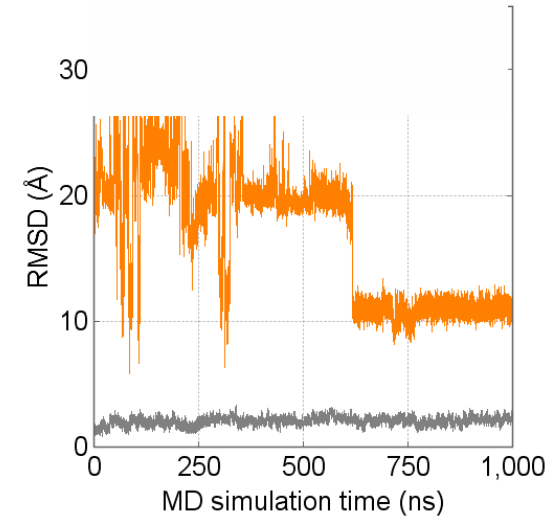
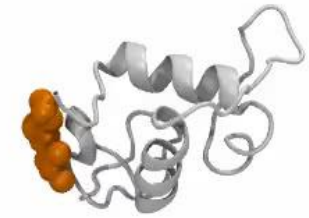
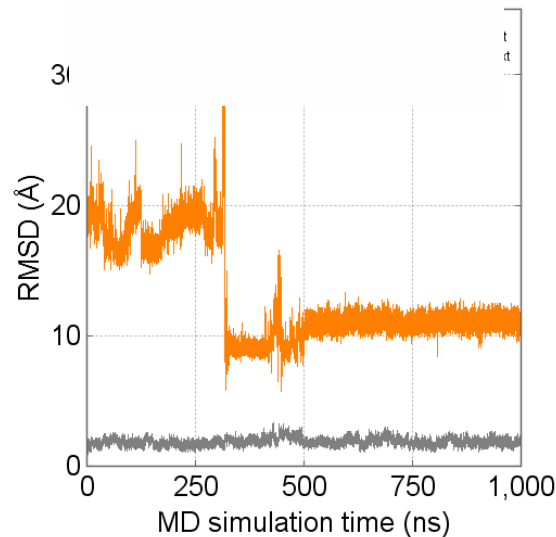
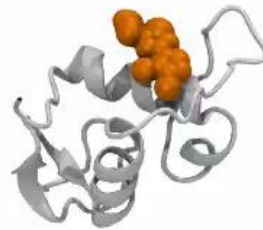
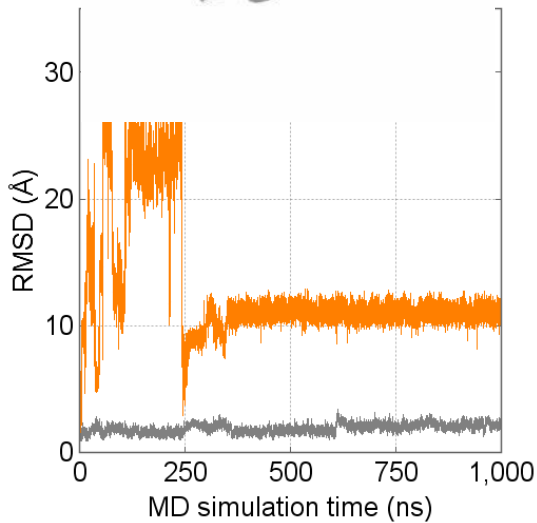
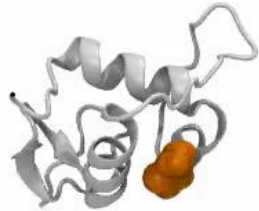
14449 Demonstrates Selectivity Toward the AR

	560	570	580	590	600	610	620
AR-DBD	TCLICGDEASGCHYGAL	TCGSCKVFFKRAA	EGKQKYL	CASRNDCTI	DKFRRKNCP	S	CRLRKCYEAG
ER-DBD	YCAVCNDYASGYHYGVWSCEGCKAFFKRSI	QGHNDYMCP	ATNQCTI	DKNRRKS	CQACRLRKCYE	V	G
GR-DBD	LCLVCSDEASGCHYGVLT	TCGSCKVFFKRAV	EGQHNYL	CAGRNDCI	VDKI	RRKNCP	ACRYRKCLQAG
PR-DBD	ICLI	CGDEASGCHYGVLT	TCGSCKVFFKRA	MEGQHNYL	CAGRNDCI	V	DKI



(Left) Enzalutamide and (Right) 14449 inhibits AR but not ER, GR and PR in luciferase assays against transiently expressed AR, GR, and PR or against endogenous ER in MCF-7 cells. AR, GR and PR activity was assessed with the ARR3tk-luciferase reporter

VPC - 14449 Firmly Binds to the AR DBD Site

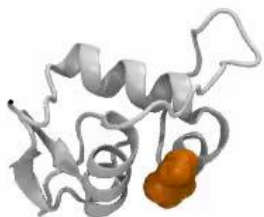


Molecular dynamics simulation was performed using explicit solvent model. The total run time 3 μ s. The MD simulation study supports that **14449 binds to DBD site stably.**

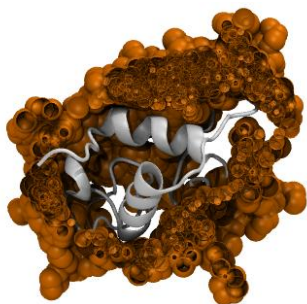
The results indicate **14449 finds its DBD binding spot** from various starting points.

Consensus Validation of the Binding Site and Poses

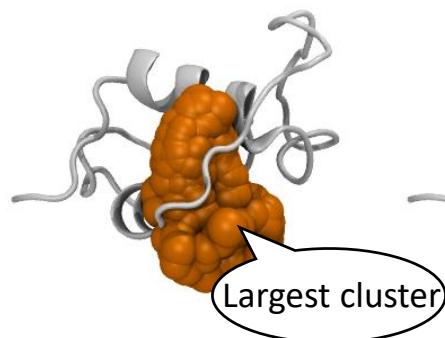
1. Multiple MD simulations



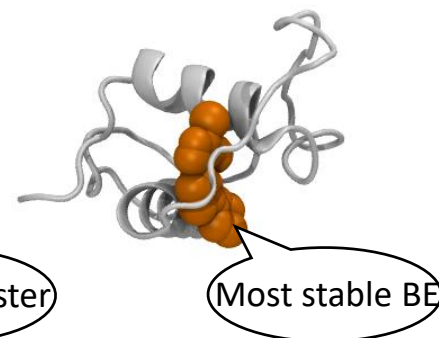
2. Sampled binding poses



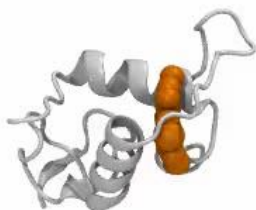
3. Cluster analysis & Binding energy calc.



4. Representative pose

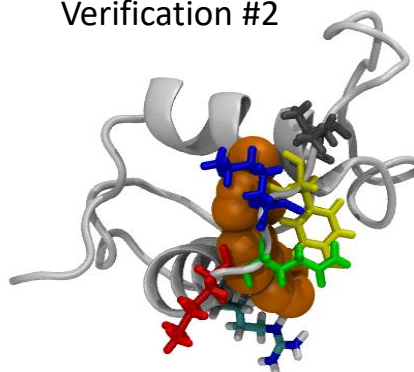


Verification #1

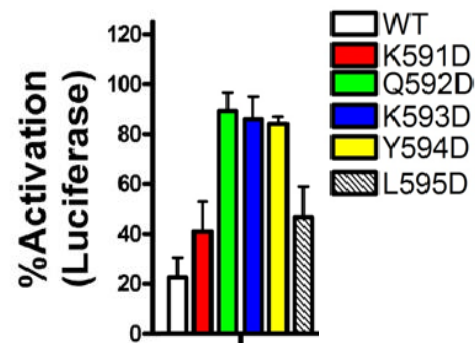


MD simulation starting from the representative pose

Verification #2



Comparison with the mutation experiment



VPC - 14449 Demonstrated sub-Optimal Stability

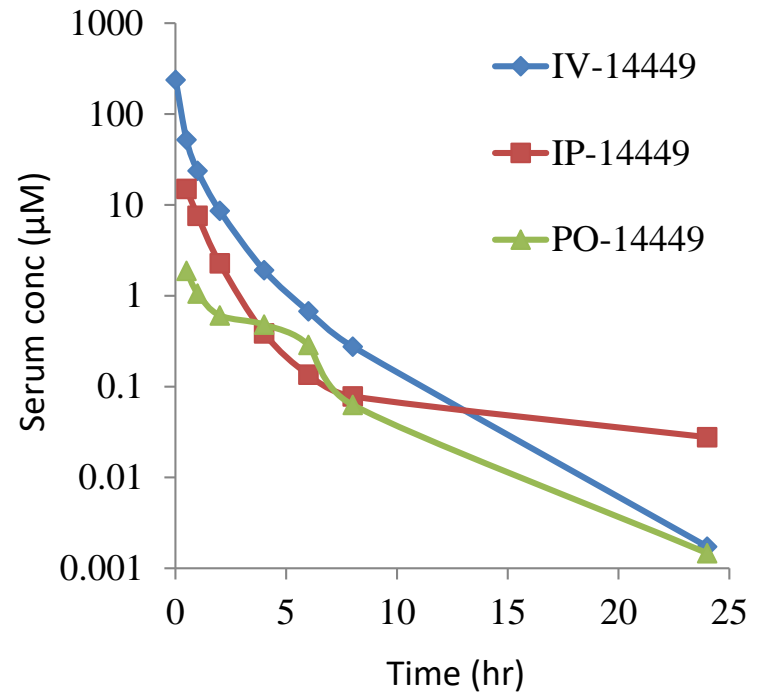


14449	0	1,06E+03	1,07E+03	1,07E+03	100	0,993	0,017	40,67	41,07	100
	10	9,12E+02	9,60E+02	9,36E+02	88					
	20	7,43E+02	7,08E+02	7,25E+02	68					
	30	6,99E+02	6,14E+02	6,57E+02	61					
	40	5,27E+02	5,60E+02	5,44E+02	51					
					98					

Compound	14449
eGFP IC50 (µM)	0.38
PSA IC50 (µM)	0.17
T1/2 Microsomes (min)	14

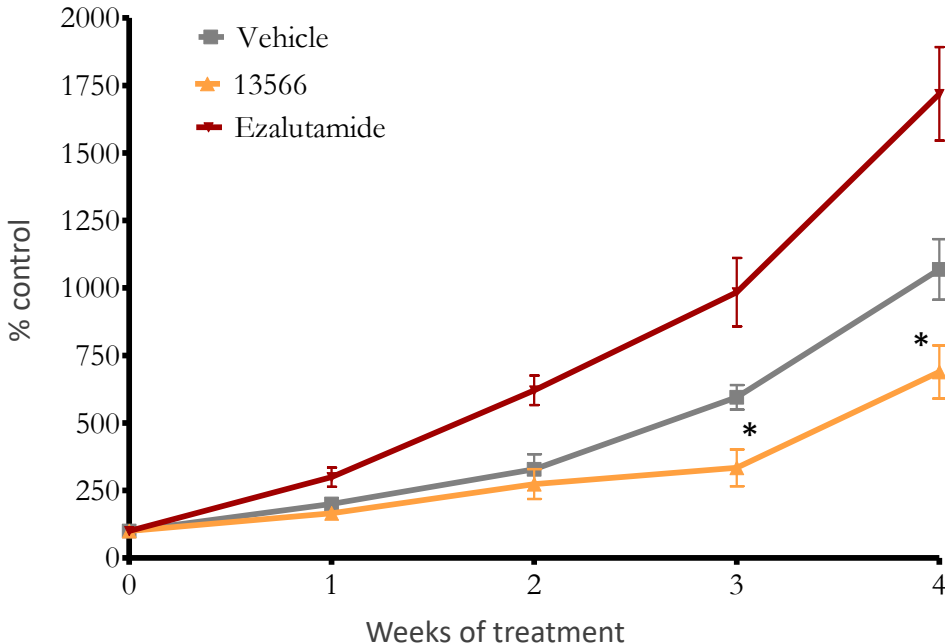
Pharmacokinetics of VPC-14449

- 9 CD1 mice 8-10 weeks old were divided into 3 groups, 3 mice each
- Route of administration: Intravenous (IV), intraperitoneal (IP) or Oral (PO)
- Dose: 100 mg/kg of 14449 formulated using 1:10 hydroxypropyl cyclodextrin: dd H₂O
- To measure serum drug levels, tail blood samples were taken following the administration, at time points corresponding to 0.0, 0.5, 1, 2, 4, 6, 8, 24hr

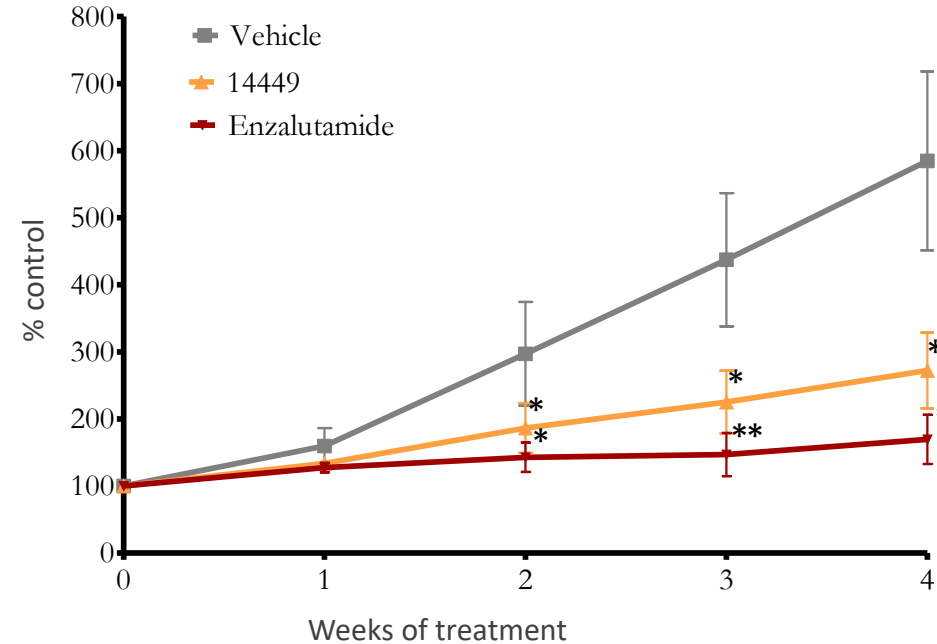


In vivo Effect of VPC - 14449

MR49F (Tumor Volume)



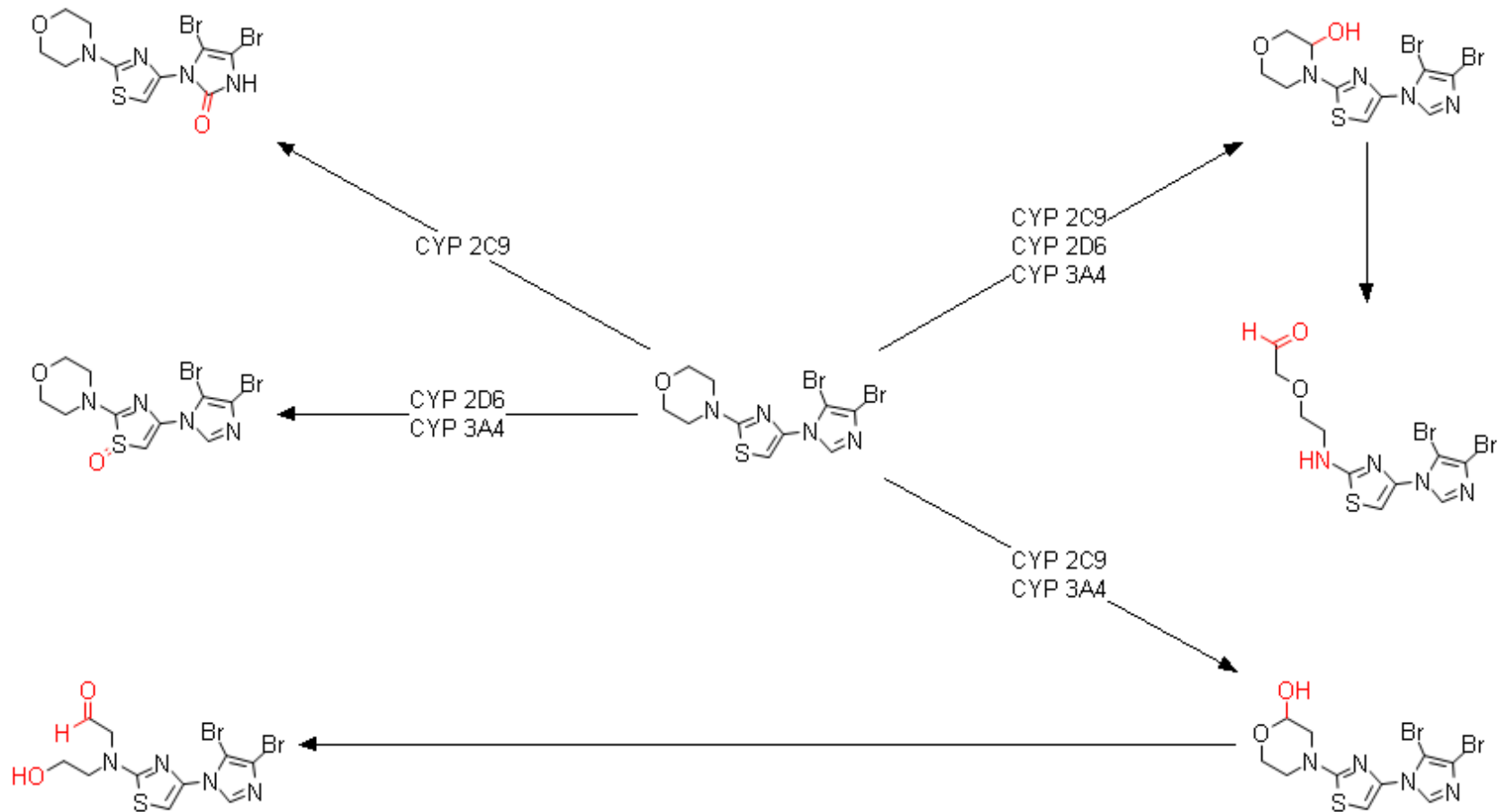
C4-2 (Tumor Volume)



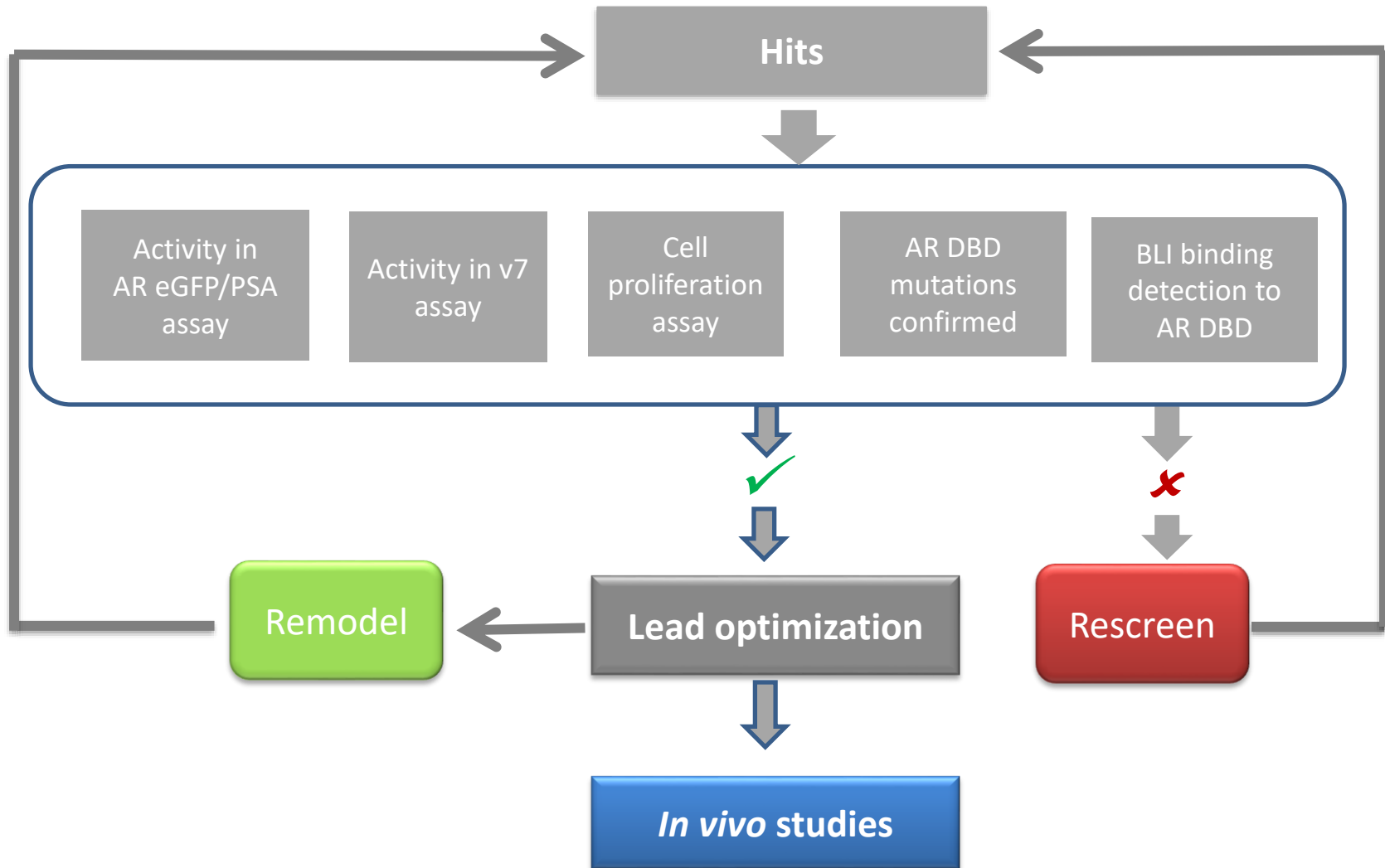
(Left) The effect of 14449 on the tumor volume of the Enzalutamide-resistant (MR49F) xenograft model.

(Right) The effect on tumor volume of castration resistant (androgen insensitive) C4-2 xenograft model.

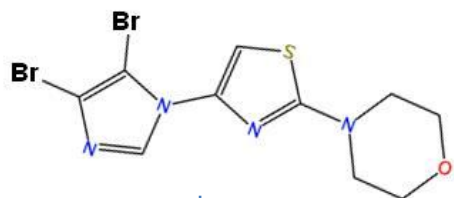
Predicted Metabolic Liabilities of VPC-14449



Iterative Screening Workflow



Second Generation VPC-14518, Improved Stability

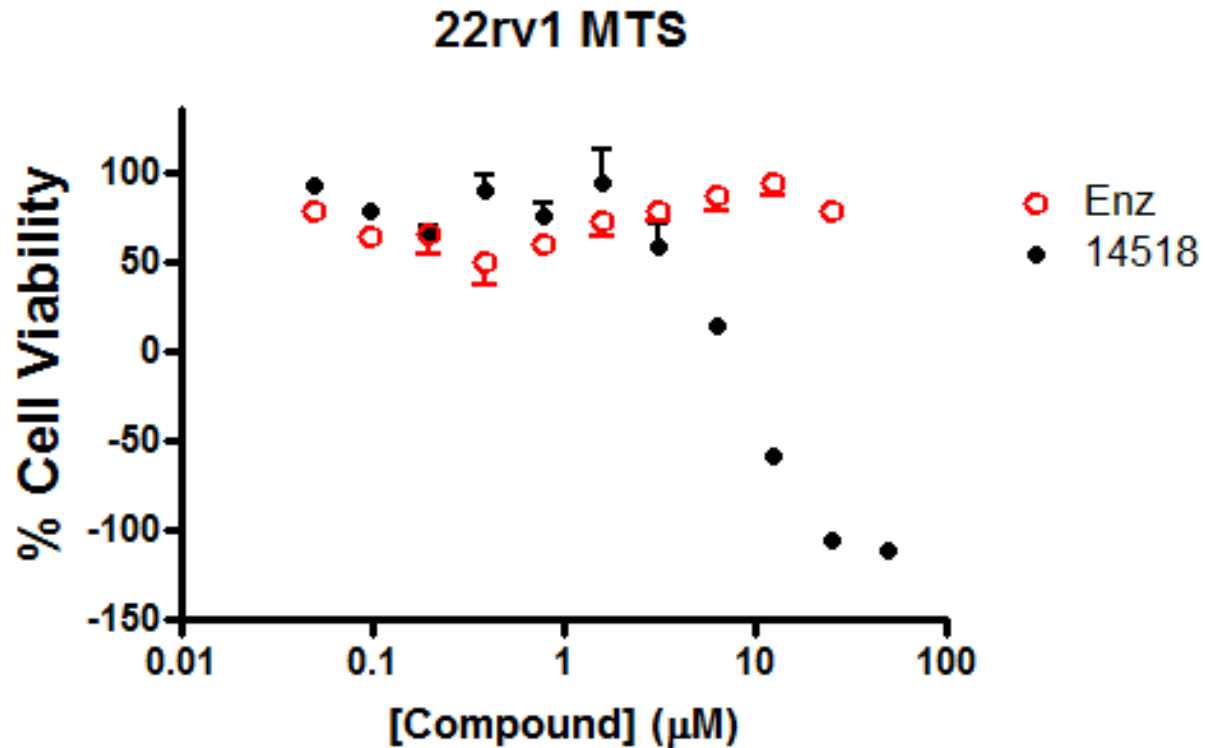


14512/14518

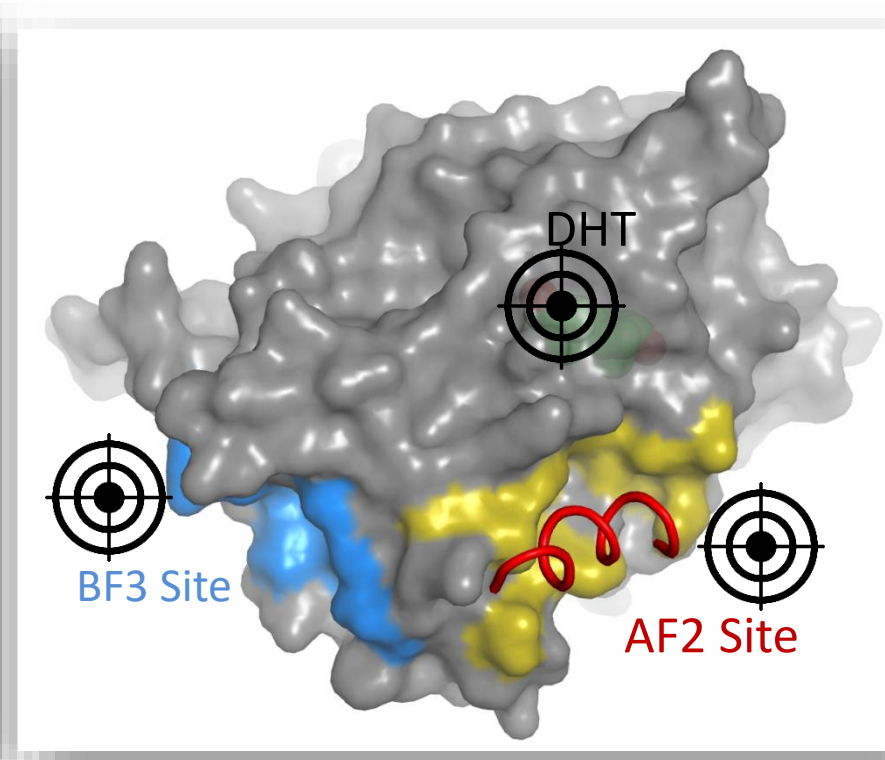
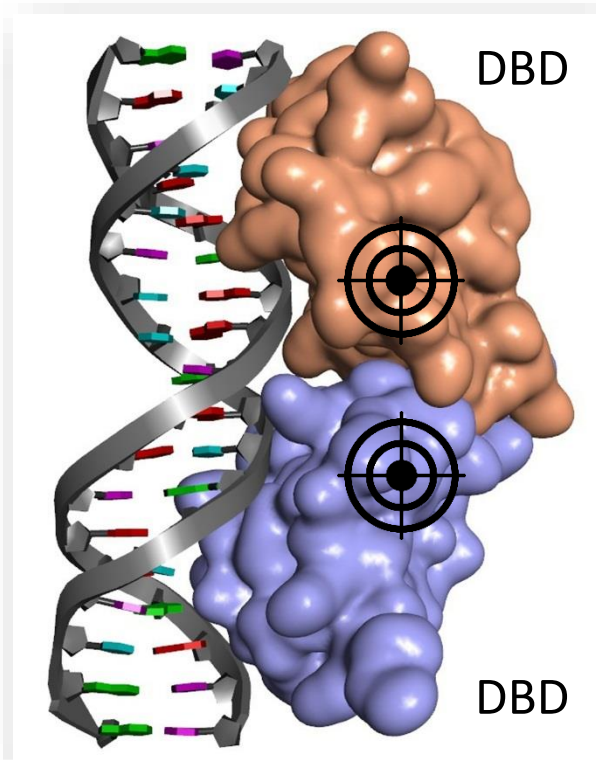
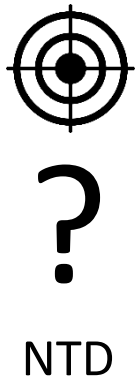
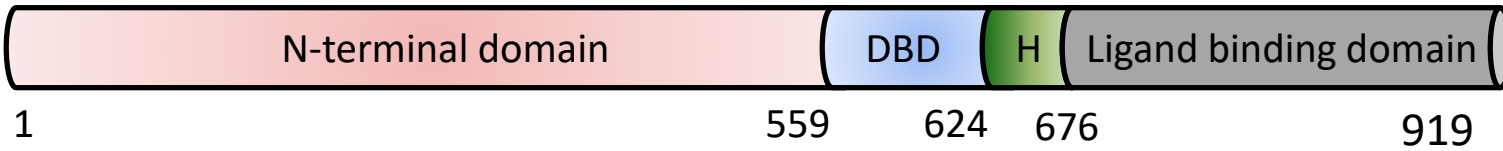
14518	0	4,79E+05	4,74E+05	4,77E+05	100	0,823	0,003	263,18	6,35	100
	10	4,66E+05	4,24E+05	4,45E+05	93					
	20	4,18E+05	4,56E+05	4,37E+05	92					
	30	4,58E+05	4,46E+05	4,52E+05	95					
	40	4,07E+05	4,22E+05	4,15E+05	87					

Compound	14449	14512	14518
eGFP IC50 (μM)	0.38	0.16	0.19
PSA IC50 (μM)	0.17	0.16	0.08
T1/2 Microsomes (min)	14	58	263

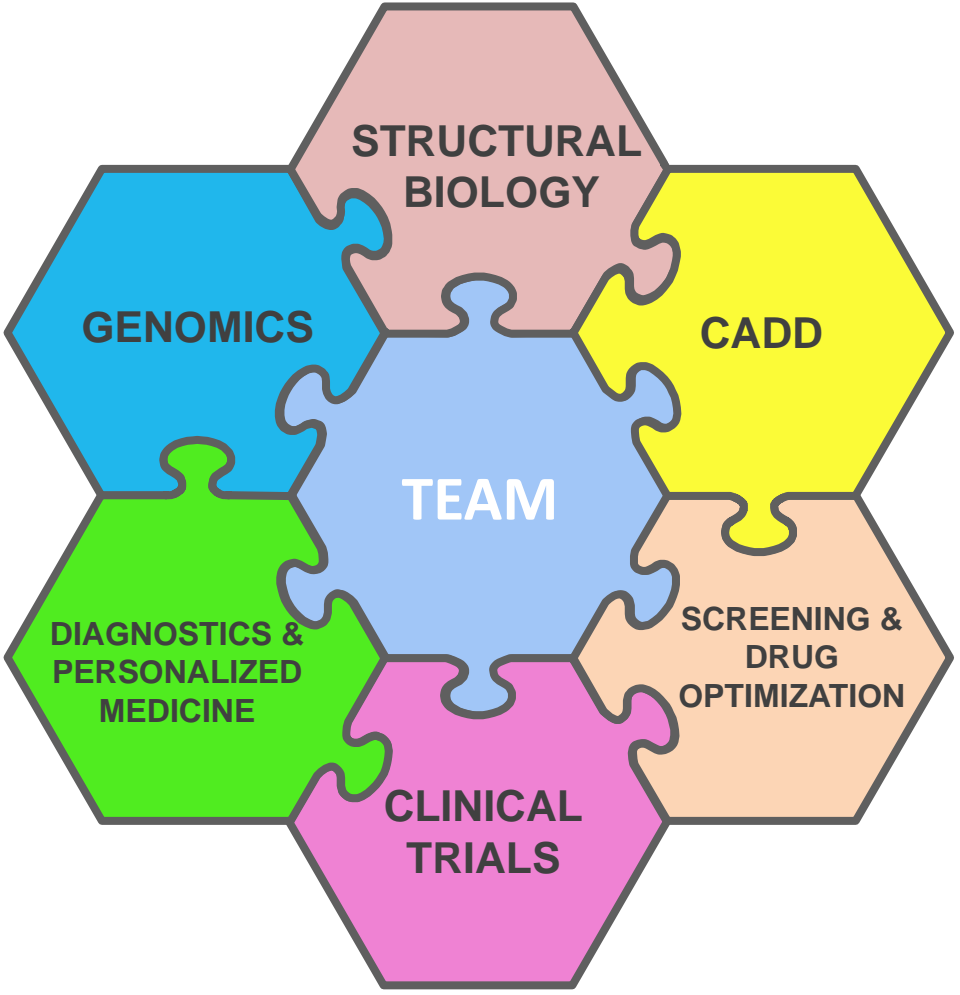
Selecting a Clinical Candidate VPC-14518



Structural Domains of AR



All the Pieces to Succeed = Guaranteed Outcome



=

- New Targets and Structures
- New Drugs
- Companion Diagnostics

IN SPORTS
VRBATA NEEDS A GOOD FEED
 Winger struggling without healthy diet of Sedinyx > C7

BUSINESSBC

TUESDAY, DECEMBER 15 | 2015 | BUSINESSCORRECTOR SCOTT McFEE@604.685.2006 | INFO@VANCOUVERNEWS.COM

S & P 500 17,000.26 ↓ 0.46
 TSX Venture 1,265.20 ↓ 9.91
 Dow Jones 103,290 ↑ 1.35
 S & P 500 17,000.26 ↓ 0.46
 Dollar 1.00 US ↑ 0.02
 Gold 1,242.70 ↑ 12.20
 Oil 49.11 ↓ 0.69
 Natural Gas 4.10 ↓

BRIEFINGS

SCIENCE

Newalta to spend less on growth
 The British environmental services company, which helps recover valuable material from waste produced by the oil and gas industry, says it will spend less on growth projects next year. The Calgary-based company said Monday it has about 100 million of undepreciated equipment in inventory. As a result, it will reduce its budget for growth capital to between \$20 million and \$30 million in 2016, down from 570 million this year. It will also spend \$10 million on maintenance capital, the same as 2015.

Oil, gas weakness curbs Trinidad
 Trinidad Drilling Ltd. has chopped its initial capital spending budget for 2016 to \$30 million — 84 per cent less than what it's spending this year — to reflect weak conditions in the oil and gas industry. The Calgary-based company says it's primarily aiming to maintain Trinidad's current operations, although it may be able to spend as much as \$45 million if certain growth opportunities arise — still 76 per cent below 2015 levels.

Pepsi revamps vending tactics
 PepsiCo Inc., facing an anti-soda backlash and health concerns about snack foods, is looking for a resurgence in an especially hard-hit part of the industry: vending machines. The company is rolling out several thousand temperature-controlled machines that offer both food and drinks under the new Hello Goodness brand, according to a statement. The units will include healthier products from PepsiCo's beverage and Frito-Lay divisions.

Ferrari designer shares link
 The Mahindra industrial group based in Mumbai, India, announced Monday it had reached a deal to buy a controlling stake in the Italian design firm Pininfarina, most famous for its designs for Ferrari, Alfa Romeo and Maserati. Shares in the 85-year-old Italian company dropped by nearly 70 per cent on the news, to close at \$1.44 U.S. Under the deal, two of the Mahindra group's units will buy 70.5 per cent of the design firm for \$1.21 U.S. a share.

Researcher Artem Cherkasov displays a computer model simulation used to develop a new treatment for drug-resistant prostate cancer at the Vancouver Prostate Centre. "Using computer simulations, we sometimes go through 50 million compounds to find a molecule that will test in a precise and accurate way," he says.

Massive cancer-drug deal one of UBC's biggest to date
 University's record agreement worth \$140 million — and counting

RANDY SHORE
 VANCOUVER

As much as that sounds — and it is a lot — the real money is in the royalties, which could exceed \$140 million by quite a bit.

BRAD WHEELER
 TECHNOLOGY TRANSFER MANAGER, UBC'S UNIVERSITY-INDUSTRY LIAISON OFFICE

Whether, technology transfer manager at the University-Industry Liaison Office and lead negotiator on the Roche license. The scientists will share 50 per cent of the test revenue.

The researchers found the three-dimensional shape of their target location in previous research and set about looking for a molecule that would bind to it.

"Drug and medicine work like a key in a lock, so we have to find the perfect key for the matching lock," said Cherkasov. "Using computer simulations, we sometimes go through 50 million compounds to find a molecule that will test in a precise and accurate way."

Roche's powerful search technique produced about two candidate molecules, which they

- Dr. Leonard Foster (PI)
- Dr. Raymond See
- Nikolay Stoynov
- Jihong Jiang
- Sukhbir Kaur
- Tian Lian
- Linda Jackson
- Dr. Natalie Strynadka (PI)
- Emily Amandoroni
- Farhad Hormozdiari
- Dr. Cenk Sahinalp (PI)
- Dr. Kendall Byler (Post doc)
- Dr. William McMaster (PI)
- Dr. Robert Brunham (PI)
- Liam Warrol

- Dr. Paul Rennie (PI)
- Dr. Emma Guns (PI)
- Dr. Martin Gleave (PI)
- Dr. Colin Collins (PI)
- Dr. Fuqiang Ban (RA)
- Dr. Takeshi Yamazaki (RA)
- Dr. Michael Hsing (Post doc)
- Dr. Robert Young (PI)
- Dr. Royal Zoraghi (RA)
- Dr. Brett Finlay
- Dr. Neil E Reiner
- Dr. Nag Kumar (Post doc)
- Ravi Munuganti
- Huifang Li
- Dr. Mohamed Hessein (RA)
- Dr. Sam Lawn (Post doc)
- Hans Adomat
- Mei Yieng Chin
- Dr. Eric Leblanc (RA)
- Dr. Kush Dalal (Post doc)
- Dr. Nada Lallous (Post doc)
- Dr. Miriam Butler (Post doc)
- Dr. Devki Nandan (RA)
- Kriti Singh
- Mani Moniri
- Helene Morin
- Fariba Ghaidi