Drugging “The Undruggable”
Augmented Reality of Academic Drug Discovery

a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA

Artem Cherkasov PhD, DSc

Disclosure

La Hoffman-Roche licenser

Aranda paid contractor

founder and/or shareholder:

ANDRONEX Pharmaceuticals

ABT Therapeutics

LAST Innovation

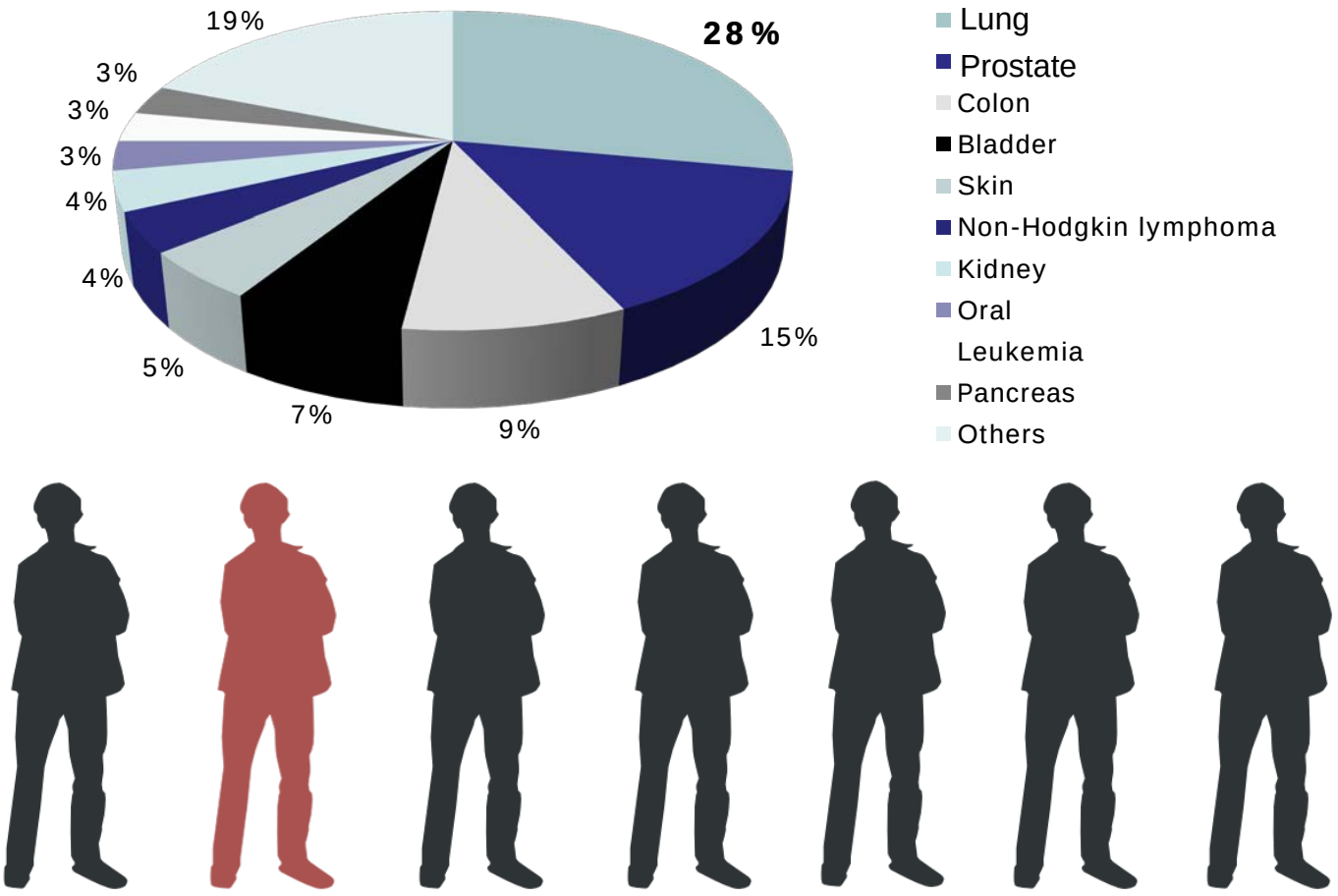
APT Therapeutics

INDEL Therapeutics

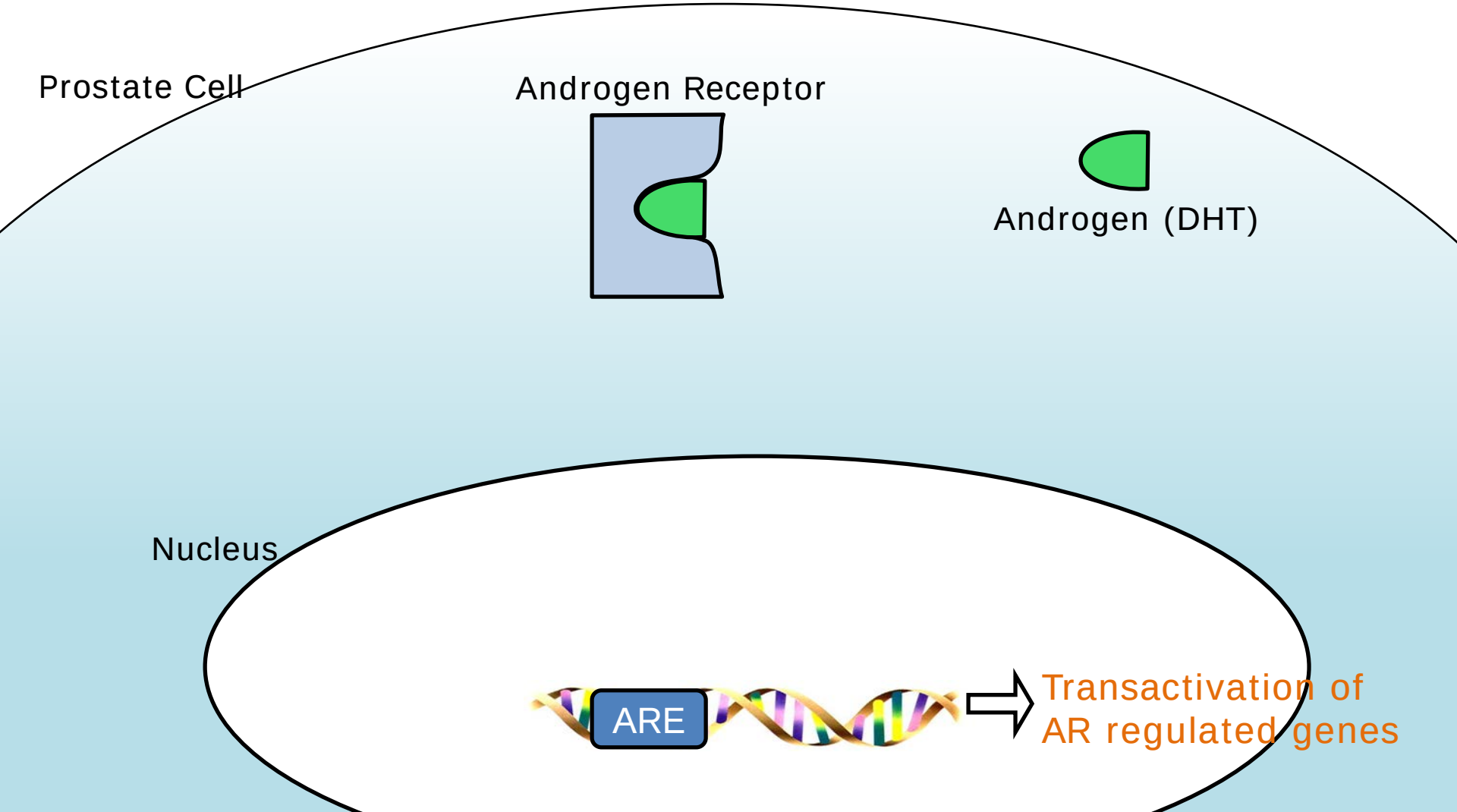
NIDA Biosciences

Prostate Cancer

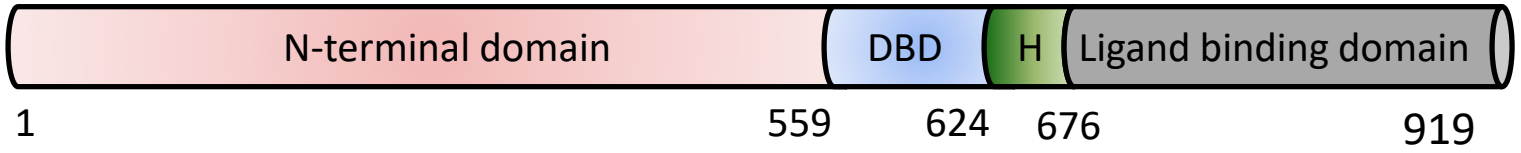
- Estimated new cancer cases in males



AR Mechanism of Action

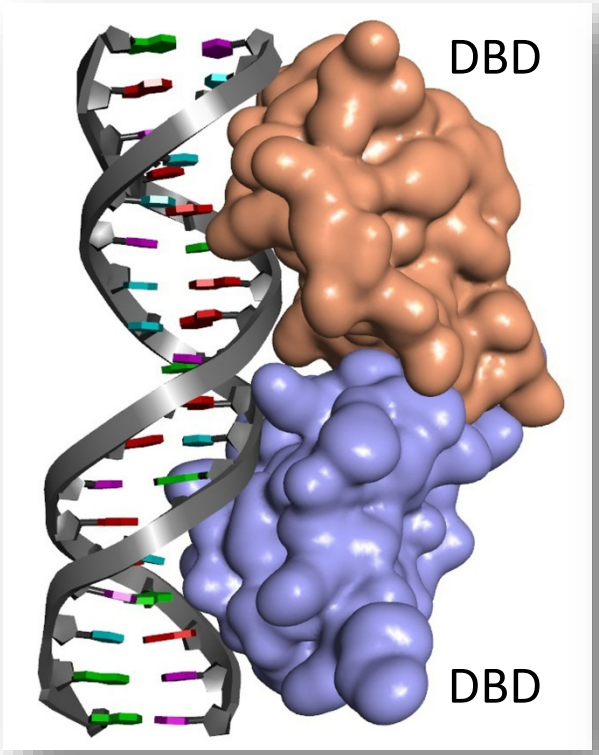


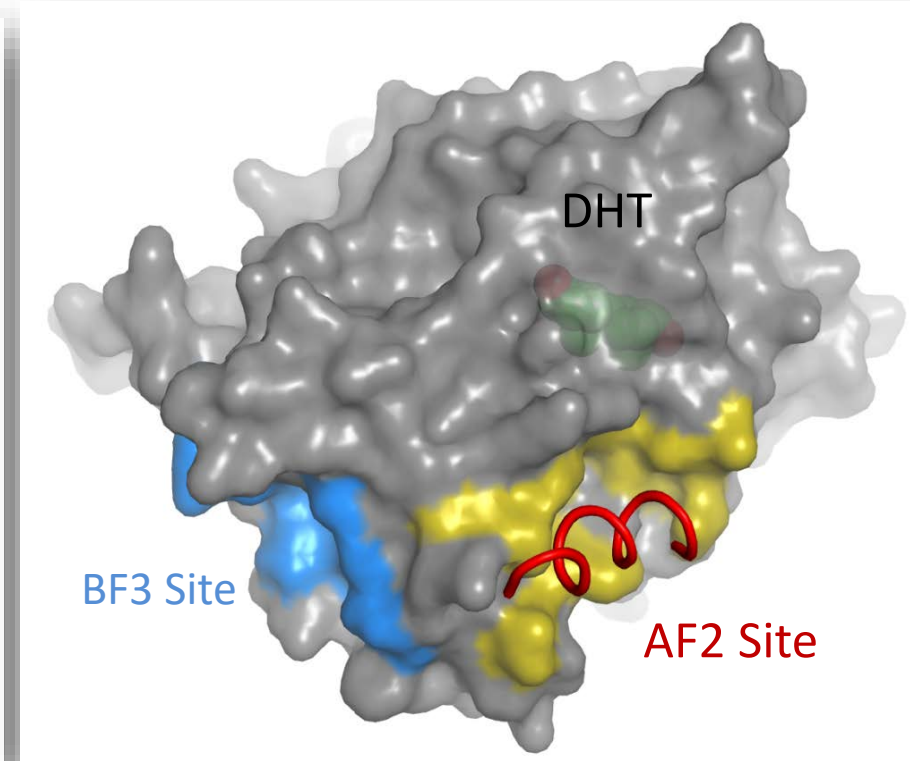
Structural Domains of AR



?

NTD



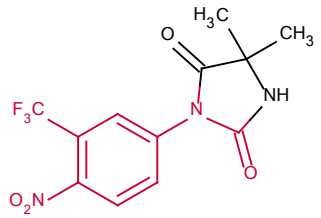


AR Conventional (LBD) Targeting

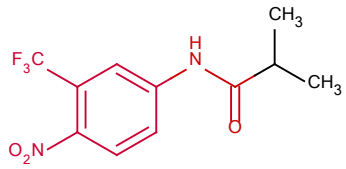
AR Inhibitors as Prostate Cancer Drugs

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

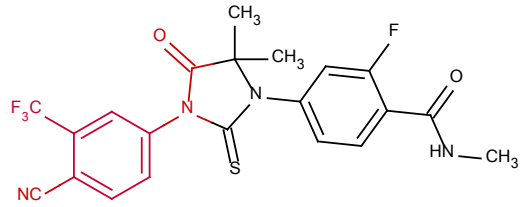
Nilutamide



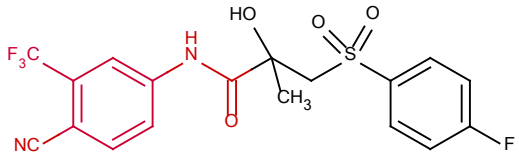
Flutamide



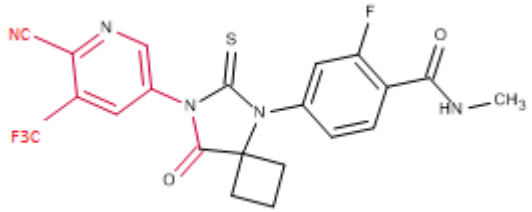
Enzalutamide (mdv3100)



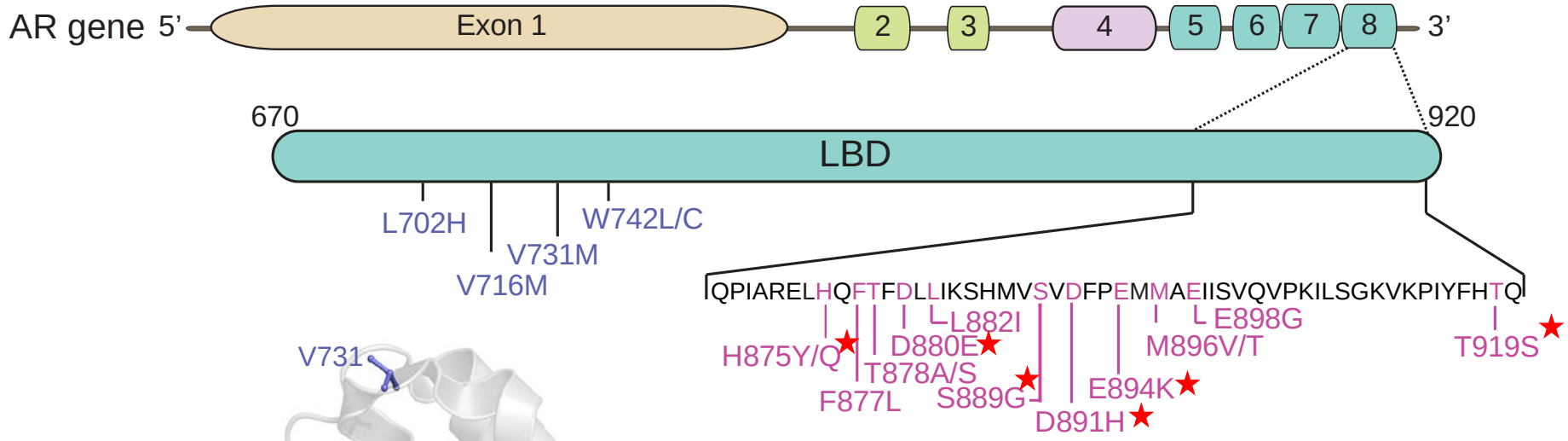
Bicalutamide

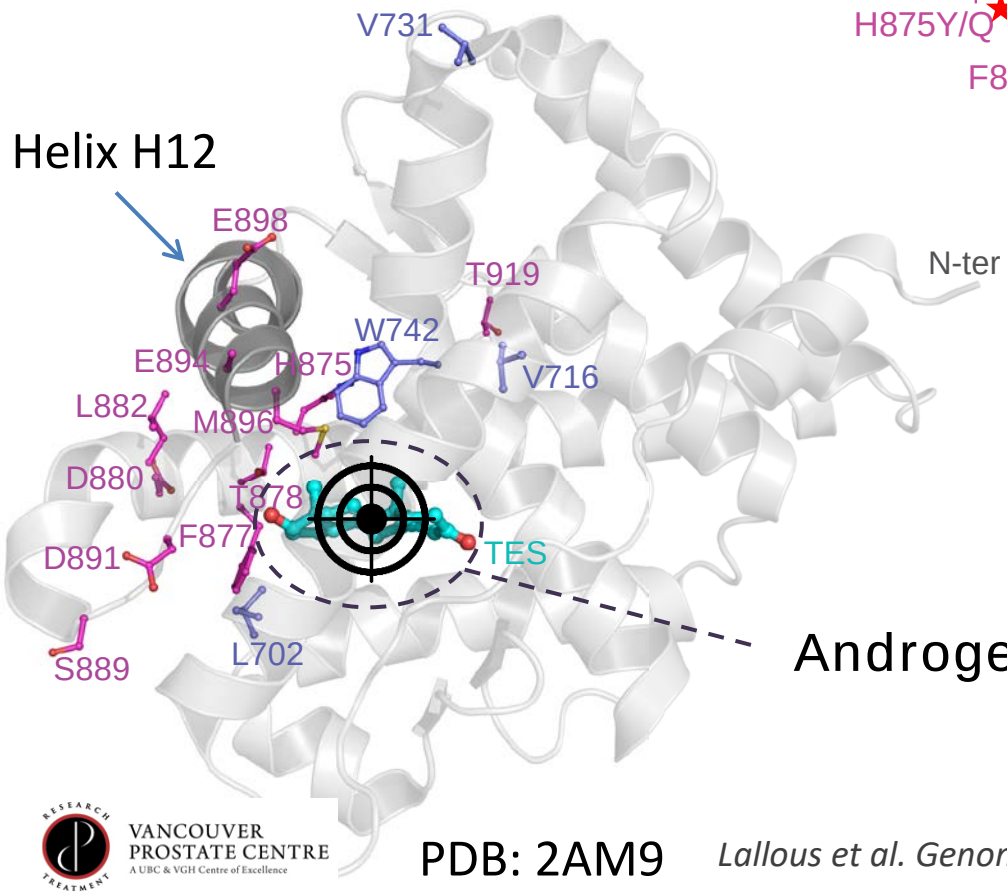


Apalutamide (arn-509)



Identification of AR mutants using liquid biopsy





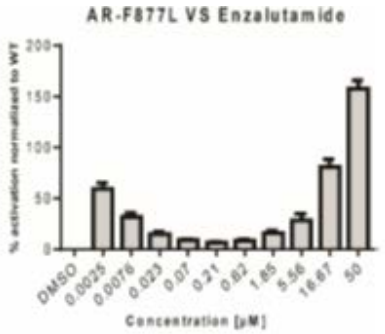
PDB: 2AM9

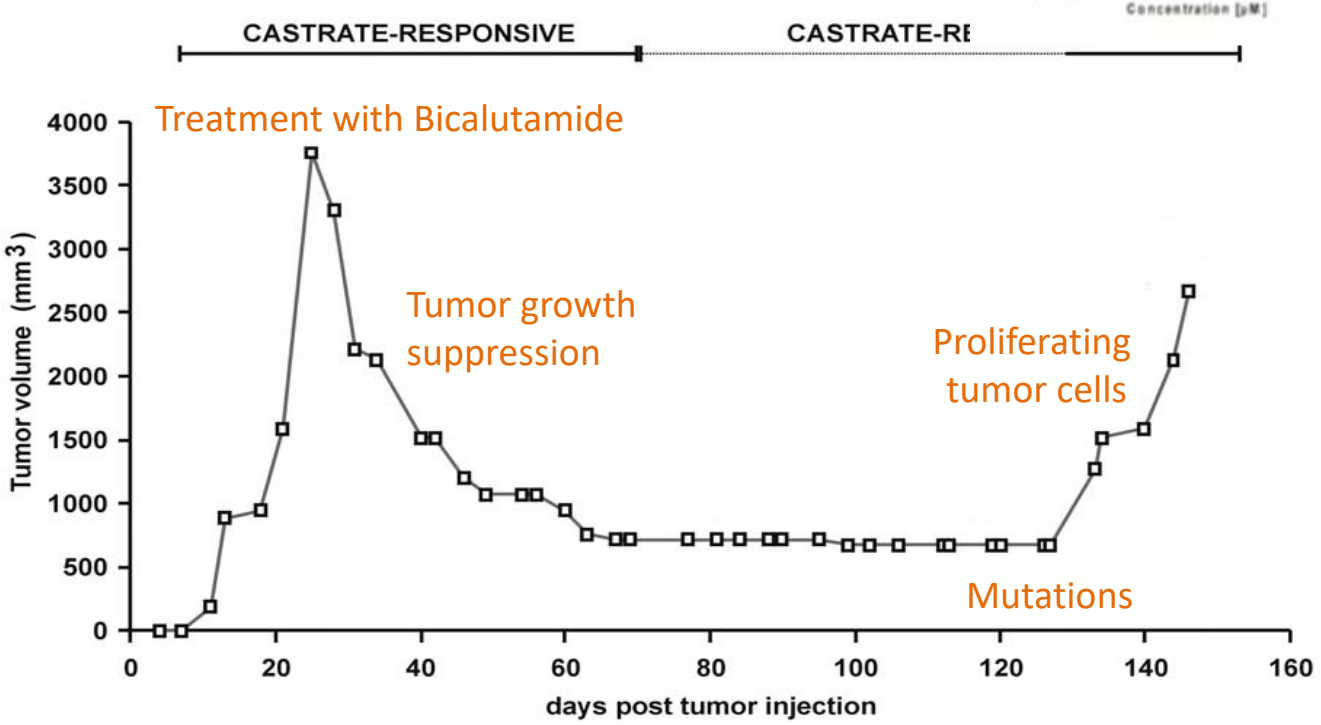
Lallous et al. Genome Biology, 2016

Factors that Causes Resistance to Anti-AR Drugs

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

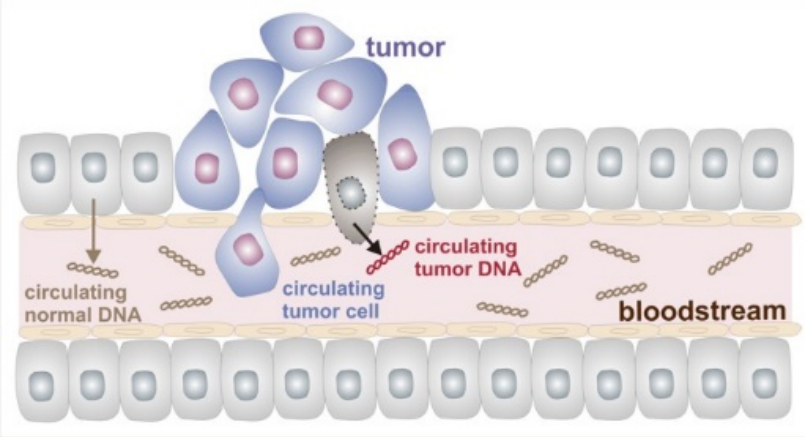
- W741C : Bicalutamide
- T877A : Flutamide
- F876L : Enzalutamide

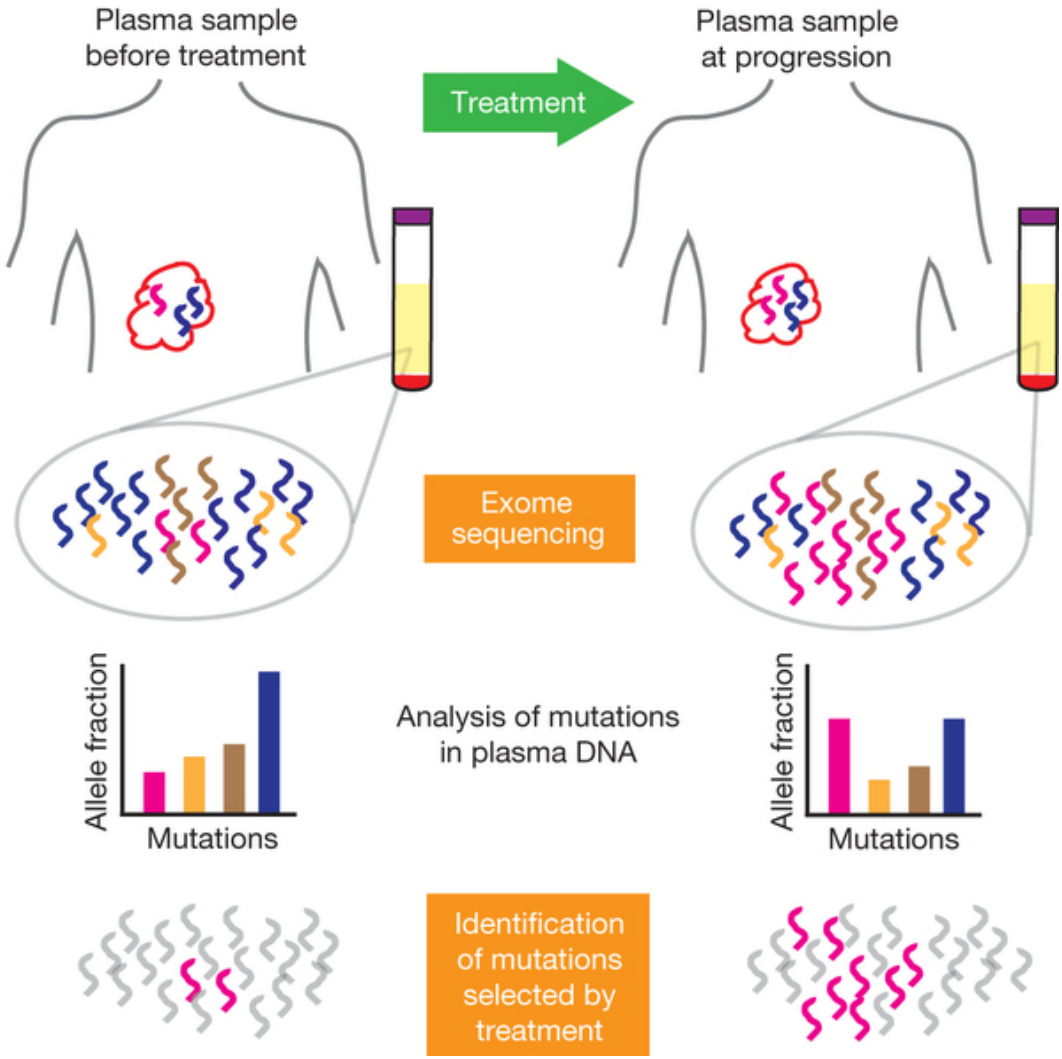




Scher et al. Endocrine-Related Cancer 2004

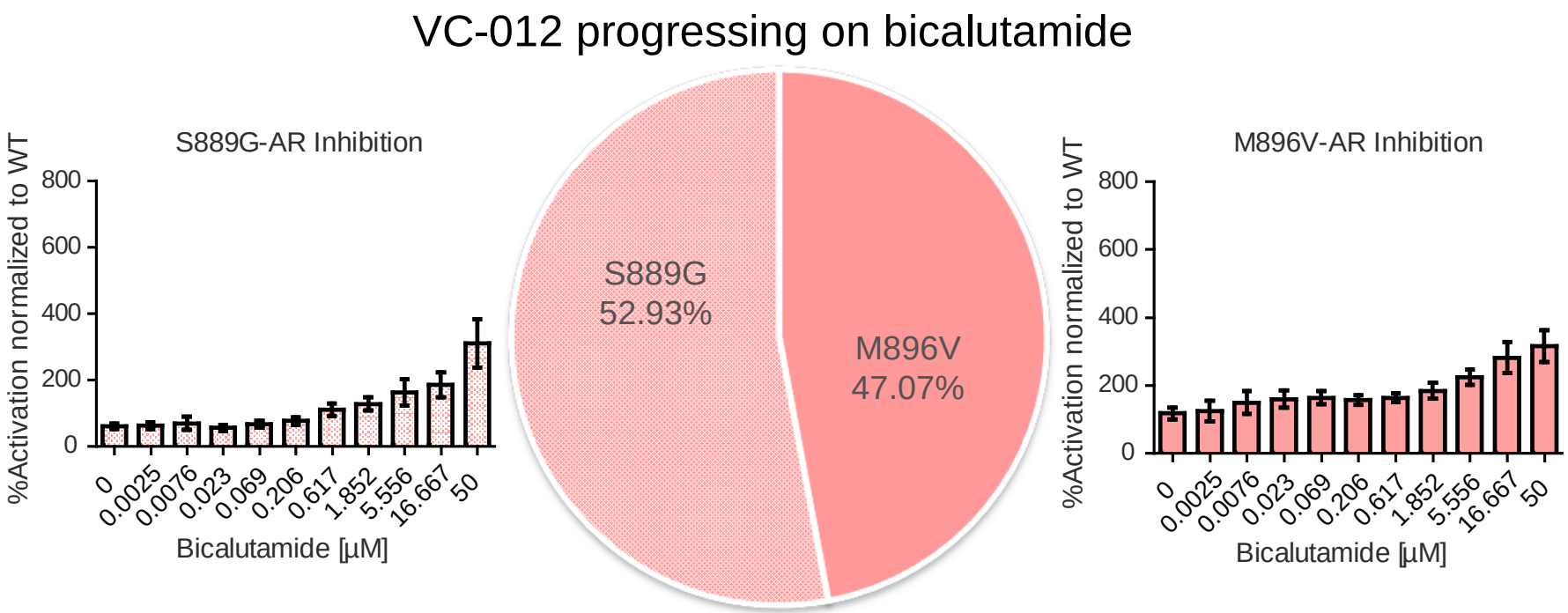
Circulating Cell Free DNA





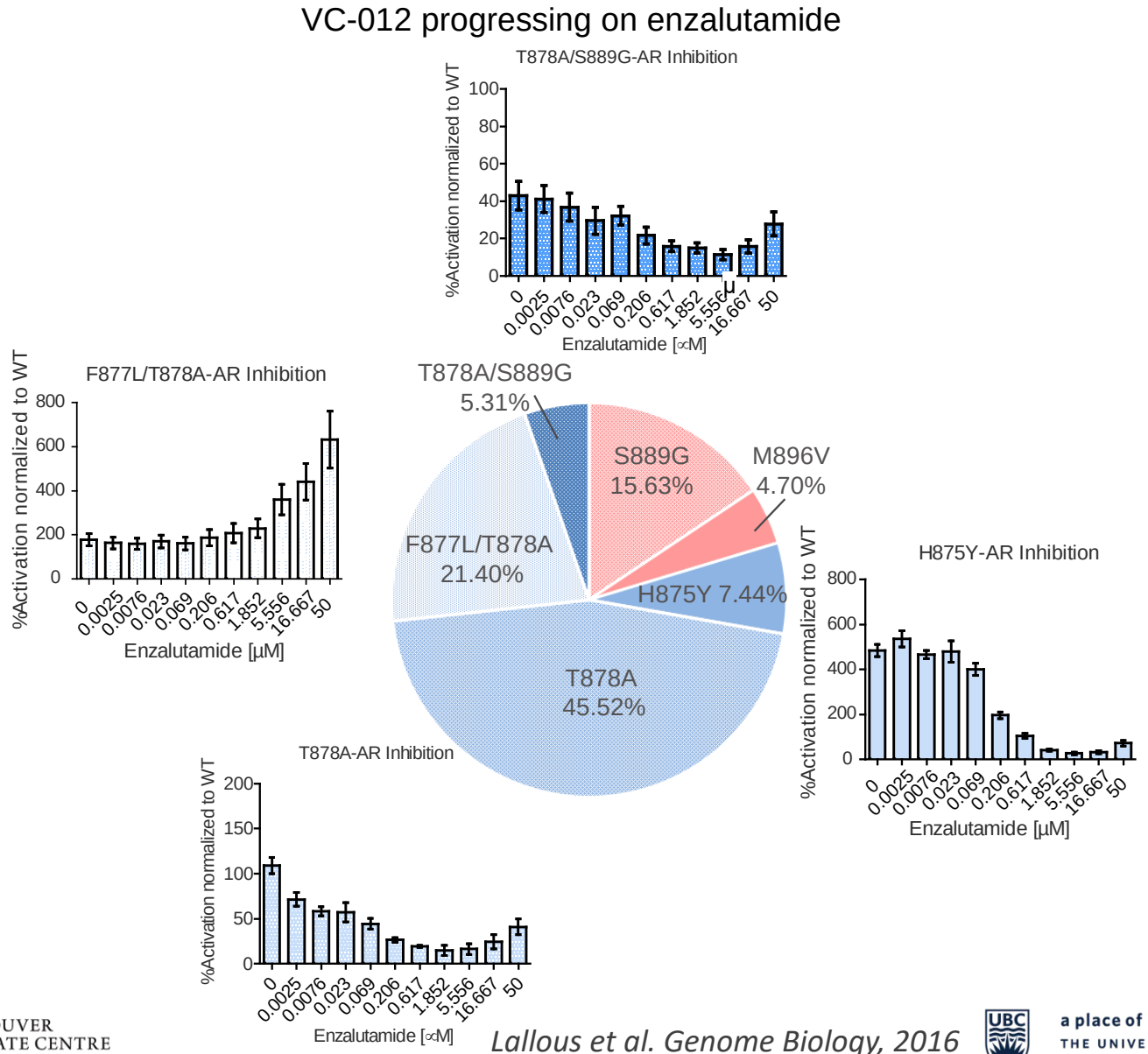
Nature 497, 108–112, 2013

Specific Case: Patient VC-012



Lallous et al. Genome Biology, 2016

Specific Case: Patient VC-012



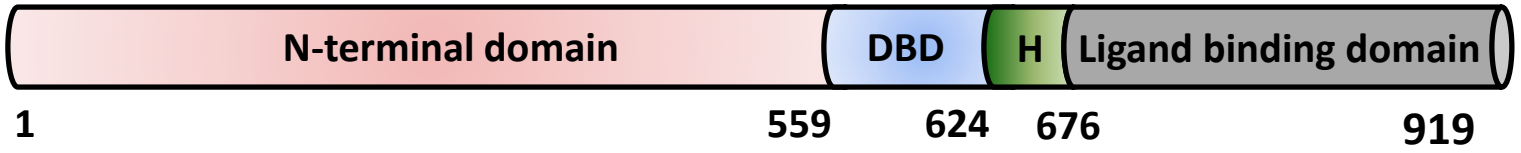
Lallous et al. Genome Biology, 2016

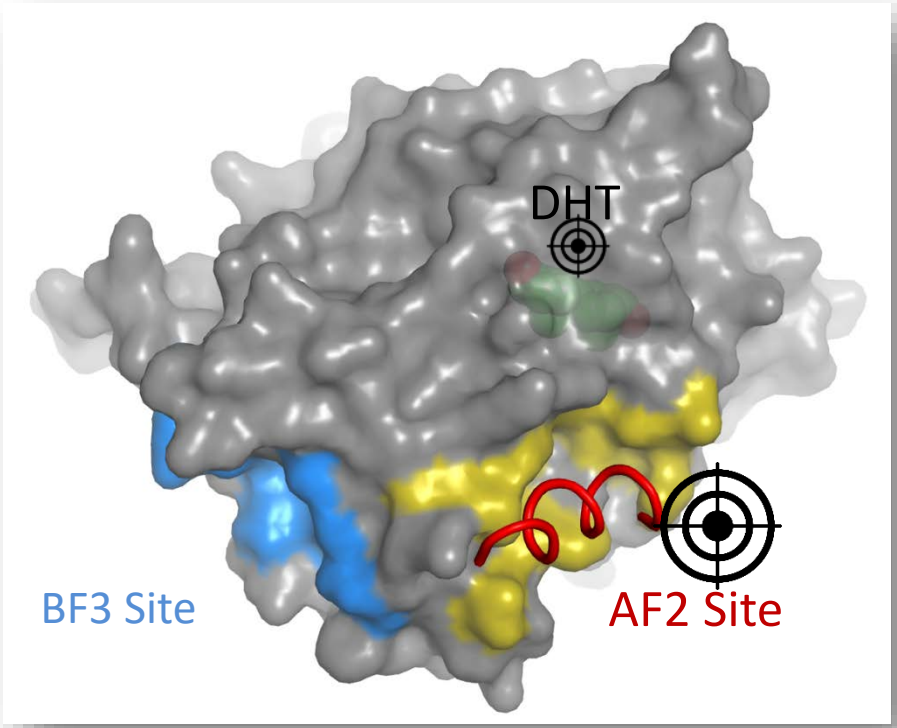
Agonist effect of anti-androgens on AR mutants

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			**A**									
		Y											
		Y		**A**									Ongoing
				A				H					
								H					
VC-005	VC-005_JWR_29Aug13								K				
VC-012	VC-012_LW_13Aug13									**V**			
	VC-012_LW_13Aug13						**G**						
	VC-012_LW_05Dec13						**G**						
										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											
												S	
VC-022	VC-022_GST_10Oct13				E								
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							

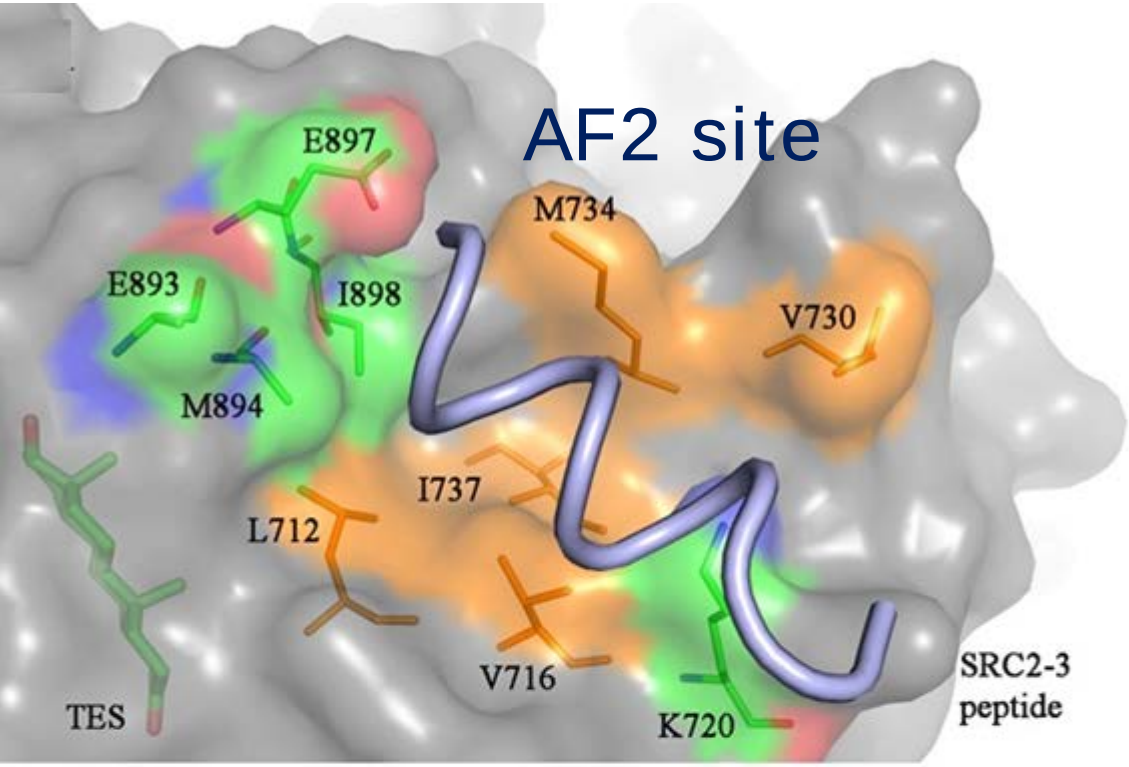
AR AF2 Targeting

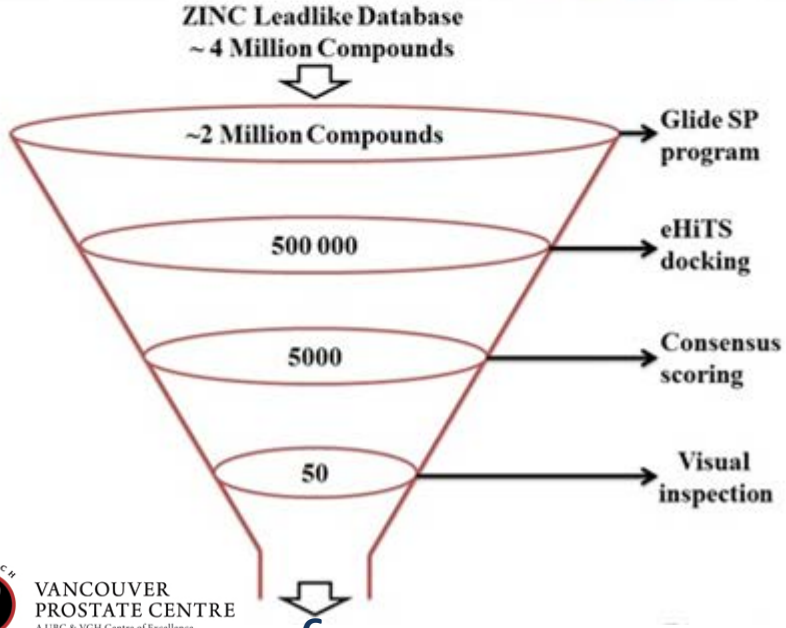
Structural Domains of AR





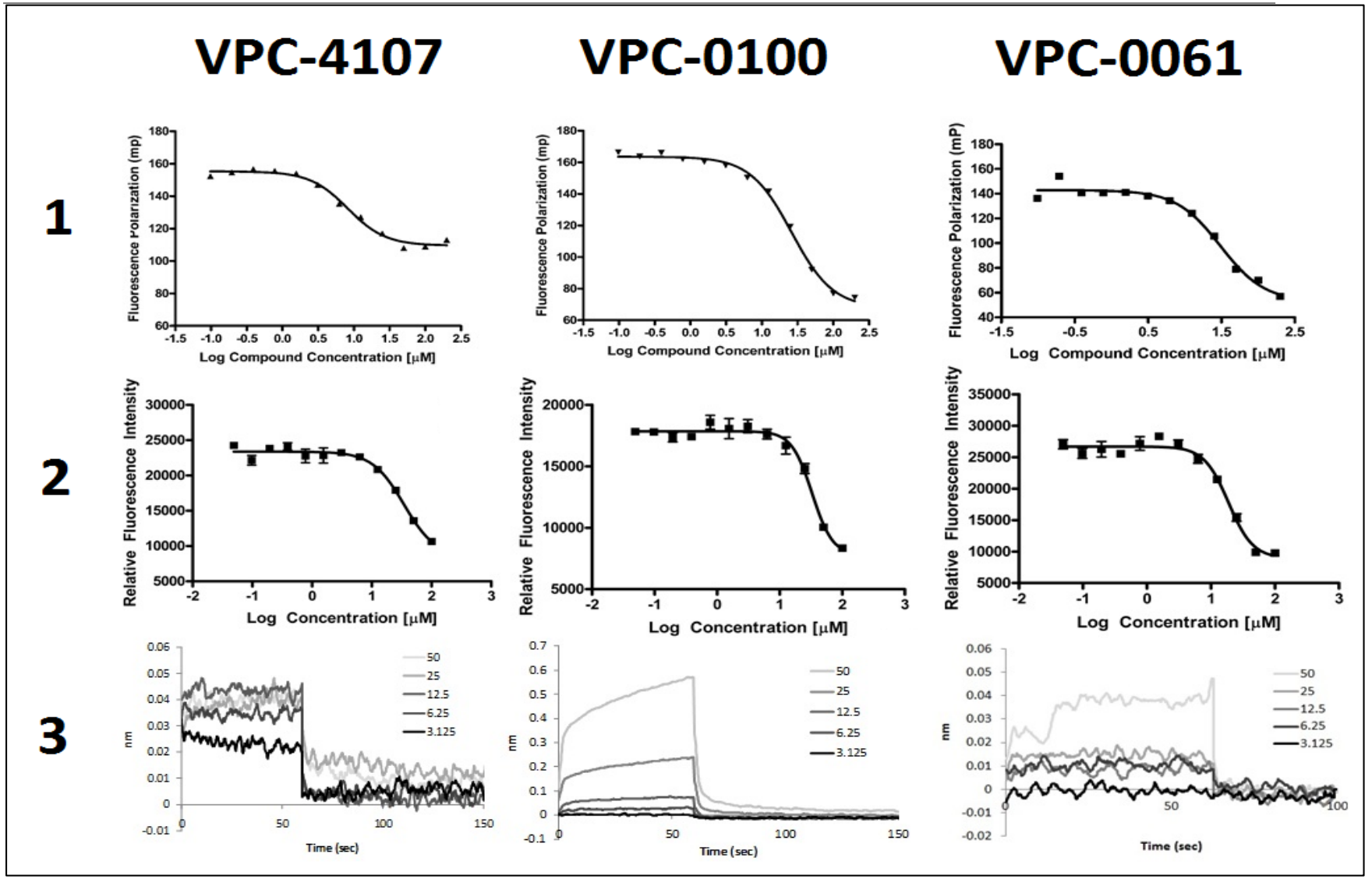
AF2 site



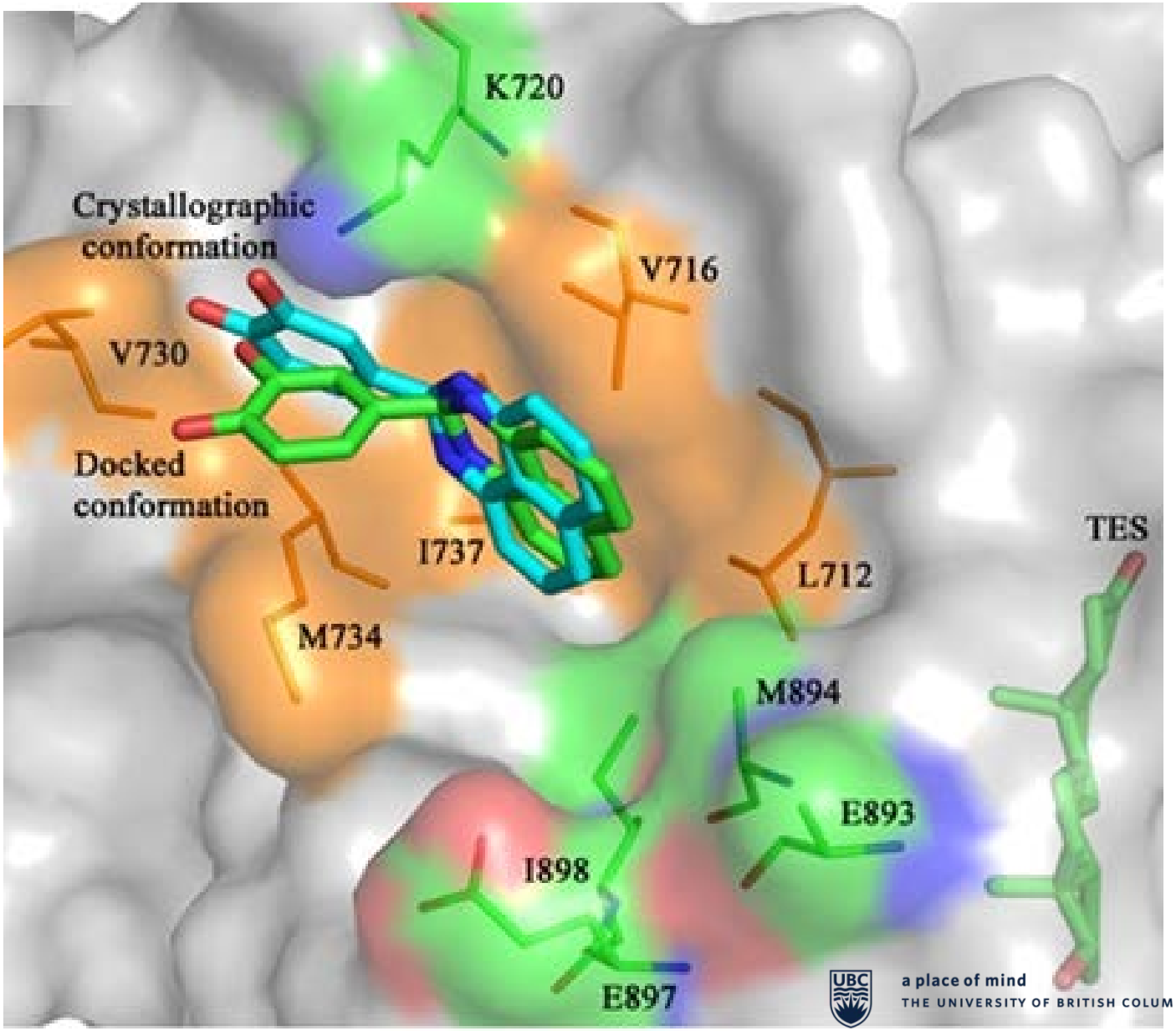


6 compounds identified with AF2
Ki = 5 - 25uM

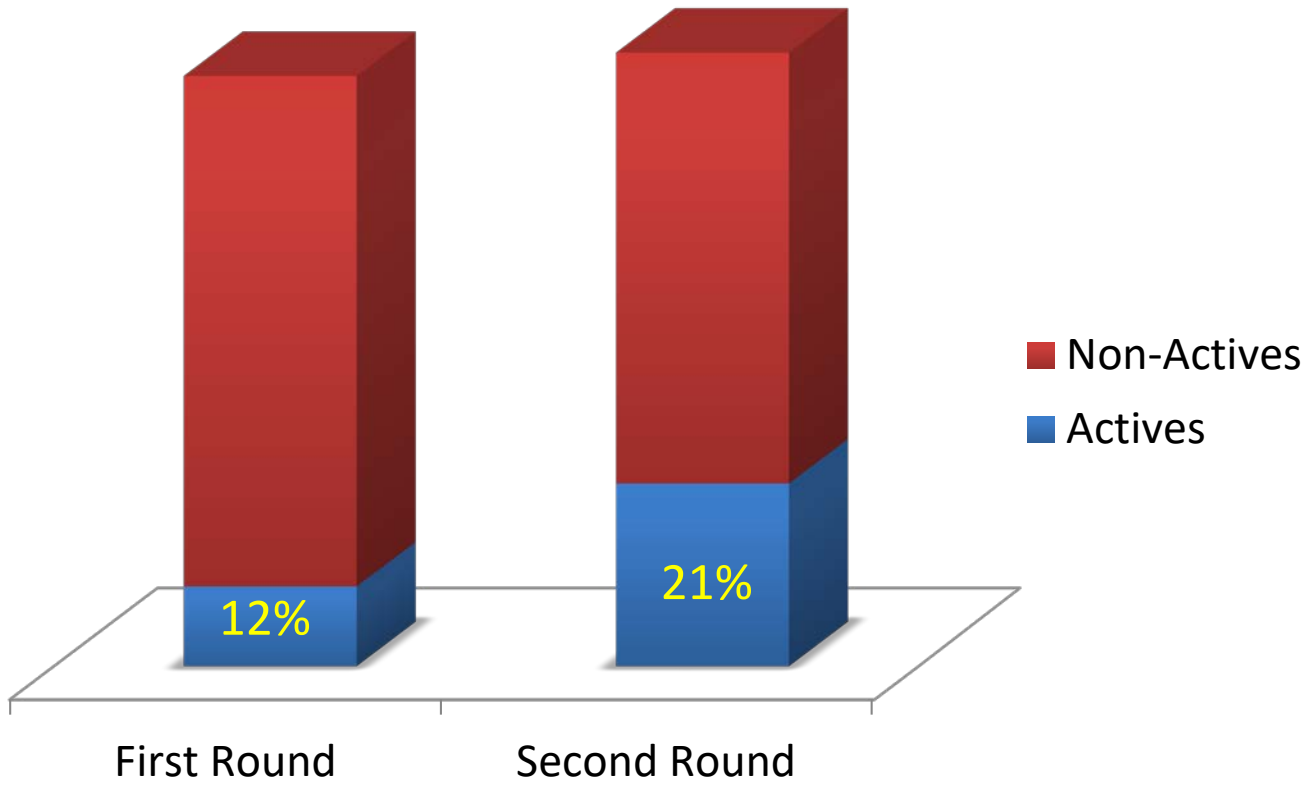
Inhibition of AF2 coactivator binding, AR transcriptional activity and SPR



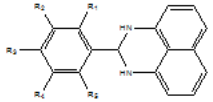
The comparison between docked and experimental orientation of CMPD61 inside the AF2 site

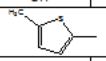


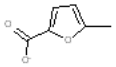
Rounds of Virtual Screening



Several Hundreds Compounds Tested: flat SAR



nal ber	EC50 (uM) (FP)	IC50 eGFP (µM)	R1	R2	R3	R4	R5
01	>200	2.5					
03	>200	Inactive	OH	Cl	H	Cl	H
04	>200	4.7	H	Br	H	H	H
05	Inactive	2.5	OH	H	NEt2	H	H
06	Inactive	0.19	CF3	H	H	H	H
07	14.7	51.48	H	Br	OH	OMe	H
08	Inactive	1.5					
09	>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	NO_2	H	H	H
16	Inactive	Inactive	H	OMe	OMe	OMe	H
/40 8	30.7	3.9	H	H	OH	H	H
18	Inactive	Inactive	Cl	H	H	NO_2	H
19	Inactive	1.682	Cl	H	H	H	F
20	Inactive	9.939	H	OCH_2Ph	H	H	H
21	Inactive	5.895	H	H	OC_6H_7	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	NEt_2	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
				H	H	H	H

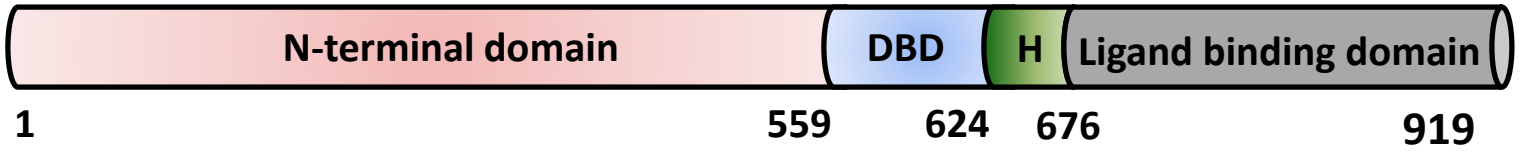
/40)	89.42	Inactive	H	OMe	OH	H	H
51	28.68	2.5	H	Cl	Cl	H	H
52	Inactive	Inactive	H	Br	OMe	H	H
53	>200	Inactive	OH	OMe	H	H	H
54	Inactive	Inactive	H	H	OEt	H	H
55	Inactive	Inactive	OMe	H	H	OMe	H
/40 1	33.47	6.9	H	OEt	OH	H	H
57	Inactive	Inactive	Cl	H	H	H	H
58	Inactive	Inactive	H	OMe	OC(O)Me	H	H
59	Inactive	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
51	30.5	23.2	H	OH	OH	H	H
07	8.2	14	H	OH	OMe	H	H
02	100	5	H	Br	OH	H	H
07		6	H	Cl	OH	H	H
08	Inactive	32					
09	Inactive	16					
10	Inactive	Inactive					
11	Inactive	4					
12	Inactive	Inactive	H	COO-	H	H	H
13	Inactive	13	H	Cl	OH	OMe	H
14	Inactive	11	H	H	CH_2OH	H	H
15	Inactive	Inactive	H	OH	COO-	H	H

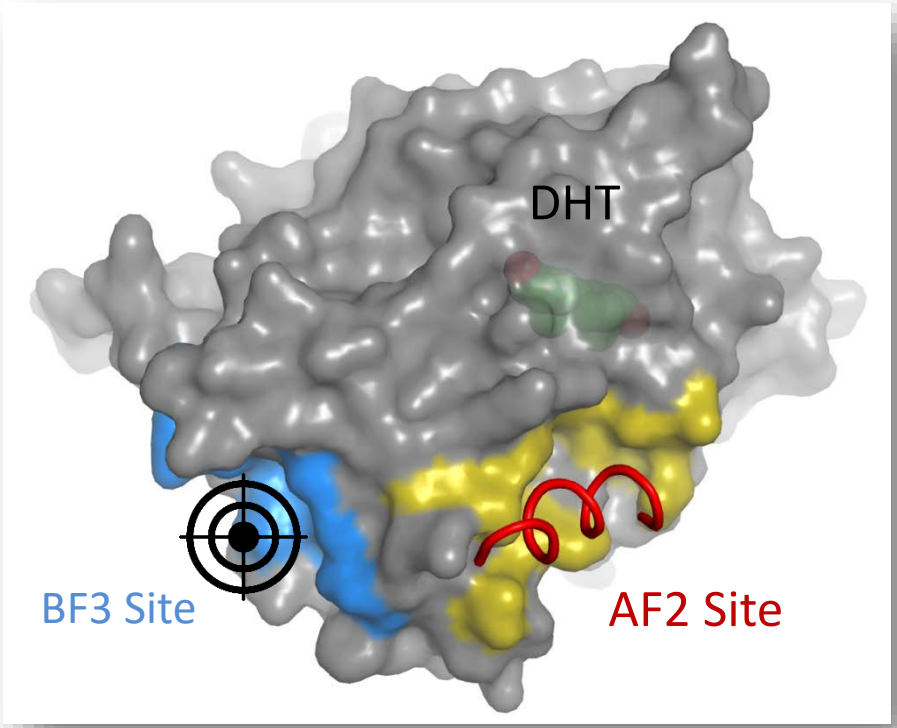
VPC-0061
IC50=30.6 uM

VPC-7051
IC50=2.5 uM

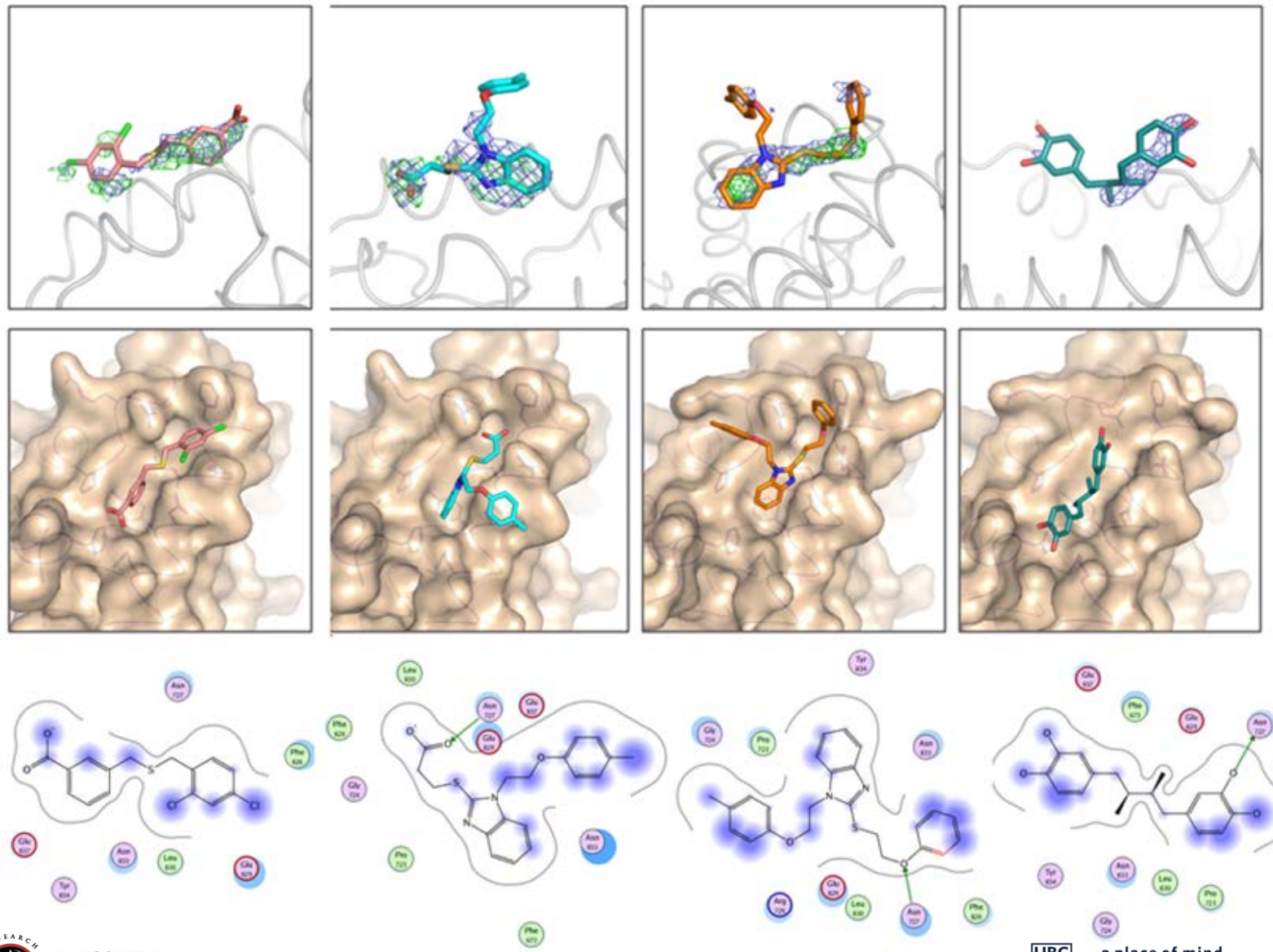
AR BF3 Targeting

Structural Domains of AR

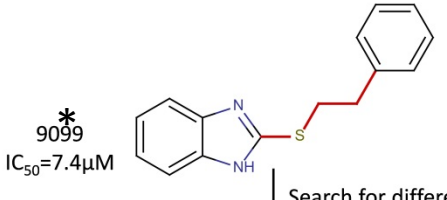




Four BF3 crystallographically confirmed hits

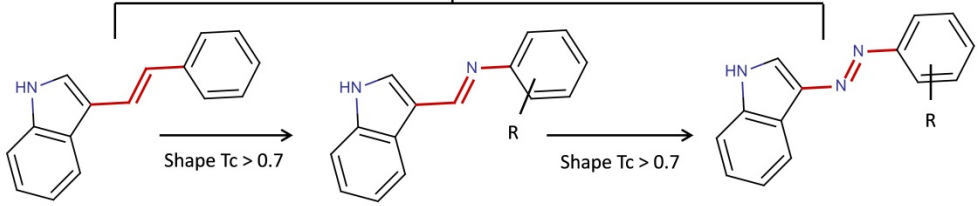


Identification of Potent BF3 Inhibitors using ROCS



Search for different linkers using ROCS

(Shape Tc > 0.8)



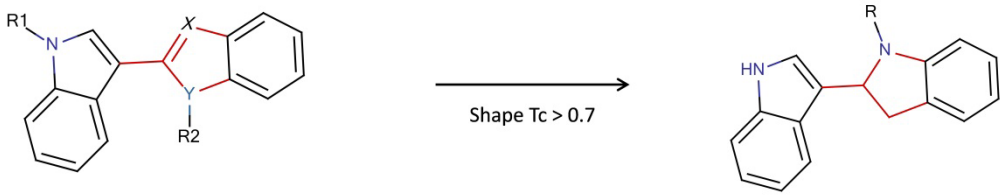
ID	IC_{50}(μM)
13235	2.21

ID	R	IC_{50} (μM)
13303	2-CF3	4.46
13304	2,4-Cl	7.27
13299	3-Me	8.16
13300	3-OMe	9.33
13310	2,3-Me	10.31
13345	1,6-Cl	13.89
13320	2-OMe	25.23
13321	2,3-Cl	25.78
13309	1,3-Br	27.21

ID	R	IC_{50} (μM)
13259	1-CF3	0.31
13256	-	0.38
13255	1-Cl	0.52
13225	1,3-Me	0.70
13254	3-Cl	1.20
13257	3-Me	4.18
13258	1-Ph	6.78

ROCS search based on 2)13235

(Shape Tc > 0.7)



ID	Group	IC_{50}(μM)
13127	X=C, Y=N	0.60
13166	X=C, Y=N, R_1R_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

VANCOUVER PROSTATE CENTRE
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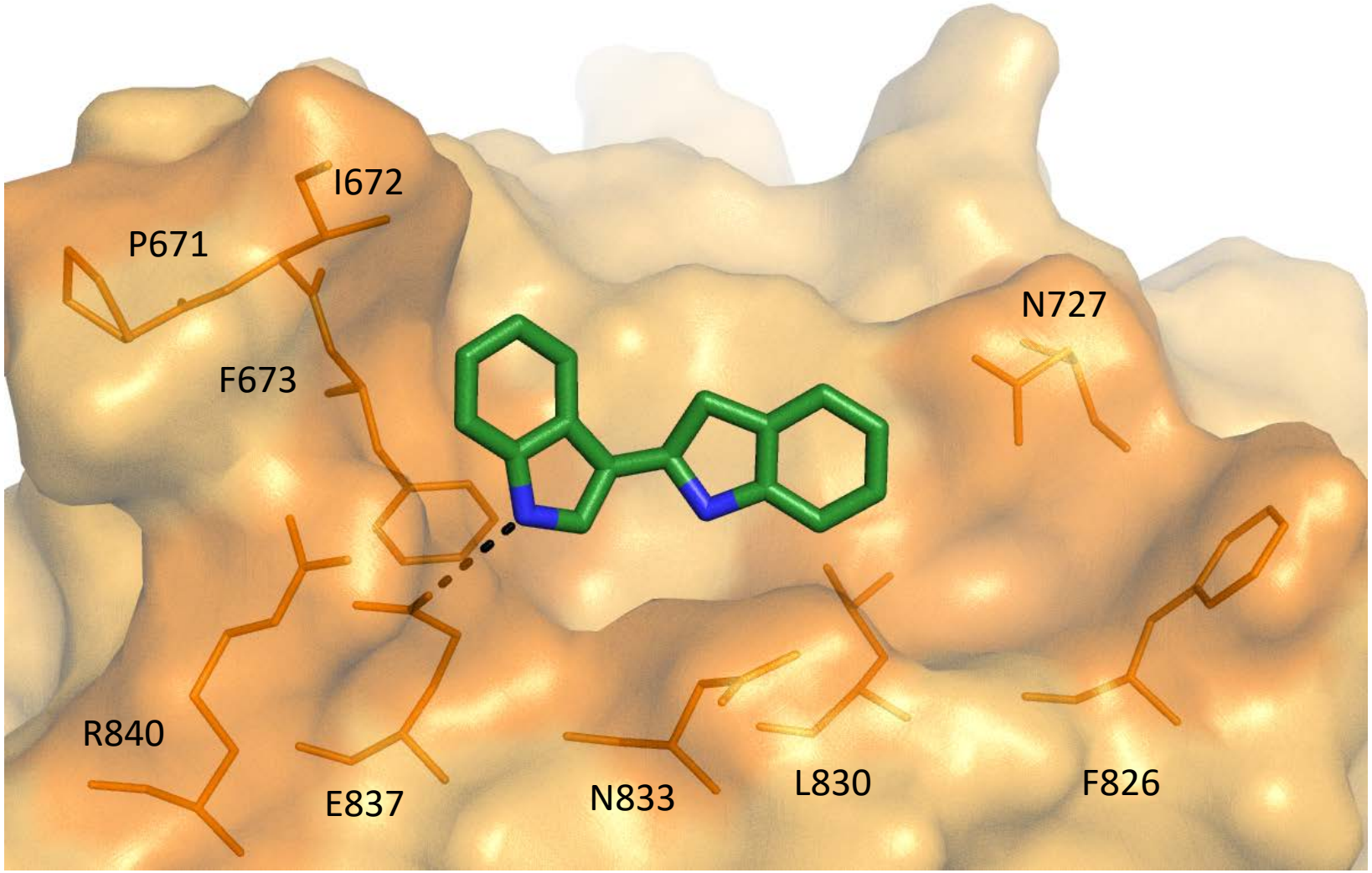
Munuganti RS et al, J Med Chem, 2013

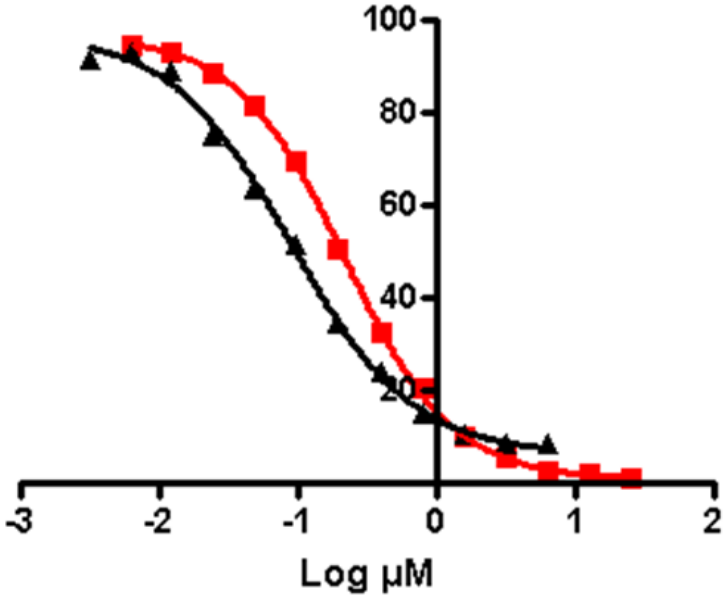
Binding Pose of VPC-13163



Effect of 13163 on MDV-resistant cell line

LNCaP

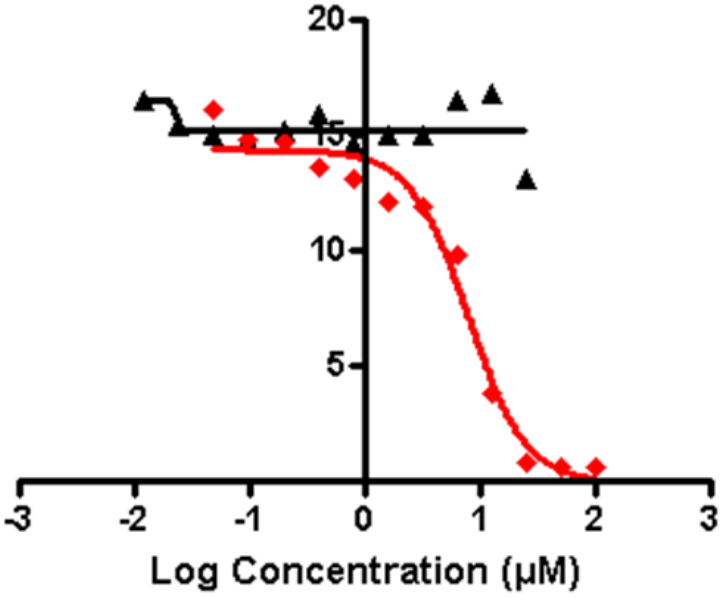
% of control
(R1881 0.1 nM)



13163: 0.216 µM
MDV3100: 0.090 µM

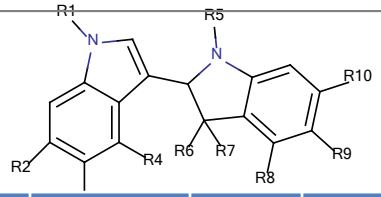
MR49F cell line

PSA units



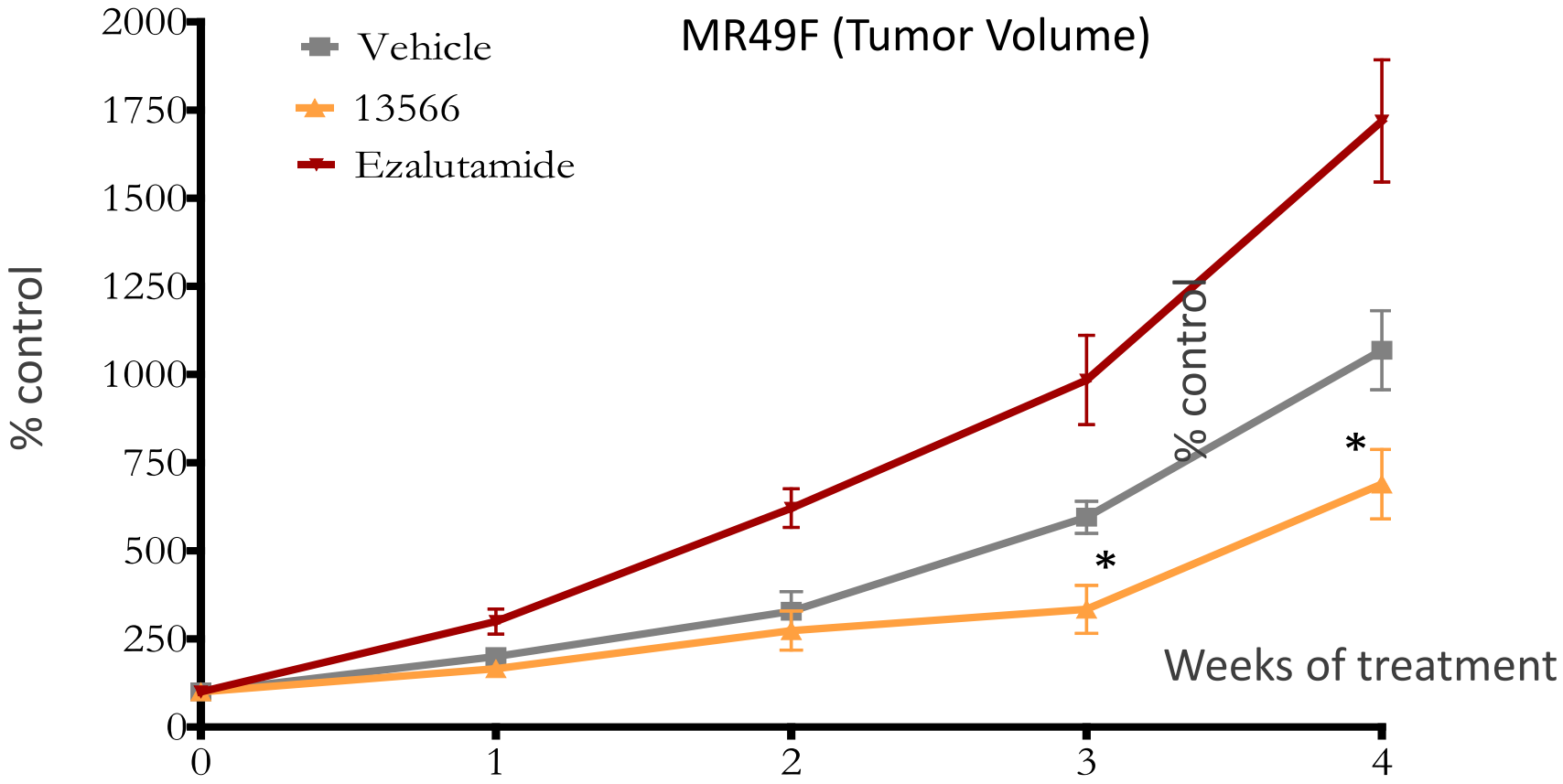
13163: 7.031 µM
MDV3100: Inactive

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			NO2			Me	Me				4.7	1.60	Mar'13
13531			F			Me	Me				0.39	0.31	Mar'13
13532					CH_2COOEt	Me	Me				2.84	3.10	Mar'13
13521		Cl				Me	Me				0.4	0.26	Feb'13
13566						**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_2H_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 – 13566

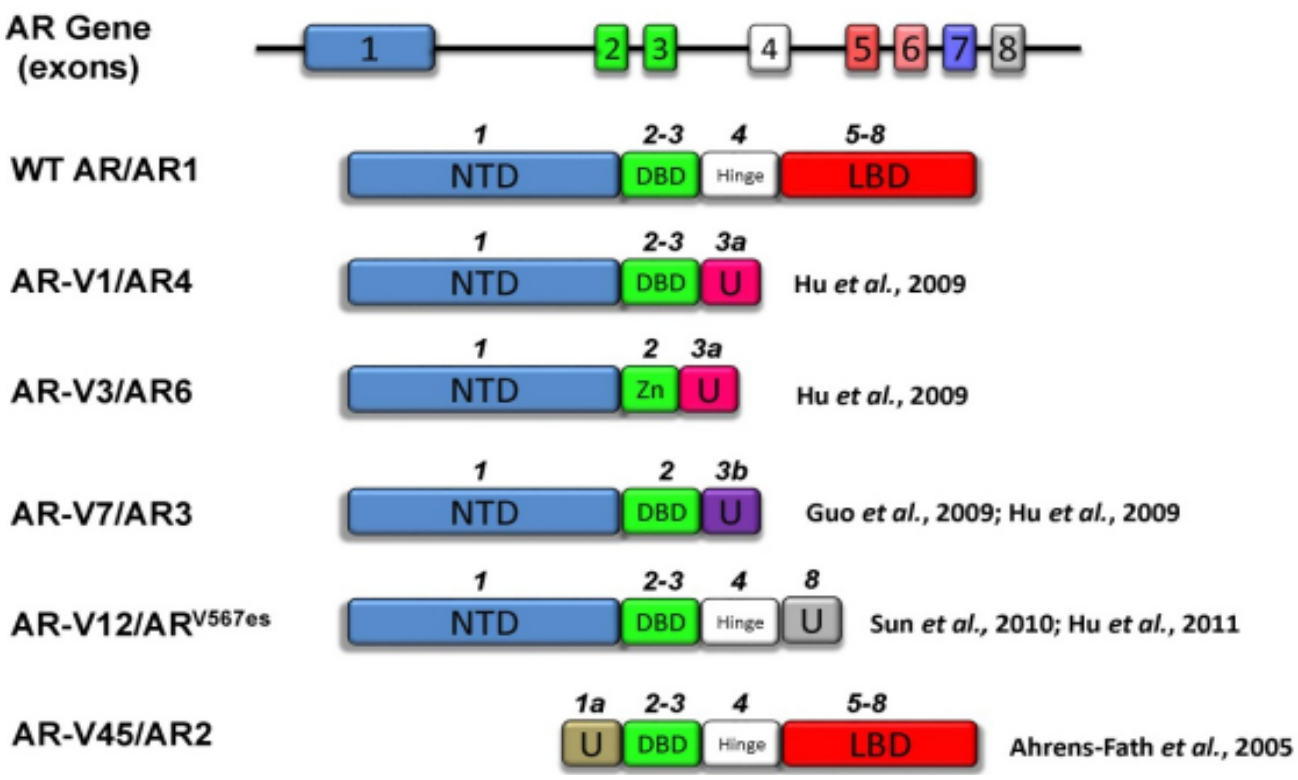


The effect of VPC-13566 compound on the tumor volume of the Enzalutamide-resistant (MR49F) xenograft model.

AR DBD Targeting

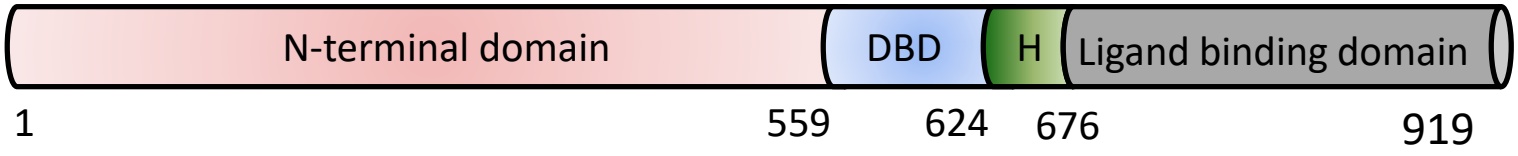
CRPC Resistance Driven by AR Splice Variants

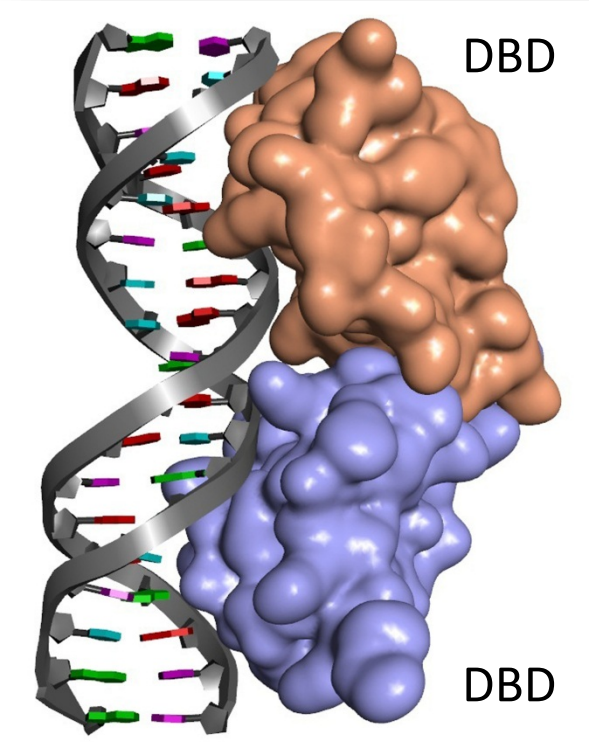
Lallous et al. Int J Biol Sci 2011; 7(6) 815-822



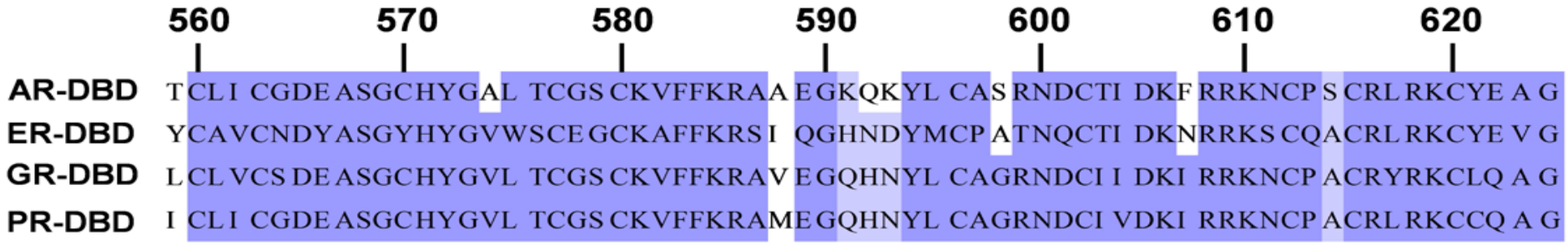
- NEED FOR DRUGS WITH NOVEL MOA, targeting both full length and splice variants of AR

Structural Domains of AR



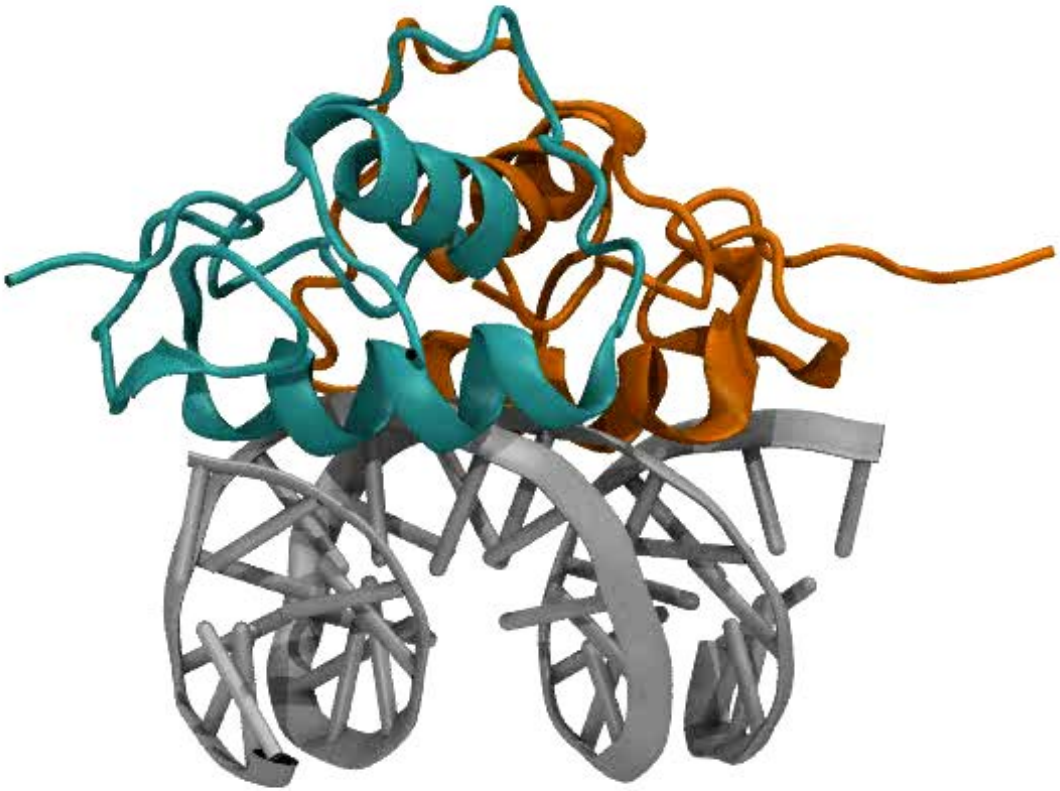


DBD is the Most Conserved Area of all NRs



Novel Strategy to Target AR

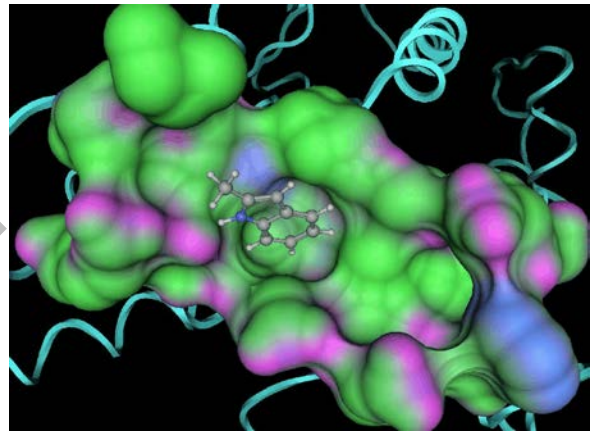
Hypothesis: Targeting alternative functional sites on AR should provide a promising strategy for treatment of PCa including its resistant forms where known mutations and splice variants hamper efficacy of the current drugs



In Silico Screening Workflow

Protein structure

Molecular docking
(50M-100M molecules)



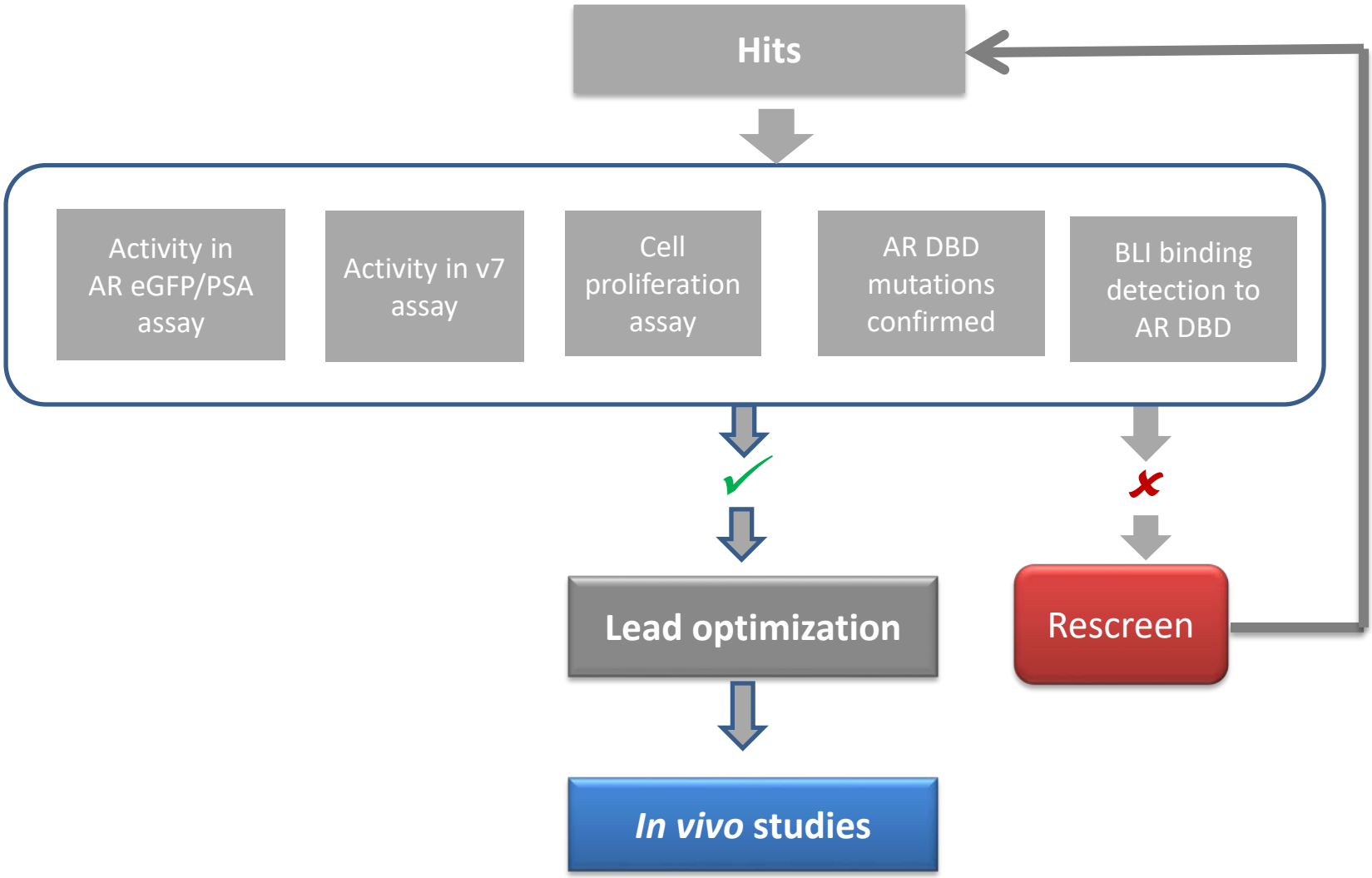
Computational protocols (~10,000)

Small Molecule Database (500,000,000)

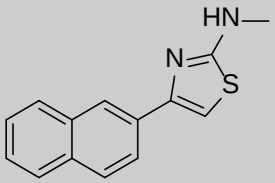
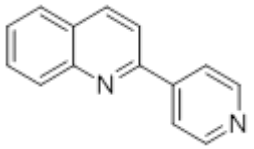
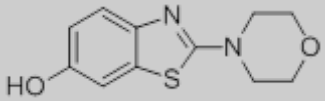
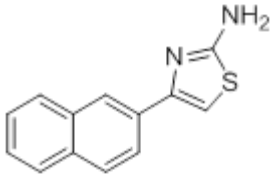
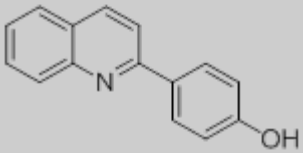
CONSENSUS SCORING !

Virtual Hits (100 to 200)

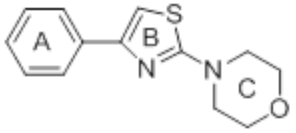
Experimental Screening Workflow

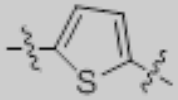
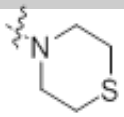
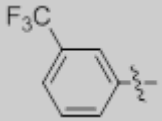
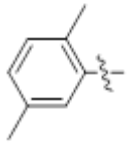
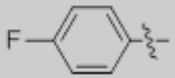


Initial in silico hits

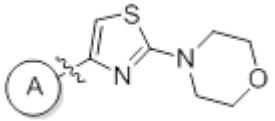
VPC-ID	Structure	eGFP IC50 (µM)	PSA IC50(µM)
14203		3.17 ± 0.3	3.91
14320		4.20 ± 0.6	2.26
14378		7.41 ± 0.4	8.08
14204		9.16 ± 0.5	10.6
14410		9.84 ± 3	N/A

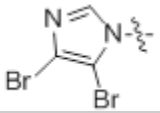
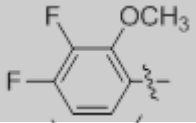
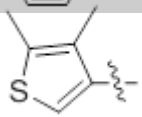
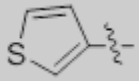
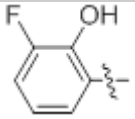
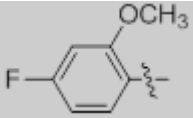
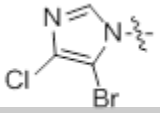
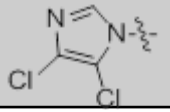
MedChem analogues, 1st round



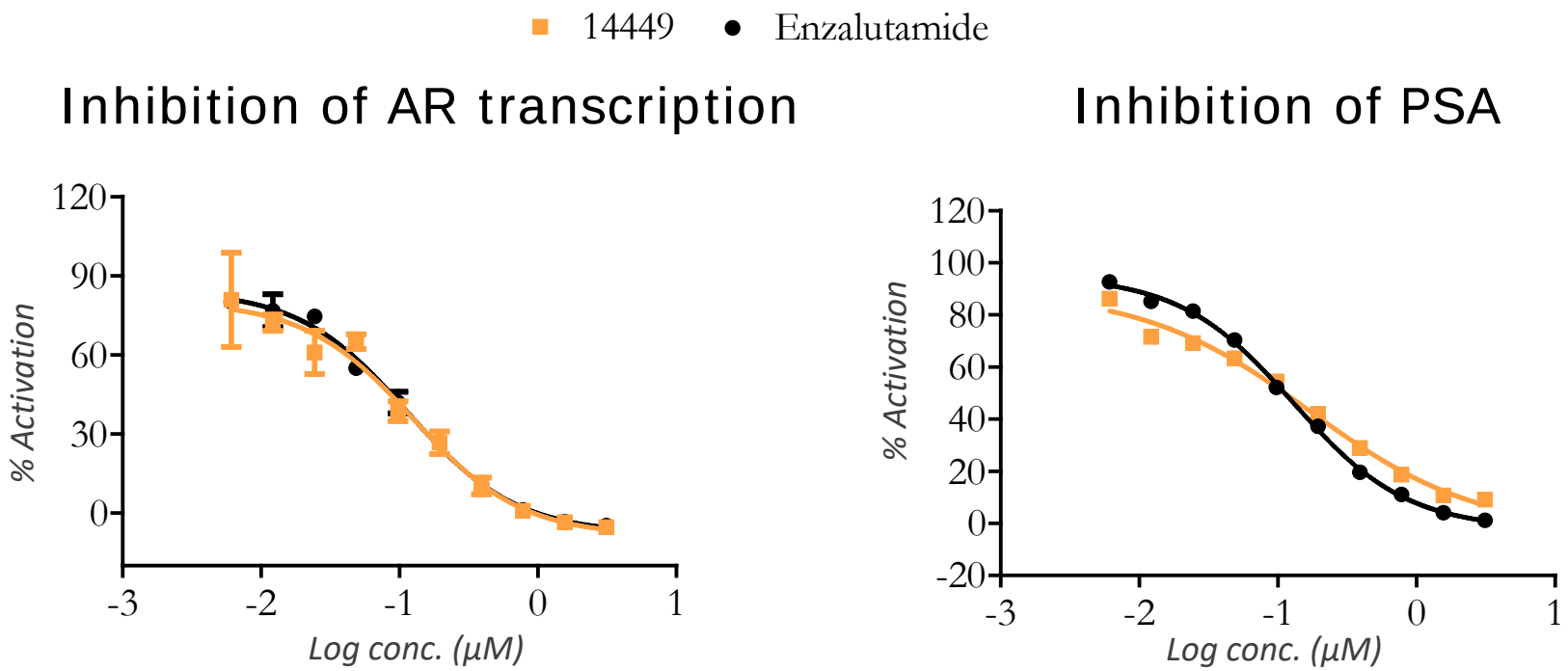
VPC-ID	A ring	B ring	C ring	eGFP IC50 (μM)	PSA IC50 (μM)
14228				0.33 ± 0.12	0.28
14103				0.52 ± 0.03	0.51
14385				0.62 ± 0.06	N/A
14292				0.61 ± 0.02	0.58
14293				0.62 ± 0.06	0.52
14255				0.65 ± 0.06	0.41

MedChem analogues, 2nd round



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

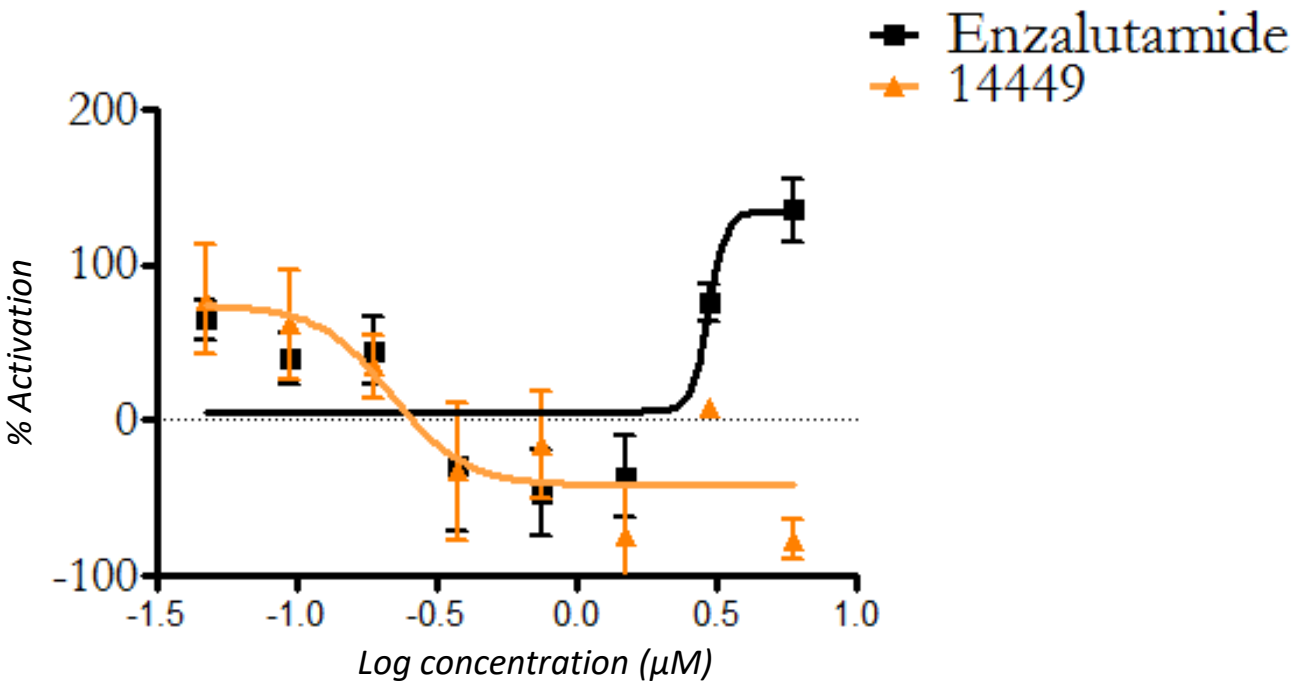
Activity Profile of the Lead VPC-14449



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

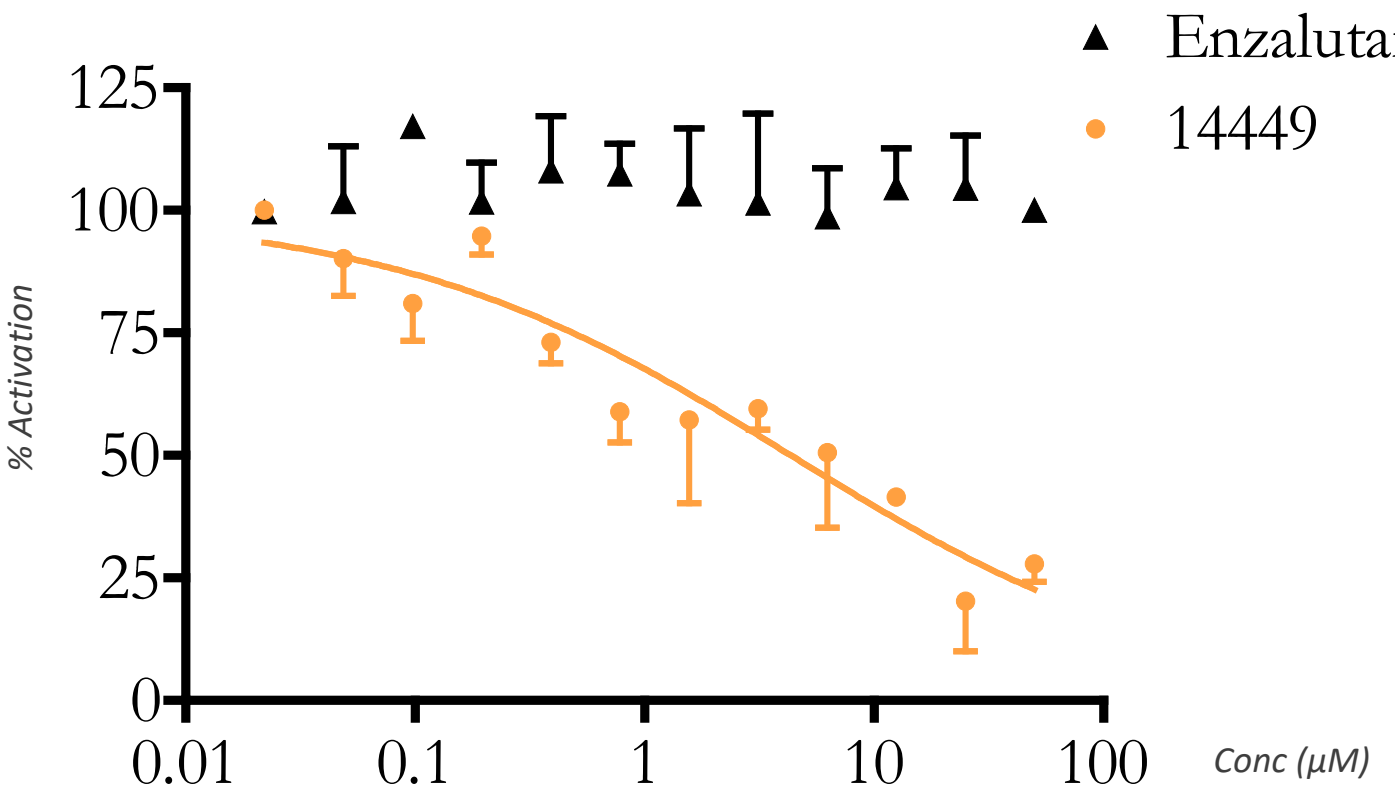
(Right) IC_{50} curve illustrating the inhibiting effect of 14449 (IC_{50} = 0.17μM) and Enzalutamide (IC_{50} = 0.08μM) on the PSA levels in LNCaP cells

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. 21µM

14449 Inhibits AR Splice Variant V7



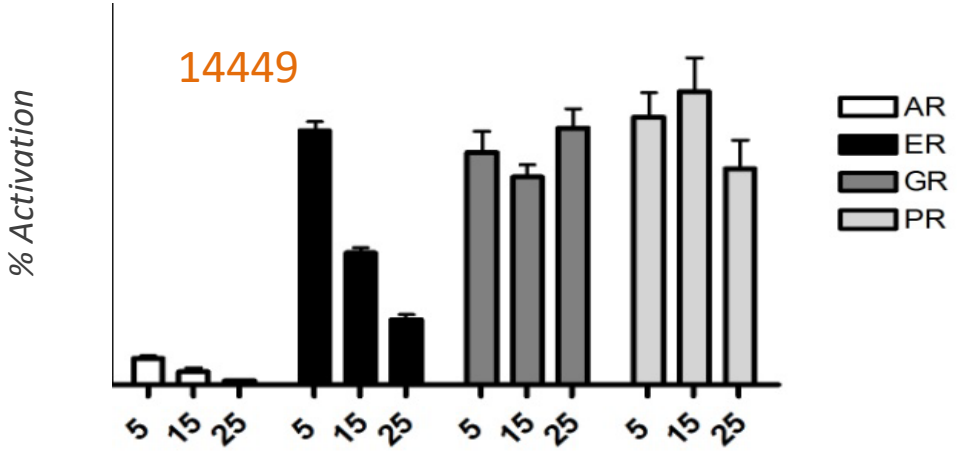
14449 inhibits the transcriptional activity of wild type AR splice variant, V7 assay. Enzalutamide has no effect on V7.

14449 Demonstrates Selectivity Toward the AR

Enzalutamide

Conc (μM)

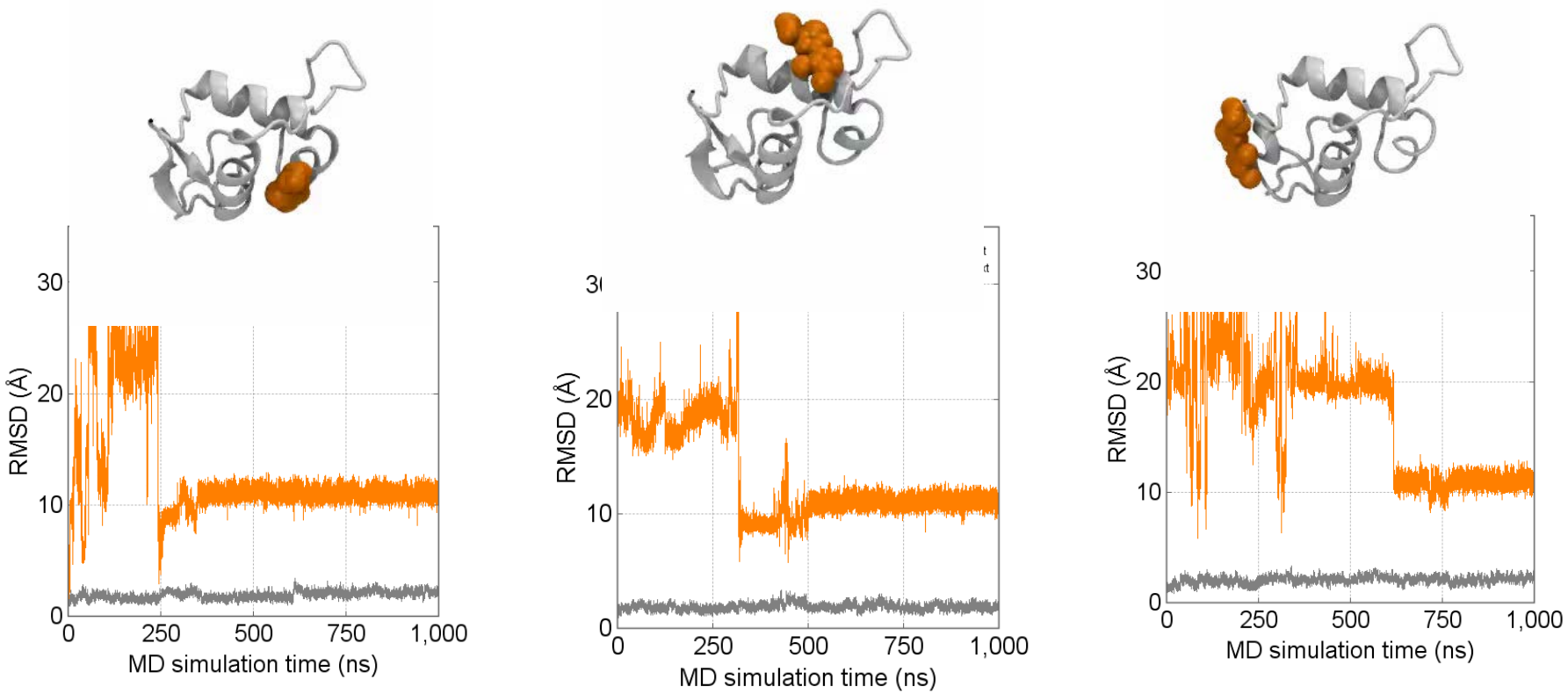
14449



Conc (μM)

(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

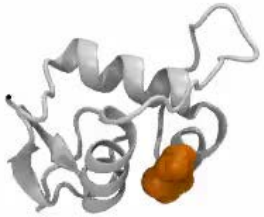


Molecular dynamics simulations was performed using explicit solvent model. The total run time 3μs. The MD simulation study supports that 14449 binds to DBD site stably.

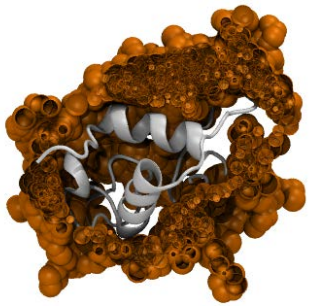
The results indicate 14449 finds its DBD binding spot from various starting points.

Consensus Validation of the Binding Site and Poses

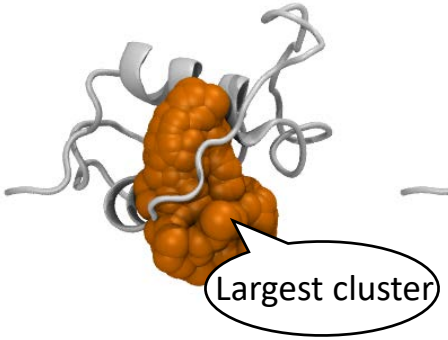
1. Multiple MD simulations



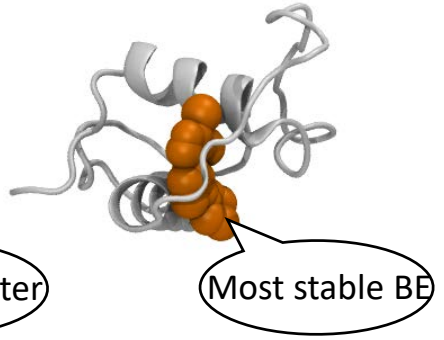
2. Sampled binding poses



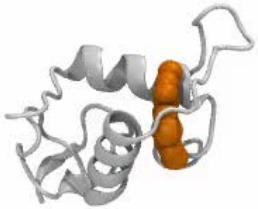
3. Cluster analysis & Binding energy calc.



4. Representative pose

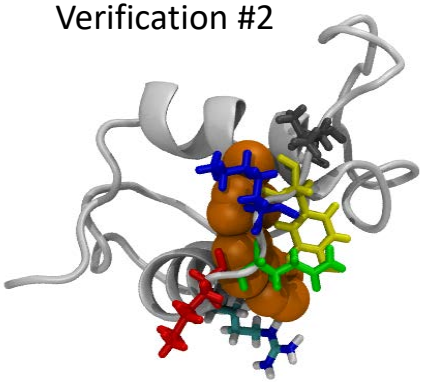


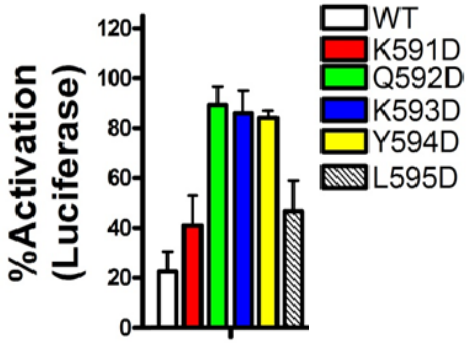
Verification #1



MD simulation starting from the representative pose

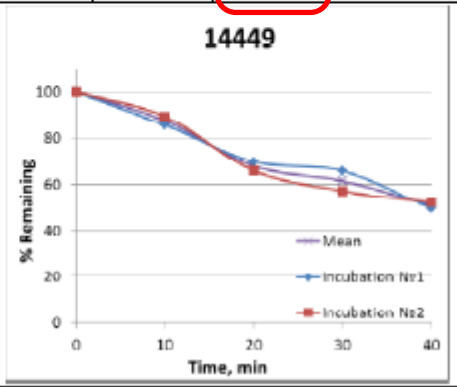
Verification #2





Comparison with the mutation experiment

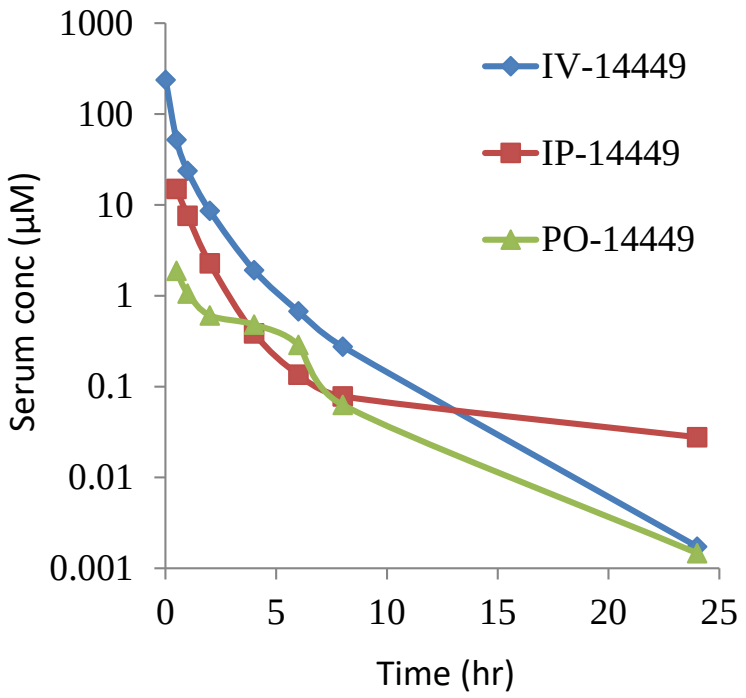
VPC - 14449 Demonstrated sub-Optimal Stability

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

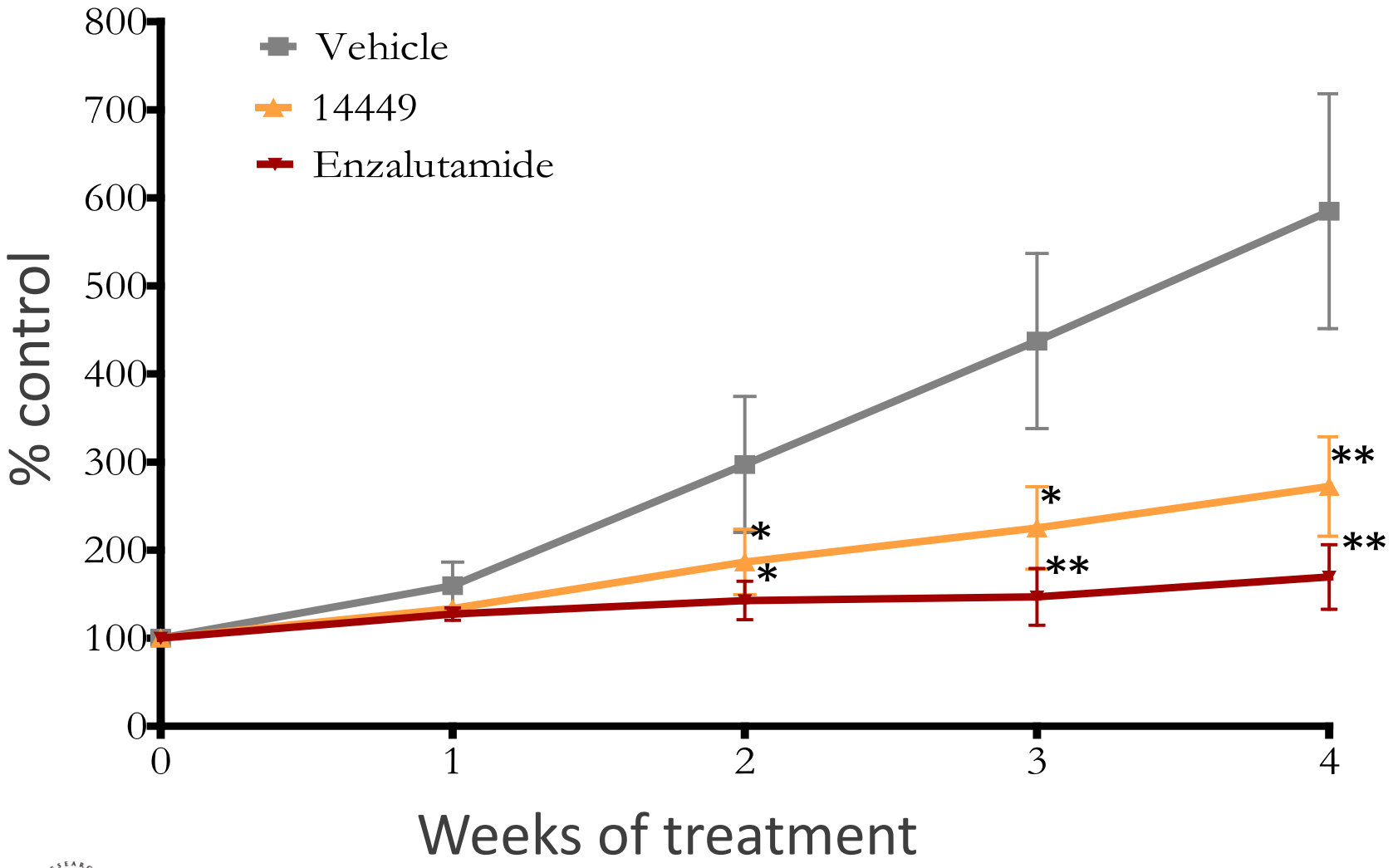
Compound	**14449**
eGFP IC50 (µM)	0.38
PSA IC50 (µM)	0.17
T1/2 Microsomes (min)	14

Pharmacokinetics of VPC-14449

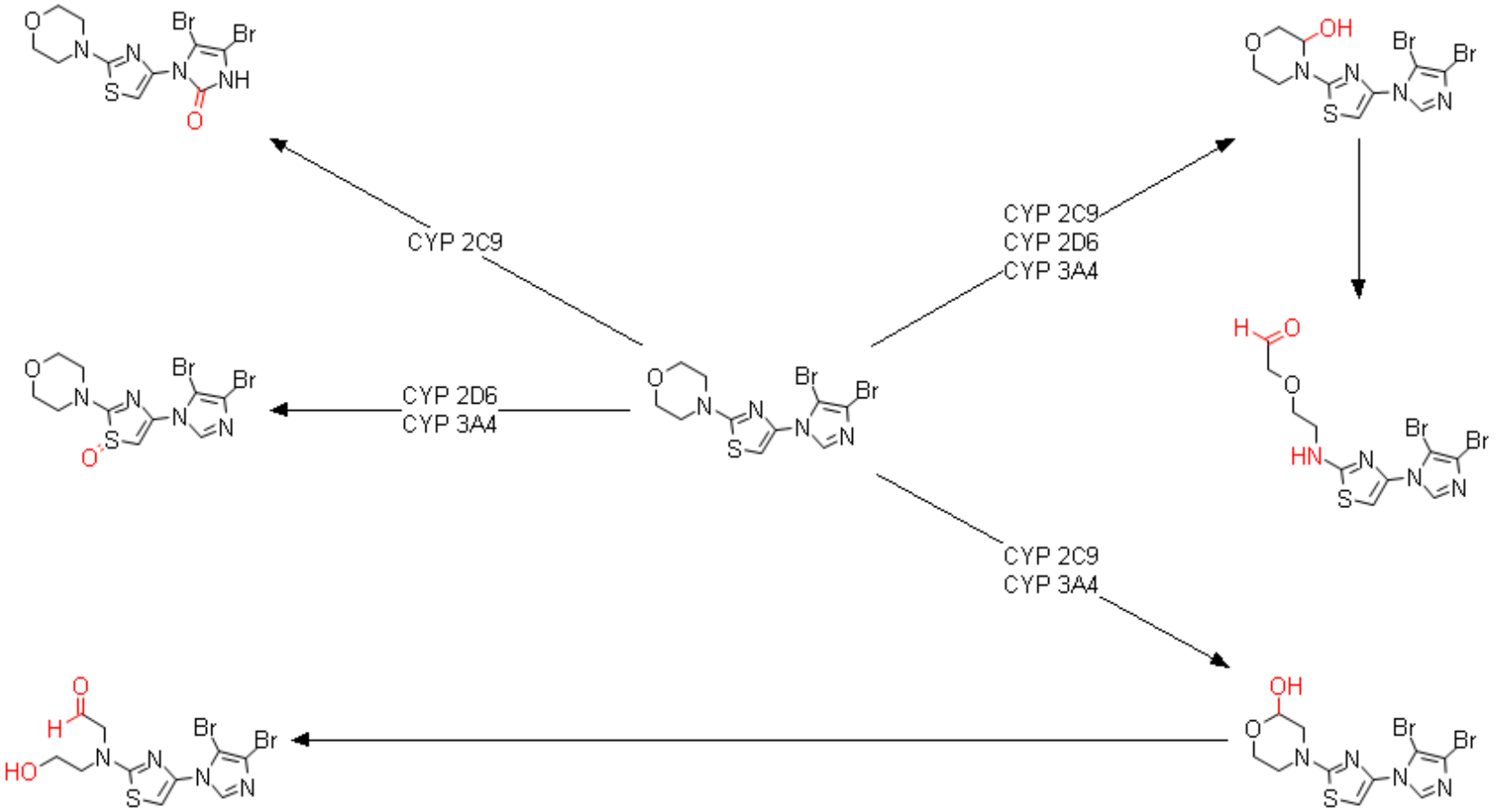
- 9 CD1 mice 8-10 weeks old were divided into 3 groups, 3 mice each
- Rout of administration: Intravenous (IV), intraperitoneal (IP) or Oral (PO)
- Dose: 100 mg/kg of 14449 formulated using 1:10 hydroxypropyl cyclodexterin: dd H2O
- To measure serum drug levels, tail blood samples were taken following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



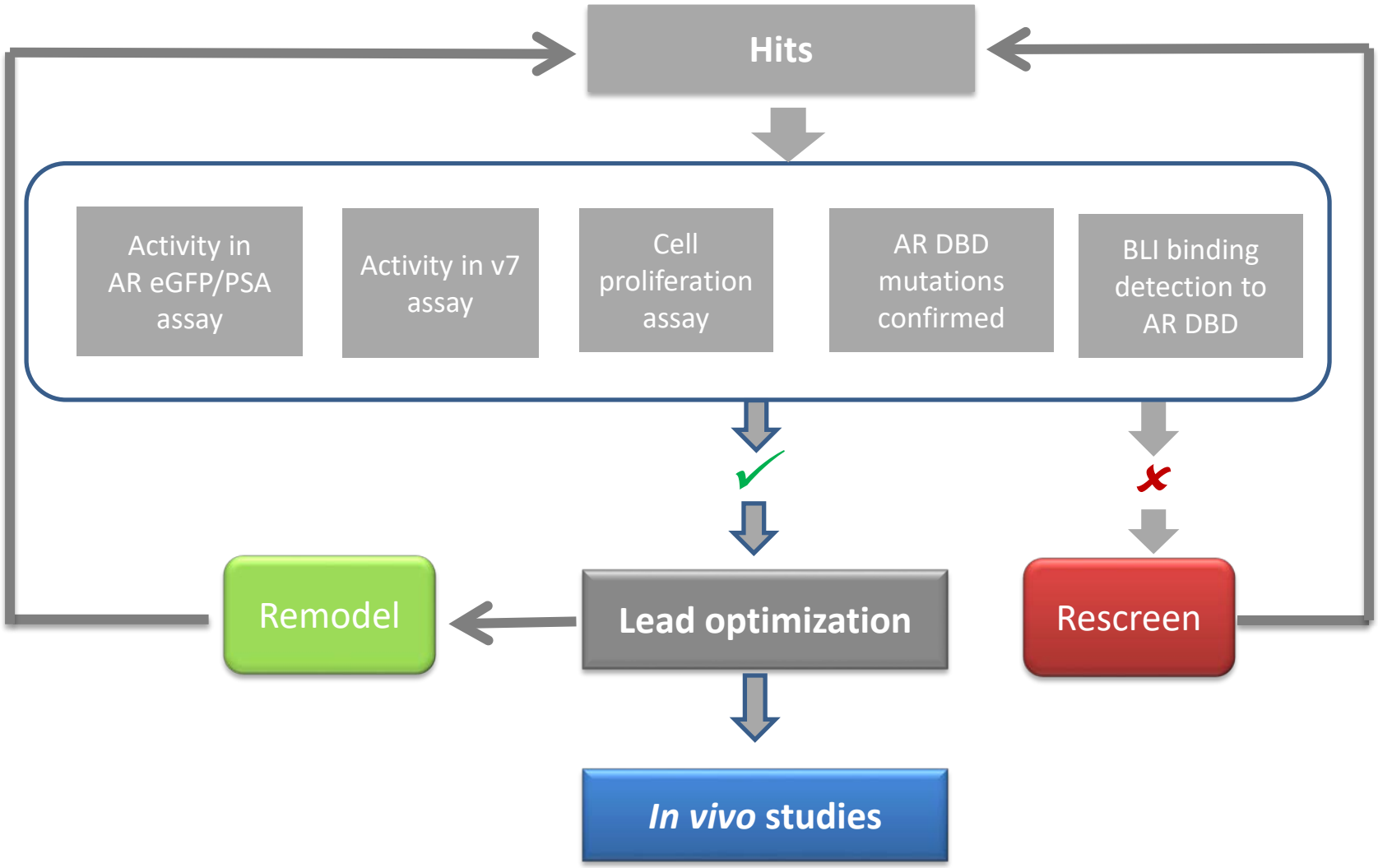
In vivo Effect of VPC – 14449 on tumor



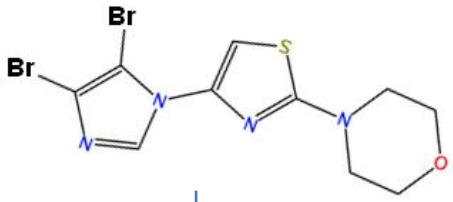
Predicted Metabolic Liabilities of VPC-14449



Iterative Screening Workflow

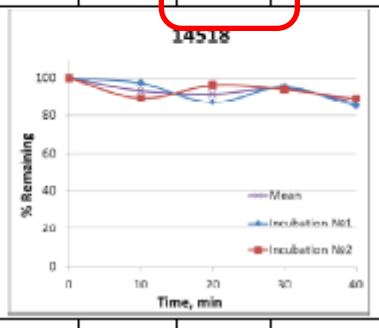


Second Generation VPC-14518, Improved Stability



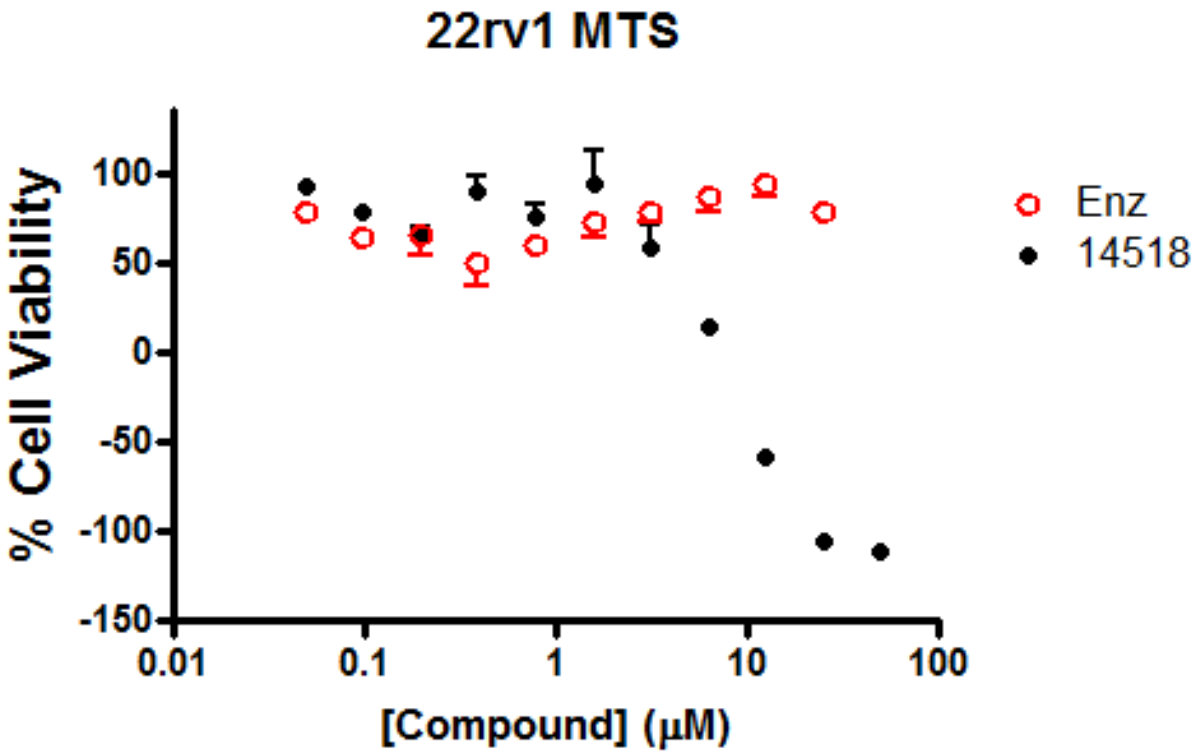
14512/14518

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					100



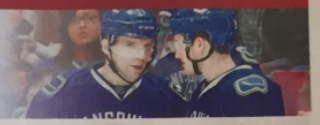
Compound	**14449**	**14512**	**14518**
eGFP IC50 (μM)	0.38	0.16	0.19
PSA IC50 (μM)	0.17	0.16	0.08
T1/2 Microsomes (min)	14	58	263

Selecting a Clinical Candidate VPC-14518



VRBATA NEEDS A GOOD FEED

Winger struggling without healthy diet of Sedinery » C7



BUSINESSBC

TUESDAY, DECEMBER 15 | 2015 | BUSINESS COORDINATOR: SCOTT NEUFELD 604-605-2636 | SNEUFELD@VANCOUVERSUN.COM

S & P/TSX	TSX Venture	Dow Jones	S & P 500	Dollar	Gold	Oil	Natural Gas
12,695.49	496.18	17,368.50	2,021.94	72.79¢ US	1,064.70	36.31	1.89
94.46 ↓	5.91 ↓	103.29 ↑	9.57 ↑	0.02 ↑	12.20 ↓	0.69 ↑	0.10 ↓

BRIEFINGS

Newalta to spend less on growth

The Newalta 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 $50 million of underutilized 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 $70 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 dual-temperature 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 tank

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 US. Under the deal, two of the Mahindra group's units will buy 76.06 per cent of the design firm for $1.21 US a share.

SCIENCE

STEVE BOSCH/PNG

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 seat 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 SUN

A promising new treatment for drug-resistant prostate cancer developed by scientists at the University of B.C. has been licensed by the pharmaceutical giant Roche for more than $140 million, the university's richest intellectual property deal in its history.

Researchers Paul Rennie and Artem Cherkasov of the Vancouver Prostate Centre designed the drug to treat prostate cancers

> *"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

Wheeler, technology transfer manager at the University-Industry Liaison Office and lead negotiator on the Roche licence.

The scientists will share 50 per cent of the net revenue

Prostate cancer is the most prevalent and potentially lethal cancer affecting men, with 24,000 new cases leading to more than 4,000 deaths per year, according to the Canadian

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

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

Cherkasov's powerful search technique produced about 200 candidate molecules, which they

Targeting AR Dimerization

ELSEVIER

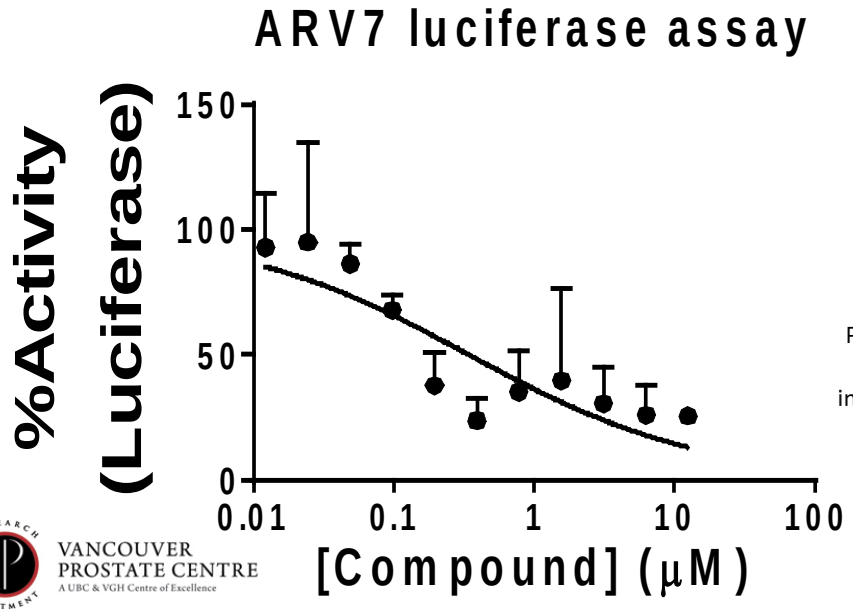
Cancer Letters

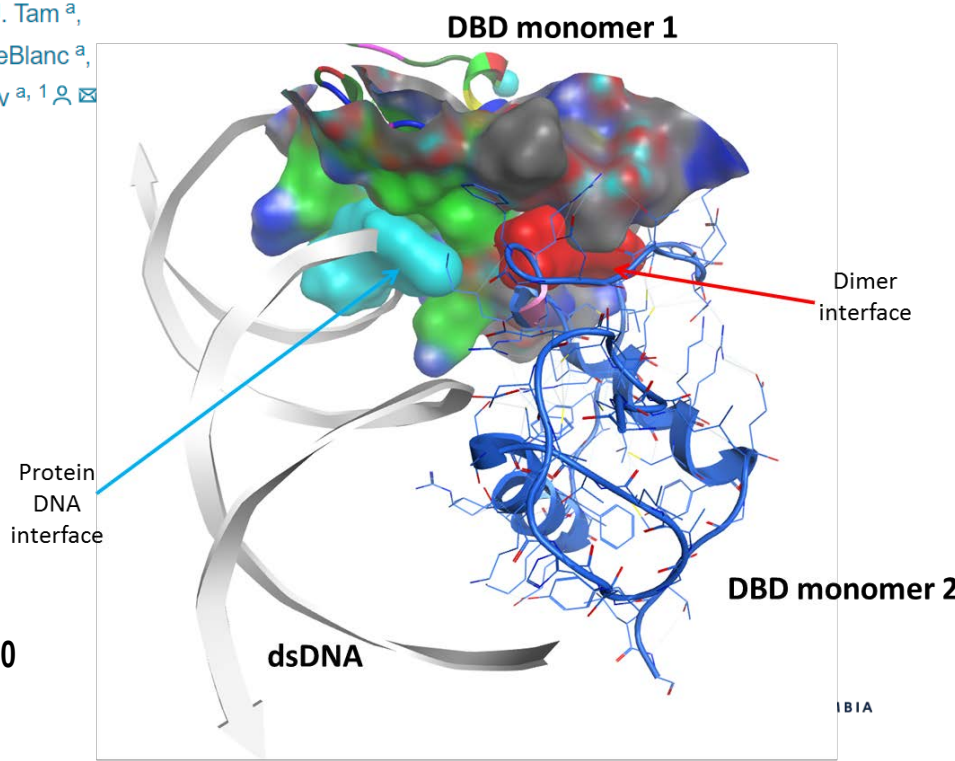
Volume 437, 28 November 2018, Pages 35-43

Original Articles

Selectively targeting the dimerization interface of human androgen receptor with small-molecules to treat castration-resistant prostate cancer

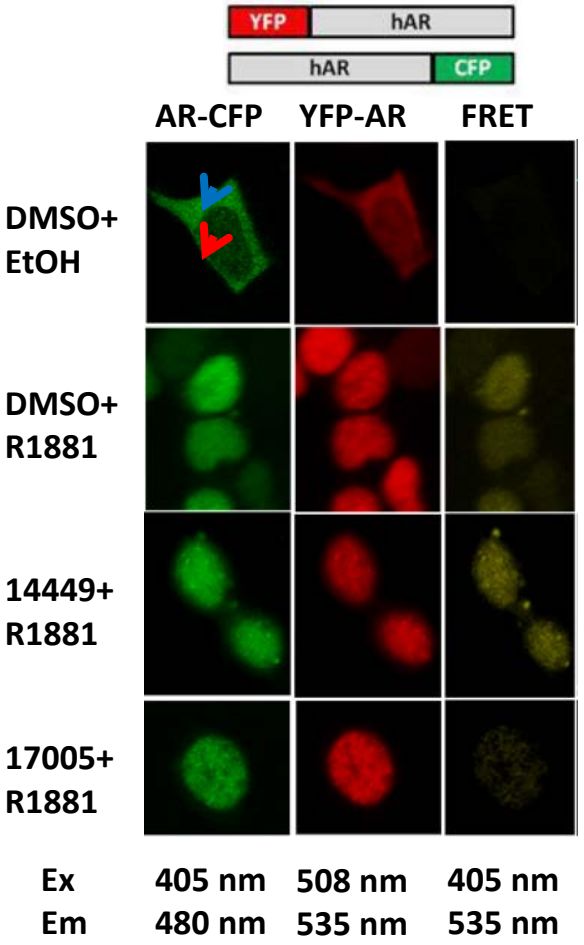
Kush Dalal [a], Fuqiang Ban [a], Huifang Li [a], Hélène Morin [a], Mani Roshan-Moniri [a], Kevin J. Tam [a], Ashley Shepherd [a], Aishwariya Sharma [a], James Peacock [a], Michael L. Carlson [b], Eric LeBlanc [a], Carl Perez [a], Franck Duong [b], Christopher J. Ong [a], Paul S. Rennie [a, 1], Artem Cherkasov [a, 1]



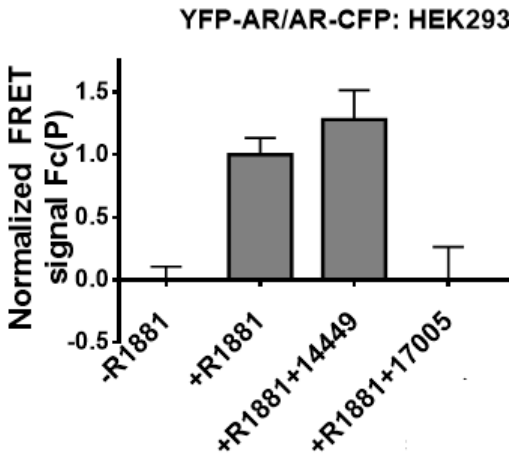


VANCOUVER PROSTATE CENTRE
A UBC & VGH Centre of Excellence

Blocking AR dimers

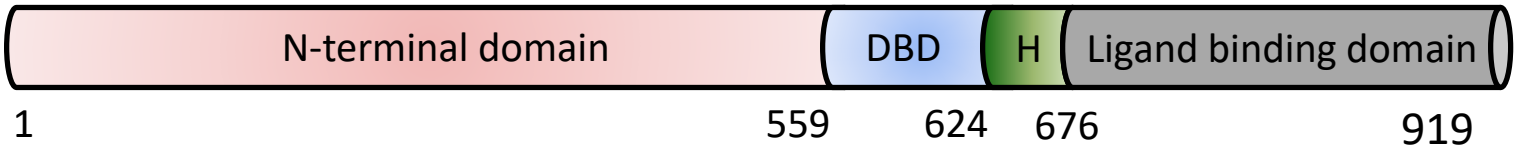


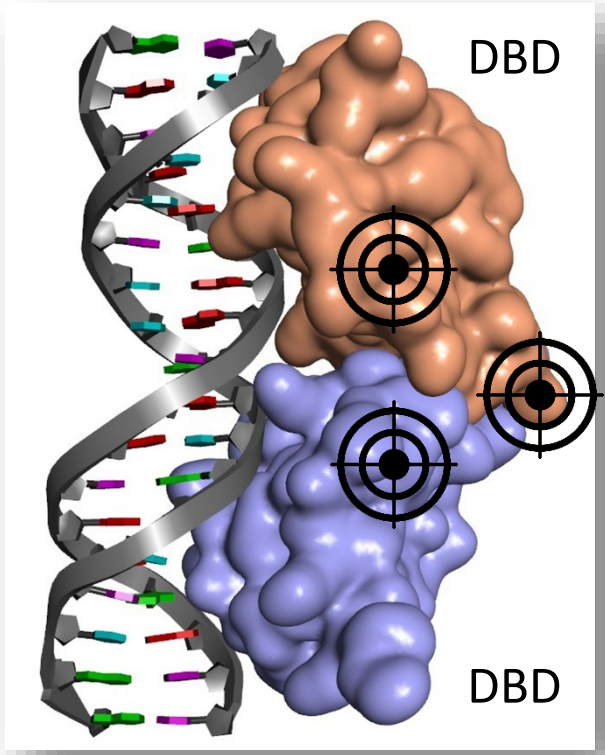
Cytosol
Nucleus

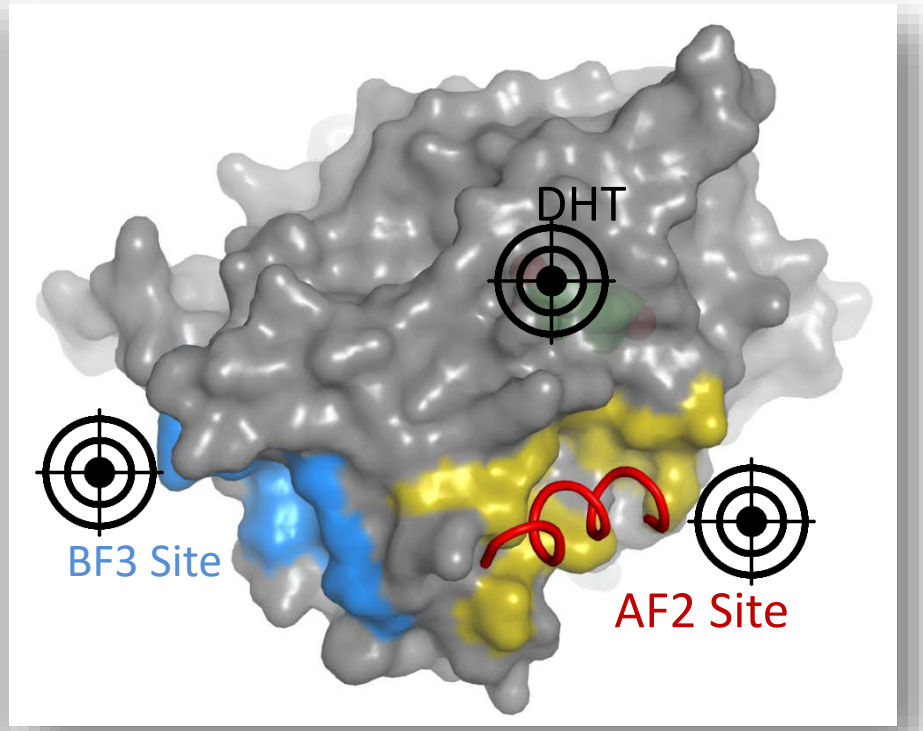


-Compounds break dimers
-No inhibition of nuclear localization
-No effect on AR expression

Structural Domains of AR







AR AF2/BF3 compounds found home

Nat Med. 2018 May ; 24(4): 427–437. doi:10.1038/nm.4500.

Selective Modulation of the Androgen Receptor Activation Function-2 Domain Rescues Degeneration in Spinal Bulbar Muscular Atrophy

Nisha M Badders[1,13], **Ane Korff**[1,9,13], **Helen C Miranda**[2], **Pradeep K Vuppala**[3,10], **Rebecca B Smith**[1], **Brett J Winborn**[1], **Emmanuelle R Quemin**[1,11], **Bryce L Sopher**[4], **Jennifer Dearman**[1], **James Messing**[1,9], **Nam Chul Kim**[1,12], **Jennifer Moore**[1], **Brian D Freibaum**[1], **Anderson P Kanagaraj**[1], **Baochang Fan**[1], **Heather Tillman**[5], **Ping-Chung Chen**[6], **Yingzhe Wang**[3], **Burgess B Freeman III**[3], **Yimei Li**[7], **Hong Joo Kim**[1], **Albert R La Spada**[2,8], and **J Paul Taylor**[1,9]

[1]Department of Cell and Molecular Biology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA

[2]Department of Pediatrics, University of California at San Diego, La Jolla, CA 92037, USA

[3]Preclinical Pharmacokinetic Shared Resource, St. Jude Children's Research Hospital, Memphis, TN 38105, USA

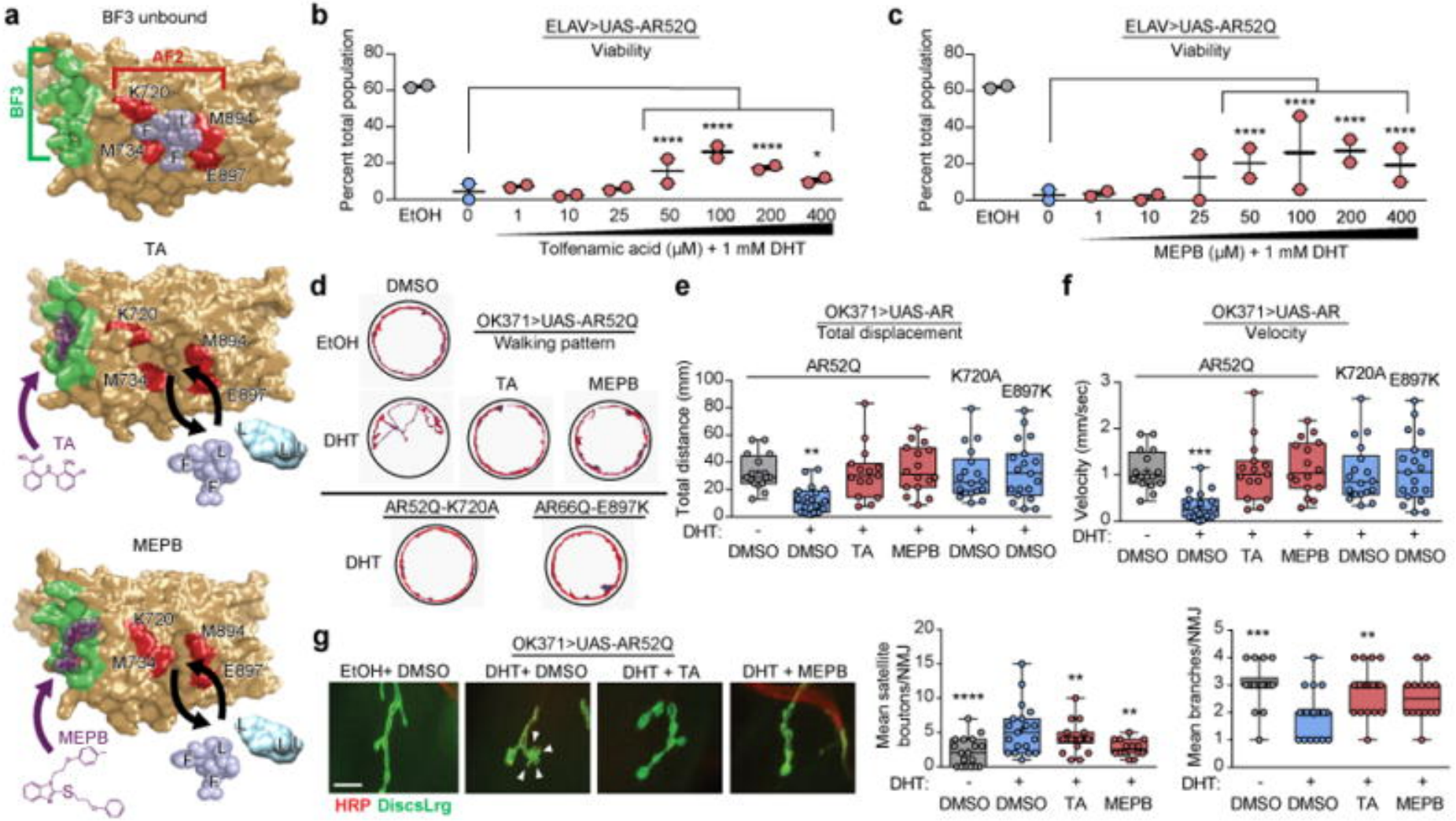
[4]Department of Neurology, University of Washington, Seattle, WA 98195, USA

[5]Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA

[6]Department of Structural Biology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA

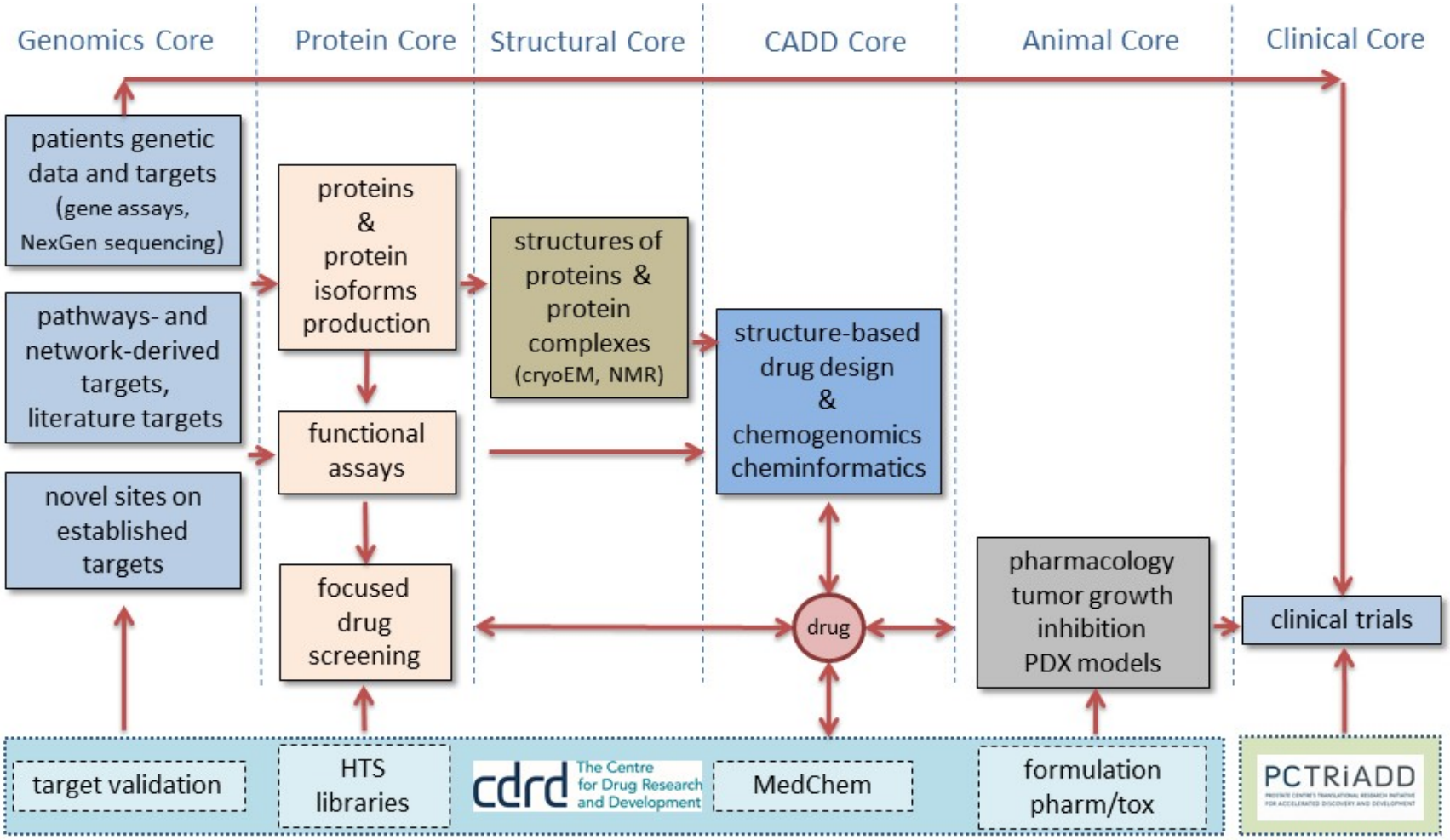
[7]Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN 38105, USA

AF2 (BF3 really…) modulation rescues degeneration in a fruit fly model of SBMA



Badders et al, Nat Med, 2018

Lab Organization & Structure



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THE UNIVERSITY OF BRITISH COLUMBIA

BC Cancer Agency
CARE + RESEARCH

Vancouver CoastalHealth
Promoting wellness. Ensuring care.

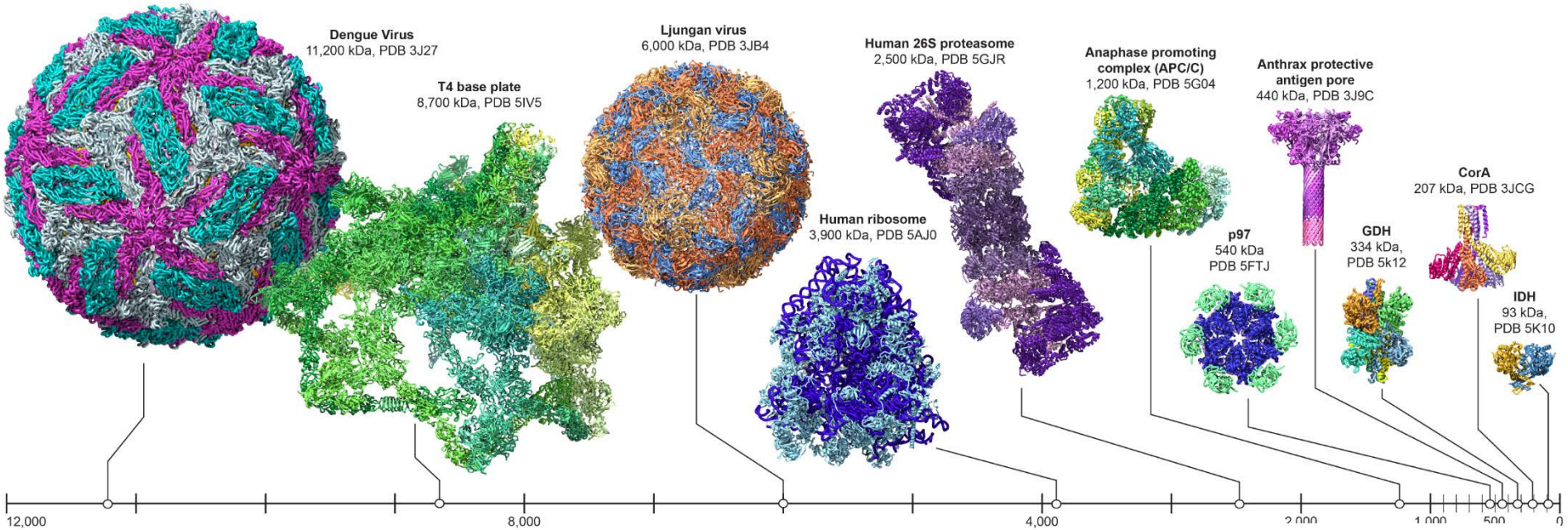
Growing diversity of cryo-EM targets

Cell

Breaking Cryo-EM Resolution Barriers to Facilitate Drug Discovery

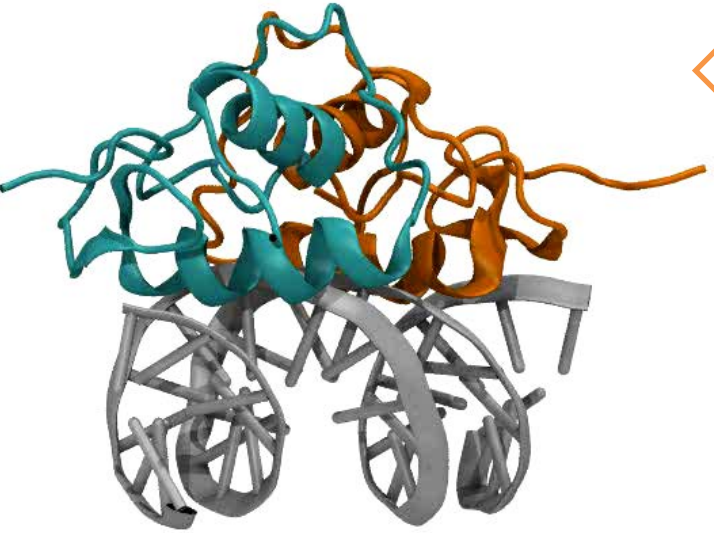
Alan Merk,[1,3] Alberto Bartesaghi,[1,3] Soojay Banerjee,[1,3] Veronica Falconieri,[1] Prashant Rao,[1] Mindy I. Davis,[2] Rajan Pragani,[2] Matthew B. Boxer,[2] Lesley A. Earl,[1] Jacqueline L.S. Milne,[1] and Sriram Subramaniam[1,*]

Size *(Kilodaltons, kDa)*

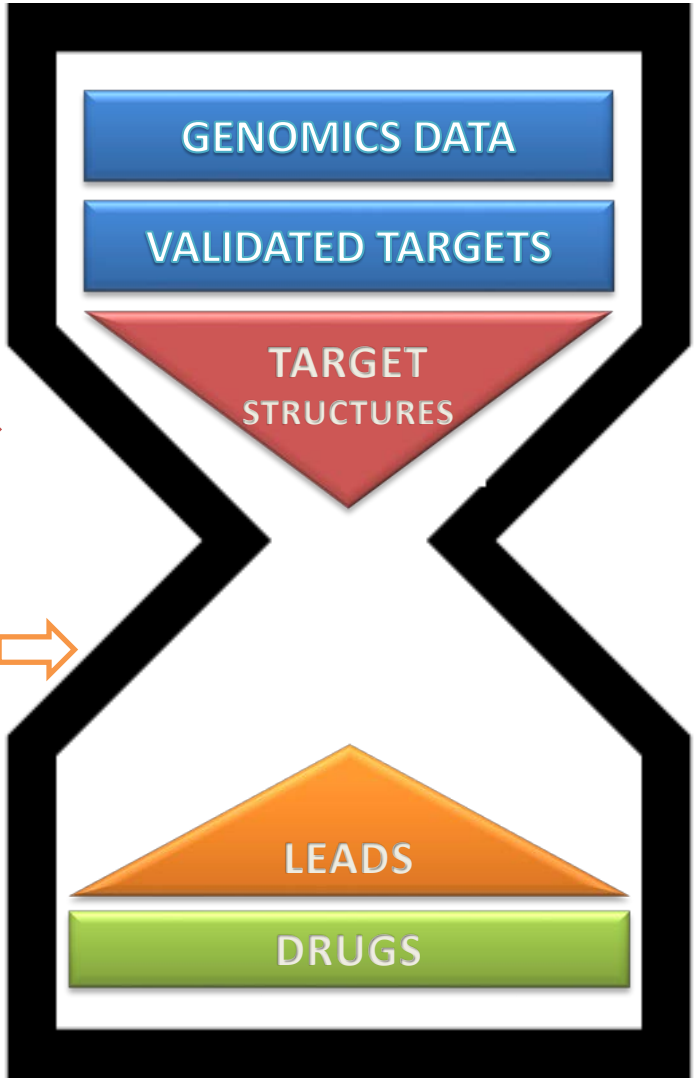


Opening Bottleneck : Target to Drug

⇦ CRYO-EM ⇨



⇦ CADD MODELING ⇨



Accelerated Drug Discovery

GENOMICS CORE

CFI # 33440 @VPC

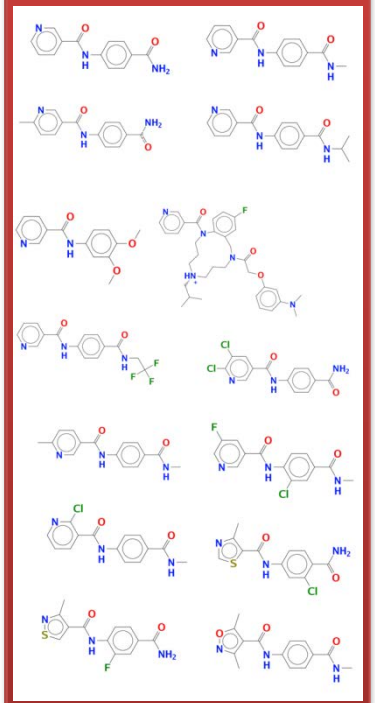
PROTEIN PLATFORM

CFI – requested

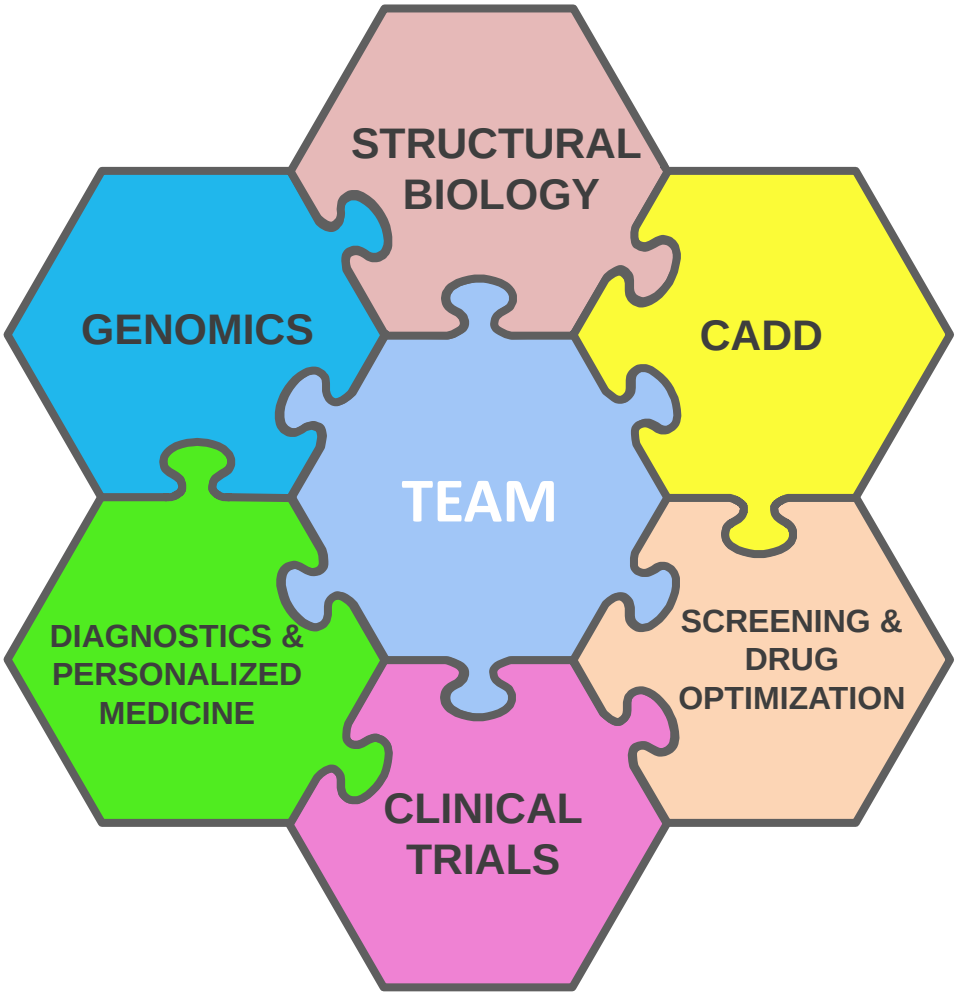
300eV cryoEM: Higher res
Low throughput, 30% down time
(CFI # 33611, @UBC ASTRID)

200eV cryoEM: Lower res ,
High throughput, no down time
CFI – requested

CADD PLATFORM



All the Pieces to Succeed = Guaranteed Outcome



=

- New Targets and Structures
- New Drugs
- Companion Diagnostics

Targets Emergence

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Accession Number : AD1061899

Title : Direct Targeting of the FKBP52 Cochaperone for the Treatment of Castration R

International Journal of *Molecular Sciences*

Article

Benzothiophenone Derivatives Target Forms of Estrogen Receptor-α in Horr Breast Cancers

Kriti Singh †, Ravi S. N. Munuganti †, Nada Lallous, Kush Dalal, J Aishwariya Sharma, Takeshi Yamazaki, Artem Cherkasov ‡ and Paul

Vancouver Prostate Centre, University of British Columbia, 2660 Oak Street,

Targeting Semaphorin 3C in Prosta With Small Molecules

Chung C W Lee, Ravi Shashi Nayana Munuganti, James W Ivy Z F Jiao, Ashley Shepherd, Liangliang Liu, Kevin J Tar Satyam Bhasin, Kevin C K Lee, Luke Gooding, Benjamin \ Tabitha Tombe, Yifan Gong, Martin E Gleave, Artem Cher Christopher J Ong

Journal of the Endocrine Society, Volume 2, Issue 12, 1 De 1381–1394, https://doi.org/10.1210/js.2018-00170

molecules

MDPI

Article

Computer-Aided Discovery of Small Molecule Inhibitors of Transcriptional Activity of TLX (NR2E1) Nuclear Receptor

ELSEVIER

European Journal of Medicinal Chemistry

Volume 160, 5 December 2018, Pages 108-119

la;

Research paper

Computer-aided drug discovery of Myc-Max inhibitors as potential therapeutics for prostate cancer

Lavinia A. Carabet [a, 1], Nada Lallous [a, 1], Eric Leblanc [a], Fuqiang Ban [a], Helene Morin [a], Sam Lawn [a], Fariba Ghaidi [a], Joseph Lee [a], Ian G. Mills [b, c], Martin E. Gleave [a], Paul S. Rennie [a, 2], Artem

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 26), pp: 42438-42454

Research Paper

Discovery and characterization of small molecules targeting the DNA-binding ETS domain of ERG in prostate cancer

Miriam S. Butler[1,*,#], Mani Roshan-Moniri[1,*,#], Michael Hsing[1,*,#], Desmond Lau[2,*,#], Ari Kim[1], Paul Yen[1], Marta Mroczek[1], Mannan Nouri[1], Scott Lien[1], Peter Axerio-Cilies[1], Kush Dalal[1], Clement Yau[1], Fariba Ghaidi[1], Yubin Guo[1], Takeshi Yamazaki[1], Sam Lawn[1], Martin E. Gleave[1], Cheryl Y. Gregory-Evans[3], Lawrence P. McIntosh[2,*], Michael E. Cox[1,*], Paul S. Rennie[1,*] and Artem Cherkasov[1,*]

[1]Vancouver Prostate Centre and the Department of Urologic Sciences, University of British Columbia, Vancouver, BC V6H 3Z6, Canada

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Dr. Robert Brunham (PI)
Liam Warrol

Dr. Paul Rennie (PI)
Dr. Emma Guns (PI)
Dr. Martin Gleave (PI)
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Dr. Fuqiang Ban (RA)
Dr. Takeshi Yamazaki (RA)
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Dr. Robert Young (PI)
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