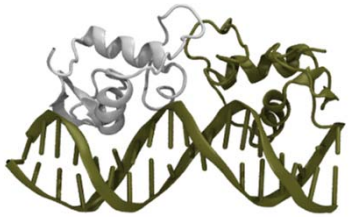
A Cheminformatics Story Behind $141,000,000 Molecule

Dr. Artem Cherkasov, PhD, DSc



<u>conflicts to disclose:</u>

La Hoffman-Roche licensee

LeadGen Ltd consultant

ANDRONEX founder and shareholder

World Leader in Prostate Cancer Research

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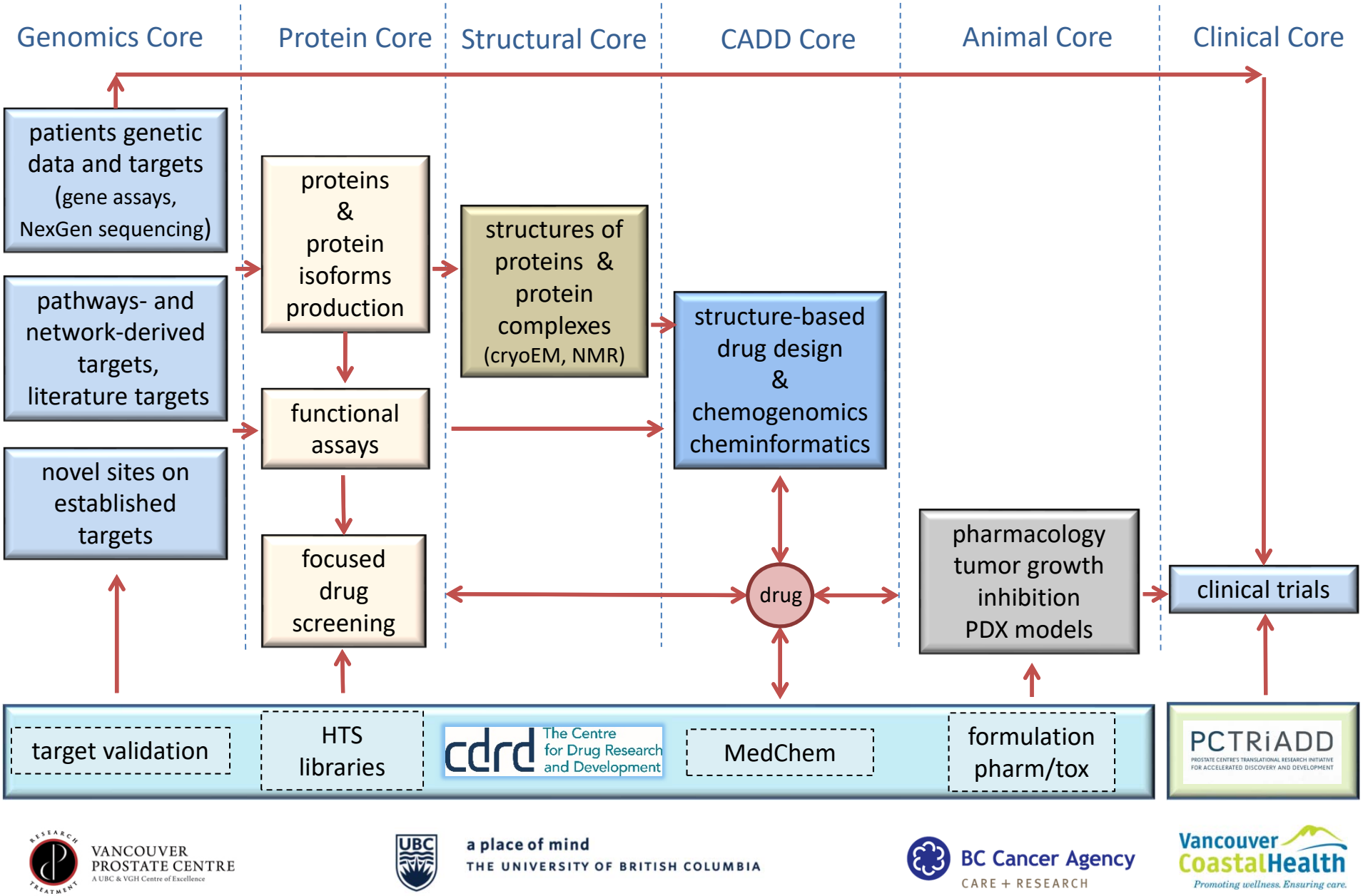

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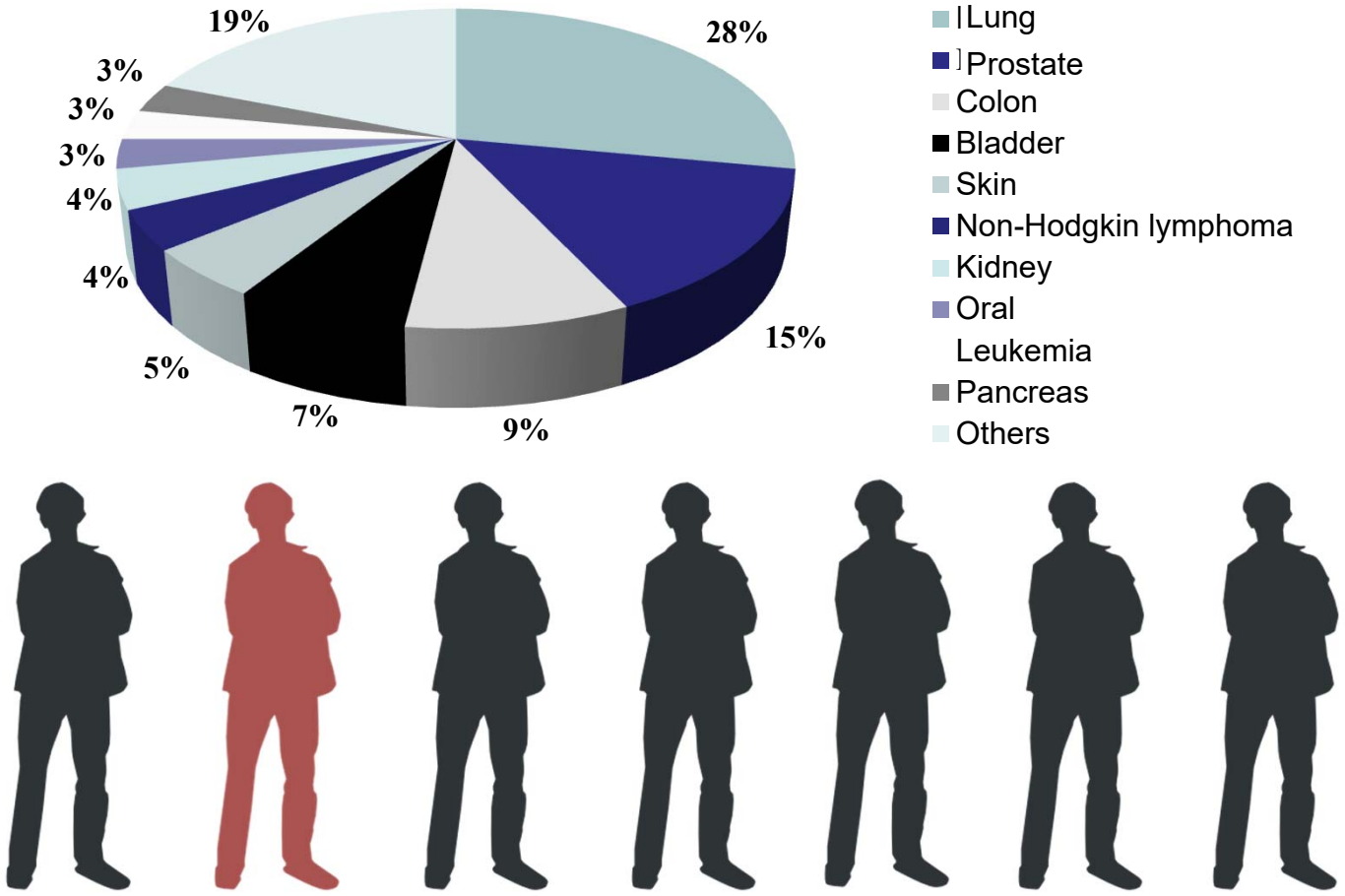
BC Cancer Agency
CARE + RESEARCH

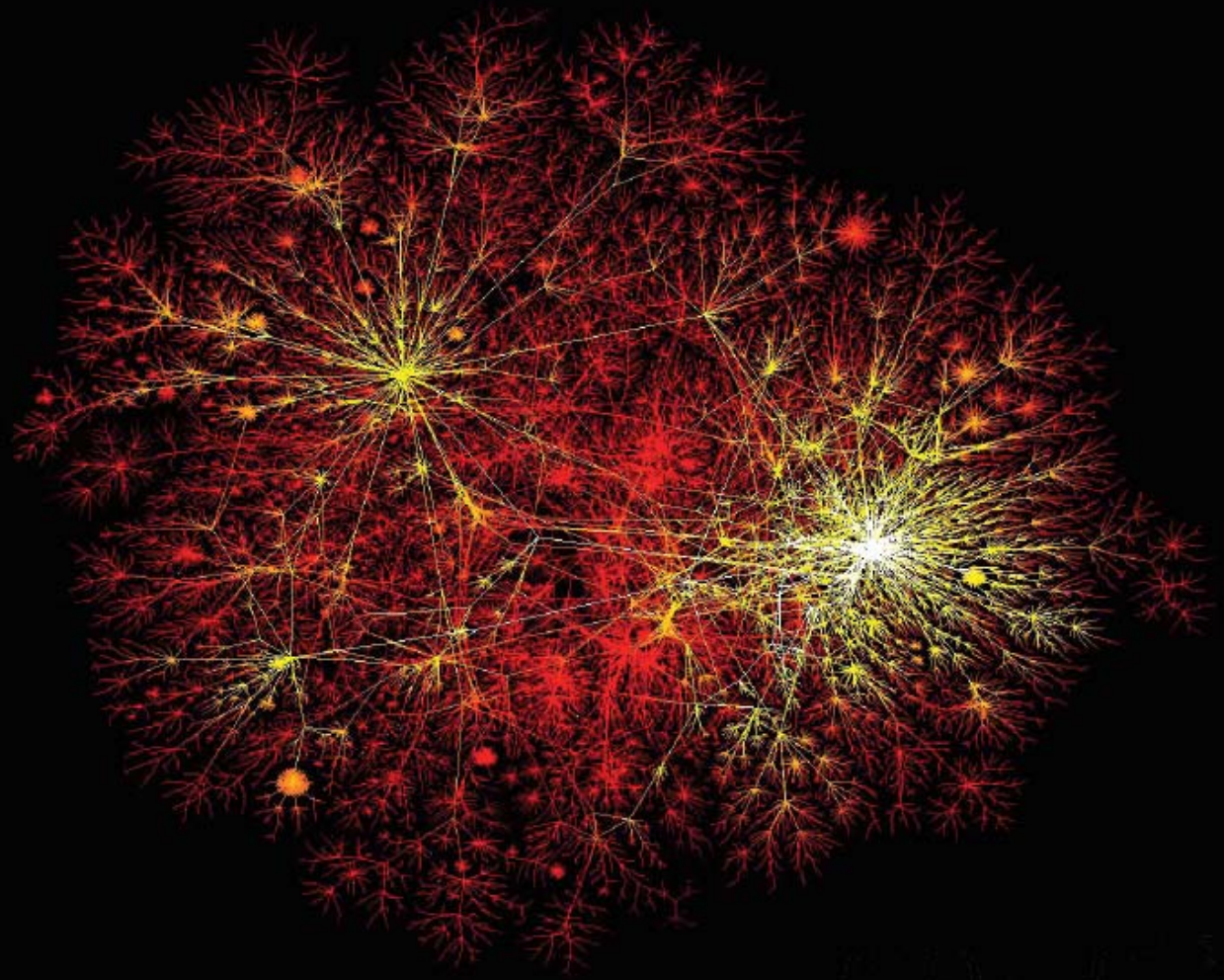
Vancouver CoastalHealth
Promoting wellness. Ensuring care.

Prostate Cancer

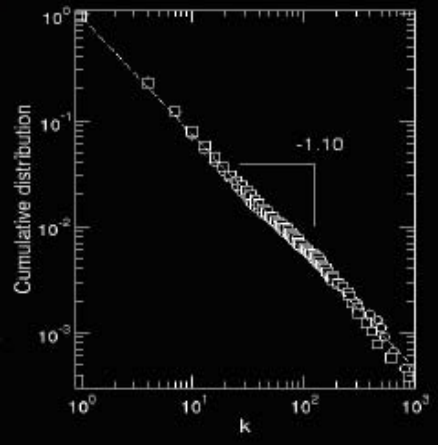
- Estimated new cancer cases in males in 2010



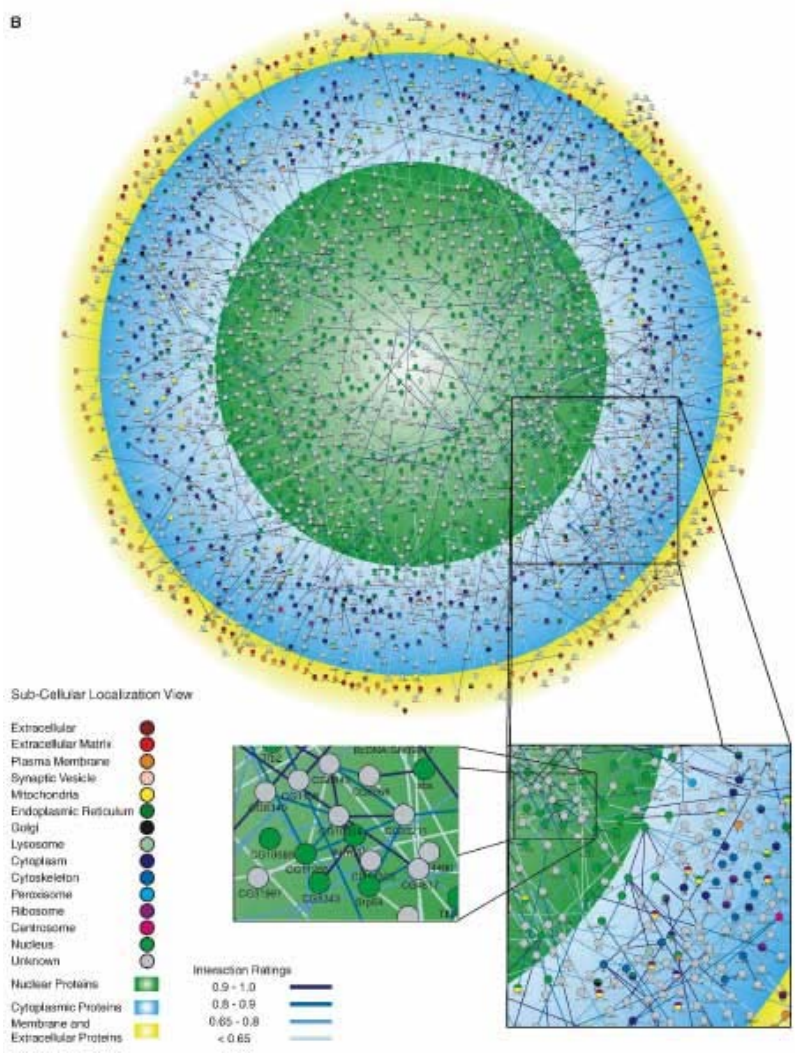
Complex networks are scale-free



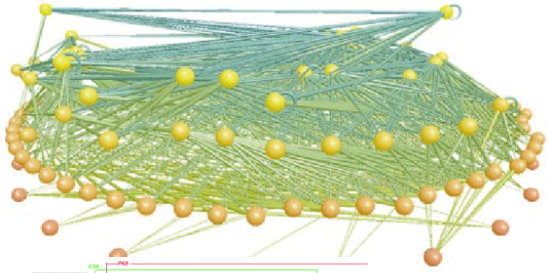
$$P(k) \sim k^{-\gamma}\phi(k/\xi)$$



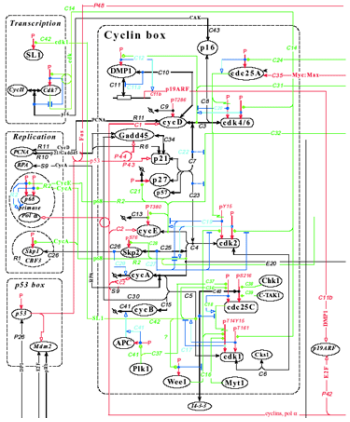
Protein interaction networks are also scale-free



The web of human sexual contacts (Liljeros et al., Nature, 411 (2001)

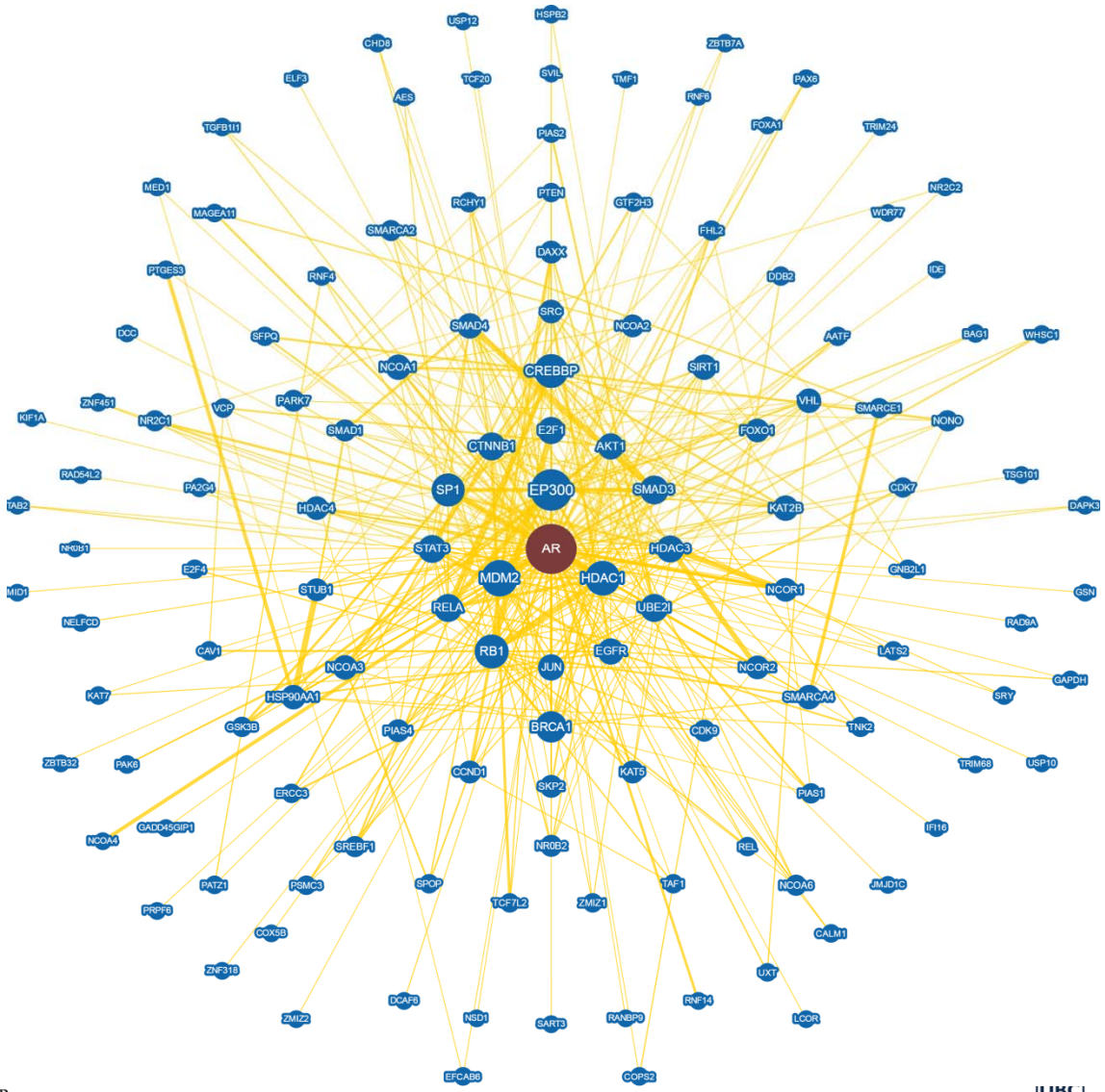


The food network

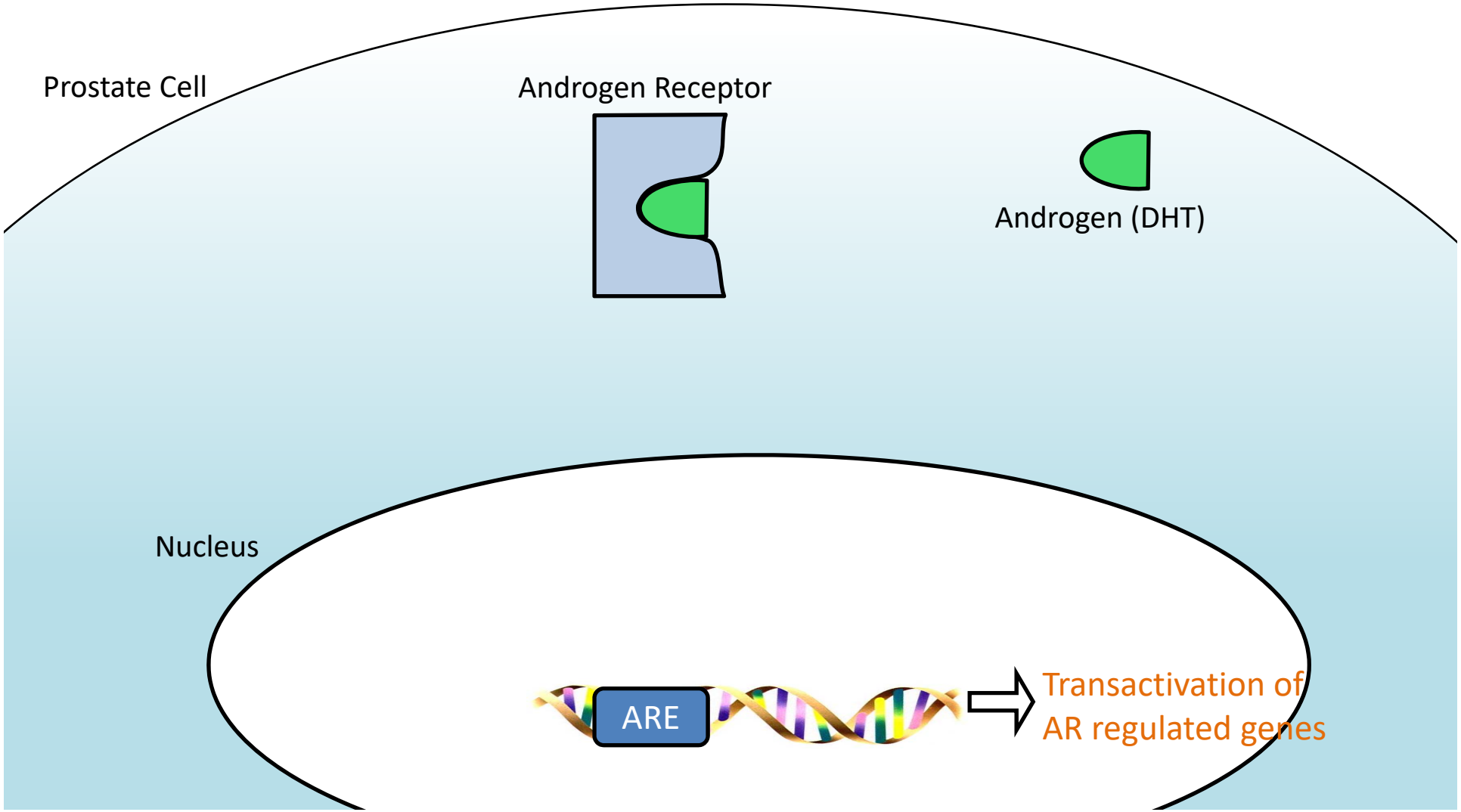


Neurons connections

AR is a Major Protein-Protein Interactions Hub



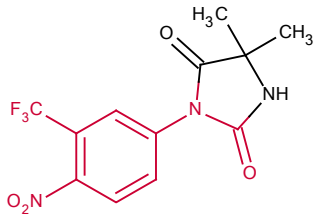
AR Mechanism of Action



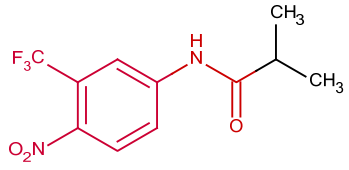
Androgen Receptor Inhibitors as Prostate Cancer Drugs

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

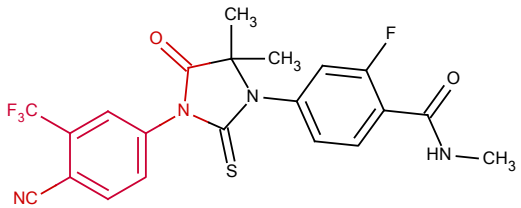
Nilutamide



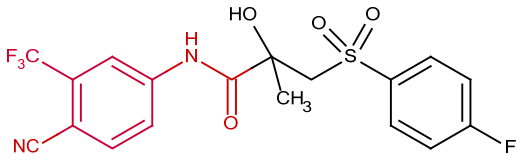
Flutamide



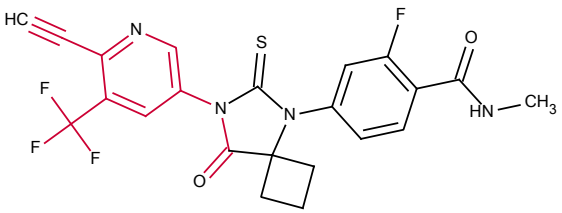
Enzalutamide



Bicalutamide



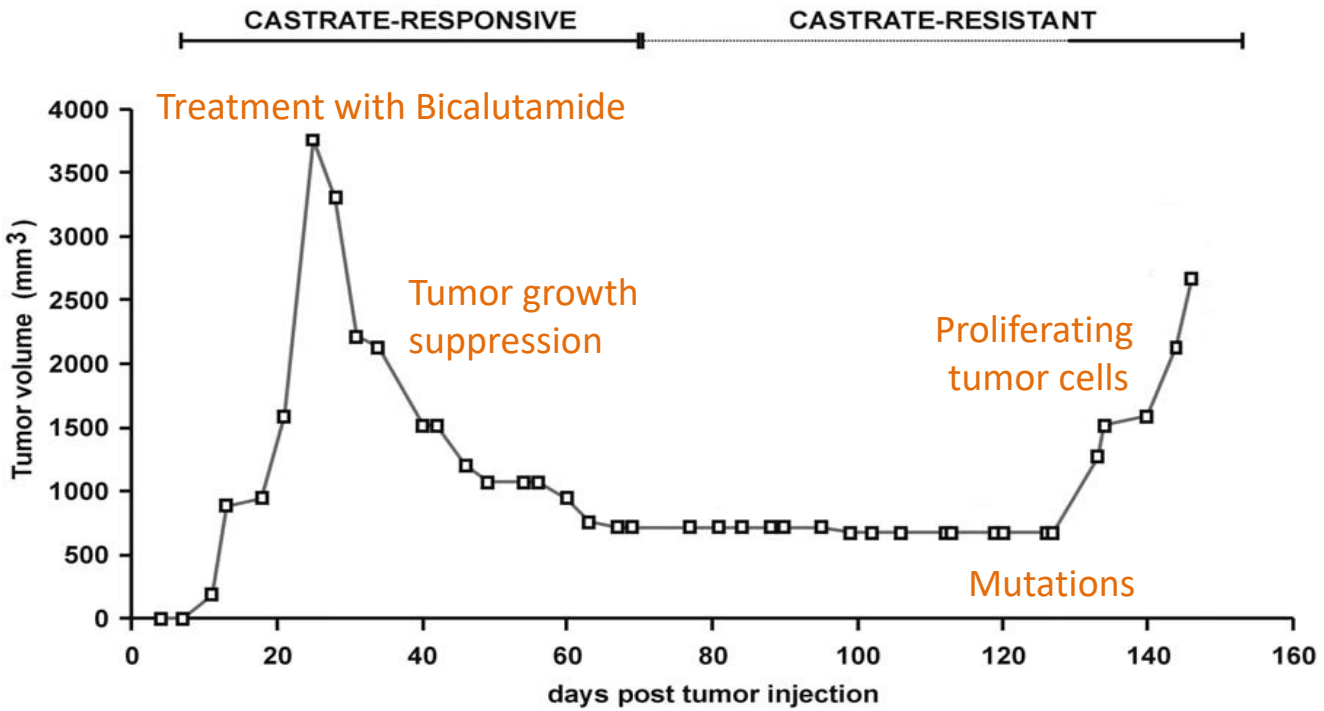
ARN-509



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

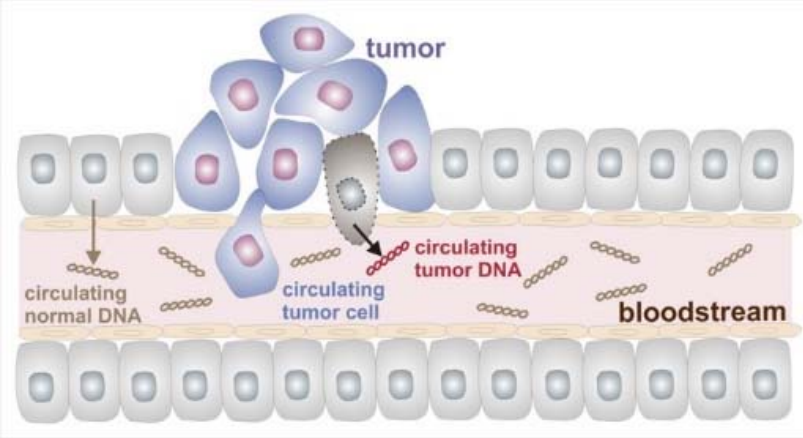


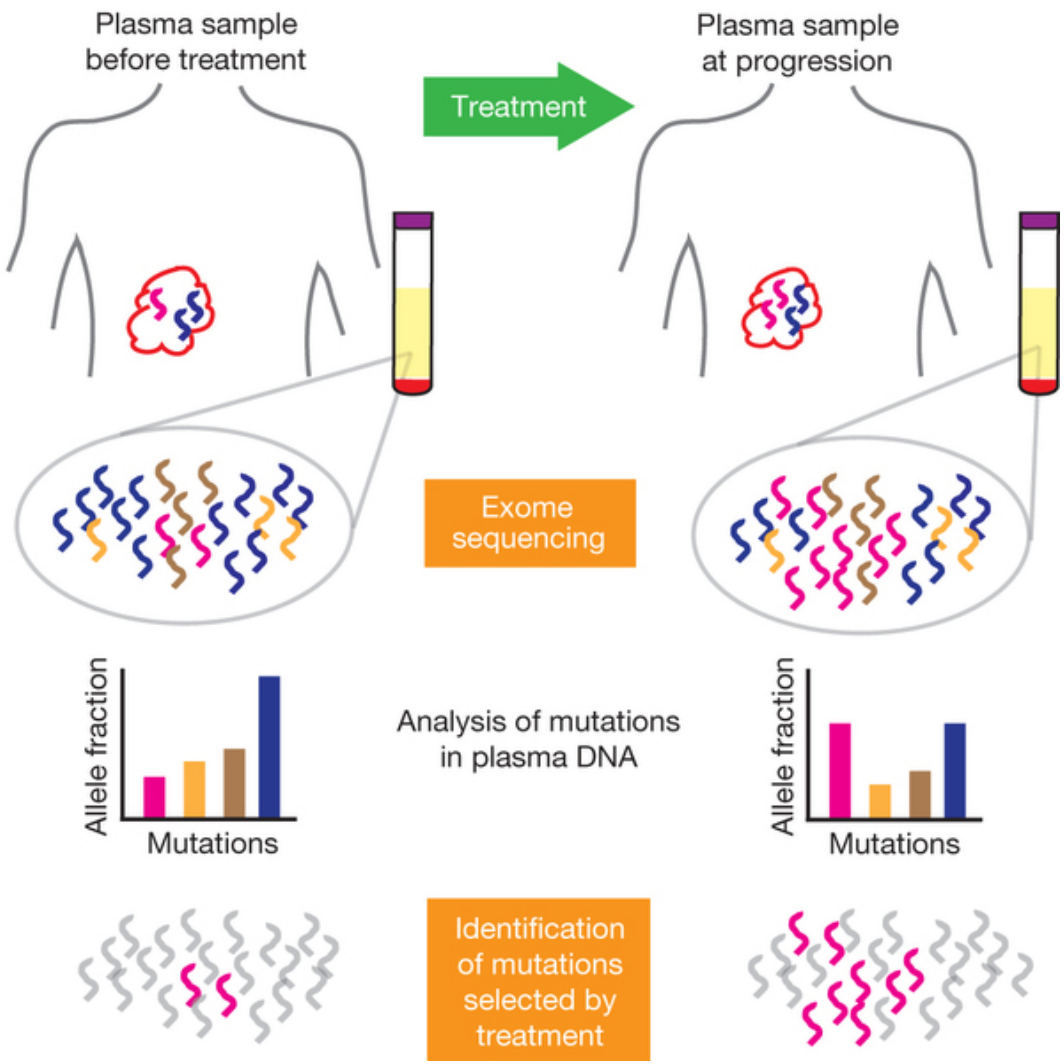
Scher et al. Endocrine-Related Cancer 2004

Lesson 1

Know your target

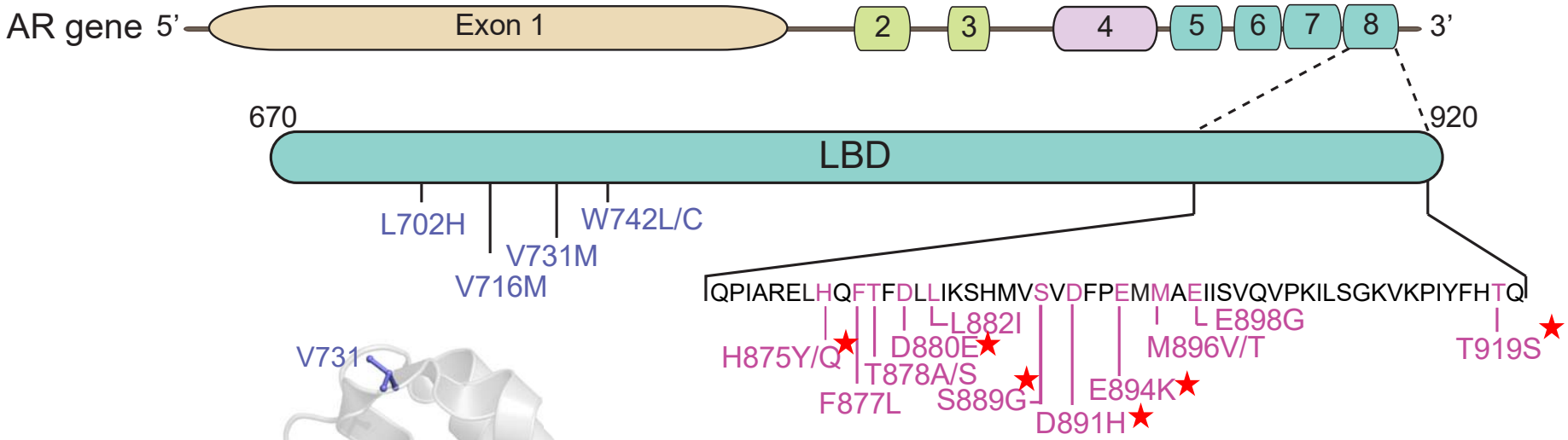
Circulating Cell Free DNA

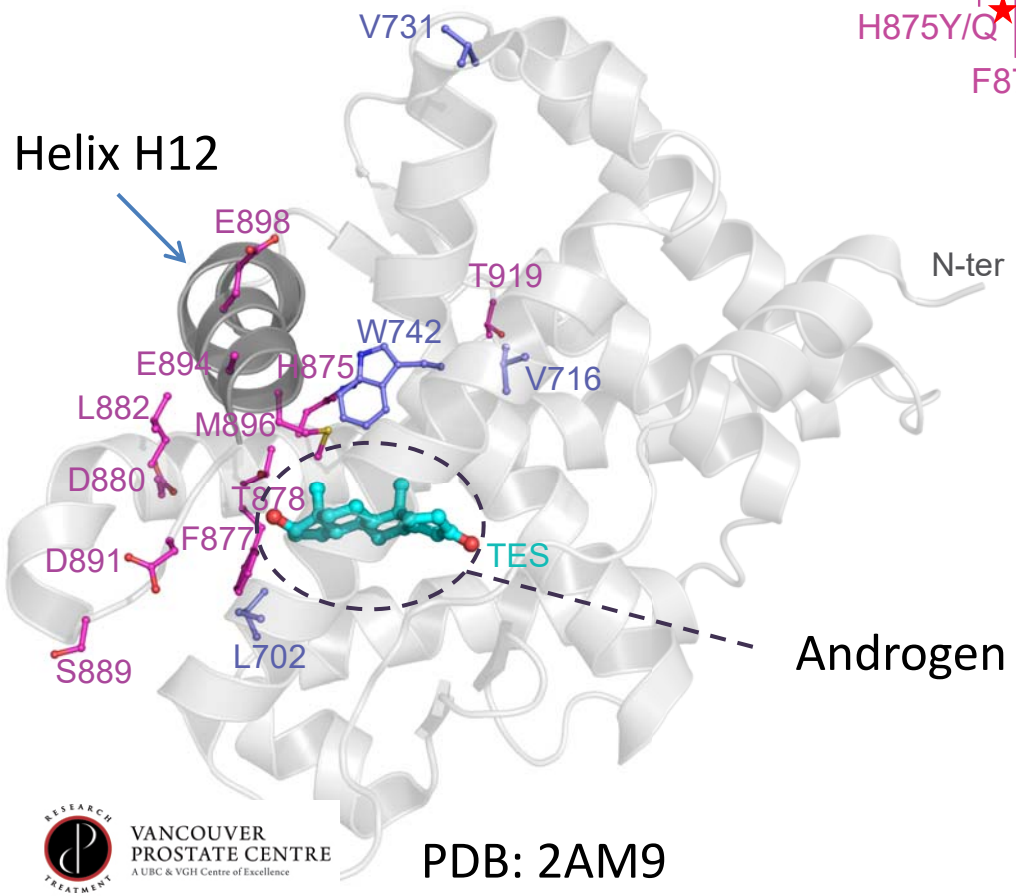




Nature 497, 108–112, 2013

Identification of AR mutants using liquid biopsy





Androgen Binding Site

Lallous et al. Genome Biology, 2016

PDB: 2AM9

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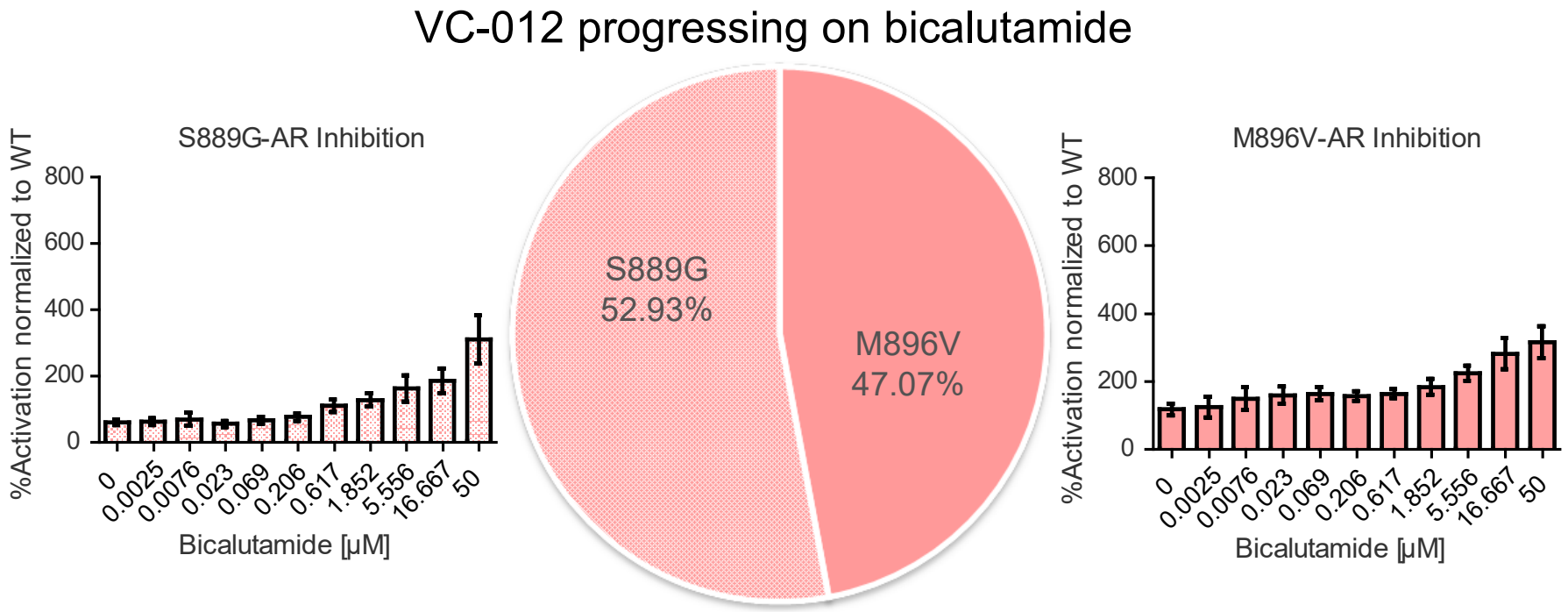
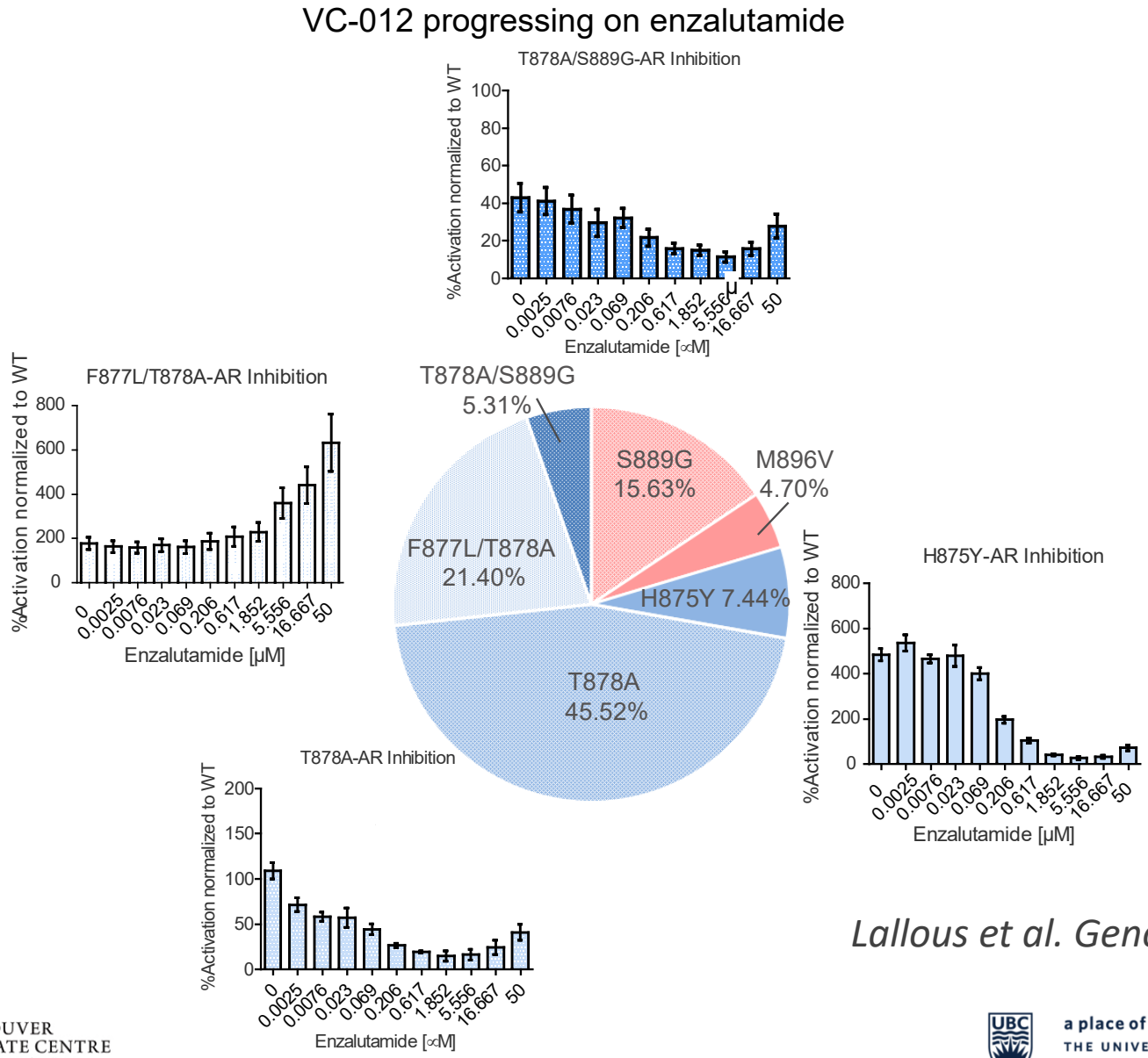
Specific Case: Patient VC-012



Lallous et al. Genome Biology, 2016

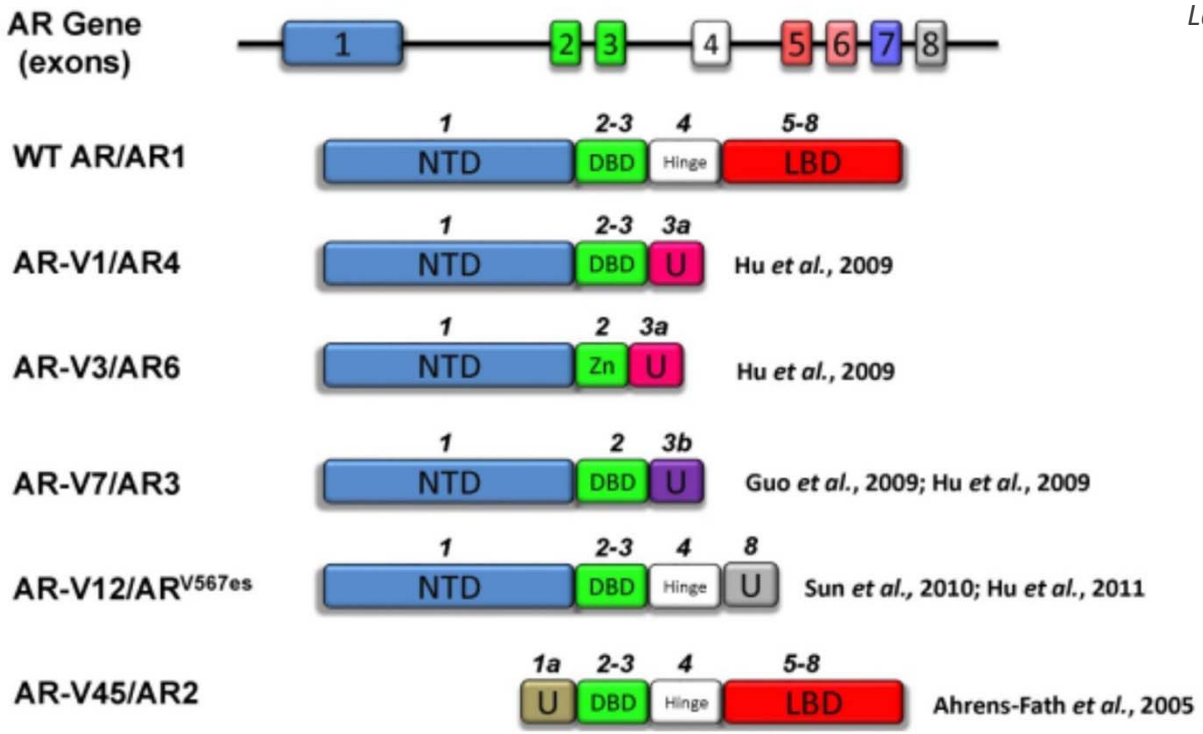
Lallous et al. Genome Biology, 2016

Specific Case: Patient VC-012



Lallous et al. Genome Biology, 2016

CRPC Resistance Driven by AR Splice Variants



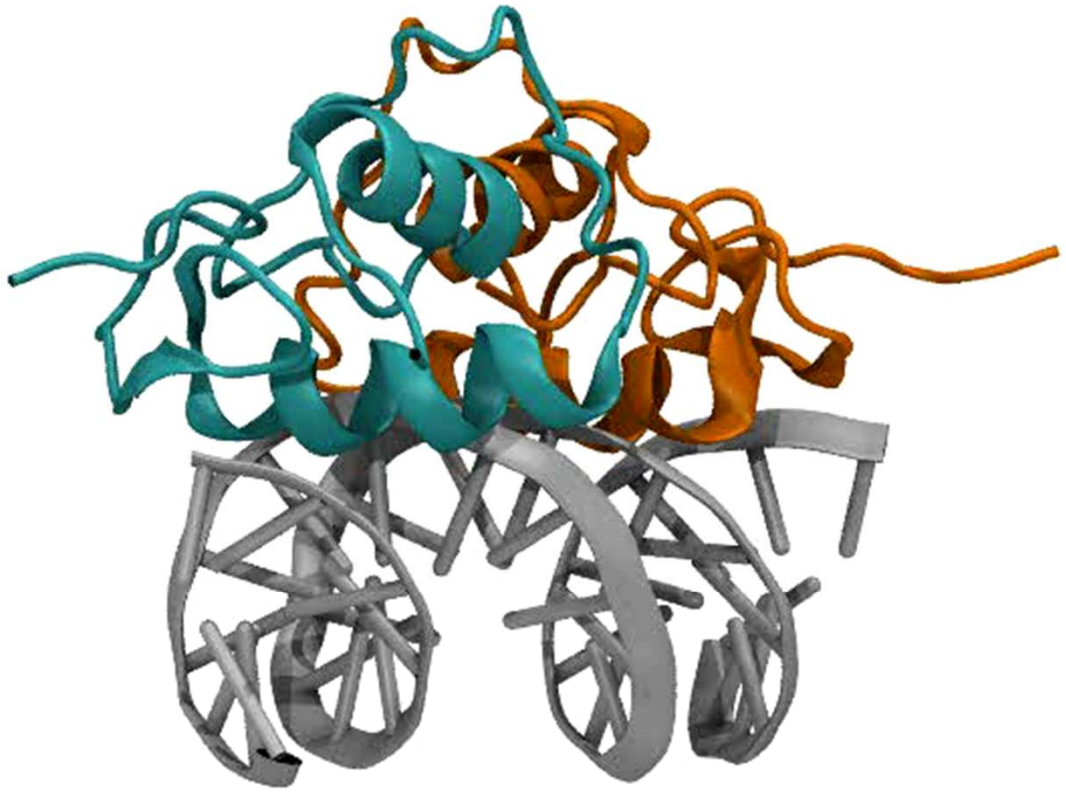
Lallous et al. Int J Biol Sci 2011; 7(6) 815-822

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

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

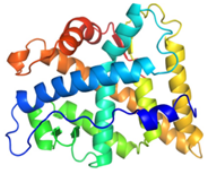


Typical ‘in silico’ Screening Pipeline

Protein structural modeling

→ Protein structure database
- PDB

→ Protein models and pockets
- MODELLER, MOE



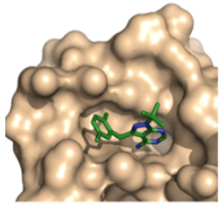
Tens of millions of small molecules

→ Small molecule database
- ZINC

→ Molecular docking
- Glide, FRED, AutoDock, eHiTs

→ Consensus voting

→ ADMET prediction
- ADMET Predictor, FAFDrugs

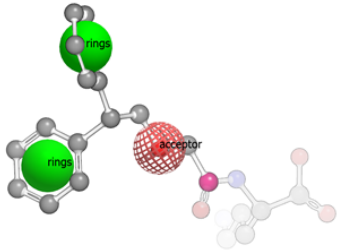


100s of virtual Hits

→ Computer-aided medicinal chemistry
- BROOD, MD, FEP

→ Chemical similarity
- 2D-fingerprints, ROCS

→ SAR and QSAR



Few leads

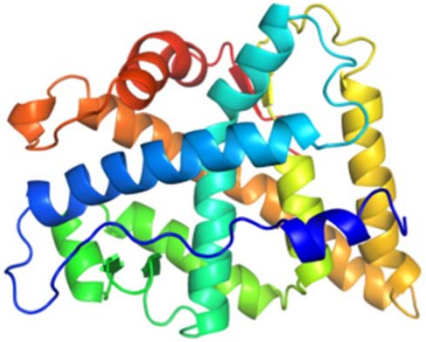
Lead Drug Candidate

Lesson 2

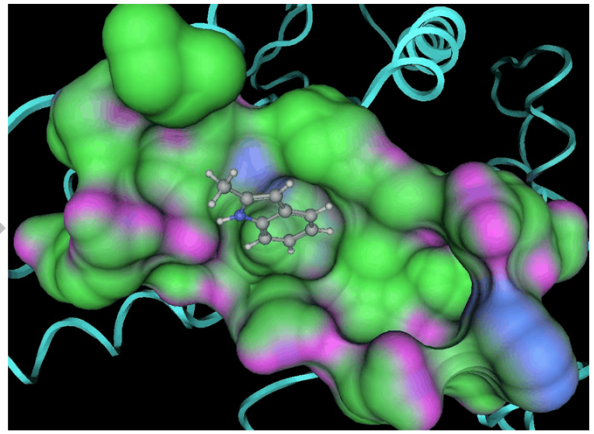
Use diverse cheminfo methods

In Silico Screening Workflow

Protein structure



Molecular docking
(~10,000,000 mol)



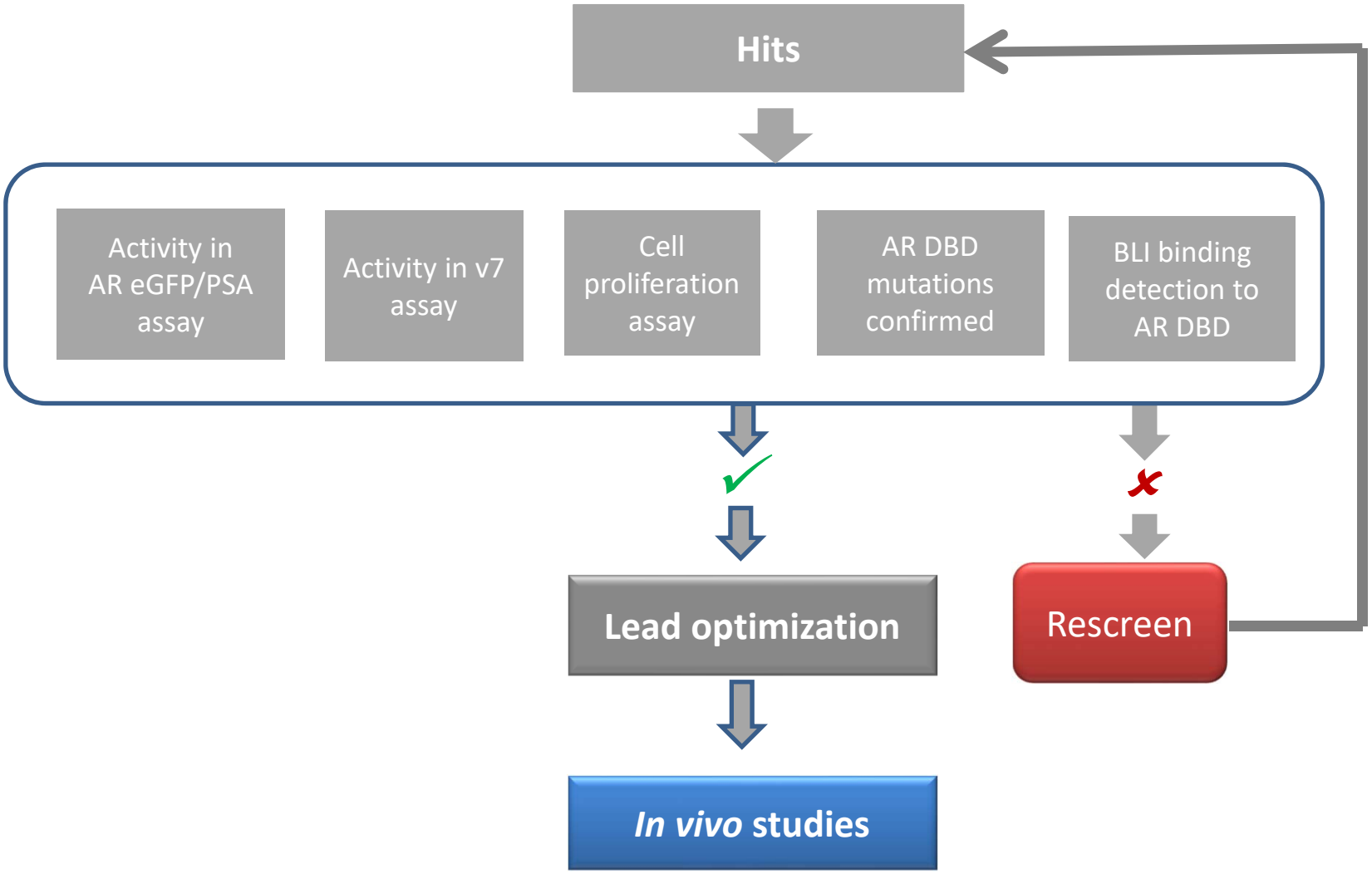
Computational protocols (~1,000,000)

Small Molecule Database (50,000,000)

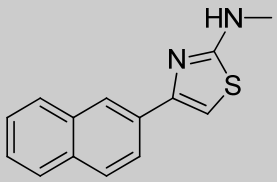
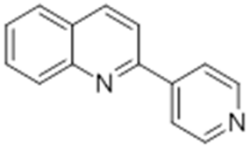
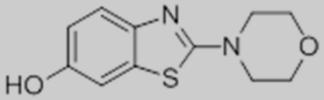
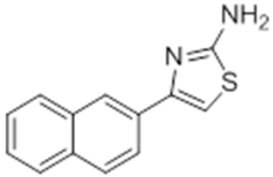
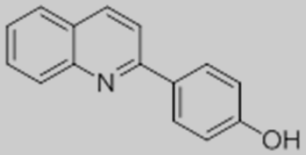
CONSENSUS SCORING !

Virtual Hits (100 to 200)

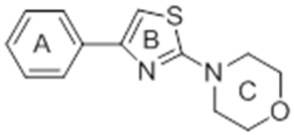
Experimental Screening Workflow

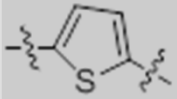
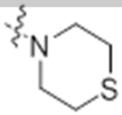
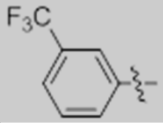
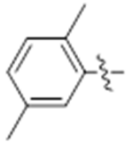
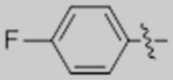


Initial *in silico* hits

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 derived analogues, 1st round

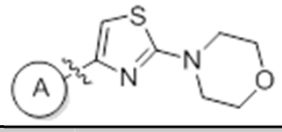


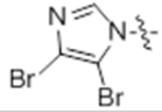
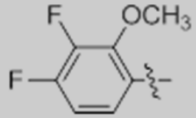
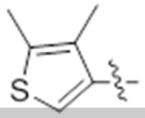
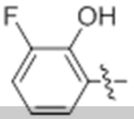
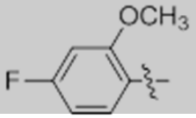
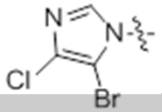
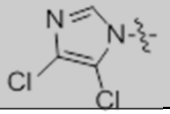
VPC-ID	A ring	B ring	C ring	eGFP IC50 (µM)	PSA IC50 (µM)
14228				0.33 ± 0.12	0.28
14103				0.52 ± 0.03	0.51
14385				0.62 ± 0.06	N/A
14292				0.61 ± 0.02	0.58
14293				0.62 ± 0.06	0.52
14255				0.65 ± 0.06	0.41

Lesson 3

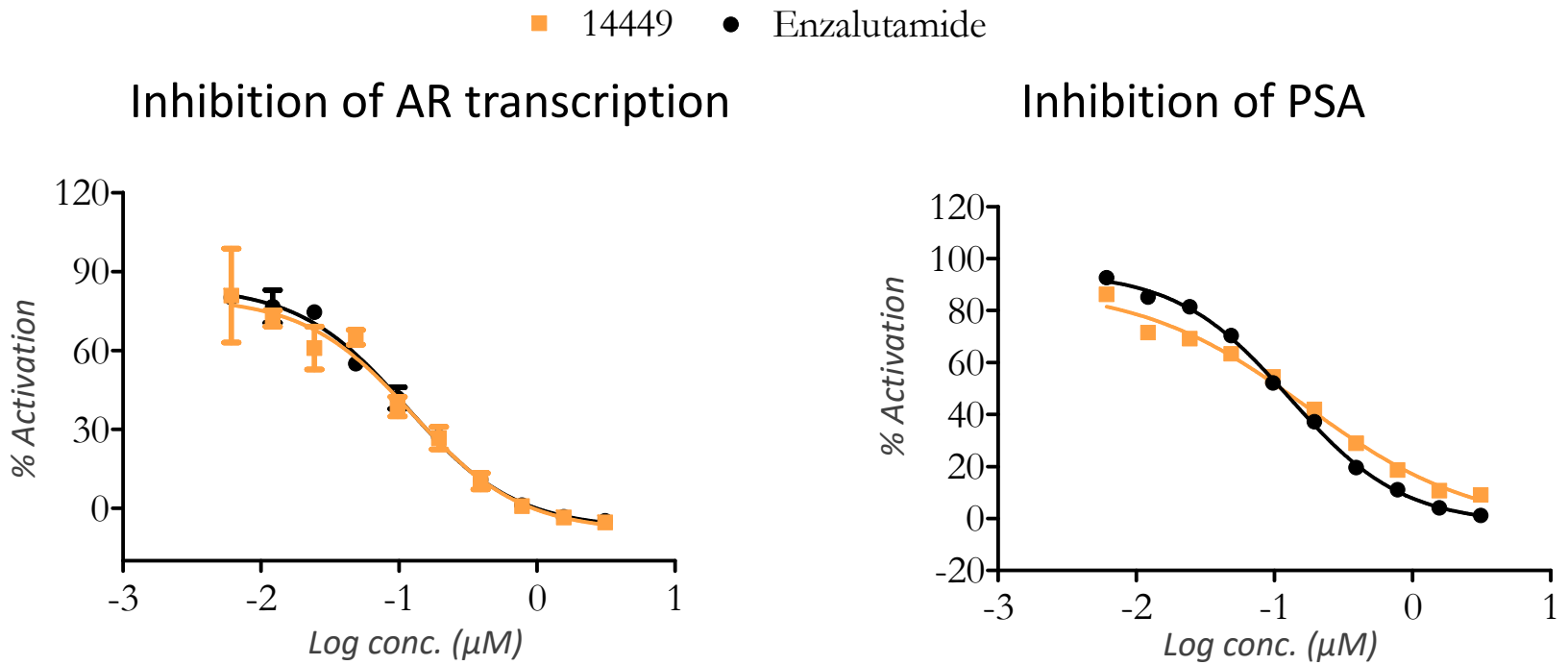
Analyse your hits, explore chemical space around them, combine structural elements, etc

2nd round of MedChem resulted in >100 Derivatives



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

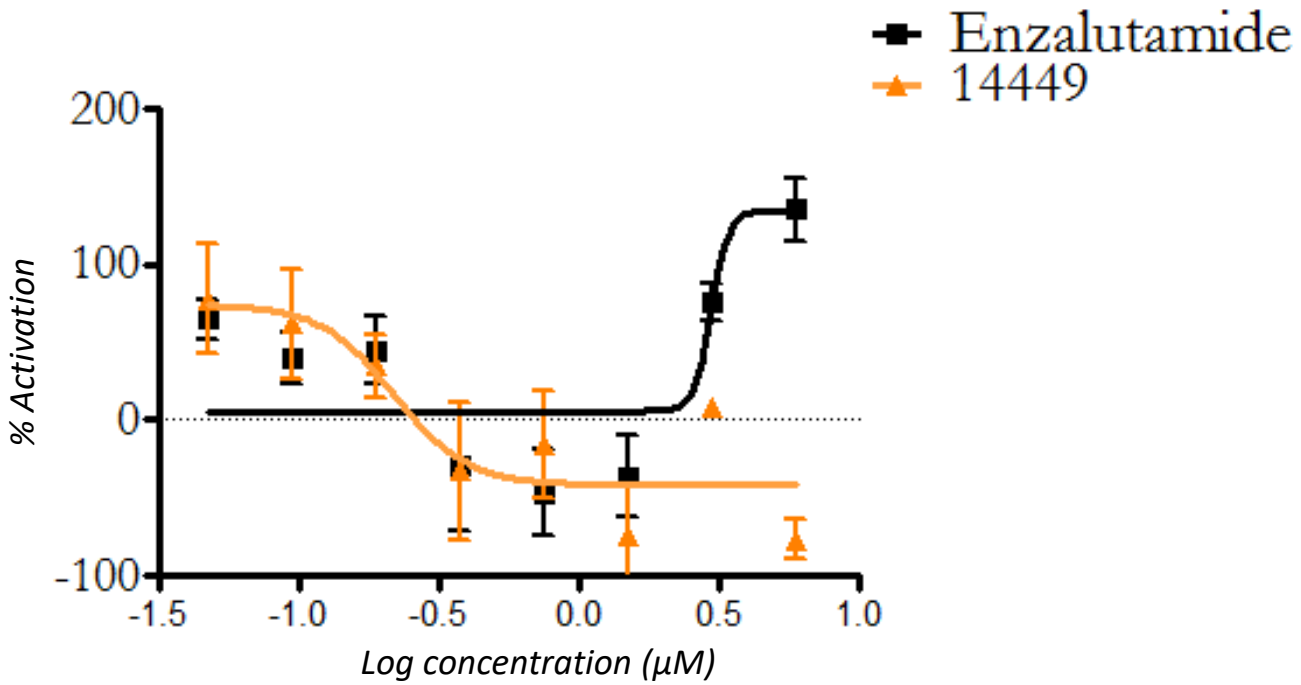
Activity Profile of the Current Lead VPC-14449



(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

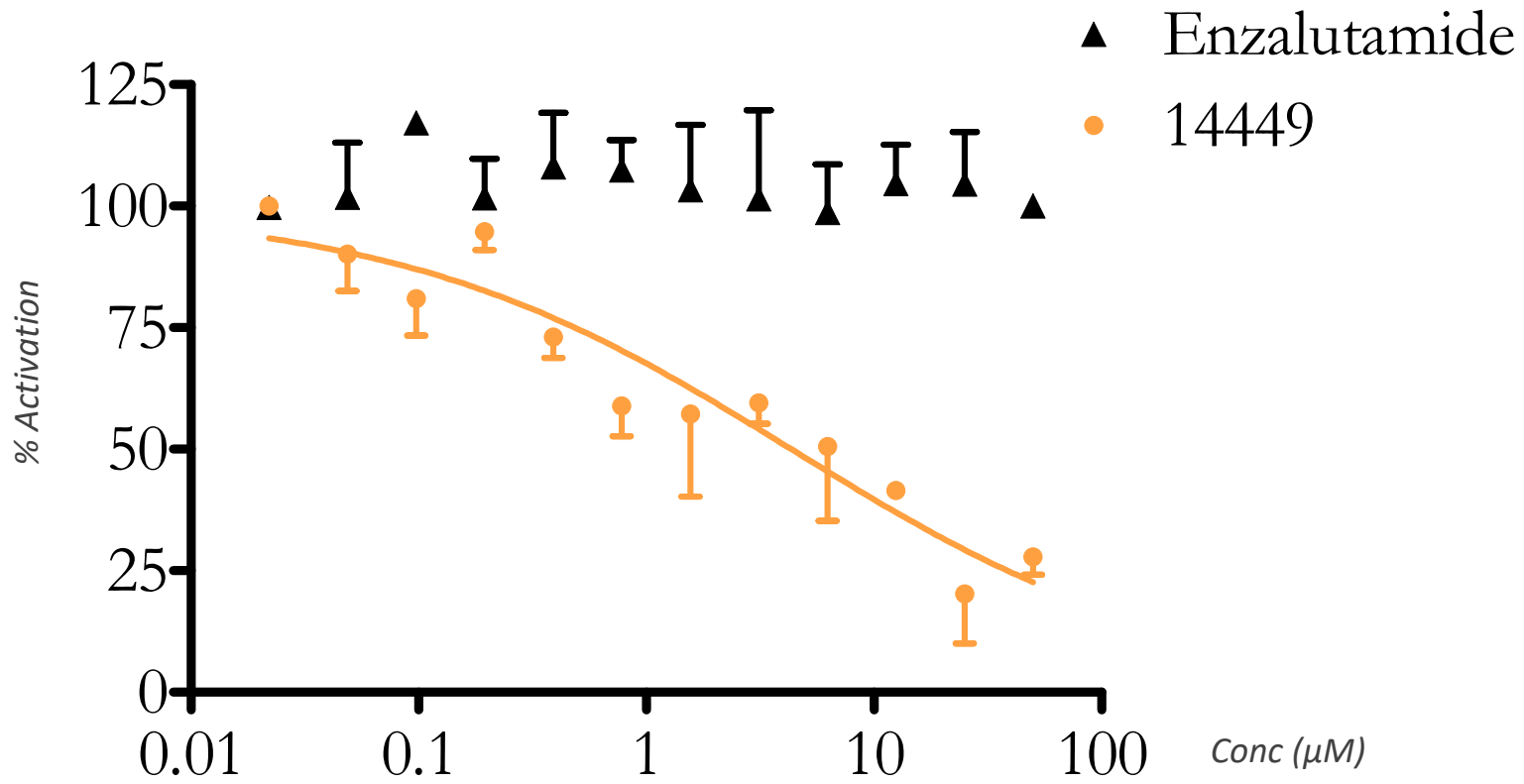
(Right) IC_{50} curve illustrating the inhibiting effect of 14449 (IC_{50} = 0.17μM) and Enzalutamide (IC_{50} = 0.08μM) on the PSA levels in LNCaP cells

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 the Activity of AR Splice Variant, V7

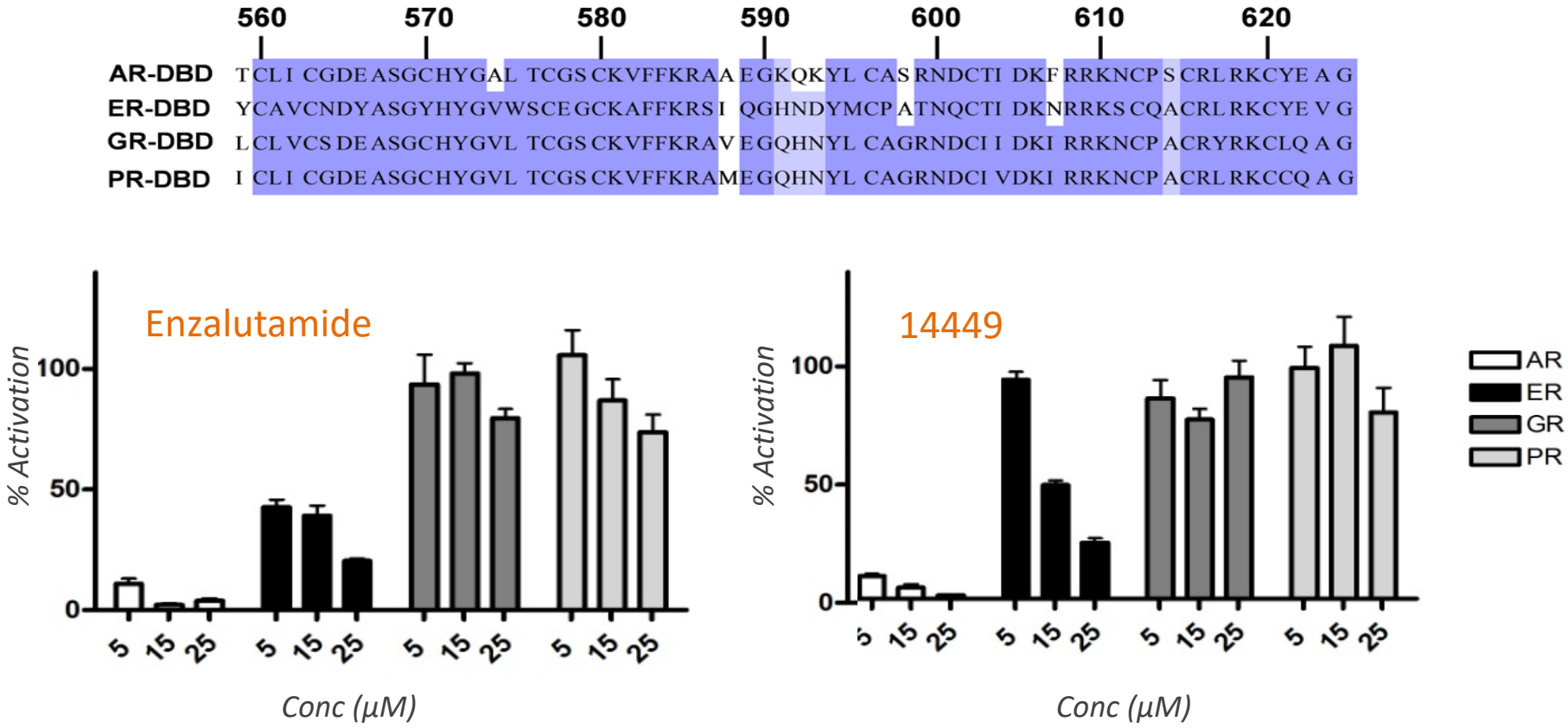


14449 inhibits the transcriptional activity of wild type AR splice variant, V7 in luciferase reporter assay. Enzalutamide has no effect on V7.

Lesson 4

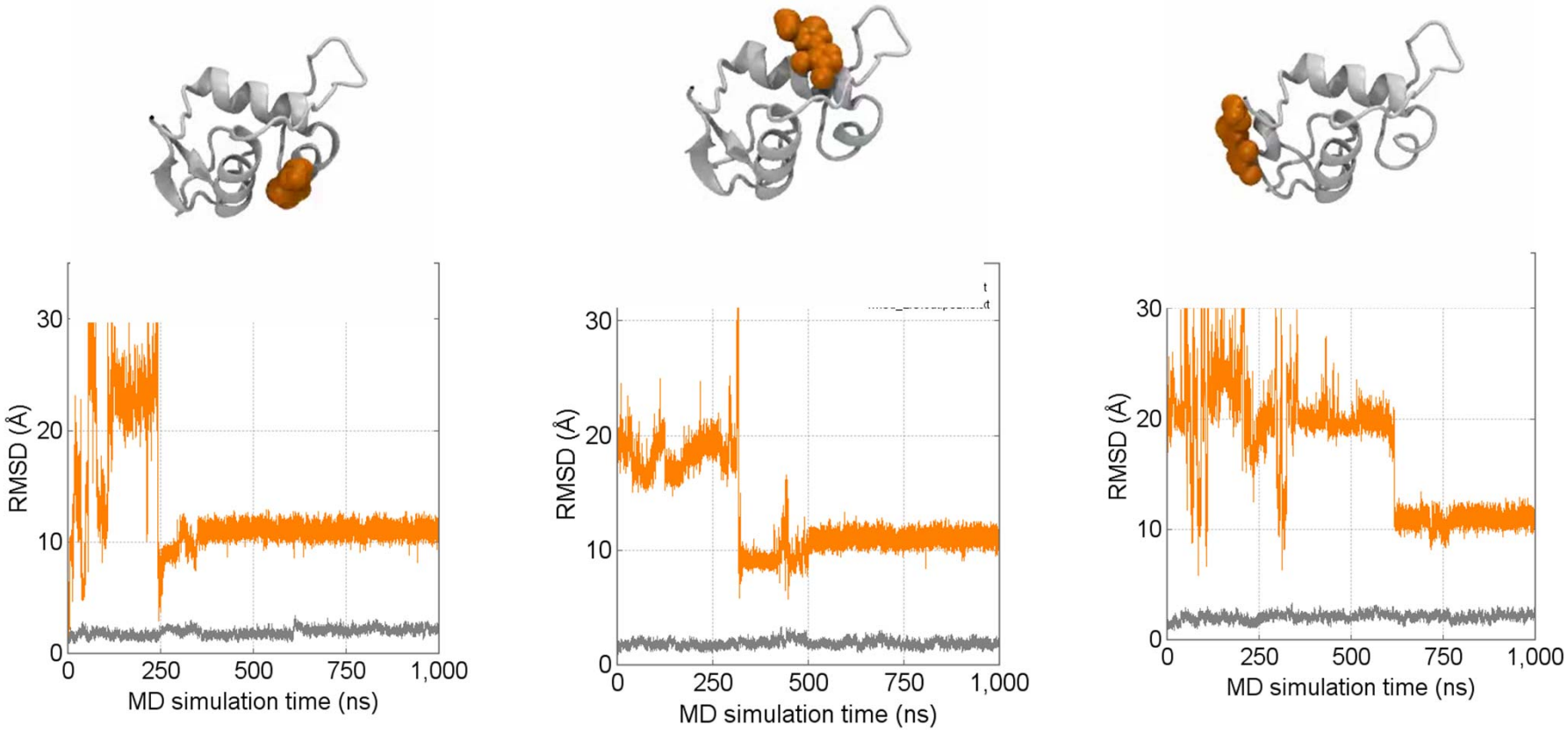
Work with experimentalists during the screening

14449 Demonstrates Selectivity Toward the AR



(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

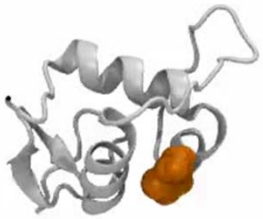
VPC - 14449 Firmly Binds to the AR DBD Target Site



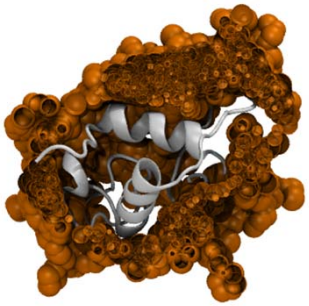
Molecular dynamics simulations was performed using explicit solvent model. The total run time 3µs. The MD simulation study supports that 14449 binds to DBD site stably. The results indicate 14449 finds its DBD binding spot from various starting points.

Consensus Validation of the Binding Site and Poses

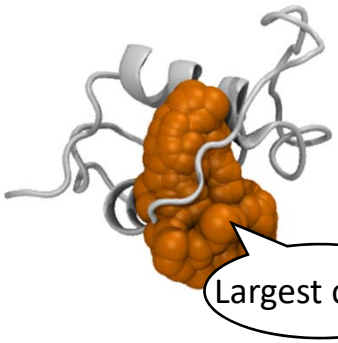
1. Multiple MD simulations



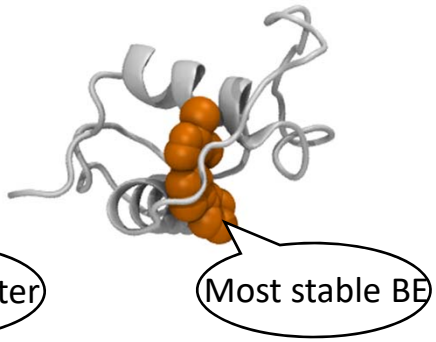
2. Sampled binding poses



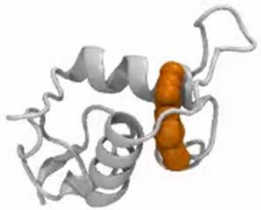
3. Cluster analysis & Binding energy calc.



4. Representative pose

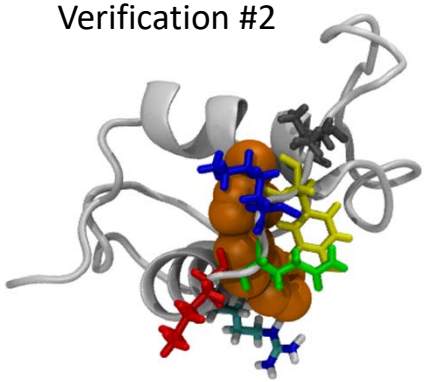


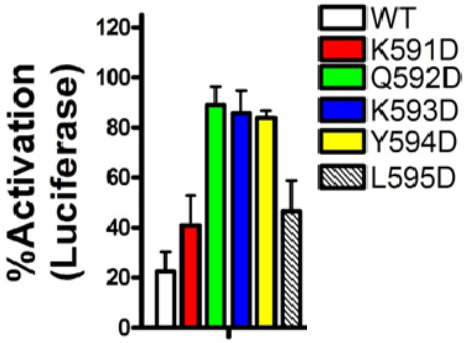
Verification #1



MD simulation starting from the representative pose

Verification #2





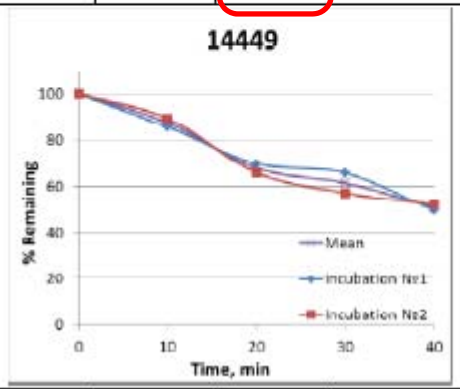
Comparison with the mutation experiment

Lesson 5

Validate your hits in details experimentally and ‘in silico’

VPC - 14449 Demonstrated sub-Optimal Stability

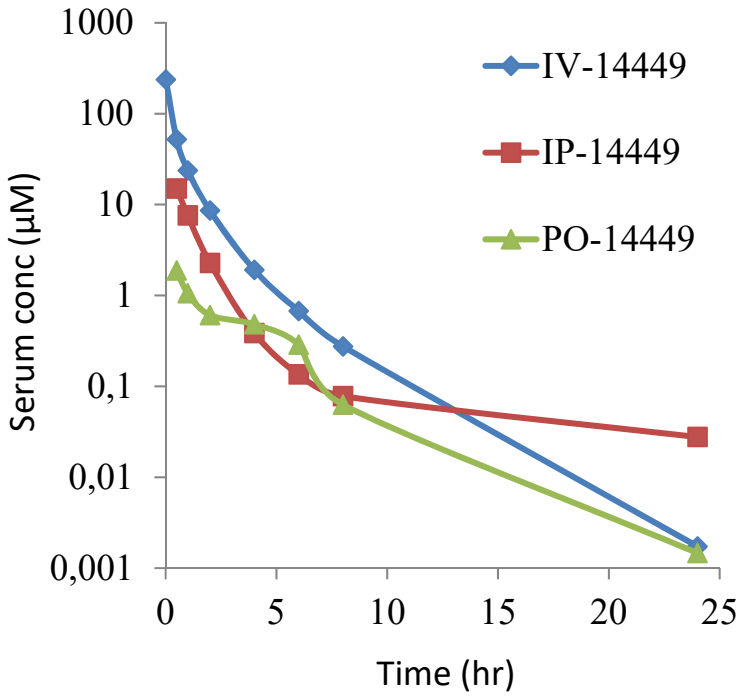
14449	0	1,06E+03	1,07E+03	1,07E+03	100	0,993	0,017	40,67	41,07	100
	10	9,12E+02	9,60E+02	9,36E+02	88					
	20	7,43E+02	7,08E+02	7,25E+02	68					
	30	6,99E+02	6,14E+02	6,57E+02	61					
	40	5,27E+02	5,60E+02	5,44E+02	51					98



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

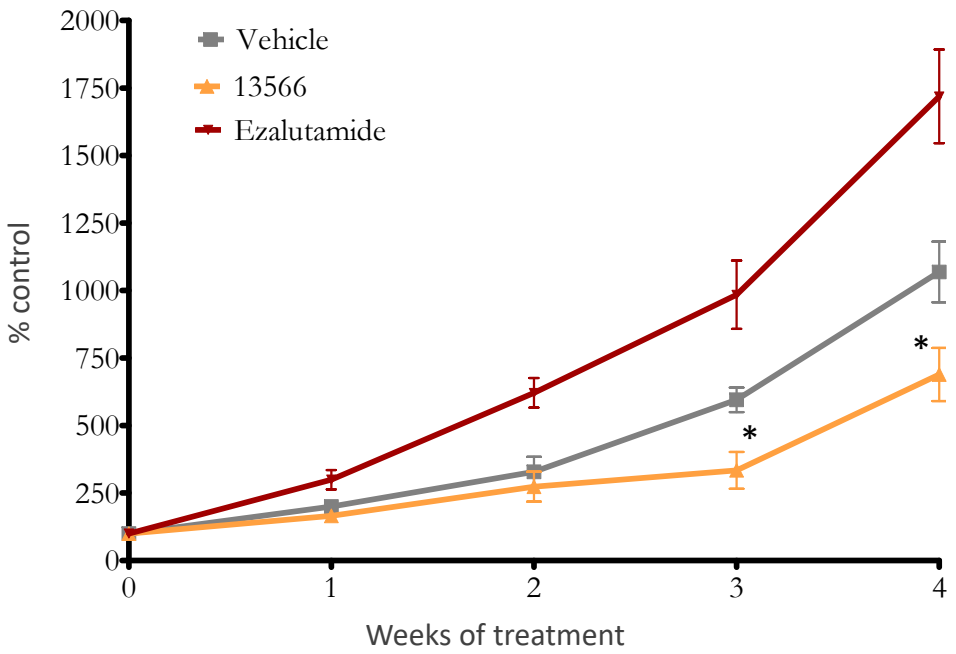
Pharmacokinetics of VPC-14449

- 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

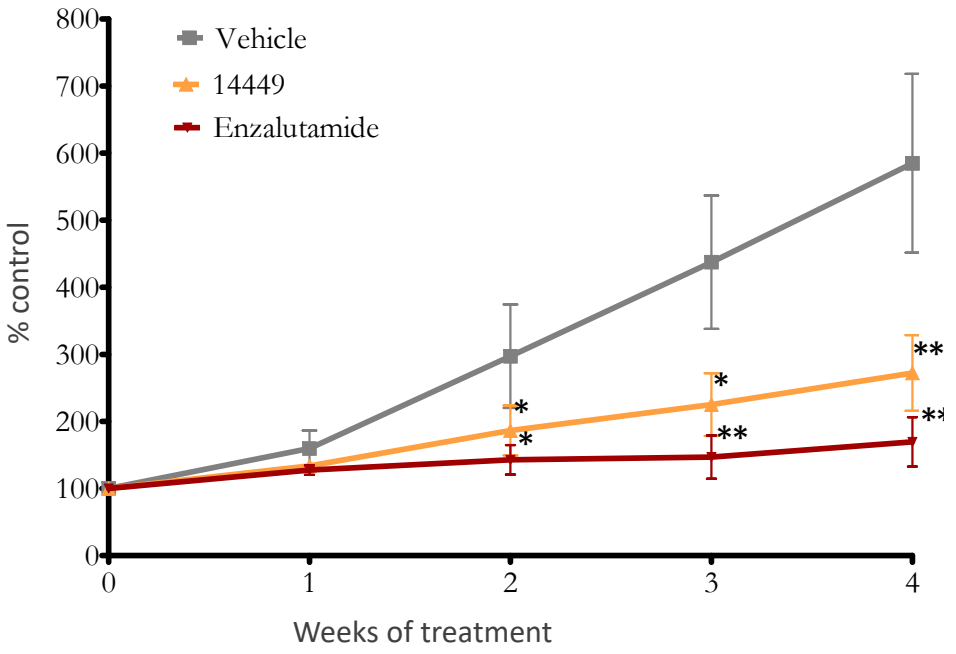


In vivo Effect of VPC - 14449

MR49F (Tumor Volume)



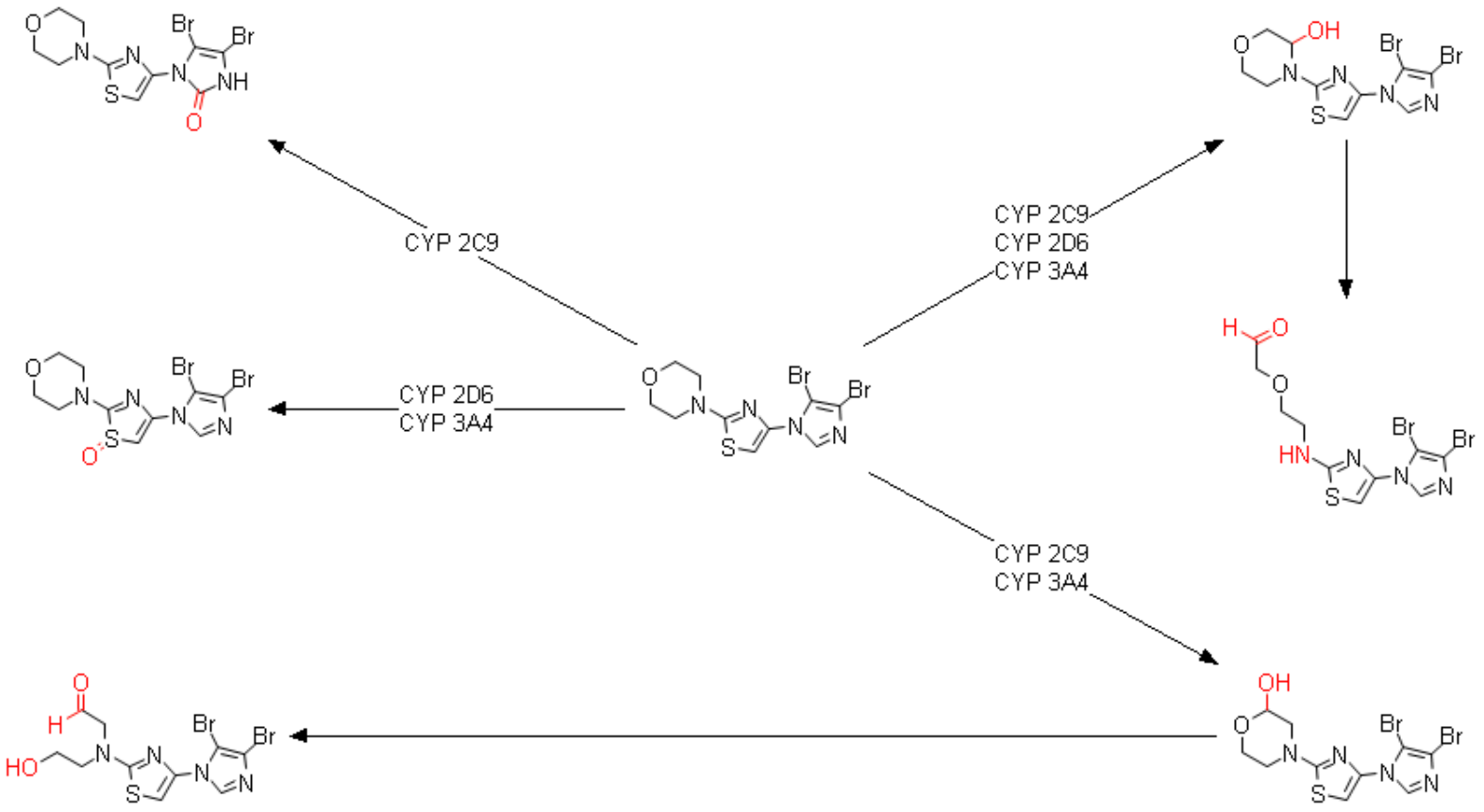
C4-2 (Tumor Volume)



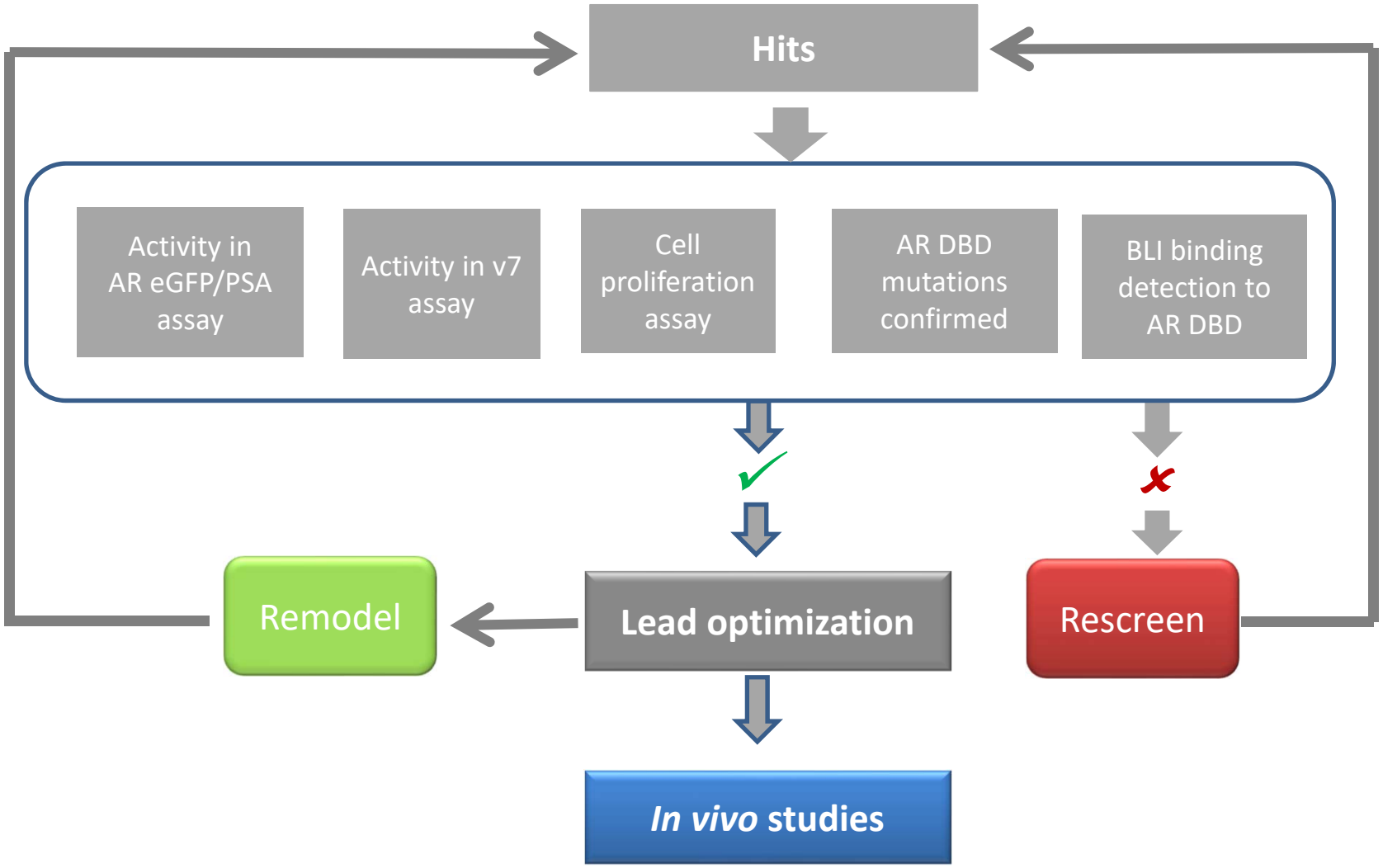
(Left) The effect of 14449 on the tumor volume of the Enzalutamide-resistant (MR49F) xenograft model.

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

Predicted Metabolic Liabilities of VPC-14449



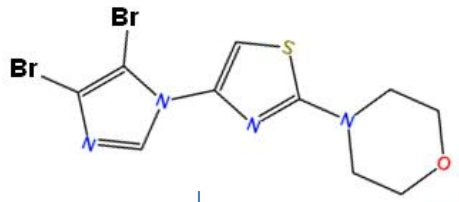
Iterative Screening Workflow



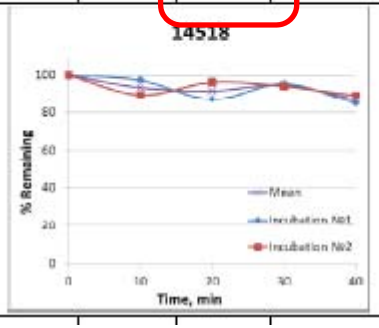
Lesson 6

Use the best practices and consensus scoring

Second Generation VPC-14518, Improved Stability and Potency

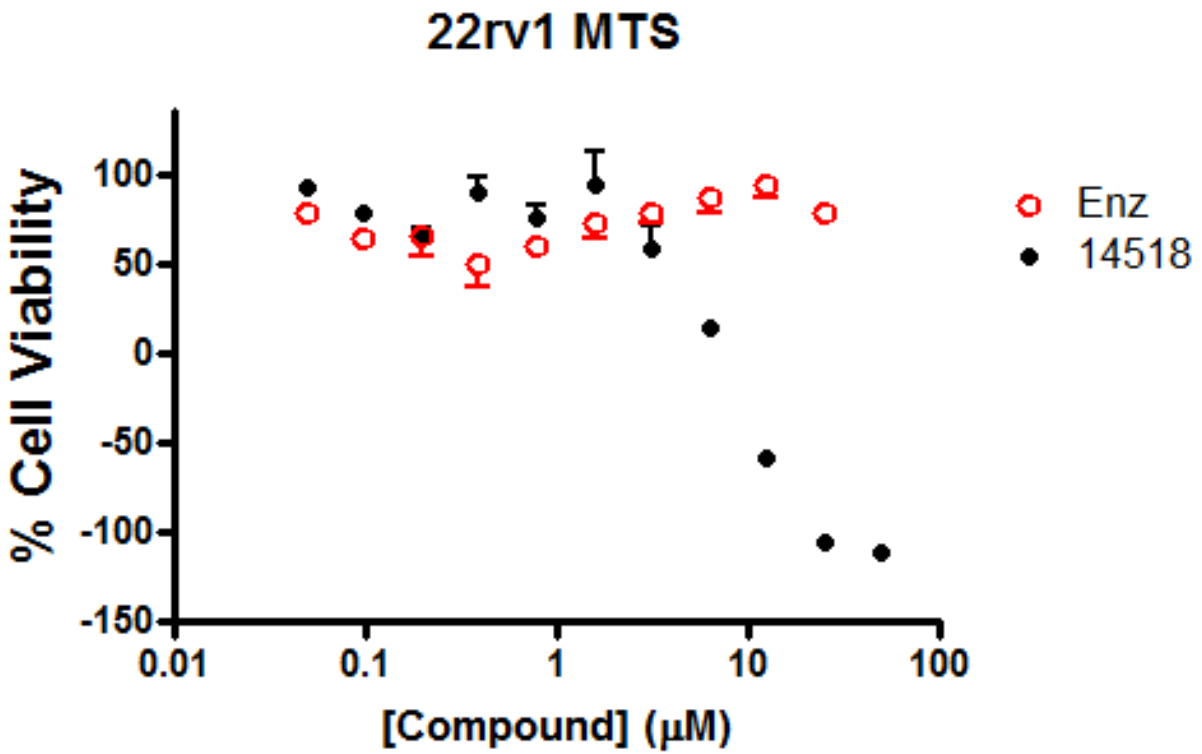


14512/14518

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



CONCLUSIONS

- → Know your target
- → Use diverse cheminfo methods
- → Analyse your hits, explore chemical space around them, combine structural elements, etc
- → Work with experimentalists closely during the screening
- → Validate your hits in details experimentally and ‘in silico’
- → Use the best practices and consensus scoring

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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

"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

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Dr. Raymond See
Nikolay Stoynov
Jihong Jiang
Sukhbir Kaur
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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)
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Dr. Takeshi Yamazaki (RA)
Dr. Michael Hsing (Post doc)
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Dr. Kush Dalal (Post doc)
Dr. Nada Lallous (Post doc)
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