Targeting Androgen Receptor with CADD

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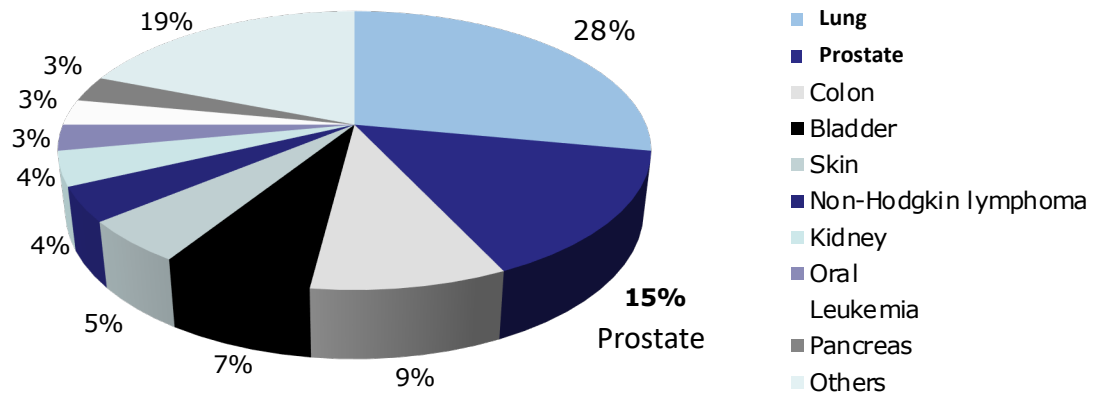
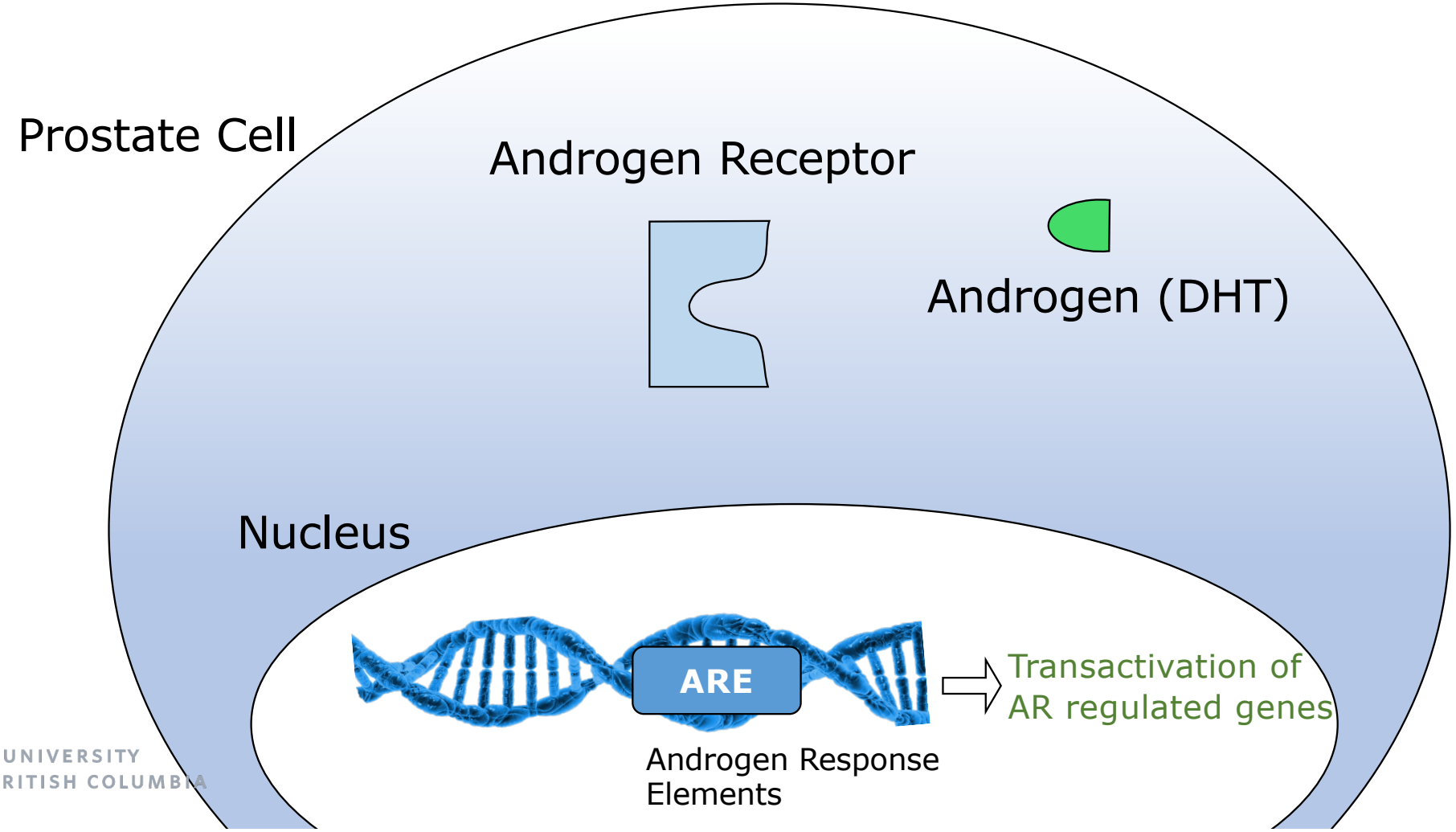
Prostate Cancer

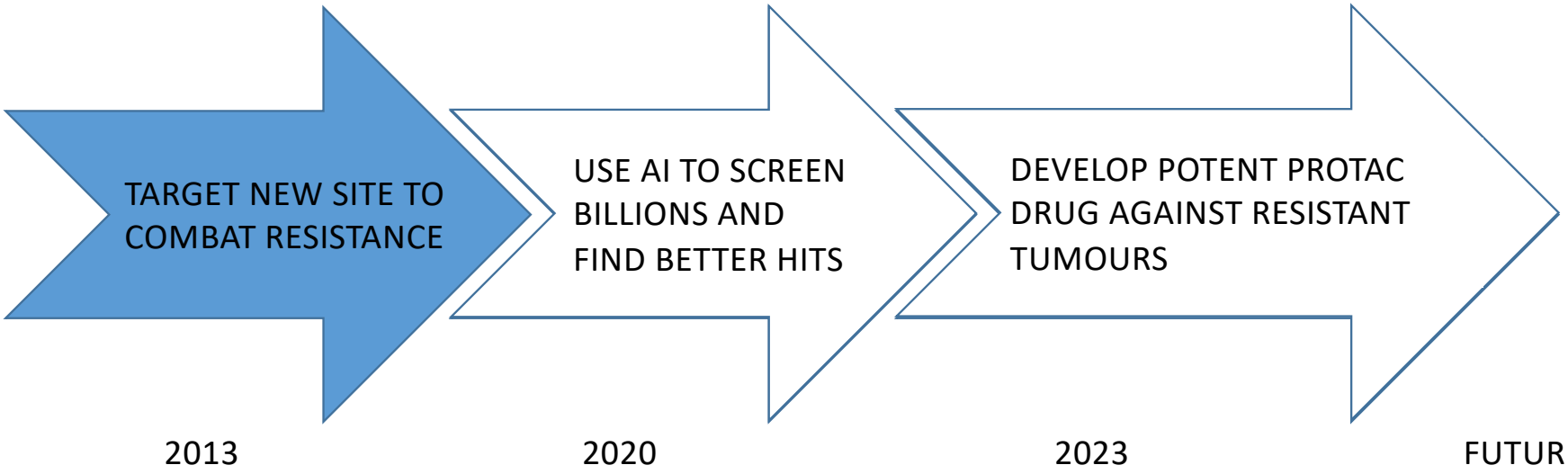
Estimated new cancer cases in males



Androgen Receptor (AR) - main driver of PC



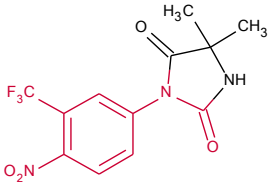
TARGETING AR JOURNEY



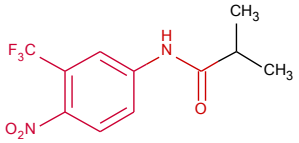
AR Inhibitors as Prostate Cancer Drugs

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

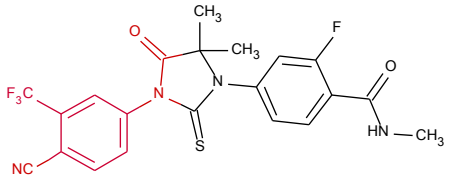
Nilutamide



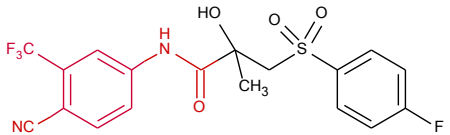
Flutamide



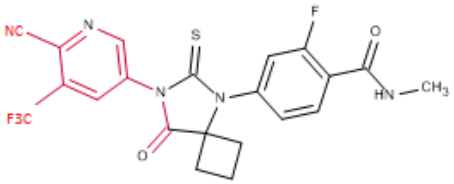
Enzalutamide (mdv3100)



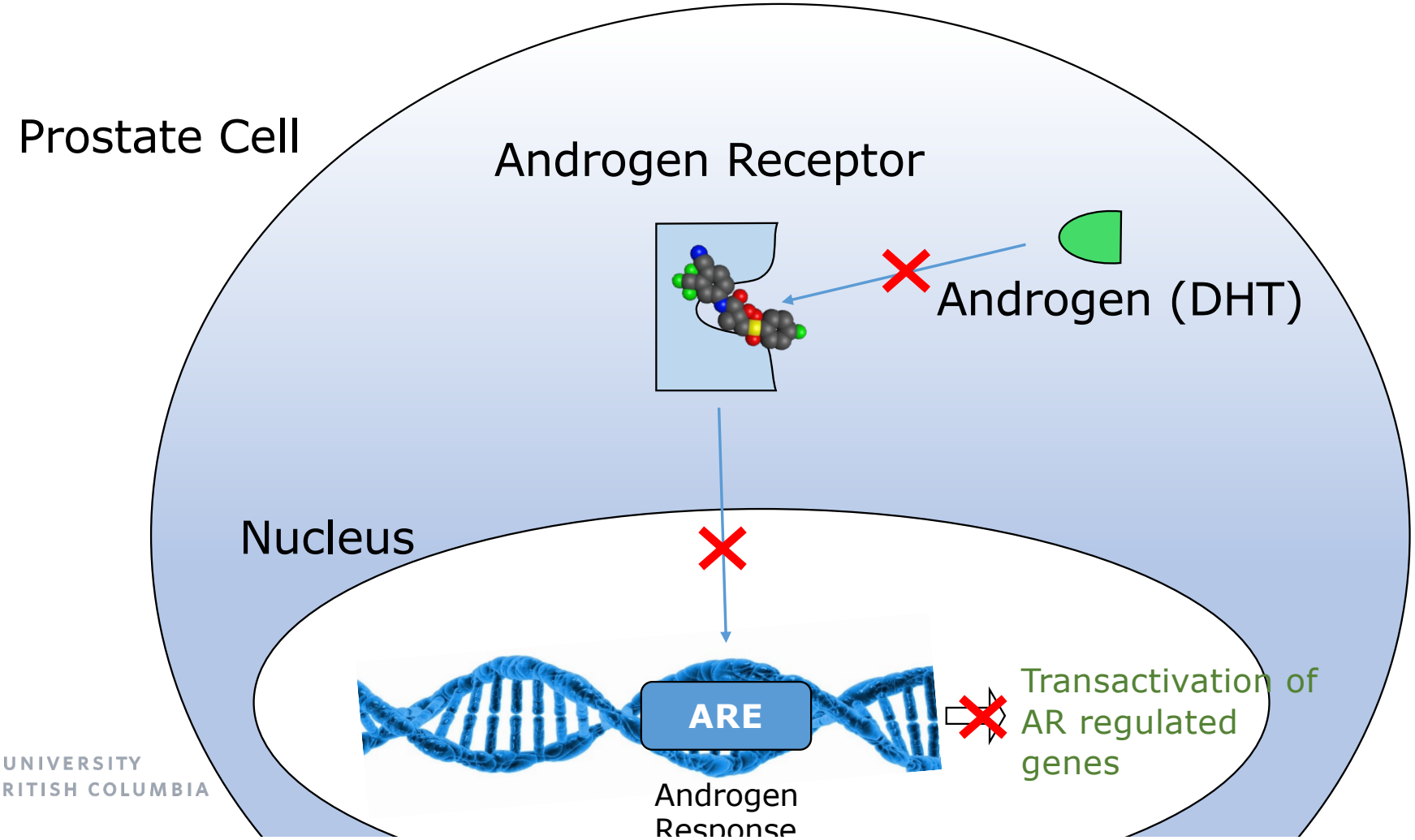
Bicalutamide



Apalutamide (arn-509)

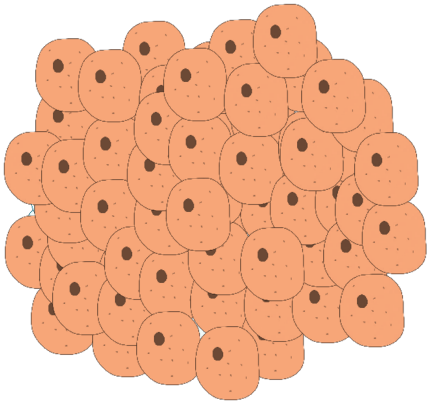


Current AR Inhibitors Mechanism of Action



Prostate Cancer Eventually Develops Drug Resistance

Mutation induced drug resistance

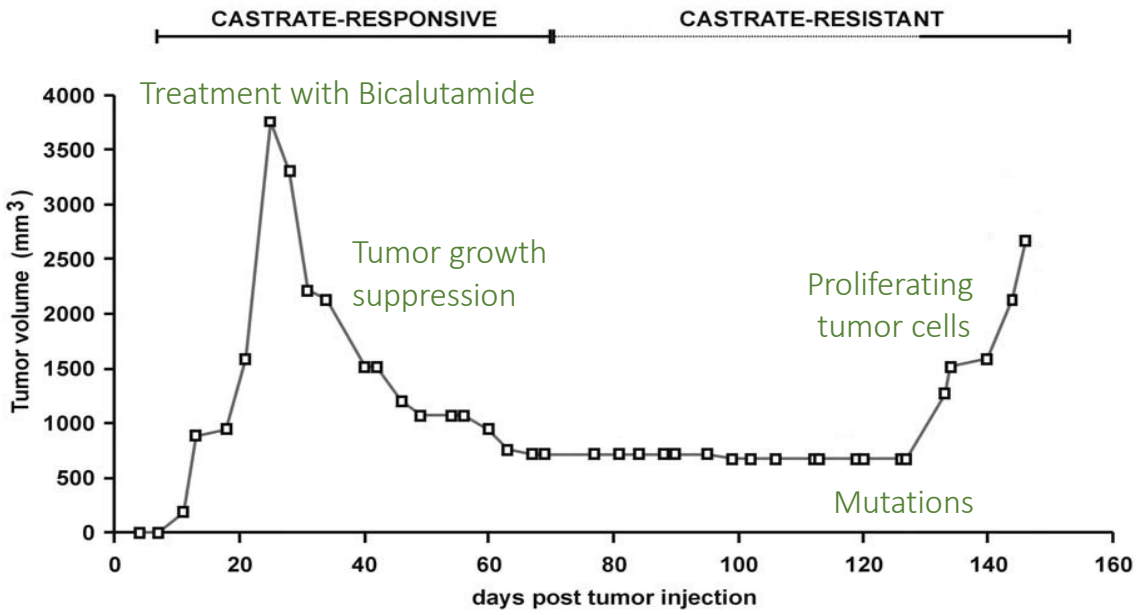


Tumor

Highly malignant treatment resistance cancer

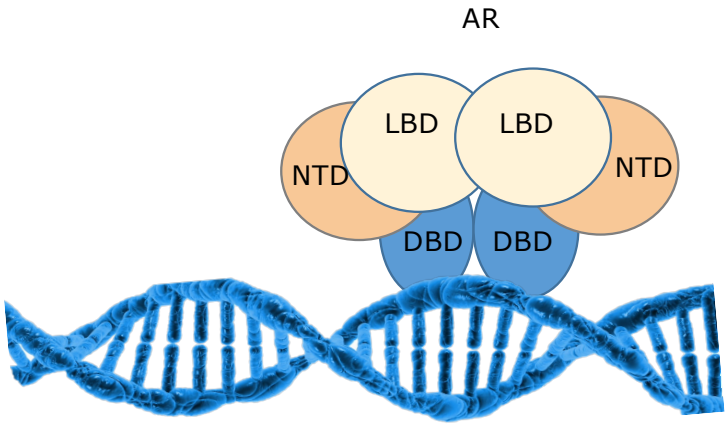
Factors that Causes Resistance to Anti-AR Drugs

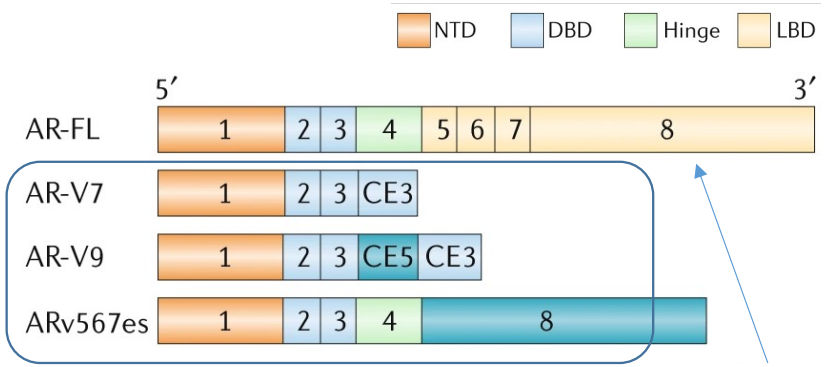
Mutations in the LBD hamper the efficacy of known anti-androgens



Scher et al. Endocrine-Related Cancer 2004

Targeting AR DNA-binding domain





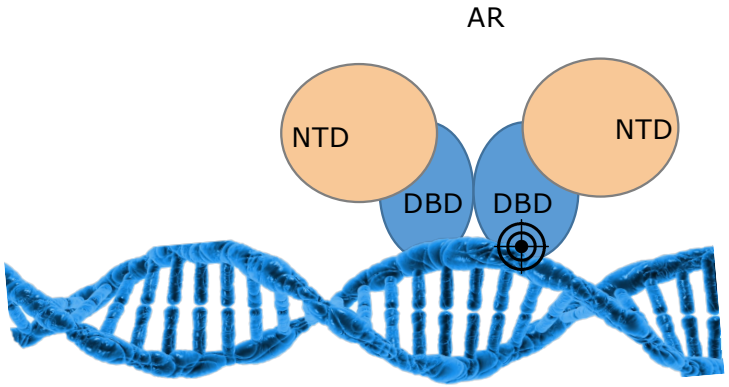
All current drugs target ligand binding domain (LBD)

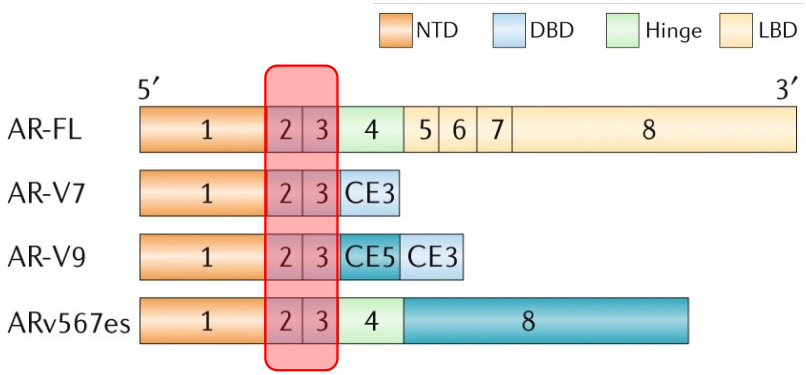
Two problems:

- Mutations within LBD lead to drug resistance
- Advanced PC expresses truncated forms of AR completely lacking the LBD

THERE IS A NEED FOR DRUGS WITH A NEW MODE OF ACTION

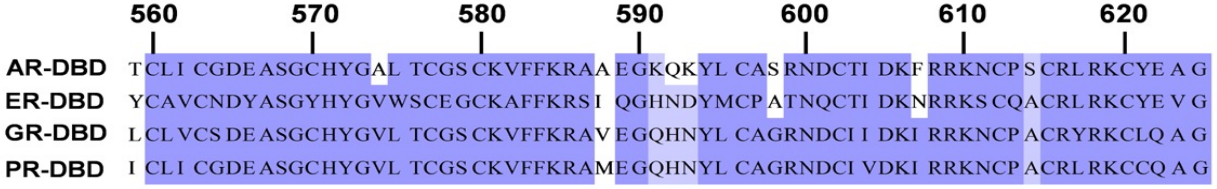
Targeting AR at the DNA binding domain



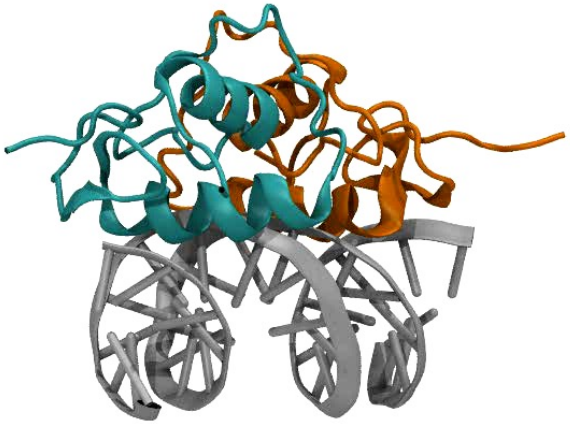


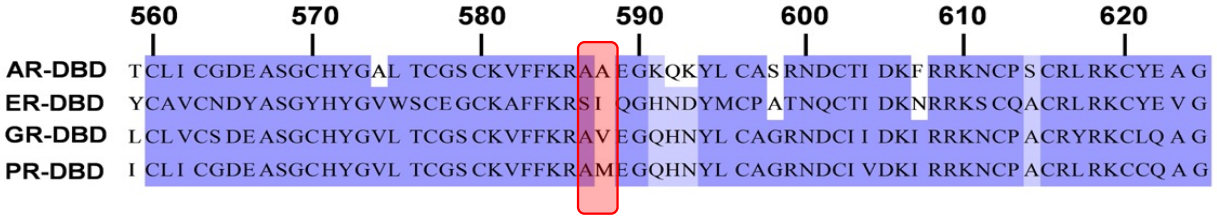
Why don't we target DBD directly?

Previously was deemed impossible due to high conservation with other receptors



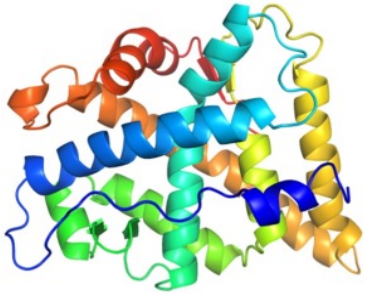
Using CADD to develop a selective drug



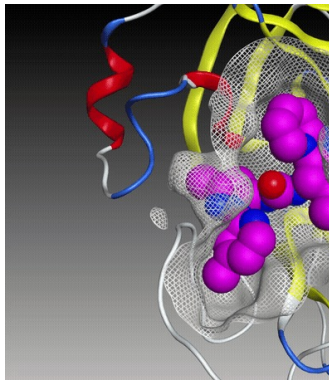


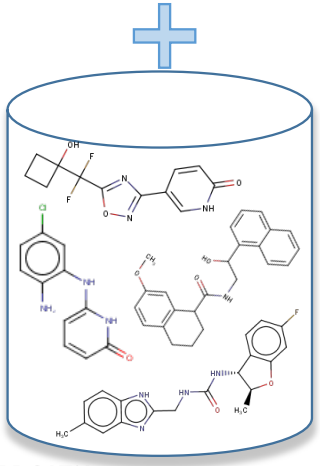
In Silico Screening Work

Protein structure



Molecular do





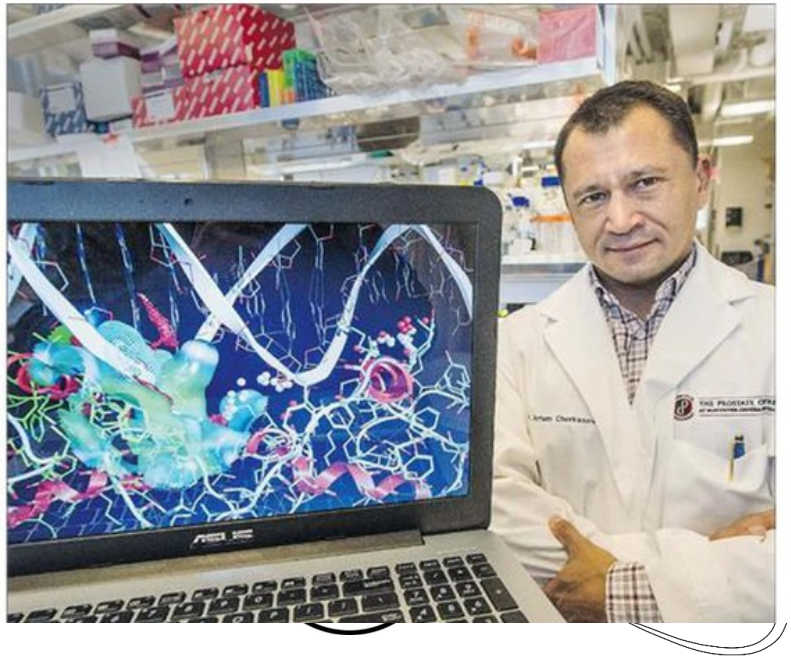
SMALL MOLECULE DATABASE

VANCOUVER SUN

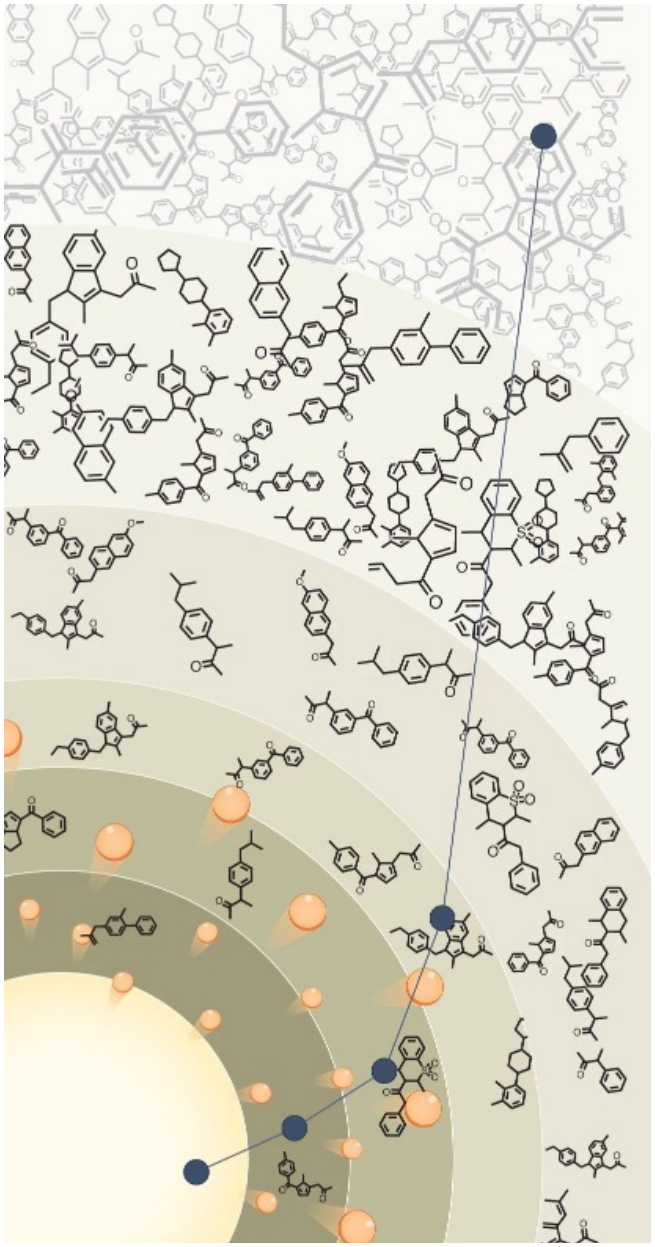
Massive cancer-drug deal one of UBC's biggest to date

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.

Randy Shore
Dec 16, 2015 • December 16, 2015 • 3 minute read



THE UNIVERSITY OF BRITISH COLUMBIA

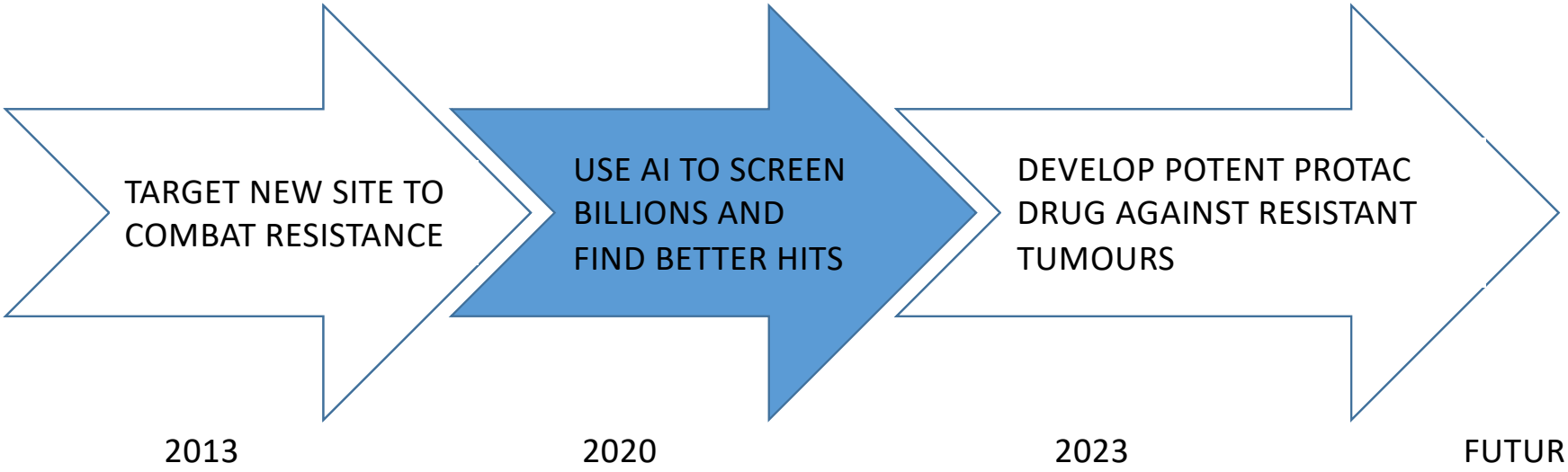


Googol?

37,000,000,000	2022
1,400,000,000	2020
220,000,000	2015
3.400,000	2012
727,842	2004

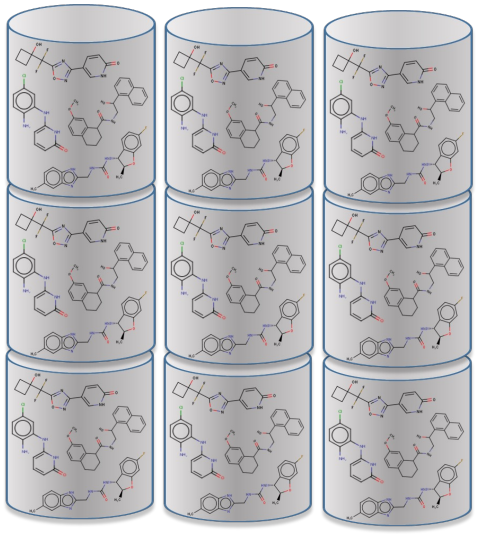
The ‘Big Bang’ of the chemical universe

TARGETING AR JOURNEY

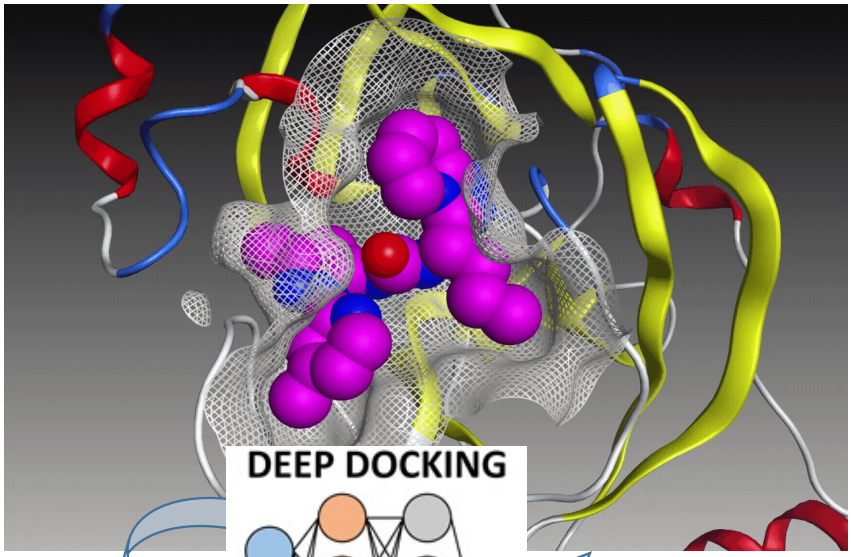


How we find drug candidates today?

TARGET PROTEIN/TARGET SITE



37 BILLION
MOLECULES



Predict docking
scores with AI models

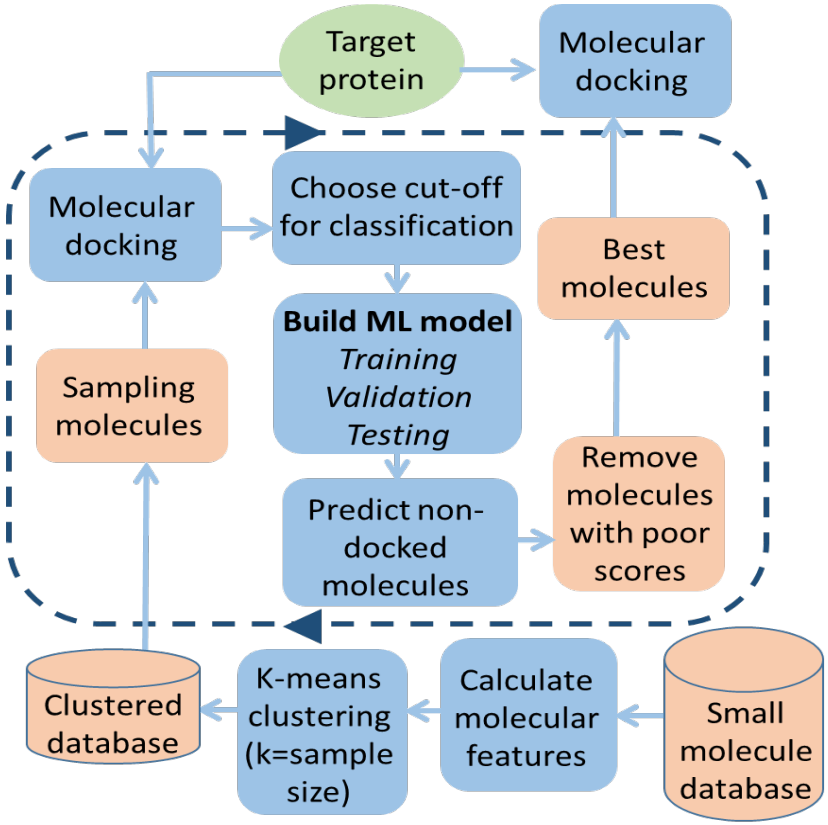
100s X
FASTER

DRUG
CANDIDATES

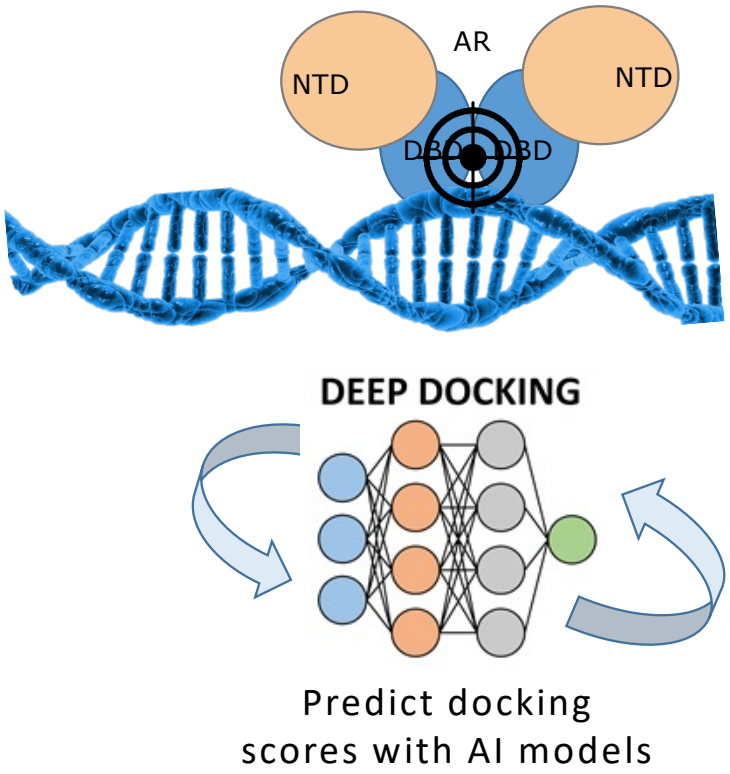
DeepDocking workflow

Accelerates docking up to x50 times

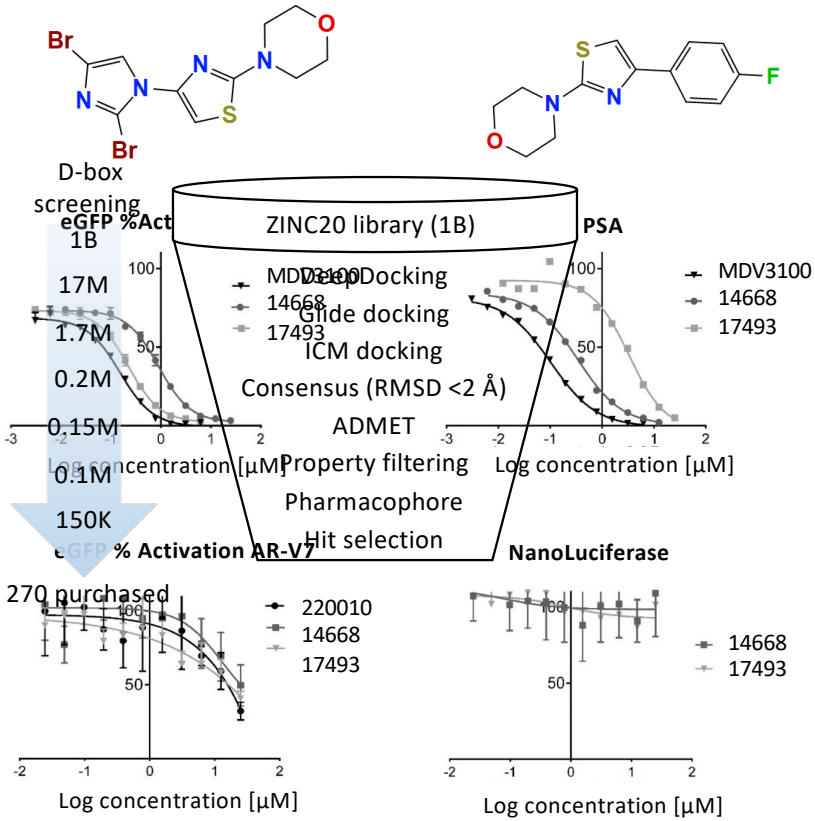
1. Dock a sample of the database
2. Build a prediction model using the docked compounds
3. Predict docking scores of undocked compounds
4. Discard compounds with poor predicted docking scores



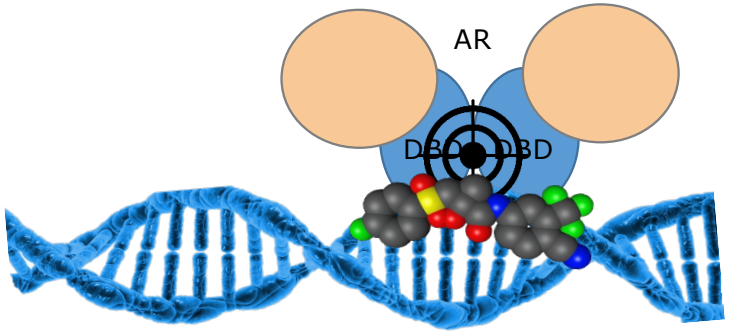
Identification of new AR drug candidates



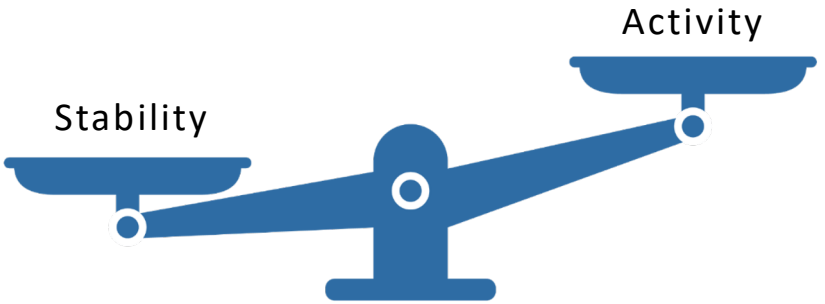
DRUG CANDIDATES



Problems with targeting AR DBD

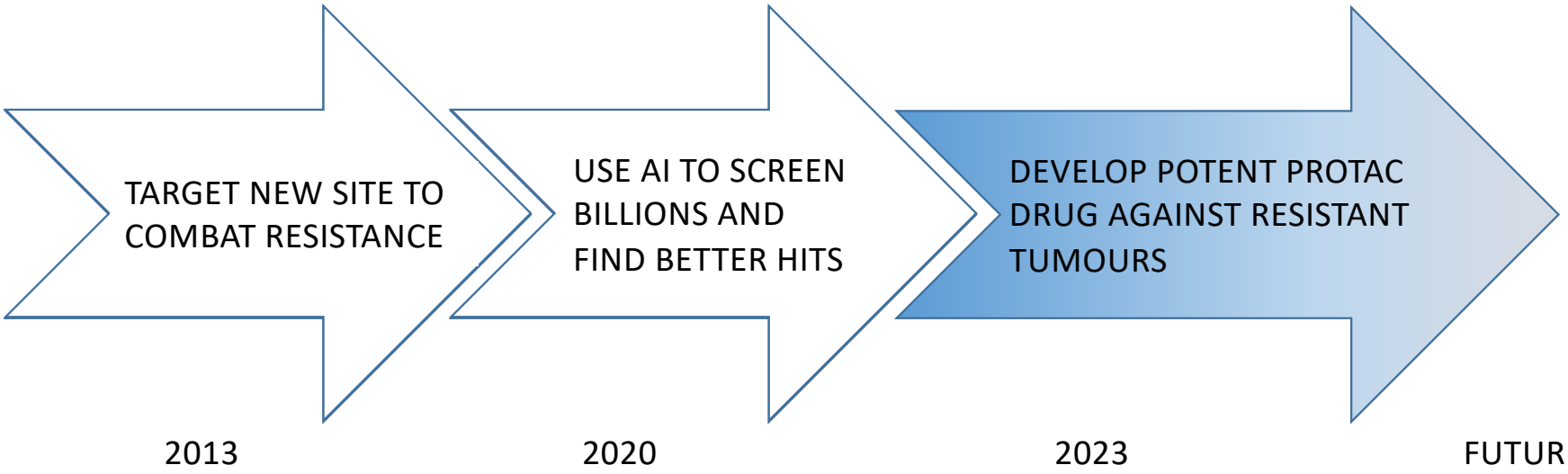


Molecules compete with a big molecule - DNA

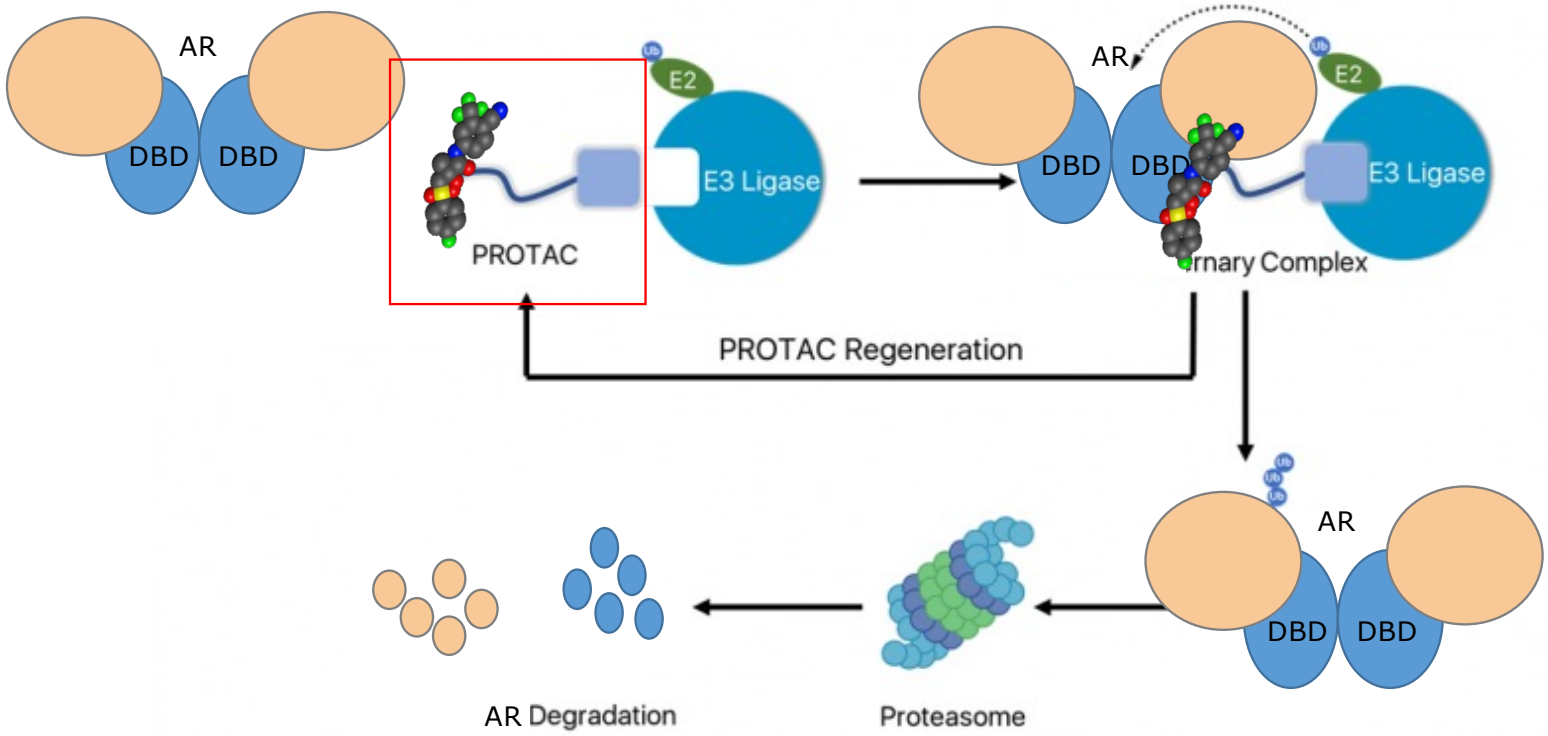


Difficult to optimize for both - activity and stability

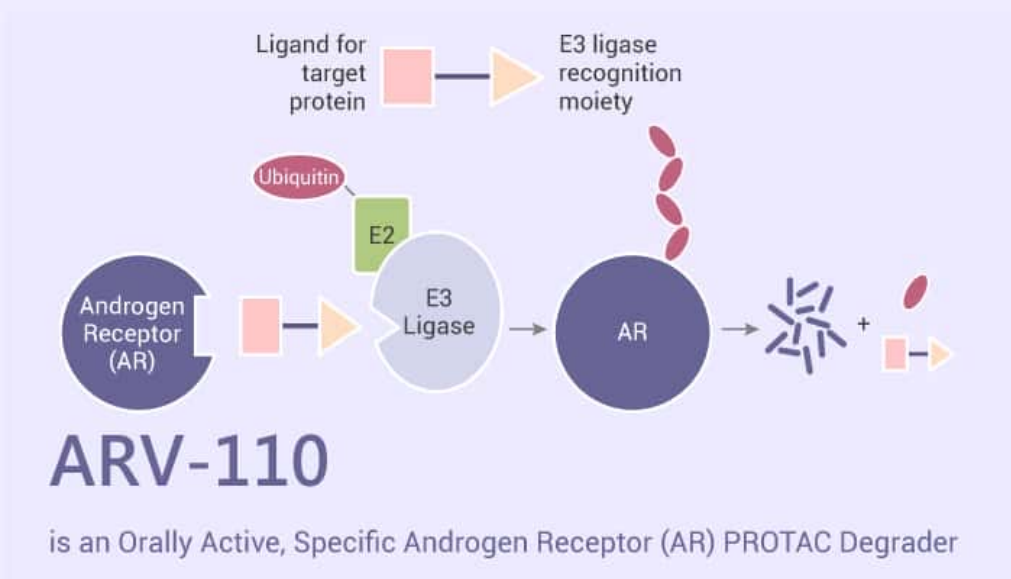
TARGETING AR JOURNEY

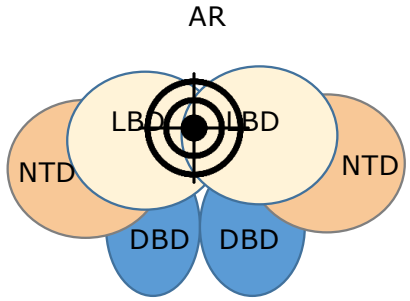


New strategy – AR DBD PROTAC



Existing AR PROTAC

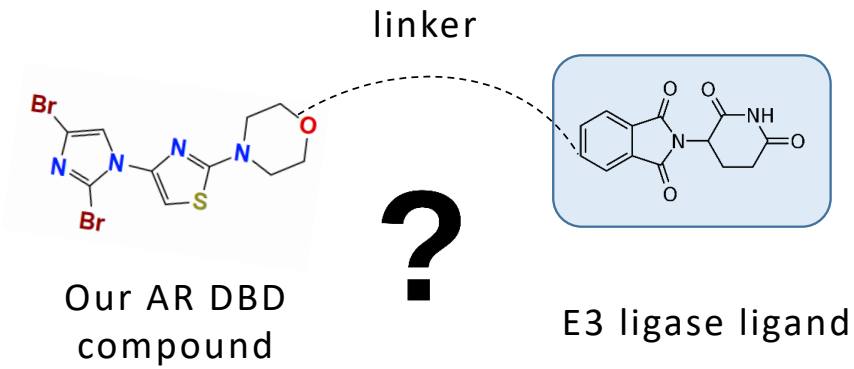




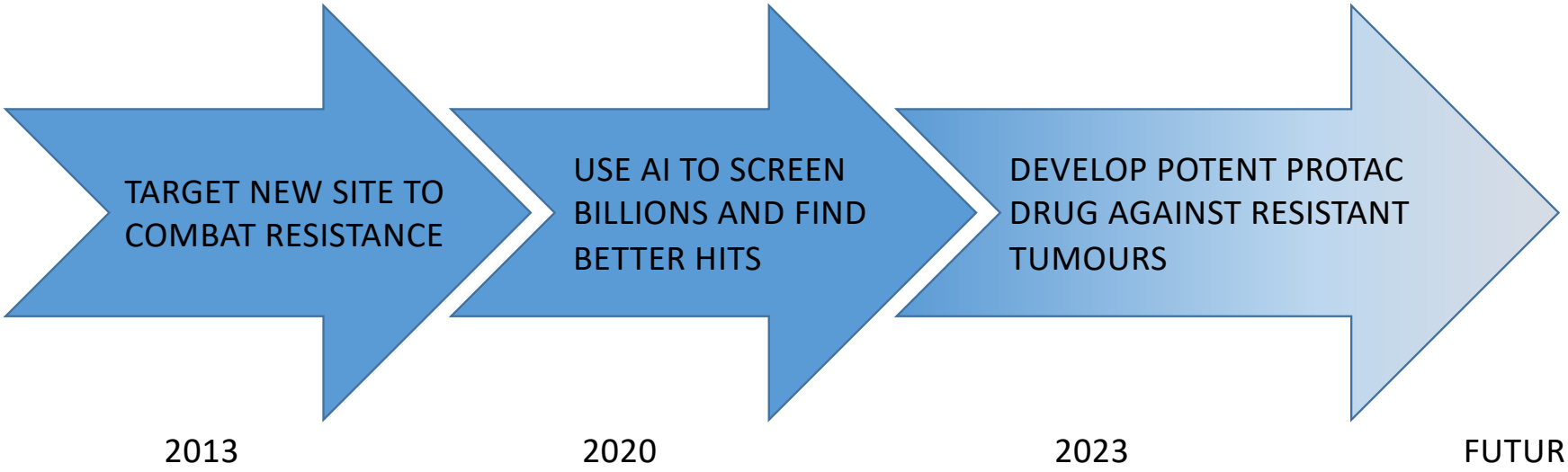
This drug targets LBD!
Ineffective against truncated forms of AR

Arvinas PROTAC® Protein Degrader Bavdegalutamide (ARV-110) Continues to Demonstrate Clinical Benefit in Men with Metastatic Castration-Resistant Prostate Cancer
Currently in Phase II Clinical Trials

Current direction – development of a selective and potent PROTAC



Developing candidate PROTAC molecule using computational modeling


TARGET NEW SITE TO COMBAT RESISTANCE
USE AI TO SCREEN BILLIONS AND FIND BETTER HITS
DEVELOP POTENT PROTAC DRUG AGAINST RESISTANT TUMOURS
2013
2020
2023
FUTURE

THANK YOU!