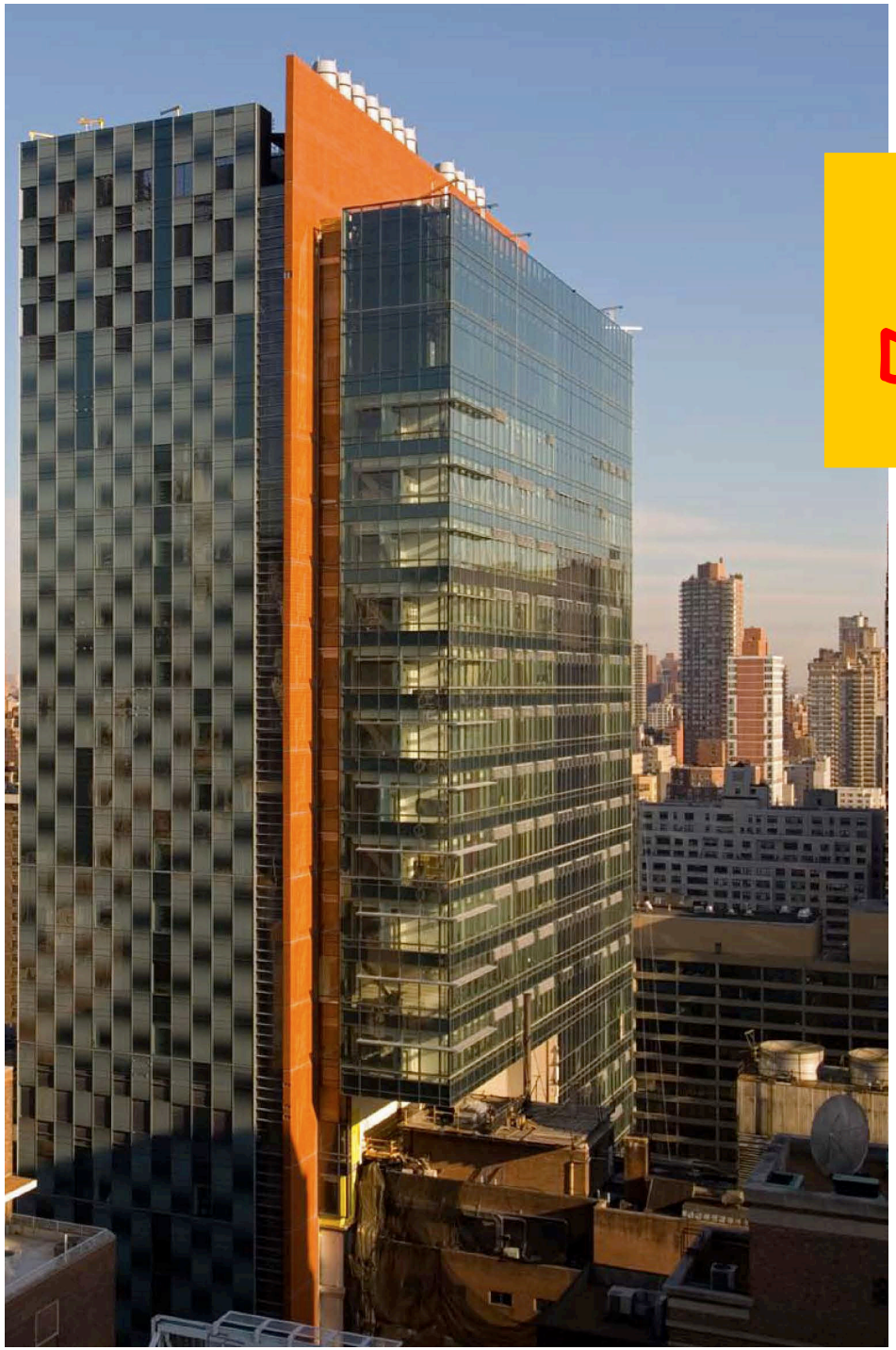


Challenges to Drug Development in Academia

Charles L. Sawyers, M.D.

Chair, Human Oncology and Pathogenesis Program (HOPP)

Investigator, Howard Hughes Medical Institute

Memorial Sloan-Kettering Cancer Center; New York, NY

Disclosure

I am a co-inventor of the drug MDV3100, now in a phase III clinical trial in prostate cancer, and I own stock in the company Medivation.

Two translational tales

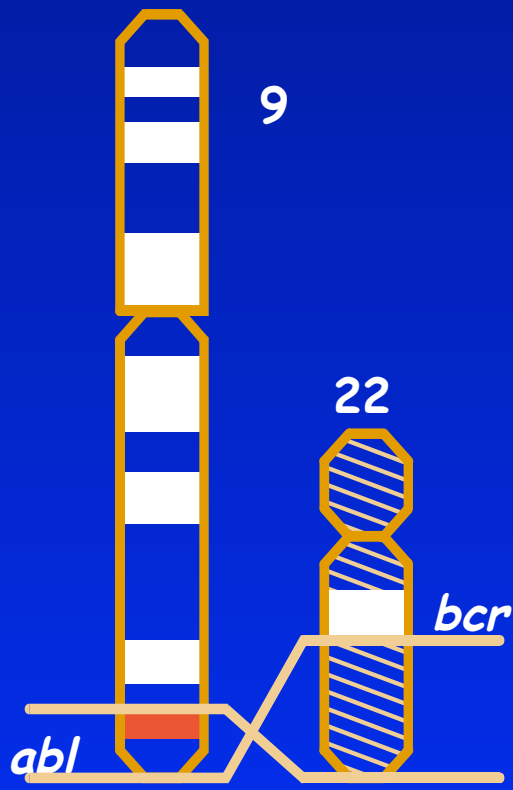
1) Dasatinib (Sprycel) in chronic myeloid leukemia:

   serendipitous marriage of a discovery in academia that reshaped a pharma-driven drug development program

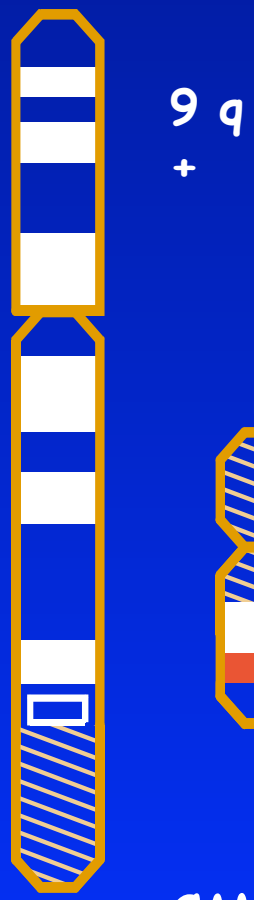
2) MDV3100 in prostate cancer:

   academia-based target validation and drug screening project that resulted in a biotech/pharma licensing deal for clinical development

The Ph Chromosome: t(9;22) Translocation



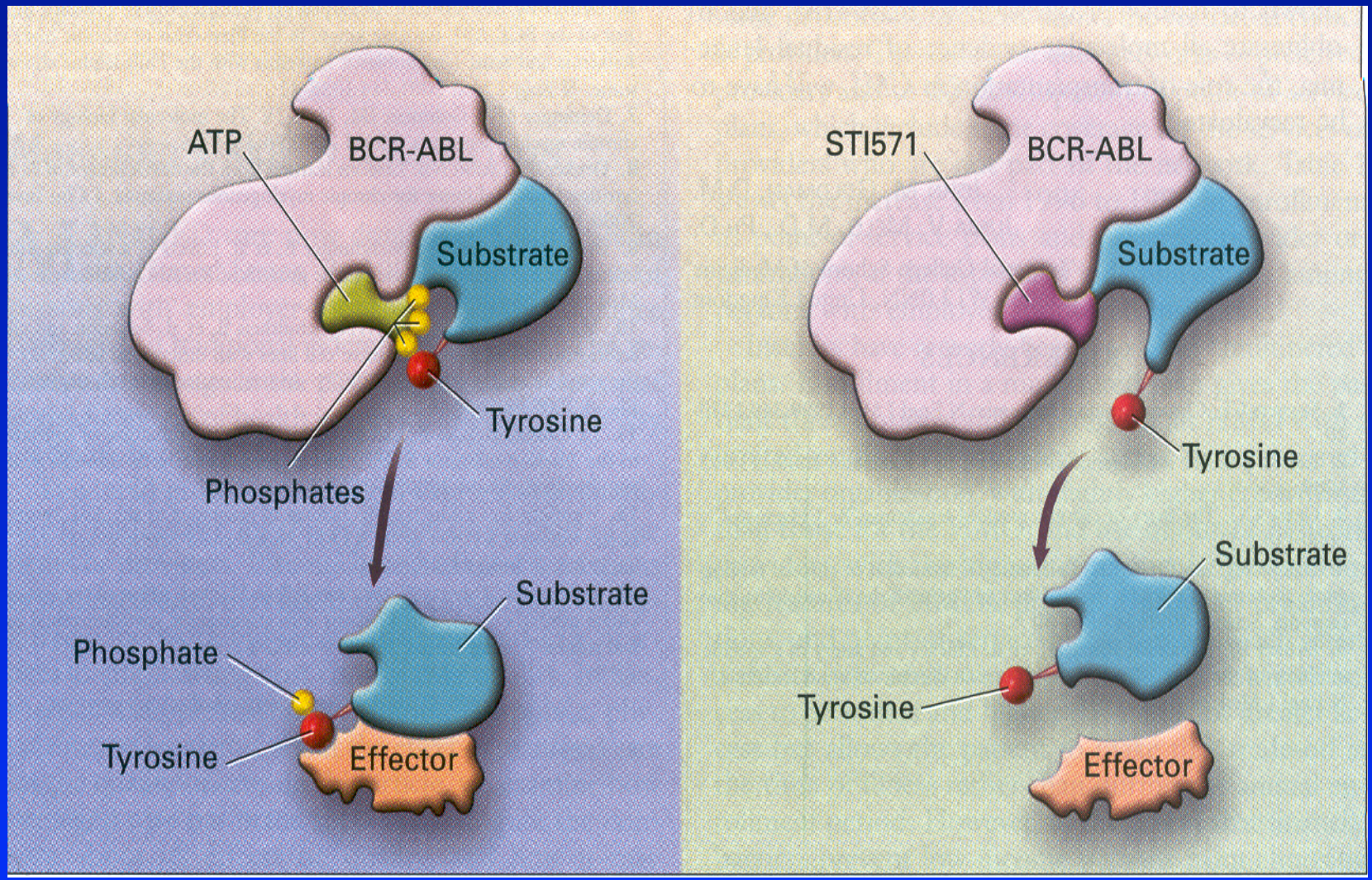
Normal



CML

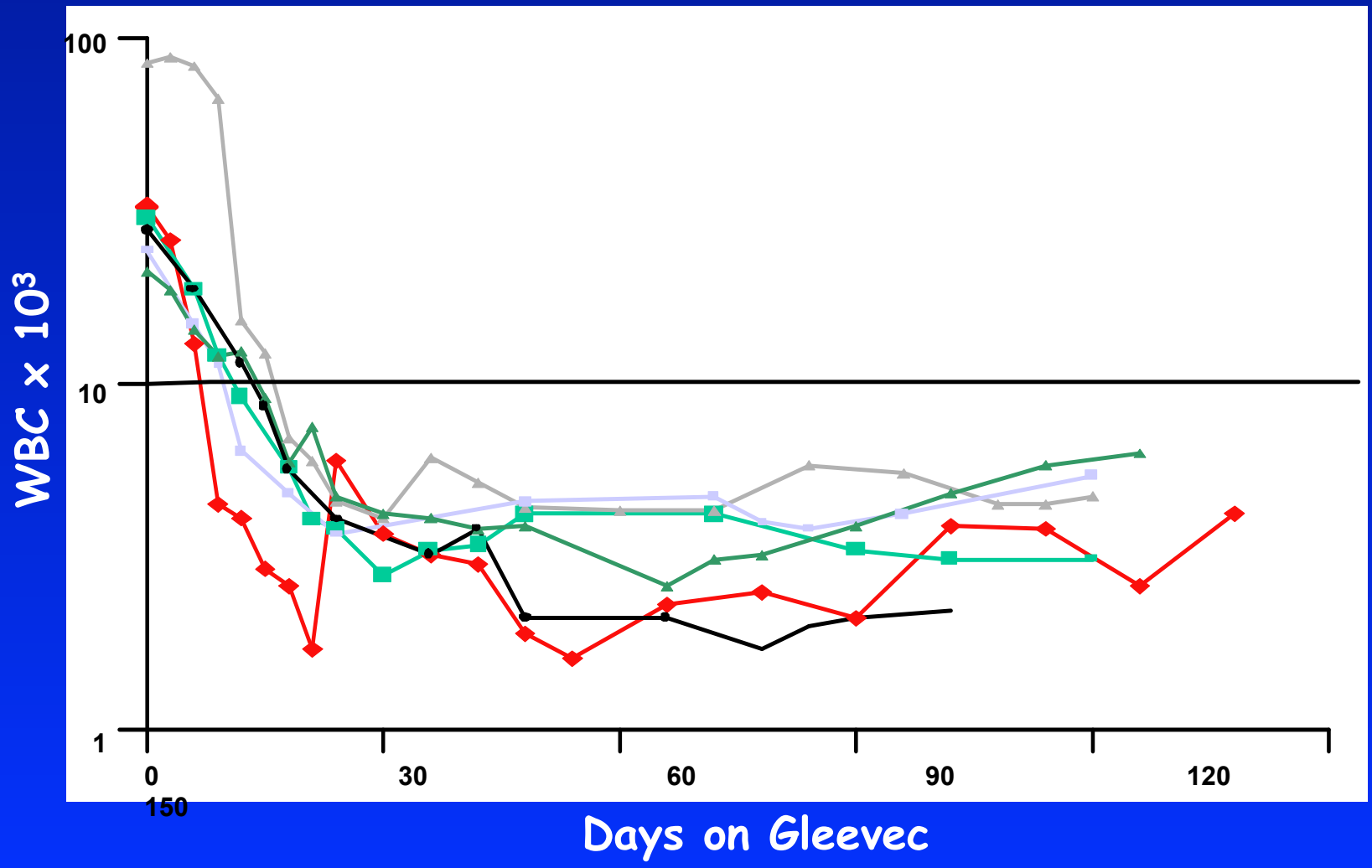
FUSION PROTEIN WITH TYROSINE KINASE ACTIVITY

Imatinib/STI571 (Gleevec) blocks BCR-ABL



Goldman JM, Melo JV. *NEJM*. 344:1084-1086

Blood counts of the first 6 patients who took 300 mg/day of Gleevec



Gleevec is not a cure:

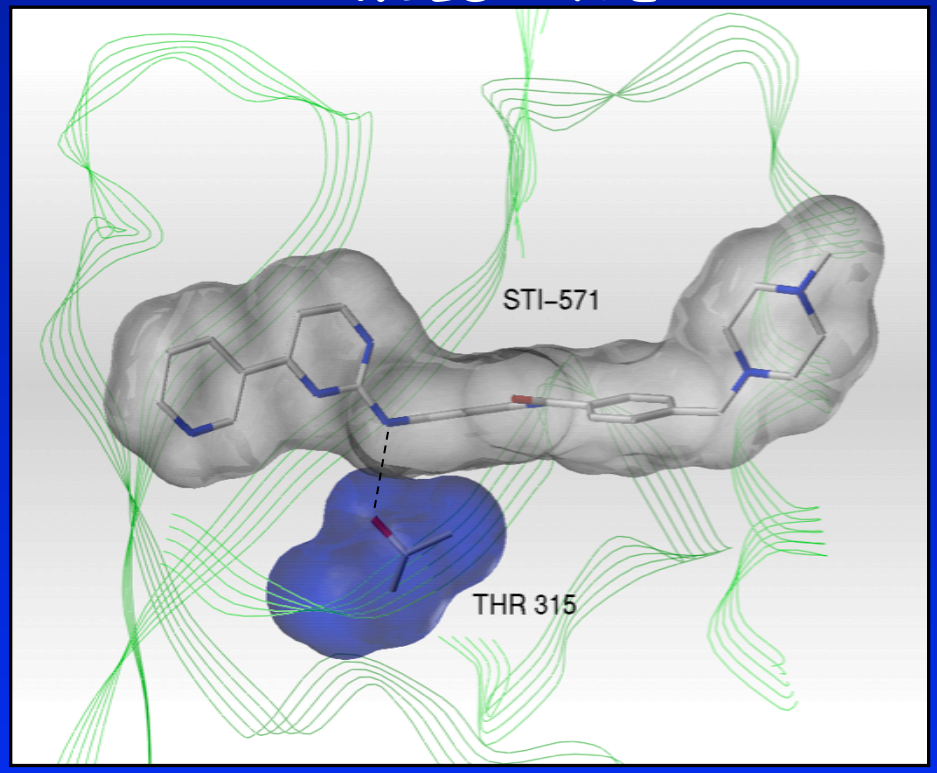
Small numbers of CML cells are detected in patients who are in “remission.”

Patients can relapse while taking Gleevec.

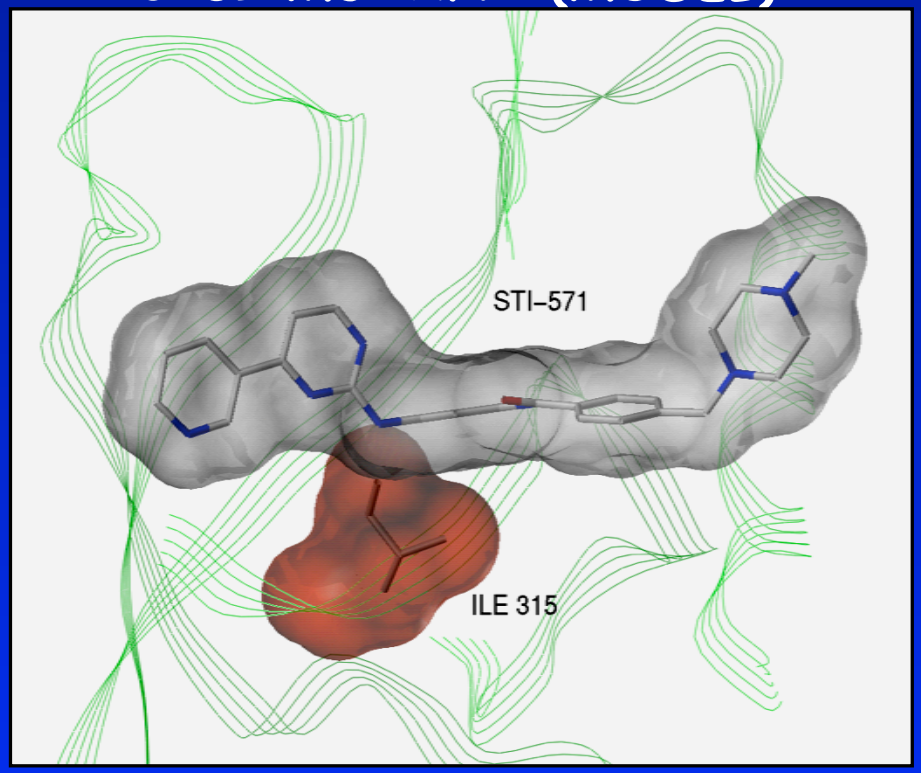
Why?

A mutation isolated from patients who relapse on Gleevec blocks drug binding to BCR-ABL

WILD-TYPE

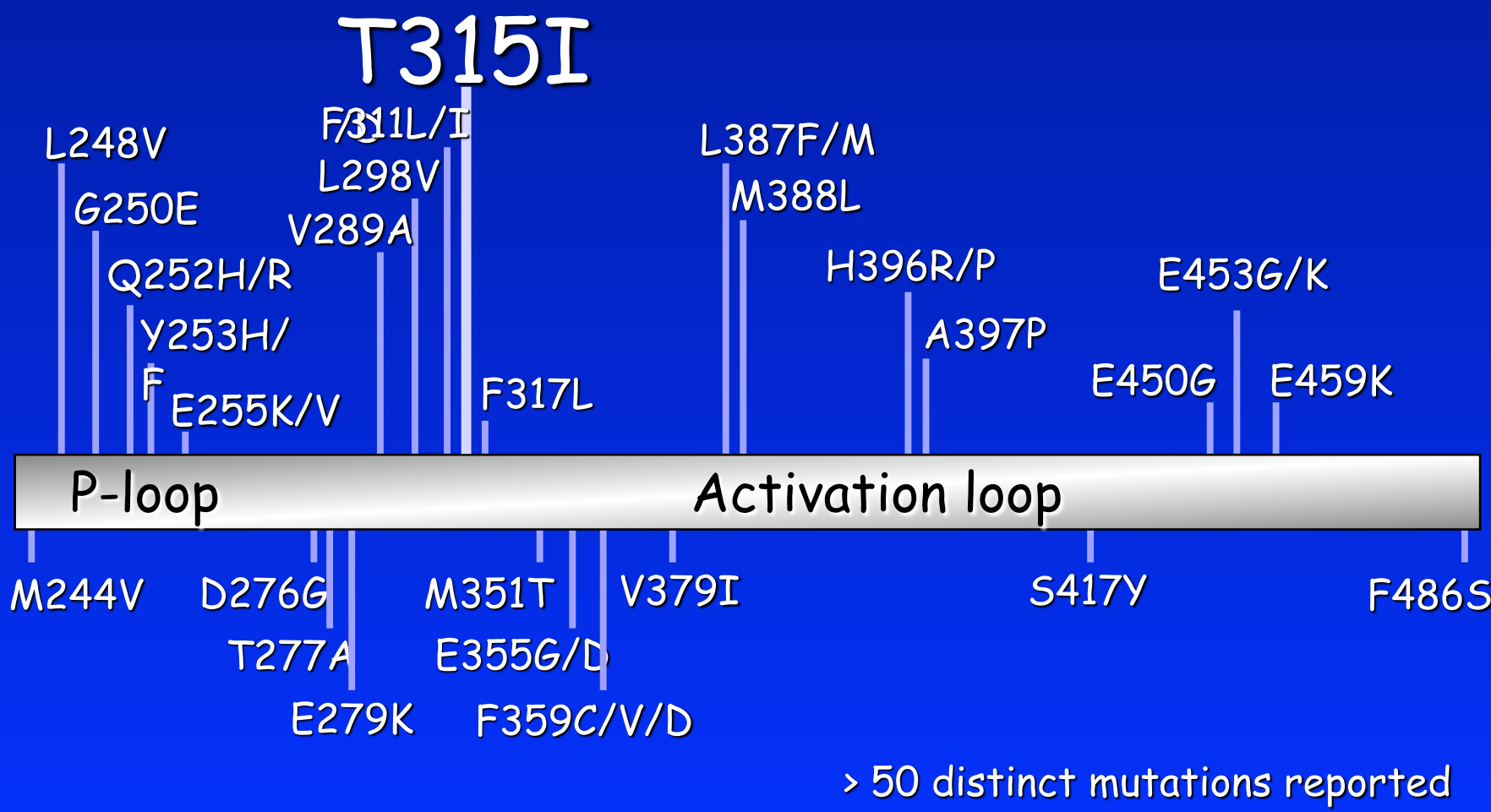


T315I MUTANT (MODEL)



(Gorre et al Science, 2001)

BCR-ABL Kinase Domain Mutations Associated with Imatinib Resistance

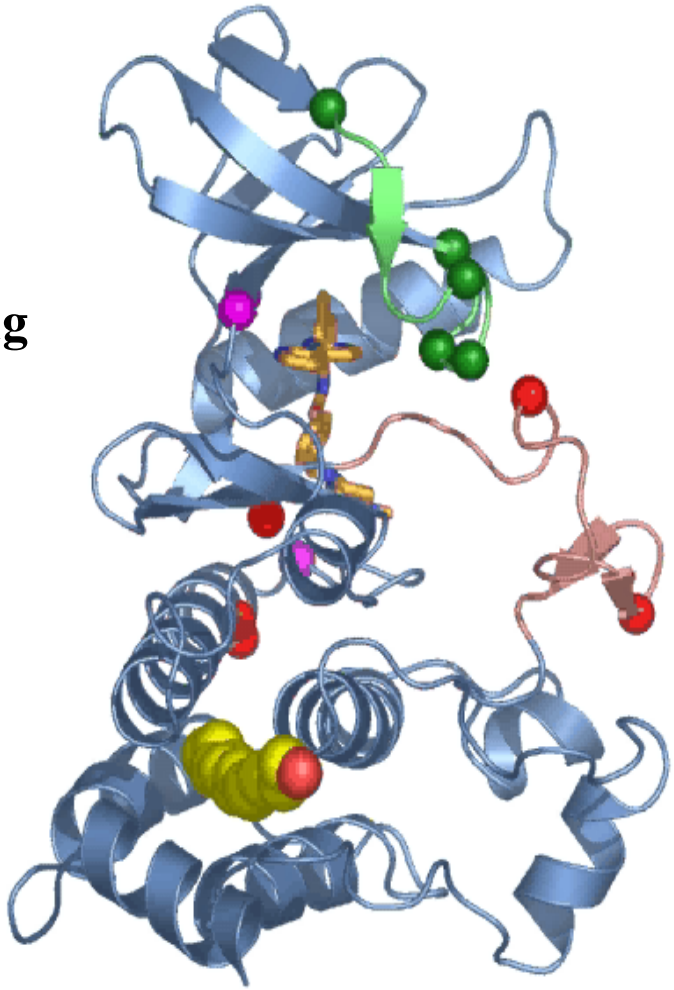


> 50 distinct mutations reported

Imatinib resistance mutations impair conformational flexibility of the ABL kinase

Location of Mutations

- **P loop**
- **Direct contact with drug**
- **hinge**



John Kuriyan, Bhushan Nagar (UC-Berkeley)

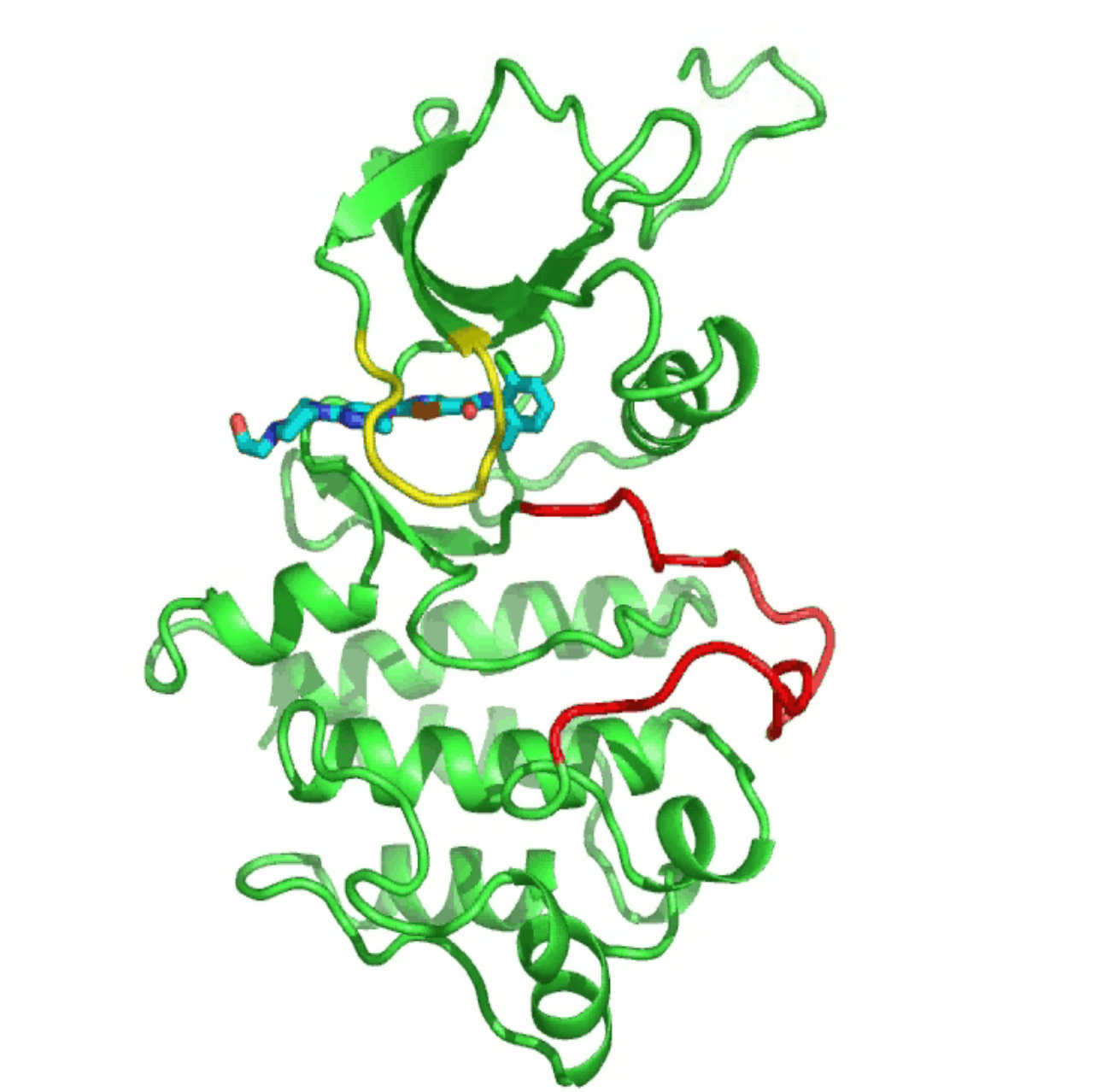
How do we deal with resistance?

Problem: Over 50 different mutations can cause resistance to Gleevec

Structural biology prediction: Mutations change the shape of BCR-ABL so that it favors the “open” conformation.

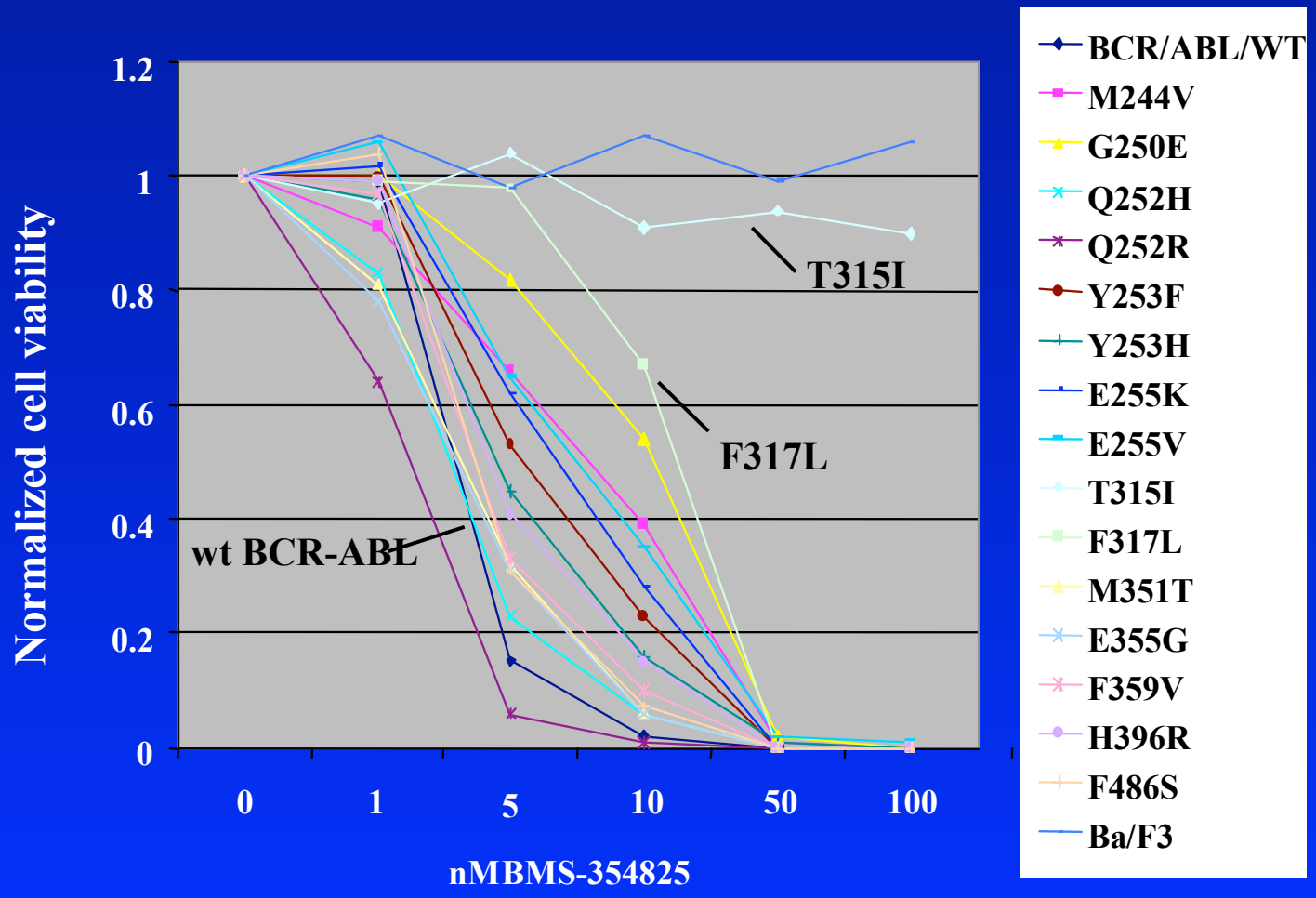
Solution: Drugs that target the “open” conformation should work in patients with Gleevec resistance.

Dasatinib



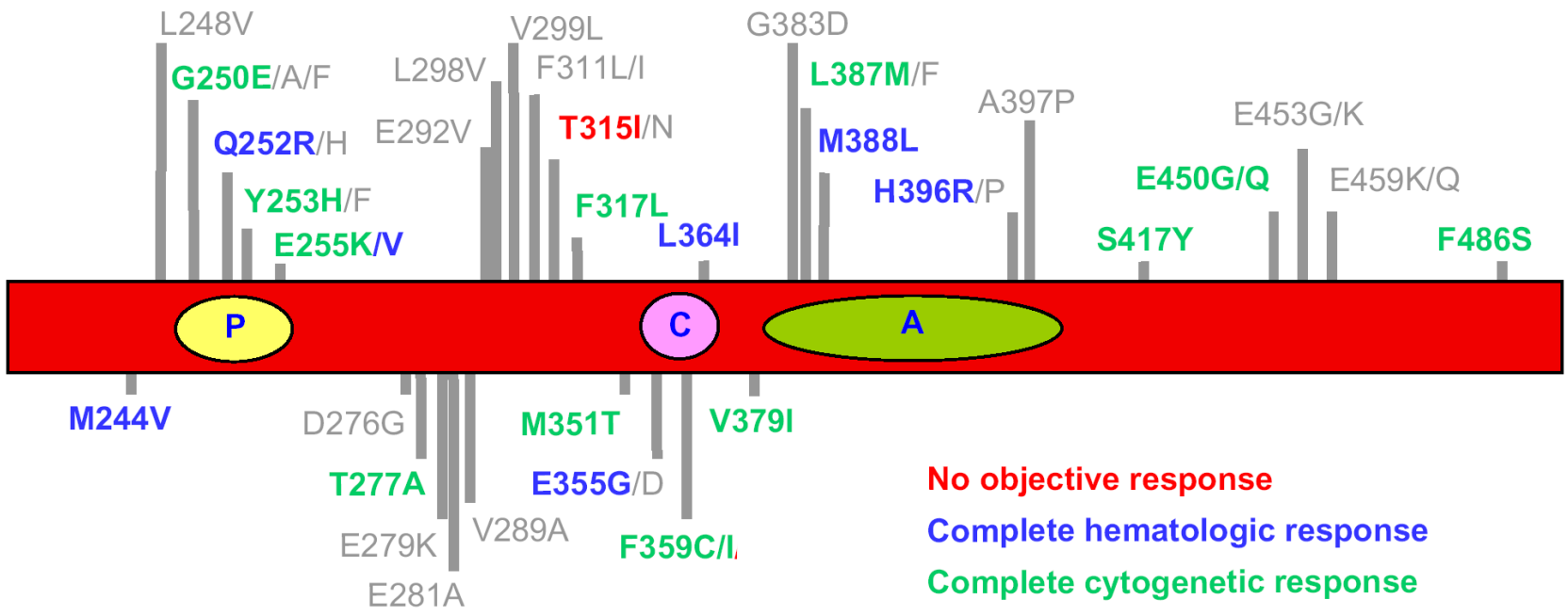
Gleevec

The SRC/ABL inhibitor dasatinib (BMS-354825) is active against all but one of the known mutations in BCR-ABL that confer imatinib resistance



Shah et al Science, 2004

BCR-ABL genotype predicts clinical response to dasatinib



Talpaz ….Sawyers, NEJM, 2006

Chronic Myeloid Leukemia: 2010

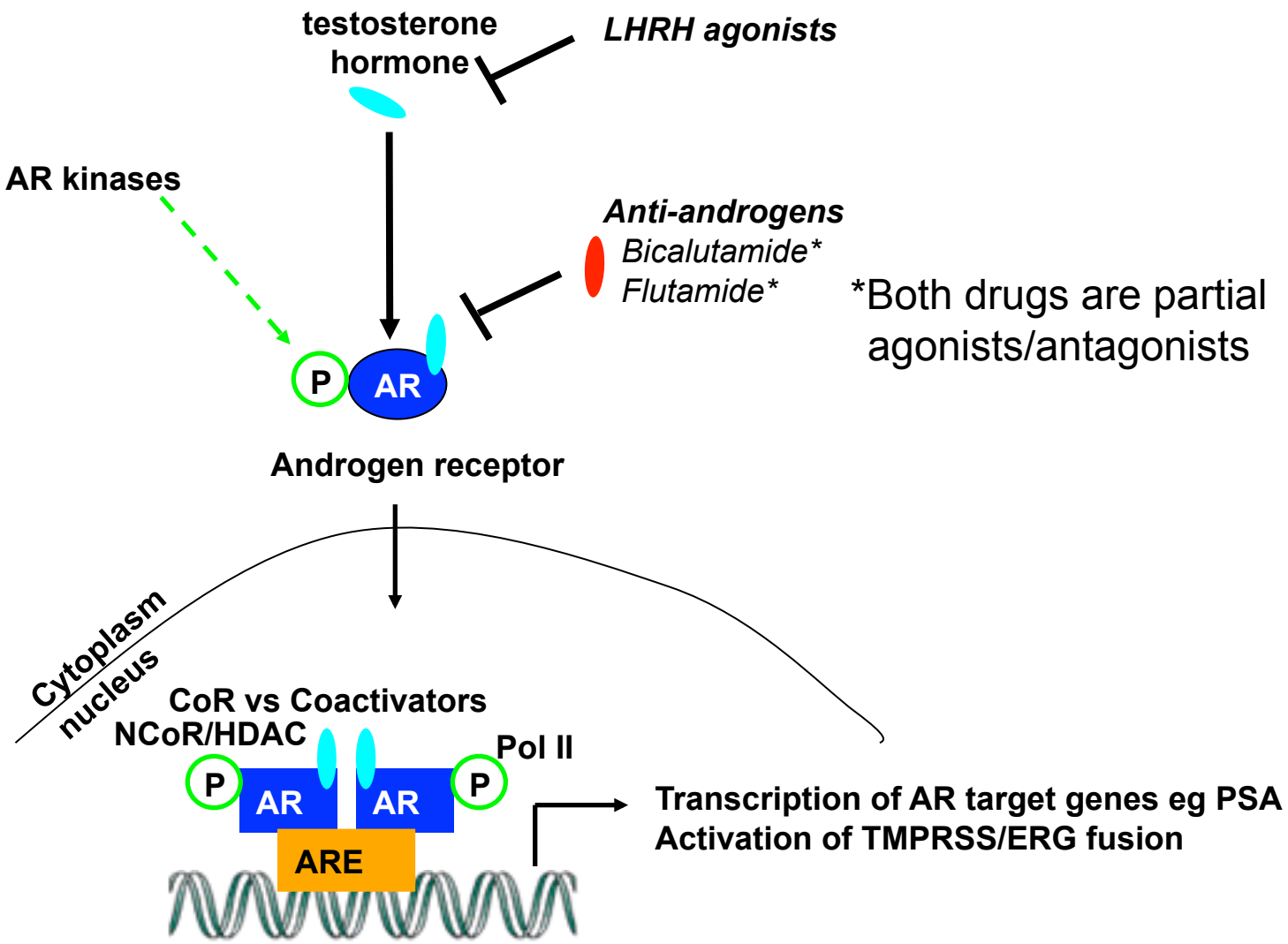
1) Imatinib has been frontline CML therapy

-75% of patients achieve complete cytogenetic response
-20% relapse within 5 years, usually with mutant BCR-ABL

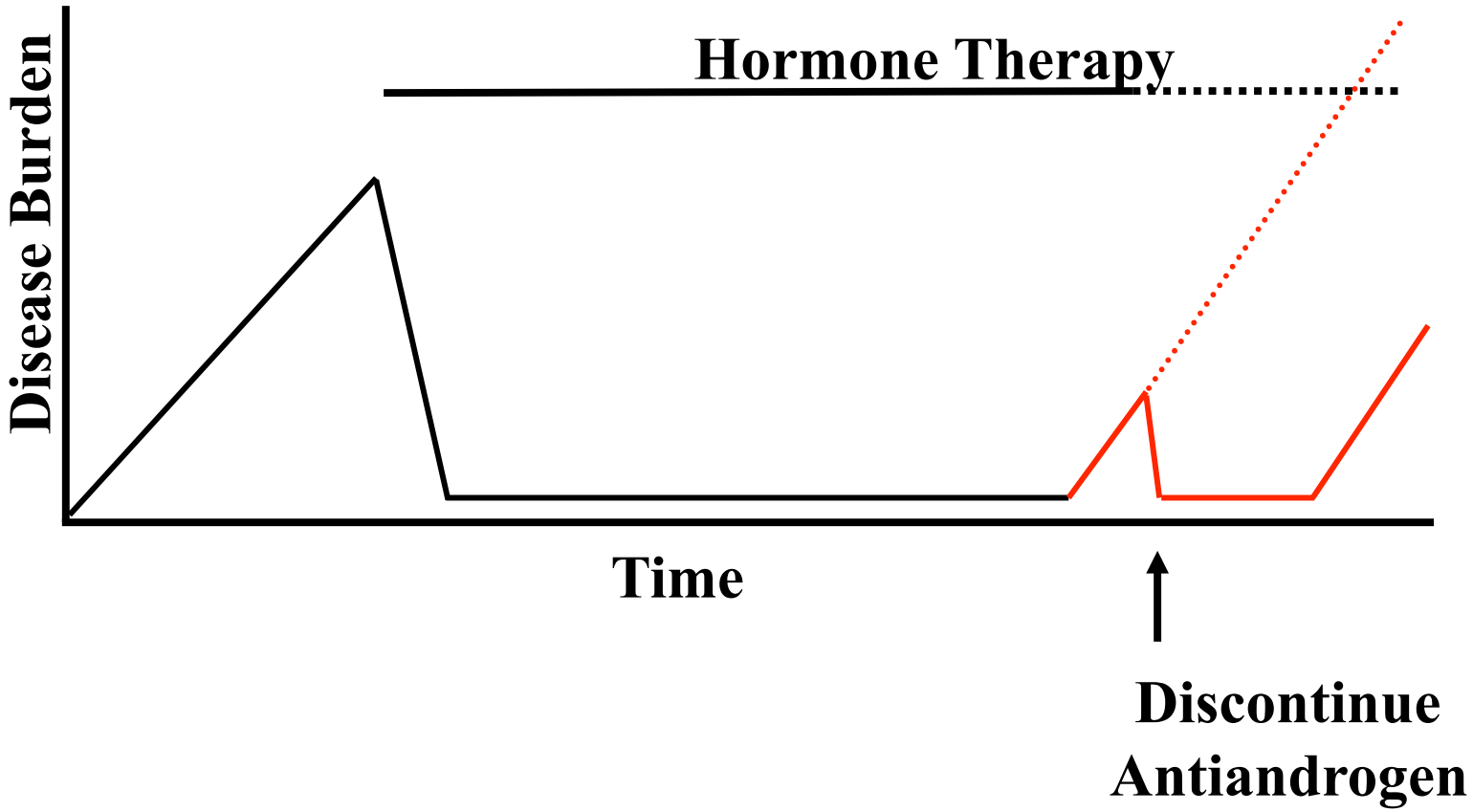
2) Dasatinib and nilotinib were initially approved as 2nd line therapy for imatinib-resistant CML (2006, 2007)

3) Upfront comparisons show than 2nd generation compounds are superior to imatinib
(Kantarjian et al NEJM 2010; Saglio et al NEJM 2010)

Inhibition of androgen receptor (AR) signaling



Typical Response to Hormone Therapy

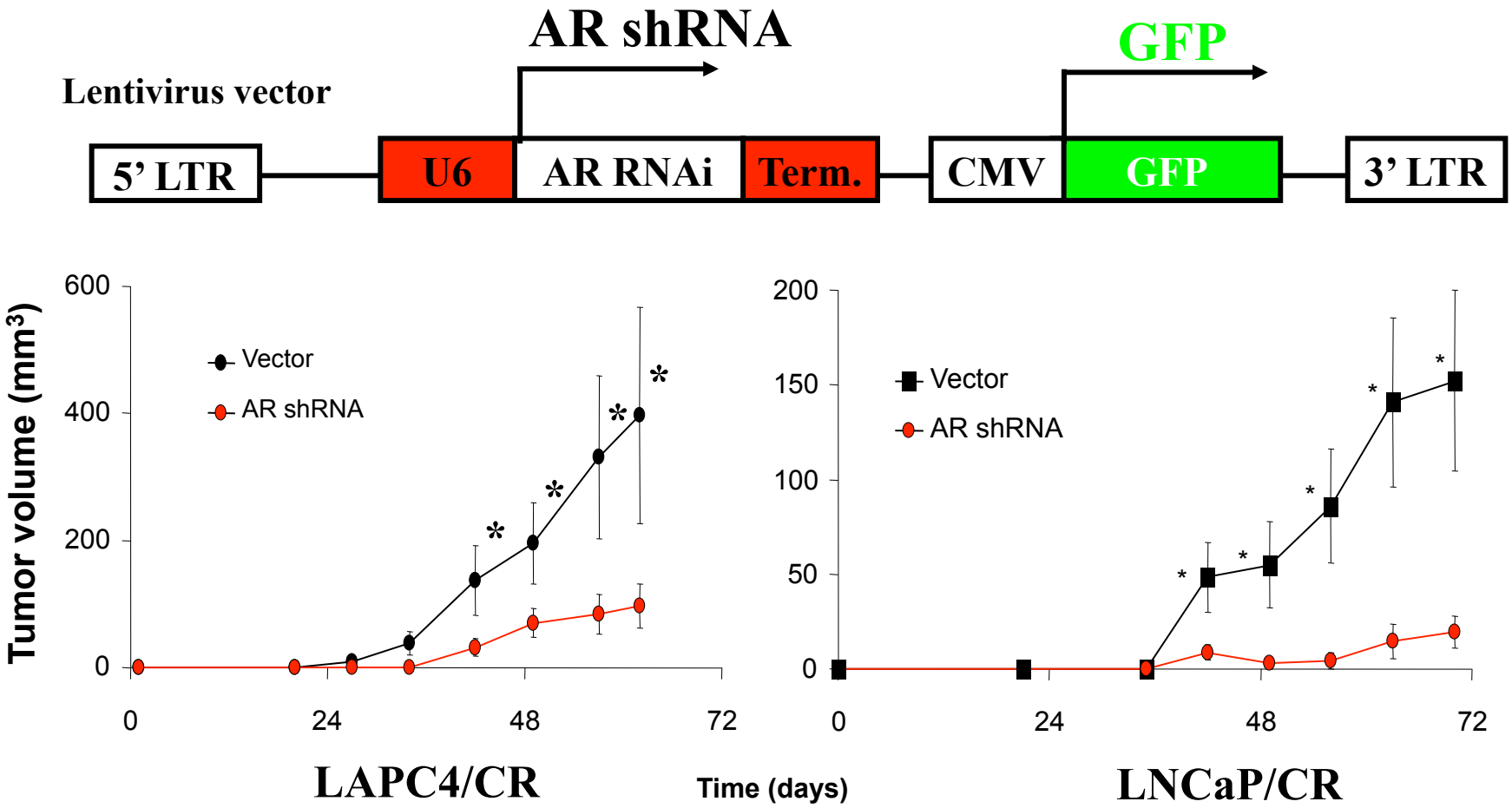


Primary Mechanism of Resistance to Castration and/or Current Antiandrogens

1) AR is overexpressed in castration resistant sublines of multiple prostate cancer xenograft models (and in patients)
2) Forced AR overexpression confers castration-resistance
3) AR knockdown impairs castration-resistant growth
4) AR antagonists act as agonists when AR levels are high

(Chen et al Nature Med, 2004)

AR is required to maintain castrate resistance *in vivo*



Growth of castrate resistant xenografts in castrate male mice

Primary Mechanism of Resistance to Castration and/or Current Antiandrogens

1) AR is overexpressed in castration resistant sublines of multiple prostate cancer xenograft models (and in patients)
2) Forced AR overexpression confers castration-resistance
3) AR knockdown impairs castration-resistant growth
4) AR antagonists act as agonists when AR levels are high

(Chen et al Nature Med, 2004)

Second generation anti-androgens must:

- be effective in cells expressing high levels of androgen receptor

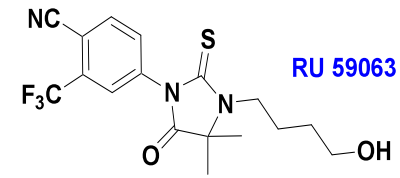
AND

- overcome the problem of antagonist/agonist conversion

Cell-based screen for compounds with greater antagonism and no agonism ("pure antagonists")

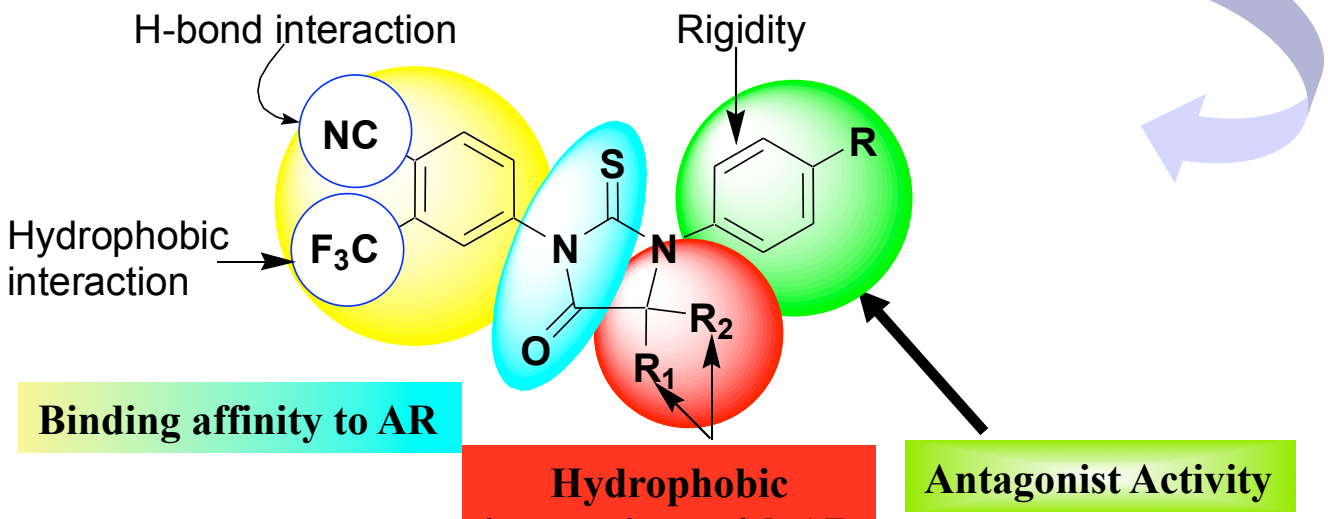
Design tools:

- Crystal structure
- Homology modeling
- Binding affinity



RU 59063

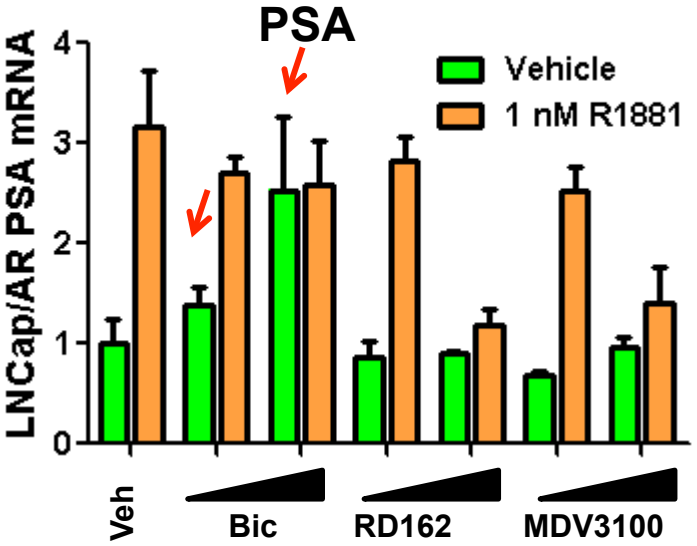
High AR binding affinity
(*Ka* = 20 nM for human AR)
But with agonistic activity

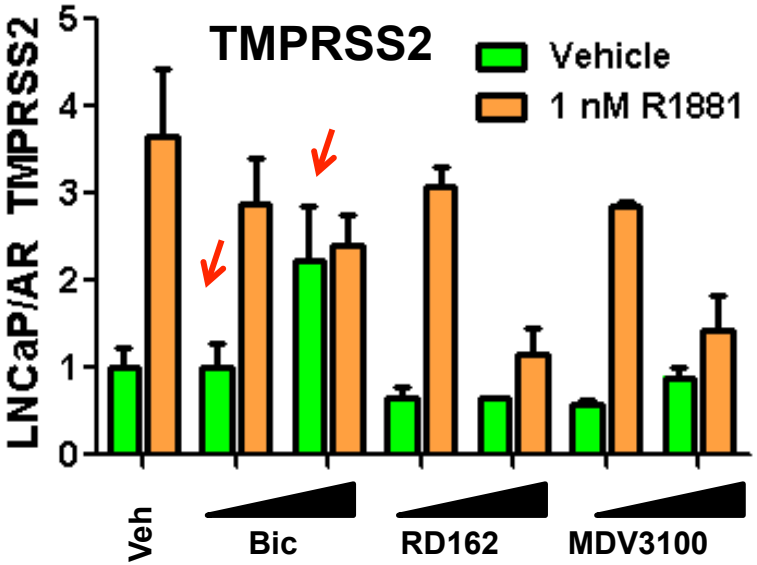


Jung et al, J Med Chem, 2010

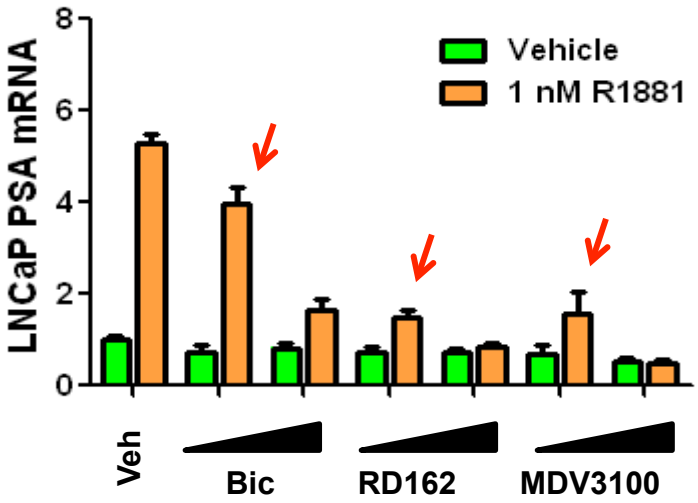
Samedy Ouk, Michael Jung (UCLA Department of Chemistry)

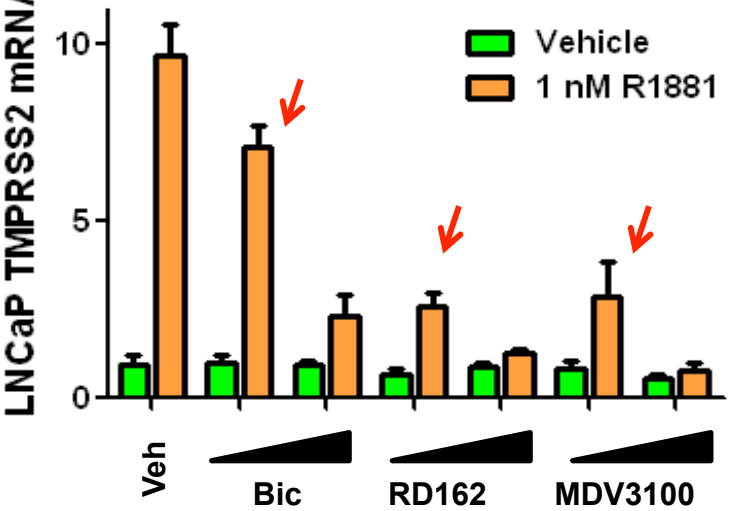
RD162 and MDV3100 do not display agonism in AR overexpressing cells





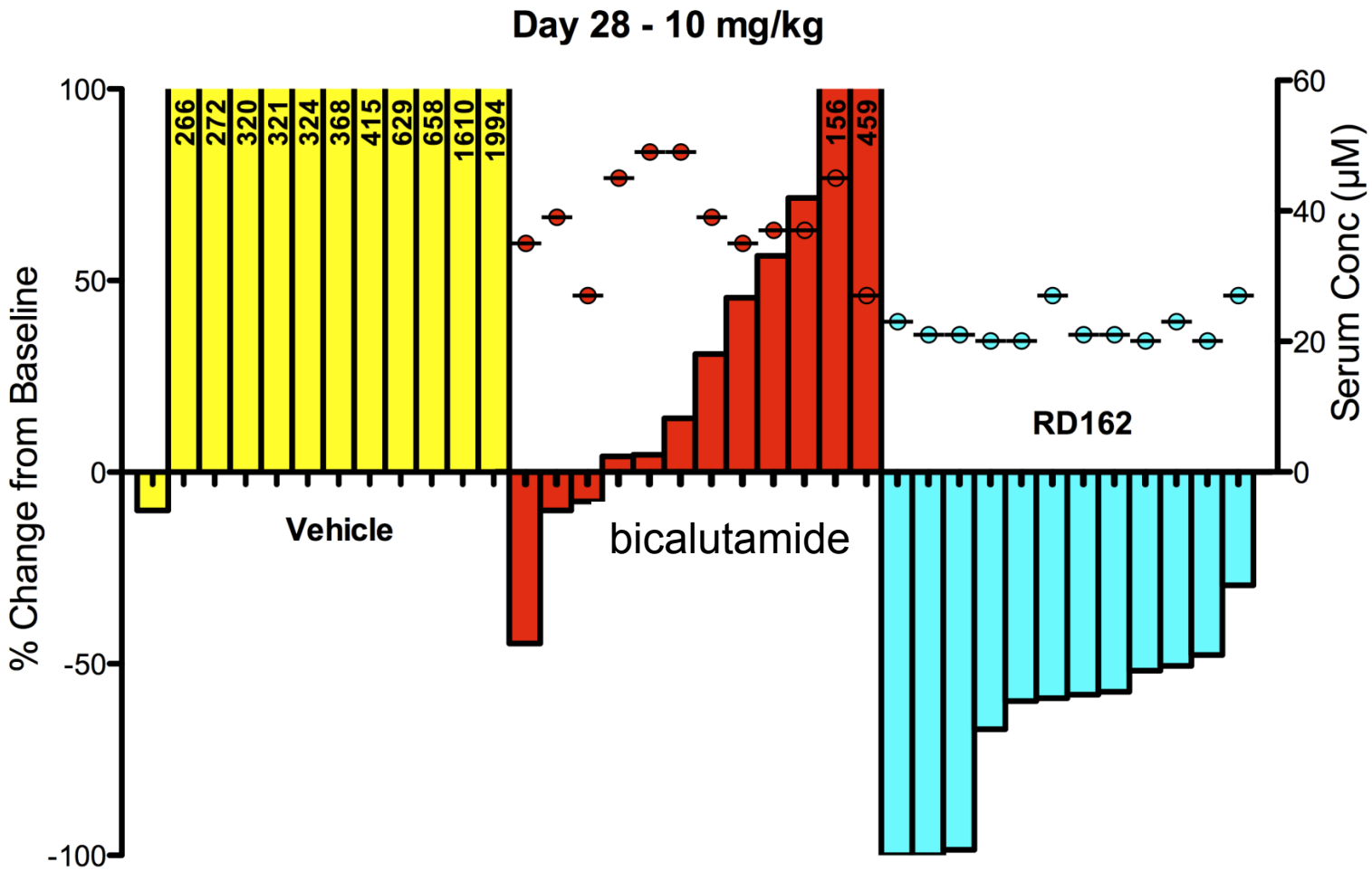
…and have more potent antagonist activity





Tran et al, Science 2009

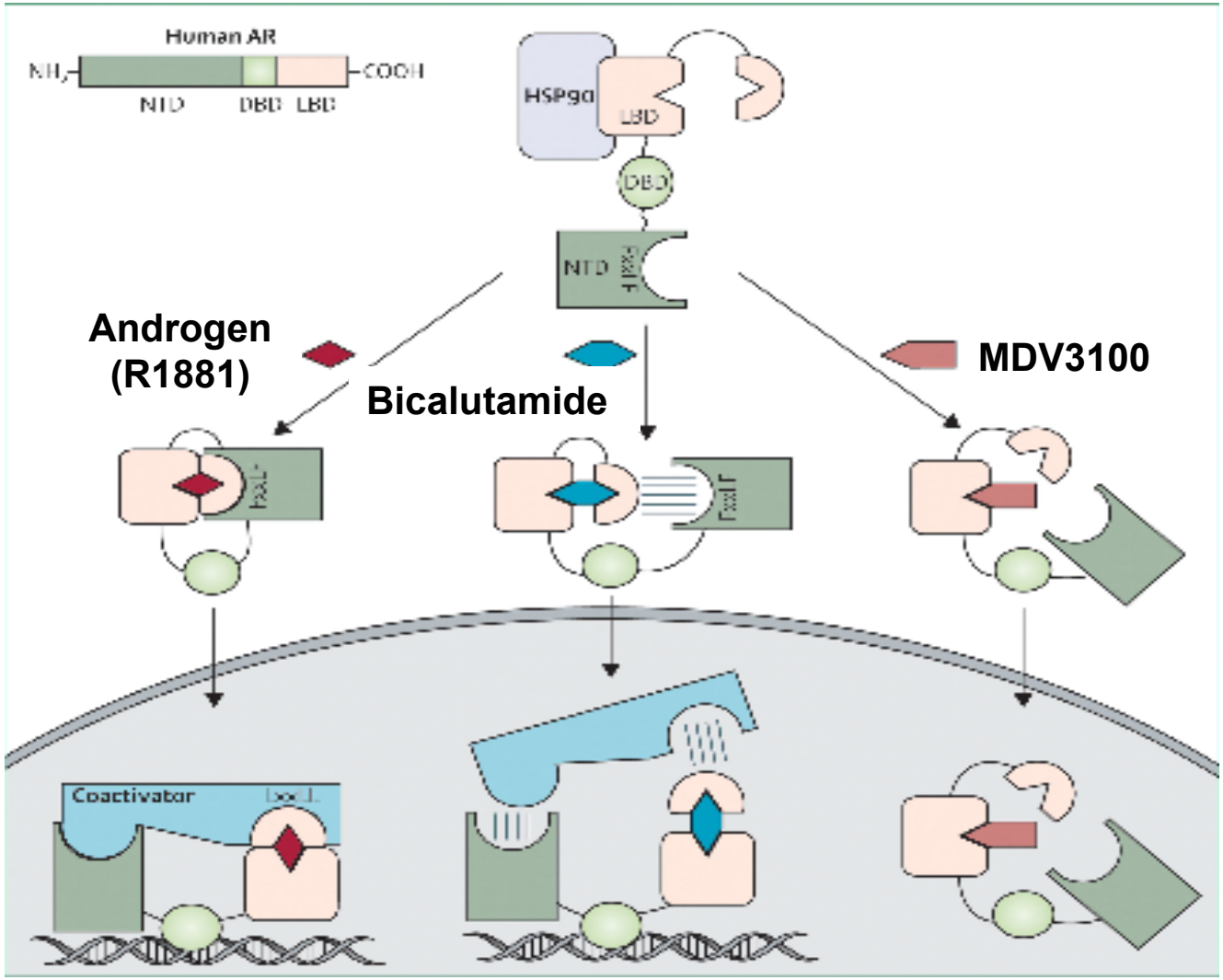
RD162 (and MDV3100) are superior to bicalutamide in the castrate-resistant LNCaP-AR xenograft model



Immunodeficient SCID castrate male mice. Tumor volume was measured in 3 dimensions.

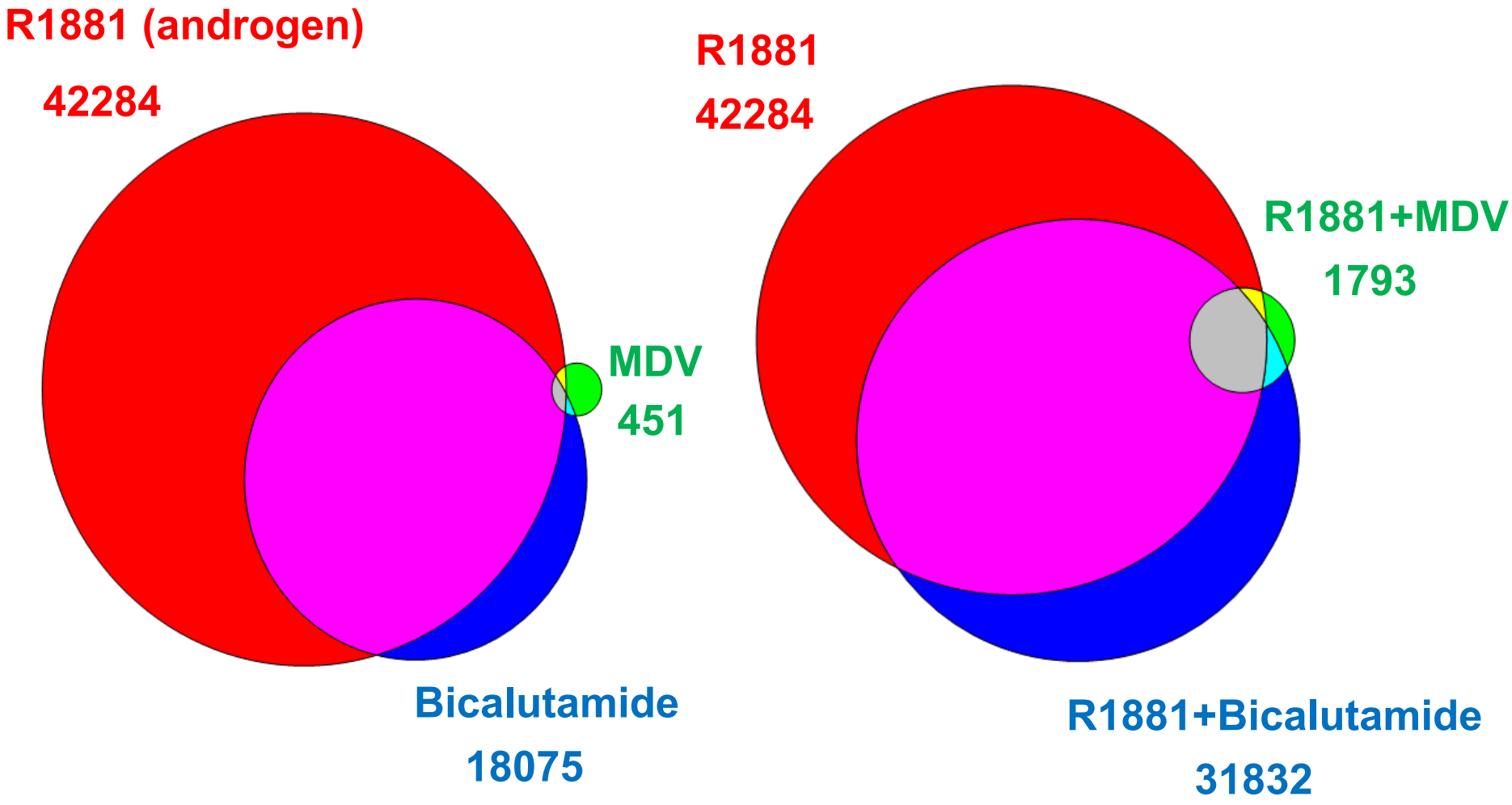
Tran et al, Science 2009

Androgen receptor activation and mechanism of antiandrogen action



Revised from Lancet Oncol. 2009 Oct;10(10):981-91.

Overlap among AR binding peaks in response to antagonists (determined by AR ChIP-Seq)



peaks found by MACS, p-value $<10^{-5}$

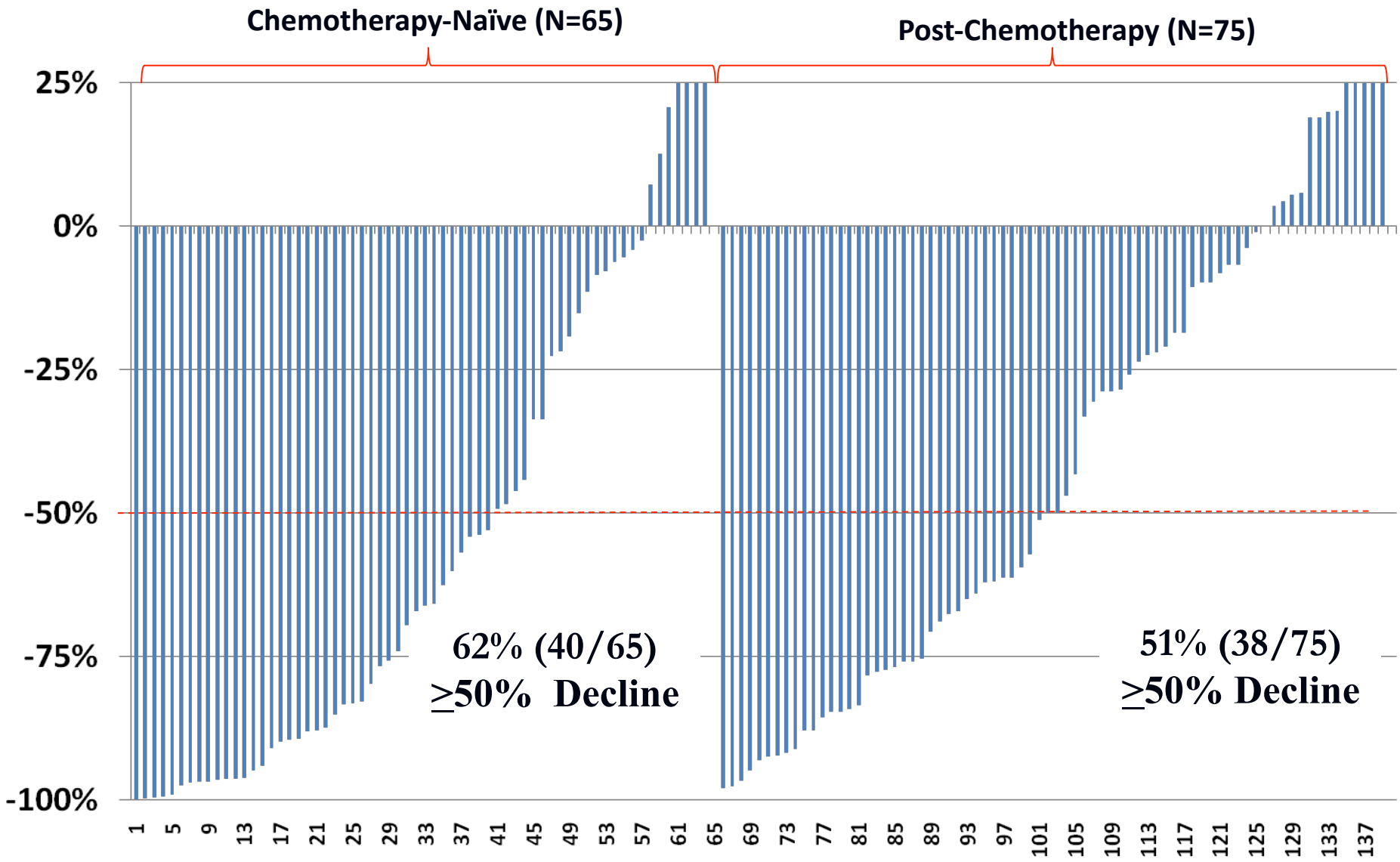
Ling Cai

A Phase 1-2 Multicenter First-in-Man Trial of MDV3100 in Castrate Resistant Prostate Cancer

1. Dose escalation, 3 patients per cohort, beginning at 30 mg/d to 600 mg/d
2. After safety was established at 60 mg/d, cohorts were expanded to 24 patients (12 chemo-naïve, 12 chemo failure)
3. First patient dosed in July, 2007
4. 140 men enrolled at 5 centers
   (MSKCC, OHSU, U Wash, DFCI, MDACC)

Scher et al Lancet, 2010

Waterfall Plot of Best Percent PSA Change from Baseline

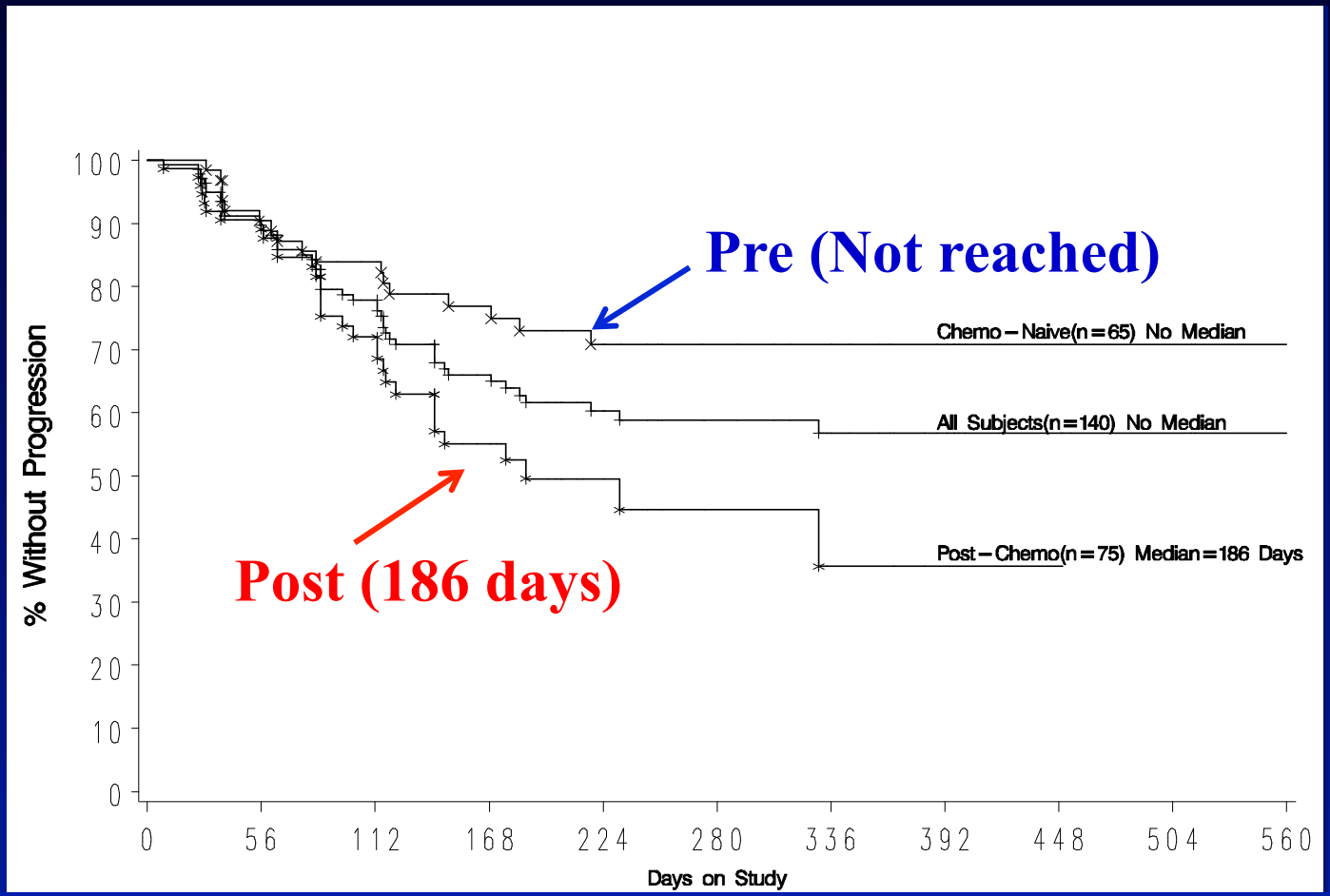


Radiographic Changes in Soft Tissue (N=59) and in Bone (N=109)

	Chemotherapy-Naïve Patients (N=65)	Post-Chemotherapy Patients (N=75)
Soft Tissue* (Best Response)	N=25	N=34
Partial Response	36% (9/25)	12% (4/34)
Stable Disease	44% (11/25)	53% (18/34)
Bone Scan (Week 12)	N=41	N=68
Stable Disease	63% (26/41)	51% (35/68)

*59 patients with evaluable soft tissue disease as defined by PCWG2 consensus
J Clin Oncol 2008.

Time to PSA Progression For Pre- and Post-Chemotherapy Treated Patients



Summary

1. Castration resistant prostate cancer remains dependent on androgen receptor (AR) function.

2. Pure AR antagonists like MDV3100 can overcome clinical resistance to partial antagonists (bicalutamide).

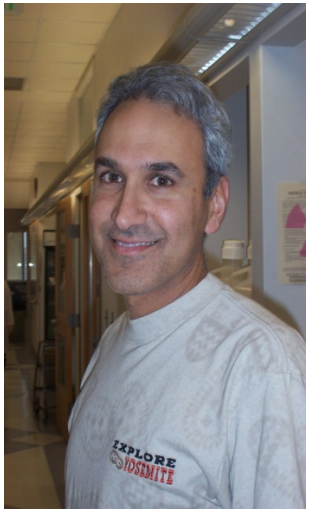
3. MDV3100 likely induces an AR conformation that precludes DNA binding.

4. MDV3100 development has progressed to a phase III registration trial in castration resistant, chemotherapy resistant prostate cancer

CML/Abl Inhibitor Project

Mercedes Gorre

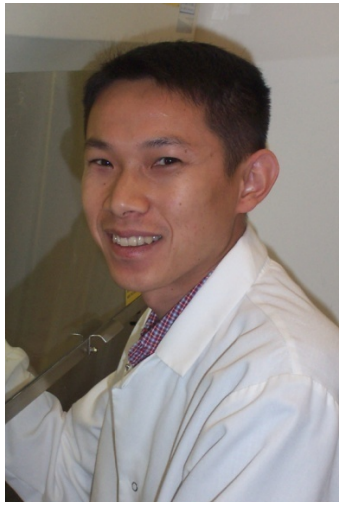
Neil Shah



Mike Burgess

John Nicoll

Chris Tran



Ron Paquette

Liz Haddad

BMS clinical trial

Moshe Talpaz
Art Decillis
Claude Nicaise
Eric Bleickardt

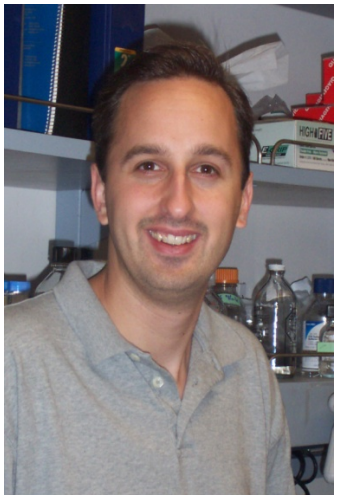
Collaborators

Bhushan Nagar
John Kuriyan
(UC Berkeley)
Frank Lee (BMS)

Prostate Cancer/Antiandrogen Project

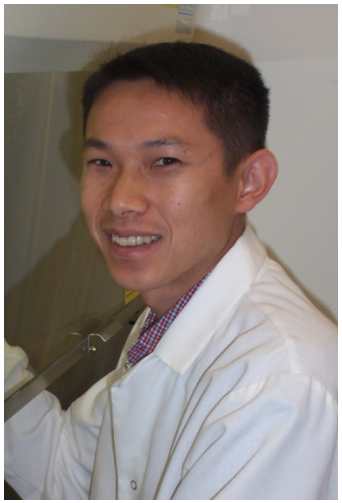
Charlie Chen

Derek Welsbie



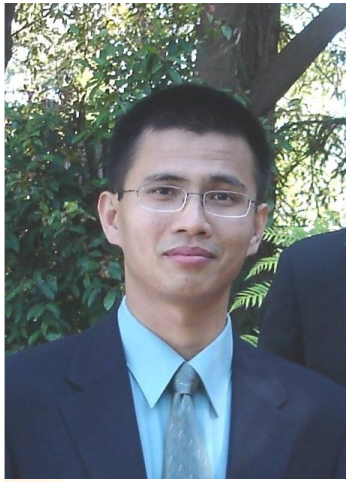
John Wongvipat

Chris Tran



Nicola Clegg

Michael Jung (Chemistry)



Samedy Ouk (Chemistry)

David Hung
Medivation