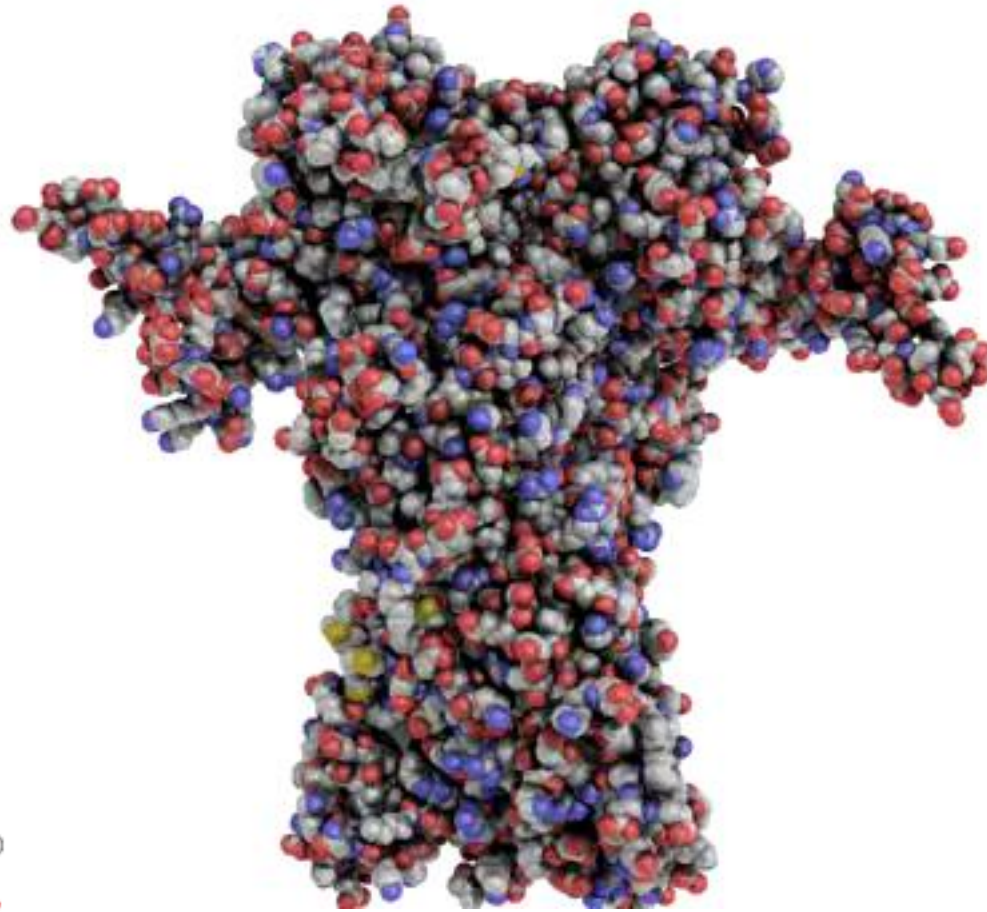
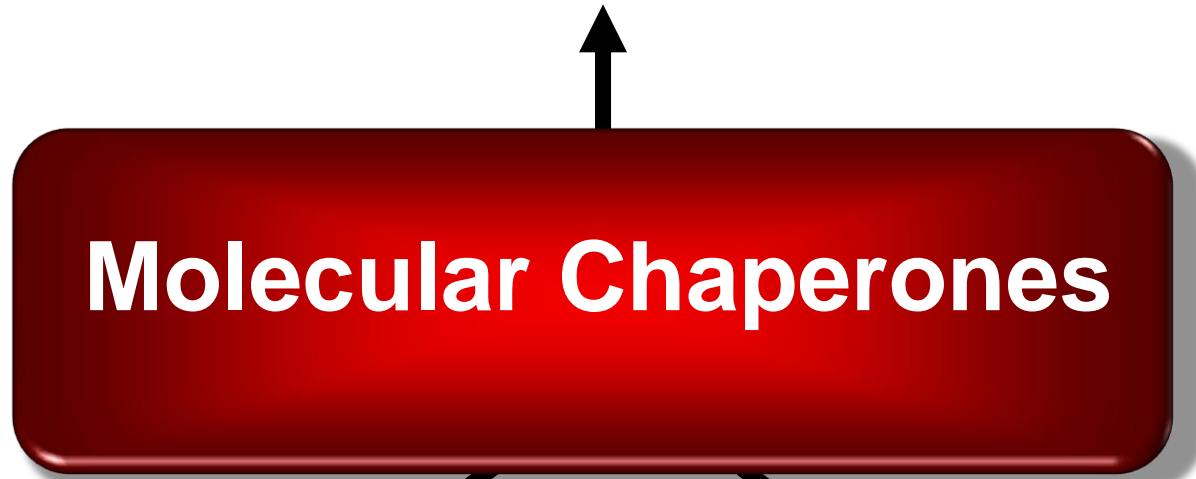


Targeting the Molecular Chaperone Hsp90 in Cancer: What Does the Biology Tell Us?



Regular Folding Pathways

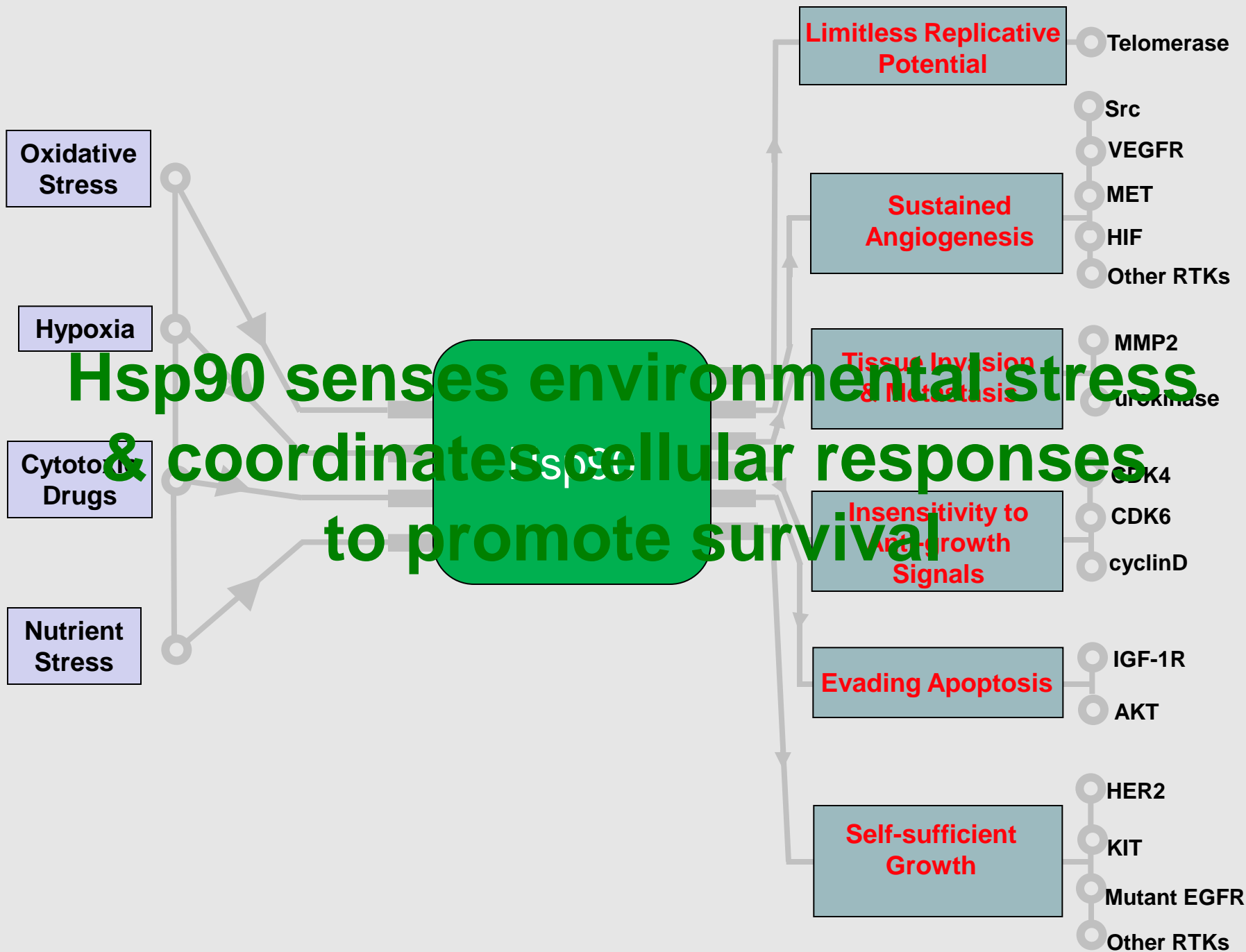


**Quality Control of
Misfolded Proteins**

**Activity & Stability
of Folded Proteins**

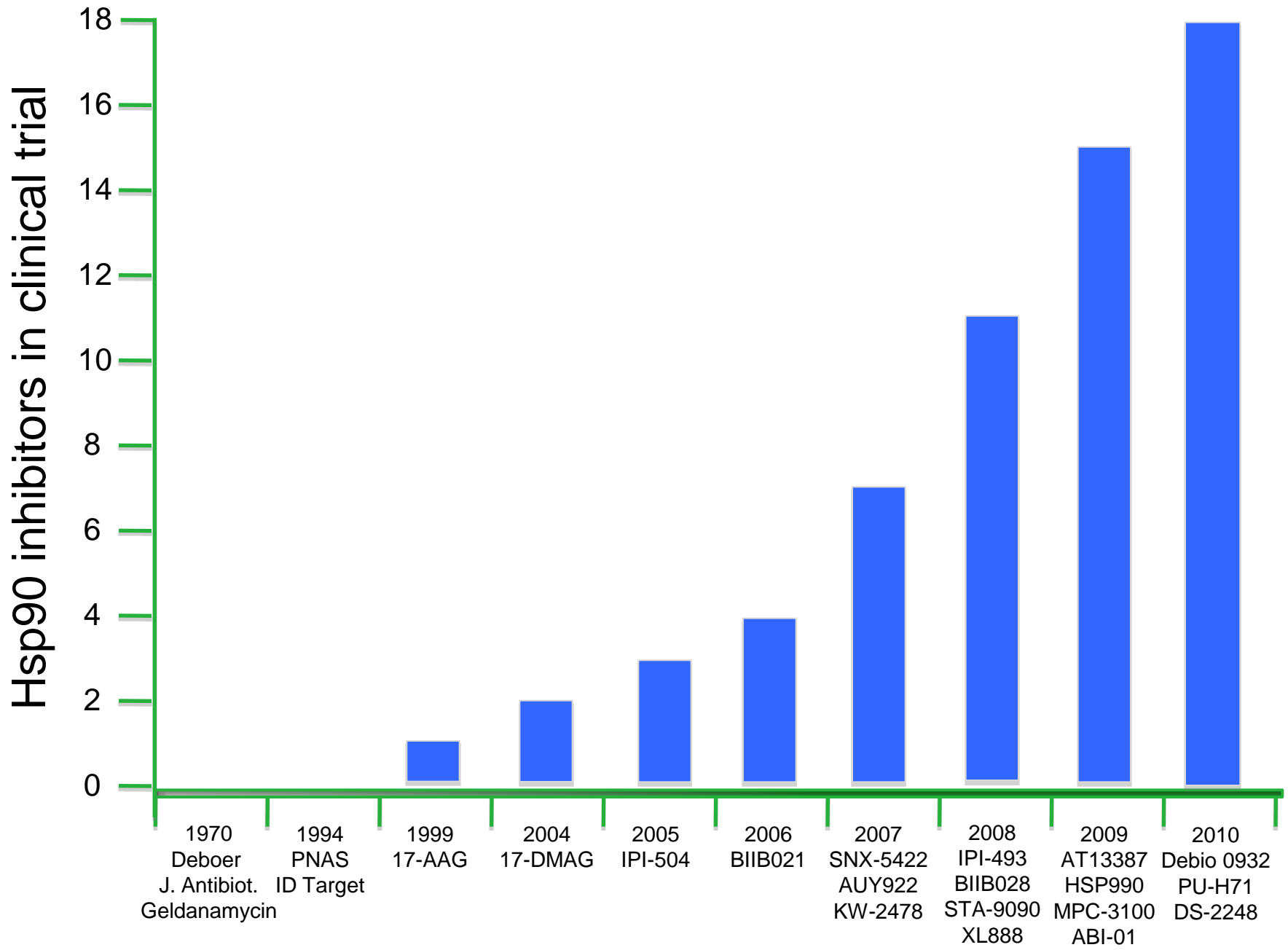
Hsp90

Why Hsp90?

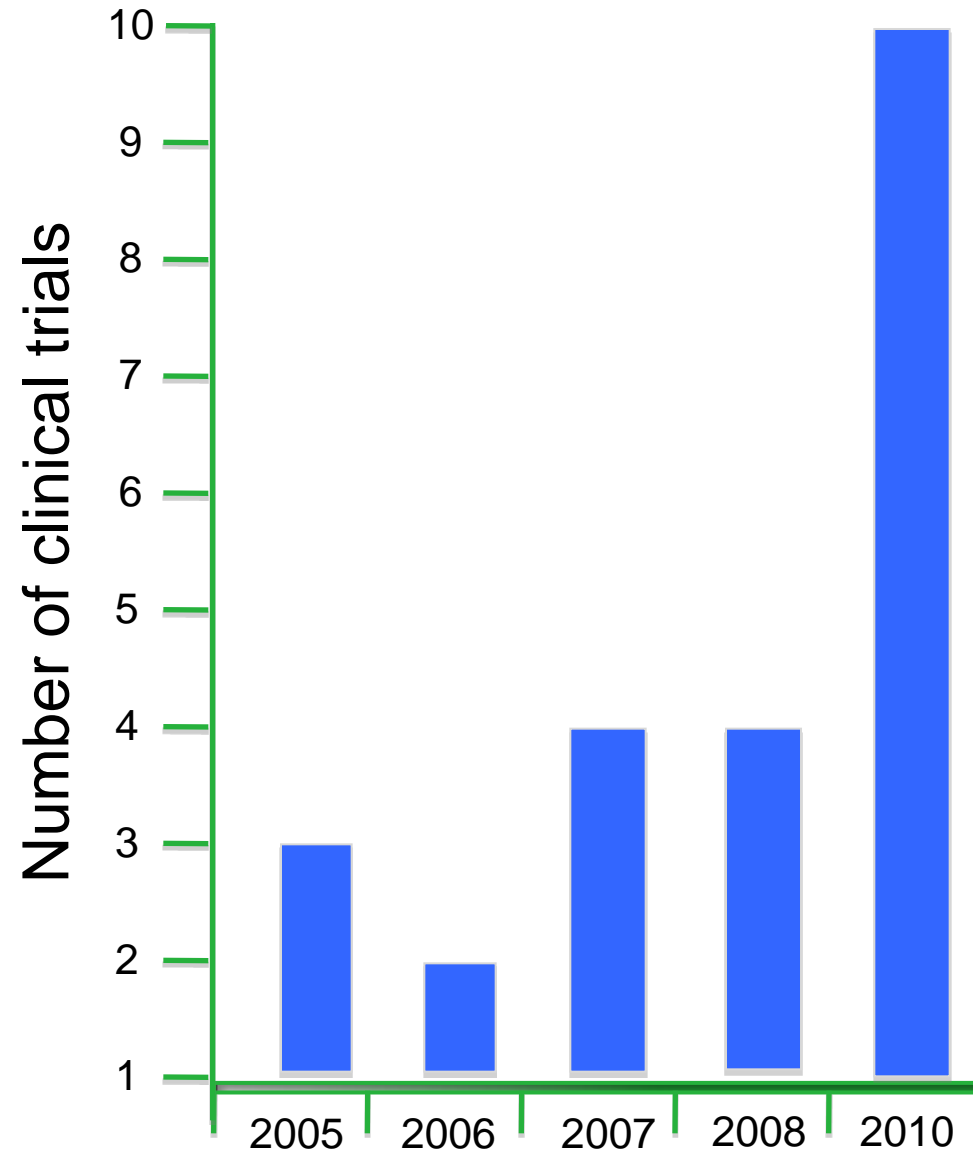


**Hsp90 clients include many
mutated oncogenic kinases:
Bcr-Abl, EGFR, MET, ALK...**

Development of Hsp90 inhibitors



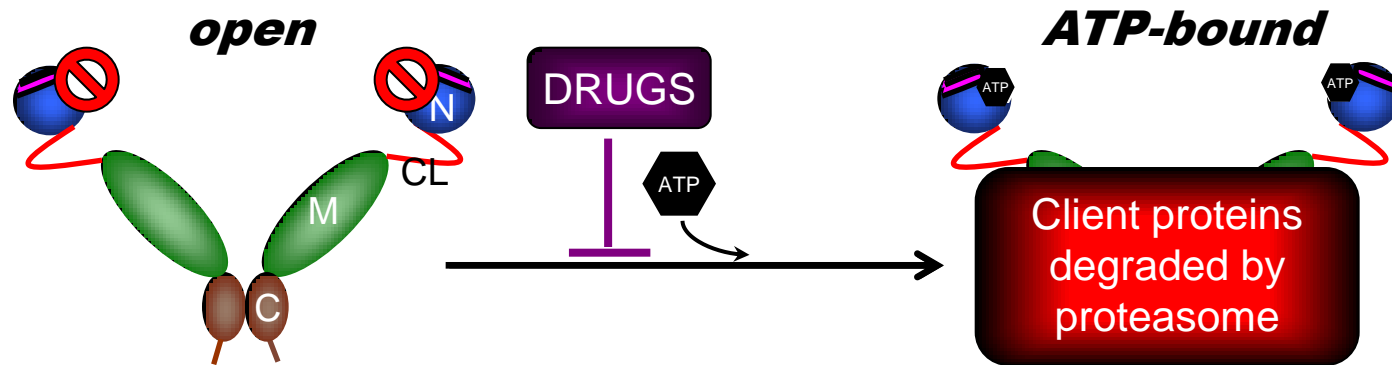
Published Hsp90 inhibitor clinical trials



Conclusions to date based on published data: **(tanespimycin (17AAG), alvespimycin (17DMAG), retaspimycin (IPI-504))**

- MTD and toxicity are strongly influenced by schedule
- Hsp90 inhibitor + trastuzumab is well tolerated and has anti-tumor activity in patients with HER2+ breast cancer whose tumors have progressed on trastuzumab alone (Modi et al., J Clin Oncol, 2007)
- Hsp90 inhibitor + sorafenib has clinical activity in kidney cancer and melanoma (Vaaishampayan et al., Clin Cancer Res, 2010)
- Single agent activity seen in 3 of 7 evaluable patients with advanced acute myeloid leukemia (Lancet et al., Leukemia, 2010)
- Hsp90 inhibitor +/- bortezomib has clinical activity and reduced peripheral neuropathy in patients with relapsed/refractory multiple myeloma (Richardson et al., Br J Haematol, 2010, x2)
- Single agent activity seen in patients with NSCLC, particularly those with ALK rearrangements (Sequist et al., J Clin Oncol, 2010)

Complex twist & turns of the chaperone cycle



Chaperone-dependent E3 ubiquitin ligase **CHIP** mediates a degradative pathway for c-ErbB2/Neu.

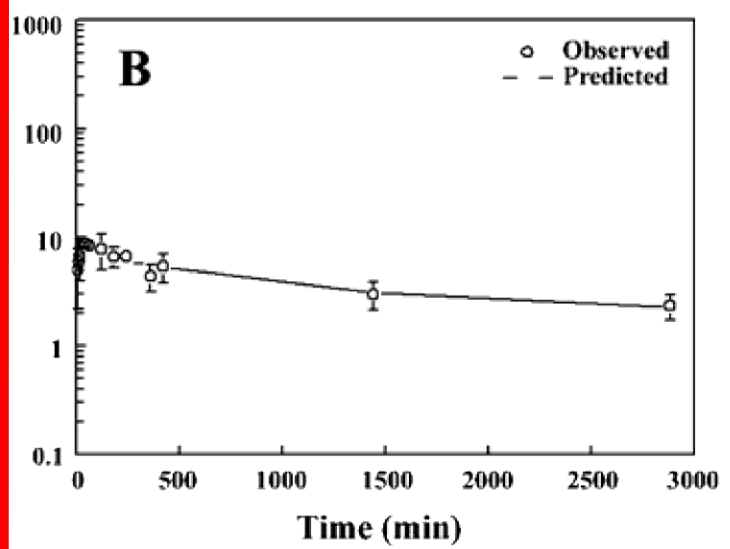
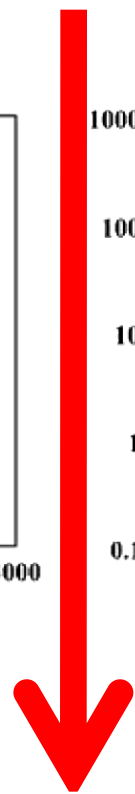
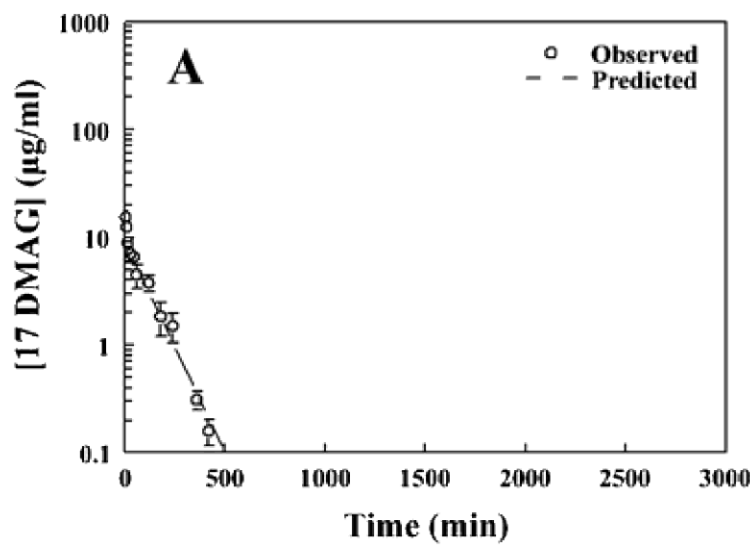
Xu et al., Proc Natl Acad Sci U S A, 2002

Regulation of Hsp90 client proteins by a **Cullin5-RING** E3 ubiquitin ligase.

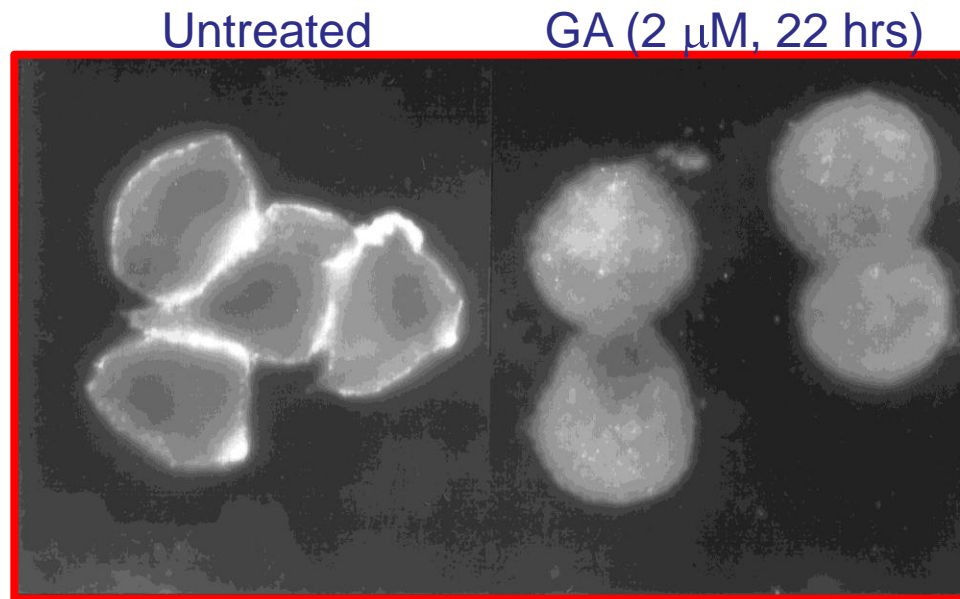
Ehrlich et al., Proc Natl Acad Sci U S A, 2009



➤ Hsp90 inhibitors are concentrated and retained in tumor



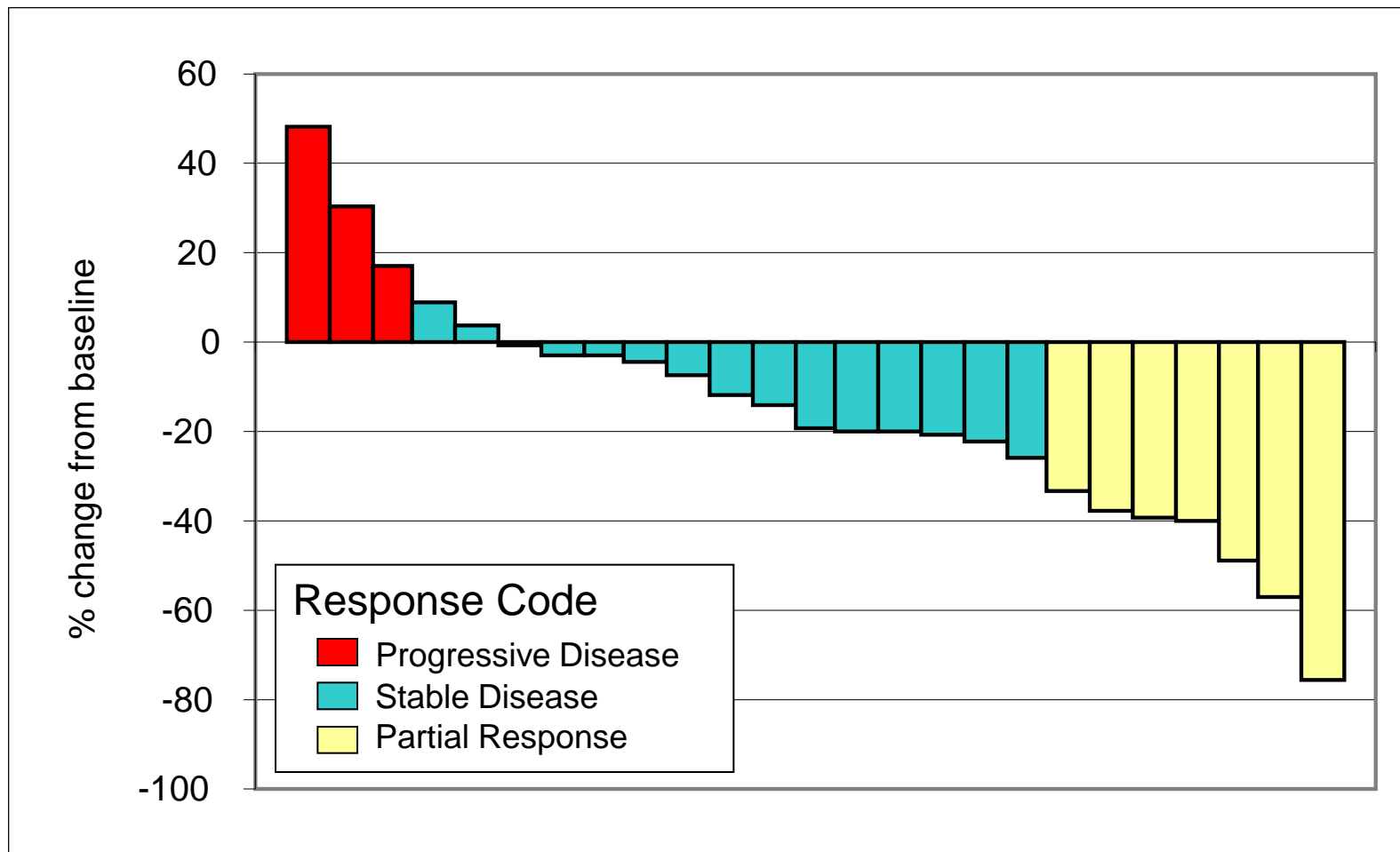
Hsp90 inhibitors promote rapid degradation of ErbB2 but not of WT EGFR



ErbB2 expression in SKBR3 cells

Chavany et al., J Biol Chem, 1996

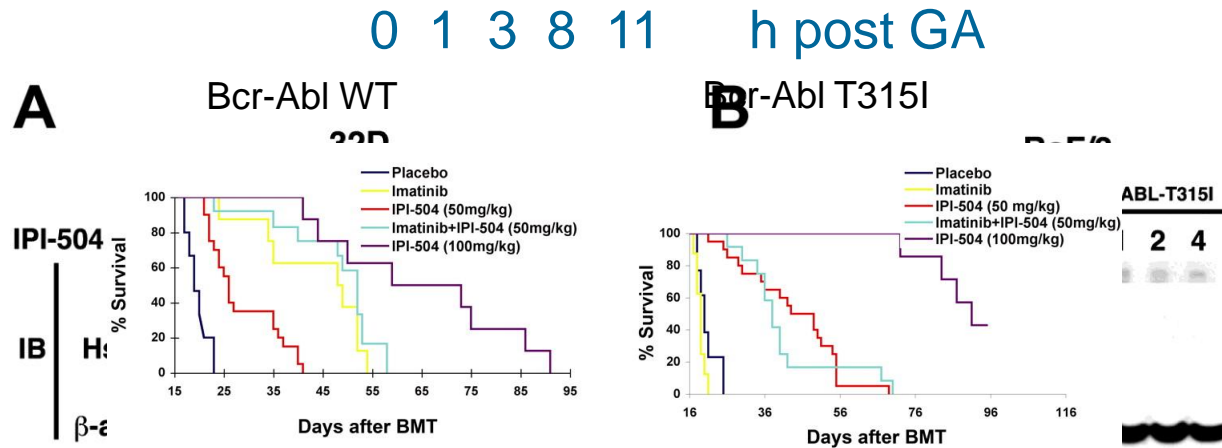
HER2+ Breast Cancer: 17-AAG + Herceptin in Patients Who Progressed on Herceptin Alone



Response rate: 26%; overall clinical benefit rate: 63%

Hsp90 inhibitors abrogate TKI resistance

Hsp90 Inhibitors Destabilize Bcr-Abl Tyrosine Kinase



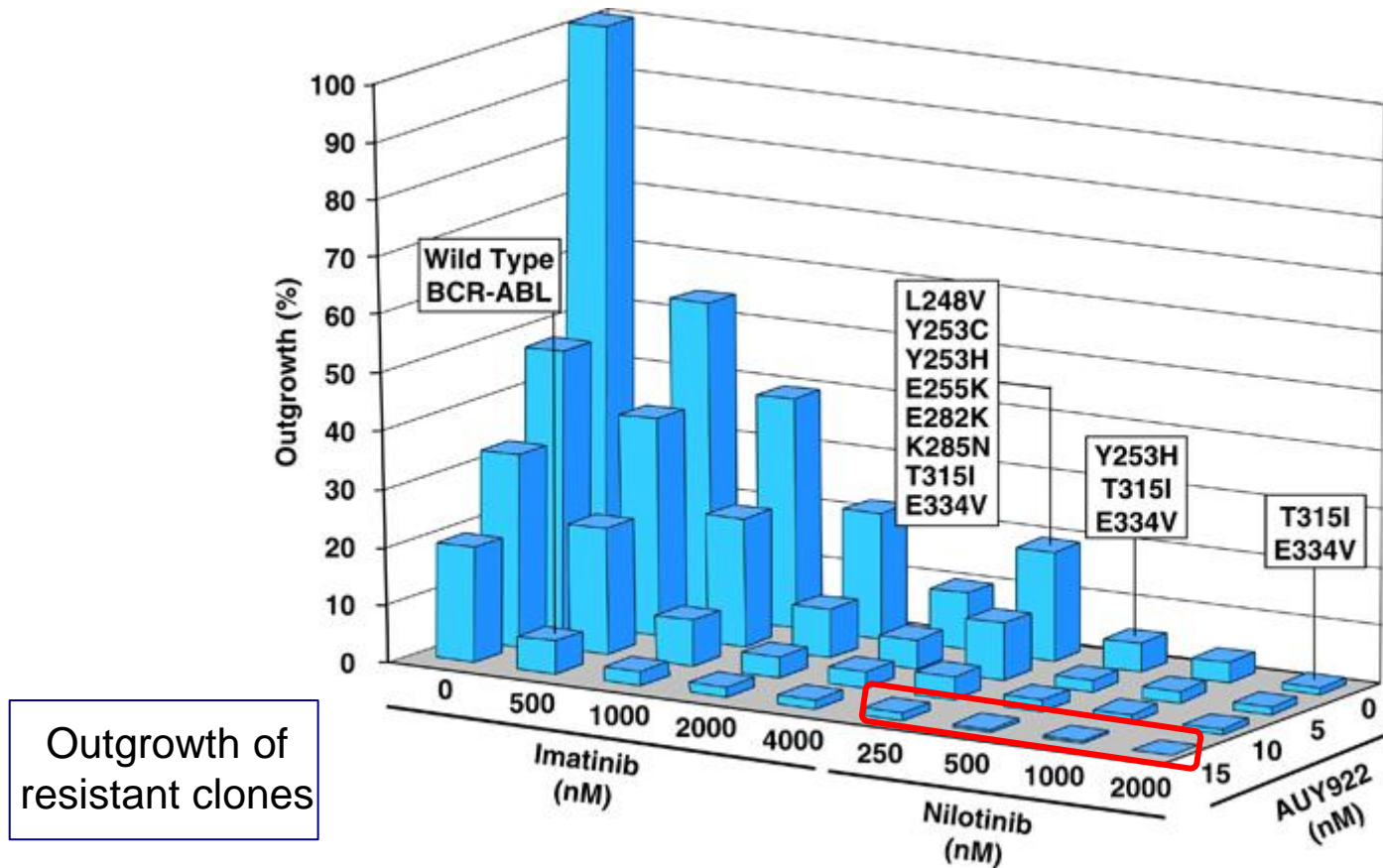
Peng et al., Blood, 2007

Peng et al., Blood, 2007

An et al., Cell Growth Differ, 2000

Blagosklonny et al., Leukemia, 2001

Hsp90 Inhibitors Destabilize Bcr-Abl Tyrosine Kinase



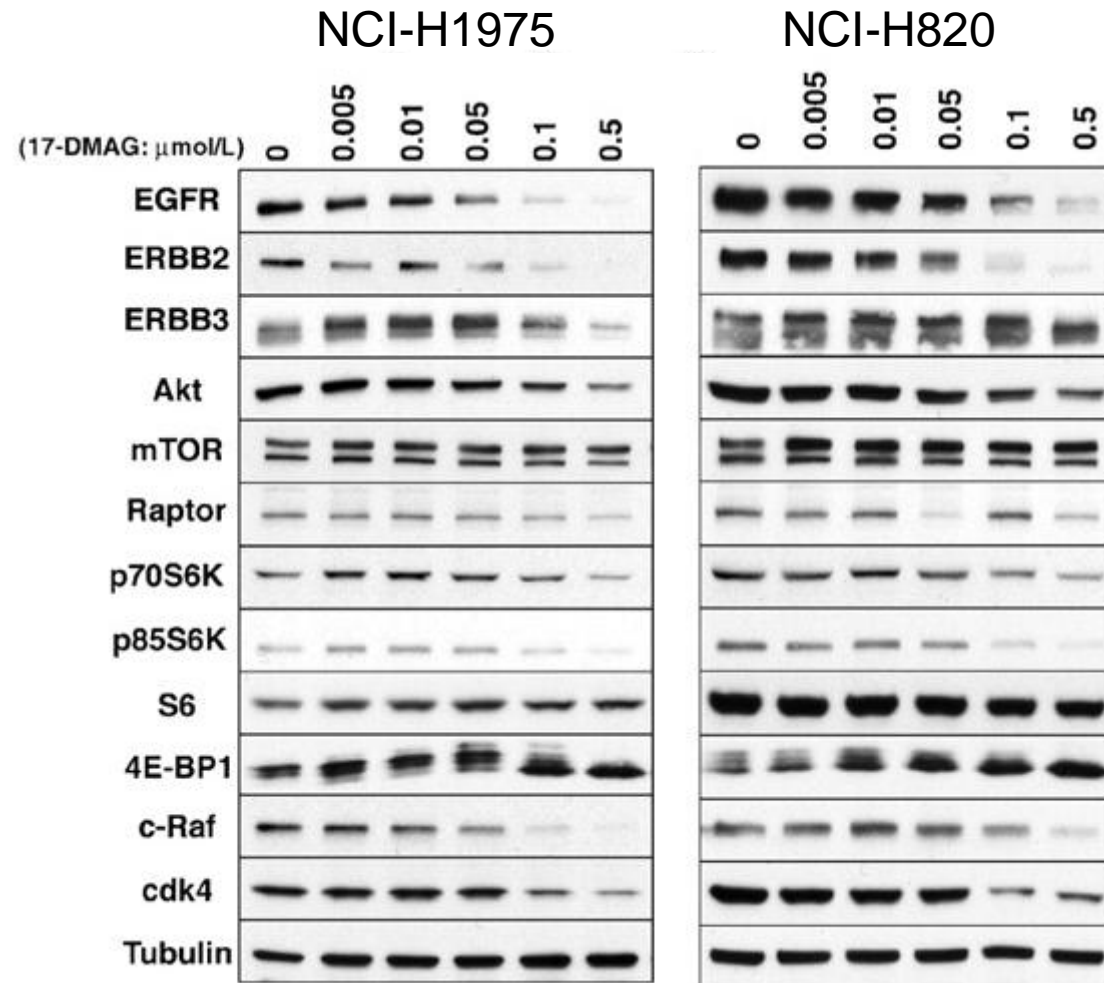
“Sequencing revealed only WT Bcr-Abl in AUY922-resistant clones”

FROM: Tauchi et al., Oncogene, 2011

Combined effects of novel heat shock protein 90 inhibitor NVP-AUY922 and nilotinib in a random mutagenesis screen

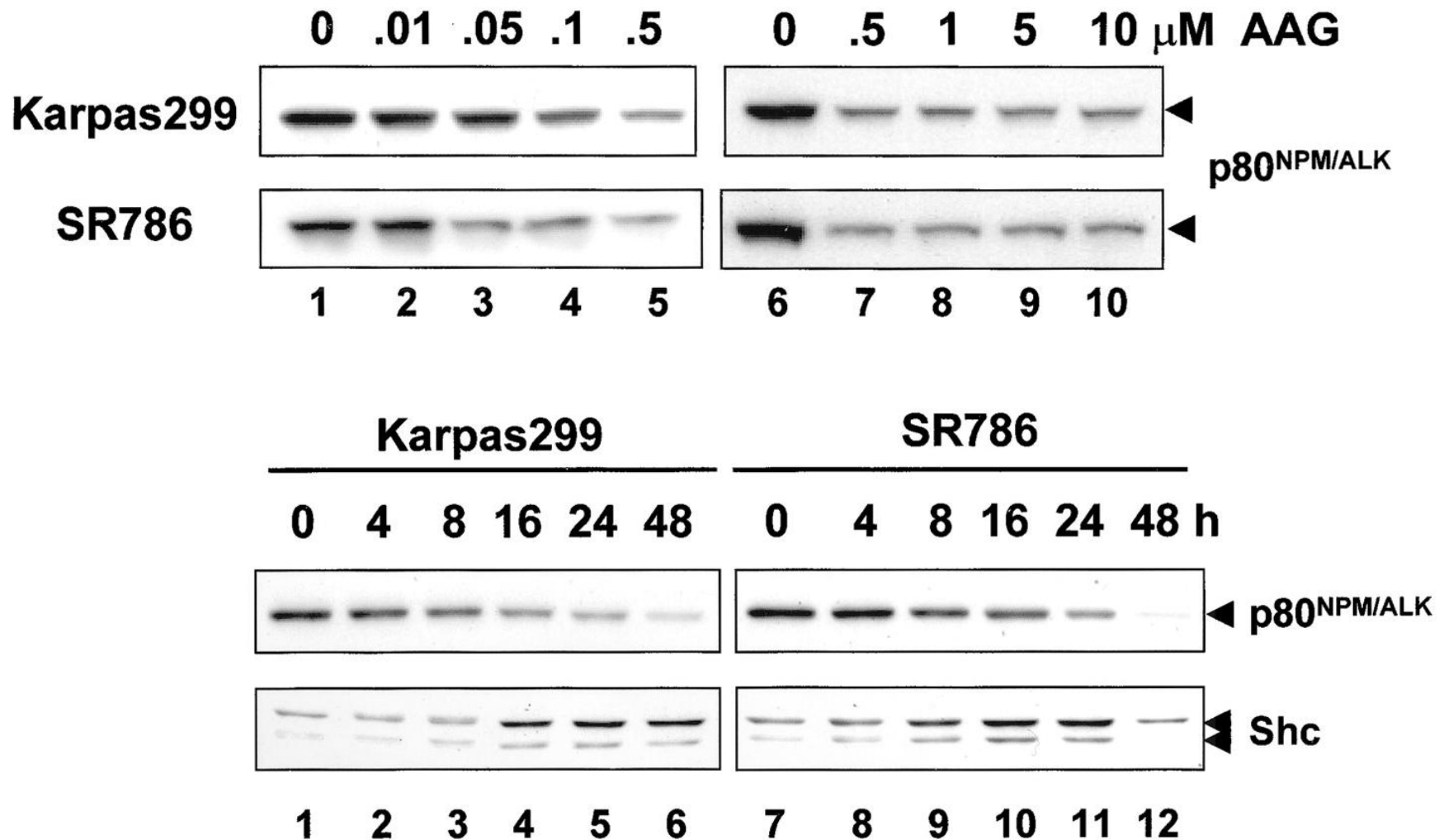
Hsp90 Inhibitors Destabilize EGFR Kinase Domain Mutants

T790M 2
mutations

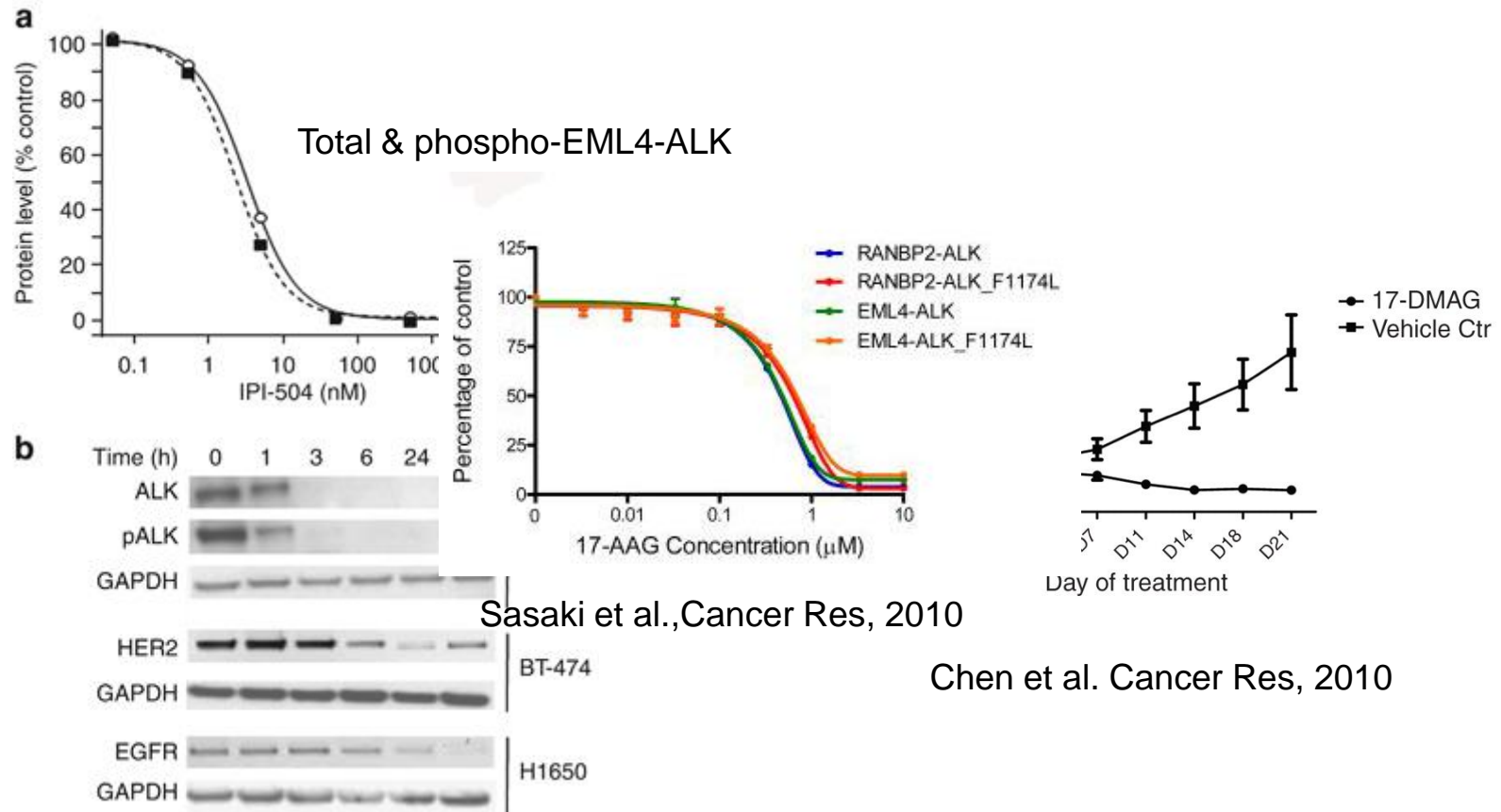


Shimamura et al., Cancer Res, 2008

Hsp90 Inhibitors Destabilize NPM-ALK in ALCL



Neuroblastoma ALK is overexpressed in 17-DMAG sensitive to Hsp90 inhibition



Sasaki et al., Cancer Res, 2010

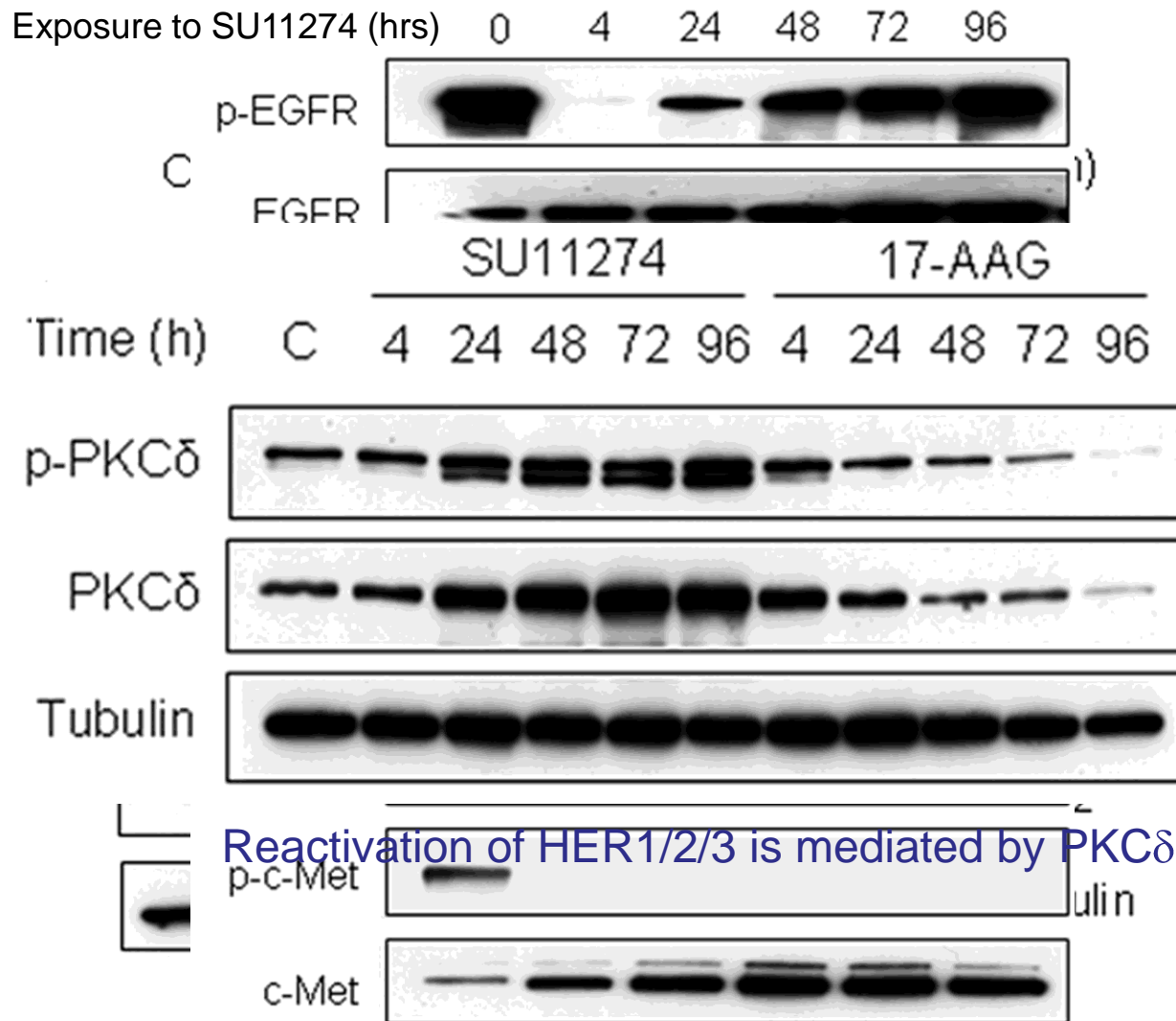
Chen et al. Cancer Res, 2010

Normant et al., Oncogene, 2011

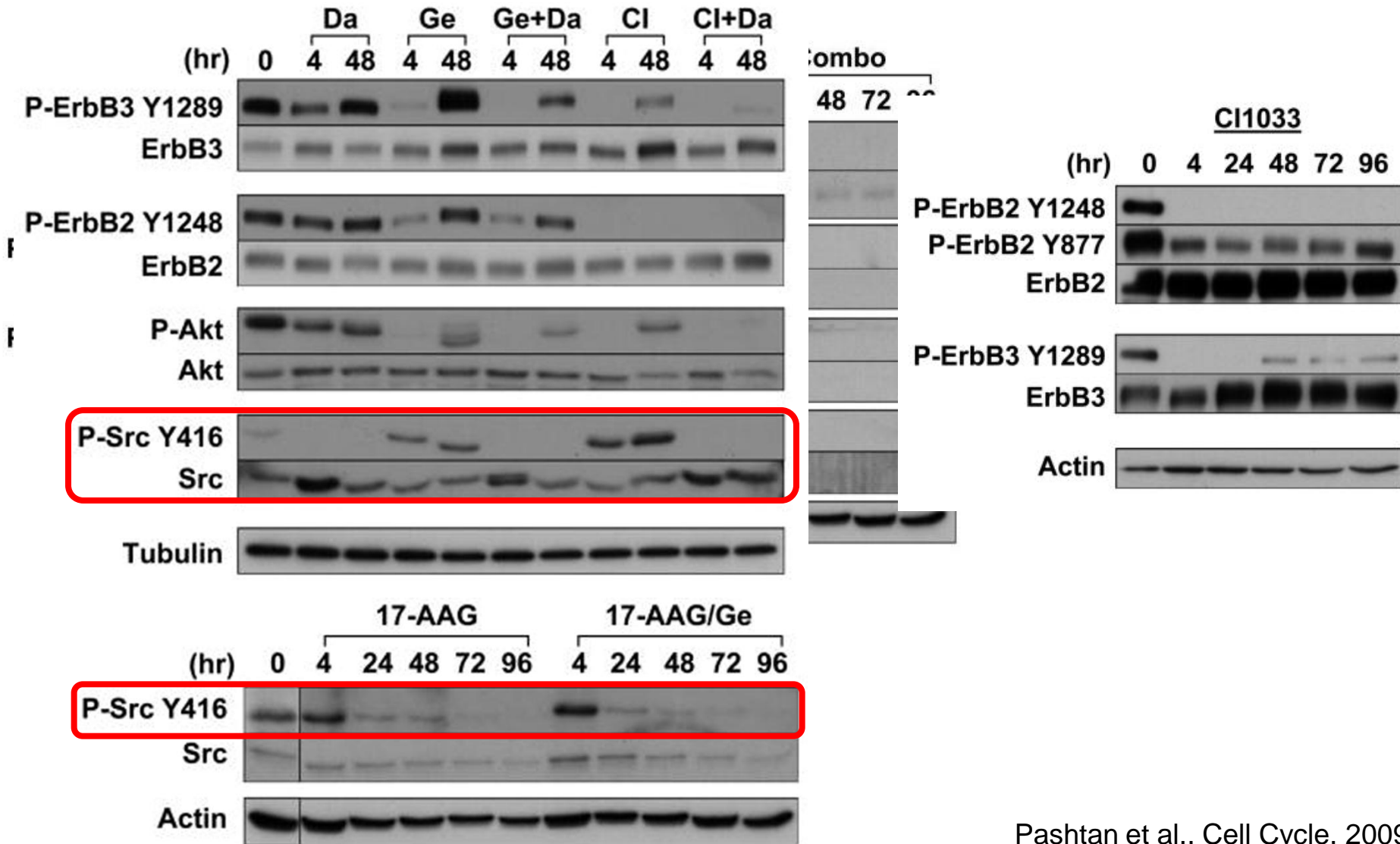
Hsp90 inhibitors abrogate TKI resistance

- By targeting TKI resistance mutations

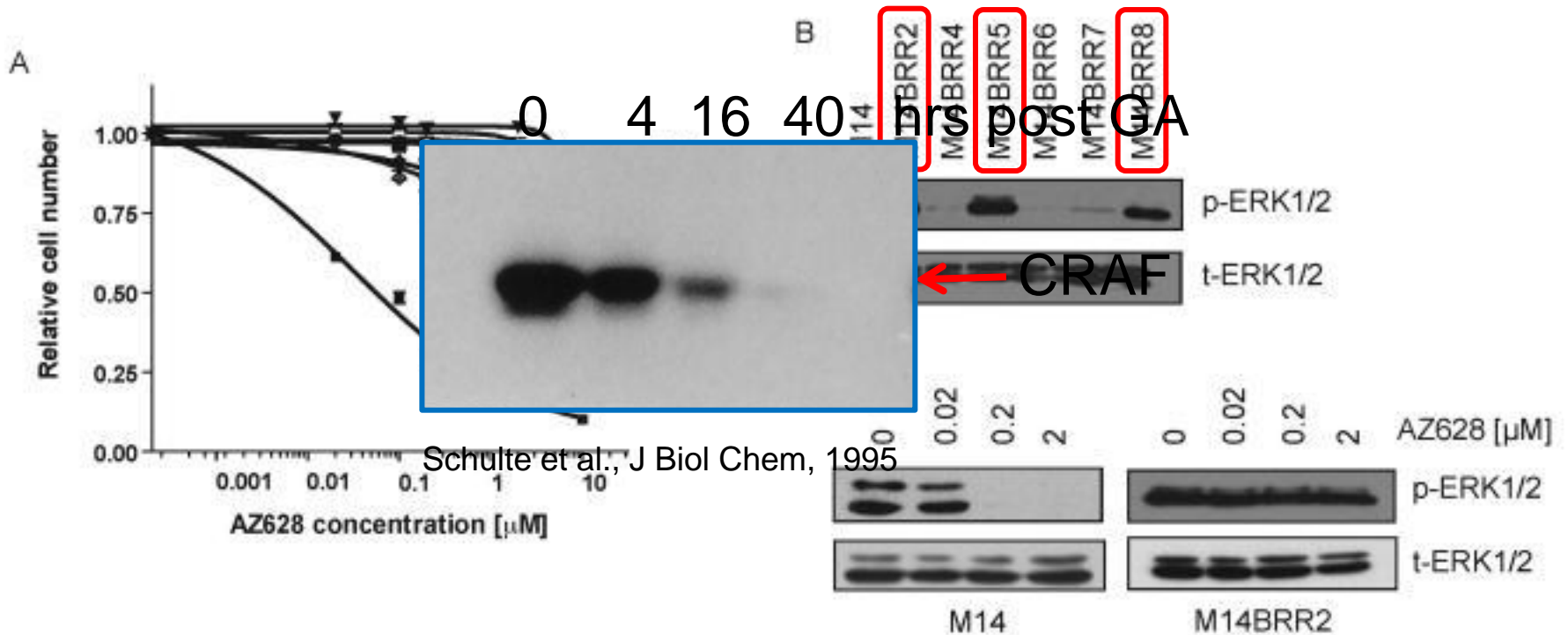
Escape from c-MET TKI



Escape from HER1/2 TKI

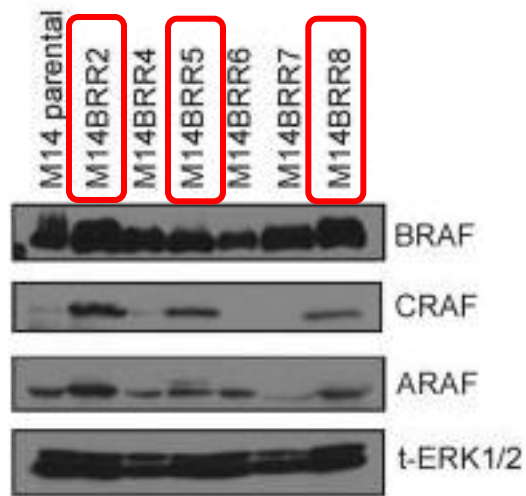


Escape from BRAF-V600E TKI

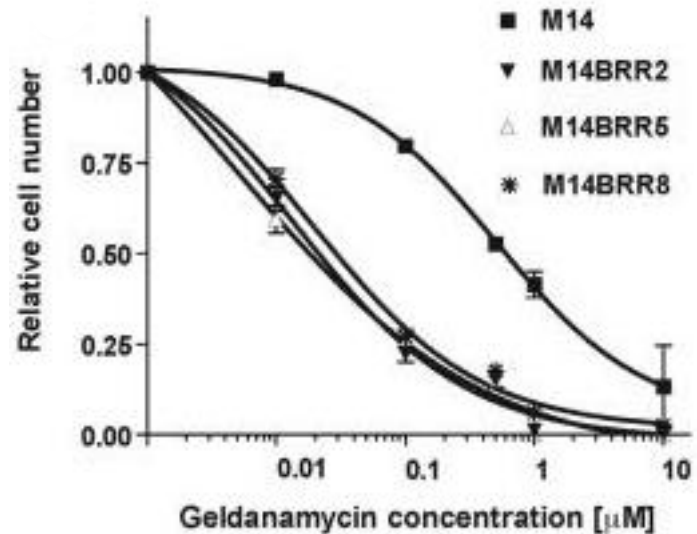
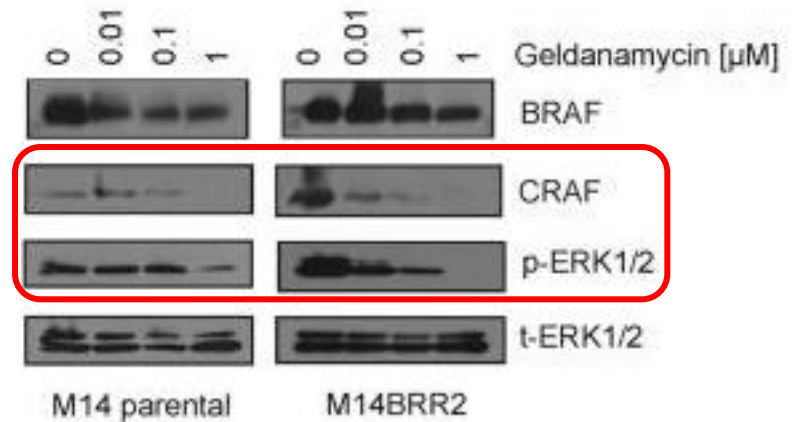


Montagut et al., Cancer Res, 2008

Escape from BRAF-V600E TKI



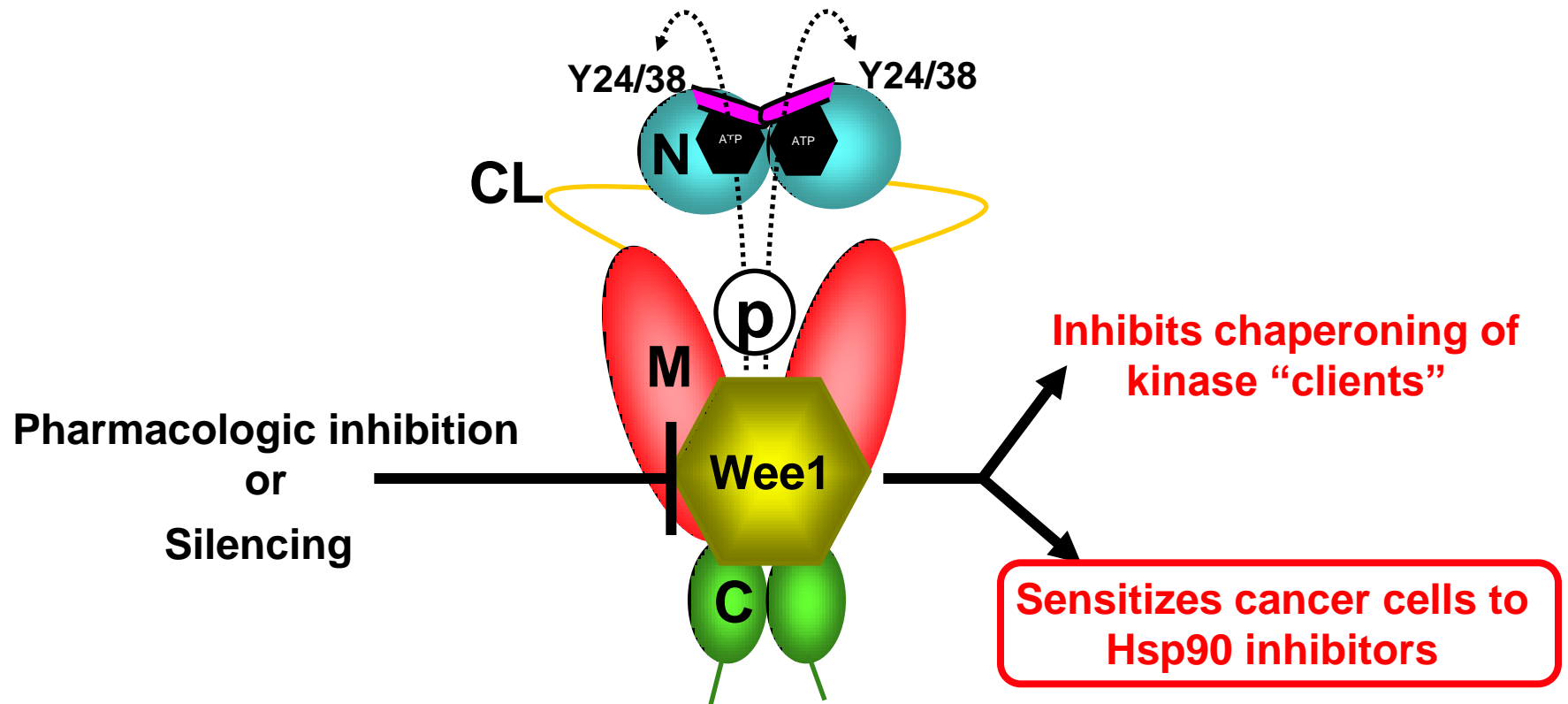
Montagut et al., Cancer Res, 2008



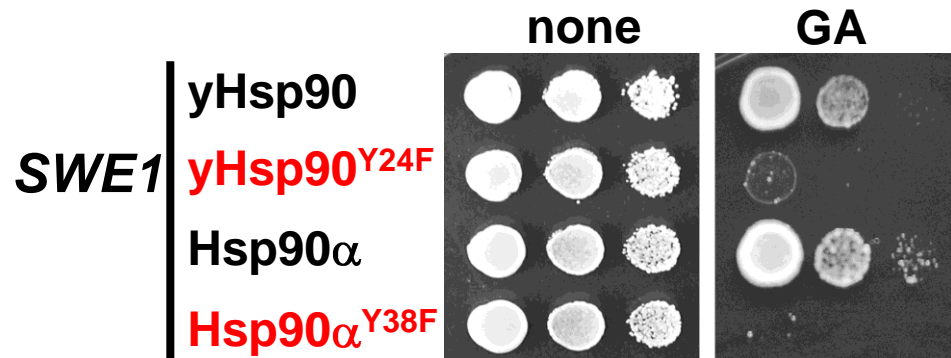
Can Hsp90 be made more sensitive to inhibitors?

Mollapour *et al.*, *Mol. Cell*, 2010

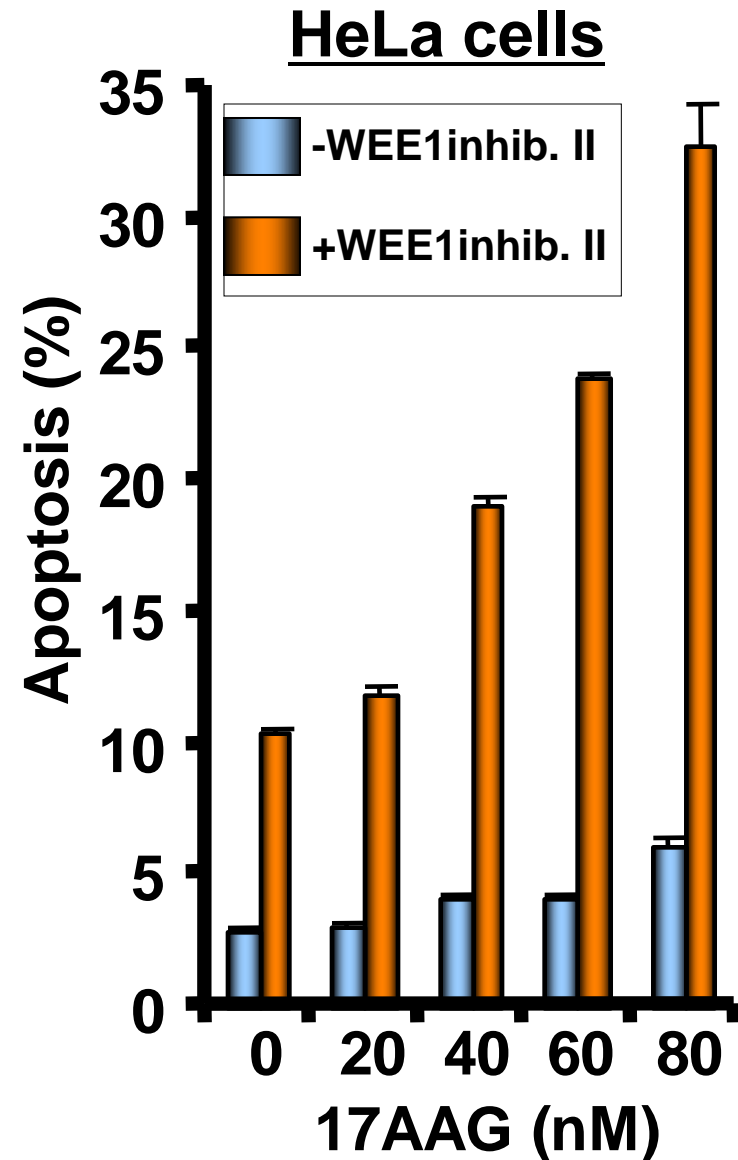
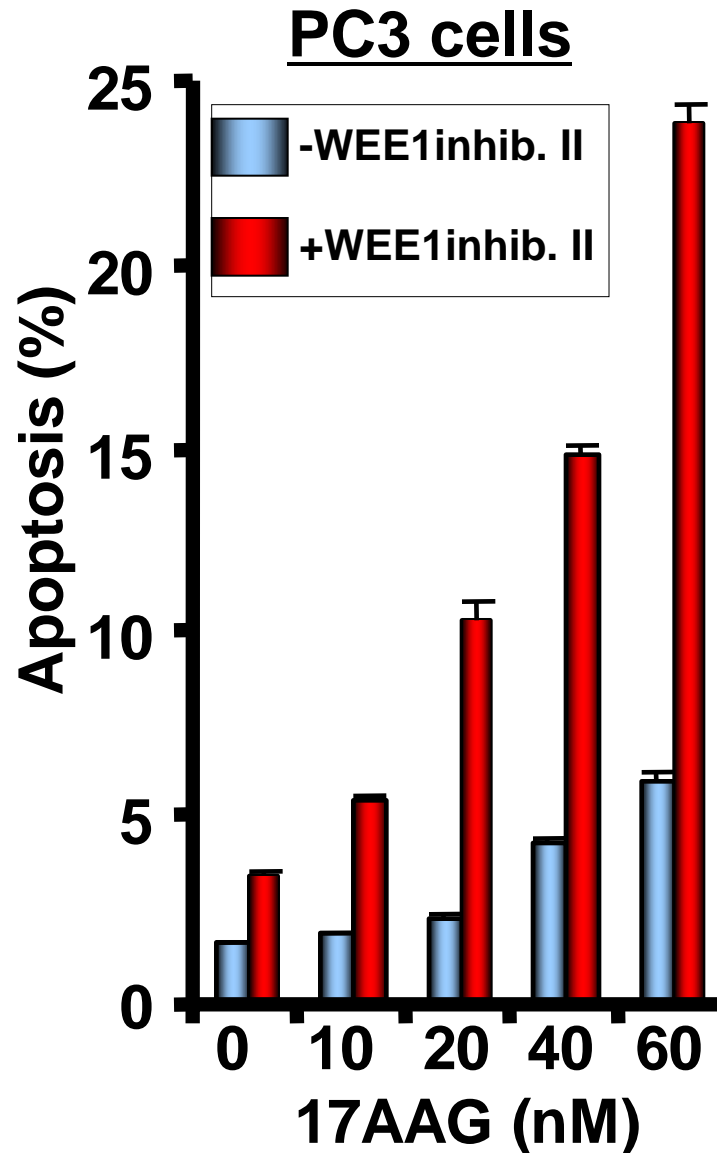
Inhibition of Wee1 sensitizes cells to Hsp90 inhibitors



Non-phospho *hsp90* yeast mutants display enhanced sensitivity to geldanamycin



Wee1 inhibition enhances cancer cell sensitivity to the Hsp90 inhibitor 17AAG



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