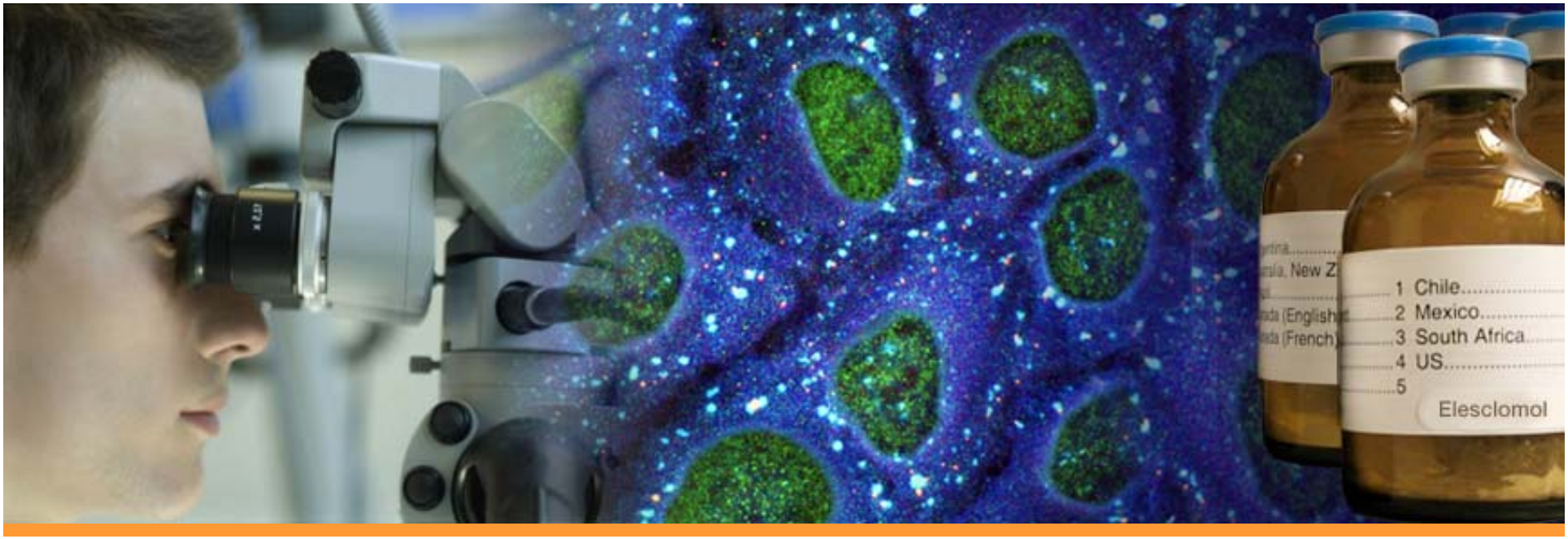
SYNTA PHARMACEUTICALS®

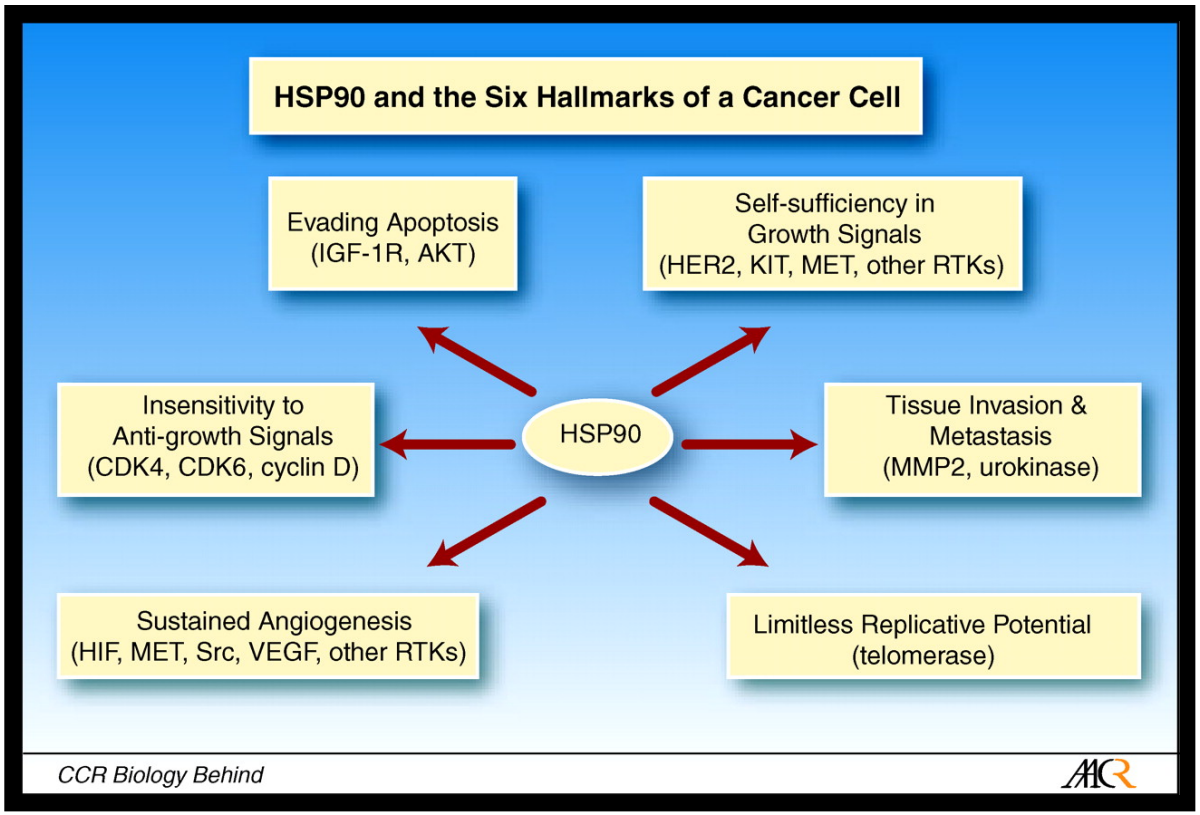


STA-9090: Second-generation Hsp90 Inhibitor

Review for Gastrointestinal Stromal Tumors

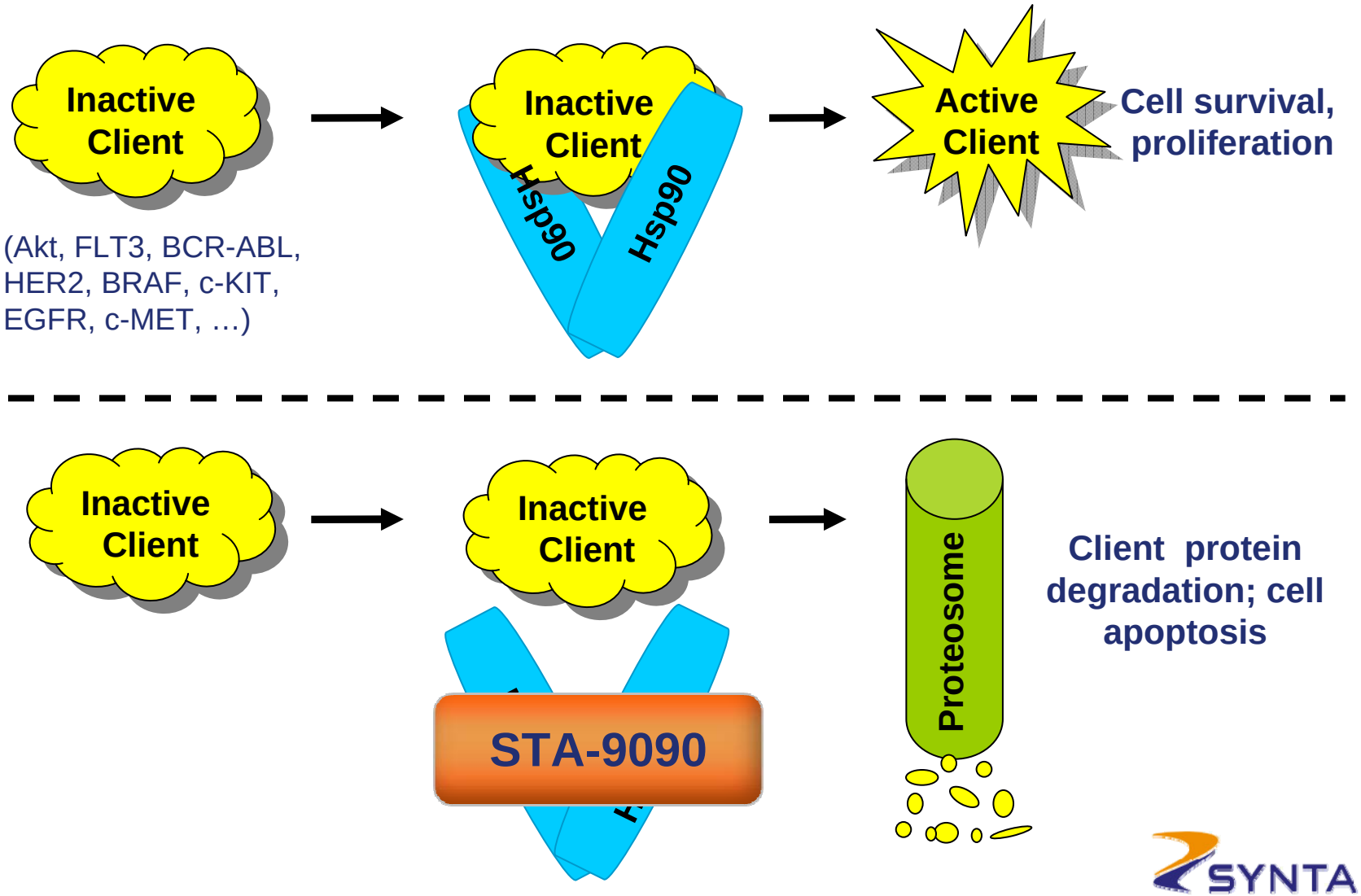
Hsp90 chaperones “client proteins” that drive many key features of cancer cells

Hsp90 helps maintain the shape and proper functioning of these proteins



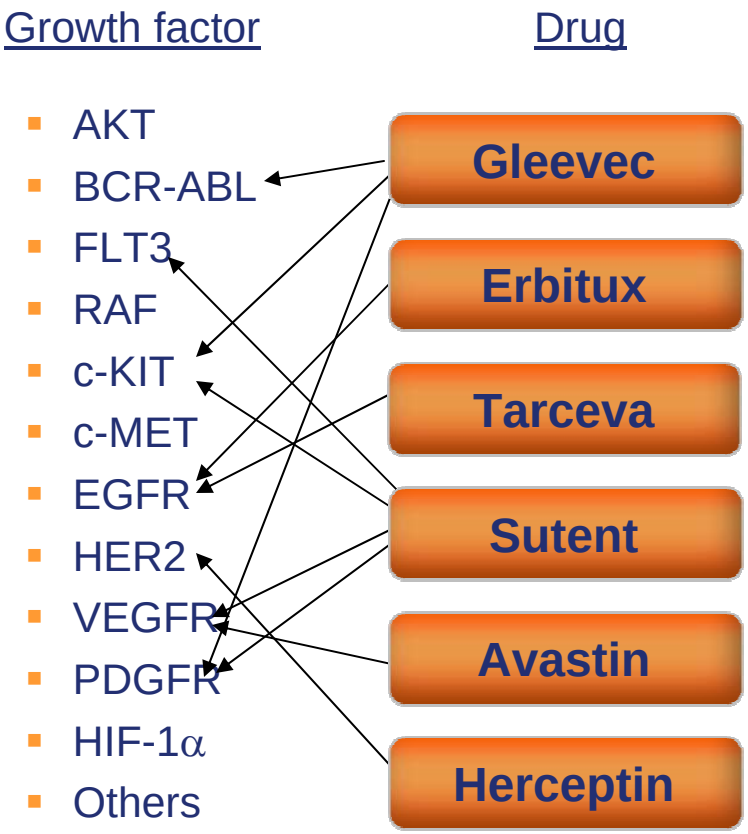
Xu, W. et al. Clin Cancer Res 2007;13:1625-1629.

Blocking Hsp90 causes degradation of client proteins, leading to tumor cell death



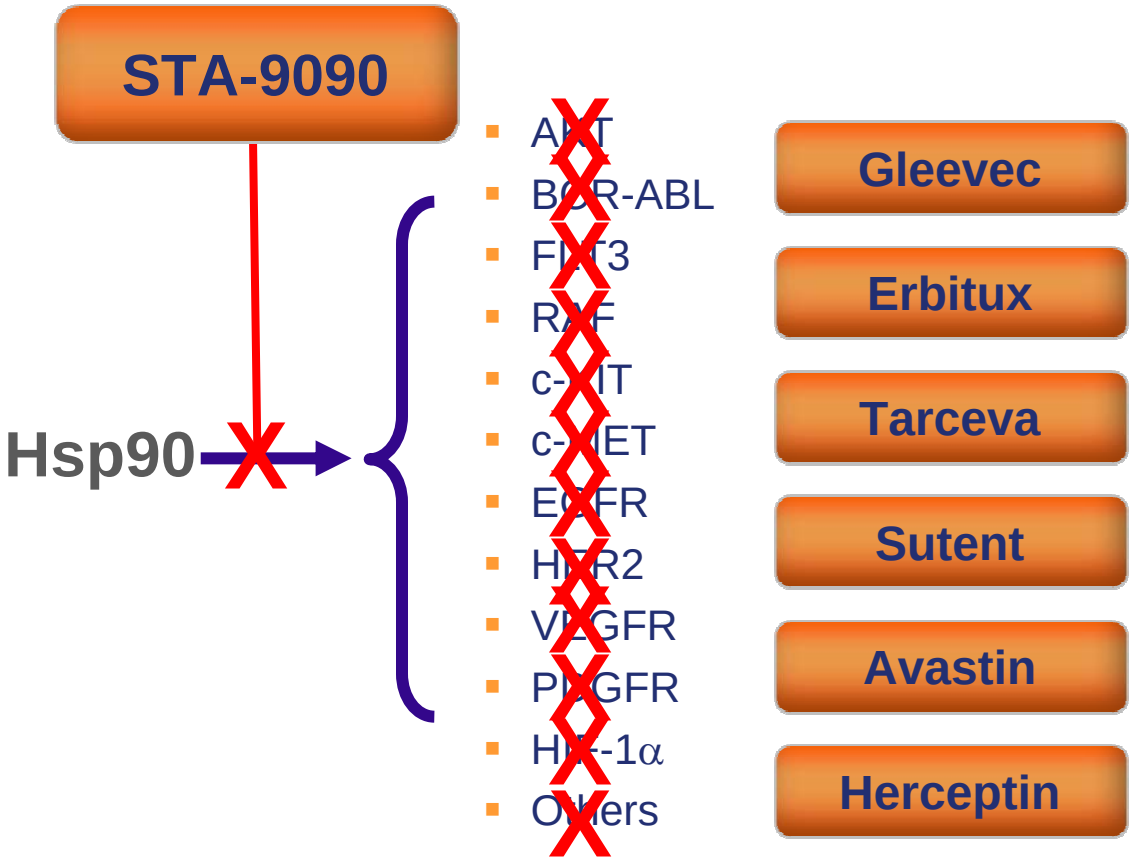
Cancer cells can have multiple, redundant drivers of growth and proliferation

The redundancy of growth factors helps cancer cells “evade” treatment by drugs that target one, or a small number, of these proteins



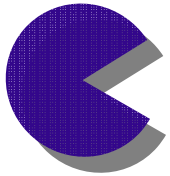
Blocking Hsp90 degrades many of these growth factors simultaneously

Eliminating multiple growth factors can help overcome drug resistance



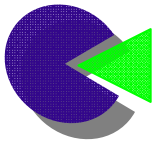
Blocking Hsp90 can also eliminate mutated client proteins, overcoming drug resistance

Protein X (e.g., kinase) drives a cancer



→ Cancer

Treat with Gleevec, Sutent, Tarceva, …



// Cancer

Resistance can emerge from mutation of the kinase

→ Cancer

Treat with STA-9090

// Cancer

The mutated protein also relies on Hsp90 for proper activation

// Cancer

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Example: overcoming resistance in GIST

In the two GIST cancer cell lines on the right, mutations have developed that make these cancers drug-resistant – the drug is unable to degrade the form of KIT protein driving the disease ("p-KIT"). STA-9090, however, can degrade the protein and kill the cancer cell.

Sunitinib-resistant KIT mutations retain biochemical sensitivity to STA-9090

J. A. Fletcher et al, G. D. Demetri; Brigham and Women's Hospital; Dana-Farber Cancer Institute; Harvard Medical School; Oregon Health and Science University: AACR-NCI-EORTC Nov 2009

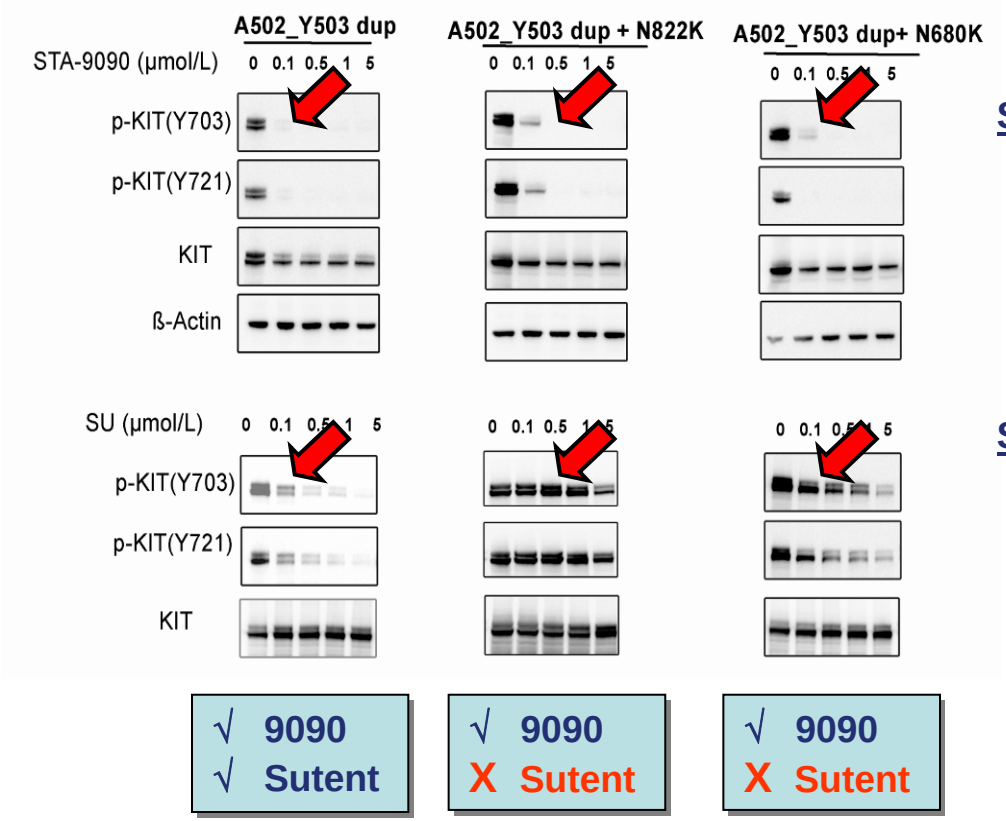

Fig. 1: Novel IM/SU-resistance mutations are inhibited by STA-9090. HEK293 cells were transfected with various KIT mutants identified in clinically-progressing GISTs. 24 hours after transfection, cells were exposed to varying concentrations of STA-9090 for 6 hours. Whole-cell lysates were immunostained for p-KIT(Y703), p-KIT(Y721), total KIT and ß-Actin. Sunitinib-resistant KIT mutations retain biochemical sensitivity to STA-9090.

Example: overcoming resistance in GIST

The highlighted cancers below, which have developed a form of KIT protein mutation that make them resistant to treatment with Gleevec, are still effectively killed by STA-9090. ("IC50" score is a measure of potency – the concentration of drug needed to kill 50% of cancer cells in a laboratory assay.)

Table 1: Cell viability IC50s in Ba/F3 cells transformed by KIT mutants with primary mutation only (Ex 9) vs primary + secondary mutations (Ex 9 + V654A).

Model	IC_{50}	STA-9090 (nM)	17-AAG (nM)	Gleevec (nM)
Ba/F3: KIT Exon 9		**15**	200	200
Ba/F3: KIT Exon 9 + V654A (ABP)		**15**	200	>1000

Table 2: Cell viability IC50s in KIT-dependent and KIT-independent (GIST62) GISTs

Cell line	IC_{50}	STA-9090 (nM)	17-AAG (nM)	Gleevec (nM)
GIST882: KIT Ex 13		**40**	200	300
GIST882B (17-AAG resistant)		**35**	>1000	300
GIST430: KIT Ex 11 + V654A (ABP)		**20**	300	>1000
GIST48: KIT Ex 11 + D820A (AL)		**20**	100	>1000
GIST62 (KIT-negative)		**>1000**	>1000	>1000

HSP90 inhibitor STA-9090 potently suppresses secondary KIT kinase-domain mutations responsible for gastrointestinal stromal tumor (GIST) progression during imatinib therapy -- J. A. Fletcher et al, G. D. Demetri; Brigham and Women's Hospital; Dana-Farber Cancer Institute; Harvard Medical School; Oregon Health and Science University; Synta. AACR-NCI-EORTC Nov 2009

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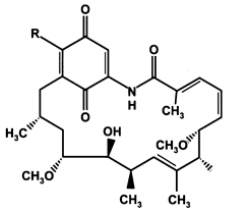
Hsp90 history: first-generation inhibitors have limitations

Heat shock proteins discovered

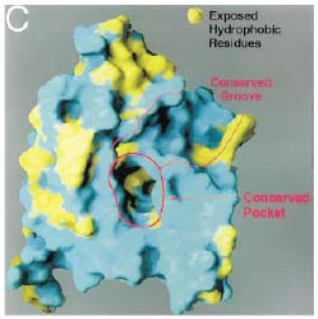


Geldanamycin purified for use as antibiotic

Antibiotic **radicicol** shown to inhibit Hsp90

1962 — 1970 — 1997 — 1998 — 2000 — 2004 — 2008 …

Crystal structure elucidated for binding pocket in Hsp90

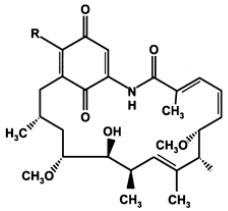


First-generation Hsp90 inhibitors (ansamycins, 17-AAG) shown to have modest potency but relatively toxic

Second-generation inhibitors seek to improve potency, safety

Heat shock proteins discovered

1962



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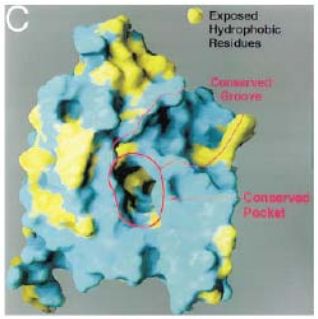

1998

First-generation Hsp90 inhibitors (ansamycins; 17-AAG) shown to have modest potency but relatively toxic

2000

2004

Second-generation, small-molecule Hsp90 inhibitors

2008 …

STA-9090

STA-9090 Clinical Status Summary

- Currently in six ongoing Phase 1, Phase 2 trials. Initial results from these trials to be presented at medical meetings in 2010
- Phase 2 clinical trial in GIST was initiated in the end of 2009 and is currently enrolling patients
- Information about the Phase 2 trial in GIST can be found at http://clinicaltrials.gov (identifier NCT01039519)

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