Mechanisms of cancer drug susceptibility and resistance

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ZRC-1863

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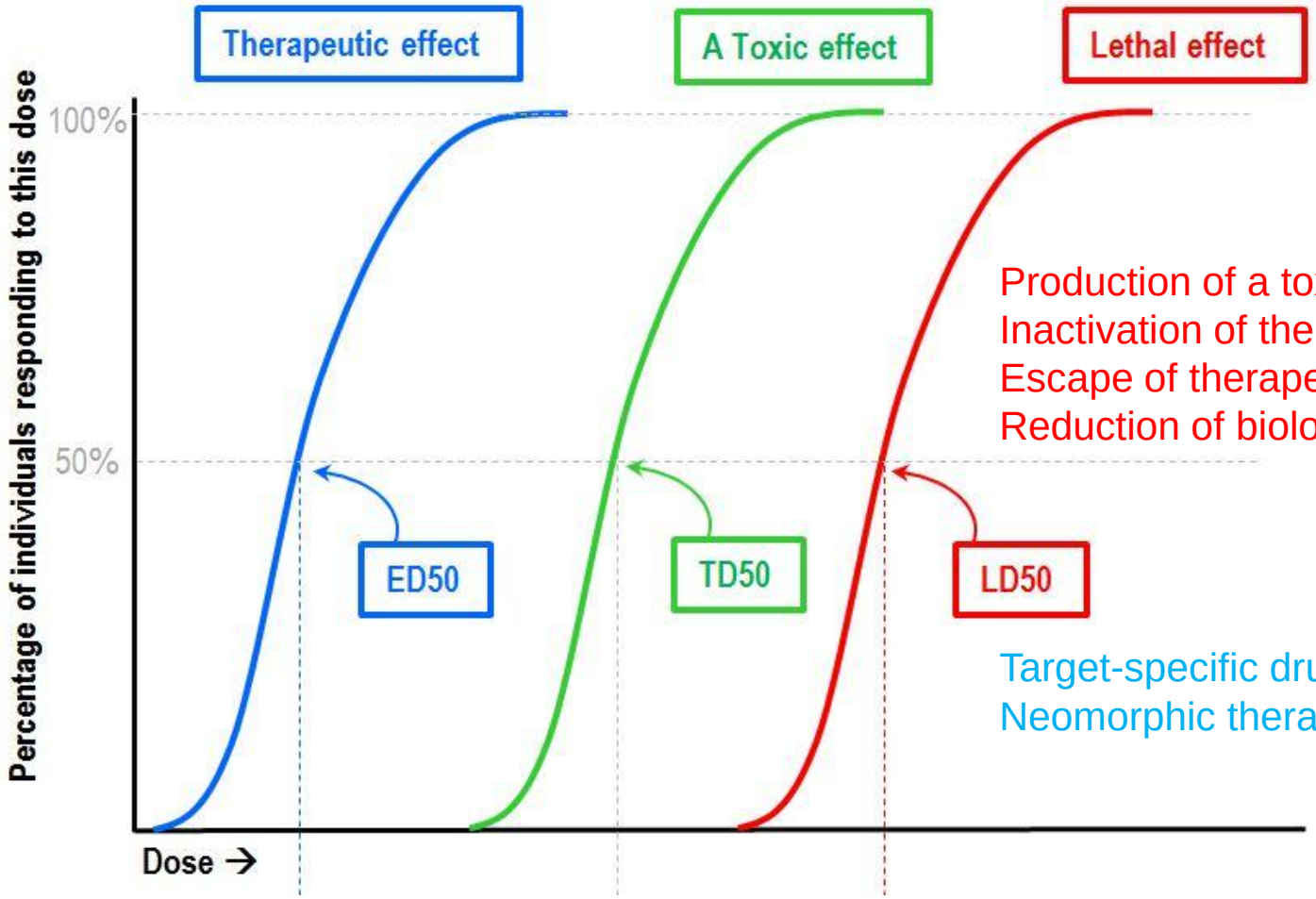
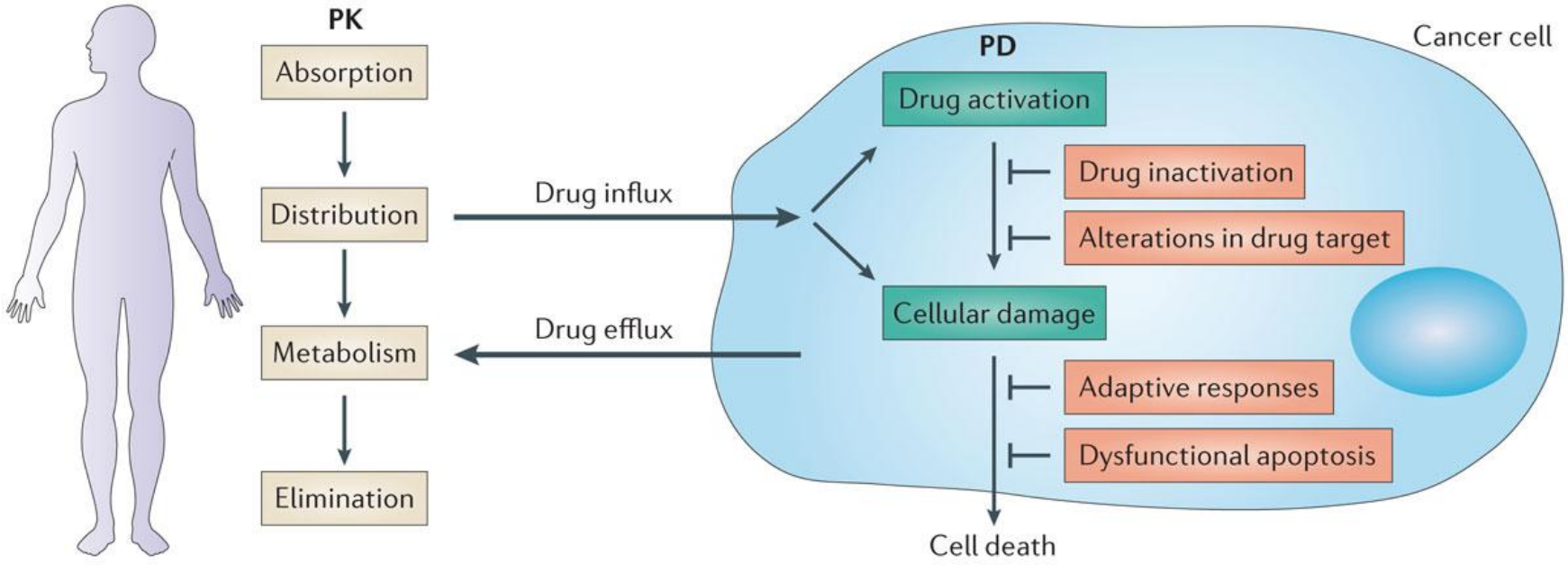
Therapeutic window



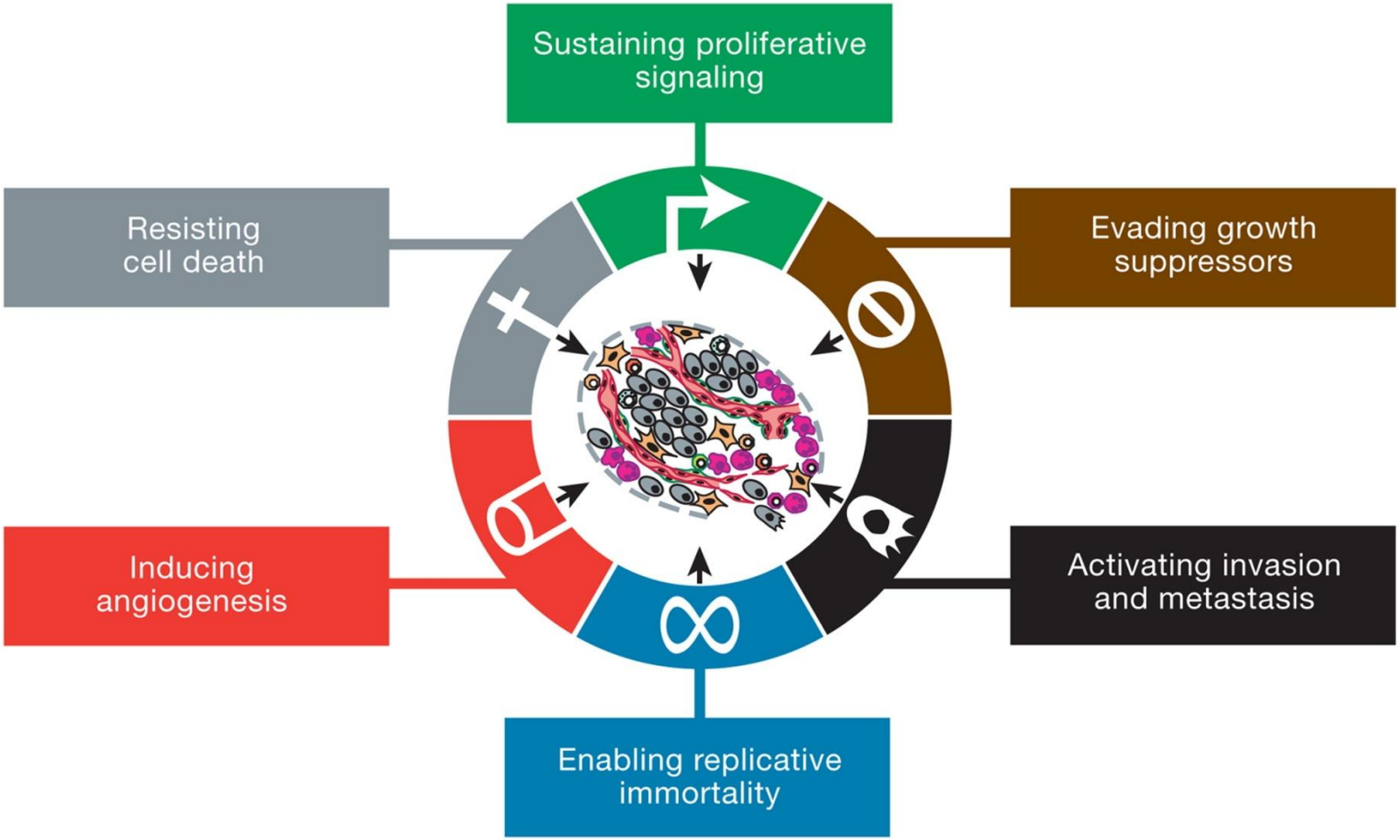
Production of a toxic metabolite
Inactivation of therapeutic drug
Escape of therapeutic target
Reduction of biologic dependency

Target-specific drug delivery/activation
Neomorphic therapeutic target

Therapeutic window



Hallmarks of cancer

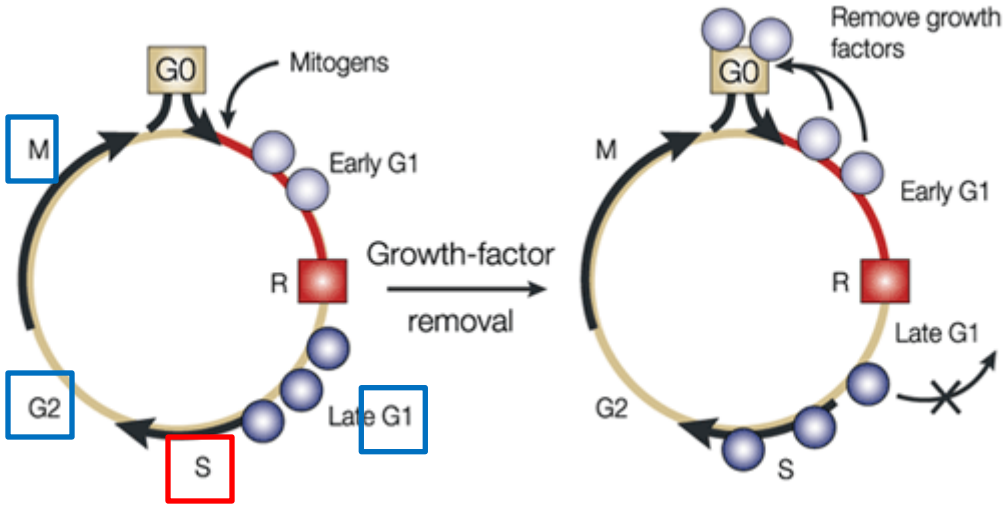


http://www.ncbi.nlm.nih.gov/pubmed/21376230

Targeting aberrant cell proliferation

Antimetabolites

Cell cycle inhibitors

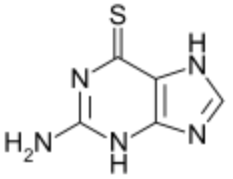


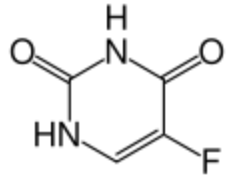
http://www.ncbi.nlm.nih.gov/pubmed/11008002
http://www.ncbi.nlm.nih.gov/pubmed/11902577

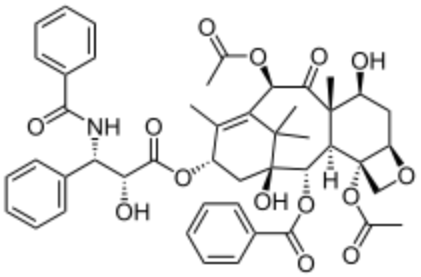
Targeting aberrant cell proliferation

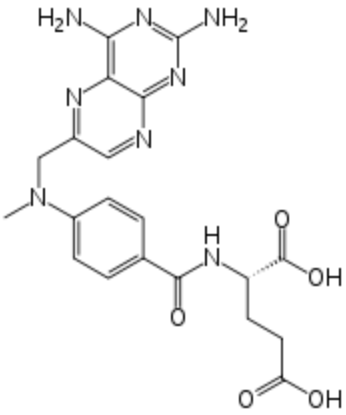
Antimetabolites

- Purine analogues (thioguanine, fludarabine)
- Pyrimidine analogues (5-fluorouracil, cytosine arabinoside)
- Antifolates (methotrexate)



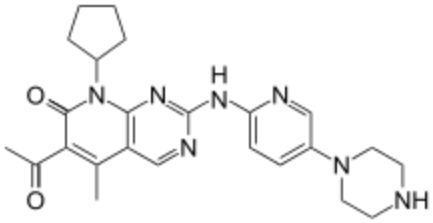






Cell cycle inhibitors

- Antimitotics (vincristine, paclitaxel)
- CDK inhibitors (palbociclib, LEE011)



http://www.ncbi.nlm.nih.gov/pubmed/11008002
http://www.ncbi.nlm.nih.gov/pubmed/11902577

Targeting aberrant cell proliferation

Therapeutic window depends on relative cell cycle kinetics of cancer as compared to non-cancer cells

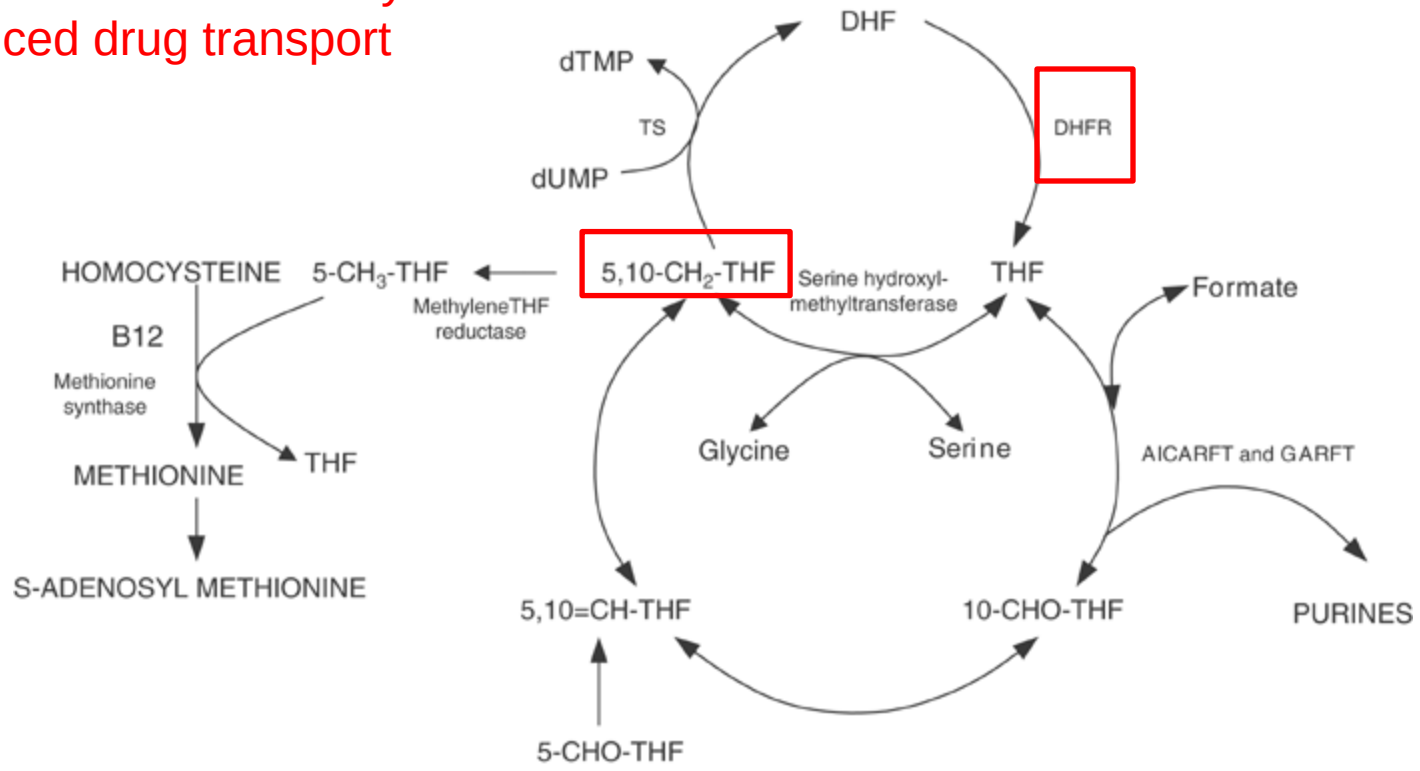
W i d e : Amplification of cyclin D or deletion of CDKN2A/p16, activating CDK4, such as in familial melanoma

Narrow: Overexpression of FPGS, leading to increased methotrexate polyglutamylation and inhibition of DHFR, such as in Down's syndrome acute lymphoblastic leukemia

http://www.ncbi.nlm.nih.gov/pubmed/15630450
http://www.ncbi.nlm.nih.gov/pubmed/14576850

Methotrexate resistance

Increased DHFR activity
Reduced drug transport



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Selective Multiplication of Dihydrofolate Reductase Genes in Methotrexate-resistant Variants of Cultured Murine Cells*

(Received for publication, November 4, 1977)

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The rate of dihydrofolate reductase synthesis in the AT-3000 line of methotrexate-resistant murine Sarcoma 180 cells is approximately 200- to 250-fold greater than that of the sensitive, parental line. We have purified cDNA sequences complementary to dihydrofolate reductase mRNA and subsequently used this probe to quantitate dihydrofolate reductase mRNA and gene copies in each of these lines. Analysis of the association kinetics of the purified cDNA with DNA from sensitive and resistant cells indicated that the dihydrofolate reductase gene is selectively multiplied approximately 200-fold in the resistant line. A similar analysis of a partially revertant line of resistant cells indicated that the loss of resistance observed when the AT-3000 line is grown in the absence of methotrexate is associated with a corresponding decrease in the dihydrofolate reductase gene copy number. In each of these lines the relative number of dihydrofolate reductase gene copies is proportional to the cellular level of dihydrofolate reductase and dihydrofolate reductase mRNA sequences.

We have also studied parental and methotrexate-resistant lines of L1210 murine lymphoma cells. Both resistance and an associated 35-fold increase in the level of dihydrofolate reductase appear to be stable properties of the resistant L1210 line since we find no decrease in either parameter in over 100 generations of growth in the absence of methotrexate. Once again, we find that the increased levels of dihydrofolate reductase in the methotrexate-resistant L1210 line are associated with a proportional increase in the number of dihydrofolate reductase gene copies. In this case the dihydrofolate reductase gene copy number appears to be relatively stable in the resistant line. Therefore, we conclude that selective multiplication of the dihydrofolate reductase gene can account for the overproduction of dihydrofolate reductase in both stable and unstable lines of methotrexate-resistant cells.

The resistance of both human neoplasms (1) and various lines of cultured cells (2–11) to the 4-amino analogs of folic acid is often associated with an increase in the cellular content of dihydrofolate reductase. We have been studying the overproduction of this enzyme in variant lines of murine Sarcoma 180 cells that were selected by a step-wise procedure for growth in the presence of high concentrations of methotrexate (a folic acid analogue). Dihydrofolate reductase comprises as much as 6% of the soluble protein in the methotrexate-resistant AT-3000 line, representing an increase of more than 200-fold over the level in the sensitive, parental cells (12). Purified dihydrofolate reductase from resistant cells appears to be identical to that from sensitive cells; and, in addition, the relative half life of the enzyme is similar to these lines (12). We have demonstrated that the increased level of dihydrofolate reductase in resistant cells is due to an increased rate of enzyme synthesis (12), and that, in turn, this increase is correlated with increased cellular levels of translatable dihydrofolate reductase mRNA (13).

One of the most interesting characteristics of the AT-3000 line is that high levels of resistance are lost when these cells are grown in the absence of methotrexate (3). Loss of resistance is associated with a decrease in the level of dihydrofolate reductase (3, 12), and a corresponding decrease in both the rate of dihydrofolate reductase synthesis (12) and the level of the specific mRNA activity (13). Several lines of evidence suggest that these decreases are due to the instability of the variation (mutation?) which leads to increased enzyme synthesis (12). Instability is also a characteristic of methotrexate

http://www.ncbi.nlm.nih.gov/pubmed/627542

Mechanism of DHFR overexpression?

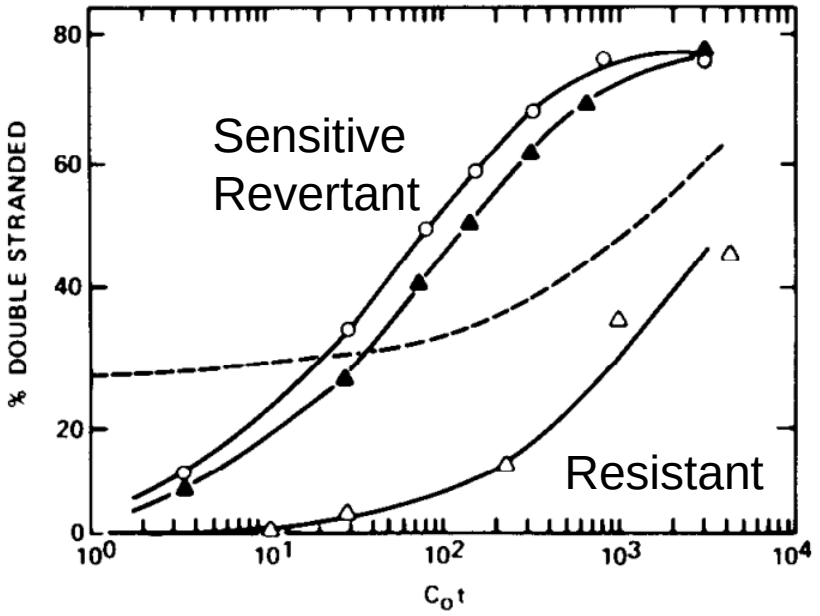
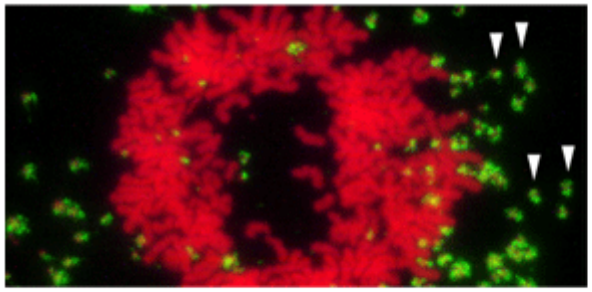


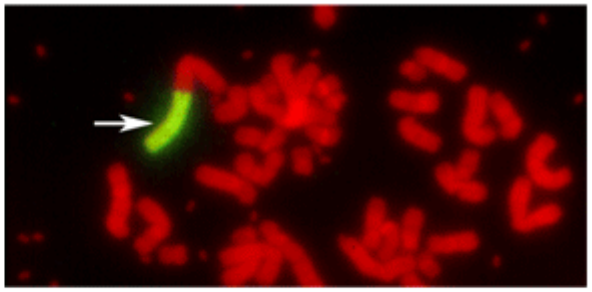
FIG. 9. Association kinetics of purified cDNA with DNA prepared from sensitive and methotrexate-resistant lines of L1210 cells. DNA prepared from various lines of L1210 cells was denatured and allowed to reanneal in the presence of a trace amount of purified [^{3}H]cDNA, and the extent of association at indicated C_0t values determined by chromatography on hydroxylapatite (see "Experimental Procedures" for details). Reassociation of the driver DNA summarized for all three reactions, - - -; association of the purified [^{3}H]cDNA with DNA from L1210S, △——△; L1210RR, ○——○; and L1210RR grown for approximately 100 cell doublings in the absence of methotrexate, ▲——▲.

http://www.ncbi.nlm.nih.gov/pubmed/627542

Genomic plasticity: Double minute chromosomes



The target genes have assumed the structure of DMs (double minutes) and been amplified



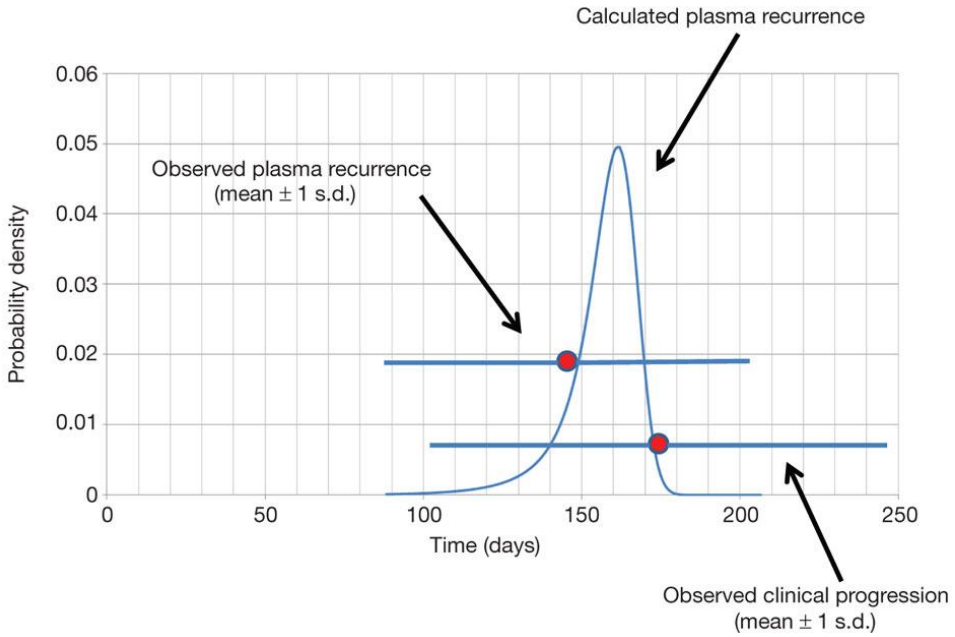
Target gene amplified by HSRs

Implication:

If cancer cells possess mechanisms that can generate large numbers of pleiomorphic states before therapeutic effect is achieved, then resistance $\propto N_{states} \times t_{mutation} / t_{therapy}$

Genomic plasticity: Fundamental cause of resistance

The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers



Implication:

If cancer cells possess mechanisms that can generate large numbers of pleiomorphic states before therapeutic effect is achieved, then resistance $\propto N_{states} \times t_{mutation} / t_{therapy}$

http://www.ncbi.nlm.nih.gov/pubmed/22722843

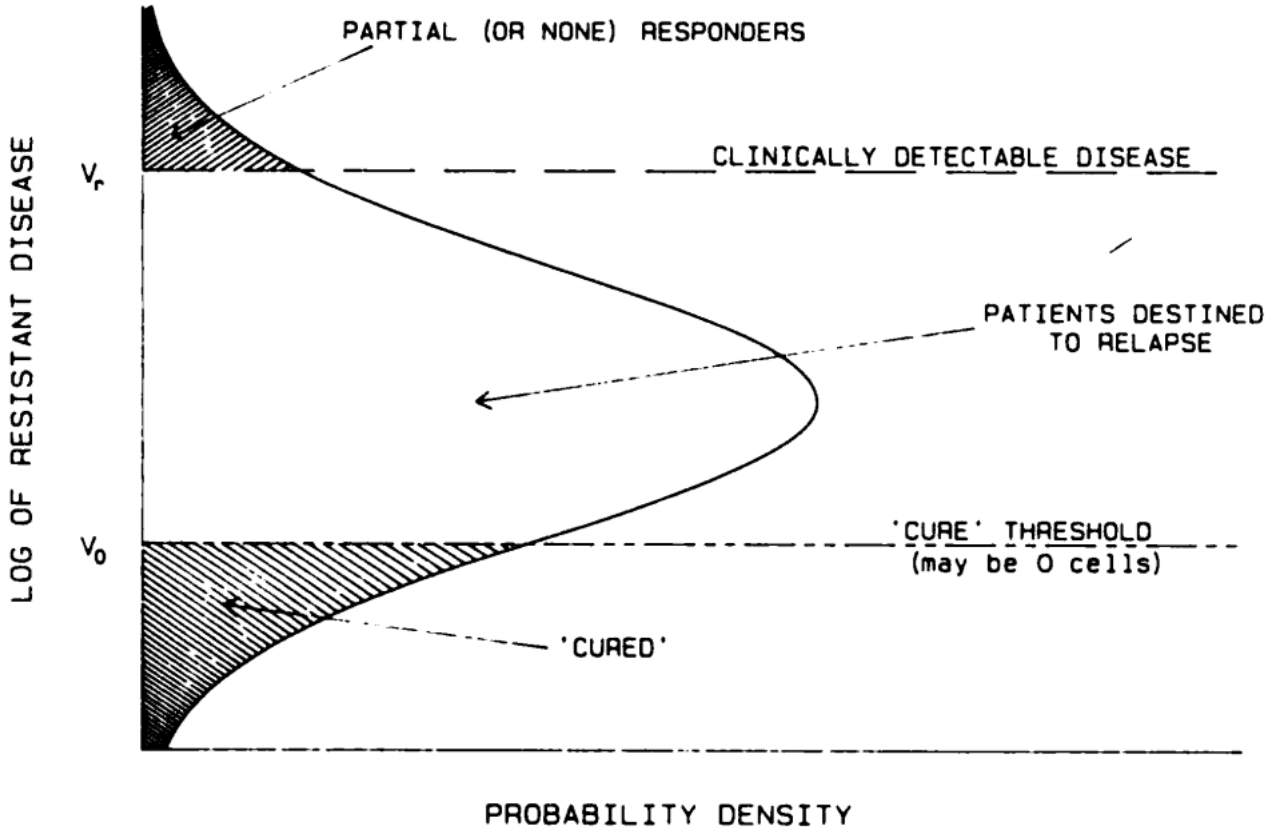
Goldie-Coldman hypothesis

Goldie & Coldman. *A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate.* Cancer Treat Rep (1979)

A mathematic model has been developed relating the drug sensitivity of a tumor to its own spontaneous mutation rate towards phenotypic drug resistance. The proportion as well as the absolute numbers of resistant cells will increase with time and the fraction of resistant cells within tumor colonies of the same size with vary depending on whether mutation occurs as an early or late event. Analysis of the model indicates that the probability of the appearance of a resistant phenotype increases with the mutation rate. Furthermore, for any population of tumors with a non-zero mutation rate the likelihood of there being at least one resistant cell will go from a condition of low to high probability over a very short interval in the tumor's biologic history.

http://www.ncbi.nlm.nih.gov/pubmed/526911

Goldie-Coldman hypothesis



http://www.ncbi.nlm.nih.gov/pubmed/526911

Goldie-Coldman hypothesis

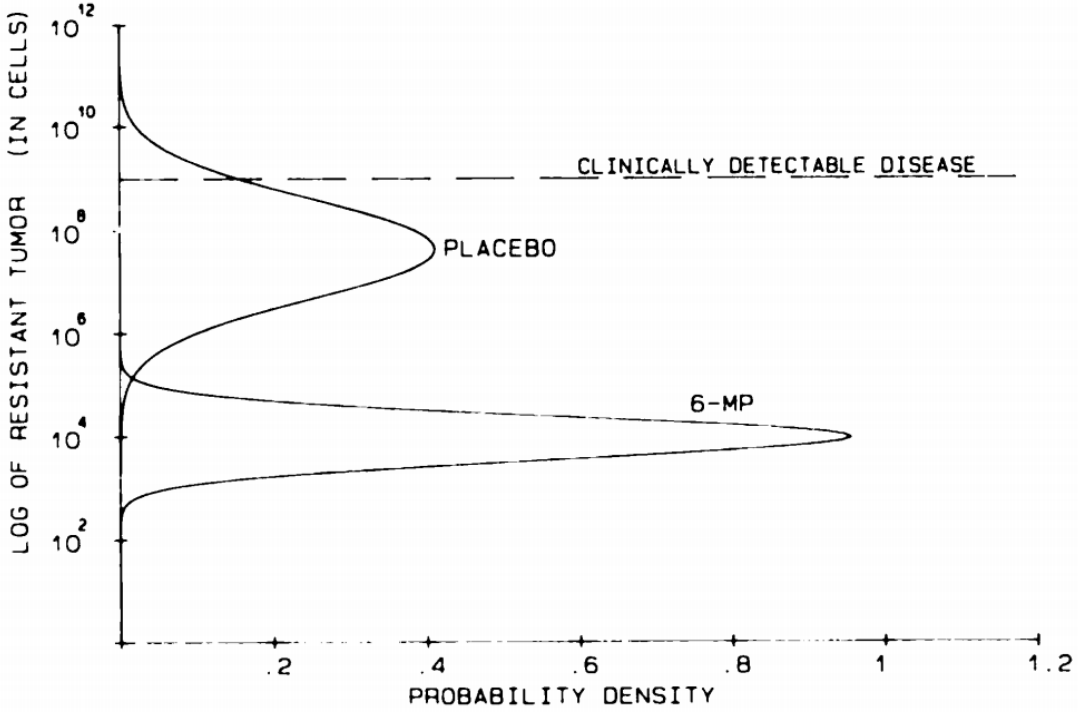
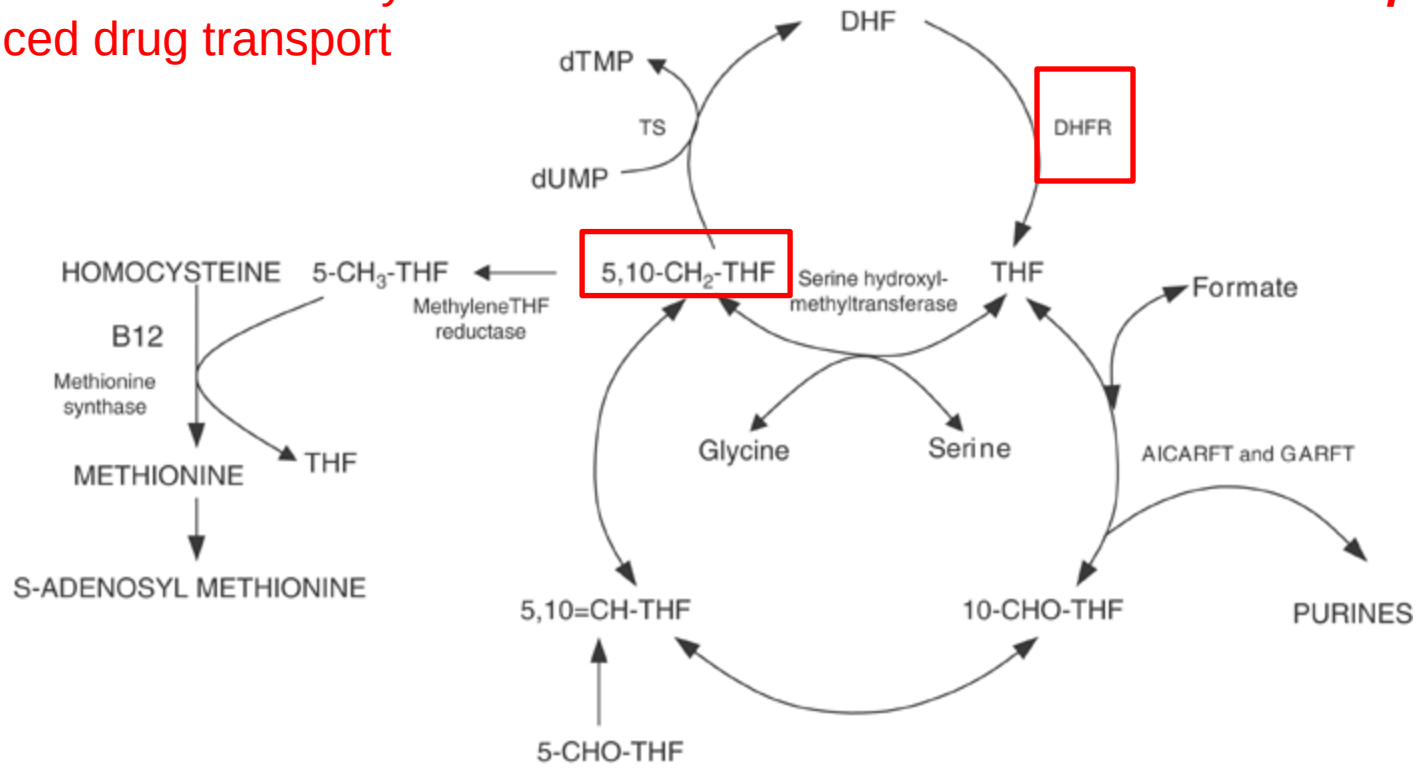


Fig. 8. Estimated distributions of resistant disease for ALL patients treated with prednisone with or without 6-MP, showing the additional 4 logs of cell-kill achieved with the 6-MP.

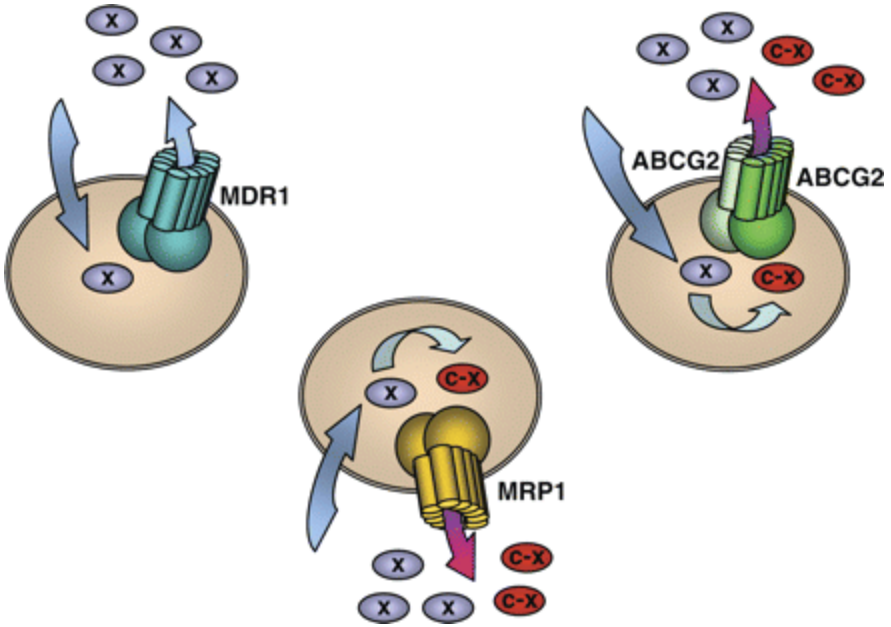
Methotrexate resistance

Increased DHFR activity
Reduced drug transport

Genomic plasticity



Mechanism of drug efflux



Physiologic function: Xenobiotic transport, quorum sensing

http://www.ncbi.nlm.nih.gov/pubmed/17015488

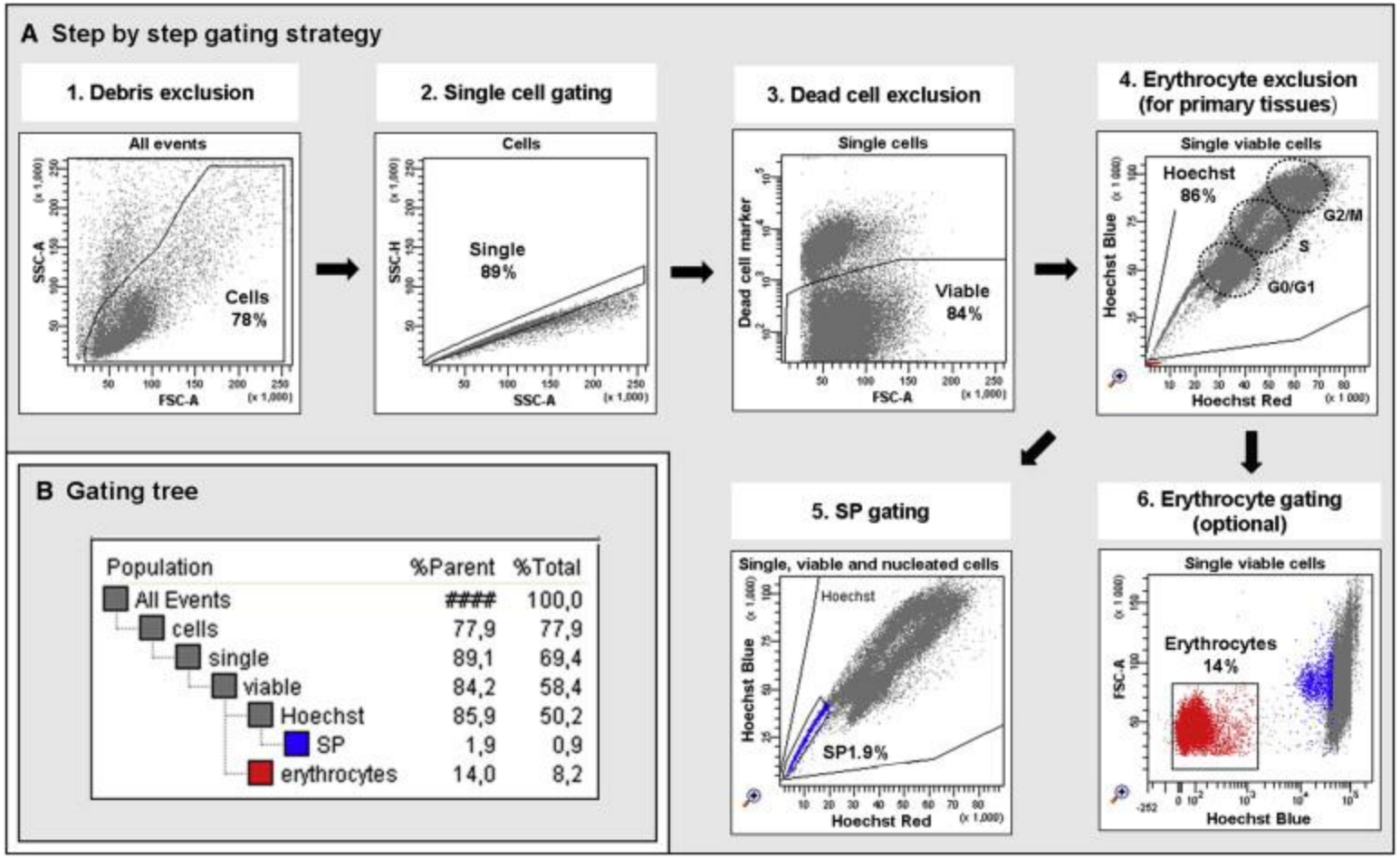
Mechanism of drug efflux

Table 1 | **ABC transporters involved in drug resistance**

Gene	Protein/alias	Chemotherapeutic drugs effluxed by transporter	Other drugs and substrates
ABCA2	ABCA2	Estramustine	–
ABCB1	PGP/MDR1	Colchicine, doxorubicin, etoposide, vinblastine, paclitaxel	Digoxin, saquinivir,
ABCC1	MRP1	Doxorubicin, daunorubicin, vincristine, etoposide, colchicine, camptothecins, methotrexate	Rhodamine
ABCC2	MRP2	Vinblastine, cisplatin, doxorubicin, methotrexate	Sulfinpyrazone
ABCC3	MRP3	Methotrexate, etoposide	–
ABCC4	MRP4	6-mercaptopurine, 6-thioguanine and metabolites; methotrexate	PMEA, cAMP, cGMP
ABCC5	MRP5	6-mercaptopurine, 6-thioguanine and metabolites	PMEA, cAMP, cGMP
ABCC6	MRP6	Etoposide	–
ABCC11	MRP8	5-fluorouracil	PMEA, cAMP, cGMP
ABCG2	MXR/BCRP	Mitoxantrone, topotecan, doxorubicin, daunorubicin, irinotecan, imatinib, methotrexate	Pheophorbide A, Hoechst 33342, rhodamine

ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanine monophosphate; MDR, multidrug resistance; MRP, multidrug-resistance-associated protein; MXR, mitoxantrone resistance protein; PMEA, 9-[2-(phosphonomethoxy)ethyl]adenine.

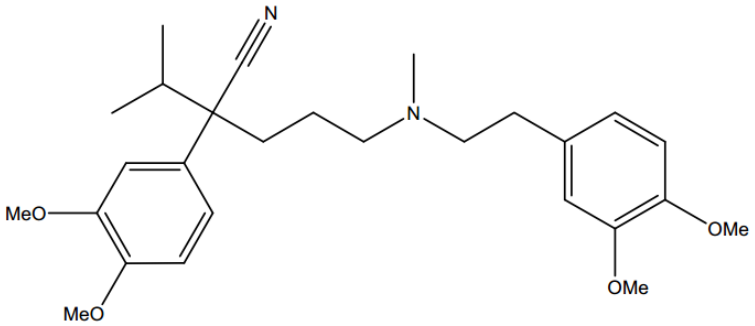
Side population: Physiologic function of MDR transporters?



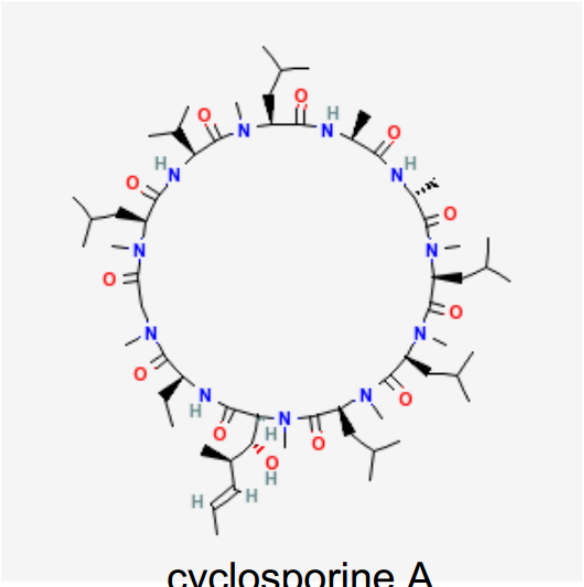
http://www.ncbi.nlm.nih.gov/pubmed/21295271

P-gp inhibitors

Class	Pharmaceutical code name	USAN name	Chemical class
1st Generation	Verapamil	–	Diphenylalkylamine Ca-channel blocker
	Cyclosporine A	–	Cyclic oligopeptide immunosuppressant
	Tamoxifen	–	Nonsteroidal anti-estrogen



verapamil



cyclosporine A

1st generation: not developped for MDR pumps inhibition, low affinity for pumps, side effects at the concentrations required to inhibit P-gp in vivo

P-gp inhibitors

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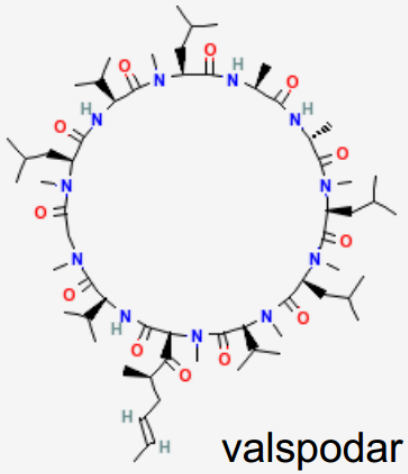
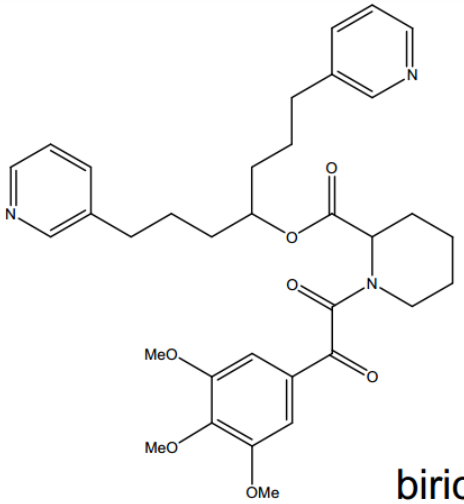
1st Generation	Verapamil	–	Diphenylalkylamine Ca-channel blocker
	Cyclosporine A	–	Cyclic oligopeptide immunosuppressant
	Tamoxifen	–	Nonsteroidal anti-estrogen
2nd Generation	PSC833	Valspodar	Non-immunosuppresive derivative of cyclosporine A
	VX-710	Biricodar	Derivative of FK-506 - macrocyclic antibiotic
	S9788	–	Triazine
	SR33557	–	Indolizin sulfone

QSAR



valspodar



biricodar

2nd generation: more potent, toxicity reduced, but anti-cancer drugs pharmacokinetic impaired (metabolisme & elimination, via interactions with cytochrome P450)

P-gp inhibitors

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1st Generation	Verapamil	–	Diphenylalkylamine Ca-channel blocker
	Cyclosporine A	–	Cyclic oligopeptide immunosuppressant
QSAR	Tamoxifen	–	Nonsteroidal anti-estrogen
2nd Generation	PSC833	Valspodar	Non-immunosuppresive derivative of cyclosporine A
	VX-710	Biricodar	Derivative of FK-506 - macrocyclic antibiotic
	S9788	–	Triazine
	SR33557	–	Indolizin sulfone
3rd Generation	GF120918	Elacridar	Acridonecarboximide
	LY335979	Zosuquidar	Cyclopropyldibenzosuberane
Combinatorial chemistry	XR9576	Tariquidar	Anthranilamide
	OC144-093	Ontogen	Diarylimidazole

3rd generation: more specific and powerful, under clinical trials

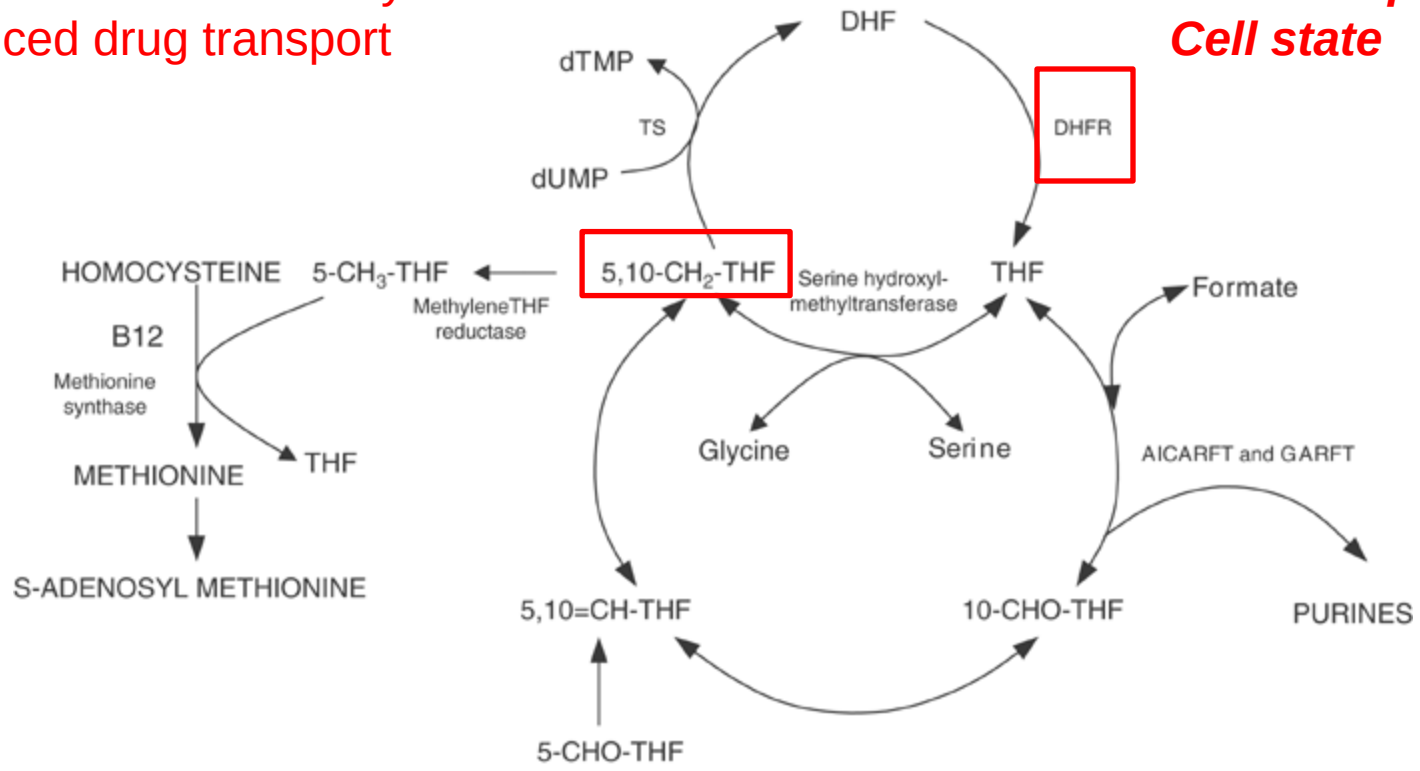
Challenge: 30-100 different MDR transporters

http://www.ncbi.nlm.nih.gov/pubmed/17208306

Methotrexate resistance

Increased DHFR activity
Reduced drug transport

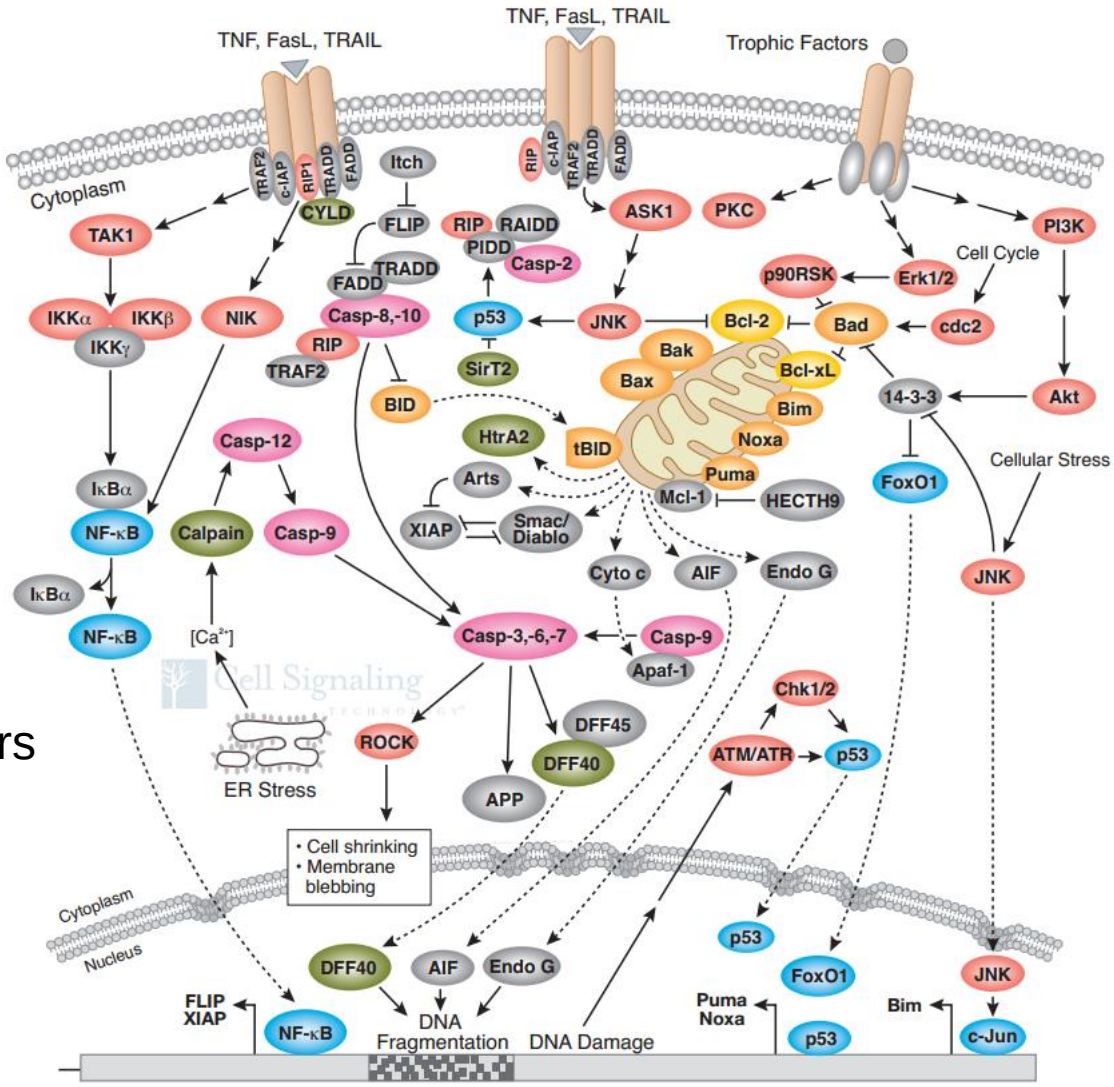
Genomic plasticity
Cell state



Targeting aberrant cell survival

Mitogenic signaling inhibitors

Apoptosis resistance inhibitors



Targeting aberrant cell survival

Mitogenic signaling inhibitors

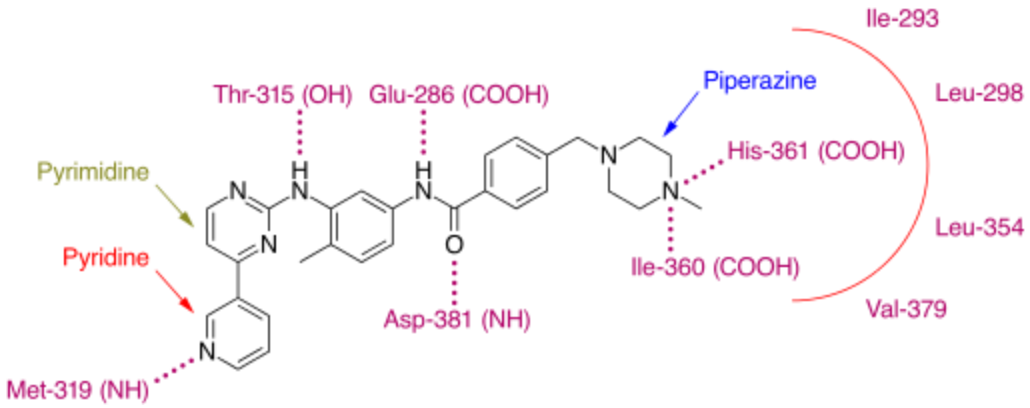
- (Receptor) tyrosine kinase inhibitors (imatinib, crizotinib)
- Neutralizing antibodies (trastuzumab/Herceptin, cetuximab/Erbitux)

Apoptosis resistance inhibitors

- BH3 mimetics (ABT-737, obatoclax)
- MDM2 inhibitors (Nutlin-3)

Target escape: TKI resistance

Binding of BCR-ABL1 by imatinib



Physical mechanisms of resistance?

Target escape: TKI resistance

Mechanisms of Autoinhibition and STI-571/Imatinib Resistance Revealed by Mutagenesis of BCR-ABL

S N	Mutations		Cellular IC_{50} (μM)
	Type Ib	Type Ia	
1	L267R/V	L248R/V	> 20.0 R
2	Y272H/C/F	Y253H/C/F	17.7 H
3	V275A	V256A	0.6
4	A288V	A269V	1.1
5	K290N	K271N	INACTIVE KINASE
6	E305K/V	E286K/V	INACTIVE KINASE
7	V308S	V289S	1.4
8	M309L/T	M290L/T	ND
9	I332A	I313A	INACTIVE KINASE
10	T334 I/S/G	T315 I/S/G	>20.0 I; 3.8 S
11	F336L	F317L	2.3
12	M337A	M318A	0.6
13	G340W	G321W	1.5
14	I379F	I360F	ND
15	F401A	F382A	INACTIVE KINASE

http://www.ncbi.nlm.nih.gov/pubmed/2654249
http://www.ncbi.nlm.nih.gov/pubmed/20072125

Target escape: TKI resistance

Mechanisms of Autoinhibition and STI-571/Imatinib Resistance Revealed by Mutagenesis of BCR-ABL

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3	V275A	V256A	0.6
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5	K290N	K271N	INACTIVE KINASE
6	E305K/V	E286K/V	INACTIVE KINASE
7	V308S	V289S	1.4
8	M309L/T	M290L/T	ND
9	I332A	I313A	INACTIVE KINASE
10	T334 I/S/G	T315 I/S/G	>20.0 I; 3.8 S
11	F336L	F317L	2.3
12	M337A	M318A	0.6
13	G340W	G321W	1.5
14	I379F	I360F	ND
15	F401A	F382A	INACTIVE KINASE

Maintenance of kinase activity and interference with inhibitor binding

http://www.ncbi.nlm.nih.gov/pubmed/2654249
http://www.ncbi.nlm.nih.gov/pubmed/20072125

Target escape: TKI resistance

Origin of escape mutants?

The Presence of Typical and Atypical BCR-ABL Fusion Genes in Leukocytes of Normal Individuals: Biologic Significance and Implications for the Assessment of Minimal Residual Disease

By Shikha Bose, Michael Deininger, Joanna Gora-Tybor, John M. Goldman, and Junia V. Melo

The number of genetic lesions necessary to generate leukemia in humans is unknown, but it is possible that certain specific abnormalities, eg, fusion genes, known to be associated with acute and chronic leukemia are produced relatively frequently in human cells but require other events to occur before the leukemia becomes manifest. We investigated this possibility by studying peripheral blood leukocytes from normal individuals and various hematopoietic cell lines for the presence and expression of the p210 and the p190 types of the BCR-ABL gene associated with chronic myeloid leukemia (CML) and acute lymphoblastic leukemia. We used two-step reverse transcriptase-polymerase chain reaction (RT-PCR) assays in which batches of 10^8 cells per sample were tested in 40 replicate reactions. We estimate that this assay is 1.5 logs more sensitive than the two-step RT-PCR assays that we use routinely to assess minimal residual disease. BCR-ABL fusion gene transcripts of various configurations were found in circulating leukocytes from 12 of the 16 healthy adults analyzed. Transcripts with an e1a2 junction (p190 BCR-ABL) were present in 11 and p210-type transcripts with b2a2 and/or b3a2 junctions were detected in 4 individuals. The same RT-PCR assays in non-CML cell lines showed the presence of classical or aberrant p210-type mRNA in 3 of 7 lines and of p190-type transcripts in all 7 lines of hematopoietic origin (HL60, KG1, U937, Kasumi, Jurkat, JVM13, and JVM25), whereas the NIH3T3 murine fibroblast line was reproducibly negative for these fusion genes. These findings confirm and extend previous reports on the detection of leukemia-associated genes in normal leukocytes and suggest that certain fusion genes are generated relatively frequently in hematopoietic cells, but only infrequently do the cells acquire the additional changes necessary to produce leukemia in humans. Although there is only a small probability that such innocent BCR-ABL–carrying leukocytes are detected by conventional RT-PCR assays, they may be the source of some sporadically positive tests in leukemia patients in long-term remission.

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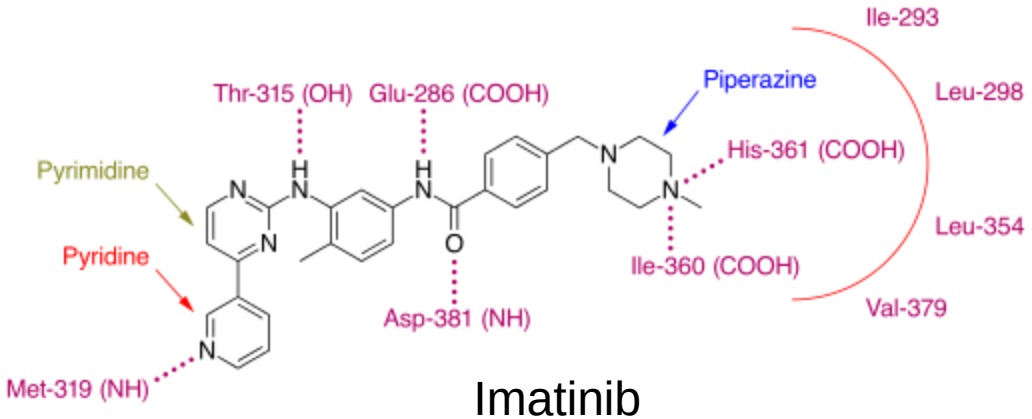
http://www.ncbi.nlm.nih.gov/pubmed/9787174

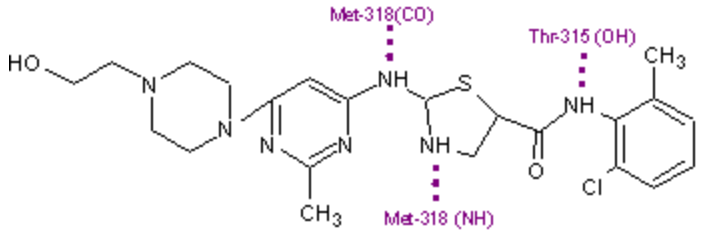
Target escape: TKI resistance

How to overcome resistance to inhibitor binding mutants?

Vary modes of inhibitor binding



Imatinib



Dasatinib

http://www.ncbi.nlm.nih.gov/pubmed/16740718

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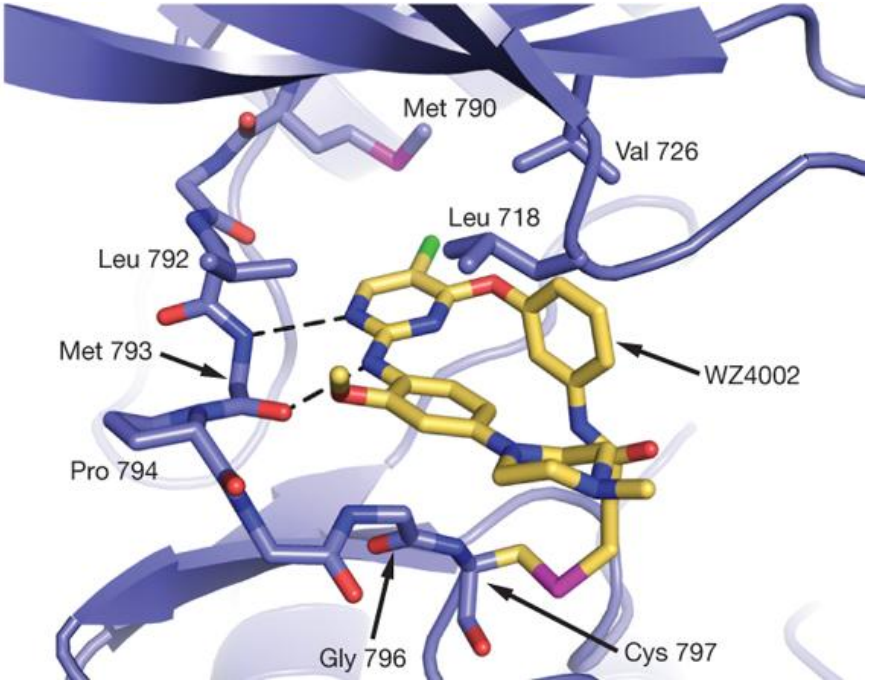


Michael addition of acrylamide to cysteine thiol to generate covalent non-competitive inhibitor

http://www.ncbi.nlm.nih.gov/pubmed/20033049

Target reactivation: TKI resistance

Autocrine activation of the MET receptor tyrosine kinase in acute myeloid leukemia

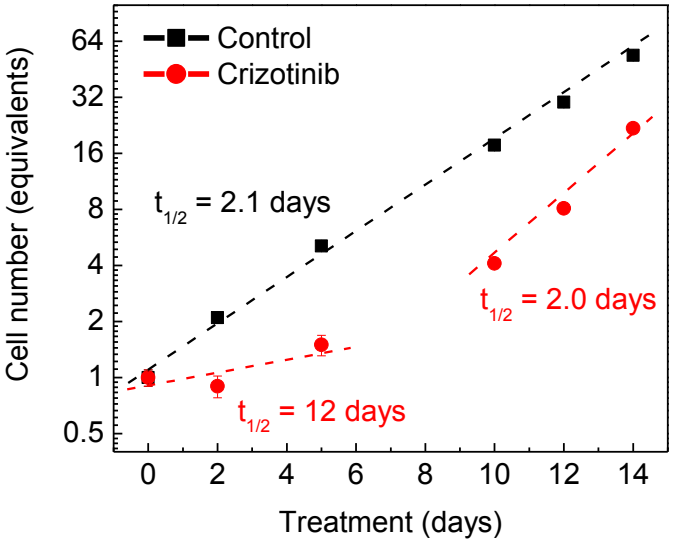
EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib

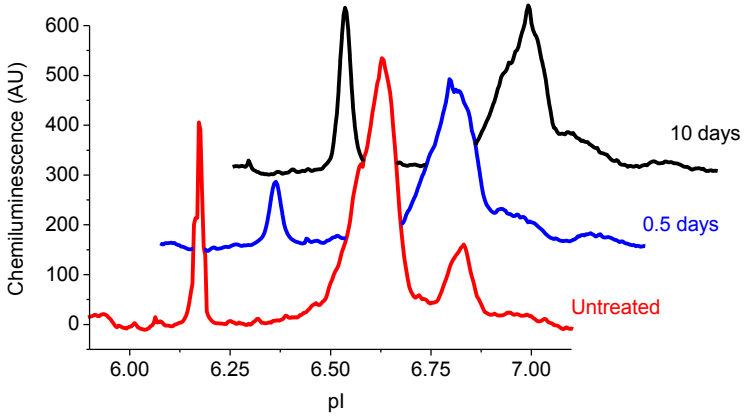
Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion

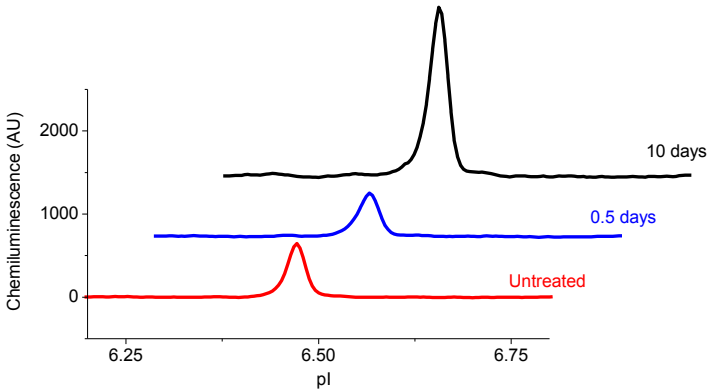
Relief of profound feedback inhibition of mitogenic signaling by RAF inhibitors attenuates their activity in BRAFV600E melanomas

http://www.ncbi.nlm.nih.gov/pubmed/22683780
http://www.ncbi.nlm.nih.gov/pubmed/22448344
http://www.ncbi.nlm.nih.gov/pubmed/23153539
http://www.ncbi.nlm.nih.gov/pubmed/22763439

Target reactivation: TKI resistance







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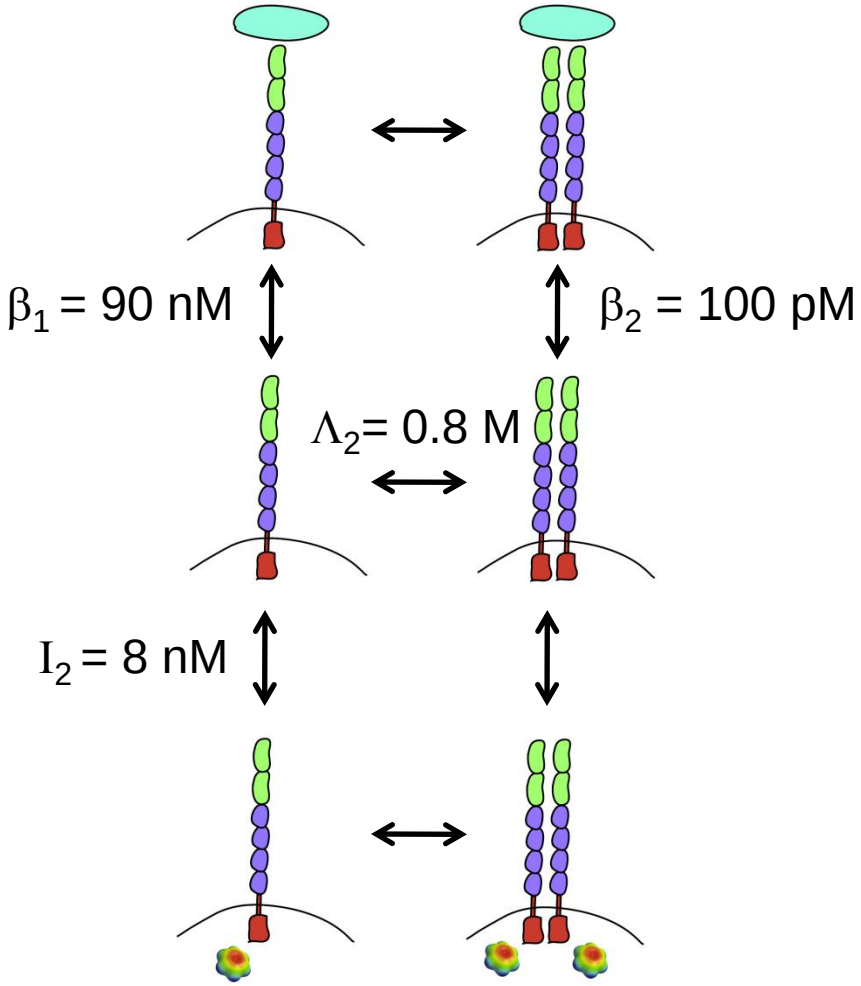
Target reactivation: TKI resistance



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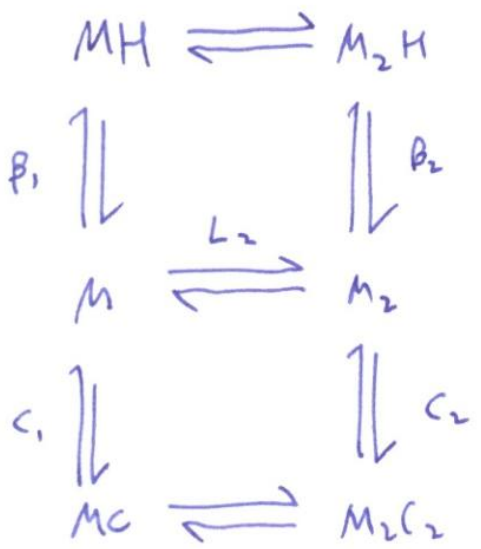


$$\beta_1 = \frac{[MH]}{[M][H]} \approx 90\ \mu M$$

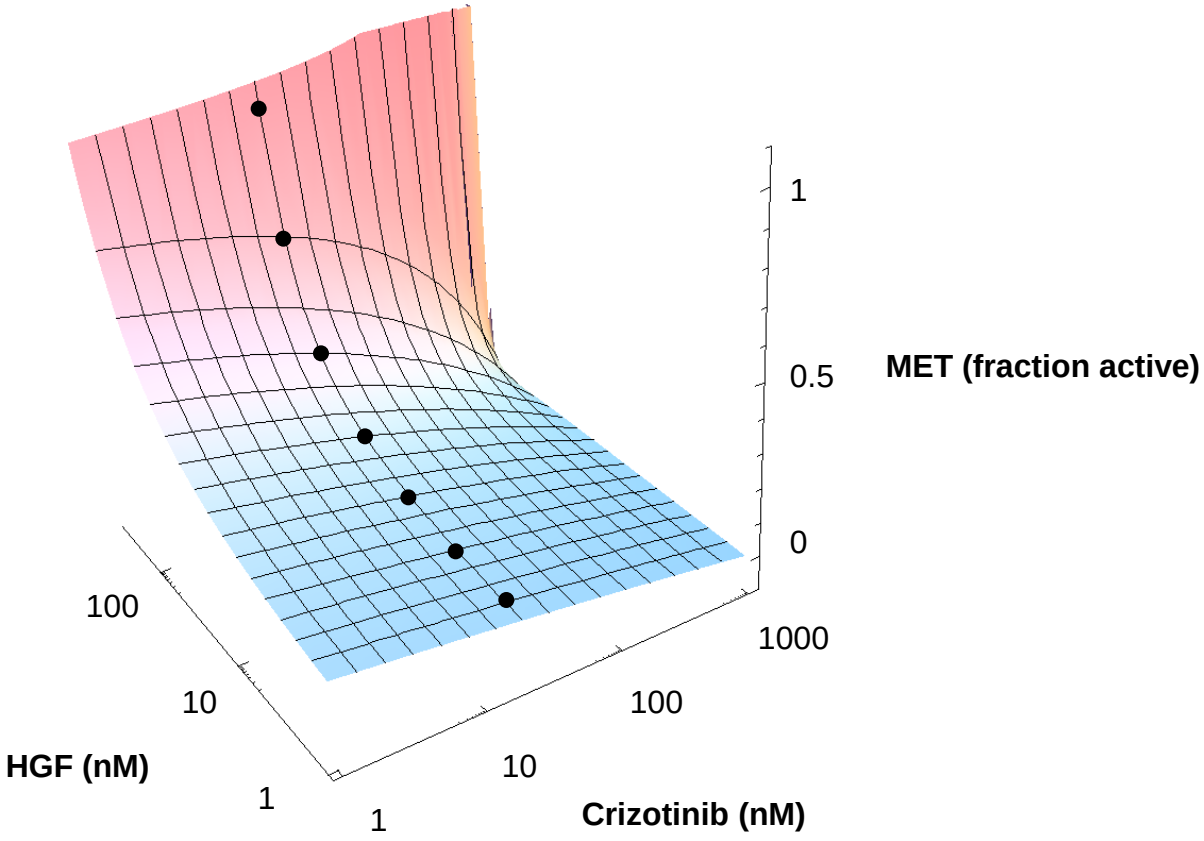
$$\beta_2 = \frac{[M_2H]}{2[M]^2[H]} \approx 100\ pM$$

$$L_2 = \frac{[M_2]}{2[M]^2} \approx 0.8\ M$$

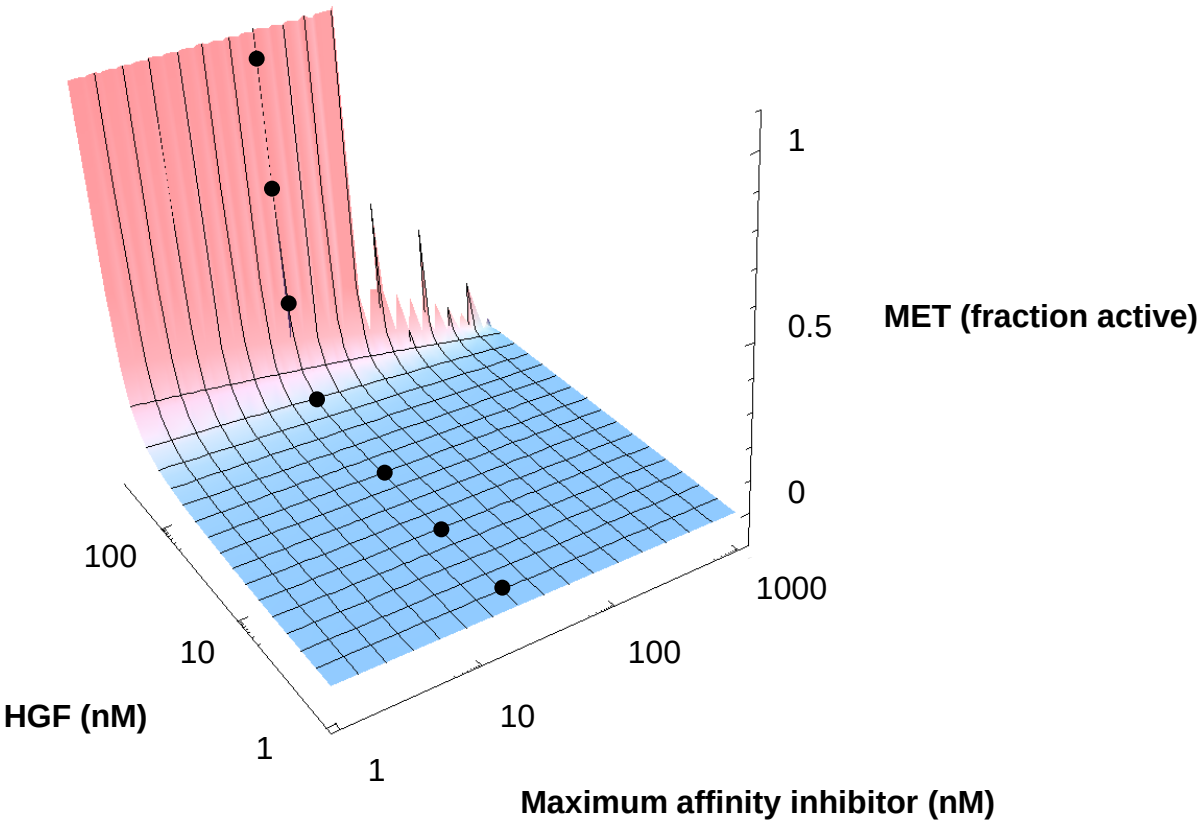
$$C_1 = \frac{[MC]}{[M][C]} \approx 8\ \mu M$$

$$C_2 = \frac{[M_2C_2]}{2[M]^2 2[C]^2}$$

Target reactivation: TKI resistance



Target reactivation: TKI resistance



Targeting aberrant cell survival

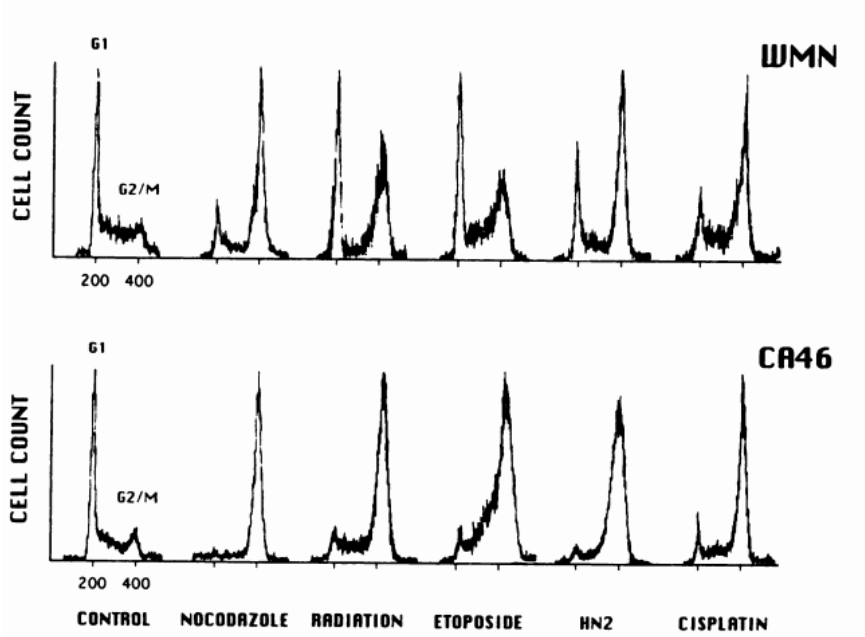
Mitogenic signaling inhibitors

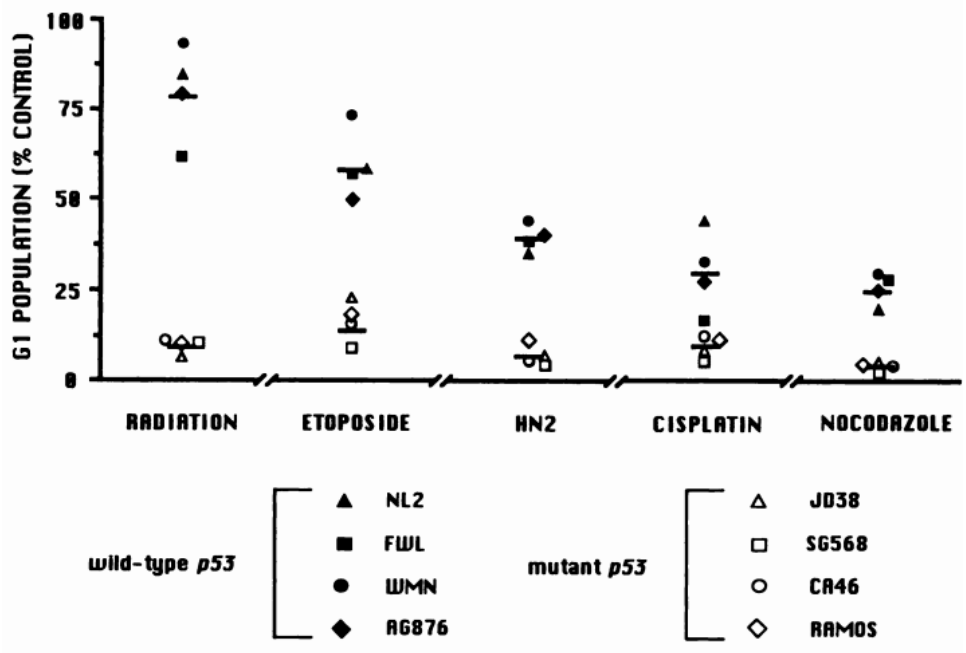
- (Receptor) tyrosine kinase inhibitors (imatinib, crizotinib)
- Neutralizing antibodies (trastuzumab/Herceptin, cetuximab/Erbitux)

Apoptosis resistance inhibitors

- BH3 mimetics (ABT-737, obatoclax)
- MDM2 inhibitors (Nutlin-3)

Homeostatic pathways control cell stress responses





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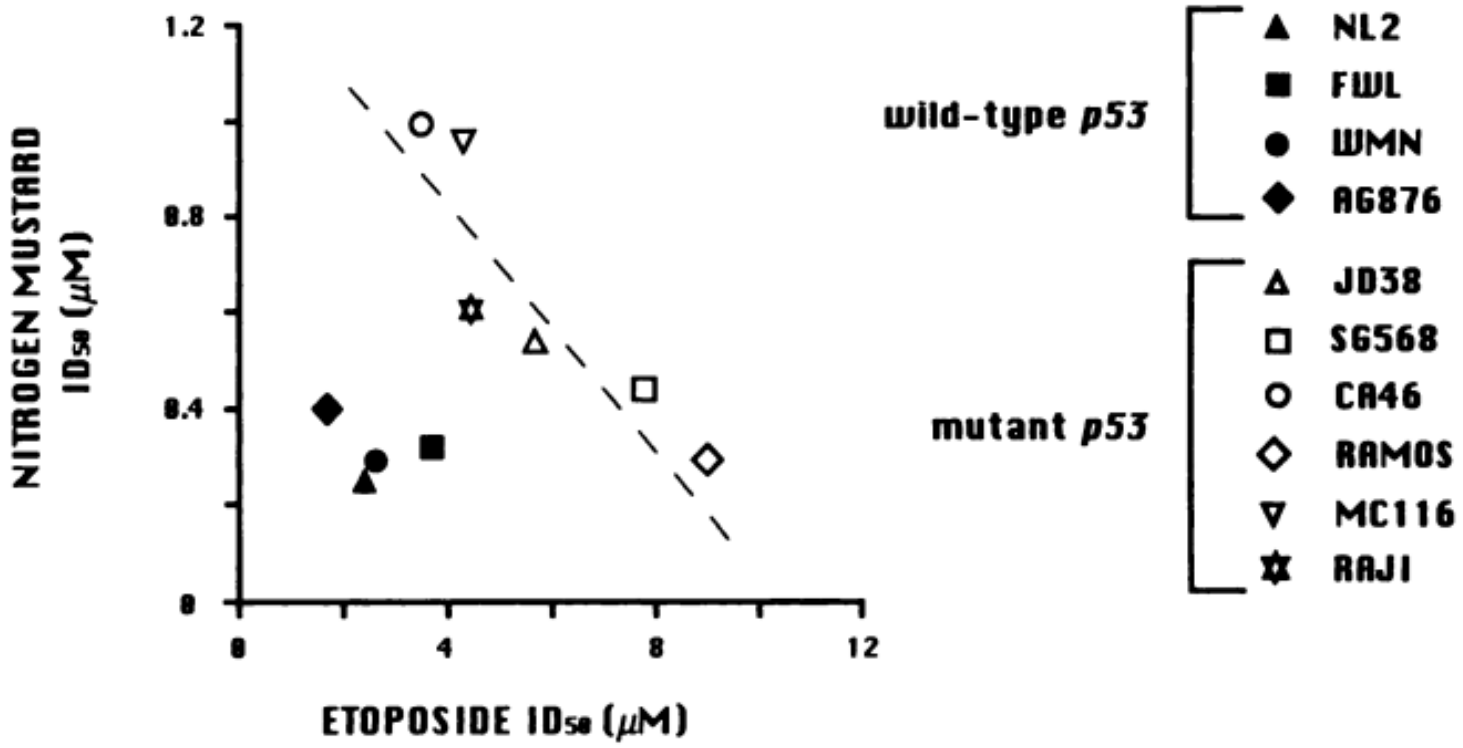
Homeostatic pathways control cell stress responses



http://www.ncbi.nlm.nih.gov/pubmed/7954409

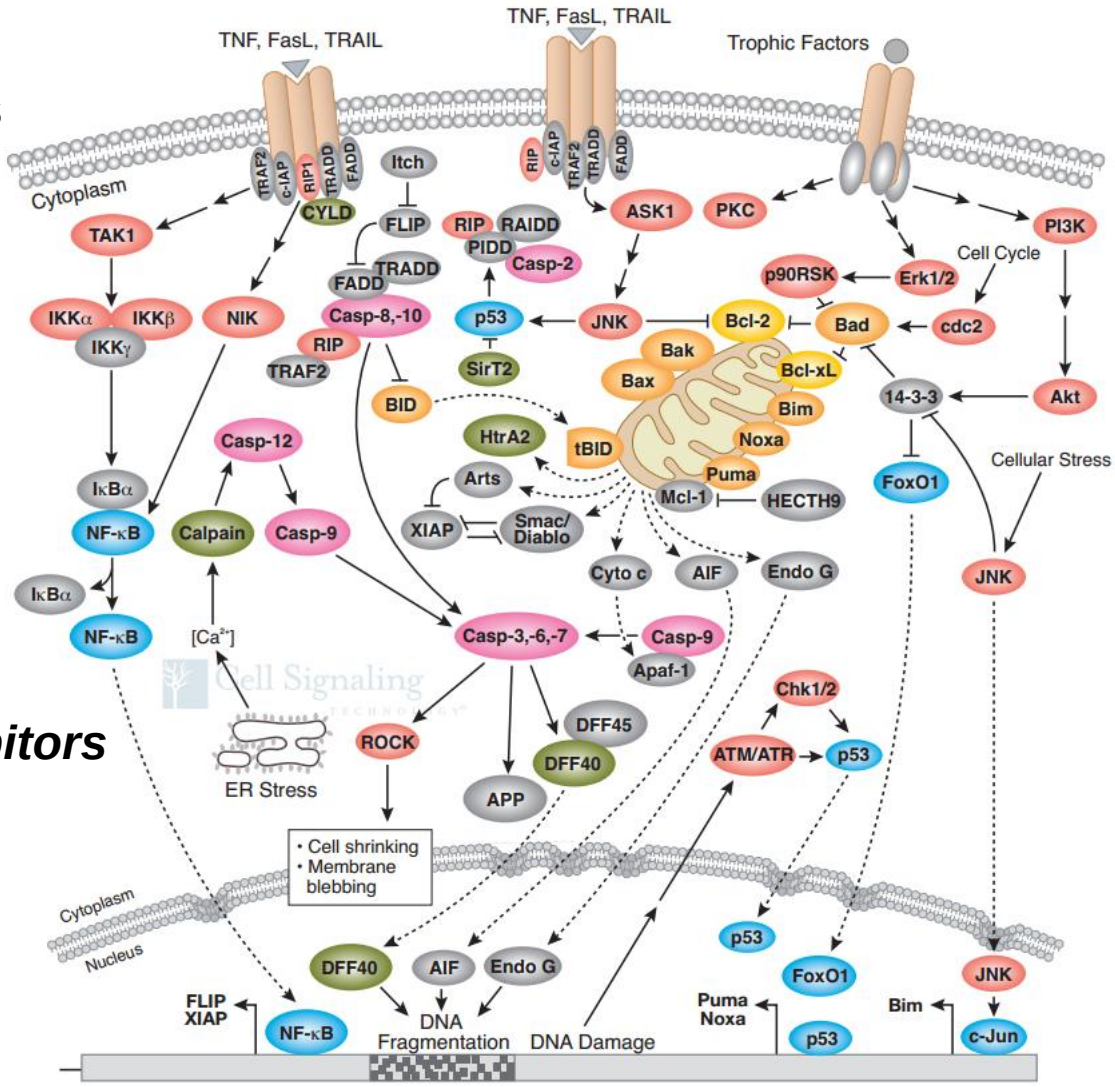
Homeostatic pathways control cell stress responses

How to overcome resistance conferred by inactivation of cell stress response pathways such as P53 signaling?

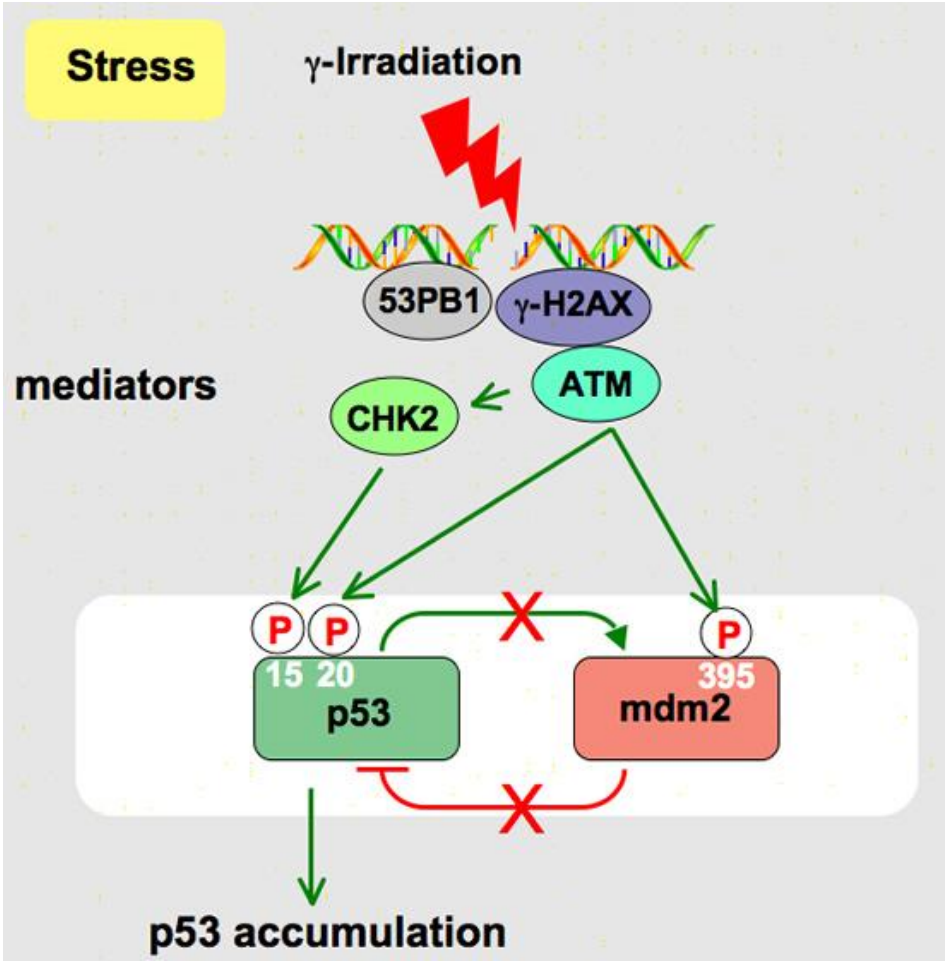
Targeting aberrant cell survival

Mitogenic signaling inhibitors

Apoptosis resistance inhibitors



Targeting aberrant cell survival



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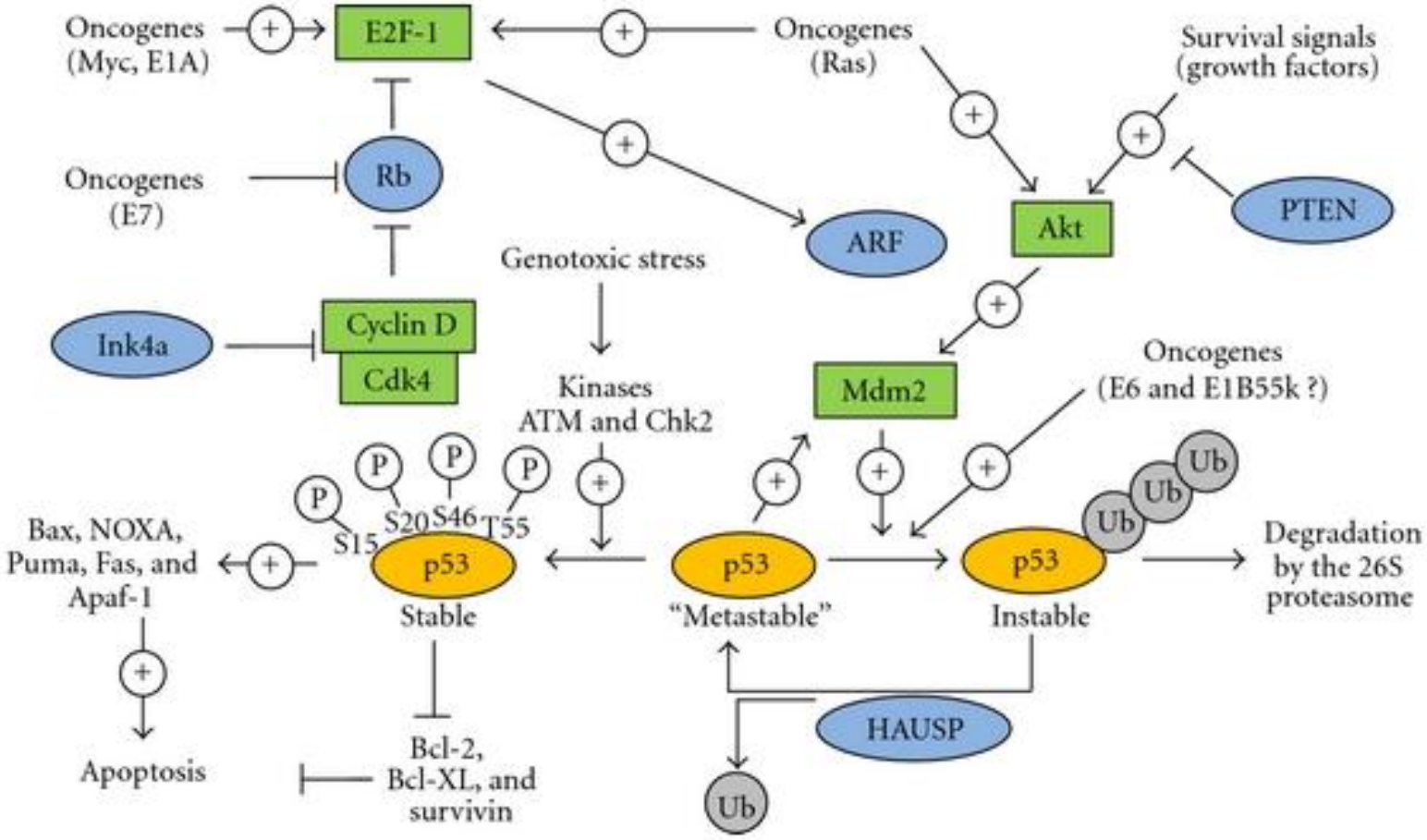
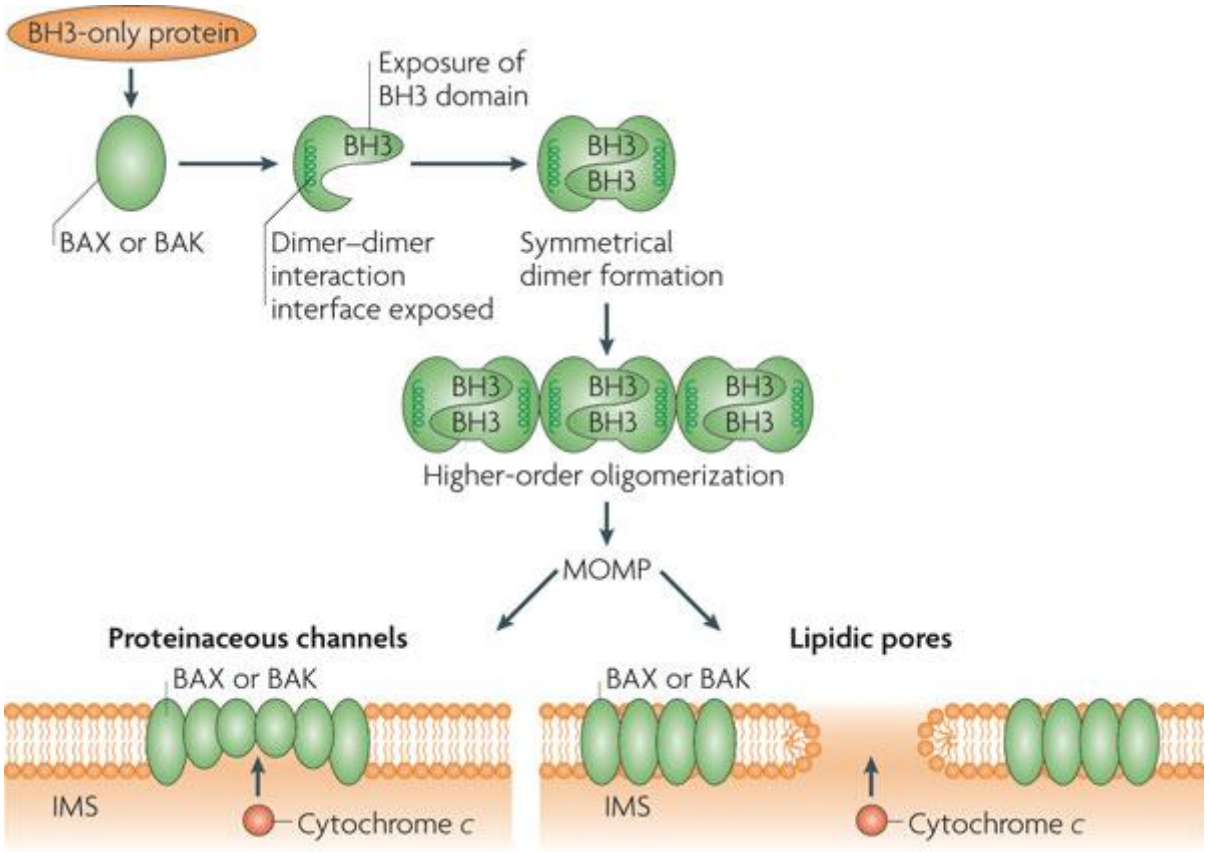
Targeting aberrant cell survival



Blockade of apoptosis resistance



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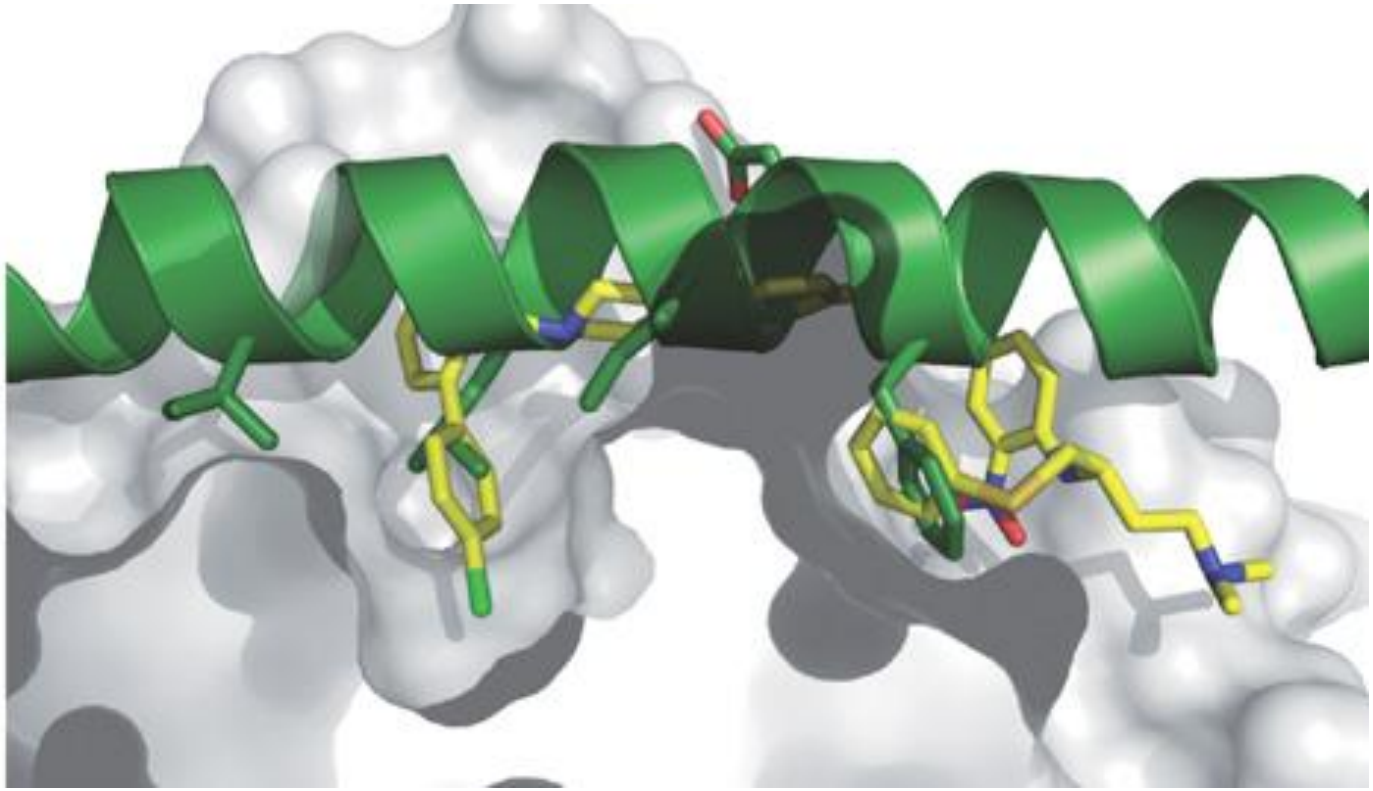
Blockade of apoptosis resistance

Overlay of BCL-X_L–ABT-737 complex with BCL-X_L–BIM BH3 complex



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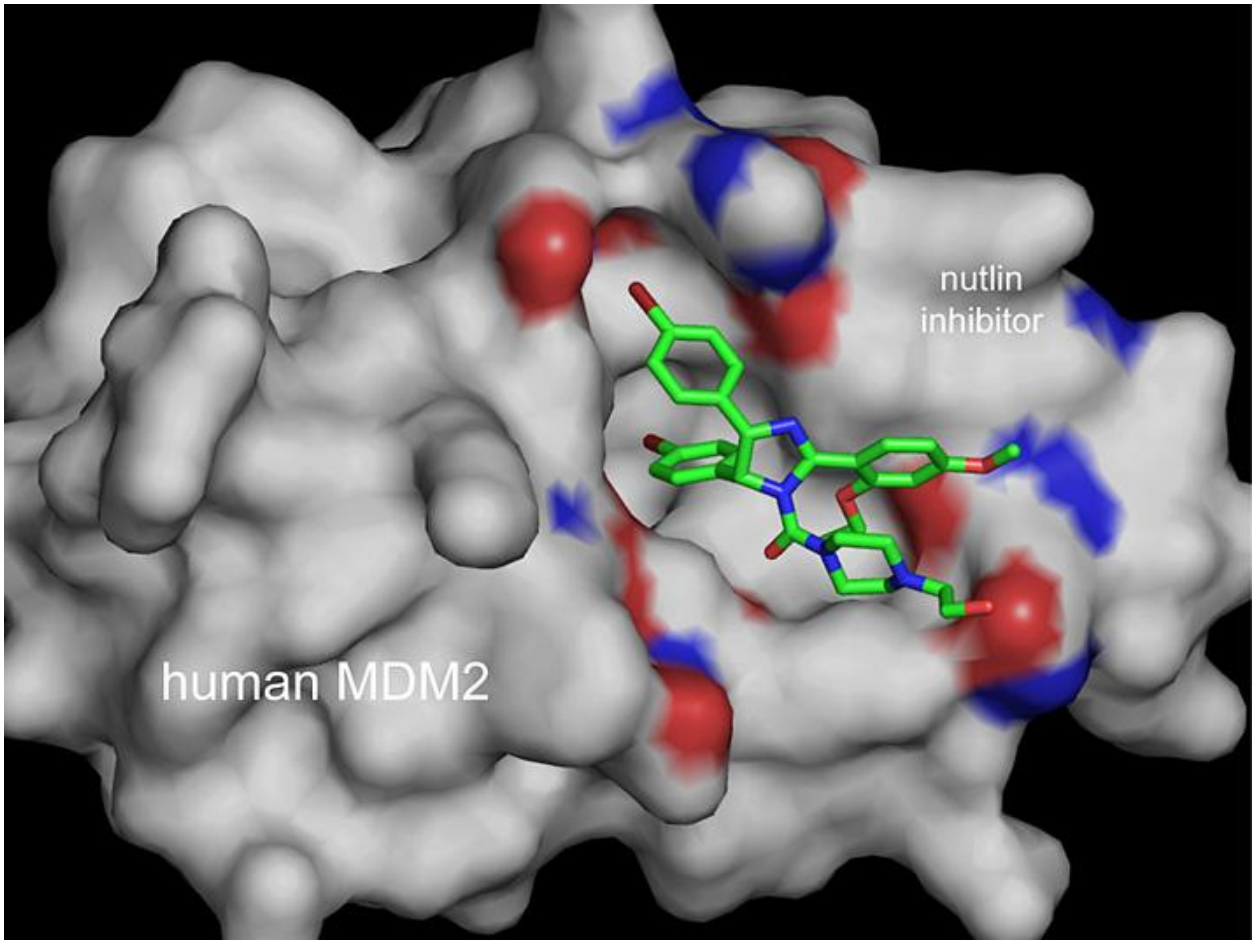
Blockade of apoptosis resistance

Competitive inhibitor of P53:MDM2 binding



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Blockade of apoptosis resistance

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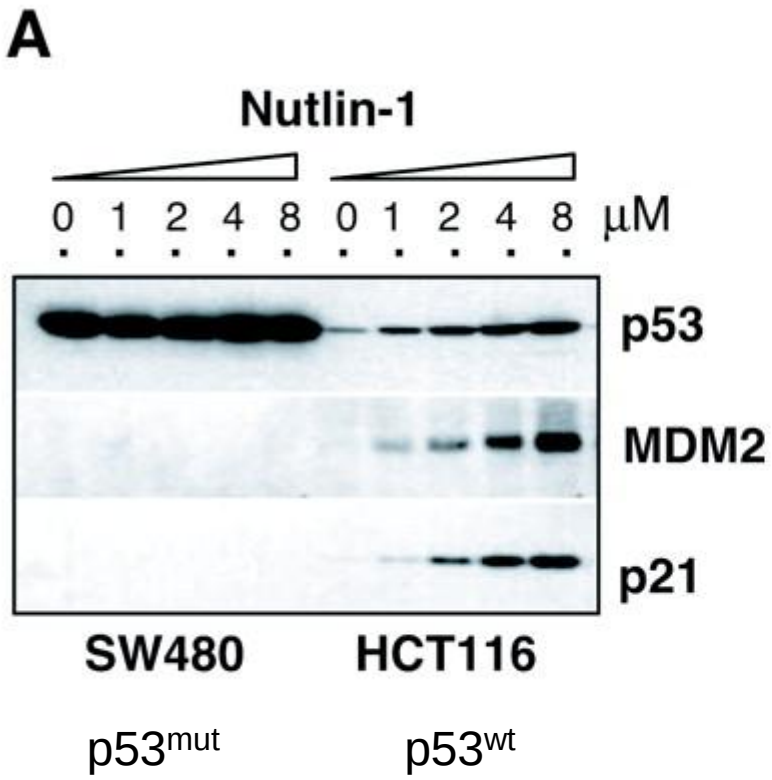

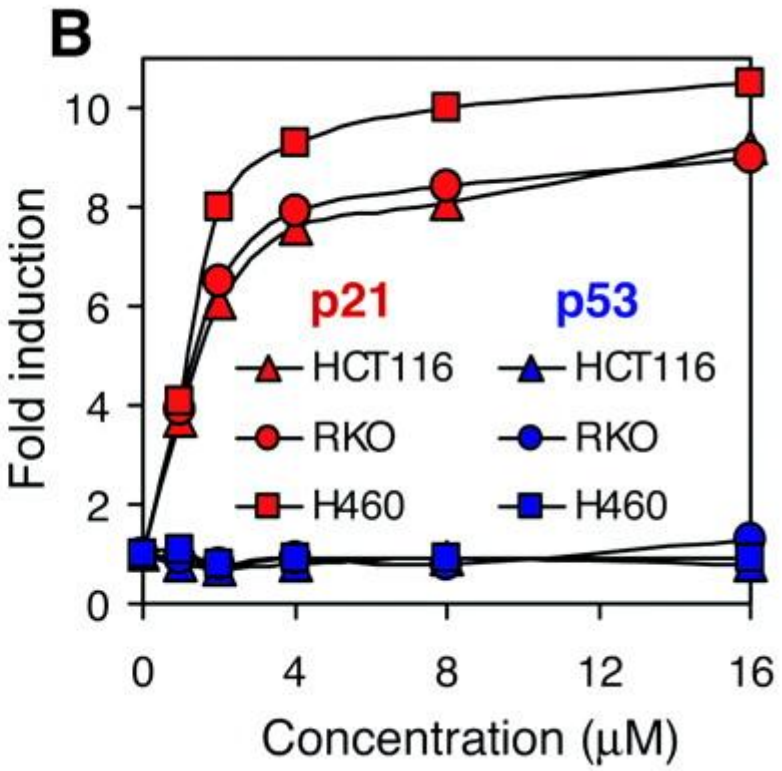

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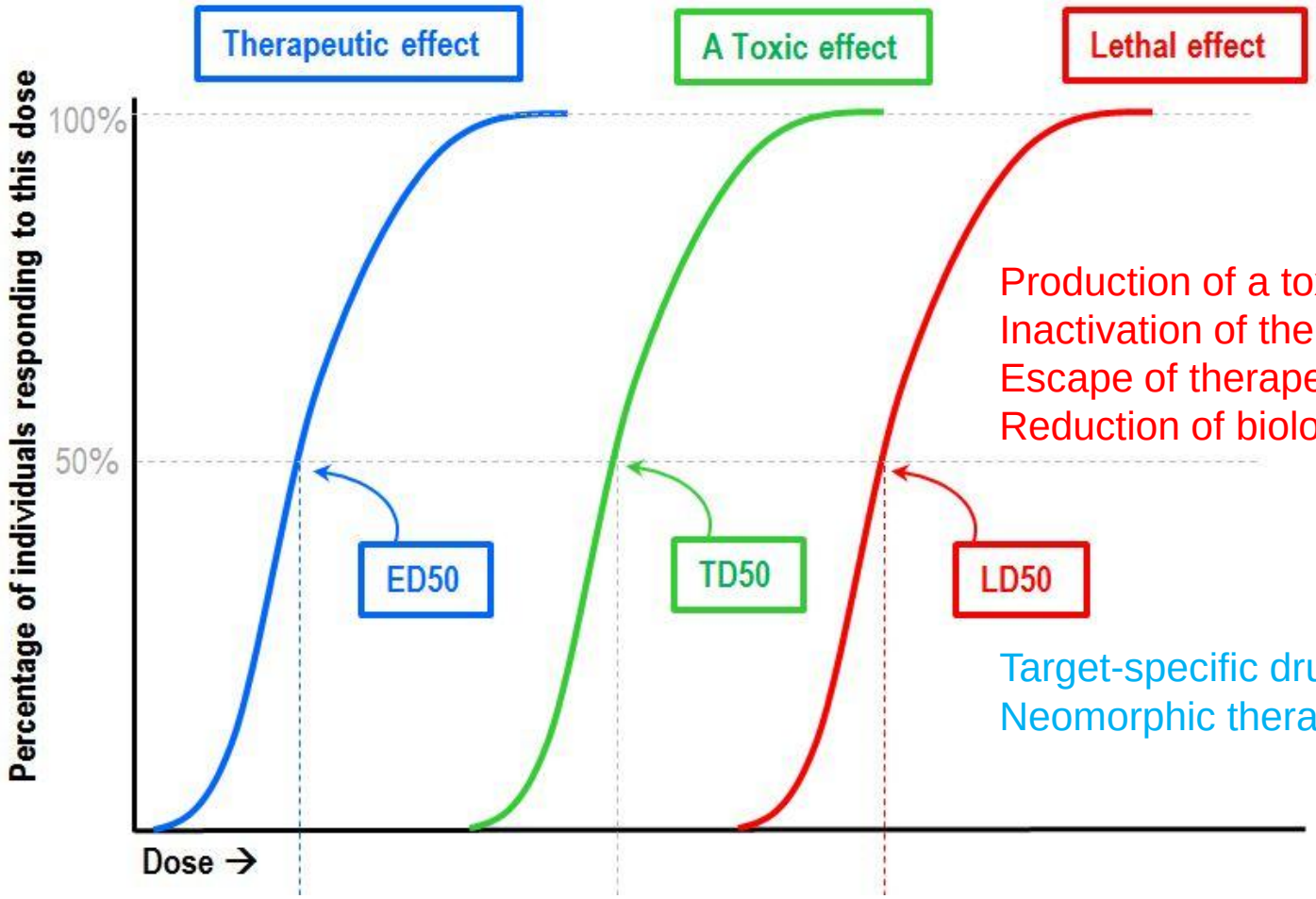
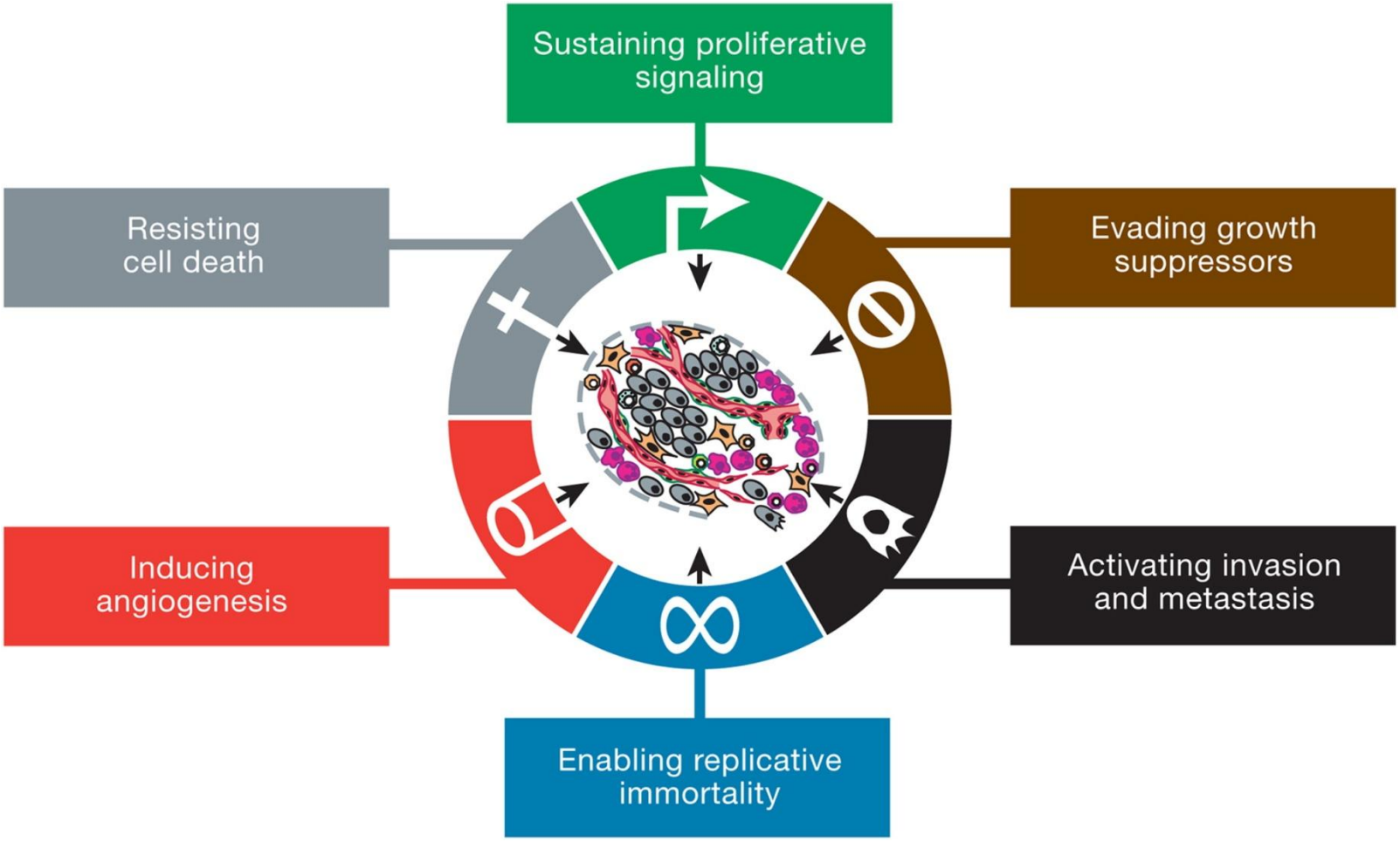
How to target *neomorphic* properties of cancer cells?



Production of a toxic metabolite
Inactivation of therapeutic drug
Escape of therapeutic target
Reduction of biologic dependency

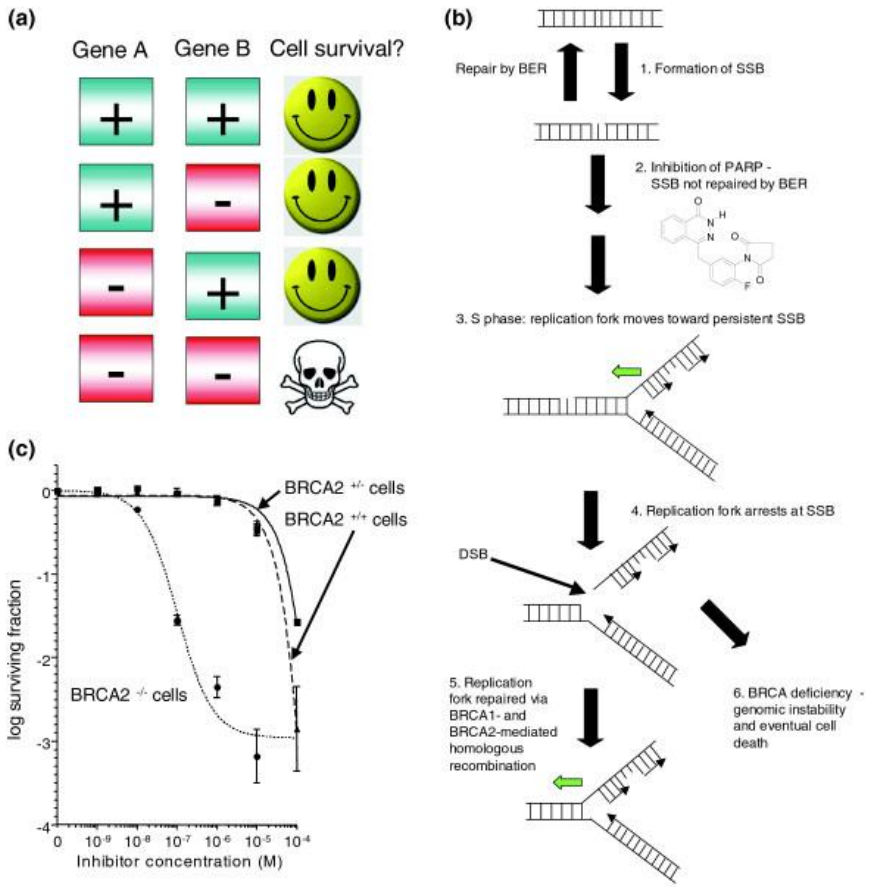
Target-specific drug delivery/activation
Neomorphic therapeutic target

How to target *neomorphic* properties of cancer cells?



How to target *neomorphic* properties of cancer cells?

Functional co-dependence (synthetic lethality)



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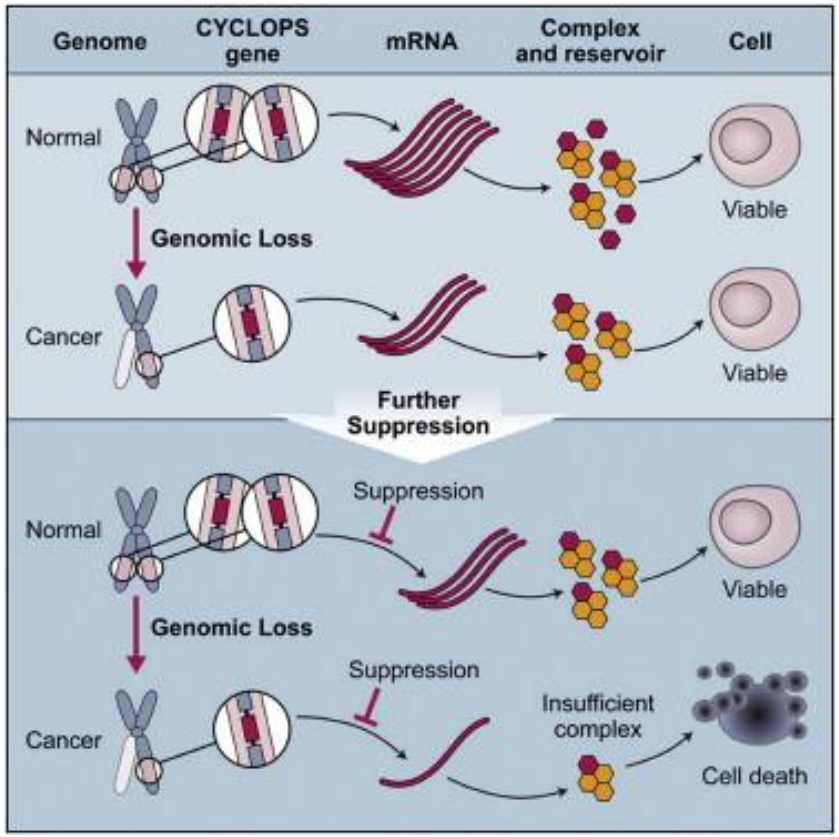
Structural co-dependence (bystander effect)



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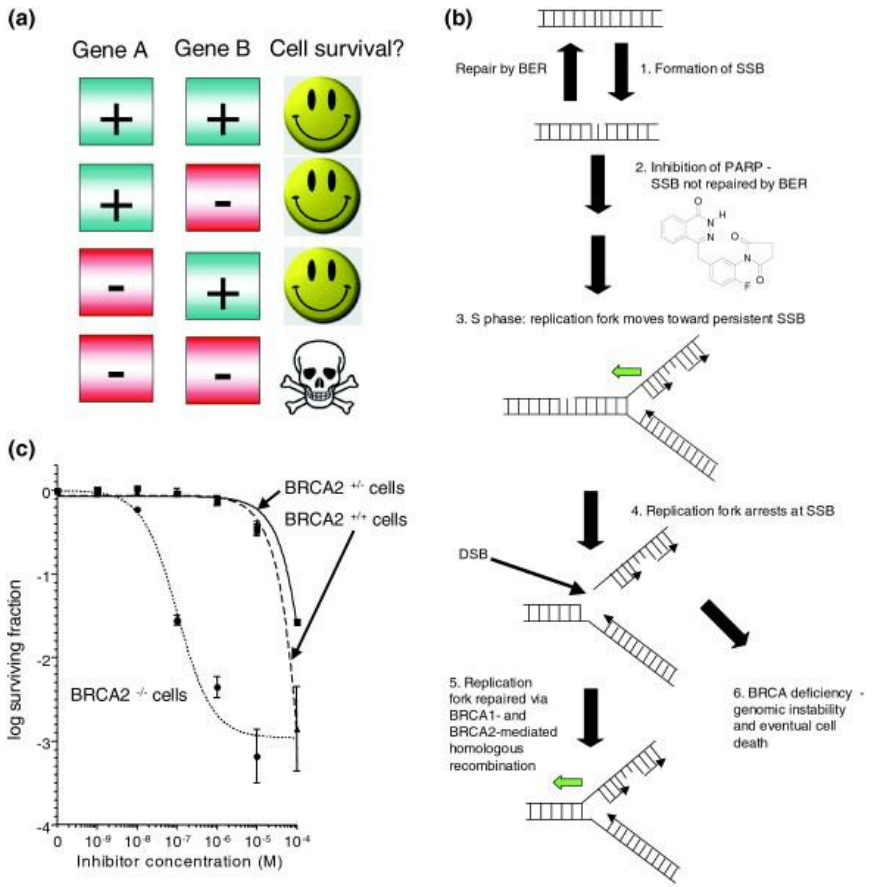
How to target *neomorphic* properties of cancer cells?

Functional co-dependence (synthetic lethality)



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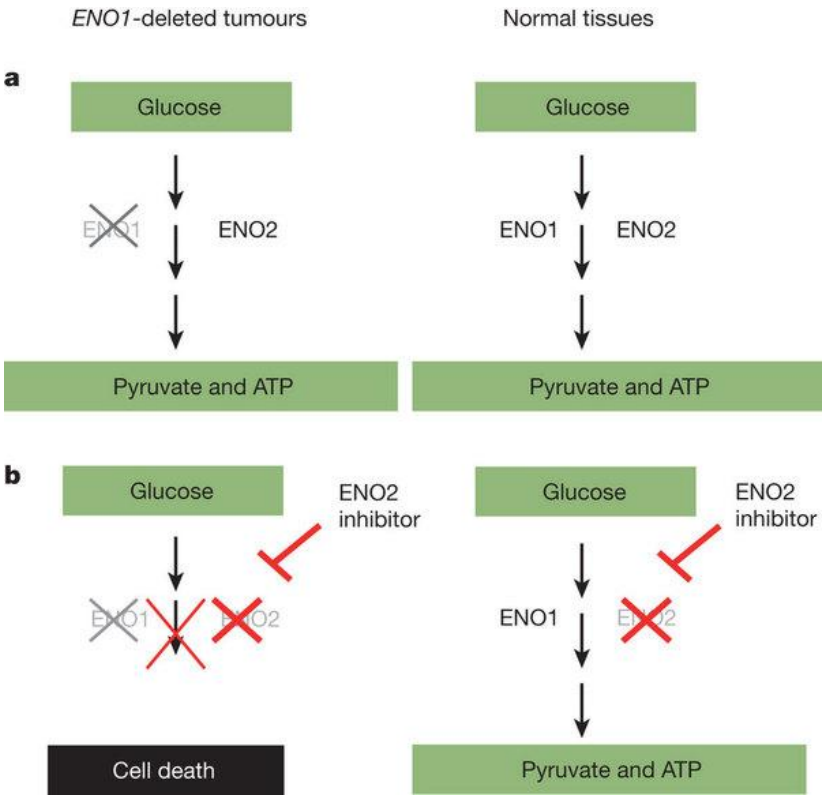

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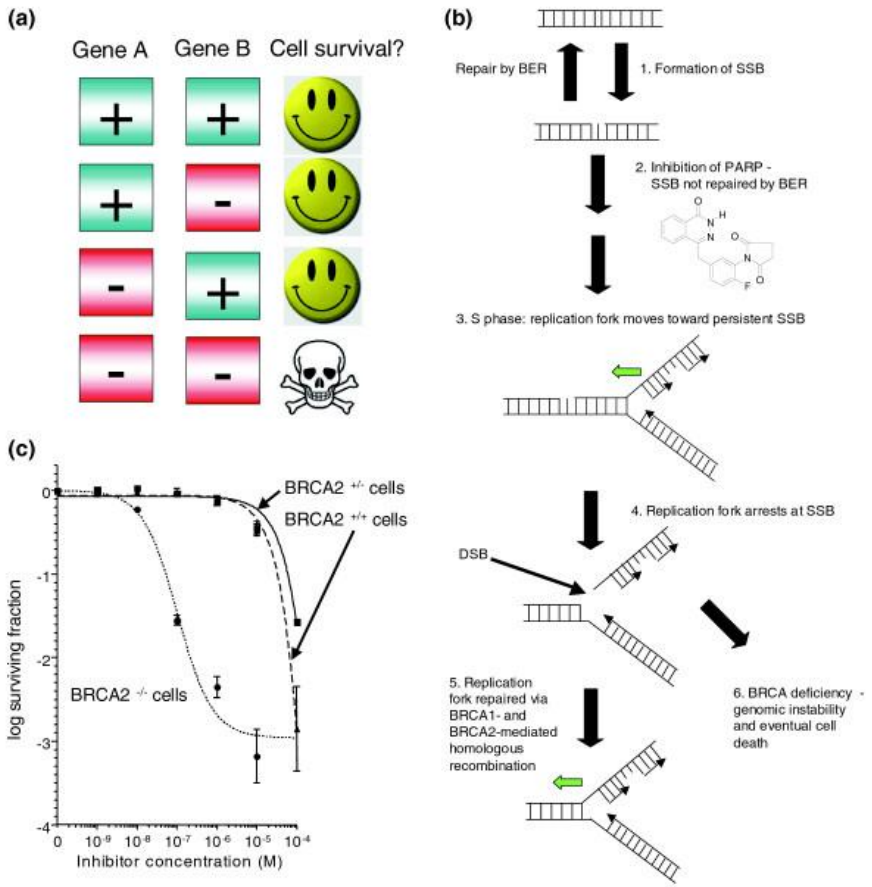

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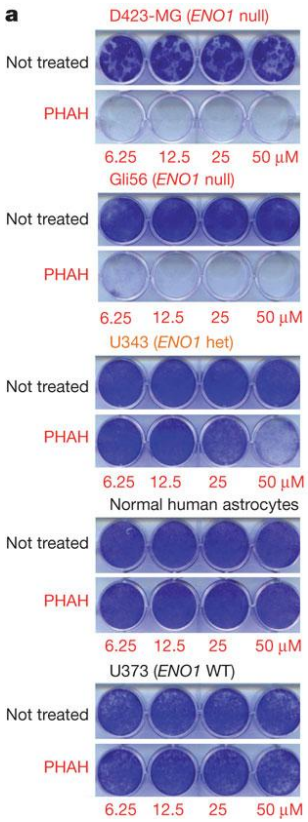
Structural co-dependence (bystander effect)



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How to target *neomorphic* properties of cancer cells?

Functional co-dependence (synthetic lethality)

Structural co-dependence (bystander effect)

Is resistance possible?

Resistance to therapy caused by intragenic deletion in *BRCA2*

Stacey L. Edwards[1], Rachel Brough[1], Christopher J. Lord[1], Rachael Natrajan[1], Radost Vatcheva[1], Douglas A. Levine[2], Jeff Boyd[3], Jorge S. Reis-Filho[1] & Alan Ashworth[1]

Cells with loss of BRCA2 function are defective in homologous recombination (HR) and are highly sensitive to inhibitors of poly(ADP-ribose) polymerase (PARP)[1,2], which provides the basis for a new therapeutic approach. Here we show that resistance to PARP inhibition can be acquired by deletion of a mutation in *BRCA2*. We derived PARP-inhibitor-resistant (PIR) clones from the human CAPAN1 pancreatic cancer cell line, which carries the protein-truncating c.6174delT frameshift mutation. PIR clones could form DNA-damage-induced RAD51 nuclear foci and were able to limit genotoxin-induced genomic instability, both hallmarks of a competent HR pathway. New BRCA2 isoforms were expressed in the resistant lines as a result of intragenic deletion of the c.6174delT mutation and restoration of the open reading frame (ORF). Reconstitution of BRCA2-deficient cells with these revertant *BRCA2* alleles rescued PARP inhibitor sensitivity and HR deficiency. Most of the deletions in *BRCA2* were associated with small tracts of homology, and possibly arose from error-prone repair caused by BRCA2 deficiency[3,4]. Similar ORF-restoring mutations were present in carboplatin-resistant ovarian tumours from c.6174delT mutation carriers. These observations have implications for understanding drug resistance in *BRCA* mutation carriers as well as in defining functionally important domains within BRCA2.

are defective in the ability to form damage-induced RAD51 foci and HR[13] and are extremely sensitive to treatment with potent inhibitors of PARP[14].

PIR clones were developed either by a continuous stepwise exposure to increasing concentrations of the PARP inhibitor KU0058948 (ref. 1) (from 1 nM to 50 μM; clones PIR1–6) or by continuous treatment with 100 nM KU0058948 (clones PIR7–12). PIR clones were highly resistant (1,370-fold) to KU0058948 (Fig. 1a). For CAPAN1, the SF_{50} (the dose at which 50% of cells survive) was 5.75 nM, in contrast with 7.35 μM for PIR1–12. PIR clones were also resistant to the DNA crosslinking agent cisplatin but not to the microtubule-stabilizing taxane docetaxel (Fig. 1a). Both KU0058948 and cisplatin are thought to exert their BRCA-selective effects by increasing the frequency of stalled and collapsed replication forks, leading to mis-repaired DSBs in the absence of effective HR[1,15], indicating that the resistance of PIR clones to KU0058948 might involve the restoration of functional HR.

The extent of stalled and collapsed replication forks and DSBs can be assessed by quantifying nuclear γ-H2AX foci[16]. KU0058948 induced the formation of γ-H2AX foci to the same extent in both CAPAN1 and PIR clones (Fig. 1b), indicating that resistance was unlikely to be explained by enhanced drug metabolism or efflux. CAPAN1 cells are deficient in the ability to form RAD51 foci after

http://www.ncbi.nlm.nih.gov/pubmed/18264088

How to target *neomorphic* properties of cancer cells?

Functional co-dependence
(synthetic lethality)

Structural co-dependence
(bystander effect)

Resistance to therapy caused by intragenic deletion in *BRCA2*

If restoration of BRCA2 expression in tumors
confers resistance to PARP inhibitors,
what does this suggest about the tumorigenic mechanism BRCA2 mutations
and their significance as therapeutic targets?

BRCA2 loss is required for tumor initiation but not tumor maintenance

http://www.ncbi.nlm.nih.gov/pubmed/18264088

Cancer drug resistance

Cytotoxic agent	Cancer type	Target	Resistance mechanism	Refs
Antimetabolites (for example, 5-FU, methotrexate, gemcitabine and cytarabine)	Breast cancer, colorectal cancer, pancreatic cancer, gastric cancer, head and neck cancer, ovarian cancer, lymphoma and leukaemia	Thymidylate synthase and DNA synthesis	Increased target expression (thymidylate synthase)	151
			MLH1 hypermethylation	152
			Activation of survival pathways (for example, ERBB signalling pathways)	101
			Increased expression of anti-apoptotic proteins (for example, FLIP, BCL-2 or MCL1)	90,75
Platinum compounds (for example, cisplatin and oxaliplatin)	Ovarian cancer, testicular cancer, sarcoma, lymphoma and small-cell lung carcinoma	DNA	Reduced cellular uptake	153
			Increased efflux	13
			Increased DNA repair	66–69
			MLH1 hypermethylation	64
Topoisomerase I inhibitors (for example, irinotecan)	Colorectal cancer and small-cell lung carcinoma	Topoisomerase I	Drug efflux	13
			Reduced target expression	25
			Topoisomerase I mutations	154
			Suppression of apoptosis	75
			Activation of survival pathways (for example, ERBB signalling pathways)	99
Topoisomerase II inhibitors (for example, doxorubicin and etoposide)	Kaposi's sarcoma, Ewing's sarcoma, lung cancer, testicular cancer, lymphoma, leukaemia and glioblastoma	Topoisomerase II	MDR1 overexpression	13
			Mutation or decreased expression of topoisomerase II	155
			Decreased apoptosis due to mutation of p53	59
Microtubule poisons (for example, paclitaxel and vinorelbine)	Lung cancer, ovarian cancer, breast cancer, head and neck cancer, Kaposi's sarcoma	Tubulin	Tubulin mutations	156–157
			MDR1 overexpression	13
			Chromosomal instability	71

5-FU, 5-fluorouracil; MDR1, multi-drug resistance protein 1.

http://www.ncbi.nlm.nih.gov/pubmed/24060863

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