Molecular Targets in Cancer Therapy

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Targeted Cancer Therapy

- Massive subject.
- Year long course would still be incomplete.
- Moving target.
- Focus of this lecture: *Principles of targeted therapy.*

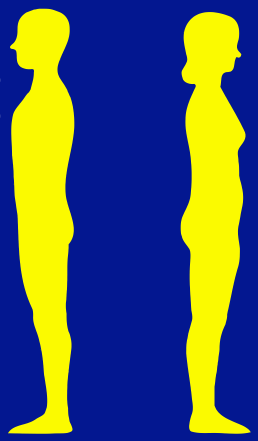
Cancer is a Problem.

- $46 **billion** per year cancer related health care costs. NCI spent $5.7 **billion** in FY2004.
- Yet, approximately 1:4 people will still die with cancer.
- Better therapy--not more.
- Understanding the molecular mechanisms of cancer---and how to use this knowledge clinically--- is the foundation for future cancer therapy.

- **Sobering cancer statistics**

Estimated US Cancer Deaths

Men 290,890		Women 272,810	
Lung & bronchus	32%	•25%	Lung & bronchus
Prostate	10%	•15%	Breast
Colon & rectum	10%	• 10%	Colon & rectum
Pancreas	5%	• 6%	Ovary
Leukemia	5%	• 6%	Pancreas
Non-Hodgkin lymphoma	4%	• 4%	Leukemia
Esophagus	4%	• 3%	Non-Hodgkin lymphoma
Liver & intrahepatic bile duct	3%	• 3%	Uterine corpus
Urinary bladder	3%	• 2%	Multiple myeloma
Kidney	3%	• 2%	Brain/ONS
All other sites	21%	•24%	All other sites



ONS=Other nervous system. Source: American Cancer Society, 2004.

What is YOUR life-time risk to get diagnosed with cancer?

Lifetime Probability of Developing Cancer, by Site, Men, US, 1998-2000

Site	Risk
All sites	1 in 2
Prostate	1 in 6
Lung & bronchus	1 in 13
Colon & rectum	1 in 17
Urinary bladder	1 in 29
Non-Hodgkin lymphoma	1 in 48
Melanoma	1 in 55
Leukemia	1 in 70
Oral cavity	1 in 72
Kidney	1 in 69
Stomach	1 in 81

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 5.1 Statistical Research and Applications Branch, NCI, 2003. http://srab.cancer.gov/devcan

Lifetime Probability of Developing Cancer, by Site, Women, US, 1998-2000

Site	Risk
All sites	1 in 3
Breast	1 in 7
Lung & bronchus	1 in 17
Colon & rectum	1 in 18
Uterine corpus	1 in 38
Non-Hodgkin lymphoma	1 in 57
Ovary	1 in 59
Pancreas	1 in 83
Melanoma	1 in 82
Urinary bladder	1 in 91
Uterine cervix	1 in 128

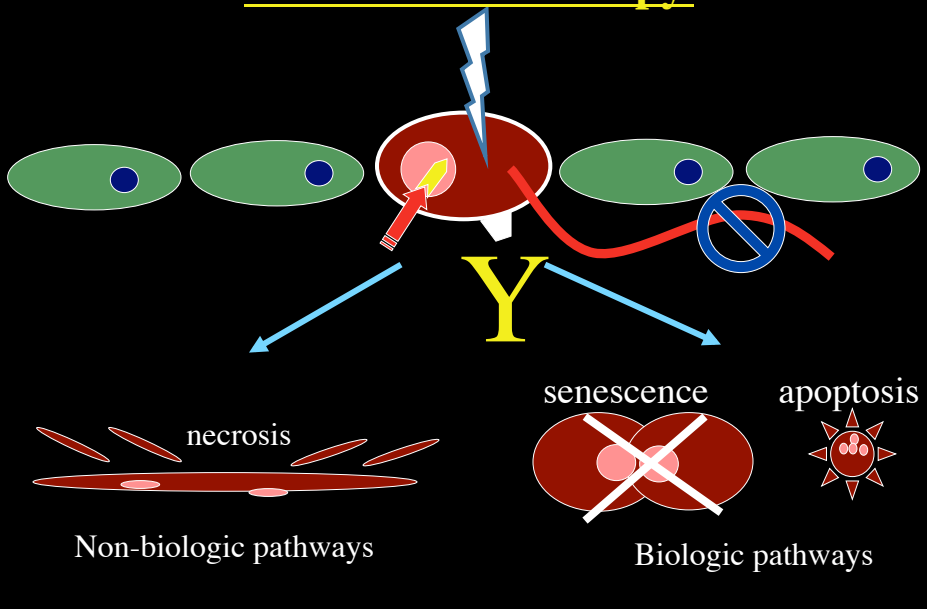
Source:DevCan: Probability of Developing or Dying of Cancer Software, Version 5.1 Statistical Research and Applications Branch, NCI, 2003. http://srab.cancer.gov/devcan

Cancer Biology Challenge: Bridging the Bench to Bedside Gap.

"The publications of scientists concerning their individual work have never been so copious---and so unreadable for anyone but their fellow specialists. This has been a great handicap to science itself, for the basic advances in scientific knowledge often spring from the cross-fertilization of knowledge from different specialties."

------Isaac Asimov, The New Intelligent Man's Guide to Science (1965)

"Therapeutic window" is the foundation for all cancer therapy.



Overview.

- How do we currently treat cancer?
- How do we evaluate new therapies?
- How do we discover new therapies?
- What are the molecular mechanisms underlying the “therapeutic window?”
- How are we translating new biologic knowledge into:
  - better therapies?
  - better clinical trials?

Current Treatment: Local Therapy

- Surgery: curative in selected circumstances.
  - Limited disease
  - technically possible

Example of Surgical Management

Esophageal cancer: survival by stage

Stage	3 years	5 years
I	80%	65%
IIA	50%	40%
IIB	30%	22%
III	20%	12%
IV	2%	0%

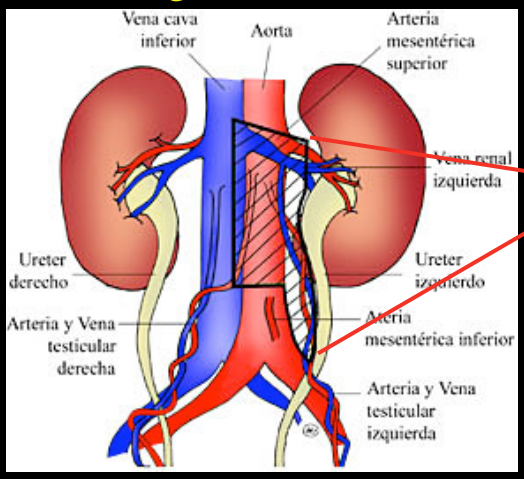
(5071 pts. Iizuki et.al.)

Current Treatment: Local Therapy

- Ionizing radiation: curative in selected circumstances.
  - DNA target
  - Dose-limiting toxicities to normal tissues

Example of radiation therapy

Stage II seminoma (limited to RP nodes)



30 Gy (1.8 Gy fractions)

85-90% cure rate

Current Treatment: Systemic Therapy

- Chemotherapy: curative in selected circumstances.
  - Oral
  - Intravenous

Systemic chemotherapy example: Hodgkin's disease

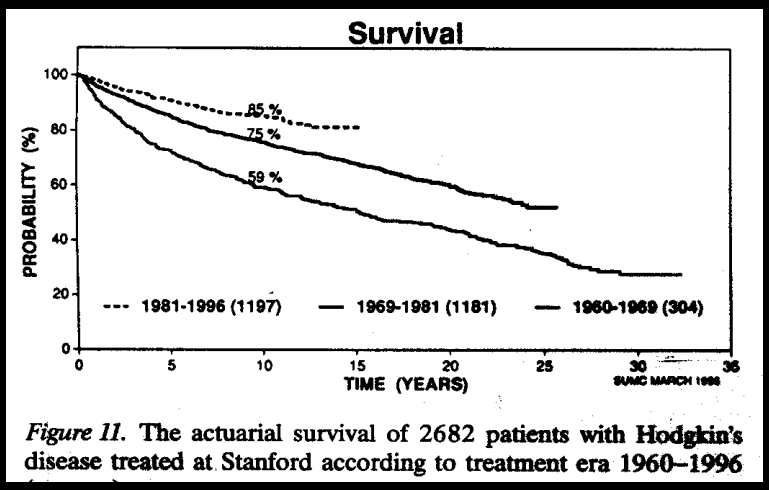


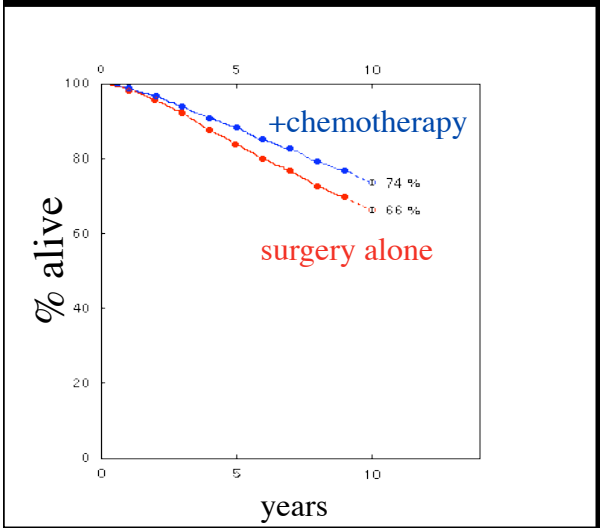
Figure 11. The actuarial survival of 2682 patients with Hodgkin's disease treated at Stanford according to treatment era 1960–1996

(Rosenberg, Annals of Oncology, 1996)

Current Treatment: Systemic Therapy

- Adjuvant therapy.
  - Systemic therapy delivered after definitive local therapy.
  - Reduce risk of relapse from microscopic disease state.
- Although curative in selected circumstances--- "treating the many to benefit the few" with toxic agents.

Adjuvant therapy example: breast cancer



Stage III breast cancer
+/-adjuvant chemo

Cancer therapy: history

- Alkylating agents. By product of U.S. secret war gas program.
  - WWII Bari Harbor explosion released mustard gas. Autopsies revealed many sailors had no lymph nodes and hypocellular bone marrow.
- 1943 Yale University treated first humans with alkylating agents (mustard agents)--marked lymphoma regression.

Major classes of chemotherapy agents in use.

- Topoisomerase inhibiting agents.
  - Induce torsional strain resulting in DNA strand breaks.
  - Examples: adriamycin, etoposide
- Antimicrotubule agents.
  - Breakdown or hyperstabilize microtubules to disrupt mitosis.
  - Examples: vinblastine, paclitaxel.
- Alkylating agents.
  - Electron-rich nucleaophiles alkylate DNA (also lesser extent proteins).
  - Examples: cyclophosphamide, ifosfamide
- Platinum containing agents.
  - Electrophile forms DNA-platinum adducts.
  - Examples: cisplatin
- Antimetabolic agents.
  - Antifolates, nucleotide analogues
  - Examples: Ara-C

Standard cancer therapy approaches with chemotherapy or radiation.

- Mechanisms of action pleiotropic (e.g. likely unknown pathways).
- All ultimately activate common biologic pathways that selectively inhibit or kill tumor cells.
- Have almost reached the limit of what standard approaches can do---need to operate in the therapeutic window (e.g don't kill patient).
- *How do we develop and evaluate better therapies?*

What is 'targeted therapy'?

FDA definition:

A drug with an approved label in which there is specific reference to a simultaneously or previously approved diagnostic test that must be performed before the patient can be considered eligible to receive the drug. The drug and the test are virtual combination products that must be used together.

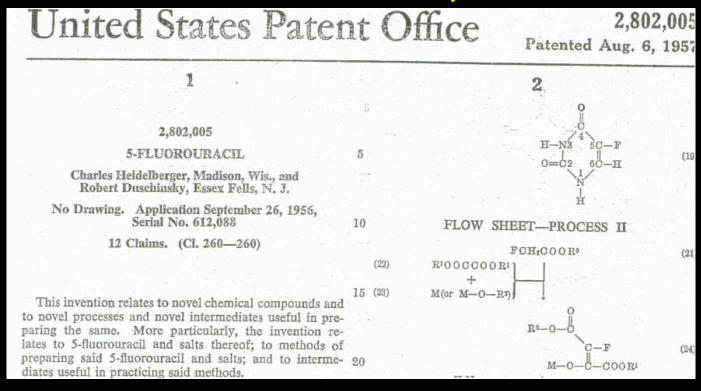
Definition by scientists and oncologists:

A drug with a focused mechanism that specifically acts on a well-defined target or biological pathway that, when inactivated, causes regression or destruction of the malignant process.

Ross et al., Am J Clin Pathol 122, 598-609 (2004)

So, are targeted therapies anything new then?

5-Fluorouracil; 5-FU



United States Patent Office

2,802,005

Patented Aug. 6, 1957

2,802,005

5-FLUOROURACIL

Charles Heidelberger, Madison, Wis., and Robert Duschinsky, Essex Fells, N. J.

No Drawing. Application September 26, 1956, Serial No. 612,088

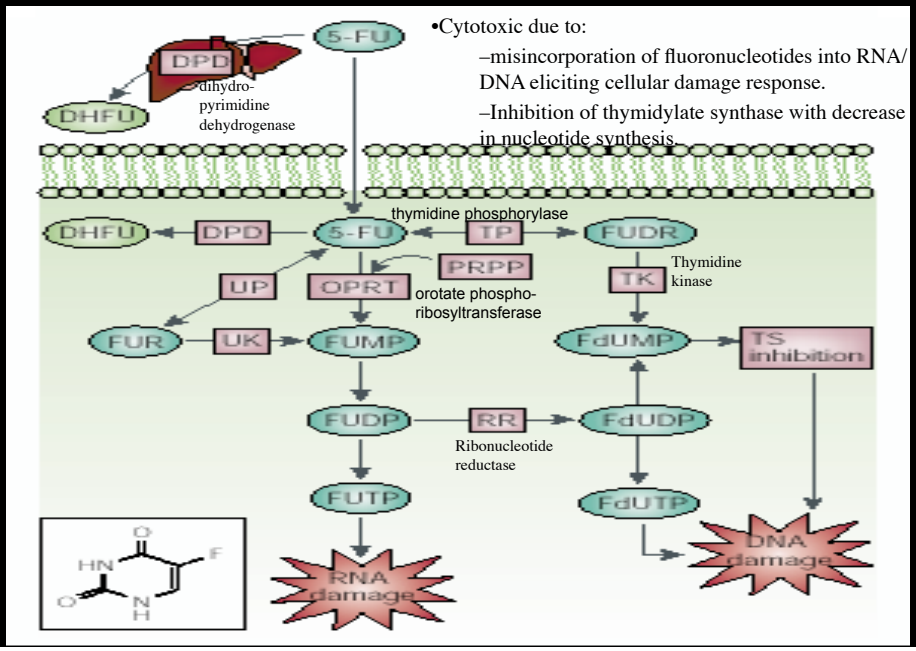
12 Claims. (Cl. 260—260)

This invention relates to novel chemical compounds and to novel processes and novel intermediates useful in preparing the same. More particularly, the invention relates to 5-fluorouracil and salts thereof; to methods of preparing said 5-fluorouracil and salts; and to intermediates useful in practicing said methods.

FLOW SHEET—PROCESS II

- •Developed in 1950s after observation that rat hepatoma utilized uracil faster than normal tissue.
- •Still used today in combination chemotherapy regimens for breast, colon, head and neck cancers.

First "targeted" therapy: 5-FU

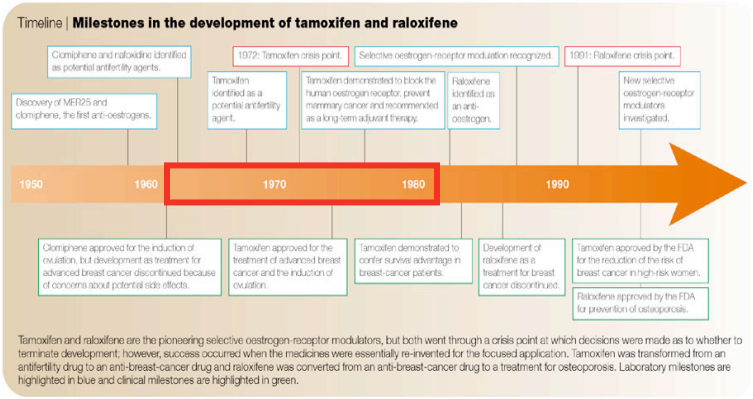


- Cytotoxic due to:
  - –misincorporation of fluoronucleotides into RNA/ DNA eliciting cellular damage response.
  - –Inhibition of thymidylate synthase with decrease in nucleotide synthesis

Tamoxifen (antiestrogen)

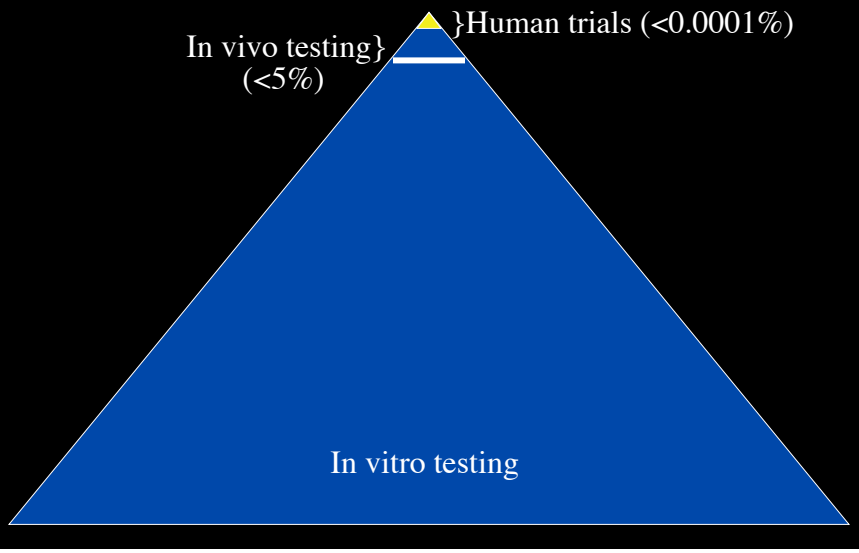
for breast cancers that are estrogen and/or progesterone receptor positive.

Approximately 400,000 breast cancer patients saved by Tamoxifen!



Jordan, Nature Reviews Drug Discovery 2, 205-213 (2003)

How do we evaluate new anticancer agents?



How do we evaluate new anticancer agents in patients? Clinical trials.

Phase I	Determine dose for Phase II/III based on toxicity and pharmacokinetics Dose escalation and size of cohorts determined by likelihood of toxicity	Is it safe? What dose?
Phase II evaluation	Determine antitumour activity Clinical endpoint determined by preclinical results Patient population defined by histology and stage of disease Dose(s) based on toxicity and pharmacokinetics	Is it active?
Phase III evaluation	Clinical benefit Patient population defined by histology and stage of disease Dose(s) based on toxicity and pharmacokinetics	Does it really work? -control arm

Phase III targeted therapies: are these the correct experiments?

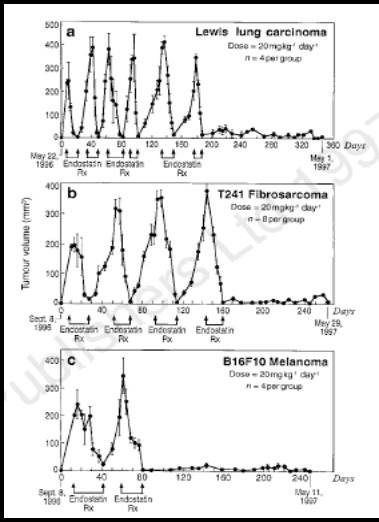
Table 1 | **Outcome of Phase III trials of targeted therapies**

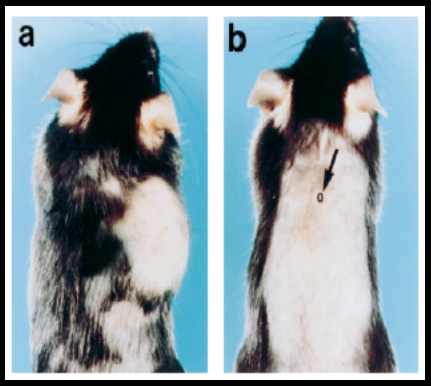
Agent	Control	Cancer	Clinical setting and tumour status	Effect of targeted therapy	References
Matrix metalloproteinase inhibitors					
Marimastat	Gemcitabine	Pancreatic	First-line therapy, locally advanced and metastatic	No survival benefit	26
Marimastat	Placebo	Gastric	Non-progressive following surgery or first-line therapy, locally advanced and metastatic	No survival benefit	17
Marimastat	Placebo	Glioblastoma	Locally advanced, unresectable cancer	No survival benefit	27
Marimastat	Placebo	Small-cell lung	Limited or extensive stage, following response to first-line therapy	No survival benefit	28
Marimastat + Gemcitabine	Gemcitabine	Pancreatic	First-line therapy, locally advanced and metastatic	No survival benefit	29
Marimastat + Carboplatin	Carboplatin	Ovarian	Locally advanced and metastatic	No enhancement of response rate	27
Marimastat	Placebo	Breast	Non-progressive following first-line chemotherapy for metastatic disease	No survival benefit	30
Marimastat	Placebo	Colorectal	Unresectable liver metastases	No survival benefit	31
Marimastat	Placebo	Glioblastoma	Unresectable multiforme	No survival benefit	32
Prinomastat + Gemcitabine/ Cisplatin	Gemcitabine/ Cisplatin	Non-small-cell lung	Unresectable locally advanced and metastatic	No survival benefit	33 34
Prinomastat + Carboplatin/ Paclitaxel	Carboplatin/ Paclitaxel	Non-small-cell lung	Unresectable locally advanced and metastatic	No survival benefit	
Prinomastat + Mitoxantrone/ Prednisone	Mitoxantrone/ Prednisone	Prostate	Metastatic, hormone refractory	No survival benefit	35
Tanomastat	Gemcitabine	Pancreatic	First-line, locally advanced and metastatic	Worse survival	36
Tanomastat	Placebo	Small-cell lung	Limited or extensive stage, following response to first-line therapy	Worse survival	37
BMS-275291 + Carboplatin/ Paclitaxel	Carboplatin/ Paclitaxel	Non-small-cell lung	First-line, locally advanced and metastatic	Accrual complete, results pending	
Neovastat	Placebo	Renal cell	Locally advanced and metastatic	Accrual complete, results pending	
Epidermal growth-factor receptor inhibitors					
Gefitinib + Carboplatin/ Paclitaxel	Carboplatin/ Paclitaxel	Non-small cell lung	First-line, locally advanced and metastatic	No survival benefit	38
Gefitinib + Cisplatin/ Gemcitabine	Cisplatin/ Gemcitabine	Non-small-cell lung	First-line, locally advanced and metastatic	No survival benefit	39
Erlotinib + Carboplatin/ Paclitaxel	Carboplatin/ Paclitaxel	Non-small-cell lung	First-line, locally advanced and metastatic	Accrual complete, results pending	
Farnesyltransferase inhibitors					
R115777 + Gemcitabine	Gemcitabine	Pancreatic	Locally advanced and metastatic	No survival benefit	40
Angiogenesis inhibitors					
Bevacizumab + Capecitabine	Capecitabine	Breast	Second- or third-line metastatic	No survival benefit	41
Semaxanib (SU5416) + Irinotecan/ 5-Fluorouracil/ Leucovorin	Irinotecan/ 5-Fluorouracil/ Leucovorin	Colorectal	First-line metastatic	No survival benefit	42

Are these the correct experiments?

- Agent doesn't work.
- Huge leap of faith:
  - Cell culture--->mouse--->human
- Wrong dose or wrong combination.
- Wrong patients.
- Wrong endpoints.
- Biologic heterogeneity.
- Don't really understand target.
- Targeted therapy won't work.

Mouse to human:easy to cure mice!





Boehm et.al.
NATURE | VOL 390 | 27 NOVEMBER 1997

Are these the correct experiments: wrong endpoint?

- Overall survival gold standard to demonstrate efficacy.
  - Cross-over design in randomized trials dilutes Phase III data.
  - Active 2nd/3rd line agents dilutes Phase III data.
- Can we use time to tumor progression (TTP) as an endpoint?
  - What is tumor progression? (e.g. size? activity?).
  - Lead time bias problem (e.g when are you looking?)
  - TTP ≠ OS

Are these the correct experiments: wrong patients?

- New agent as upfront therapy?
  - Difficult to compare experimental agent verses standard therapy if standard therapy has a known survival benefit (no matter how poor).
- New agents usually tested in 2nd/3rd line settings in highly advanced cancers.
  - Tumors already globally resistant from clonal evolution/selection from prior therapies.
- Target validation.
  - Is the target there?
  - Is target being inhibited?
- *Are we missing active agents by testing in the wrong patients?*

Are these the correct experiments: tumor heterogeneity?

- Cancers for most part classified by histology.
- Same tumor types display vastly different biology (seemingly completely different diseases):
  - Breast cancer:-ER+ verses ER-; +/- her2/neu.
  - Lymphoma: diffuse large cell: 50% curable.
- Therefore, Phase III trials for "specific" cancers actually studying multiple diseases. Difficult to demonstrate OS benefit without huge trial.
- *Subset of patients who benefit? Probably--but we can't prove it with these methods!*

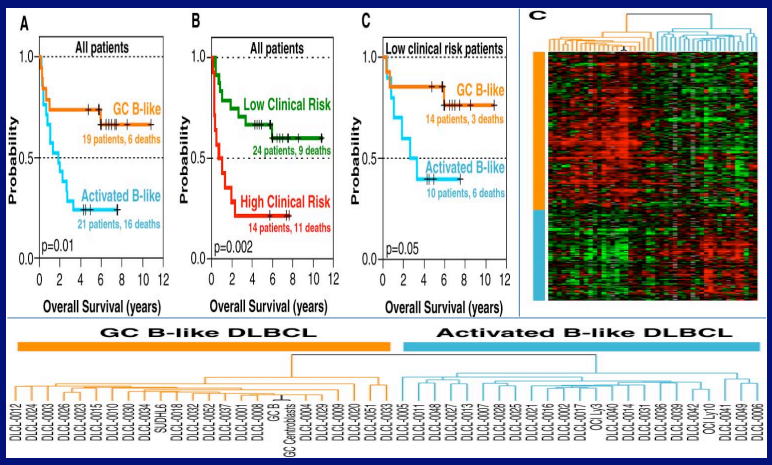
Currently:
clinical trials use staging as a crude surrogate for tumor biology.

Table 2 | **Staging cancer by determining the extent of disease spread**

Tumour size (T)	Lymph node status (N)	Metastatic status (M)
T0: impalpable	N1: spread to regional lymph nodes	M0: no detectable metastases
T1: 0–2 cm	N2: 3 distant lymph nodes affected	M1: metastases present
T2: 2–5 cm		
T3: over 5 cm and fixation to underlying muscle		
T4: any size, with fixation to chest wall or skin		

This procedure requires a combination of pathological, clinical and radiological data. The pathology data relate to size of tumour and involvement of regional nodes. The data are combined to determine final stage, tumour size (T), nodal status (N) and presence or absence of distant metastases (M).

Future:
Molecular re-classification of tumors



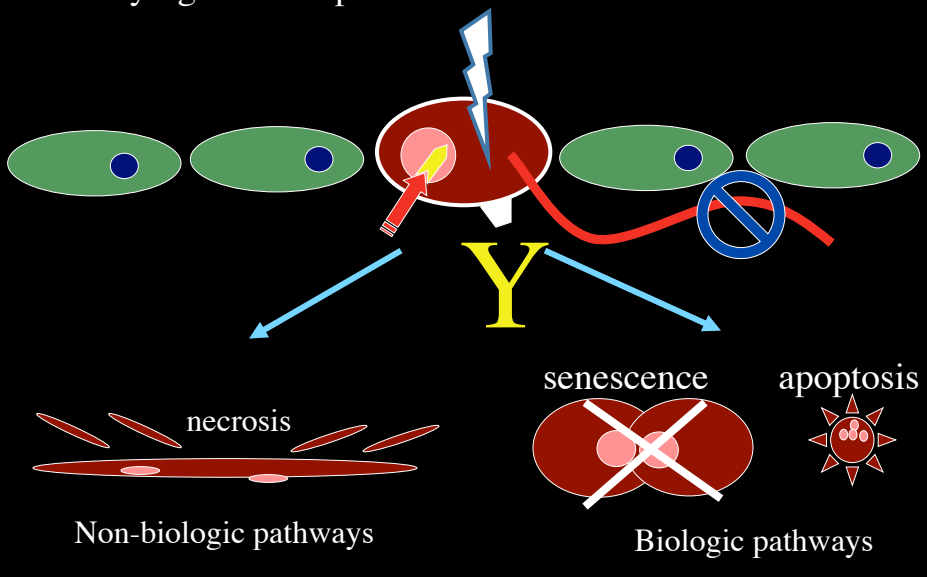
DLBC-lymphomas are actually different diseases!

Alizadeh et al., Nature 403:503(2000).

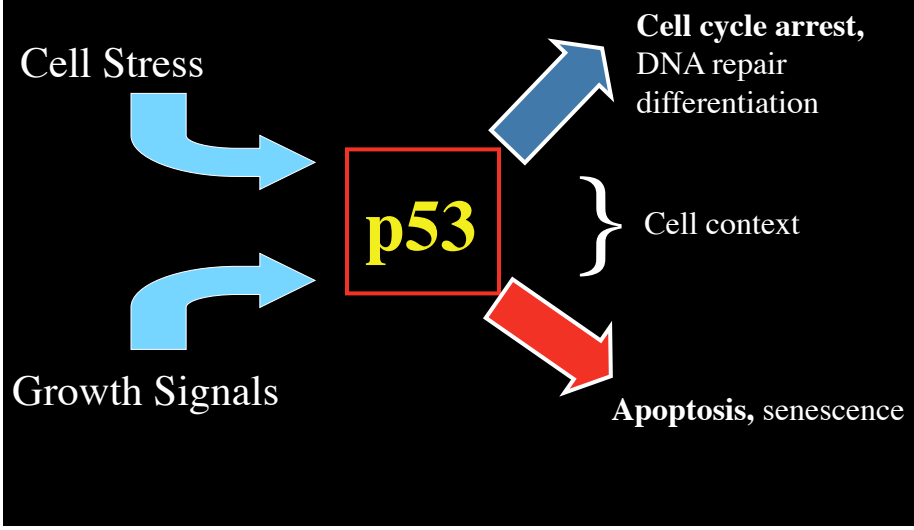
Molecular re-classification will change the practice of oncology.

- Immediate: identifying patient subsets for prognosis.
- Long-term: understanding biology will drive discovery of new agents.

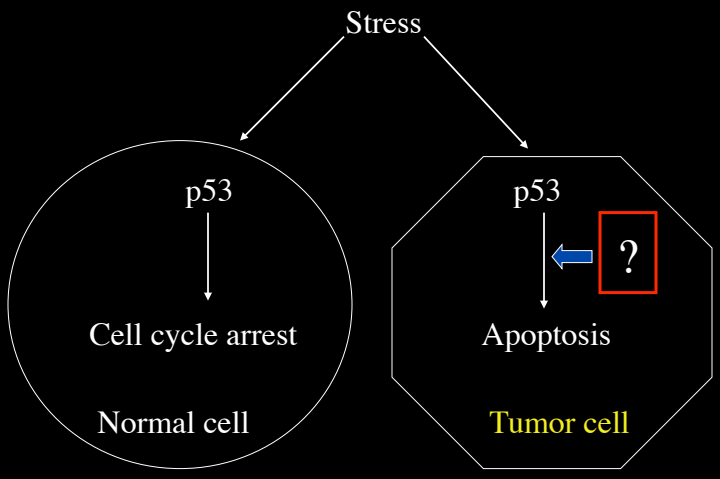
Cancer therapy: What are the molecular mechanisms underlying the therapeutic window?



p53: pivotal role in the cellular stress response and tumor suppression.



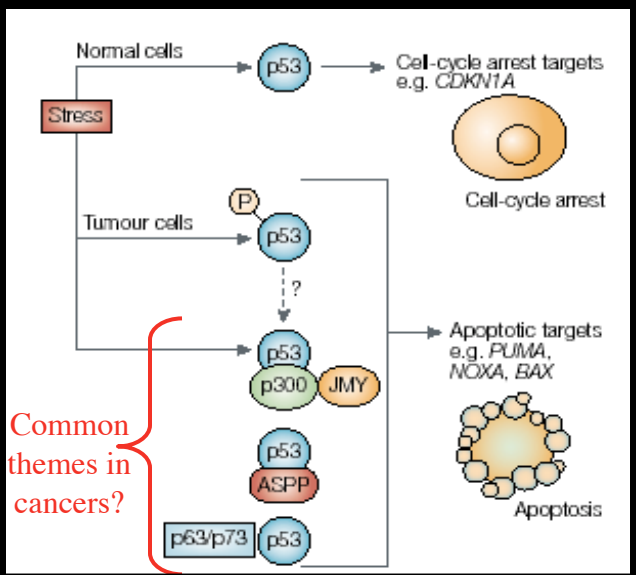
Treatable cancers: tumor cell context can increase sensitivity to apoptotic signals.



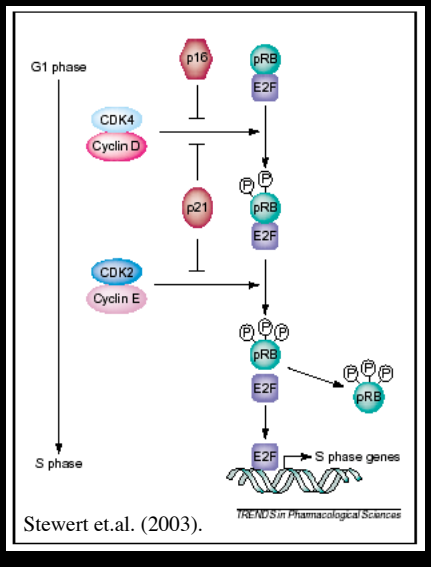
Holy grail of cancer therapy is to amplify/restore sensitivity in tumors that have a disabled apoptotic pathway.

Treatable cancers: tumor cell context can increase sensitivity to apoptotic signals.

Vousden and Lu. Nature Reviews: Cancer 2:594(2002).



Tumor cell context: inappropriate proliferation a common theme of cancer.



Stewert et.al. (2003).

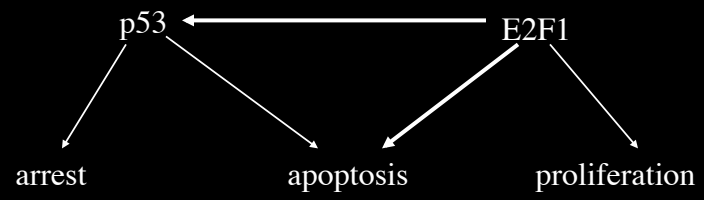
- Dysregulation of Rb/E2F pathway an essential step in cancer formation.

Examples:
- -Rb loss
- -Overexpression of D-type cyclins
- -Loss of p16/INK4A

*All leading to unregulated E2F activity and inappropriate S-phase entry.

Coupling proliferation and increased sensitivity to apoptotic signals.

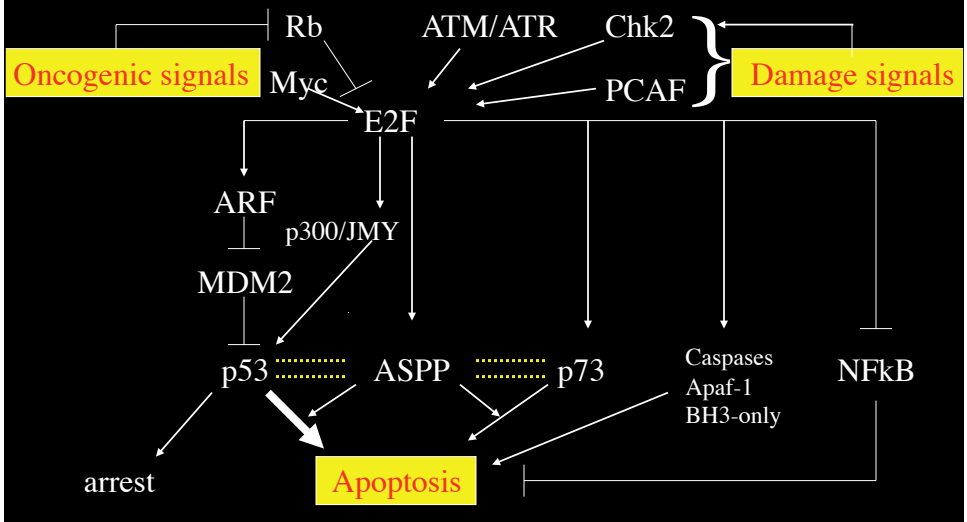
E2F1 sends cooperative signals to sensitize cells to apoptotic signals via both p53 dependent and p53 independent pathways.



E2F1 major mechanism coupling proliferation and apoptosis.

Coupling proliferation and increased sensitivity to apoptotic signals:

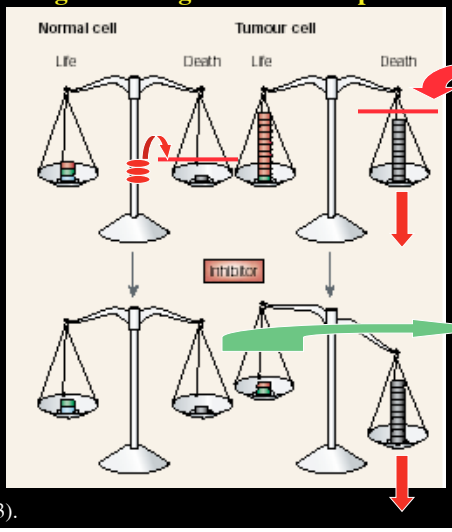
parallel pathways lower the apoptotic threshold.



Coupling proliferation and increased sensitivity to apoptotic signals:

it's all about thresholds providing context.

Tumors "living on the edge" is the therapeutic window for treatment



Killing input can tip over death threshold.

Growth inhibitor can tip over death threshold.

Modified from: Nature Reviews Cancer 3:11 (2003).

Features of the ideal anticancer target

Crucial to the malignant phenotype

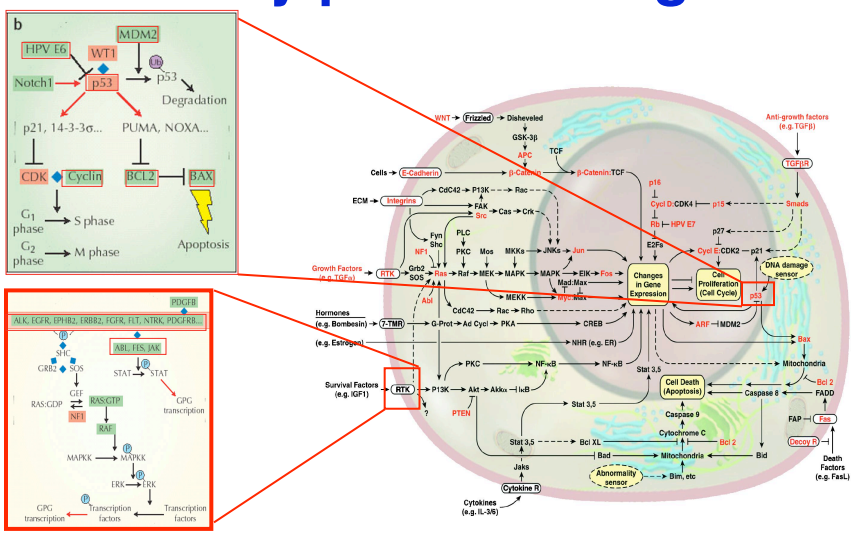
Hitting the target does not cause problems in vital organs and tissues

Reproducibly measured in readily obtained clinical samples

Correlated with clinical outcome

Ross et al., Am J Clin Pathol 122, 598-609 (2004)

Many potential targets!



RED = altered in cancer cells

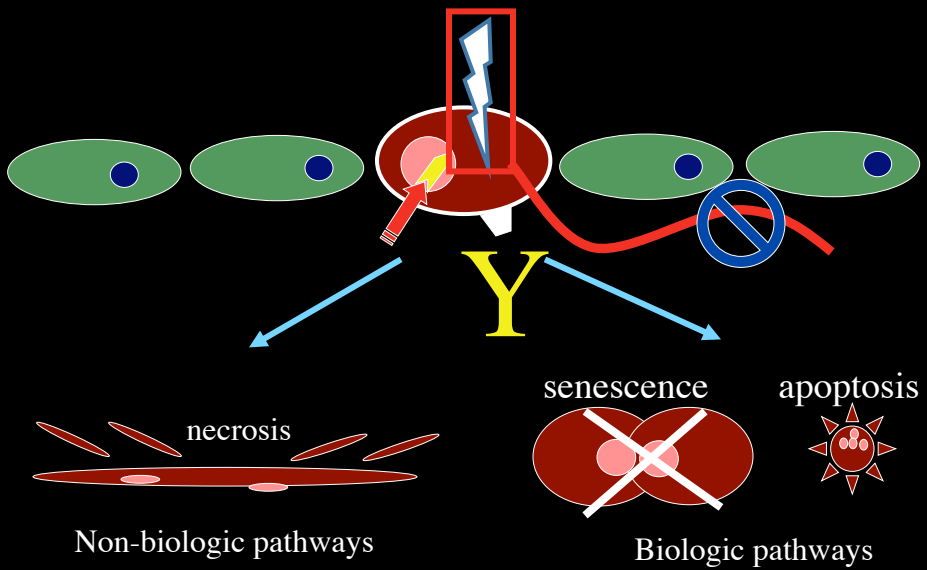
Vogelstein & Kinzler, Nature Medicine 10, 789-799 (2004)

Hanahan, D., and Weinberg, R.A., The Hallmarks of Cancer, Cell 100, 57-70 (2000)

How do we discover new agents?

- Brute force assays.
  - E.g. NCI anticancer screen of human tumor cell lines for in vitro activity of naturally occurring compounds produced Paclitaxel (Taxol).
- Molecular targeted assays.
  - E.g. Tyrosine kinase inhibitors screen produced STI-571 (Gleevec).
- Good ideas.

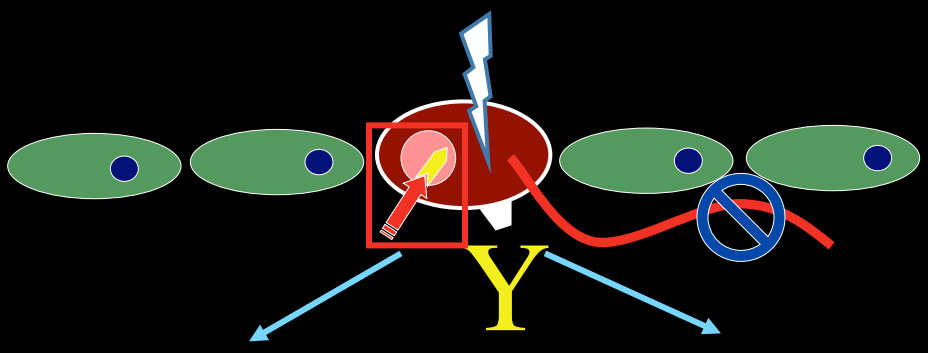
Cancer therapy: cytotoxic screen



Example brute force cytotoxic screen:Taxol

- 114,000 plant extracts screened at NCI from 1960 to 1981.
  - 1962:Bark of Pacific NW Yew tree (Taxus brevifolia), sent in by three grad students.
  - 1967: Extract slowed tumor growth in mice.
  - 1970: Taxol molecular structure solved. Effect on microtubule dynamics demonstrated.
  - 1984: First human trials.
  - 1992: FDA approved.
- Major drug today: active in ovarian, breast, lung and others.
- But took *30 years!*

Cancer therapy: targeted screen



necrosis

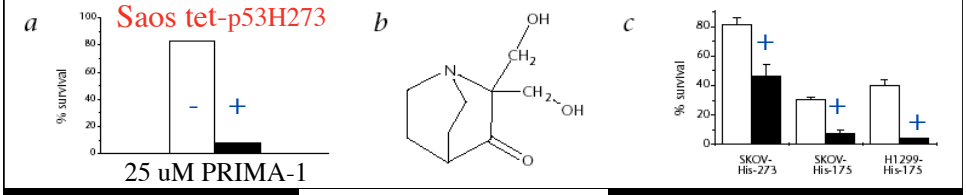
senescence

apoptosis

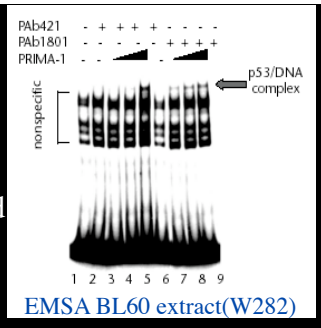
Non-biologic pathways

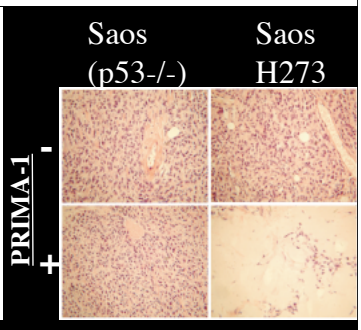
Biologic pathways

Example targeted screen: restoring p53 function (PRIMA-1).



- Chemical library screen for growth inhibition specific for mutant p53.
- P53 Reactivation and Induction of Massive Apoptosis-1

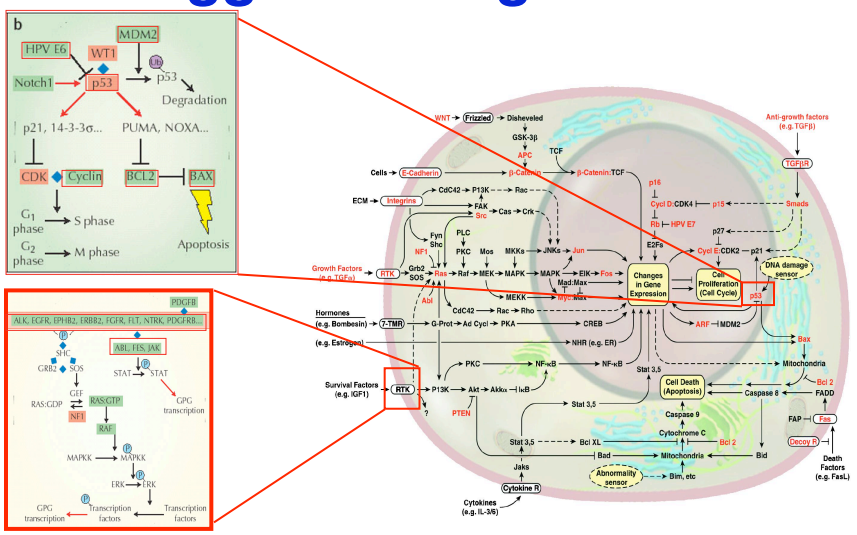




- Ongoing Phase I Clinical trial of PRIMA-1 in patients with urinary bladder cancer

Nature Medicine 8:282 (2002).

"Druggable" targets: kinases



RED = altered in cancer cells

Vogelstein & Kinzler, Nature Medicine 10, 789-799 (2004)

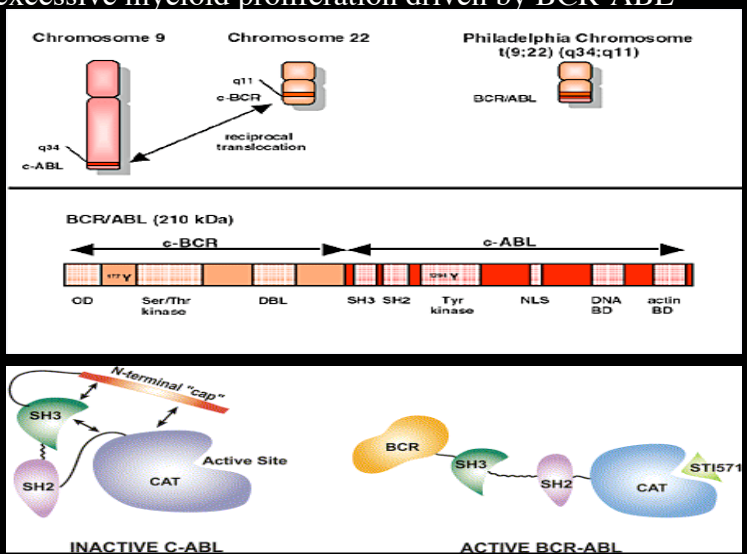
Hanahan, D., and Weinberg, R.A., The Hallmarks of Cancer, Cell 100, 57-70 (2000)

"Druggable" targets: kinase inhibitors.

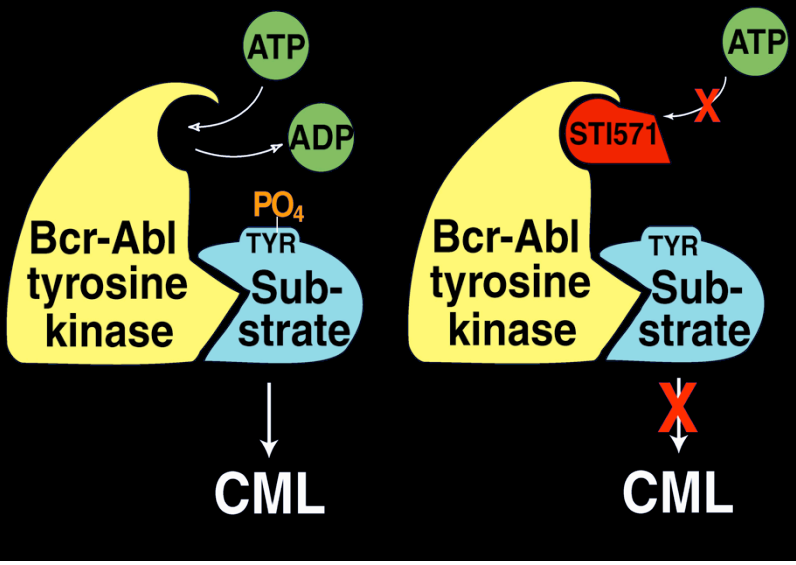
- 1990s: 2-phenylaminopyrimidines identified in screening program for PKC selective inhibitors.
- Chemical synthesis used to generate series of compounds that:
  - Modified specificity
  - Increased solubility
- CGP57148 (aka STI-571, Gleevec) an ATP-competitive inhibitor specific for Abl, c-kit, PDGFR tyrosine kinases.

Gleevec and CML

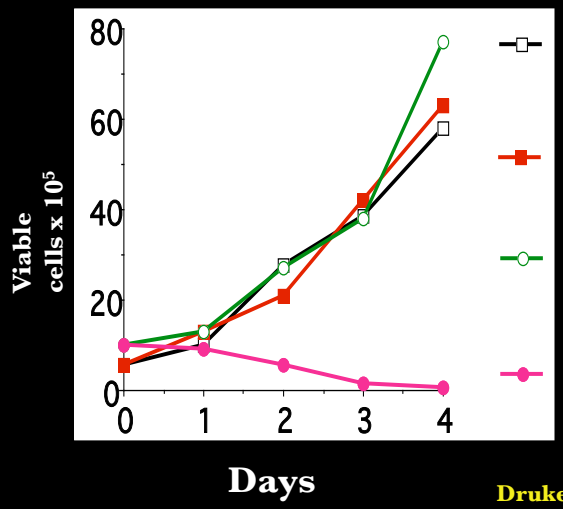
Chronic myelogenous leukemia: hematologic stem cell disorder of excessive myeloid proliferation driven by BCR-ABL



Bcr-Abl as a Therapeutic Target for CML

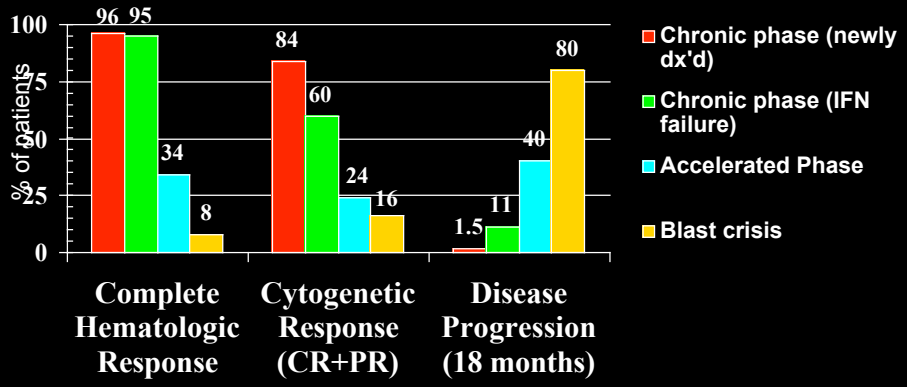


STI571 Specifically Inhibits The Growth of Cells With Bcr-Abl



Druker et al, Nat Med 2:561, 1996

Gleevec works in CML



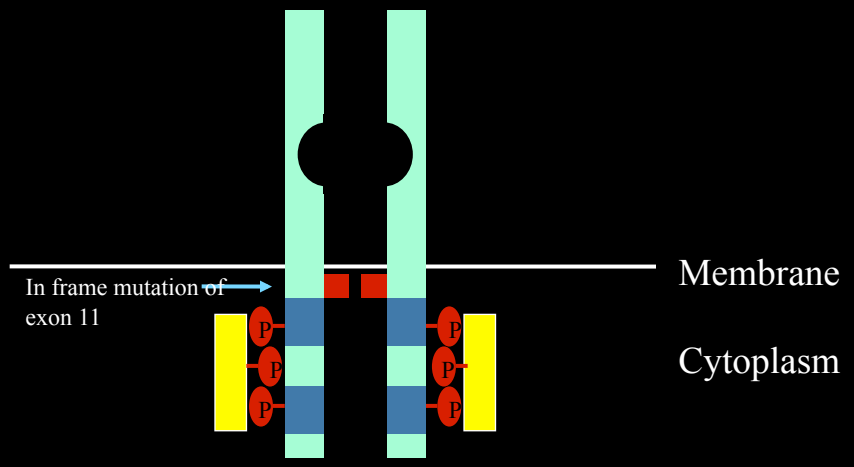
Gleevec.

- Results in Phase I trial rapidly expanded to Phase II/III trials. FDA approved 2001 after *record setting 3 month review.*
- Gleevec is now standard first-line therapy for CML

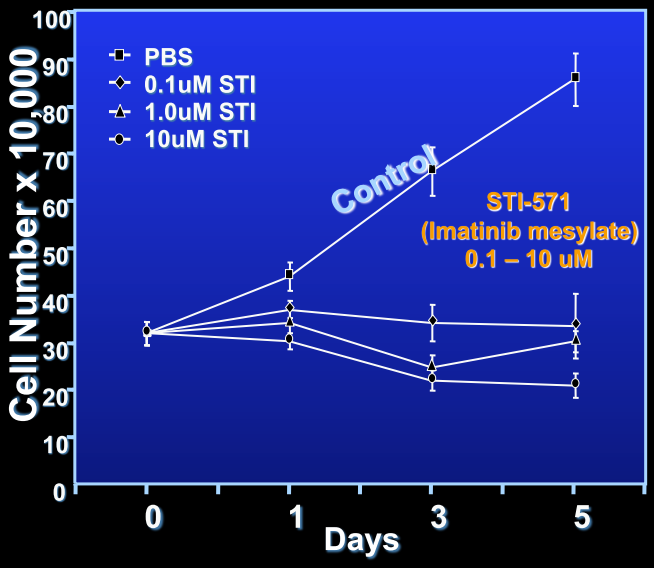
CML and GIST paradigm: the *molecular lesion* defines the tumor.

- GIST (GI stromal tumor): Mesenchymal gut neoplasms histologically ***completely different*** than CML
- c-KIT: 145-kd transmembrane GP member TK_{III} family. Normal cellular homologue of a viral oncogene.
- Protein normally expressed heme progenitors, mast + germ cells, interstitial cells of Cajal
- c-kit activation stimulates cell growth & survival.

Ligand-independent Activation of Mutant KIT (Exon 11): blocked by Gleevec.



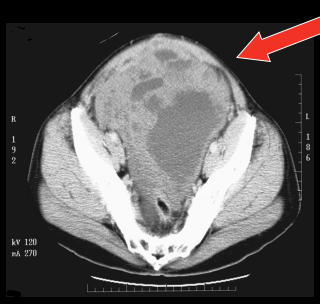
Gleevec Inhibits Proliferation of Human GIST Cells in Vitro



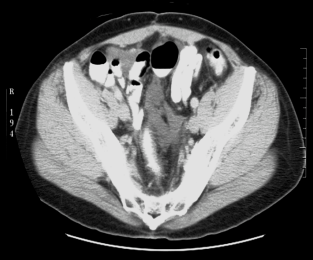
Tuveson, et al. *Oncogene* 2001.

Gleevec works in GIST.

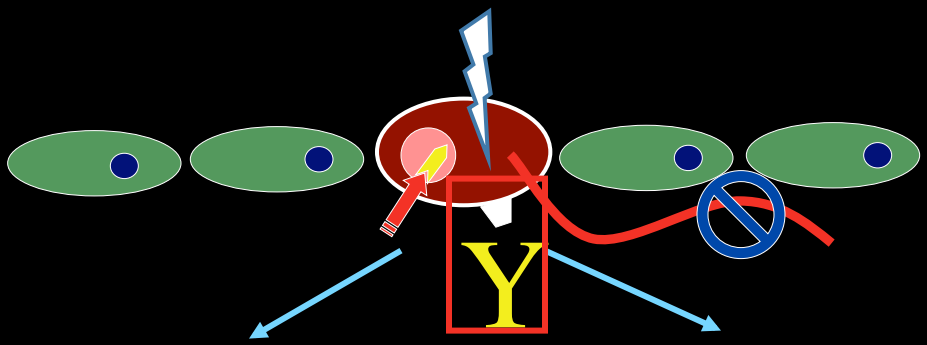
8/16/00

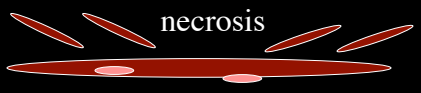


2/6/01



Cancer therapy: good idea "screen"

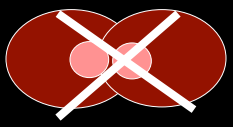




necrosis

Non-biologic pathways

senescence



apoptosis

Biologic pathways

HER-2/neu and breast cancer

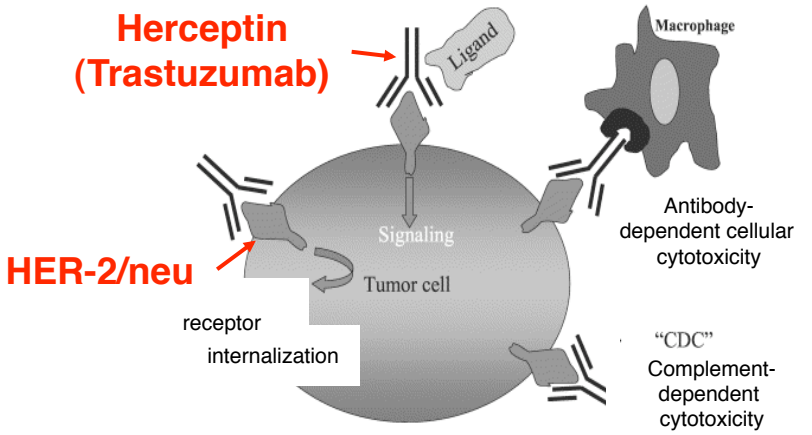
Science. 1987 Jan 9;235(4785):177-82.

Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene.

Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL.

The HER-2/neu oncogene is a member of the erbB-like oncogene family, and is related to, but distinct from, the epidermal growth factor receptor. This gene has been shown to be amplified in human breast cancer cell lines. In the current study, alterations of the gene in 189 primary human breast cancers were investigated. **HER-2/neu was found to be amplified from 2- to greater than 20-fold in 30% of the tumors.** Correlation of gene amplification with several disease parameters was evaluated. **Amplification of the HER-2/neu gene was a significant predictor of both overall survival and time to relapse in patients with breast cancer.** It retained its significance even when adjustments were made for other known prognostic factors. Moreover, HER-2/neu amplification had greater prognostic value than most currently used prognostic factors, including hormonal-receptor status, in lymph node-positive disease. These data indicate that this gene may play a role in the biologic behavior and/or pathogenesis of human breast cancer.

Anti-HER-2/neu mAb (Herceptin/Traztuzumab) kills tumor cells in vitro.



possible mechanisms

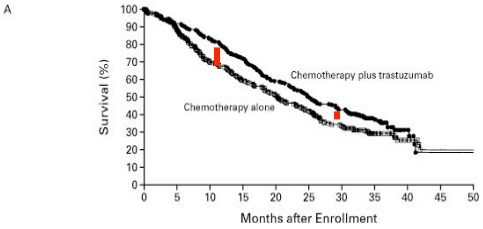
Kim, J.A., American Journal of Surgery 186, 264-268 (2003)

The NEW ENGLAND JOURNAL of MEDICINE

Volume 344:783-792 March 15, 2001

Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2

Dennis J. Slamon, M.D., Ph.D., Brian Leyland-Jones, M.D., Steven Shak, M.D., Hank Fuchs, M.D., Virginia Paton, Pharm.D., Alex Bajamonde, Ph.D., Thomas Fleming, Ph.D., Wolfgang Eiermann, M.D., Janet Wolter, M.D., Mark Pegram, M.D., Jose Baselga, M.D., and Larry Norton, M.D.



Results

… a lower rate of death at 1 year (22 percent vs. 33 percent, P=0.008)…

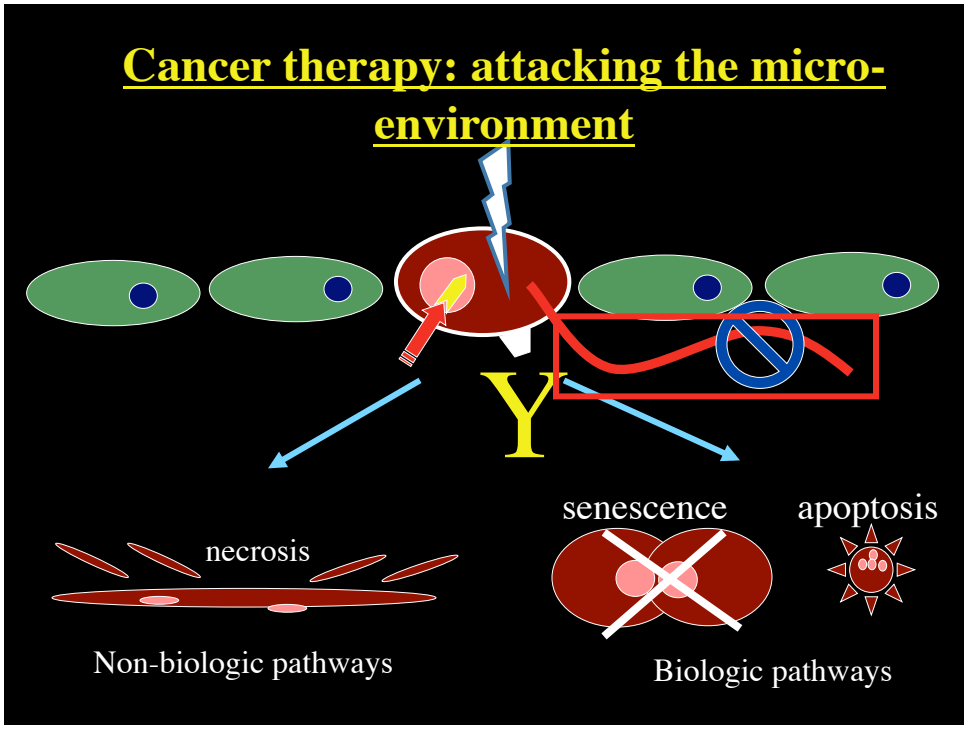
National Cancer Institute
U.S. National Institutes of Health | www.cancer.gov

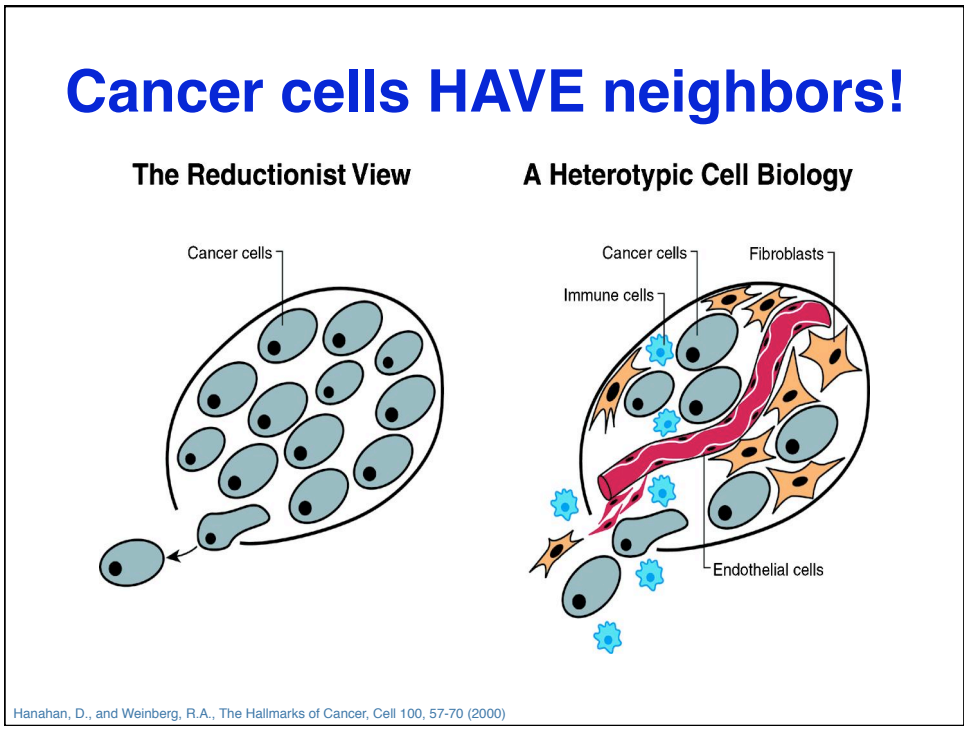
Posted: 04/25/2005

Herceptin® Combined With Chemotherapy Improves Disease-Free Survival for Patients With Early-Stage Breast Cancer

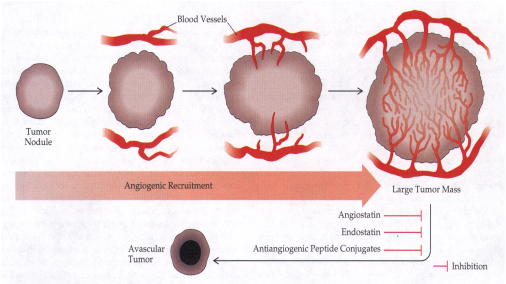
ADJUVANT THERAPY

"…..patients in the clinical trials who received trastuzumab in combination with standard combination chemotherapy had ***a 52 percent decrease in disease recurrence*** compared to patients treated with chemotherapy alone."


Cancer therapy: attacking the micro-environment
Y
necrosis
senescence
apoptosis
Non-biologic pathways
Biologic pathways


Cancer cells have neighbors!
The Reductionist View
A Heterotypic Cell Biology
Cancer cells
Cancer cells
Fibroblasts
Immune cells
Endothelial cells
Hanahan, D., and Weinberg, R.A., The Hallmarks of Cancer, Cell 100, 57-70 (2000)

Angiogenesis and cancer



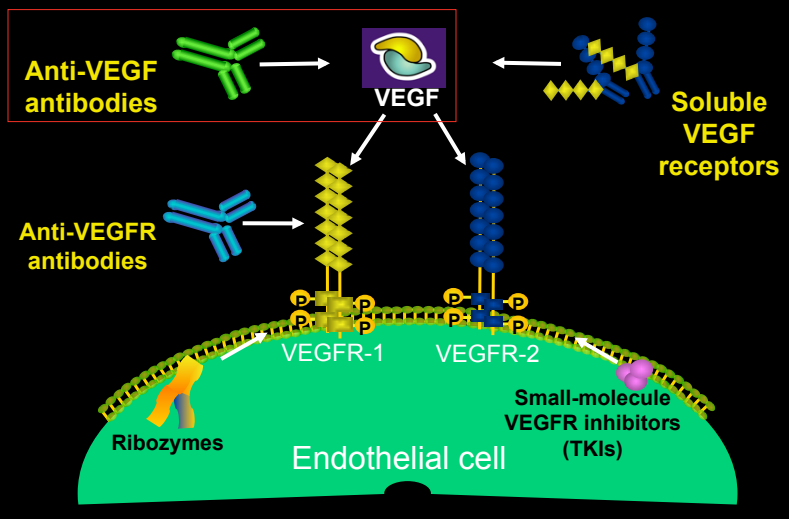
Cells have to be within 100 μm of a capillary in order to survive.

Genetic events leading to increased angiogenesis are not that clear.

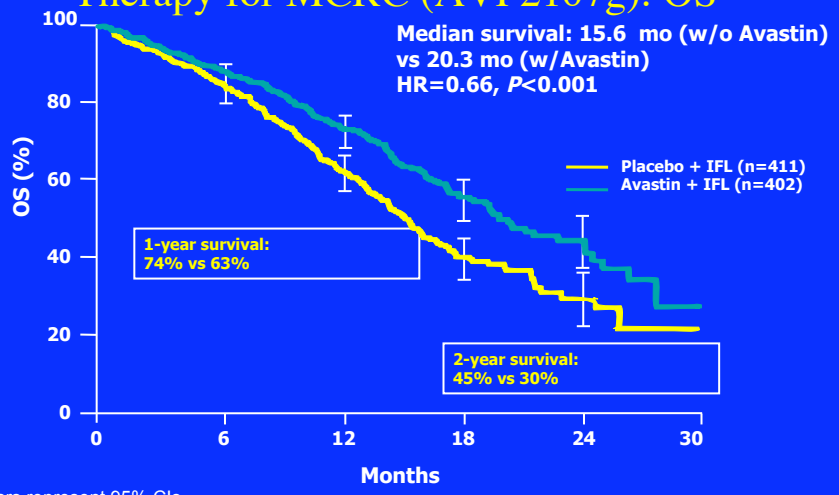
BUT: even without understanding all basic mechanisms, exciting therapeutic strategies have been identified.

Haber, D.A., Scientific American Medicine, Section 12 II (1999)

Agents Targeting the VEGF Pathway: bevacizimab



Phase III Trial of Avastin + IFL as First-Line Therapy for MCRC (AVF2107g): OS



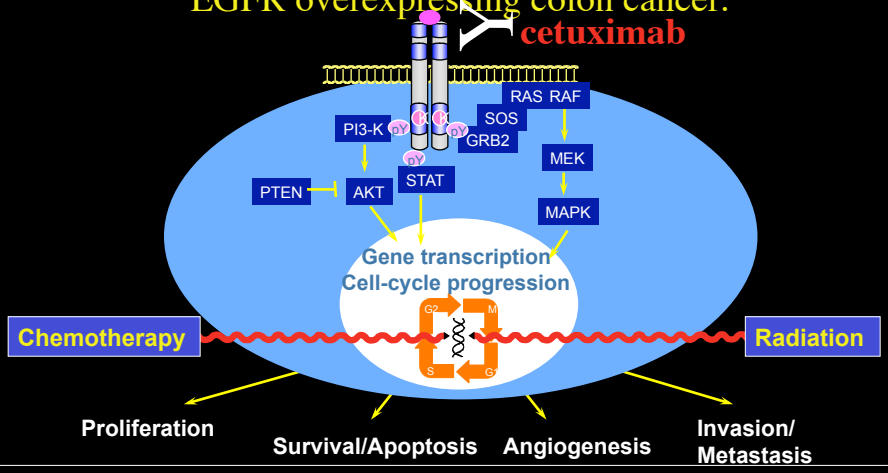
Error bars represent 95% CIs.

Avastin® (bevacizumab) PI. December 2004.
Data on file (SR2), Genentech, Inc. 2005.
Hurwitz et al. *N Engl J Med*. 2004;350:2335.

Are we learning biological lessons from ongoing clinical trials?

Bench to bedside.....to bench again?

Clinical Trial: anti-EGFR antibody plus chemotherapy in EGFR overexpressing colon cancer.



- IgG1 monoclonal antibody targeting the extracellular domain of human EGFR with high affinity (K_d, 0.5 nM)
- Prevents binding of EGF or TGF-α to EGFR and presumably preventing activation of intracellular tyrosine kinase

What lessons did we learn from this trial?

Lesson: no insider trading!

Cetuximab response rates ***did not*** correlate with EGFR overexpression.

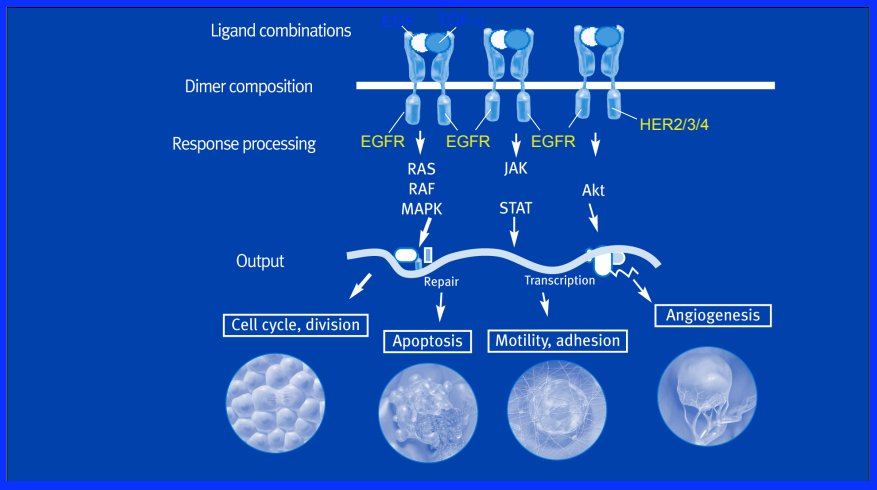
	Cetuximab (n=111)	Cetuximab + Irinotecan (n=218)	*P* Value
PR (%)	11	23	.0074
TTP (mo)	1.5	4.1	<. 0001

More to story than just overexpressed EGFR??

*Cunningham et al. NEJM 7/04.

The EGF Receptor: (HER1 or c-Erb-1)

EGFR a member of a subfamily of type I receptor tyrosine kinases (including HER2, HER3 and HER4)

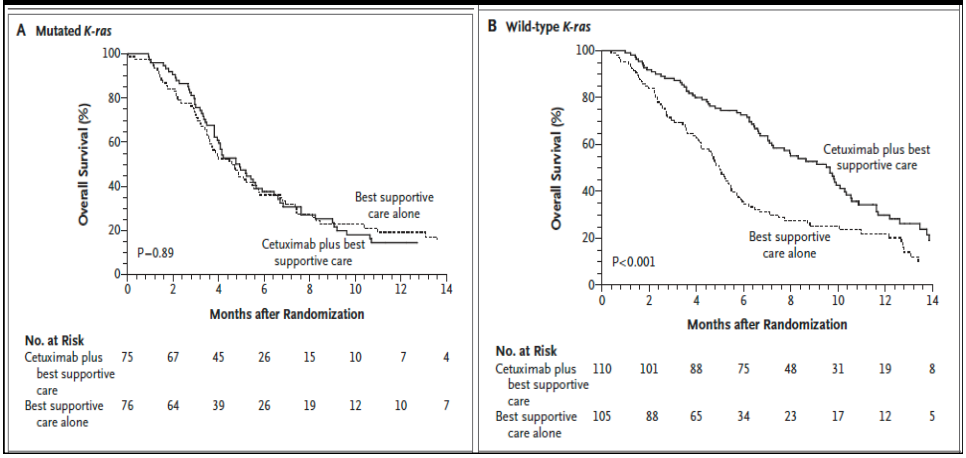


EGF = epidermal growth factor; TGF-α = transforming growth factor-alpha; EGFR = epidermal growth factor receptor.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 23, 2008 VOL. 359 NO. 17

K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer



VOLUME 26 · NUMBER 35 · DECEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Wild-Type *BRAF* Is Required for Response to Panitumumab or Cetuximab in Metastatic Colorectal Cancer

Federica Di Nicolantonio, Miriam Martini, Francesca Molinari, Andrea Sartore-Bianchi, Sabrina Arena, Piercarlo Saletti, Sara De Dosso, Luca Mazzucchelli, Milo Frattini, Salvatore Siena, and Alberto Bardelli

From the Laboratory of Molecular Genetics, The Oncogenomics Center,

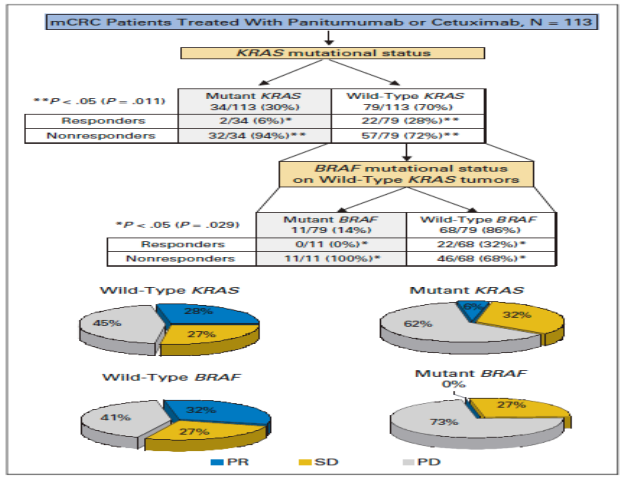
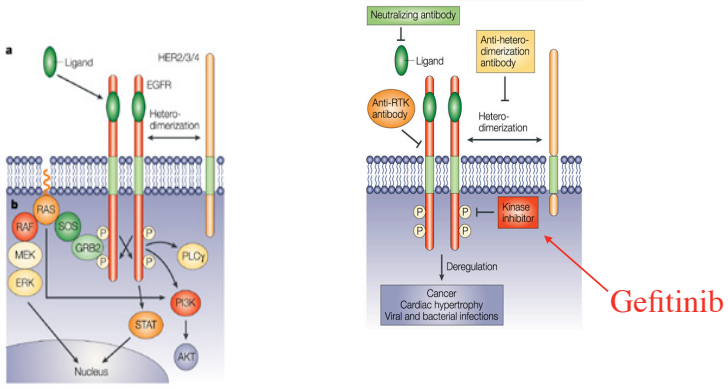


Fig 1. *KRAS* and *BRAF* mutations correlate with lack of response to treatment with monoclonal antibodies targeting epidermal growth factor receptor. The number of responders and nonresponders (stable disease [SD] + progressive disease [PD]) is indicated according to *KRAS* or *BRAF* mutational status. The percentage of patients displaying partial response (PR), SD, or PD is shown in the pie charts. mCRC, metastatic colorectal cancer.

Iressa (Gefitinib) for Non-Small Cell Lung Cancer

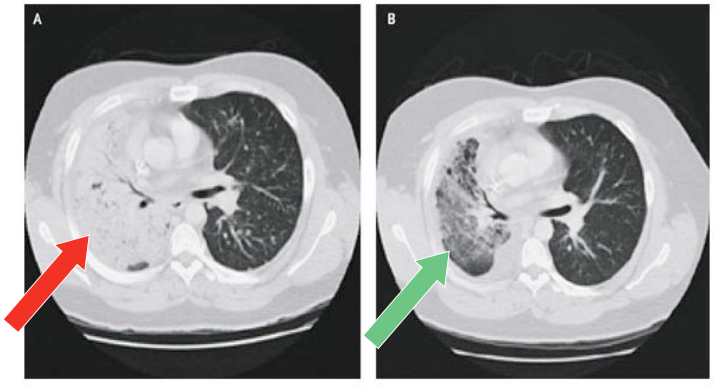
Tyrosine kinase inhibitor targeting EGFR.



Gschwind et al., Nature Reviews Cancer 4, 361-370 (2004)

Mostly no responses, but 10% with clinical responses, some dramatic.

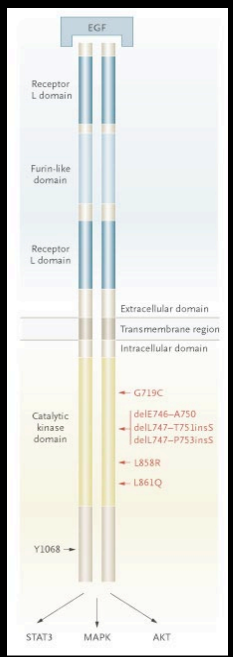
Pre-gefitinib Post-gefitinib



Target validation?
Tumor heterogeneity?

Lynch et al., NEJM 350, 2129-2139 (2004)

Bench to bedside...and back to bench.



The NEW ENGLAND JOURNAL of MEDICINE

Volume 350:2129-2139 May 20, 2004

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib *Thomas J. Lynch et.al.*

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

Science 304:1497 (June 2004)

Gefitinib-Sensitizing *EGFR* Mutations in Lung Cancer Activate Anti-Apoptotic Pathways

Raffaella Sordella, Daphne W. Bell, Daniel A. Haber, Jeffrey Settleman*

Science 305:1163 (August 2004)

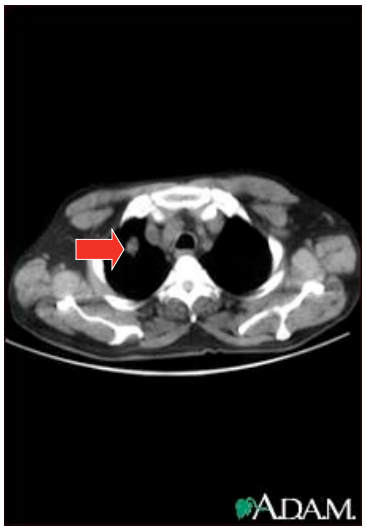
Some sobering thoughts.....

- Are the dramatic responses exceptional examples of rare cancers *dependent* on an activating oncogenic lesion?
- Is this paradigm applicable to highly deregulated cancers that are *independent* from an activating oncogenic lesion?
- Advanced cancers have yet to be cured with new targeted agents.

Some sobering thoughts.....

Can cancer cells

simply outnumber excellent therapies?



A mass visible on CT scan (~1cm^3):

10^9 cells

Cancer metastatic at diagnosis:

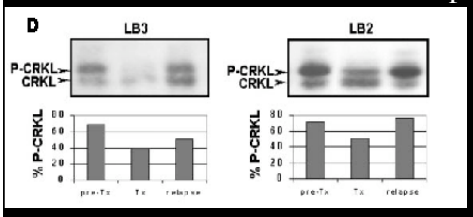
10^{10} cells

If one chemo/targeted therapy cycle kills 99.9% of all cancer cells:

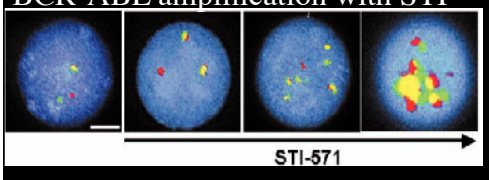
10^7 cells still there

Some sobering thoughts.... resistance mechanisms in Gleevec failures/relapses.

STI fails to inhibit Bcr-Abl in relapse

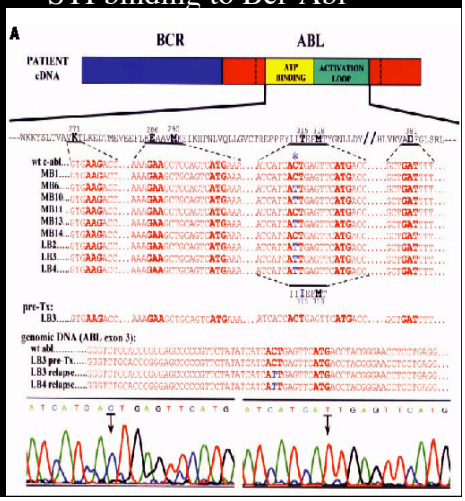


BCR-ABL amplification with STI



Gorre et.al., Science 293:876 (2001).

Kinase point mutant disrupts STI binding to Bcr-Abl



Summary

- Biology, biology, biology! The foundation of all molecularly targeted therapies.
- Entering an exciting new era in cancer biology and therapy---the basic science work of the last several decades is translating into effective therapies.

Summary

- Biology, biology, biology! The foundation of all molecularly targeted therapies.
- Entering an exciting new era in cancer biology and therapy---the basic science work of the last several decades is translating into effective therapies.

However, major hurdles remain for molecularly targeted therapies.

Major hurdles: bench

- What are the mechanisms of resistance?
  - cancers are turning out to be quite clever even against molecularly targeted agents.
- What are the targets for most cancers?
  - Breast with Her2/neu amplification
  - Lung with EGFR mutations
  - CML
  - GIST

  } minority of cancers!

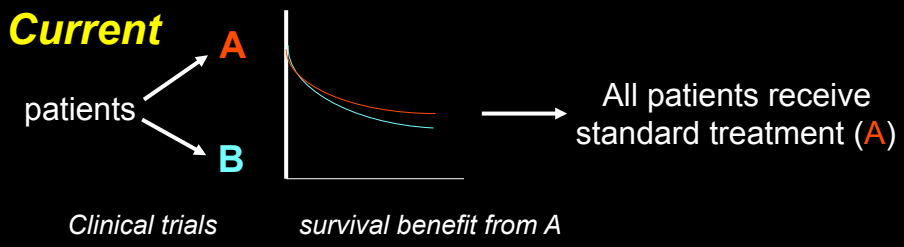
  } minority of patients!
- Are all relevant targets druggable?
  - e.g. loss of tumor suppressor

Major hurdles: bedside

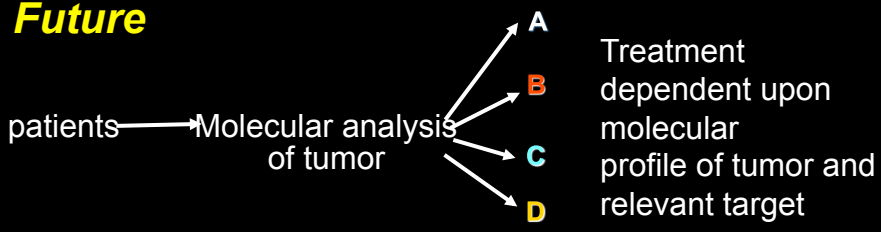
- Need robust molecular diagnostics.
  - Highly accurate and reproducible.
  - Work in "real-life" clinical settings.
- Need to match molecularly targeted drugs with molecularly defined patients--or will not be able to demonstrate efficacy in heterogeneous populations (e.g. do the correct experiment!)
  - Modify phase I trials to address ***proof of concept***
    - Does drug hit the intended target?
    - What dose of drug required to inhibit the target (not max tolerated dose)?

A New Paradigm for Cancer Therapy

Current



Future



Cancer Biology Challenge: Bench to Bedside--and back to Bench.

•Medical Genetics 605: Mechanisms of Cancer Journal Club (free lunch!)
• Tumor Boards