


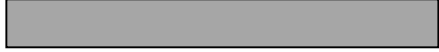






Causes of death, 2001:

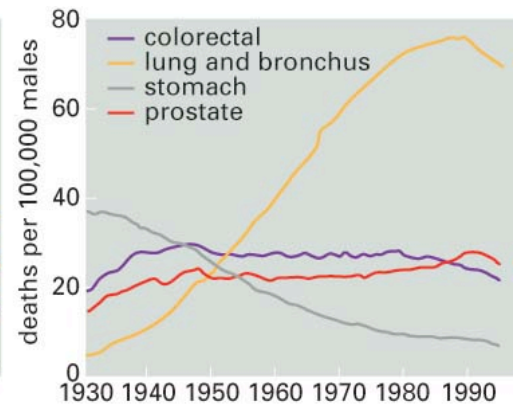
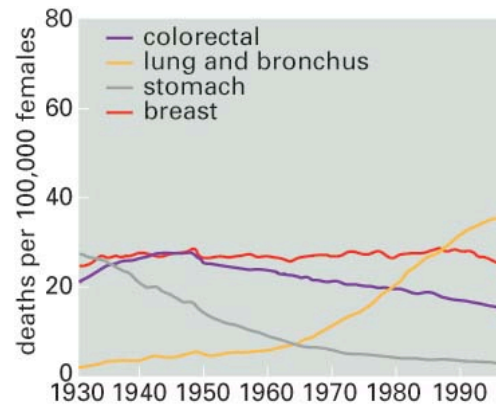
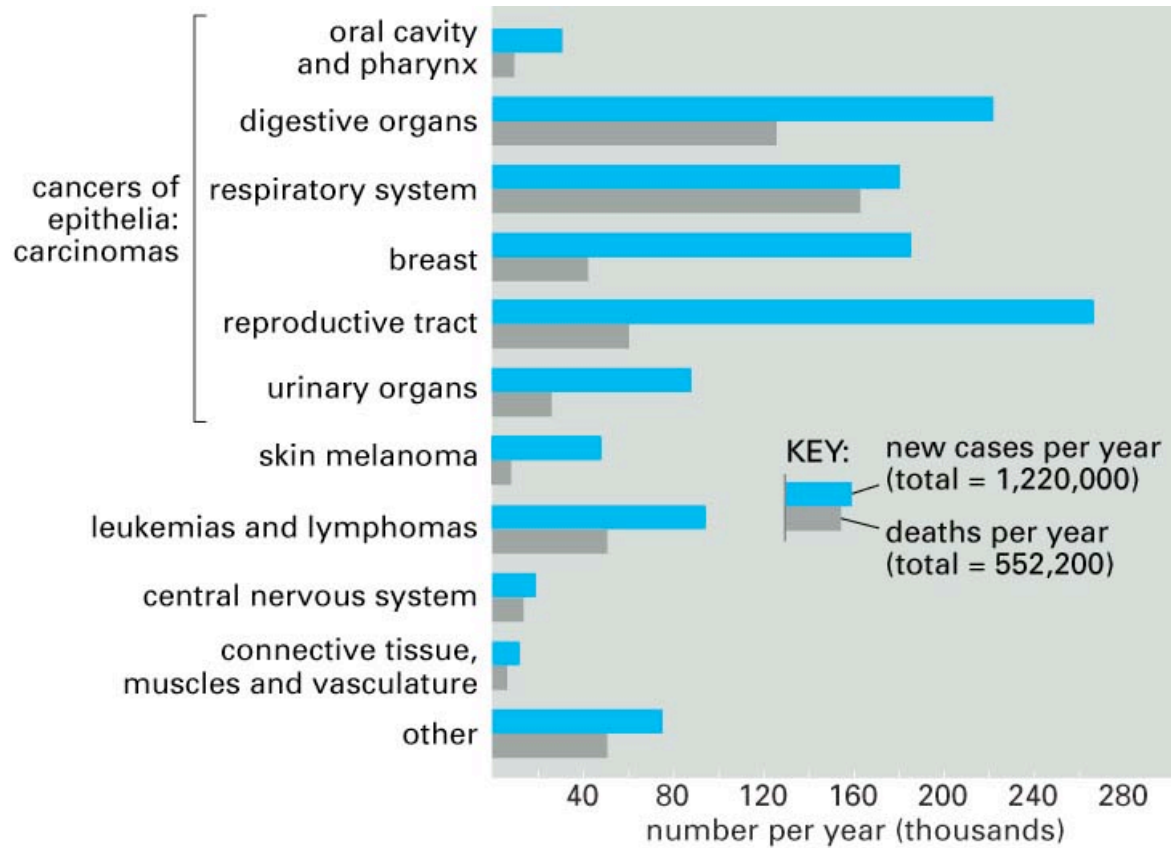
| | |
|-------------|---------------|
| Population: | 6,122,210,000 |
| Deaths: | 56,554,000 |

USA

6. 1. **Infectious and parasitic diseases: 14.9 million**

1. 2. **Heart diseases: 11.1 million**

2. 3. **Cancers: 7.3 million**

3. 4. **Stroke: 5.5 million**

4. 5. **Respiratory diseases: 3.6 million**

5. 6. **Accidents, fires, drowning, etc.: 3.5 million**

7. 7. **Maternal and perinatal: 3.0 million**

8. 8. **Violence (war, homicide, suicide): 1.6 million**


World Health Organization
World Health Report 2002

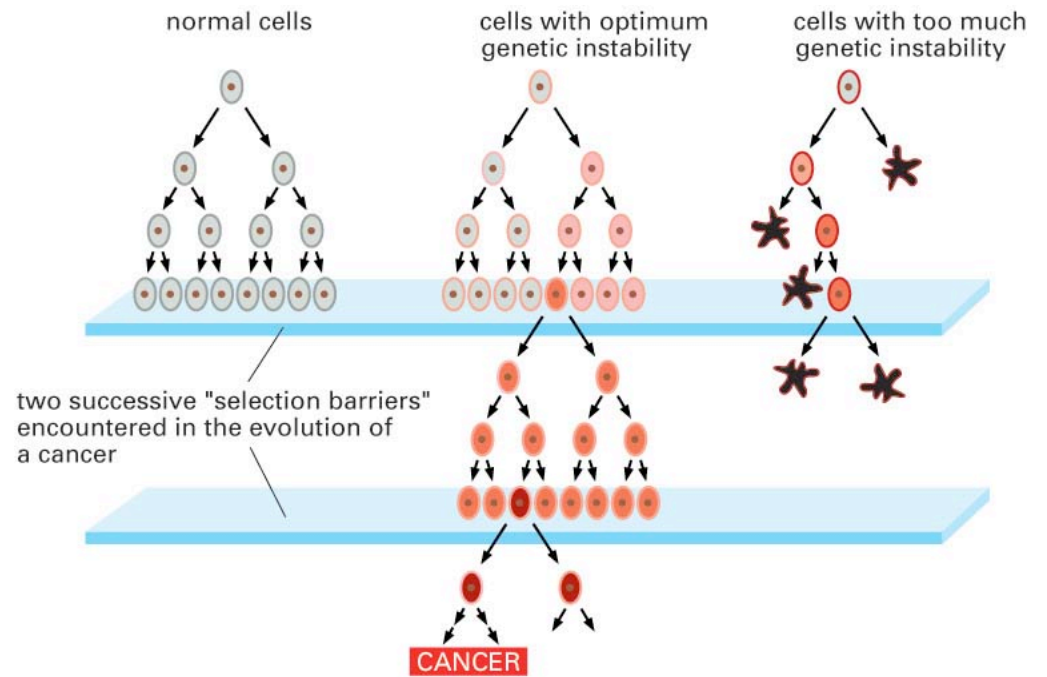
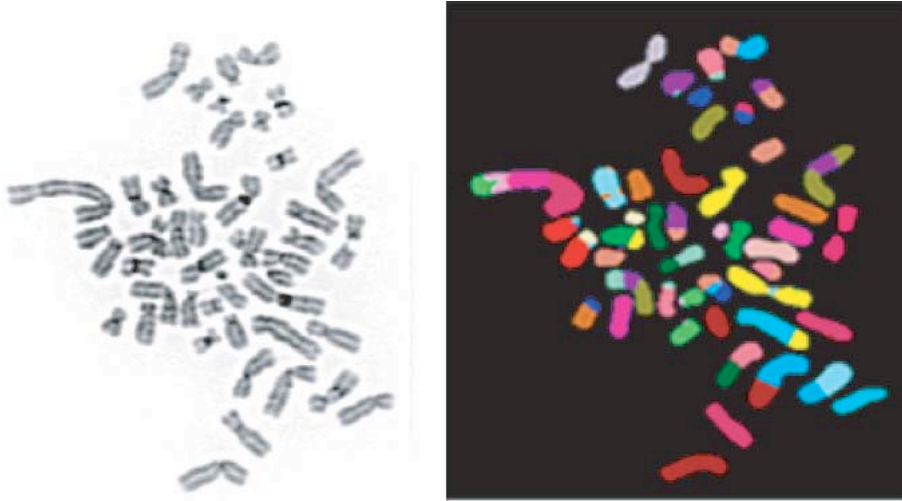
Cancer Incidence



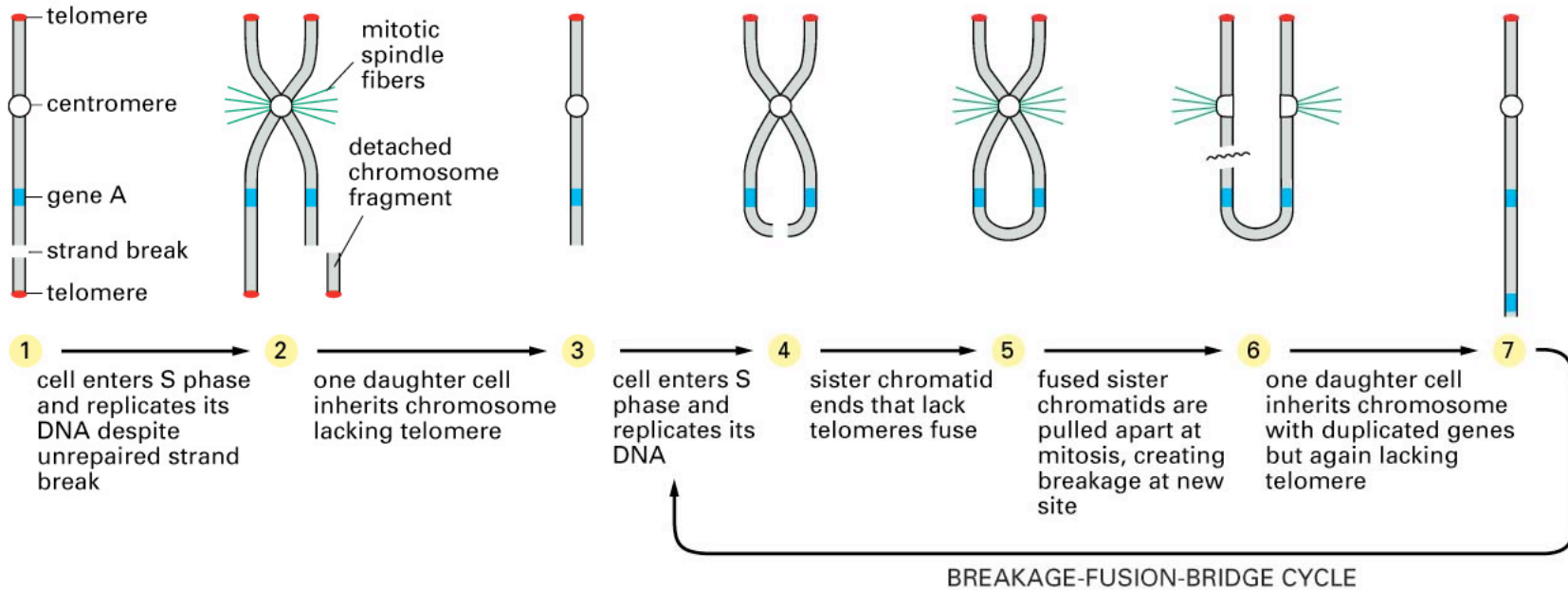
Essential Characteristics of Cancer Cells

1. Rapid/dysregulated cell division
2. Avoid apoptosis/differentiation
3. Avoid senescence by telomere shortening
4. Genomically unstable (Mut L/S HNPCC vs. FAP)
5. Invasive
6. Survive Elsewhere (10^{-3} to 10^{-6} ; *e.g.* angiogenesis)

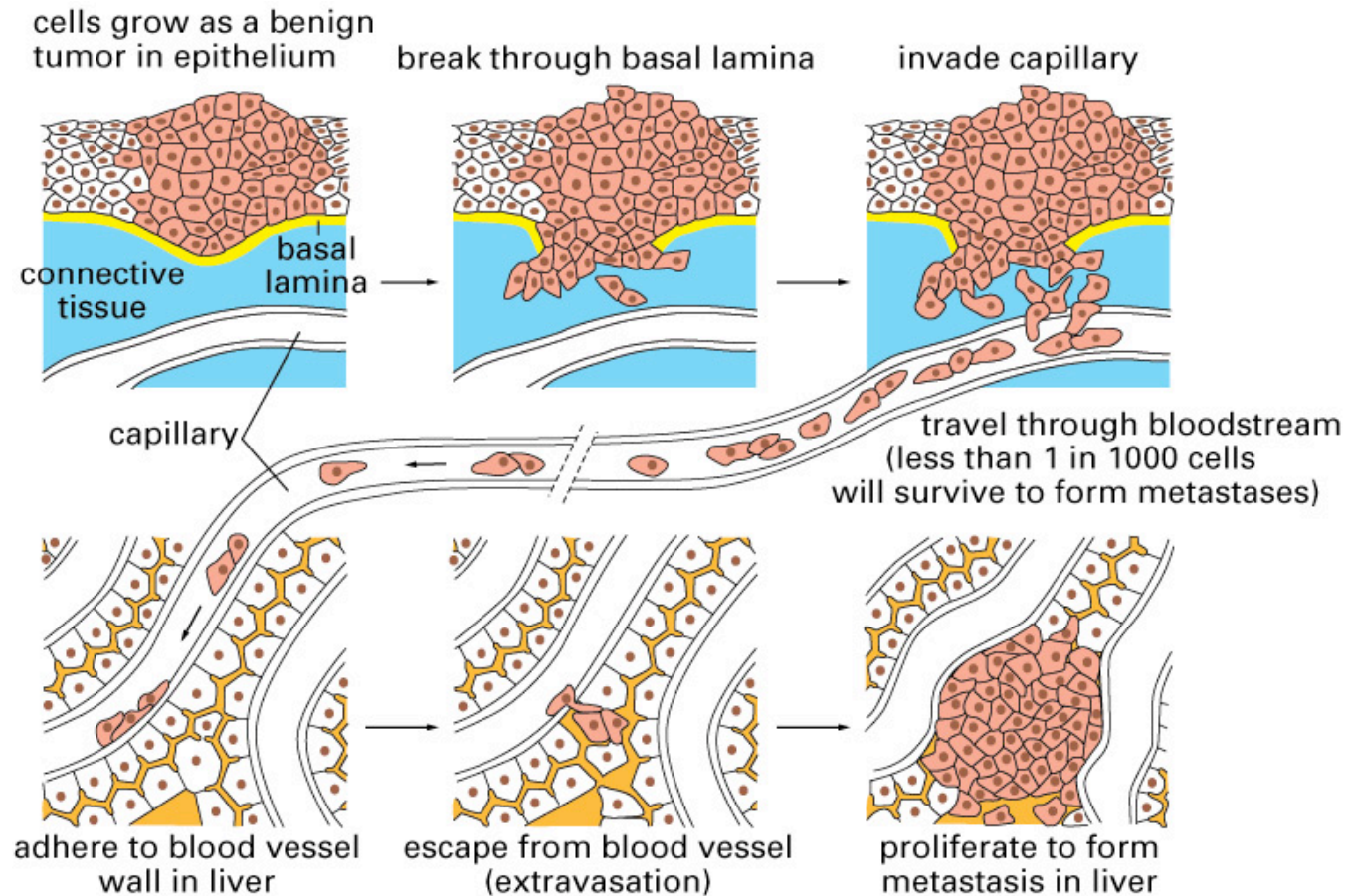
Genomic Instability



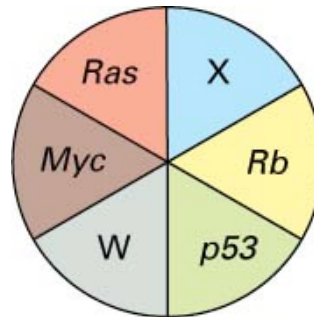
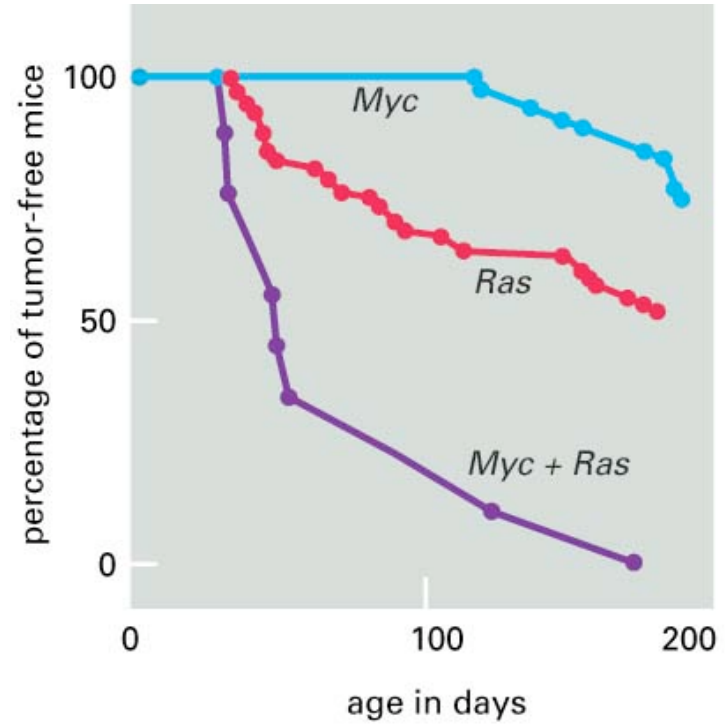
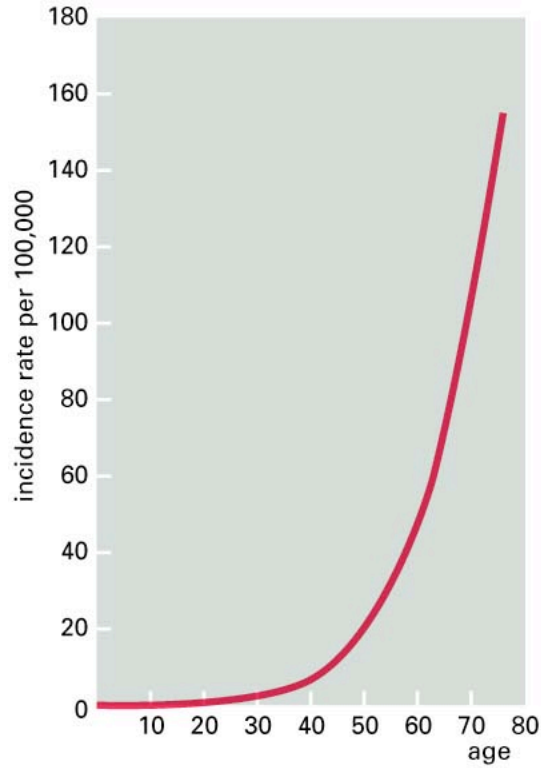
Break-Fusion-Bridge and Telomeres



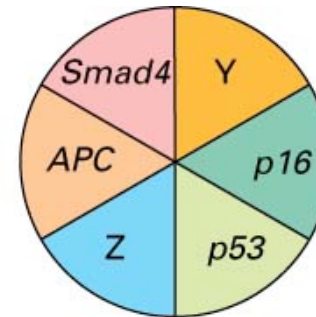
Invasiveness and Ectopic Survival



Multiple Hits are Required/Cancer Heterogeneity



TUMOR 1



TUMOR 2

Environment versus Genetics

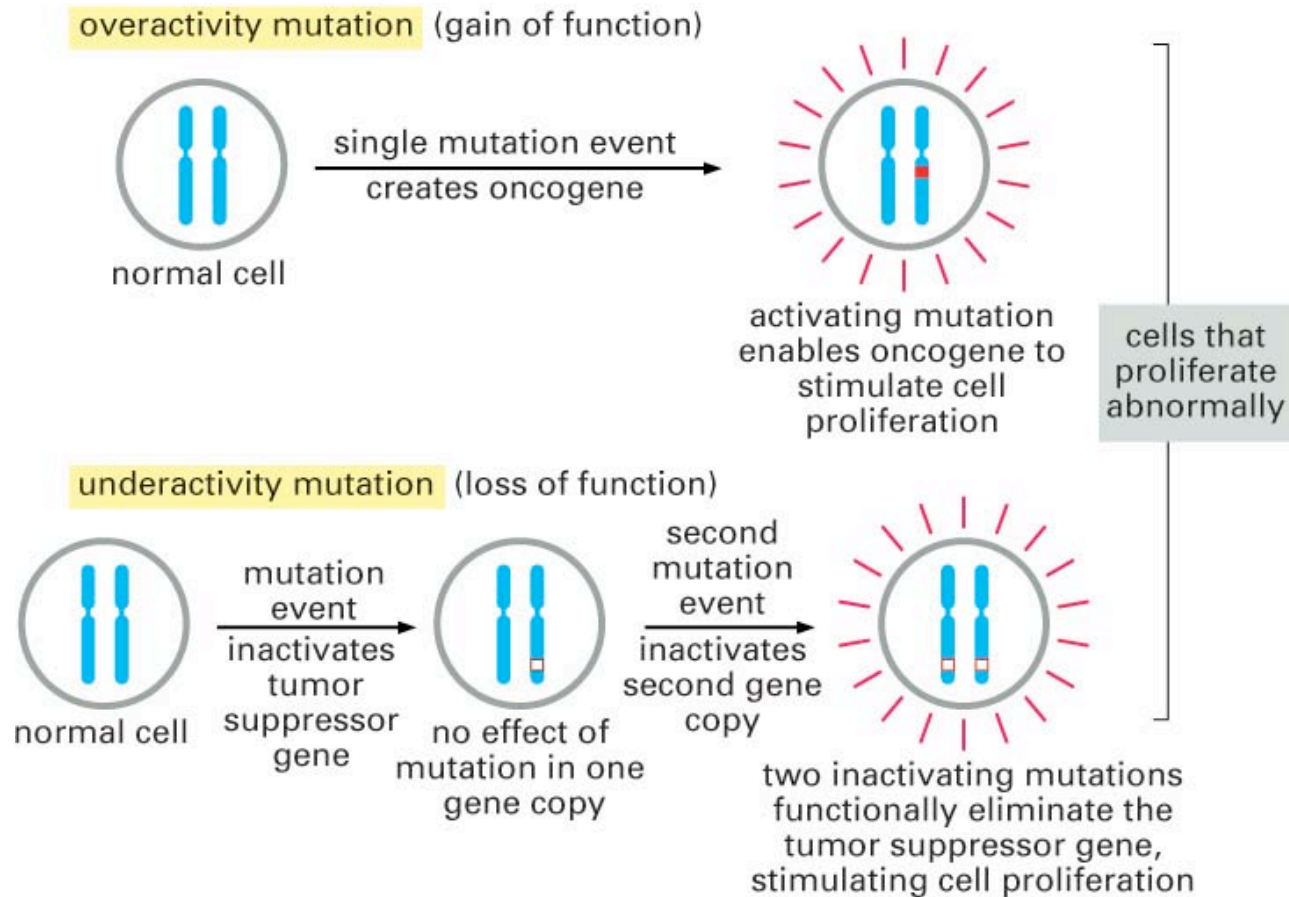
Variation Between Countries in the Incidence of Some Common Cancers

| SITE OF ORIGIN OF CANCER | HIGH-INCIDENCE POPULATION | | LOW-INCIDENCE POPULATION | |
|-----------------------------|--------------------------------------|------------|--------------------------|------------|
| | LOCATION | INCIDENCE* | LOCATION | INCIDENCE* |
| Lung | USA (New Orleans, blacks) | 110 | India (Madras) | 5.8 |
| Breast | Hawaii (Hawaiians) | 94 | Israel (non-Jews) | 14.0 |
| Prostate | USA (Atlanta, blacks) | 91 | China (Tianjin) | 1.3 |
| Uterine cervix | Brazil (Recife) | 83 | Israel (non-Jews) | 3.0 |
| Stomach | Japan (Nagasaki) | 82 | Kuwait (Kuwaitis) | 3.7 |
| Liver | China (Shanghai) | 34 | Canada (Nova Scotia) | 0.7 |
| Colon | USA (Connecticut, whites) | 34 | India (Madras) | 1.8 |
| Melanoma | Australia (Queensland) | 31 | Japan (Osaka) | 0.2 |
| Nasopharynx | Hong Kong | 30 | UK (Southwestern) | 0.3 |
| Esophagus | France (Calvados) | 30 | Romania (urban Cluj) | 1.1 |
| Bladder | Switzerland (Basal) | 28 | India (Nagpur) | 1.7 |
| Uterus | USA (San Francisco Bay Area, whites) | 26 | India (Nagpur) | 1.2 |
| Ovary | New Zealand (Polynesian Islanders) | 26 | Kuwait (Kuwaitis) | 3.3 |
| Rectum | Israel (European and USA born) | 23 | Kuwait (Kuwaitis) | 3.0 |
| Larynx | Brazil (São Paulo) | 18 | Japan (rural Miyagi) | 2.1 |
| Pancreas | USA (Los Angeles, Koreans) | 16 | India (Poona) | 1.5 |
| Lip | Canada (Newfoundland) | 15 | Japan (Osaka) | 0.1 |
| Kidney | Canada (NWT and Yukon) | 15 | India (Poona) | 0.7 |
| Oral cavity | France (Bas-Rhin) | 14 | India (Poona) | 0.4 |
| Leukemia | Canada (Ontario) | 12 | India (Nagpur) | 2.2 |
| Testis | Switzerland (urban Vaud) | 10 | China (Tianjin) | 0.6 |

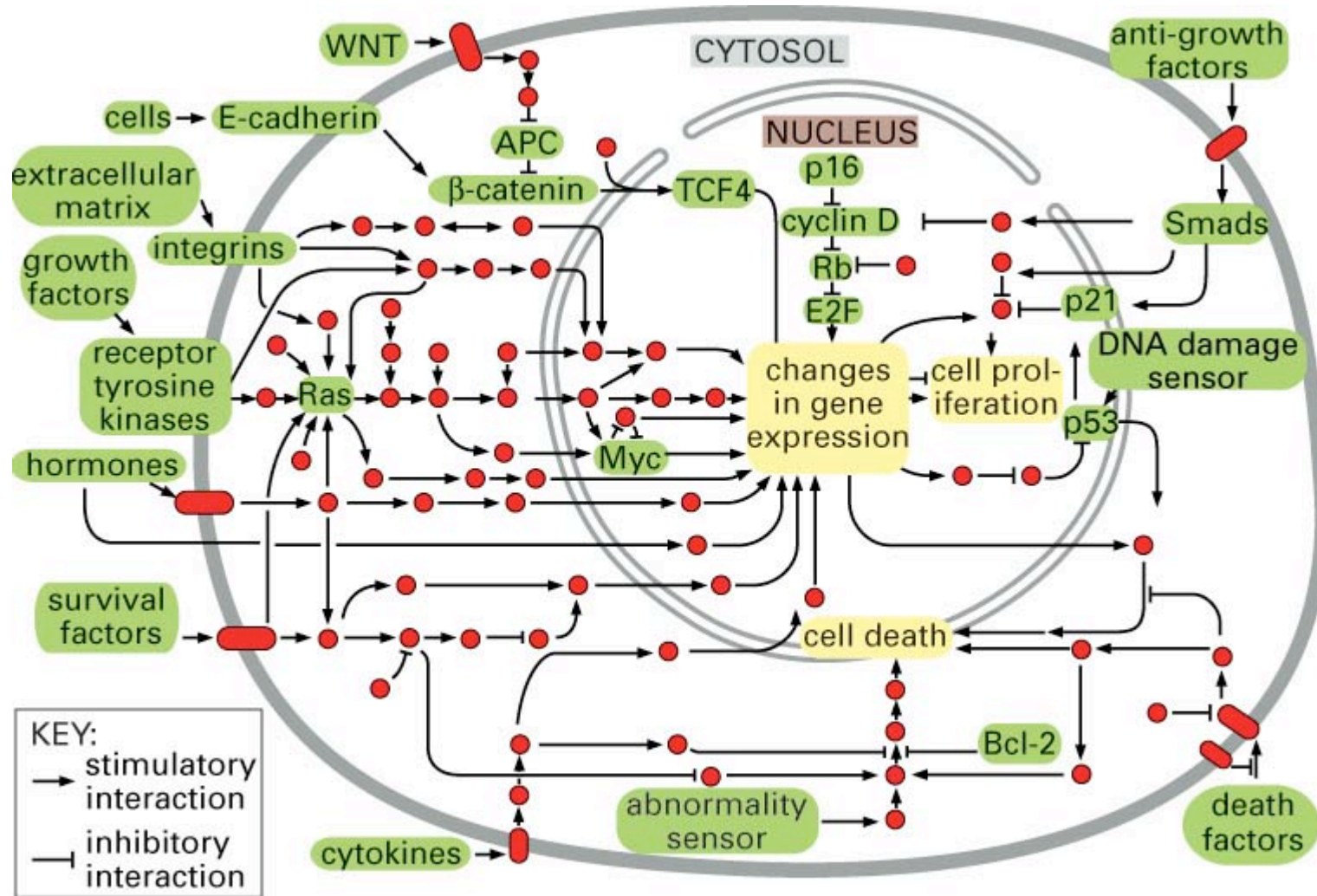
*Incidence = number of new cases per year per 100,000 population, adjusted for standardized population age distribution (so as to eliminate effects due merely to differences of population age distribution). Figures for cancers of breast, uterine cervix, uterus, and ovary are for women; other figures are for men. (Adapted from V.T. DeVita, S. Hellman, and S.A. Rosenberg (eds.), *Cancer: Principles and Practice of Oncology*, 4th edn. Philadelphia: Lippincott, 1993; based on data from C. Muir et al., *Cancer Incidence in Five Continents*, Vol. 5. Lyon: International Agency for Research on Cancer, 1987.)

80-90% estimated delayable based on environmental factors! But what are they?

Oncogenes vs. Tumour Suppressors



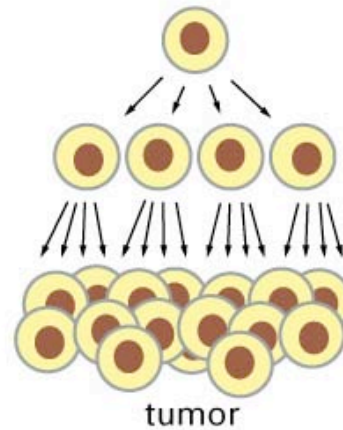
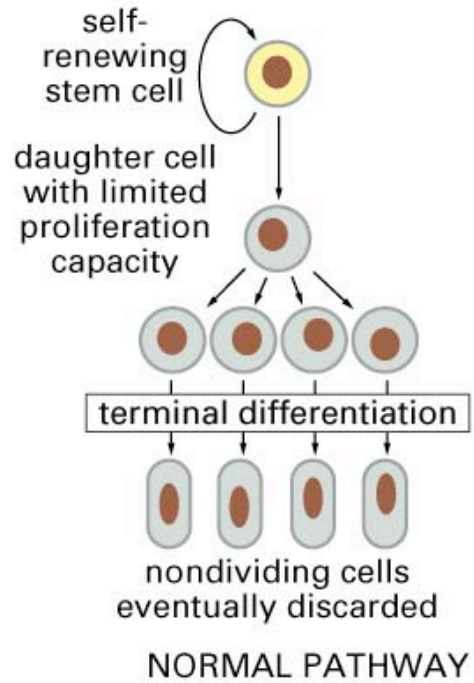
Developmental Pathways in Cancer



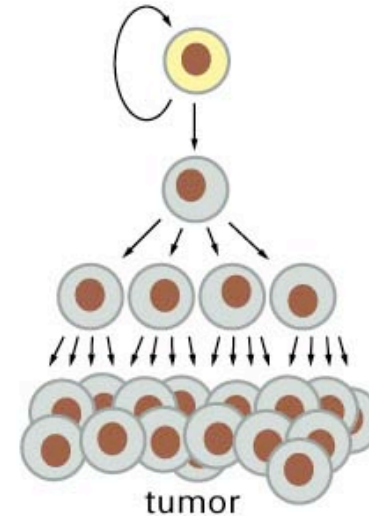
Wnt, Hedgehog, Notch/Delta, TGF β , RTK's

Questions:

1.



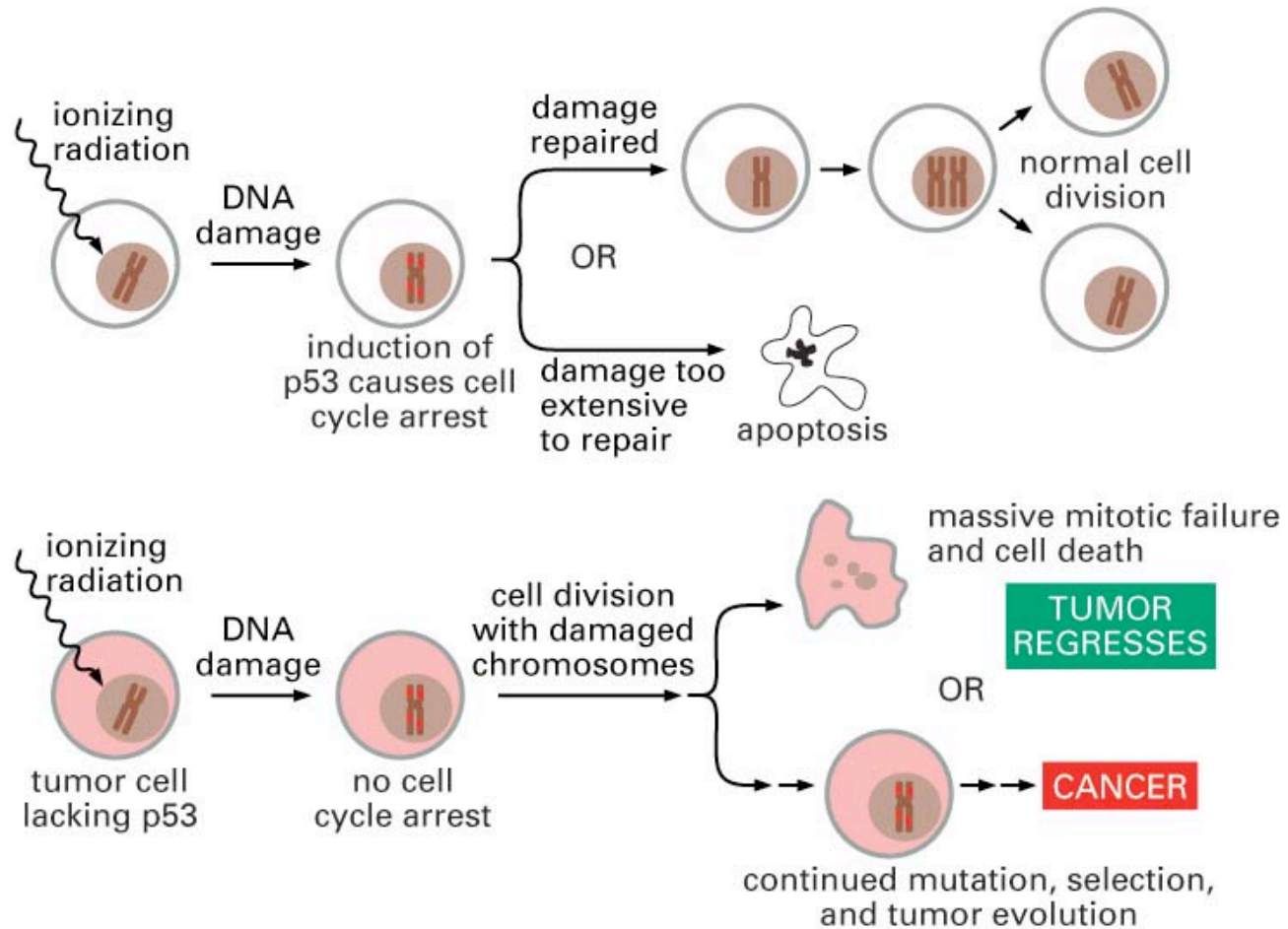
STEM CELL FAILS TO PRODUCE ONE NON-STEM-CELL DAUGHTER IN EACH DIVISION AND THEREBY PROLIFERATES TO FORM A TUMOR



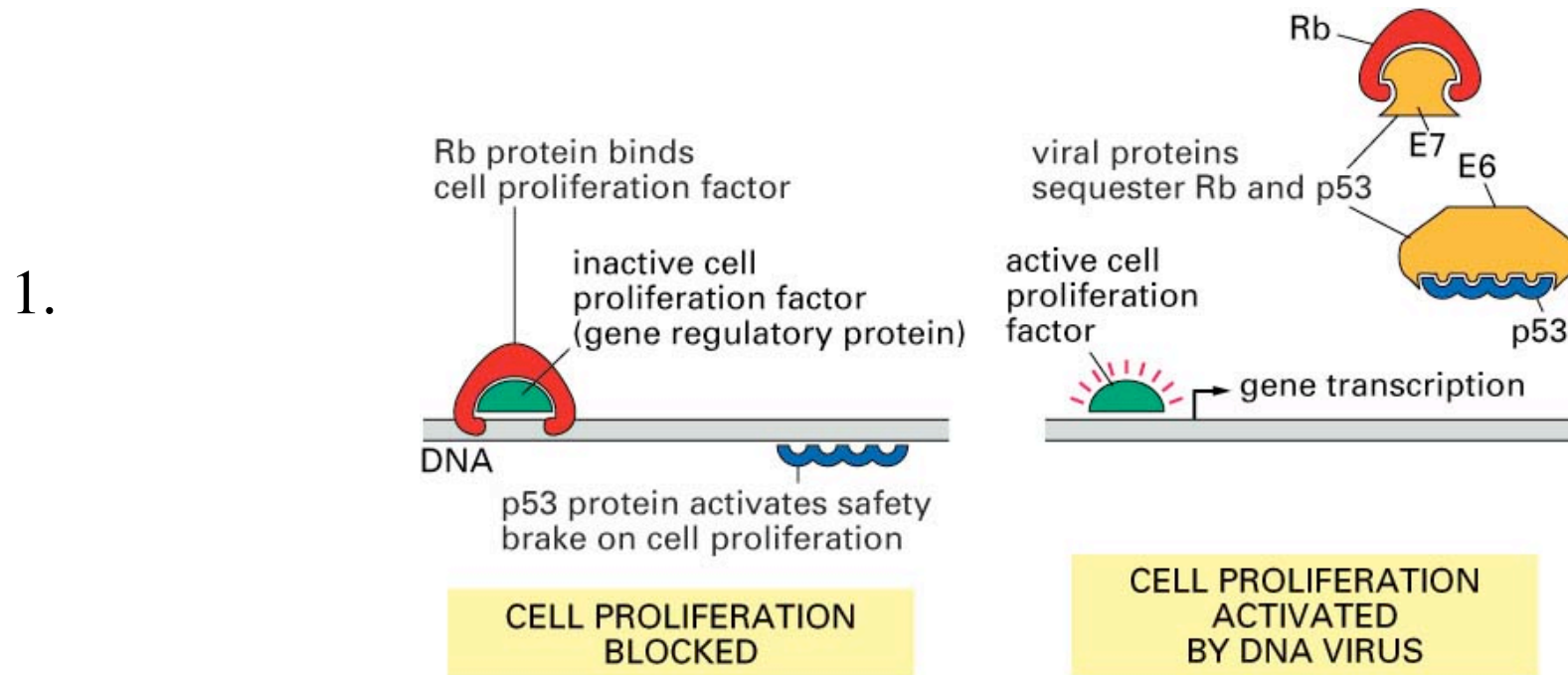
DAUGHTER CELLS FAIL TO DIFFERENTIATE NORMALLY AND INSTEAD PROLIFERATE TO FORM A TUMOR

2. Does transformation require persistence of the initiating genetic perturbation?

Conventional Cytotoxic Chemotherapy



Alternate Directed Therapies



2. Anti-Receptor mAb's (*e.g.* Herceptin) or soluble ligand/receptor proteins (*e.g.* Avastin)

3. Kinase Enzyme Inhibitors

30 Yr. Progress: the Case for Early Detection

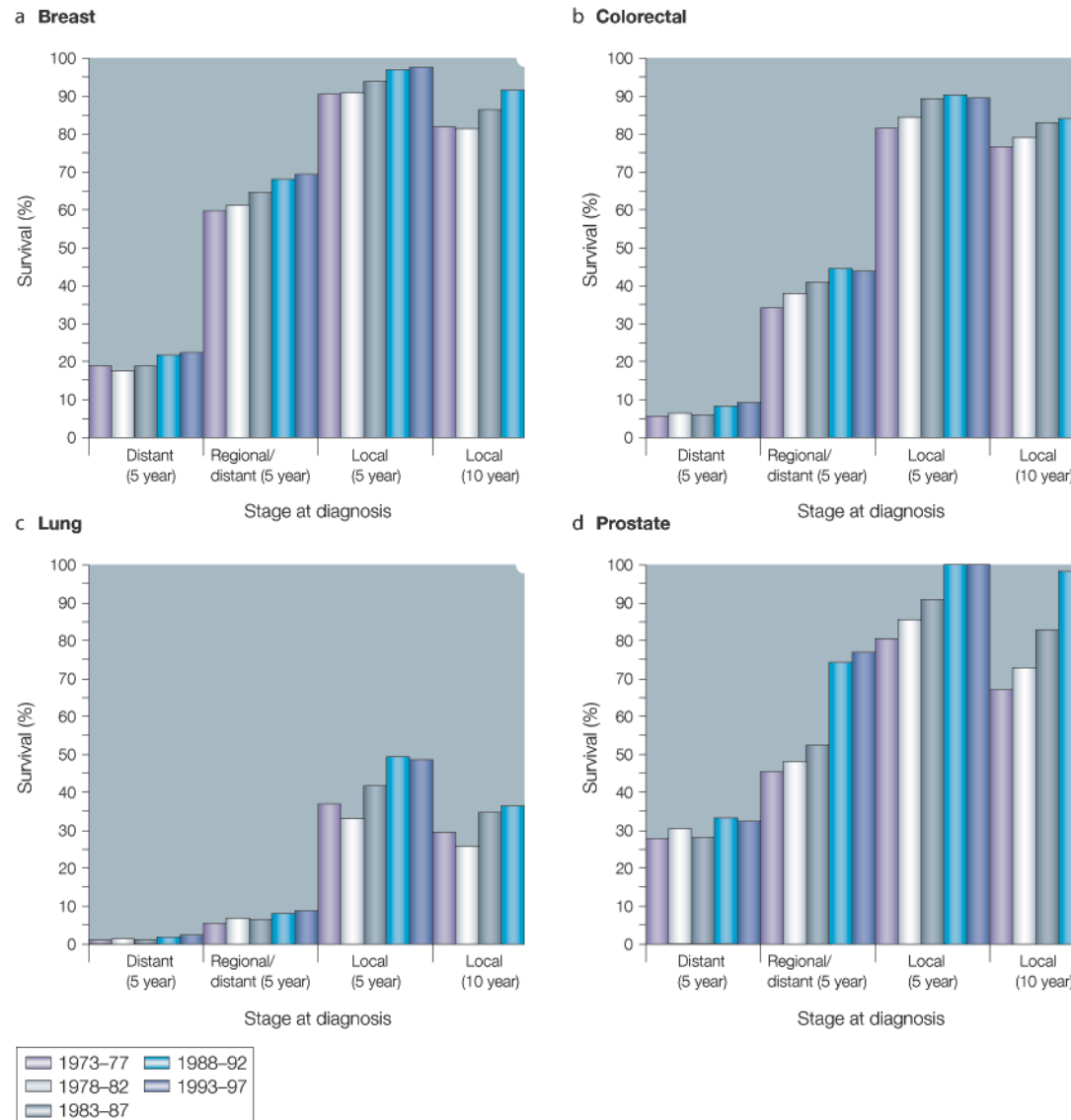
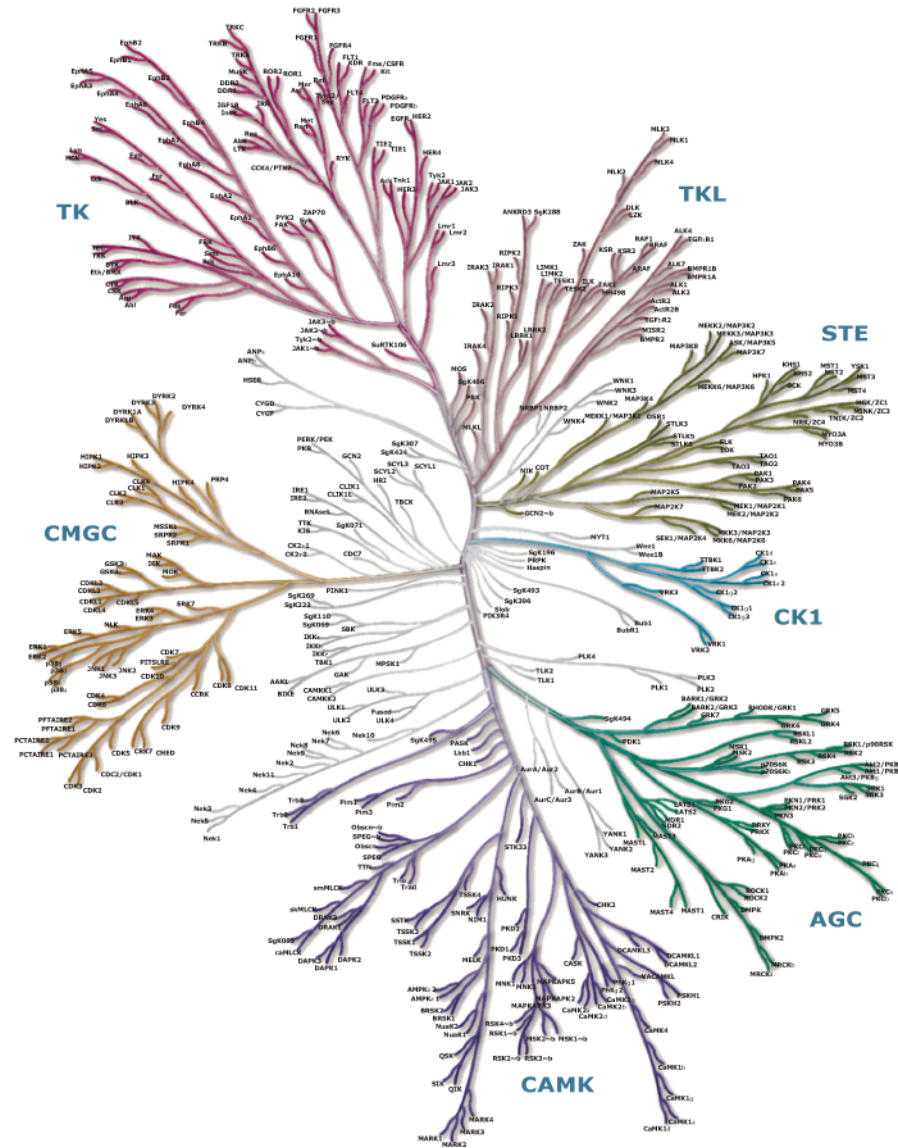
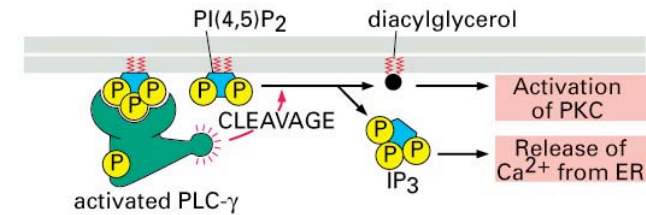
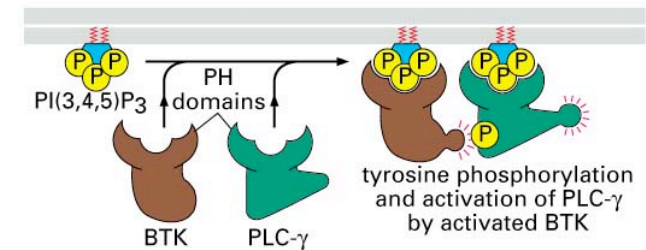
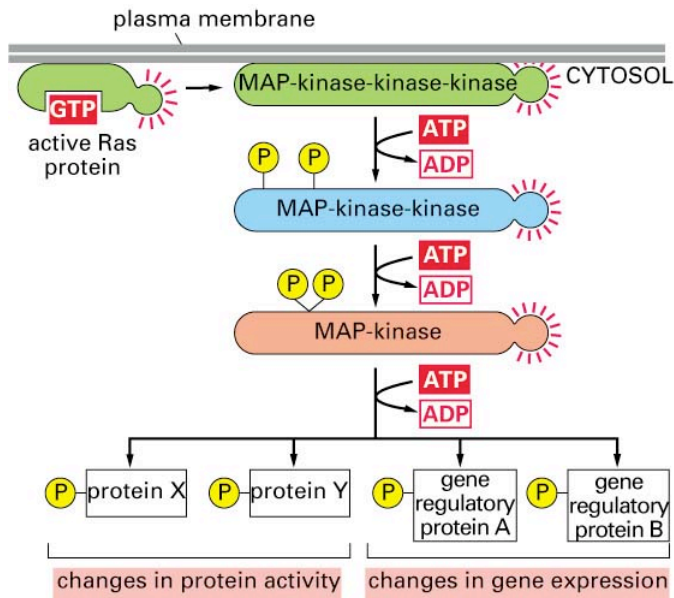
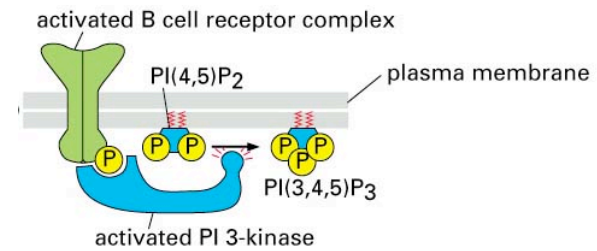
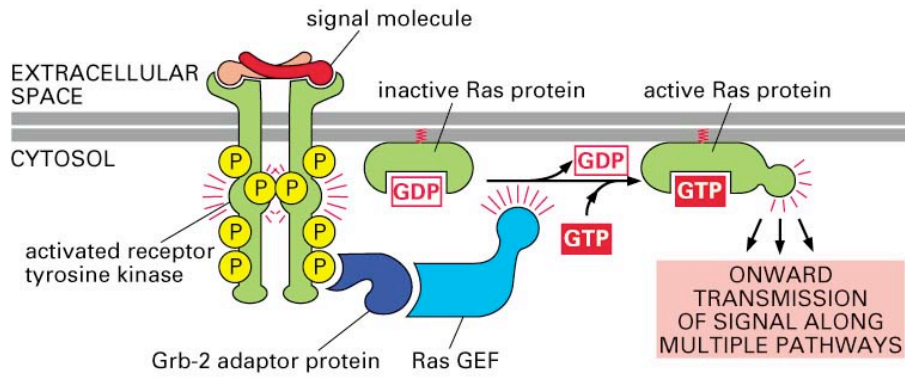


Figure 1 | Relative survival (5 year or 10 year) among cancer cases diagnosed with distant, regional or distant, and localized disease by year of diagnosis. a | Breast cancer; b | colorectal cancer; c | lung cancer; d | prostate cancer. Source: Surveillance, Epidemiology and End Results (SEER)¹. Stage is SEER historic stage.

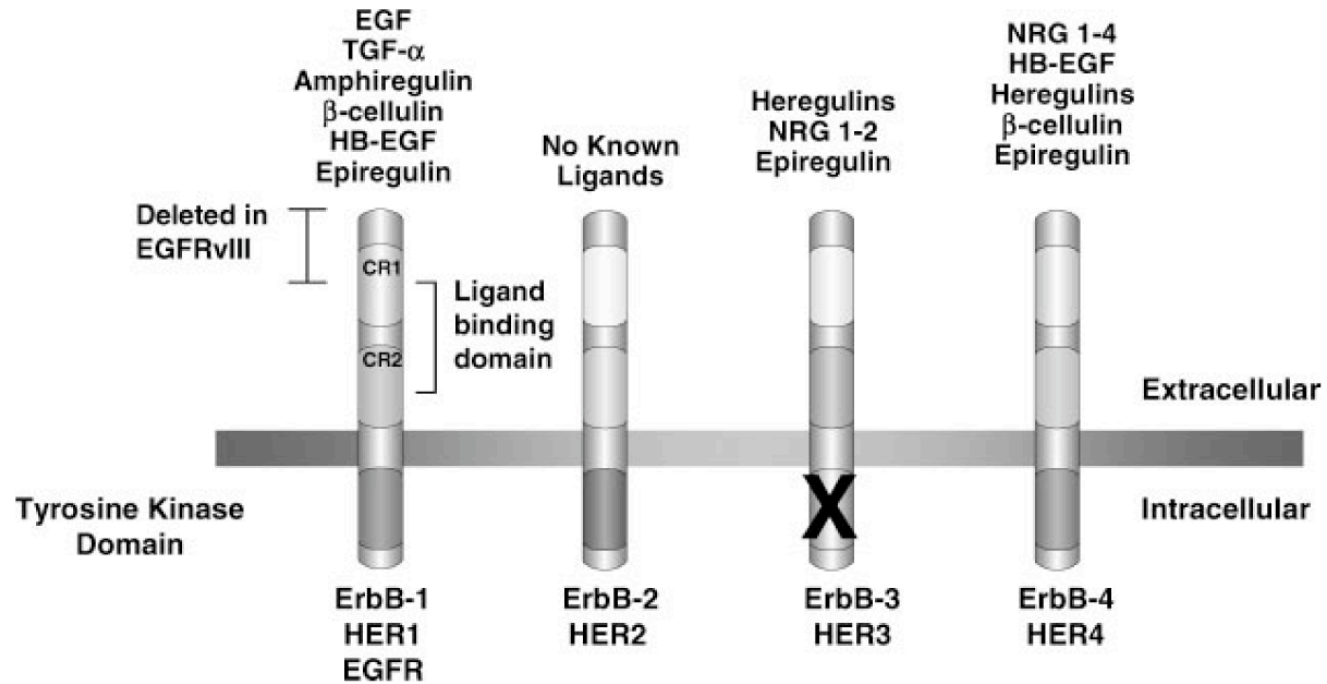
Human Kinome



TK Signaling Pathways



Erb RTK Family



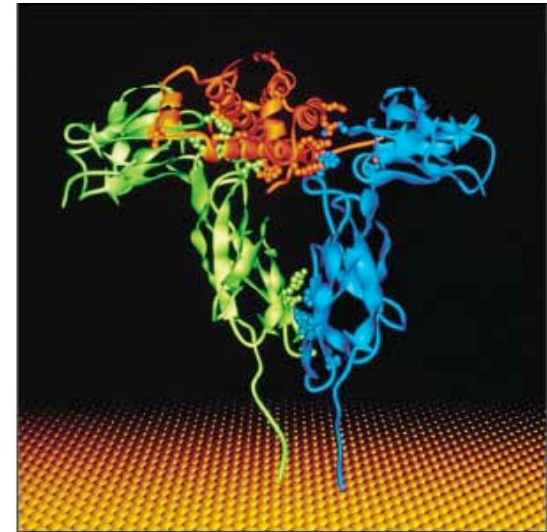
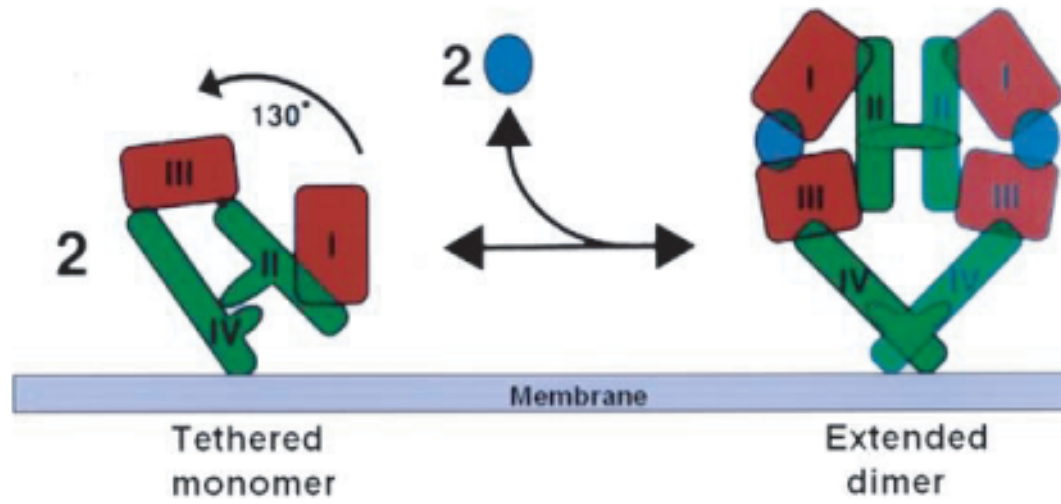
Erb Receptor Cancer Involvement

Malignancies overexpressing wild-type and mutated forms of erbB receptors

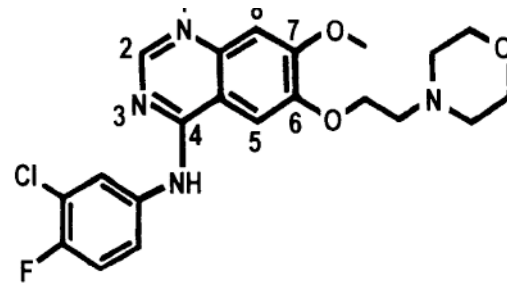
| erbB1 | erbB2 | erbB3 | erbB4 |
|--|---|--|--|
| Breast (14%–91%) [§] | Breast (10%–37%) [§] | Breast | Breast |
| Ovary (30%–75%) [§] | Ovary (20%–32%) [§] | Ovary | Ovary [§] |
| Renal (50%–90%) | Renal (24%–40%) | Renal | |
| Lung (NSCLC) (40%–80%) [§] | Lung (NSCLC) (3%–56%) [§] | Lung (NSCLC) [§] | Lung (NSCLC) |
| Head and neck (squamous) (30%–75%) [§] | Head and neck (squamous) (32%–62%) [§] | Head and neck (squamous) [§] | Head and neck (squamous) [§] |
| Colorectal (25%–77%) | Colorectal (7%) [§] | | |
| Pancreas (30%–50%) [§] | | | Pancreas |
| Glioma (40%–50%) [§] | | | |
| Bladder (31%–48%) [§] | Bladder (7%–36%) | | |
| Esophagus [§] | Esophagus (13%–73%) | | |
| Stomach [§] | Stomach (5%–55%) [§] | | |
| Prostate | Prostate [§] | Prostate | Prostate |
| Melanoma | Melanoma | Melanoma | Melanoma |
| Thyroid | | Thyroid | Thyroid |
| Endometrial [§] | Endometrial [§] | | |
| Skin (squamous cell) | | | Skin (squamous) |
| Lung (small cell) | | | Lung (small cell) |
| Cervical [§] | | | |
| Sarcomas | | | |
| | | | Chronic myelogenous leukemia |

[§]Clinical studies have linked overexpression and/or mutation of this erbB receptor to a worse prognosis.

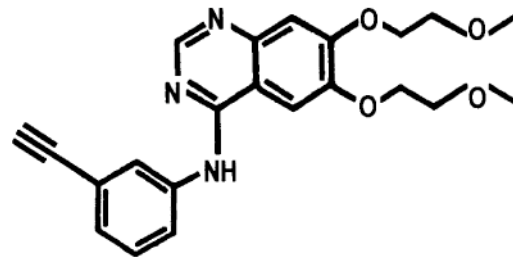
Erb Signaling Mechanism



Erb 1 Inhibitors

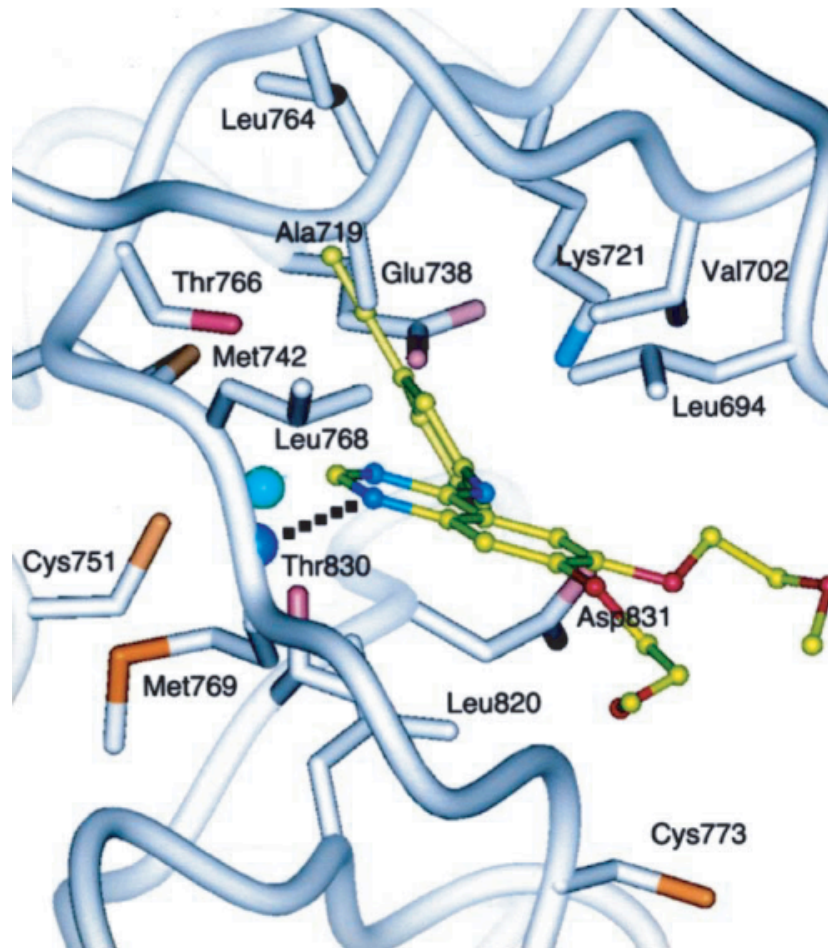


ZD1839
(gefitinib, Iressa)

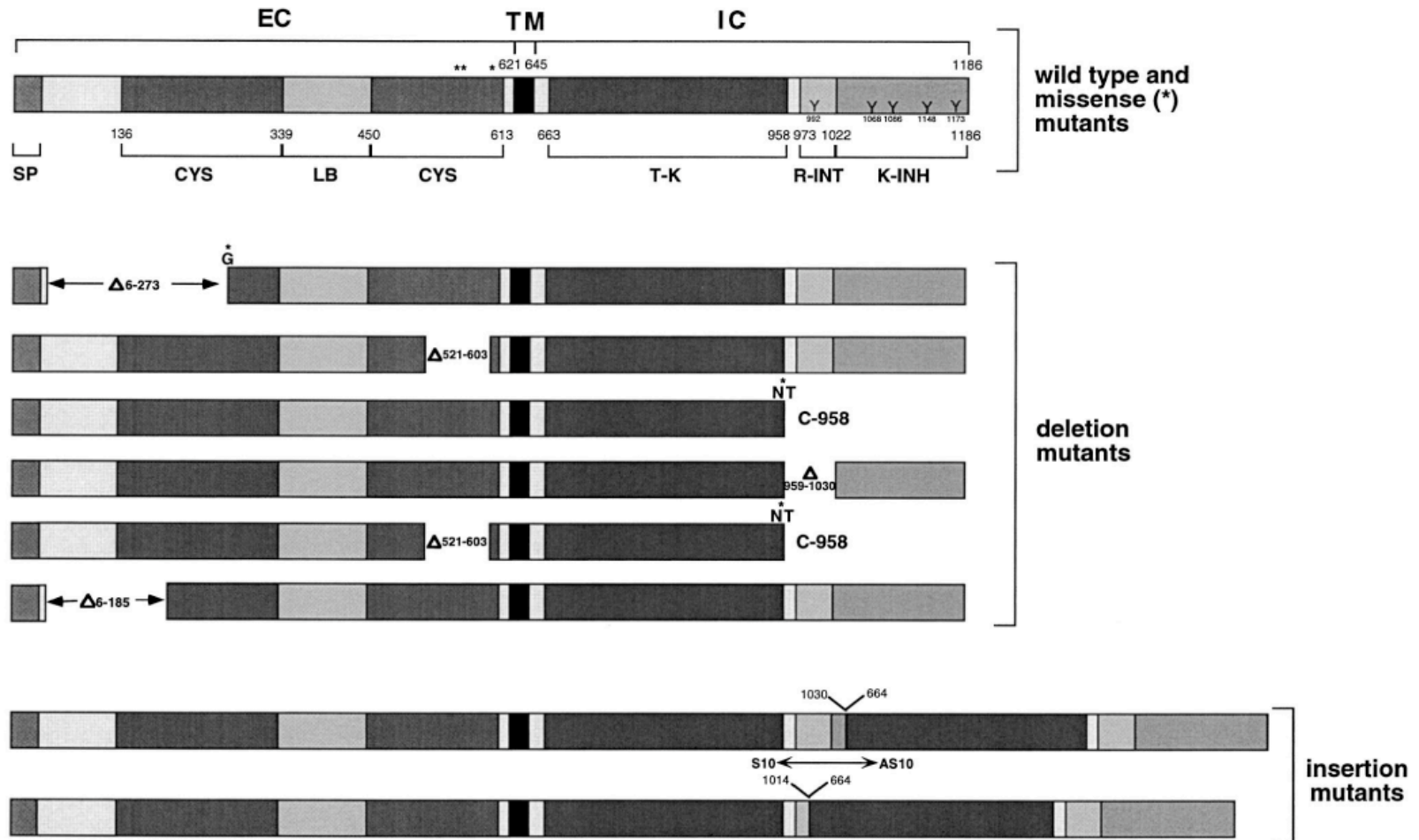


OSI-774
(erlotinib, Tarceva)

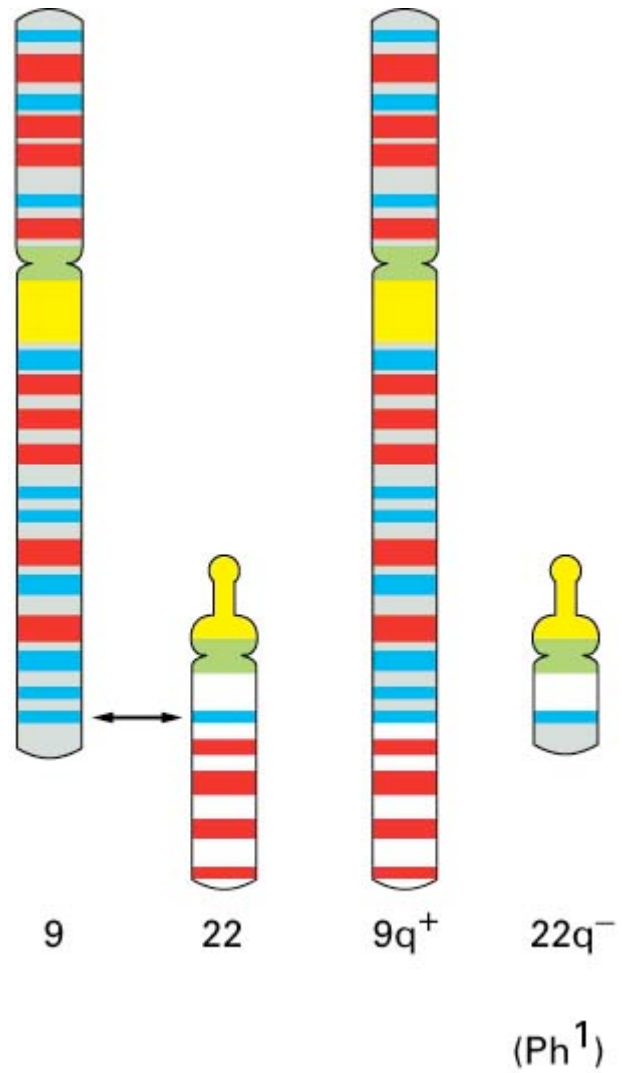
Tarceva On Erb1



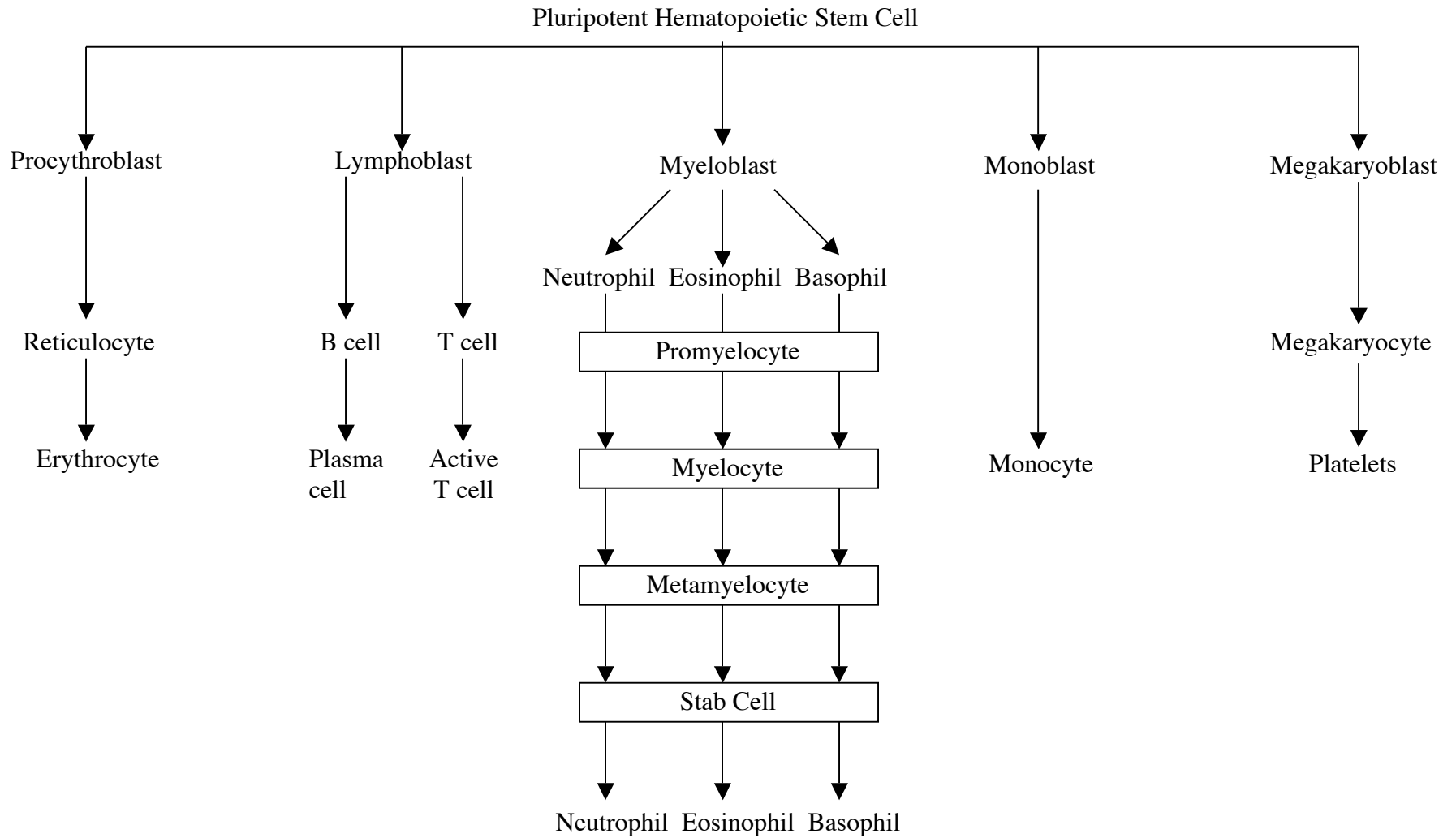
Erb1 Mutations in Glioblastoma



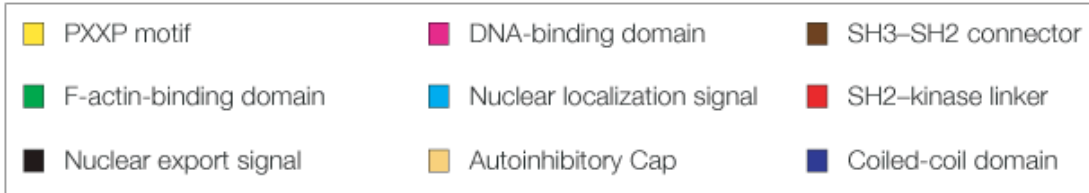
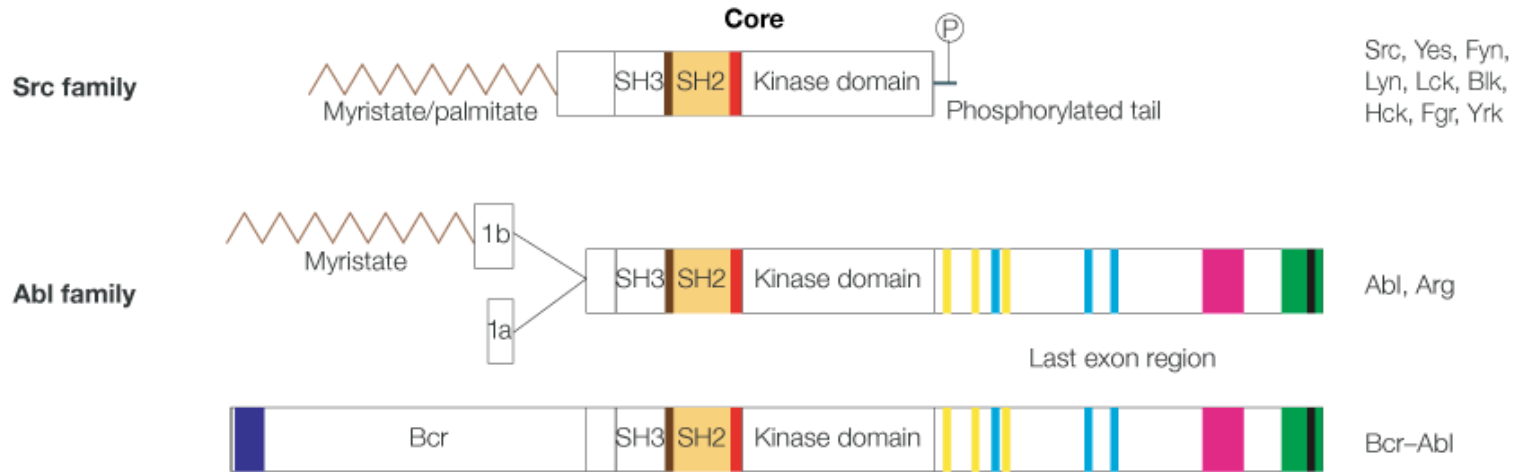
Philadelphia Chromosome Rearrangement



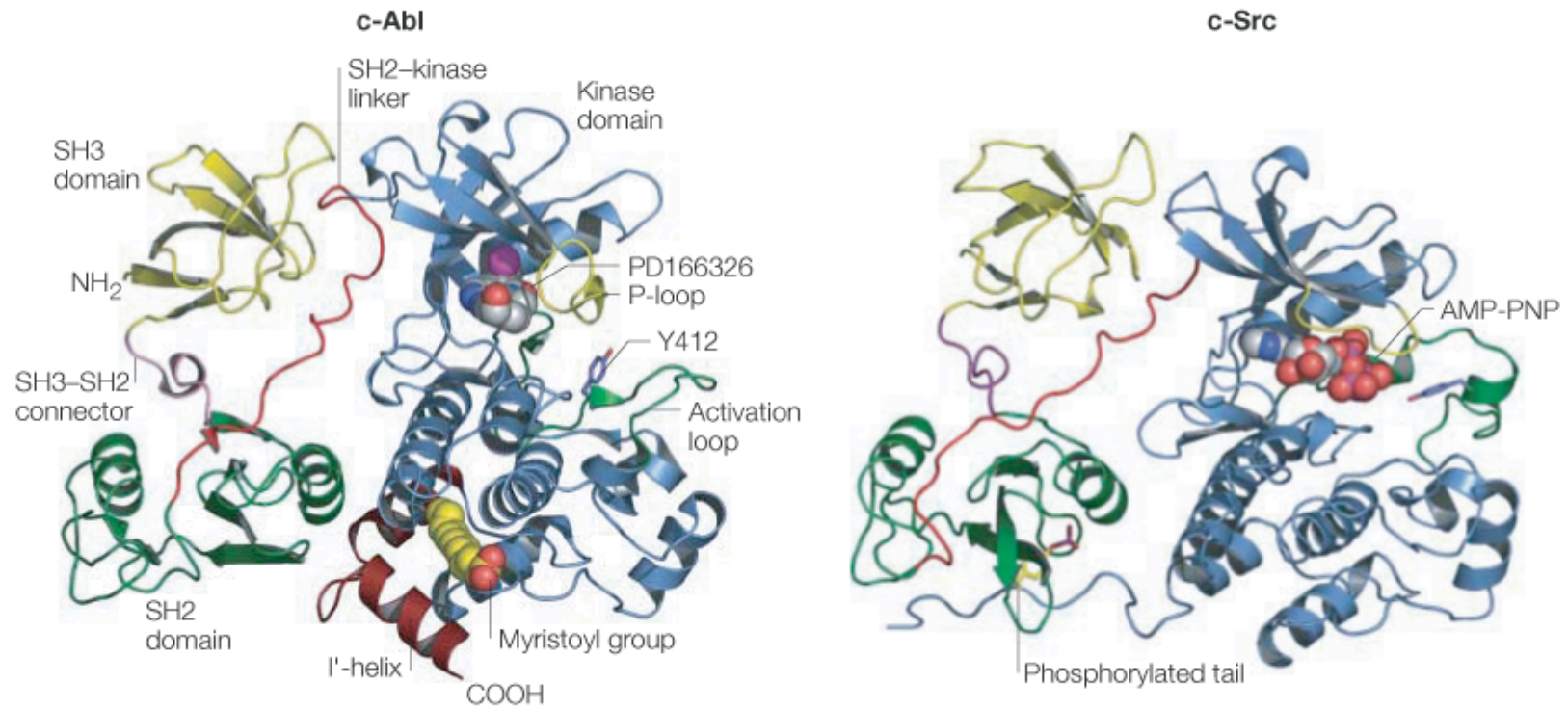
Blood Cell Differentiation



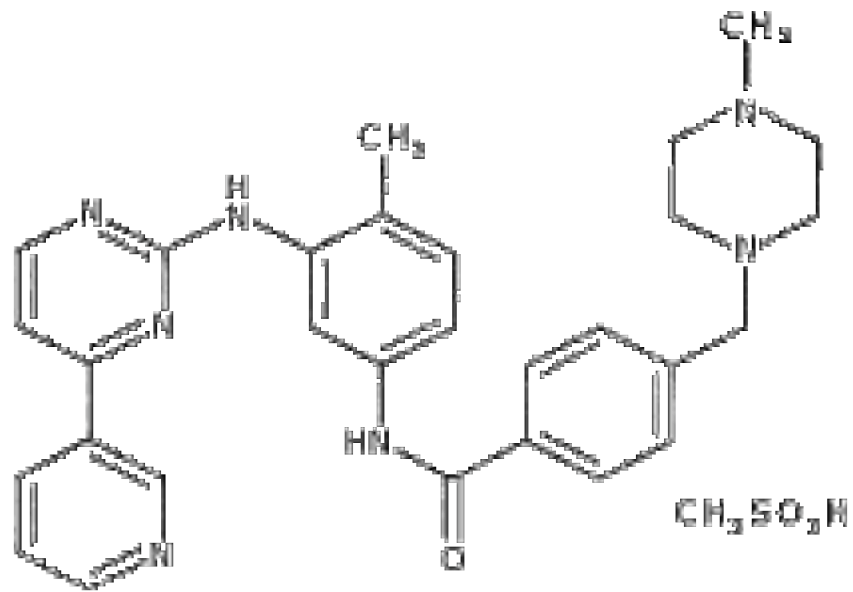
Abl Domains



Abl Autoinhibition

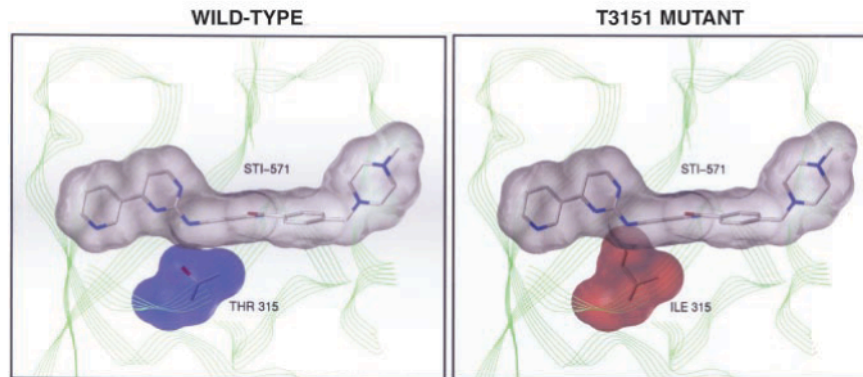
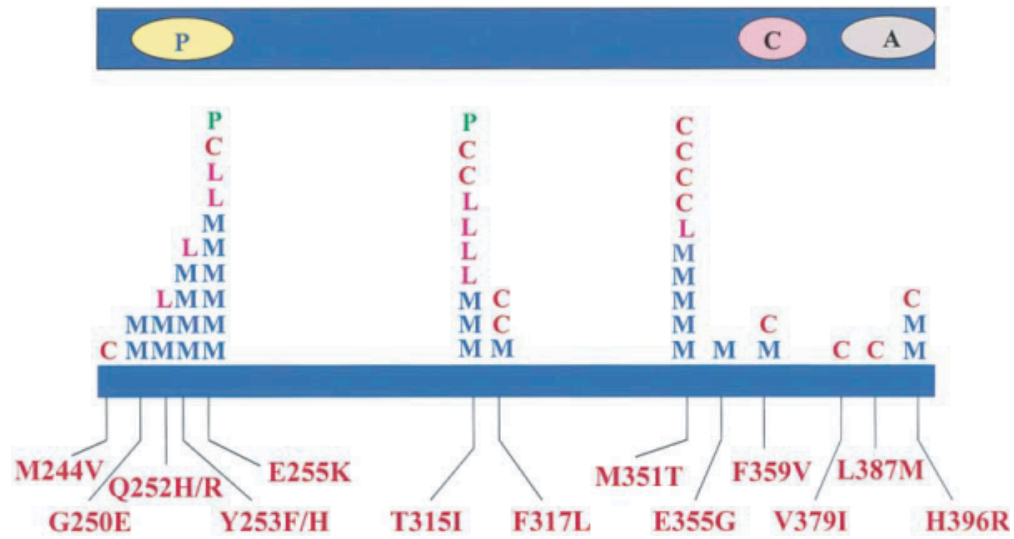


Gleevec

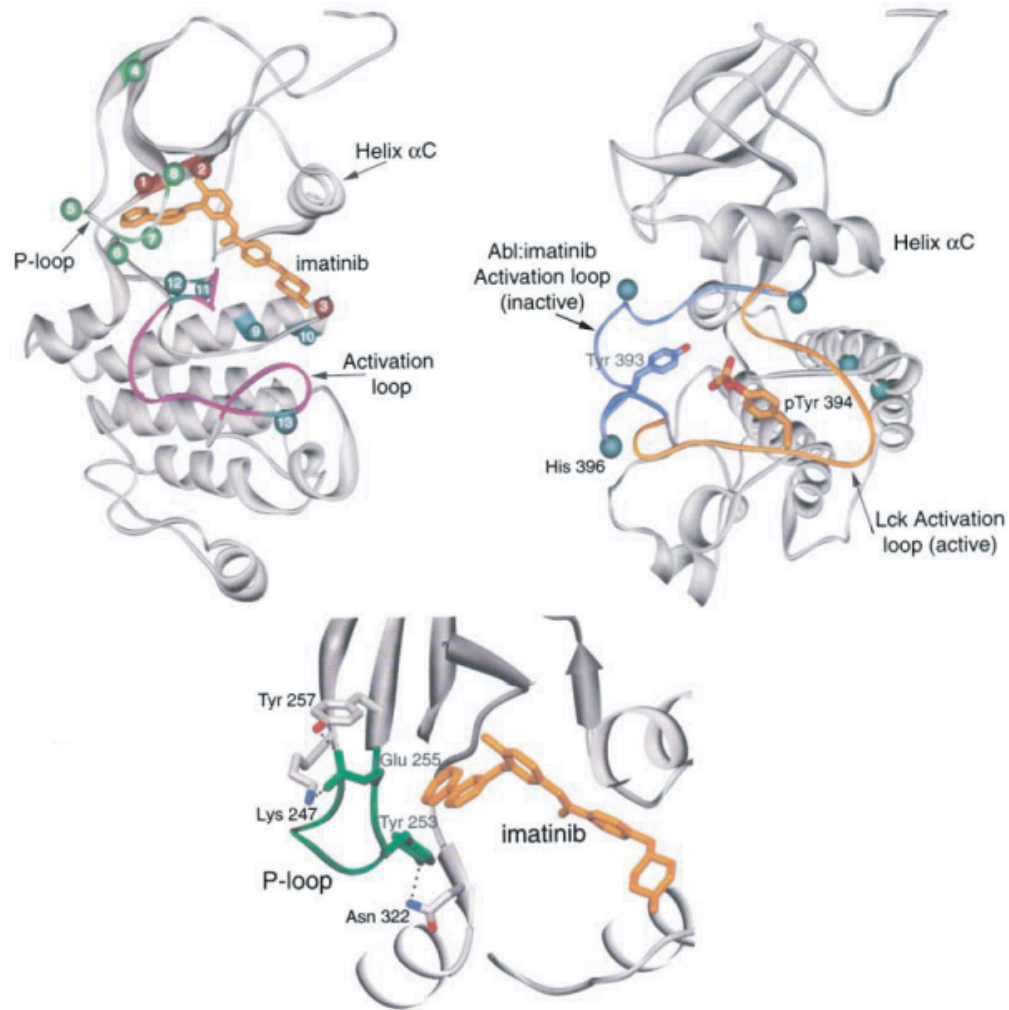


Gleevec Resistance Mutations in Abl

BCR-ABL kinase domain



Structural Basis for Gleevec Resistance



Questions:

Erb RTK K.O. in mice is embryonic lethal.

Abl TK K.O. in mice induces perinatal lethality, defects of eye/head formation, and hematopoietic problems.

Based on what evidence should one choose a target for inhibition?

Papers

Lynch TJ, et al. (2004). "Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib." *N Engl J Med*. **350**(21):2129-39.

Fabian MA, et al. (2005). "A small molecule-kinase interaction map for clinical kinase inhibitors." *Nat Biotechnol*. **23**(3):329-36.