Oncogenes, Bcr-Abl1 & ErbB2

Dr.G.MATHAN
Assistant Professor
Department of Biomedical Science
Bharathidasan University
Tiruchirappalli, Tamil Nadu

What is proto-oncogene?

➢A **proto-oncogene** is a normal gene that can become an oncogene due to mutations or increased expression. The resultant protein may be termed an **oncoprotein**.

➢Proto-oncogenes code for proteins that help to regulate cell growth and Differentiation.

➢**Abl is one of the first proto-oncogenes cloned (1981)**

➢**Abl Oncogene fused to BCR in Philadelphia Chromosome of chronic myelogenous leukemia (CML).**

- **Two main types of oncogenes:**
  - ***Viral oncogene*: gene from the retrovirus itself**
  - ***Non-Viral oncogene (Cellular oncogene):* genes derived from the genes of the host cell that are in an inactive form usually. Occasionally if the gene incorporates with the viral genome will form a highly oncogenic virus.**

How does a Proto-oncogene become an Oncogene?

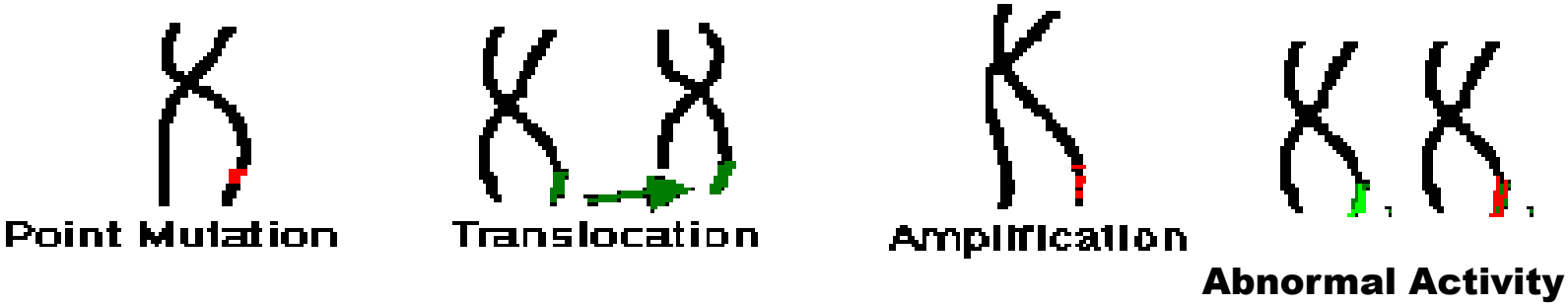
Proto-Oncogene → Oncogene

1.Mutation

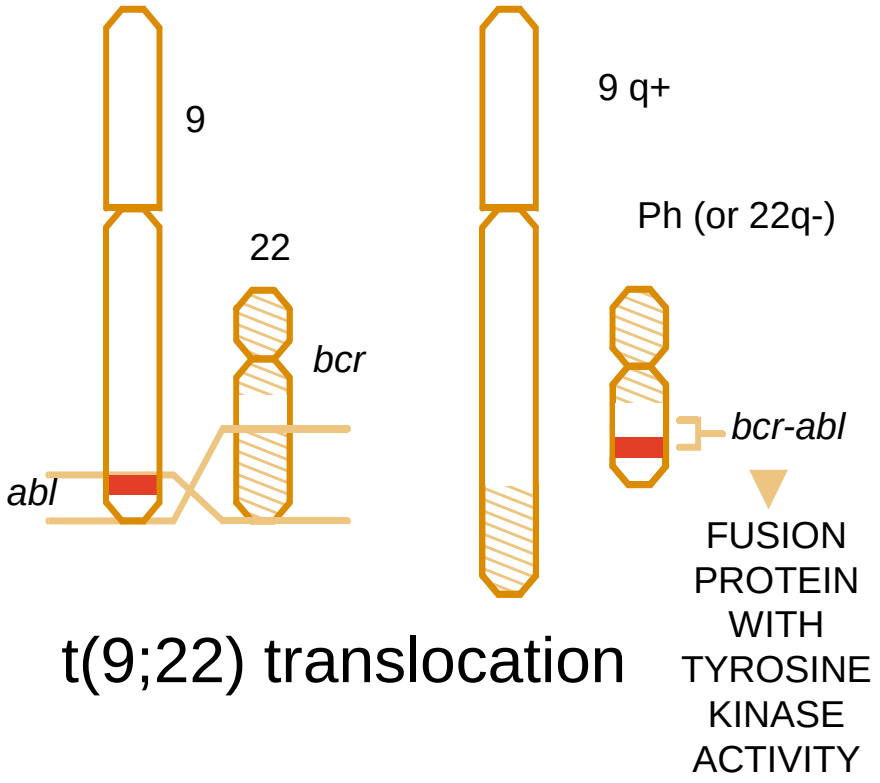
2.Gene Translocation

3. Amplification

4. Abnormal Activity

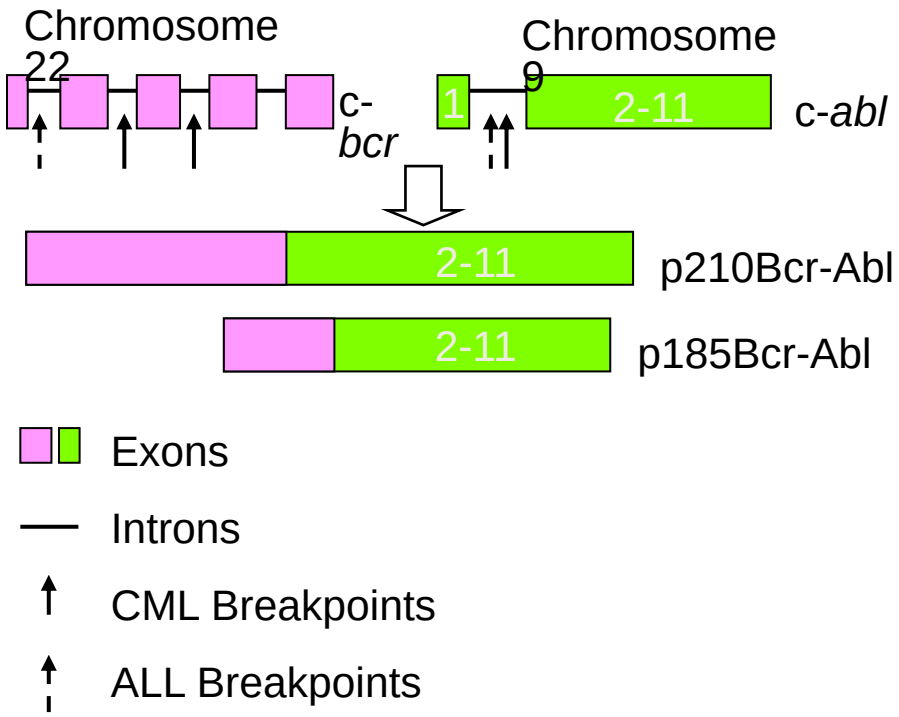


The Ph Chromosome and the bcr-abl Gene



t(9;22) translocation

bcr-abl gene structure



- **The molecular weight of the protein can range from 185 to 210 kDa**
- Bcr-Abl codes for a receptor tyrosine kinase which is constitutively active, leading to uncontrolled cell proliferation.

Different breakpoints in *bcr* results in different types of human leukemia

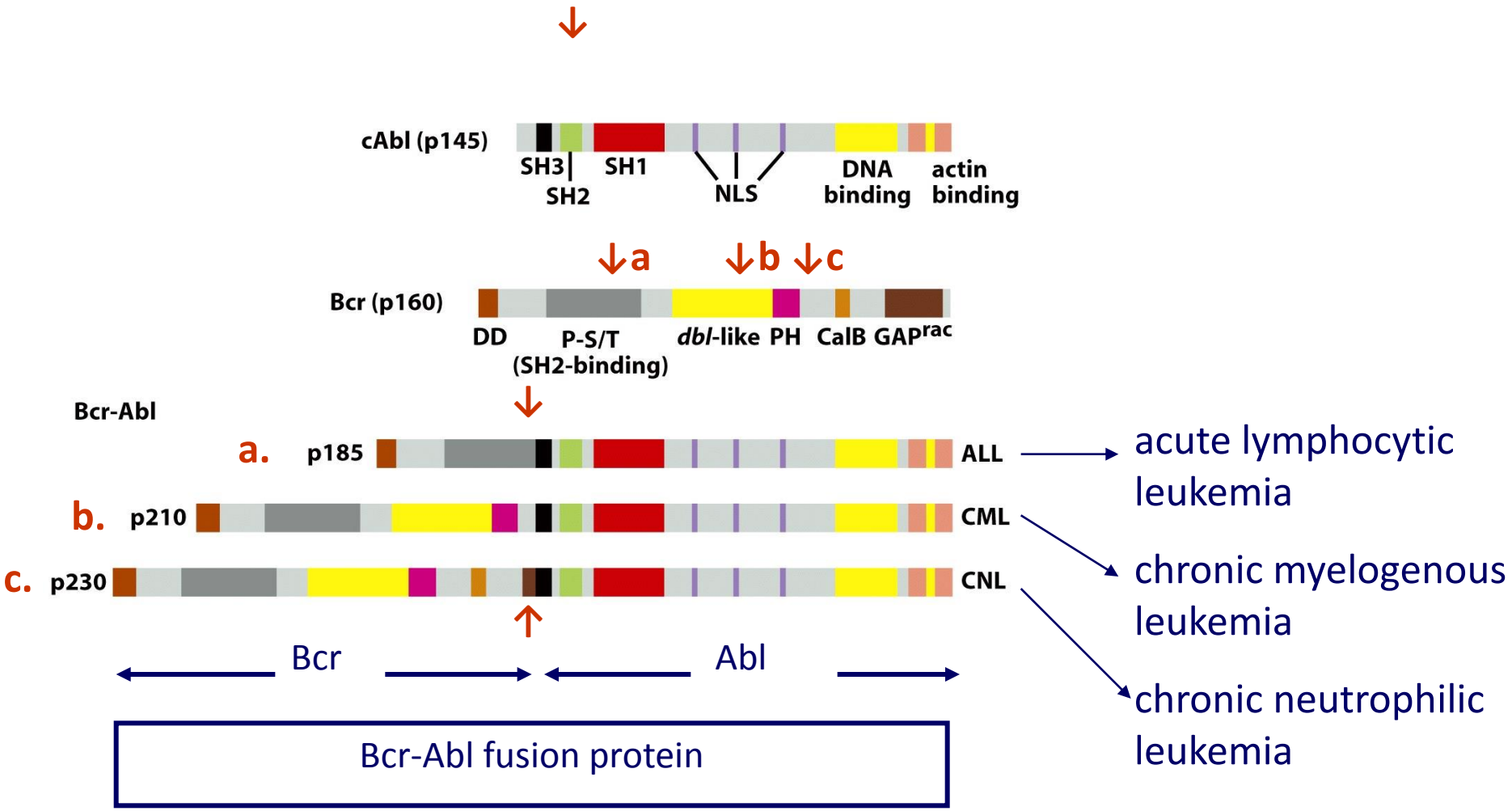
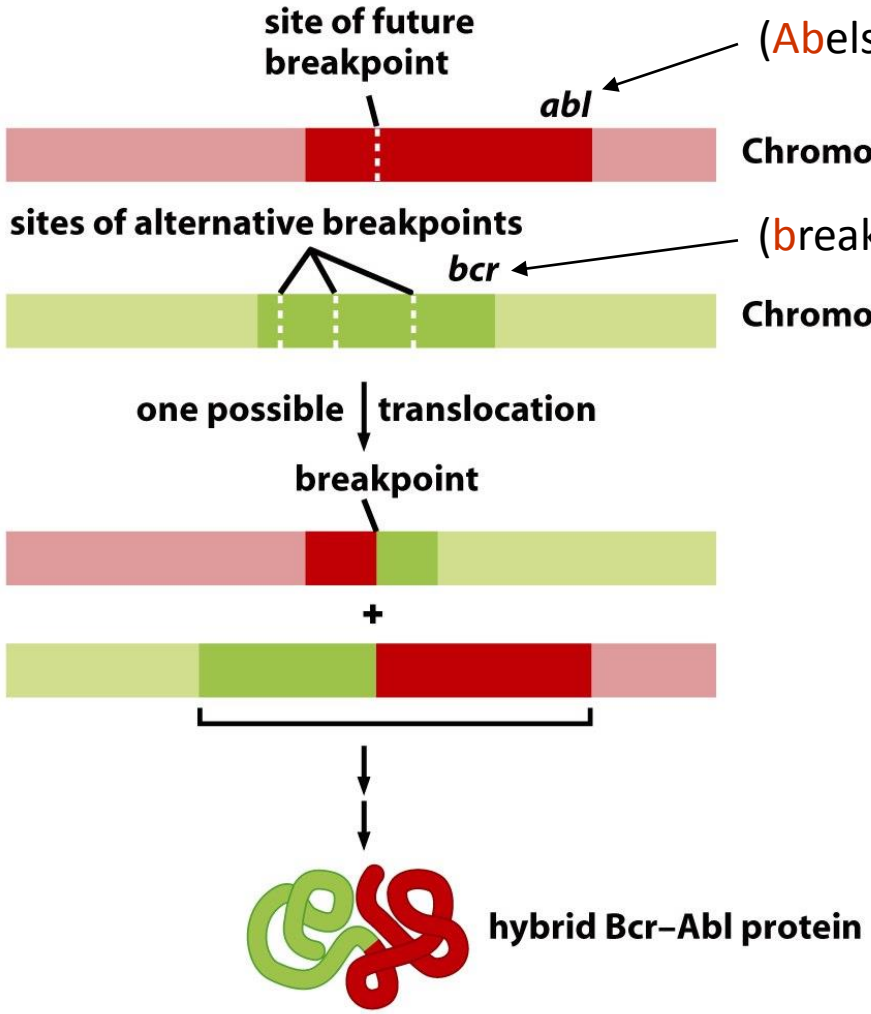


Figure 4.15b *The Biology of Cancer* (© Garland Science 2007)

Formation of the *bcr-abl* oncogene after t(9; 22) (q34; q11) translocation

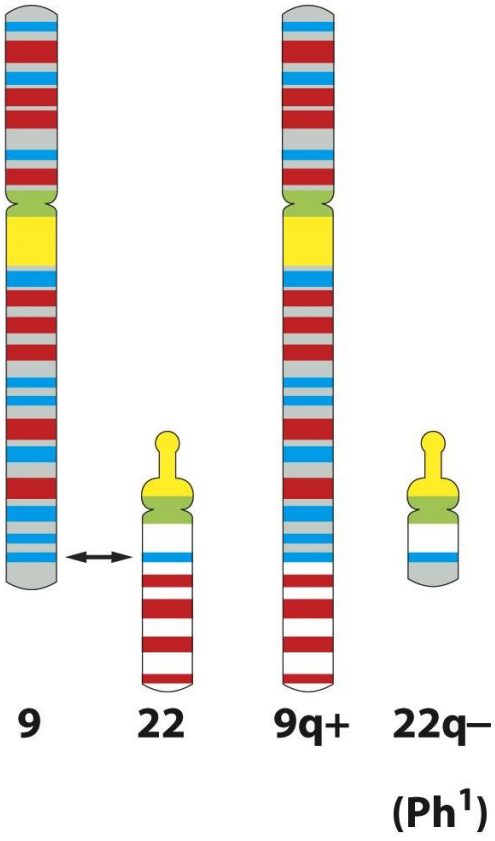


(Abelson murine leukemia virus)

(breakpoint cluster region)

Figure 4.15a *The Biology of Cancer* (© Garland Science 2007)

The great majority (> 95 %) of chronic myelogenous leukemia (CML) has t(9; 22) (q34; q11) translocation



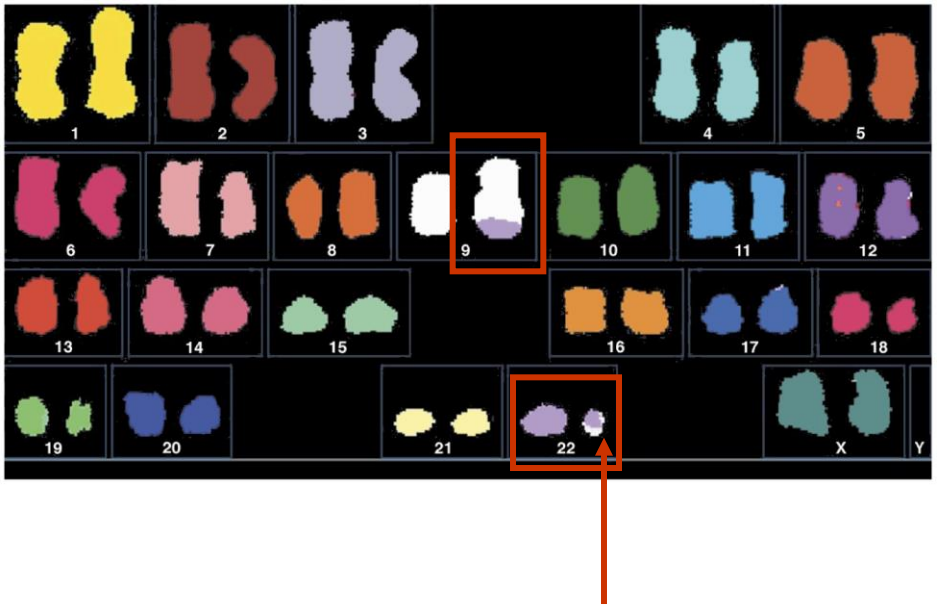


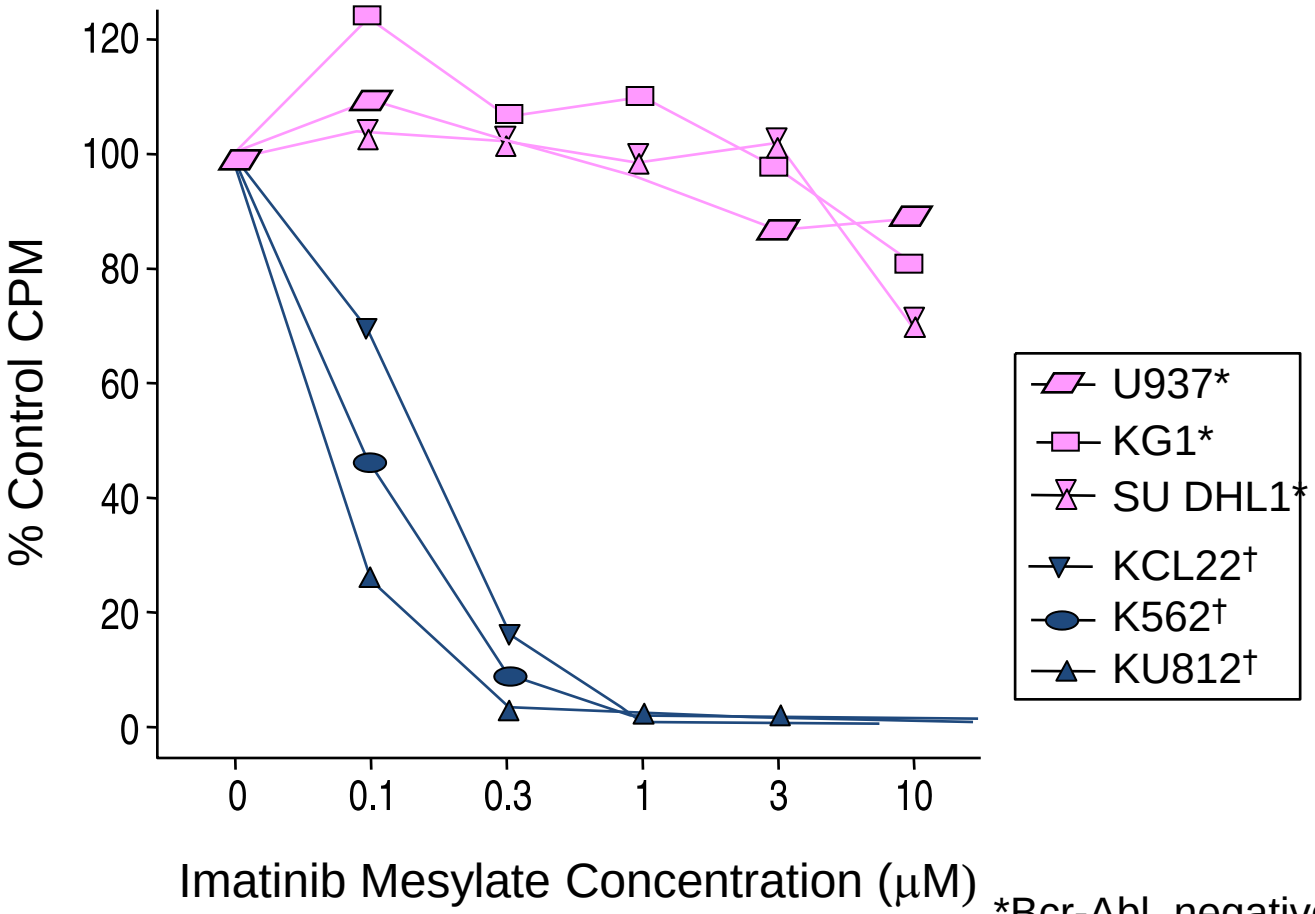
Figure 2.23a *The Biology of Cancer* (© Garland Science 2007)

Table 4.5 Translocations in human tumors that cause the formation of oncogenic fusion proteins of novel structure and function

Oncogene	Neoplasm
bcr/abl	chronic myelogenous leukemia; acute lymphocytic leukemia
dek/can	acute myeloid leukemia
E2A/pbx1	acute pre-B-cell leukemia
PML/RAR	acute promyelocytic leukemia
?/erg	myeloid leukemia
irel/urg	B-cell lymphoma
CBFβ/MYH11	acute myeloid leukemia
aml1/mtg8	acute myeloid leukemia
ews/fli	Ewing sarcoma
lyt-10/Cα1	B-cell lymphoma
hrx/enl	acute leukemias
hrx/af4	acute leukemias
NPM/ALK	large-cell lymphomas

Adapted from G.M. Cooper, Oncogenes, 2nd ed. Boston and London: Jones and Bartlett, 1995.

Imatinib Mesylate Inhibits the Growth of Bcr-Abl–Positive Cells

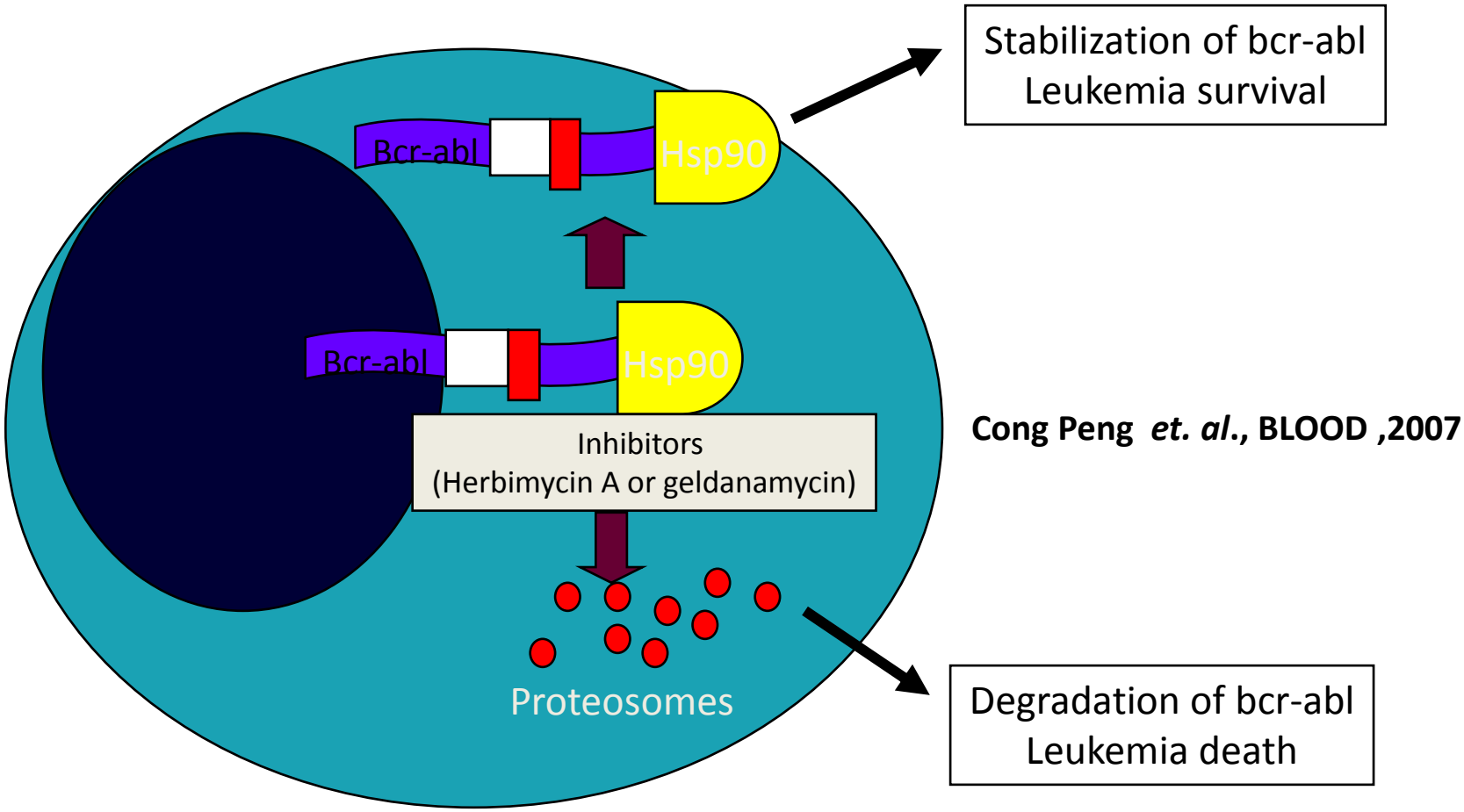


*Bcr-Abl–negative cell lines.

†Bcr-Abl–positive cell lines.

Gambacorti-Passerini C et al. *Blood Cells Mol Dis*. 1997;23:380-394.

Selective apoptosis of CML by Hsp90 inhibitors



Cong Peng *et. al*., BLOOD ,2007

Philadelphia chromosome–positive chronic myelogenous leukemia (CML) where all available kinase inhibitors in clinic are ineffective against the BCR-ABL mutant, T315I.
As an alternative approach to kinase inhibition, an orally administered heat shock protein 90 (Hsp90) inhibitor**, IPI-504**, was evaluated in a murine model of CML.

Transfection of DNA provides a strategy for detecting nonviral oncogenes

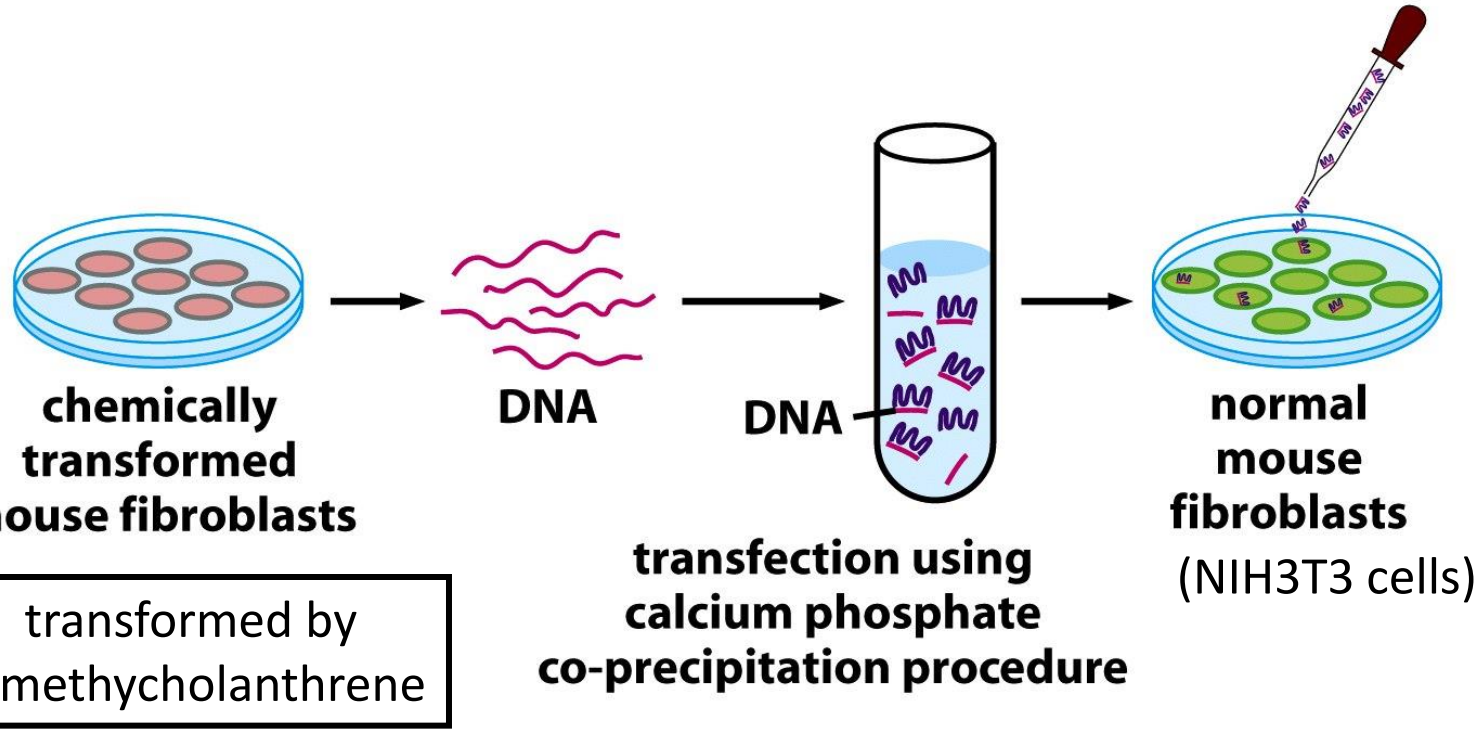
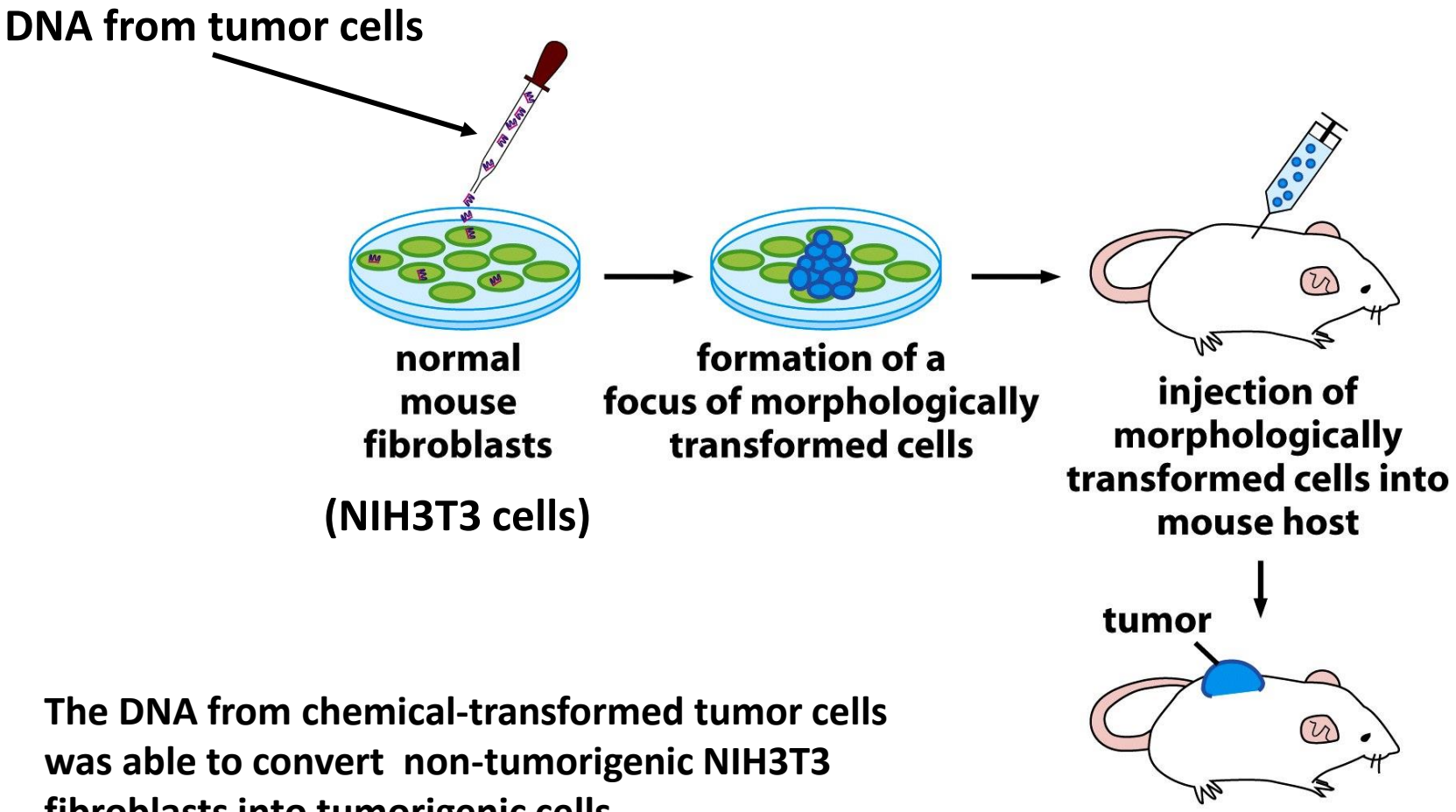


Figure 4.2 (part 1 of 2) *The Biology of Cancer* (© Garland Science 2007)

Oncogenes discovered in human tumor cell lines are related to those carried by transforming retroviruses

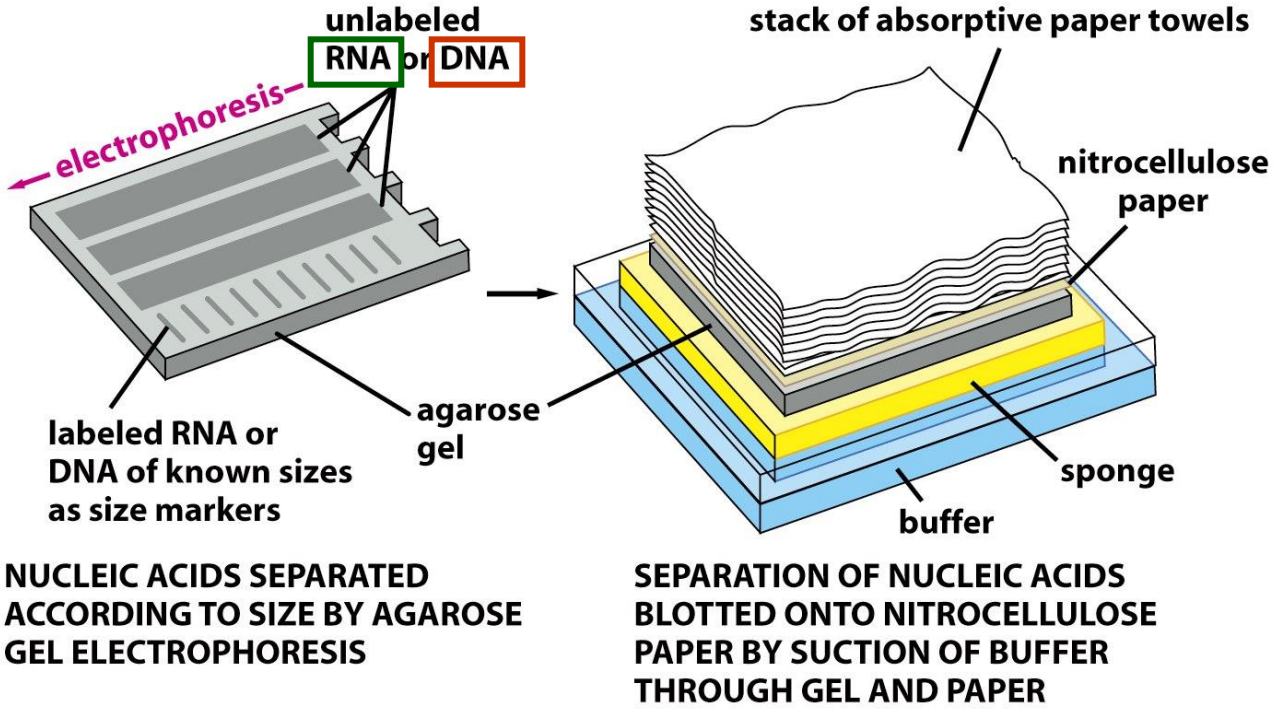


The DNA from chemical-transformed tumor cells was able to convert non-tumorigenic NIH3T3 fibroblasts into tumorigenic cells.

Figure 4.2 (part 2 of 2) *The Biology of Cancer* (© Garland Science 2007)

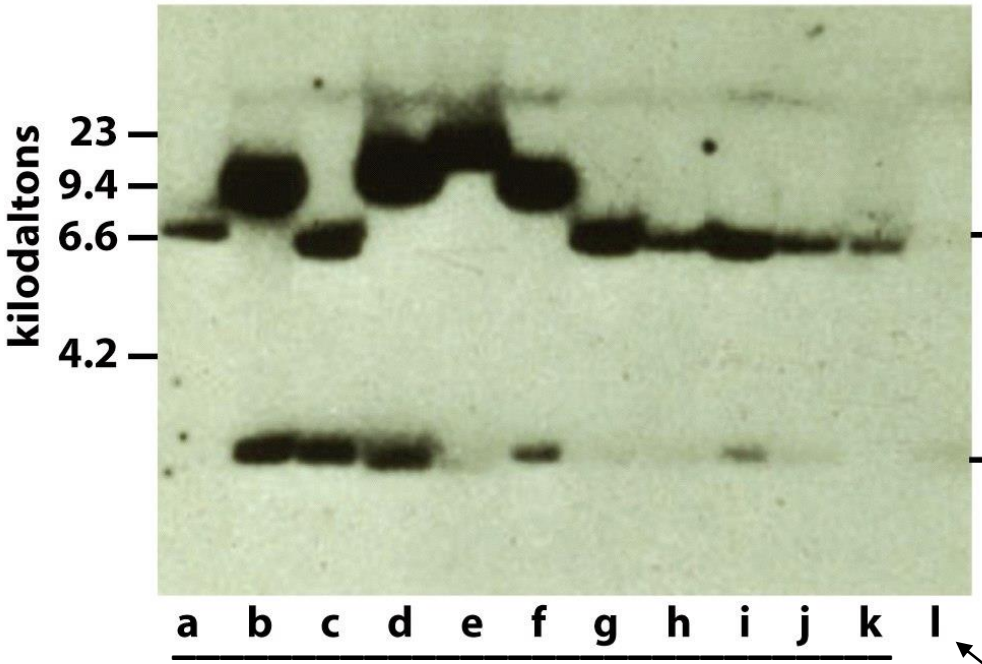
Oncogenes discovered in human tumor cell lines are related to those carried by transforming retroviruses

Southern blotting (DNA)
Northern blotting (RNA)



Homology between transfected oncogenes and retroviral oncogenes

probe used: H-ras oncogene present in Harvey rat sarcoma virus



11 (a ~ k) NIH3T3 cell lines transfected with DNA extracted from a **human** bladder carcinoma cell line

Figure 4.5 *The Biology of Cancer* (© Garland Science 2007)

ErbB- Gene symbol

- The gene symbol, ErbB, is derived from the name of a viral oncogene to which these receptors are homologous: Erythroblastic Leukemia Viral Oncogene.

- v-ErbBs are homologous to EGFR, but lack sequences within the ligand binding ectodomain.

- Insufficient ErbB signaling in humans is associated with the development of neurodegenerative diseases, such as multiple sclerosis and Alzheimer's Disease.

Receptor Tyrosine Kinases

- The Receptor Tyrosine Kinases (RTKs) are membrane receptors.

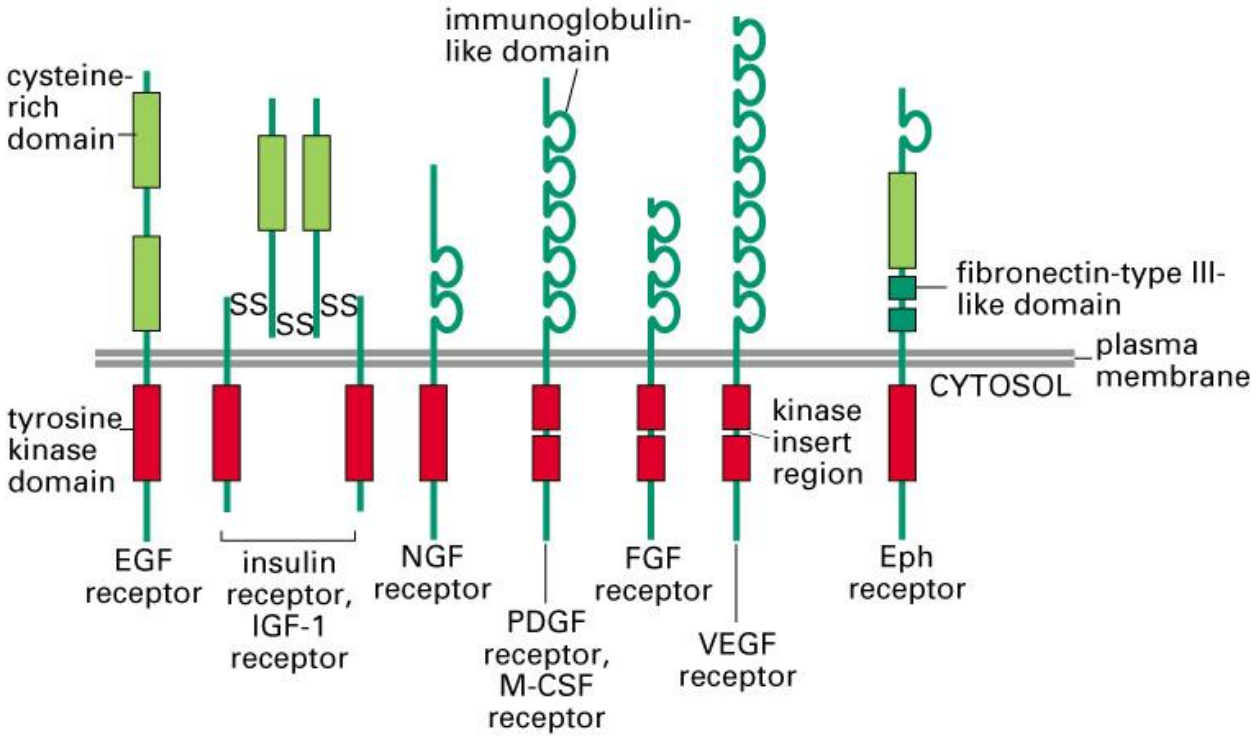
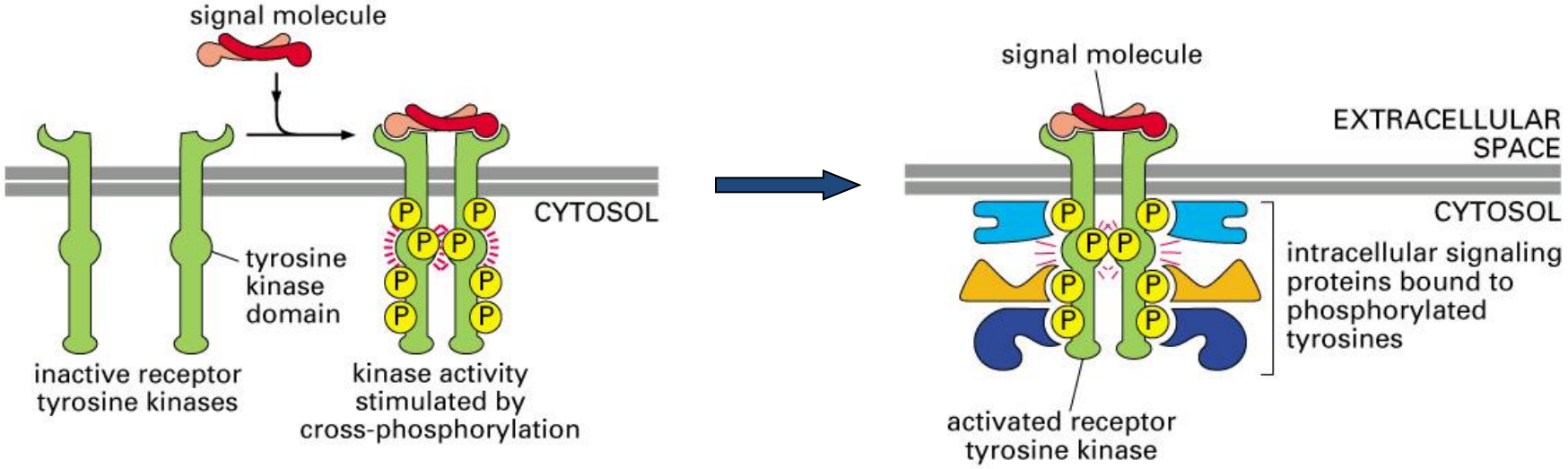


Figure 15–49. Molecular Biology of the Cell, 4th Edition.

Receptor Tyrosine Kinases

- Most of these recepors are activated by ligand-induced dimerization, resulting in increased kinase activity of the TK domain.

- This results in trans-autophosphorylation of the cytoplasmic domains.

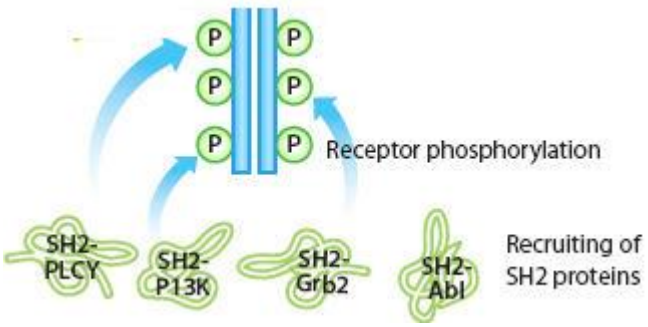


Receptor Tyrosine Kinases

- Most of these recepors are activated by ligand-induced dimerization, resulting in increased kinase activity of the TK domain.

- This results in trans-autophosphorylation of the cytoplasmic domains.

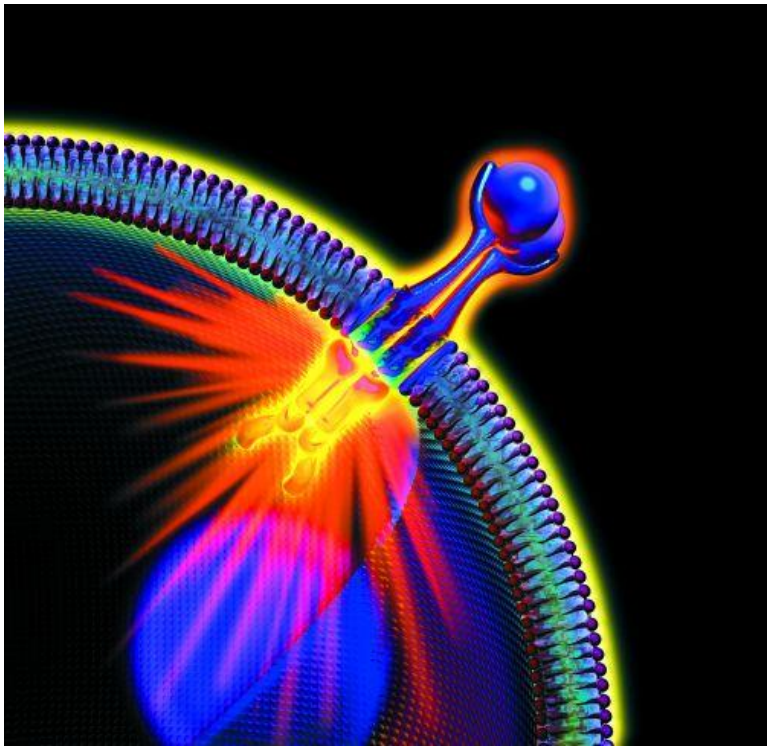
- The phospho-tyrosines can then recruit SH2 domains of different signaling proteins.



EGFR

- EGFR is an RTK protein. It was the first receptor that was linked directly to cancer.

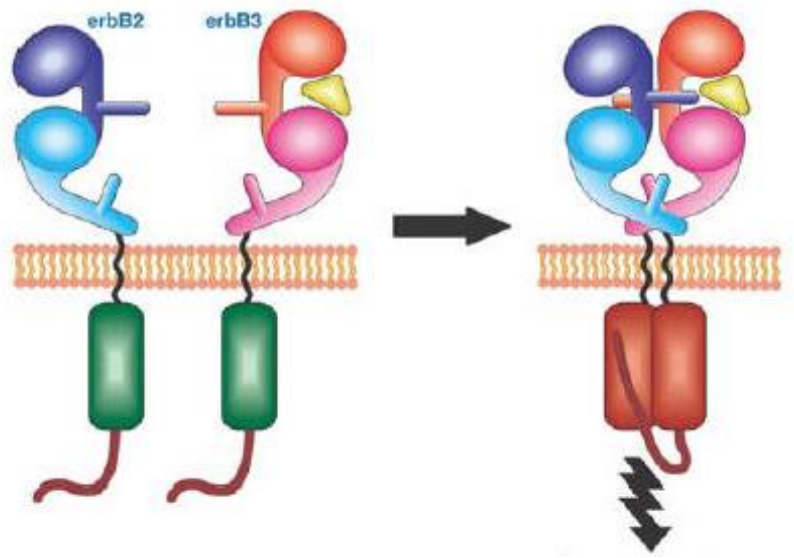
- Mutations in EGFR which result in overactivity are associated with several types of cancers.



The ErbB family

- EGFR belongs to the ErbB family which contains four RTKs.

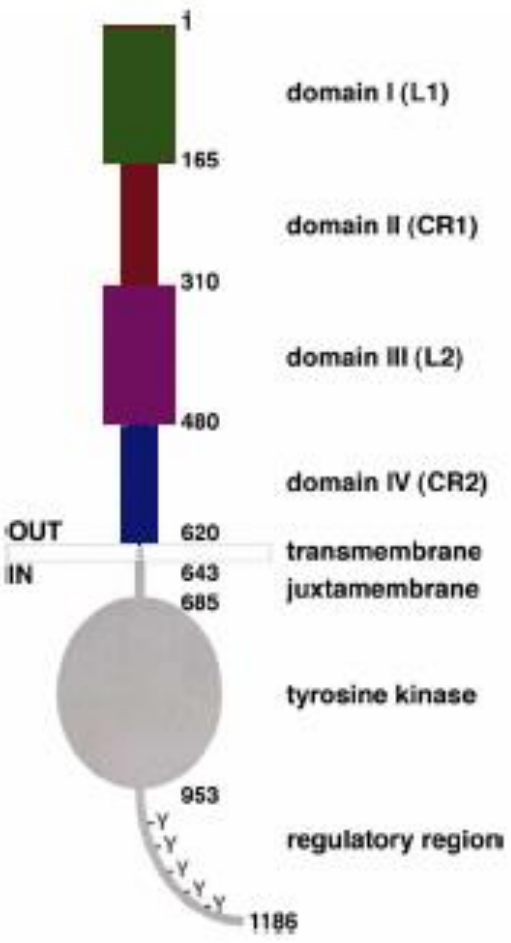
- They are capable of forming homo- or heterodimers and possibly higher-order oligomers, following activation by their ligands.



The ErbB protein family consists of 4 members

- **Epidermal growth factor receptor (EGFR) family**
- ErbB-1, also named epidermal growth factor receptor (EGFR)
- ErbB-2 stands for "Human Epidermal growth factor Receptor 2" and is a protein giving higher aggressiveness in breast cancers.
- Also named , **HER2/neu** (HER2 in humans and neu in rodents)
- ErbB-3, also named HER3
- ErbB-4, also named HER4

Domain organization



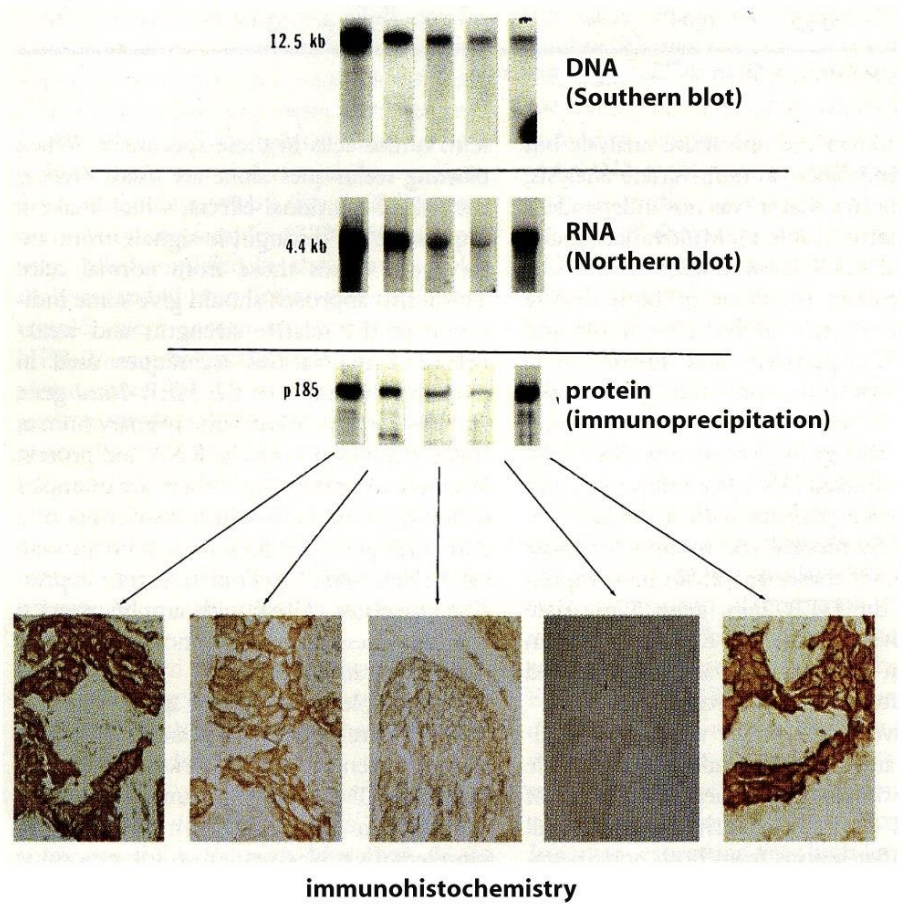
The four erbB receptors are closely related glycoproteins. They consist of:

1) An extracellular ligand binding region (**620 residues**)
2) A single transmembrane domain (**23 residues**)
3) Juxtamembrane (**40 residues**)
4) An intracellular tyrosine kinase domain (**260 residues**)
5) C-terminal regulatory region (**232 residues**)

ErbB

- ErbB-1 is overexpressed in many cancers.
- Drugs such as panitumumab, cetuximab, gefitinib, erlotinib are used to inhibit it.
- ErbB-2 (HER-2) is often overexpressed in breast cancer.
- It is revealed that patients with ER+/HER2+ breast cancers may actually benefit more from drugs that inhibit the PI3K/AKT molecular pathway

erbB2/HER2/neu oncogene can be amplified or overexpressed in human breast carcinoma cells



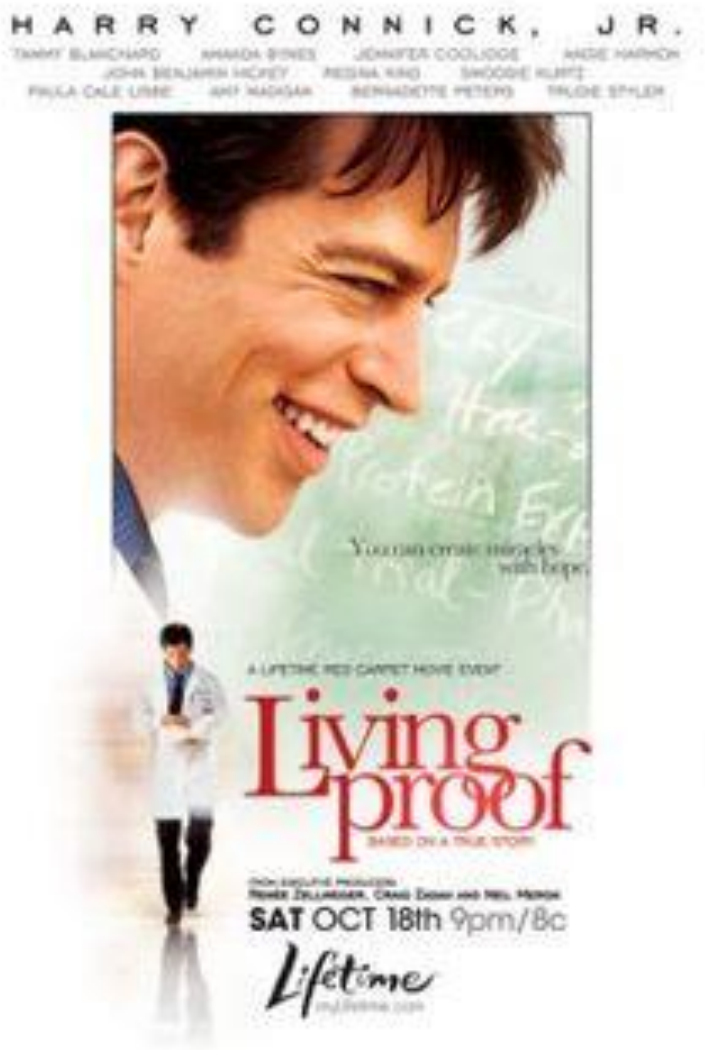
erbB2/neu oncogene is amplified

erbB2/neu mRNA is overexpressed

increased level of *erbB2/neu*-encoded protein

Figure 4.6c *The Biology of Cancer* (© Garland Science 2007)

Dr. Dennis Slamon and the book *HER-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer* by Robert Bazell.



- Breast Cancer drug Herceptin, over the course of 8 years from 1988 to 1996.
- Dr. Slamon is a research doctor at UCLA Medical Center (Los Angeles), where he has developed the experimental drug Herceptin, which he believes will become a treatment for breast cancer.

Herceptin-- The corporate view

Herceptin®
Trastuzumab
anti-HER2 monoclonal antibody

Genentech
In Business for Life

In HER2-driven metastatic breast cancer

Lay a strong foundation to extend survival

Please choose one of the following:

Patient and Caregiver | Healthcare Professional | International Visitors

WARNINGS:
CARDIOMYOPATHY
HERCEPTIN administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in all patients prior to and during treatment with HERCEPTIN. Discontinuation of HERCEPTIN treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patients who received HERCEPTIN in combination with anthracyclines and cyclophosphamide. (Please see full Prescribing Information, including Boxed WARNING.)

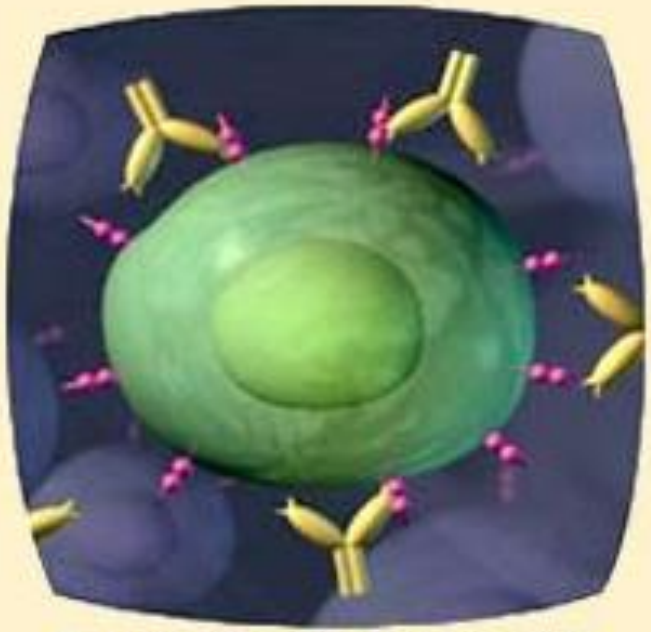
HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS
INFUSION REACTIONS
PULMONARY EVENTS
HERCEPTIN administration can result in severe hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary events. Rarely, these have been fatal. In most cases, symptoms occurred during or within 24 hours of administration of HERCEPTIN. HERCEPTIN infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of HERCEPTIN treatment should be strongly considered for patients who develop anaphylaxis, angioedema, or acute respiratory distress syndrome. (Please see full Prescribing Information, including Boxed WARNING.)

Genentech

How Herceptin Works

What is a monoclonal antibody?

An *antibody* is a protein made by the body's own natural immune system. They are directed against foreign and infectious agents, called antigens. *Monoclonal antibodies* engineered through biotechnology are produced to provide specific anti-tumor action within the human body.



Monoclonal antibodies targeting
a HER2 protein overexpressing cell

Genentech.com

Thanks for your attention

Acknowledgement

- The Presentation is being used for educational and non commercial purpose
- Thanks are due to all those original contributors and entities whose pictures used for making this presentation.