# Cancer genes to drugs

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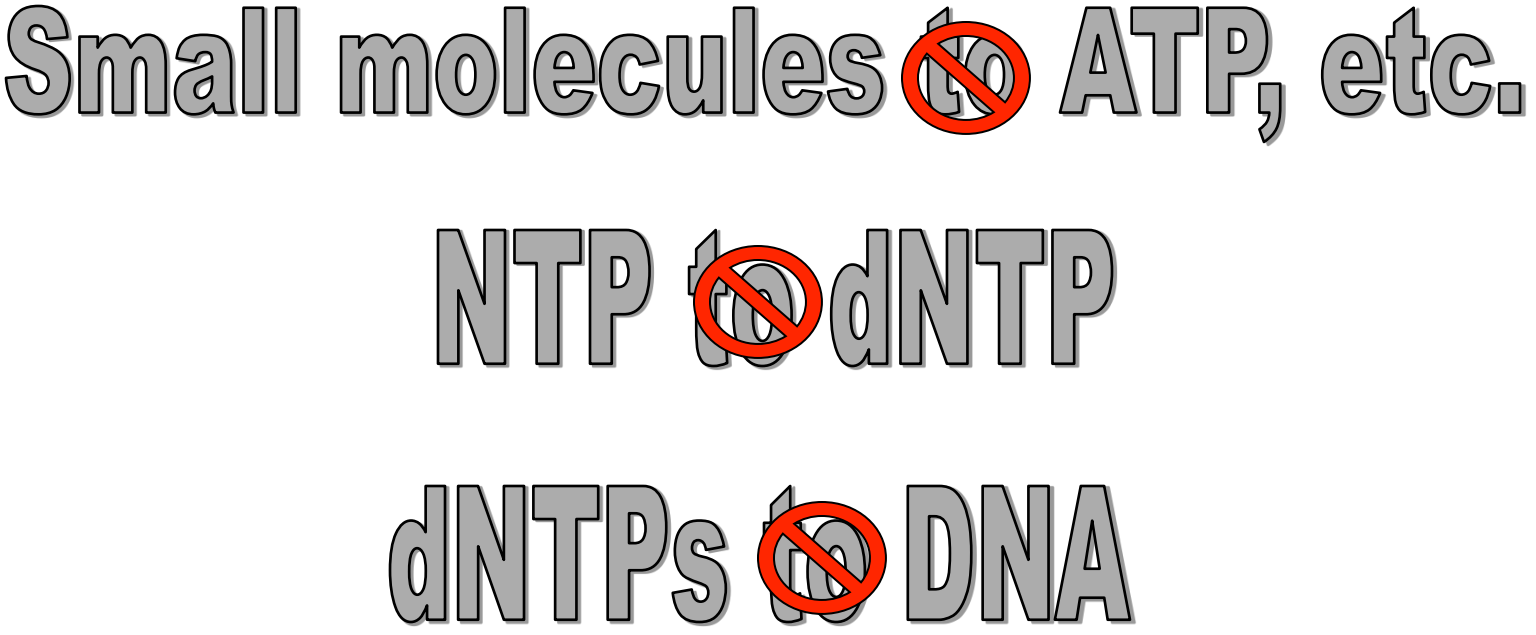
# Traditional Chemotherapy

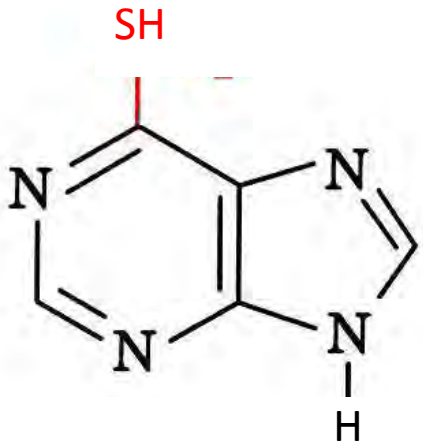
- The earliest of these (before 1970) led to a Nobel Prize in Physiology and Medicine in 1988.
  - (James Black, Gertrude Elion and George Hitchings)
- The first outcomes of the War on Cancer
  - Started with funding legislation in 1971
- Aimed at killing rapidly growing cells
- Toxic to normal cells that need to proliferate
- For solid tumors, these drugs remain in use and have had spectacular success in a few cancers.
- Tumor removal (when possible) is still preferred.

# Early Chemotherapy

- Targets – rapidly growing cells.



# A purine analog




**6-Mercaptopurine**. The molecule inhibits several purine synthesis steps.


**Allopurinol**

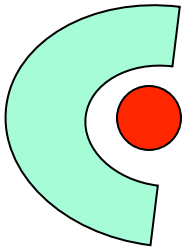
With allopurinol (above, to block degradation) 6-mercaptopurine stays in the body long enough to be effective.

# Drugs targeted to gene defects?

- Types of genes – reminder
- Accelerators – often Kinase enzymes
  - Add a phosphate to other proteins or molecules
- Receptors (exposed on the cell surface)
  - Recognize growth signals from outside
- Factors that alter gene expression
  - Bind to specific regions of the DNA
- Brakes (tumor suppressors)
  - DNA repair and damage recognition
  - Enzymes that turn off signals

# Small molecule drugs

- Small molecule inhibitors.
- These are often termed “ib”
- They are usually specific.
- Some of these small molecule drugs are initially effective, but cancer cells can sometimes acquire mutations that make them less effective over time.



# Gleevec

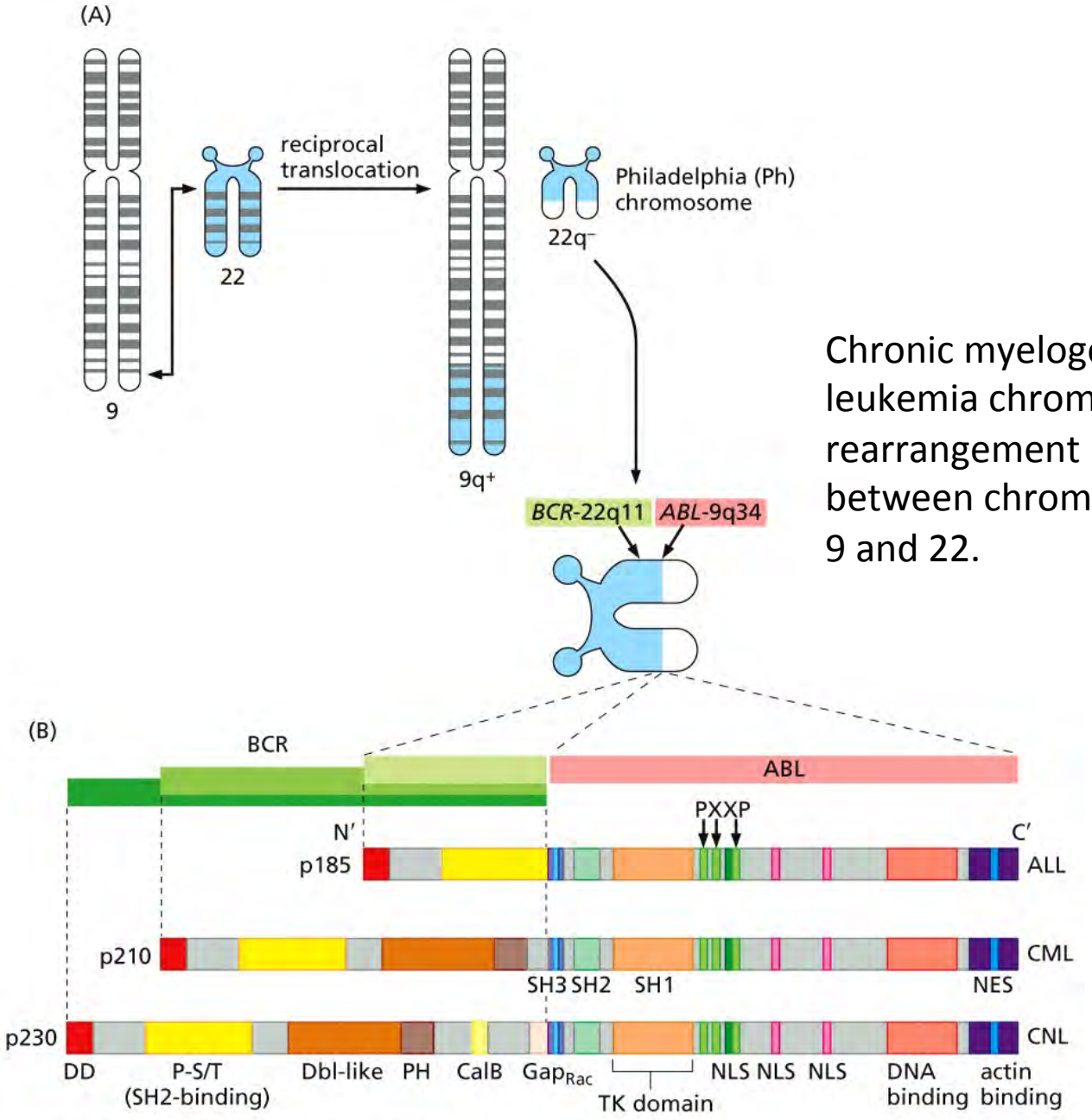



Figure 16.22 The Biology of Cancer (© Garland Science 2014)

Chronic myelogenous leukemia chromosome rearrangement between chromosomes 9 and 22.

Instead of blocking ATP binding, it stabilizes an inactive conformation

# Lots of accelerators are enzymes

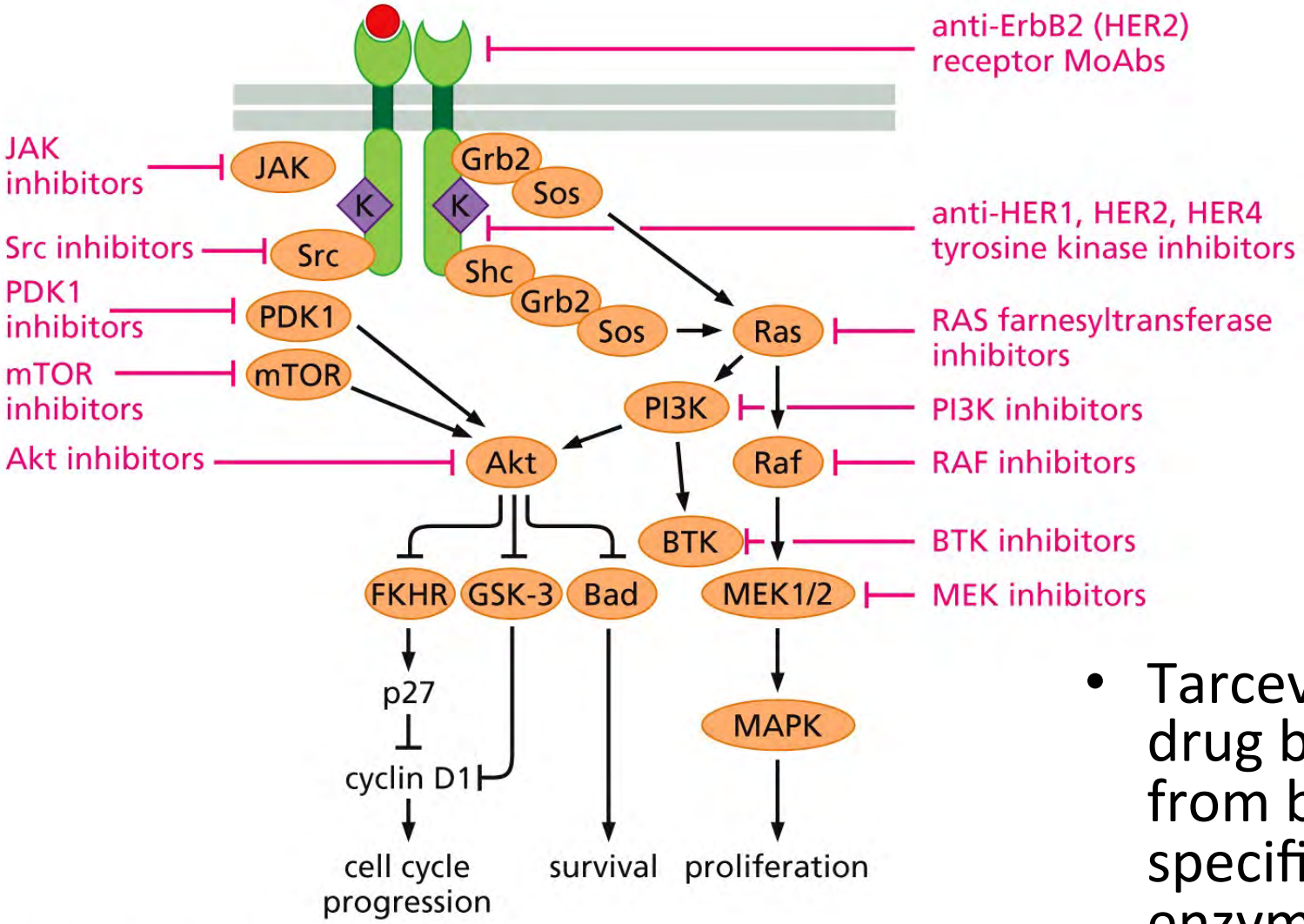



Figure 16.9 The Biology of Cancer (© Garland Science 2014)

- Tarceva. This drug blocks ATP from binding to specific kinase enzymes.

# Blocking protein-protein interactions

- Other driver (oncogene and tumor suppressor) mutations alter protein-protein interactions. Generally these are considered harder to block with small drugs.

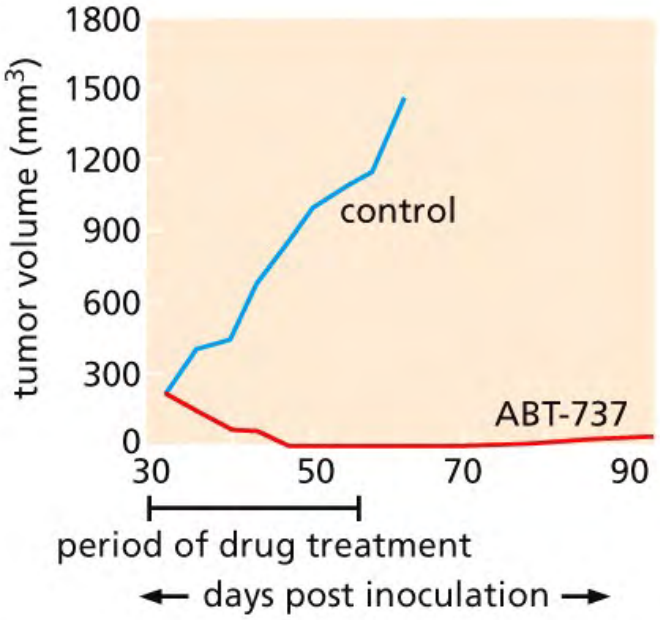
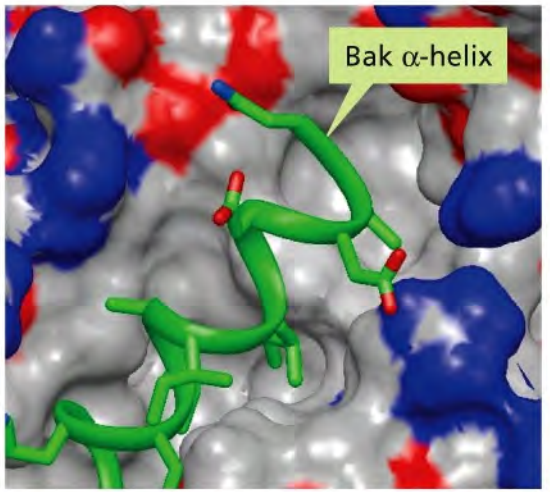
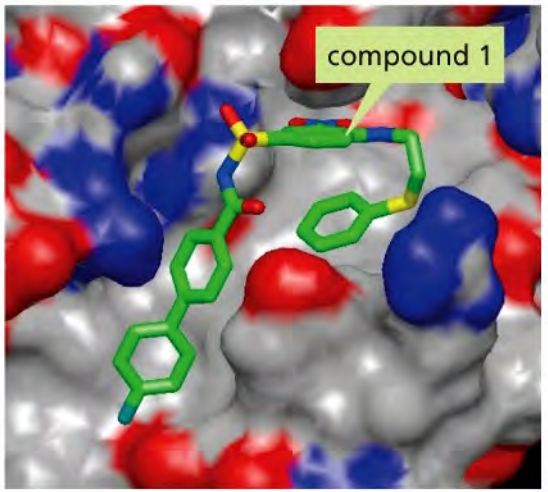



Figure 16.11c The Biology of Cancer (© Garland Science 2014)



# Some cancer cells make pumps to dump the drugs back out.

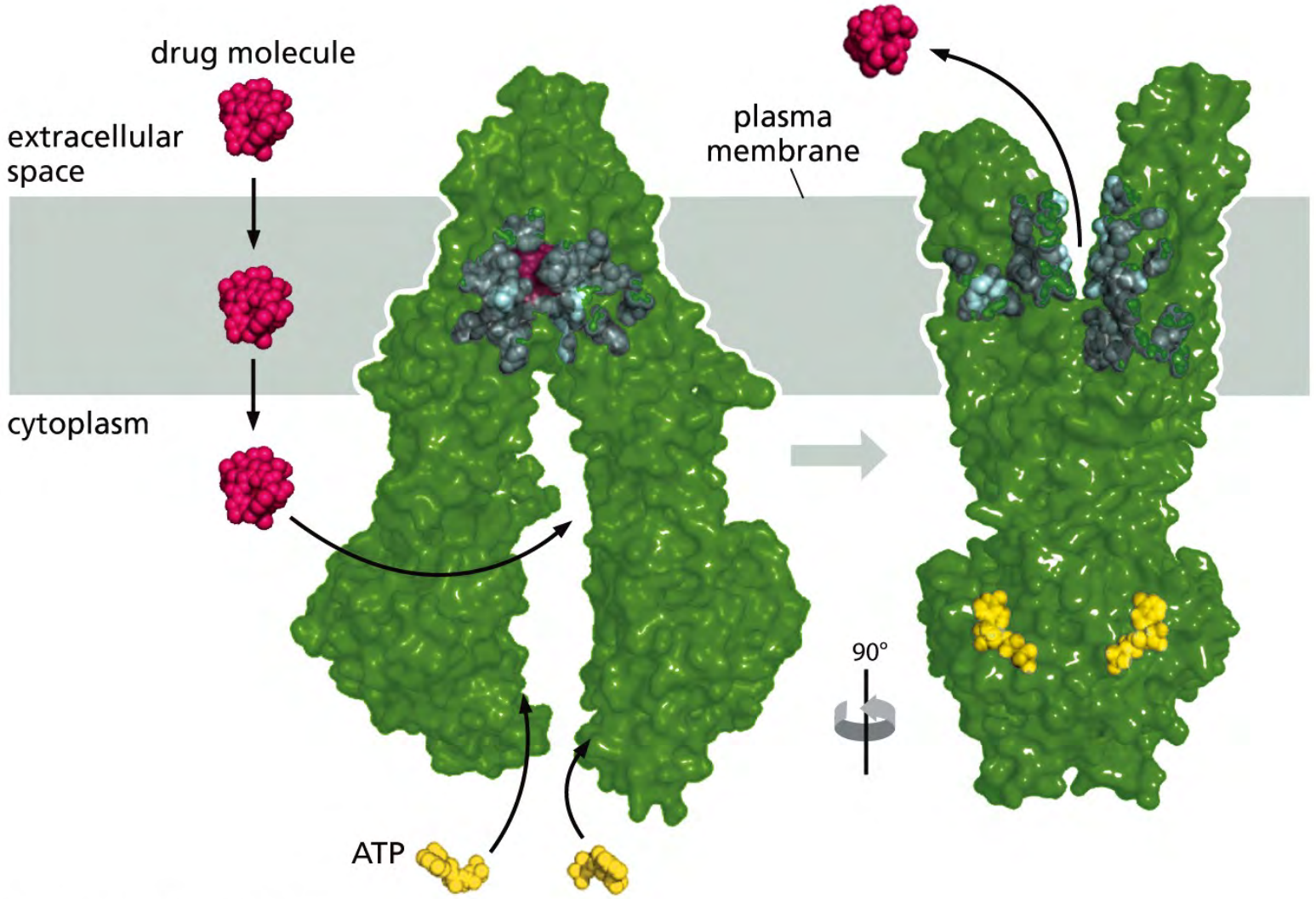
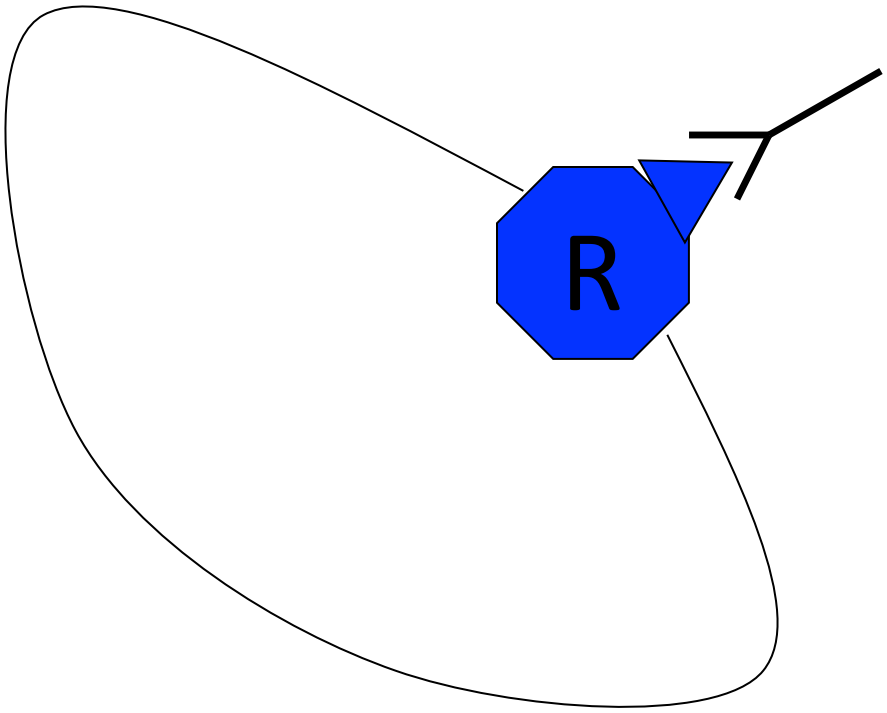



Figure 16.21 The Biology of Cancer (© Garland Science 2014)

# Drug Antibodies

- Antibodies against growth factor receptors or mutated overactive forms of the receptors.

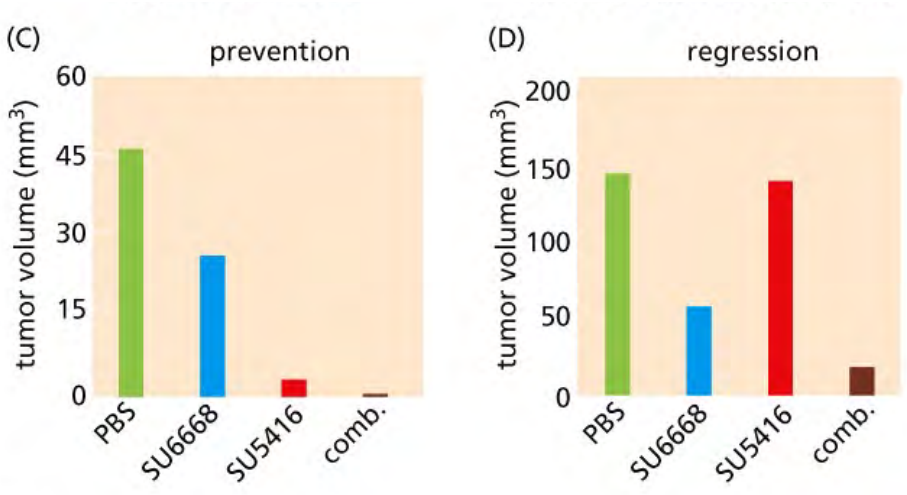



✓Antibodies might recruit the immune system

✓Antibodies might block ligand binding to remaining receptors

✓Antibodies might block receptor function

# Blocking blood vessels




- Avastin – an antibody based blocking agent, survival for one to several months longer.

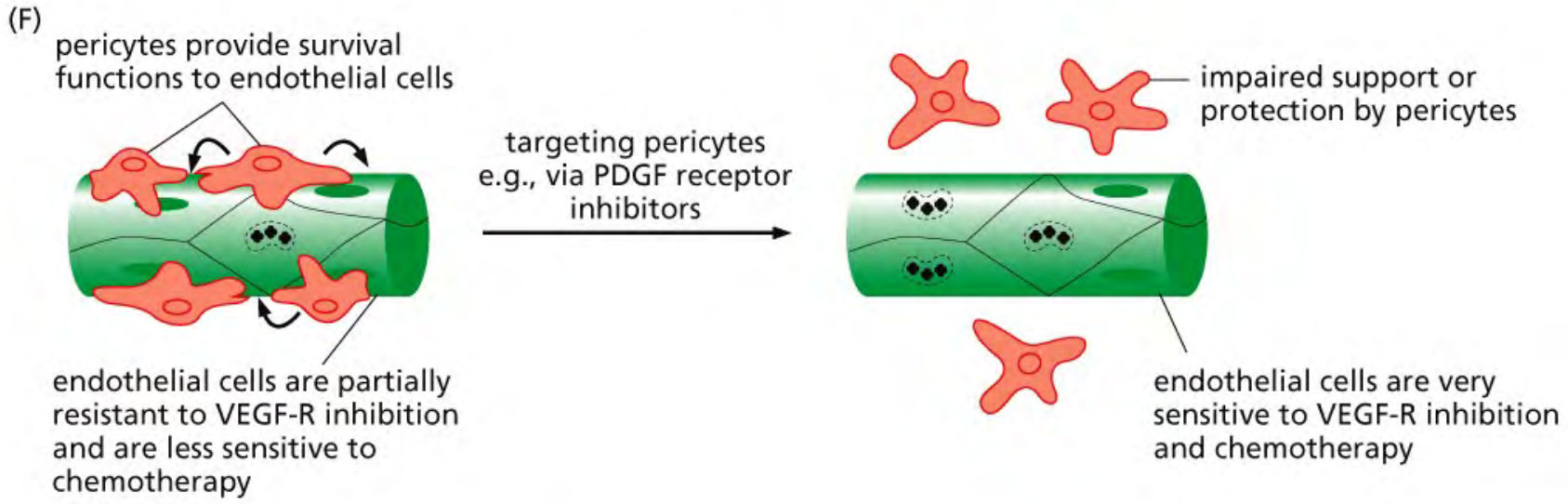
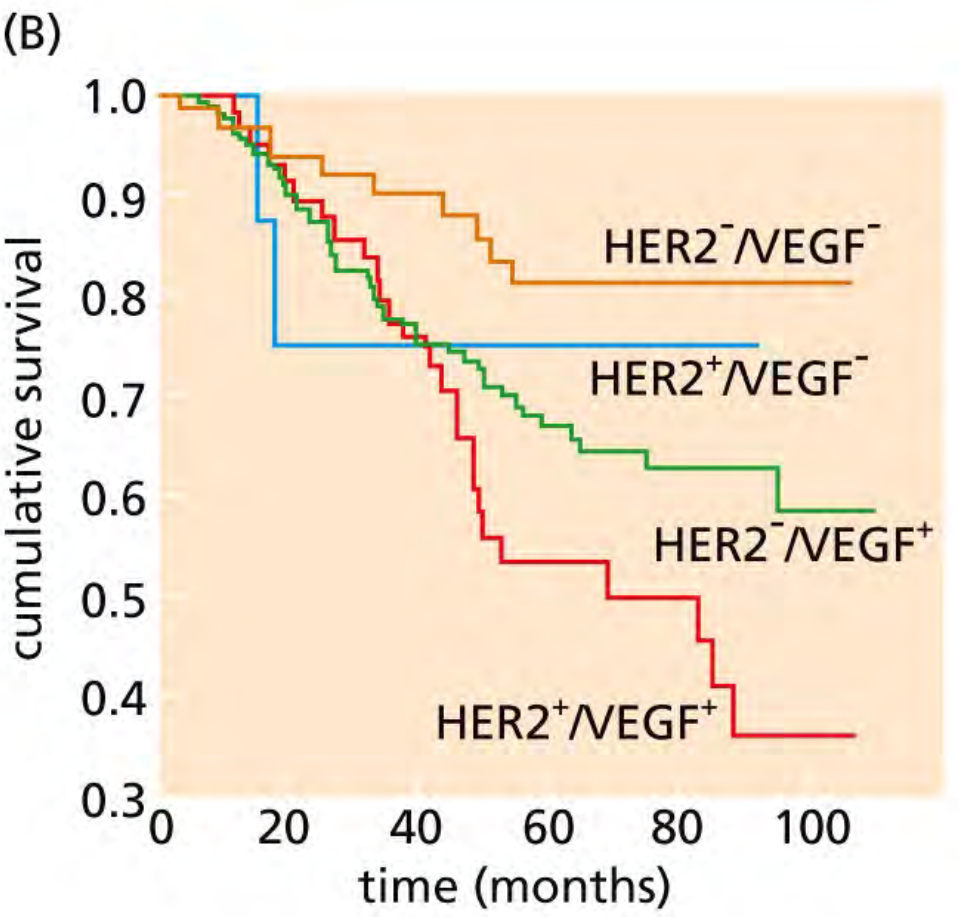



Figure 13.46 The Biology of Cancer (© Garland Science 2014)

# 65 or more breast cancer drugs

- Trastuzumab – Herceptin – induces cell death after binding to the overexpressed receptor
- Triple negative (progesterone, estrogen, Her2)




Biology of Cancer, Weinberg

http://www.cancer.gov/about-cancer/treatment/drugs/breast#2

# Let's talk

- Based on what I just said – what do you think someone might want to know about their tumor before getting treatment?
- Who should have access to genetic and protein expression information?
- Does that differ from access to genetic information generally?

# Long term goals

- Ultimately, targeting the stem cells that are cancerous rather than only the most rapidly growing cells will be important.
- Development of specific drugs based on specific cancer situations is also continuing (personalized medicine).
- http://www.cancer.gov/