

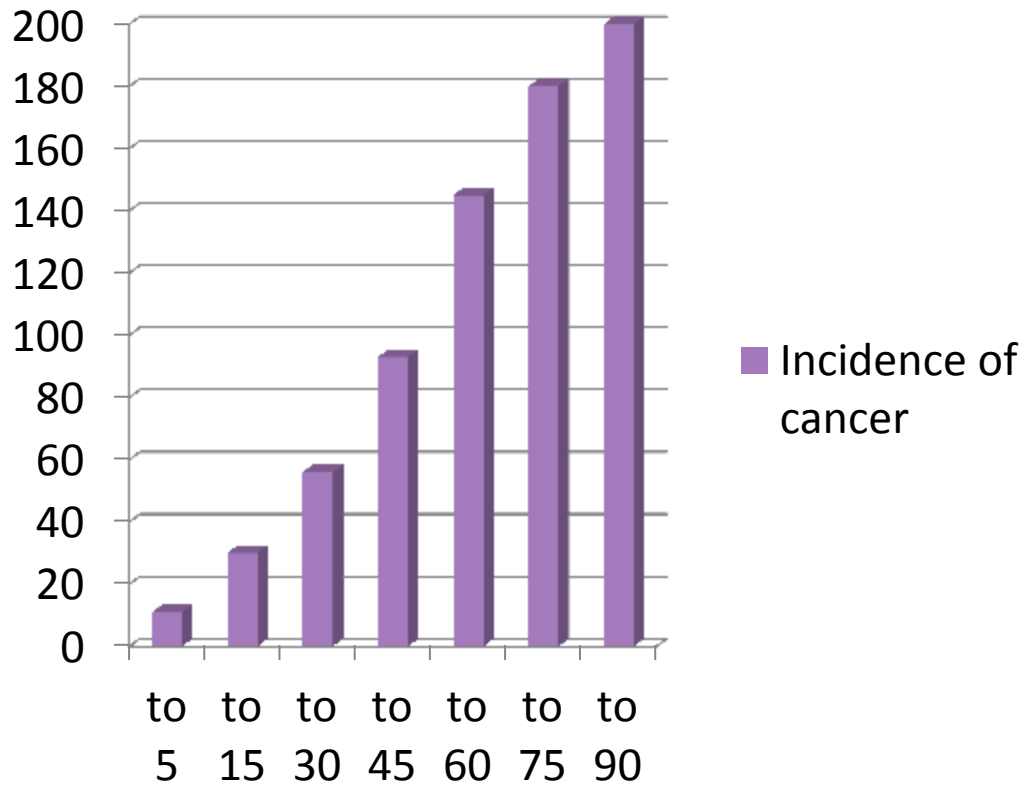
Cancer and Oncogenes
Bioscience in the 21st Century

Linda Lowe-Krentz

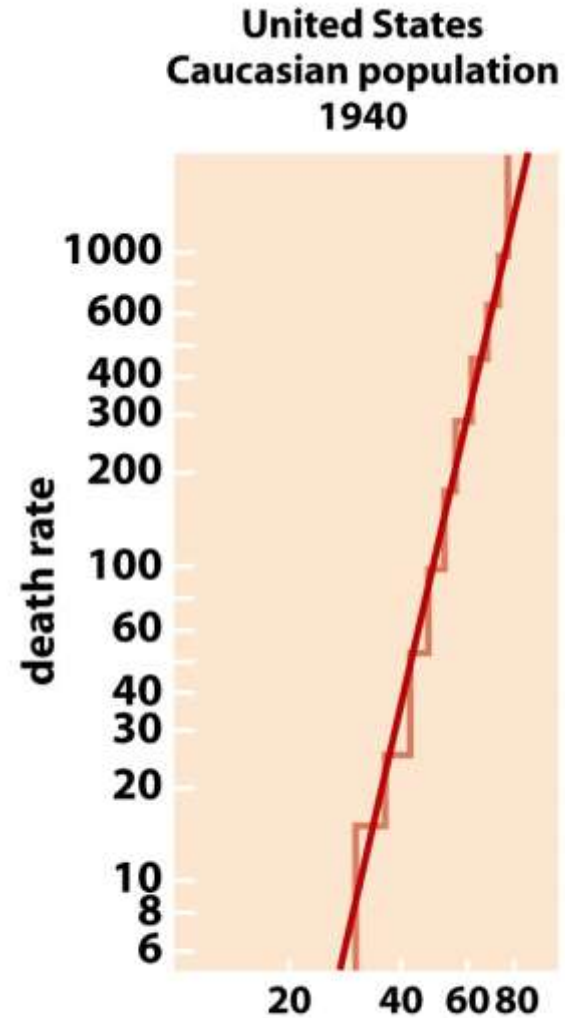
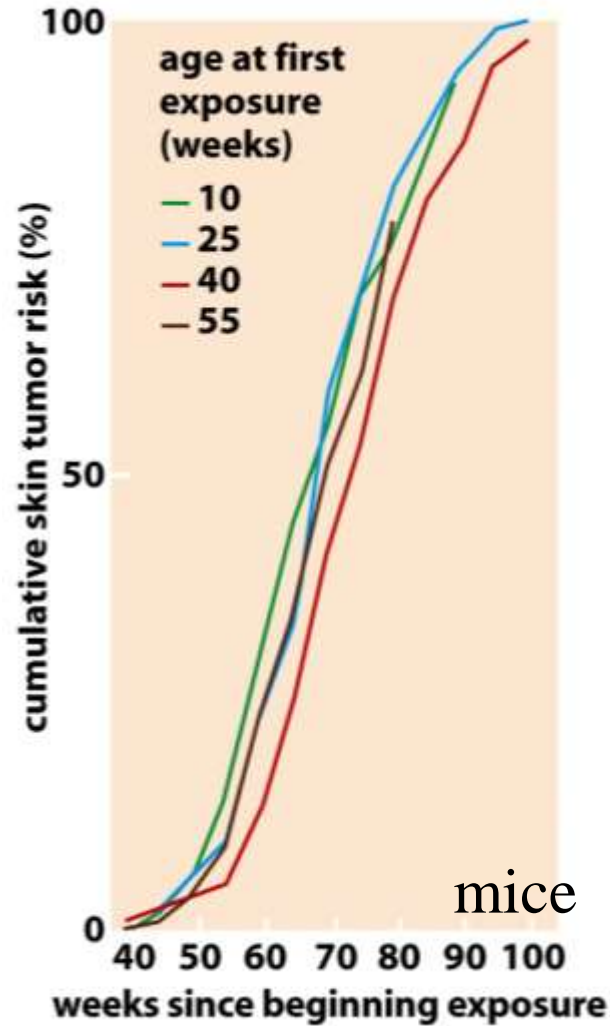
October 11, 2013

- Just a Few Numbers
- Becoming Cancer
- Genetic Defects
- Drugs

Our friends and family



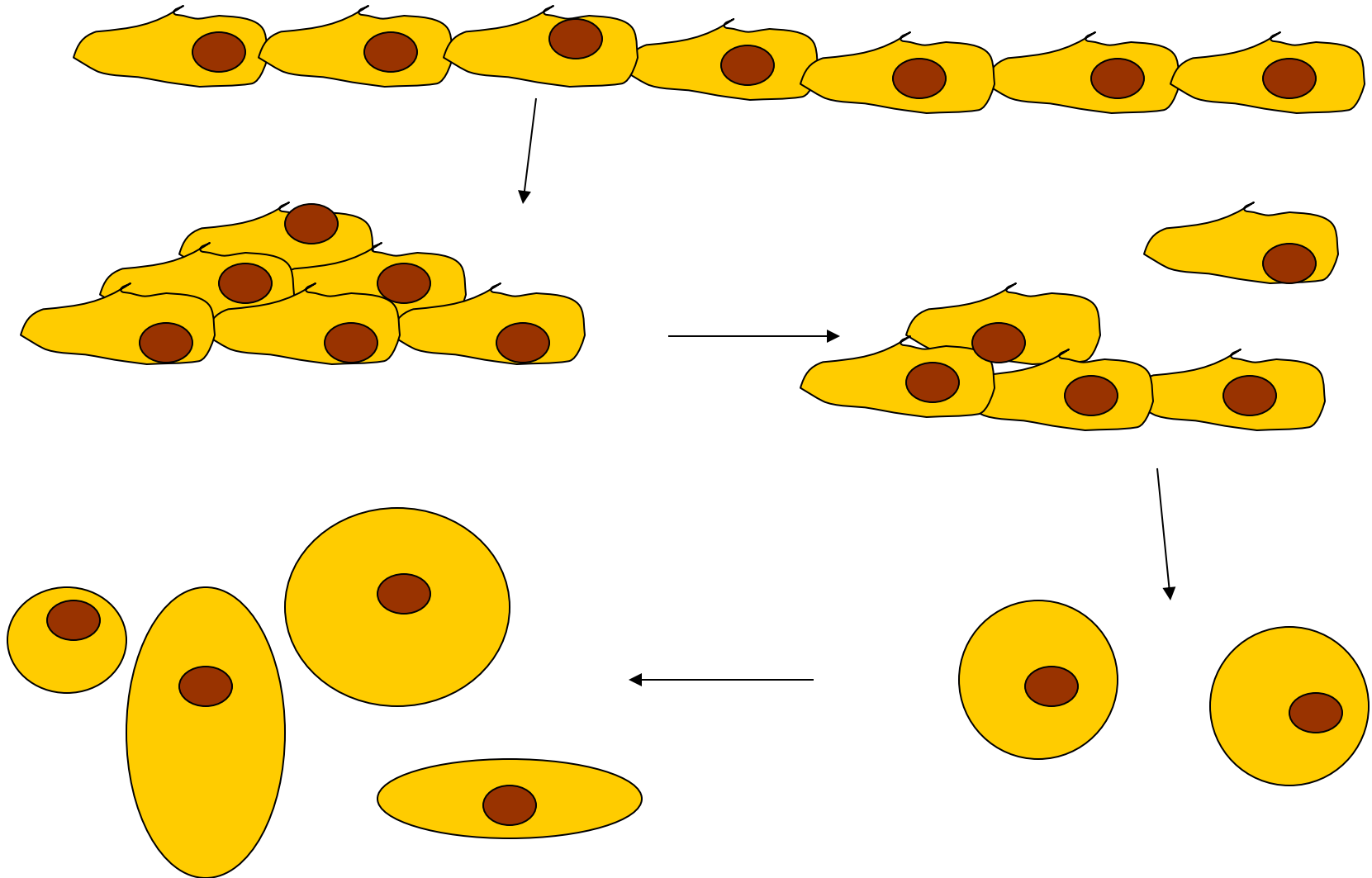
Other similar data



Mutations collected

- Original hypothesis – 2 mutations, one in signaling and one in the nucleus.
- Statistical analysis says more like 5 or 6 mutations probably contribute to cancer.
- Typically at least one mutation is in a cell growth pathway.

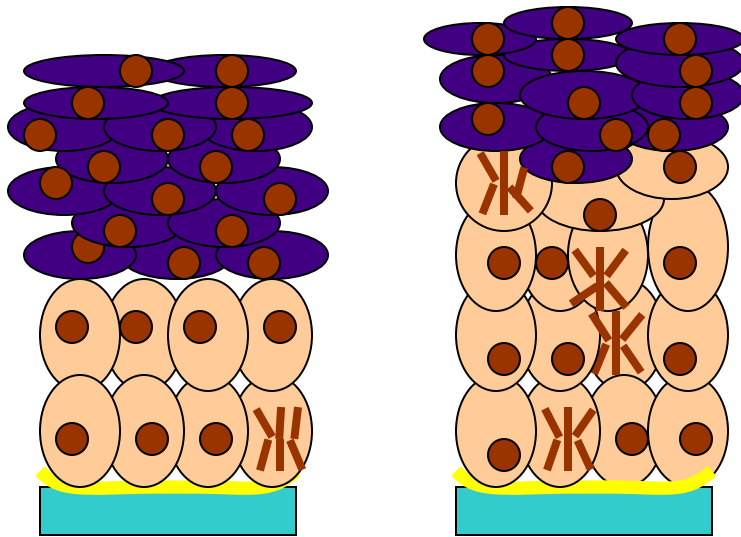
Evolution of a cancer cell



Abilities acquired

- Grow rapidly
- Dissociate from neighboring cells
- Invade adjacent tissue
- Recruit vasculature and invade blood vessels or lymphatic system
- Escape immune system
- Arrest in a new location
- Get into target tissue
- Proliferate in new location

Normal Dysplasia



Pre-malignant,
appear abnormal

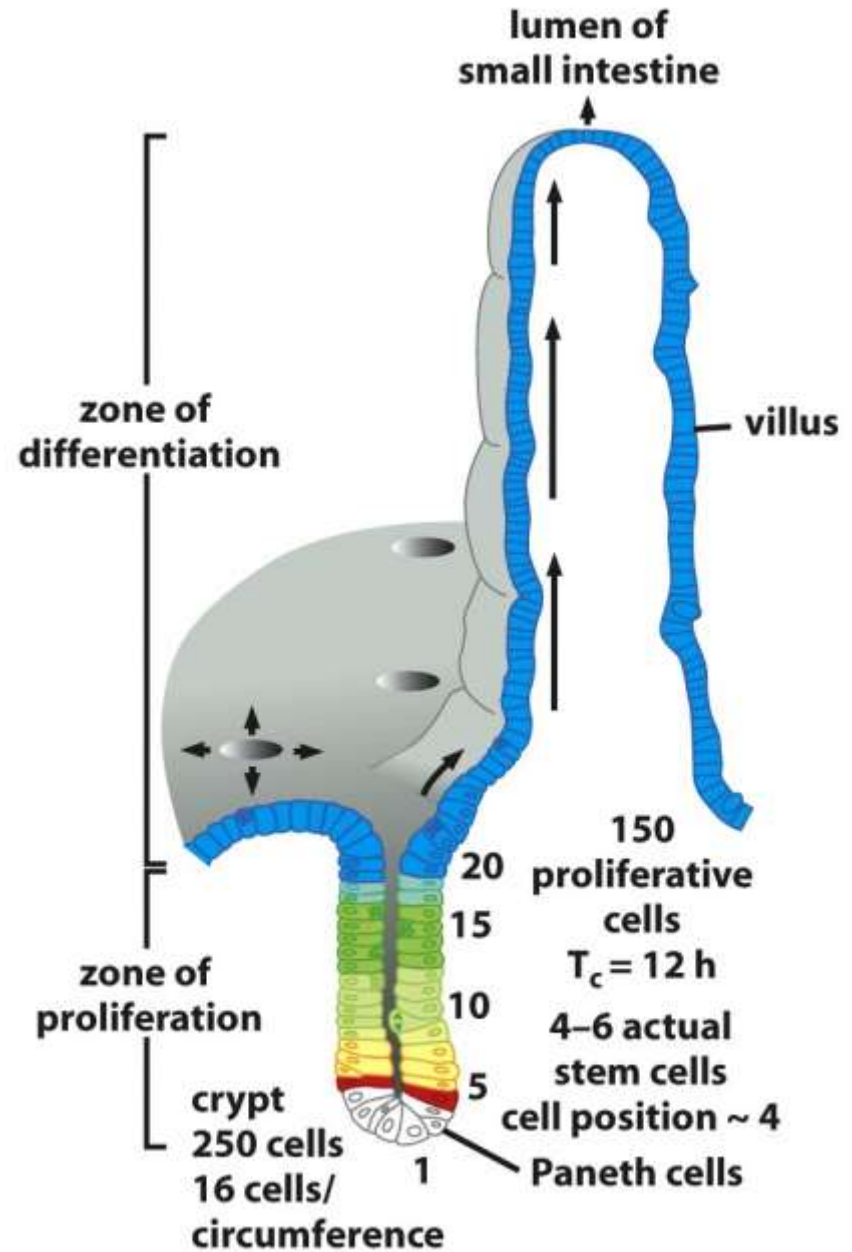
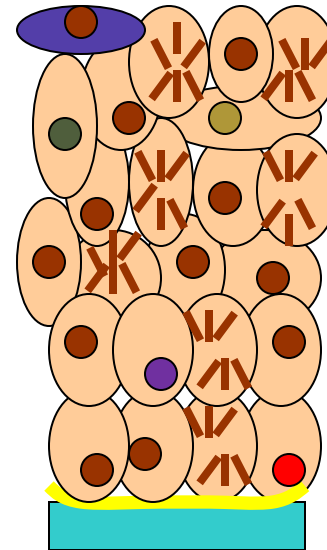


Figure 12-2a The Biology of Cancer (© Garland Science 2007)

Carcinoma

Increased cell proliferation

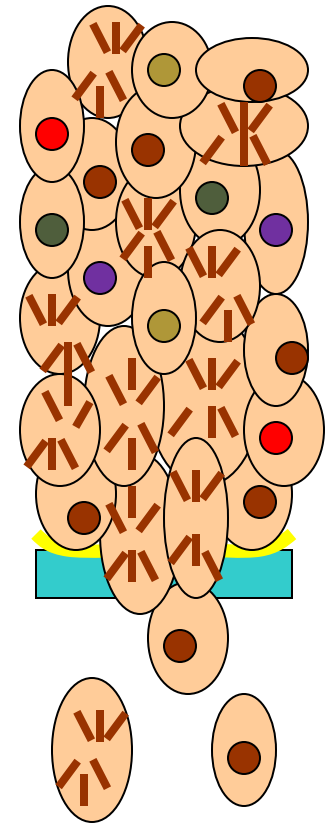
Additional possible
changes here include
decreased ability to catch
mistakes



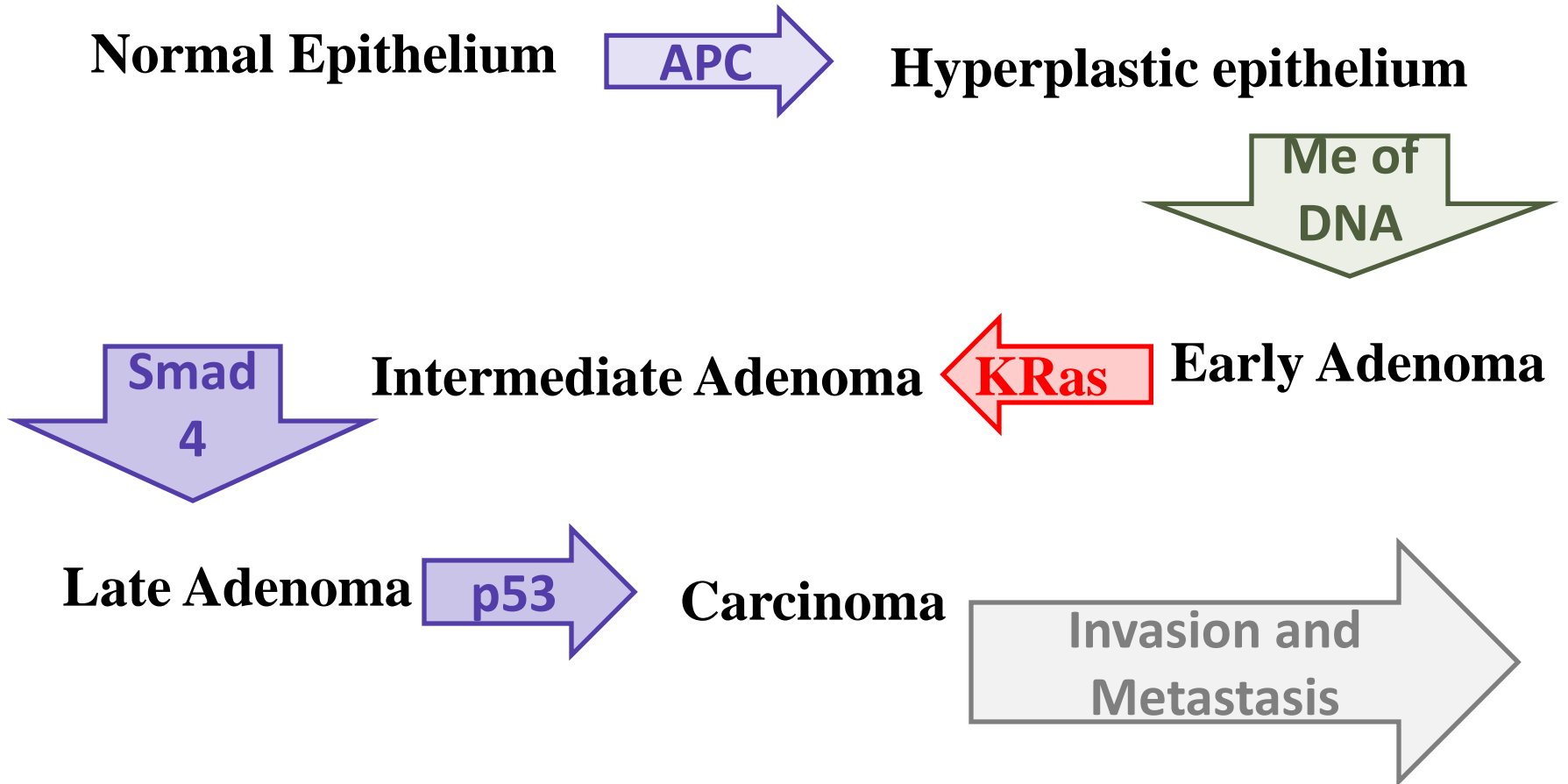
Malignant

Epithelial to
mesenchymal transition.

Cells are able to change
characteristics and gain
the ability to migrate
across barriers or
through membranes.



One pathway



Cancer Evolution

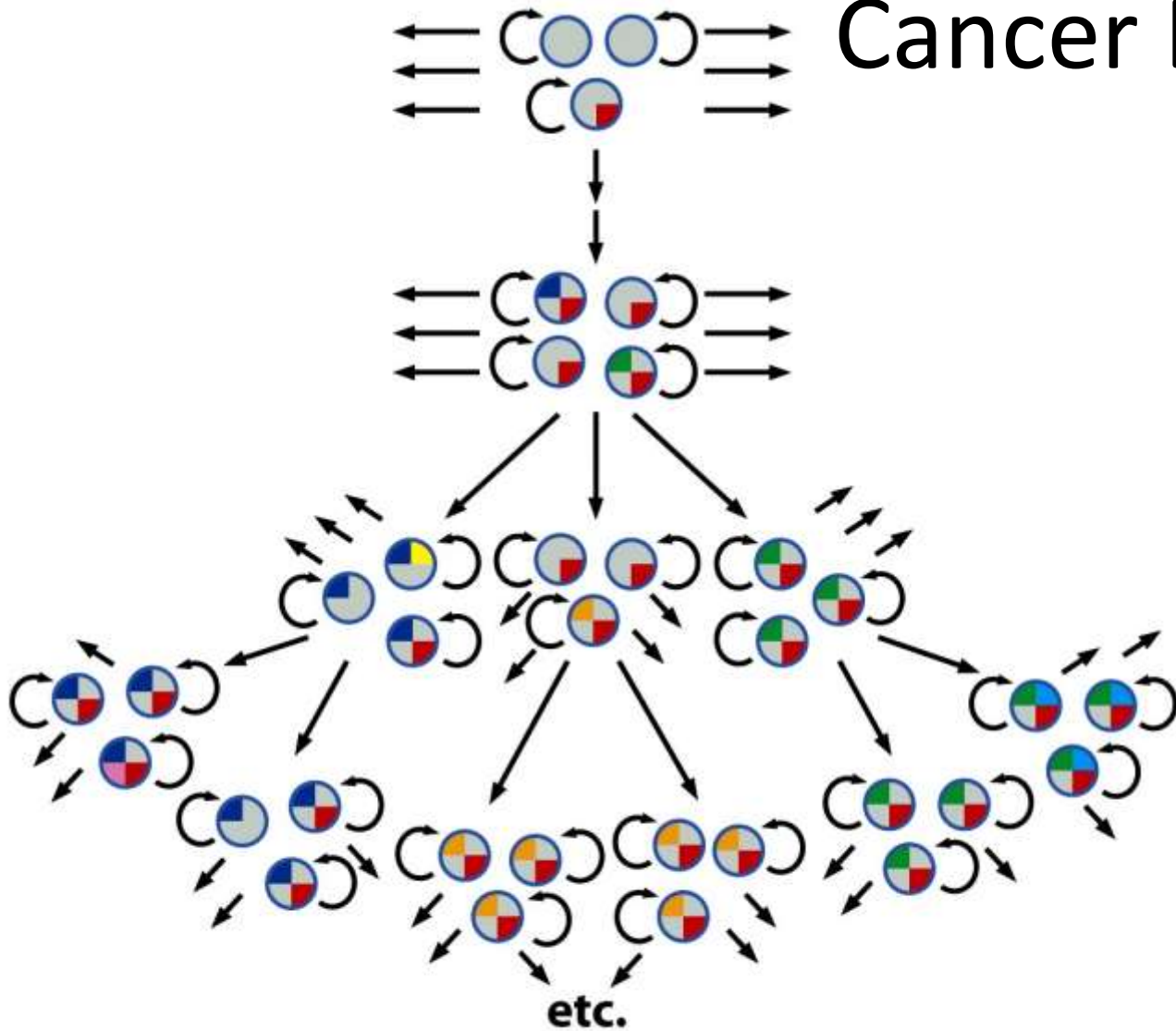
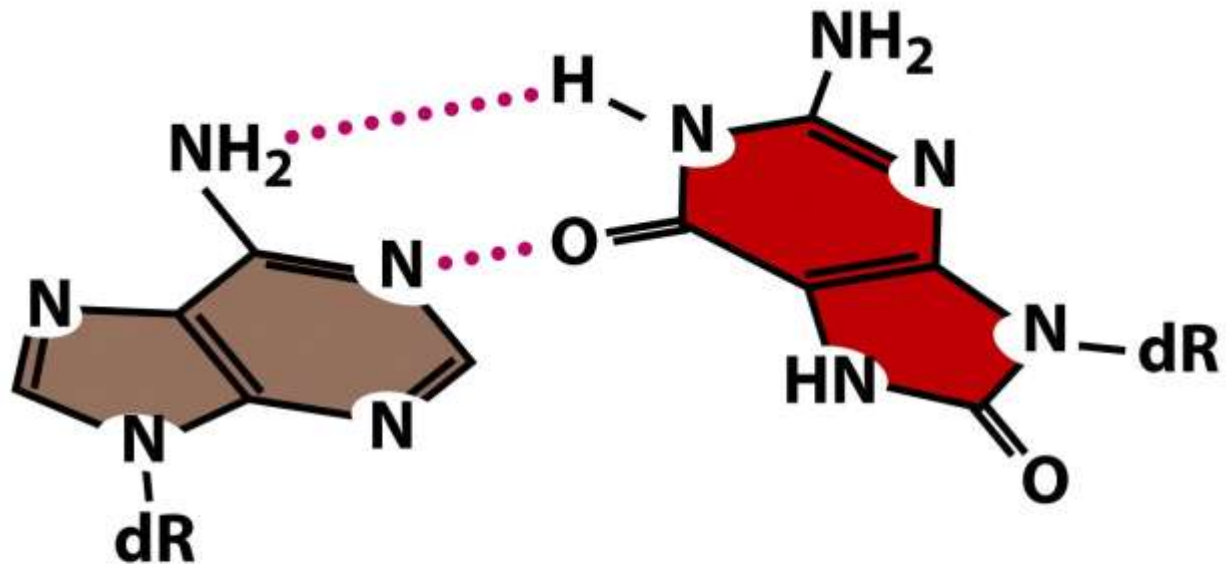


Figure 11-18 The Biology of Cancer (© Garland Science 2007)

Oxidative damage outcomes



**mispairing of 8-oxo-dG
with deoxyadenosine (dA)**

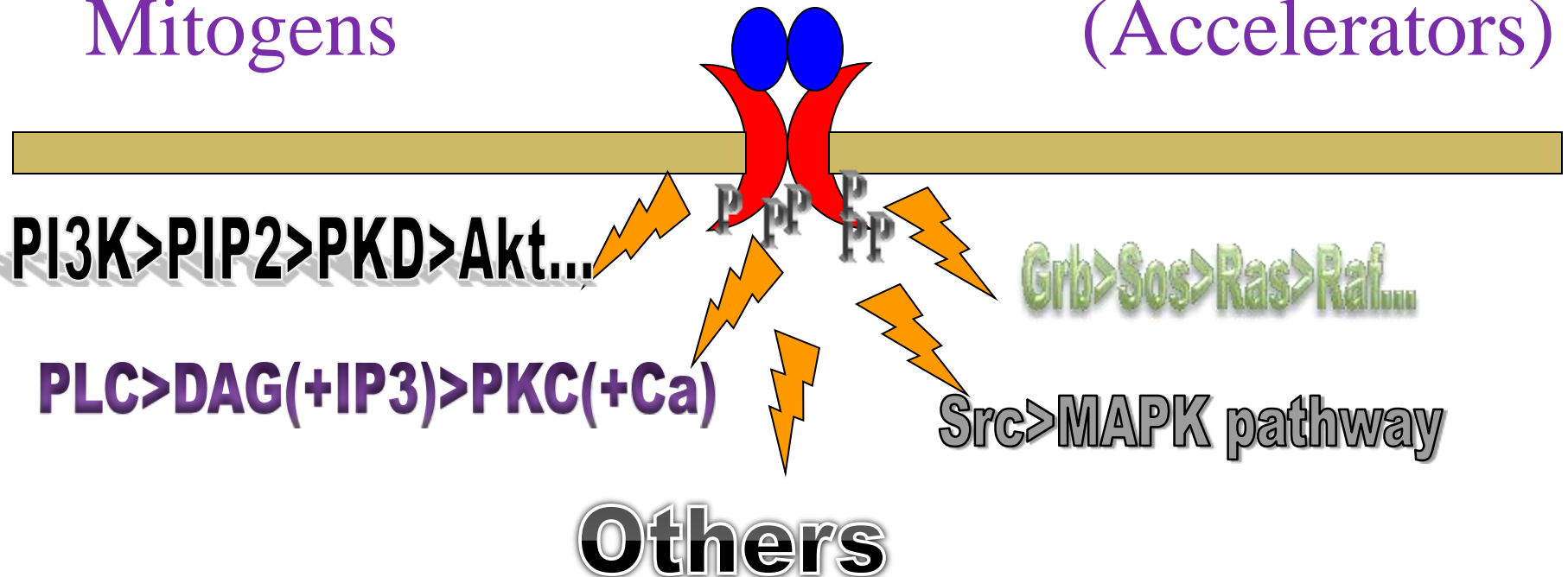
But repair enzymes fix most problems

- If you cannot fix all of the DNA damage, mistakes accumulate more rapidly and cancer usually starts earlier.
- An example when repair is not complete is individuals with Li-Fraumeni syndrome whose cells do not recognize damage (faulty p53).
- Another example is Xeroderma Pigmentosum, where patients cannot repair UV damage and get skin cancer more rapidly than most people – with much less exposure

Growth factors and the cell cycle

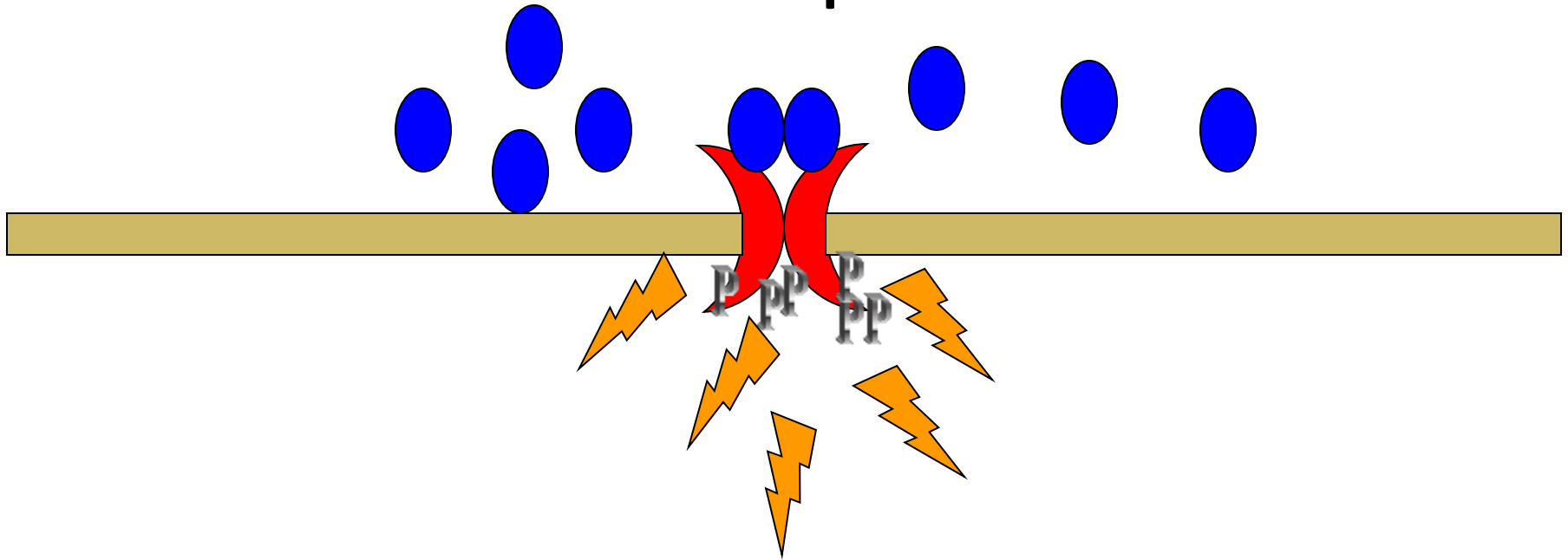
Mitogens

(Accelerators)



Together these pathways control a complicated set of events that result in a balance of proteins and other factors leading to cell growth and division.

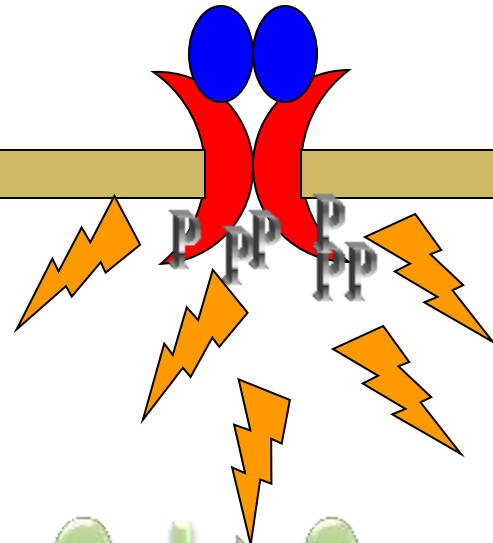
SCF is over produced



In many Small Cell Lung Carcinoma patients, lots of SCF (stem cell factor) is produced and the cells also contain the growth factor receptor for this molecule. Therefore, continuous growth signaling occurs.

Ras signaling and cancer

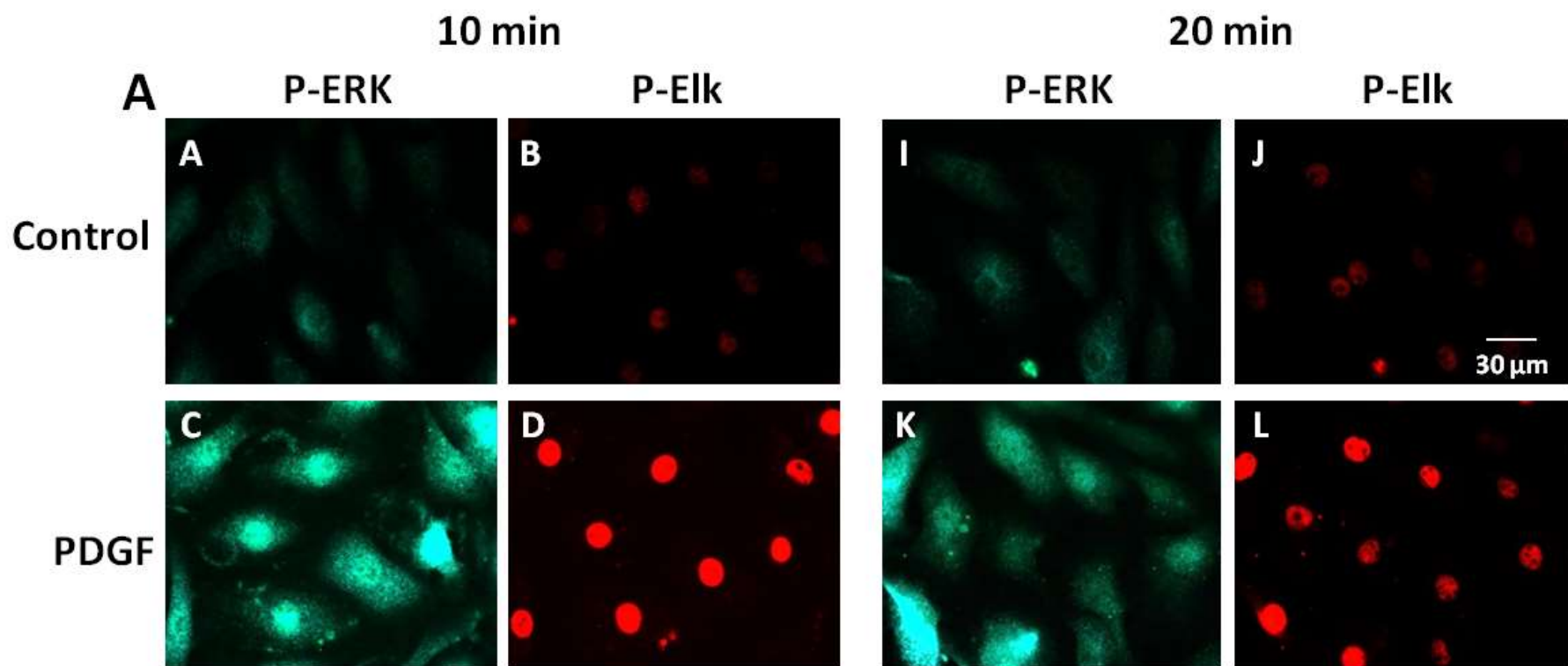
Many mistakes
in this pathway
have been
identified.



Grb>Sos>Ras>Raf

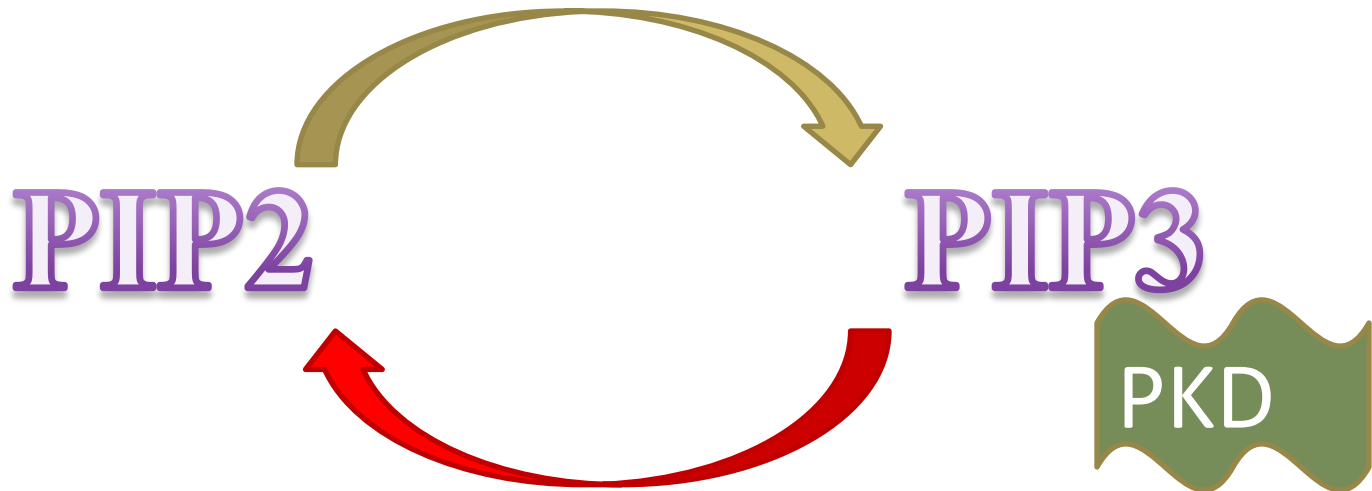
Fos ← Ets ← MAPK ← MAPKK

Grb>Sos>Ras>Raf> MAPKK>MAPK>ETS



PI3K > PIP2 > PKD > Akt...

PI3K (Adds phosphate)



(Removes phosphate)

Types of genes that get mutated

- Oncogenes – gain of function (accelerators)
 - Hybrid proteins that change function
 - Over-production of a protein
 - Activity increases
 - **CANCER ONLY NEEDS ONE BAD COPY**
- Suppressor – loss of function (brakes)
 - They can't stop growth
 - **USUALLY YOU LOSE BOTH GENES** if there is a defect leading to cancer

Massive changes in the nucleus

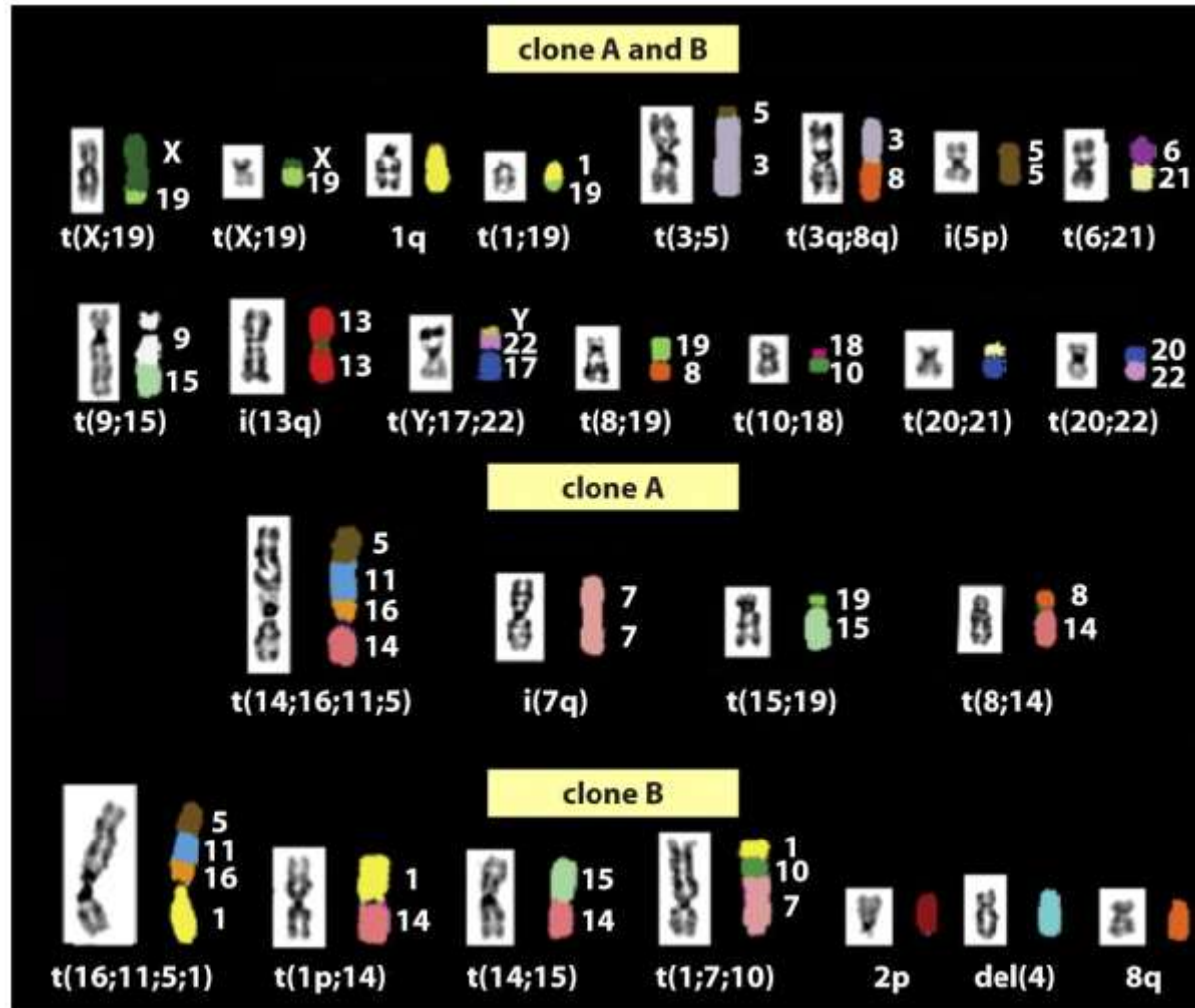


Figure 10-38 The Biology of Cancer (© Garland Science 2007)

Translocations, duplications, deletions

Early Chemotherapy

- Targets – rapidly growing cells.

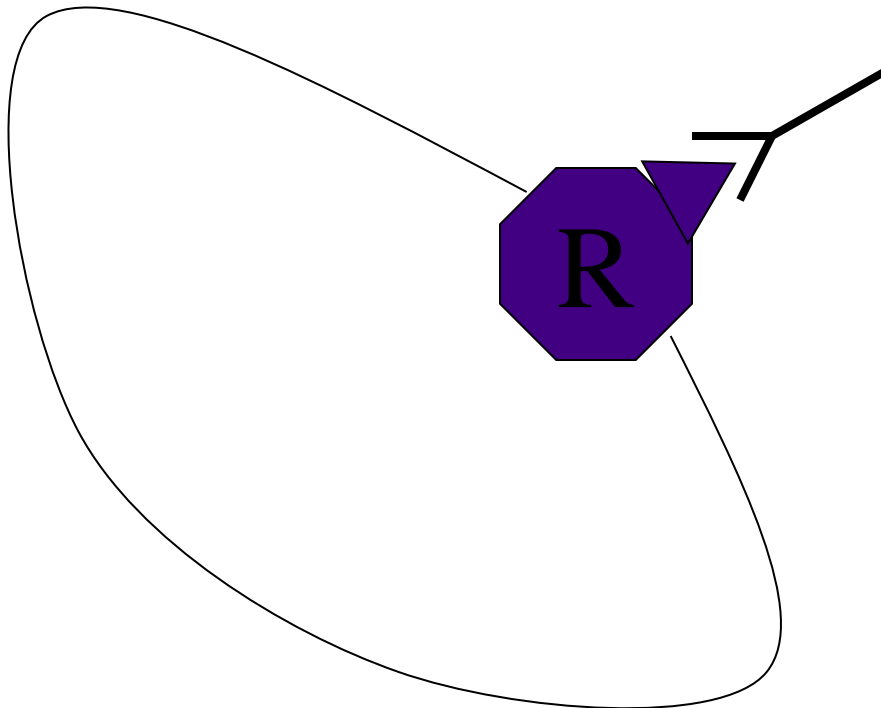
Small molecules ~~to~~ ATP, etc.

NTP ~~to~~ dNTP

dNTPs ~~to~~ DNA

Drug Antibodies

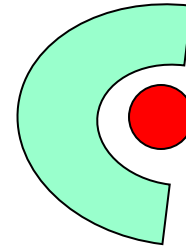
- Antibodies against growth factor receptors or mutated overactive forms of the receptors.



- ✓ Antibodies might recruit the immune system
- ✓ Antibodies might block ligand binding to remaining receptors
- ✓ Antibodies might block receptor function

Small molecule drugs

- Small molecule inhibitors.



- Some of these small molecule drugs are initially effective, but cancer cells can sometimes acquire mutations that make them less effective over time. Some cancer cells make pumps to dump the drugs back out.

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/>