Cancer and Oncogenes
Bioscience in the 21st Century

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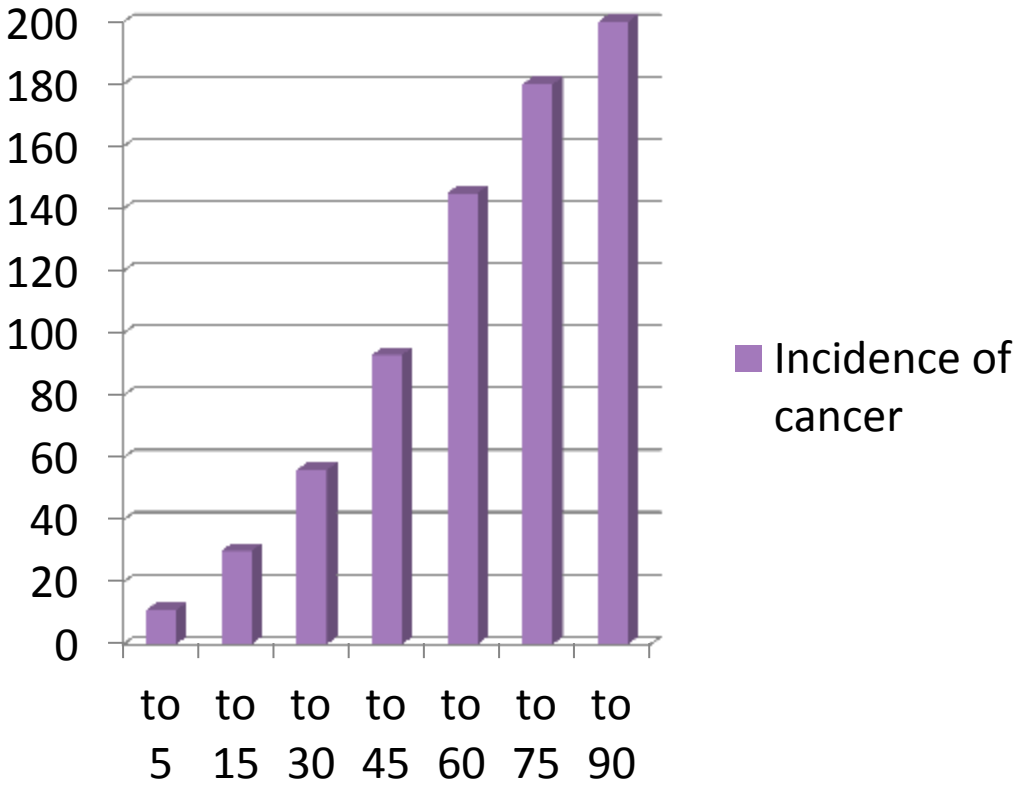
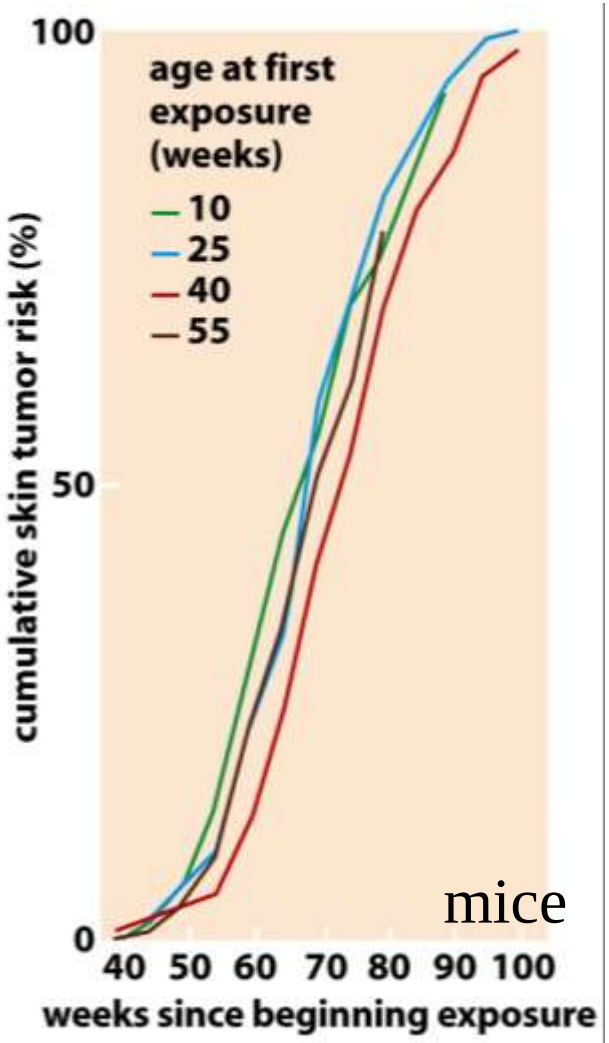
October 11, 2013

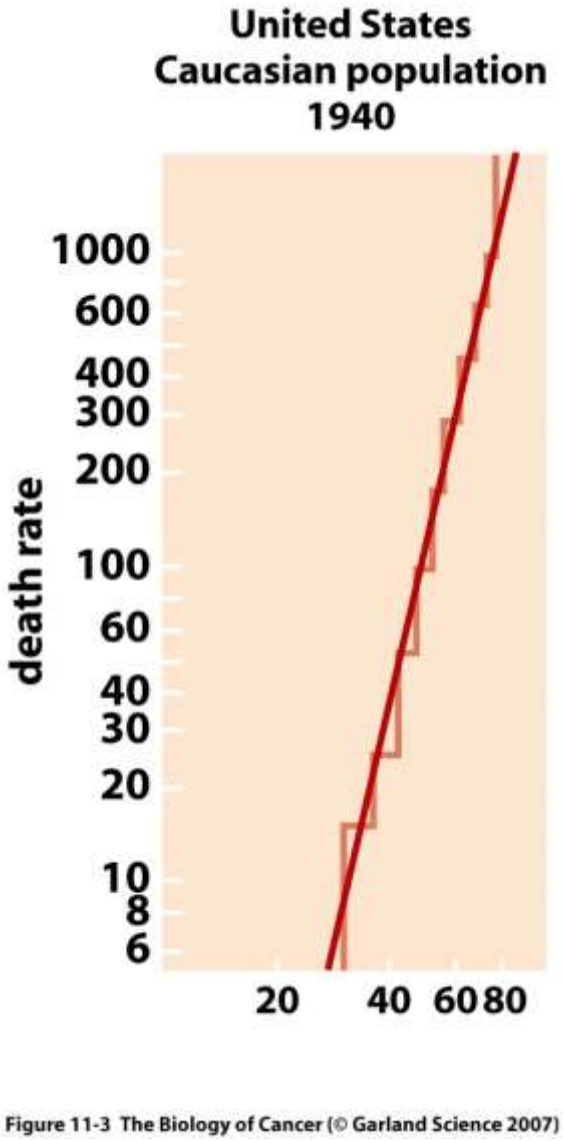
- Just a Few Numbers
- Becoming Cancer
- Genetic Defects
- Drugs

Our friends and family



Other similar data





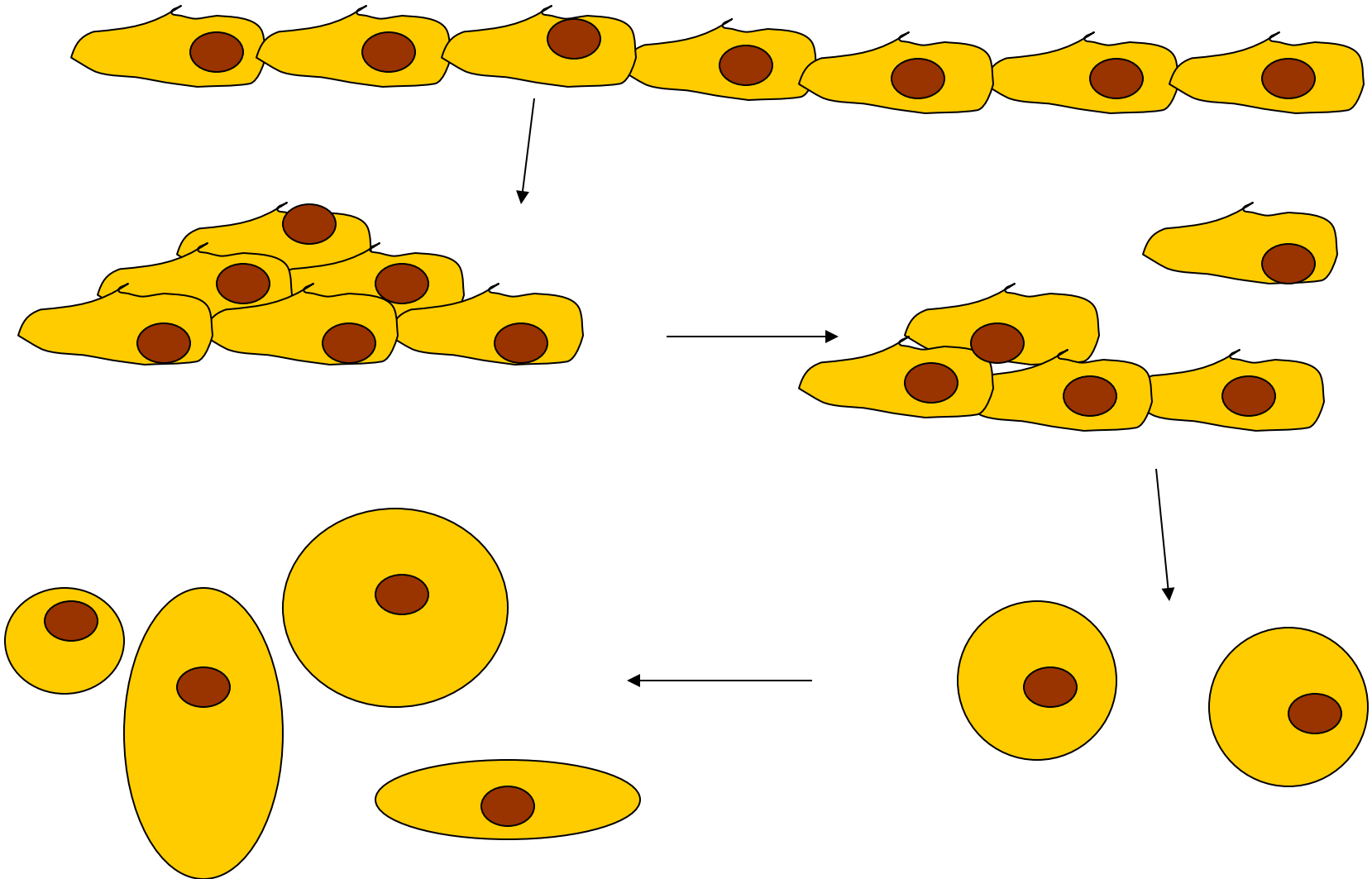
Weinberg, the Biology of Cancer

Figure 11-3 The Biology of Cancer (© Garland Science 2007)

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.

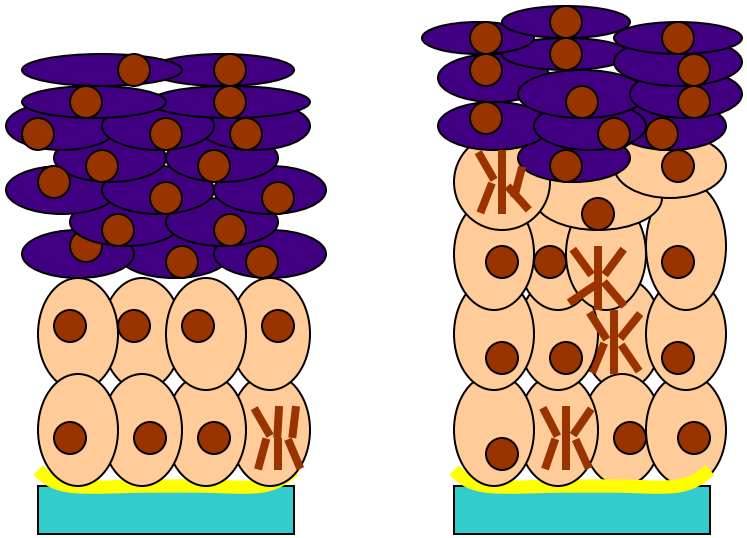
Evolution of a cancer cell



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

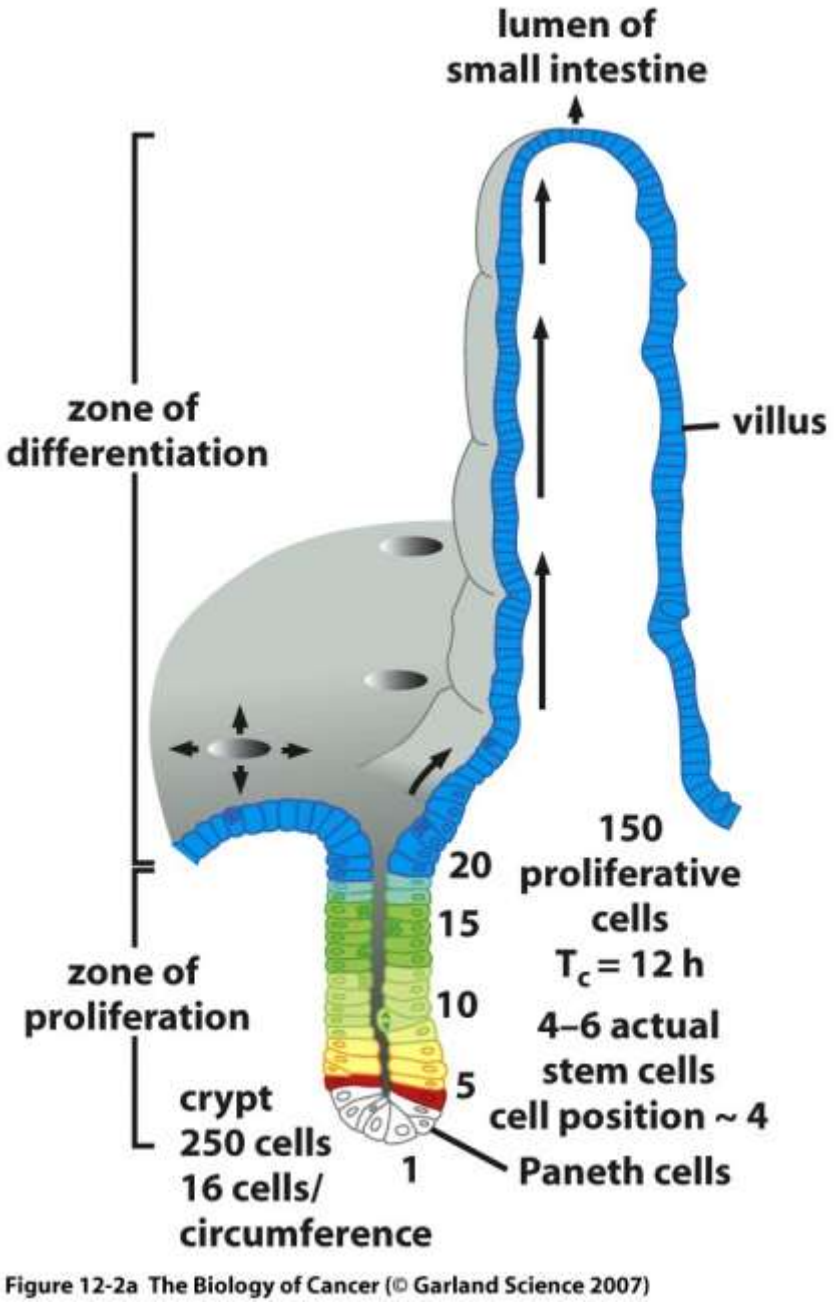
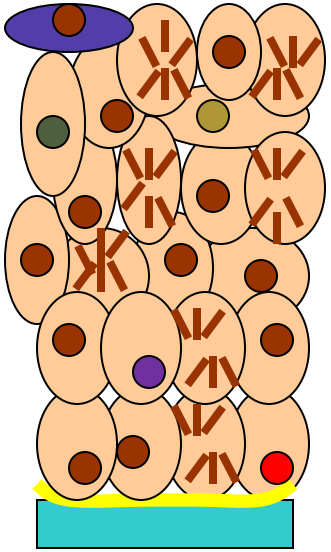


Figure 12-2a The Biology of Cancer (© Garland Science 2007)

Carcinoma

Increased cell proliferation

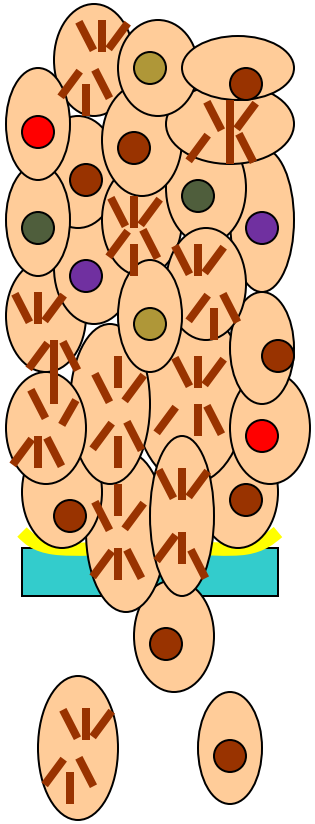
Additional possible changes here include decreased ability to catch mistakes



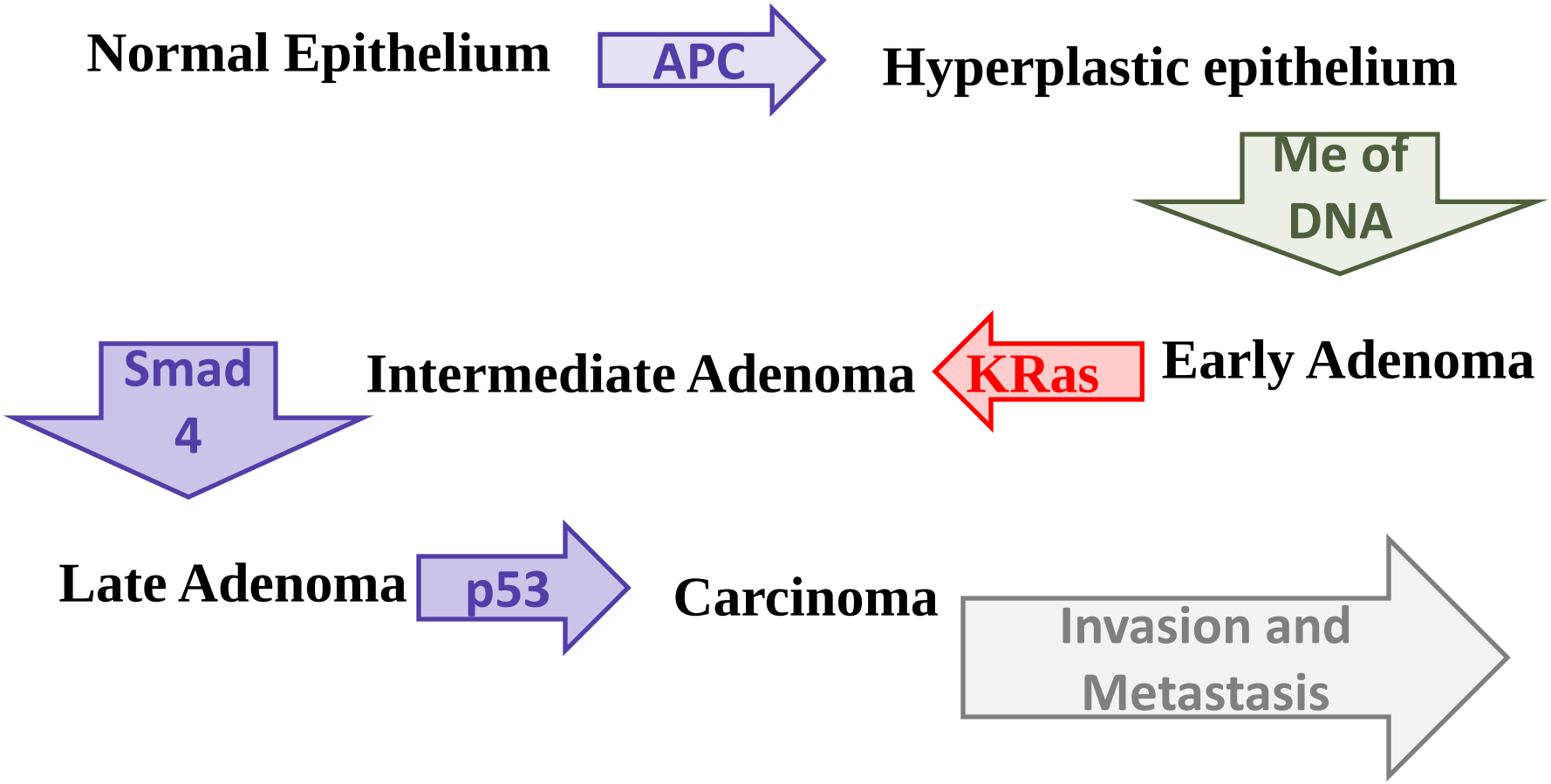
Malignant

Epithelial to mesenchymal transition.

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



One pathway


Normal Epithelium
APC
Hyperplastic epithelium
Me of DNA
Smad 4
Intermediate Adenoma
KRas
Early Adenoma
Late Adenoma
p53
Carcinoma
Invasion and Metastasis

Cancer Evolution

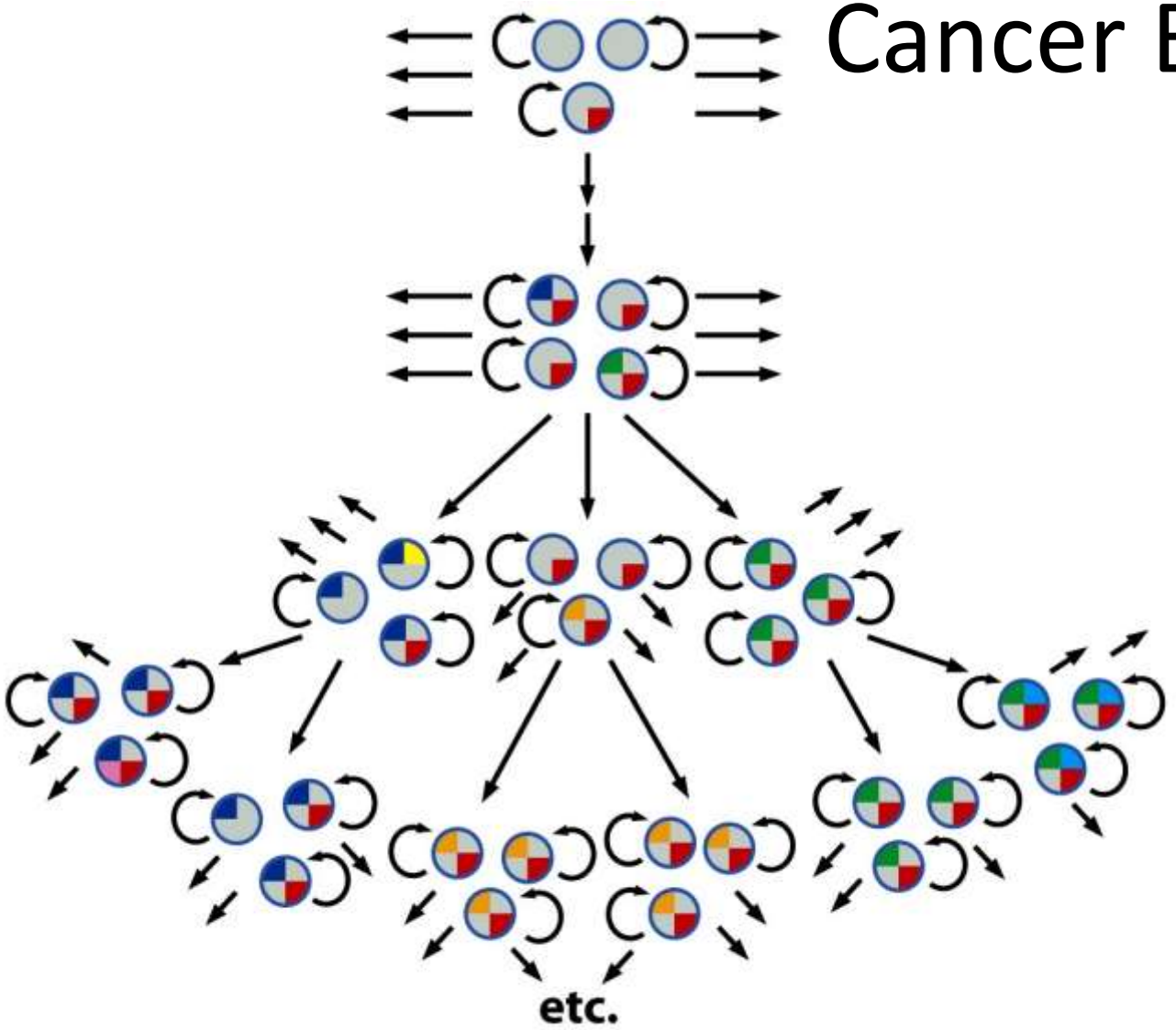
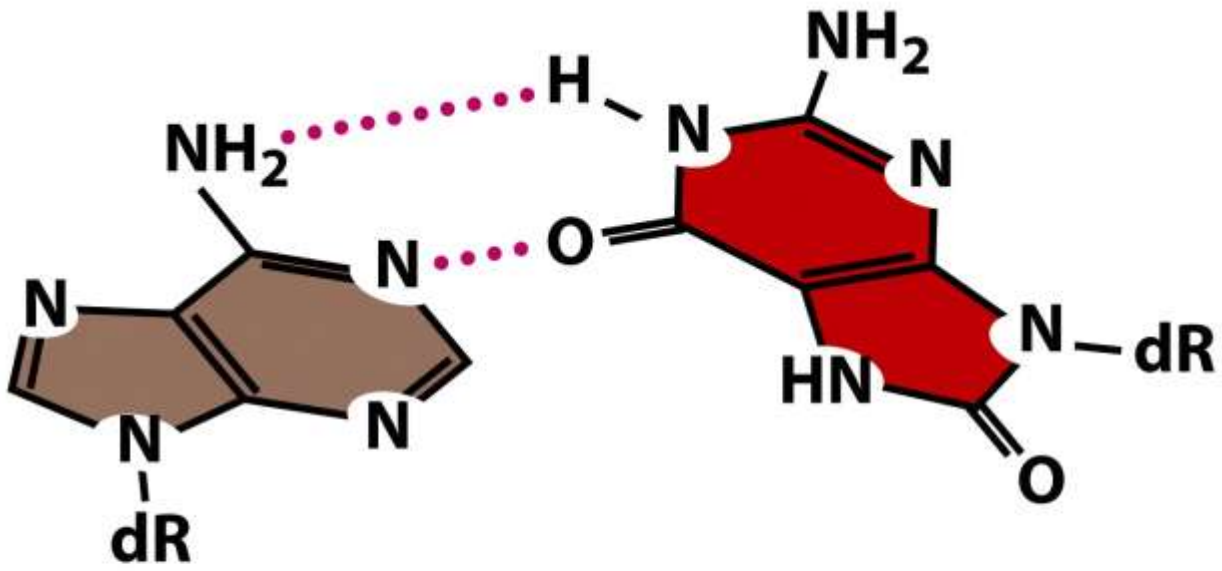


Figure 11-18 The Biology of Cancer (© Garland Science 2007)

http://scienceblog.cancerresearchuk.org/2012/08/03/the-queen-in-the-hive-scientists-find-more-evidence-for-cancer-stem-cells/

Oxidative damage outcomes



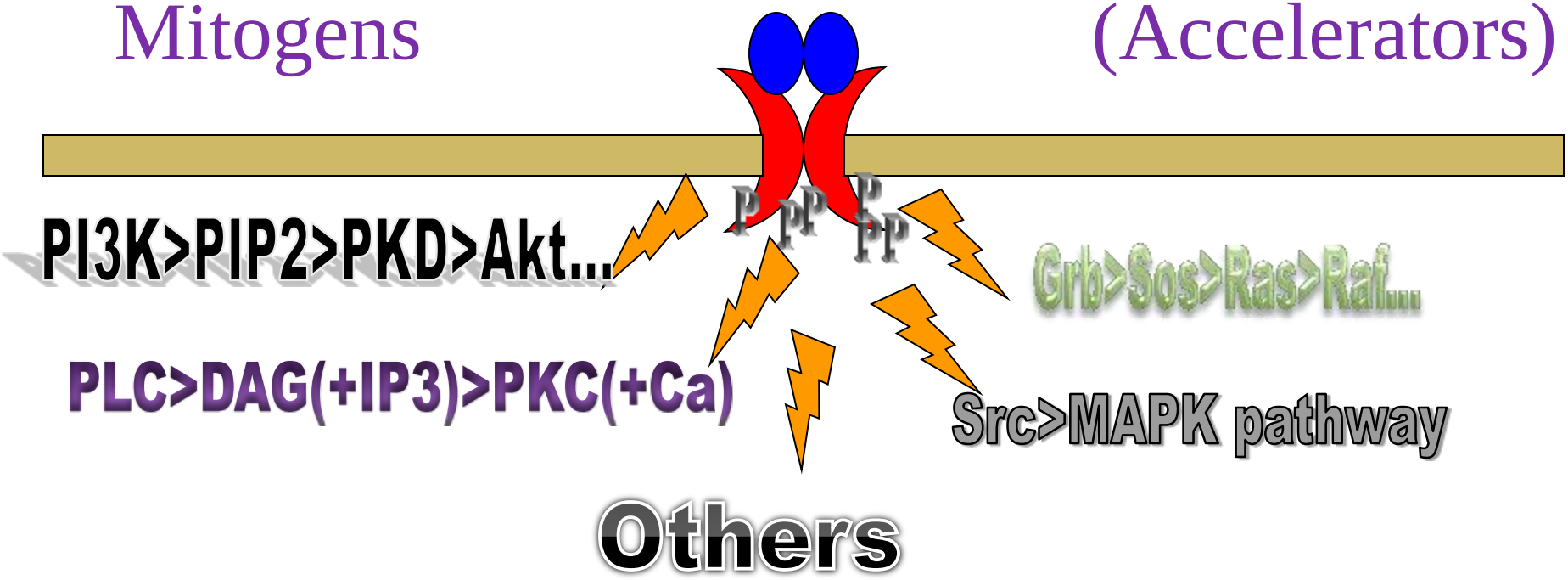
mispairing of 8-oxo-dG with deoxyadenosine (dA)

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

But repair enzymes fix most problems

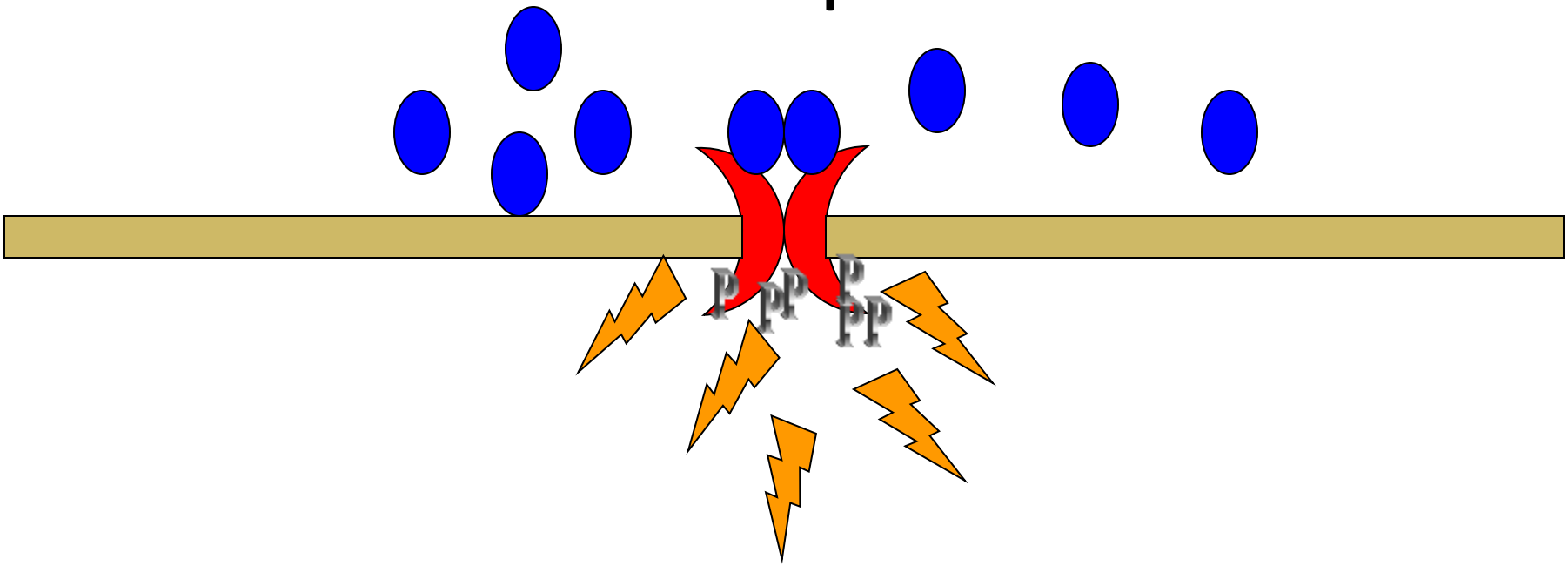
- If you cannot fix the all of the DNA damage, mistakes accumulate more rapidly and cancer usually starts earlier.
- An example when repair is not complete is individuals with Li-Fraumeni syndrome whose cells do not recognize damage (faulty p53).
- Another example is Xeroderma Pigmentosum, where patients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

Growth factors and the cell cycle



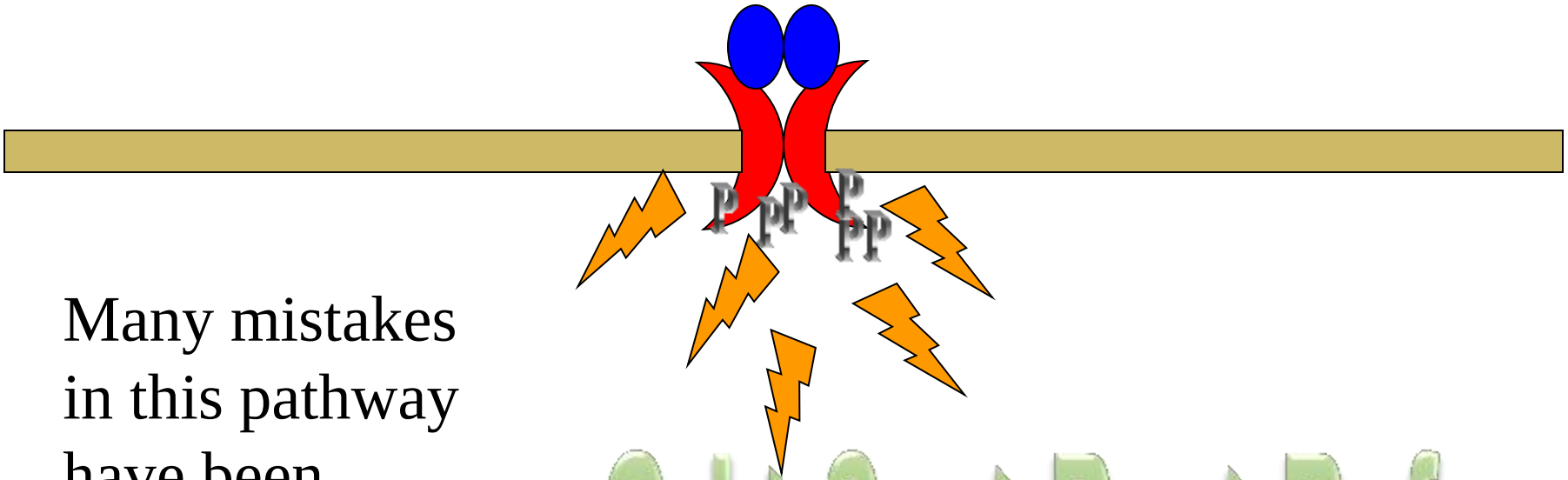
Together these pathways control a complicated set of events that result in a balance of proteins and other factors leading to cell growth and division.

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

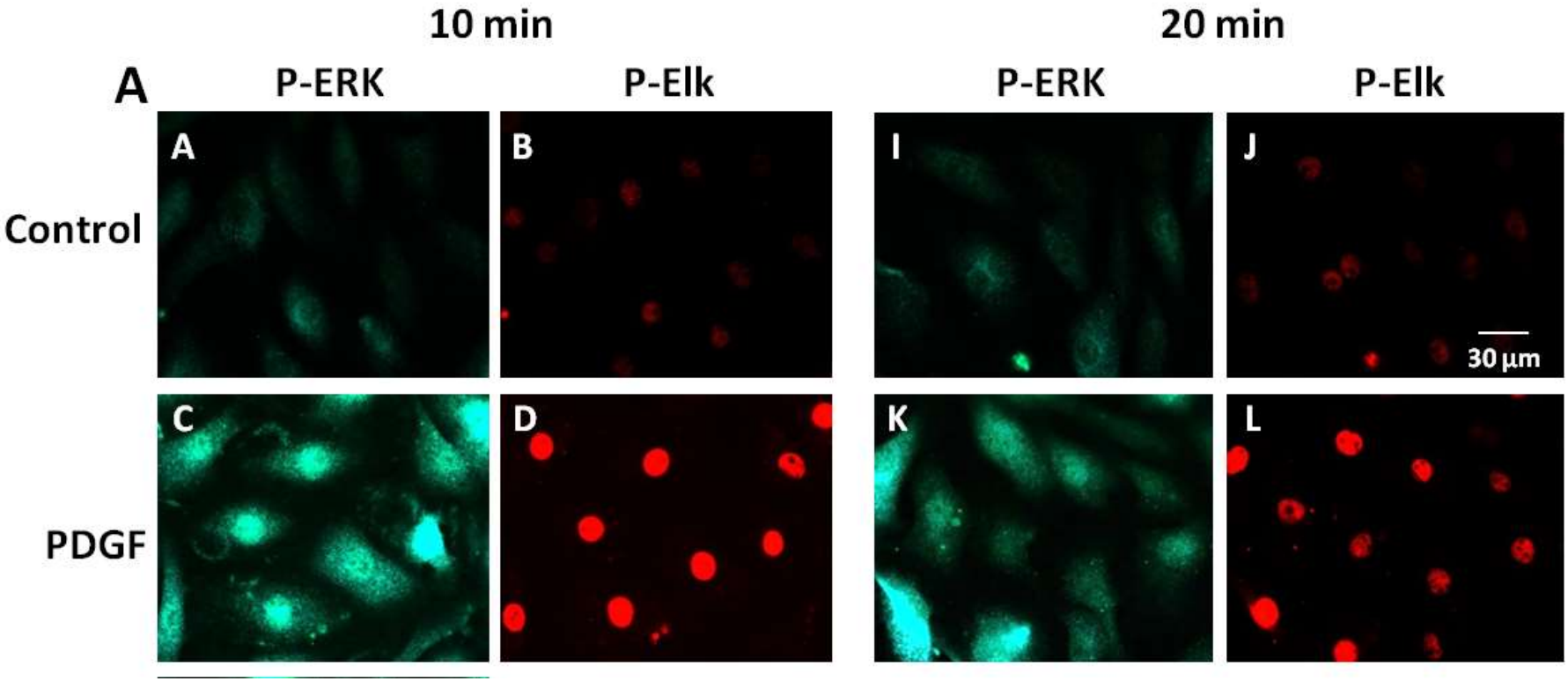


Many mistakes in this pathway have been identified.

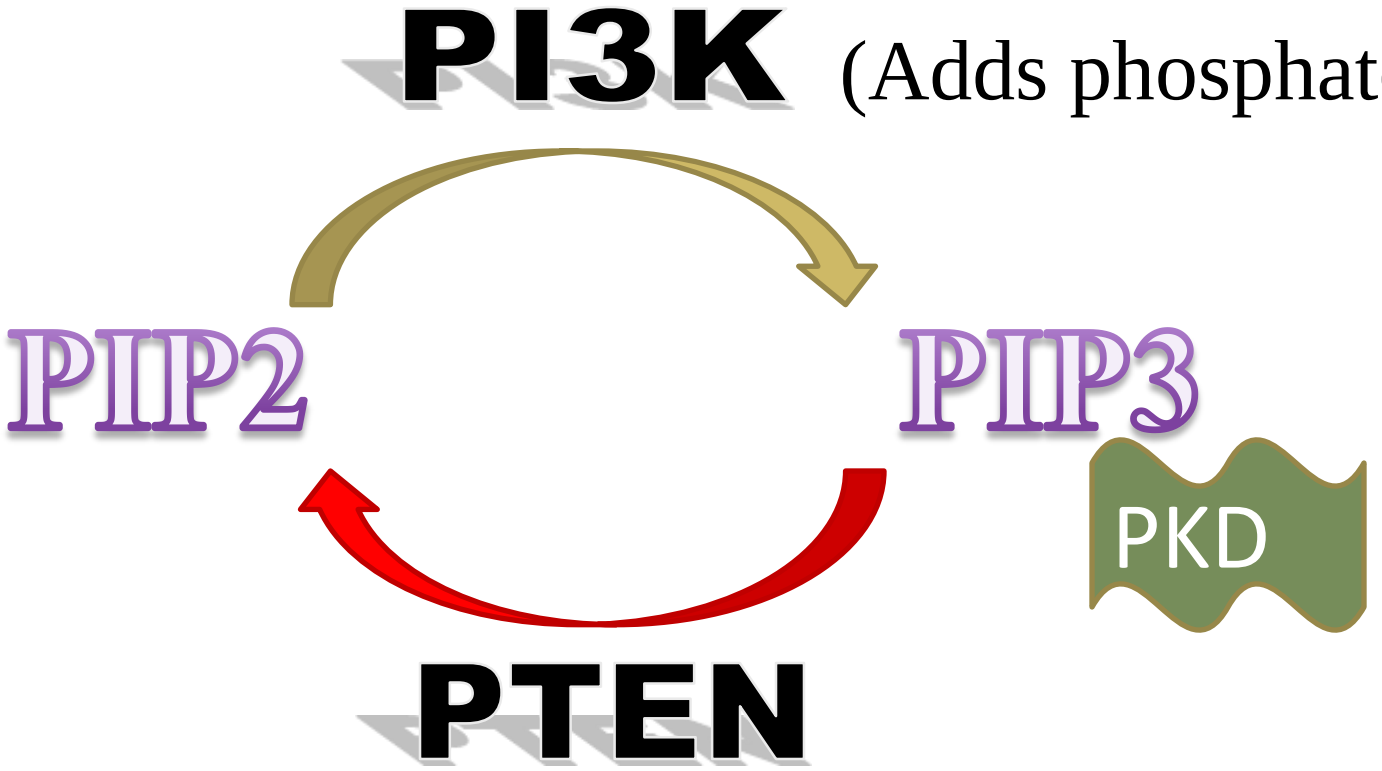
Grb>Sos>Ras>Raf

Fos ⟵ Ets ⟵ MAPK ⟵ MAPKK

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



PI3K>PIP2>PKD>Akt...



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

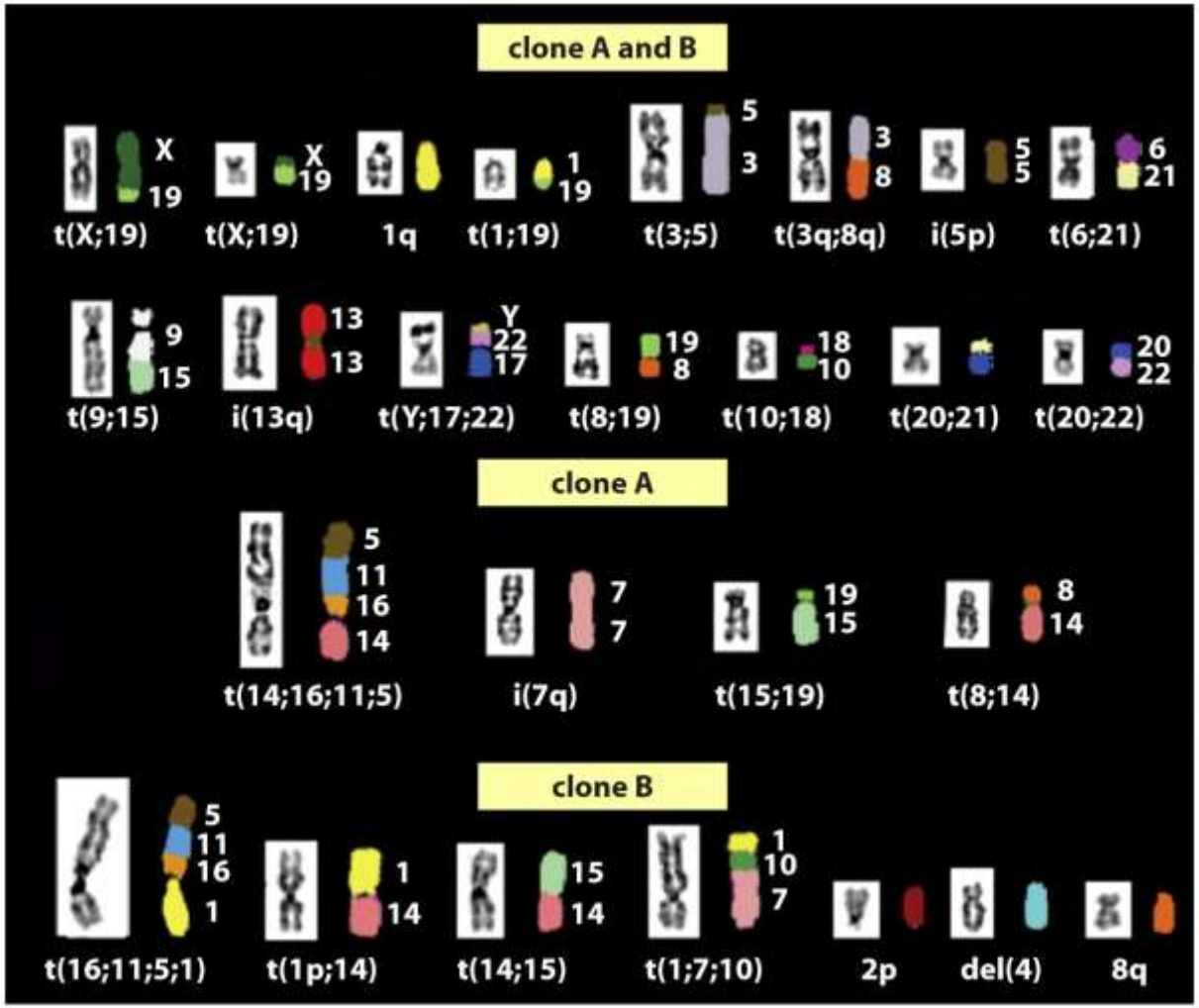
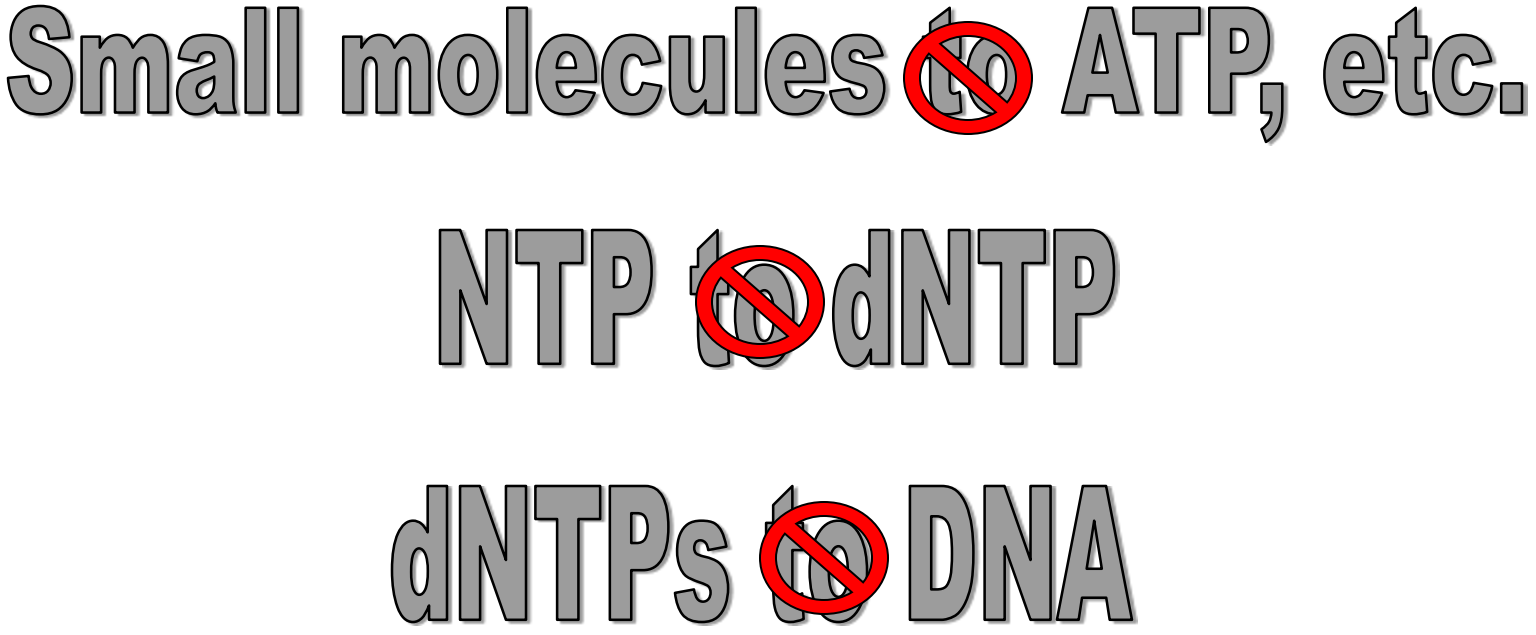


Figure 10-38 The Biology of Cancer (© Garland Science 2007)

Translocations, duplications, deletions

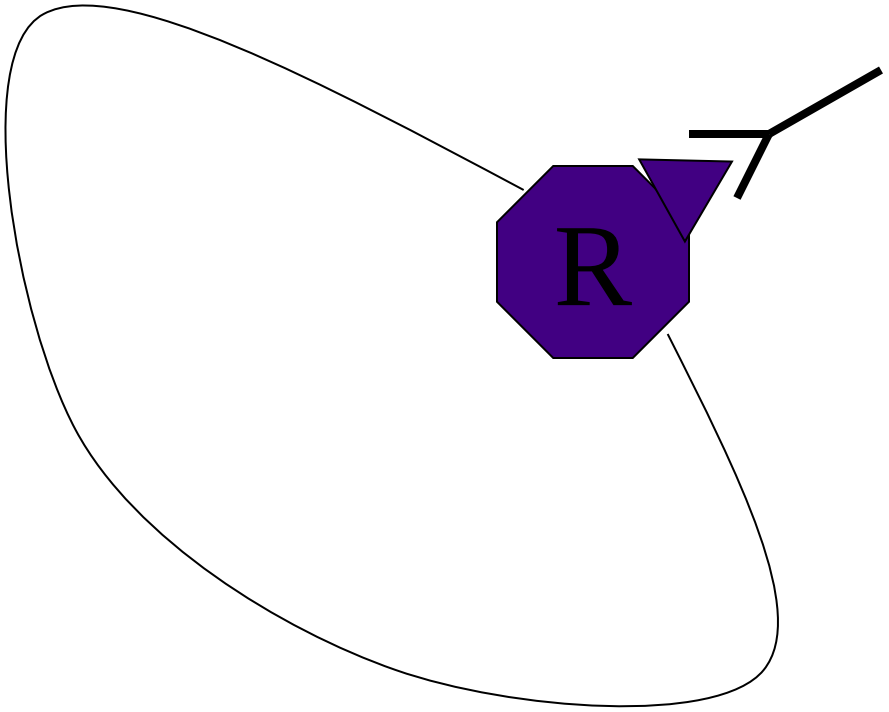
Early Chemotherapy

- Targets – rapidly growing cells.



Drug Antibodies

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



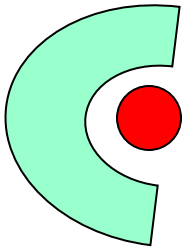
✓Antibodies might recruit the immune system

✓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/