

# Introduction to Systems Biology of Cancer

## Lecture 1

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DREAM Challenges



Bathsheba at Her Bath,  
Rembrandt van Rijn, 1654

The dark shadow in the left  
breast may be a cancer.

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# What is Cancer?

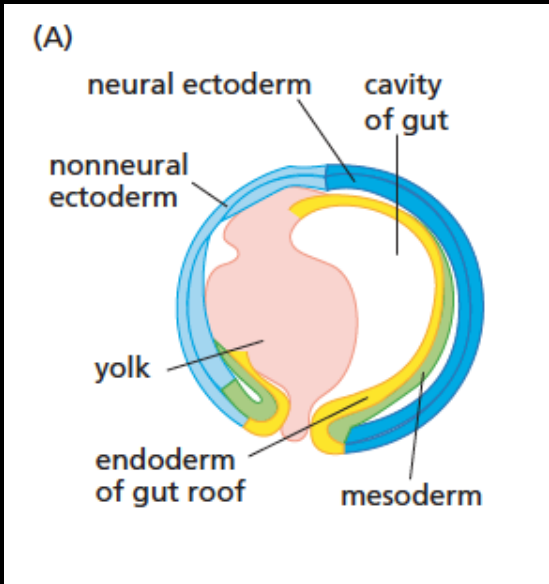
# Big picture view

- Cancer is a pathology characterized by uncontrolled cell growth (in the case of solid tumors) and invasion.
- Leukemia is a liquid tumor that originates from hematopoietic cells
- Cancer can be benign and malignant.
  - Benign tumors: uncontrolled growth but non-invasion
  - Malignant tumors are invasive and can migrate to other organs (metastasis). 90% of cancer deaths are due to metastasis.
- Cancer can affect most of the tissues in the body.

# Classification of Cancer

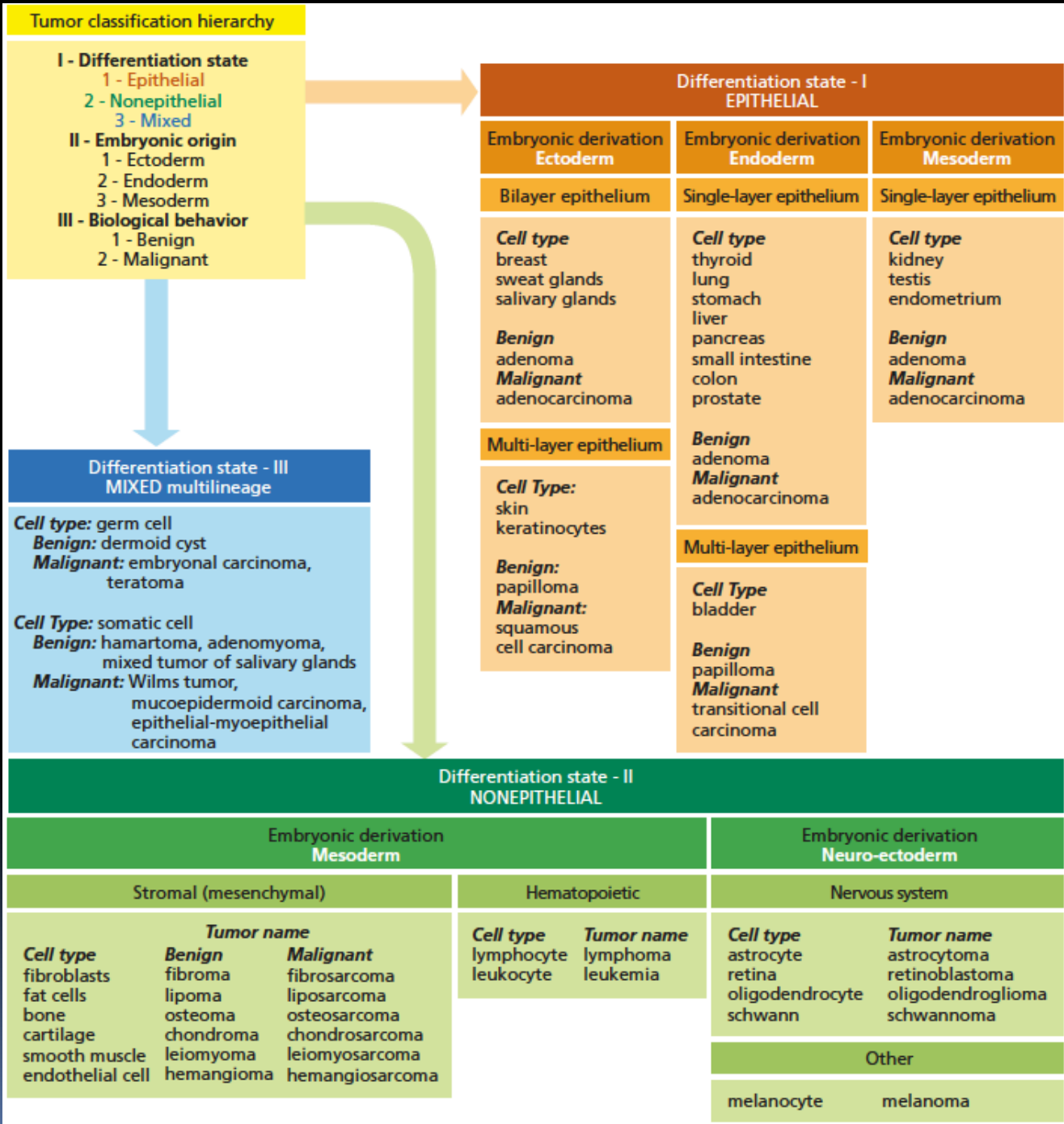
- Derive from epithelial normal cells (80%):
  - Carcinomas (breast, ovary, cervix, prostate, lung, pancreas, colon, etc.)
- Arise from non-epithelial normal cells:
  - Derive from connective or supportive tissue (bone, cartilage, fat, muscle, blood vessels): Sarcomas
  - Derive from hematopoietic tissues (blood forming cells): Lymphomas and Leukemias
  - Derive from Central and Peripheral nervous system: Gliomas, Neuroblastoma, Schwannomas and Meduloblastomas

# Embryonic Cell Layers



All tissues of higher organisms develop from 3 embryonic compartments:

Ectoderm,  
Mesoderm,  
Endoderm

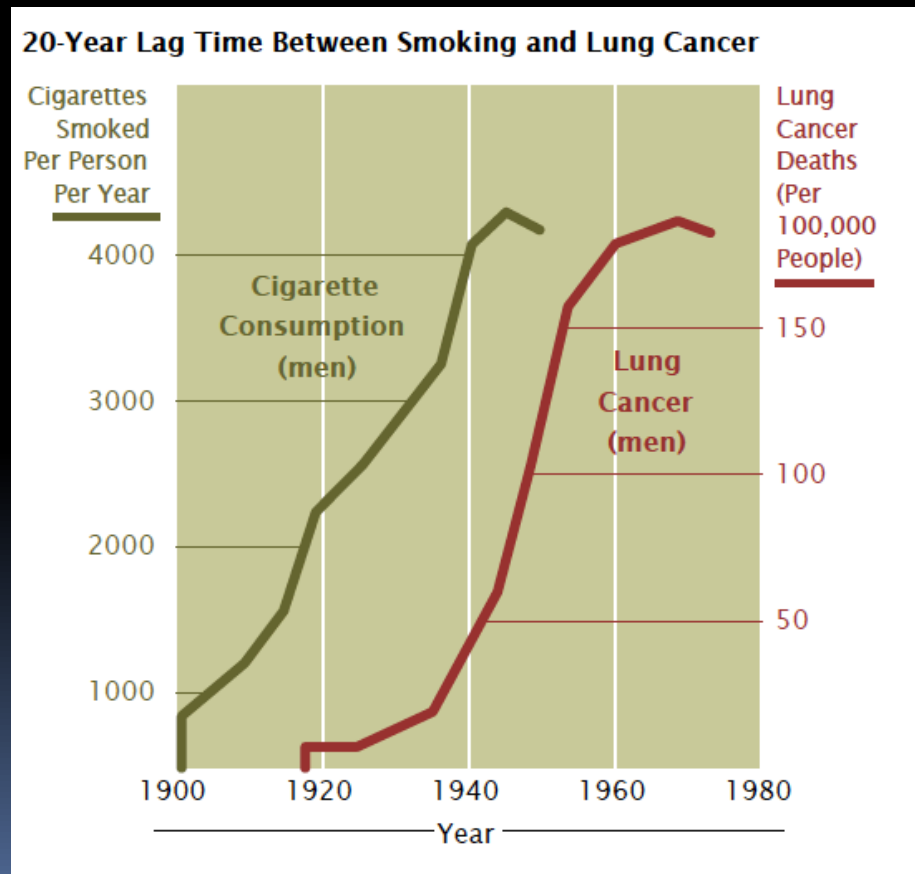


# Facts about a killer

- Cancer is the second killer disease (second to heart disease)
- Kills more than AIDS, malaria and tuberculosis combined (1 of 8 deaths is due to cancer)
- By 2030 it is anticipated that there will be 17 million deaths a year.
- Breast cancer affects 1 woman out of 9 during a life span

# Facts about a killer

- ~25% of cancer deaths are due to tobacco



# History of the name

- The first mention of cancer was documented in Egypt around 1600 BC. The Edwin Smith Papyrus, found in 1860 in Egypt, described eight cases of ulcers of the breast. The first doctors wrote of the mysterious disease: “There is no treatment!”
- Father of medicine Hippocrates (460-370BC) described cancer and gave it the greek name karkinos (crab).
- Roman phylosopher Celsus (25BC-50AD) translated it into latin as cancer (latin for crab).
- Greek physician Galen (130-200AD) used the greek term onkos (meaning masses or swelling) to refer to malignant tumors.
- In the 1500’s the word Tumor started to be used. It comes from the latin (tumere) and means to swell



# Causes of cancer in history

## Blame it on God

- Ancient Egyptians blamed cancers on the gods.

## Humoral theory

- Hippocrates thought that the body had 4 *humors* (body fluids): blood, phlegm, yellow bile, and black bile. Too much or too little of any of the humors caused disease. An excess of black bile in various body sites was thought to cause cancer.
- Galen's embraced this theory, which remained the unchallenged standard through the Middle Ages for over 1,300 years. During this period, the study of the body, including autopsies, was prohibited for religious reasons.

# Causes of cancer in history

## **Blastema theory**

- In 1838, German pathologist Johannes Muller demonstrated that cancer is made up of cells and not fluids, but he believed that cancer cells did not come from normal cells. Muller proposed that cancer cells developed from budding elements (blastema) between normal tissues.
- His student, father of cellular pathology Rudolph Virchow (1821-1902), determined that all cells, including cancer cells, are derived from other cells.

## **Trauma theory**

- From the late 1800s until the 1920s, trauma was thought by some to cause cancer. This belief was maintained despite the failure of injury to cause cancer in experimental animals.

# Causes of cancer in history

## **Infectious disease theory**

- In the 17th and 18th centuries, some believed that cancer was contagious. The first cancer hospital in France was forced to move from the city in 1779 because people feared cancer would spread throughout the city. Although human cancer, itself, is not contagious, we now know that certain viruses, bacteria, and parasites can increase a person's risk of developing cancer.

# Modern Development of Cancer Causes

## Chemical Carcinogenesis

- In 1915, Katsusaburo Yamagiwa and Koichi Ichikawa at Tokyo University, induced cancer in lab animals for the first time by applying coal tar to rabbit skin.

THE JOURNAL OF CANCER RESEARCH, VOL. III, NO. 1

EXPERIMENTAL STUDY OF THE PATHOGENESIS OF CARCINOMA<sup>1</sup>

KATSUSABURO YAMAGIWA AND KOICHI ICHIKAWA

*From the Pathological Institute of the Medical College of the Imperial University, Tokyo, Japan*

Received for publication, May 24, 1917

*A. The result with regard to the rabbits in four earlier experiments which have survived over 70 days*

NUMBER OF RABBITS AND EARS IN EACH EXPERIMENT		NUMBER OF EARS BEARING FOLLICULO-EPITHELIOMA AMONG THE SURVIVING RABBITS	PERCENTAGE RESULT BETWEEN 2 AND 3
Rabbits	Ears		
15	23	20	<i>per cent</i> 87
6	6	4	67
7	13	7	54
10	10	1	10

*B. The result with regard to rabbits which have survived over 150 days*

9	13	13	100
3	3	3	100
4	7	7	100
6	6	1	17

- Many more years passed before tobacco was “rediscovered” as the most destructive source of chemical carcinogens known to man.

# Modern Development of Cancer Causes

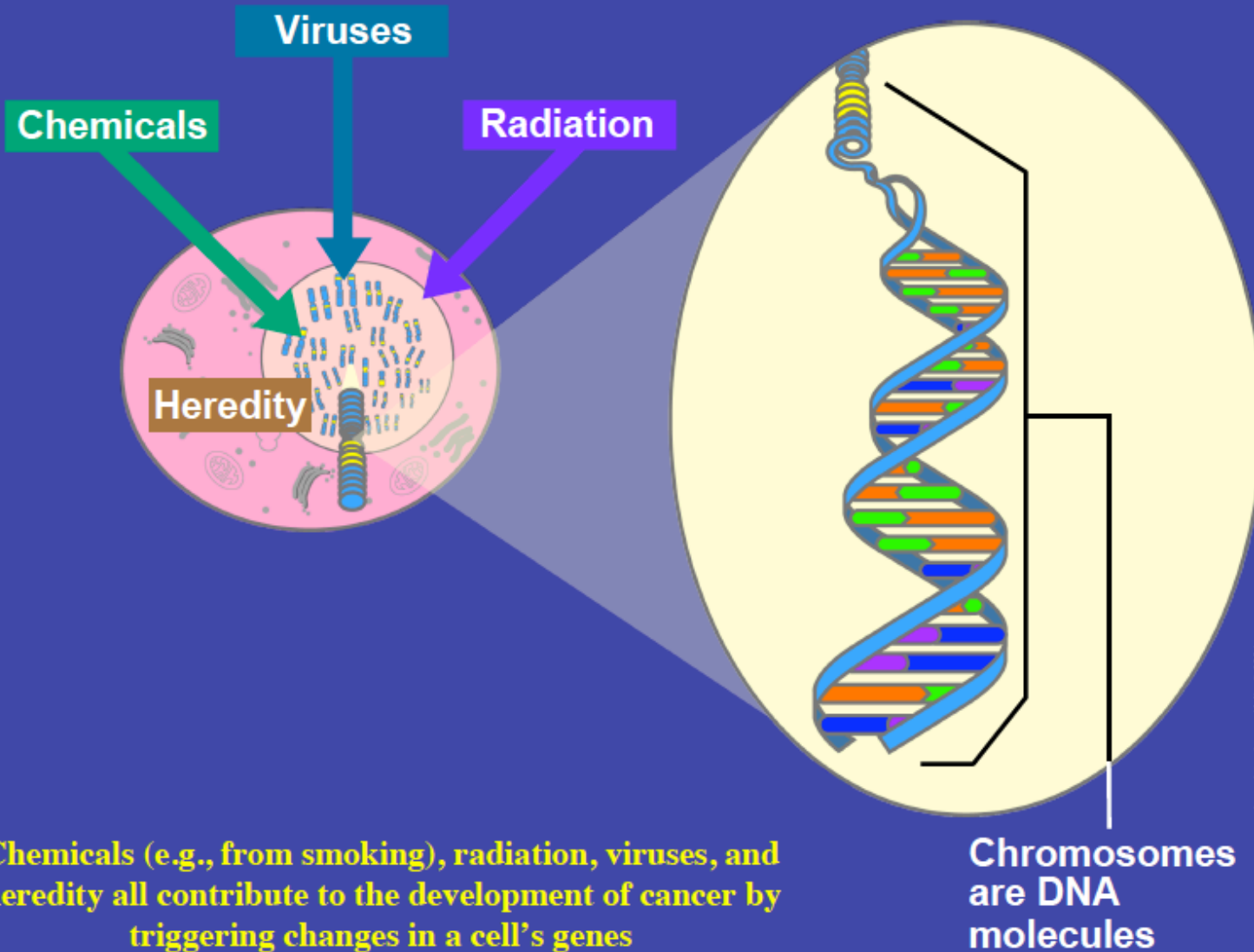
## Viral Carcinogenesis

- In 1911, Peyton Rous, at the Rockefeller Institute in New York, described a type of cancer (sarcoma) in chickens caused by what later became known as the Rous sarcoma virus. He was awarded the Nobel Prize for that work in 1968.
- Several viruses are now linked to cancer in humans, for example:
  - Long-standing infection with the hepatitis B or C viruses can lead to cancer of the liver.
  - People with HIV have greater increased risk of developing several cancers, especially Kaposi sarcoma and non-Hodgkin lymphoma.
  - Human papilloma viruses (HPVs) have been linked to many cancers, especially those of the cervix, vulva, vagina, anus, and penis. Today there are vaccines to help prevent HPV infection.
  - In the developing world nearly 20% of cancers are due to infections such as hepatitis B, hepatitis C, and human papillomavirus (HPV)

# Cancer is a disease of the genome

- In 1953 Watson and Crick elucidated the structure and function of the DNA. Molecular biology was born and
- As the understanding of DNA and genes increased, it was clear that chemicals and radiation, or the introduction of new DNA sequences by viruses, often led to DNA damage.
- This damage, it was found, mapped to the same genes affected in families who had hereditary predisposition to cancer (10 - 15% of cancers).
- Most of the things that caused cancer (carcinogens) caused genetic damage (mutations) that looked a lot like the mutations that could be inherited and could result in the same types of cancer if more mutations were introduced.
- During the 1970s, scientists discovered 2 particularly important families of genes related to cancer oncogenes and tumor suppressor genes.

# Genes and Cancer



# Accumulation of alterations

- Cancer onset is characterized by an accumulation of alterations (caused by aging, tobacco, chemical agents, radiation, viruses, etc.) that generate
  - Chromosome rearrangements
  - Amplifications and deletions
  - Point mutations
- Some of these mutations are passenger mutations: generating any trouble
- Other mutations hit cancer critical genes.



# Accumulation of alterations

- COSMIC: Catalogue of Somatic Mutations in Cancer  
<http://cancer.sanger.ac.uk/census> (572 entries)
  - Cancer Gene Census: lists genes whose mutations are causal
  - >1% of all human genes are implicated via mutation in cancer.  
~90% have somatic mutations in cancer
  - ~20% bear germline mutations that predispose to cancer
  - 10% show both somatic and germline mutations.

# COSMIC Database

[Home](#) ▾[About](#) ▾[Licensing](#) ▾[Data Download](#) ▾[News](#) ▾[Help](#) ▾[Login](#) ▾[Census](#) **[Breakdown](#)** [Abbreviations](#)Show [All](#) ▾ entriesSearch:  [?](#)

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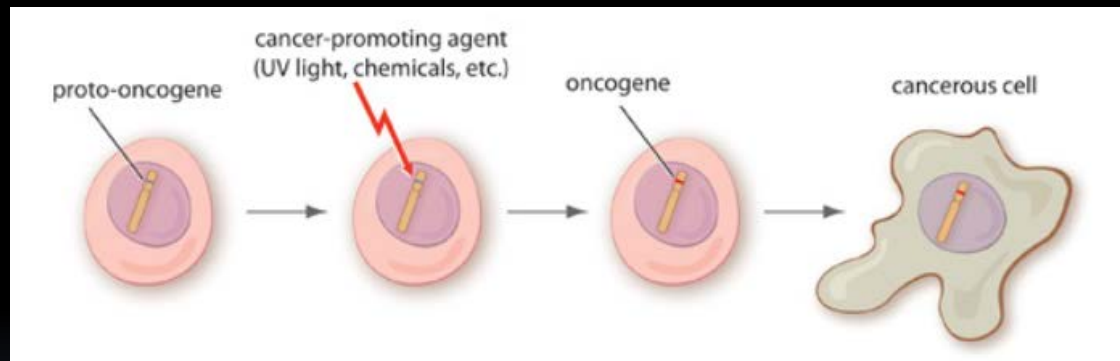
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<a href="#">Frameshift Mutations</a>	131
<a href="#">Gene Symbol</a>	573
<a href="#">Germline Mutations</a>	88
<a href="#">Large Deletions</a>	39
<a href="#">Missense Mutations</a>	198
<a href="#">Nonsense Mutations</a>	117
<a href="#">Other Mutations</a>	35
<a href="#">Somatic Mutations</a>	534
<a href="#">Splicing Mutations</a>	75
<a href="#">Translocations</a>	355

Showing 1 to 12 of 12 entries

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# Oncogenes

- Normal cellular genes with the potential to become oncogenes are called **proto-oncogenes**
- When a proto-oncogene becomes activated by a genomic alteration, it becomes an **oncogene**



## Possible Genomic Alterations:

Mutation: Point Mutation (SNP) or Insertion

Amplification

Translocation

# Francis Peyton Rous

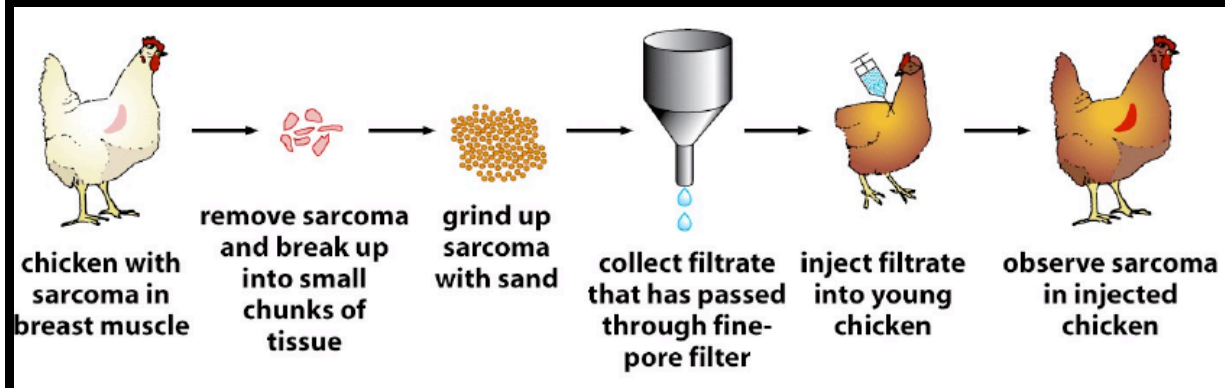
Some **viruses** can transform normal cells



1910

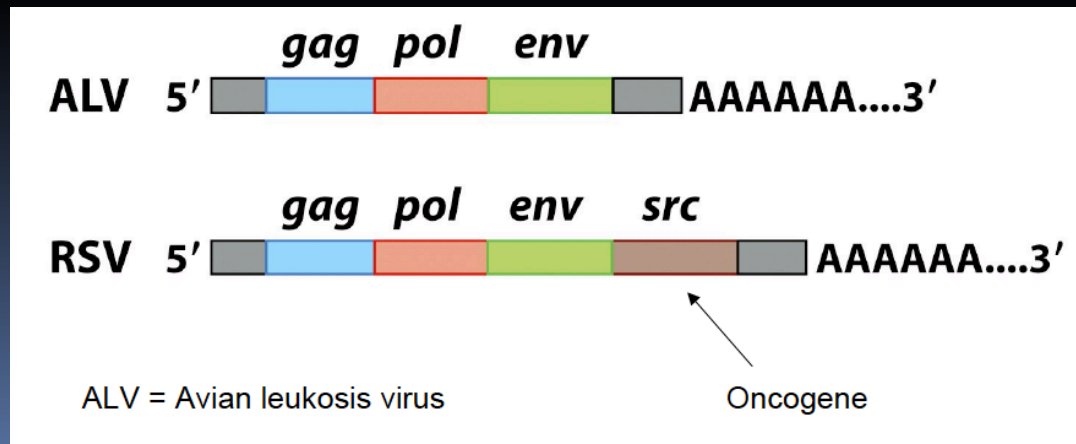


1966  
Nobel prize in  
Physiology and medicine



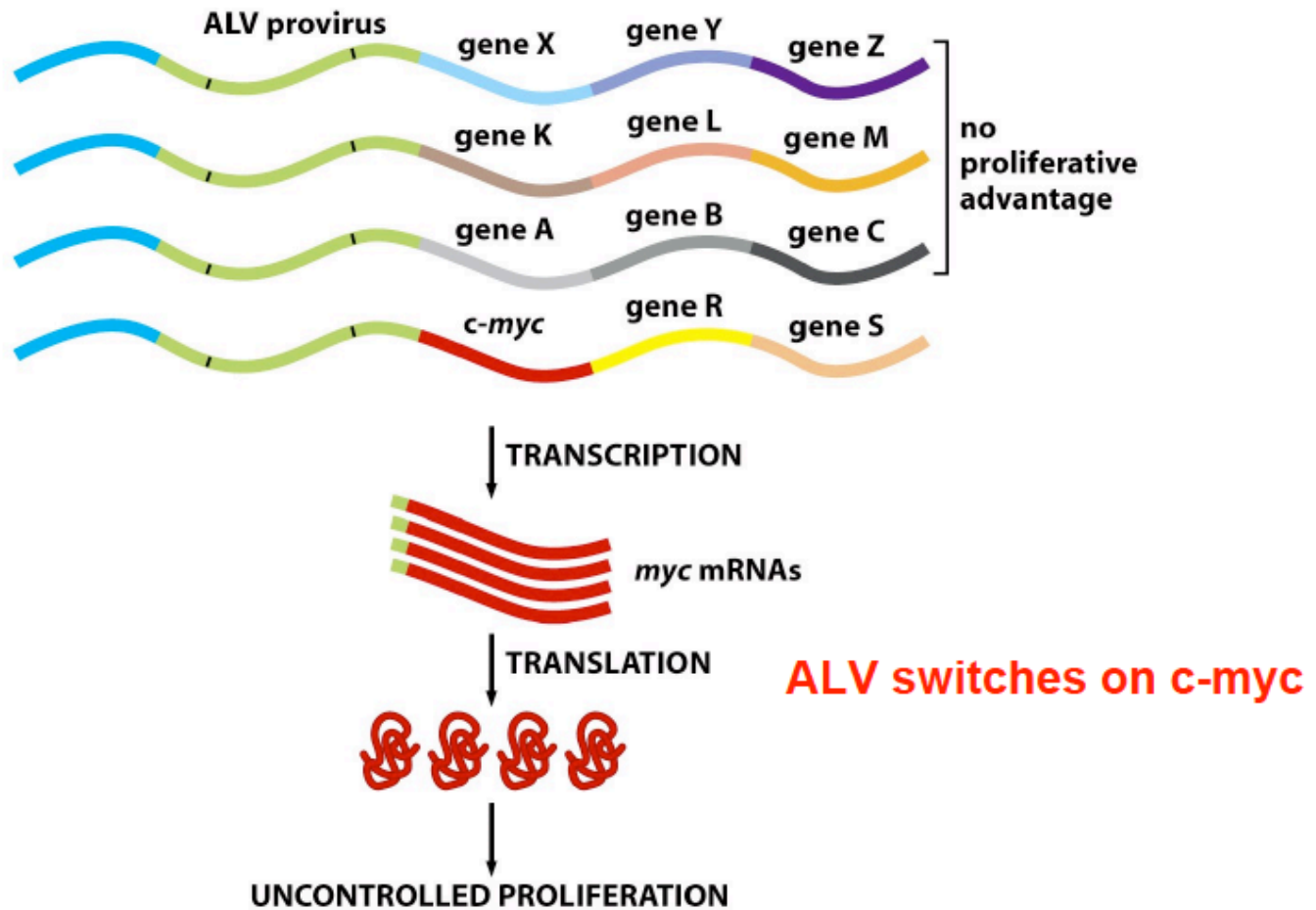
Bishop and Varmus: SRC (the first Oncogene Discovered ~1970) was a host gene that got activated by the virus the first Oncogene.

The cancer gene is in the normal cell: doesn't come from outside!



# Mutagenesis by viral insertion

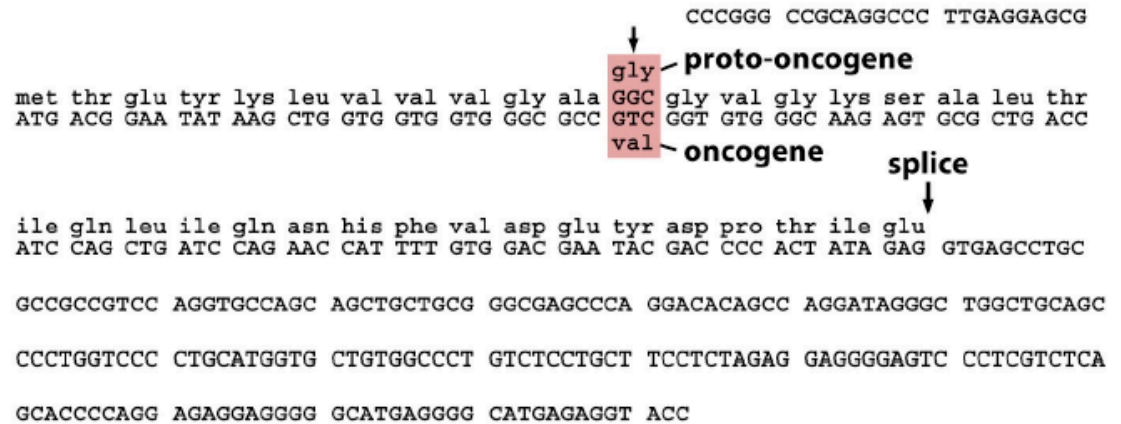
ALV provirus may become integrated with the c-myc oncogene



Point mutations in the RAS gene occurs at a particular codon in the gene in many cancers. It renders it constitutively active

## Activation of oncogenes

### Mutation responsible for H-ras oncogene activation



Human bladder cancer oncogene - 12th codon of H-ras ,mutation converts glycine codon to valine codon

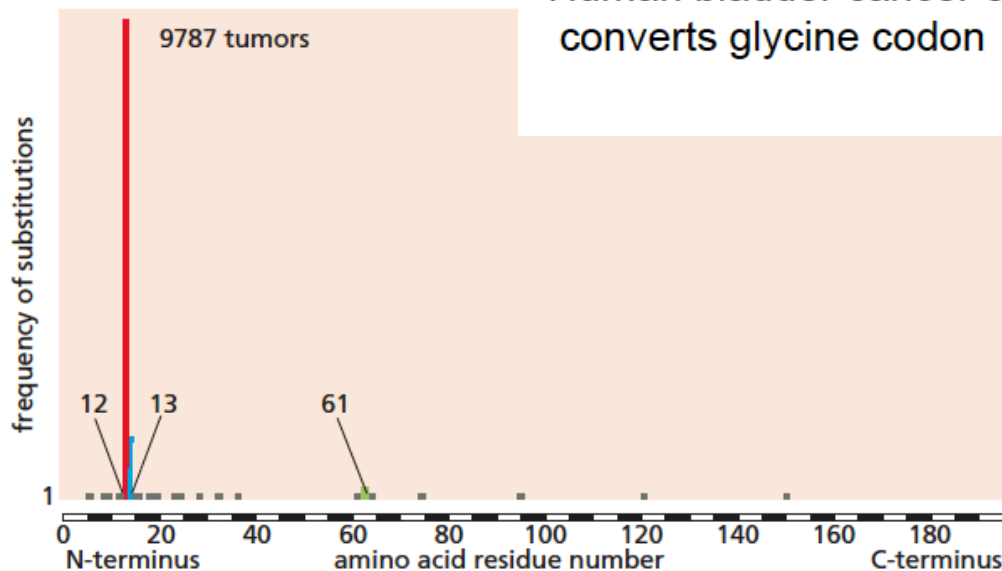
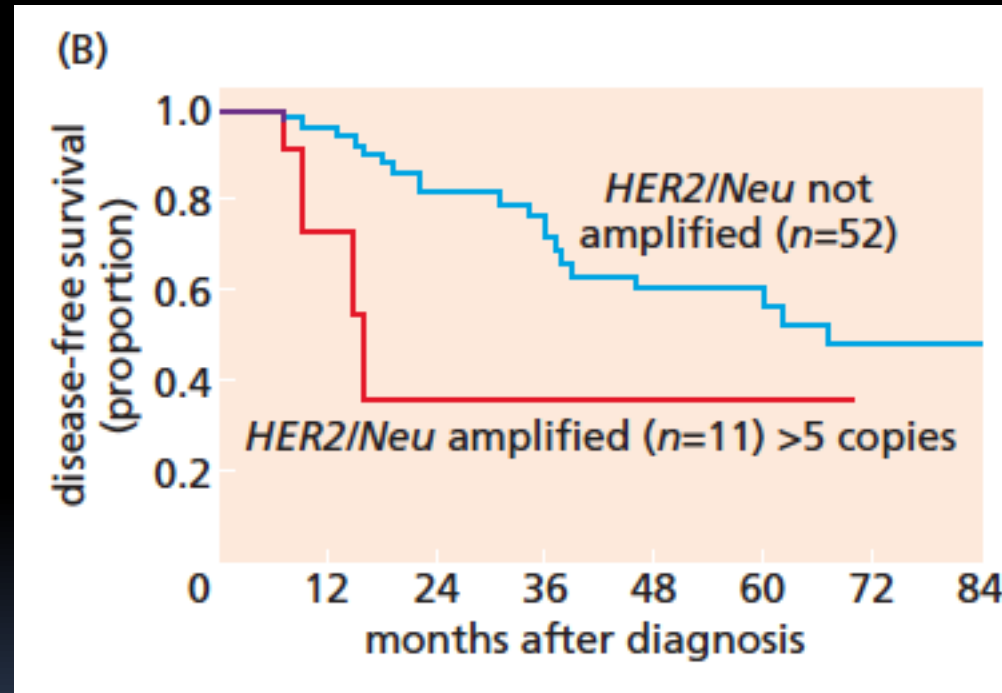
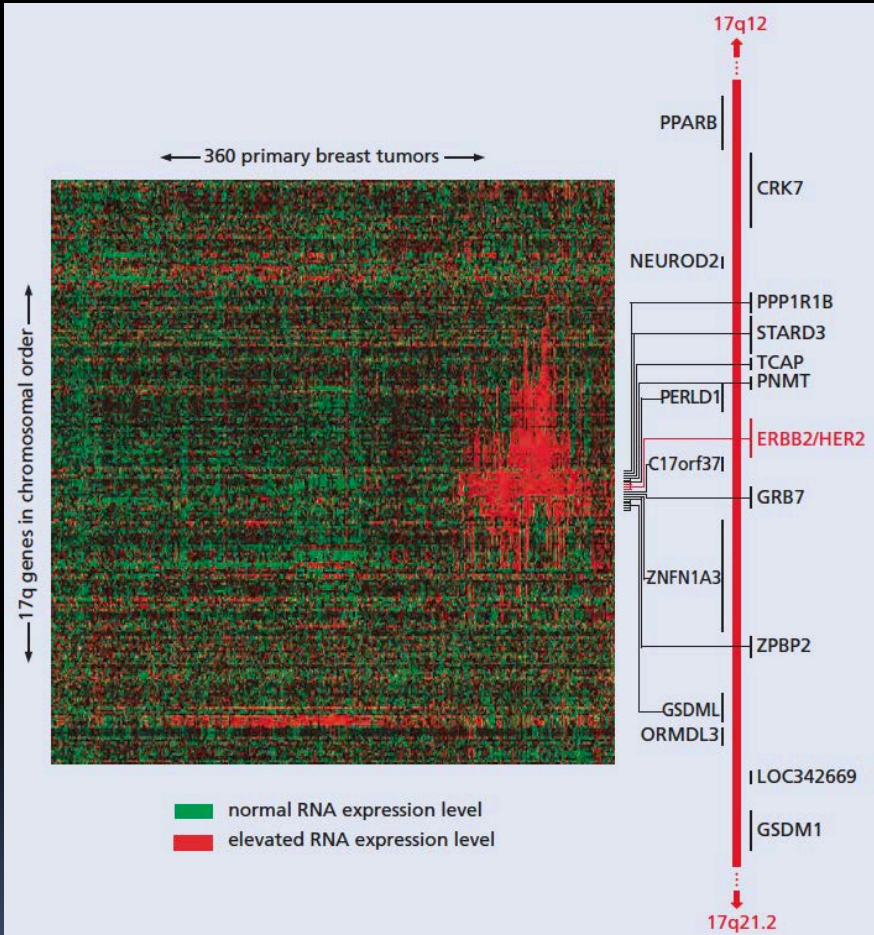


Figure 4.10 *The Biology of Cancer* (© Garland Science 2007)

# Another example of oncogene alteration: Amplification of HER2

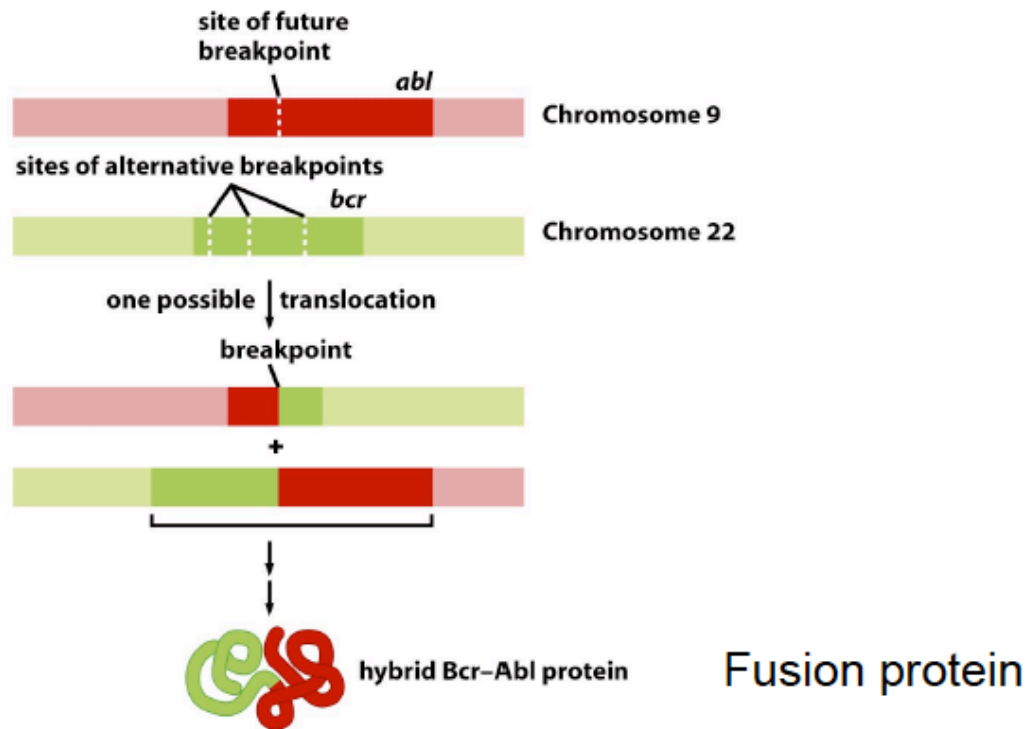
Reported in 1987 for the first time, today we know that HER2 is amplified in 30% of human breast cancers.



While normal cells have ~20,000 HER2 receptors, there may be up to 2.5M receptors in a positive cancer cell (Barillot et al, CSB or Cancer).

# Translocation-mediated oncogene activation

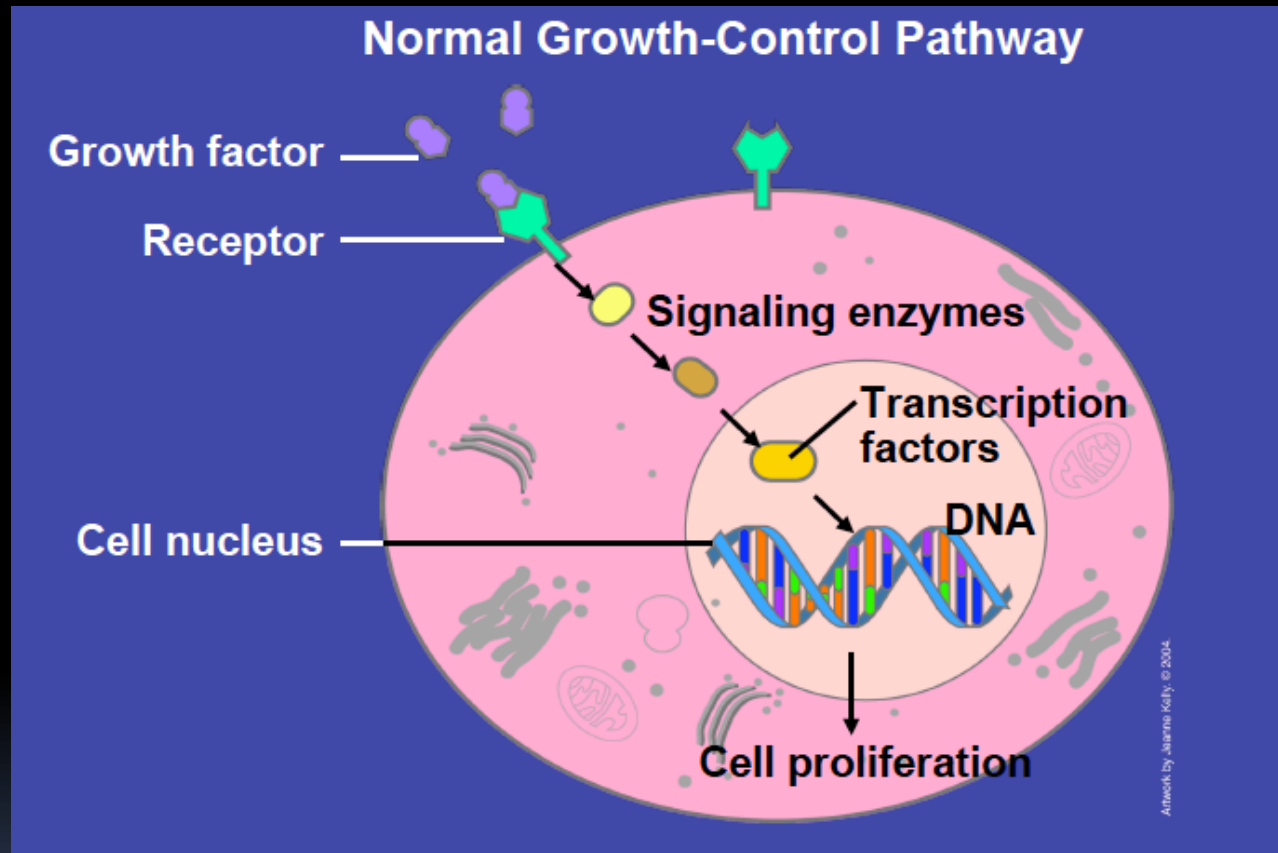
Reciprocal translocations between human Chr 9 (*abl*) and 22 (*bcr*)



Bcr-abl oncogene formation gives rise to acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML) or chronic neutrophilic leukemia (CNL)



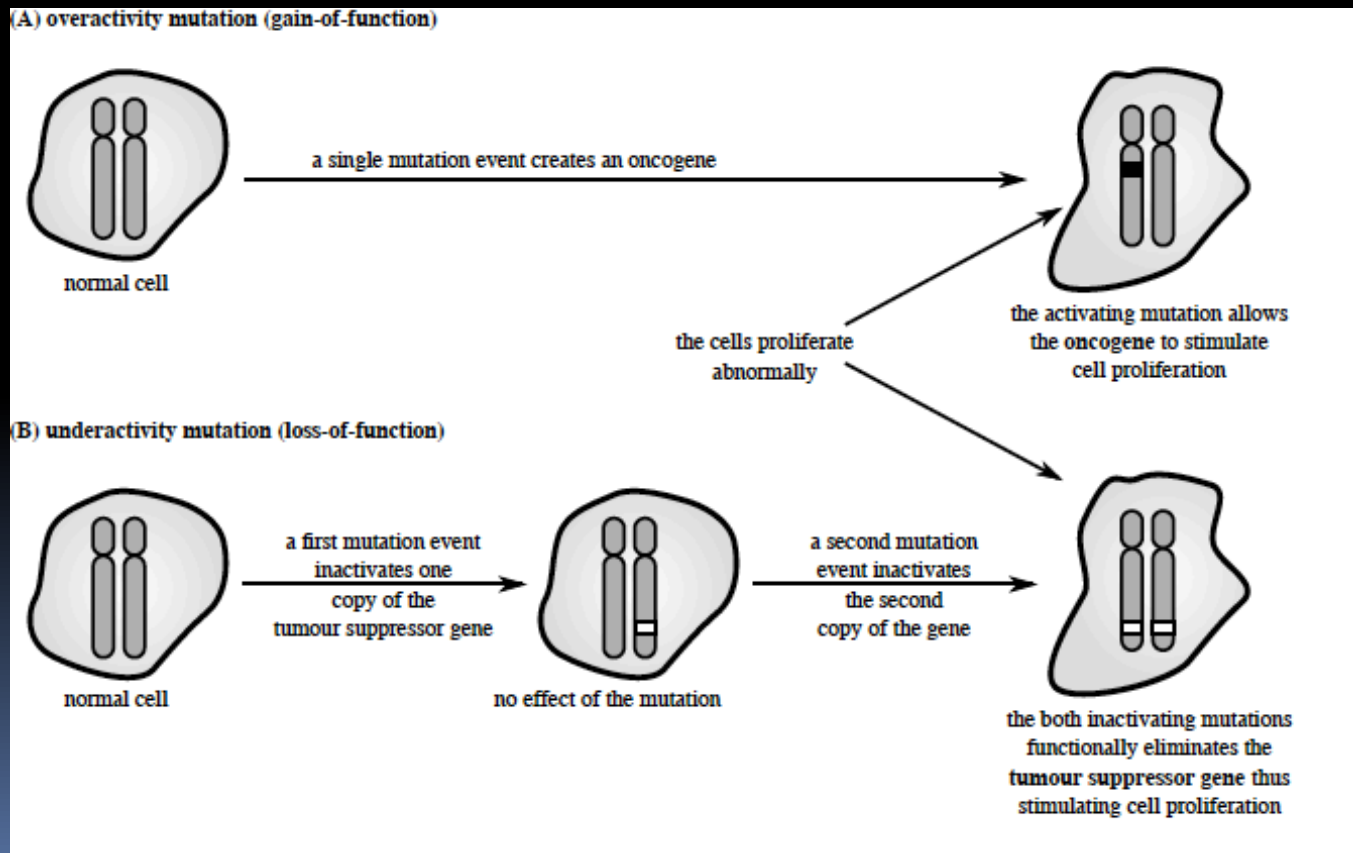
# What role do oncogenes typically play in the normal cell machinery?



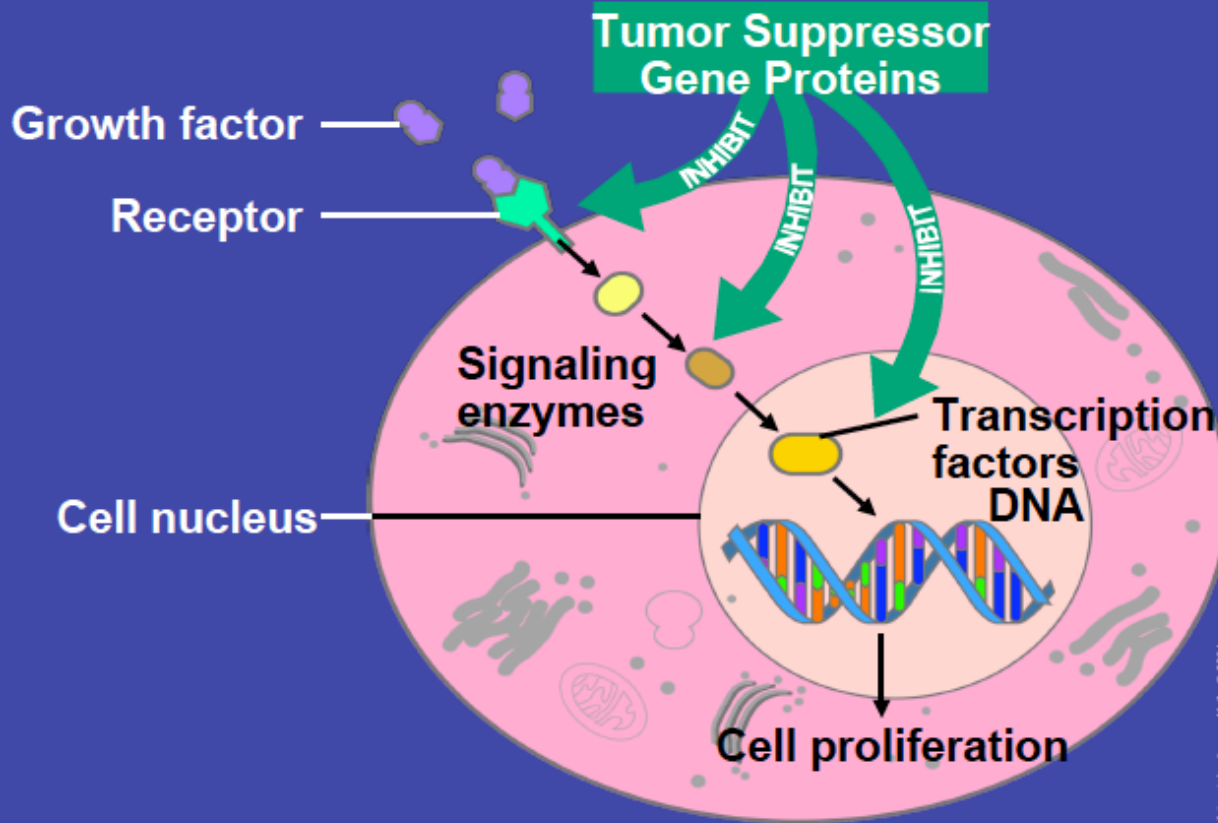
Proto-oncogenes can encode proteins that are used in cell proliferation or apoptosis. These can be growth factors, receptors, signaling enzymes, and transcription factors

# Tumor Suppressors

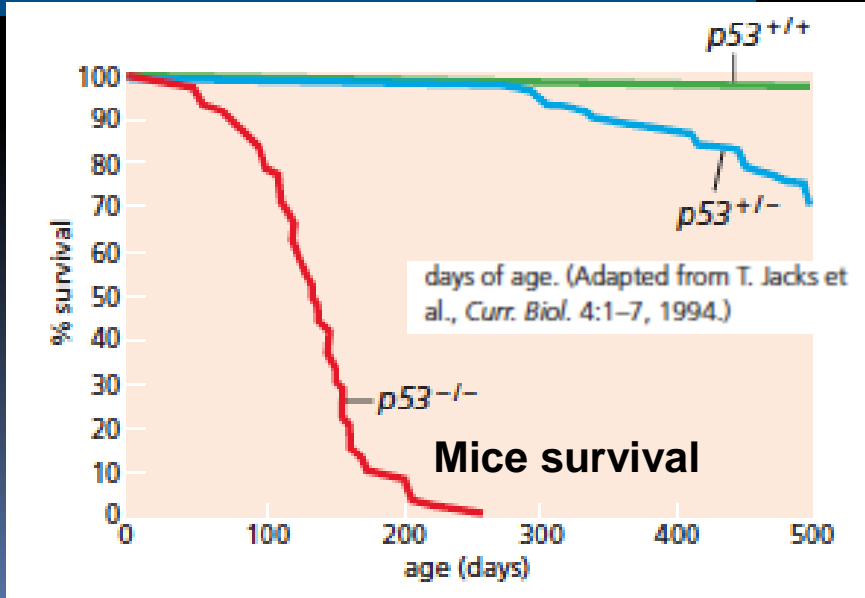
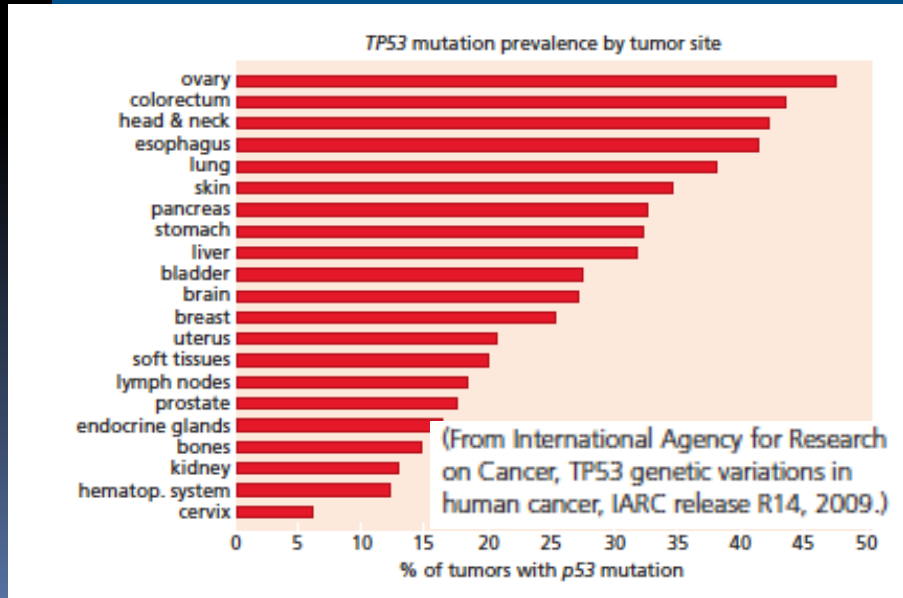
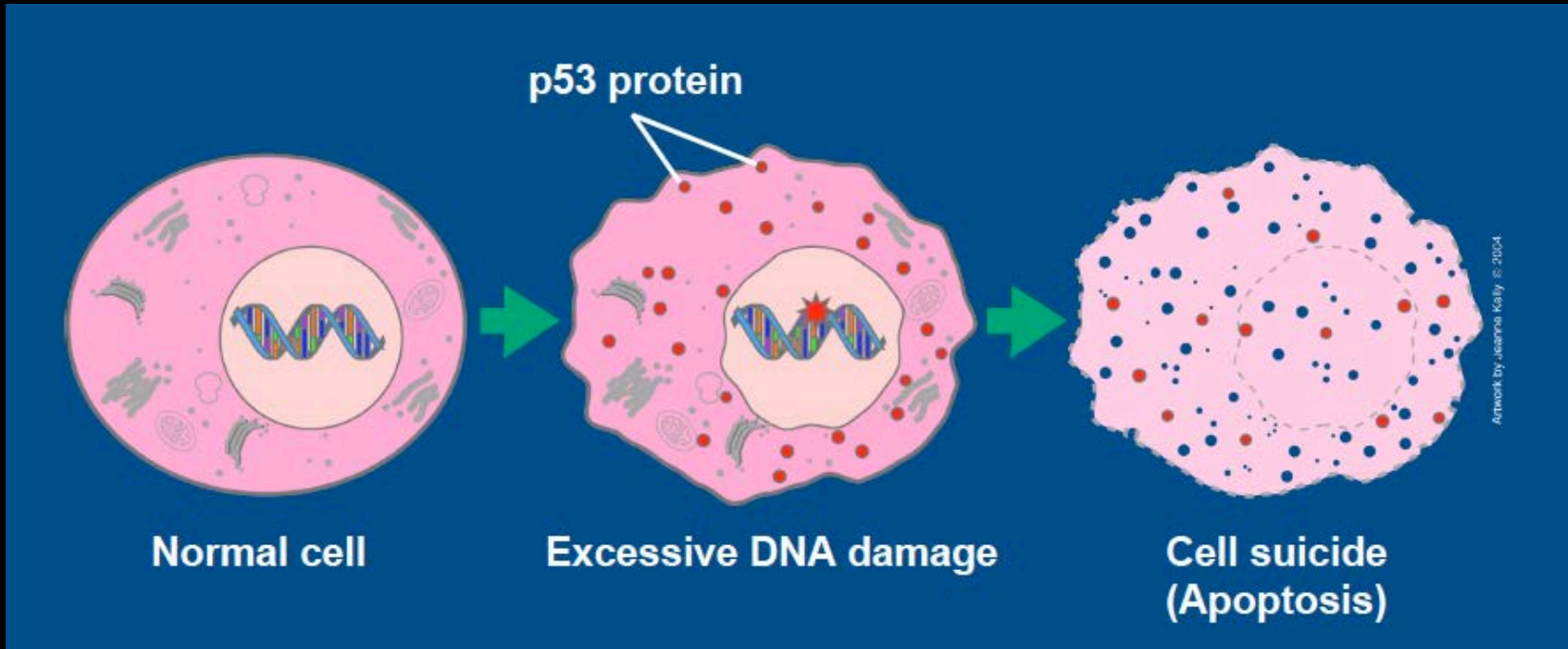
Tumor Suppressors genes are normal genes whose **ABSENCE** can lead to cancer tumor suppressor genes protect the cell.



# Tumor Suppressor Genes Act Like a Brake Pedal

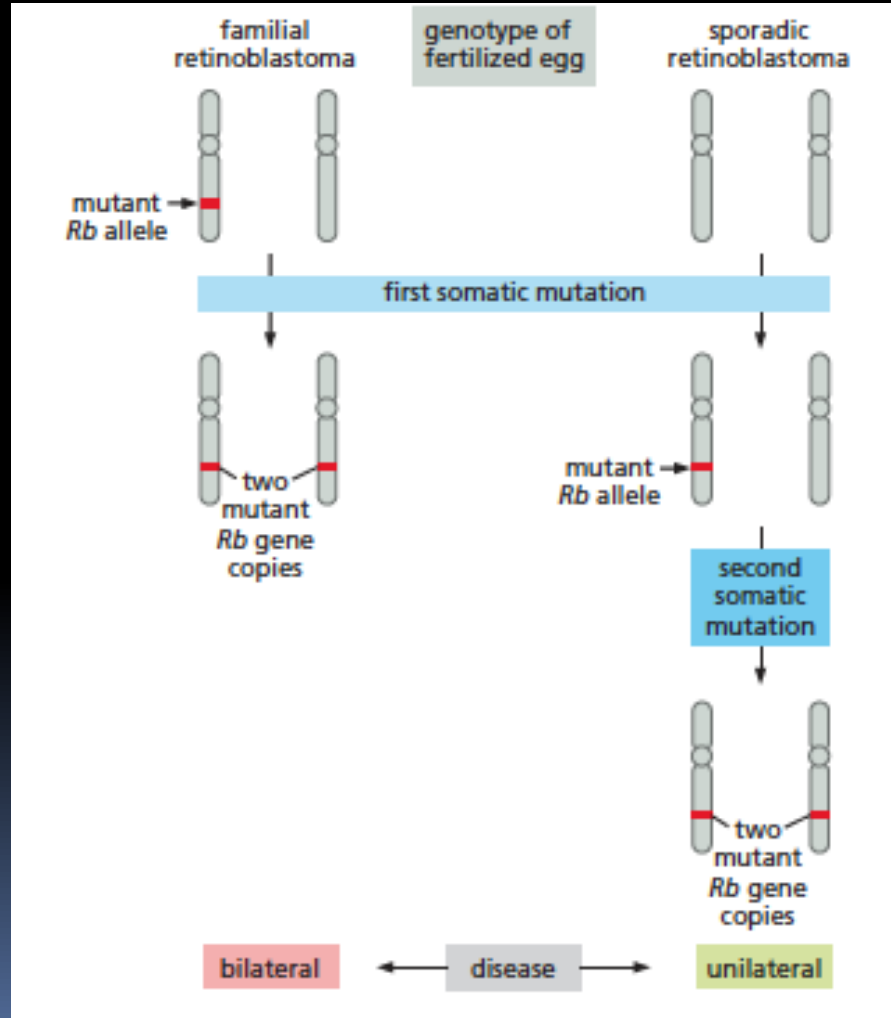


# The first tumor suppressor gene discovered was p53



# The 2<sup>nd</sup> tumor suppressor gene discovered was Rb

- Carriers of mutated RB gene have 90% of developing Retinoblastoma (vs 1/20,000 in the general population)



# Rb was useful to postulate the 2 hit model

- Carriers of mutated RB gene have 90% of developing Retinoblastoma (vs 1/20,000 in the general population)

*Proc. Nat. Acad. Sci. USA*  
Vol. 68, No. 4, pp. 820–823, April 1971

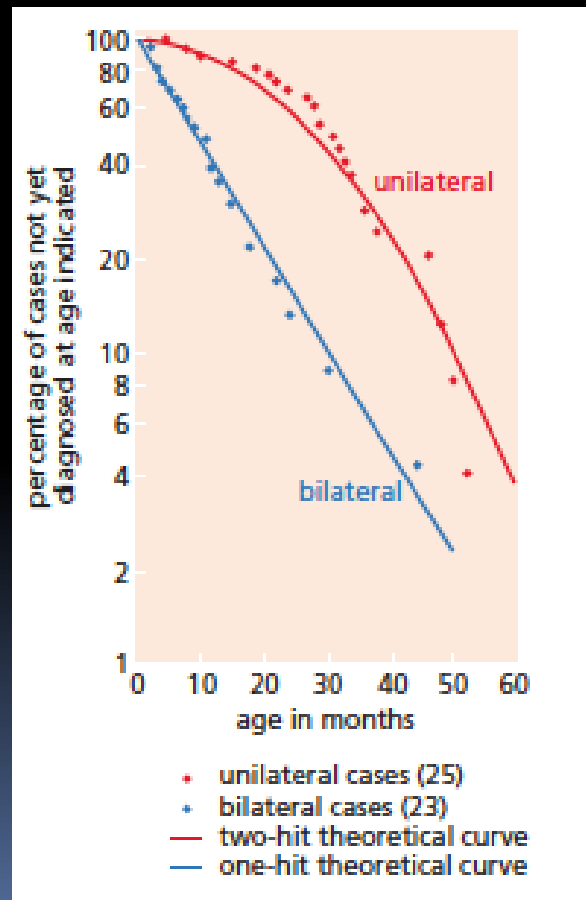
## Mutation and Cancer: Statistical Study of Retinoblastoma

ALFRED G. KNUDSON, JR.

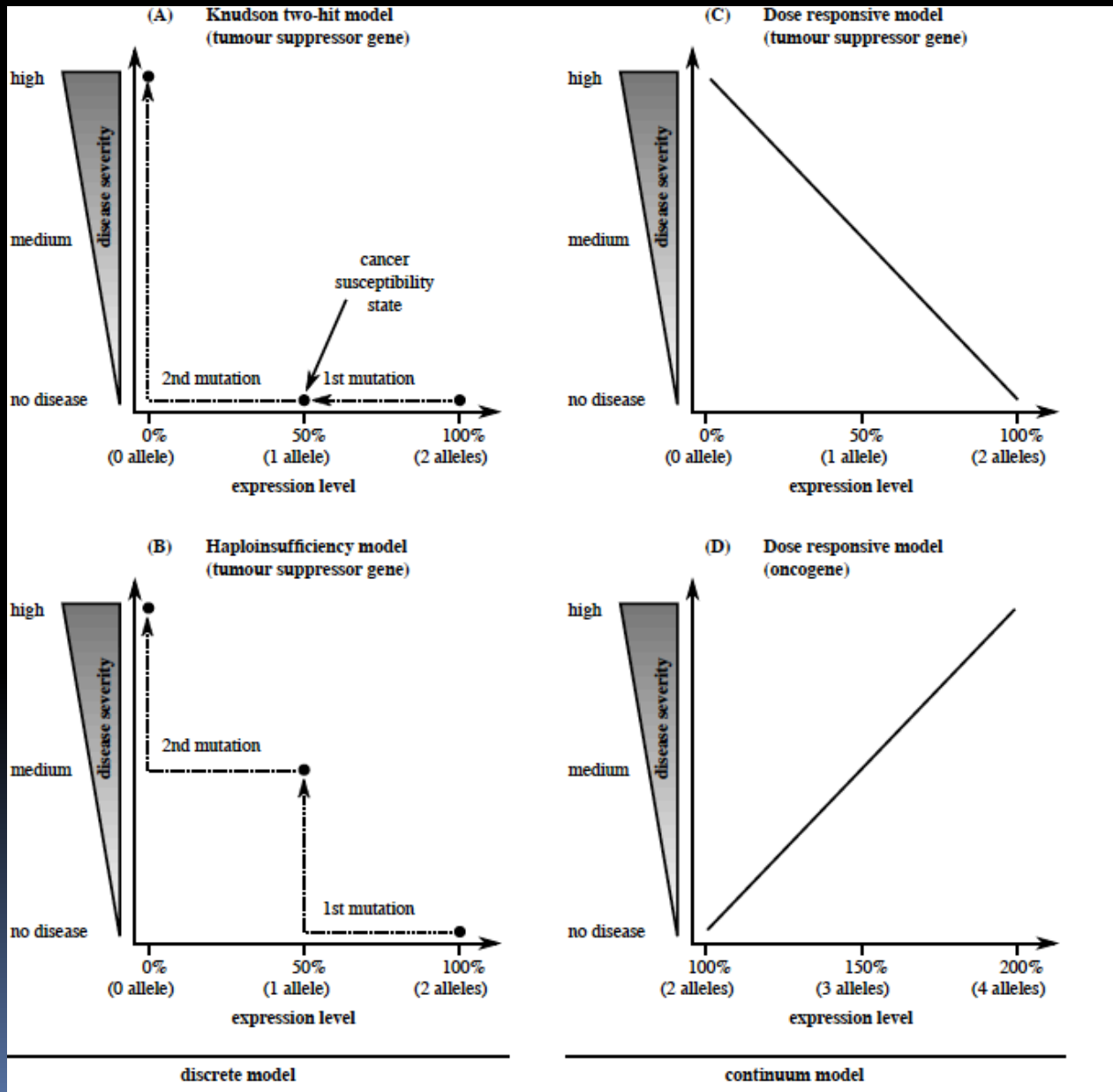
Graduate School of Biomedical Sciences and M. D. Anderson Hospital and Tumor Institute,  
The University of Texas at Houston, Houston, Texas 77025

Communicated by James V. Neel, February 8, 1971

**Figure 7.5 Kinetics of appearance of unilateral and bilateral retinoblastomas** Alfred Knudson Jr. studied the kinetics with which bilateral and unilateral retinoblastomas appeared in children. He calculated that the bilateral cases (tumors in both eyes) arose with one-hit kinetics, whereas the unilateral tumors (affecting only one eye) arose with two-hit kinetics. Each of these hits was presumed to represent a somatic mutation. The fact that the two-hit kinetics involved two copies of the *Rb* gene was realized only later. Percentage of cases not yet diagnosed (ordinate) at age (in months) indicated (abscissa). (From A.G. Knudson Jr., *Proc. Natl. Acad. Sci. USA* 68:820–823, 1971.)



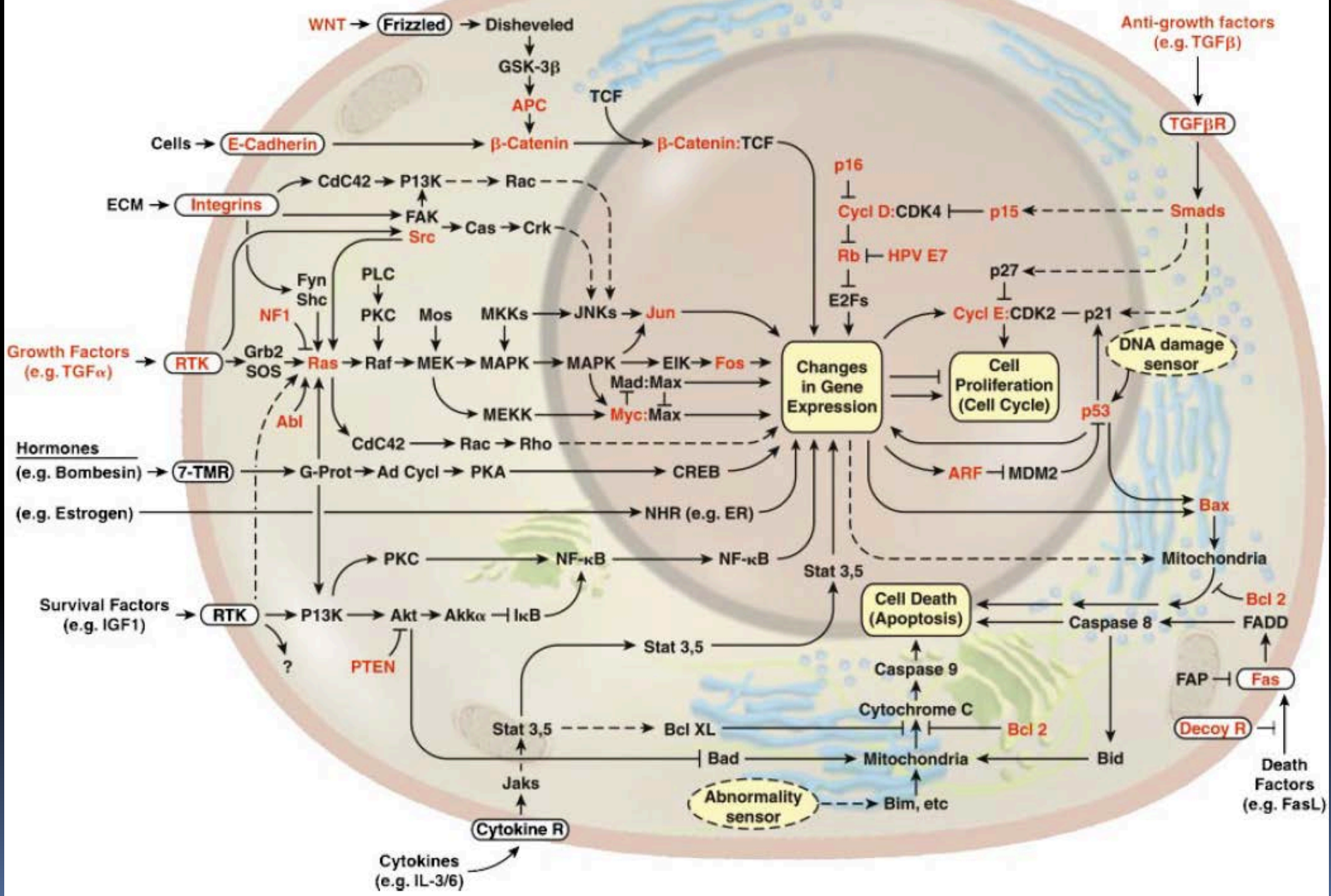
# Other models of tumor suppression



# Cancer is a disease of the network

- The cell has ~20,000 genes. Not all are active in a given cell type.
- These genes are organized in networks reminiscent of integrated circuits from where a biological function emerges.



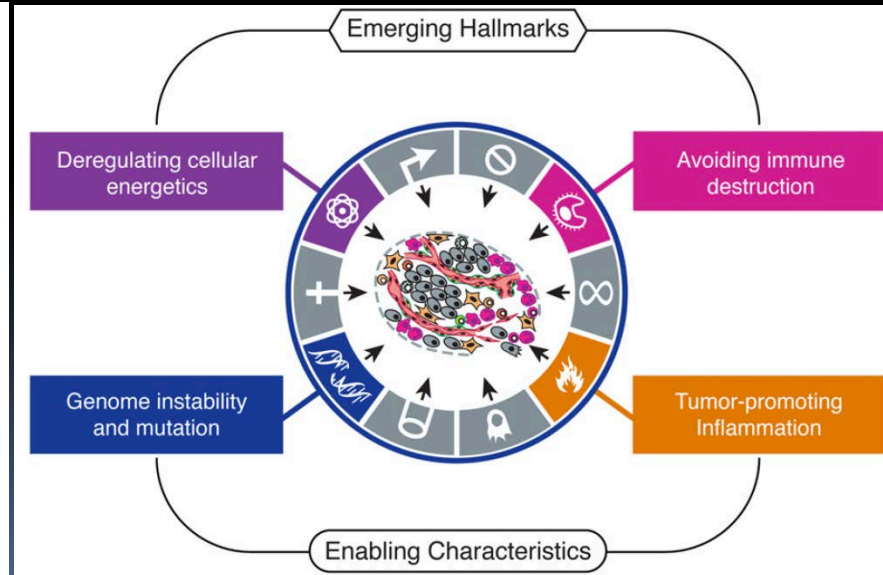
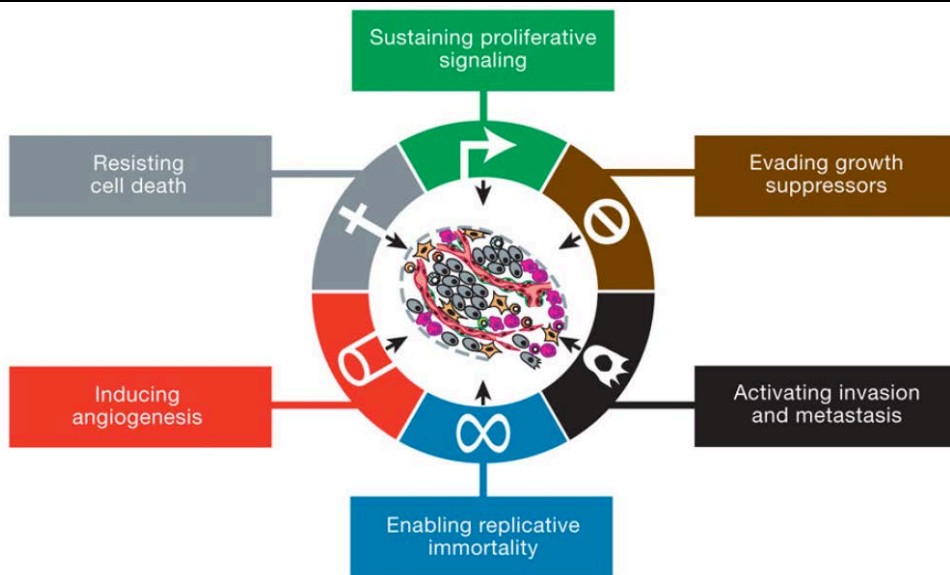


# Cancer is a disease of the network

- Cancer Gene Census lists ~600 genes associated with cancer.
- These genes are organized in networks reminiscent of integrated circuits from where a biological function emerges.
- There are a limited number of biological functions: Cell Survival, proliferation, death, metabolism needed to survive
- Mutated genes (~600) in cancer, suppresses some of these functions (e.g. cell death) and enhances others (proliferation) to attain its aggressive growth. These are the so-called hallmarks of cancer (Hanahan and Weinberg)

# Hallmarks of cancer

- Acquired cellular capabilities that allow the cells to survive, proliferate and disseminate.



# Enabling Characteristics

- Genome instability and mutation
  - Is the source of multistep tumor progression: succession of clonal expansion triggered by random acquisition of enabling mutations.
  - Some clonal expansions may be triggered by epigenetics mechanisms: DNA methylation and histone modifications.
  - Many mutations appear to be randomly located in different patients.
  - Some are recurrent and maybe causal.

# Enabling Characteristics

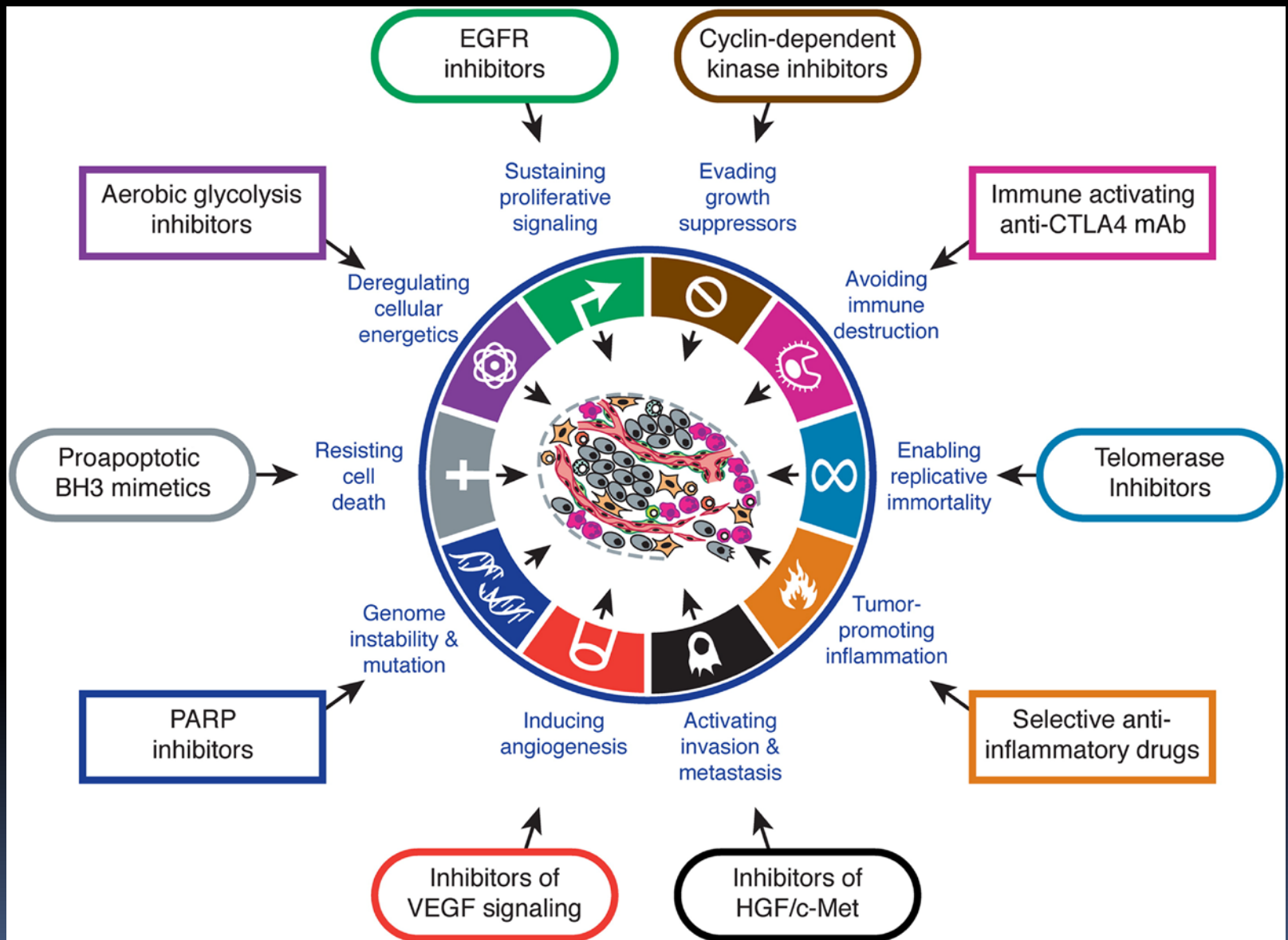
- Tumor-Promoting Inflammation
  - virtually every neoplastic lesion contains immune cells present at densities ranging from subtle to gross inflammation.
  - Such immune responses is thought to reflect an attempt by the immune system to eradicate tumors
  - The tumor responds trying to evade immune destruction
- Inflammation supplies growth factors, survival factors, pro angiogenic factors to the tumor microenvironment.
- inflammatory cells can release chemicals, notably reactive oxygen species, that are actively mutagenic for nearby cancer cells.

# Emerging Hallmark

- Reprogramming Energy Metabolism
  - Under aerobic conditions, normal cells process glucose, first to pyruvate via glycolysis in the cytosol and thereafter to carbon dioxide in the mitochondria
  - under anaerobic conditions, glycolysis is favored and relatively little pyruvate is dispatched to the oxygen-consuming mitochondria
  - even in the presence of oxygen, cancer cells can reprogram their glucose metabolism, by limiting their energy metabolism to glycolysis, leading to “aerobic glycolysis.”
  - Aerobic glycolysis is 18 fold less efficient.
- increased glycolysis allows the diversion of glycolytic intermediates into various biosynthetic pathways, including those generating nucleosides and amino acids; this facilitates assembling new cells.
- energy metabolism is an emerging hallmark as there are unresolved issues surrounding its functional independence from the core hallmarks.

# Targeted Therapeutics

- In 1900's Paul Ehrlich proposed the magic bullet theory: cancer cells have specific receptors that could be targeted with a drug
- In the language of the hallmarks, if a hallmark is truly important for the biology of tumors then its inhibition using targeted therapies should impair tumor growth and progression.



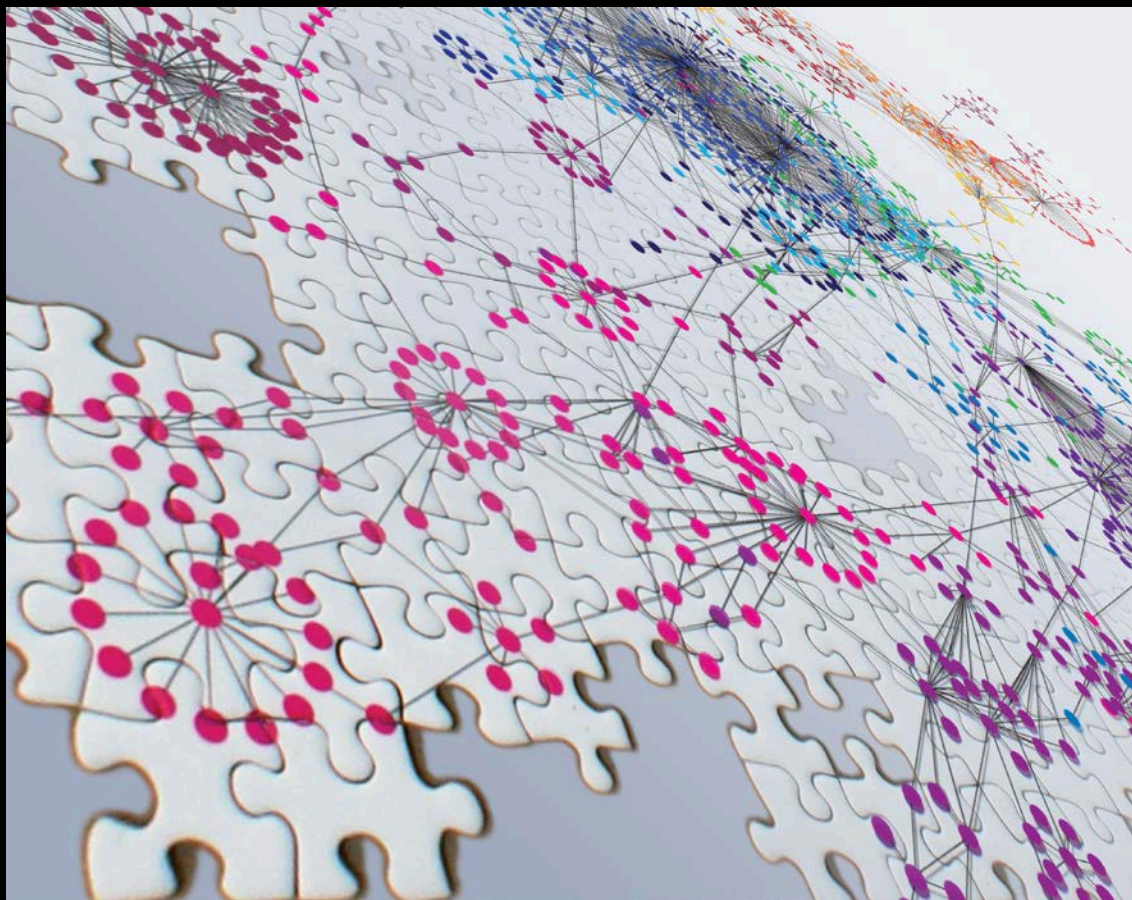


# Targeted Therapeutics

- In the 1980's research on signaling pathways revived the idea.
- It worked only partially. For example:
  - Trastuzumab inhibited HER2 in Breast Cancer
  - Imatinib inhibited BCR-ABL1 in Chronic Myeloid Leukemia
- In fact, resulting clinical responses have generally been transitory, being followed by almost-inevitable relapses.
- Patients treated with these drugs develop resistance due in part to the network nature of cancer
- Intuition is not enough to figure out which points of the network should be targeted.

# Targeted Therapeutics

- The reason is that there is redundancy compensating the mechanisms that are inhibited.
- Also if some function is targeted for inhibition, other may be enhanced. For example, targeting angiogenesis results in the creation of local metastasis. Or enhancing apoptosis may result in enhanced proliferation.
- Co-targeting multiple core and emerging hallmark capabilities is a way to improve treatment



What is Systems Biology?

# What is systems biology?

The study of the **mechanisms** underlying complex biological processes as **integrated systems** of many interacting components.

Activity of SB involves:

1. collection of large sets of experimental data
2. proposal of mathematical models
3. quantitative predictions
4. estimate quality of model by comparing with experiment

Leroy Hood, 1999

# What is systems biology? Alternative definition

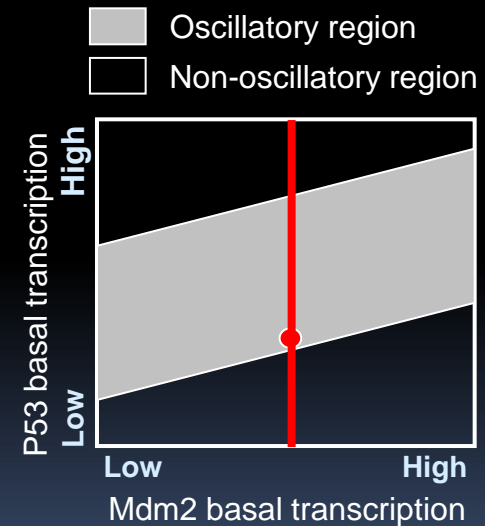
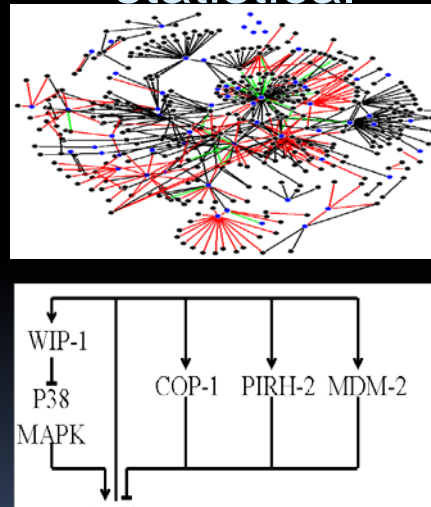
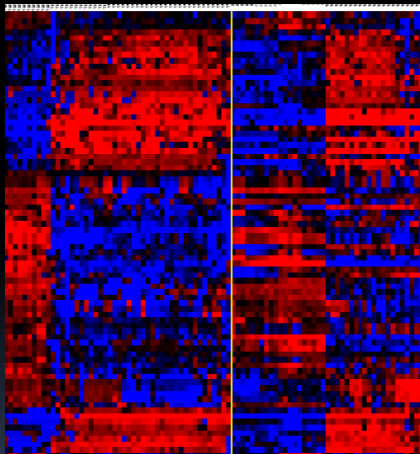
Is the discipline that results when a physicist thinks s/he is doing biology.

# Systems Biology deals with four main tasks

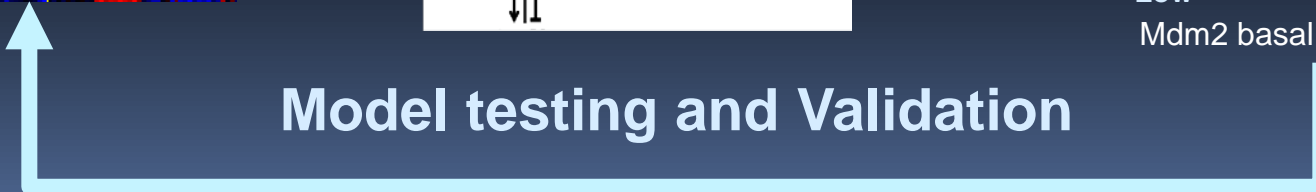
Measurements  
New High  
Throughput **Omics**  
technologies

Modeling  
Data  
exploration,  
deterministic  
statistical

System  
Characterization &  
Predictions:  
Clinical & Biological



Model testing and Validation



# A day in the life of a systems biologist

## Get a data set

- the gene expression of 1000 patients (transcriptomics)
- or the phosphorylation state of 100 proteins under different stimuli (phosphoproteomics)

## Look at it globally (to find gross patterns) and locally (to find pathway specific patterns)

- Cluster the data
- Find the genes that behave in a special way
- Put the data in the context of prior knowledge

## Generate hypothesis, test them statistically. Validate

- Do my hypothesis show statistically significant results
- What experiments can I do to test my hypothesis

## What can a systems biologist do in cancer research

- Molecular Classification of tumors, for better diagnosis and prognosis
- Create mechanistic models that can help identify causes and potential drug targets
- Propose treatments specifically tailored for a patient.

*Two decades from now having fully charted the wiring diagrams of every cellular signaling pathway, it will be possible to lay out the complete “integrated circuit of the cell”... We will then be able to apply the tools of mathematical modeling to explain how specific genetic lesions serve to reprogram this integrated circuit.....We imagine that cancer biology and treatment ... will become a science with a conceptual structure and logical coherence that rivals that of chemistry or physics.*

*Hanahan and Weinberg, “The hallmarks of cancer”, Jan 2000*



## Proposed homework

Read: Hanahan and Weinberg, *The Hallmarks of Cancer*, Cell, Vol. 100, 57–70, January 7, 2000. Bring 1 important take home message

Or

Read: Knudson two hit model paper: A. Knudson, *Mutation and Cancer: Statistical Study of Retinoblastoma*, Proc. Nat. Acad. Sci. USA, Vol. 68, No. 4, pp. 820-823, April 1971. Try to make sense of the two hit model.

Or

Explore the COSMIC ([cancer.sanger.ac.uk/cosmic](http://cancer.sanger.ac.uk/cosmic)) Gene Cancer Census ([cancer.sanger.ac.uk/census](http://cancer.sanger.ac.uk/census)) database. Bring 1 tumor suppressor and 1 oncogene.