BASIC & TRANSLATIONAL ONCOLOGY ERASMUS COURSE 2020

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Department of Experimental and Clinical Medicine
University of Florence

"Basic and translational oncology"
Italian-French Erasmus Intensive Course in Oncology organized in collaboration with
European Master of Genetics - University Paris7-Paris5

	MONDAY 20/01/2020	TUESDAY 21/01/2020	WEDNESDAY 22/01/2020	THURSDAY 23/01/2020	FRIDAY 24/01/2020
	Auditorium B (Morgagni)	Auditorium B (Morgagni)	Auditorium B (Morgagni)	Auditorium B (Morgagni)	Auditorium B (Morgagni)
9.30-10.30	Annarosa Arcangeli Introduction to Oncology	Paola Defilippi The p140Cap adaptor protein as a molecular hub for limiting breast cancer and neuroblastoma aggressiveness	Annarosa Arcangeli The bases of Clinical Oncology	Giovanni Navalesi Clinical Trials in oncology in the era of the Precision Medicine	EXAM
10.30-11.30	Christine Delprat Cancer Immunotherapy innovation	Silvestro Conticello Mutations: from evolution to cancer	Luigi Messori Metal based drugs for cancer treatment: the case of gold compounds	Giulia Meoni Clinical cancer advance: Immunotherapy	
11.30-12.30	Laura Gragnani Pathogenesis of HCV-related lymphoproliferative disorders	Laura Maggi Principles of immunology and immunotherapy	Giulia Bon Drug resistance in solid tumors	Lapo Bencini Overview of pancreatic cancer multimodal management	
12.30-13.30	Mattia Rediti Translational research in Breast Cancer	Martina Chiu Cancer-associated alteration of Glutamine metabolism: the cases of hematological neoplasia	Silvia Sordi Breast Cancer... from Biology to Surgery	Luca Saragoni Preneoplastic and neoplastic lesions of the stomach	
13.30-15.00	LUNCH BREAK				
15.00-16.00	Claudia Duranti Monoclonal and engineered antibodies in cancer therapy	Mjriam Capula New experimental models & pharmacological studies in pancreatic cancer	Elena Lastraioli Molecular Aspects of Cancer Diagnostics	STUDENTS' PRESENTATIONS	
16.00-17.00	Hugo de Jonge The HGF/SF-cMet signalling complex - a complex interaction	Tiziano Lottini Mouse models and Ultrasound and Photoacoustic imaging in preclinical research	Giuseppe Perrone Morphological and Molecular classification of Breast Cancer		

Cancer Biology: The Basics

- **The vocabulary**
- **Impact of cancer on human population**
- **Hallmarks of cancer**
- **Molecular bases of cancer**

Definitions

- Willis (1952):" A neoplasm is an abundant mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change"

Definitions

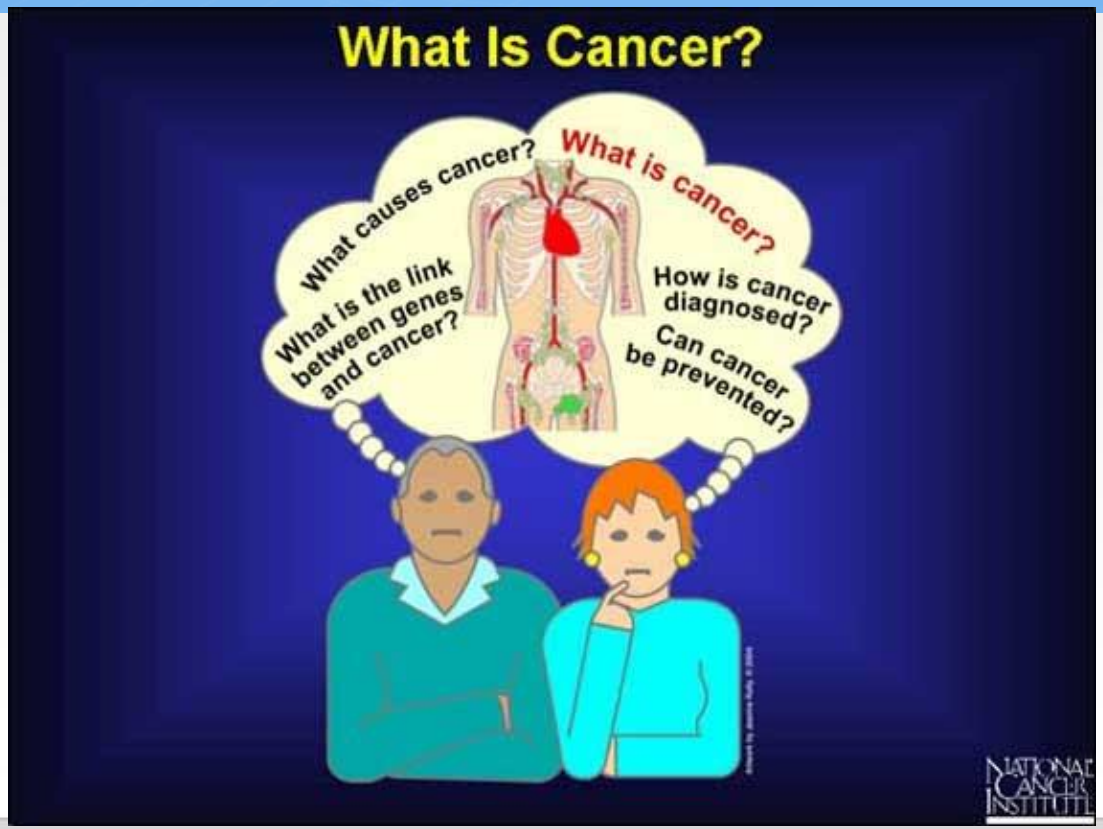
- **When I published the results of my experiments on the development of double-fertilized sea-urchin eggs in 1902, I added the suggestion that malignant tumors might be the result of a certain abnormal conditions of the chromosomes, which may arise from multipolar mitosis. ……So I have carried on for a long time the kind of experiments I suggested, which are so farwithout success, but my convinction remains unshaken.**

- Theodor Boveri, pathologist, 1914

The Vocabulary

- Hyperplasia – increased number of cells
- Hypertrophy – increased size of cells
- Dysplasia – disorderly proliferation
- Neoplasia – abnormal new growth
- Anaplasia – lack of differentiation
- Tumor – originally meant any swelling, but now equated with neoplasia
- Cancer- malignant tumor
- Metastasis –growth at a distant site

What is cancer?



What Is Cancer?

- Cancer is a group of diseases caused by the uncontrolled multiplication of abnormal cells in the body, a process called **neoplasia**.
- Abnormal new tissues called **neoplasms** are formed.
- **Neoplasms** usually form masses called **tumors** that may be **benign** (non cancerous) or **malignant** (cancerous).
- **Malignant** or **cancerous tumors** grow rapidly, are **invasive** (to surrounding tissue) and **metastatic** (traveling via blood/lymph to invade distant tissues).
- Cancers destroy healthy tissues causing loss of function and death.

- Cancers are genetic disorders caused by accumulation of somatic mutations (gene & chromosome) in a person's cells.
- Inherited mutations give a predisposition for certain cancers.

Biology of tumor growth: benign and malignant neoplasms

TABLE 7–2 Comparisons Between Benign and Malignant Tumors

Characteristics	Benign	Malignant
Differentiation/anaplasia	Well differentiated; structure may be typical of tissue of origin	Some lack of differentiation with anaplasia; structure is often atypical
Rate of growth	Usually progressive and slow; may come to a standstill or regress; mitotic figures are rare and normal	Erratic and may be slow to rapid; mitotic figures may be numerous and abnormal
Local invasion	Usually cohesive and expansile well-demarcated masses that do not invade or infiltrate surrounding normal tissues	Locally invasive, infiltrating the surrounding normal tissues; sometimes may be seemingly cohesive and expansile
Metastasis	Absent	Frequently present; the larger and more undifferentiated the primary, the more likely are metastases

TABLE 7–1 Nomenclature of Tumors

Tissue of Origin	Benign	Malignant
Composed of One Parenchymal Cell Type		
Tumors of mesenchymal origin		
Connective tissue and derivatives	Fibroma	Fibrosarcoma
	Lipoma	Liposarcoma
	Chondroma	Chondrosarcoma
	Osteoma	Osteogenic sarcoma
Endothelial and related tissues		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Synovium		Synovial sarcoma
Mesothelium		Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood cells and related cells		
Hematopoietic cells		Leukemias
Lymphoid tissue		Lymphomas
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma
Tumors of epithelial origin		
Stratified squamous	Squamous cell papilloma	Squamous cell or epidermoid carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Epithelial lining of glands or ducts	Adenoma	Adenocarcinoma
	Papilloma	Papillary carcinomas
	Cystadenoma	Cystadenocarcinoma
Respiratory passages	Bronchial adenoma	Bronchogenic carcinoma
Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
Liver cells	Liver cell adenoma	Hepatocellular carcinoma
Urinary tract epithelium (transitional)	Transitional cell papilloma	Transitional cell carcinoma
Placental epithelium	Hydatidiform mole	Choriocarcinoma
Testicular epithelium (germ cells)		Seminoma
		Embryonal carcinoma
Tumors of melanocytes	Nevus	Malignant melanoma
More Than One Neoplastic Cell Type—Mixed Tumors, Usually Derived from One Germ Cell Layer		
Salivary glands	Pleomorphic adenoma (mixed tumor of salivary origin)	Malignant mixed tumor of salivary gland origin
Renal anlage		Wilms tumor
More Than One Neoplastic Cell Type Derived from More Than One Germ Cell Layer—Teratogenous		
Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma

Definitions

- Neoplasms results from heritable genetic alterations that are passed down to the progeny of the tumor cells.
- These genetic changes allow excessive and unregulated proliferation that becomes autonomous (independent of physiologic growth stimuli), although tumors generally remain dependent on the host for their nutrition and blood supply

Cancer: From the View of Cancer Cell Biology

"Tumor formation arises as a consequence of alterations in the control of cell proliferation and disorders in the interactions between cells and their surroundings that result in nvasion and metastasis."

Christopher Marshall

Cell 64:313-326

Cancer Biology: The Basics

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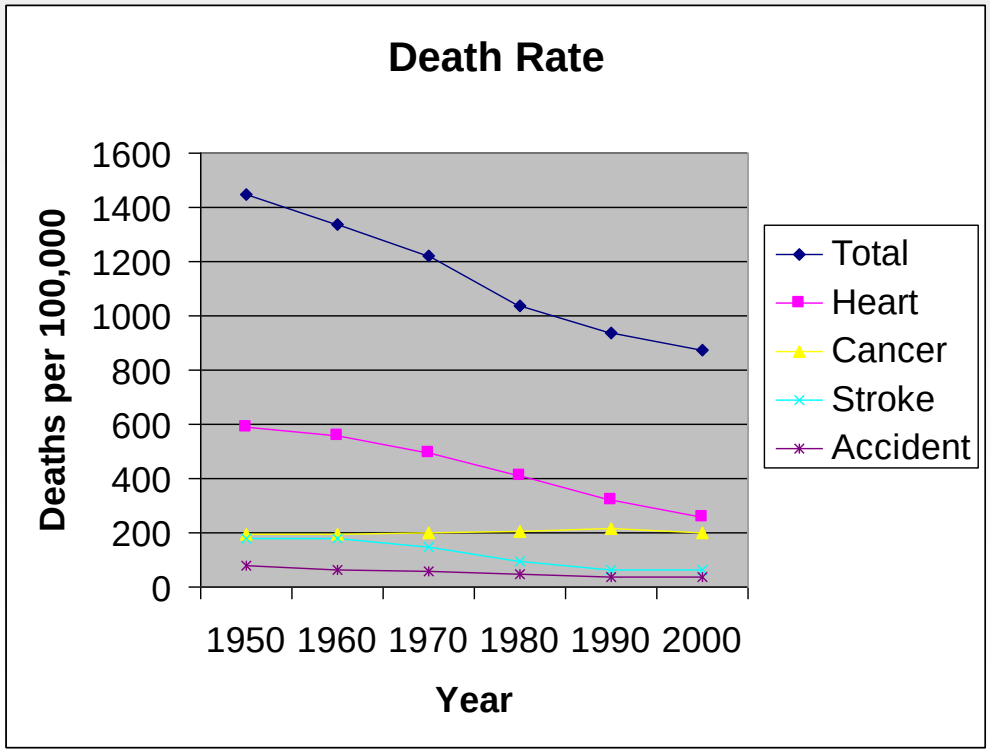
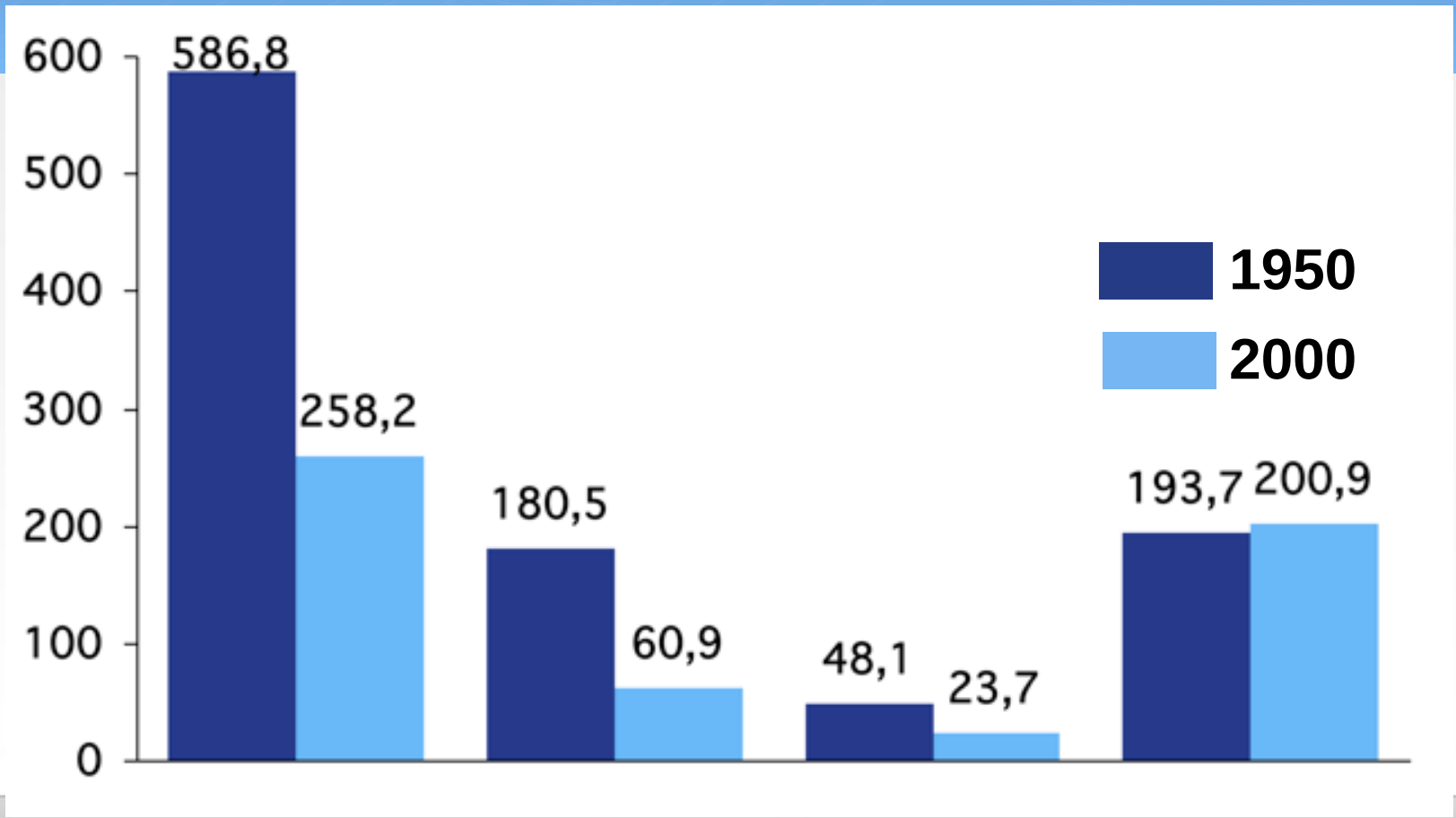
Leading Causes of Death

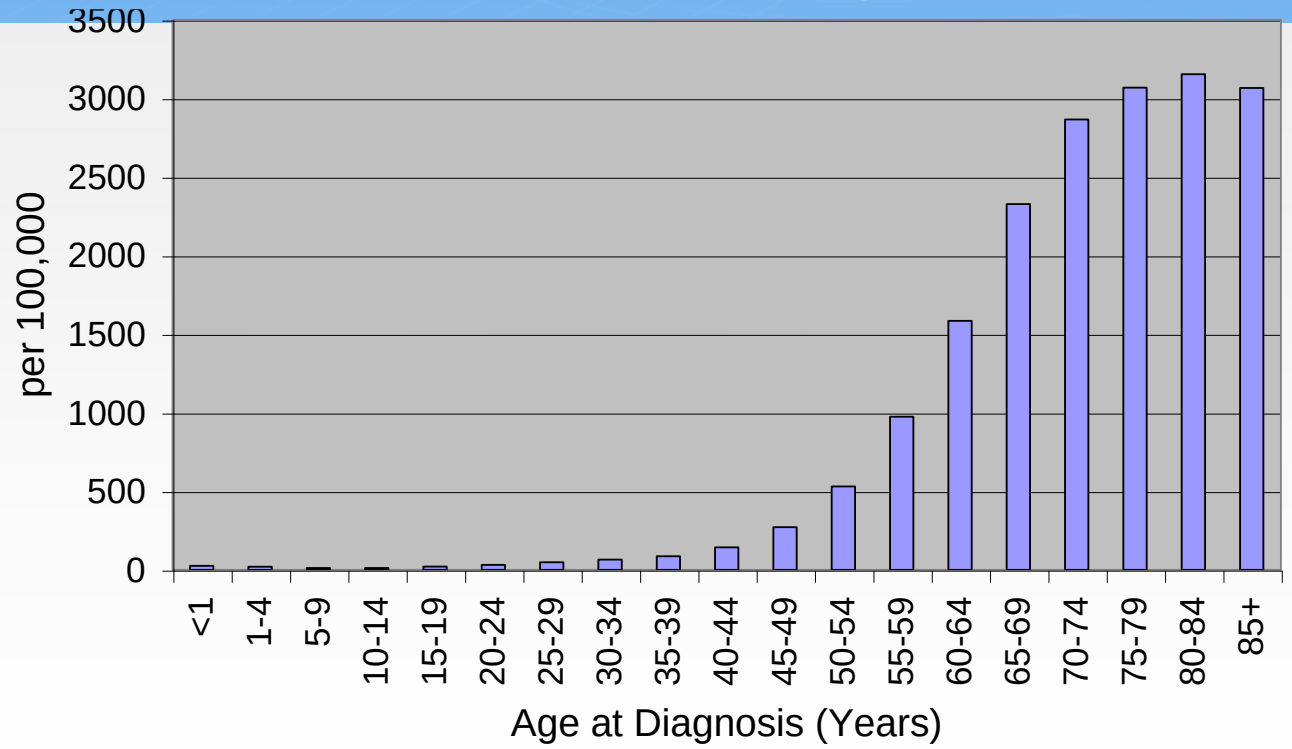


from CDC

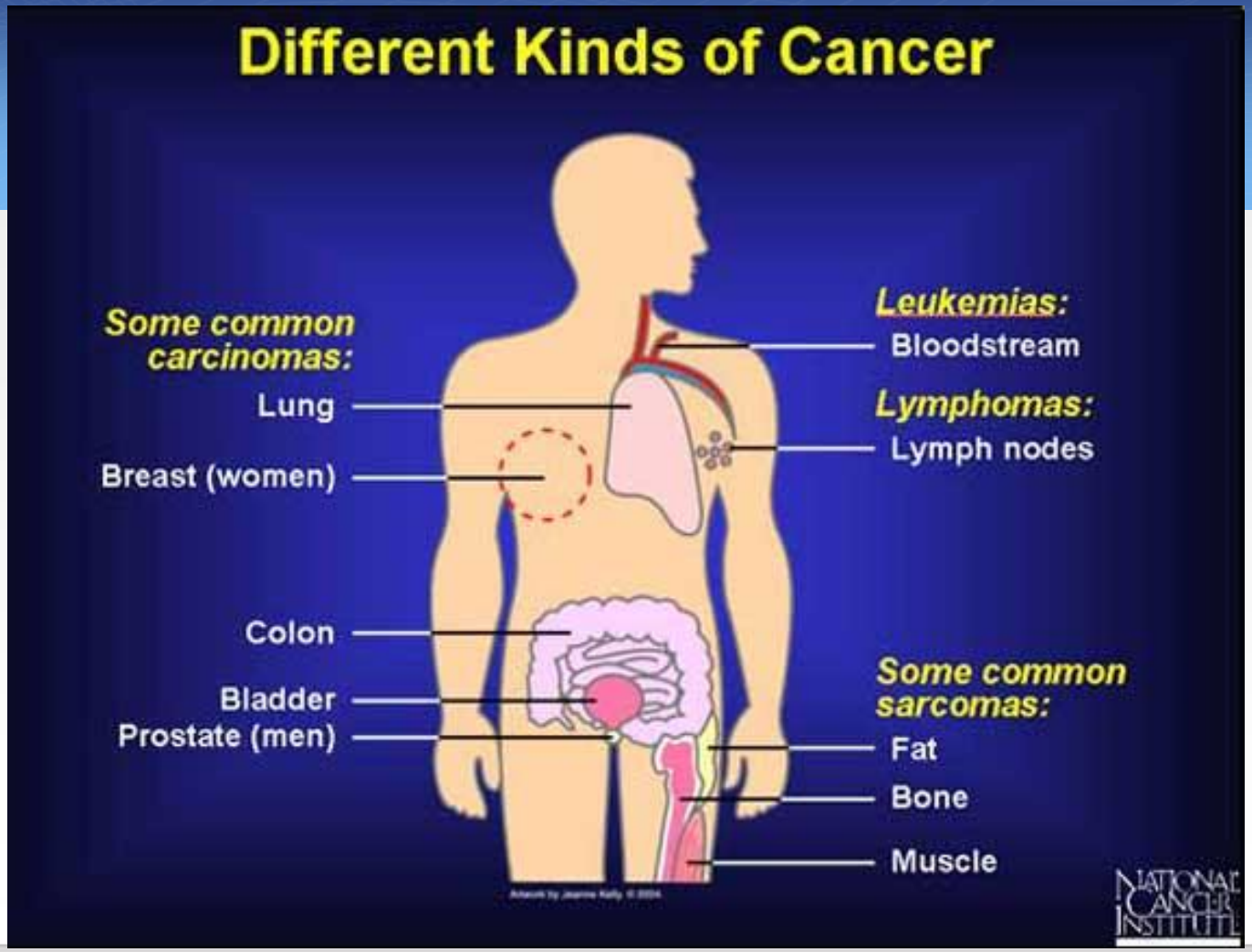
Change in Causes of Death



Invasive Cancer versus Age



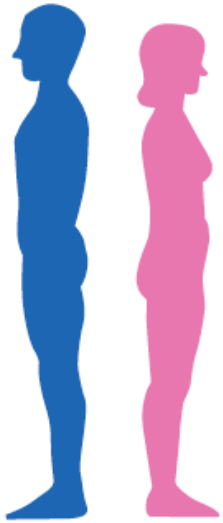
data from National Cancer Institute
http://www.cdc.gov/cancer/npcr/uscs/report/


Different Kinds of Cancer
Some common carcinomas:
Lung
Breast (women)
Colon
Bladder
Prostate (men)
Leukemias:
Bloodstream
Lymphomas:
Lymph nodes
Some common sarcomas:
Fat
Bone
Muscle
NATIONAL CANCER INSTITUTE

Estimated New Cases*

Males				Females		
Prostate	217,730	28%		Breast	207,090	28%
Lung & bronchus	116,750	15%		Lung & bronchus	105,770	14%
Colon & rectum	72,090	9%		Colon & rectum	70,480	10%
Urinary bladder	52,760	7%		Uterine corpus	43,470	6%
Melanoma of the skin	38,870	5%		Thyroid	33,930	5%
Non-Hodgkin lymphoma	35,380	4%		Non-Hodgkin lymphoma	30,160	4%
Kidney & renal pelvis	35,370	4%		Melanoma of the skin	29,260	4%
Oral cavity & pharynx	25,420	3%		Kidney & renal pelvis	22,870	3%
Leukemia	24,690	3%		Ovary	21,880	3%
Pancreas	21,370	3%		Pancreas	21,770	3%
All Sites	**789,620**	**100%**		**All Sites**	**739,940**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	86,220	29%		Lung & bronchus	71,080	26%
Prostate	32,050	11%		Breast	39,840	15%
Colon & rectum	26,580	9%		Colon & rectum	24,790	9%
Pancreas	18,770	6%		Pancreas	18,030	7%
Liver & intrahepatic bile duct	12,720	4%		Ovary	13,850	5%
Leukemia	12,660	4%		Non-Hodgkin lymphoma	9,500	4%
Esophagus	11,650	4%		Leukemia	9,180	3%
Non-Hodgkin lymphoma	10,710	4%		Uterine Corpus	7,950	3%
Urinary bladder	10,410	3%		Liver & intrahepatic bile duct	6,190	2%
Kidney & renal pelvis	8,210	3%		Brain & other nervous system	5,720	2%
All Sites	**299,200**	**100%**		**All Sites**	**270,290**	**100%**

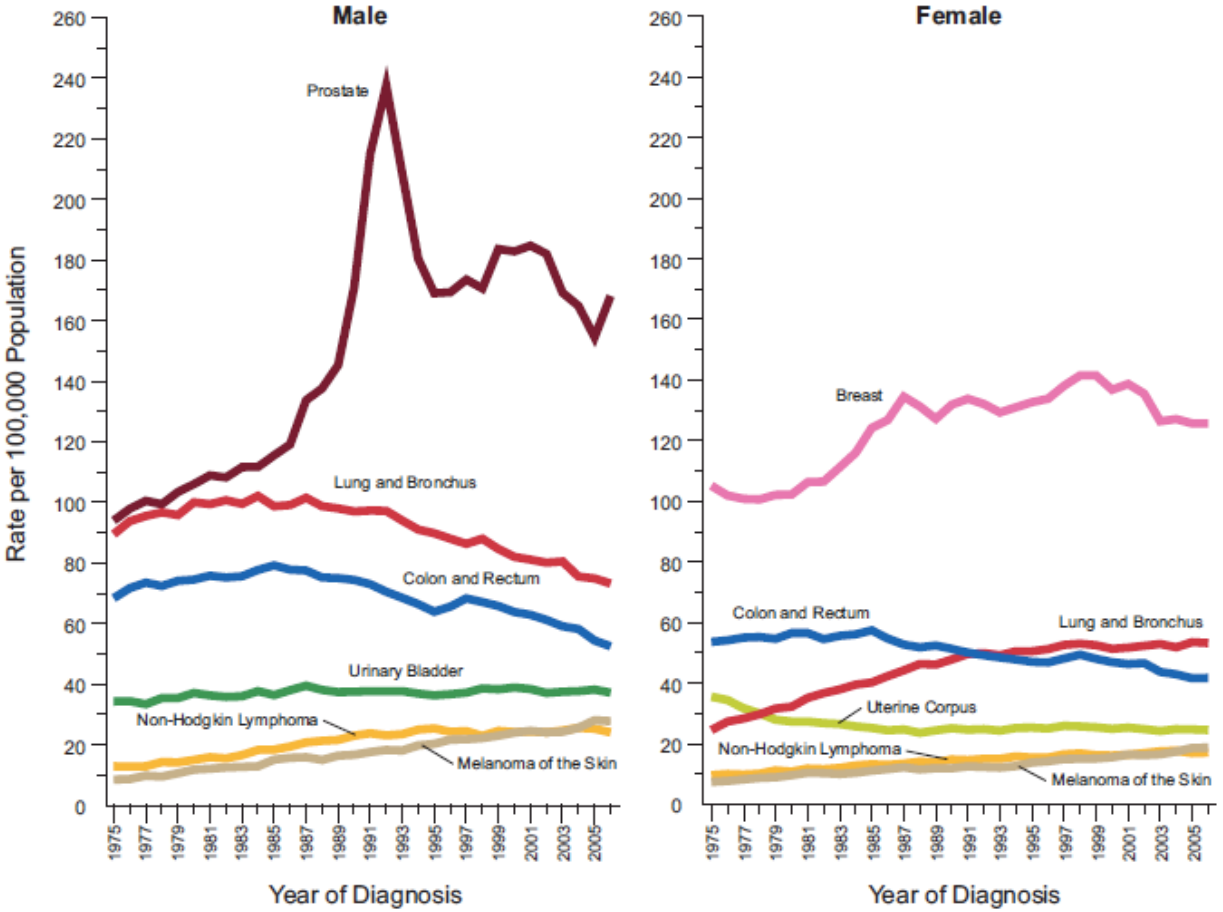
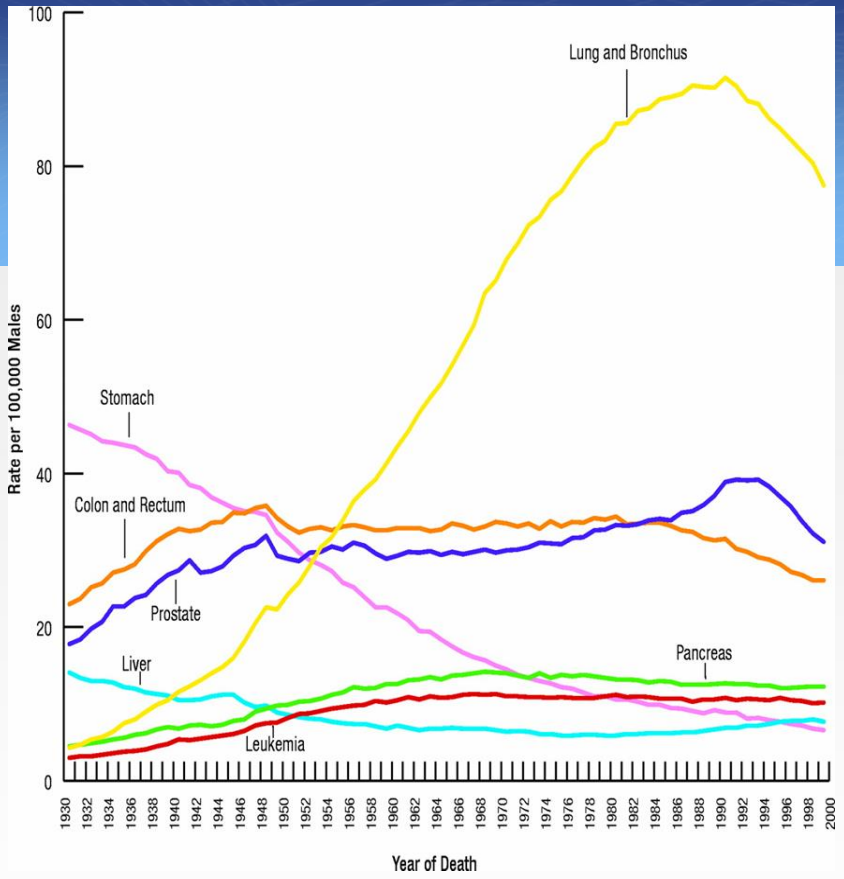


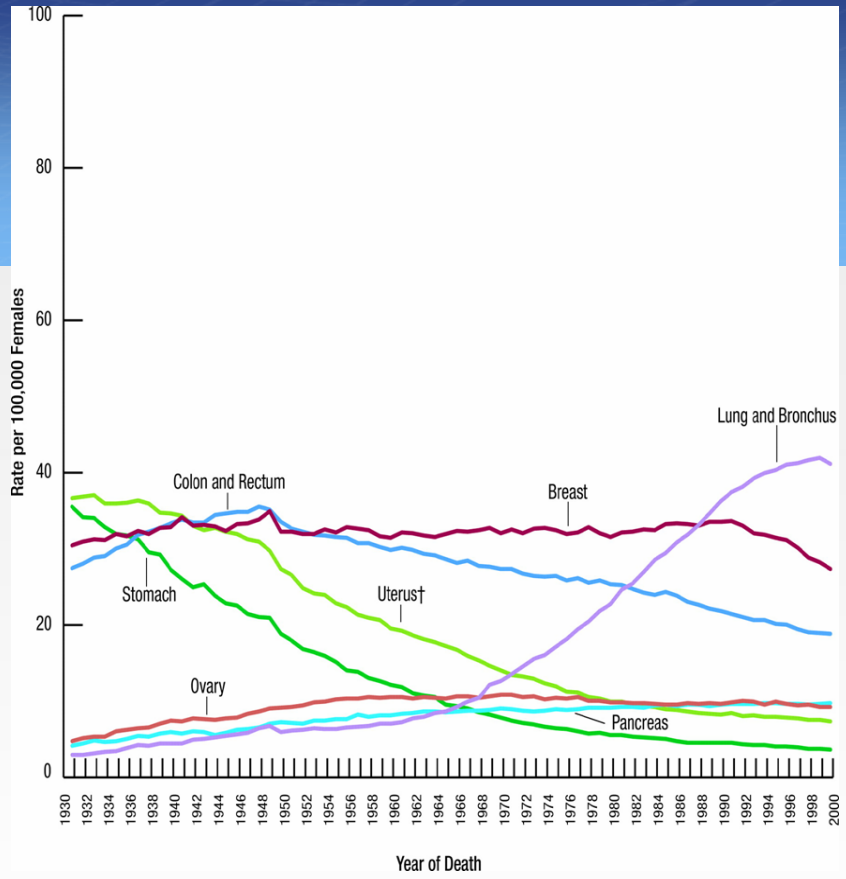
FIGURE 3. Annual Age-Adjusted Cancer Incidence Rates* for Selected Cancers by Sex, United States, 1975 to 2006.

*Rates are age adjusted to the 2000 US standard population and adjusted for delays in reporting. Source: Surveillance, Epidemiology, and End Results (SEER) program (available at: www.seer.cancer.gov). Delay-adjusted incidence database: SEER Incidence Delay-Adjusted Rates, 9 Registries, 1975-2006. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Statistical Research and Applications Branch; 2009. Released April 2009, based on the November 2008 SEER data submission.

Cancer Death Rates



MALE



FEMALE

from American Cancer Society

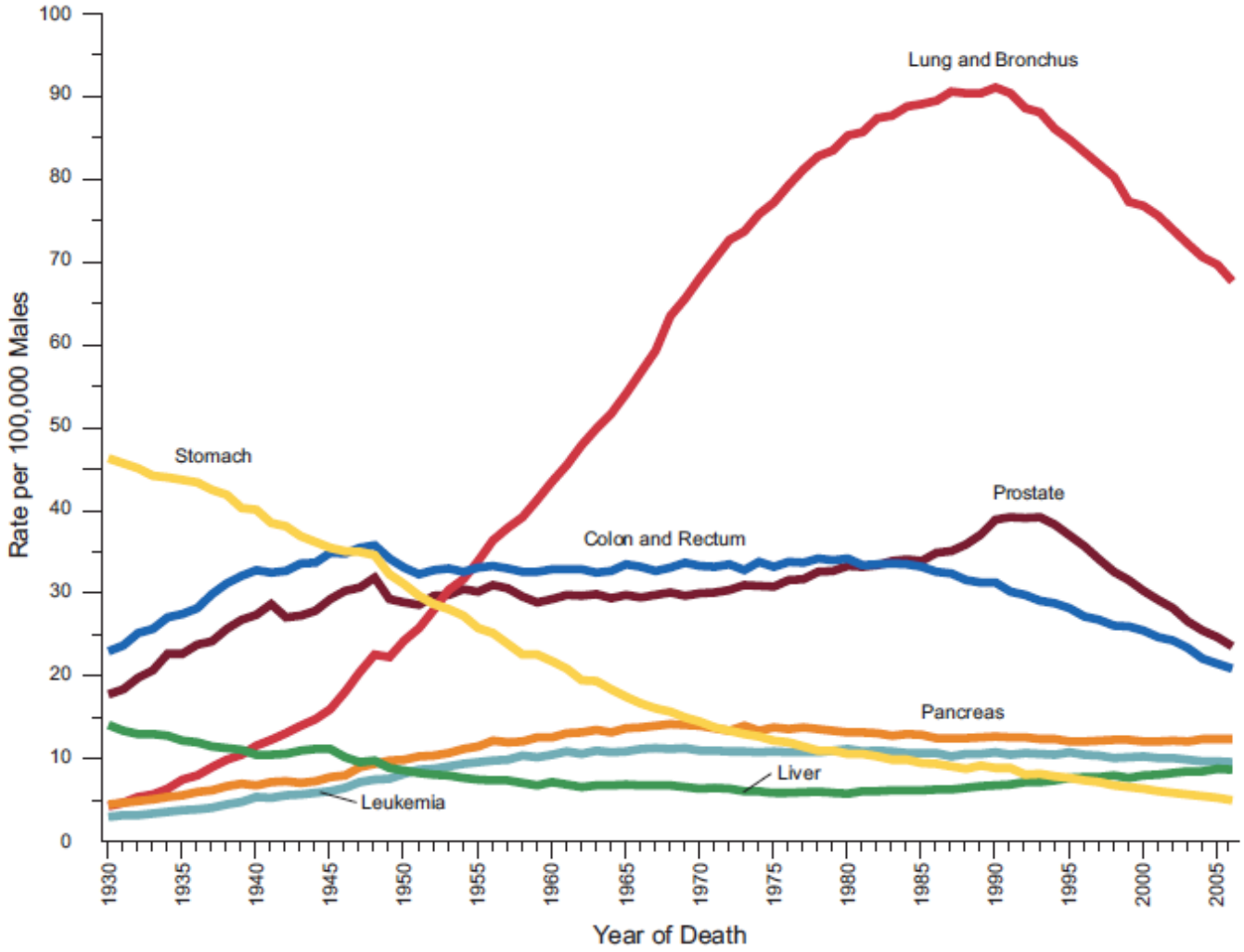


FIGURE 4. Annual Age-Adjusted Cancer Death Rates*Among Males for Selected Cancers, United States, 1930 to 2006.

*Rates are age adjusted to the 2000 US standard population. Due to changes in International Classification of Diseases (ICD) coding, numerator information has changed over time. Rates for cancers of the lung and bronchus, colon and rectum, and liver are affected by these changes. Source: US Mortality Data, 1960 to 2006, US Mortality Vol. 1930 to 1959. National Center for Health Statistics, Centers for Disease Control and Prevention.

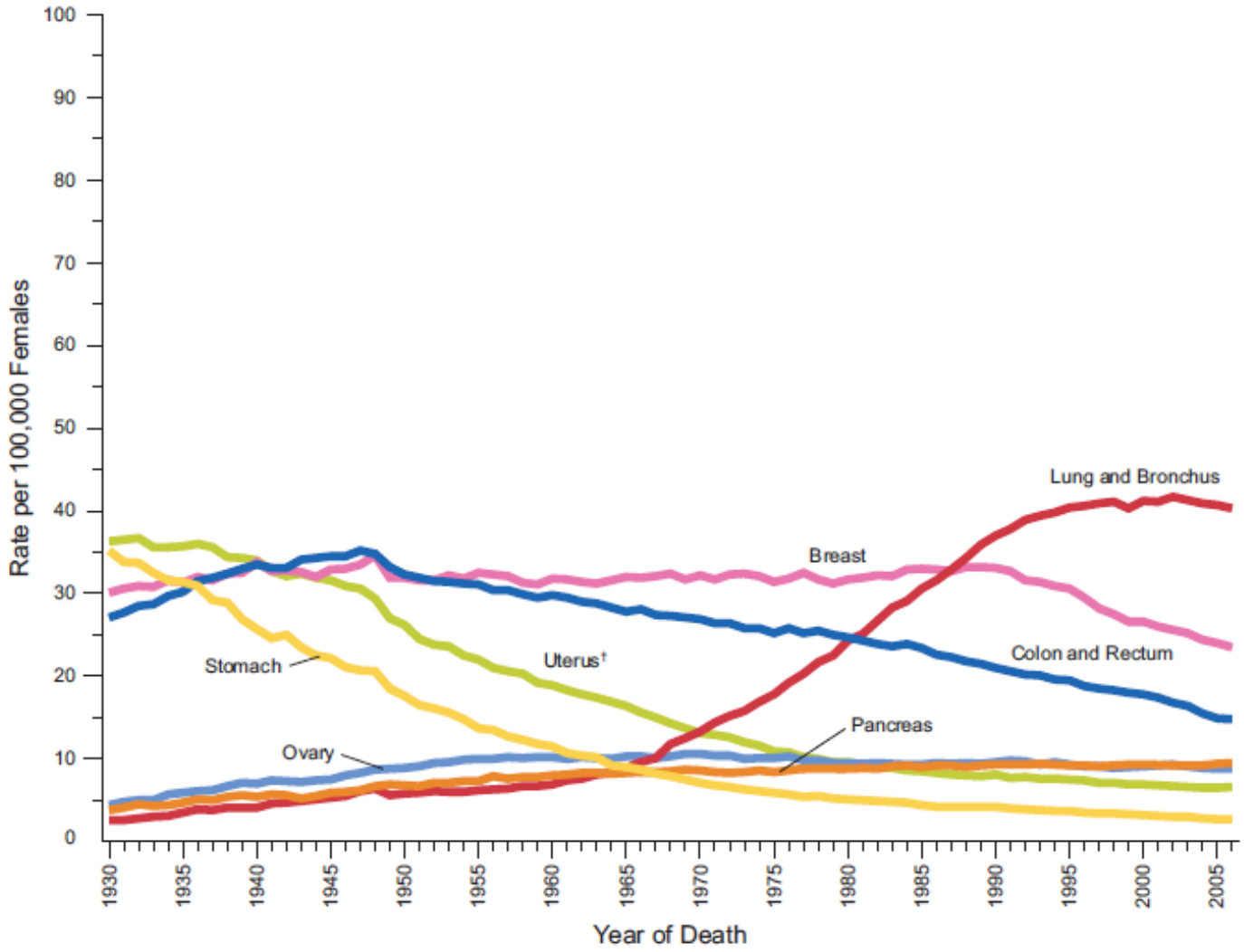


FIGURE 5. Annual Age-Adjusted Cancer Death Rates* Among Females for Selected Cancers, United States, 1930 to 2006.

*Rates are age adjusted to the 2000 US standard population.

†Uterus includes uterine cervix and uterine corpus. Due to changes in International Classification of Diseases (ICD) coding, numerator information has changed over time. Rates for cancers of the uterus, ovary, lung and bronchus, and colon and rectum are affected by these changes. Source: US Mortality Data, 1960 to 2006, US Mortality Volumes 1930 to 1959. National Center for Health Statistics, Centers for Disease Control and Prevention.

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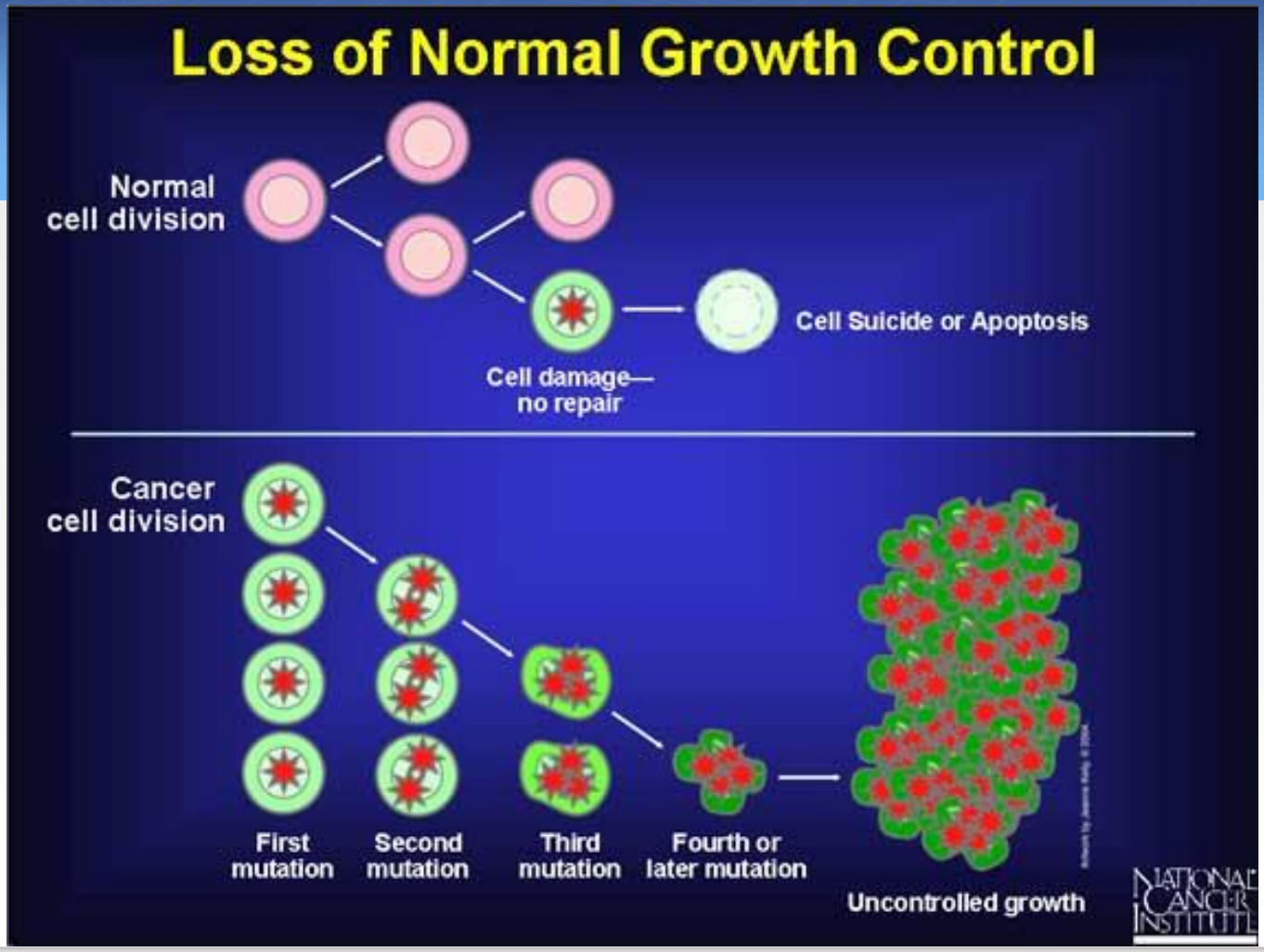
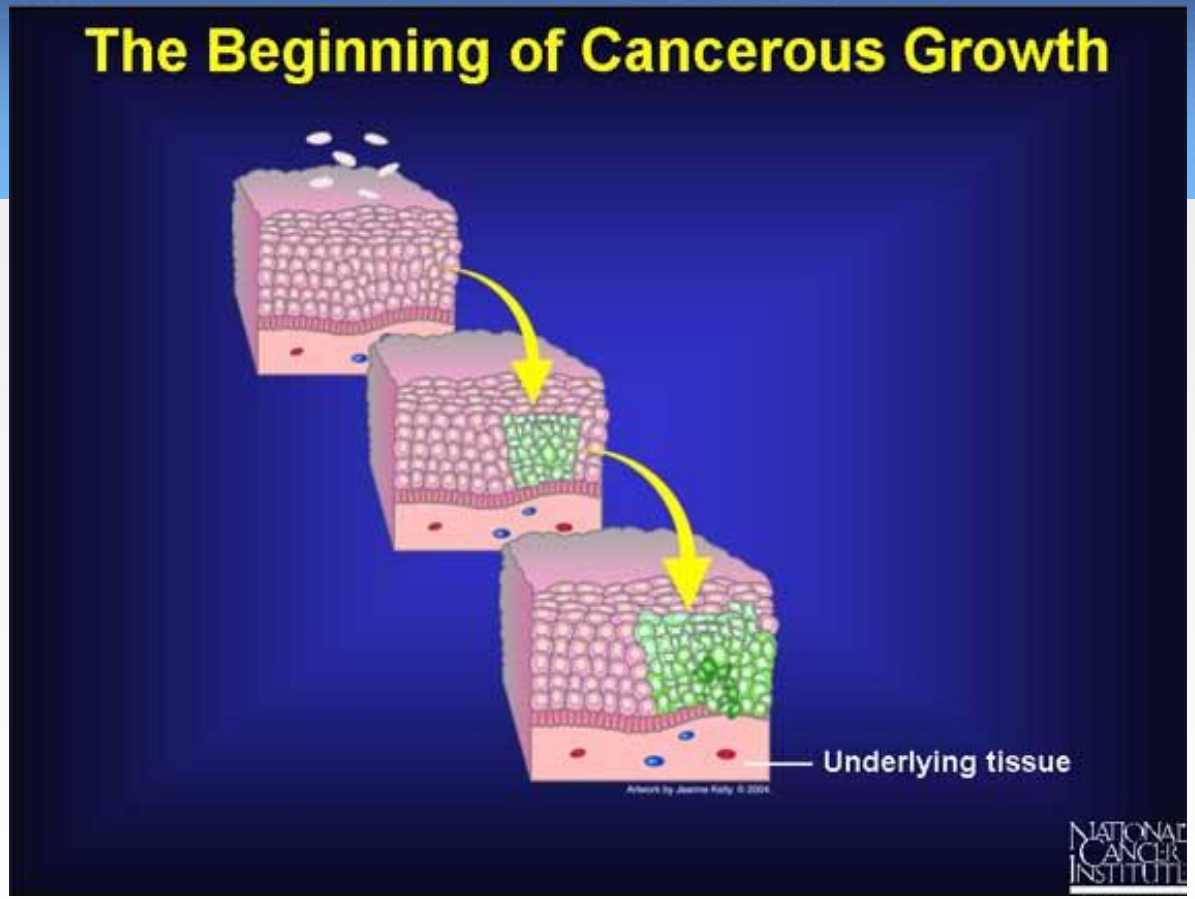
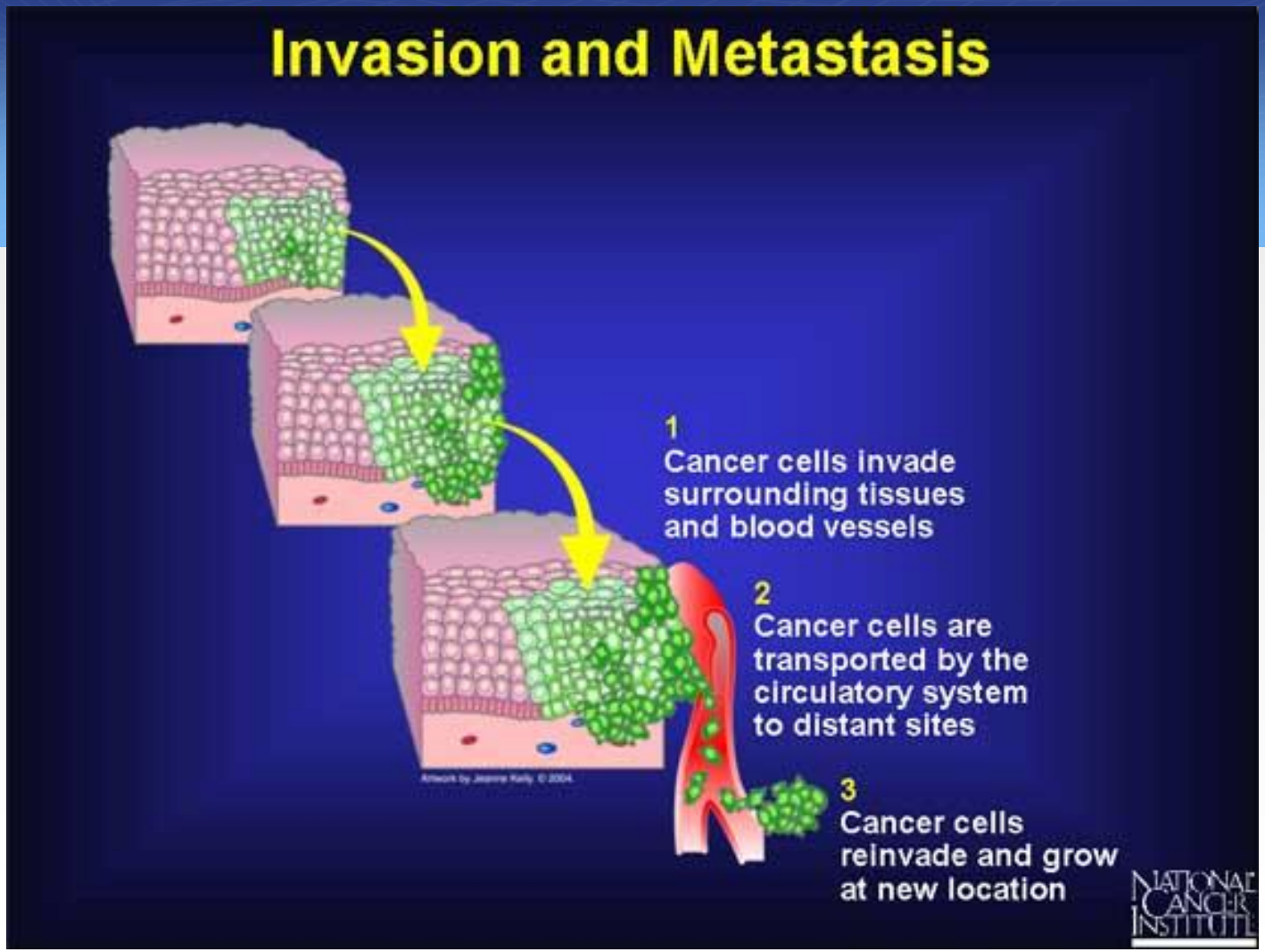
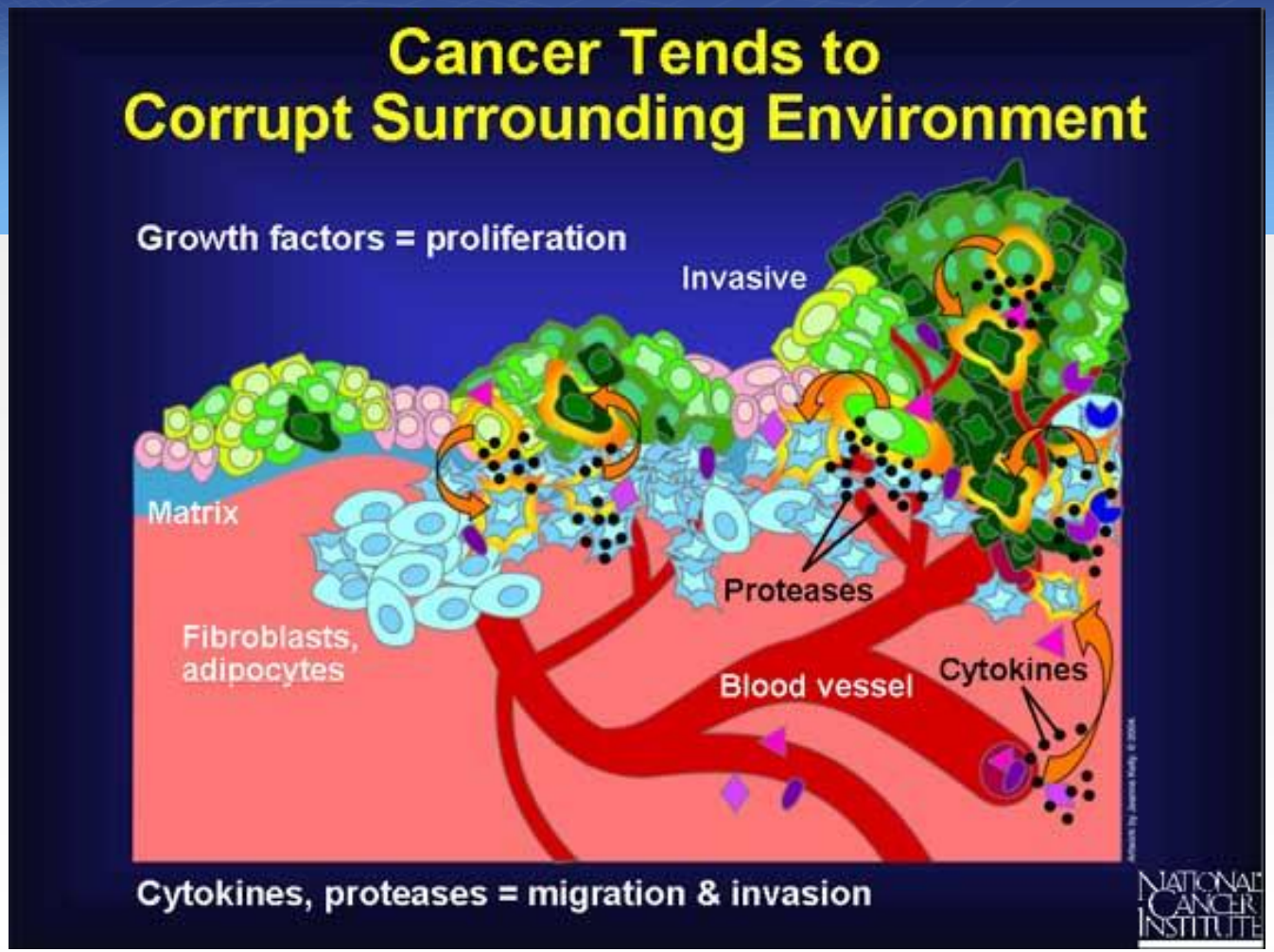

Loss of Normal Growth Control
Normal cell division
Cell Suicide or Apoptosis
Cell damage—no repair
Cancer cell division
First mutation
Second mutation
Third mutation
Fourth or later mutation
Uncontrolled growth

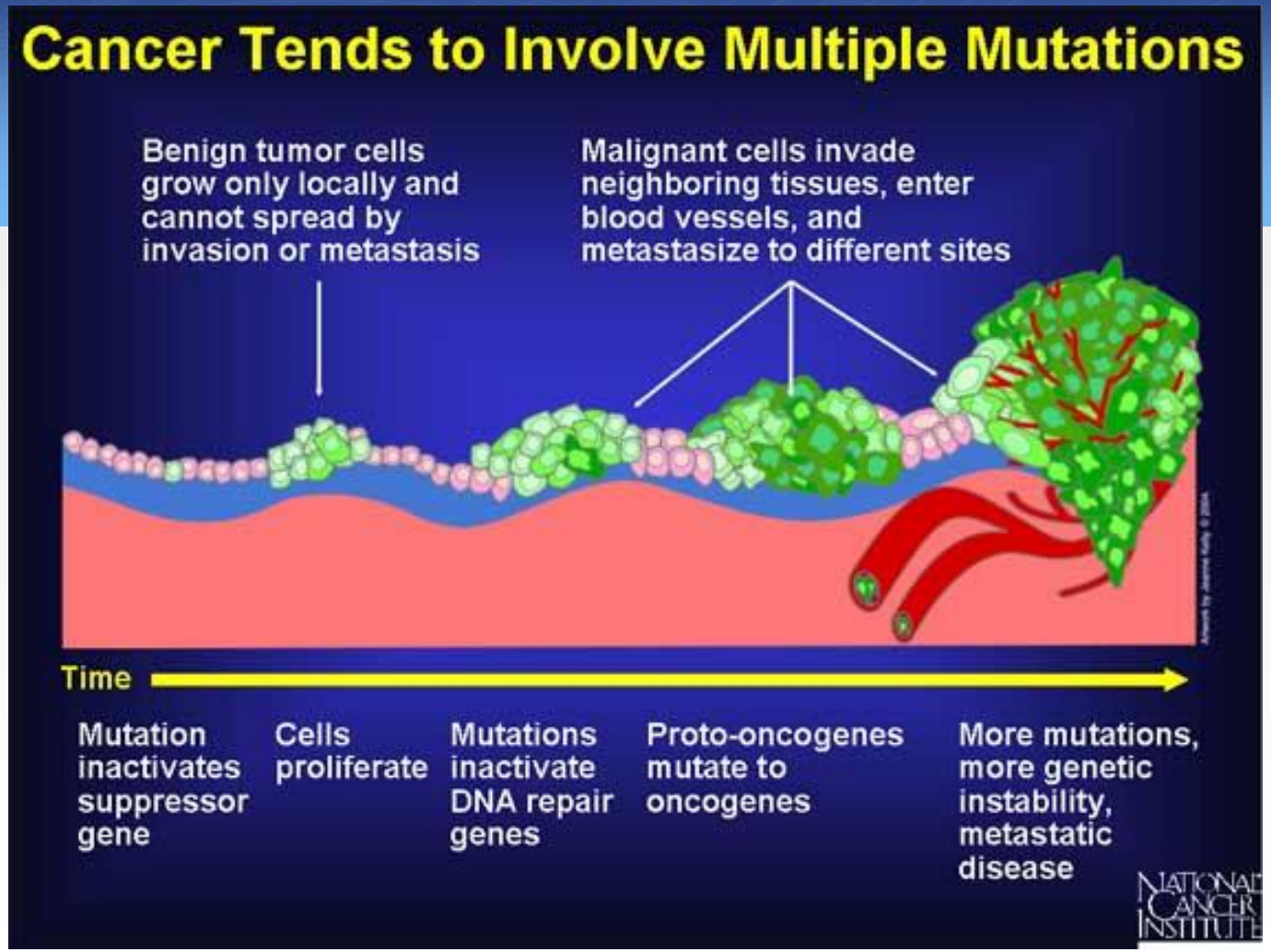

The Beginning of Cancerous Growth
Underlying tissue


Invasion and Metastasis
1
Cancer cells invade surrounding tissues and blood vessels
2
Cancer cells are transported by the circulatory system to distant sites
3
Cancer cells reinvade and grow at new location
NATIONAL CANCER INSTITUTE


Cancer Tends to
Corrupt Surrounding Environment
Growth factors = proliferation
Invasive
Matrix
Proteases
Fibroblasts,
adipocytes
Blood vessel
Cytokines
Cytokines, proteases = migration & invasion
NATIONAL
CANCER
INSTITUTE

BENINGN TUMOR…….MALIGNANT TUMOR (CANCER)

- **PRIMARY TUMORIGENESIS (……PROLIFERATION)**
- **SECONDARY TUMORIGENESIS (…….INVASIVE GROWTH…….METASASIS)**


Cancer Tends to Involve Multiple Mutations
Benign tumor cells grow only locally and cannot spread by invasion or metastasis
Malignant cells invade neighboring tissues, enter blood vessels, and metastasize to different sites
Time
Mutation inactivates suppressor gene
Cells proliferate
Mutations inactivate DNA repair genes
Proto-oncogenes mutate to oncogenes
More mutations, more genetic instability, metastatic disease
NATIONAL CANCER INSTITUTE

Biology of tumor growth: benign and malignant neoplasms

TABLE 7–2 Comparisons Between Benign and Malignant Tumors

Characteristics	Benign	Malignant
Differentiation/anaplasia	Well differentiated; structure may be typical of tissue of origin	Some lack of differentiation with anaplasia; structure is often atypical
Rate of growth	Usually progressive and slow; may come to a standstill or regress; mitotic figures are rare and normal	Erratic and may be slow to rapid; mitotic figures may be numerous and abnormal
Local invasion	Usually cohesive and expansile well-demarcated masses that do not invade or infiltrate surrounding normal tissues	Locally invasive, infiltrating the surrounding normal tissues; sometimes may be seemingly cohesive and expansile
Metastasis	Absent	Frequently present; the larger and more undifferentiated the primary, the more likely are metastases

Cancer: From the View of Cancer Cell Biology

"Tumor formation arises as a consequence of alterations in the control of cell proliferation and disorders in the interactions between cells and their surroundings that result in nvasion and metastasis."

Christopher Marshall

Cell 64:313-326

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Characteristics of Cancer Cells

- **Cancer cells are genetically altered via gene or chromosome mutations so:**

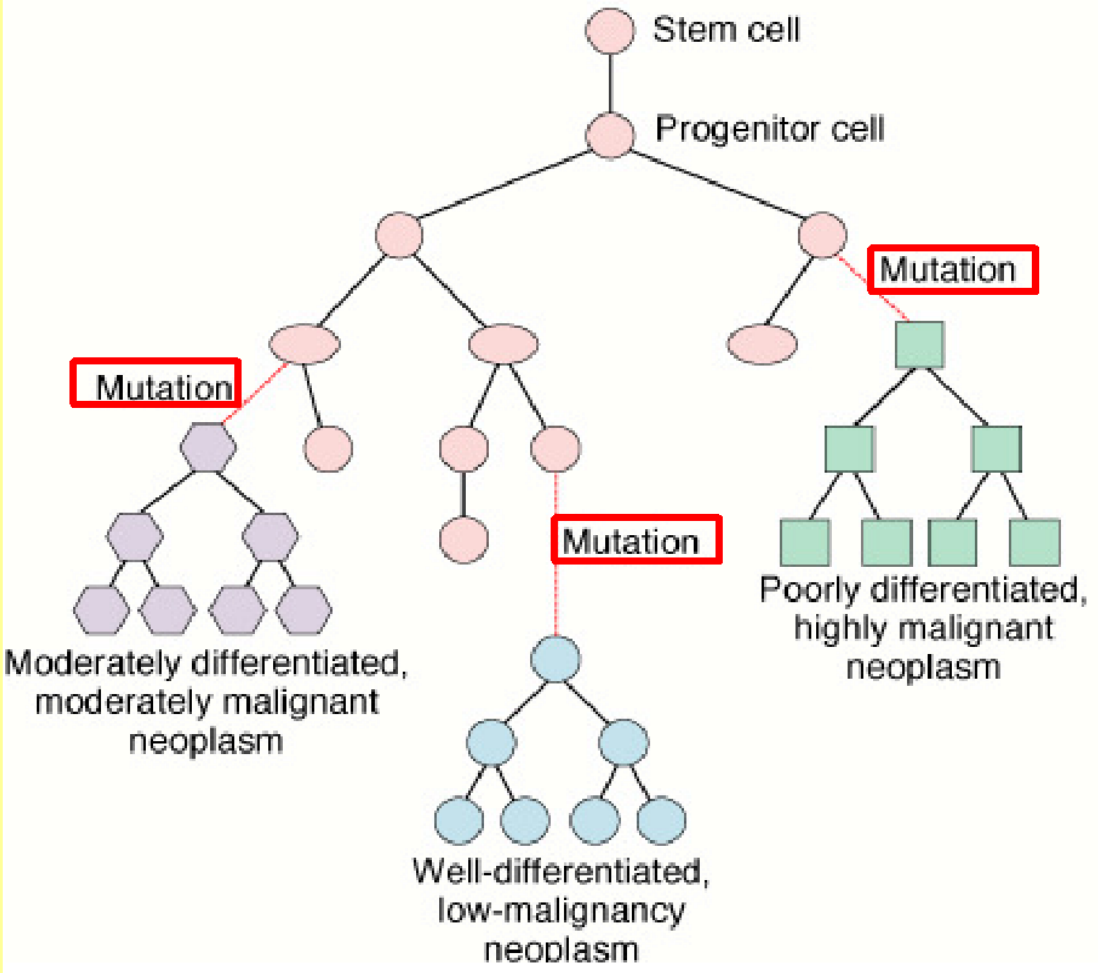
  - lack normal controls over cell division or apoptosis.

  - may express inappropriate genes (e.g. for telomerase, enzyme that maintains length of DNA for continued division)

  - are genetically unstable due to loss of DNA repair mechanisms (so are more susceptible to radiation damage than normal cells).
- **Divide excessively (proliferate) & indefinitely producing neoplasms.**
- **Live indefinitely (do not show apoptosis).**
- **Lose the normal attachment to other cells so become metastatic** (travelling via blood/lymph to invade distant sites).
- **Secrete signals for angiogenesis** (growth of blood vessels into tumor).

Cancer Cells are Undifferentiated & Malignant

- **Cancer cells are undifferentiated** to varying degrees (even anaplastic, like stem cells) so divide & do not perform the normal function of mature cells.
- **The less differentiated the cancer cell the more malignant the cancer** (the more rapidly growing is the tumor).



Cell, Vol. 100, 57–70, January 7, 2000,

The Hallmarks of Cancer

Review

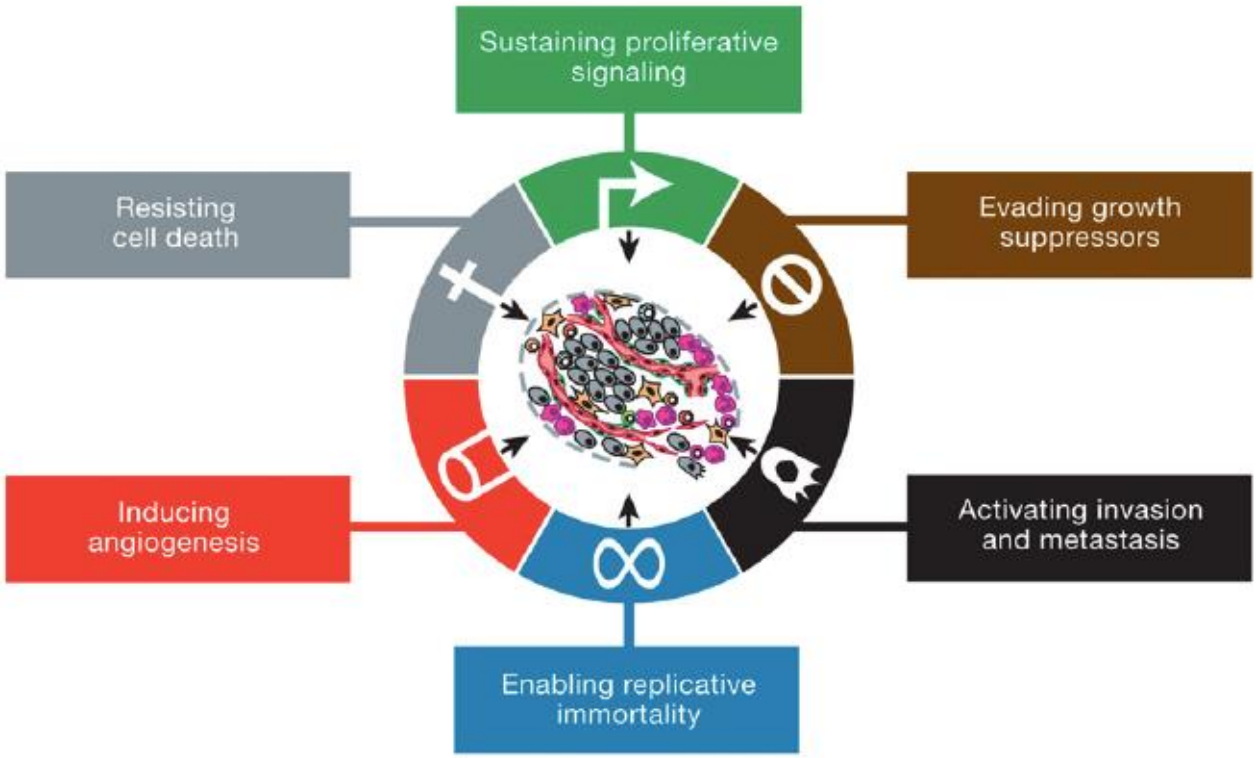
Douglas Hanahan* **and Robert A. Weinberg†**
*Department of Biochemistry and Biophysics and Hormone Research Institute
University of California at San Francisco
San Francisco, California 94143
†Whitehead Institute for Biomedical Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02142

evolve progressively from normalcy via a series of premalignant states into invasive cancers (Foulds, 1954).

These observations have been rendered more concrete by a large body of work indicating that the genomes of tumor cells are invariably altered at multiple sites, having suffered disruption through lesions as subtle as point mutations and as obvious as changes in chromosome complement (e.g., Kinzler and Vogelstein, 1996). Transformation of cultured cells is itself a

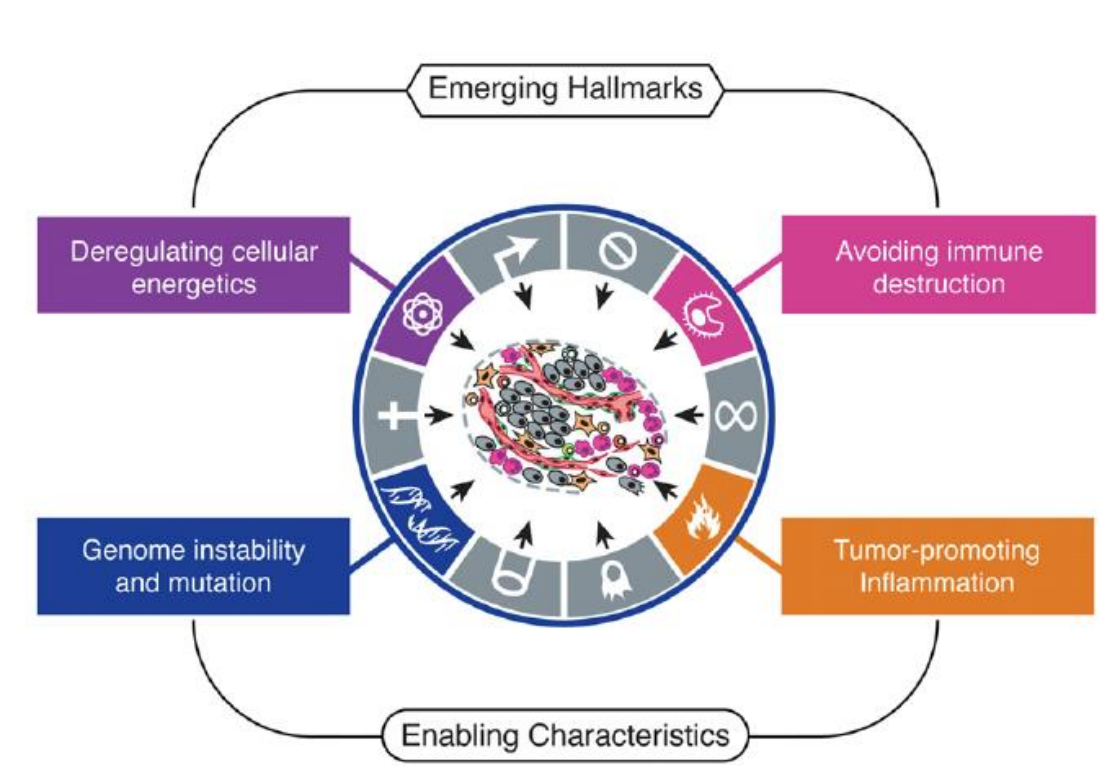
Hallmarks of Cancer

Hanahan and Weimberg, Cell, 2000



Hallmarks of Cancer: The Next Generation

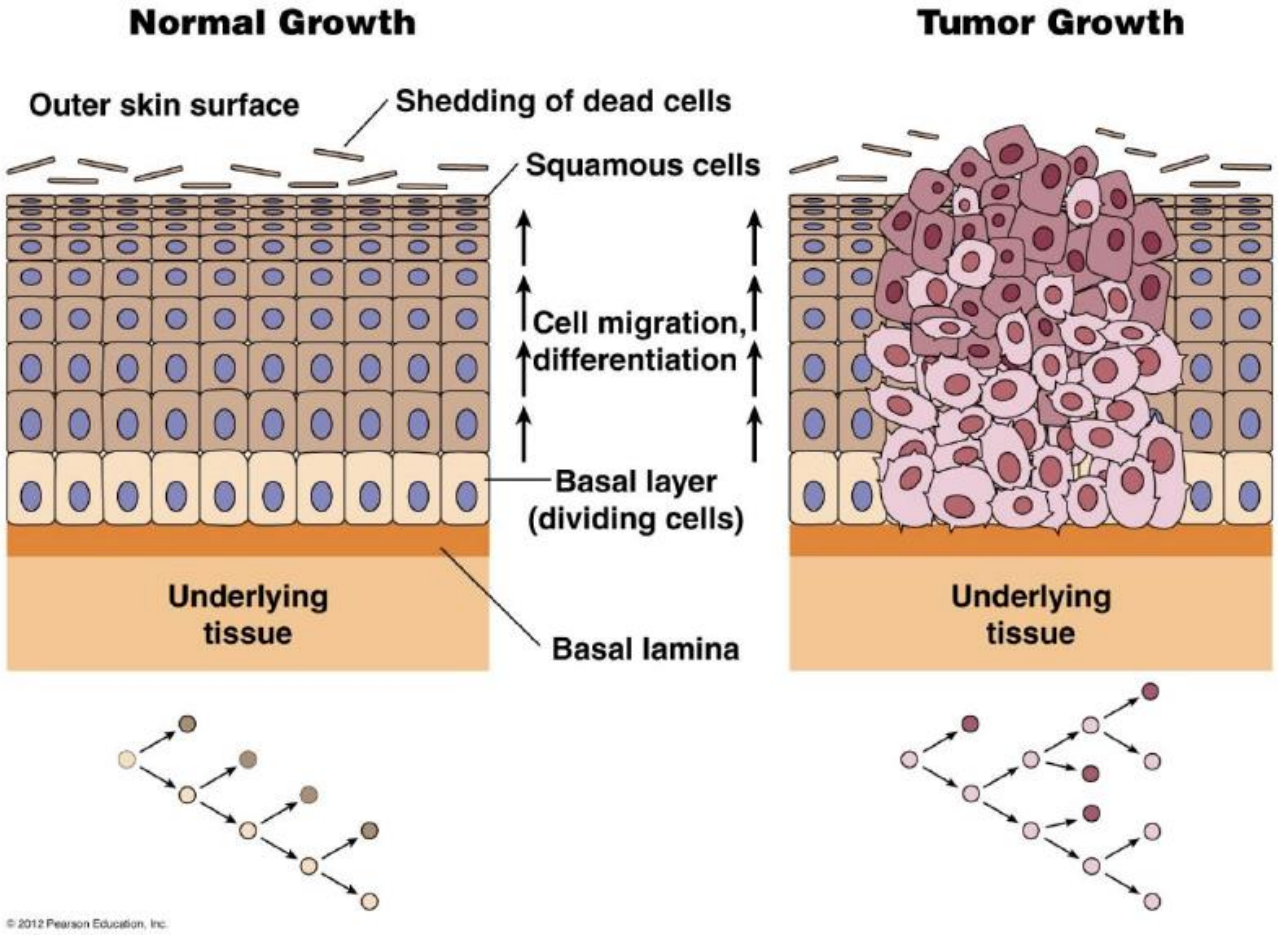
Hanahan and Weimberg, Cell, 2011



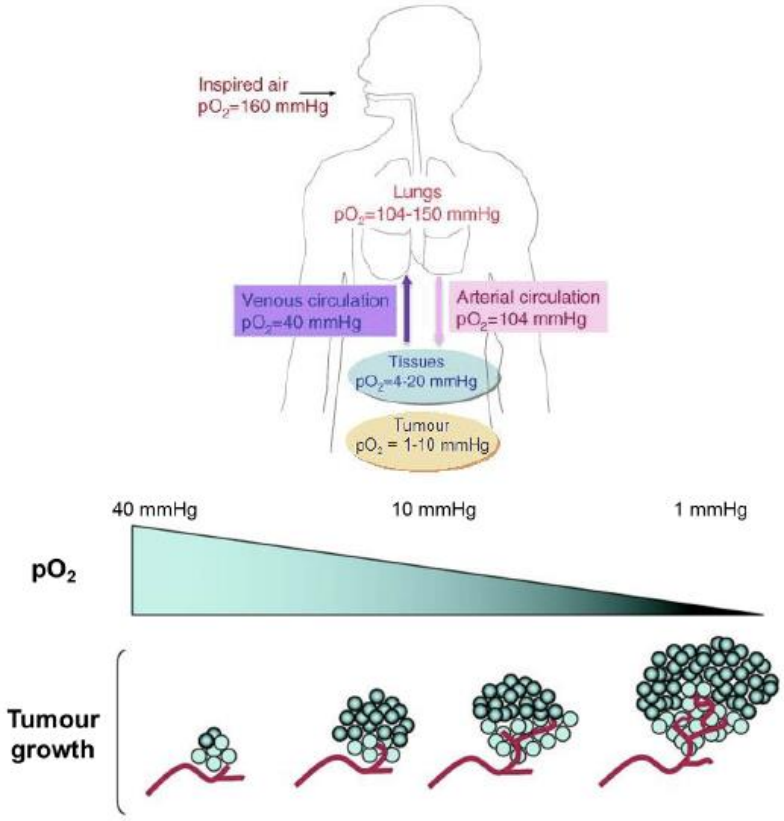
Hallmarks of cancer

1. Sustaining proliferative signalling
2. Evading growth suppressors

→ **Uncontrolled growth (primary tumourigenesis)!**

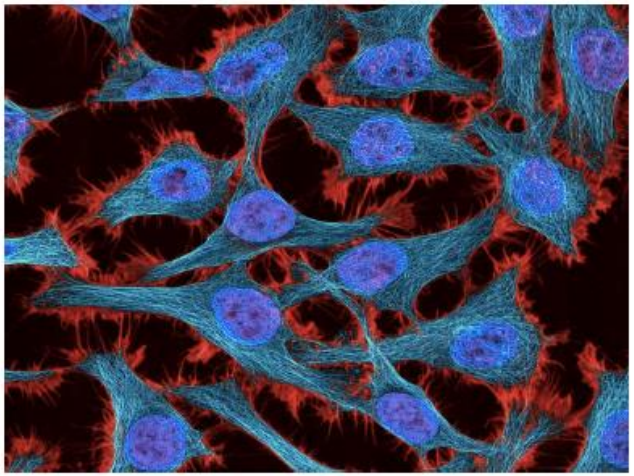

Normal Growth
Tumor Growth
Outer skin surface
Shedding of dead cells
Squamous cells
Cell migration, differentiation
Basal layer (dividing cells)
Basal lamina
Underlying tissue
Underlying tissue
© 2012 Pearson Education, Inc.

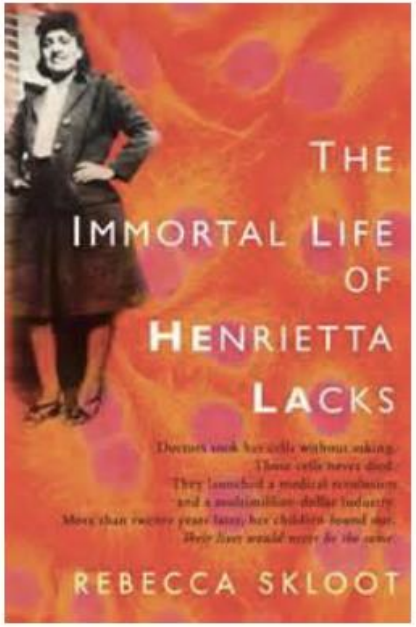
Tumour growth -> Hypoxia



Hallmarks of cancer

3. Resisting cell death (‘apoptosis’)
4. Enabling replicative immortality



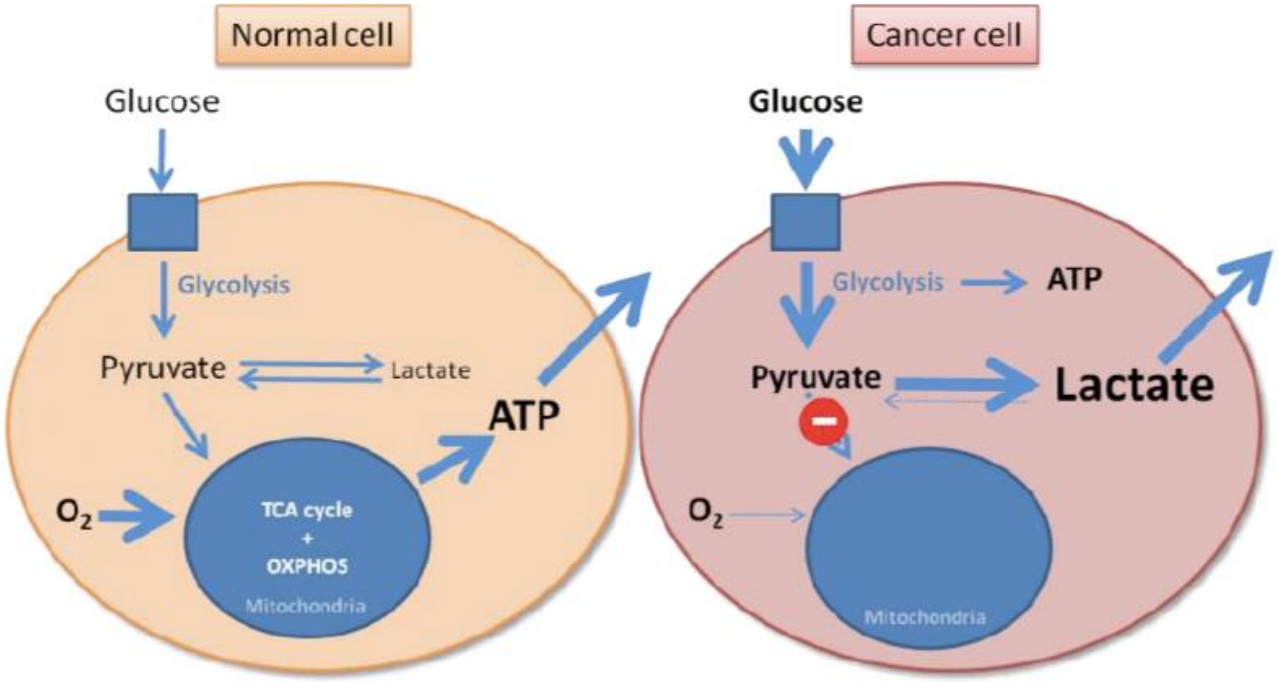


Hallmarks of cancer

5. Deregulating cellular energetics

→ Aerobic glycolysis
(Warburg effect)

Warburg effect

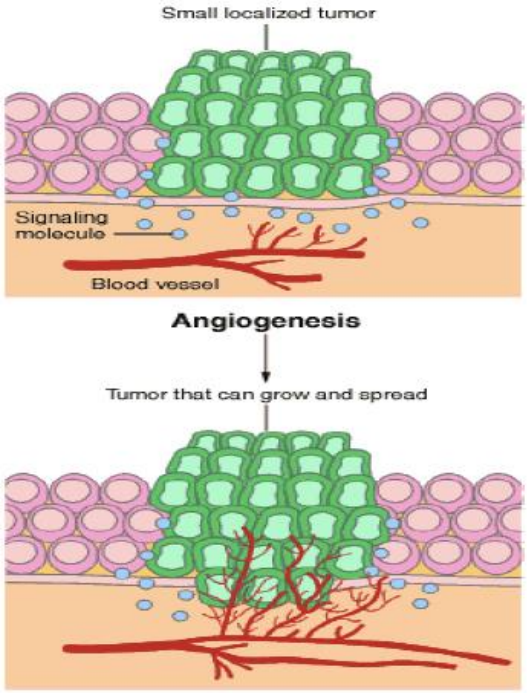


36 mol ATP/mol glucose

2 mol ATP/mol glucose

Hallmarks of cancer

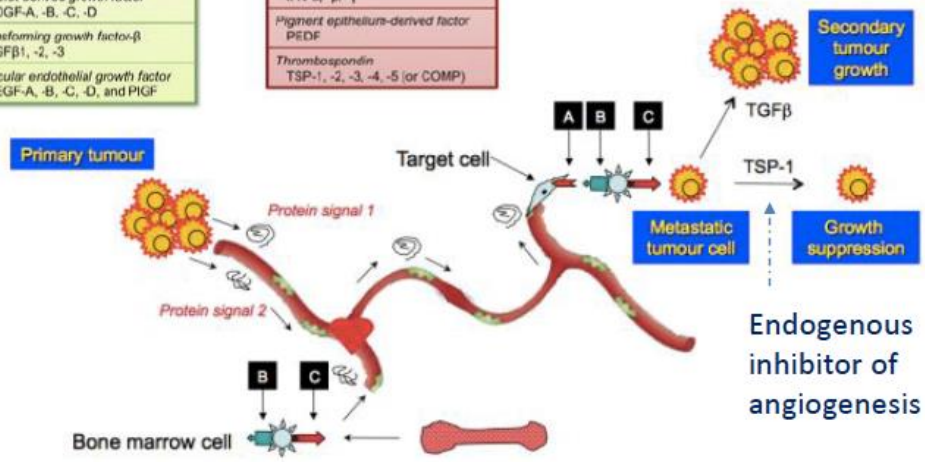
6. Inducing angiogenesis



Balance of angiogenesis

Promoter
Chemokines CXC-1, -2, -3, -5, -6, -7, -8
Fibroblast growth factor FGF-1, -2
Hepatocyte growth factor HGF
Hypoxia-inducible factor HIF-1, -2, -3
Platelet-derived growth factor PDGF-A, -B, -C, -D
Transforming growth factor-β TGFβ1, -2, -3
Vascular endothelial growth factor VEGF-A, -B, -C, -D, and PlGF

Inhibitor
Angiopoietin Ang-1, -2
Angiostatin
Chemokines CXC-4, -9, -10, -11, -12, -14
Endostatin
Interferon IFN-α, -β, -γ
Pigment epithelium-derived factor PEDF
Thrombospondin TSP-1, -2, -3, -4, -5 (or COMP)

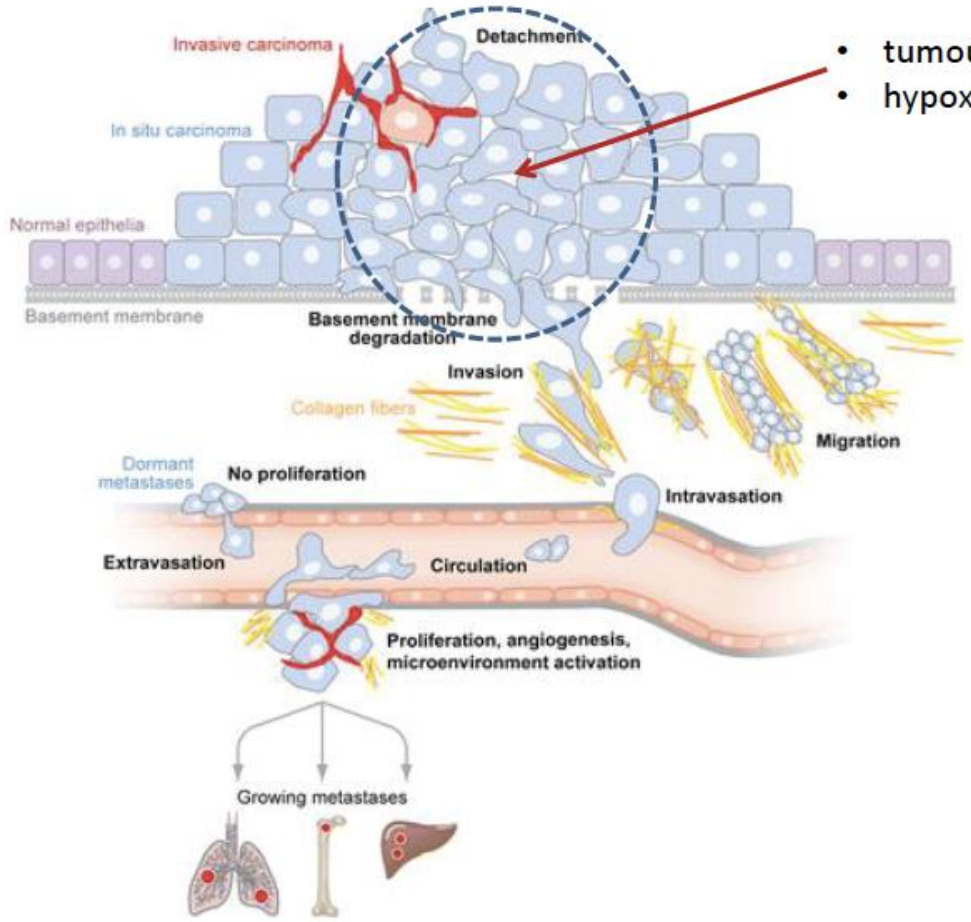


Endogenous inhibitor of angiogenesis

Hallmarks of cancer

7. Activating invasion & metastasis

METASTATIC CASCADE



- tumour m-e
- hypoxia

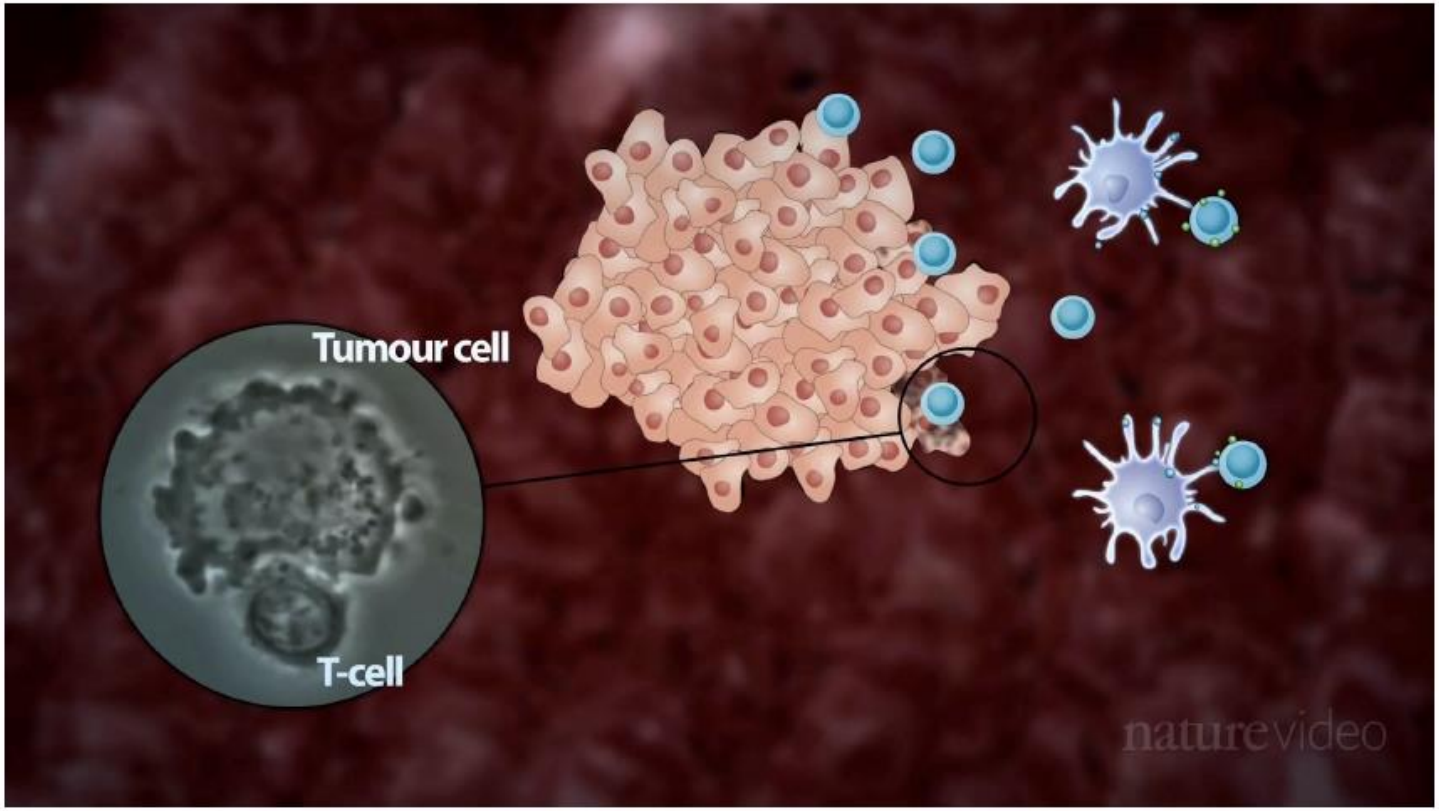
Hallmarks of cancer

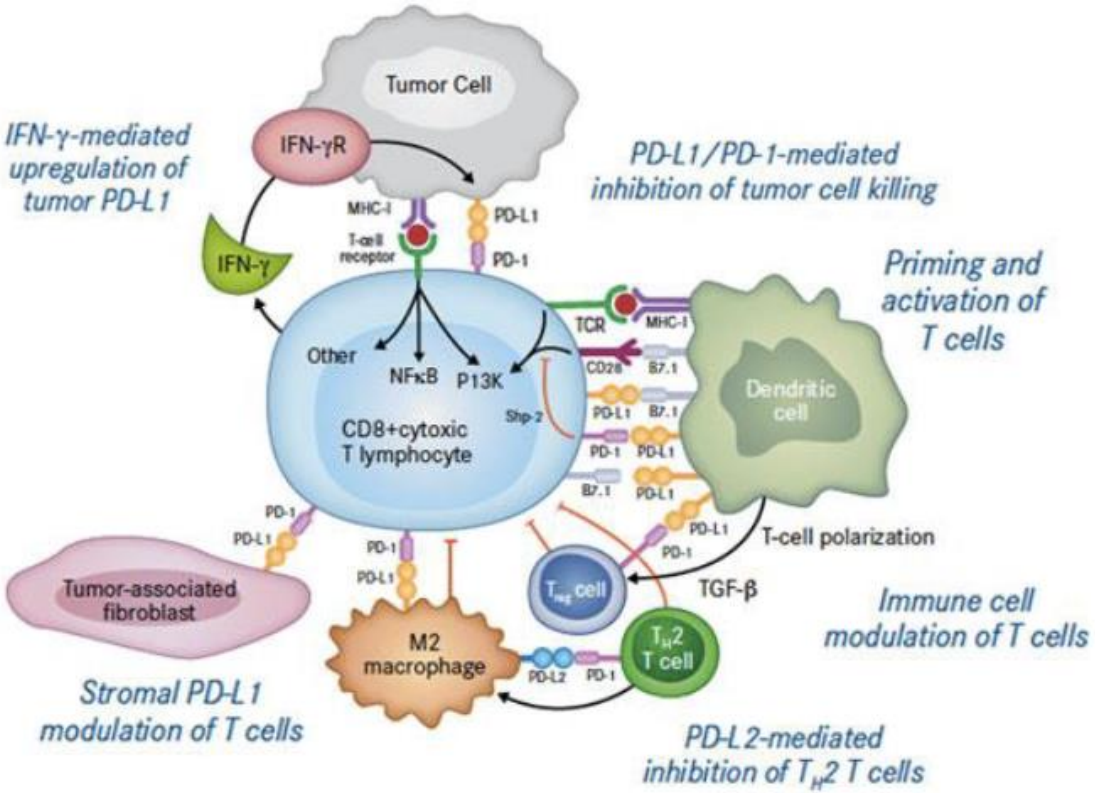
8. Avoiding immune destruction

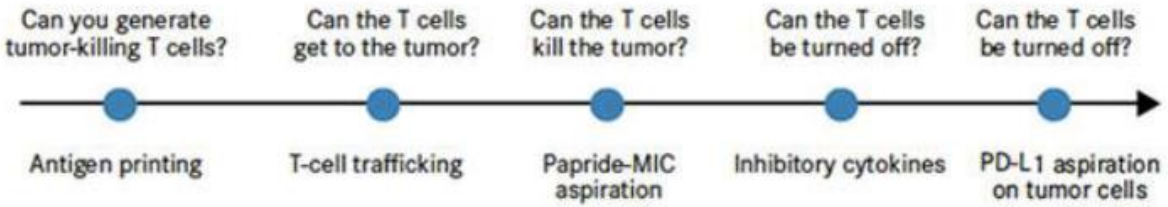
(nb. tumour-promoting inflammation)

→ Immuno-oncology

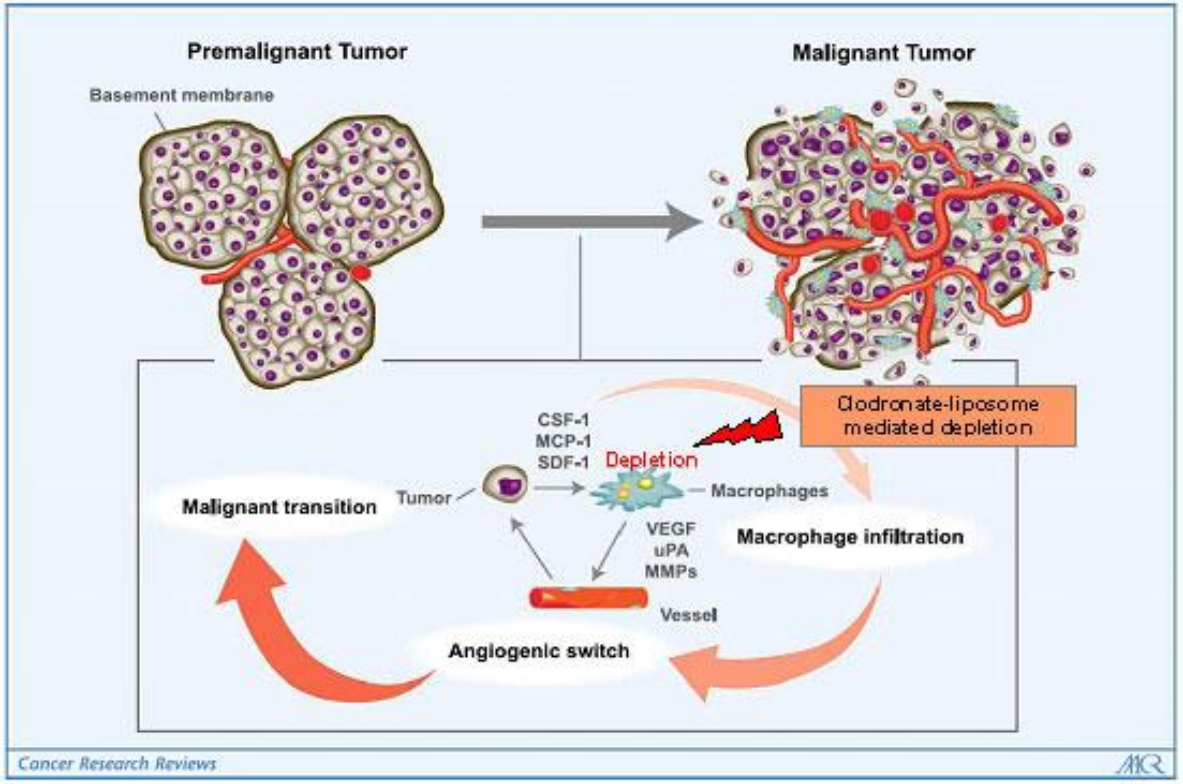
TUMOUR – IMMUNE CELL INTERACTION



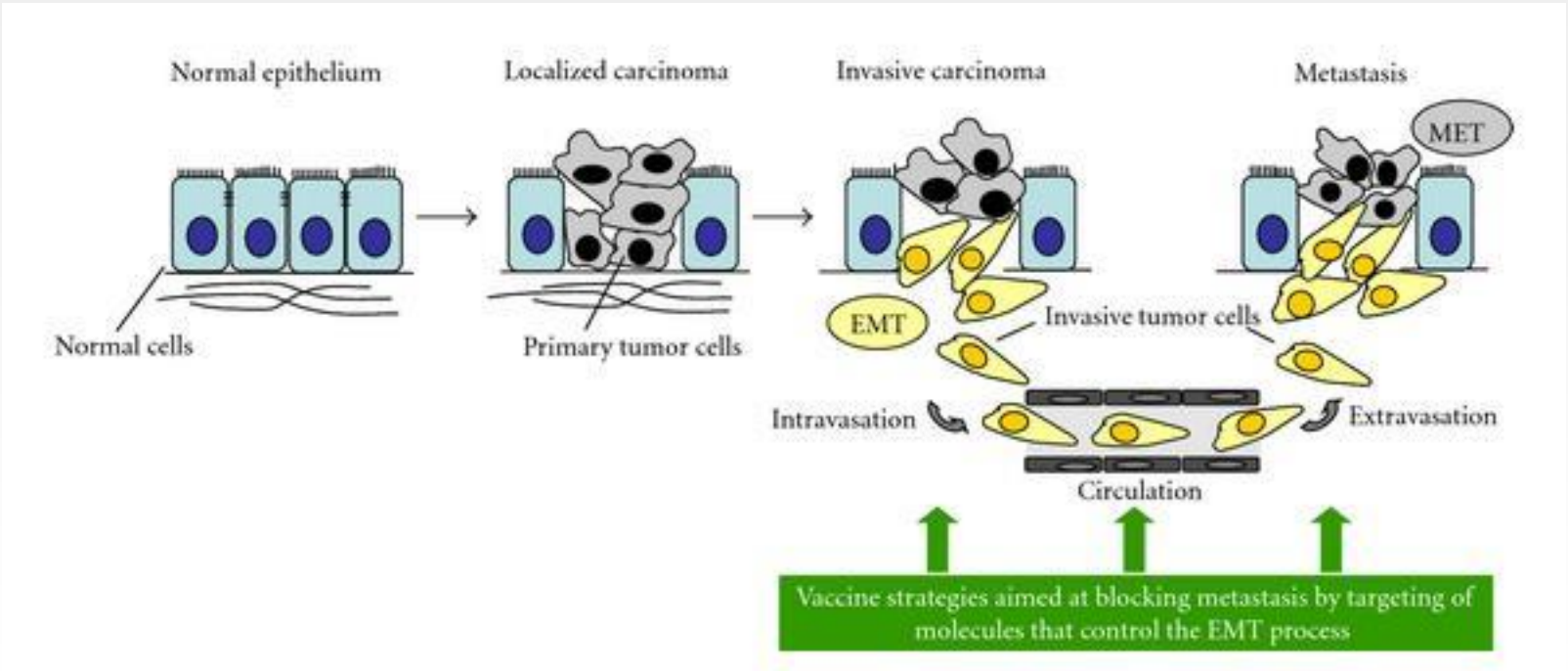

Tumor Cell
IFN-γ-mediated upregulation of tumor PD-L1
IFN-γR
IFN-γ
MHC-I
T-cell receptor
PD-L1
PD-1
PD-L1/PD-1-mediated inhibition of tumor cell killing
Priming and activation of T cells
TCR
MHC-I
CD28
B7.1
Dendritic cell
Other
NFκB
P13K
Shp-2
CD8+cytoxic T lymphocyte
T-cell polarization
TGF-β
Tumor-associated fibroblast
M2 macrophage
Treg cell
TH2 T cell
PD-L2
Immune cell modulation of T cells
Stromal PD-L1 modulation of T cells
PD-L2-mediated inhibition of TH2 T cells

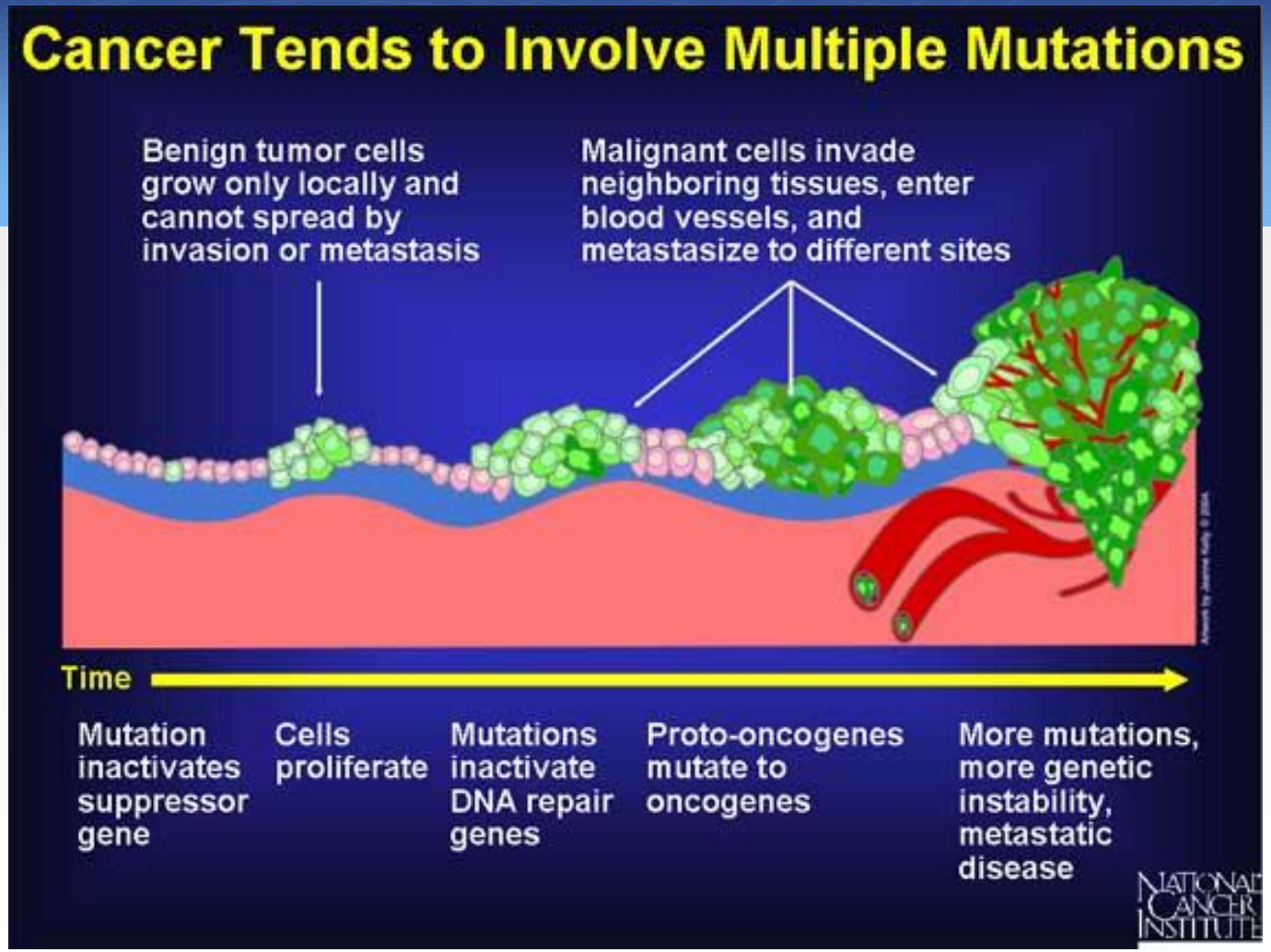

Can you generate tumor-killing T cells?
Can the T cells get to the tumor?
Can the T cells kill the tumor?
Can the T cells be turned off?
Can the T cells be turned off?
Antigen printing
T-cell trafficking
Papride-MIC aspiration
Inhibitory cytokines
PD-L1 aspiration on tumor cells

The “cancer tissue”



Tumour progression




Cancer Tends to Involve Multiple Mutations
Benign tumor cells grow only locally and cannot spread by invasion or metastasis
Malignant cells invade neighboring tissues, enter blood vessels, and metastasize to different sites
Time
Mutation inactivates suppressor gene
Cells proliferate
Mutations inactivate DNA repair genes
Proto-oncogenes mutate to oncogenes
More mutations, more genetic instability, metastatic disease
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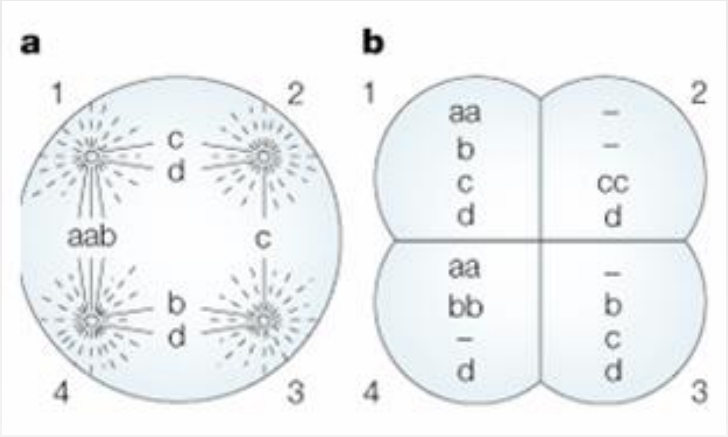
Cancer Biology: The Basics

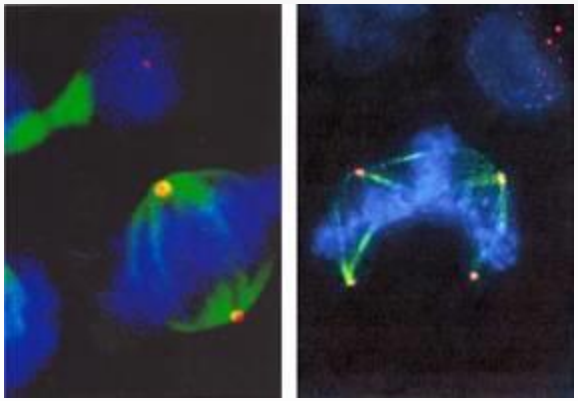
- **The vocabulary**
- **Impact of cancer on human population**
- **Hallmarks of cancer**
- **Molecular bases of cancer**

Genetic Theory of Cancer

Theodor Boveri, 1914



dispermic fertilization in sea urchin



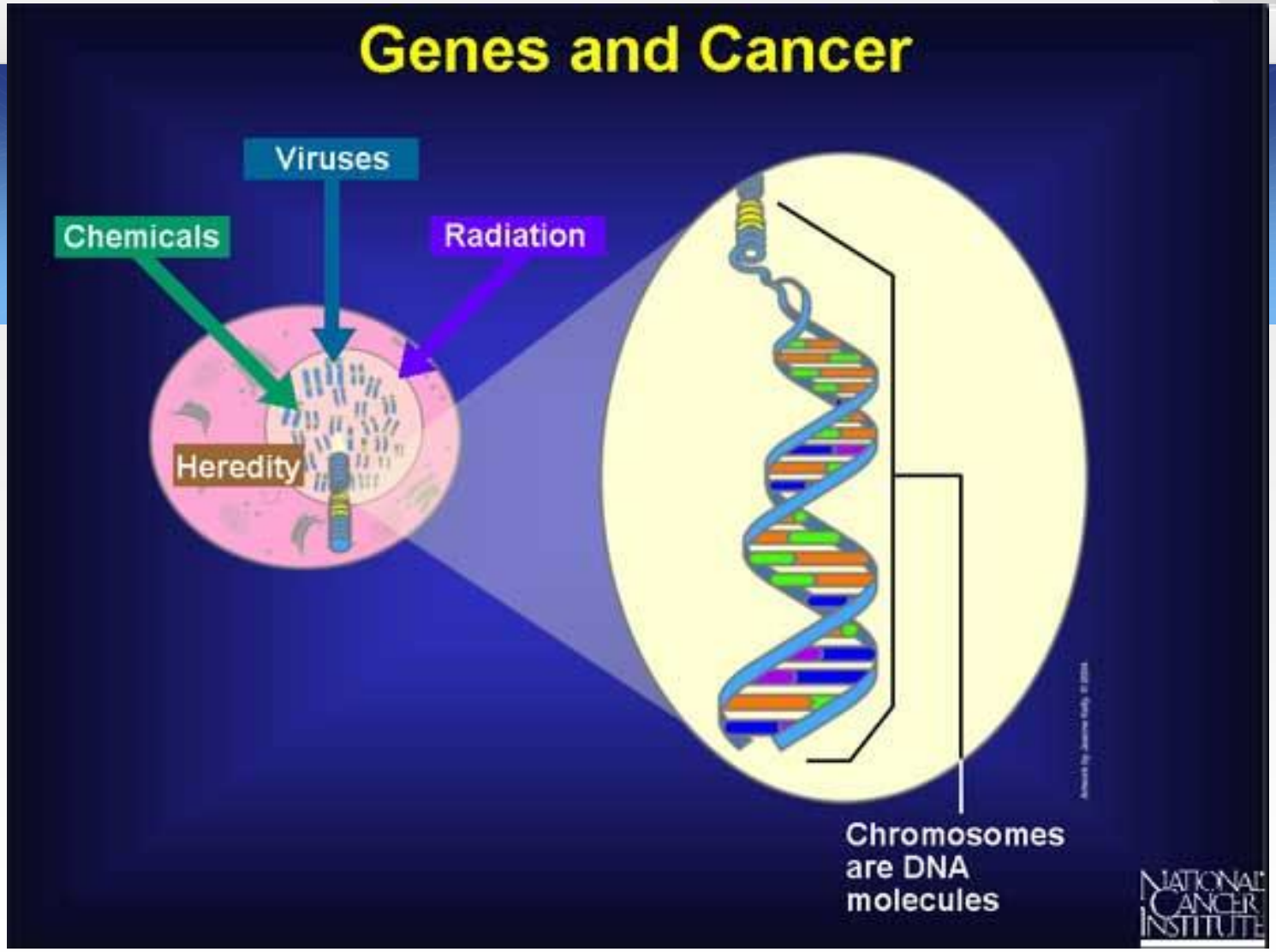
normal cancer

IF by Bill Brinkley

- When I published the results of my experiments on the development of double-fertilized sea-urchin eggs in 1902, I added the suggestion that malignant tumors might be the result of a certain abnormal conditions of the chromosomes, which may arise from multipolar mitosis. ……So I have carried on for a long time the kind of experiments I suggested, which are so far without success, but my convinction remains unshaken. *Theodor Boveri, pathologist, 1914*

Cancer is a Genetic Disease

- Somatic mutations occur in most cancers.
- Inherited germline mutations occur in rare familial cancer syndromes.
- Increases in mutation rate or genomic instability increase frequency of cancer.
- Aneuploidy is a hallmark of cancer cells.
- Genetic selection at the level of single cells.


Genes and Cancer
Viruses
Chemicals
Radiation
Heredity
Chromosomes are DNA molecules
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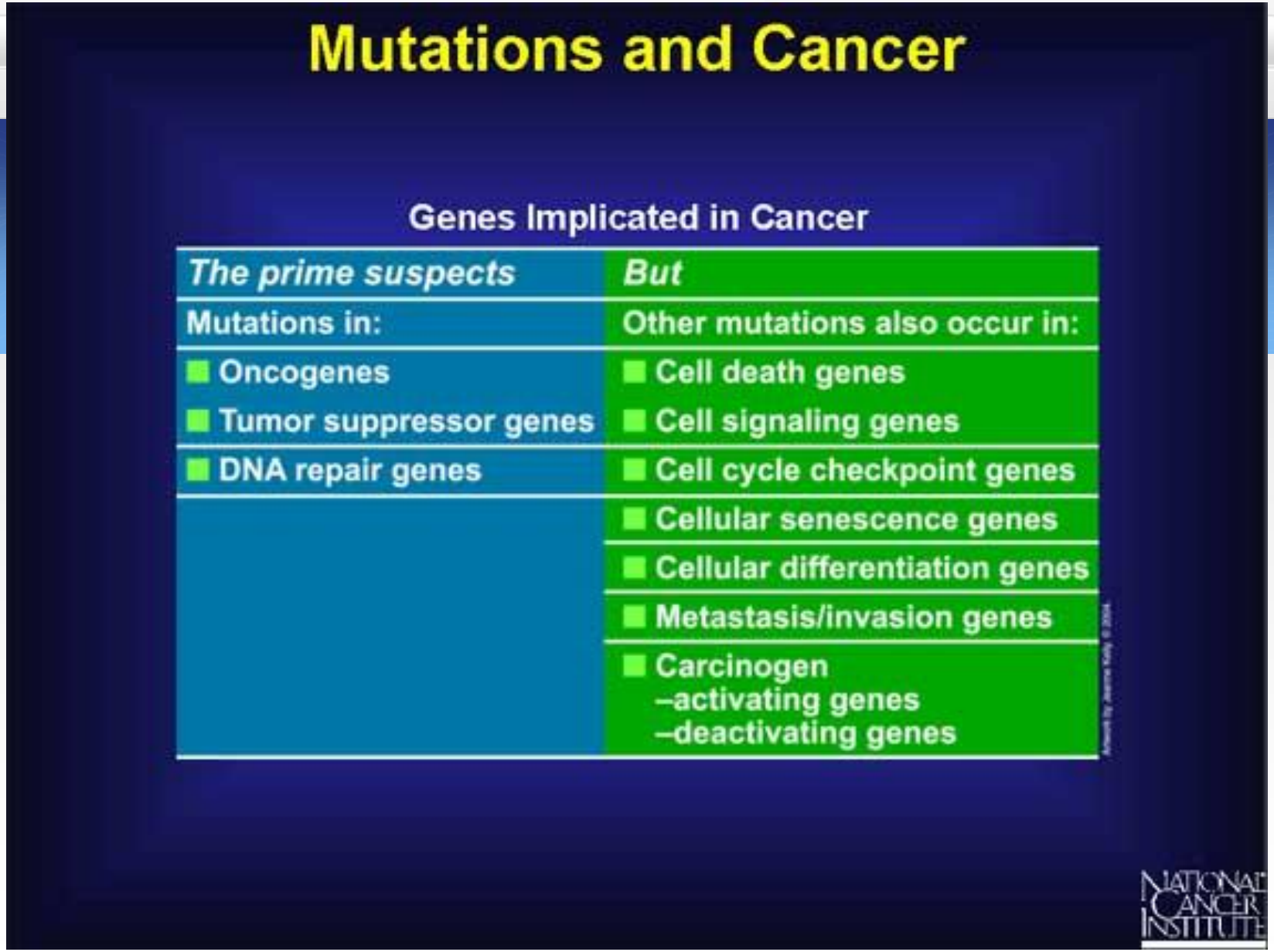
Mutations and Cancer



Cancer and genes:

Three classes of genes are frequently mutated in cancer:

- Proto-oncogenes ($\Rightarrow$ oncogenes)
- Tumor suppressor genes
- Mutator genes

Proto-oncogenes ⇒ oncogenes:

Proto-oncogenes

- Proto-oncgenes are genes that possess normal gene products and stimulate normal cell development.

Oncogenes

- Oncogenes arise from mutant proto-oncogenes.
- Oncogenes are more active than normal or active at inappropriate times and stimulate unregulated cell proliferation.

Some tumor viruses that infect cells possess oncogenes:

- RNA tumor viruses = possess viral oncogenes (derived form cellular proto-oncogenes) capable of transforming cells to a cancerous state.
- DNA tumor viruses = another class of tumor viruses; do not carry oncogenes, but induce cancer by activity of viral gene products on the cell (no transformation per se).

Types & effects of different types of mutations:

1. **Point mutations**: occur in protein coding or controlling sequences.

2. **Deletion**: frameshifts may lead to defective proteins.

3. **Gene amplification**: random over-replication of small segments of DNA results in extra copies (up-regulates cell growth).

Mutator genes:

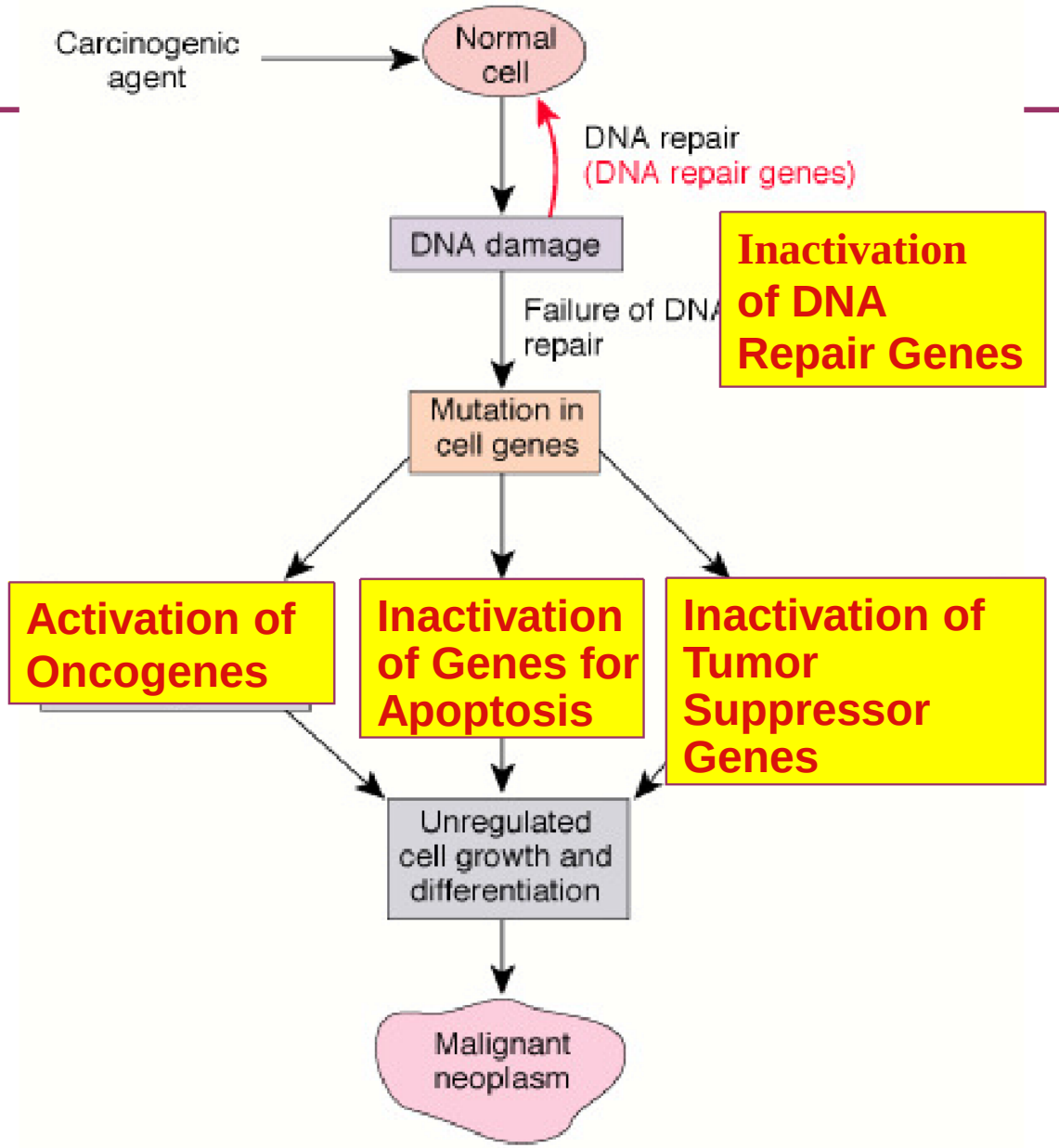
- Mutator gene increases spontaneous mutation rate of other genes.

- Mutator gene products are involved in DNA replication and repair; mutations make the cell error prone.

EPIGENETICS:

A revolution in understanding and managing cancer in the post-genomic era:

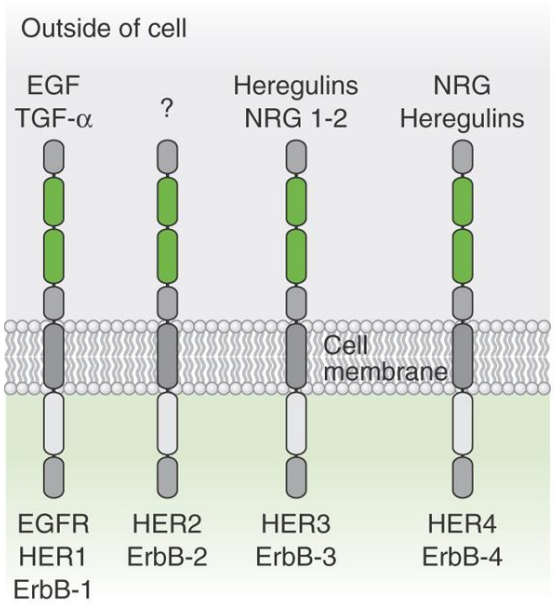
How Carcinogens Cause Cancer



Molecular Abnormalities in Solid Tumors, HER2/neu

- The *HER2/neu* gene encodes one of a family of human epidermal growth-factor receptors.
- This gene is frequently amplified in breast cancer cells, resulting in increased amounts of HER2 cell surface protein.
- HER2-expressing tumors are sensitive to herceptin, a monoclonal antibody therapy.
- HER2 protein is detected by immunohistochemistry (IHC).
- *HER2/neu* gene amplification is detected by fluorescence in situ hybridization (FISH).

The EGFR Gene Family



Molecular Abnormalities in Solid Tumors, EGFR

- The EGFR oncogene encodes another of the same family of epidermal growth factor receptors.
- This gene is mutated or amplified in several types of cancer cells.
- Tumors with activating mutations in EGFR are sensitive to tyrosine kinase inhibitors (TKI).
- EGFR protein is detected by IHC.
- EGFR gene and chromosome abnormalities are detected by FISH.
- EGFR gene mutations are detected by SSCP, SSP-PCR, or direct sequencing.

Molecular Abnormalities in Solid Tumors, *K-ras*

- The Kirsten rat sarcoma viral oncogene (*K-ras*) encodes a key component of cell signaling.
- Mutations in *K-ras* are the most common oncogene mutations in cancer.
- *K-ras* mutations are associated with tumor malignancy and may affect response to some therapies.
- *K-ras* gene mutations are detected by SSCP or direct sequencing.

Molecular Abnormalities in Solid Tumors, *TP53*

- The 53-kilodalton tumor suppressor gene (*TP53*) encodes a transcription factor.
- *TP53* is mutated in half of all types of cancer.
- Loss of *TP53* function is an indicator of poor prognosis in colon, lung, breast, and other cancers.
- Mutant p53 protein is detected by IHC.
- *TP53* gene mutations are detected by a variety of methods, including SSCP and direct sequencing.

Other Genes Associated with Solid Tumors

- Ewing sarcoma, *EWS*
- Synovial sarcoma translocation, chromsome 18; synovial sarcoma breakpoint 1 and 2, *SYT-SSX1, SYT-SSX2*
- Paired box–Forkhead in rhabdomyosarcoma, *PAX3-FKHR, PAX7-FKHR*
- Ataxia telangiectasia mutated gene, *ATM*
- Von Hippel-Lindau gene, *VHL*
- V-myc avian myelocytomatosis viral-related oncogene, neuroblastoma-derived, *MYCN* or *n-myc*
- Rearranged during transfection (*RET*) protooncogene

Inherited Cancer Gene Mutations

- Inherited tumor suppressor gene mutations are recessive for the malignant phenotype.
- Tumor suppressor gene mutations are dominant with respect to increased risk of malignancy.
- Loss of heterozygosity exposes the recessive mutant allele in a hemizygous state.
- This is explained by the two-hit hypothesis.

Inherited Breast Cancer Risk

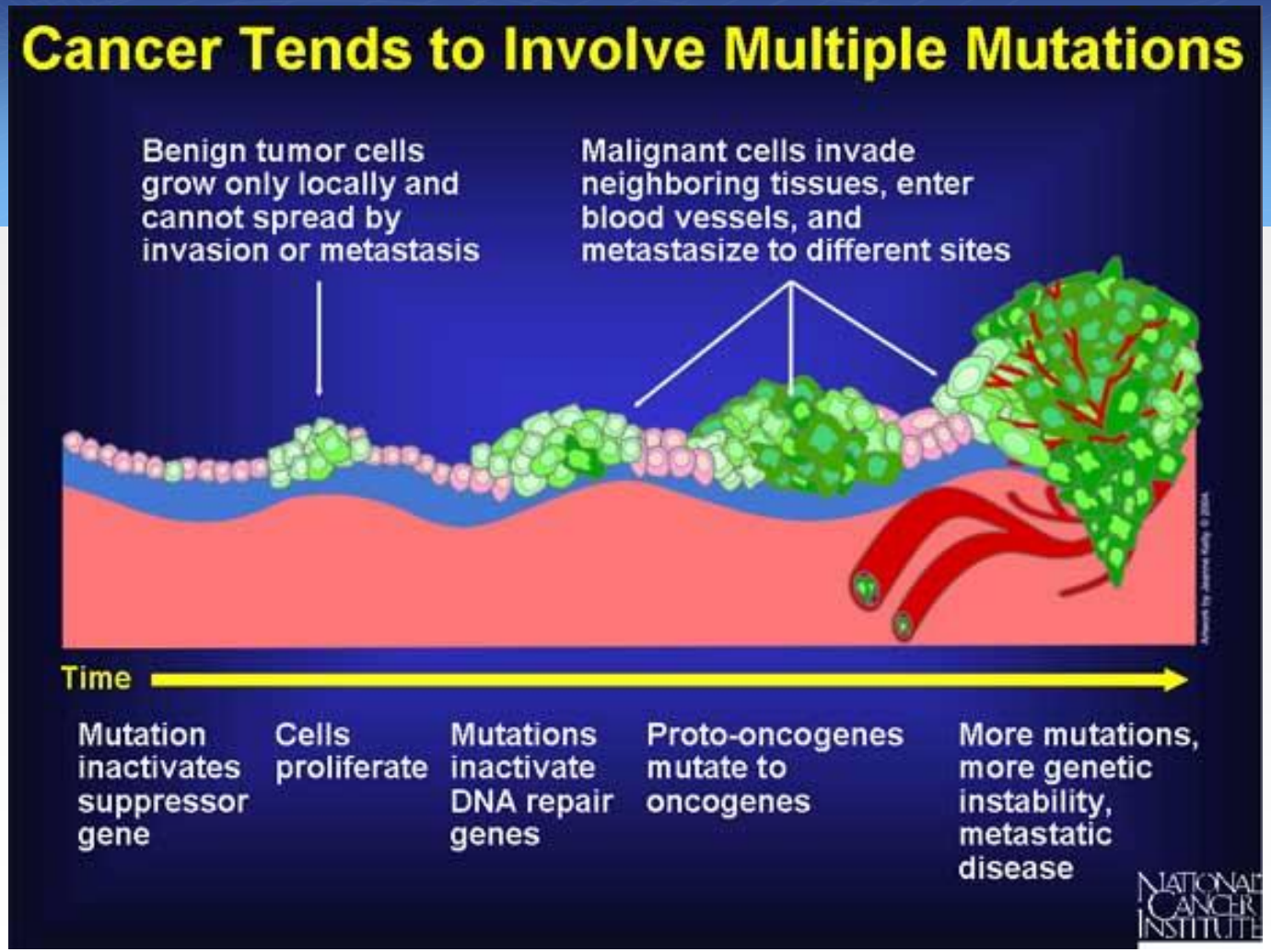
- BRCA1 and BRCA2 are tumor suppressor genes encoding proteins that participate in DNA repair.
- Inherited mutations in BRCA1 or BRCA2 significantly increase risk of breast cancer at an early age.
- Frequently occurring mutations, including 187delAG and 5382insC in BRCA1 and 6174delT in BRCA2, are detected by SSP-PCR and other methods.
- Most mutations are detected by direct sequencing of both genes.

Genetic Pathways to Cancer

Cancers develop through an accumulation of **somatic** (**not a single**) **mutations** in **proto-oncogenes** and **tumor suppressor genes**.

Multiple Mutations in Cancer

- Most malignant tumors cannot be attributed to mutation of a single gene.
- Tumor formation, growth, and metastasis depend on the accumulation of mutations in several different genes.
- The genetic pathways to cancer are diverse and complex.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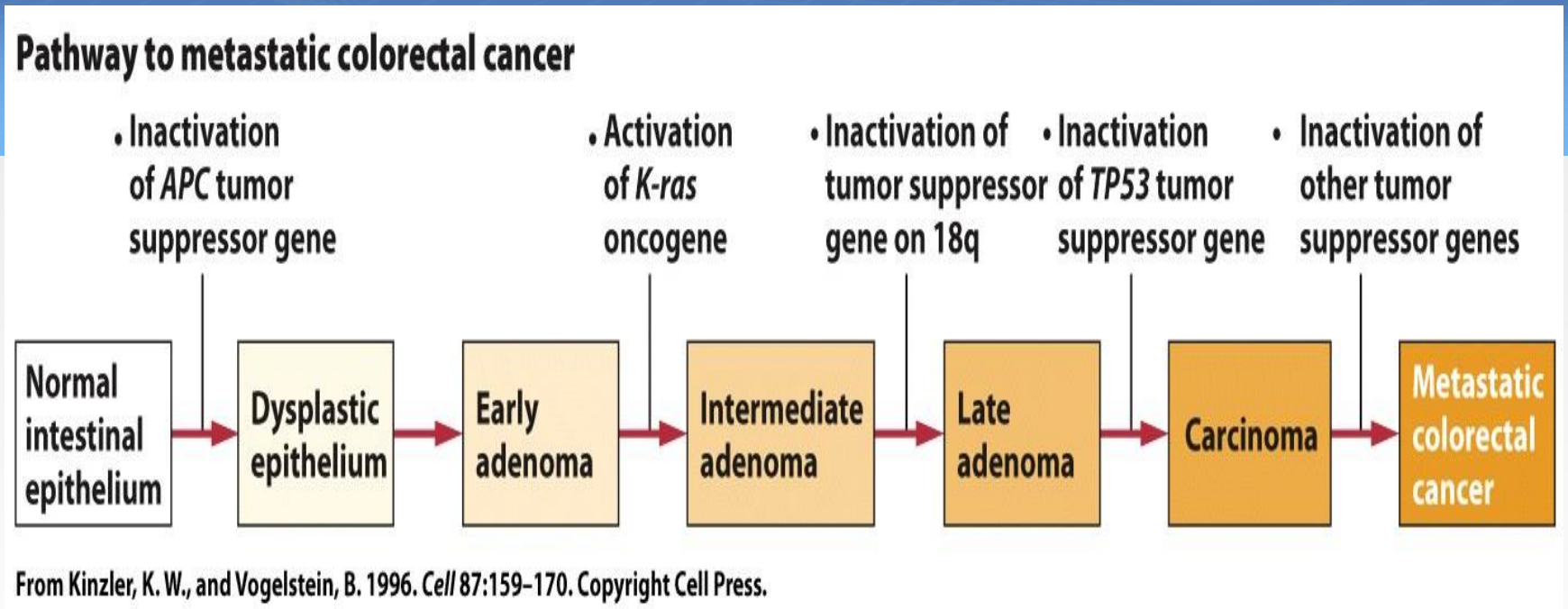


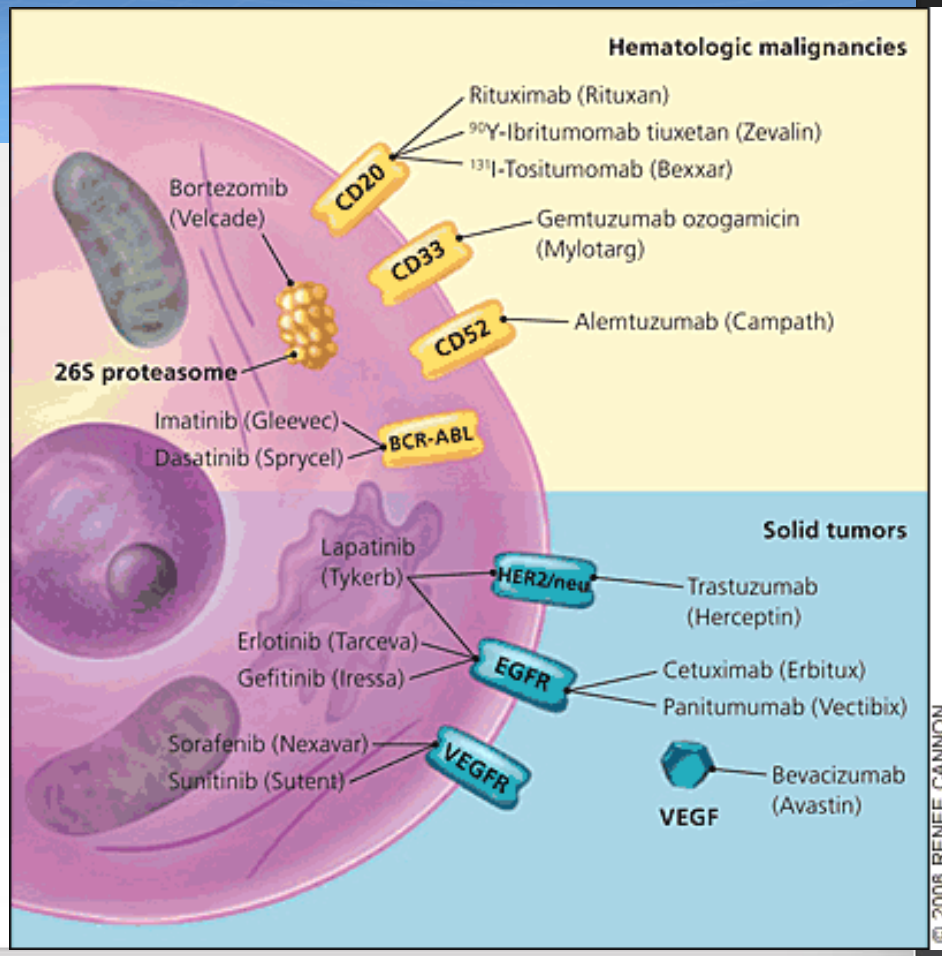
Carcinoma-epithelial cells.
Adenoma-glandular cells.

Somatic Mutation and Cancer

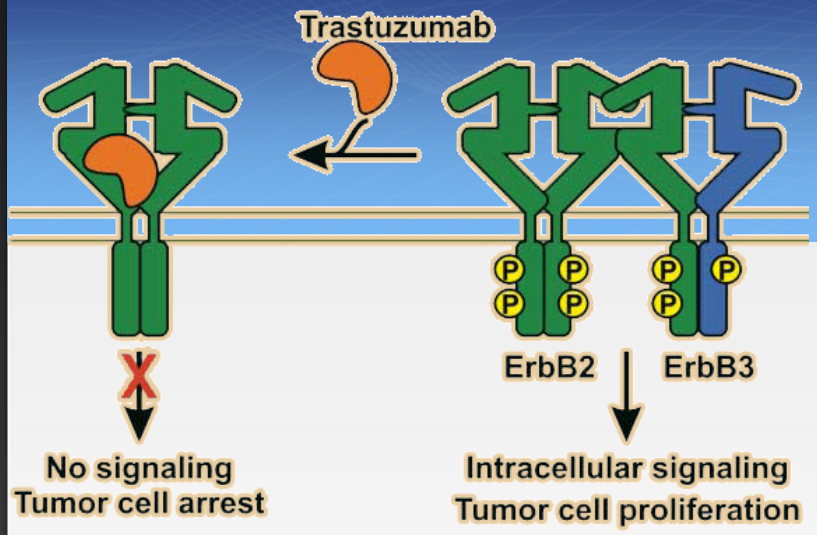
- Somatic mutation is the basis for the development and progression of all types of cancer.

- As mutations accumulate and cells become unregulated, genetic instability increases the likelihood that the cells will develop the hallmarks of cancer.

Target therapy



Herceptin



Badache and Hynes, Cancer Cell 2004

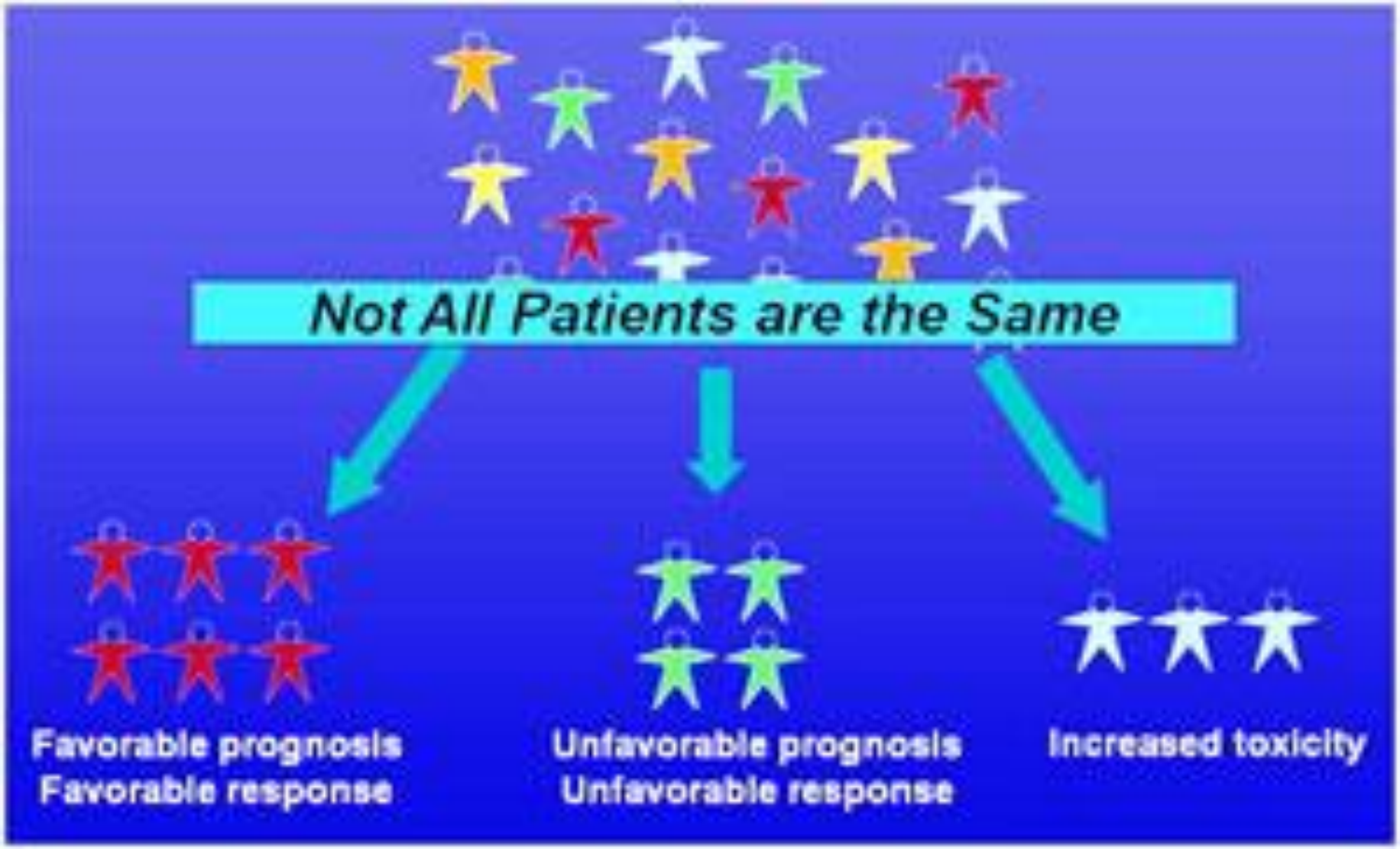
Trastuzumab is a humanized monoclonal antibody anti-ErbB-2

Efficacy on primary tumors with ErbB-2 amplification:

- Inhibits angiogenesis
- induces cytotoxicity
- increase response to chemioterapy
- Inhibits the activation of ErbB-2

Metastatic tumors develop resistance to Herceptin within 12 months

Increase of PI3K activation


Not All Patients are the Same
Favorable prognosis
Favorable response
Unfavorable prognosis
Unfavorable response
Increased toxicity

CONCLUSION

- Cancer is a complex, multi stage, disease
- Cancer can be defined by several hallmarks
- Different genetic alterations (mutations, translocations, epigenetic alterations) underlie cancer hallmarks
- Two main concepts have biological and clinical relevance: the “cancer tissue” and “tumour progression”
- Clinical management of cancer patients has improved thanks to the increasing knowledge of cancer biological and molecular bases