The Nature of Cancer

Rodrigo Romero

Course objectives

<u>Understand key concepts in cancer research</u>

- How cancer arises and progresses (a multidisciplinary perspective)

  Genomics, Signal transduction, Microenvironment, Metabolism, Lineage plasticity, Immunology

- How cancer is treated

- How cancer is studied in the lab and clinic (from mouse to human)

WHO WANTS TO BE A MILLIONAIRE

$500,000

Which of the following diseases claimed the most lives in 2017

A HIV/AIDS

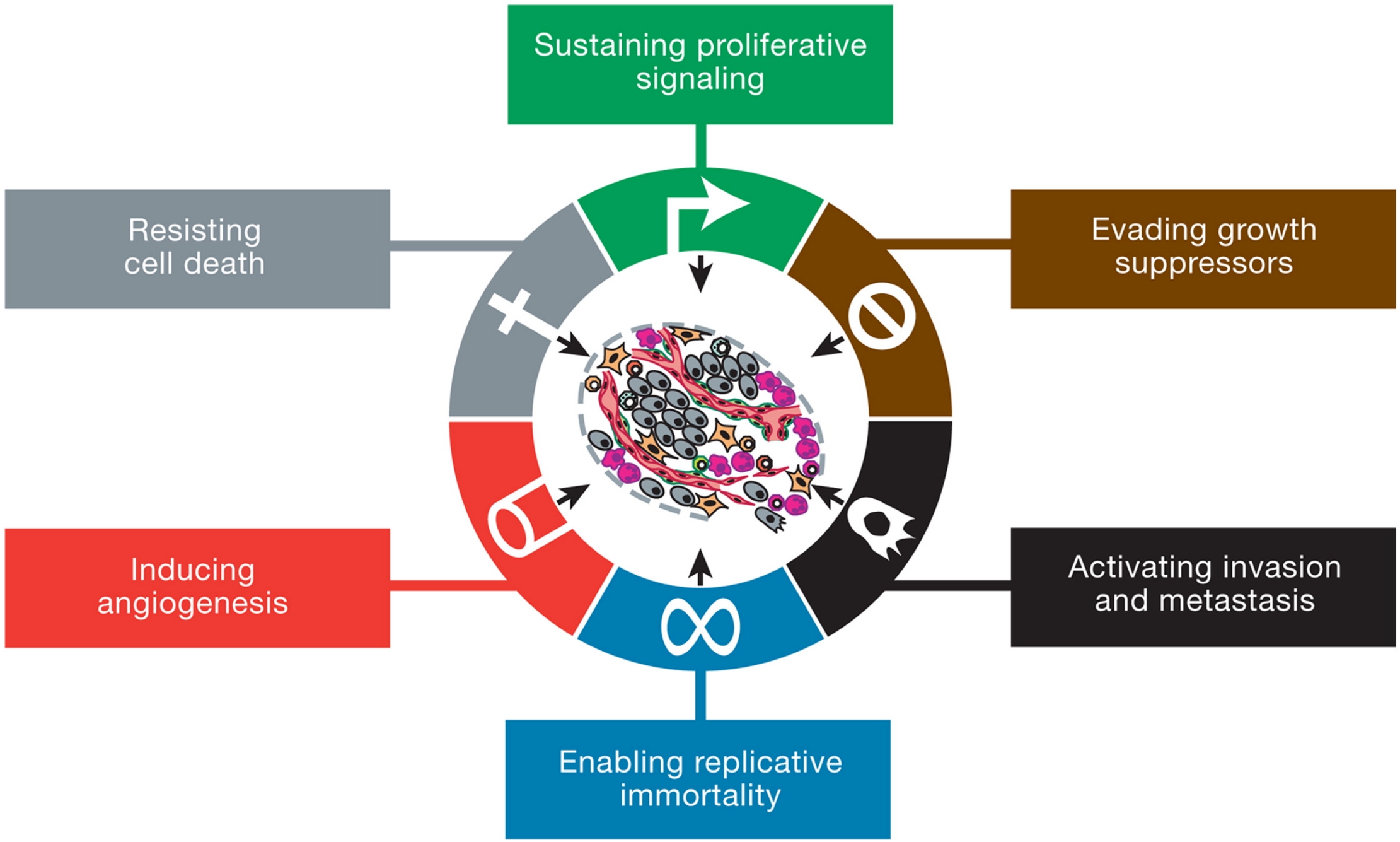
B Tuberculosis

C Malaria

D Cancer

Question: what is cancer?

Hallmarks of Cancer: a unifying framework



The Hallmarks of Cancer. Hanahan and Weinberg, *Cell* 2000

Lecture outline:

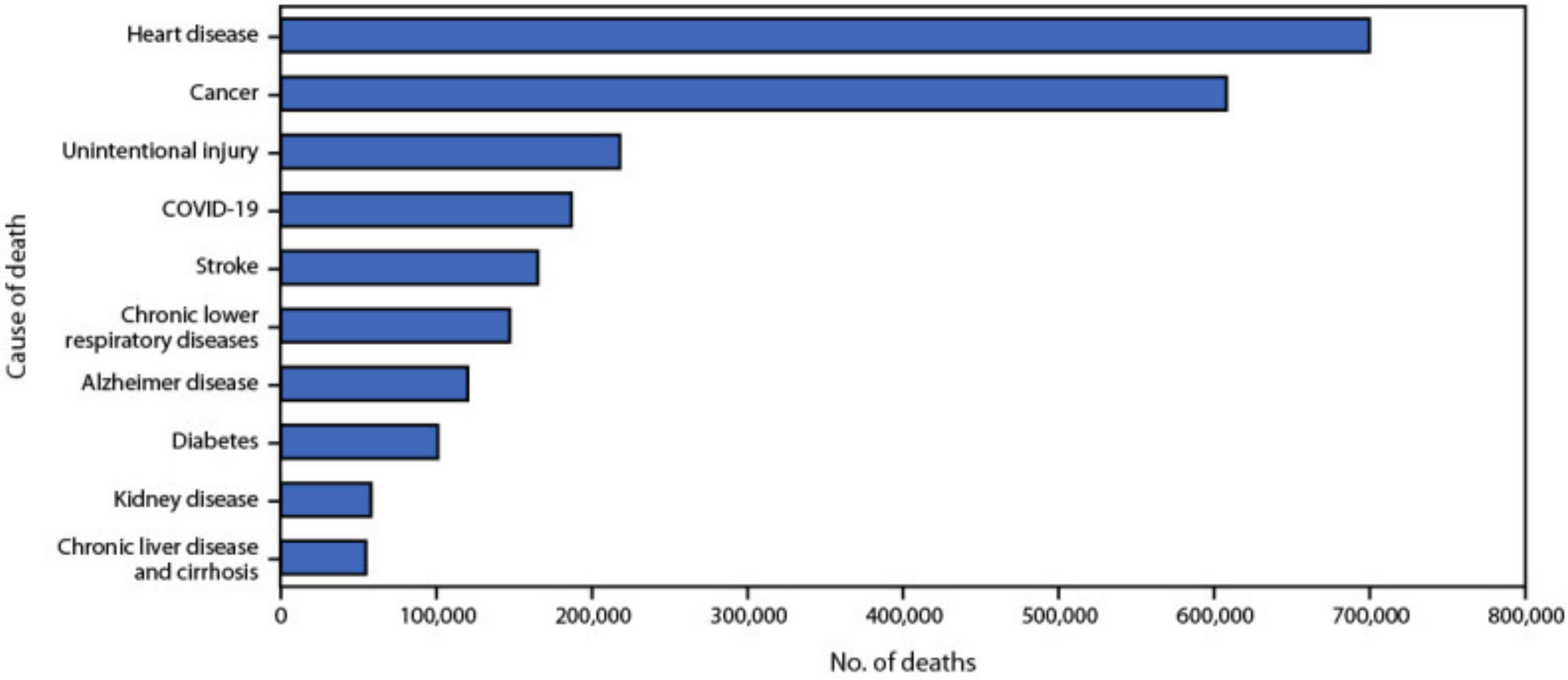
Oncogenes and the origins of cancer

1. Some cancer epidemiology
2. Cellular and tissue origins of cancer
3. Cancer is a progressive disease
4. Genetic mutations are prerequisite for cancer formation
5. Viral origins of cancer lead to the discovery of oncogenes
6. Clonal evolution theory of mutations and cancer

1. Some cancer epidemiology

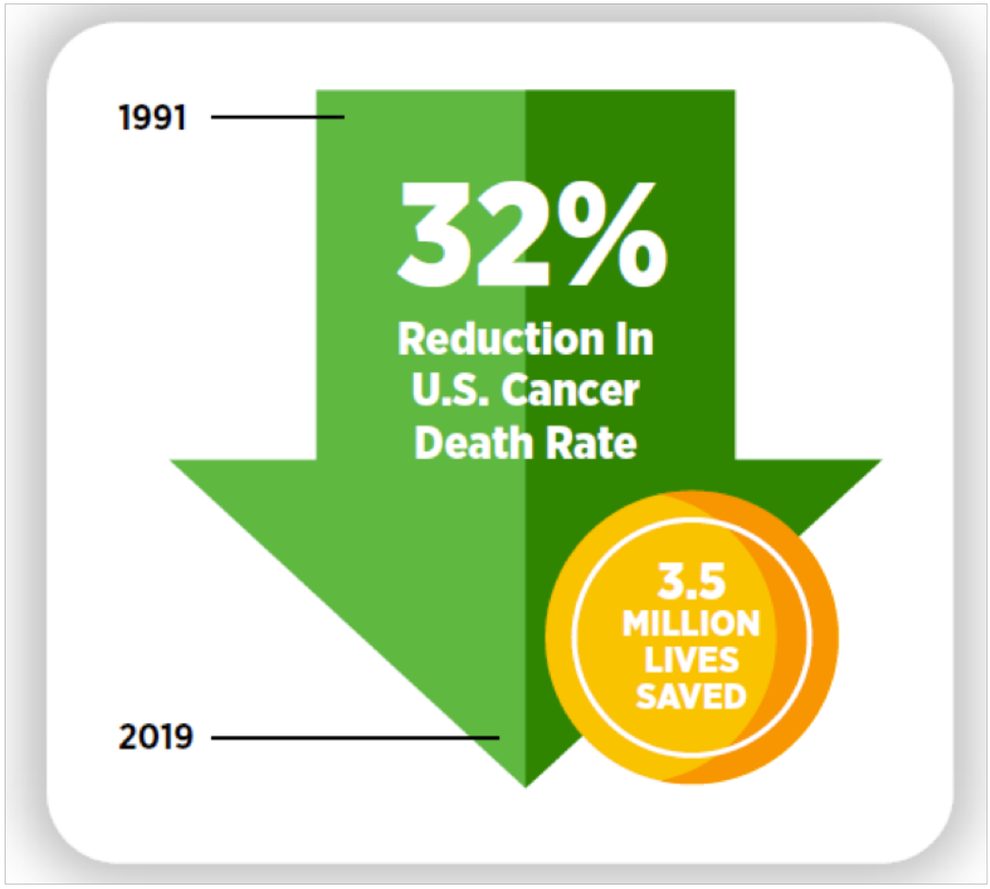
Cancer is the second leading cause of death

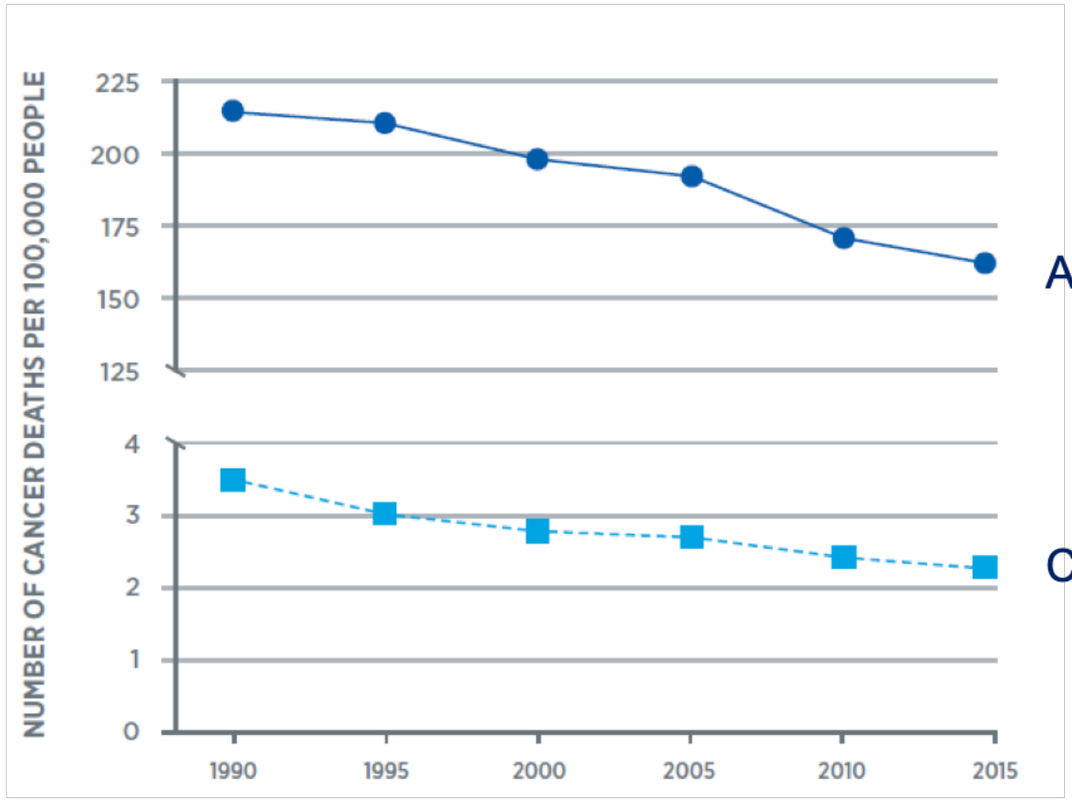
1 in 4 dies of cancer



Provisional Mortality Data—United States, 2022 Ahmad, FB, et al., *MMWR Morb Mortal Wkly Rep* 2023

Cancer deaths are declining

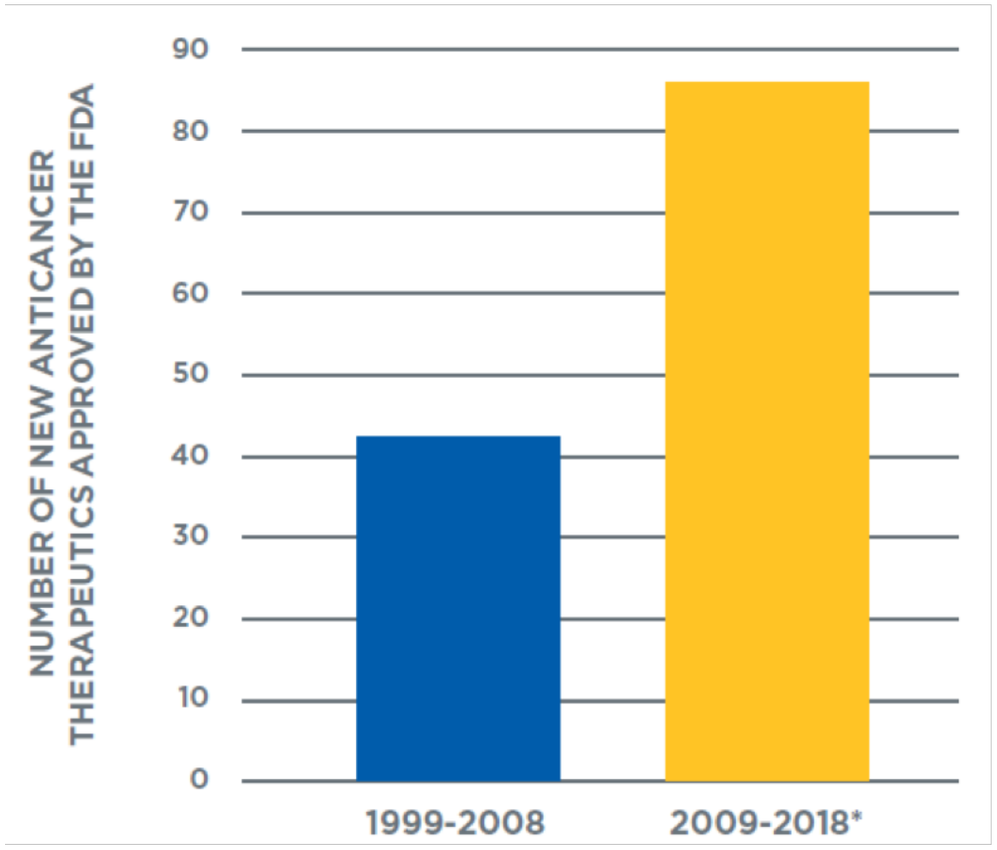


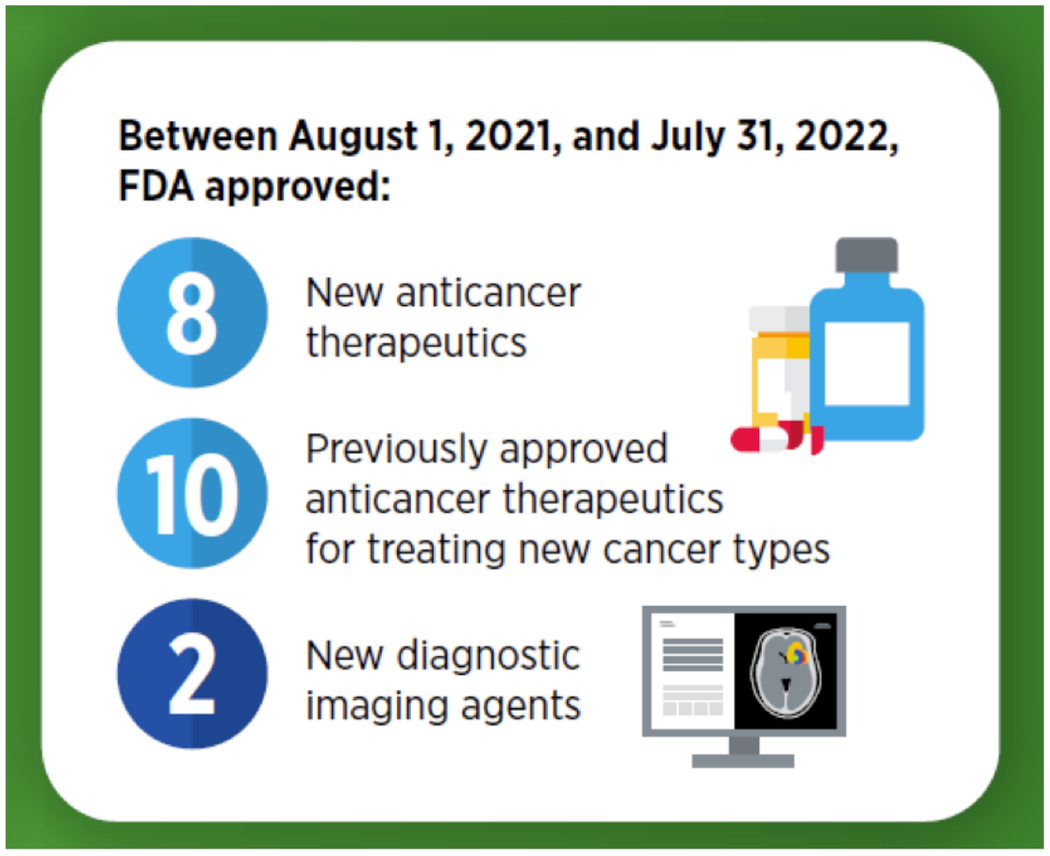


Adults

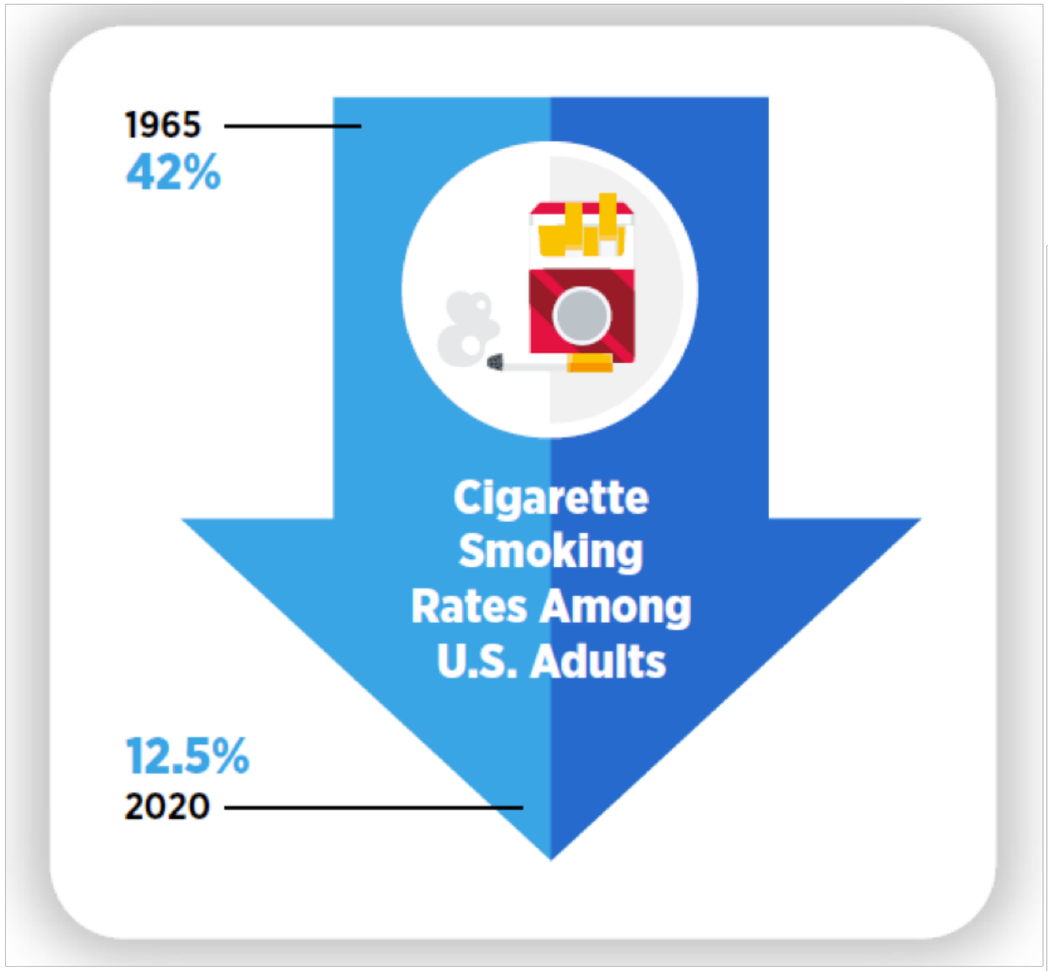
Children

New drugs are developed every year





Risk factors are changing



A study in 1,500 cancer survivors conducted over a 9-year period found that **survivors who led an active lifestyle had 66 percent lower rates of all-cause mortality** compared to those who led a sedentary lifestyle.

Early onset cancer is increasing

Rising rate of young people getting cancer

Cumulative percent change in cancer incidence rates per 100,000 from 1975 by age group

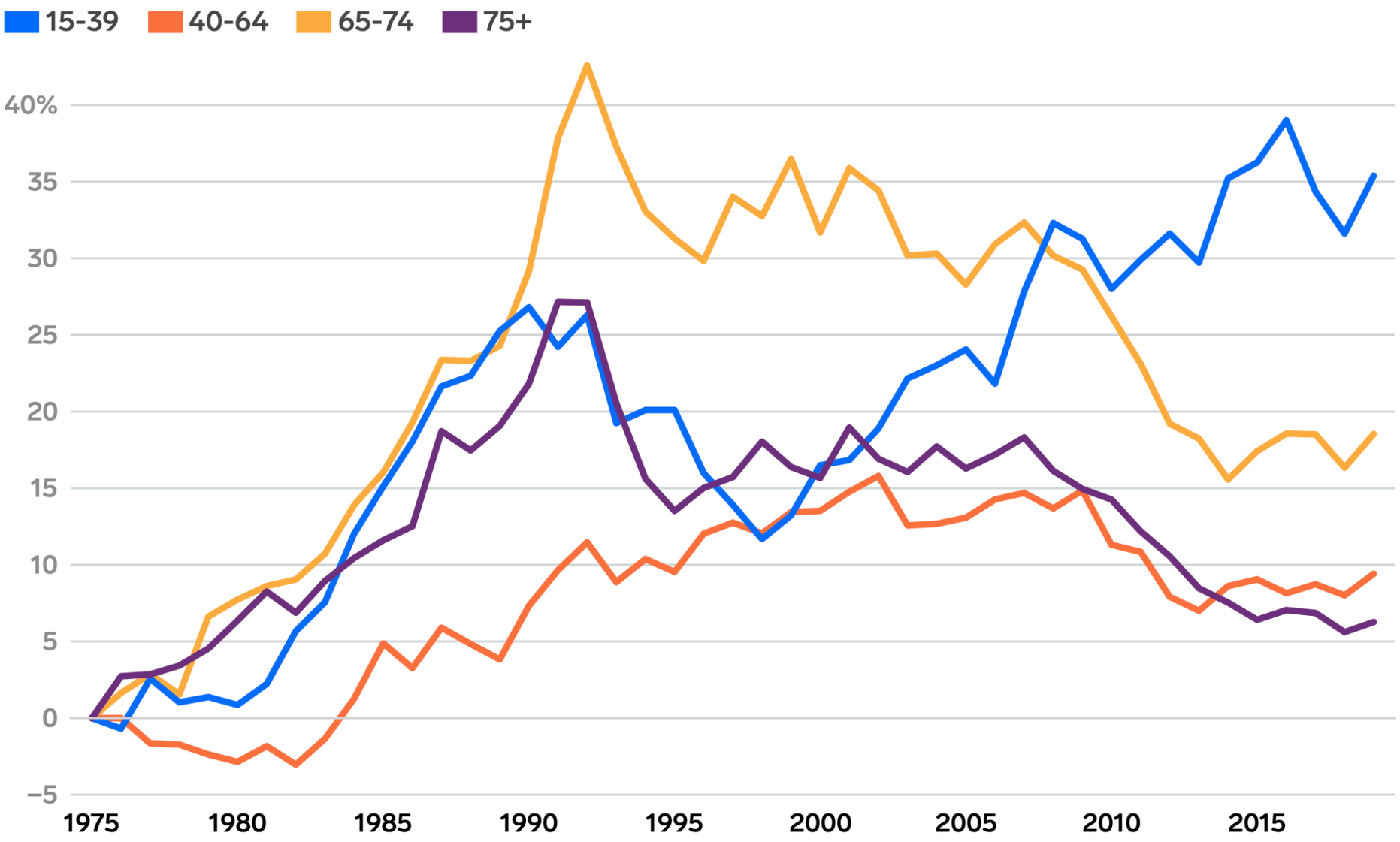


Chart: Madison Hoff/Business Insider • Source: National Cancer Institute

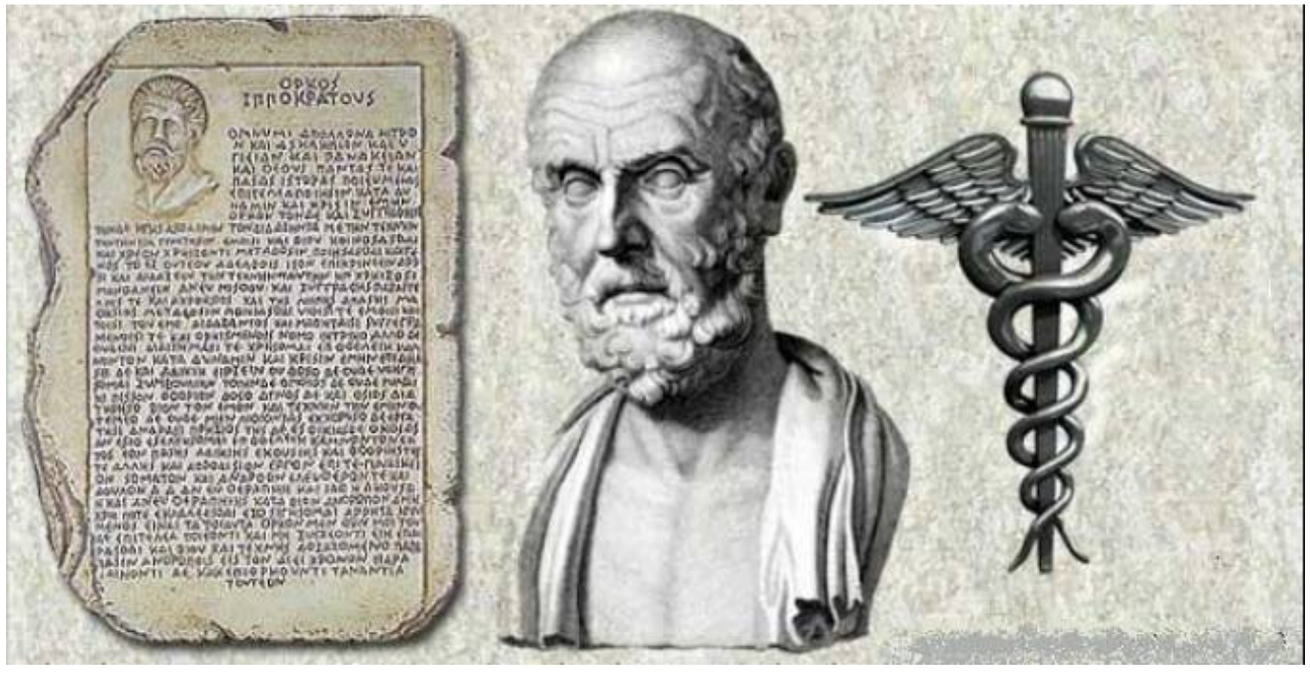
BUSINESS INSIDER

2. Cellular origins of cancer

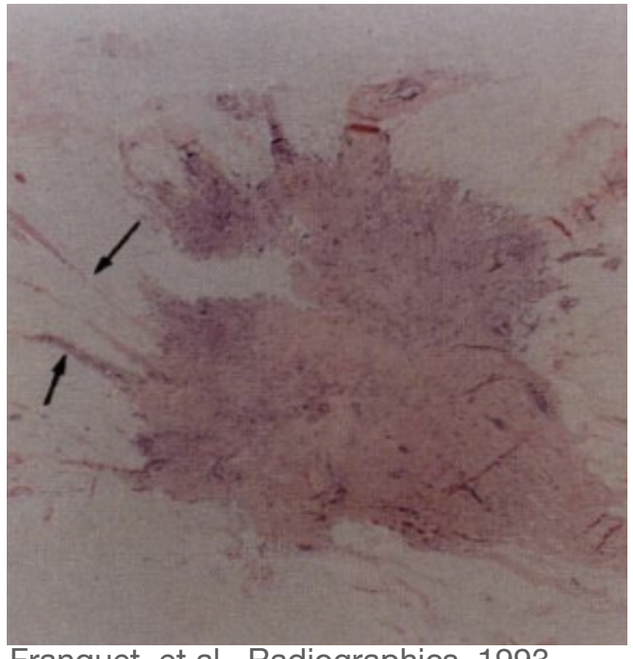
Going back a few thousand years . . .

Documented by ancient Egyptians

Approached scientifically by Hippocrates of ancient Greece



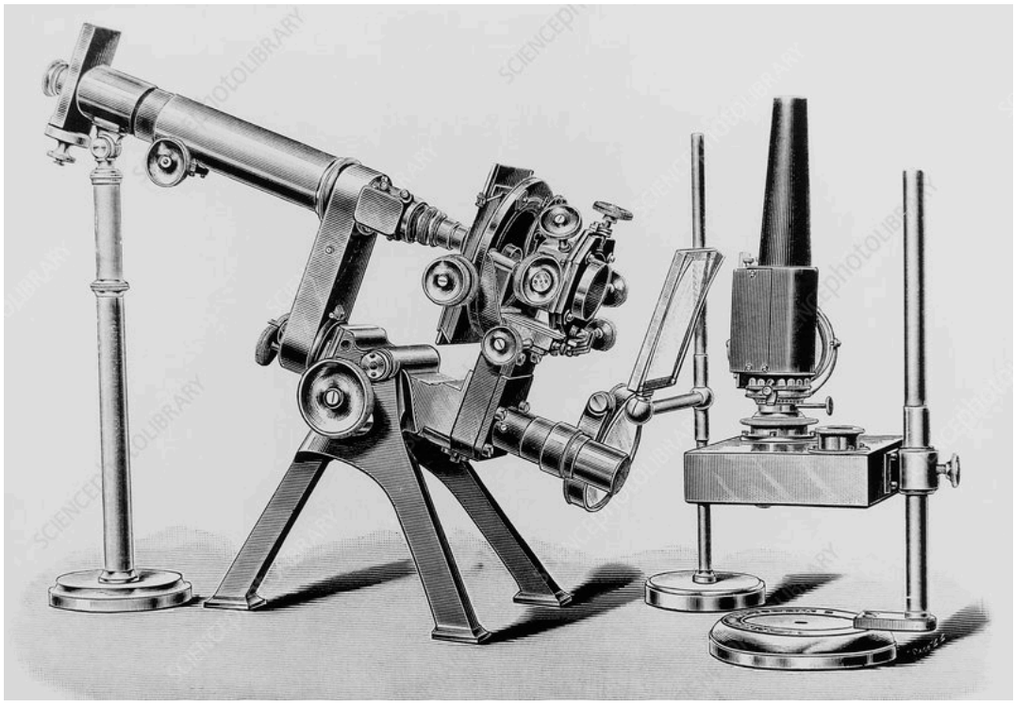
https://greekreporter.com/2022/06/09/how-was-cancer-treated-in-ancient-greece-2/



Franquet, et al., Radiographics, 1993

- Karkinoma (Karkinos = crab)
- Understood benign versus malignant
- Cancer thought to be foreign invasion until 19th century

Histology changed our understanding of cancer

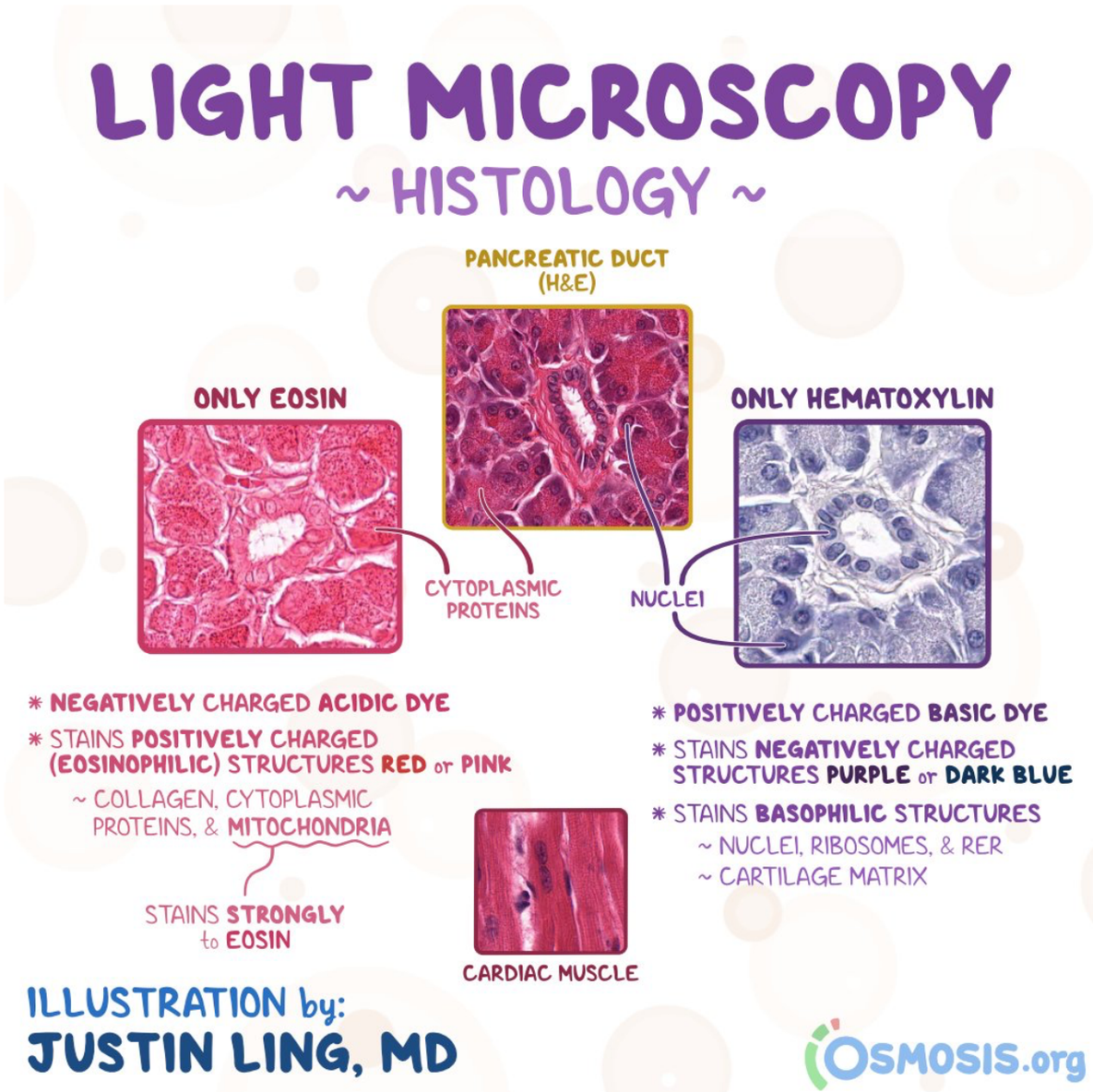


https://www.sciencephoto.com/media/1046296/view/19th-century-microscope

Histology: the study of microscopic structures of tissues

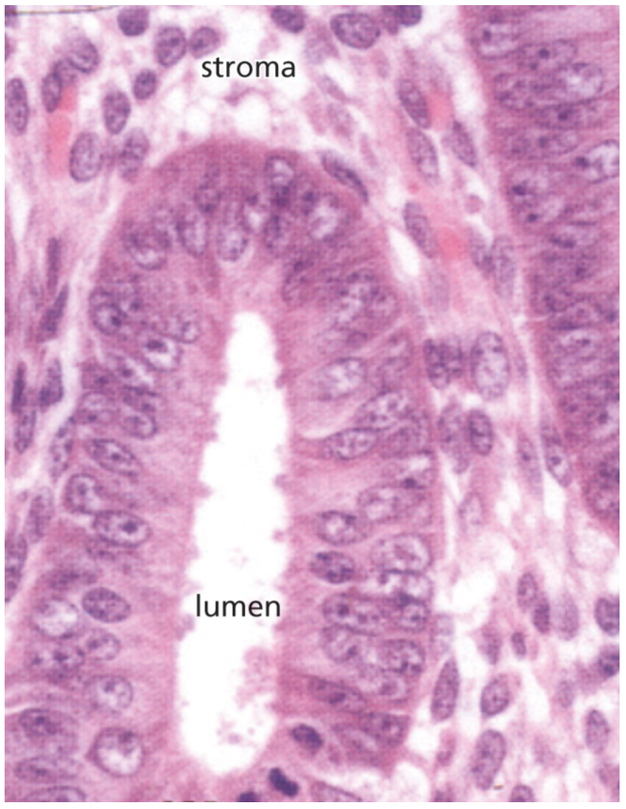
Histopathology: the microscopic study of diseased tissues

Hematoxylin and Eosin (H&E): staining of tissue sections



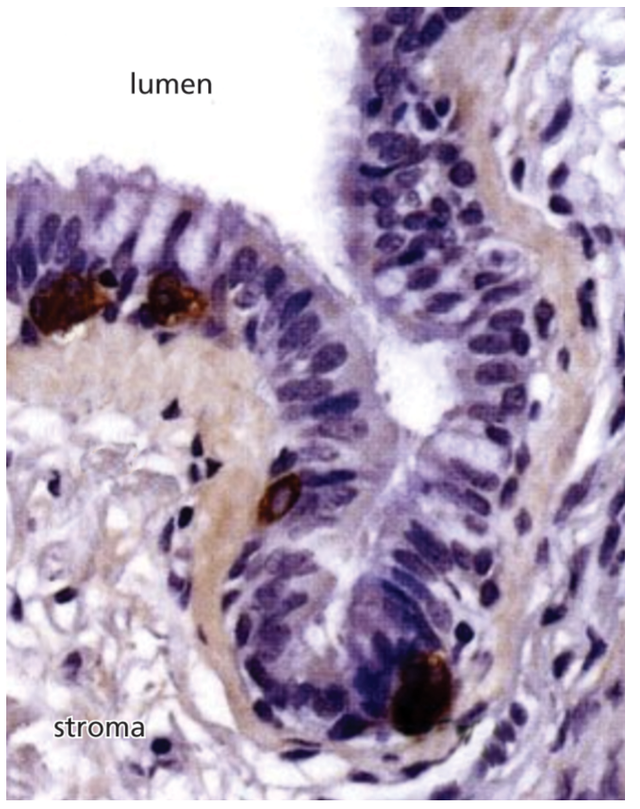
From where does cancer arise?

Uterus (endometrium)

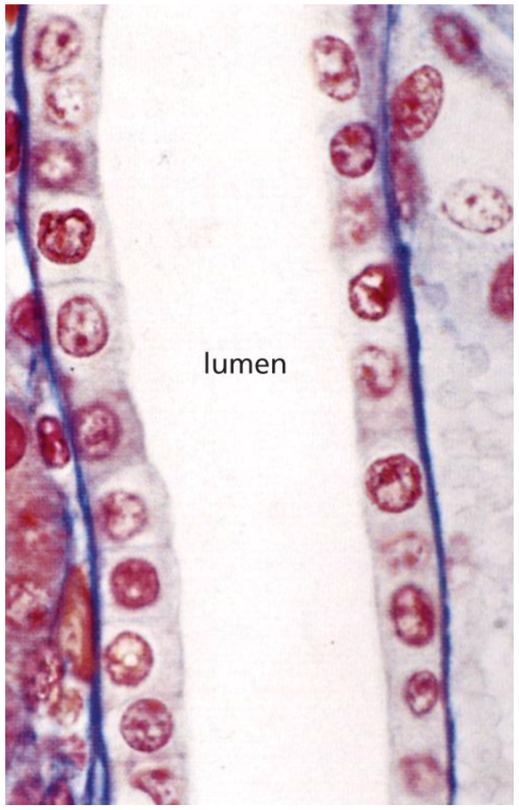


Gallbladder

Lung bronchiole



Kidney



***The Biology of Cancer**, 3rd edition.* Robert Weinberg

Ducts of breast, prostate, pancreas

Villi and crypts of small intestine and colon

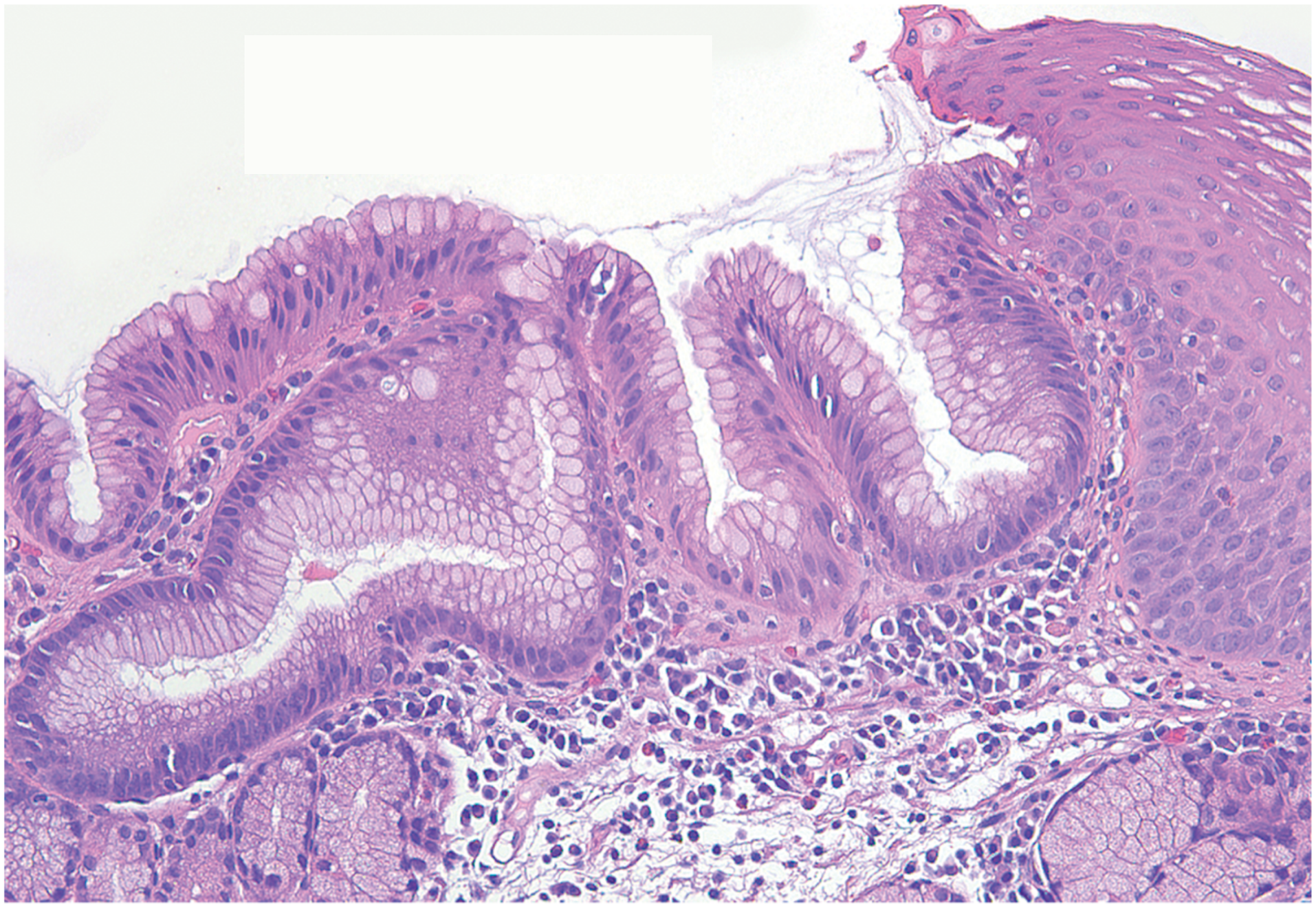
Lining of mouth, esophagus, stomach, bladder, ovary, cervix, etc.

Hepatocytes of the liver

Epidermis (skin!)

What do all these tissues have in common?

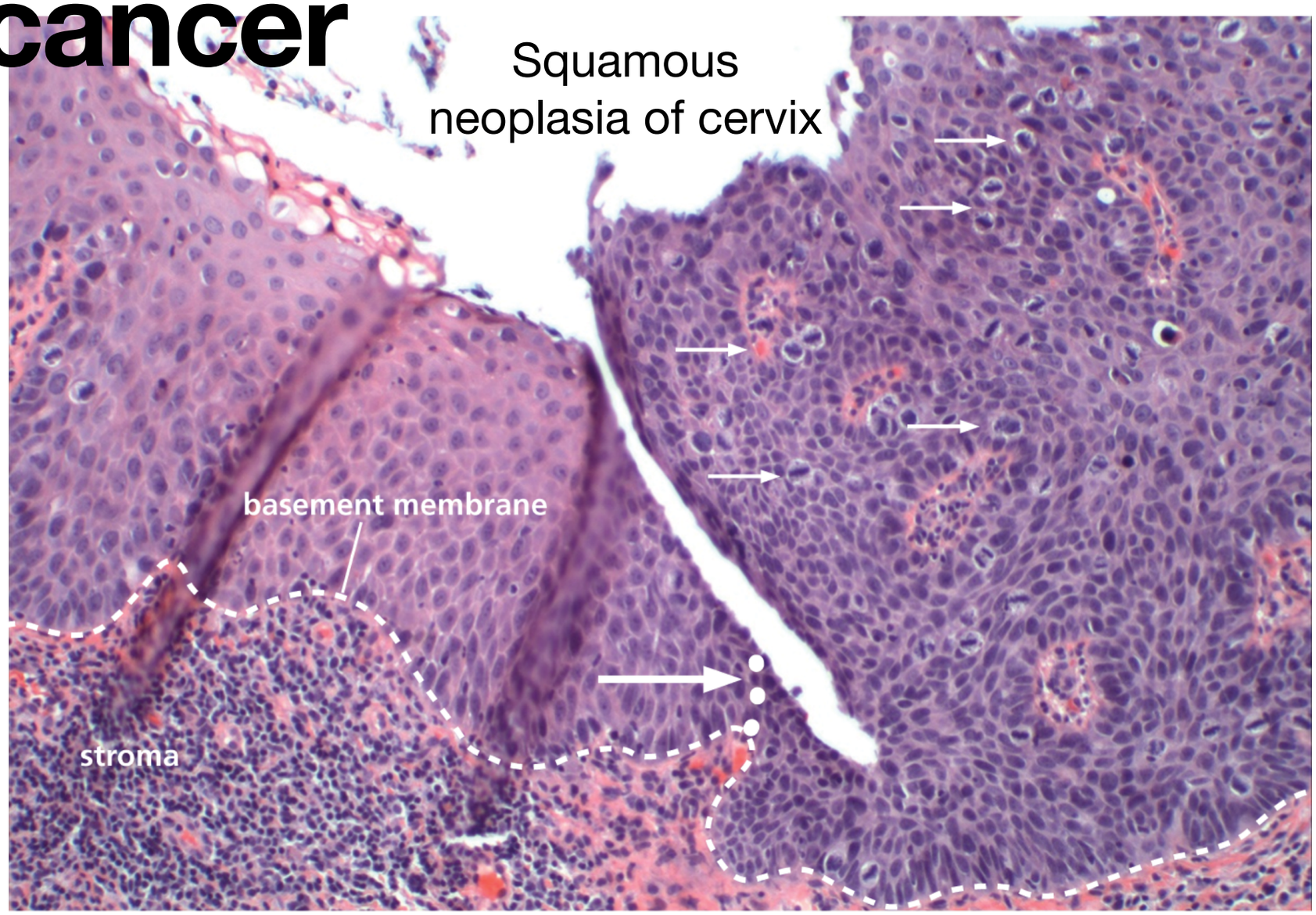
Pre-cancer



***The Biology of Cancer**, 3rd edition.* Robert Weinberg

Metaplasia: “beyond growth”, replacement of one differentiated cell type with another differentiated cell type not normally associated with a tissue

Pre-cancer



***The Biology of Cancer**, 3rd edition.* Robert Weinberg

Neoplasia: “new growth”, broad term for benign/malignant growths

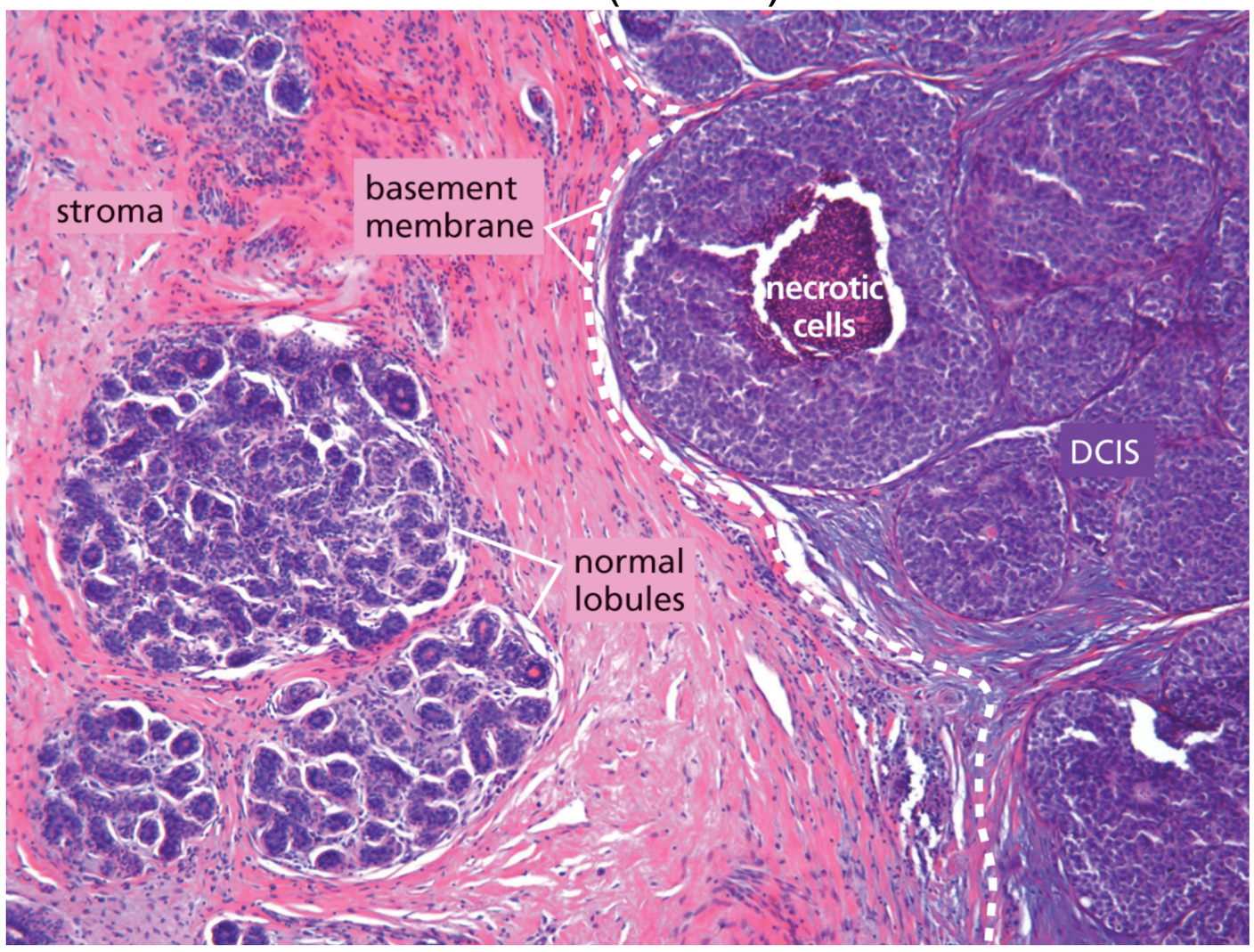
Hyperplasia: “excessive growth”, thickening or increasing size

Dysplasia: “abnormal growth”, cytologically and structurally abnormal

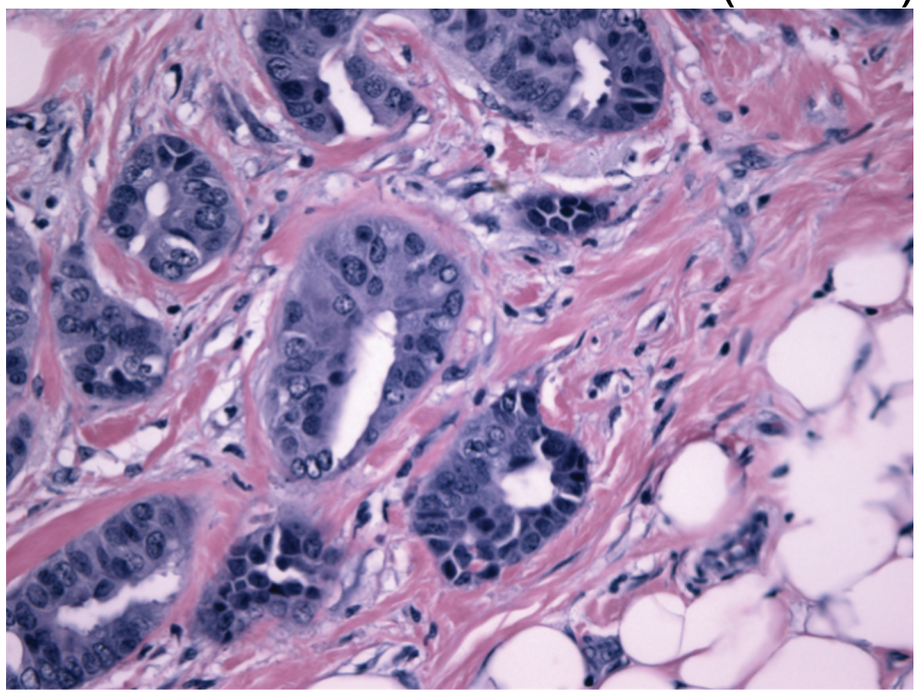
Cancers of the epithelia (carcinomas)

90% of all cancer, 80% of deaths

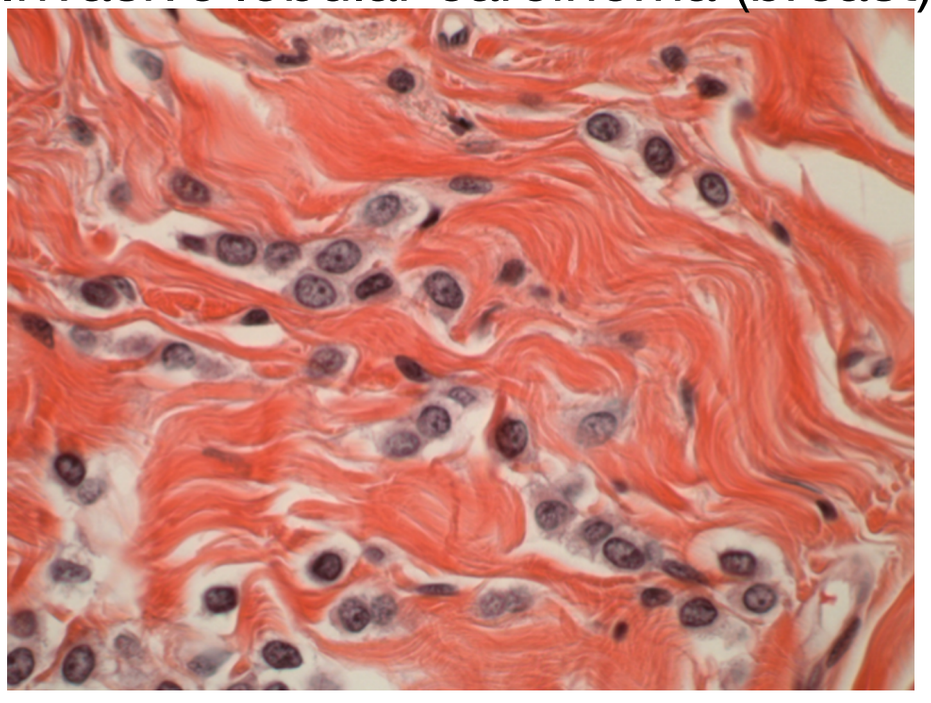
Ductal carcinoma in situ (breast)



Invasive ductal carcinoma (breast)



Invasive lobular carcinoma (breast)

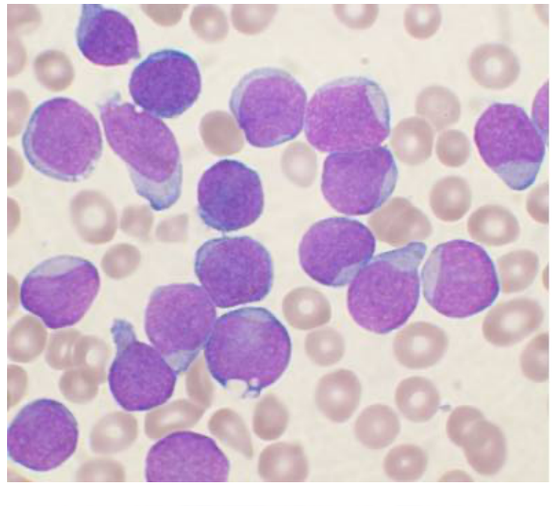


***The Biology of Cancer**, 3rd edition.* Robert Weinberg

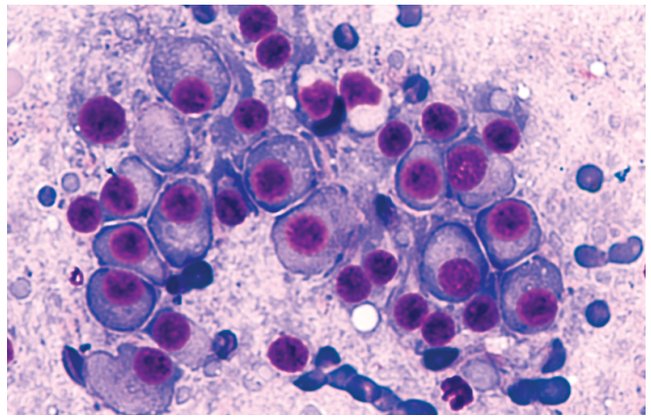
Cancers of the blood (hematologic)

8-10% of all cancer, 7% of deaths

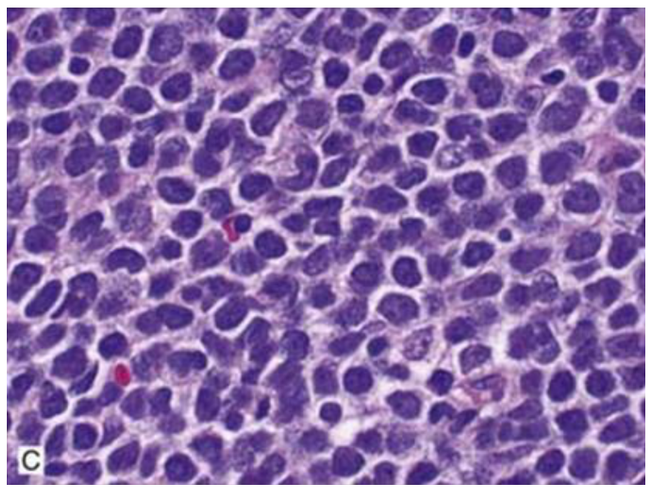
Leukemias: blood cancer, circulating “liquid tumors”



Myelomas: blood cancer, develops in bone marrow



Lymphomas: blood cancer, solid tumors localized to lymphoid tissues (e.g., thymic lymphoma)



By The original uploader was VashiDonsk at English Wikipedia.

***The Biology of Cancer**, 3rd edition.* Robert Weinberg

***Thoracic Pathology:** A Volume in the High Yield Pathology Series 1st Edition,* Aliya N. Husain

Cancers of bone and soft tissue (sarcomas)

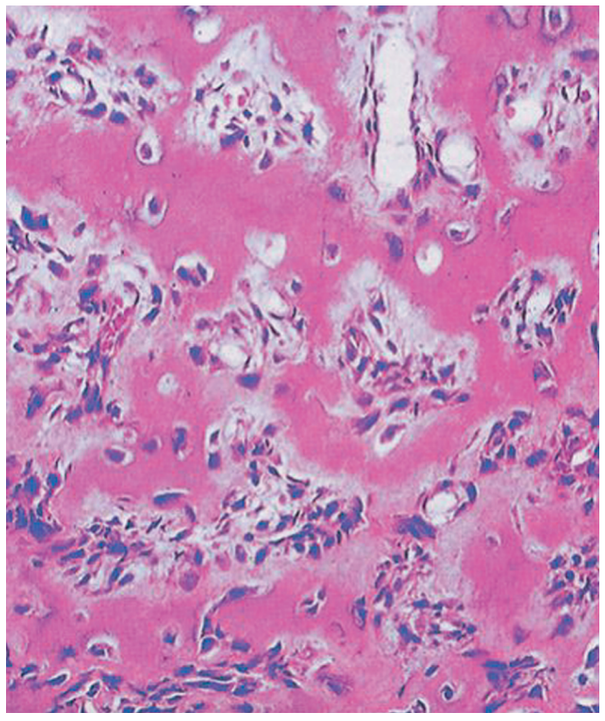
~1% of all cancer, <1% of deaths

Derive from mesenchymal cell types (bone/cartilage, connective tissues, lymphatic and blood vessels, fat, muscle)

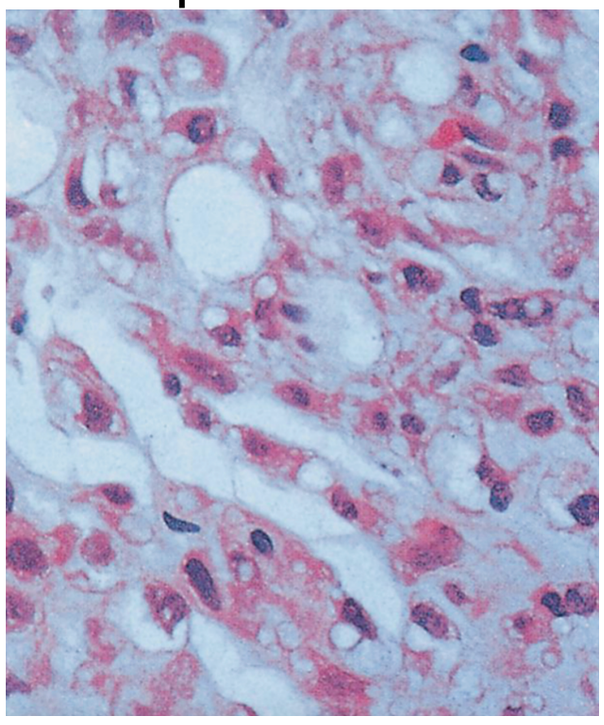
Rare, but some forms extremely aggressive, minimal treatment options

15-20% of childhood cancer

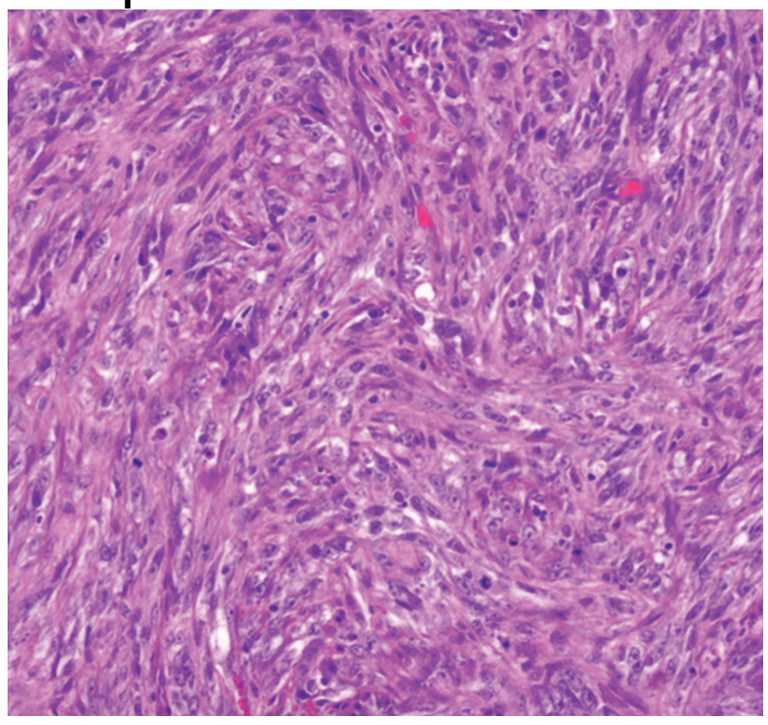
Osteosarcoma



Liposarcoma



Dedifferentiated spindle cell sarcoma



***The Biology of Cancer**, 3rd edition.* Robert Weinberg

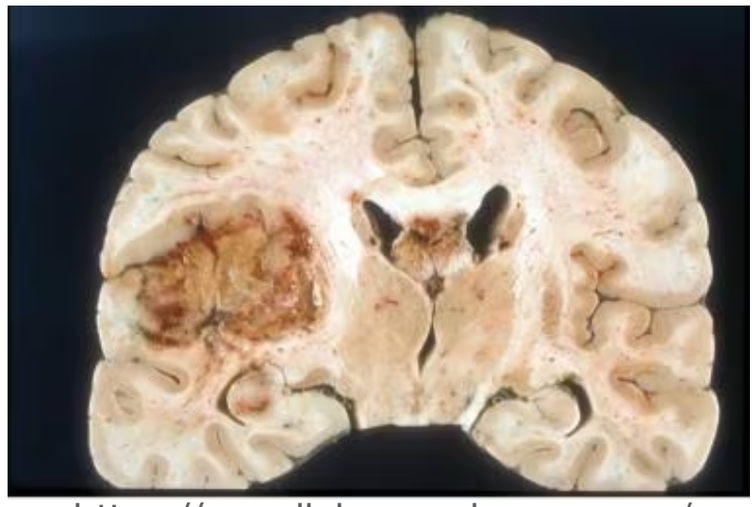
Cancers of nervous system (neuroectodermal)

1.3% of all cancer, 2.5% of deaths

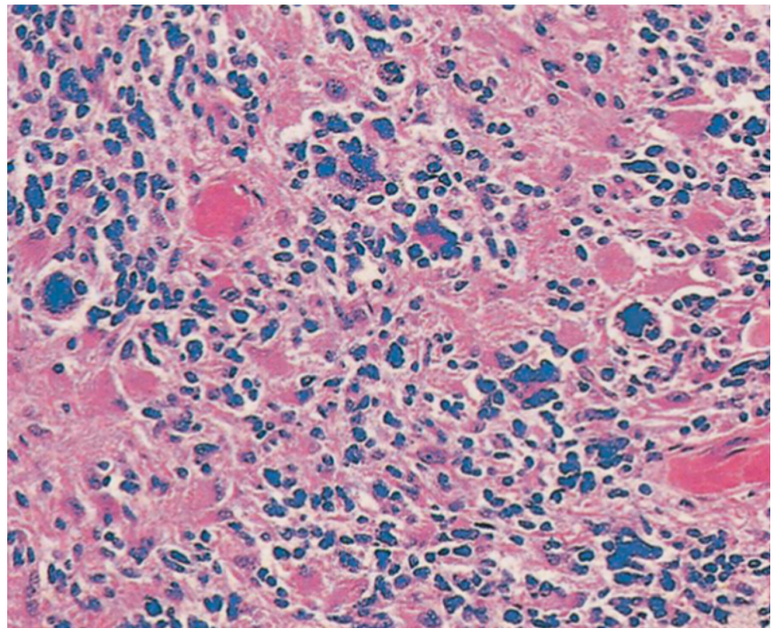
Form from components of central and peripheral nervous system:

Name of tumor	Lineage of founding cell
Glioblastoma multiforme	highly progressed astrocytoma
Astrocytoma	astrocyte (type of glial cell)[a]
Meningioma	arachnoidal cells of meninges[b]
Schwannoma	Schwann cell around axons[c]
Retinoblastoma	cone cell in retina[d]
Neuroblastoma[e]	cells of peripheral nervous system
Ependymoma	glial cells lining ventricles of brain[f]
Oligodendroglioma	oligodendrocyte covering axons[g]
Medulloblastoma	granular cells of cerebellum[h]

Glioblastoma



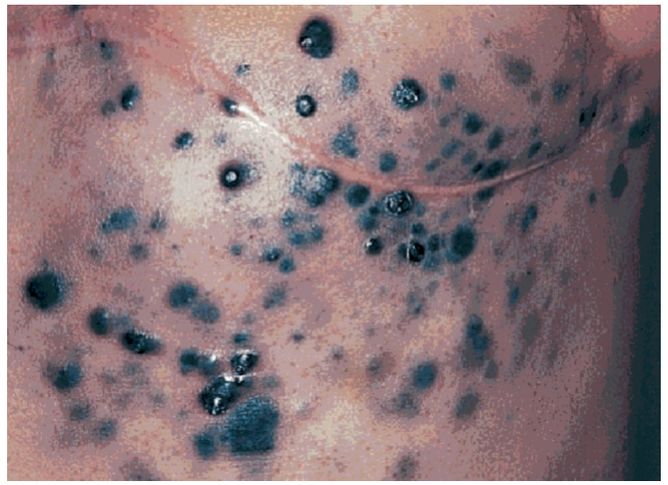
https://emedicine.medscape.com/article/283252-overview



***The Biology of Cancer**, 3rd edition.* Robert Weinberg

Other notable cancers of unique cell types

Melanoma: cancer arising from pigment producing cells in skin (melanocytes)

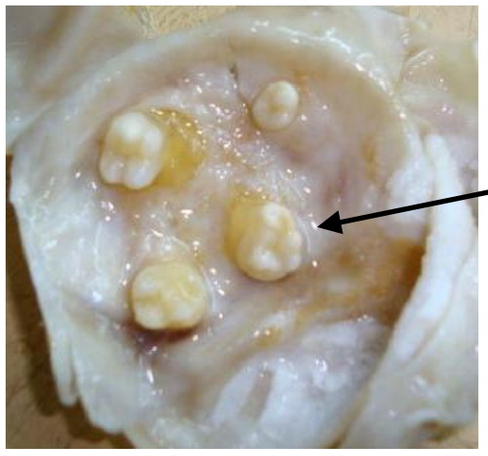


***The Biology of Cancer**, 3rd edition.* Robert Weinberg

Small cell lung cancer: likely arise from endodermal stem cells of lung

Transdifferentiate into neuroendocrine (secretory)-like cells

Teratomas: arise from diploid germ cell precursors, retain embryonic stem cell pluripotency

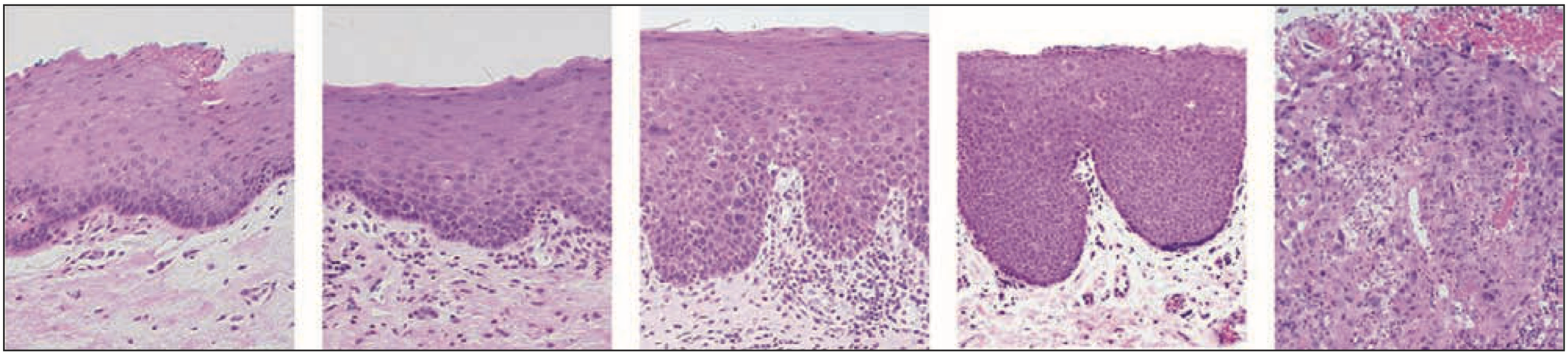


Ingale, Y, et al., ***Case Rep Dent***, 2013

3. Cancer is a progressive disease (a histopathological perspective)

Cancer is a progressive disease

Oral squamous cell carcinoma progression



Hyperplasia → Mild dysplasia → Moderate dysplasia → Severe Dysplasia/CIS → Invasive SCC

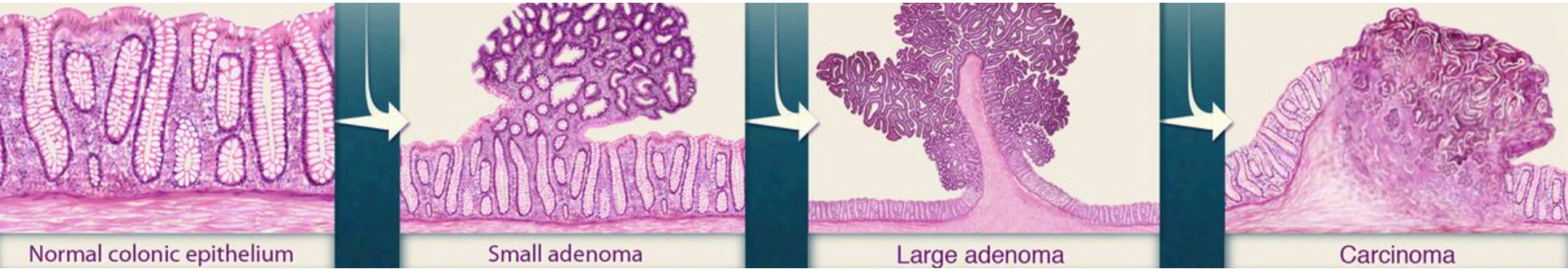
Low-grade dysplasia
Generally low cancer risk

High-grade dysplasia
Generally high
cancer risk

Poh, CF, et al., ***JCDA***, 2008

Cancer is a progressive disease

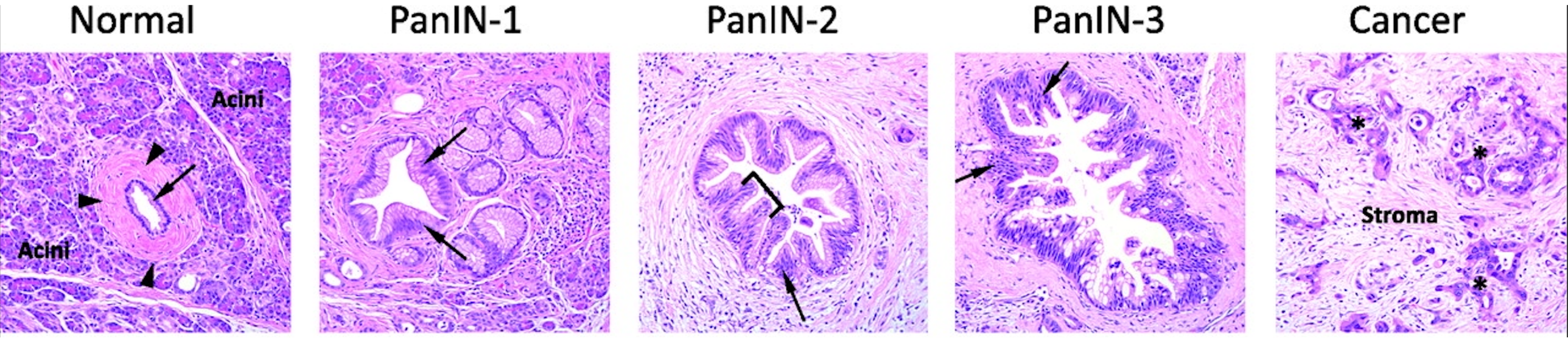
Colon adenocarcinoma



Vogelstein, B, et al. ***Science*** 2013

Cancer is a progressive disease

Pancreatic ductal adenocarcinoma



Iacobuzio-Donahue, ***Gut*** 2012

4. Genetic mutations drive cancer

Cancer is a “genetic disease”

Cancer is a disease of mutations to our DNA

- Those that we are born with (germline)
- Those that occur after birth (somatic)

Hereditary cancers

- Familial component noted since the 1600s
- Retinoblastoma
- Lynch Syndrome
- Familial Adenomatous Polyposis (FAP)
- Many others

Cancer is a “genetic disease”

- Cancer is a disease of mutations to our DNA
    - Those that we are born with (germline)
    - Those that occur after birth (somatic)

Chemicals: Benzene → leukemia

UV radiation → skin cancer

Radium → Osteosarcoma

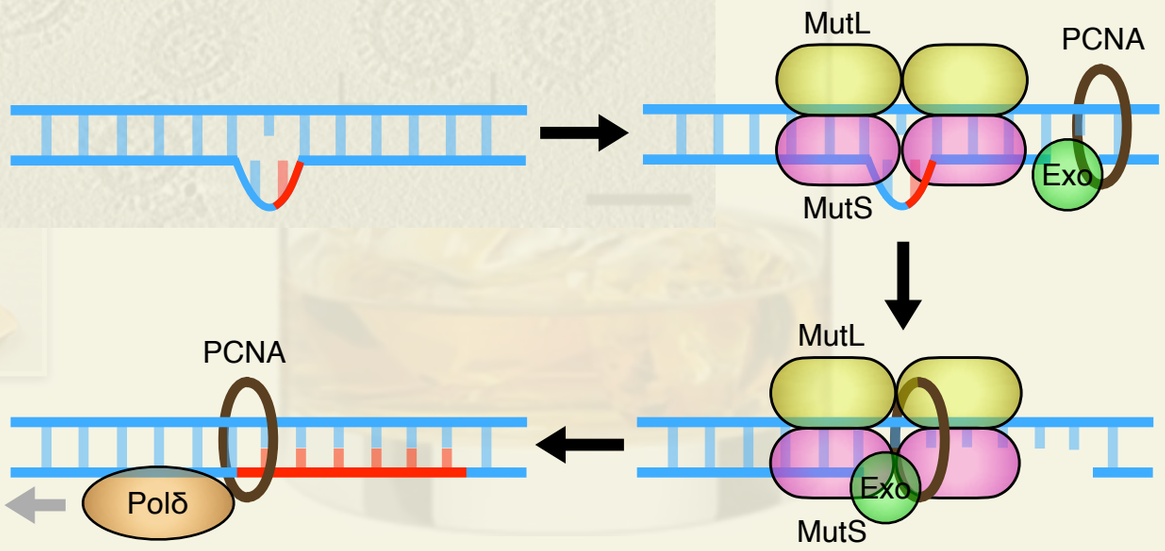
Tobacco → lung, kidney, bladder cancer

Viruses: HPV → cervical cancer

Random “bad luck” during cell division

Sources of mutations

DNA mismatch repair



Sources of mutations

Exogenous chemical and environmental (carcinogens)

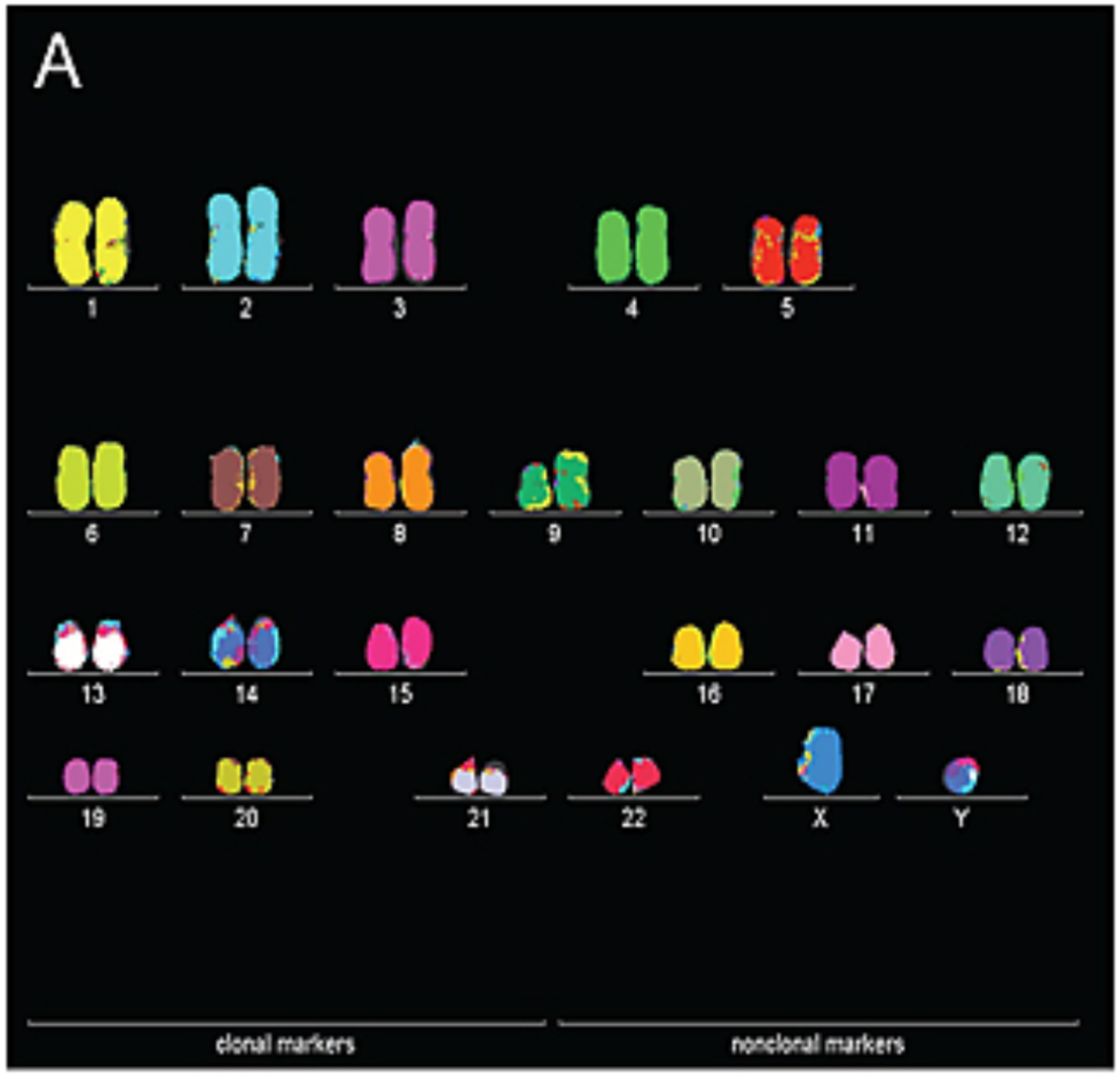
- Carcinogens (benzo-A-pyrene in cigarettes)
- UV light from the sun
- Dietary
- Viruses, bacteria

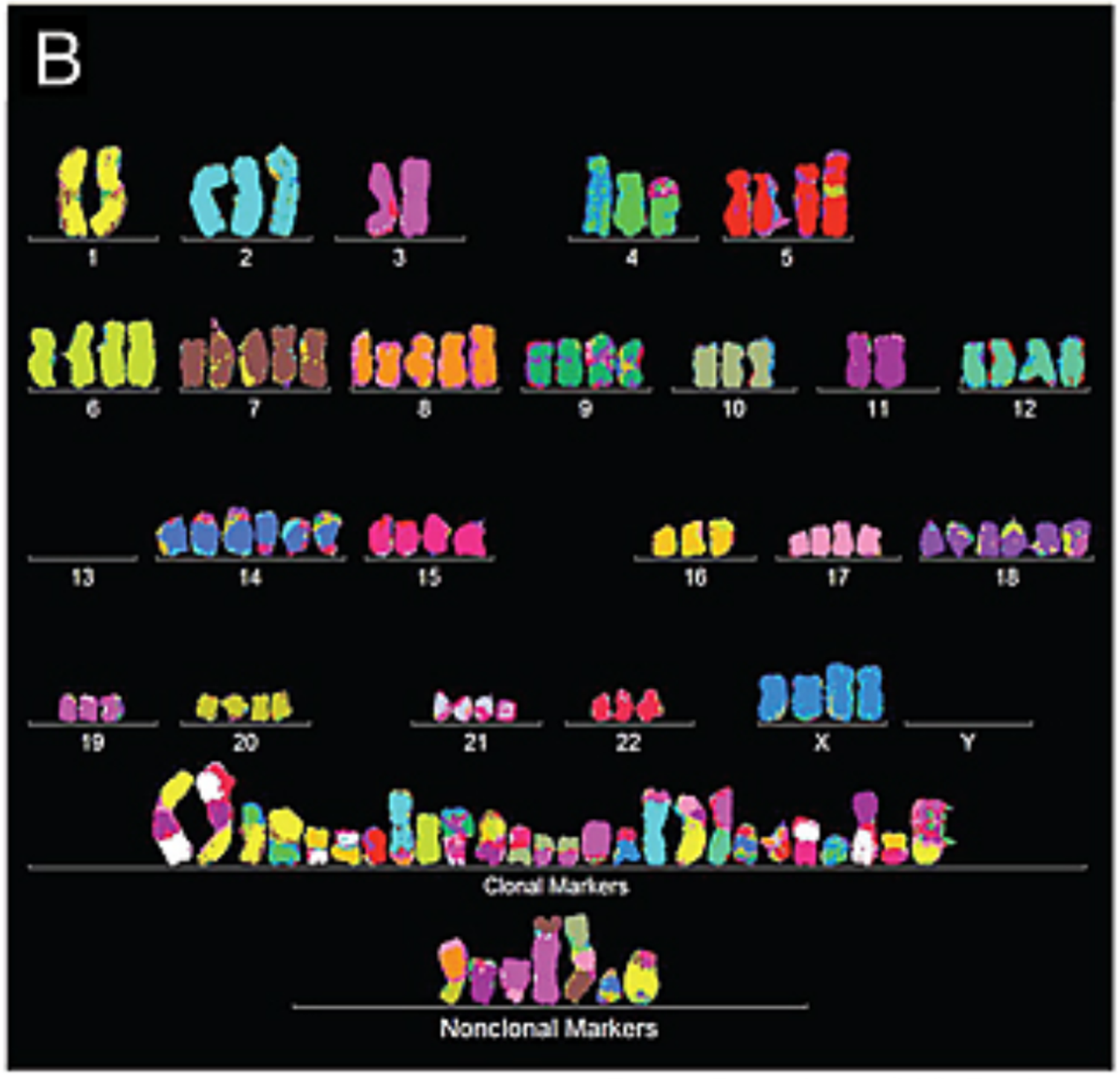
Endogenous

- Defects in DNA repair mechanisms (e.g., DNA mismatch repair)
- Replication errors during cell division (DNA breaks, aneuploidy)
- Metabolism within cell (reactive oxygen species)

Earliest evidence of abnormal DNA in cancer

- Abnormal numbers of chromosomes (aneuploidy)
- Observed over 100 years ago (before we knew what is DNA)!





Peter Duesberg/UC Berkley

Earliest evidence of abnormal DNA

Aneuploidy

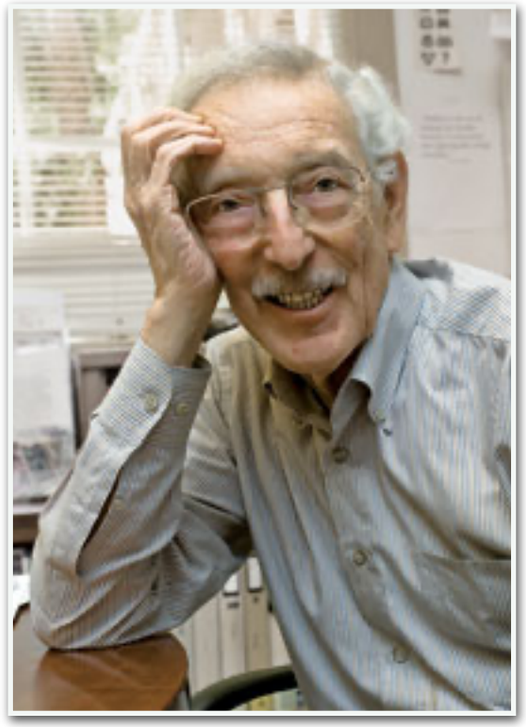
- Whole chromosome gains
- Whole chromosome losses
- Deletions/amplifications of smaller regions
- Rearrangements (e.g., translocations)
- Catastrophic changes all at once (chromothripsis: Greek for chromosome “shattering”)

Carcinogens are mutagens

The Ames test (1970s):

Test in laboratory mice

Test in cells (originally bacteria)



Bruce Ames

Proc. Nat. Acad. Sci. USA
Vol. 70, No. 8, pp. 2281–2285, August 1973

Carcinogens are Mutagens: A Simple Test System Combining Liver Homogenates for Activation and Bacteria for Detection

(frameshift mutagens/aflatoxin/benzo(a)pyrene/acetylaminofluorene)

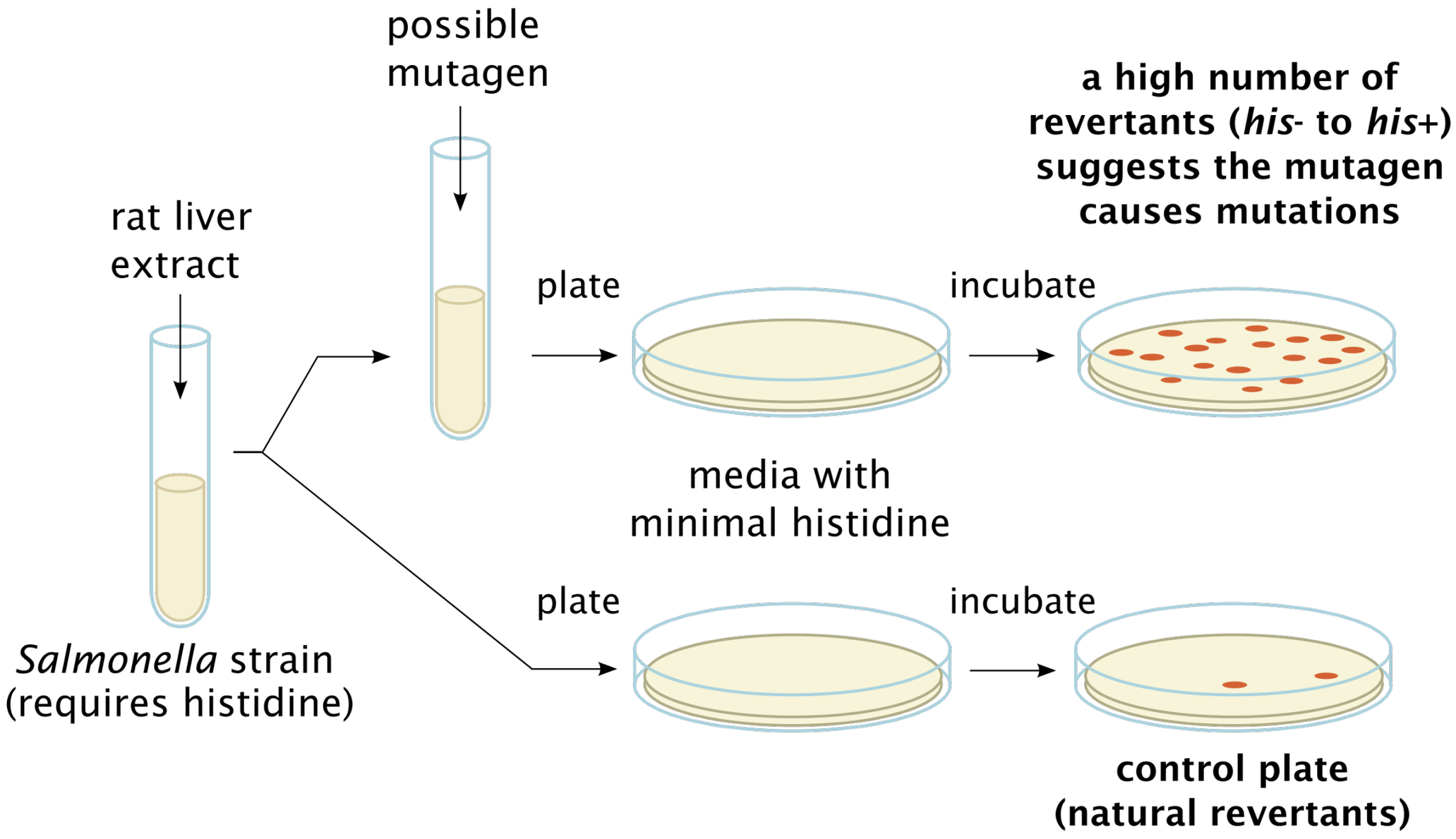
BRUCE N. AMES, WILLIAM E. DURSTON, EDITH YAMASAKI, AND FRANK D. LEE

Biochemistry Department, University of California, Berkeley, Calif. 94720

Contributed by Bruce N. Ames, May 14, 1973

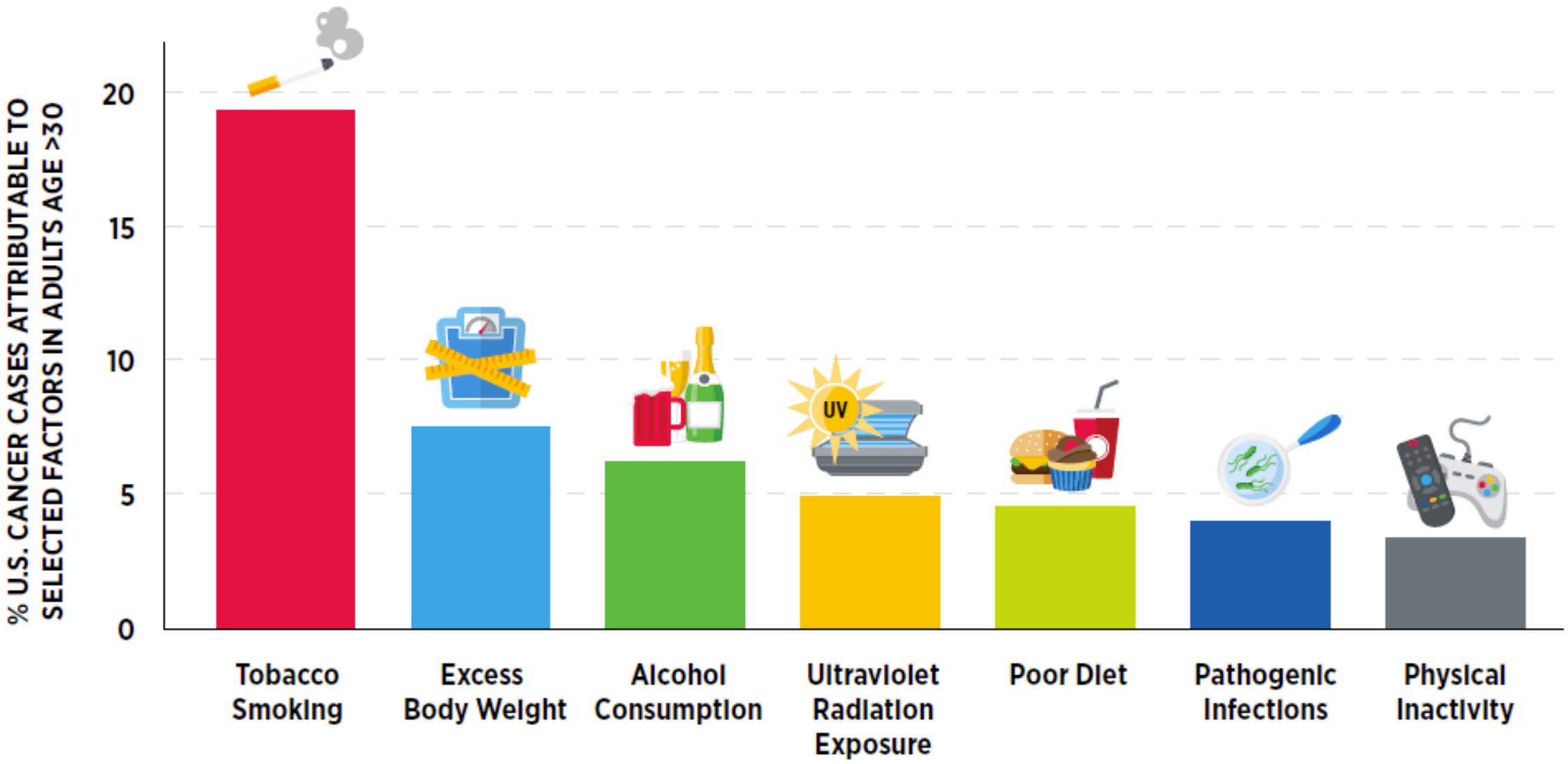
Carcinogens are mutagens

The Ames test (1970s):



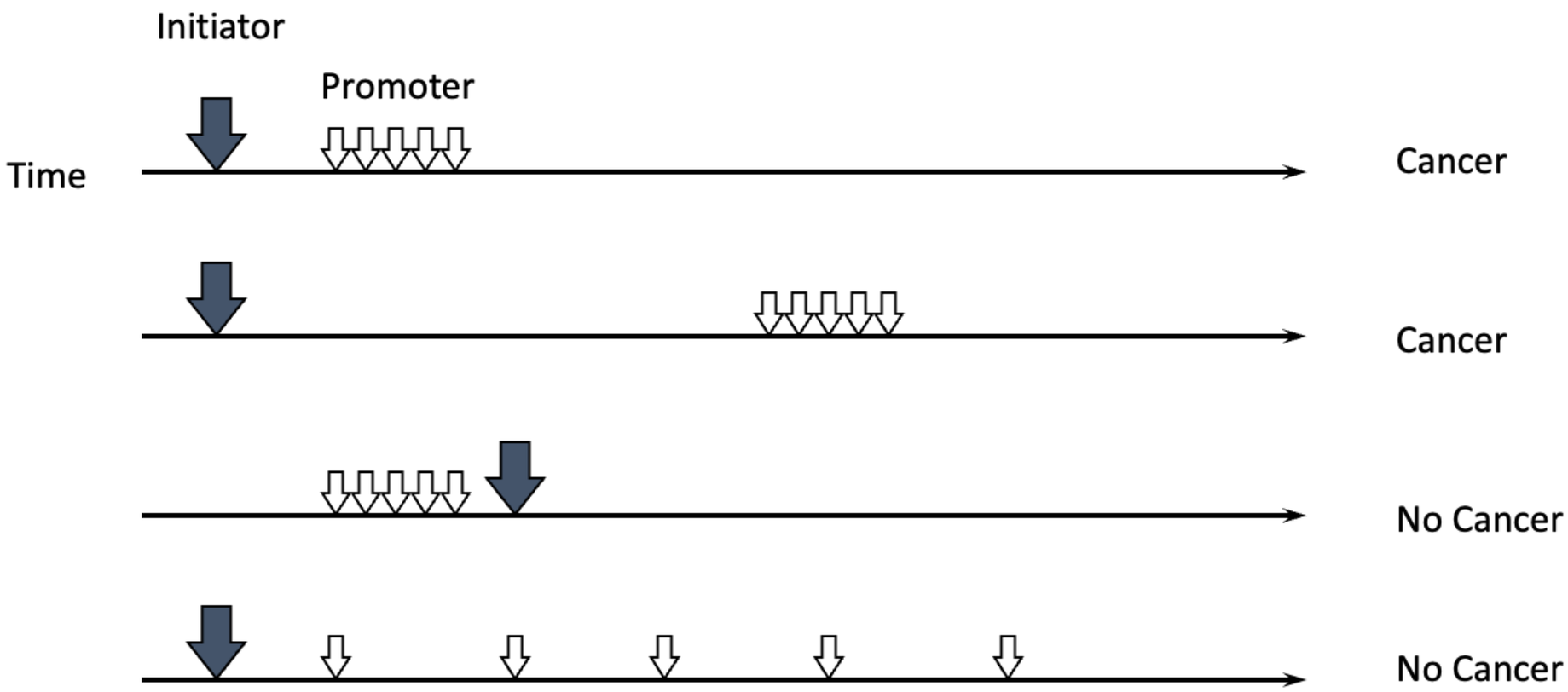
https://en.wikipedia.org/wiki/Ames_test

Carcinogens are mutagens . . . well mostly!



Which of these cancer risk factors mutate and which promote?

Mutations are not enough: the initiator/ promoter model



1940s -- Berenblum and Shubik develop model of carcinogenesis by painting polycyclic aromatic hydrocarbons and croton oil on mouse skin.

Known and suspected promoting agents

Agent or process	Cancer site
Hormones	
Estrogen	endometrium
Estrogen and progesterone	breast
Ovulation	ovary
Testosterone	prostate
Drugs	
Oral contraceptives, anabolic steroids	liver
Analgesics	renal pelvis
Diuretics	kidney
Infectious agents	
Hepatitis B/C viruses	liver
Schistosoma haematobium—blood fluke	bladder
Schistosoma japonicum—blood fluke	colon
Clonorchis sinensis—liver fluke	biliary tract
Helicobacter pylori—bacterium	stomach
Malarial parasites	B cell
Tuberculosis bacillus	lung

Agent or process	Cancer site
Chemical agents	
Betel nut, lime	oral cavity
Chewing tobacco	oral cavity
Bile	small intestine
Salt	stomach
Acid reflux	esophagus
Physical or mechanical trauma	
Asbestos	mesothelium, lung
Gallstones	gallbladder
Coarsely ground corn	stomach
Head injury	meninges
Chronic irritation/inflammation	
Tropical ulcers[a]	skin
Chronic ulcerative colitis	colon
Chronic cystitis	bladder
Chronic pancreatitis	pancreas

Which of these are associated with inflammation?

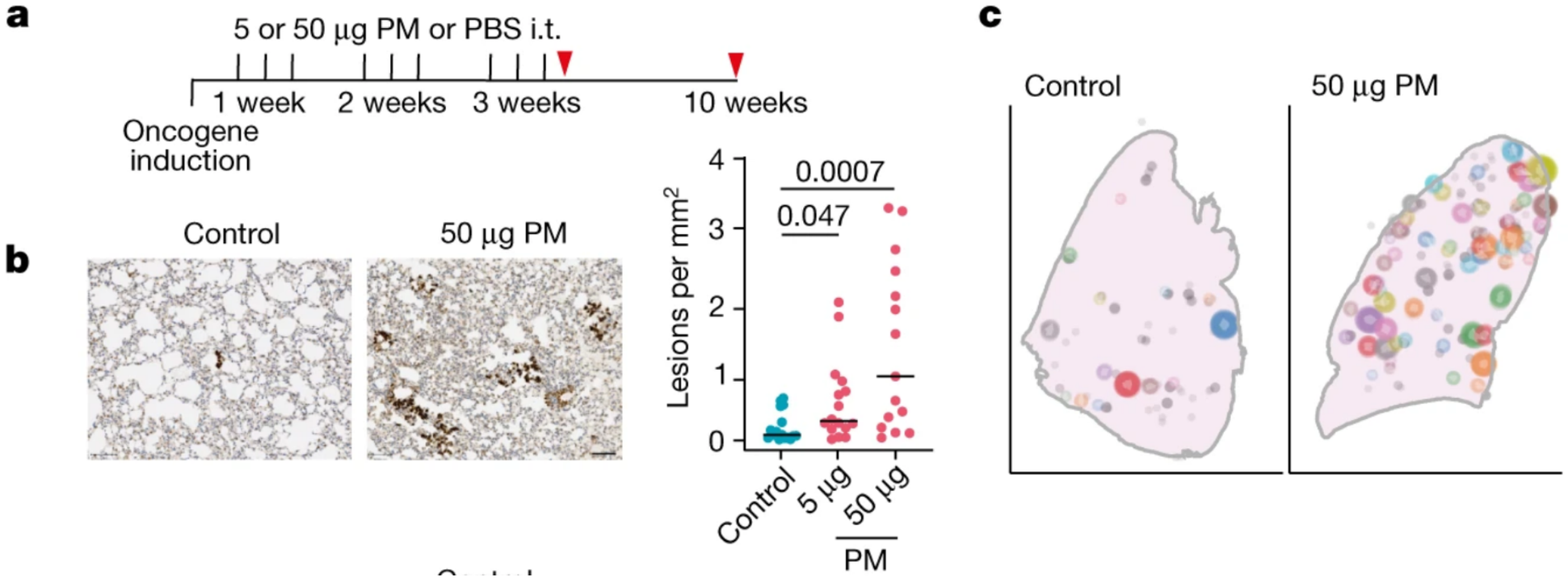
Air pollution (PM2.5) is a cancer promoter

Promoting agents

e.g., Particulate Matter measuring ≤ 2.5 μm (PM2.5)

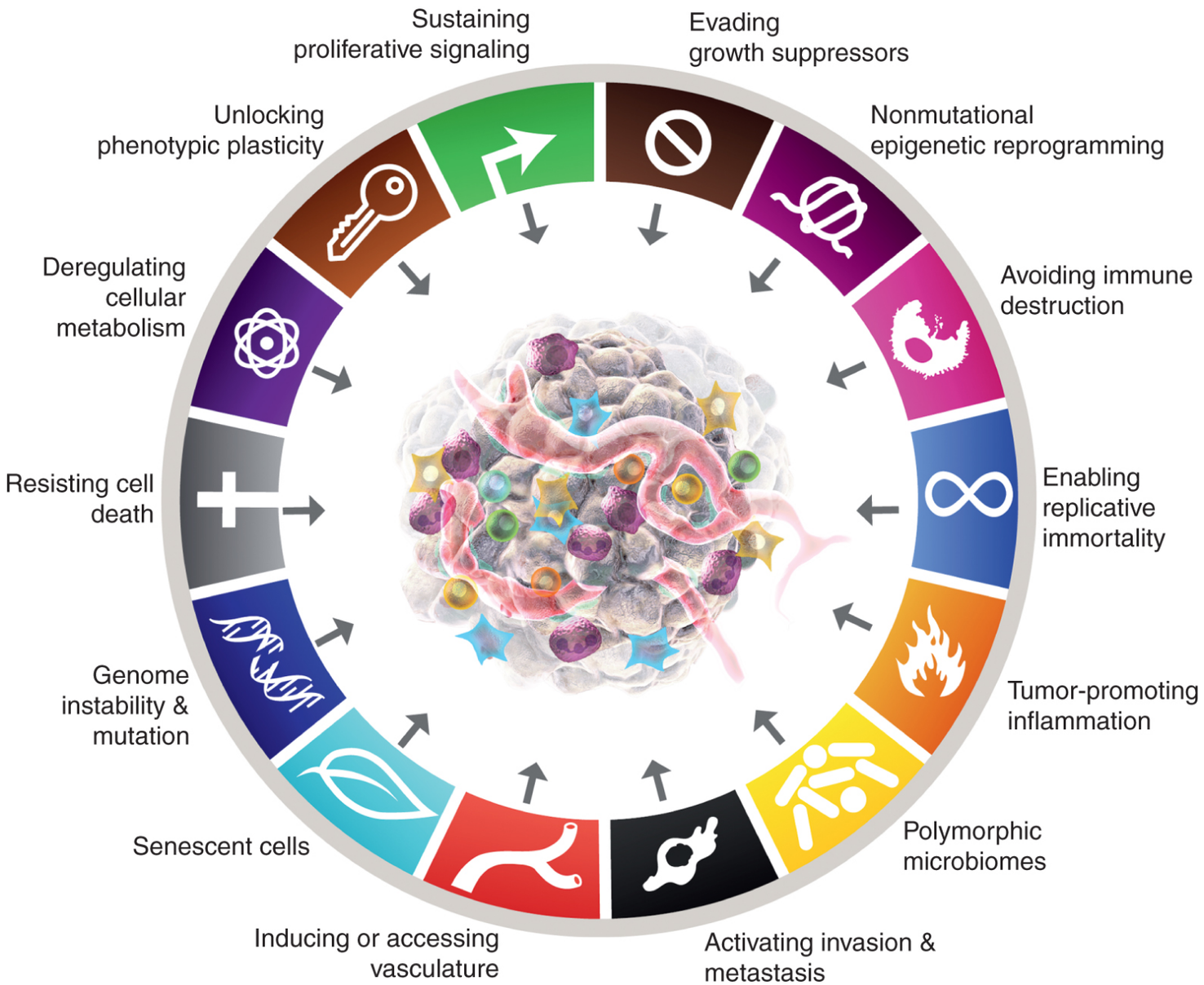
Fig. 2: PM promotes lung tumorigenesis.

From: Lung adenocarcinoma promotion by air pollutants



Hill, W, et al., ***Nature***, 2023

Mechanisms of promoting agents remains very poorly understood



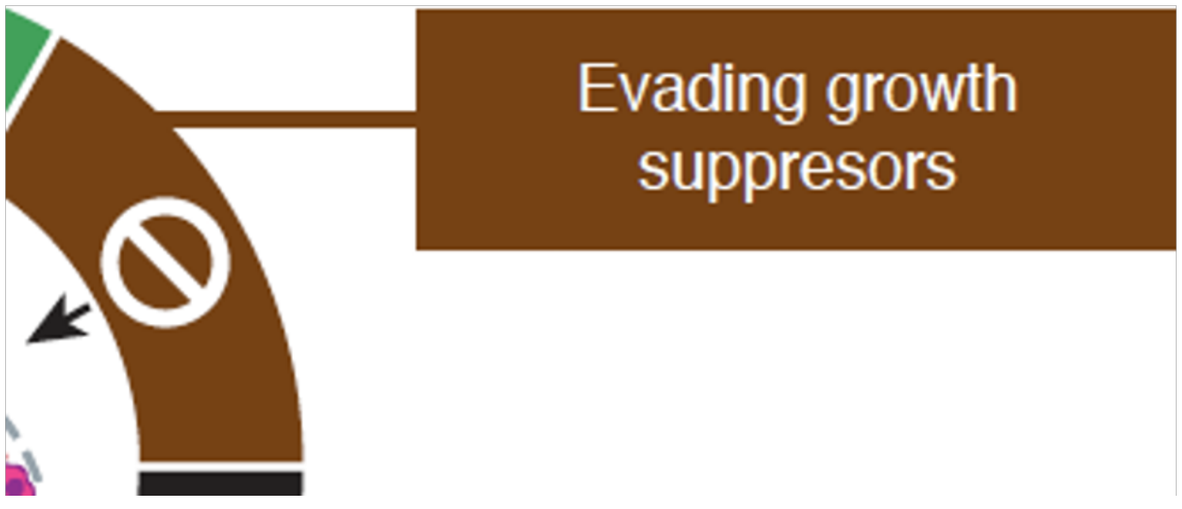
Hallmarks of Cancer: New Dimensions. Hanahan, *Cancer Discovery* 2022

Back to mutations . . .

How do mutations cause cancer?

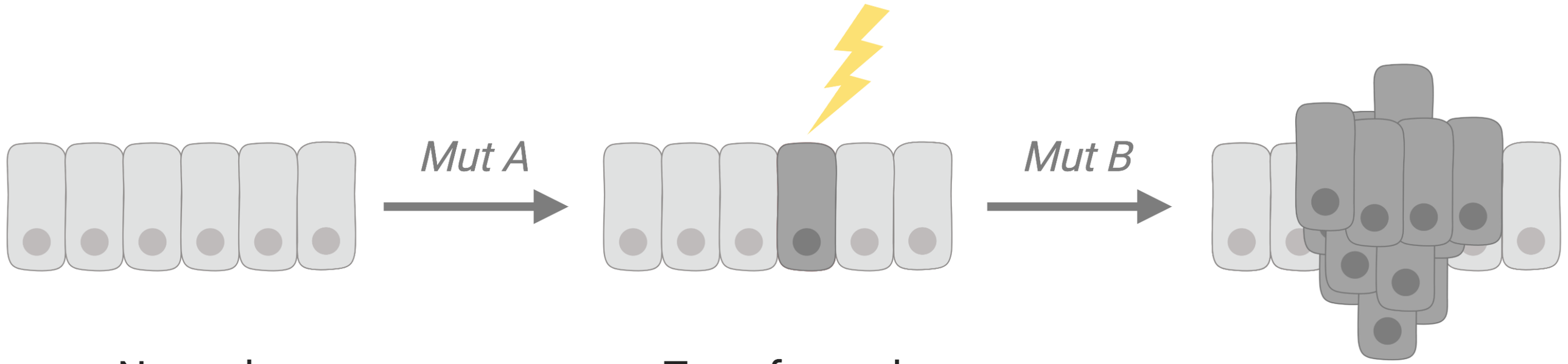
Oncogenes

Tumor suppressors



Tumorigenesis is a multistep process characterized by alterations in oncogenes and tumor suppressor genes

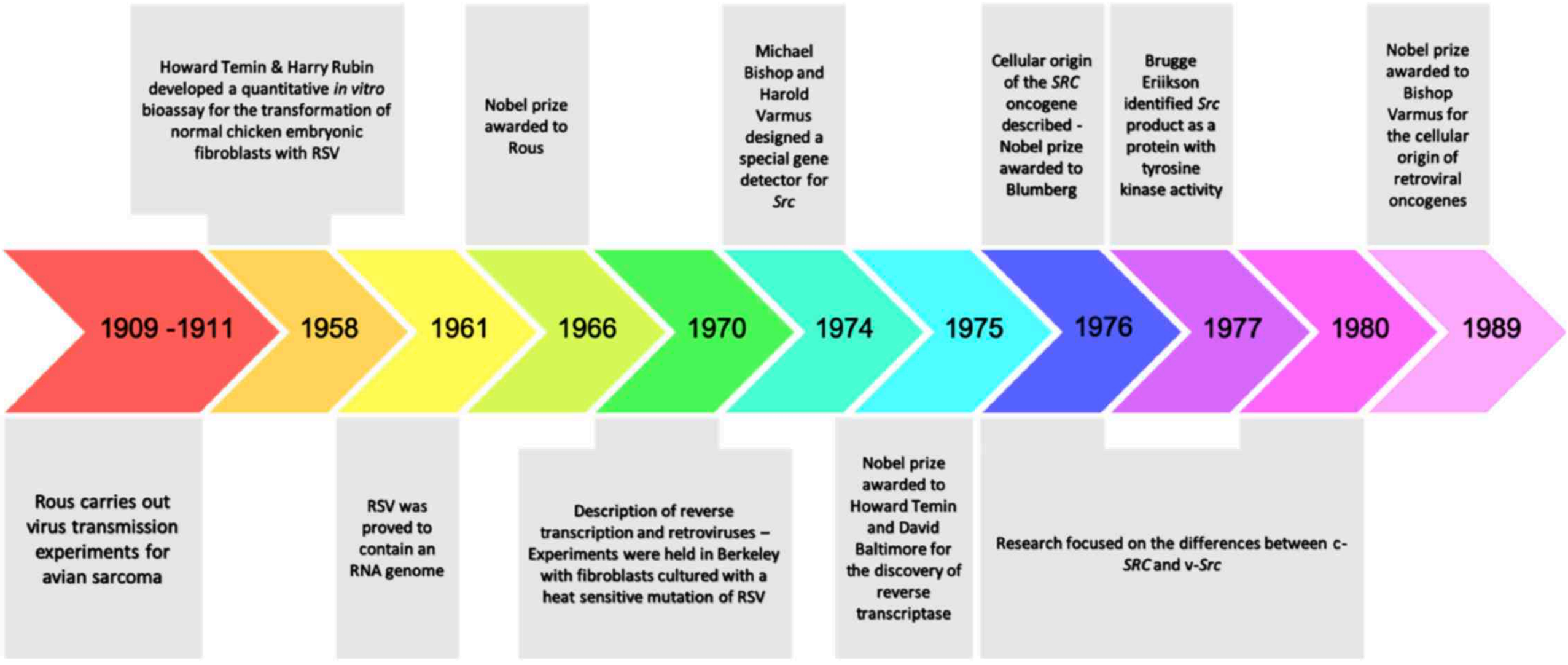
Oncogenes



Tumor Suppressor Genes

5. Viral origins of cancer lead to the discovery of oncogenes

Viral oncogenes and cancer



Simatou, A, et al., Mol & Clin Onc, 2020

Rous Sarcoma Virus (RSV): an important clue to the molecular cause of cancer

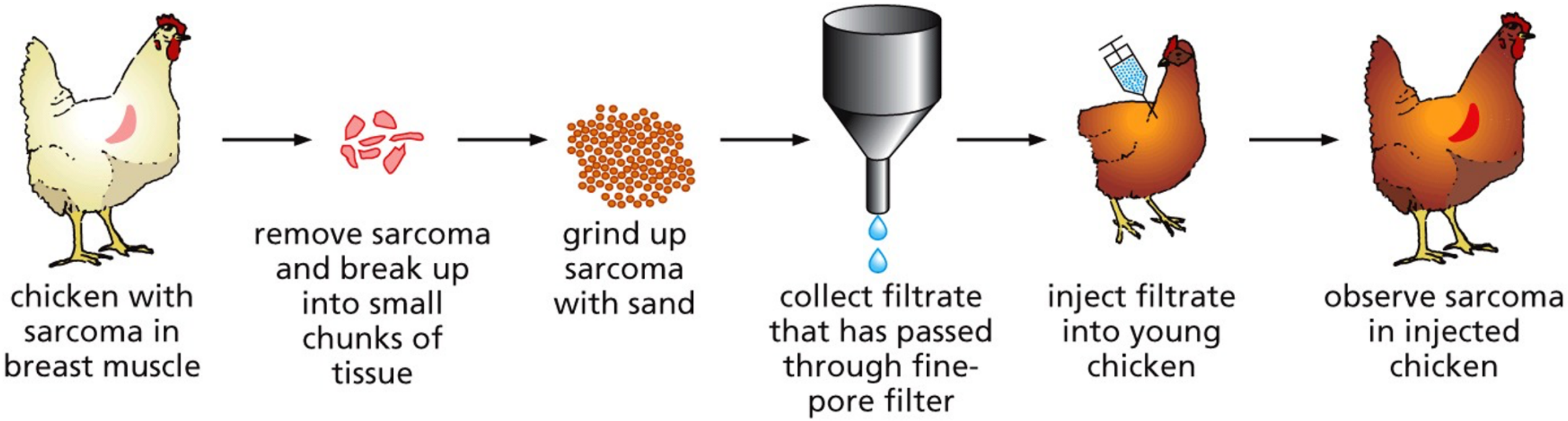


Figure 3.2 The Biology of Cancer (© Garland Science 2014)

Identification of the *Src* oncogene

Src gene sequence present in Rous Sarcoma Virus (RSV), not in related avian leukosis virus (ALV)

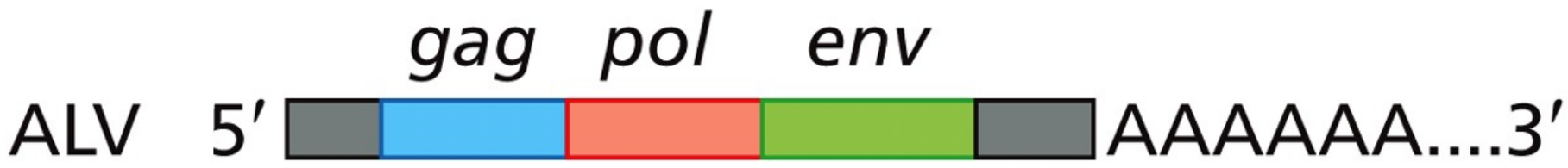


Figure 3.19 The Biology of Cancer (© Garland Science 2014)

Identification of the *Src* proto-oncogene

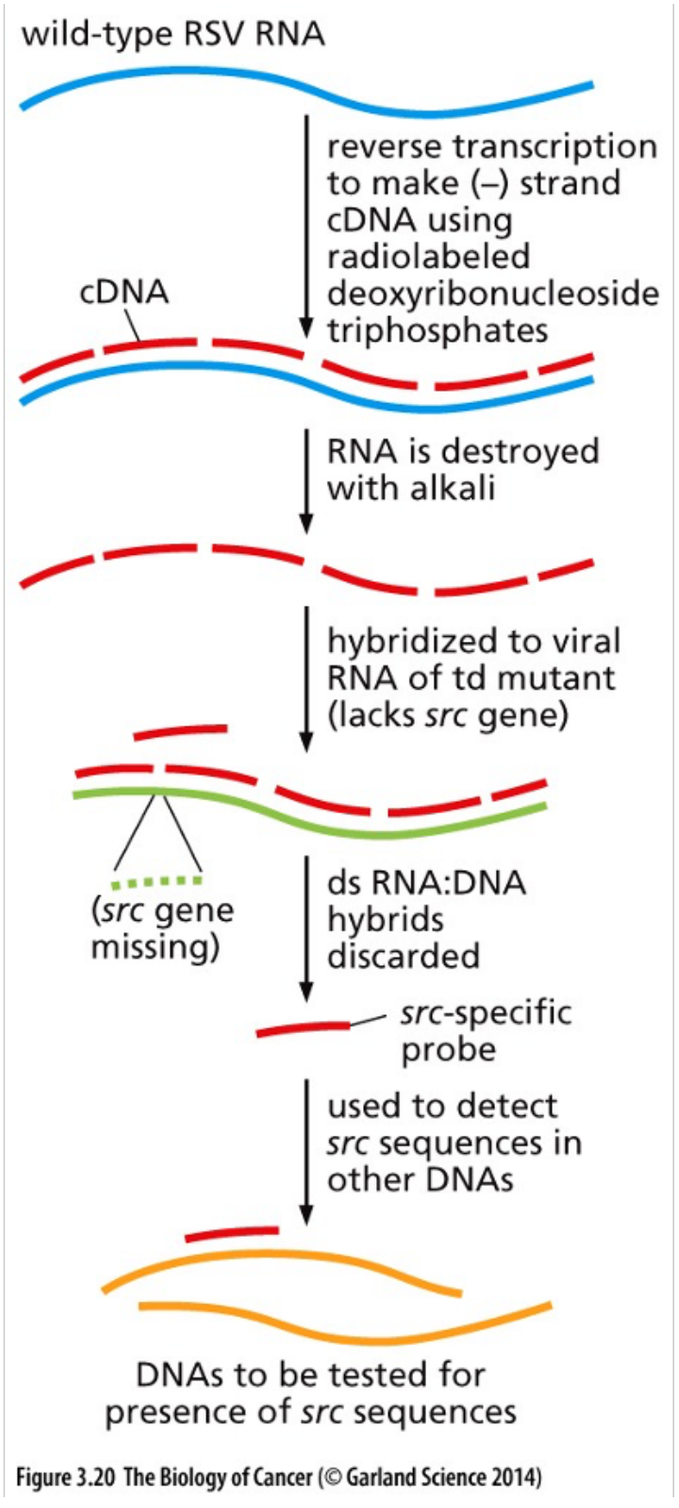
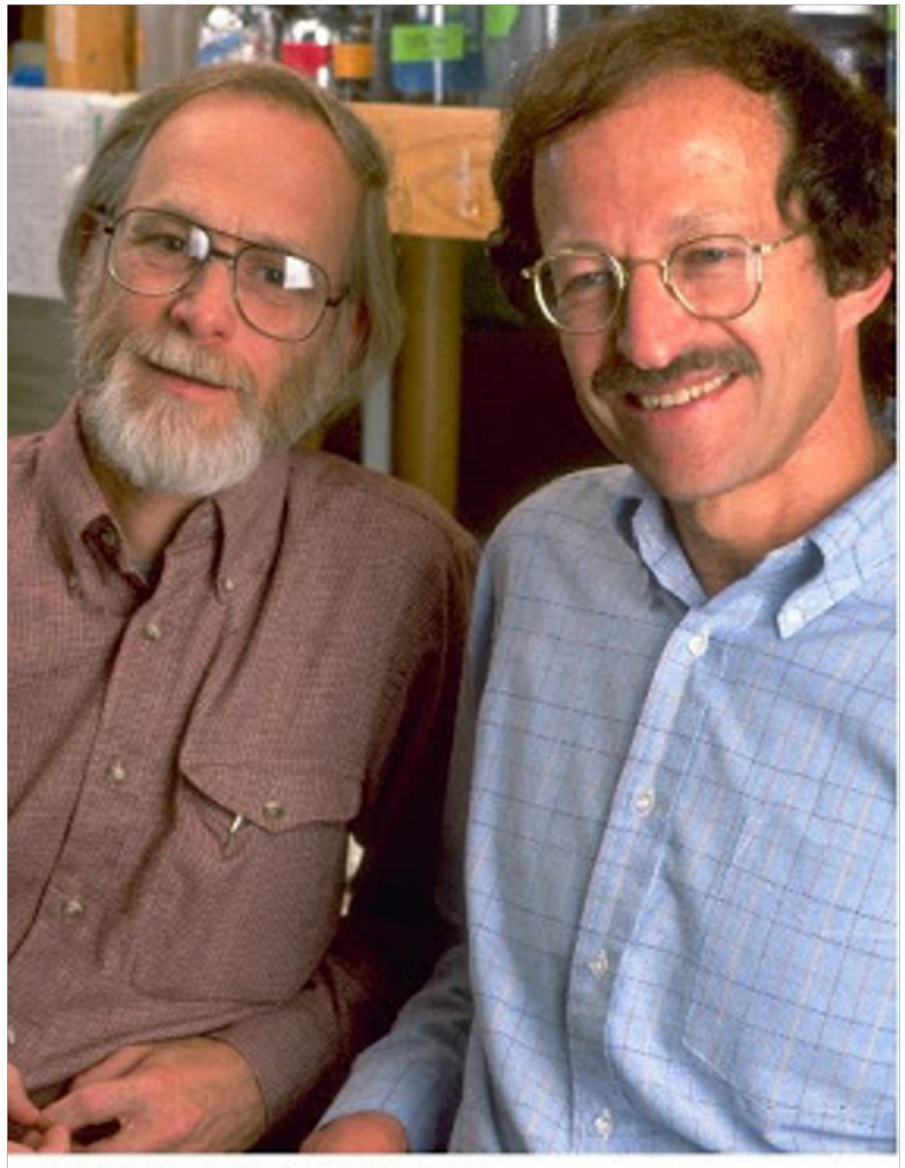


Figure 3.20 The Biology of Cancer (© Garland Science 2014)



J. Michael Bishop (1936 -)
Harold E. Varmus (1939 -)

Nobel prize 1989

Viral oncogenes result from uptake of host DNA in viral genome

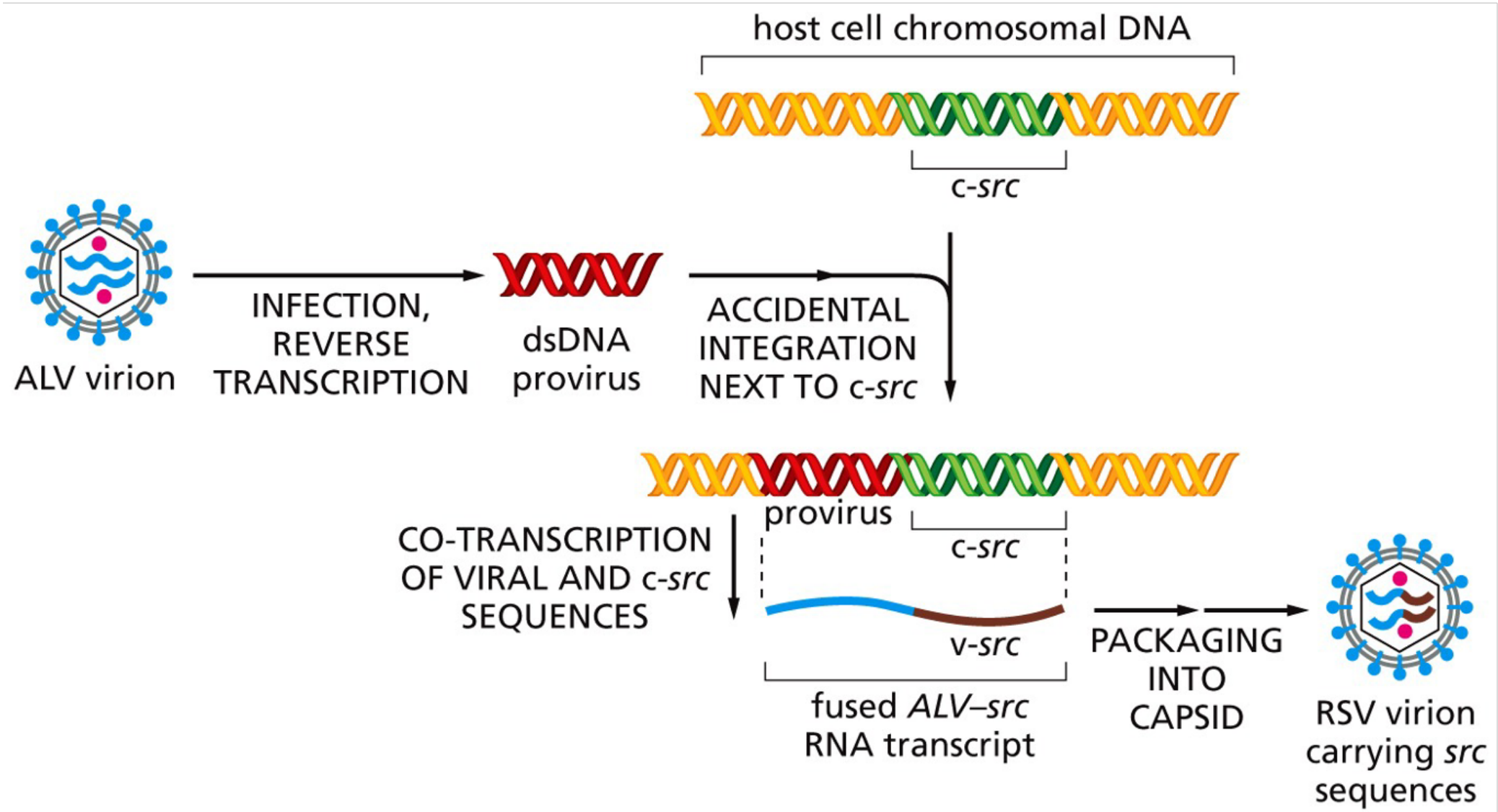


Figure 3.22 The Biology of Cancer (© Garland Science 2014)

Identification of *H-ras* proto-oncogene

Mechanism of activation of a human oncogene

Clifford J. Tabin, Scott M. Bradley, Cornelia I. Bargmann & Robert A. Weinberg

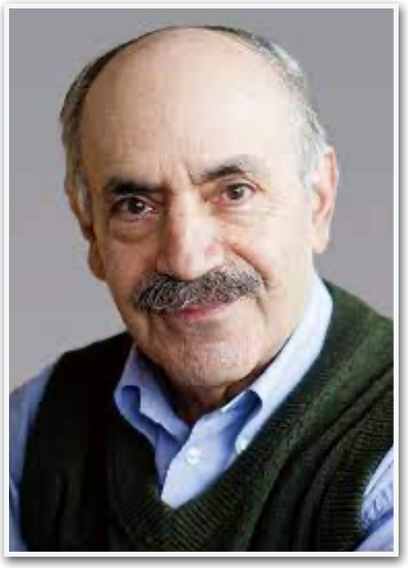
Whitehead Institute for Biomedical Research, Center for Cancer Research and Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA

Alex G. Papageorge & Edward M. Scolnick

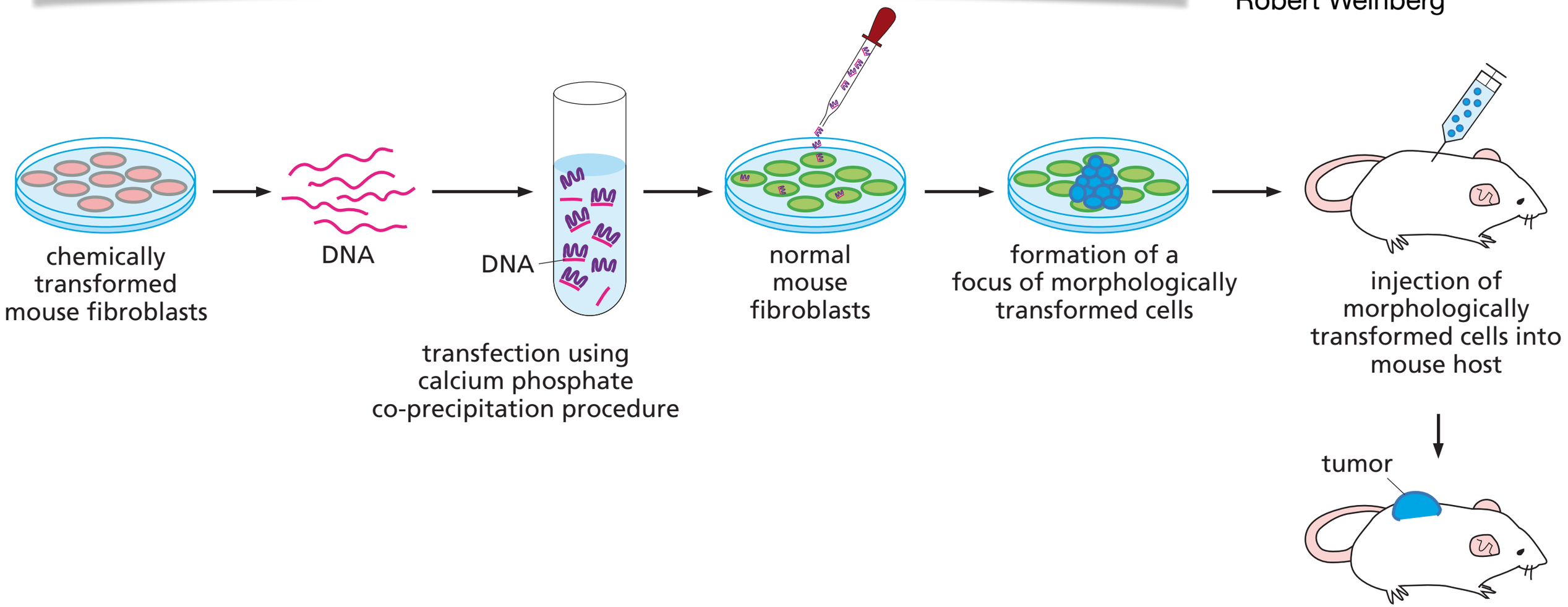
Merck Laboratories, West Point, Pennsylvania 19486, USA

Ravi Dhar, Douglas R. Lowy & Esther H. Chang*

Laboratories of Molecular Virology and Dermatology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205, USA
* Present address: Department of Pathology, Uniformed Services University for the Health Sciences, Bethesda, Maryland 20014, USA



Robert Weinberg



Weinberg - The Biology of Cancer (2014)

Transformation of mouse cells by human tumor DNA

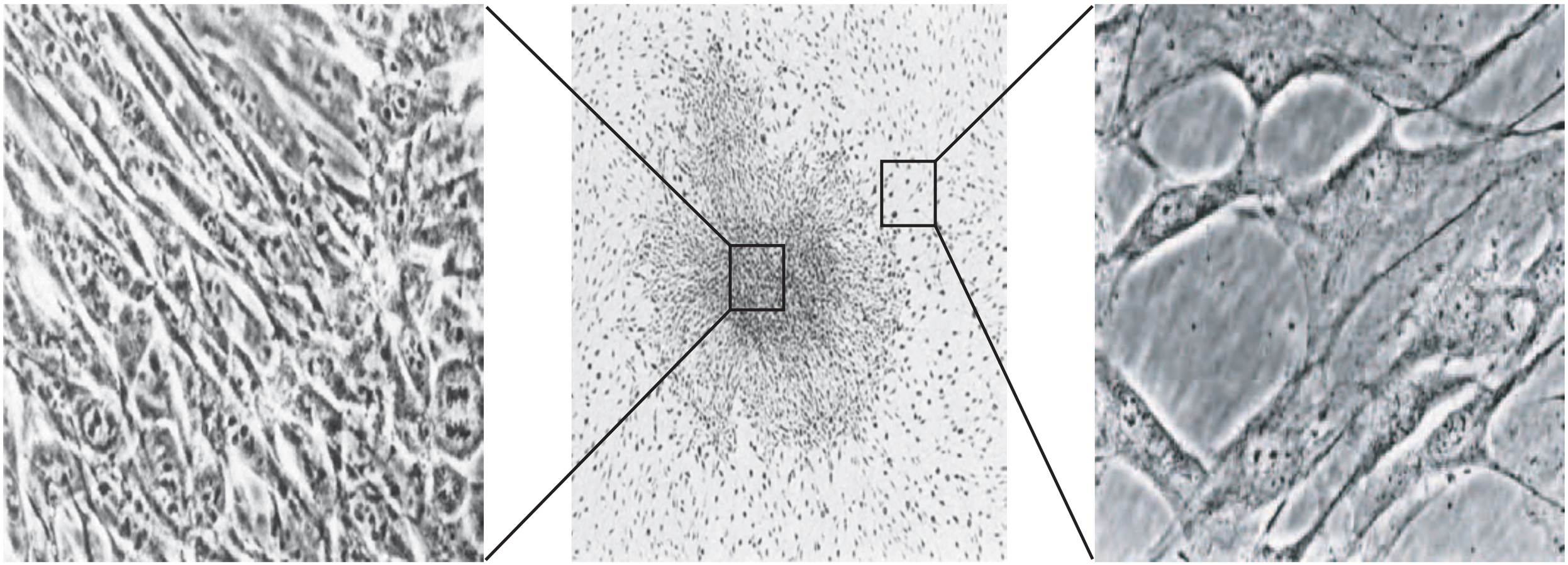


Figure 4.2 Transformation of mouse cells by human tumor DNA The introduction via transfection of various human tumor DNAs into NIH 3T3 cells yielded foci of transformants. Seen at low magnification (*middle*) is a focus generated by transfection of DNA from the T24 human bladder carcinoma cell line. At high magnification the transformed cells within this focus (*left*), like many transformed fibroblasts, are spindle-shaped, refractile, and piled up densely on one another. At the same magnification, the cells in the surrounding monolayer of untransformed NIH 3T3 cells (*right*), like normal fibroblasts, have wide, extended cytoplasms and are not piled on one another. (From M. Perucho et al., *Cell* 27:467–476, 1981.)

Identification of *H-ras* proto-oncogene

Mechanism of activation of a human oncogene

Clifford J. Tabin, Scott M. Bradley, Cornelia I. Bargmann & Robert A. Weinberg

Whitehead Institute for Biomedical Research, Center for Cancer Research and Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA

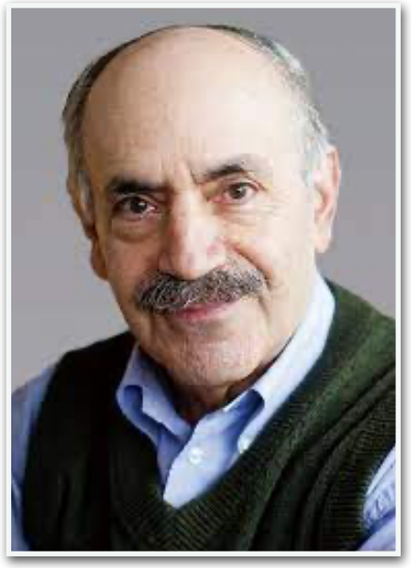
Alex G. Papageorge & Edward M. Scolnick

Merck Laboratories, West Point, Pennsylvania 19486, USA

Ravi Dhar, Douglas R. Lowy & Esther H. Chang*

Laboratories of Molecular Virology and Dermatology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205, USA
* Present address: Department of Pathology, Uniformed Services University for the Health Sciences, Bethesda, Maryland 20014, USA

Nature, 1982



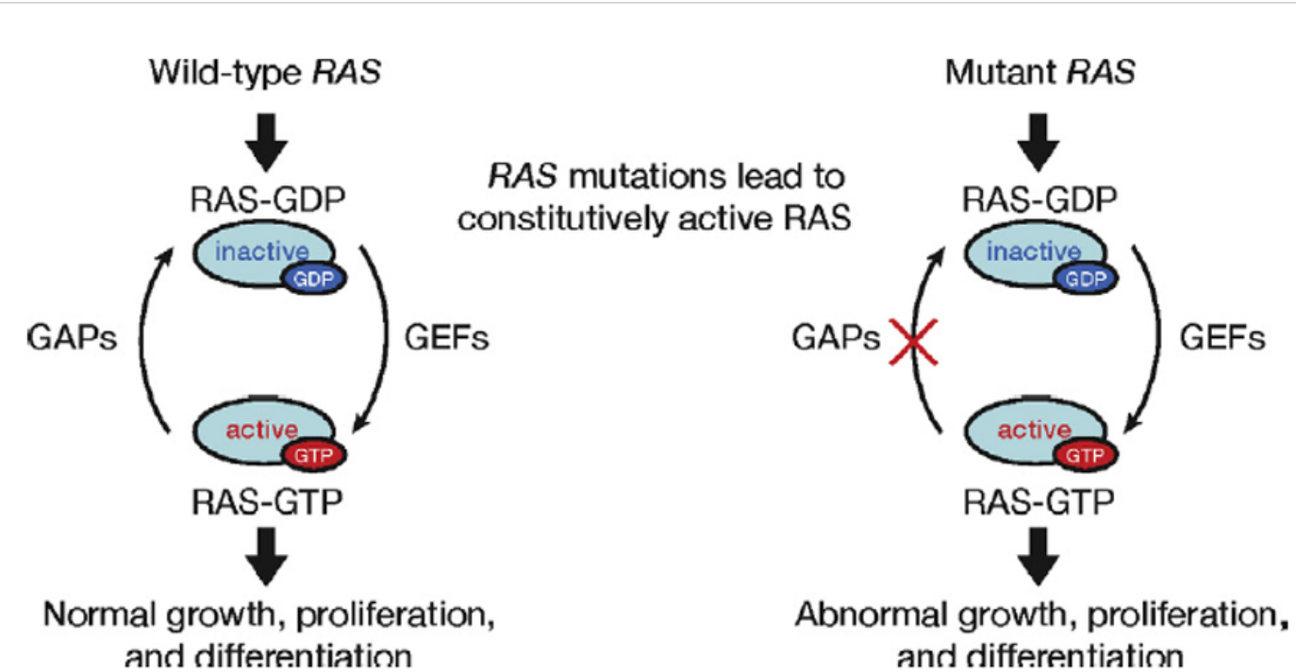
Robert Weinberg

Harvey **Ra**t **S**arcoma virus oncogene (mutant Hras) identified in a human bladder cancer cell line

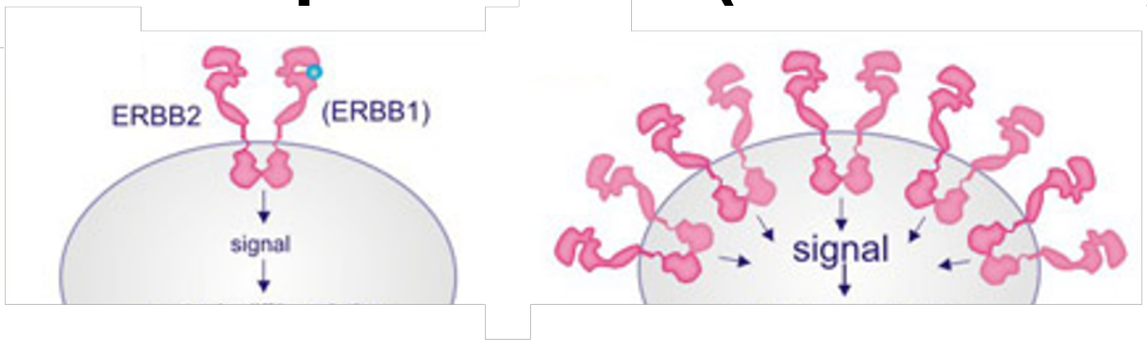
```
                                                    CCCGGG CCGCAGGCCC TTGAGGAGCG
                                                    gly  <- proto-oncogene
met thr glu tyr lys leu val val val gly ala GGC gly val gly lys ser ala leu thr
ATG ACG GAA TAT AAG CTG GTG GTG GTG GGC GCC GTC GGT GTG GGC AAG AGT GCG CTG ACC
                                                    val  <- oncogene
                                                                    splice
                                                                      v
ile gln leu ile gln asn his phe val asp glu tyr asp pro thr ile glu
ATC CAG CTG ATC CAG AAC CAT TTT GTG GAC GAA TAC GAC CCC ACT ATA GAG GTGAGCCTGC

GCCGCCGTCC AGGTGCCAGC AGCTGCTGCG GGCGAGCCCA GGACACAGCC AGGATAGGGC TGGCTGCAGC

CCCTGGTCCC CTGCATGGTG CTGTGGCCCT GTCTCCTGCT TCCTCTAGAG GAGGGGAGTC CCTCGTCTCA

GCACCCCAGG AGAGGAGGGG GCATGAGGGG CATGAGAGGT ACC
```

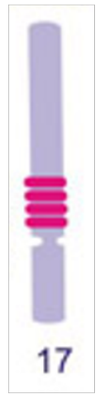
Proto-oncogenes can be activated by mutations and amplifications

Activating point mutations



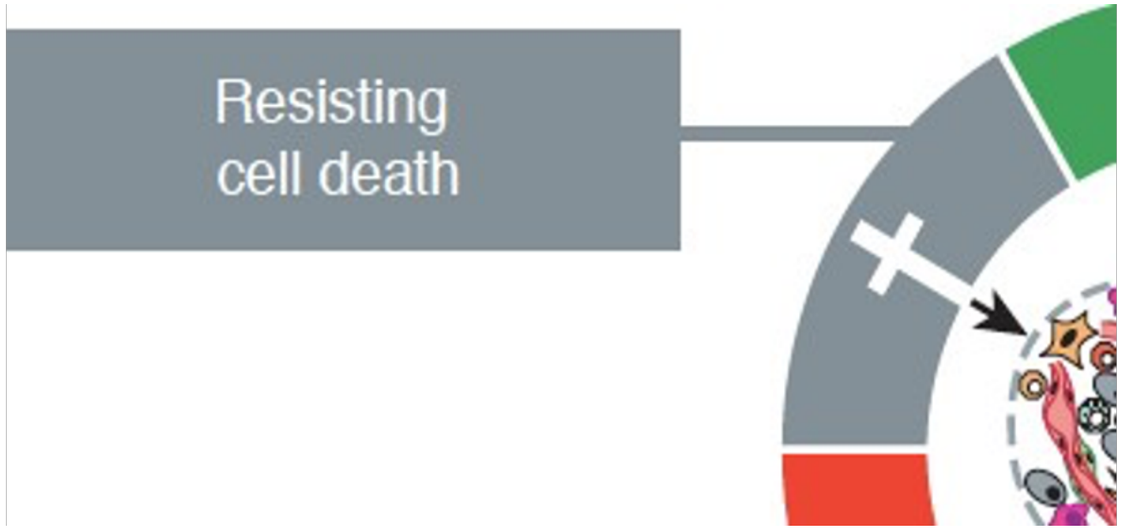
Gene amplifications (*Erbb2*/*Her2*)

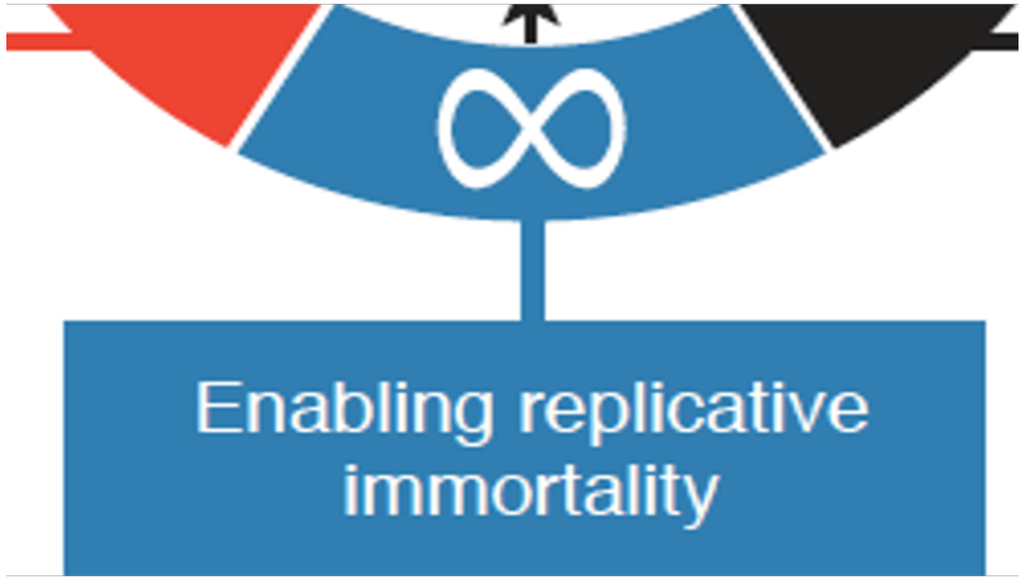


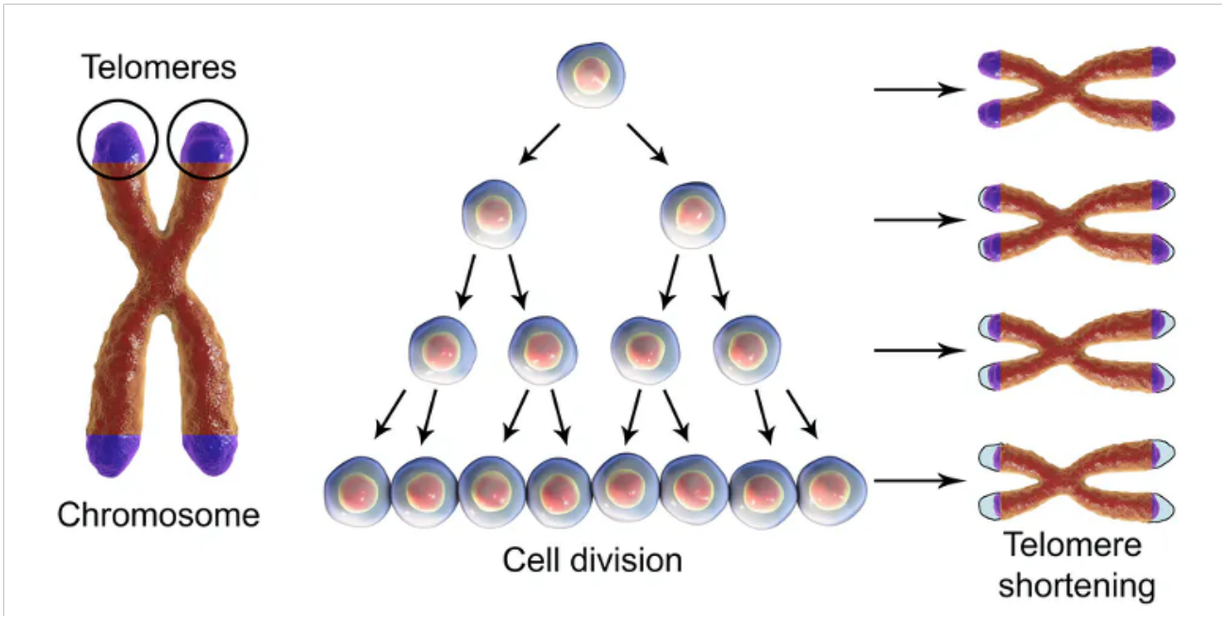


Where do you think proto-oncogenic mutations tend to occur? What type of function is being selected for?

Additional hallmarks cooperate with driver oncogenes







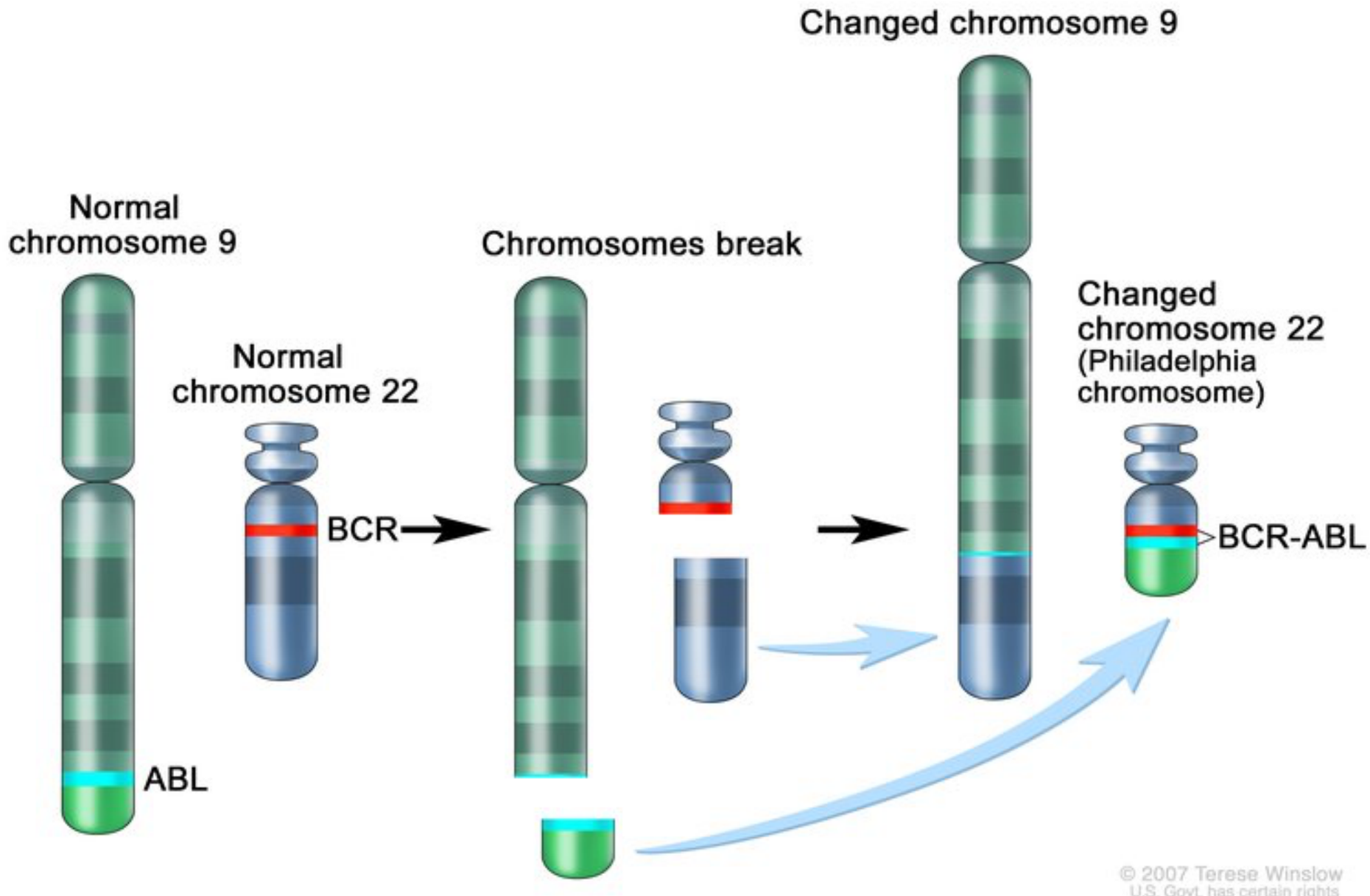
More proto-oncogenes traced from viral oncogenes

Name of virus	Species	Oncogene	Type of oncoprotein	Homologous oncogene found in human tumors
Rous sarcoma	chicken	*src*	non-receptor TK	colon carcinoma[a]
Abelson leukemia	mouse	*abl*	non-receptor TK	CML
Avian erythroblastosis	mouse	*erbB*	receptor TK	gastric, lung, breast[b]
McDonough feline sarcoma	cat	*fms*	receptor TK	AML[c]
H-Z feline	cat	*kit*	receptor TK[d]	gastrointestinal stromal
Murine sarcoma 3611	mouse	*raf*	ser/thr kinase[e]	bladder carcinoma
Simian sarcoma	monkey	*sis*	platelet-derived growth factor (PDGF)	many types[f]
Harvey sarcoma	mouse/rat	H-*ras*[g]	small G protein	bladder carcinoma
Kirsten sarcoma	mouse/rat	K-*ras*[g]	small G protein	many types
Avian erythroblastosis	chicken	*erbA*	nuclear receptor[h]	liver, kidney, pituitary
Avian myeloblastosis E26	chicken	*ets*	transcription factor	leukemia[i]
Avian myelocytoma	chicken	*myc*[j]	transcription factor	many types
Reticuloendotheliosis	turkey	*rel*[k]	transcription factor	lymphoma

***The Biology of Cancer**, 3rd edition.* Robert Weinberg

Philadelphia Chromosome

First consistent chromosomal alteration (translocation) associated with cancer (leukemias) (1960)



Question: are oncogenes/oncogenic mutations dominant or recessive?

Oncogenes can affect several Hallmarks of Cancer

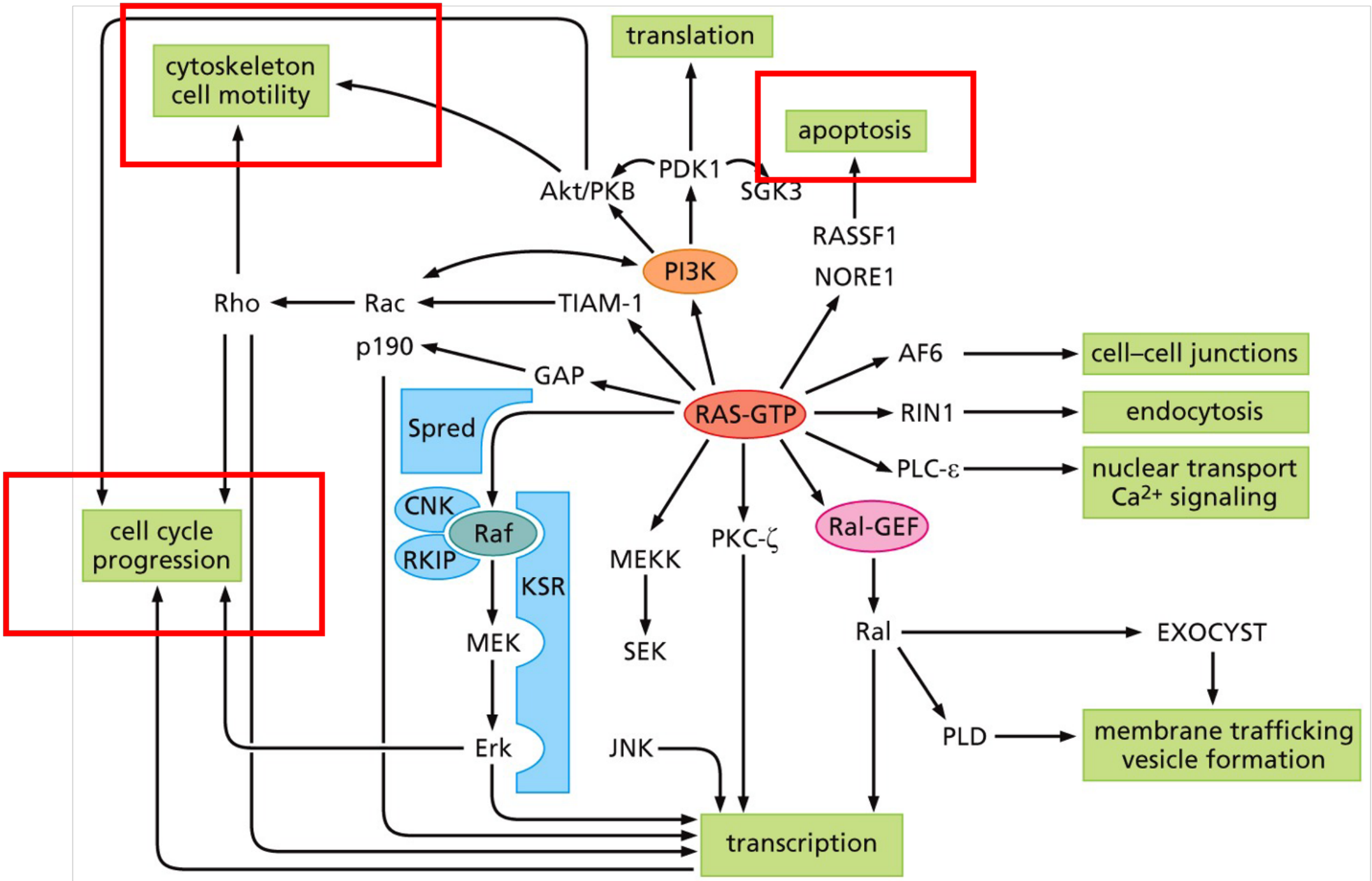
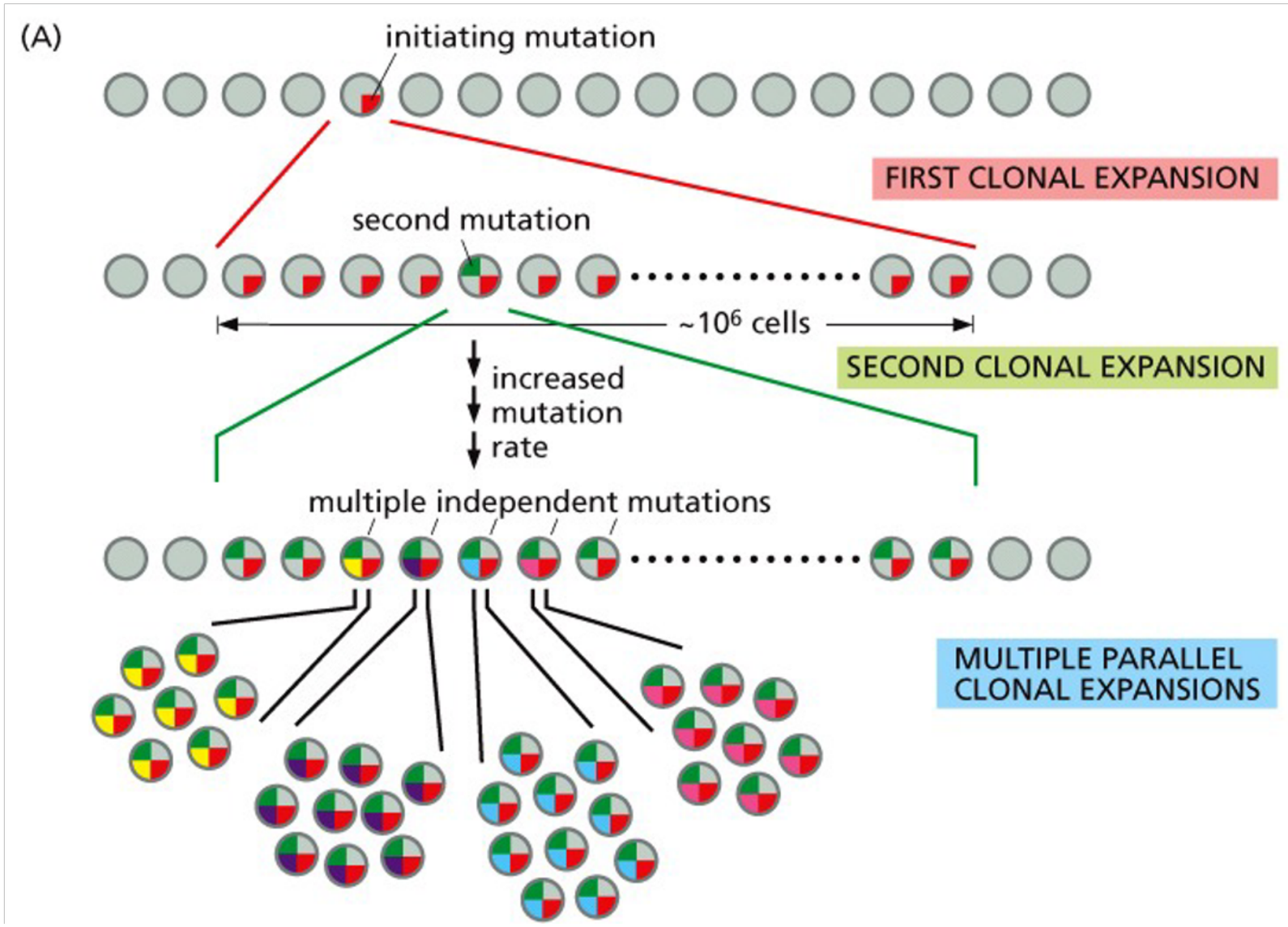
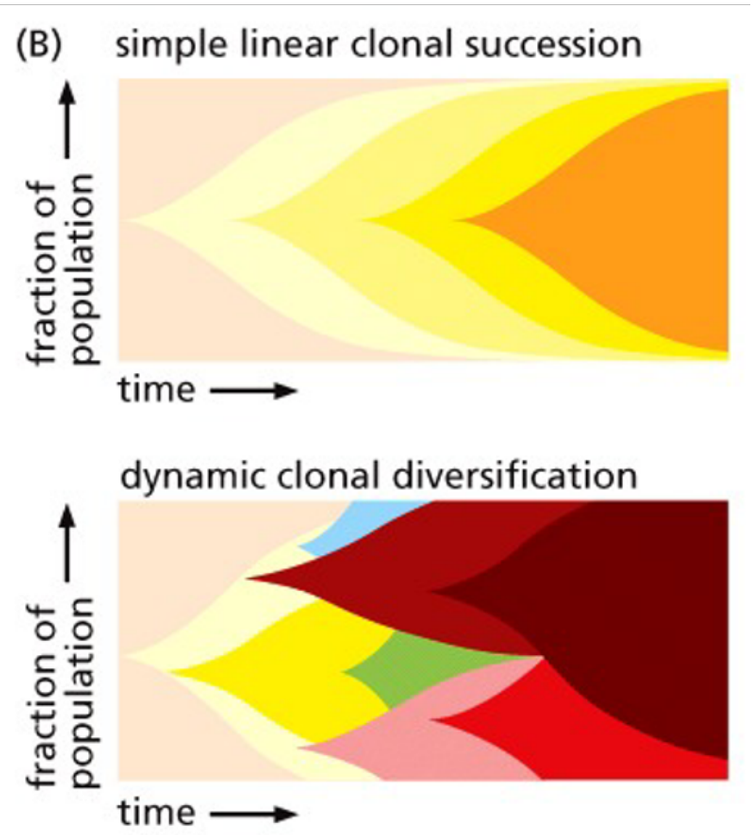


Figure 6.33 The Biology of Cancer (© Garland Science 2014)

6. Clonal evolution theory of cancer

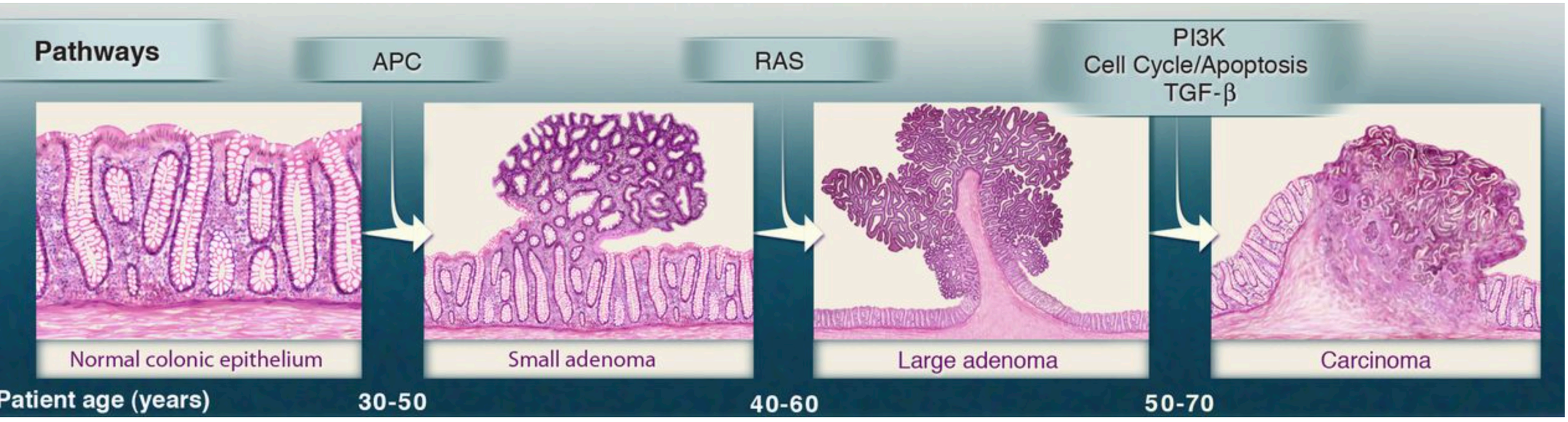
Cancer is a multi-step process



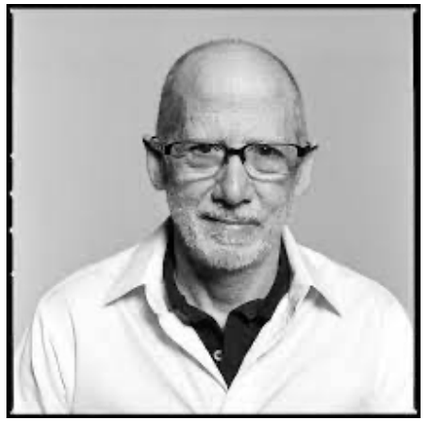


Cancer is a multi-step process

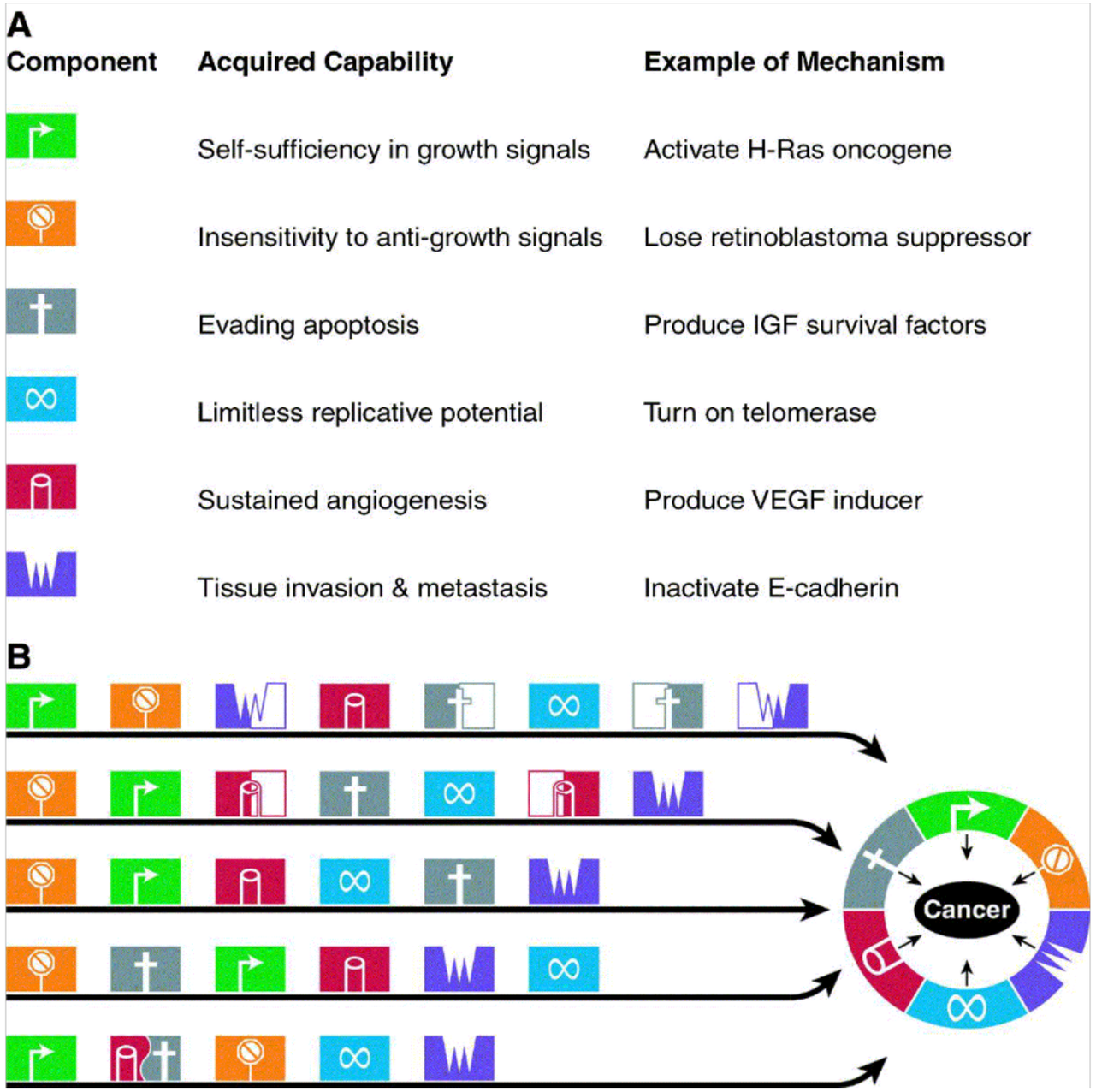
Colorectal cancer:



Vogelstein, B, et al. ***Science*** 2013



Key concept: cancer progresses through acquisition of multiple genetic changes

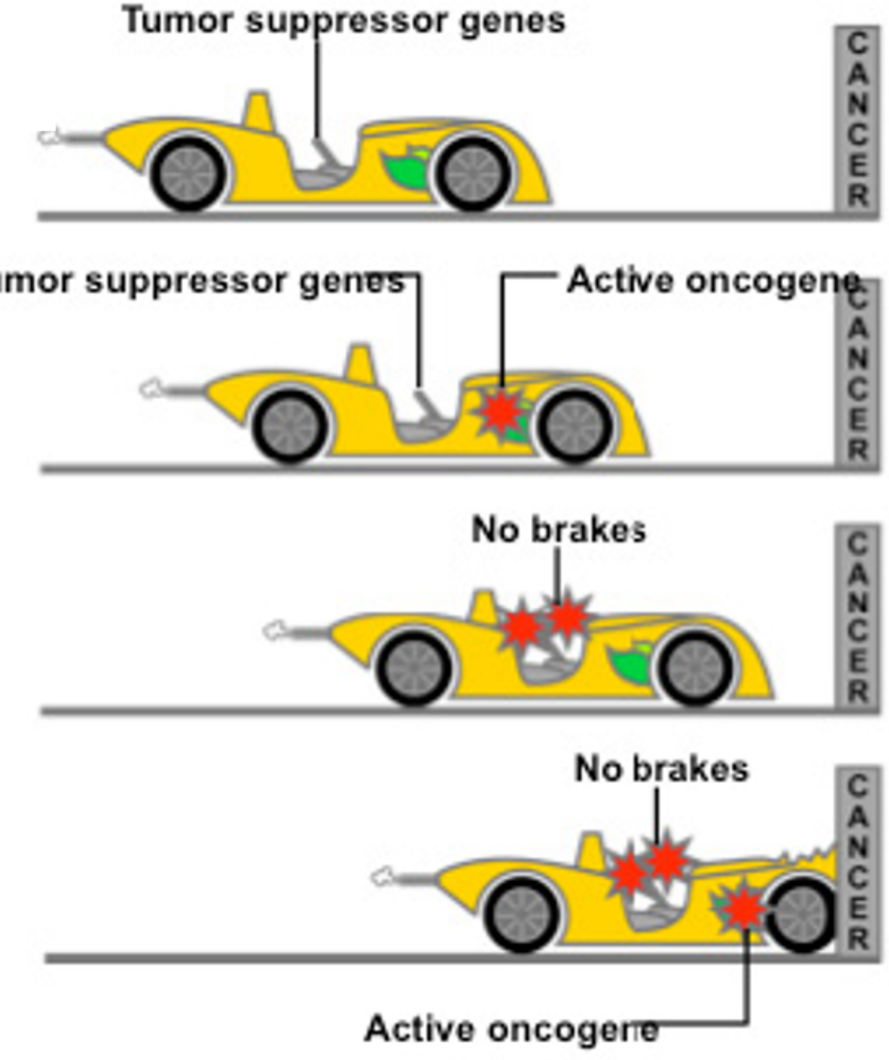


But also epigenetic and environmental changes . . .

Next up: Tumor suppressors and their dysregulation in cancer!

Key differences between oncogenes and tumor suppressor genes: brake vs. accelerator

Oncogenes	Tumor suppressor genes
Mutation in one of the two alleles is sufficient	Both alleles must be affected
Gain of function of a protein that signals cell proliferation	Loss of function of protein
Mutation arises in somatic cells, not inherited	Mutation present in germ cell (inherited) or in somatic cell



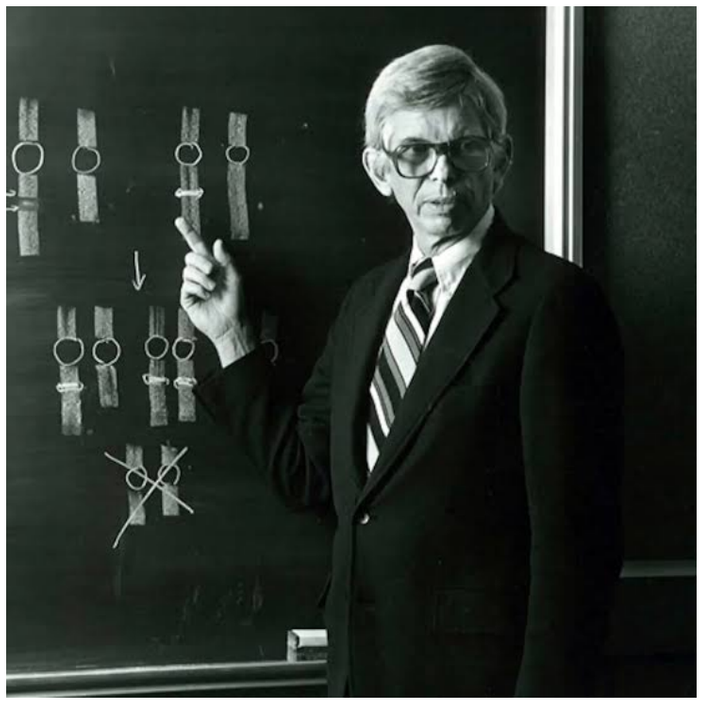
Representative TSGs

Table 1. Representative Tumor Suppressor Genes

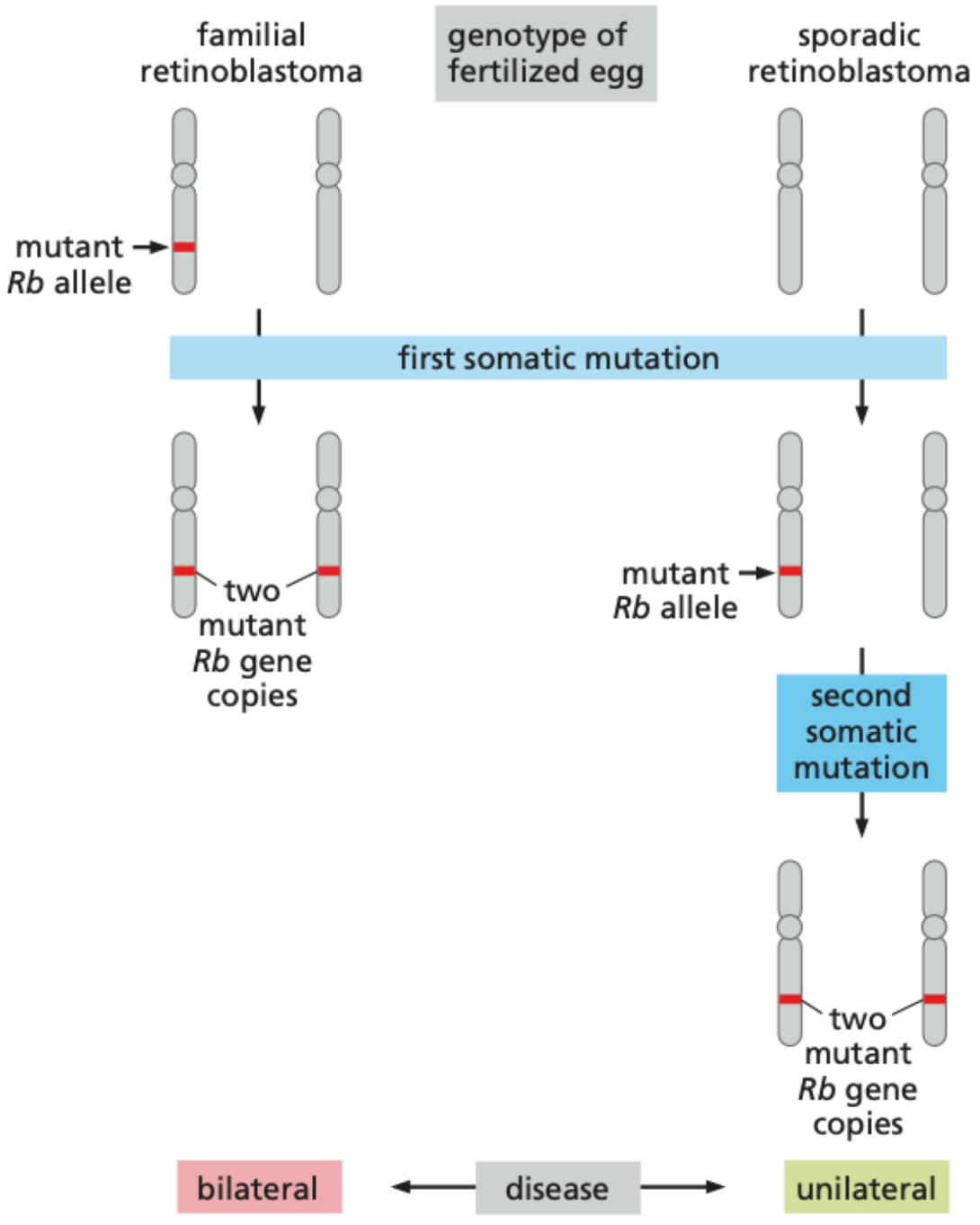
Gene	Function	Familial Cancer Association	Other Major Tumor Types
p53	Transcription factor	Li-Fraumeni syndrome	>50% of cancers
RB	Transcriptional corepression	Retinoblastoma	Many
INK4a (p16)	Cdk inhibitor (RB activation)	Melanoma	Many
ARF	Mdm2 antagonist (p53 activation)	Melanoma	Many
APC	Wnt/Wingless signaling	Familial adenomatous polyposis	Colorectal cancer
PTCH	Hedgehog signaling (receptor)	Basal cell nevus (Gorlin) syndrome	Medulloblastoma, basal cell carcinoma, rhabdomyosarcoma
SMAD4/DPC4	TGF-β signaling (Transcription factor)	Juvenile polyposis (hamartomas)	Pancreatic and colon cancer
PTEN	Lipid phosphatase (phosphoinositide metabolism)	Cowden syndrome	Glioblastoma, endometrial, thyroid, and prostate cancers
TSC1,2	GTPase activating protein complex (mTOR inhibition)	Tuberous sclerosis (hamartomas)	Renal cell carcinoma (rare), angiofibromas
NF1	GTPase activating protein for Ras	Neurofibromatosis	Sarcomas, gliomas
WT1	Transcription factor	Wilm's tumor	
MSH2 and MLH1	DNA mismatch repair	Hereditary nonpolyposis colorectal cancer (Lynch syndrome)	Endometrial, gastric, ovarian, bladder cancer
ATM	DNA damage sensor (protein kinase)	Ataxia telangiectasia (T-cell lymphoma)	Lymphoreticular malignancies
NBS1	DNA repair, S phase checkpoint control	Nijmegen breakage syndrome (T cell lymphoma)	Lymphoreticular malignancies
CHK2	Protein kinase (G1 checkpoint control)	Li-Fraumeni syndrome	
BRCA1, BRCA2	DNA repair	Familial breast and ovarian cancer	
FA genes	DNA repair, S phase checkpoint	Fanconi Anemia	Acute myelogenous leukemia
VHL	E3 ligase recognition factor for HIFα	Von Hippel-Lindau syndrome	Renal cell carcinoma, cerebellar hemangiosarcoma

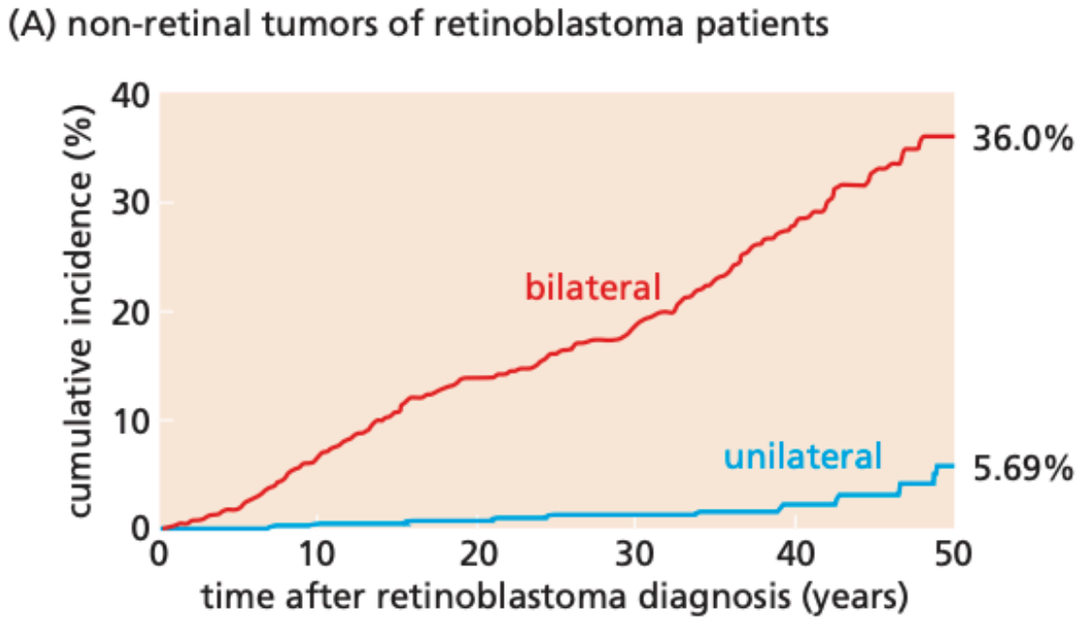
Sherr - Cell (2004)

Knudson's Two Hit Hypothesis



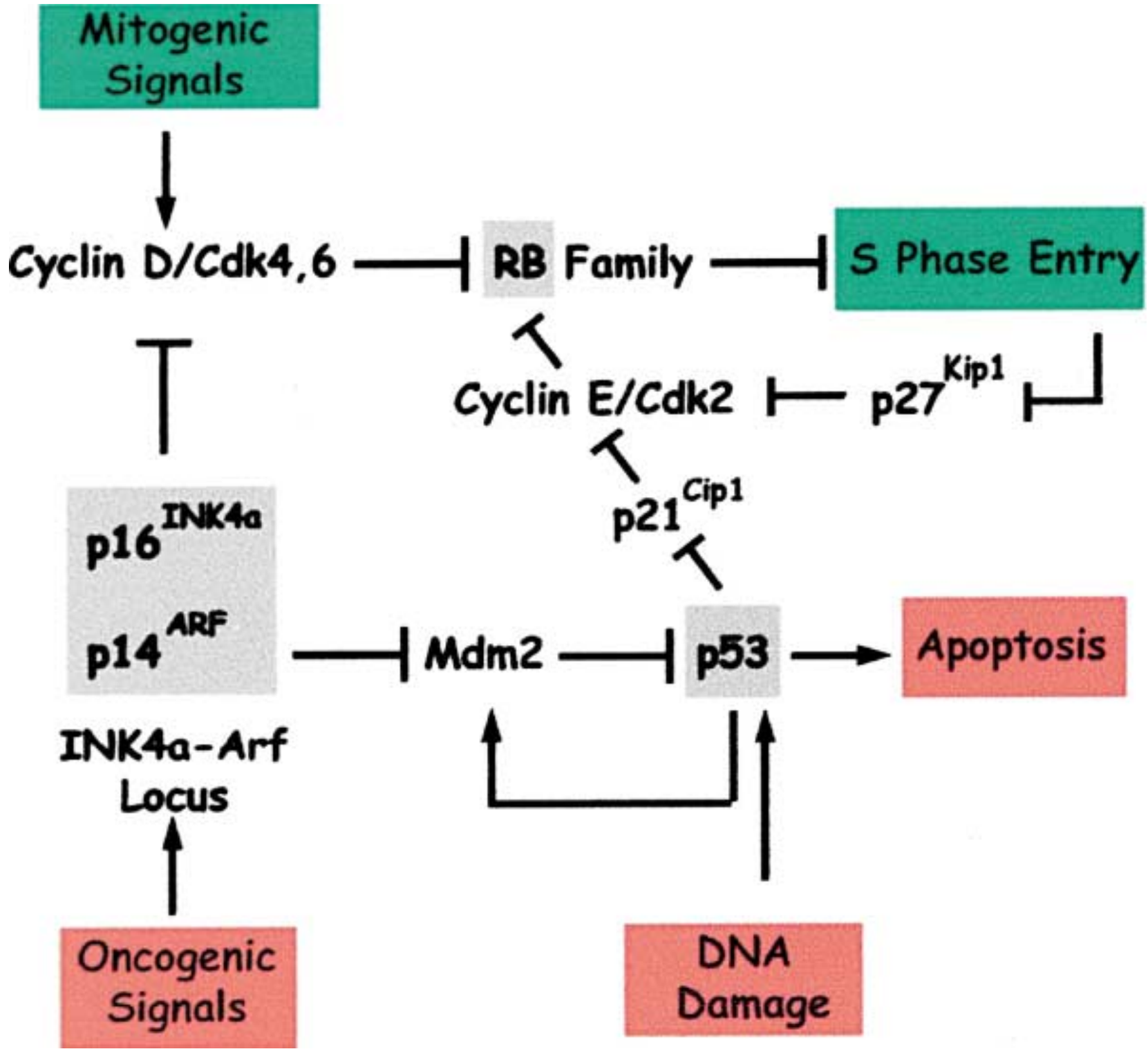
Alfred G. Knudson Jr.





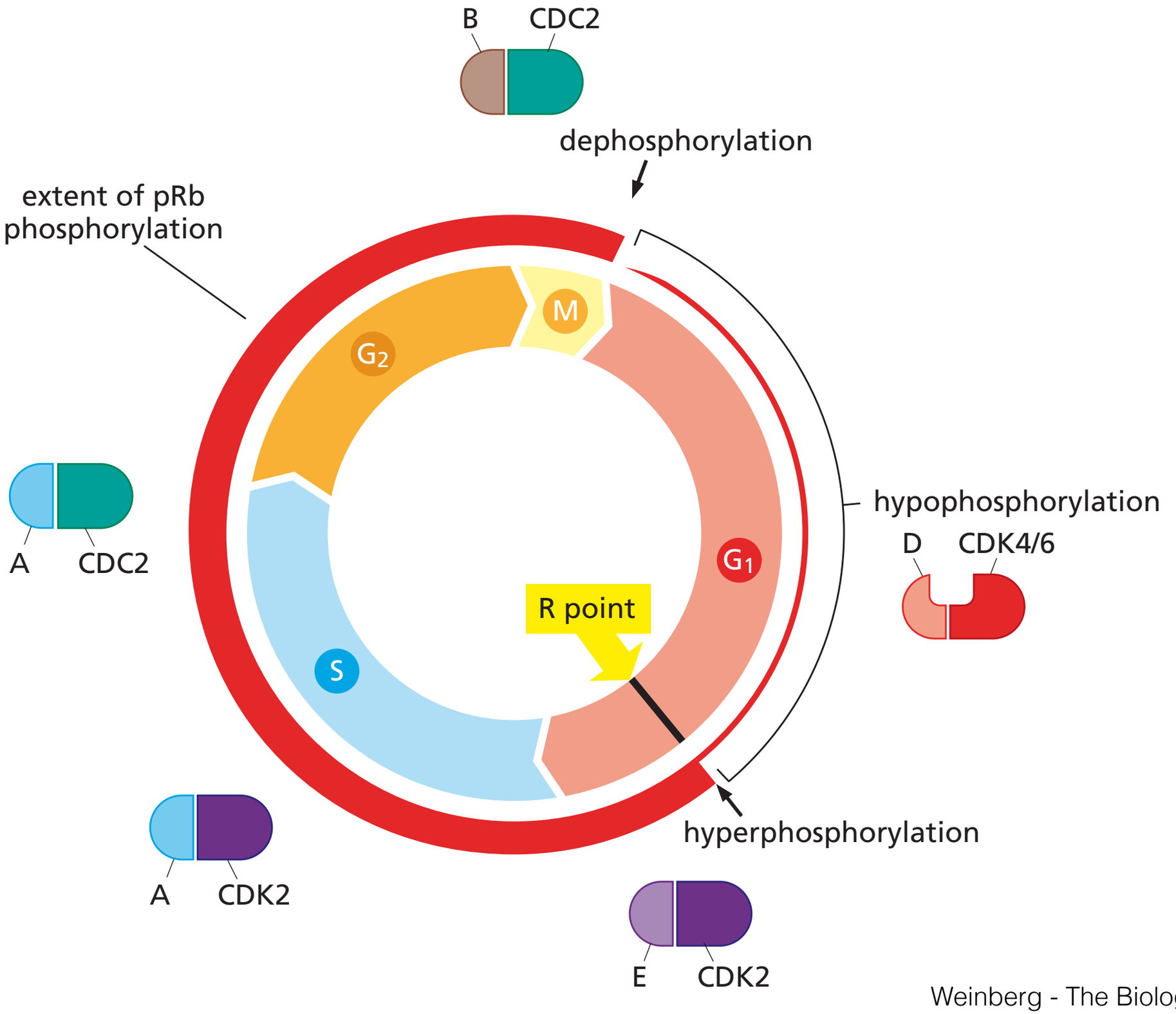
Weinberg - The Biology of Cancer (2014)

RB and p53 Regulate Cell Cycle Checkpoint Controls



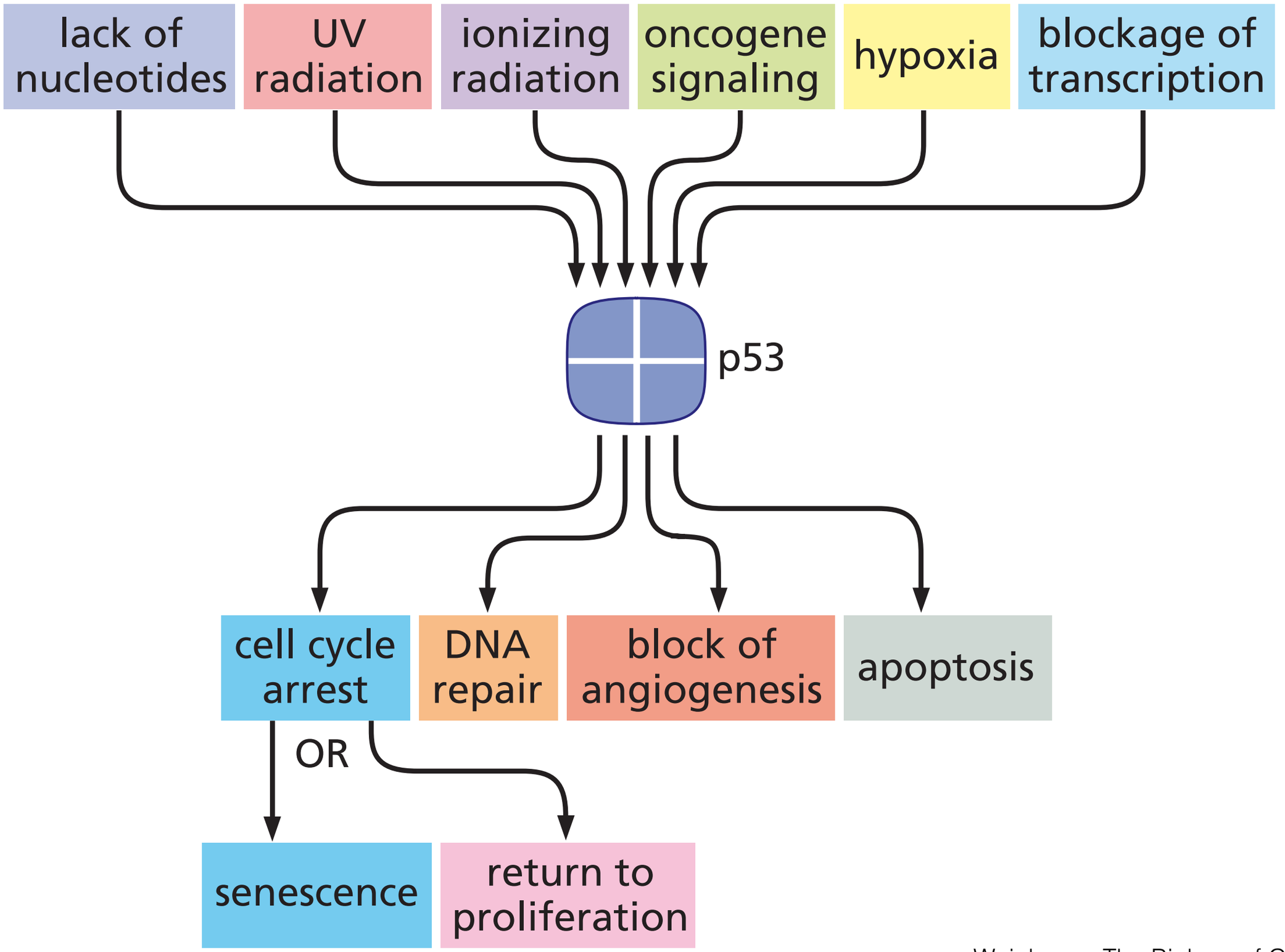
Sherr - Cell (2004)

Cell cycle–dependent phosphorylation of RB



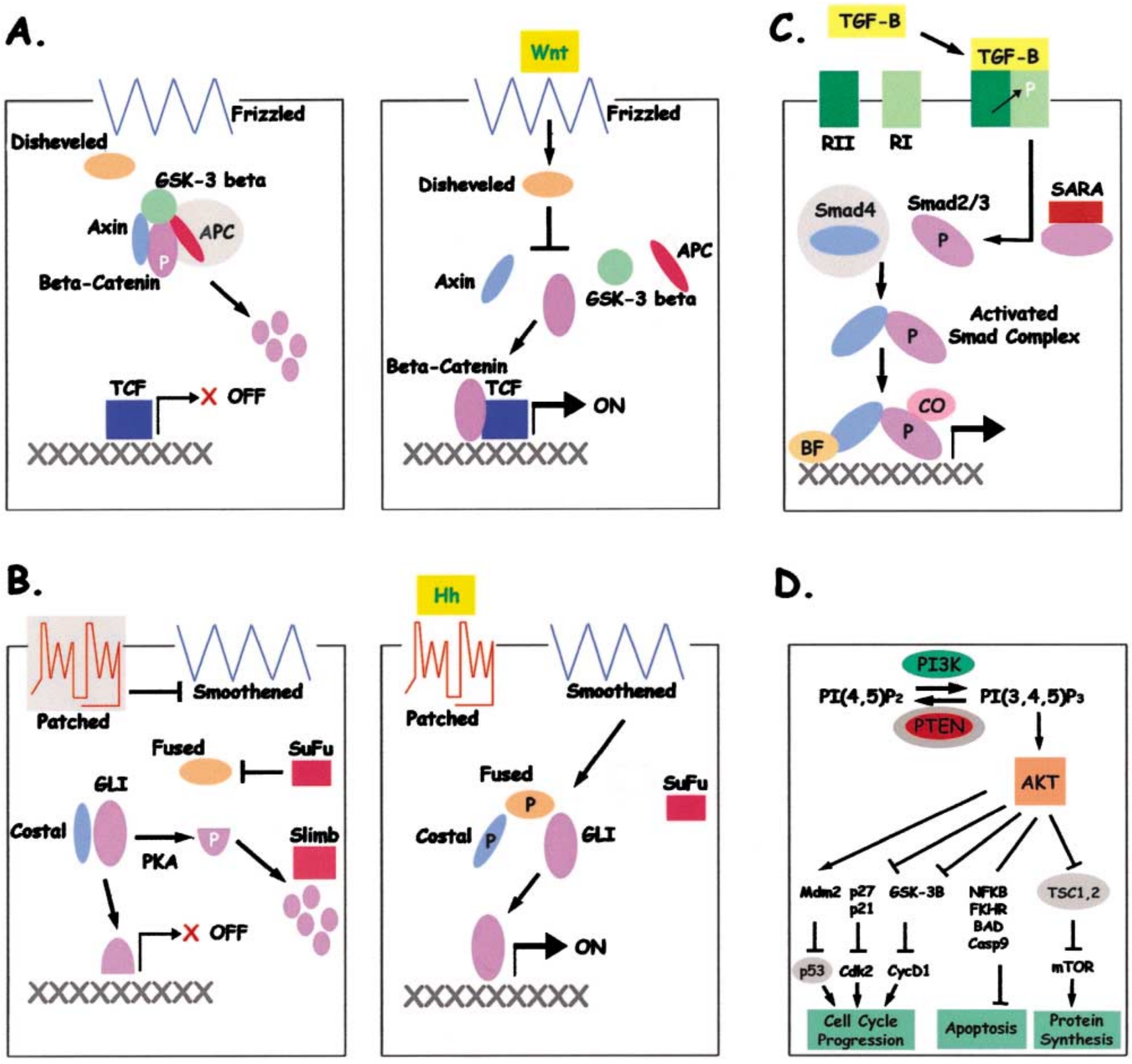
Weinberg - The Biology of Cancer (2014)

The p53 transcription factor responds to a variety of stress signals



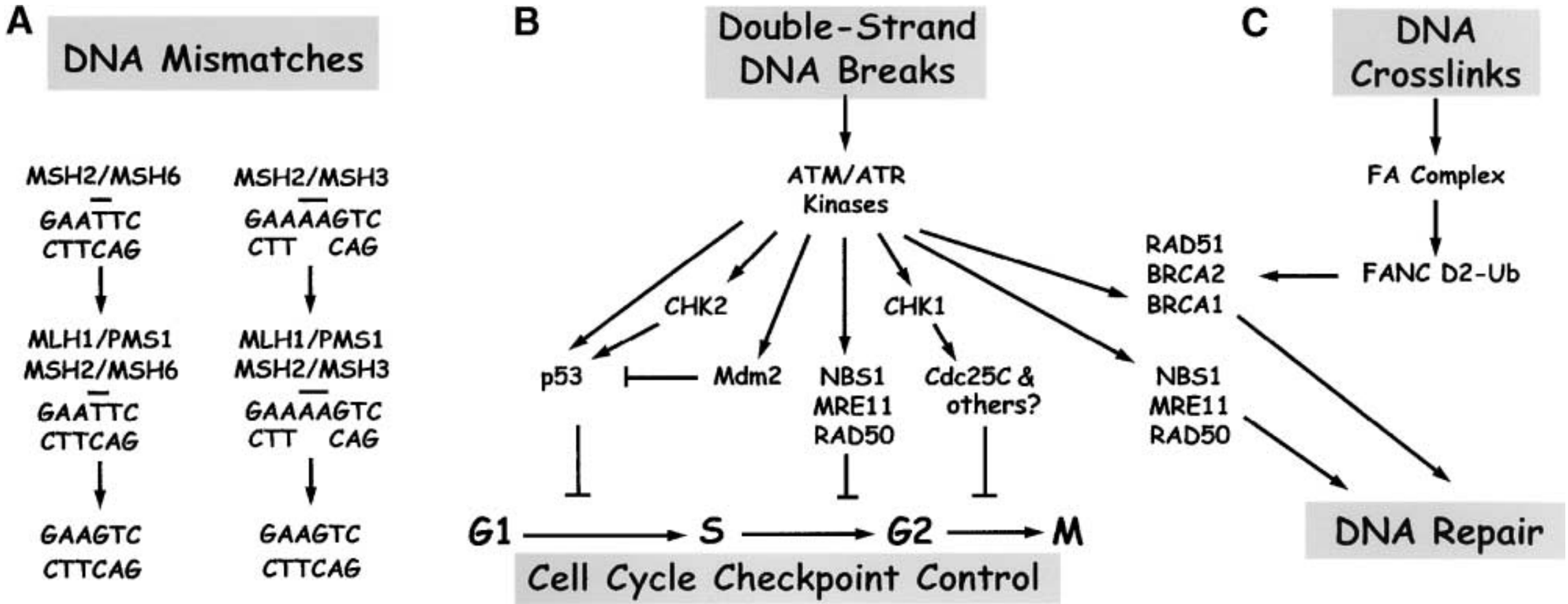
Weinberg - The Biology of Cancer (2014)

Tumor Suppressor Proteins Regulating Ligand-Mediated Signaling Pathways



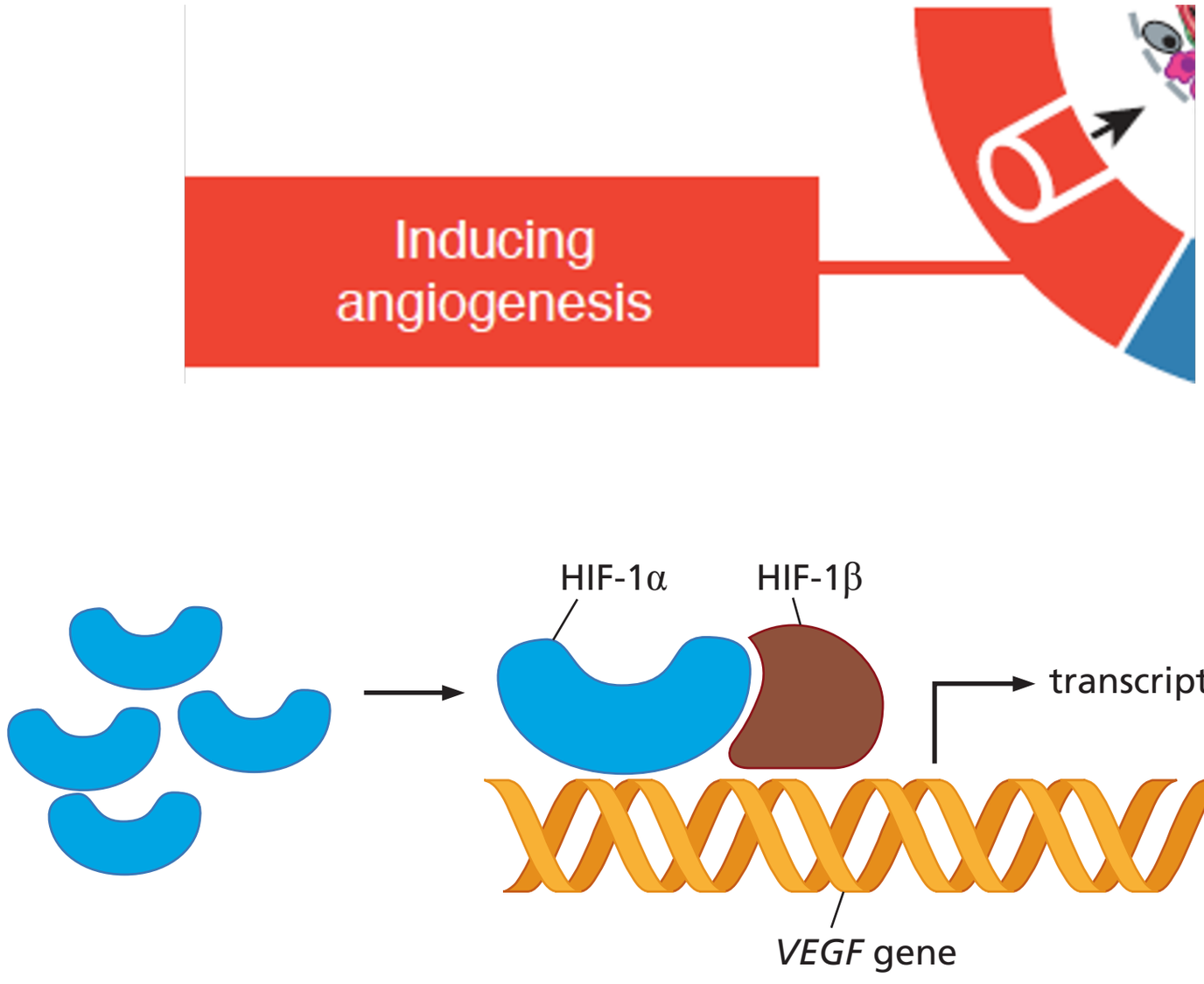
Sherr - Cell (2004)

Tumor Suppressors Involved in the DNA Damage Response



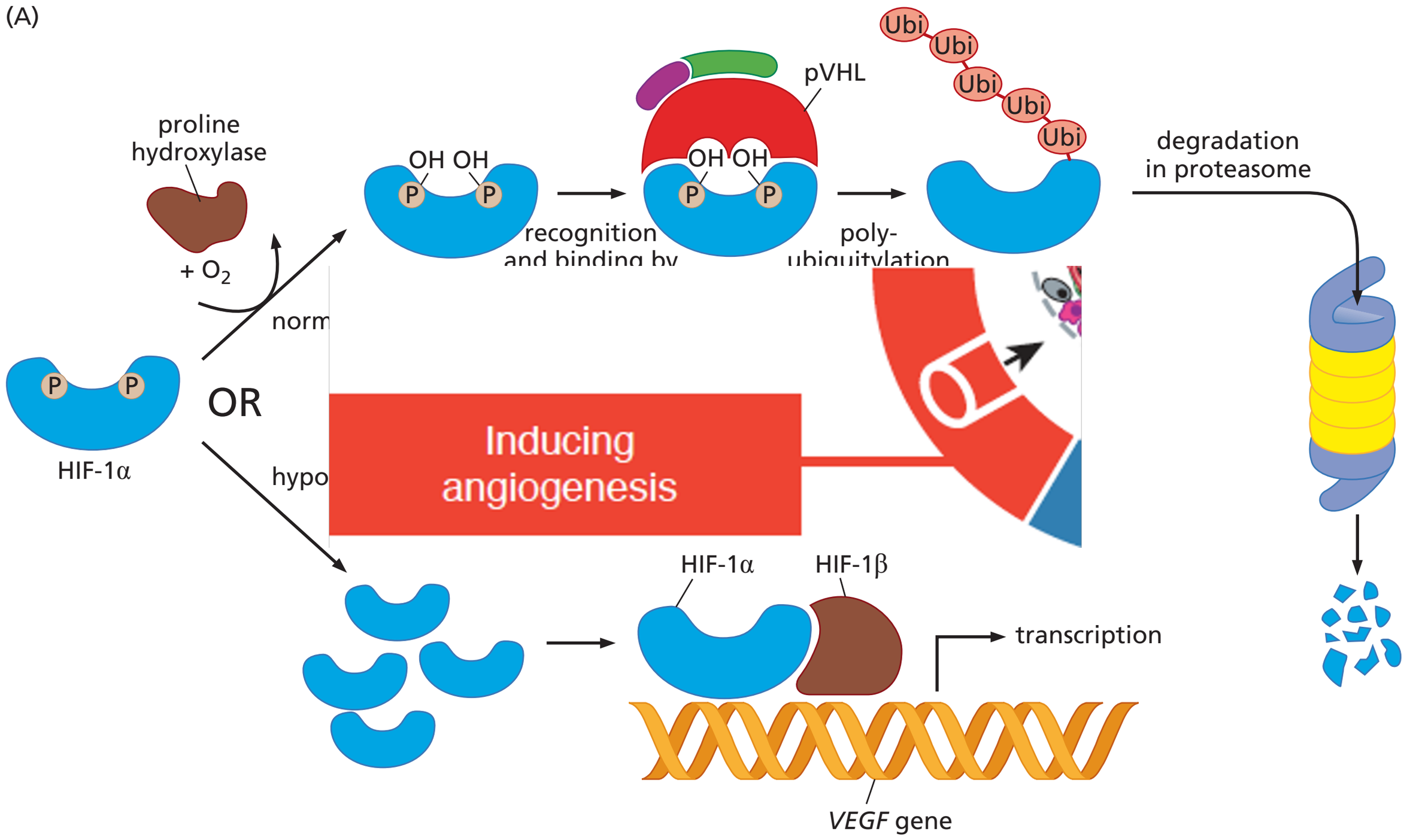
Sherr - Cell (2004)

HIF-1 and its regulation by pVHL



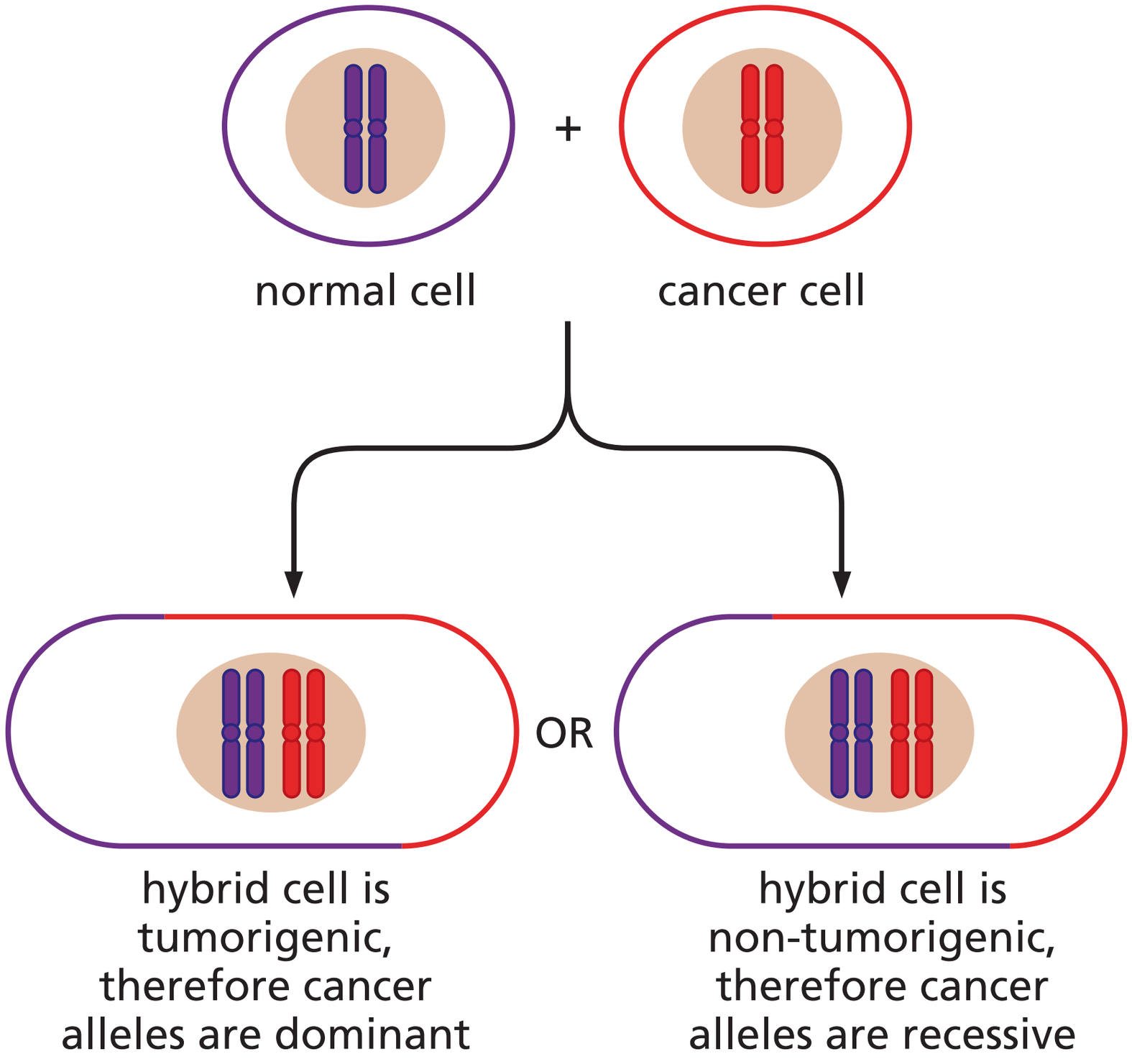
Weinberg - The Biology of Cancer (2014)

HIF-1 and its regulation by pVHL



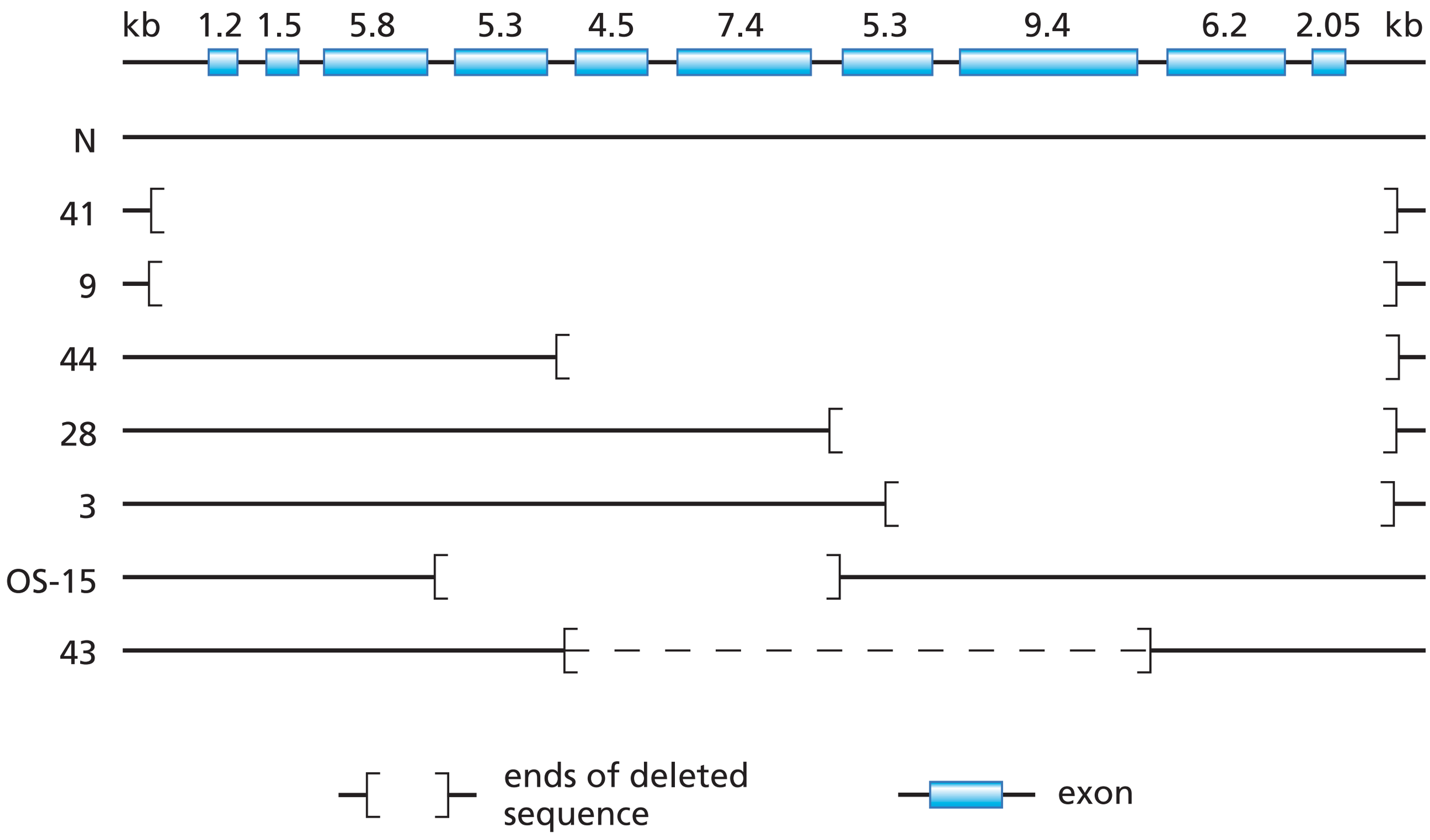
Weinberg - The Biology of Cancer (2014)

Tumor suppression is largely a dominant phenotype



Weinberg - The Biology of Cancer (2014)

Tumor suppressor genes (e.g. *RB1*) can be inactivated via genetic deletions



Weinberg - The Biology of Cancer (2014)

Tumor suppressor genes can be inactivated via genetic deletions

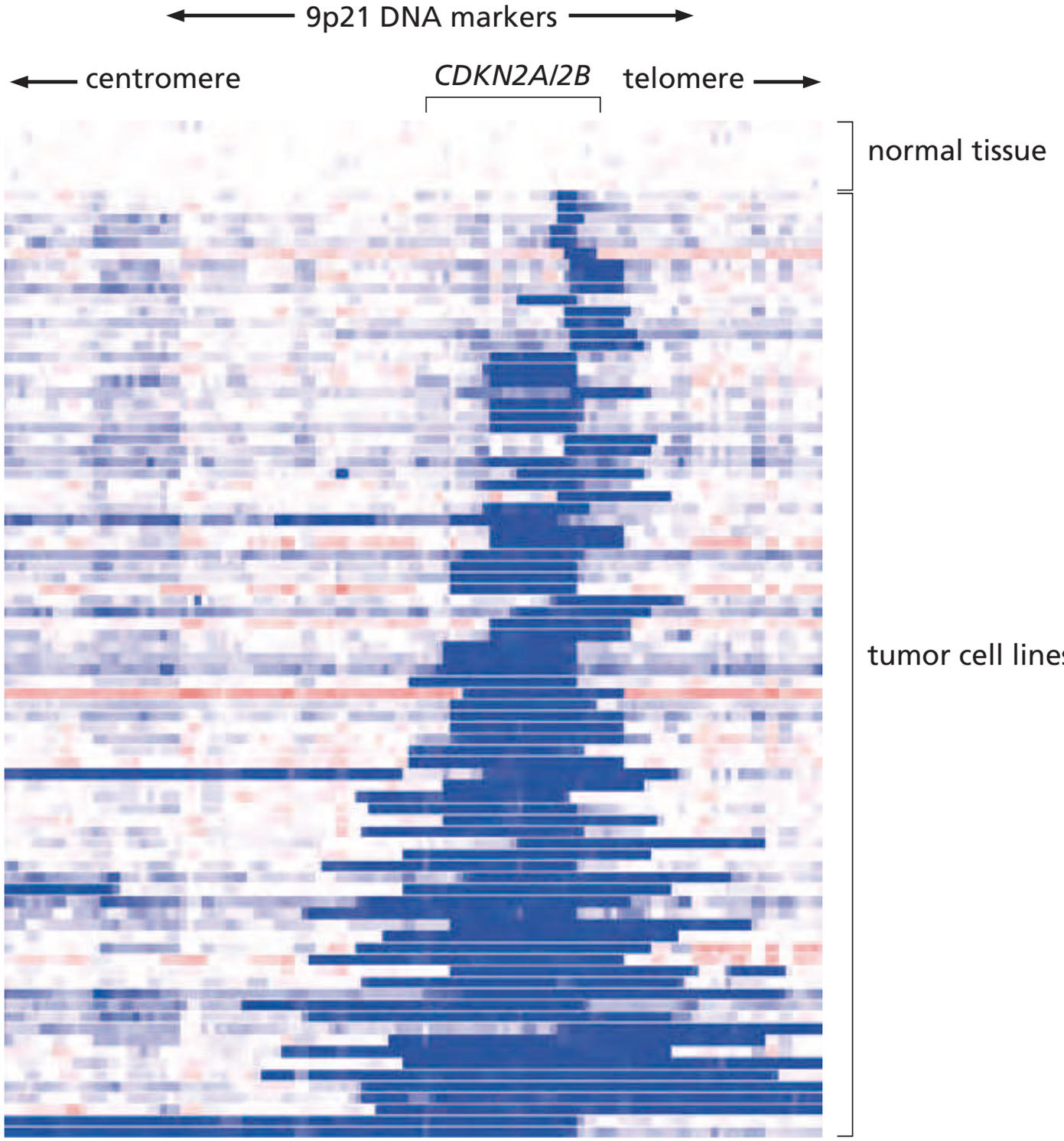


Figure 7.14 Measurement of deleted chromosomal segments carrying tumor suppressor genes One strategy for localizing and identifying TSGs depends on mapping overlapping regions of relatively small deletions that affect a chromosomal arm. This has become practical with the identification of large numbers of sequence markers that can be planted at sites across the entire human genome and the use of high-throughput sequencing technologies. Here, a set of 250,000 probes was used; the probes were planted at an average density of one per 12 kb across the genome. DNAs of 80 tumor cell lines (arrayed top to bottom, names deleted) were analyzed for the presence or absence of sequences reactive with the probes. Short homozygous deletions (*dark blue bars*) affecting one or both of the adjacent pair of TSGs mapping to chromosome 9p21—*CDKN2A* and *CDKN2B*—have been found to occur frequently. In contrast, nearby chromosomal sequences to the right and left are rarely affected by either significant amplification (*light red squares*) or deletions (*light blue squares*). (From S.M. Rothenberg et al., *Cancer Res.* 70:2158–2164, 2010.)

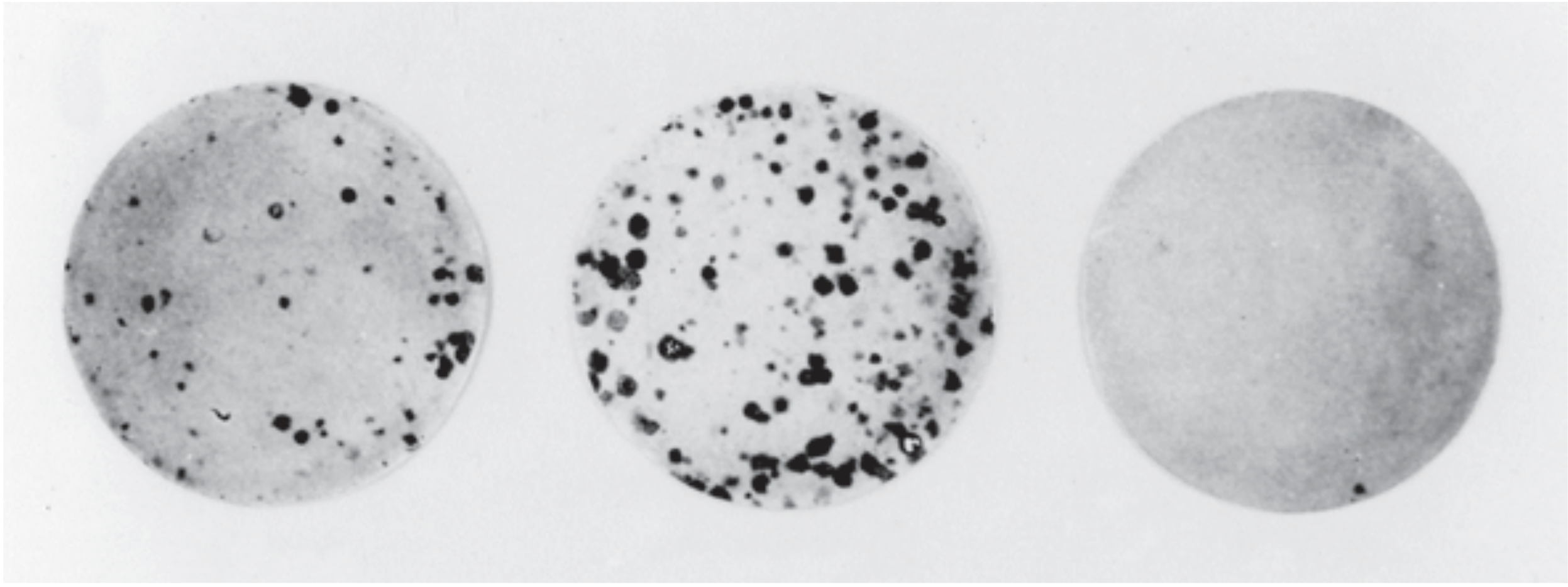
Examples of validated tumor suppressor genes

Table 7.1 Examples of human tumor suppressor genes that have been cloned

Name of gene	Chromosomal location	Familial cancer syndrome	Sporadic cancer	Function of gene product
SDHB	1p36.1	paraganglioma	—	succinate dehydrogenase
CHD5	1p36.31	cutaneous melanoma	many types	histone reader, transcriptional inducer
HRPT2	1q25–32	parathyroid tumors, jaw fibromas	parathyroid tumors	chromatin protein
FH	1q42.3	familial leiomyomatosis[a]	—	fumarate hydratase
FHIT	3p14.2	—	many types	diadenosine triphosphate hydrolase
BAP1	3p21.1	mesothelioma, melanoma	mesothelioma, uveal melanoma	ubiquitin hydrolase
RASSF1A	3p21.3	—	many types	multiple functions
TGFBR2	3p2.2	HNPCC	colon, gastric, pancreatic carcinomas	TGF-β receptor
VHL	3p25–26	von Hippel–Lindau syndrome	renal cell carcinoma	ubiquitylation of HIF
hCDC4	4q32	—	endometrial carcinoma	ubiquitin ligase
APC	5q21–22	familial adenomatous polyposis coli	colorectal, pancreatic, and stomach carcinomas; prostate carcinoma	β-catenin degradation
NKX3.1	8p21.2	—	prostate carcinoma	homeobox TF
miR-124a[b]	8p23.1	—	many types	suppresses CDK6
$p16^{INK4A}$ [c]	9p21	familial melanoma	many types	CDK inhibitor
$p14^{ARF}$ [d]	9p21	—	all types	p53 stabilizer
PTC	9q22.3	nevoid basal cell carcinoma syndrome	medulloblastomas	receptor for hedgehog GF
let 7a (*miRNA*)[e]	9q22.32	—	many types	suppresses Ras, Myc
TSC1	9q34	tuberous sclerosis	—	inhibitor of mTOR[f]
BMPR1	10q21–22	juvenile polyposis	—	BMP receptor
ANXA7	10q21	—	breast, prostate, stomach	endocytosis
PTEN[g]	10q23.3	Cowden's disease, breast and gastrointestinal carcinomas	glioblastoma; prostate, breast, and thyroid carcinomas	PIP_3 phosphatase
WT1	11p13.5–6	Wilms tumor	Wilms tumor	TF
MEN1	11p13	multiple endocrine neoplasia	—	histone modification, transcriptional repressor
BWS/CDKN1C	11p15.5	Beckwith–Wiedemann syndrome	—	$p57^{Kip2}$ CDK inhibitor
SDHD[h]	11q23.1	paraganglioma, pheochromocytoma	pheochromocytoma	mitochondrial protein
CBL	11q23.3	juvenile myelomonocytic leukemia	adult myelomonocytic leukemia	SH2-containing ubiquitin ligase
RB	13q14.2	retinoblastoma, osteosarcoma	retinoblastoma; sarcomas; bladder, breast, esophageal, and lung carcinomas	transcriptional repression; control of E2Fs
miR-15a/16-1	13q14.3	—	B-cell lymphoma	suppresses Bcl-2, Mcl-1, cyclin D1, Wnt3a
miR-127	14q32.31	—	many types	suppresses Bcl-6
CYFIP1	15q11.2	—	lung, breast, colon, bladder carcinomas	actin cytoskeleton organization
TSC2	16p13.3	tuberous sclerosis	—	inhibitor of mTOR[f]
CBP	16p13.3	Rubinstein–Taybi syndrome	AML[i]	TF co-activator
CYLD	16q12–13	cylindromatosis	—	deubiquitinating enzyme
CDH1	16q22.1	familial gastric carcinoma	invasive cancers	cell–cell adhesion
BHD/FLCN	17p11.2	Birt–Hogg–Dube syndrome	kidney carcinomas, hamartomas	regulator of mTOR[f]
TP53	17p13.1	Li–Fraumeni syndrome	many types	TF
NF1	17q11.2	neurofibromatosis type 1	colon carcinoma, astrocytoma, acute myelogenous leukemia	Ras-GAP
PRKAR1A	17q22–24	multiple endocrine neoplasia[j]	multiple endocrine tumors	subunit of PKA
DPC4[k]	18q21.1	juvenile polyposis	pancreatic and colon carcinomas	TGF-β TF
LKB1/STK11	19p13.3	Peutz–Jegher syndrome	hamartomatous colonic polyps	serine/threonine kinase
RUNX1	21q22.12	familial platelet disorder	AML	TF
SNF5[l]	22q11.2	rhabdoid predisposition syndrome	malignant rhabdoid tumors	chromosome remodeling
NF2	22q12.2	neurofibroma-predisposition syndrome	schwannoma, meningioma; ependymoma	cytoskeleton–membrane linkage
WTX	Xq11.1	—	Wilms tumor	β-catenin degradation

Weinberg - The Biology of Cancer (2014)

Oncogene-TSG cooperation in transformation



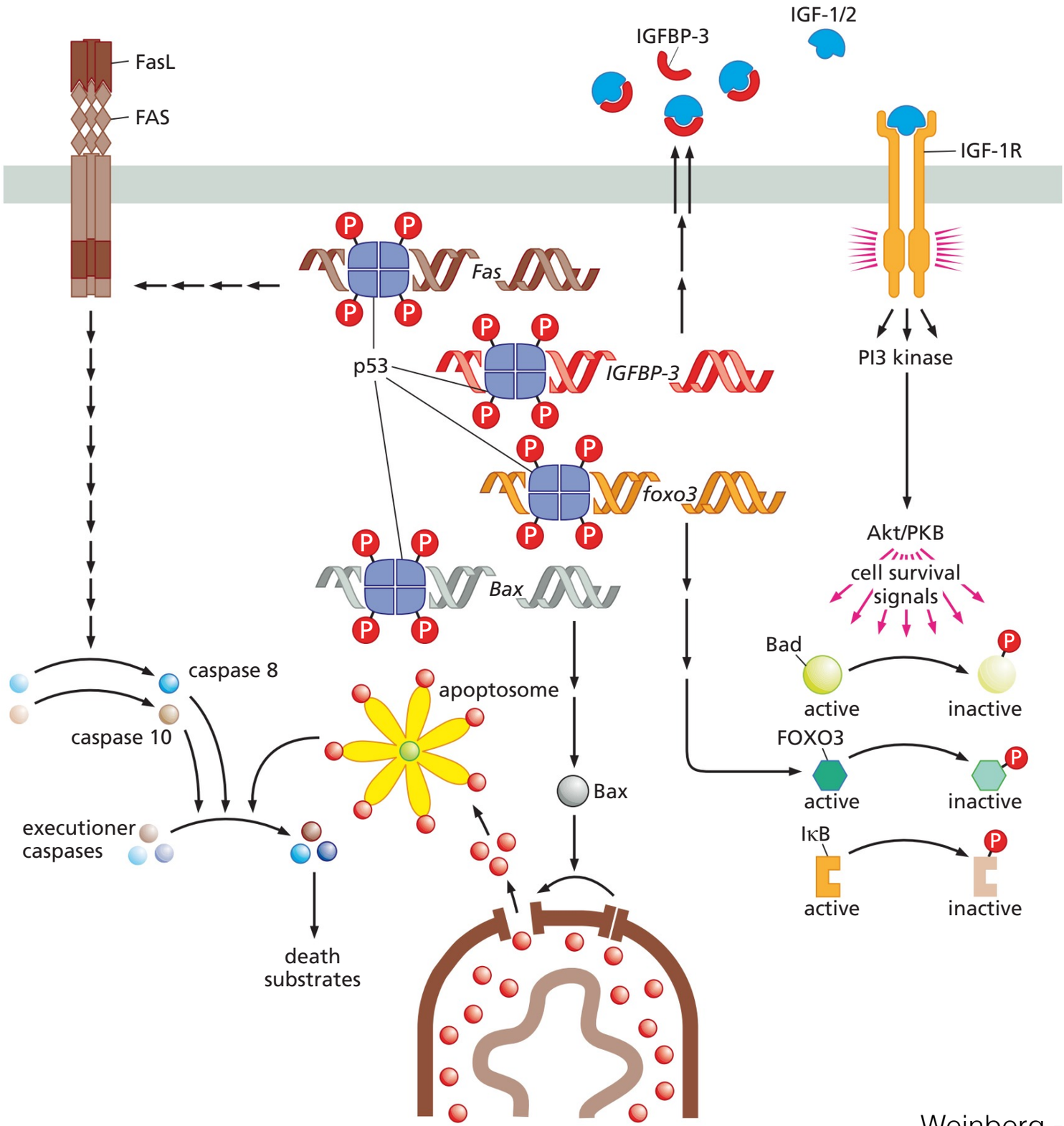
ras + *p53*
deletion mutant

ras + *p53* val-135
point mutant

ras + *p53*
wild type

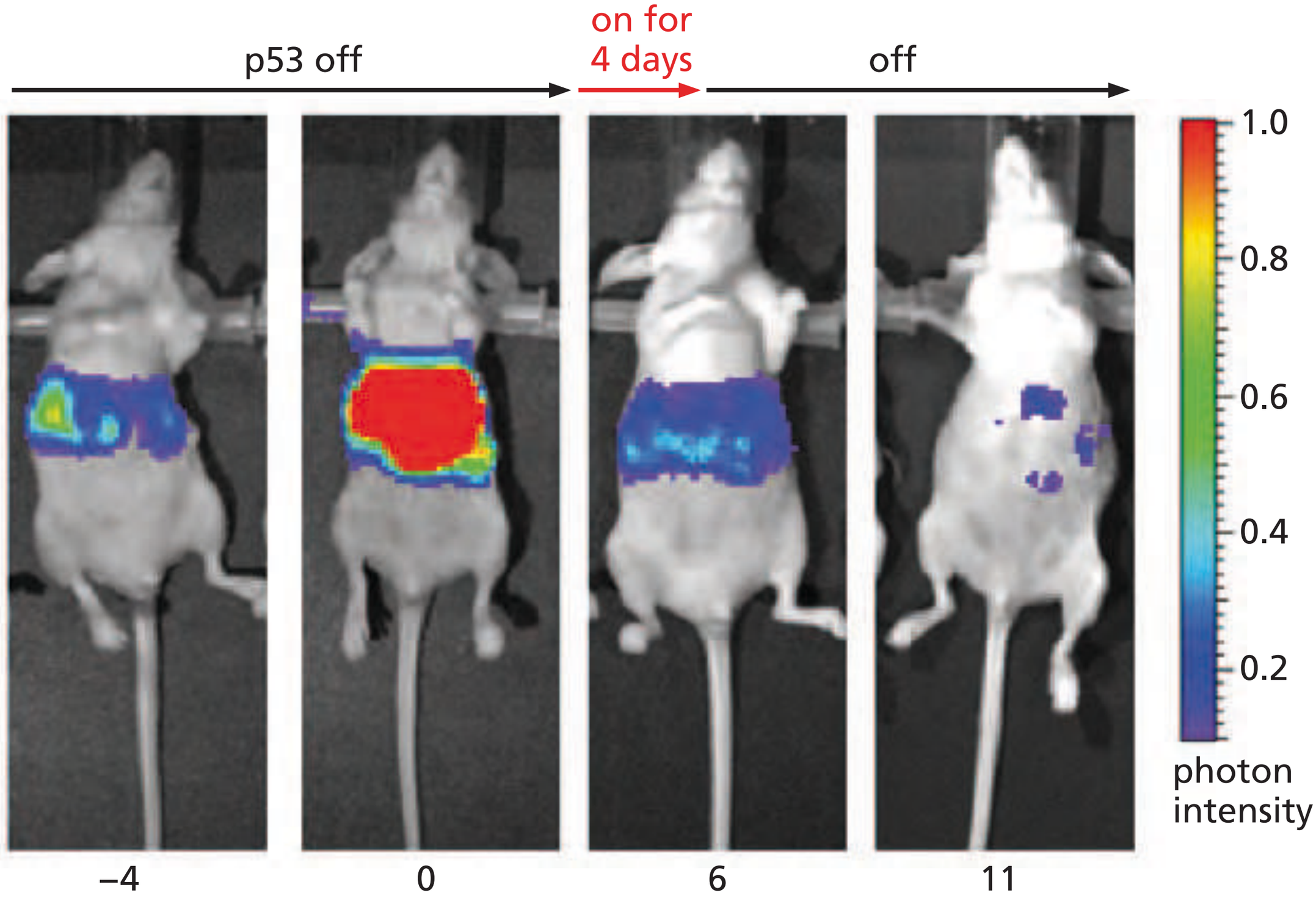
Weinberg - The Biology of Cancer (2014)

Activation of apoptosis by p53



Weinberg - The Biology of Cancer (2014)

Reactivation of p53 induces senescence



Weinberg - The Biology of Cancer (2014)

Hallmarks of Cancer: a unifying framework

Oncogenes

Tumor suppressors

Tumor epigenetics

Tumor epigenetics

Cancer metabolism

Tumor immunology

Tumor suppressors

Tumor suppressors

Cancer genomics

Tumor immunology

Tumor suppressors

Tumor immunology

Tumor microenvironment

Tumor microenvironment

Hallmarks of Cancer: New Dimensions. Hanahan, *Cancer Discovery* 2022

•Cancer cells evade immune destruction is by delivering signals that hold immune cells in check.

•New anti-cancer treatments have attempted to stop these immune checkpoint signals.

✓Ipilimumab (Yervoy)- Melanoma

✓Nivolumab (Opdivo) _NSCLC

✓Pembrolizumab (Keytruda)- Melanoma.

Unlocking
phenotypic plasticity

Nonmutational
epigenetic reprogramming

Therapy Sensitive

Therapy Resistant

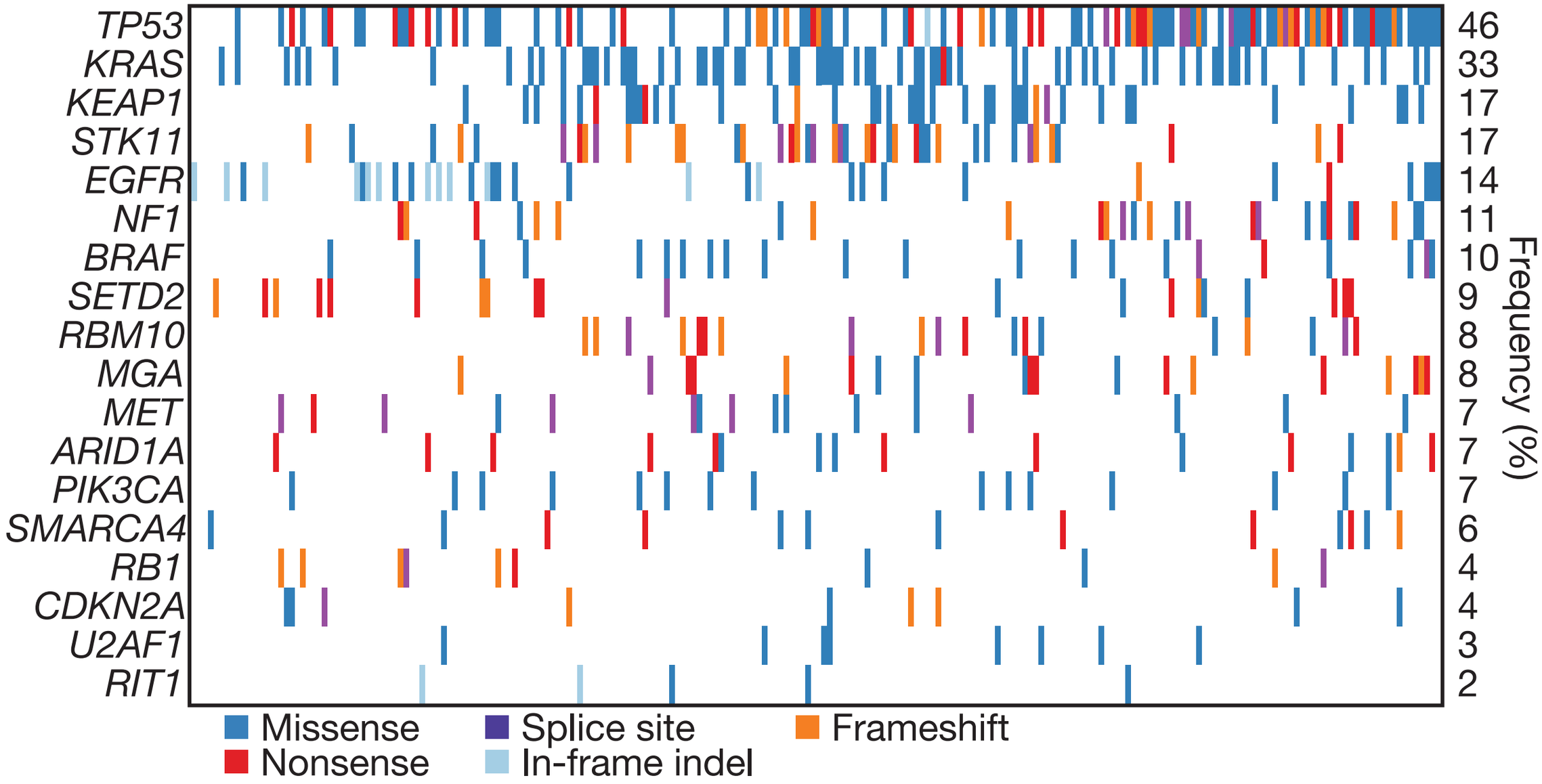
Lineage Plasticity

Tumor cells

Non-immune
stromal cells

Immune cells

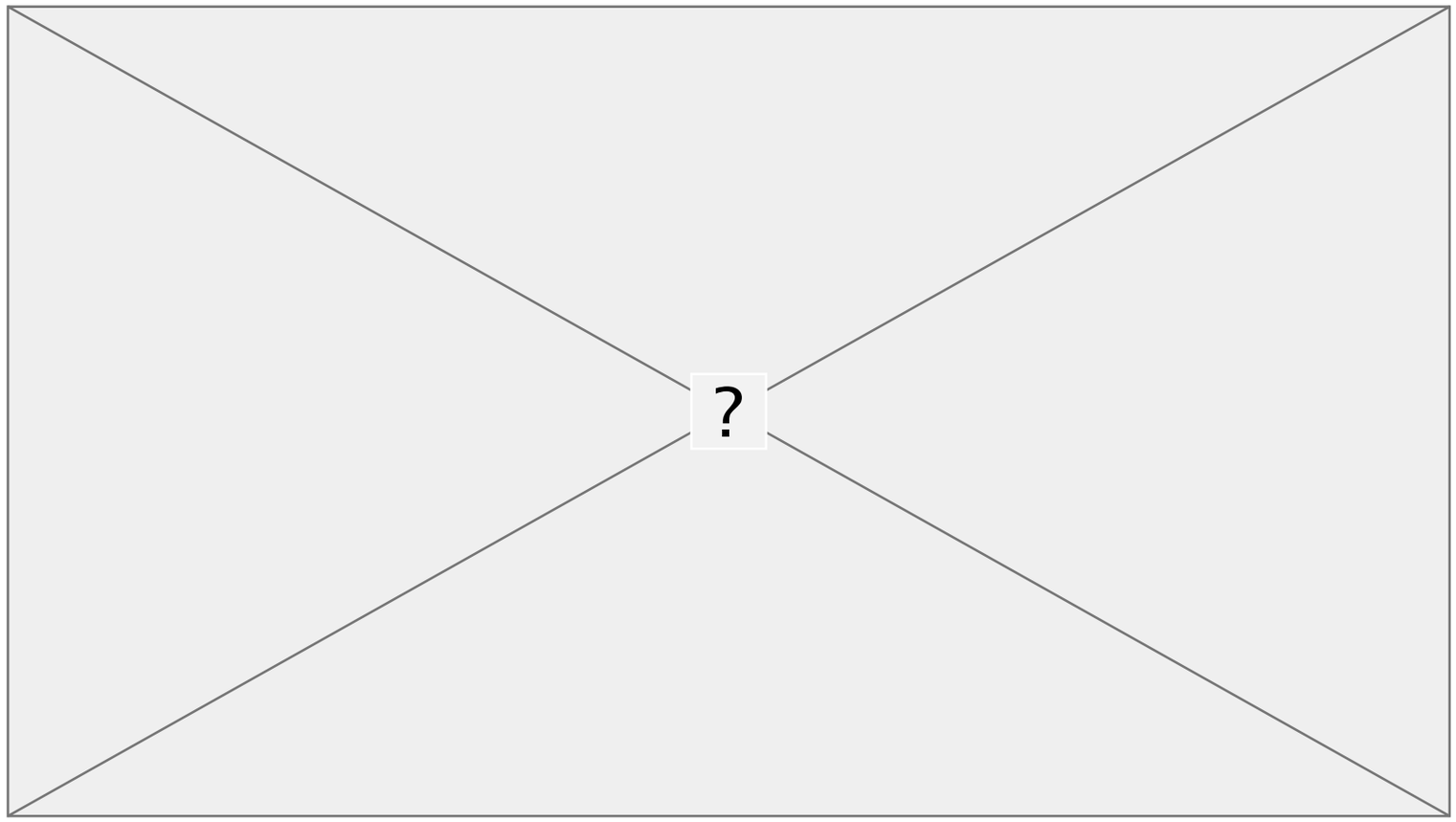
Cancer Genomics



- Average cancer genome: Hundreds of mutations!
- ~5-20 ONC/TSG mutations “Driver Mutations”
- Remainder: “Passenger Mutations”

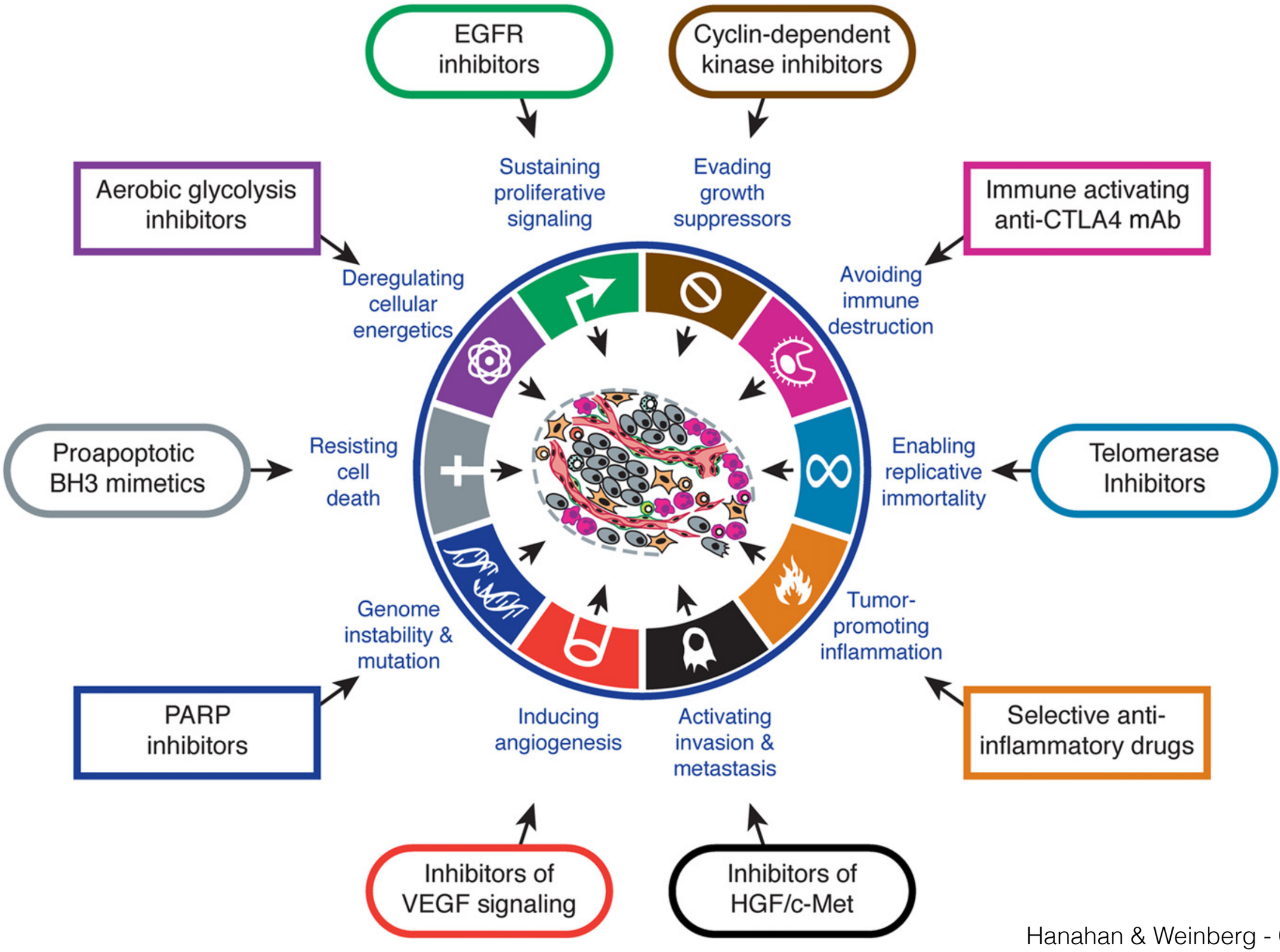
Lung Adenocarcinoma TCGA, Nature 2014

Cancer Prevention



- Human papilloma virus (HPV): High risk type

Precision Oncology



Hanahan & Weinberg - Cell (2011)