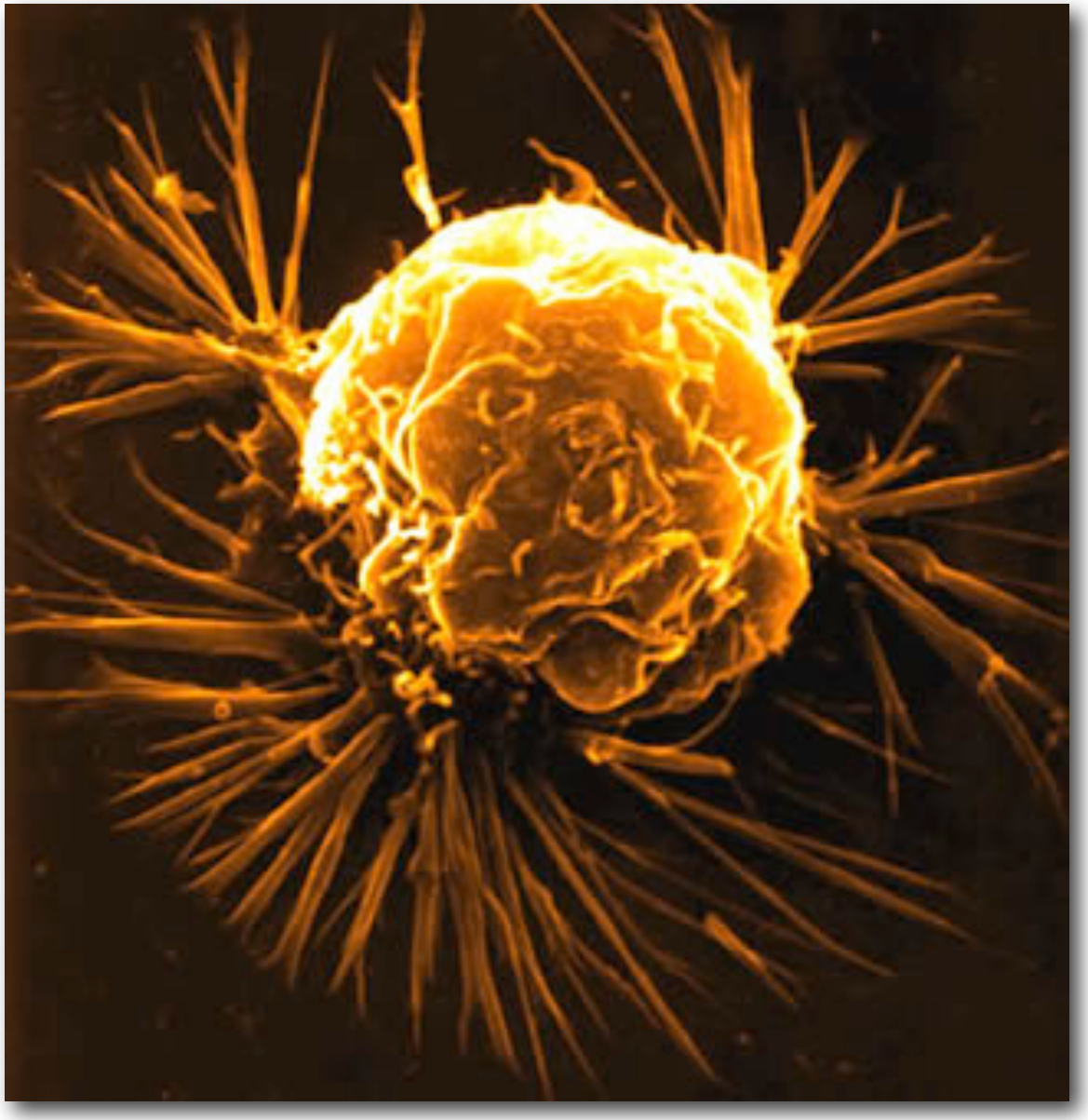
Cancer Genes
&
Cancer Genetics

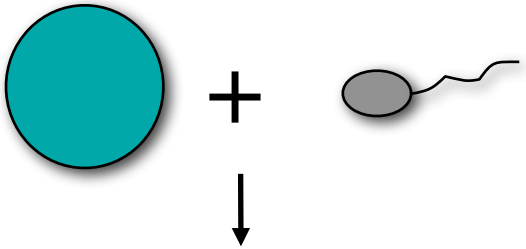
NO office hours this Friday (5-1). Please set up an appointment if you any questions.
roelink@berkeley.edu

READING: pp. 202-220



Somatic Cells/Germ line mutations

This nothing to do with bugs



Mutations

passed on to progeny, all tissues, Mendelian

GERM LINE
female: eggs (precursors)
male: sperm

Mutations

usually little effect, cell death for damaged cell; however, all cancers arise from somatic cell mutation, one cell confined to one tissue

SOMATIC CELLS
embryo proper
all tissues

Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin

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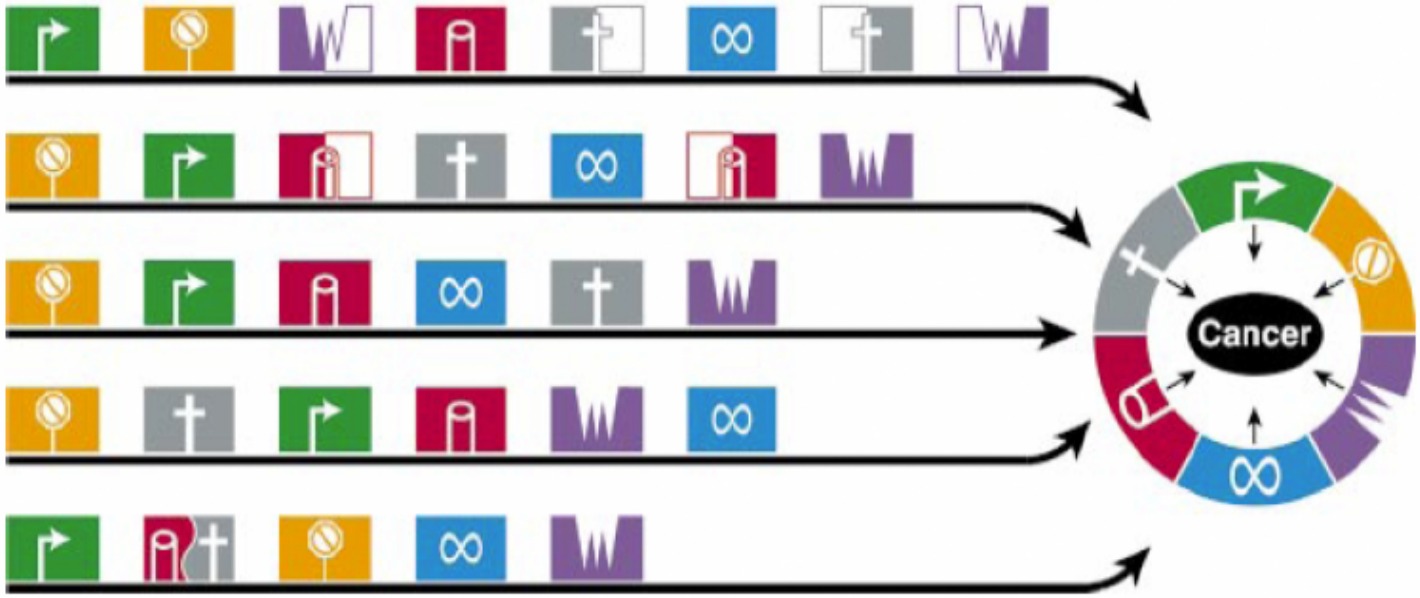
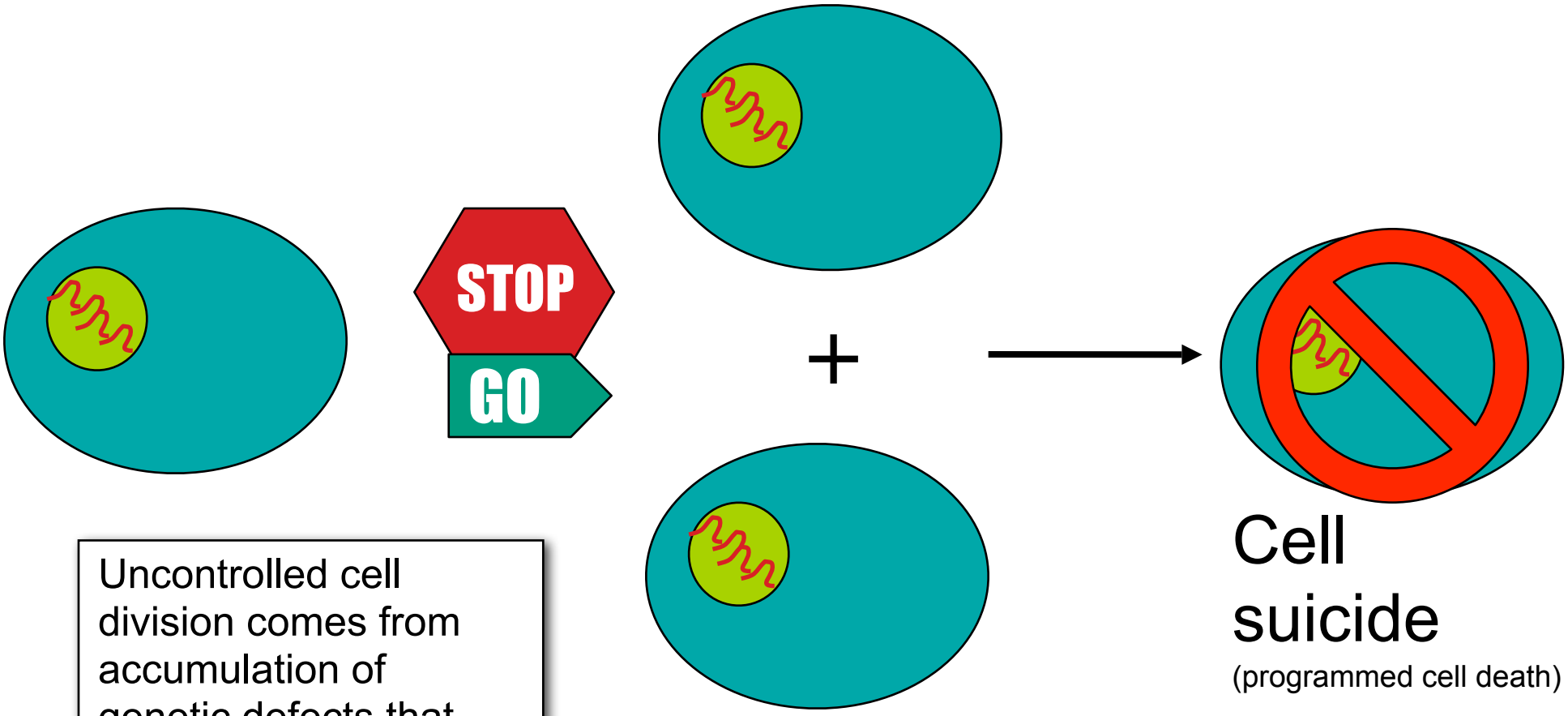


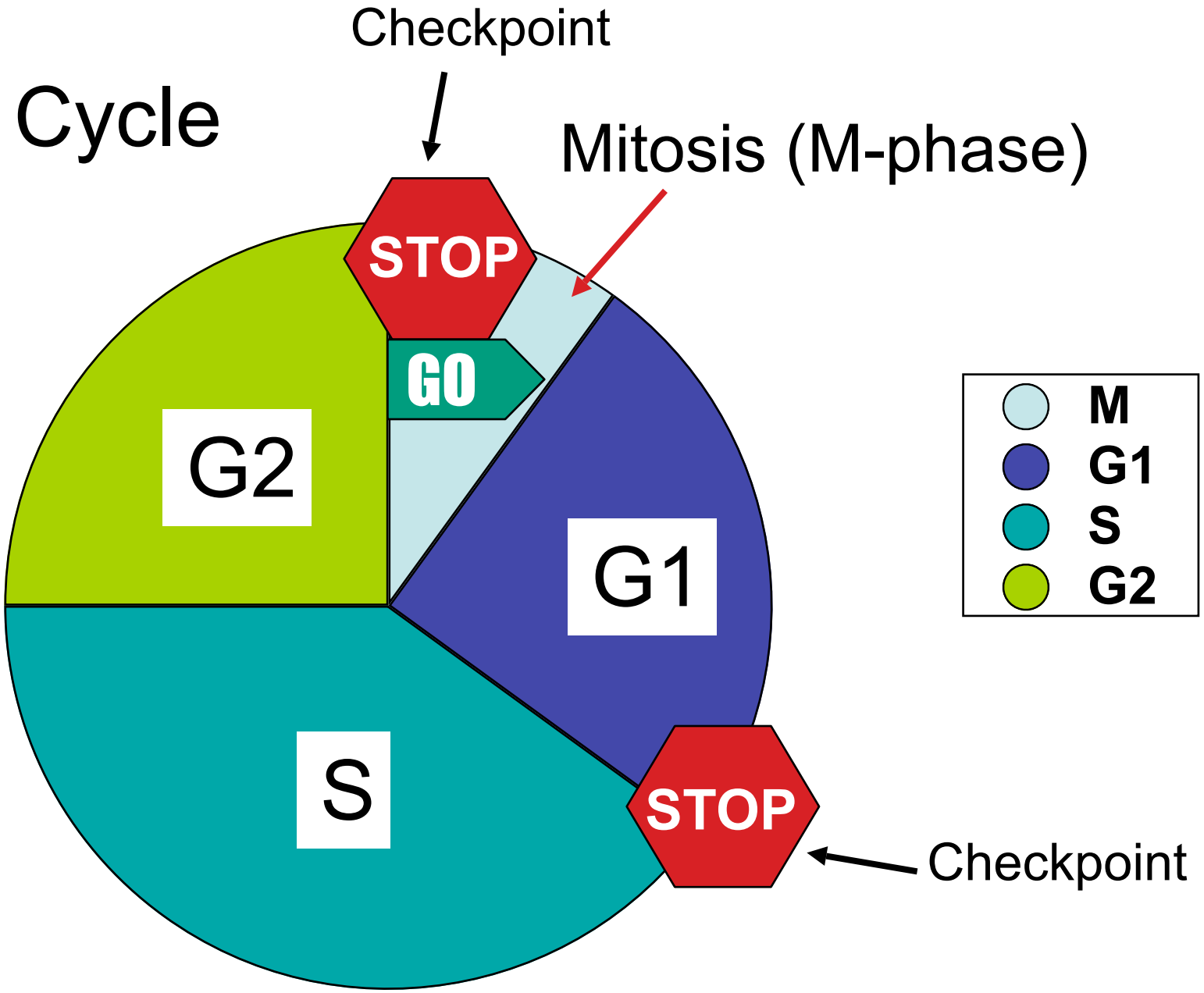
Cell Proliferation and Death



Uncontrolled cell division comes from accumulation of genetic defects that lead to too much "go" signal, too little "stop" signal, and loss of cell suicide

proliferation and programmed cell death tightly regulated to ensure the integrity of organs and tissues

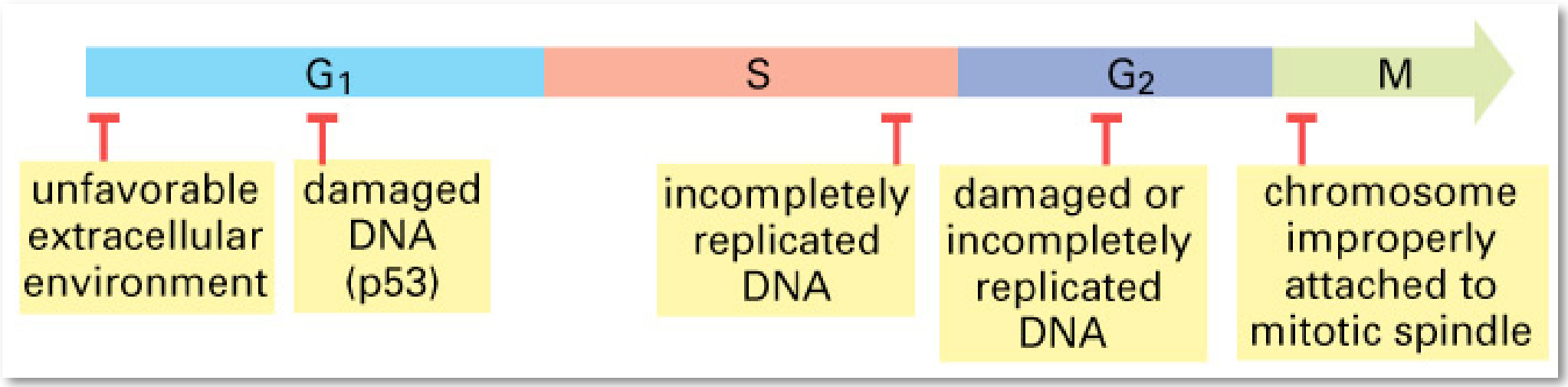
The Cell Cycle



tumor suppressors (-) STOP

proto-oncogenes (+) GO

Checkpoints ensure the cell cycle proceeds without errors



Cancer Genes

Accumulation of multiple mutations

Potential cancer genes - about 100 (0.3% of total) genes

Inappropriate signals about need for cell division (hormonal signaling pathways: growth factors)

Malfunctions in (CDK-cyclin) complexes controlling cell cycle transitions

Checkpoint breakdowns leading to DNA instability

Loss of programmed cell death (cell suicide)

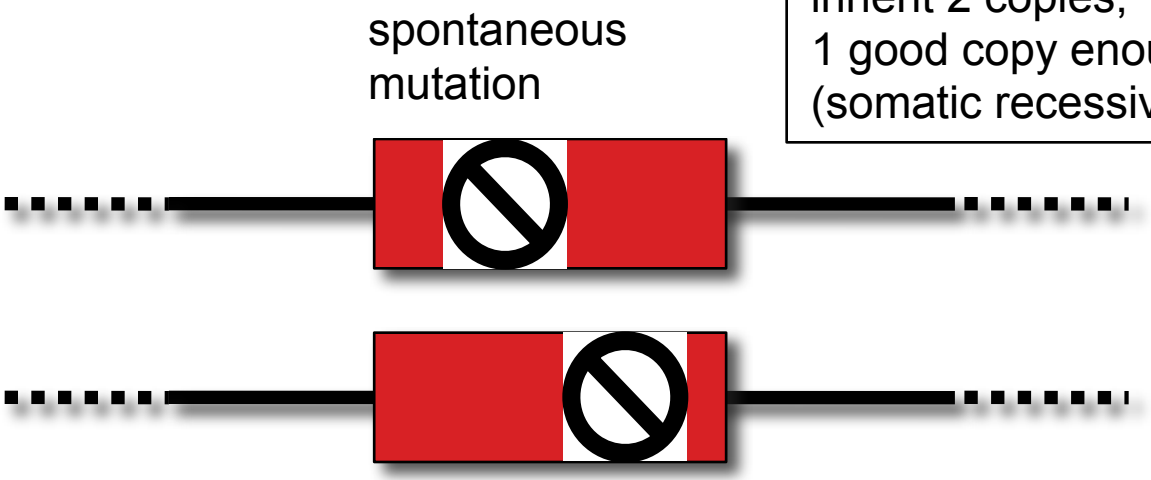
Invasion/Metastasis

Part 1: Tumor Suppressor Genes

Function
STOP signal at cell cycle checkpoint; DNA repair or apoptosis

Loss-of-Function (LOF)
no checkpoint stop; no DNA repair; cell cycle continuously cycles

inherit 2 copies;
1 good copy enough
(somatic recessive)



(inherited mutation all breast cells)

BRCA example

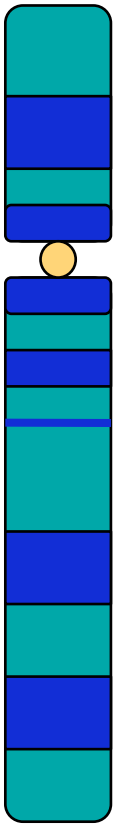
Inherited BRCA1 mutation
breast cancer frequency
20% by age 40y
50% by age 50y
85% by age 60y

1 inherited germline mutation
+
1 spontaneous somatic mutation

Breast Cancer Genes

tumor suppressor genes

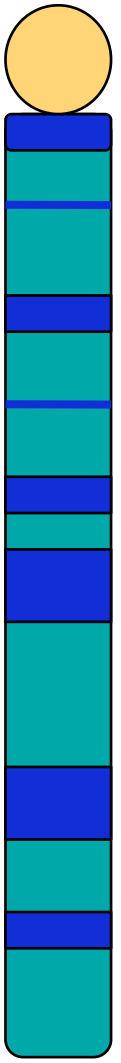
Breast cancer (inherited)	10%
BRCA1 or BRCA2 mutations	8%
US citizens	0.2%
Askenazi Jews	2.5%
All cases under 50	7%
Under 40	10%



BRCA 1
(location = D17S74)

Ch 17

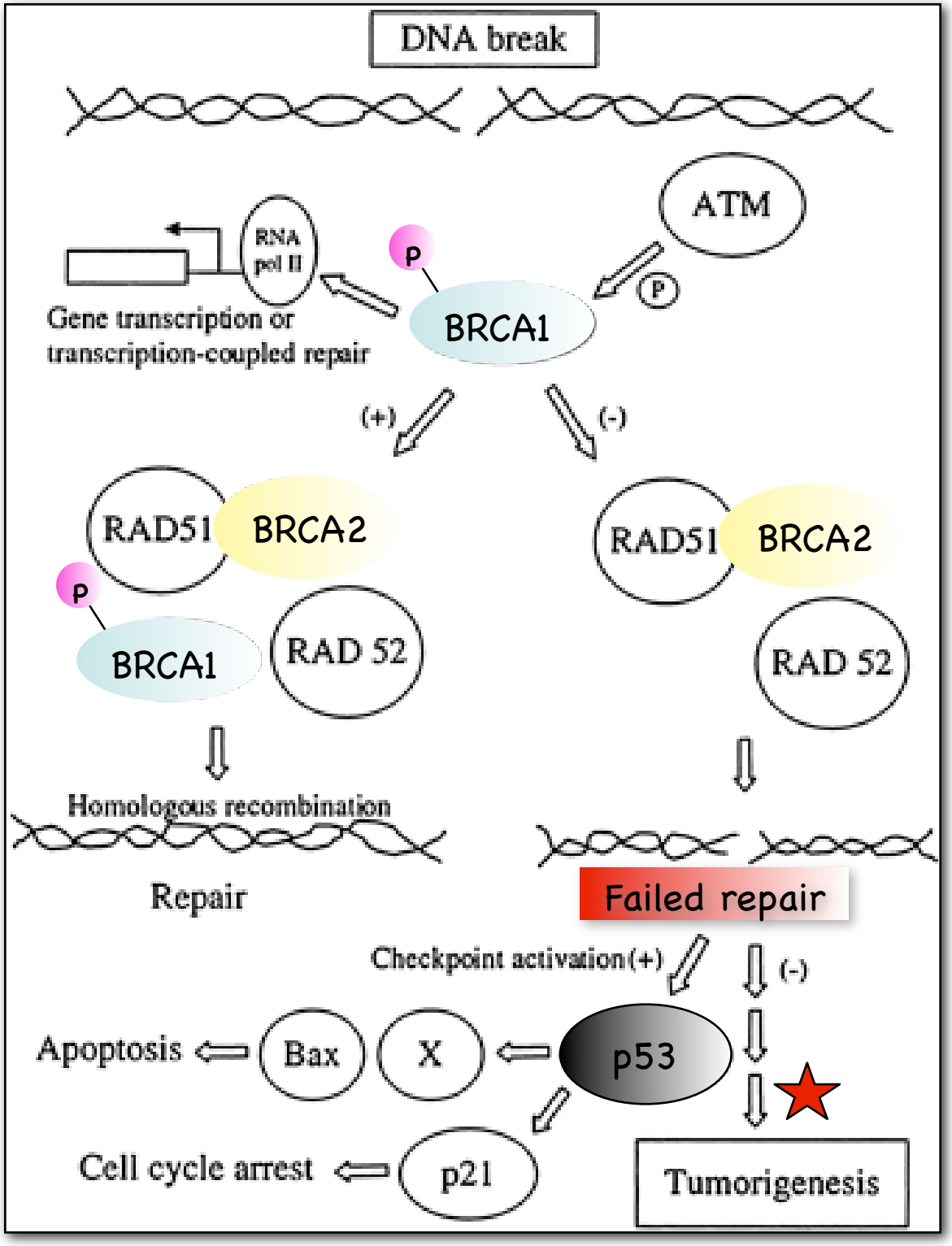
BREast CAncer (early onset) 1
BREast CAncer (early onset) 2



BRCA 2
(q12-13)

Ch 13

NIH website



Function of BRCA proteins.

DNA damage, BRCA1 regulates repair:
a) gene transcription
b) transcription-coupled DNA repair
c) homologous recombination
(double-strand break repair)

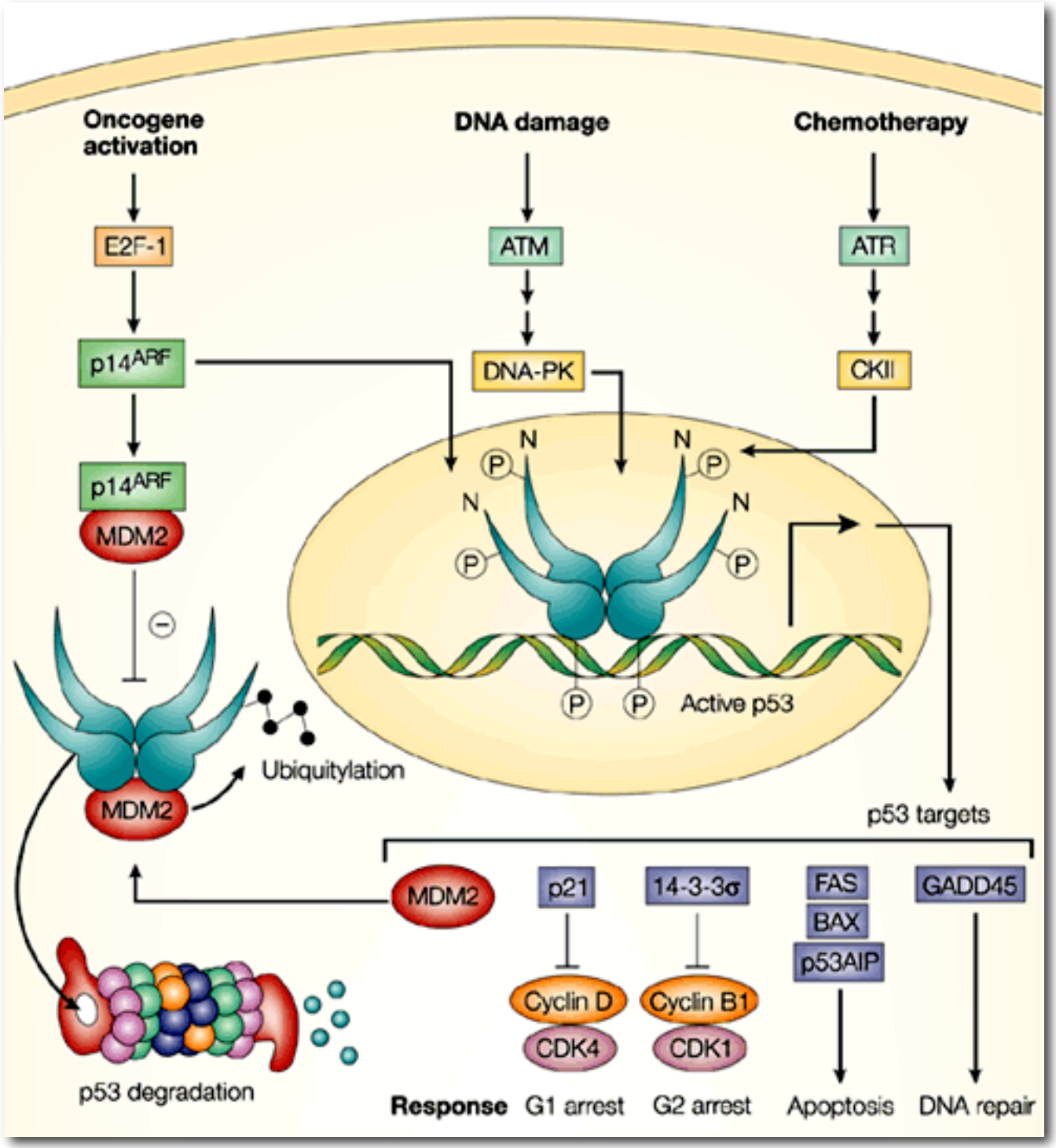
Defective BRCA1 (or BRCA2) - no repair

Activation of the p53-mediated cell cycle checkpoint(s):
a) Apoptosis (cell suicide)
b) Cell cycle arrest
c) Tumorigenesis

p53: The “guardian” of the genome

Li-Fraumeni Syndrome (p53 heterozygote)

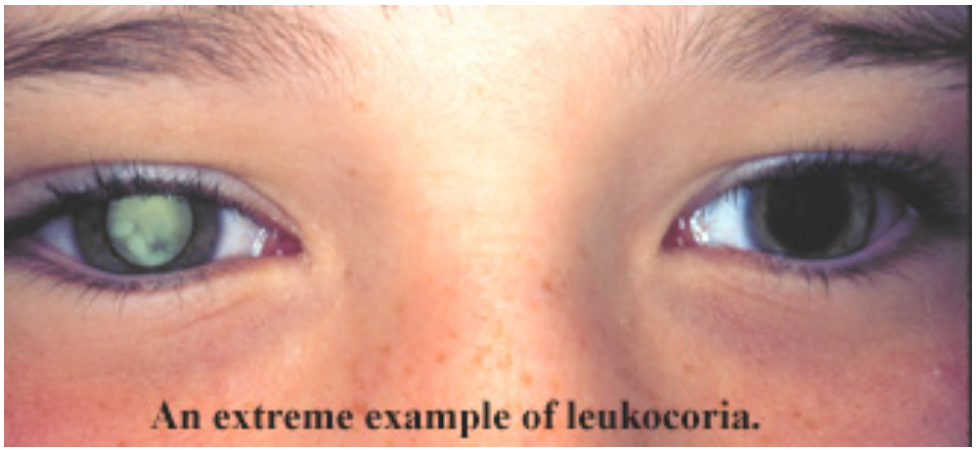
- several kinds of cancer are involved,
- cancer often strikes at a young age, and
- cancer often strikes several times throughout the life of an affected person.

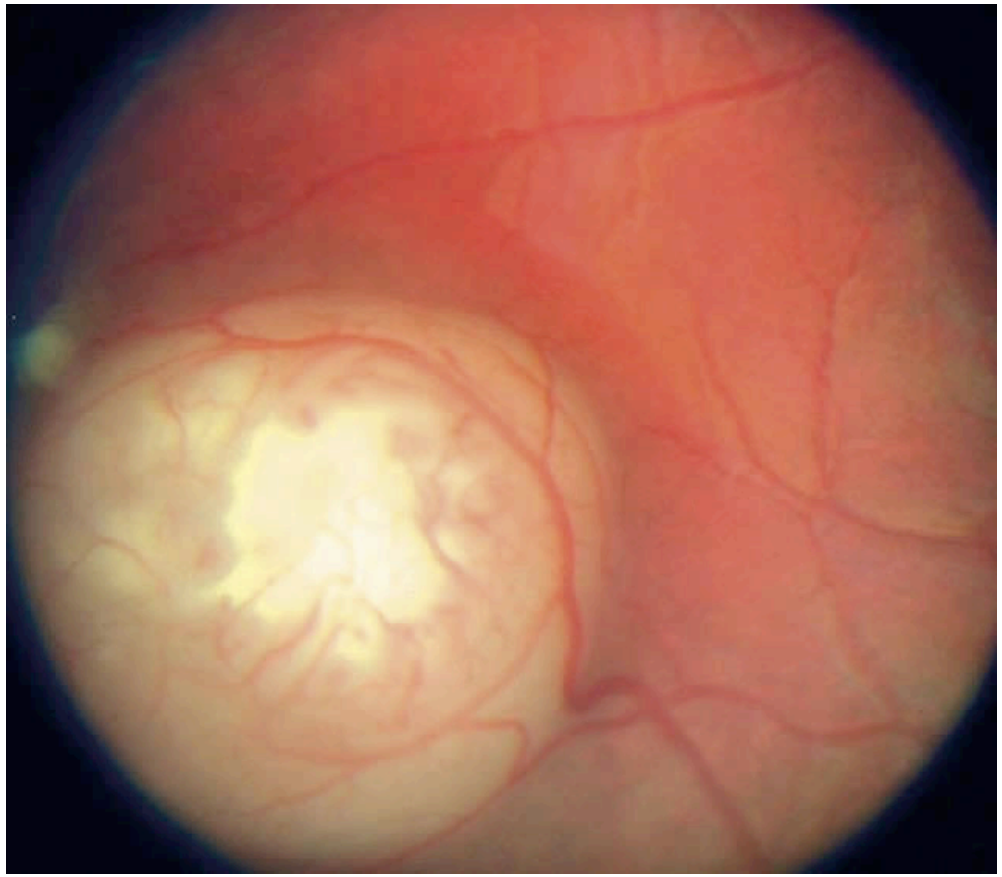


>50% (!) of human tumors have abnormal p53 activity

pRb was the first ‘classic’ tumor suppressor

The disease; retinoblastoma



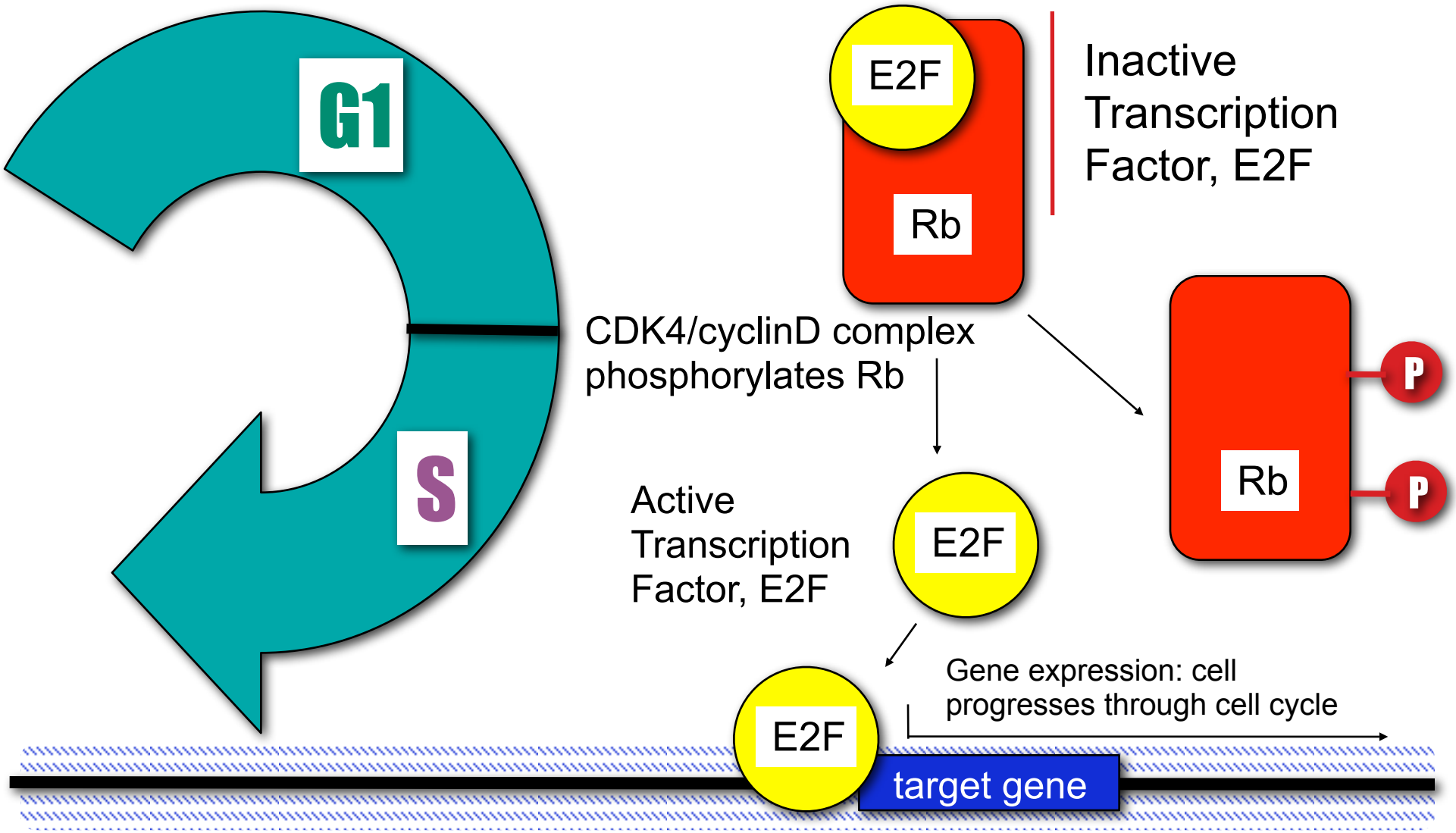


Retinoblastoma is a cancer which develops in the cells of the retina
-one of the less common cancers of childhood
-accounts for only about 3 out of every 100 cancers occurring in children under the age of 15 years

Children present with:
-an abnormal appearance of the pupil which reflects light as a white reflex, like a cat's eye.
-a squint.

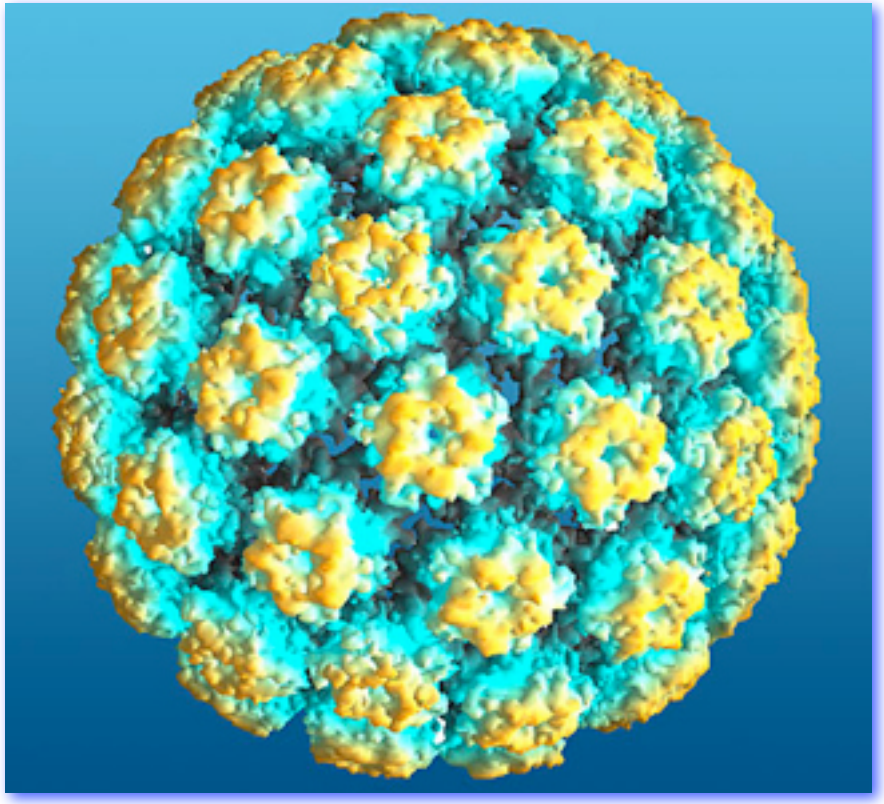
Tumor-Suppressor Gene: Rb (Retinoblastoma)

(eye tumor example)



Human Papiloma Virus (HPV)

AGE 14 to 19y (female) 25% HPV prevalence
AGE 20 to 24y (female) 45% HPV prevalence



Genital Warts
Cervical Cancer
Penile Cancer

14,000 U.S. women/year diagnosed cervical cancer
3,900 U.S. women/year die

National Cervical Cancer Coalition (NCCC)
and Journal of the American Medical Association

HPV Types

HPV - Family of about 100 DNA-based viruses

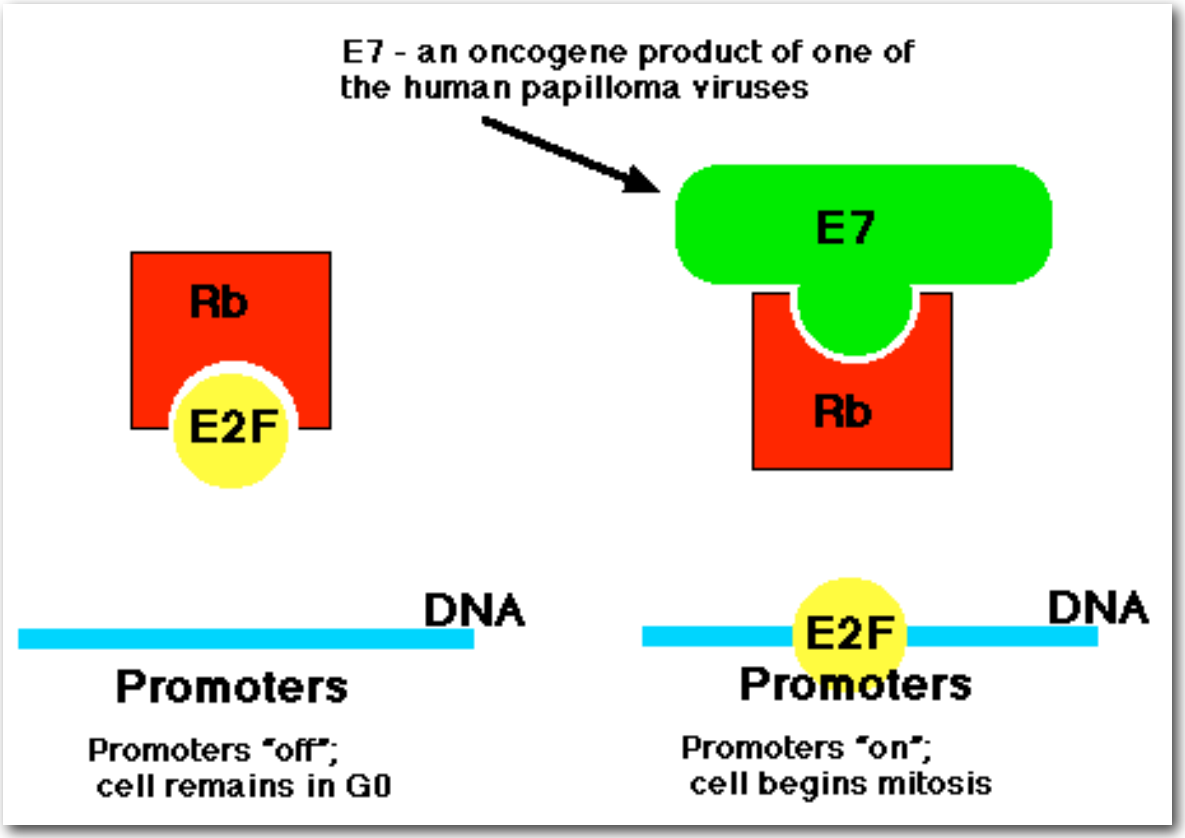
A group of about 30-40 HPVs typically transmitted through sexual contact

Genital Warts

types 6 and 11 (90% of all cases)

Cervical Cancer

types 16, 18, 31 and 45



HPV-induced cancers often have viral sequences integrated into the cellular DNA.

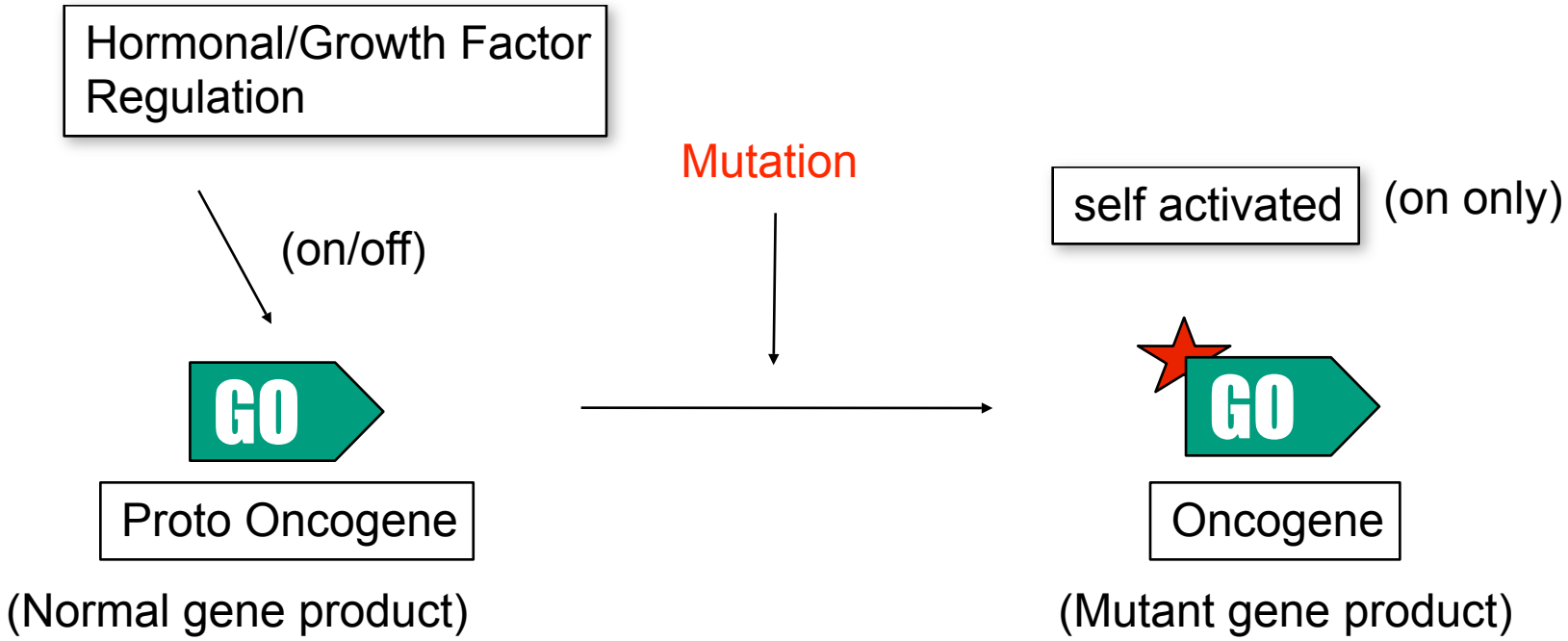
Some of the HPV "early" genes, such as E6 and E7, known to act as Oncogenes that promote tumor growth and malignant transformation.

GARDASIL™

[Quadrivalent Human Papillomavirus (Types 6,11,16,18) Recombinant Vaccine]

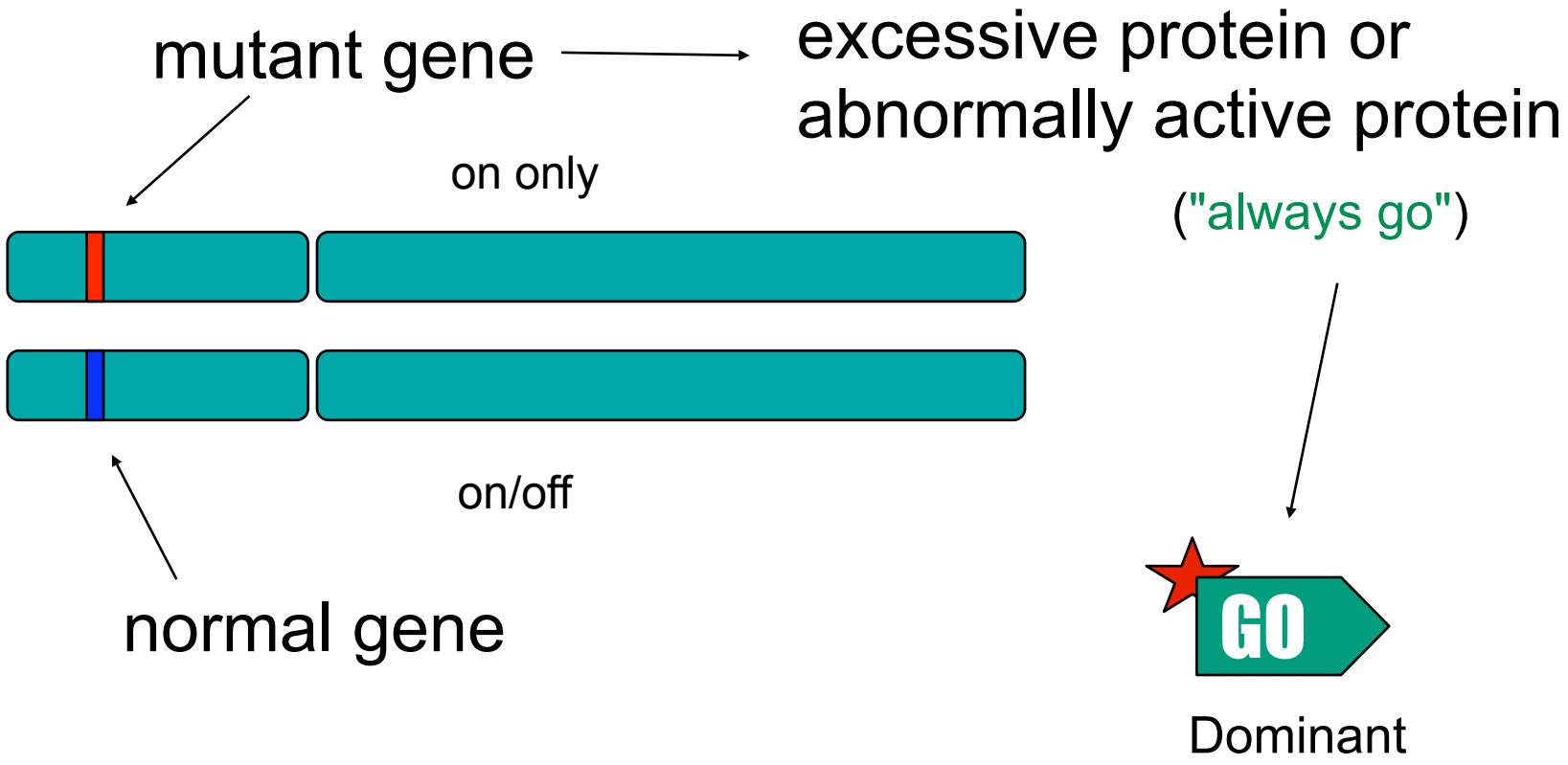
Your Choice

Part 2: Proto-Oncogenes (the **GO** signal)



Dominant Oncogene

("Gain of Function" mutation)



Possible ways to activate proto-oncogenes

Three basic types

Protein Structure Changed

a) increased enzyme activity
b) loss of regulation

Protein Concentration Increased

a) increased expression (through misregulation)
b) increased protein stability, prolonging its existence
c) gene duplication/amplification

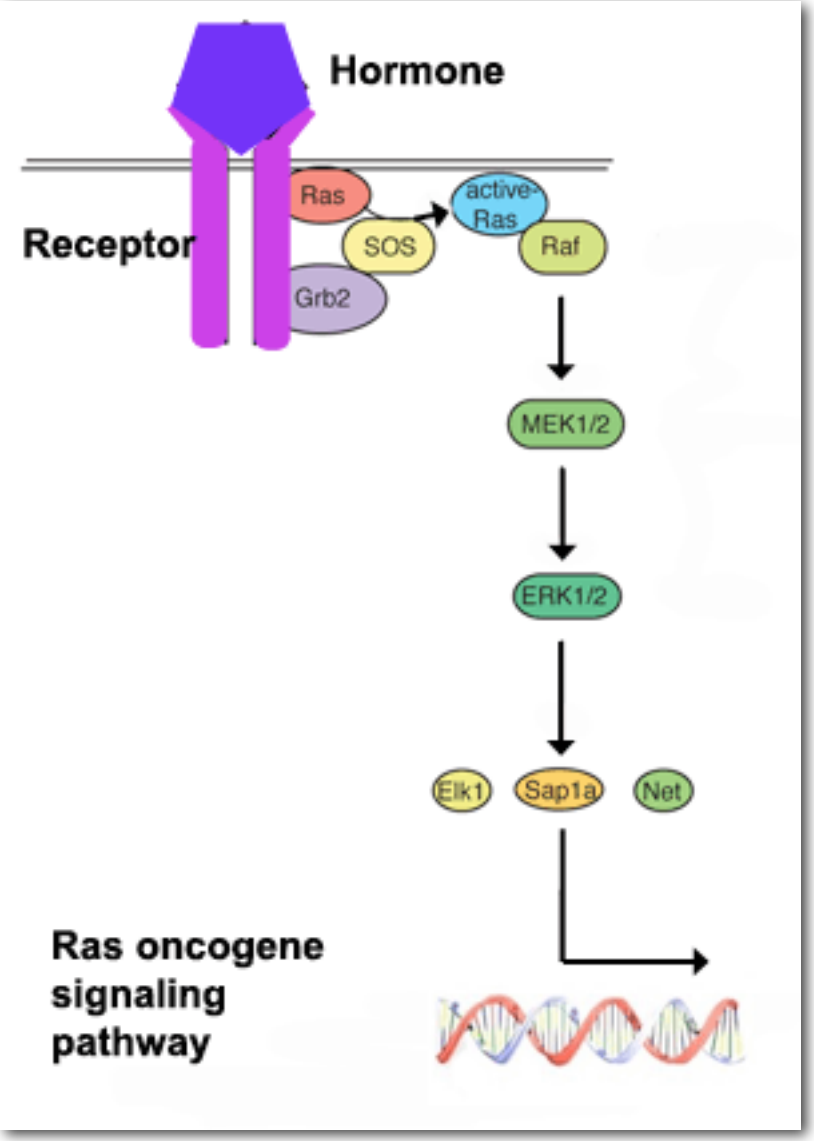
Make a “new” gene often van chromosomal tranlocation

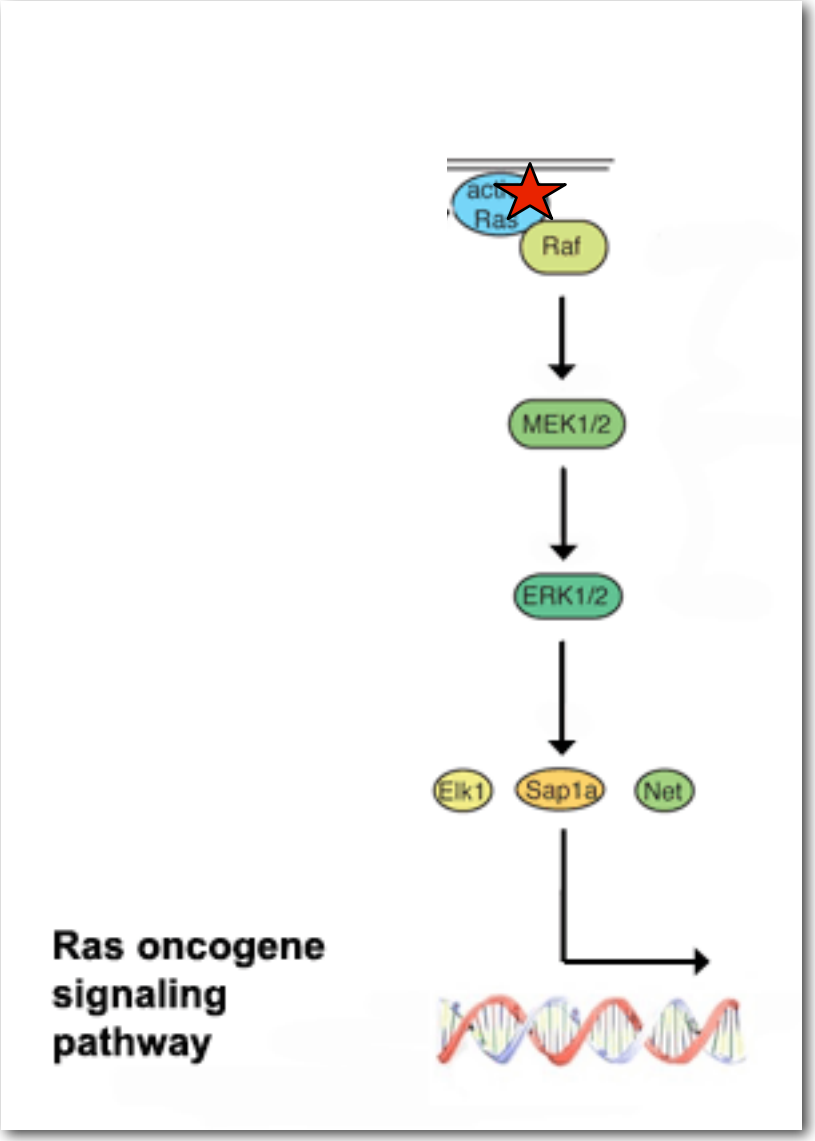
a) expression in wrong cell type or at wrong times
b) constitutively active hybrid protein
(responsible for adult leukemia in hematopoietic stem cell)

Protein Structure Changed
Point Mutation, single bp change singe aminoacid change

Oncogene: RAS

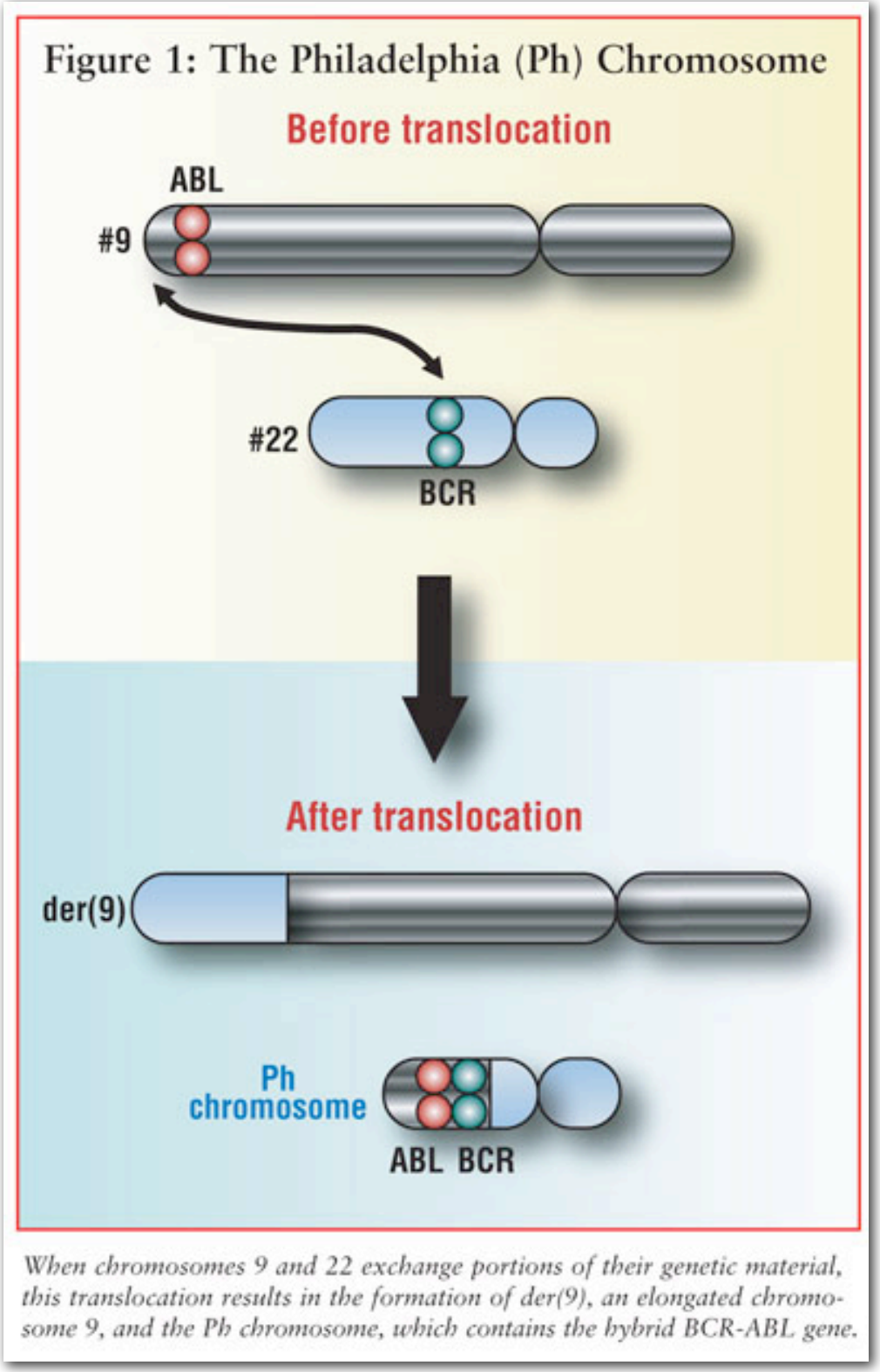
3 highly related genes in the genome

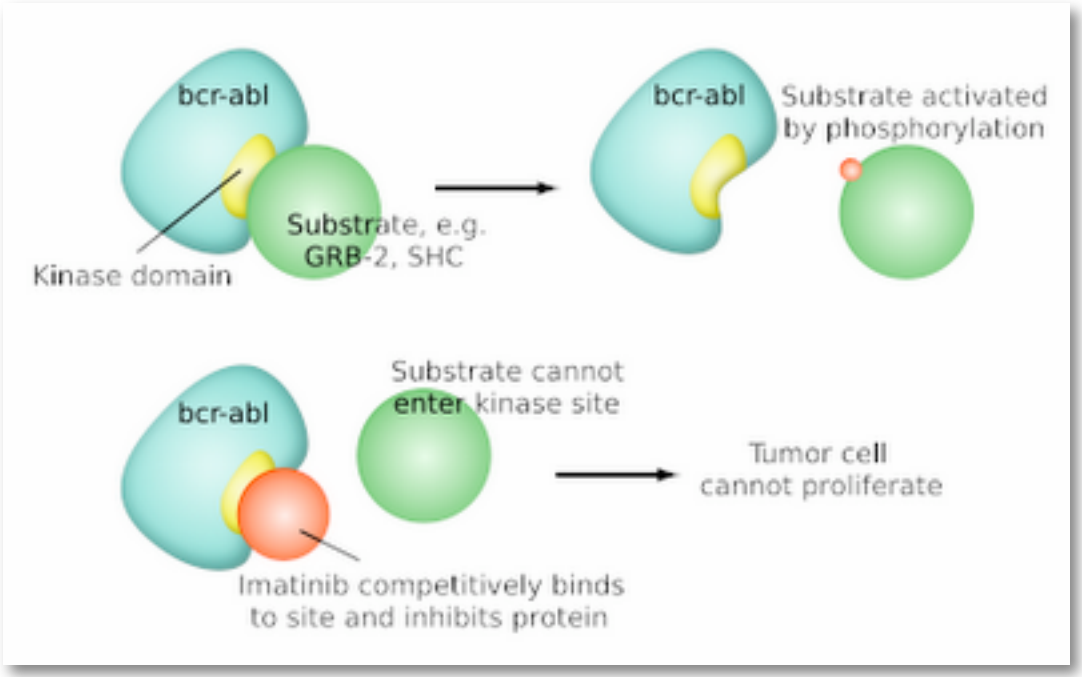




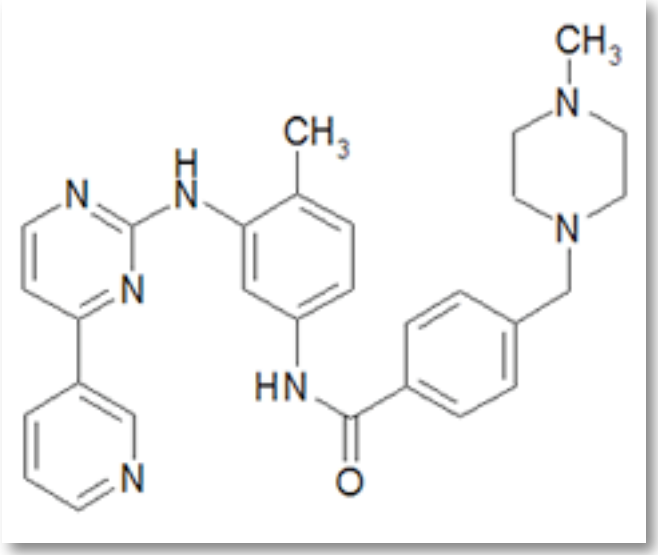
Chromosomal Translocation

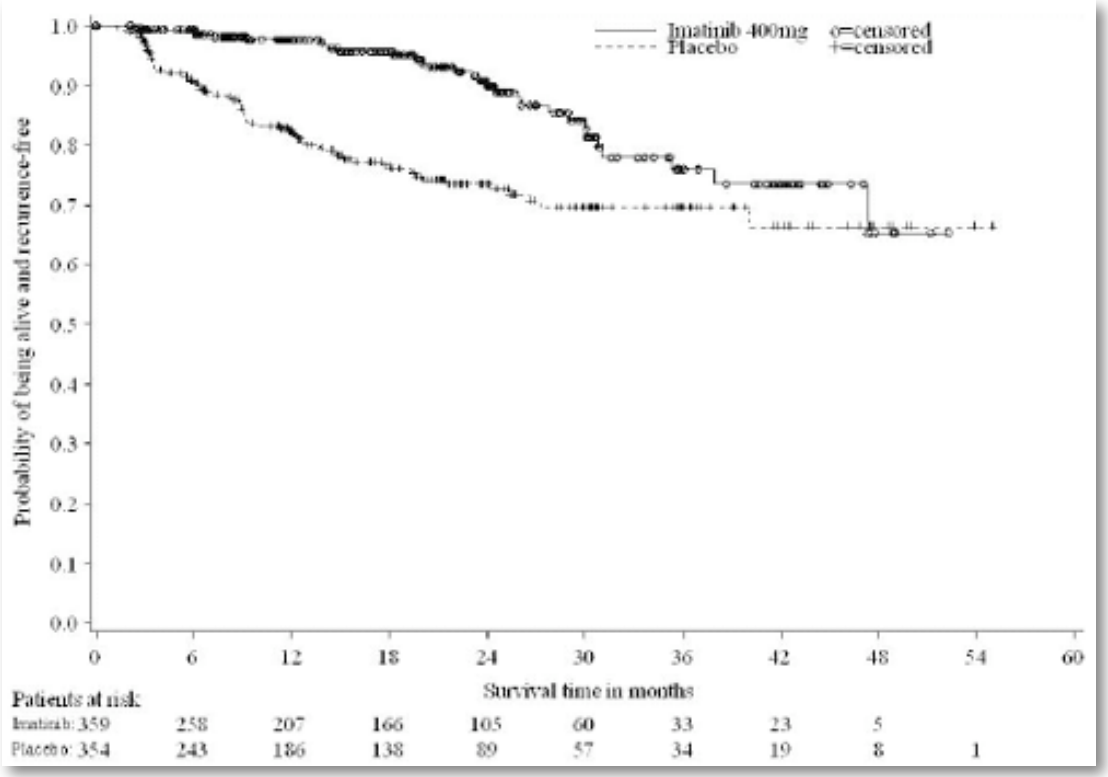
BCR-Abl





Gleevec (amatinib), one of the first examples of “designer” anti cancer drugs





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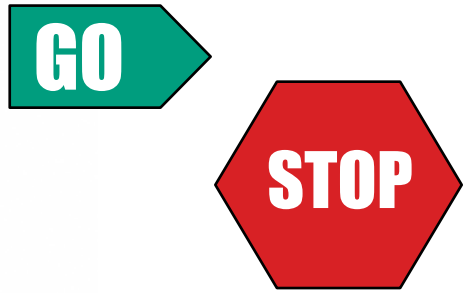

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