Molecular Basis Of Neoplasia

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PA 7.2

- **Describe the molecular basis of cancer**

SPECIFIC LEARNING OBJECTIVES

At the end of the session , the II MBBS student shall be able to

- Explain the concept of Monoclonality in tumor cell
- Enumerate the Characteristic features of Malignant cell at Molecular level / Cellular level
- Enumerate types of proto-oncogenes and Discuss the relationship between protooncogenes and oncogenes at cellular level.
- Enumerate common Tumor Suppressor genes.
- Compare and contrast protooncogenes and tumor suppressor genes

- -Explain the role of ‘DNA Repair Genes’ in Cancer.
- Describe role of Telomerase in Cancer
- Enumerate and Discuss Genetic Changes (Karyotypic abnormalities) in Tumor.
- Explain the mechanism of Evasion of Apoptosis by Cancer cell

Molecular basis of Cancer

Non lethal genetic damage lies at the heart of carcinogenesis.

Genetic damage /Mutation

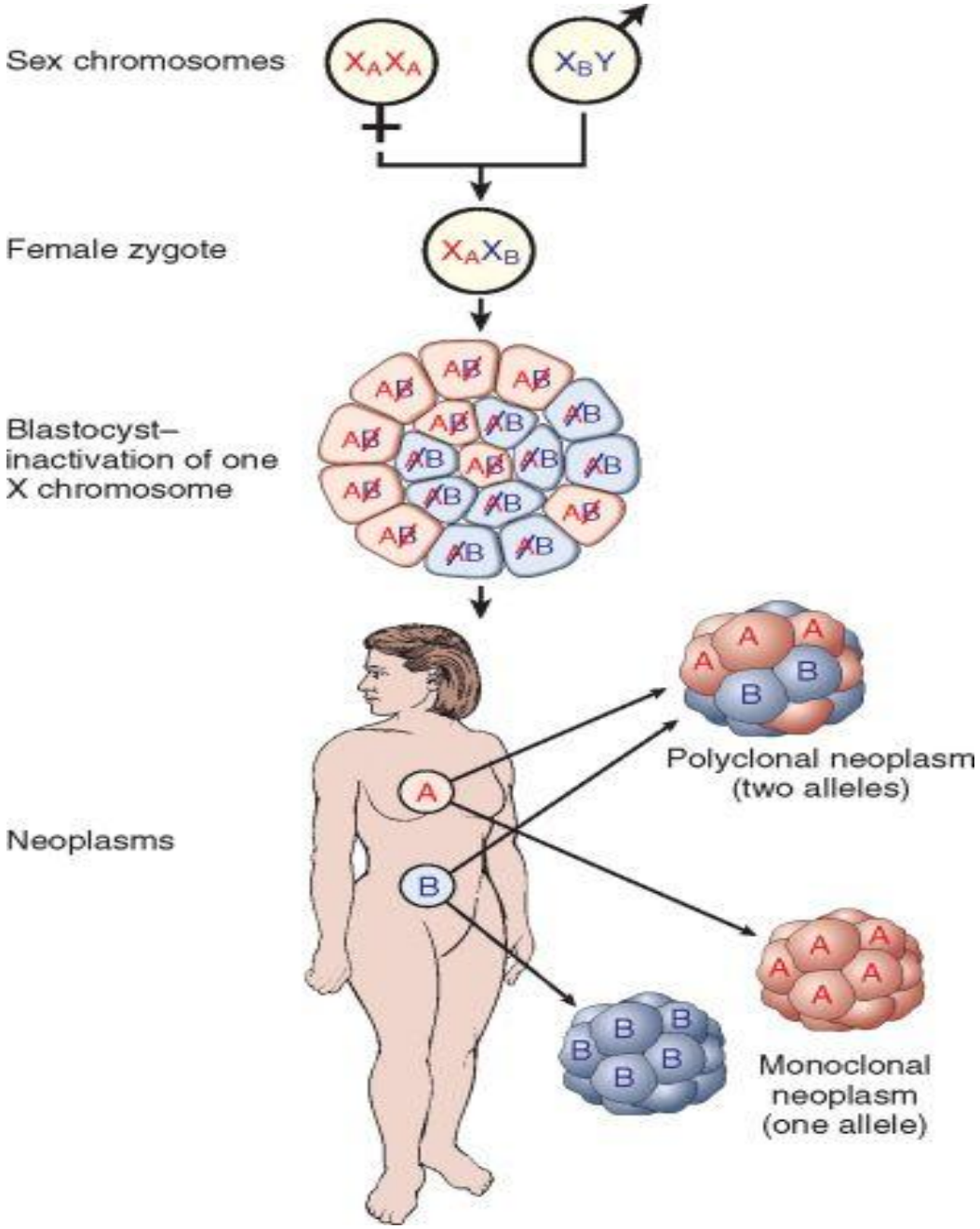
I .**Acquired**

- chemicals
- radiation
- viruses

II. **Inherited**

A tumor is formed by Clonal expansion of a single precursor cell that has incurred the genetic damage.

i.e. **Tumors are monoclona**l.


Sex chromosomes
X_AX_A
X_BY
Female zygote
X_AX_B
Blastocyst–
inactivation of one
X chromosome
Neoplasms
A
B
Polyclonal neoplasm
(two alleles)
Monoclonal
neoplasm
(one allele)

Cellular and Molecular Hallmarks of Cancer

EIGHT fundamental changes that determine malignant phenotype.

I. Self sufficiency in growth signals
II. Insensitivity to growth inhibitory signals
III. Altered cellular metabolism (Warburg effect)
IV. Evasion of apoptosis
V. Limitless replicative potential
VI. Sustained angiogenesis
VII. Ability to invade & metastasize
VIII. Ability to evade the host immune response

Principle targets of Genetic damage

Four classes of normal regulatory genes

I. Growth promoting **proto – oncogenes**

II. Growth inhibiting **suppresor genes**

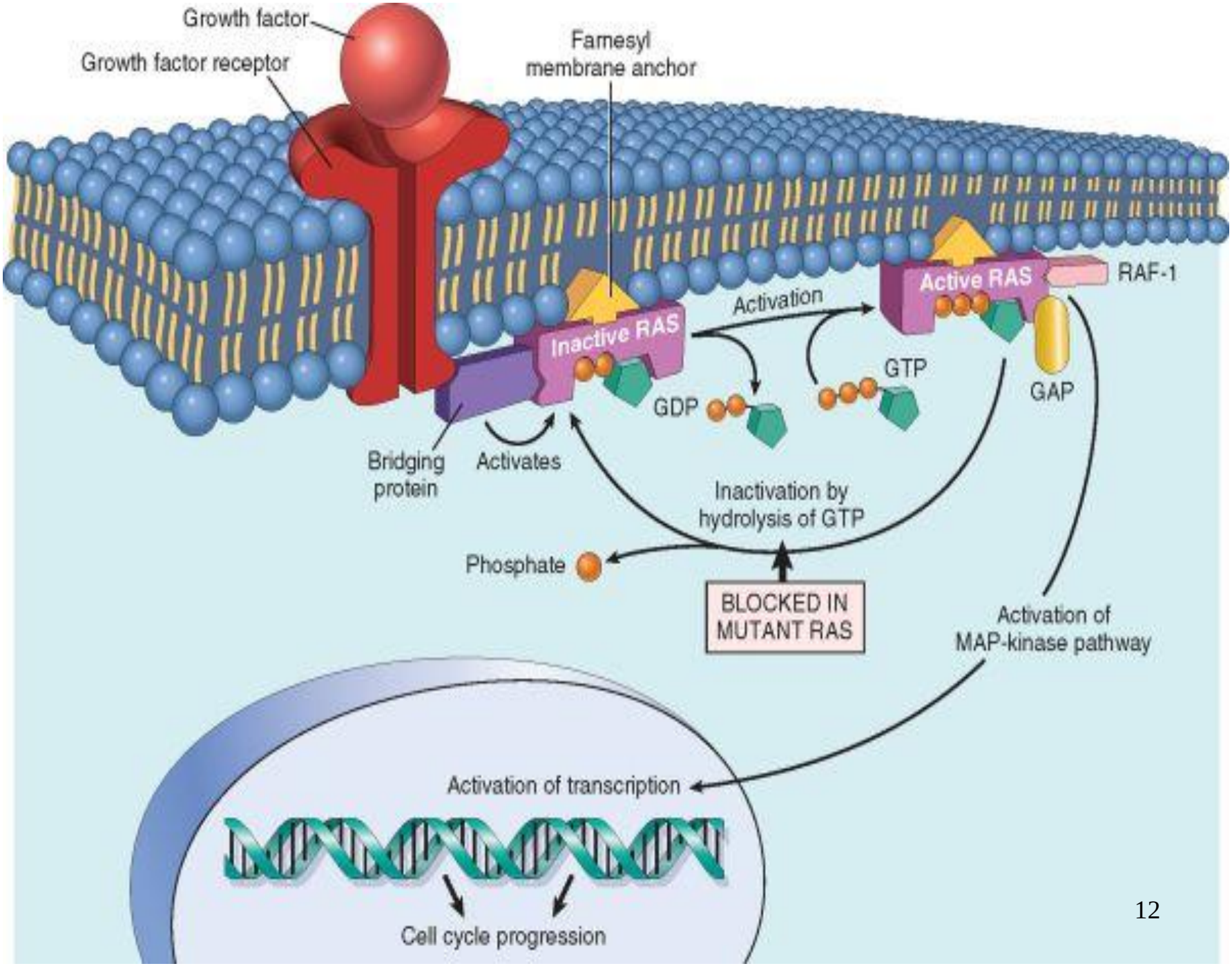
III. Genes that regulate programmed cell death – **Apoptosis**

IV. Genes involved **in DNA repair**

- **Proto-oncogenes**: normal cellular genes whose products promote cell proliferation
- **Oncogenes** are mutated genes that cause excessive cell growth, even in the absence of growth factors and other growth promoting external cue
- **Oncoproteins**: a protein encoded by an oncogene that drives increased cancer cell proliferation

Proteins encoded by proto-oncogenes may function as

- growth factors
- growth factor receptors
- proteins involved in signal transduction
- nuclear regulatory proteins
- cell cycle receptors


Growth factor
Growth factor receptor
Farnesyl membrane anchor
Inactive RAS
Activation
Active RAS
RAF-1
GTP
GDP
GAP
Bridging protein
Activates
Inactivation by hydrolysis of GTP
Phosphate
BLOCKED IN MUTANT RAS
Activation of MAP-kinase pathway
Activation of transcription
Cell cycle progression

Mechanisms of activation of c-oncs

I**. Point mutations & Deletion**

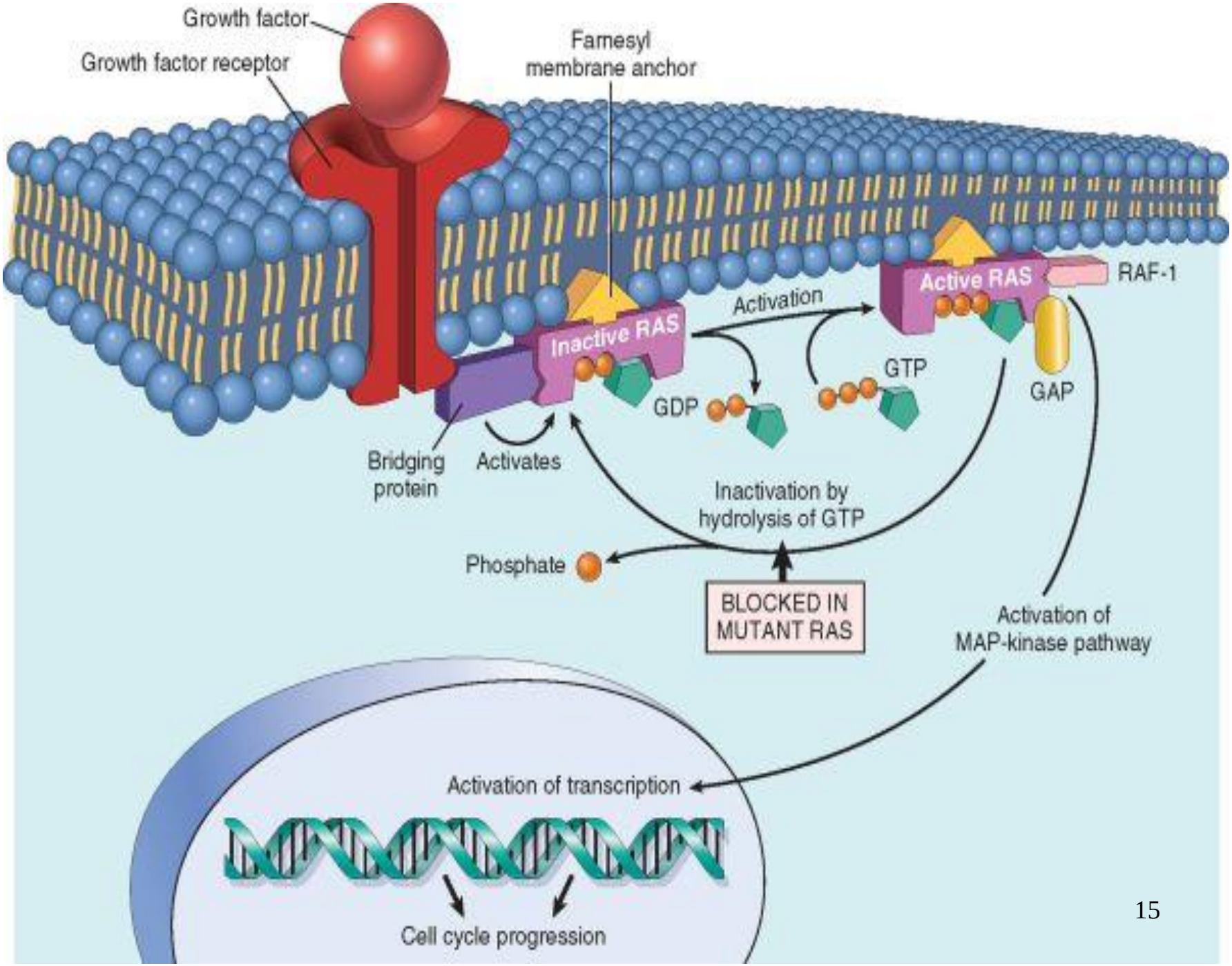
Ras proto-oncogene undergoes point mutation & is associated with colon,lung & pancreatic tumors.

II. **Chromosomal Translocation**

translocation of c-myc proto-oncogene from its site on chromosome 8 to a portion on chromosome 14, seen in 75% cases of Burkitt's Lymphoma

III. **Gene Amplification**

amplification of N-myc gene in human neuroblastoma


Growth factor
Growth factor receptor
Farnesyl membrane anchor
Inactive RAS
Activation
Active RAS
RAF-1
GTP
GDP
GAP
Bridging protein
Activates
Inactivation by hydrolysis of GTP
Phosphate
BLOCKED IN MUTANT RAS
Activation of MAP-kinase pathway
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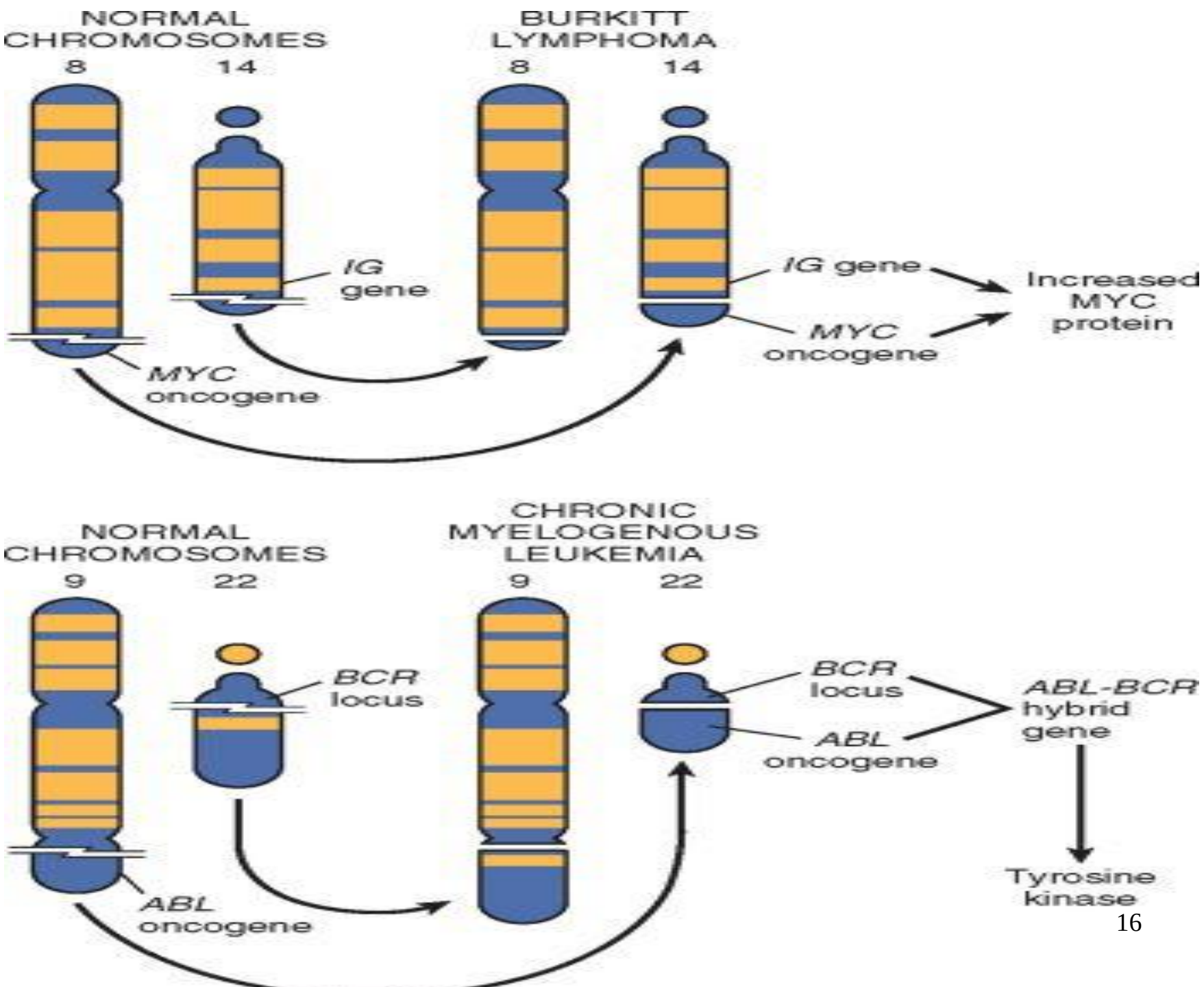
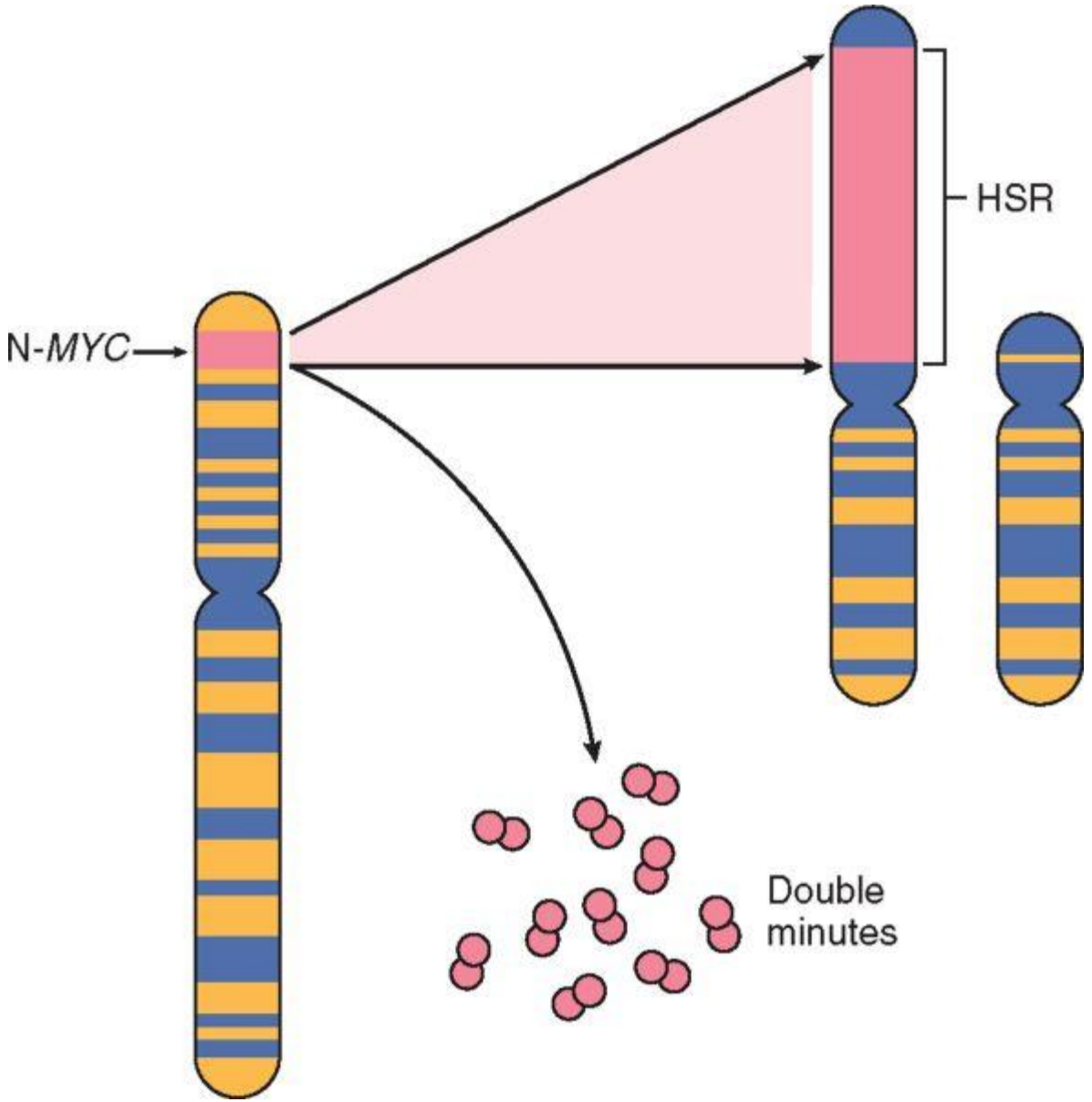
Cell cycle progression


NORMAL CHROMOSOMES
8
14
IG gene
MYC oncogene
BURKITT LYMPHOMA
8
14
IG gene
MYC oncogene
Increased MYC protein
NORMAL CHROMOSOMES
9
22
BCR locus
ABL oncogene
CHRONIC MYELOGENOUS LEUKEMIA
9
22
BCR locus
ABL oncogene
ABL-BCR hybrid gene
Tyrosine kinase


N-*MYC*
HSR
Double
minutes

Type	Proto oncogene	Mode of activation	Tumors
Growth factors PDGF B chain	SIS	Overexpression	Astrocytoma Osteosarcoma
Growth factor receptor EGF family	ERB-B1 ERB-B2	Overexpression Amplification	SCC of Lung Ca Breast & Ca Ovary
Proteins in signal transduction GTP binding	K-RAS	Point mutation	Colon, lung, pancreatic tumors

Type	Proto-oncogene	Mode of activation	Tumors
Nuclear regulatory Proteins Transcriptional activators	C-myc	Translocation	Burkitt's Lymphoma
Cell cycle regulators Cyclins	Cyclin D	Translocation	Mantle Cell Lymphoma

Tumor suppressor genes/ Anti-oncogenes

- Pair of genes which perform the physiologic function of regulation of cell growth
- ***Apply breaks to cell proliferation.***
- Deletion or mutation of antioncogenes result in removal of brakes, inhibitory effect to cell growth is gone.

Rb gene - Retinoblastoma

P53 – Ca lung,Ca colon,

Others

i) APC gene – Familial Adenomatous Polyposis Coli **gatekeeper gene**

ii) WT1 gene – Hereditary Wilms Tumor

iii) NF 1gene – Neurofibromatous type I

iv) BRCA 1& BRCA 2 genes – Breast cancer

RETINOBLASTOMA- RB GENE

Knudson Two Hit hypothesis of oncogenesis

In Hereditary cases – one genetic damage(1st hit) is inherited from an affected parent & is therefore present in all somatic cells of the body.

Whereas the 2nd mutation (2nd hit) occurs in one of the many retinal cells.(which already carry the 1st mutation) .

In Sporadic cases – both hits occur somatically within a single retinal cells,whose progeny then form the tumor.

- Both normal alleles of the RB locus must be inactivated for the development of Retinoblastoma.

- Patients with familial Retinoblastoma are also at greatly increased risk of developing Osteosarcoma & some other soft tissue sarcomas.

P 53- MOLECULAR POLICEMAN

Ionizing radiation/carcinogens/mutagen →

Normal p53 → DNA damage → G1 arrest →

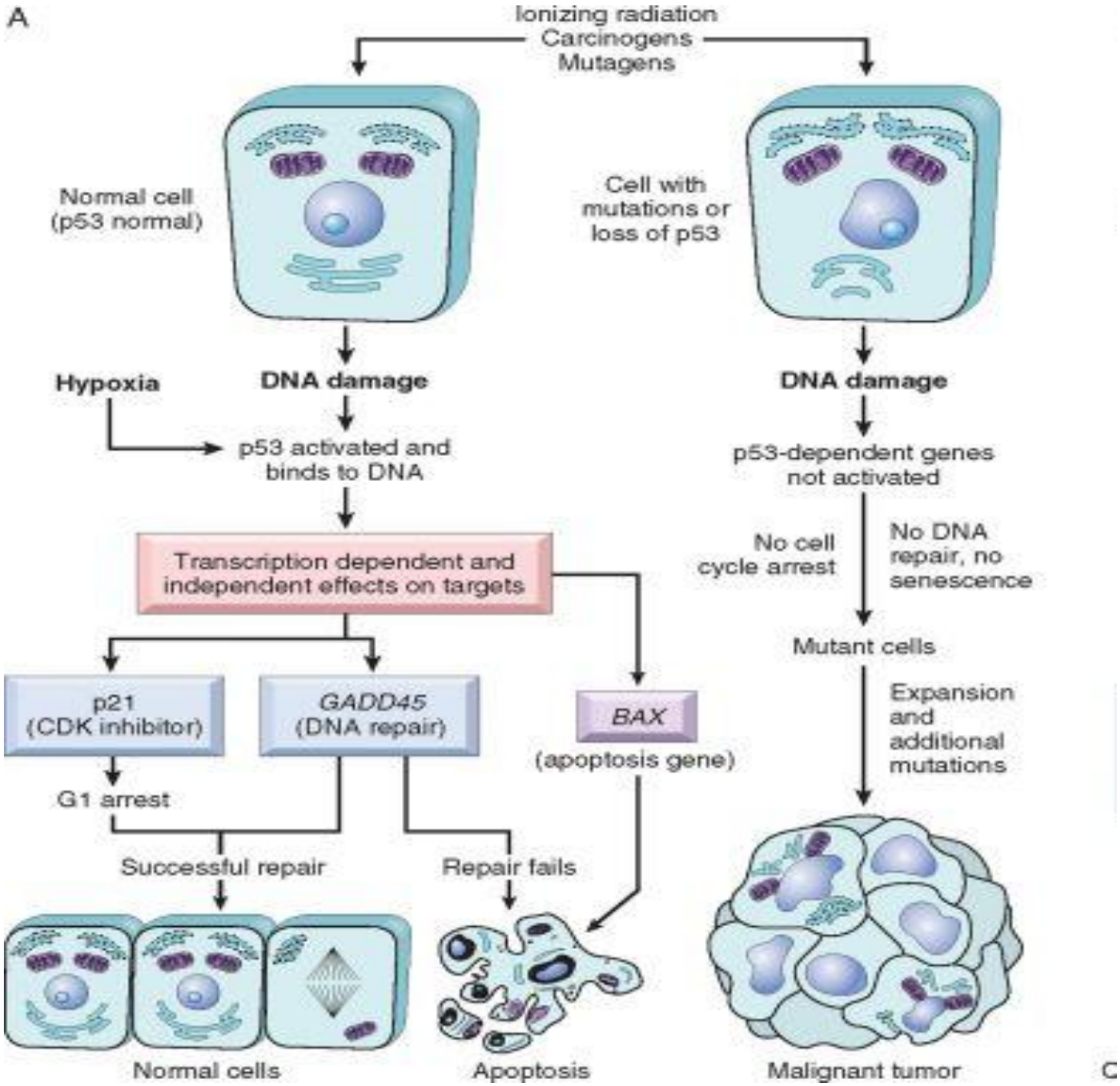
Successful repair →Normal cell

Ionizing radiation/carcinogens/mutagen →

Loss of p53 → DNA damage →DNA repair →

repair fails →Apoptosis

Guardian of genome


A
Ionizing radiation
Carcinogens
Mutagens
Normal cell
(p53 normal)
Cell with
mutations or
loss of p53
Hypoxia
DNA damage
DNA damage
p53 activated and
binds to DNA
p53-dependent genes
not activated
No cell
cycle arrest
No DNA
repair, no
senescence
Transcription dependent and
independent effects on targets
Mutant cells
p21
(CDK inhibitor)
GADD45
(DNA repair)
BAX
(apoptosis gene)
Expansion
and
additional
mutations
G1 arrest
Successful repair
Repair fails
Normal cells
Apoptosis
Malignant tumor
C

ONCOGENES

- Mutated form of normal proto-oncogene
- Dominant: mutation of a single copy may transform cell
- Point mutation, translocation, amplification, overexpression
- Allows cell proliferation by increased growth promotion pathways
- Level of action-cell surface, cytoplasm, nucleus

TUMOR SUPPRESSOR GENES

- Mutated form of normal growth suppressor genes
- Recessive: mutation of both alleles required for transformation
- Deletion, point mutation, loss of function
- Allows cell proliferation by removal of brakes in cell proliferation
- Level of action-cell surface, cytoplasm, nucleus

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 division	Loss of function of a protein
Mutation arises in somatic cells, not inherited	Mutation present in germ cell (can be inherited), or in somatic cell
Some tissue preference	Often strong tissue preference (eg effect of *RB* gene in the retina)

Data from Levine AJ: The p53 tumor suppressor gene. N Engl J Med 1992;326:1350.

DNA repair genes

- ✓ Ionizing radiation, sunlight, dietary carcinogens
- ✓ ROS generated by cell metabolism
- ✓ Errors occuring spontenously during DNA replication.
- ✓ Those born with inherited mutations of DNA repair proteins are at a greatly increased risk of developing cancer → **Genomic instability syndrome**

Genomic instability occurs when both copies of these genes are lost.

Defects in DNA repair System

a) Mismatch repair – spell checkers/proof readers: HNPCC syndrome

b) Nucleotide excision repair – UV rays cause cross linkage of pyrimidine residues :Xeroderma Pigmentosum

c) Recombination repair – Fanconi's anaemia

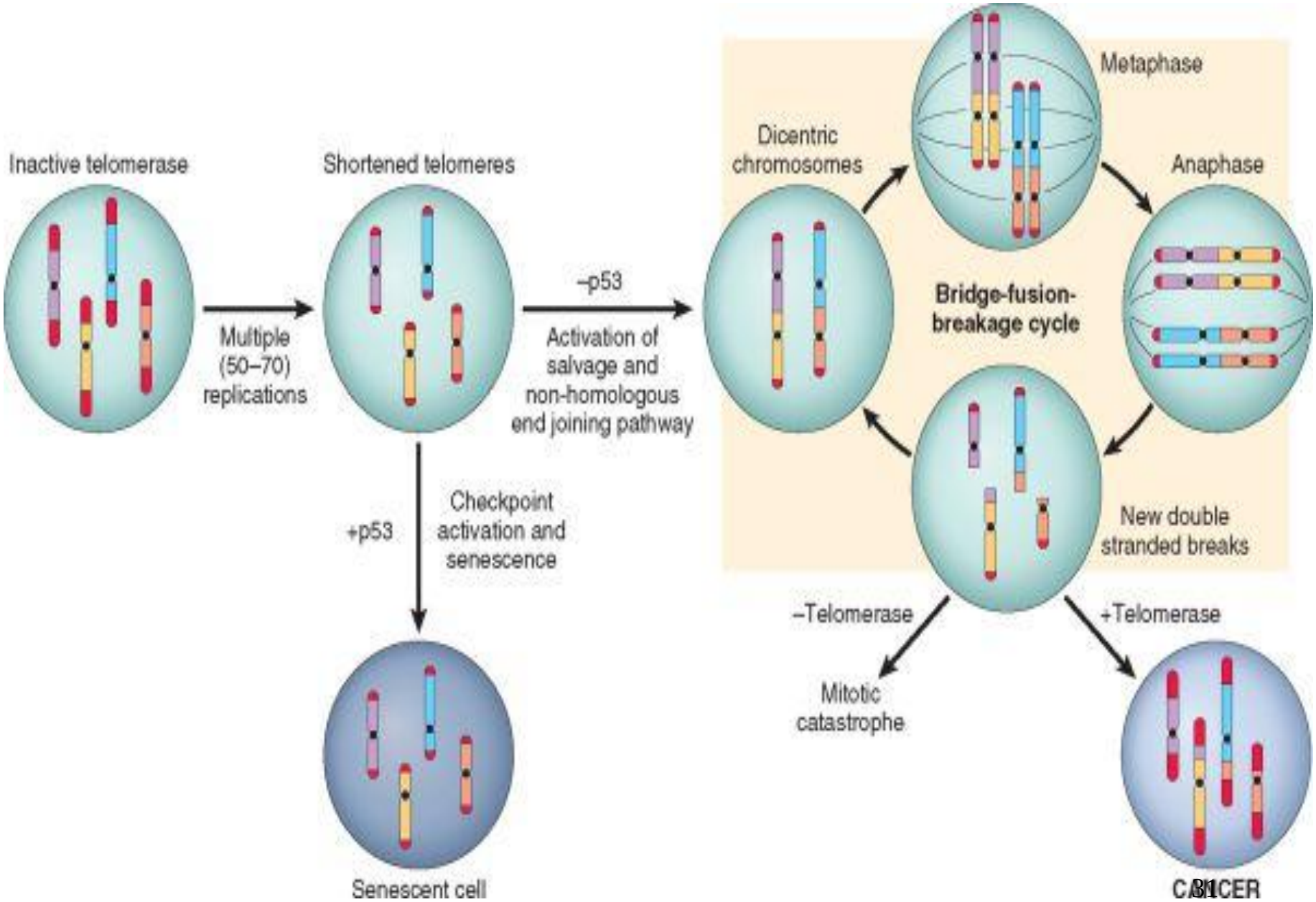
Bloom syndrome

Ataxia telangiactasia

TELOMERASE IN CANCER

Telomerase – maintains normal telomere length.

- After fixed no. of divisions telomeres are lost & the cells cease to undergo mitosis.
- Cancer cells have upregulated telomerase, maintaining telomere length.


Inactive telomerase
Shortened telomeres
Multiple (50–70) replications
–p53
Activation of salvage and non-homologous end joining pathway
+p53
Checkpoint activation and senescence
Senescent cell
Dicentric chromosomes
Metaphase
Anaphase
Bridge-fusion-breakage cycle
New double stranded breaks
–Telomerase
+Telomerase
Mitotic catastrophe
CANCER

Genes that regulate Apoptosis

Mutations in the genes that regulate apoptosis.

bcl-2 → protects cells from apoptosis

i.e. anti- apoptotic

Mutations in bcl - 2 → overexpression of bcl-2, increase in the lifespan of cells, causing B cell lymphoma.

The Warburg Effect

- Even in the presence of ample oxygen, cancer cells demonstrated a distinctive form of cellular metabolism characterized by high levels of glucose uptake and increased conversion of glucose to lactose (fermentation)via the glycolytic pathway
- Aerobic glycolysis
- Otto Warburg received Nobel prize in 1931

PET scan- Positron Emission Tomography

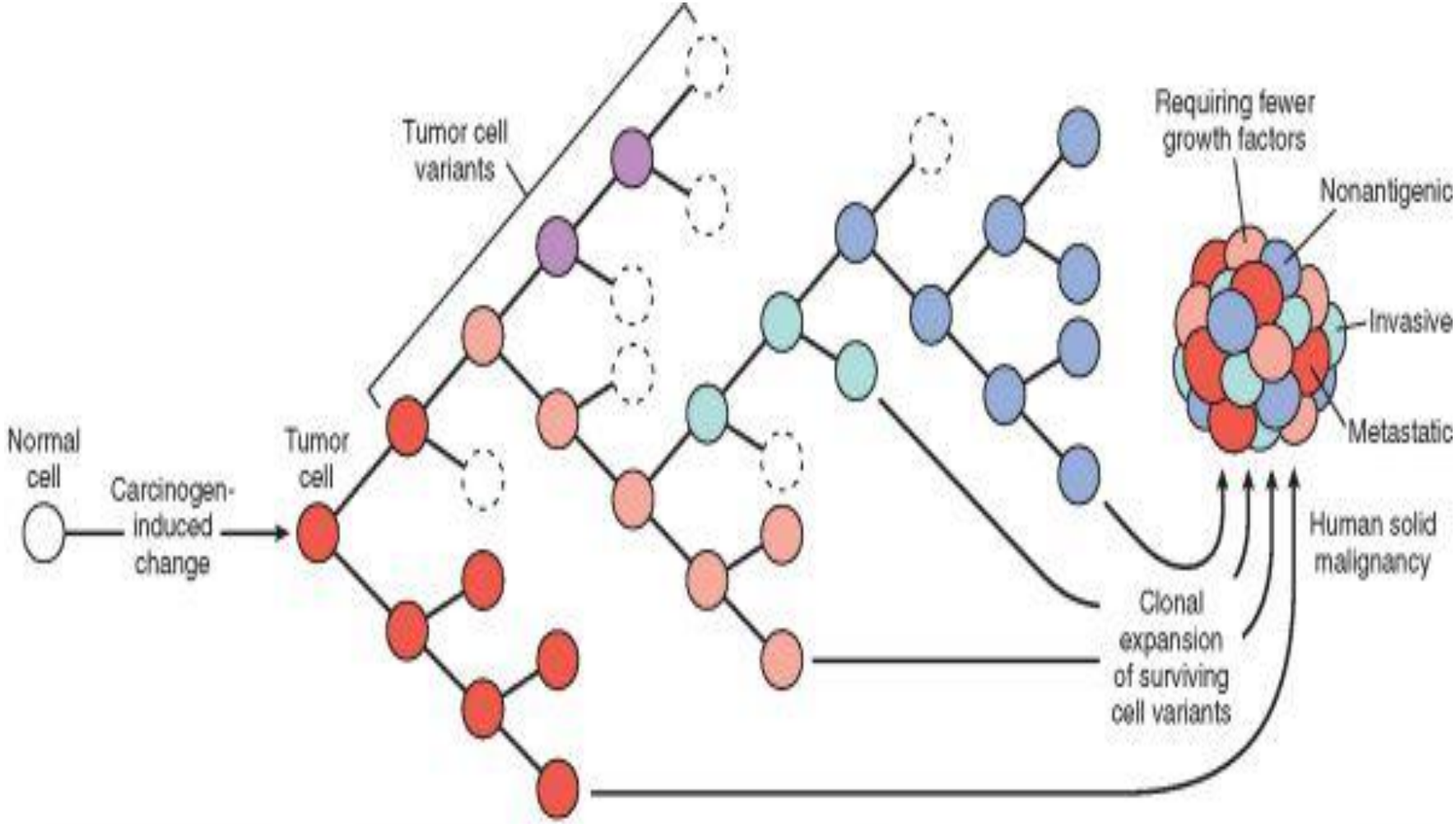
- “glucose hunger” is used to visualize tumors via PET scanning, in which patients are injected with “ F –fluorodeoxyglucose, a non metabolizable derivative of glucose that is preferentially taken up into tumor cells (as well as normal actively dividing tissues such as the bone marrow)
- Most tumors are PET positive and rapidly growing ones are markedly so

Development of sustained angiogenesis

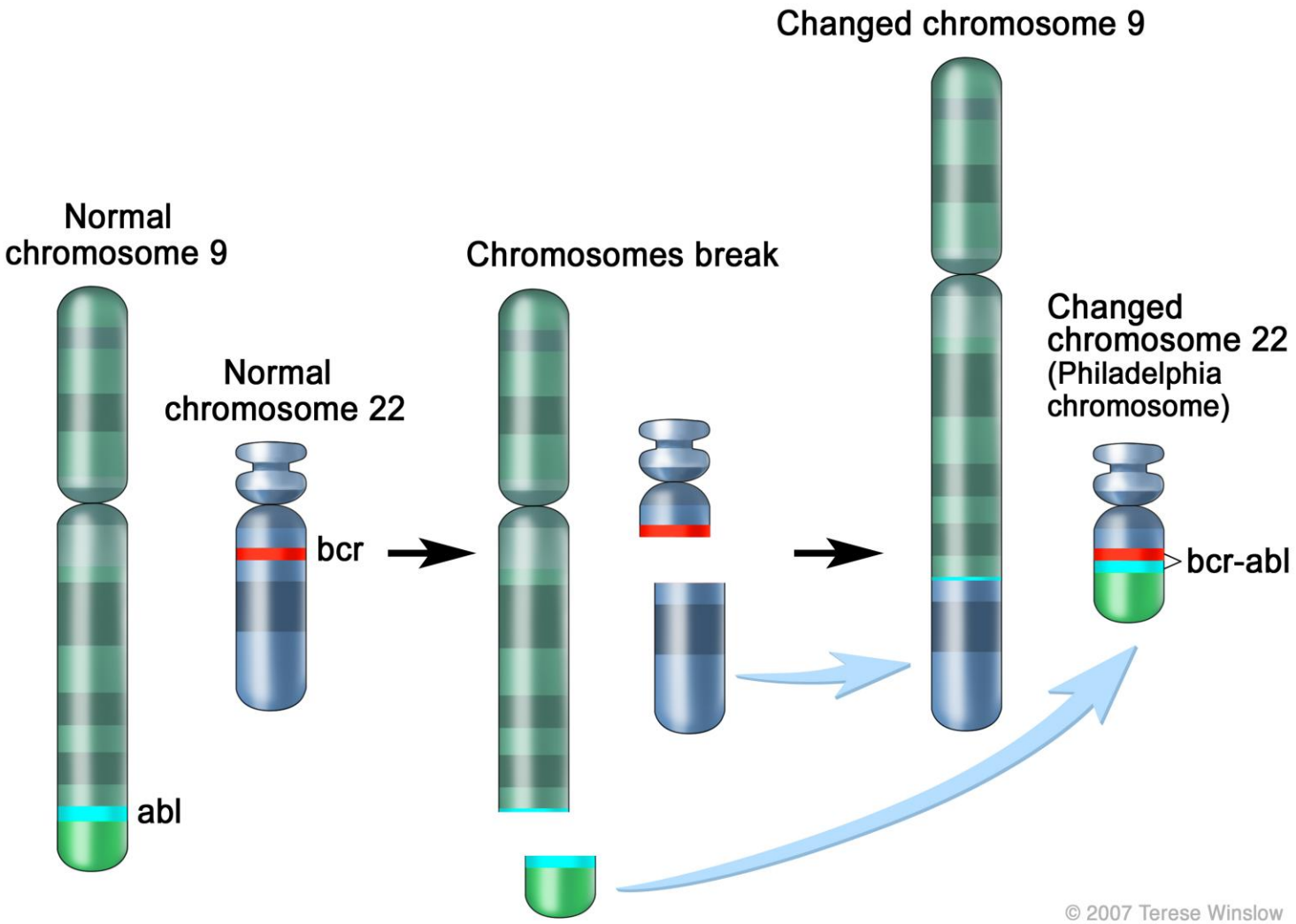
- ✓ Tumors stimulate angiogenesis.
- ✓ Angiogenesis – supplies nutrient & o_2 secretes growth factors
- ✓ Angiogenesis requisite for tumor growth & metastasis.

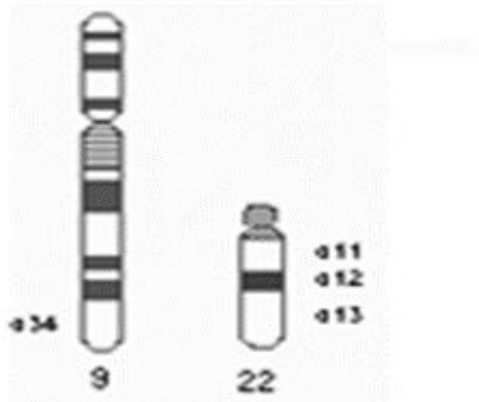
Carcinogenesis is a multistep process at both phenotypic & genetic levels

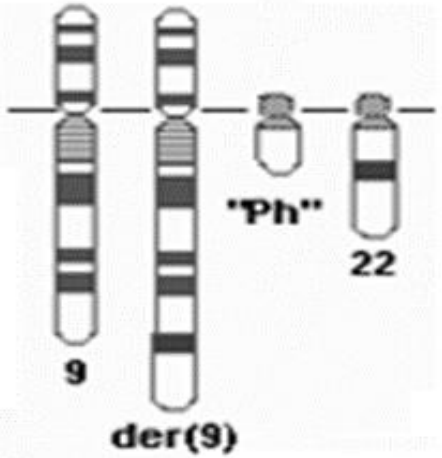
- tumor progression

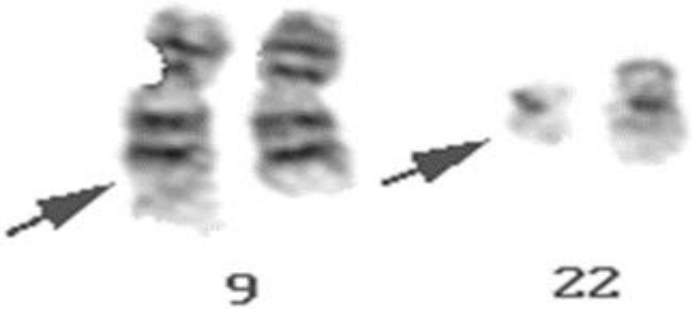


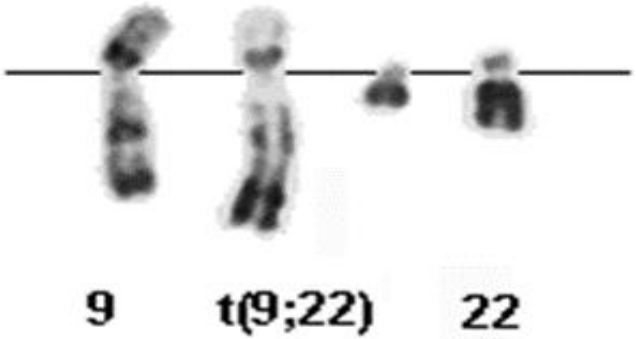
TRANSFORMATION	PROGRESSION	PROLIFERATION OF GENETICALLY UNSTABLE CELLS → TUMOR CELL VARIANTS HETEROGENEITY

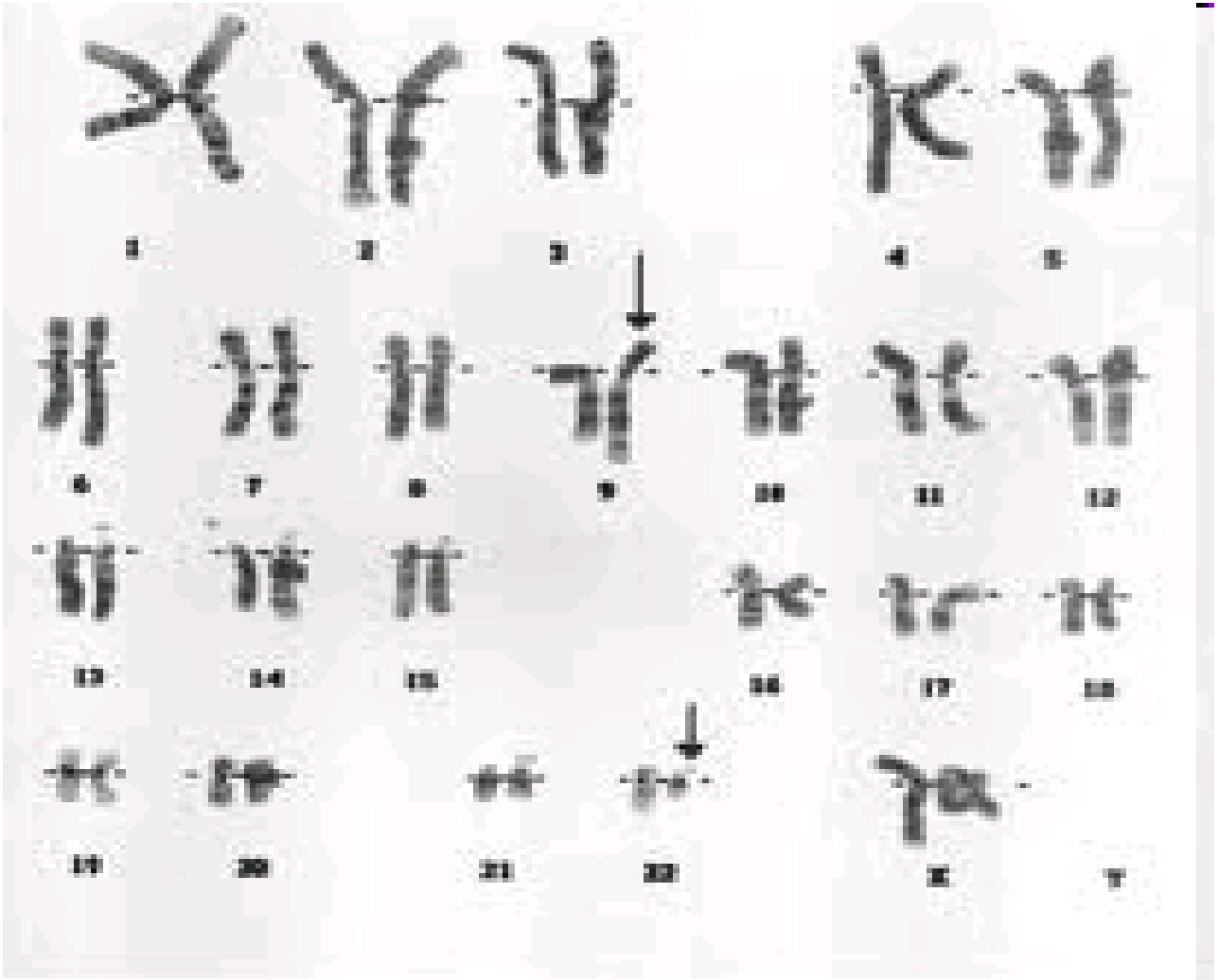



q34
q11
q12
q13
9
22

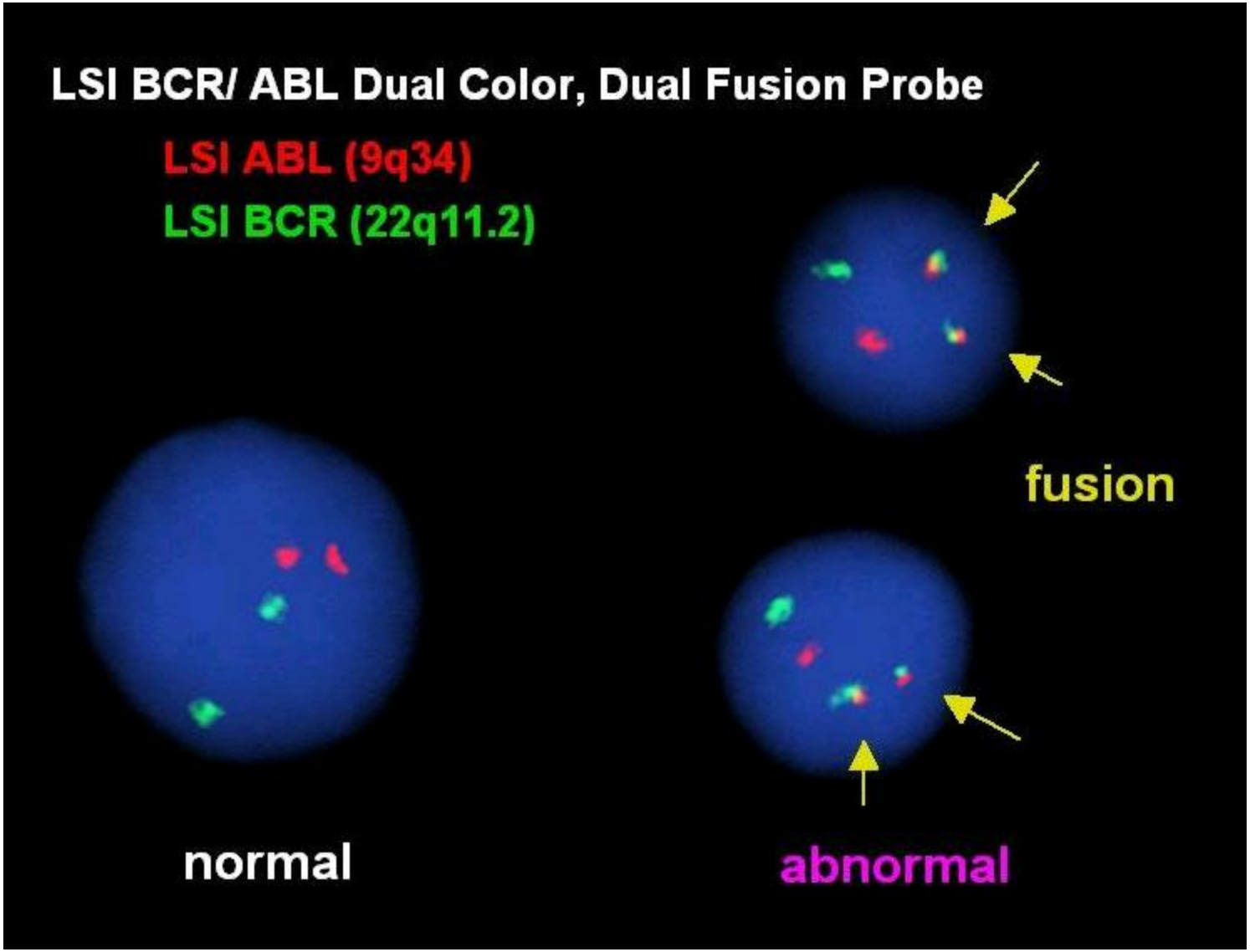

"Ph"
22
9
der(9)


9
22


9
t(9;22)
22



The abnormality seen by Nowell & Hungerford on chromosome 22, Now known as the Philadelphia Chromosome.


LSI BCR/ ABL Dual Color, Dual Fusion Probe
LSI ABL (9q34)
LSI BCR (22q11.2)
fusion
normal
abnormal