
بسم الله الرحمن الرحيم

- Proto-oncogene: A gene which may mutate to become an oncogene.

- Oncogene: A gene, one or more forms of which is associated with cancer.

How does a proto-oncogene become an oncogene?

- Virus integration
- Mutations
- Gene amplification
- Chromosomal translocations

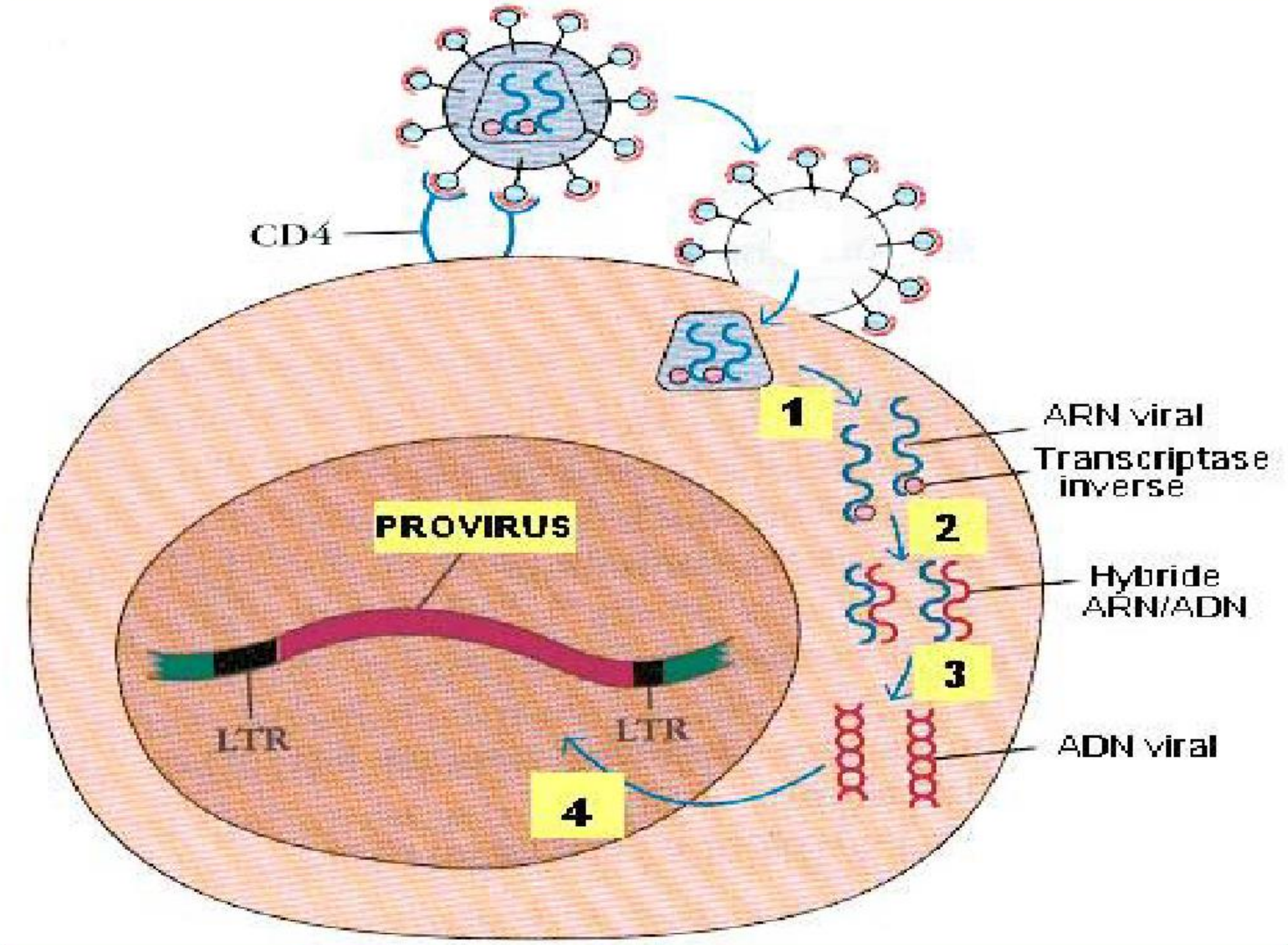
I- Virus Integration

- Many viruses can infect normal cells and convert them into malignant cells (transformation)

- The first virus of this type is RSV (Rous sarcoma virus)
- Viral oncogene v-src is found within the viral genome .

- The normal copy of the src gene in the host is termed c-src (cellular src).It is encoded in the chromosomal DNA of the host cell ,It does not cause cancer.

- However, once incorporated into a viral genome,this gene can become a viral oncogene that promotes cancer.


CD4
1
ARN viral
Transcriptase inverse
2
Hybride ARN/ADN
3
ADN viral
PROVIRUS
LTR
LTR
4

1. Over expression of c-onc gene with virus replication.
2. Further mutations in c-onc gene

Virus

Host Cell

Viral integration

Viral Replication

RSV has acquired the src gene by capturing it from a host chromosome.

- During its life cycle, a retrovirus uses reverse transcriptase to make a DNA copy of its genome, which → integrated as a provirus into the host cell genome.
- This integration may occur next to a proto-oncogene .
- During transcription of the proviral DNA, the neighboring proto-oncogene may be included in the RNA transcript recombine with an RNA retroviral genome within the cell → to yield a retrovirus that contains an oncogene

Two explanation of this phenomenon

- Many copies of the virus made during viral replication overexpression of the src gene.
- Alternatively,the v-src gene may accumulate additional mutations that convert it to an oncogene

Promoteur cellulaire
faible et régulable

gène c-myc

Exon1 Exon2 Exon3

① niveau basal d'expression faible

Promoteurs viral
fort et constitutif (non régulable)

Exon1 LTR LTR Exon2 Exon3

génome viral

② Insertion provirale
fort niveau d'expression

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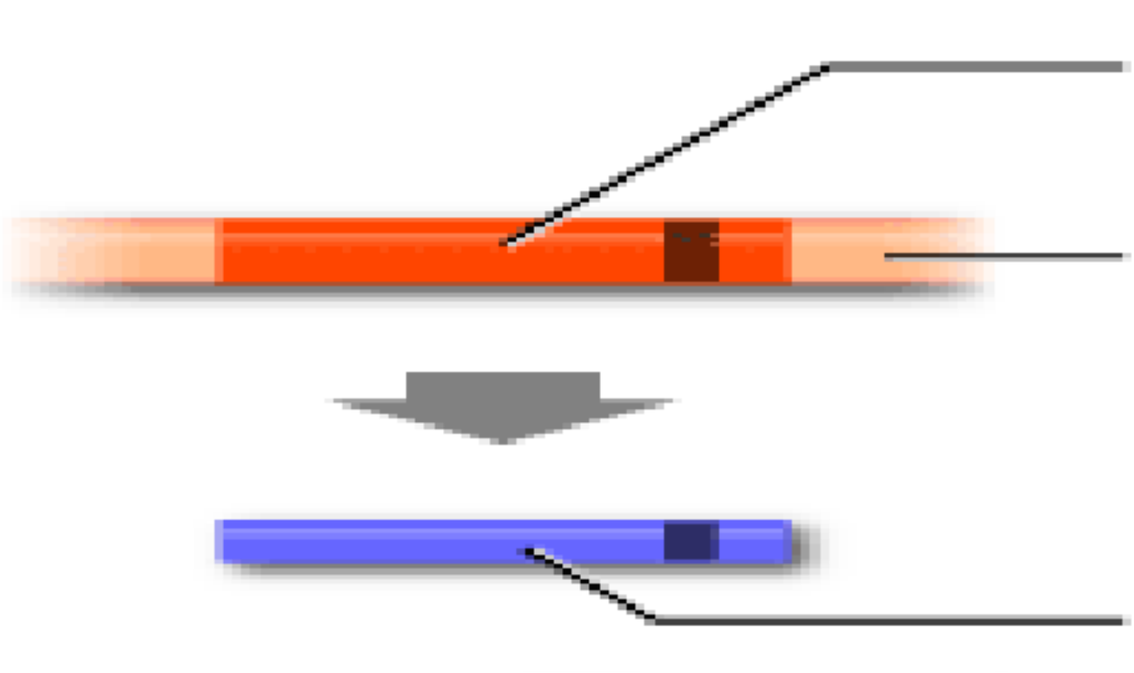
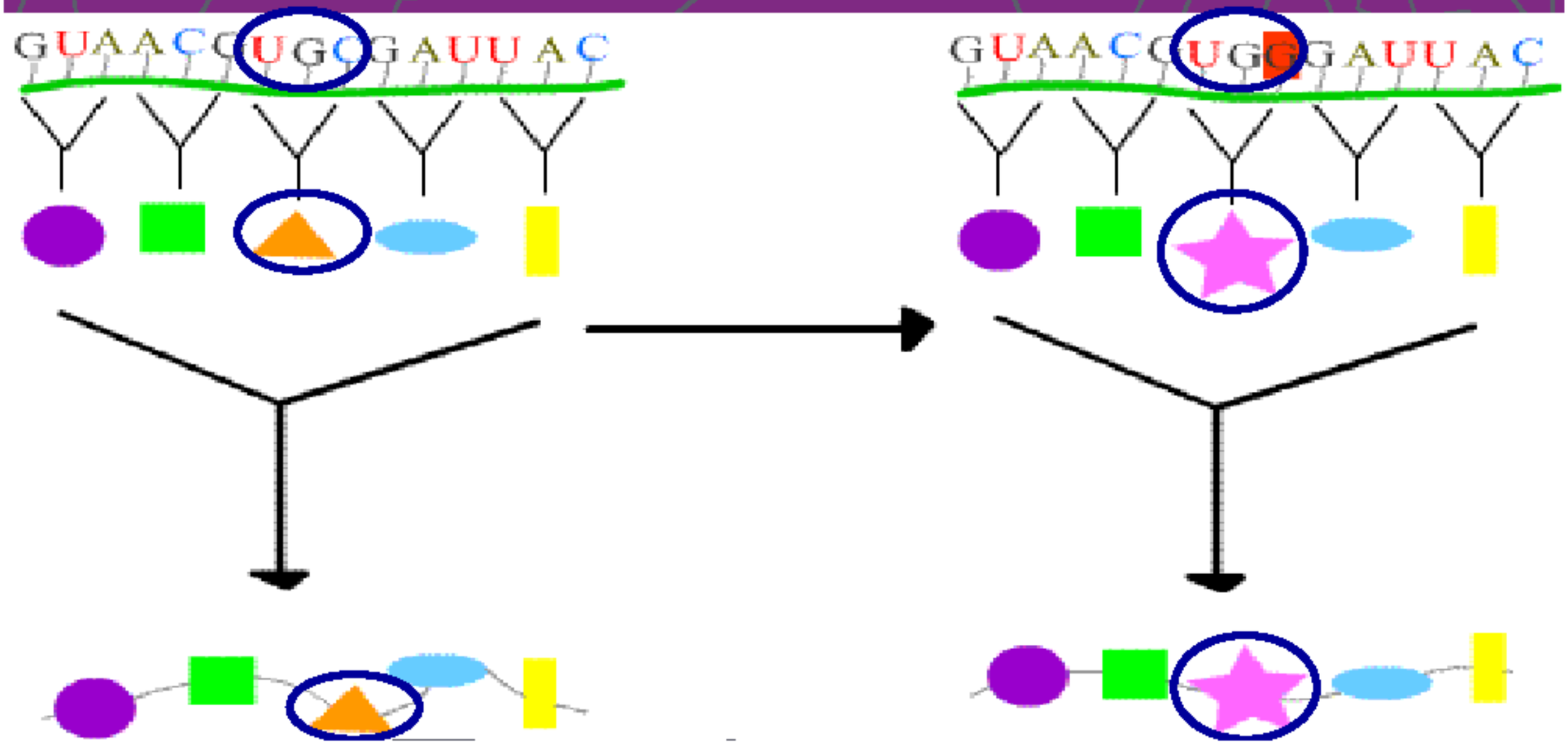
II-Mutations

Point mutation: A mutation affecting a single nucleotide pair. It can be used up to the insertion or to the deletion of a small number of nucleotide pairs.

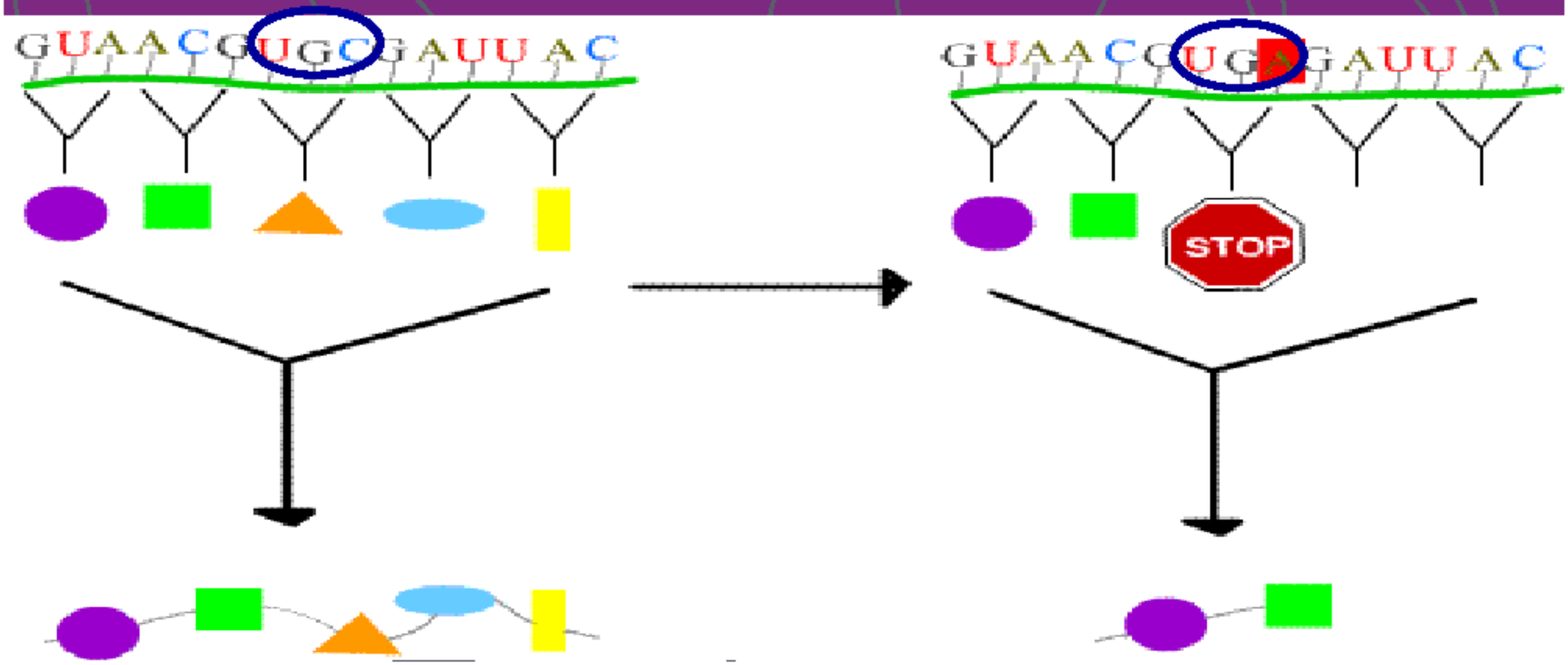


Types
- Missense
- Nonsense
- Frameshift

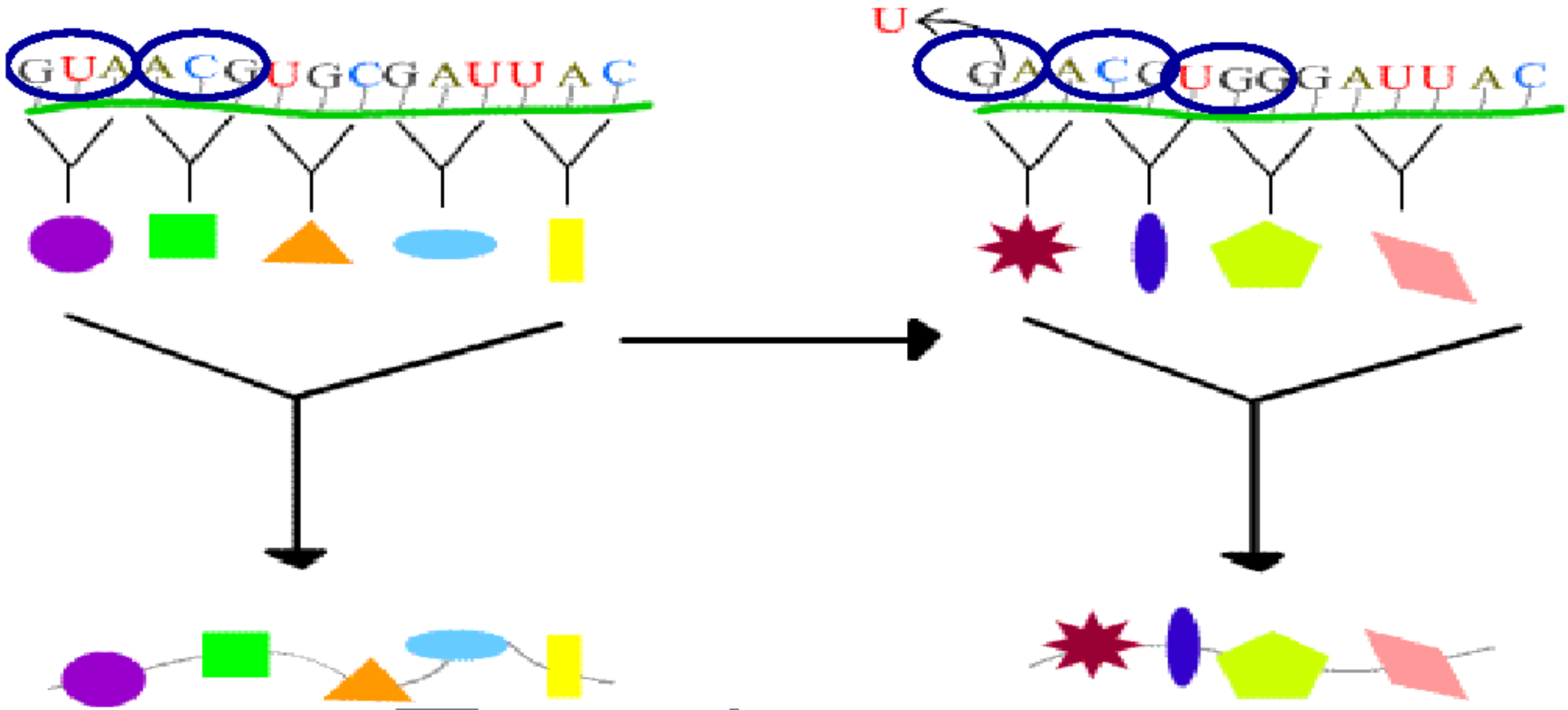
1. ***Missense mutations:*** The new codon causes an incorrect amino acid to be inserted into the protein. The effects on the function of the protein depend on what is inserted in place of the normal amino acid.



2. ***Nonsense mutations:*** The new codon causes the protein to prematurely terminate, producing a product that is shortened and often does not function.



3. ***Frameshift mutations:*** The loss or gain of 1 or 2 nucleotides causes the affected codon and all of the codons that follow to be misread.



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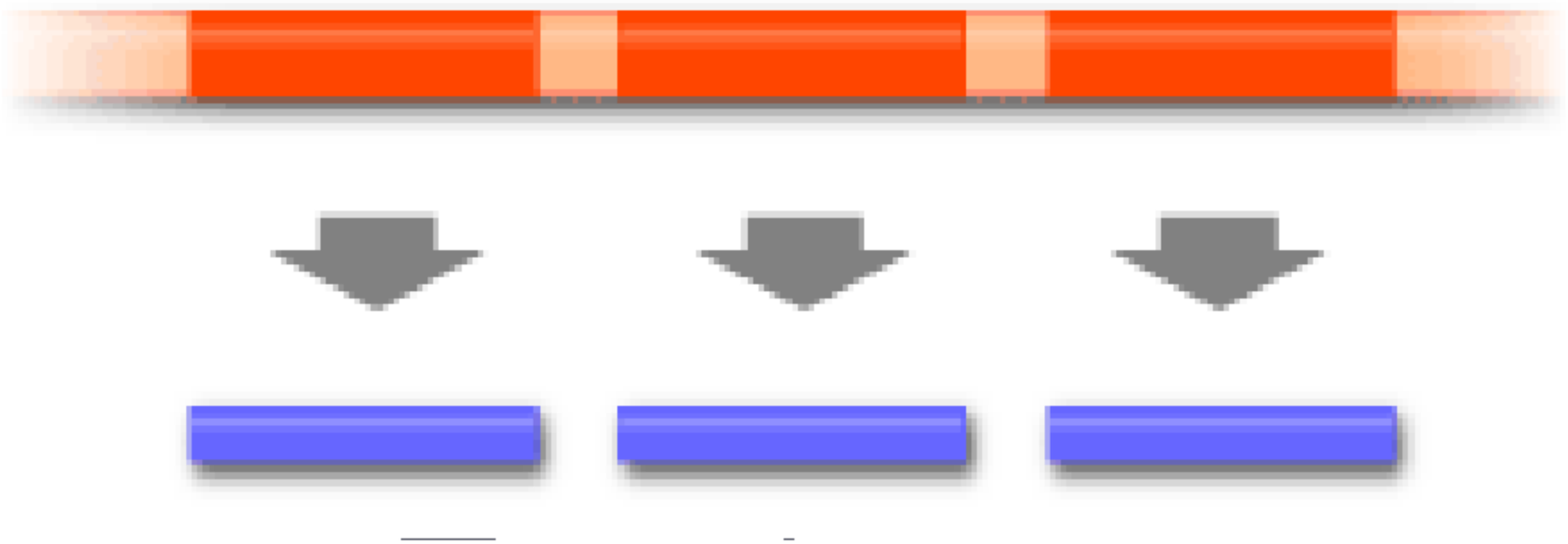
III-Gene Amplification

An increase in the number of copies of a specific DNA fragment → normal protein produced in much higher amount.



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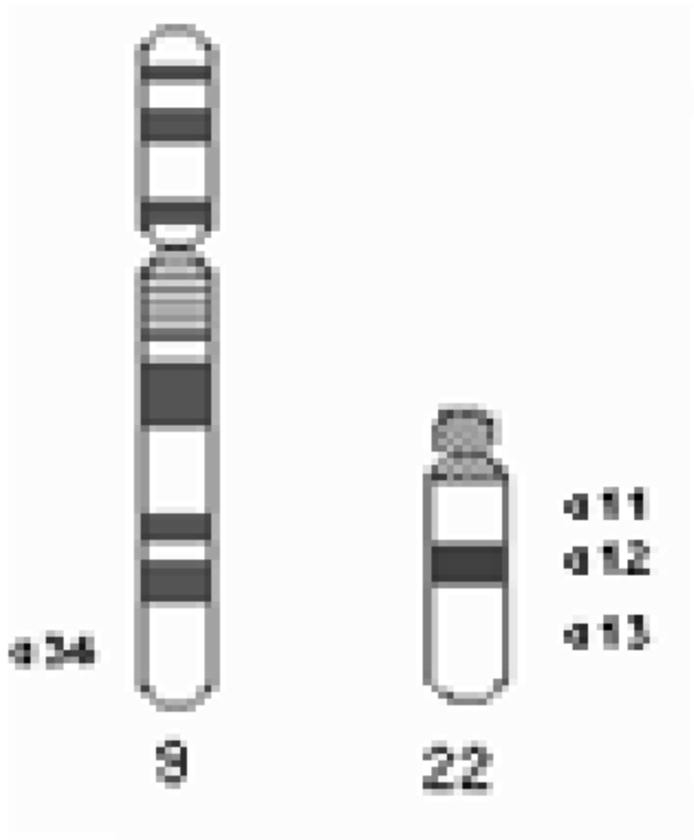
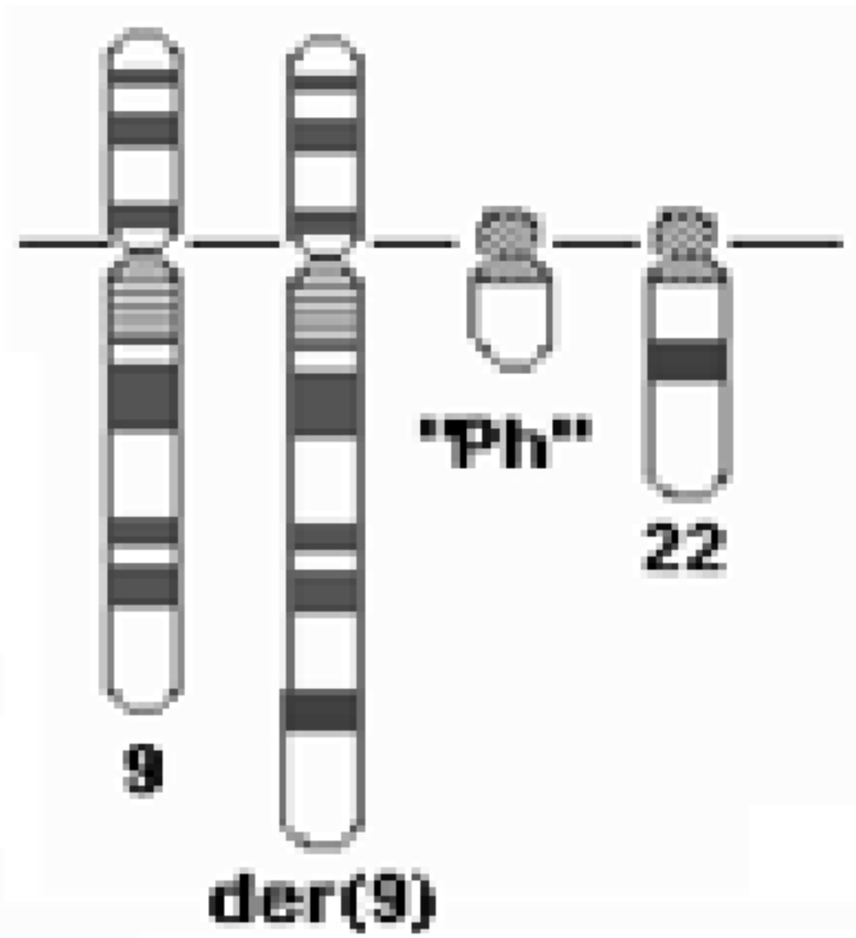
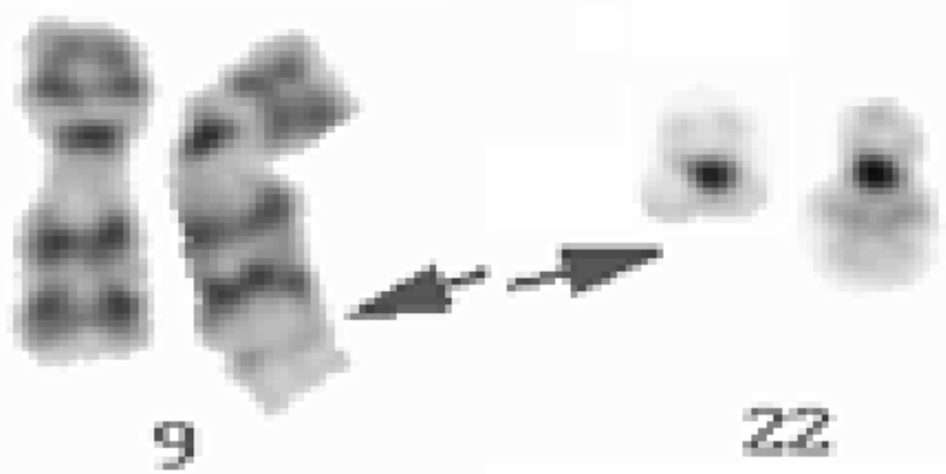
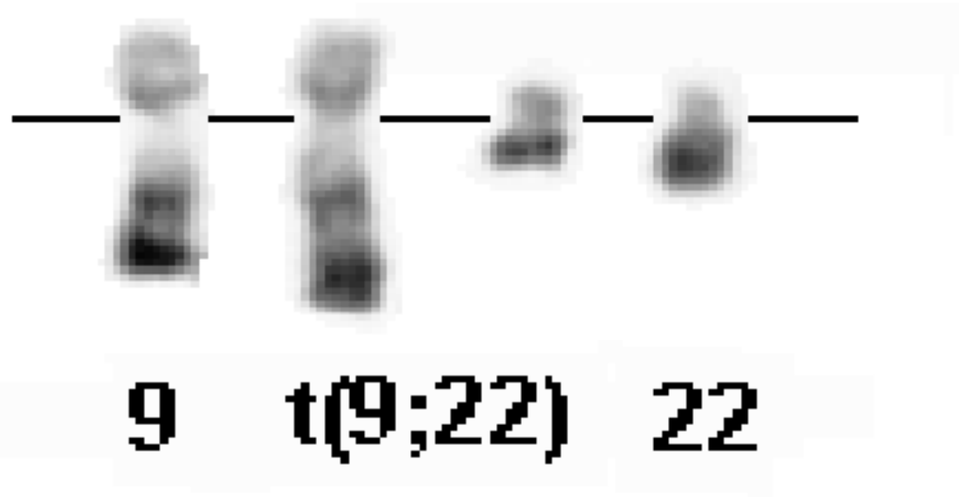
IV- Structural Anomalies (Translocations)

Chromosomes can appear to break, and broken ends can rejoin in various ways: to make a structural aberration (exchanges).


q34
q11
q12
q13
9
22


"Ph"
22
9
der(9)


9
22


9
t(9;22)
22

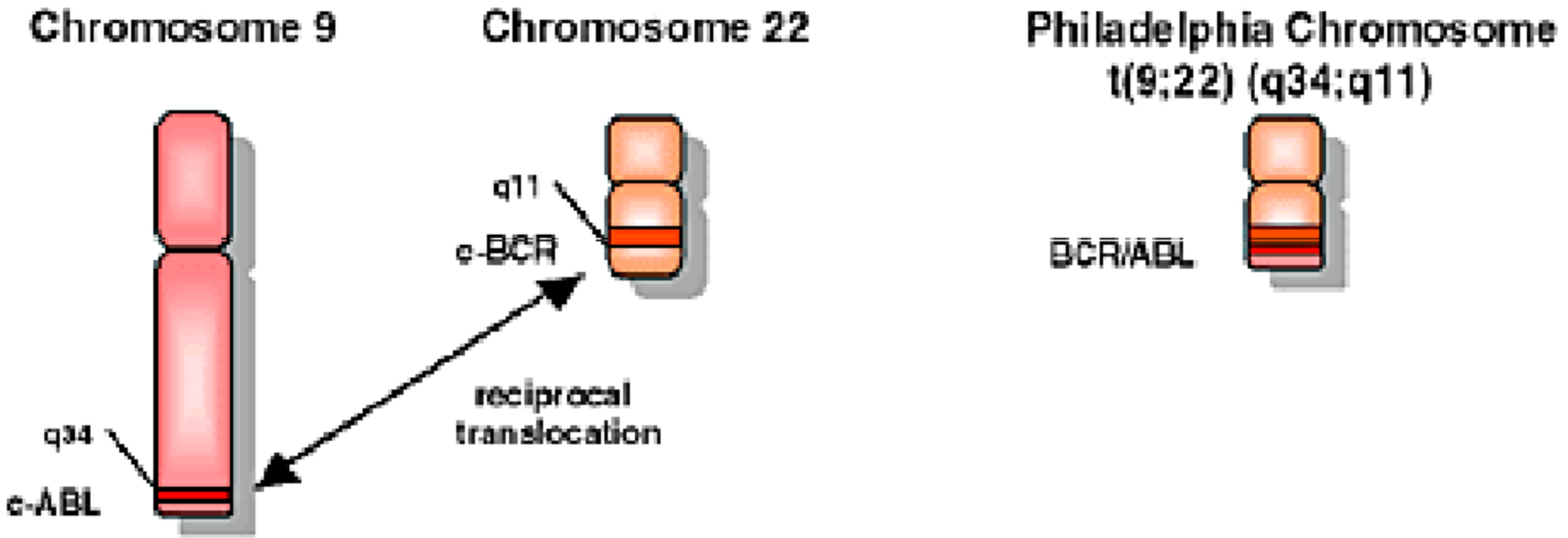
Chromosomal translocations can produce oncogenes in several ways:

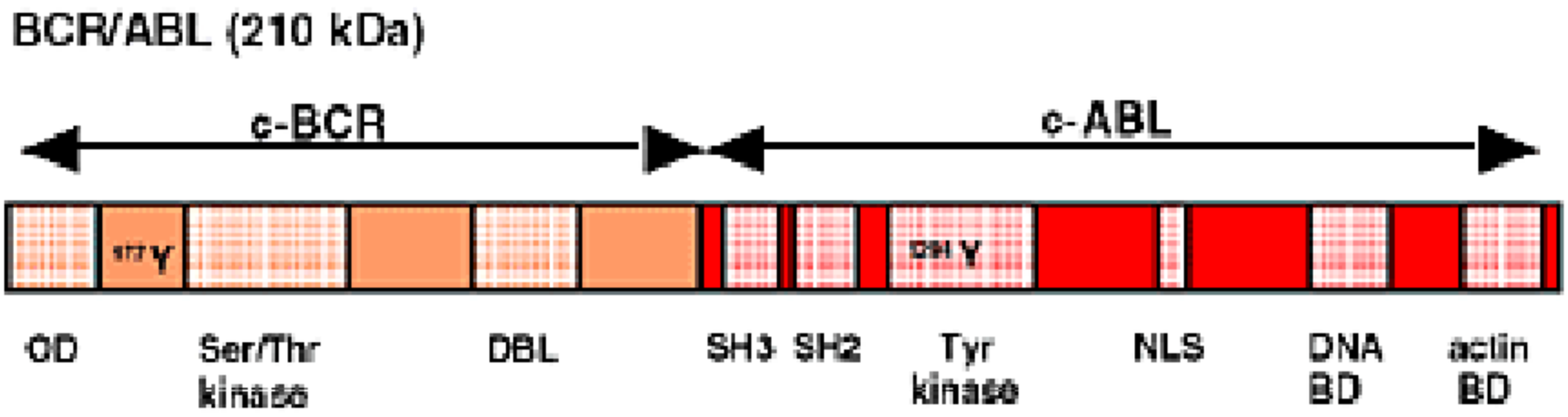
- Firstly, fusion proteins
- Secondly, the fusion of one chromosome to another can result in a strong promoter being placed upstream of a gene that would normally be either absent or present only in very low quantities.

Chromosomal translocations can produce oncogenes in several ways:

- *Firstly*, fusion proteins chromosomal translocations → fusion proteins that can be oncogenes for a number of reasons.

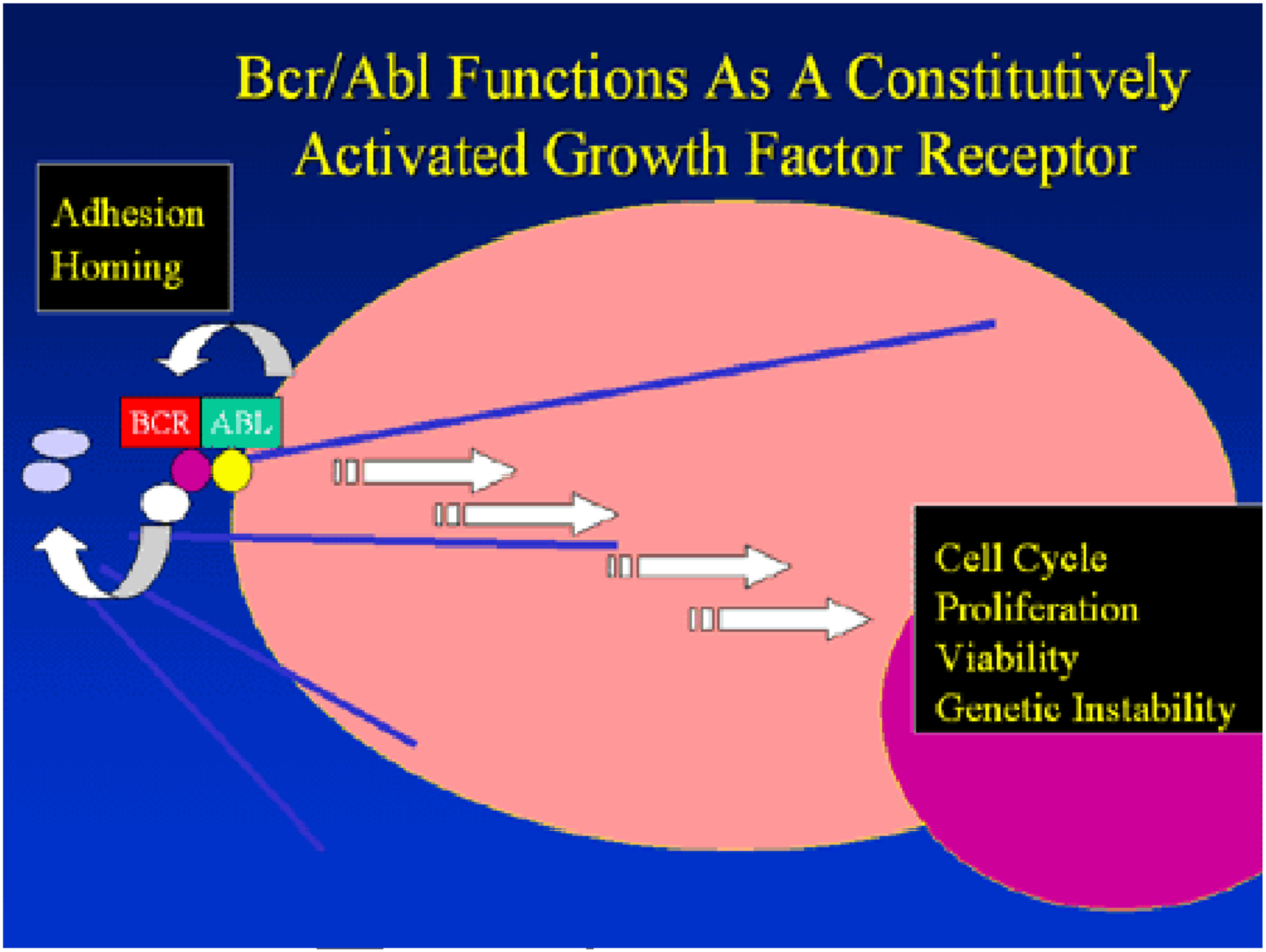
1. If it is a highly transcribed protein, then expression of the fusion protein will be high.eg,(PML/RARA) protein.
2. If it is a signalling protein ,the fusion protein will consist of a molecule with signalling capacity Such is the case of the Bcr-Abl fusion protein.


Chromosome 9
Chromosome 22
Philadelphia Chromosome
t(9;22) (q34;q11)
q11
c-BCR
BCR/ABL
reciprocal
translocation
q34
c-ABL

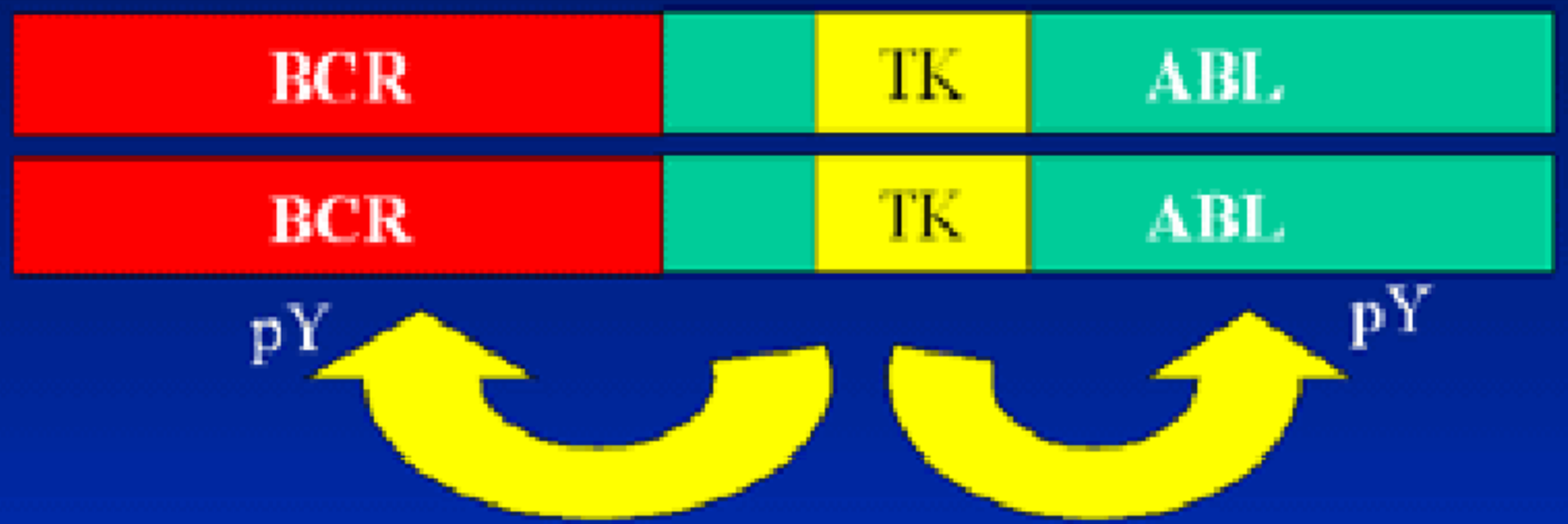

BCR/ABL (210 kDa)
c-BCR
c-ABL
OD
Ser/Thr
kinase
DBL
SH3
SH2
Tyr
kinase
NLS
DNA
BD
actin
BD

- Abl is a tyrosine kinase that requires cytokine stimulation to be activated.
- Conversely, the *bcr* gene contains no kinase activity. When a translocation occurs between chromosome 9 (containing the *abl* gene) and chromosome 22 (containing the *bcr* gene), the fusion product contains Bcr and the kinase domain of Abl. Consequently, active tyrosine kinase and controlled cell division.

Bcr/Abl Functions As A Constitutively Activated Growth Factor Receptor

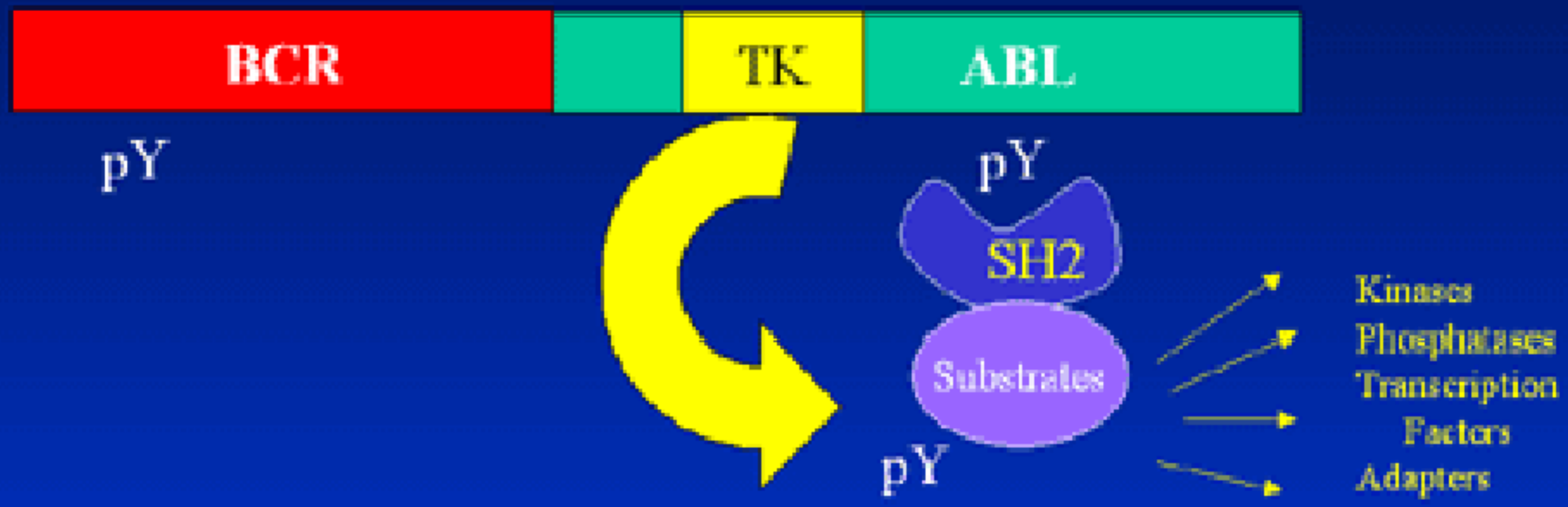


Bcr/Abl



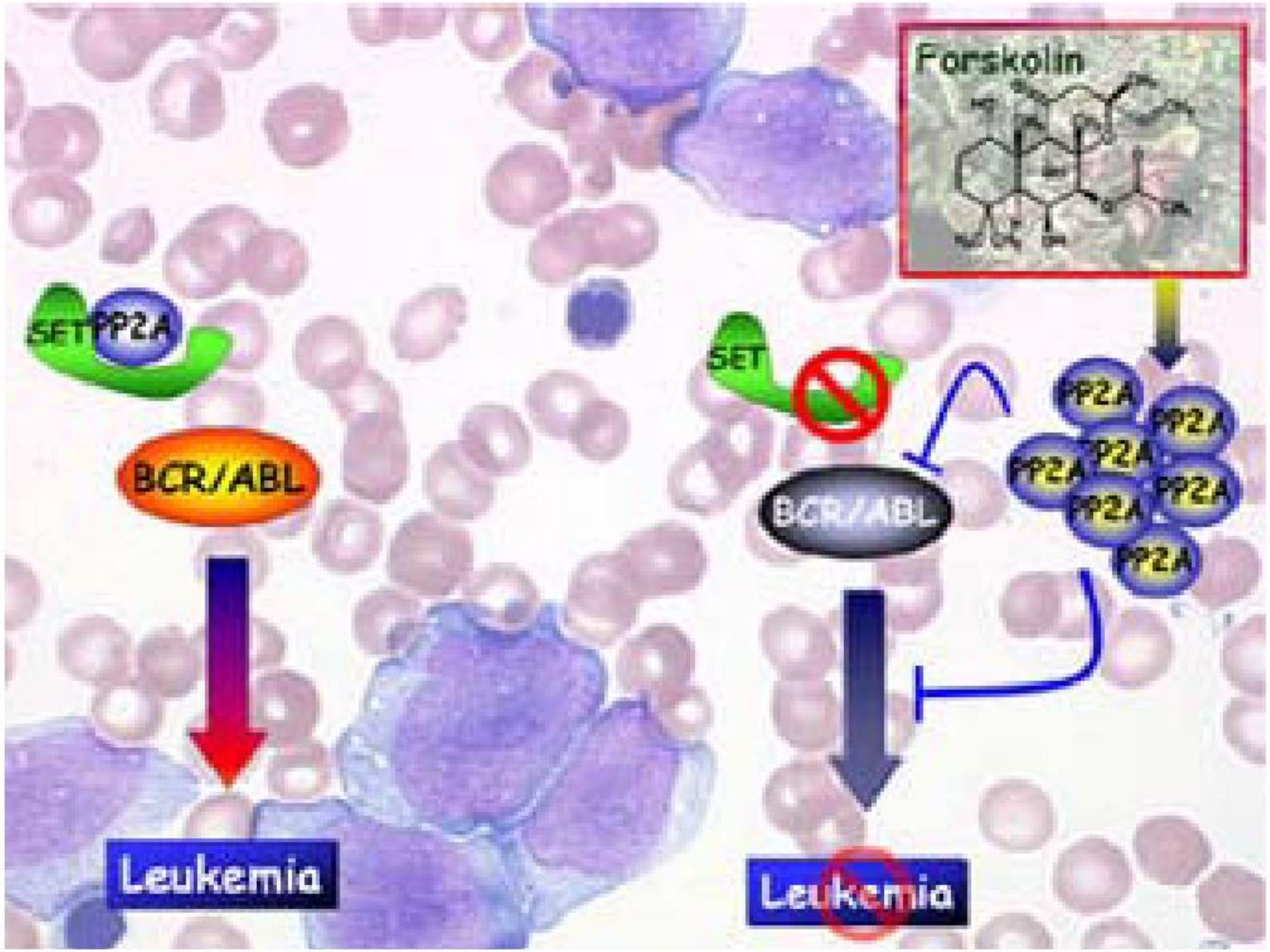
Autophosphorylation
Attraction of substrates through SH2 domains
New substrates brought in through adapters
Signal transduction activated

Bcr/Abl



- Complexes of Signaling Molecules Formed
- Multiple Adapter Molecules Conscripted
- Many Pathways Related to Growth Factor Receptors Activated

- Bcr/Abl Functions as Activated Growth Factor Receptor.
- It also starts the cascade of phosphorylation and other biochemical events, which traverse the cytoplasm, end up in the nucleus, and regulate the key effects on the biology of the cell that are related to intermediate and then distal signaling pathways
- Bcr/Abl induces proliferation, It has important and potent effects in inhibiting apoptosis and promoting viability, and, unfortunately for patients with CML, it also induces genetic instability and leads to disease progression over a period of years.

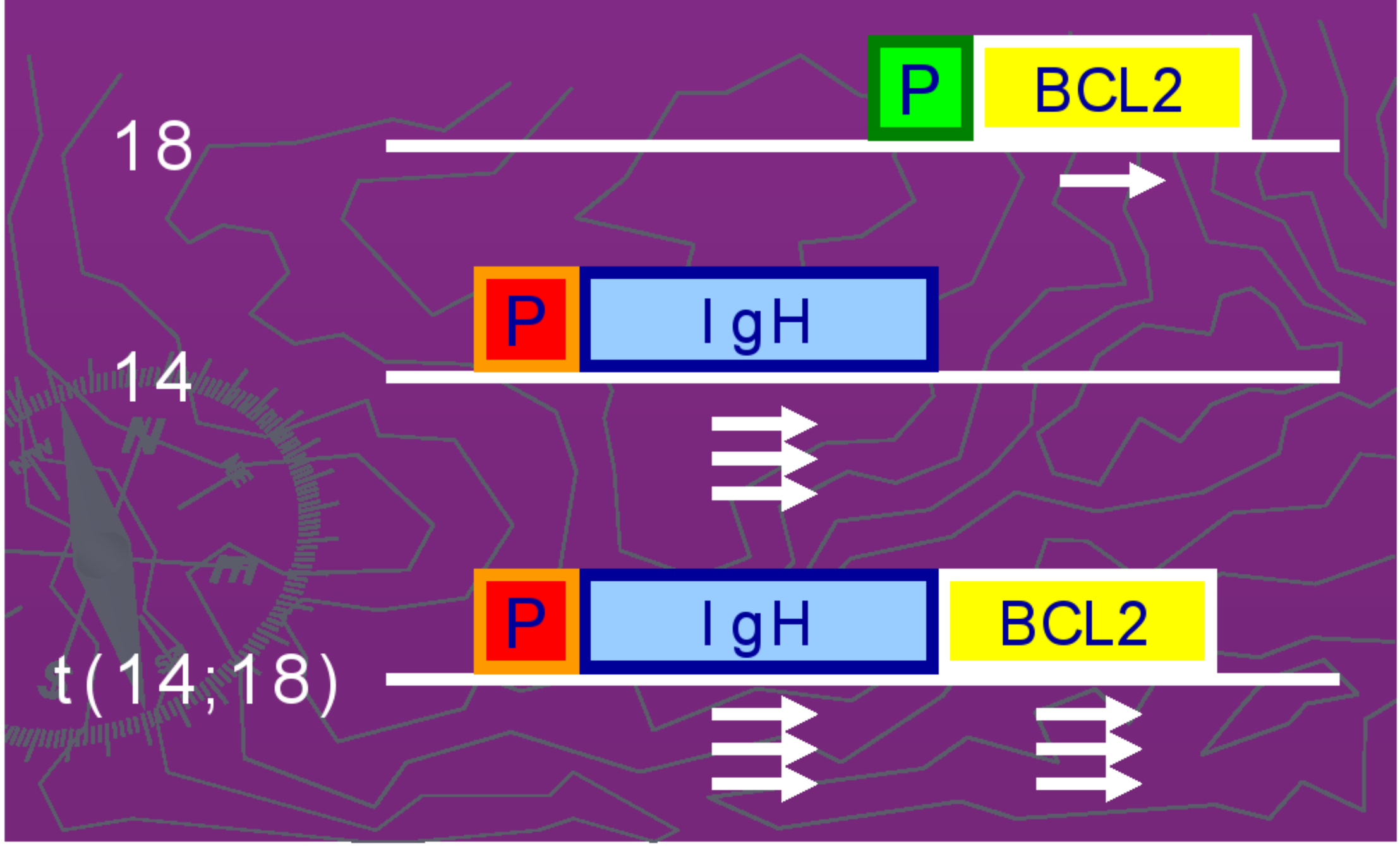

Forskolin
SET
PP2A
BCR/ABL
Leukemia
SET
BCR/ABL
PP2A
PP2A
PP2A
PP2A
PP2A
PP2A
Leukemia

Chromosomal translocations can produce oncogenes in several ways:

- Firstly, fusion proteins
- Secondly, the fusion of one chromosome to another can result in a strong promoter being placed upstream of a gene that would normally be either absent or present only in very low quantities.

t(14;18)

in follicular lymphoma



Protoncogene

- Virus integration
- Mutations
- Gene amplification
- Chromosomal translocations

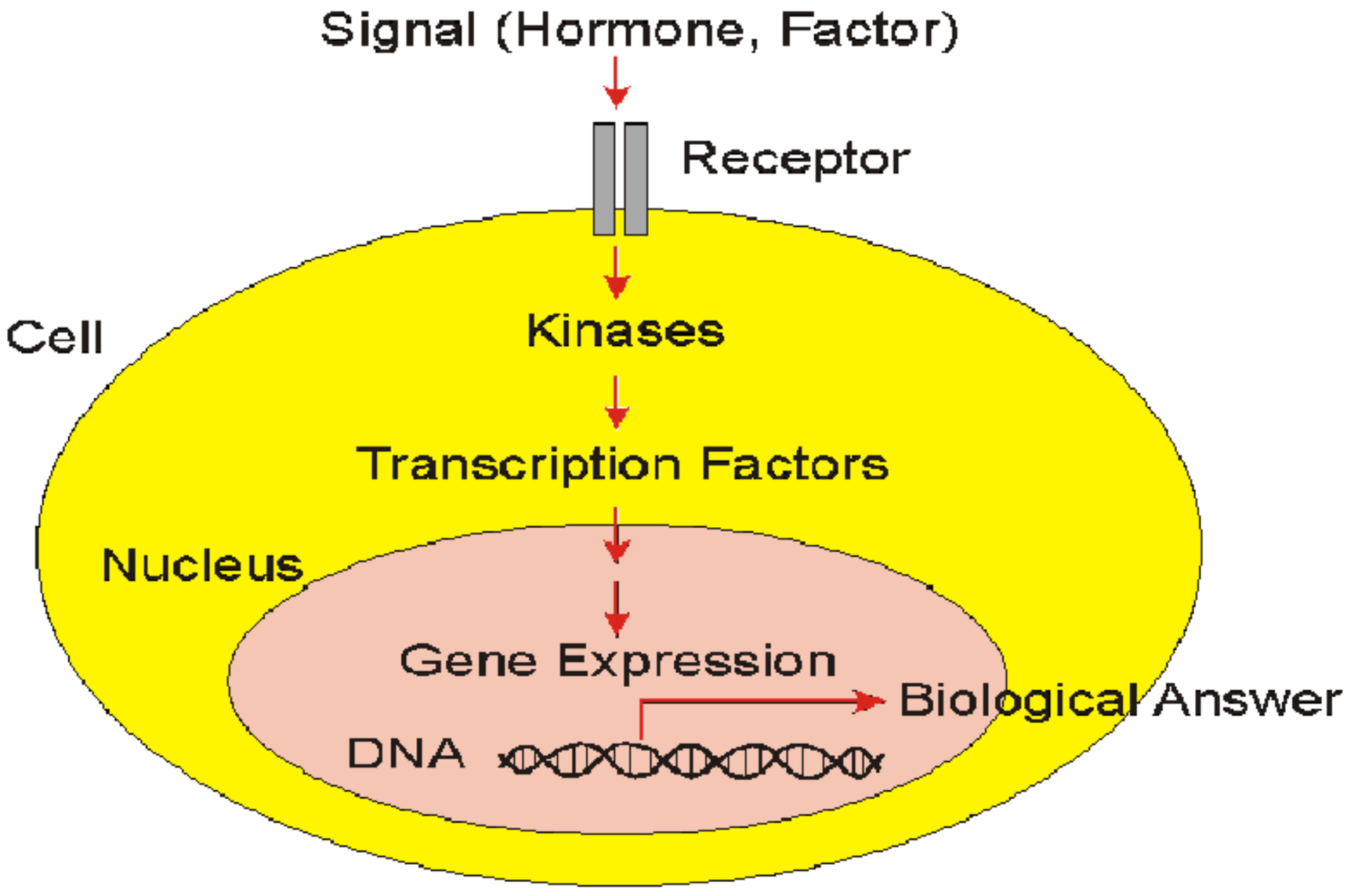
Oncogene

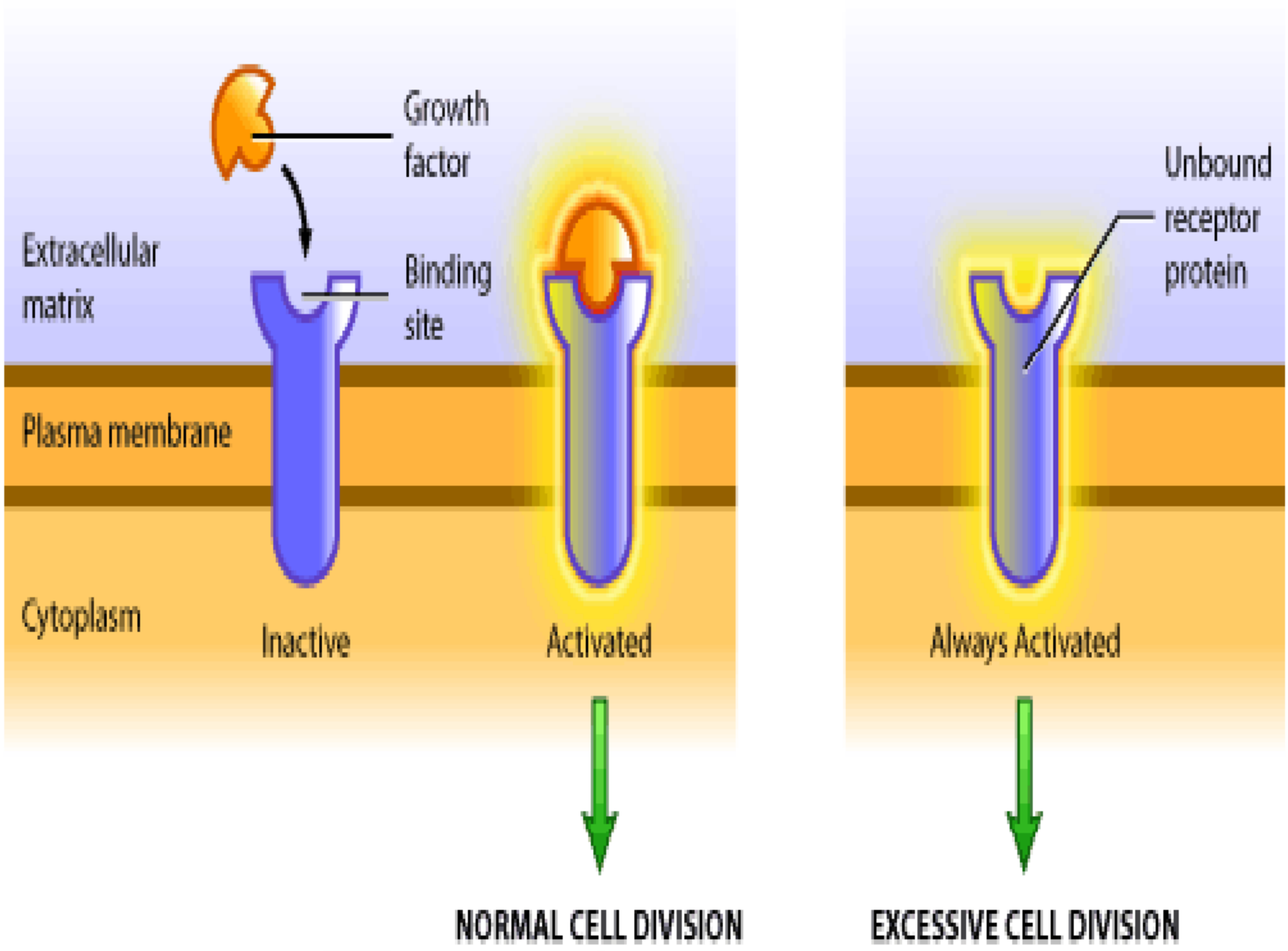
Tumor

- Abnormal signal transduction
- Cell cycle dysregulation
- Inhibition of apoptosis

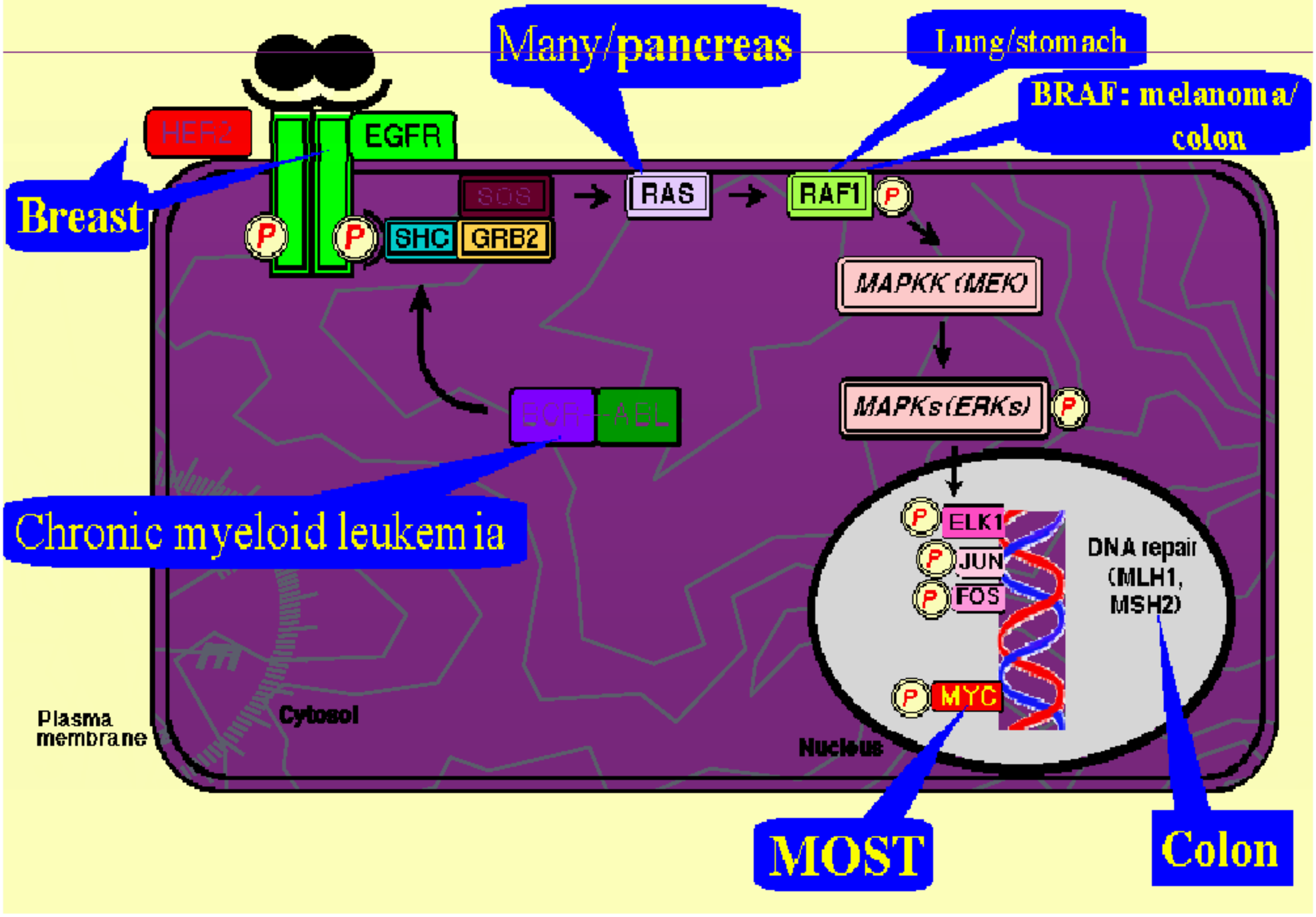
1. Signal transduction

- It Is a carefully regulated event, requiring the activation of one protein to activate another.




Growth factor
Extracellular matrix
Binding site
Plasma membrane
Cytoplasm
Inactive
Activated
Unbound receptor protein
Always Activated
NORMAL CELL DIVISION
EXCESSIVE CELL DIVISION

ONCOGENE/CANCER ASSOCIATIONS



- The oncogenic form of *egfr* produces a receptor that does not require binding of growth factor, but instead is constitutively active (In this way the oncogene product is capable of always activating the pro-growth pathway in the absence of pro-growth signals.

- The activated EGF-R dimer complexes with the adapter protein, Grb, coupled to SOS. The Grb-SOS complex can These protein interactions bring SOS in close proximity to Ras, allowing for Ras activation This subsequently activates transcription factors, such as c-fos, AP-1, and, that promote gene expression and contribute to cell proliferation.

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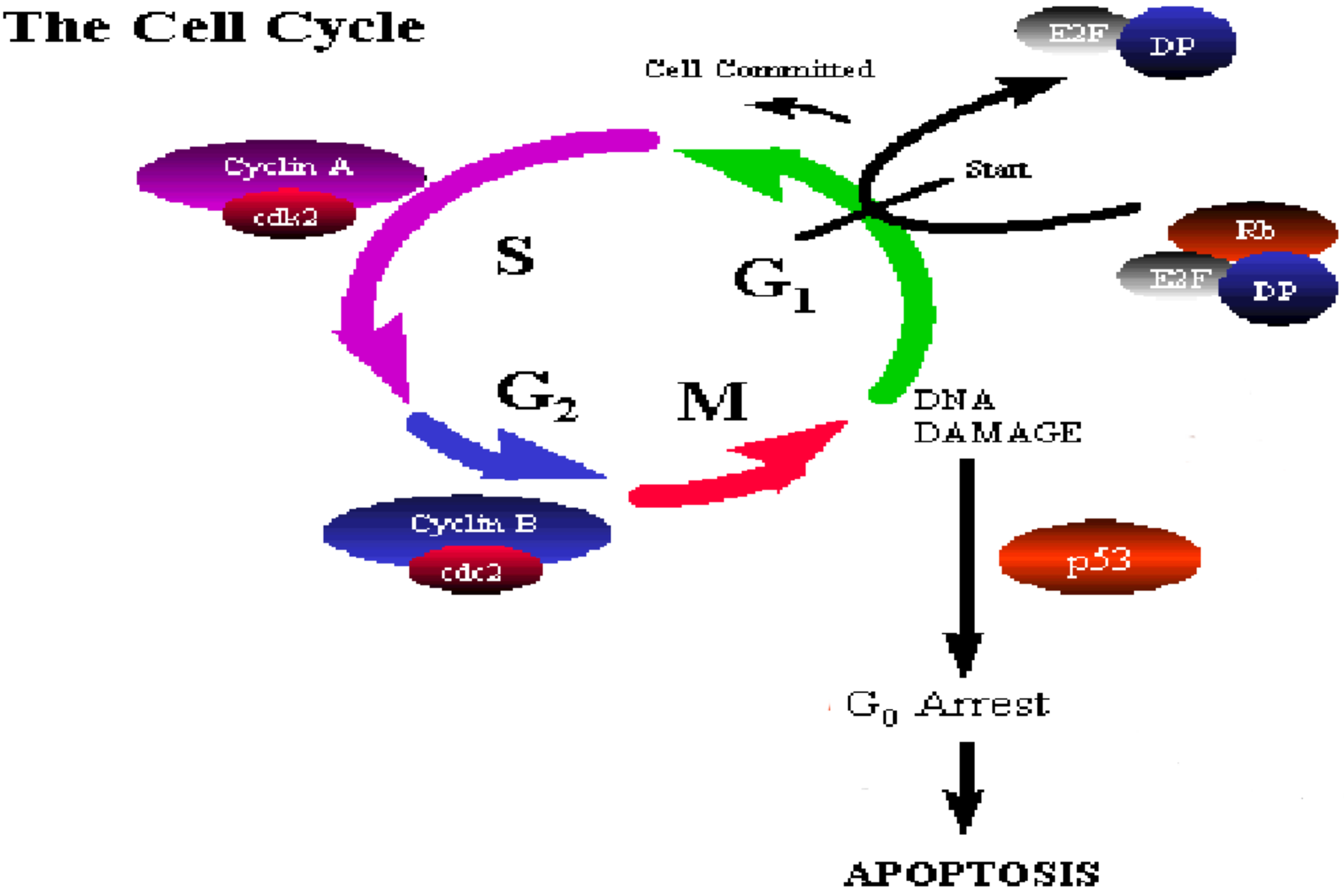
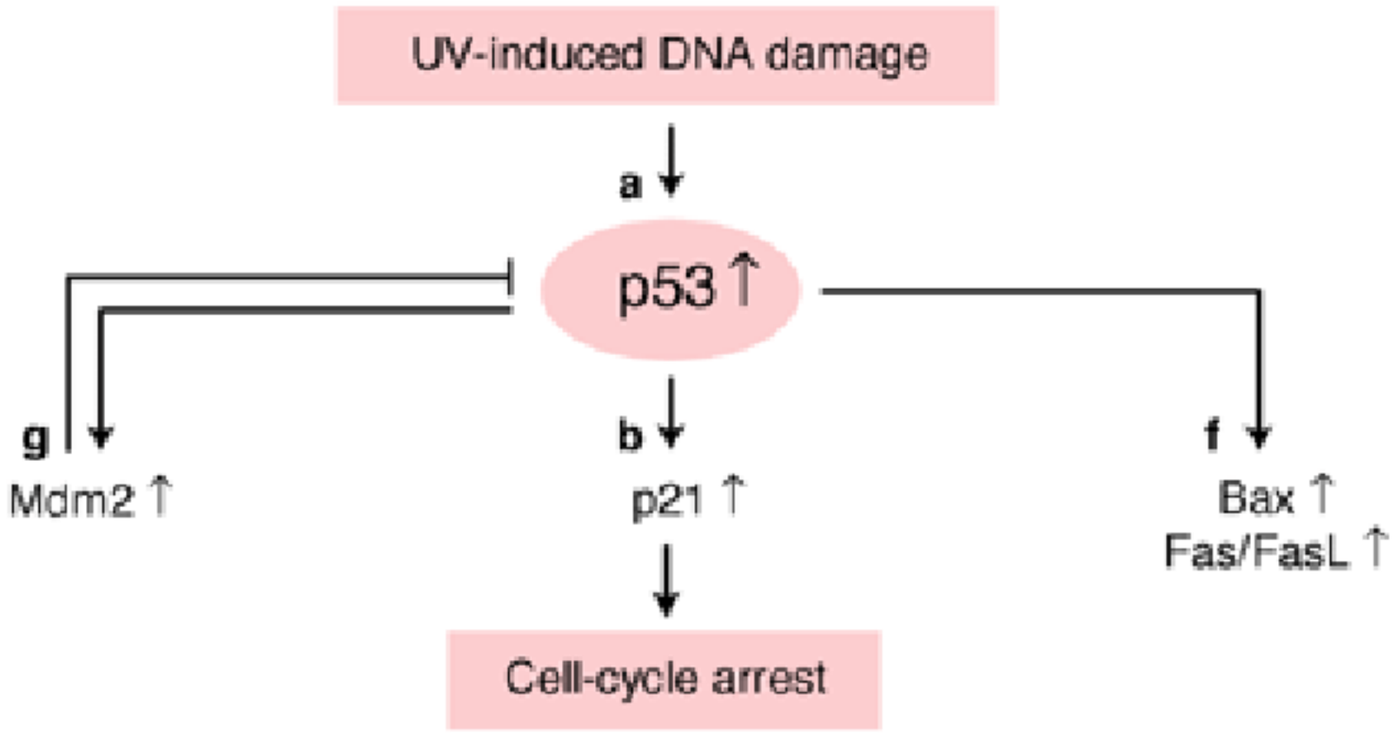
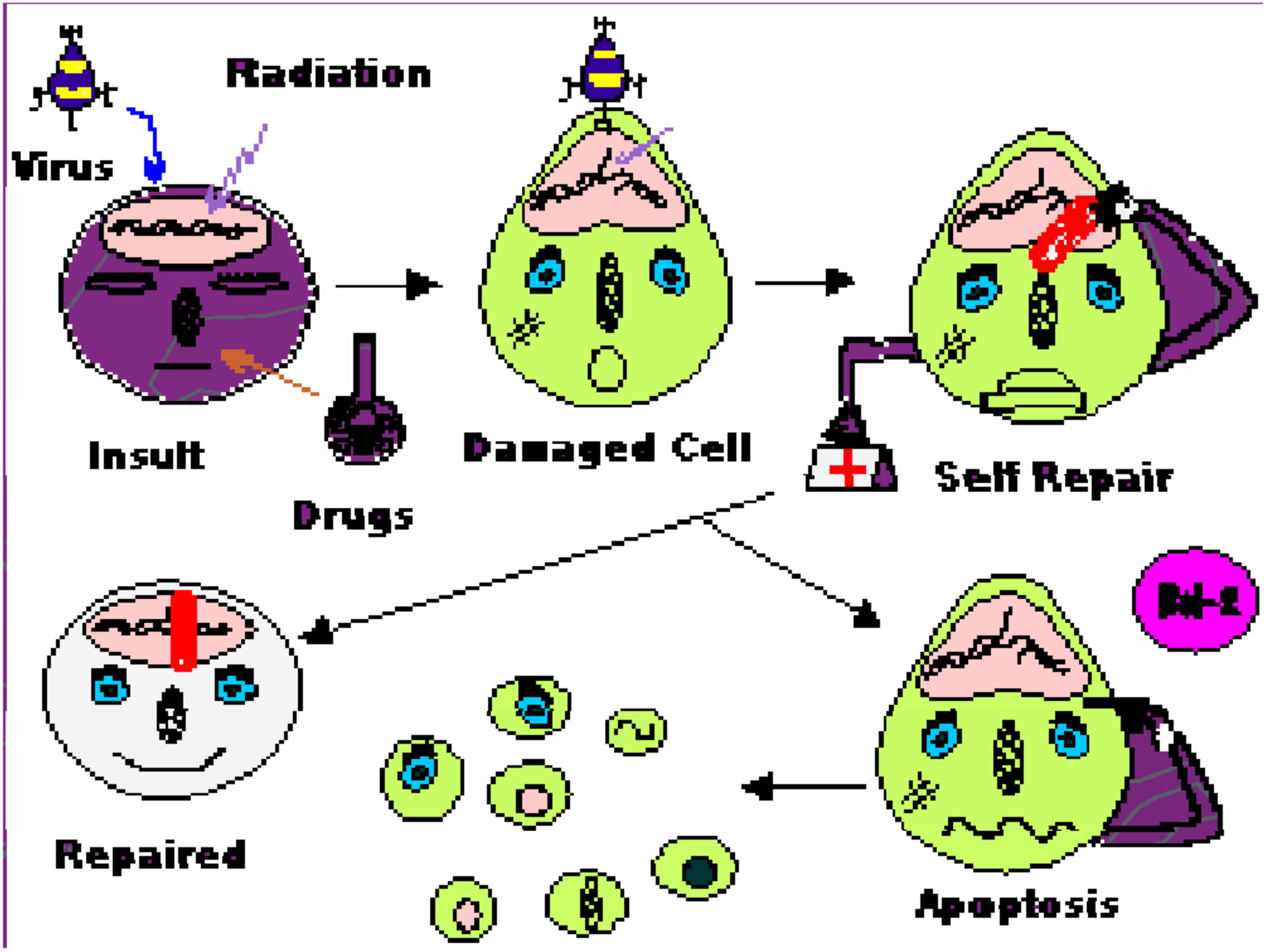
The Cell Cycle





The central role of p53 in cell-cycle arrest, DNA repair and apoptosis following UV irradiation


Radiation
Virus
Insult
Damaged Cell
Self Repair
Drugs
Repaired
Apoptosis

mutant p53

X-Ray

DNA repair

DNA damage → failure to P53

cell can replicate

with damaged DNA

more mutations

accumulate

cancerous cell

P53

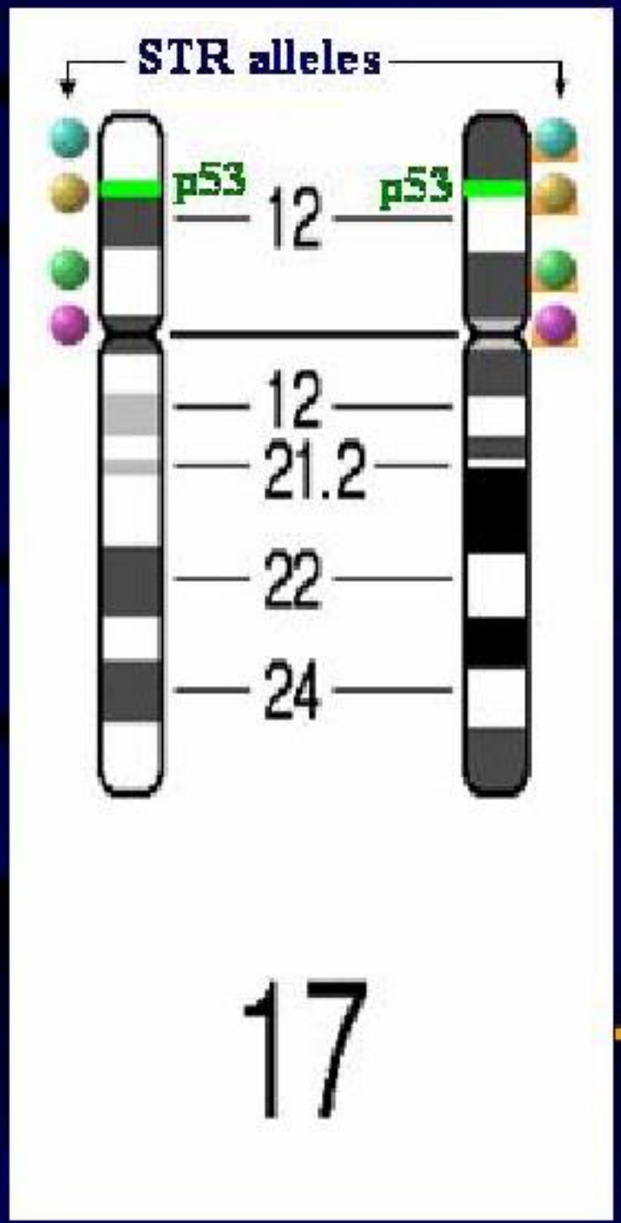
- The active p53 protein is a transcriptional regulator that is activated in response to DNA damage. Activated wild-type p53 serves double duty, preventing progression of the cell cycle until the DNA damage is repaired and, under some circumstances, inducing apoptosis.
- In the absence of a functional *p53* gene, the p53 apoptosis pathway does not become activated, and the cell cycle progresses even in the absence of DNA repair. This progression elevates the overall frequency of mutations,

▶Rb gene

In retinoblastoma, the gene encoding the Rb protein, considered in the regulation of the cell cycle, is mutated.

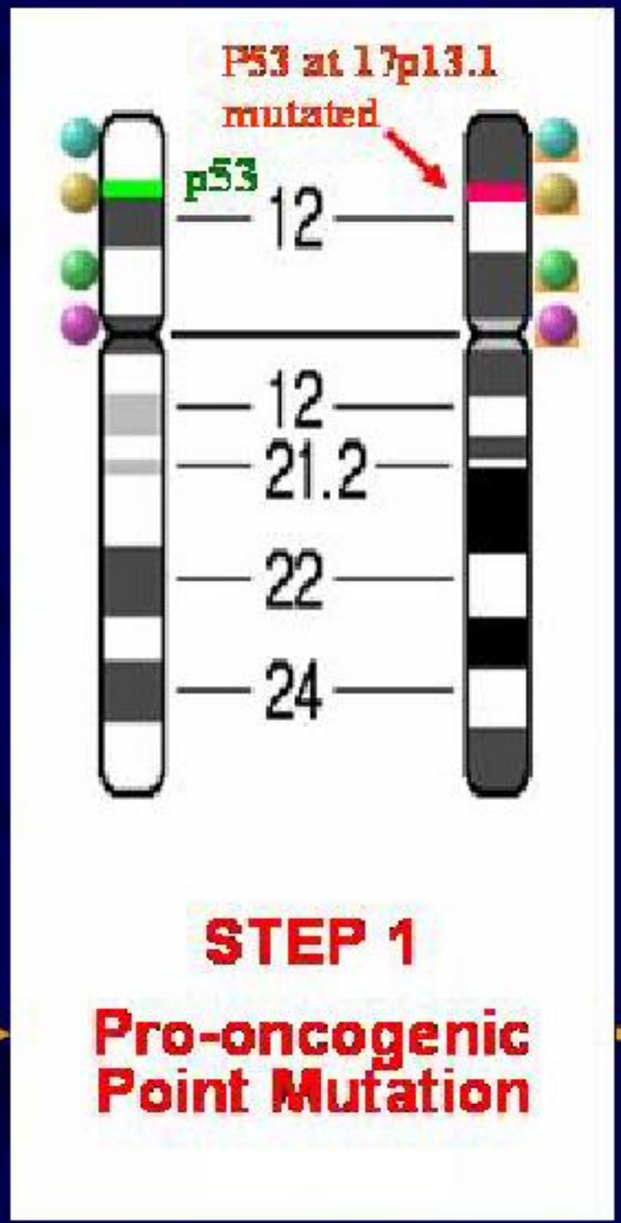
- Loss of heterozygosity !!

LOH in Knudson's "Double-Hit" Tumorigenesis Model



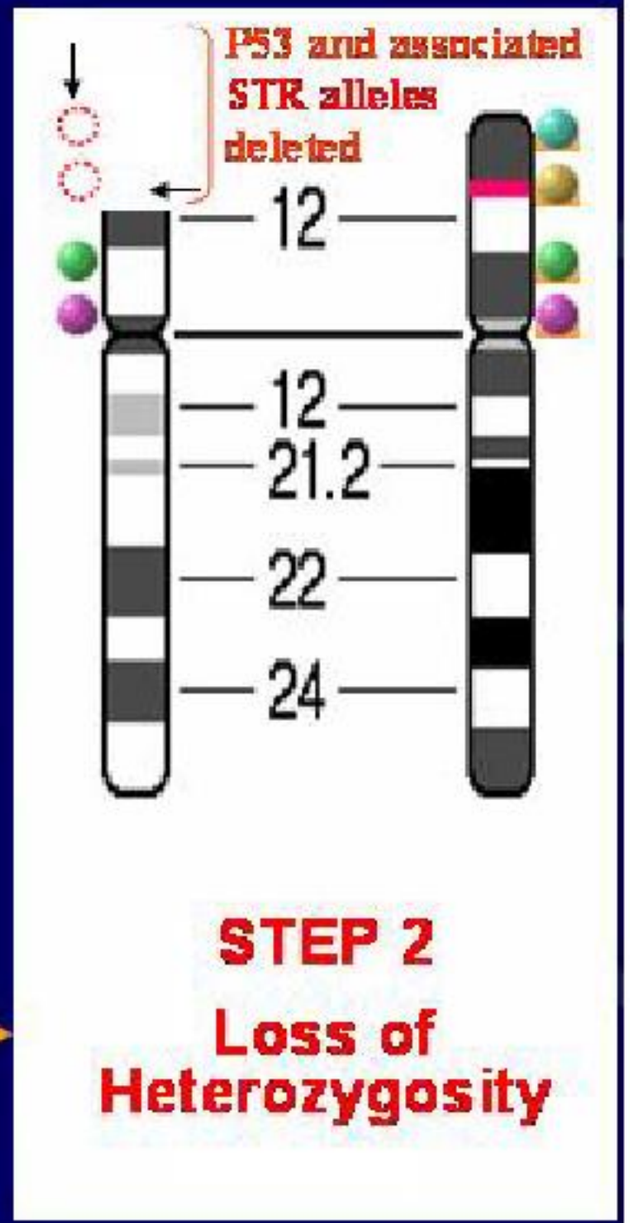
STEP 1

Pro-oncogenic Point Mutation



STEP 2

Loss of Heterozygosity



Li-Fraumeni Syndrome: germline p53 mutation

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Oncogene

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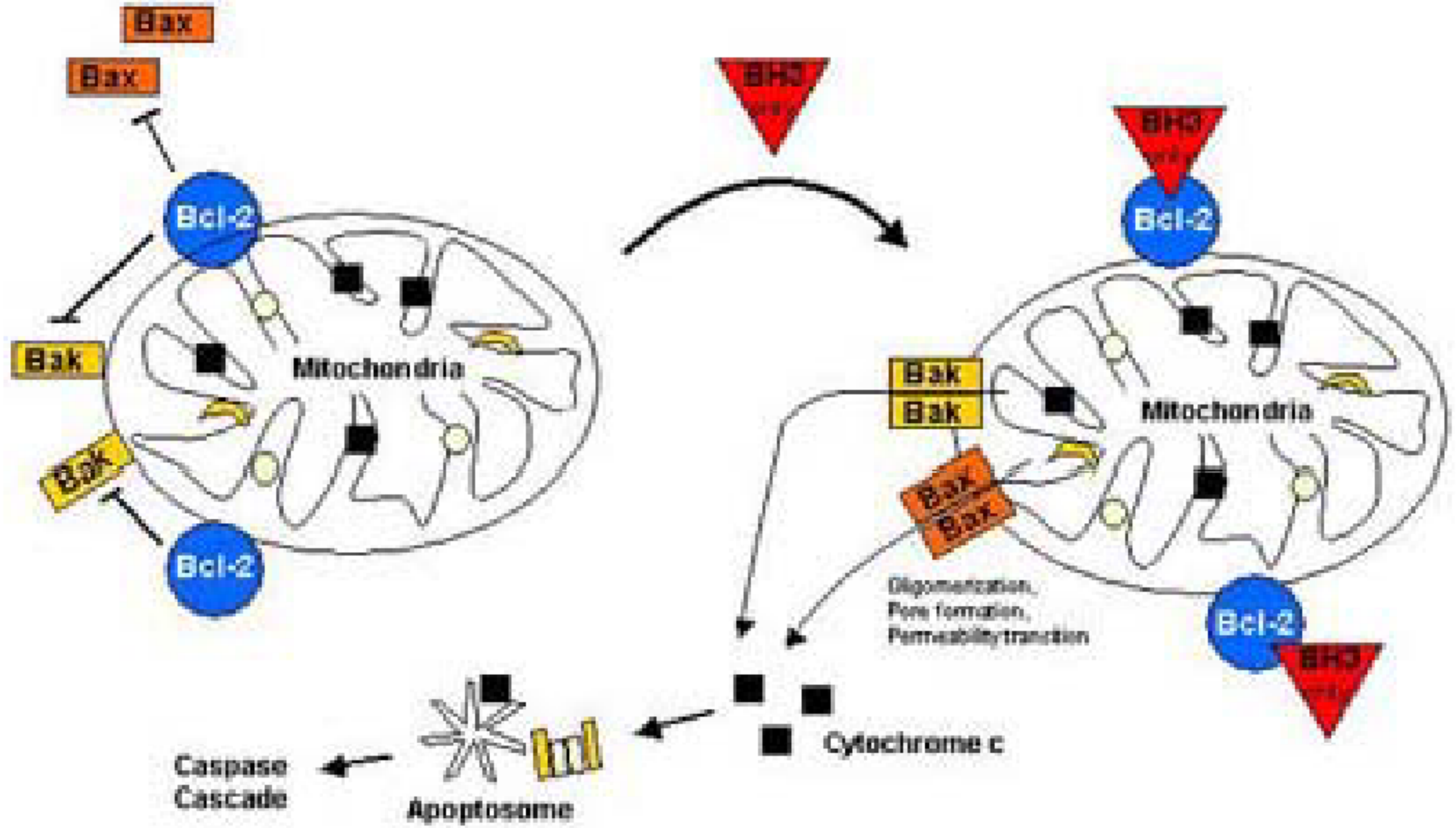
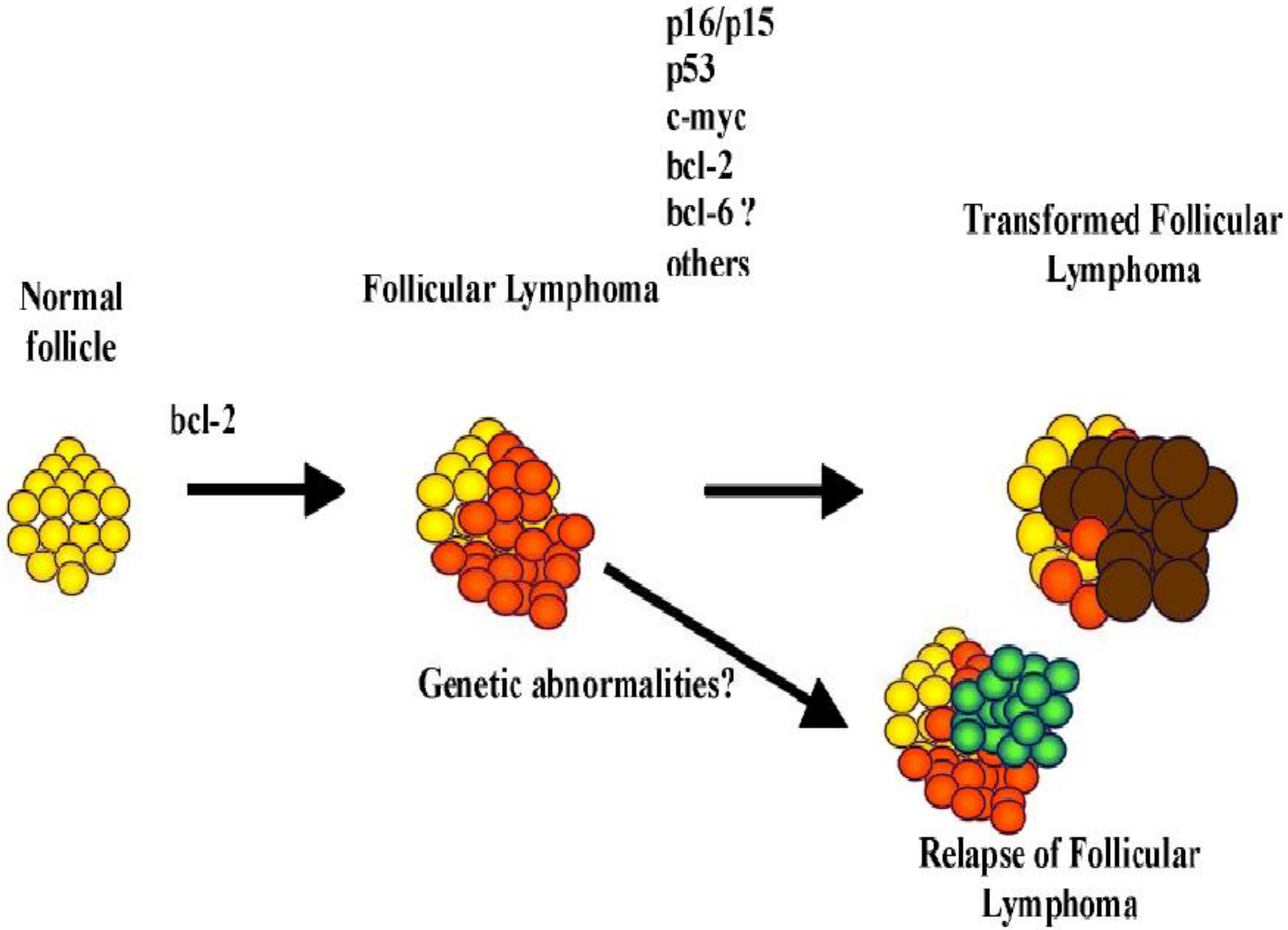
Inhibition of Apoptosis



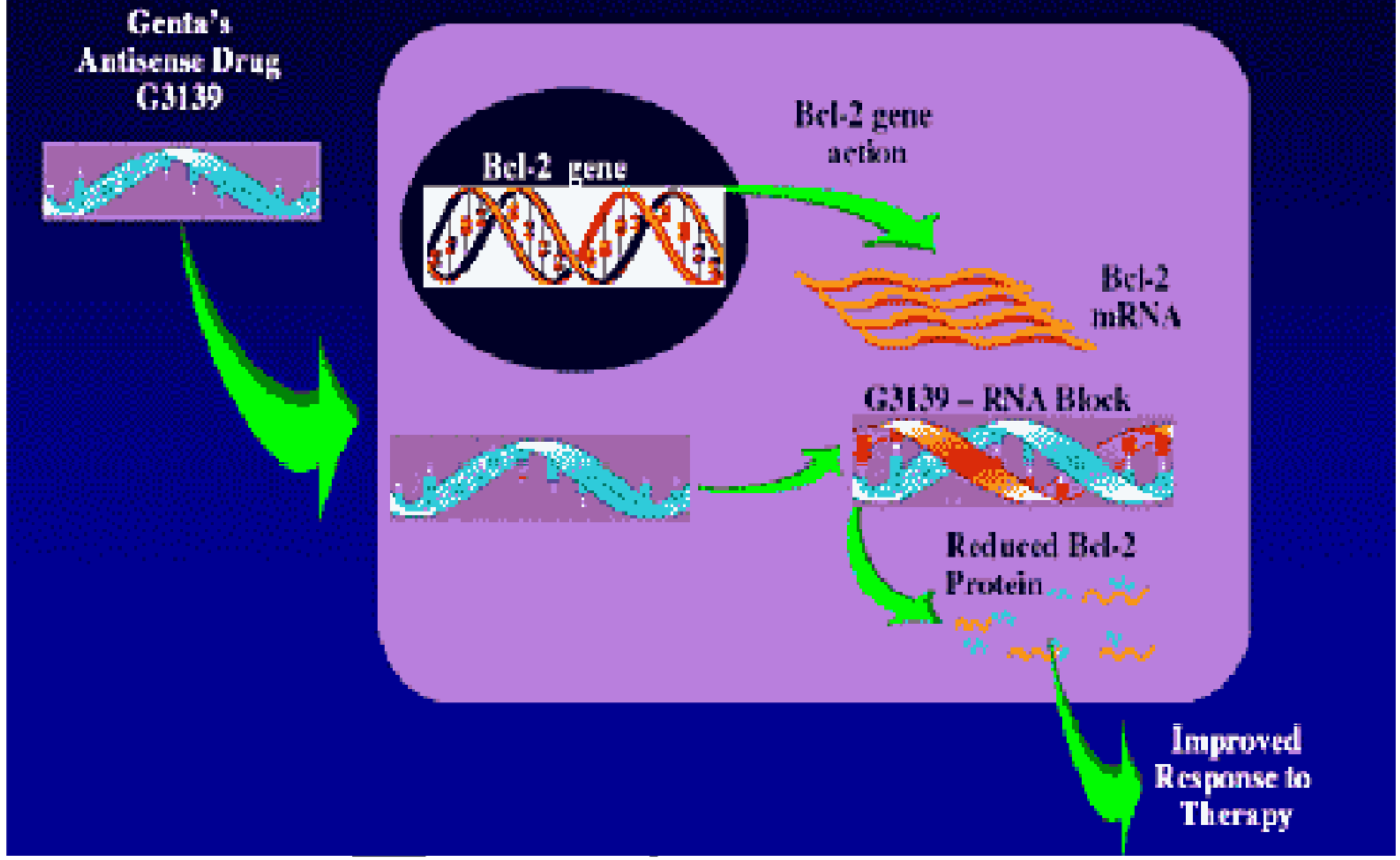
Mode of Action of BCL2

Cell survives

Apoptosis


p16/p15
p53
c-myc
bcl-2
bcl-6 ?
others
Normal follicle
bcl-2
Follicular Lymphoma
Transformed Follicular Lymphoma
Genetic abnormalities?
Relapse of Follicular Lymphoma

Genta's Antisense G3139 Blocks Bcl-2



Protoncogenes lead to cancer within these pathways.

- Signal transduction: includes
  - over-production of a growth factor
  - constitutively active receptors
  - intermediary molecules
- Apoptosis: by increased expression of proteins that inhibit apoptosis.
- Cell cycle regulation: by loss of tumor supressor gene

SUMMARY

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Tumor

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- Inhibition of apoptosis


THANK YOU