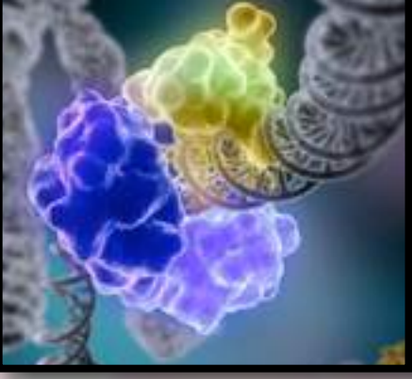
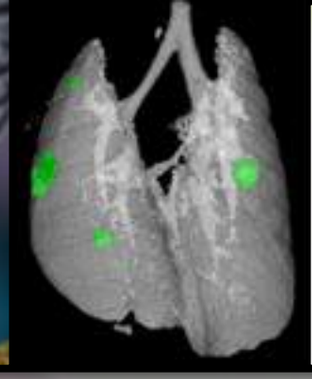

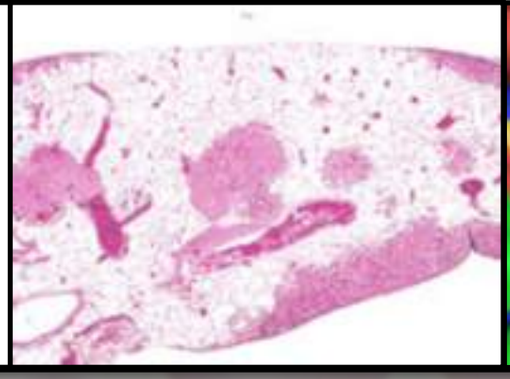
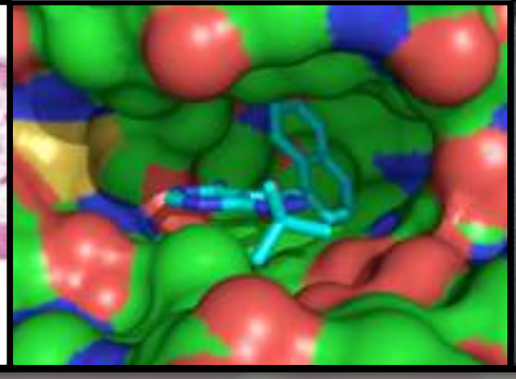

# (Oncogenic) signaling networks and signal transduction

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Medical Clinic I, Hematology/Oncology
CECAD, Research Area C
Clinical and Molecular Oncology

# Oncogenic signaling

- Regulation of the normal cell cycle

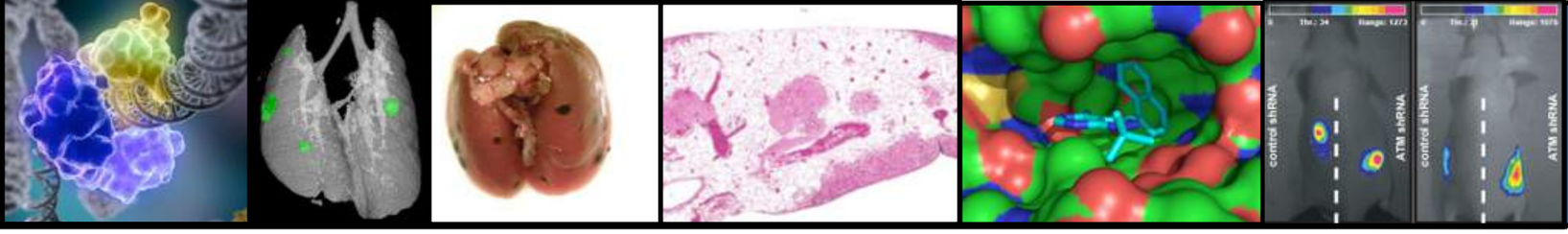
- Cell cycle checkpoints

- Oncogenes are activated by different mechanisms

- Tumor suppressor genes are inactivated by different mechanisms

- Loss of heterozygosity can be achieved by multiple mechanisms

- Oncogenic events cooperate to drive tumorigenesis

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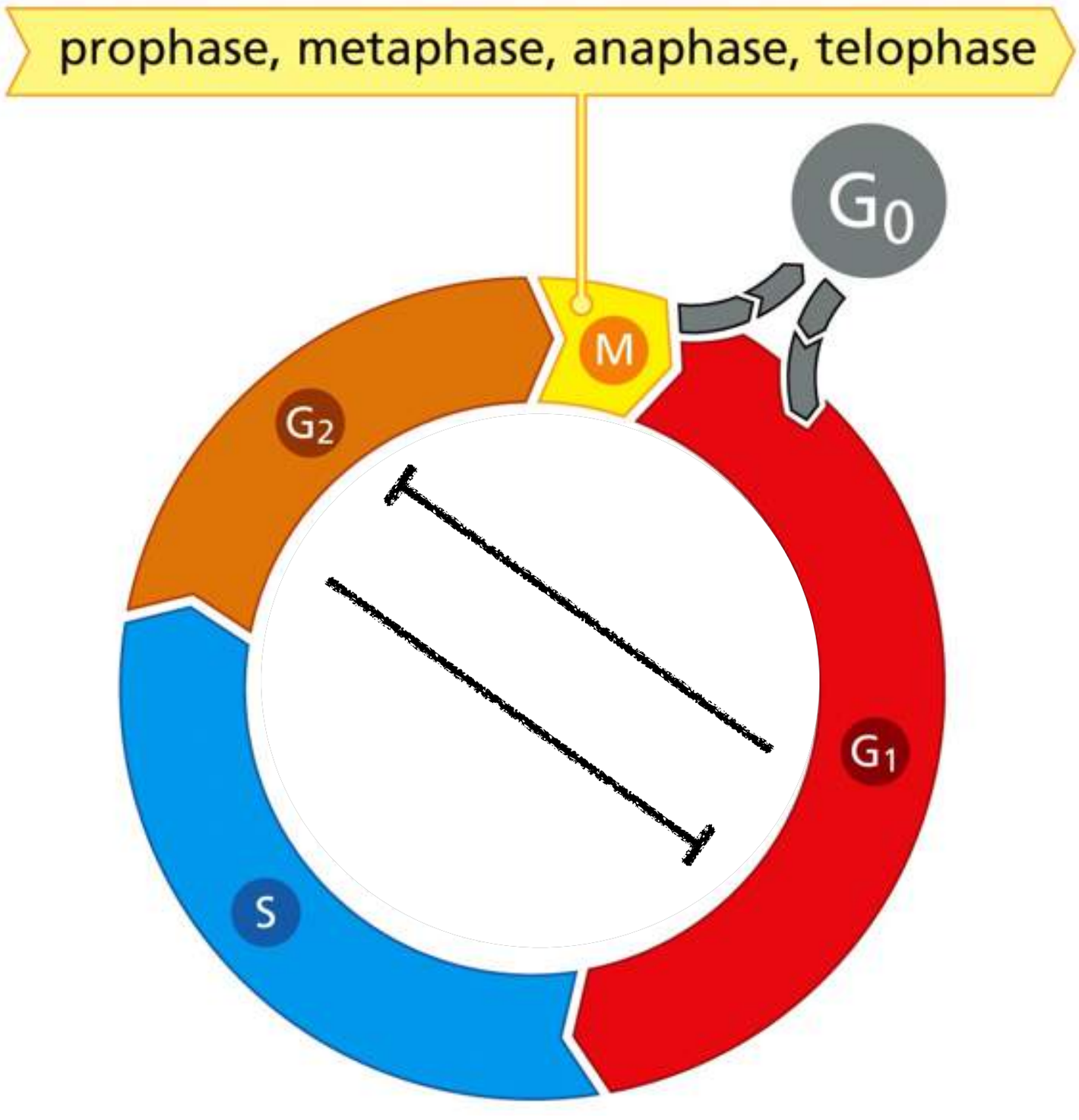
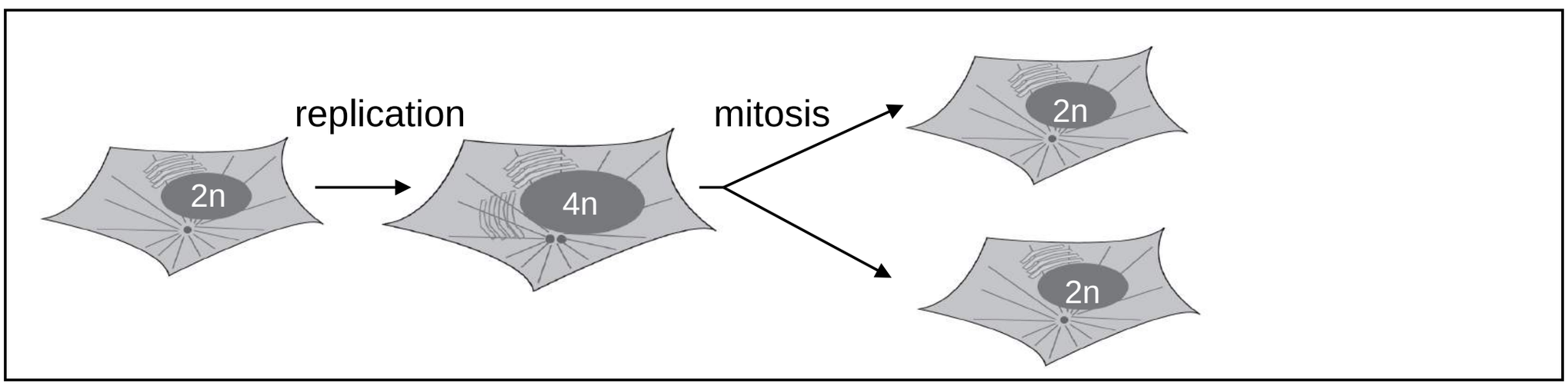
# Malignant transformation

# The eukaryotic cell cycle is subdivided into distinct phases

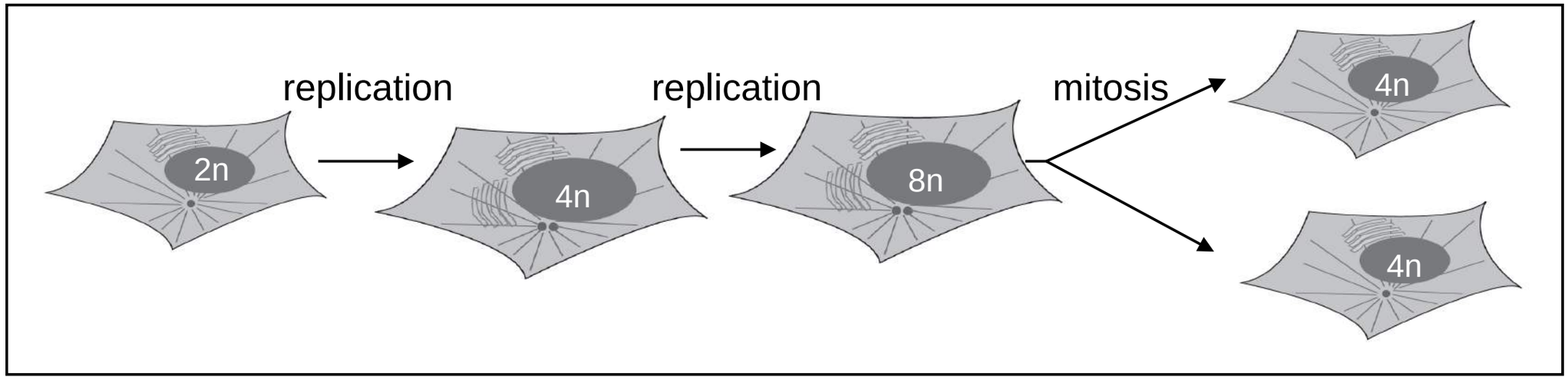


# Cell cycle progression has to be strictly regulated

ideal




aberrant

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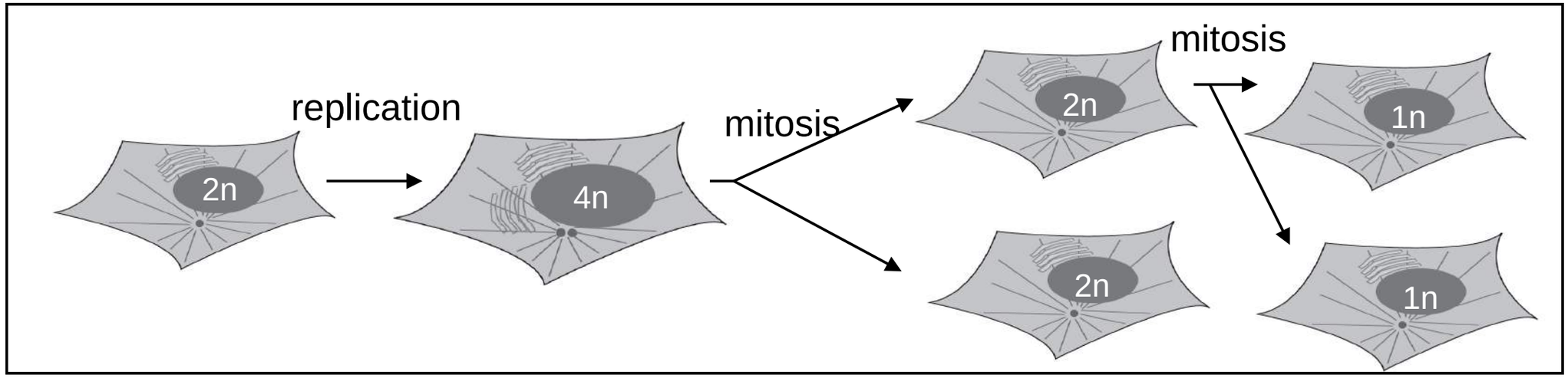
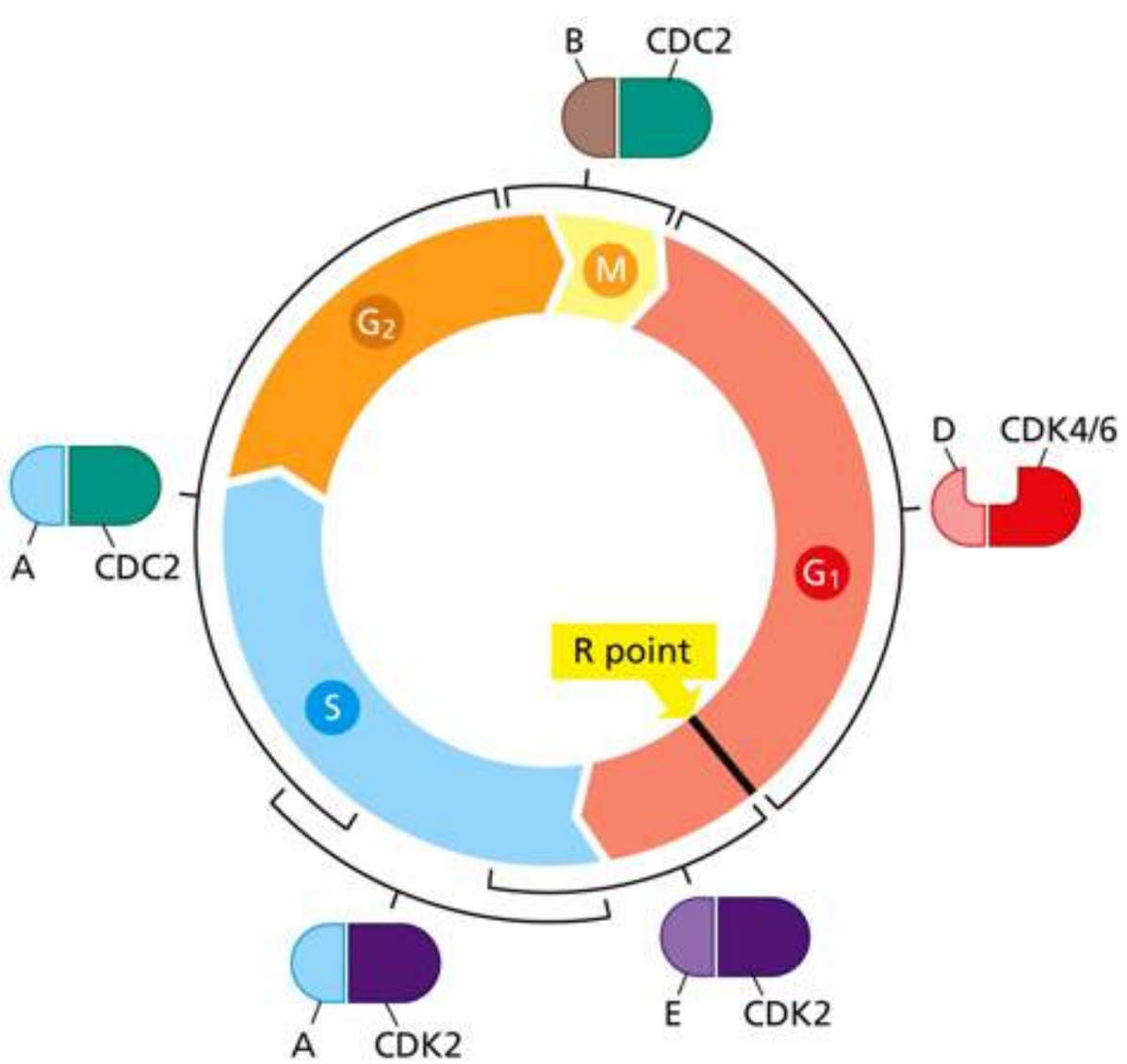
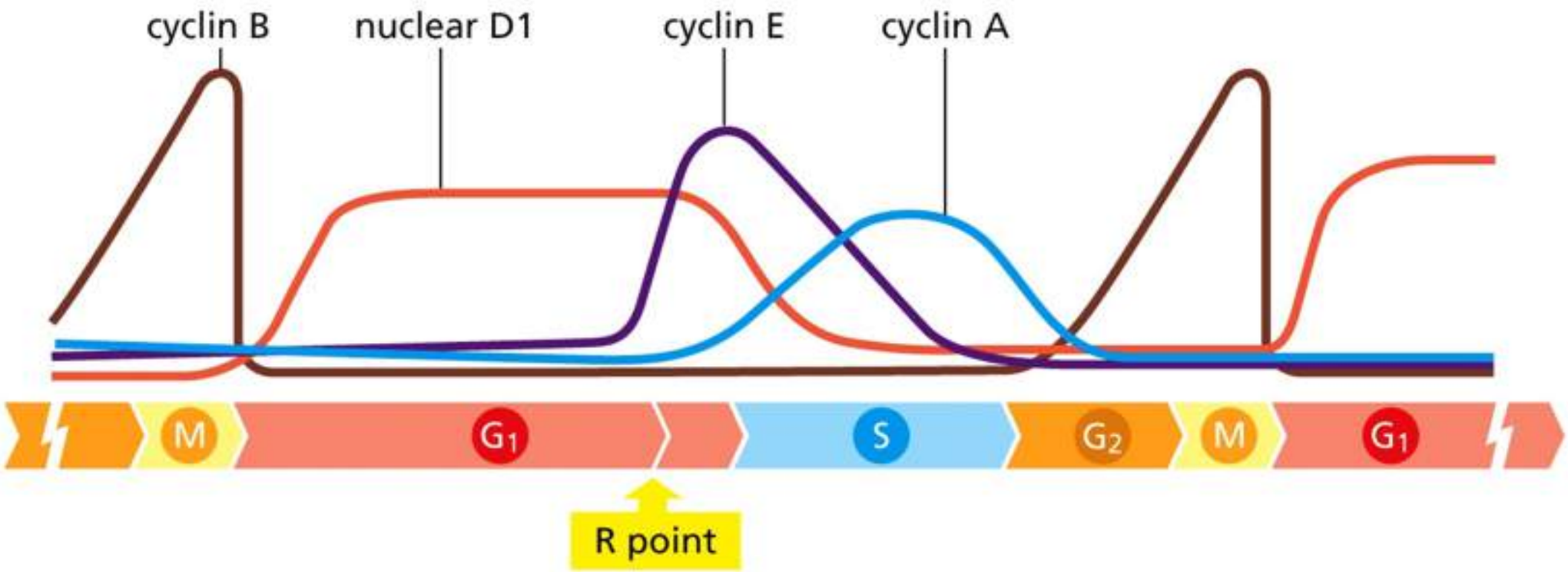
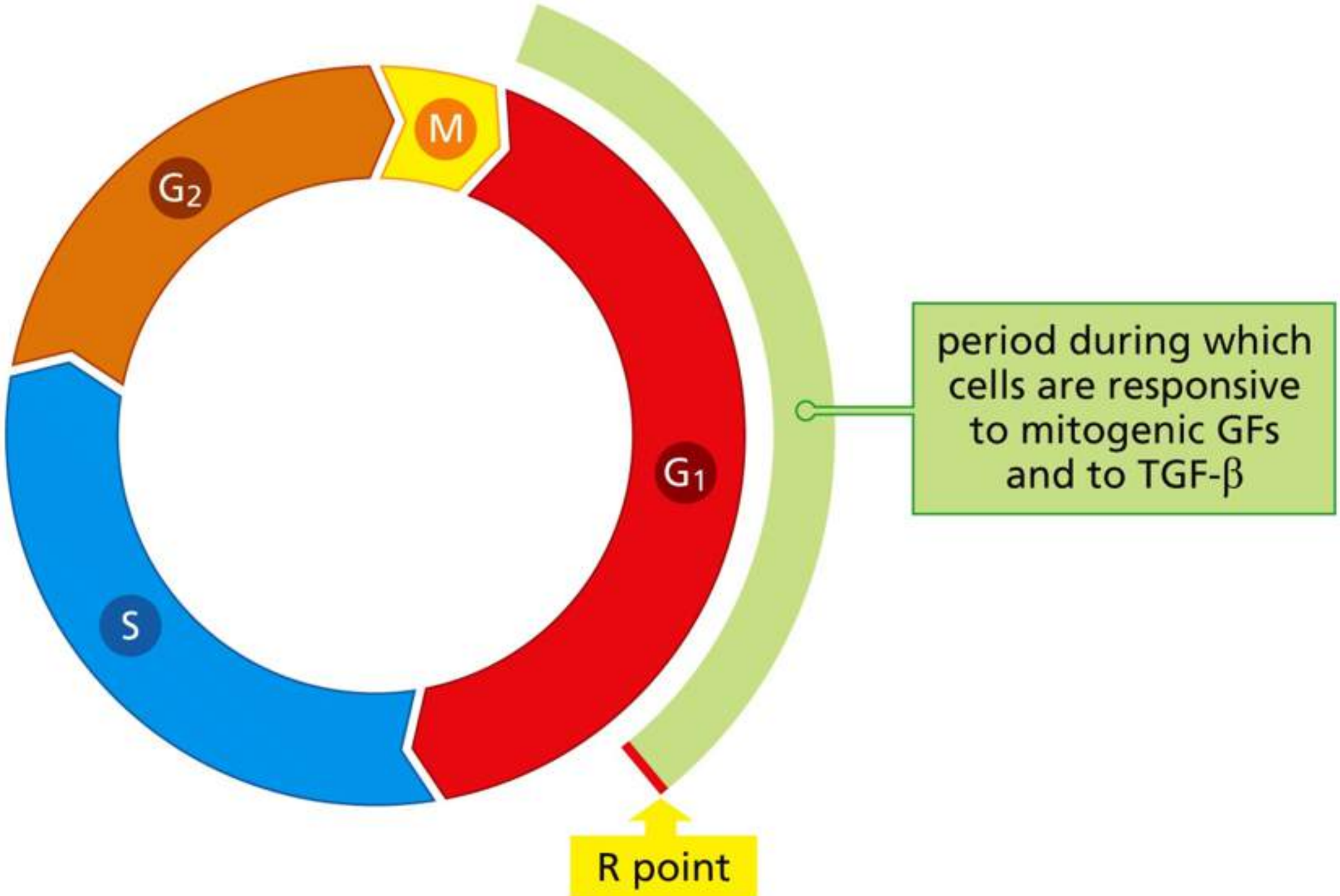


# The mammalian cell cycle is driven by cyclin-dependent kinases (CDKs)

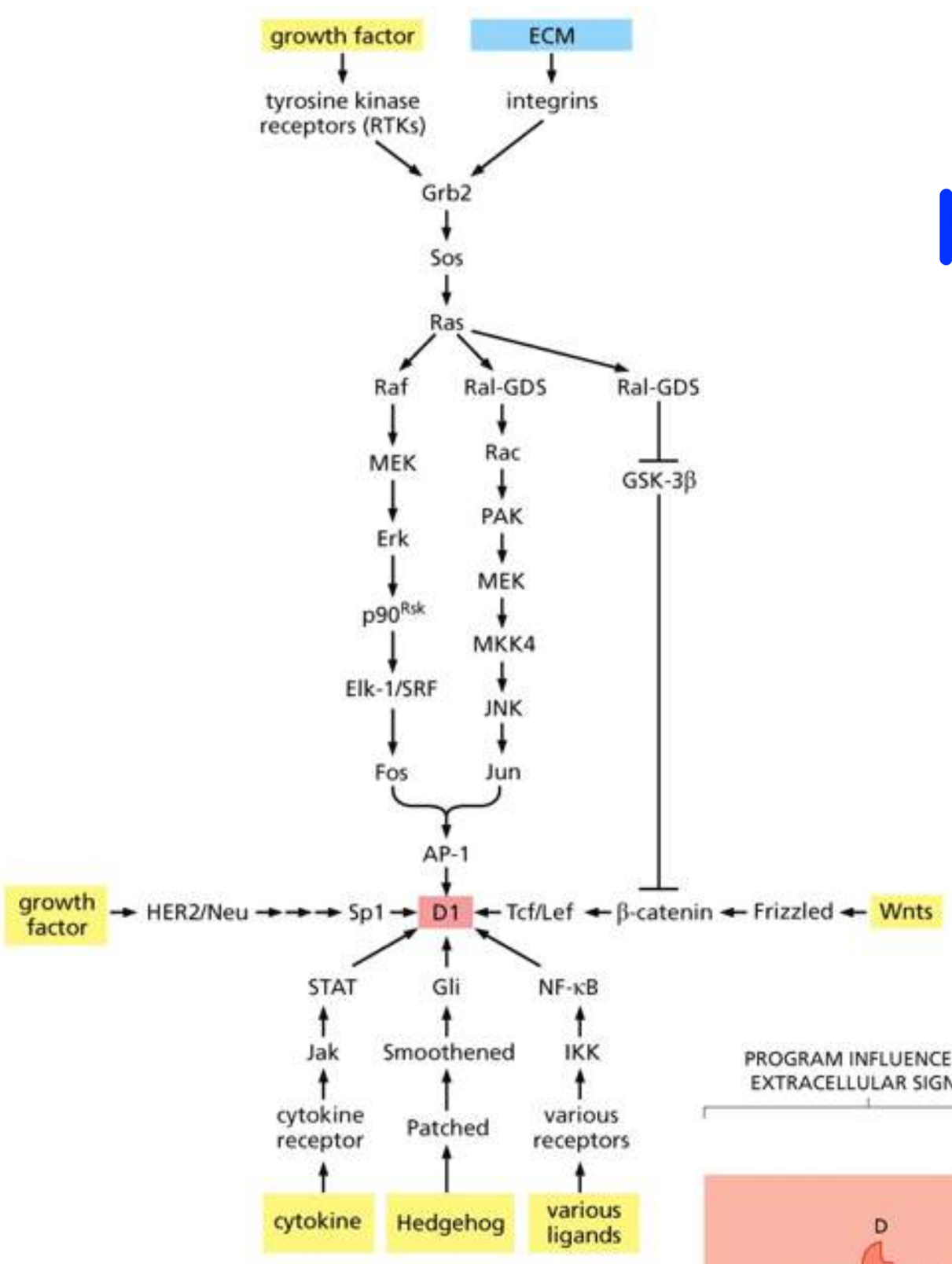


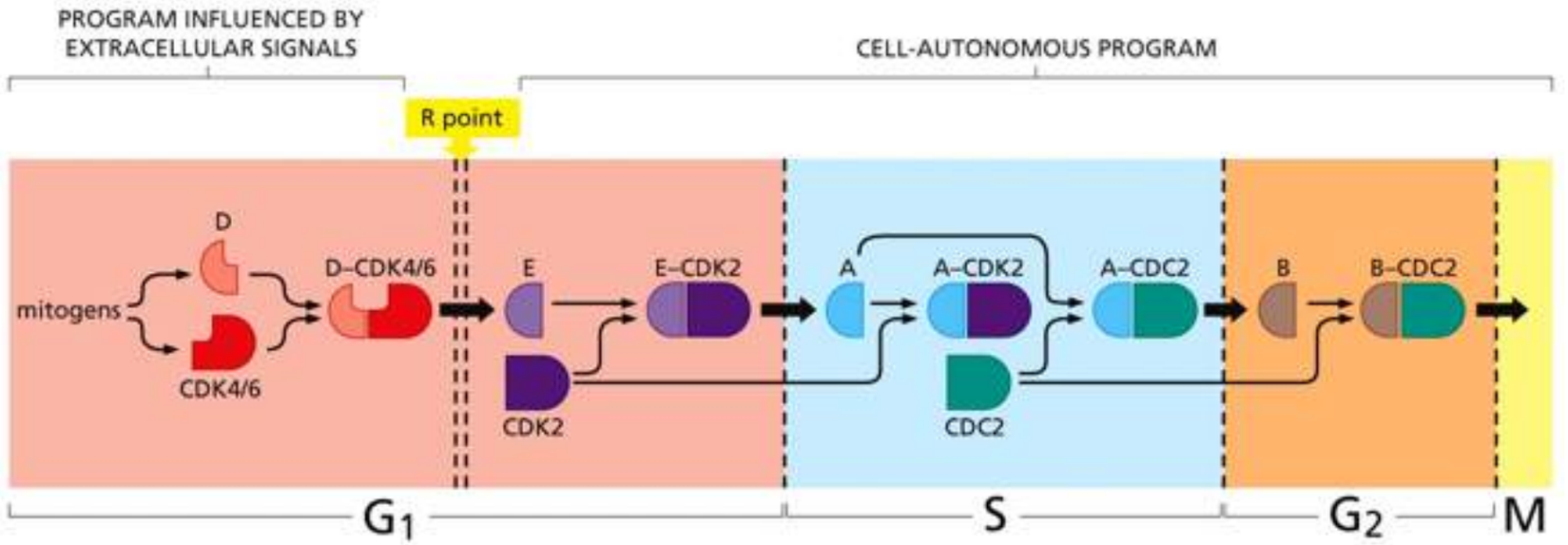



# Mammalian cells are responsive to growth signals only during the $G_1$ phase



# Numerous pro-proliferative pathways converge on cyclin D synthesis

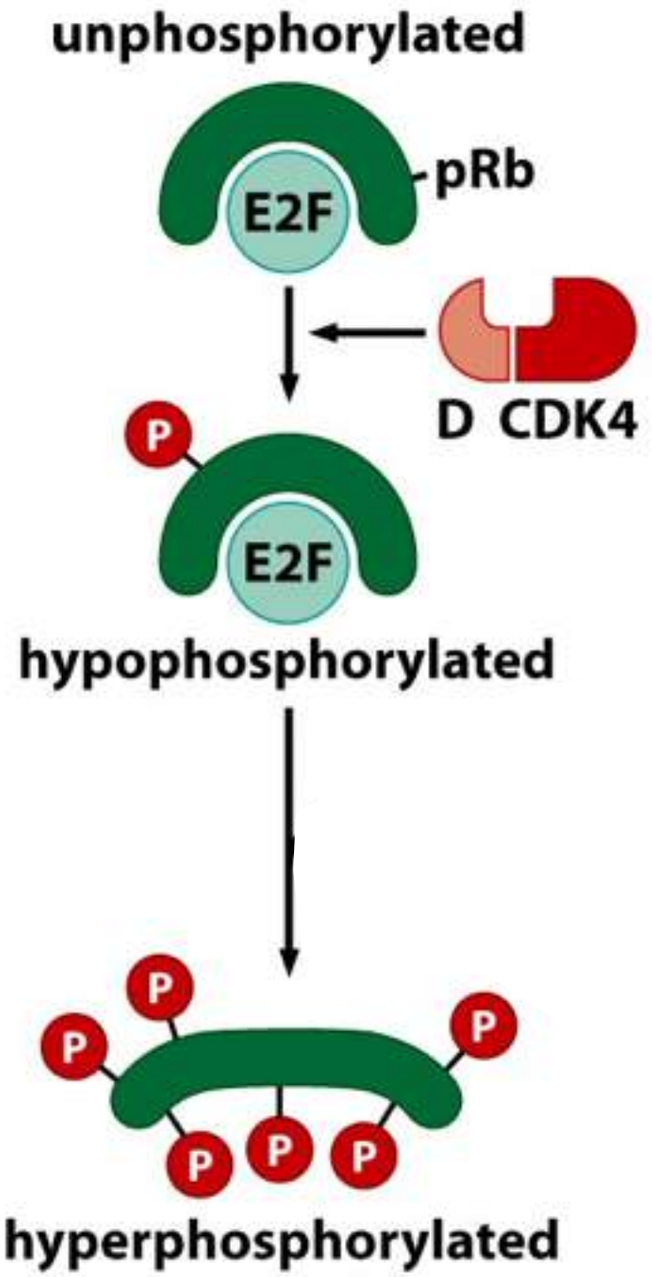


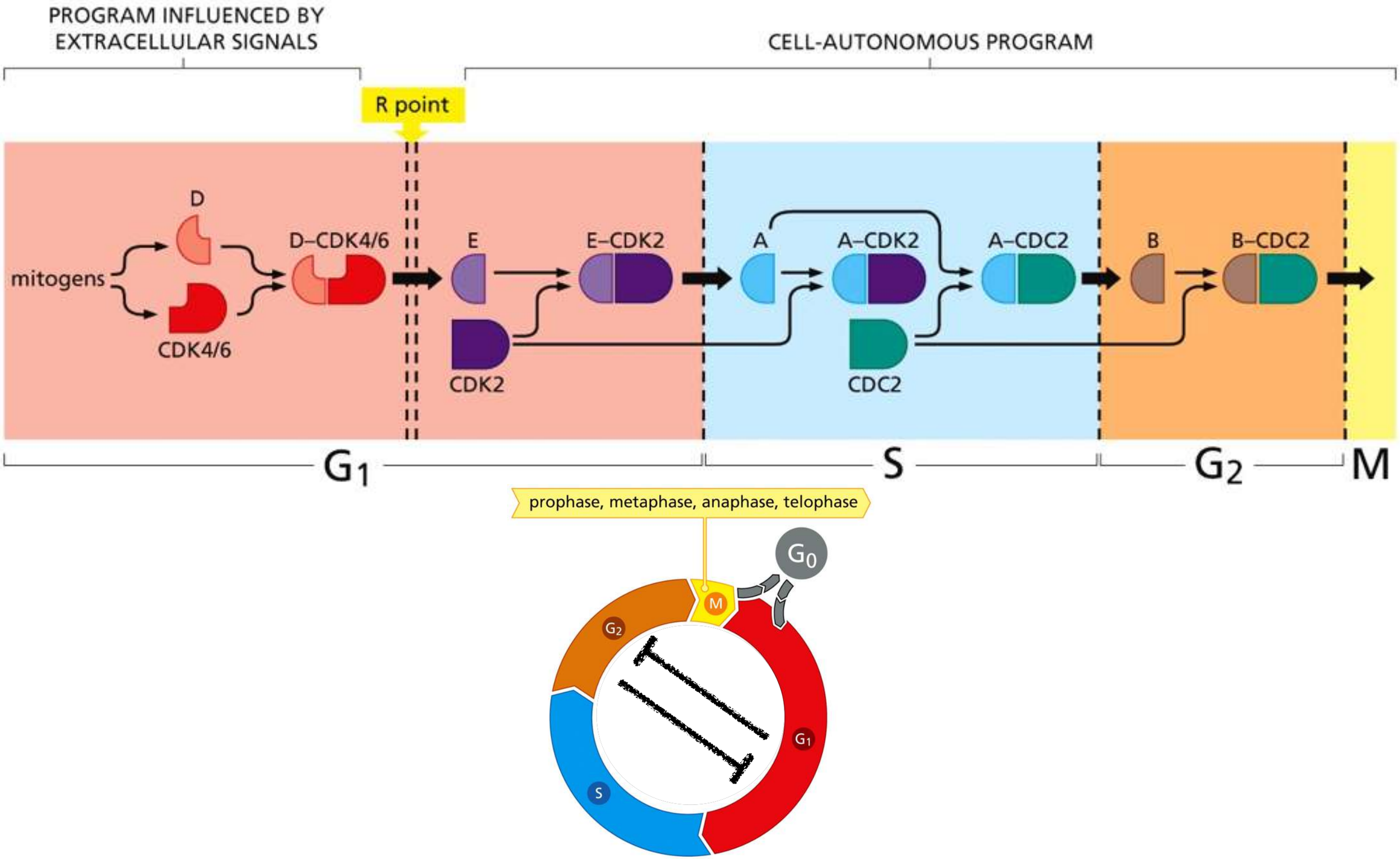
# The molecular trigger for S-phase entry

-

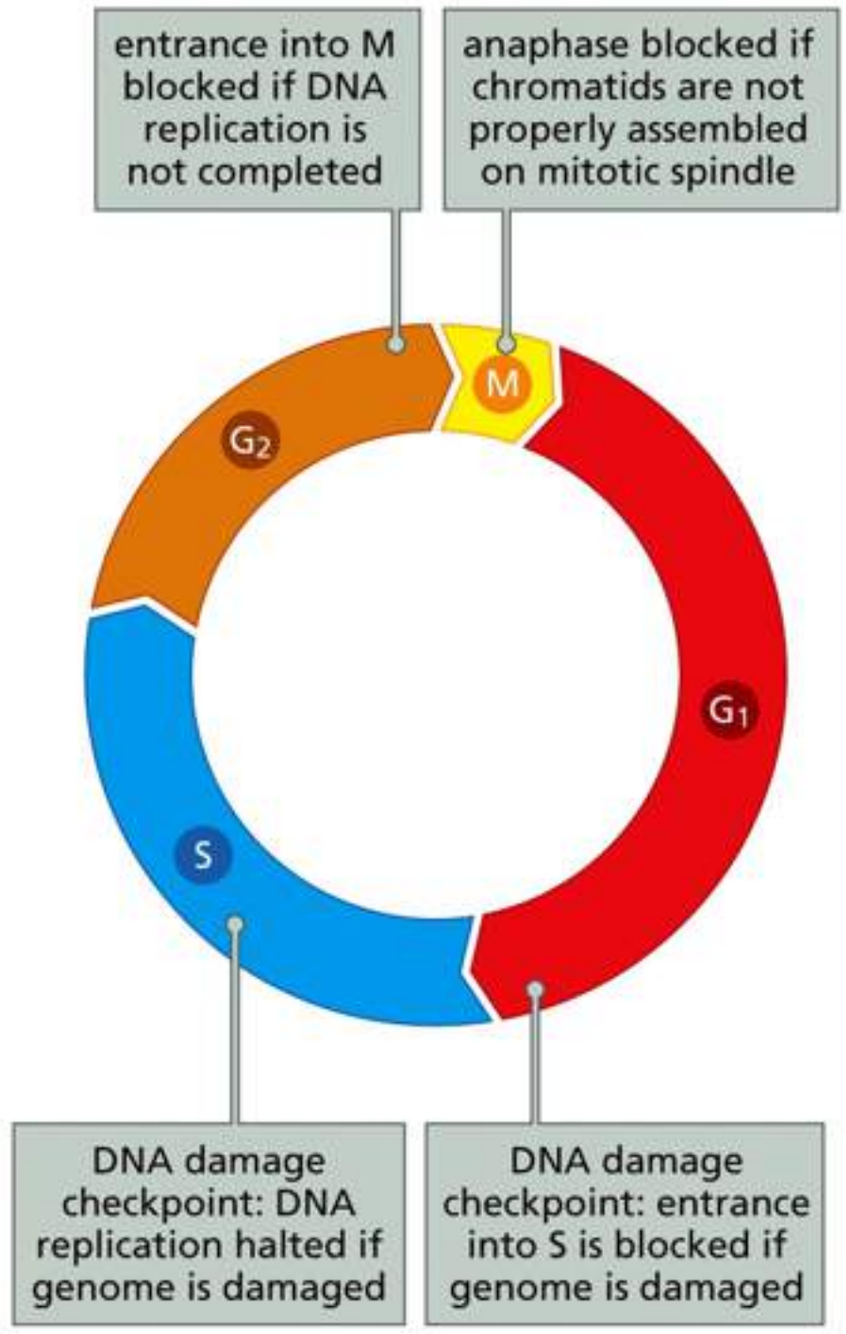
# the R(estriction) point



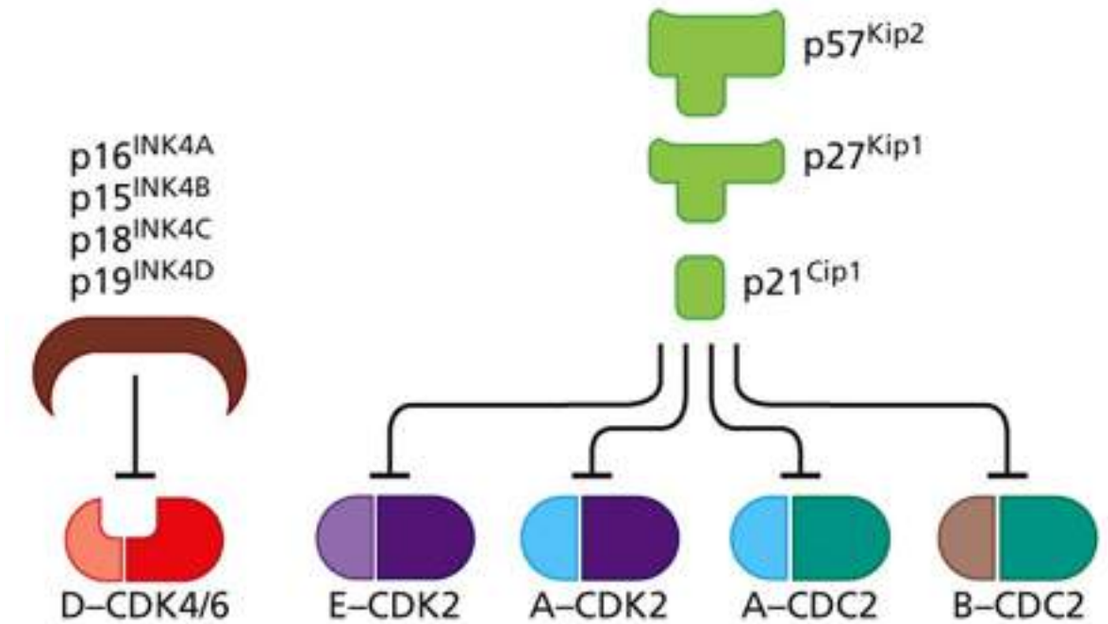
# Once the R-point is breached, cells are independent of extracellular growth signals



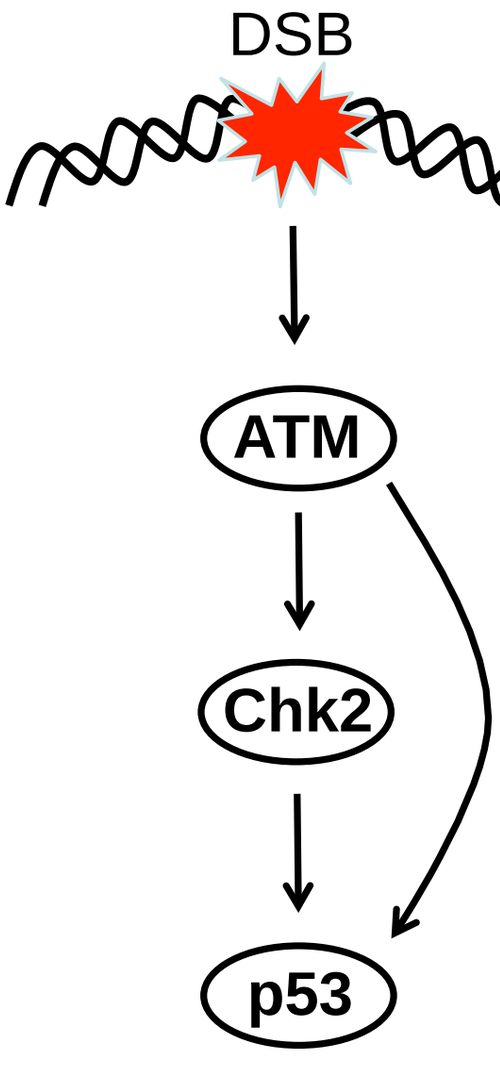
# Mammalian cells have evolved checkpoints to prevent cell cycle progression in case of danger after passing through the R-point

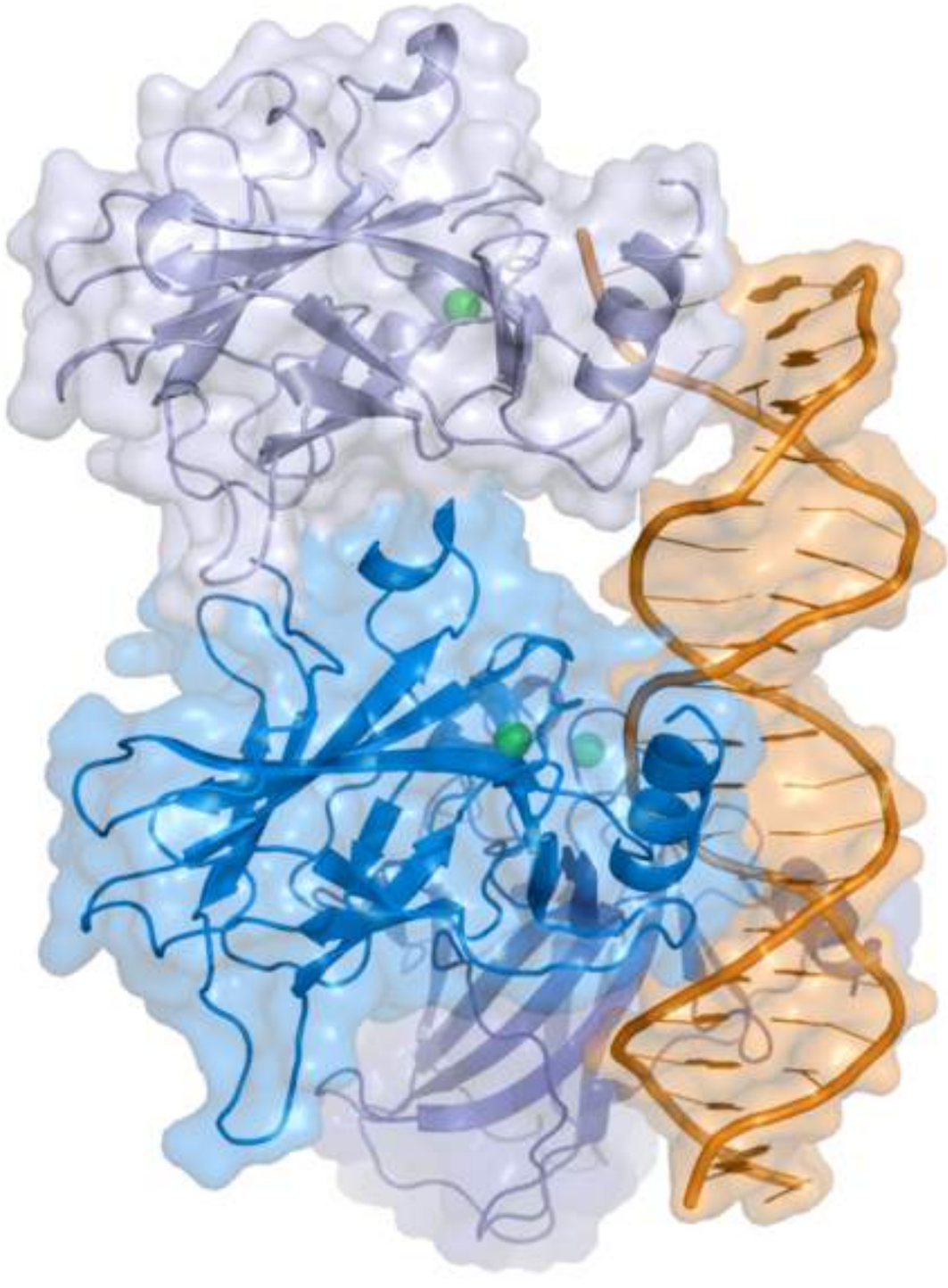


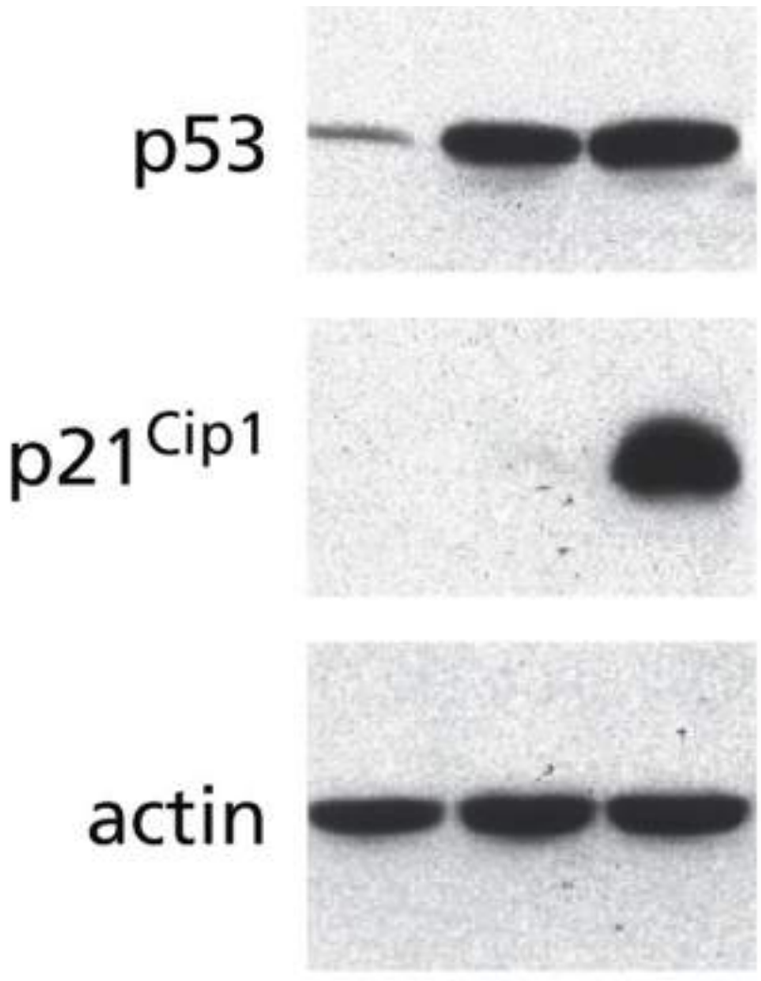
# Checkpoint activation leads to CDK inhibition



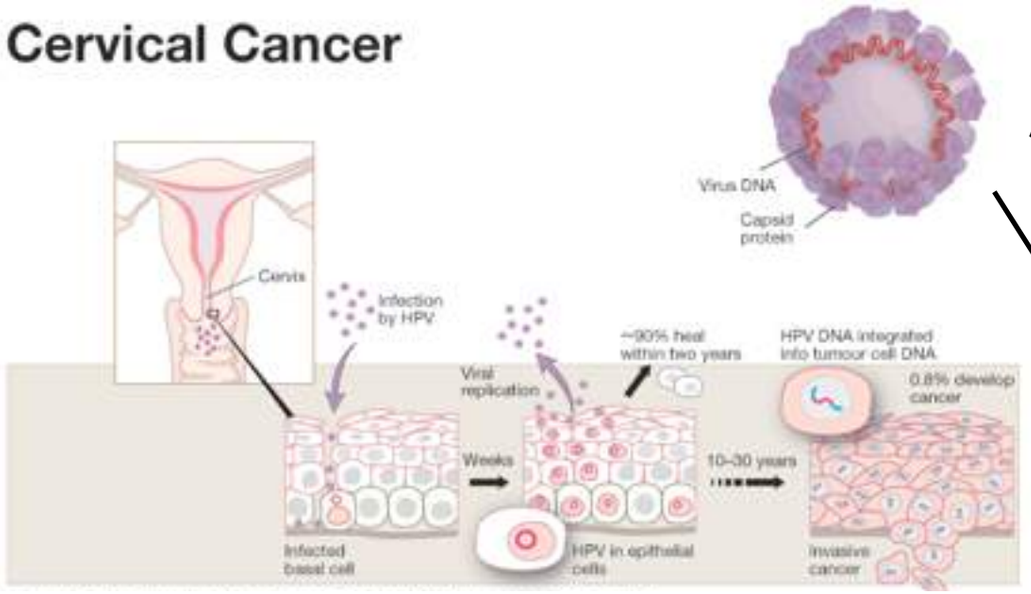
# p53 is a major component of the checkpoint machinery



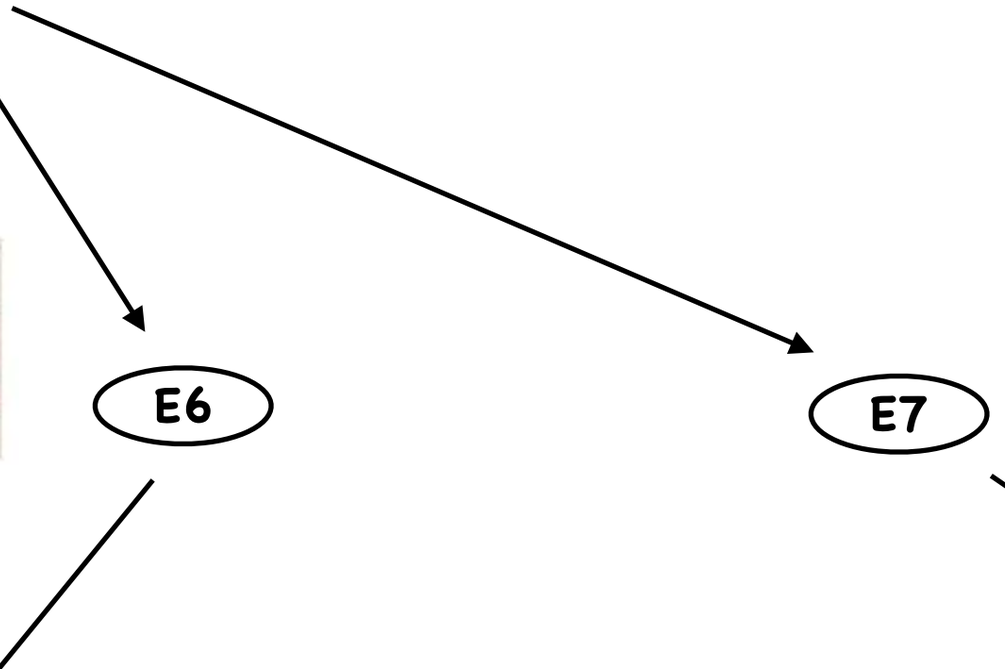


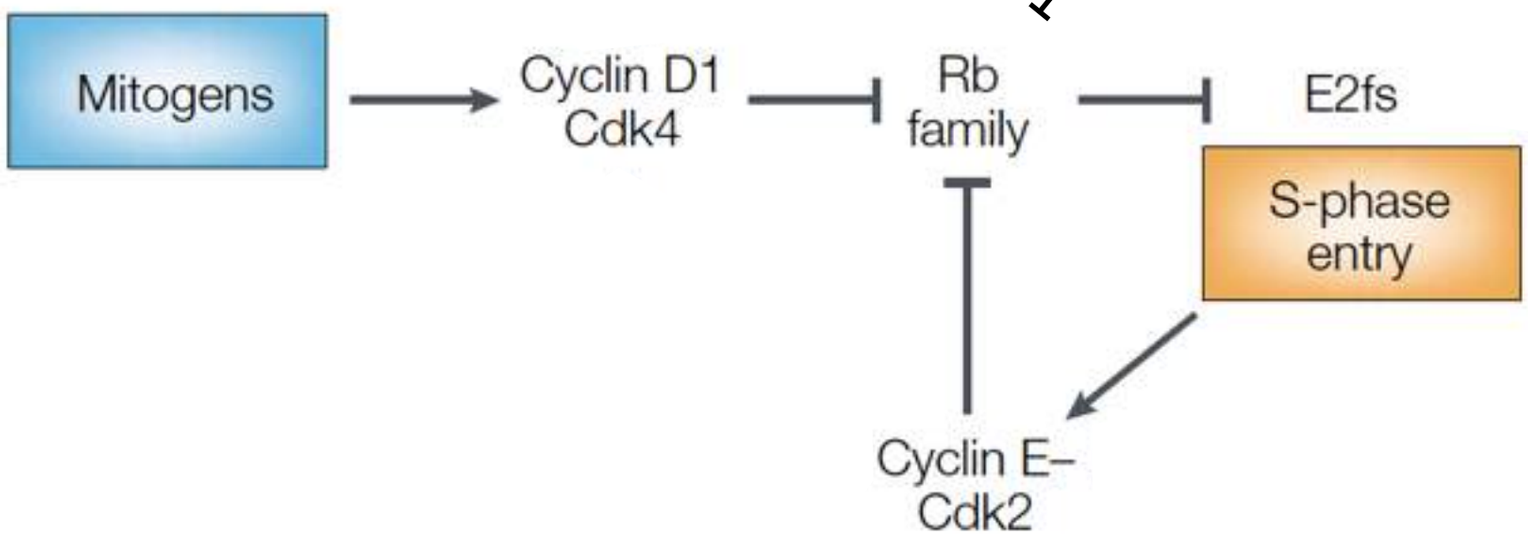
# Excessive CDK4/6 activity, loss of RB1 or E2F hyper-activation induces a fail safe mechanism







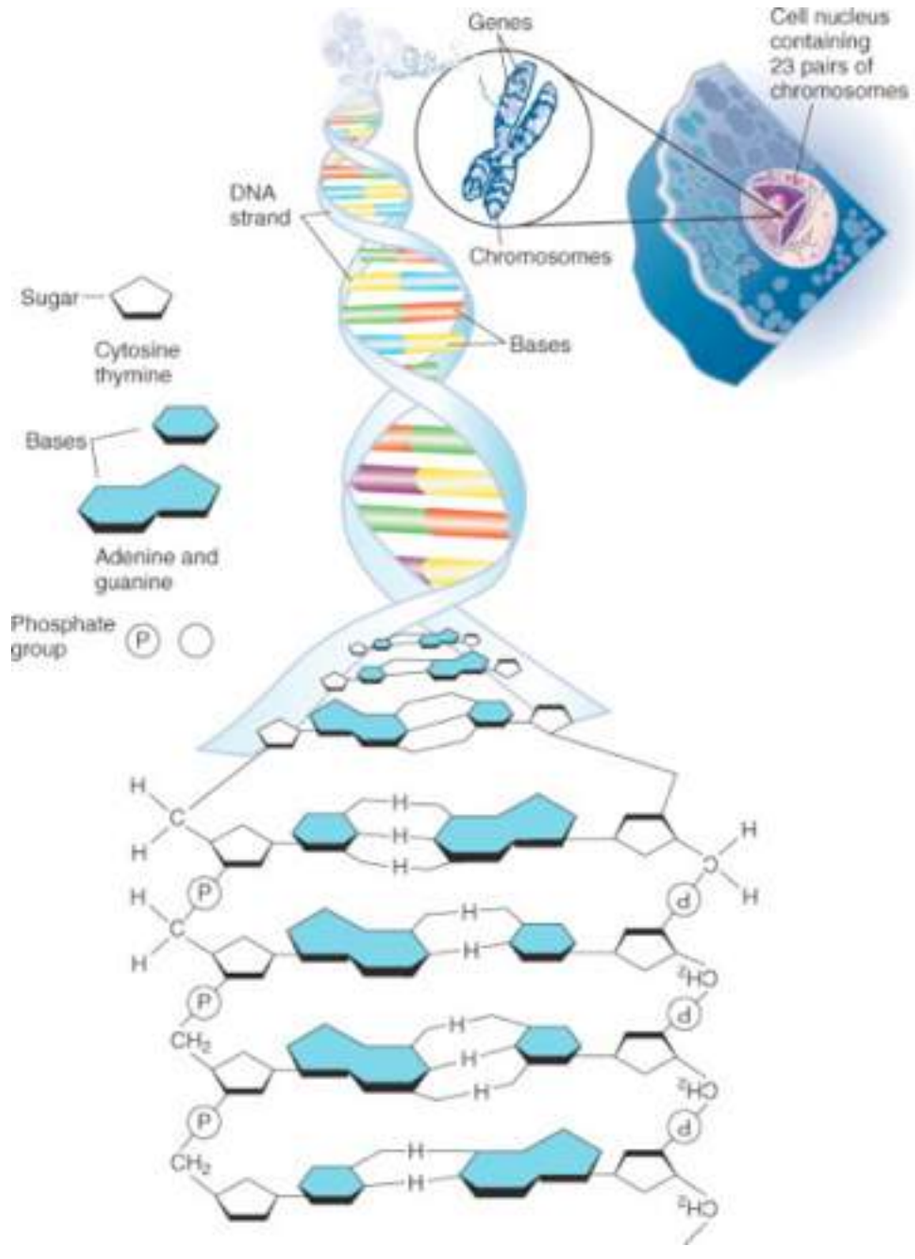


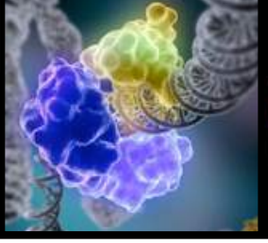
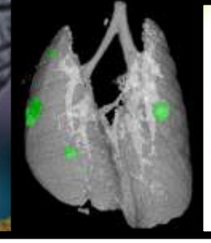



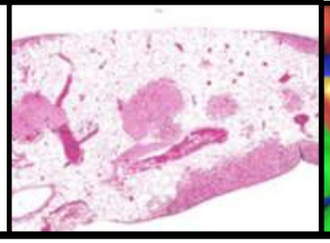
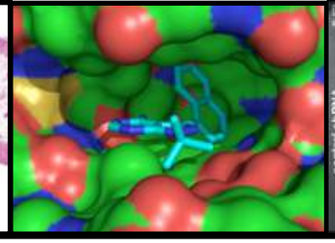
## Take home message #1:

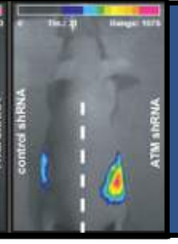
**The eukaryotic cell cycle is organized in distinct phases and progression through the cycle is driven by CDKs.**

# Cancer is a genetic disease



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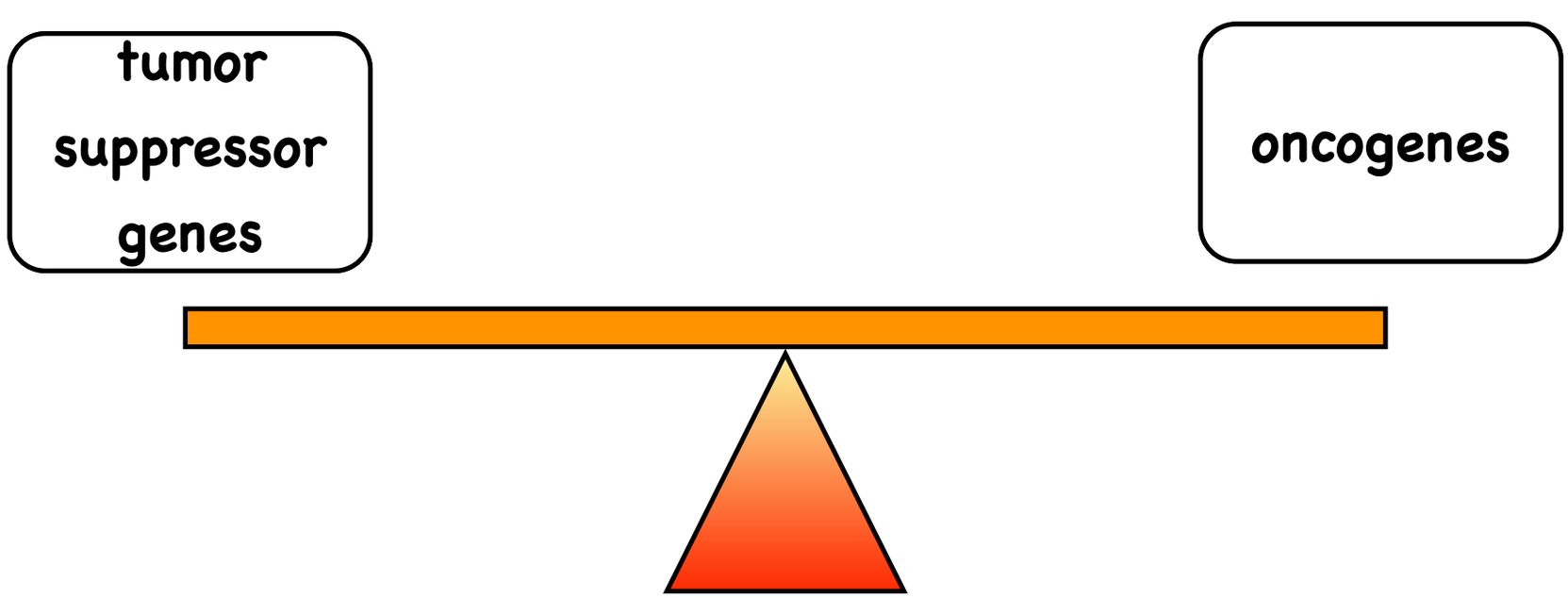
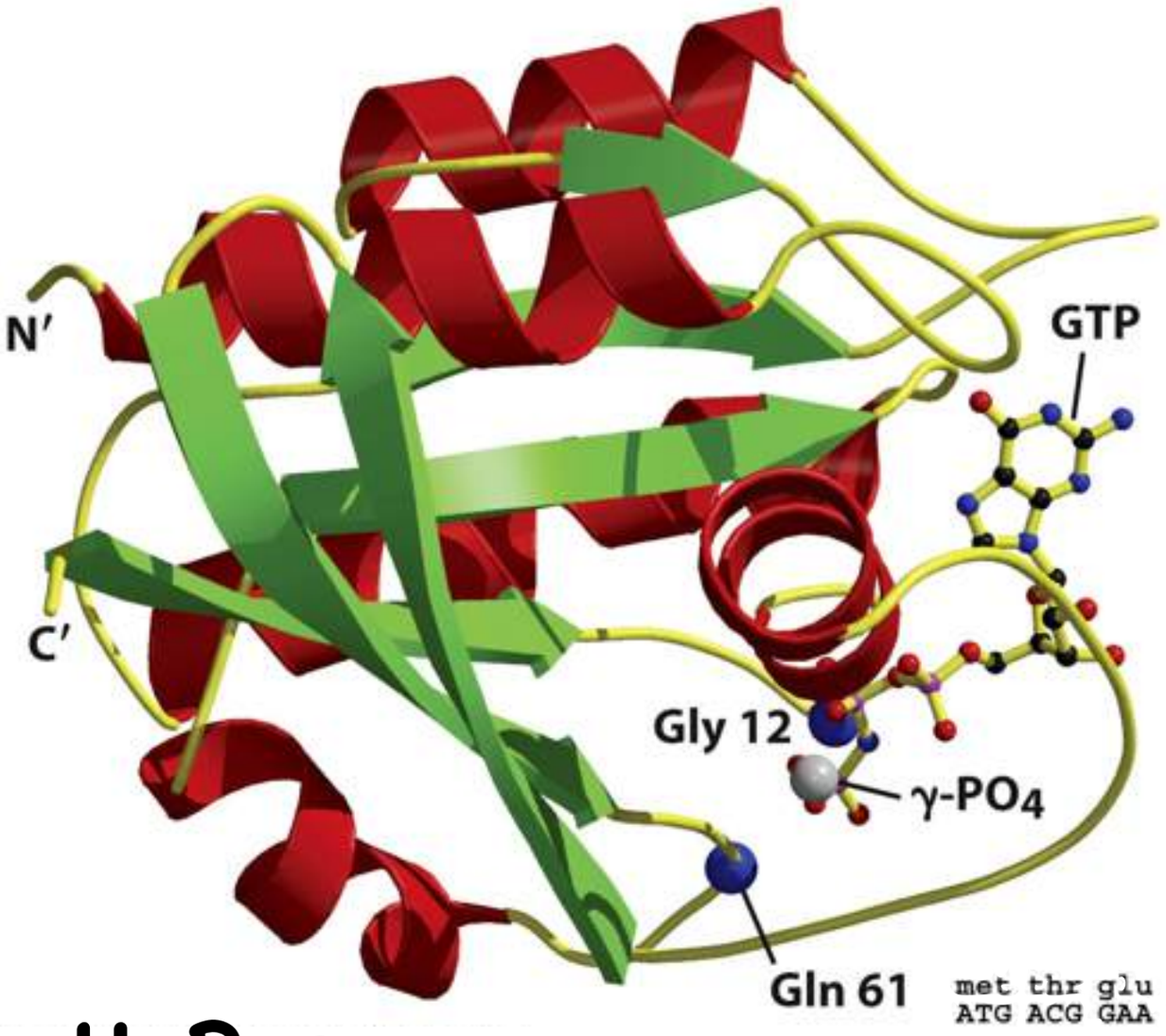
# Cancer is a genetic disease




What are the genetic events that ultimately lead to malignant transformation?

# Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure

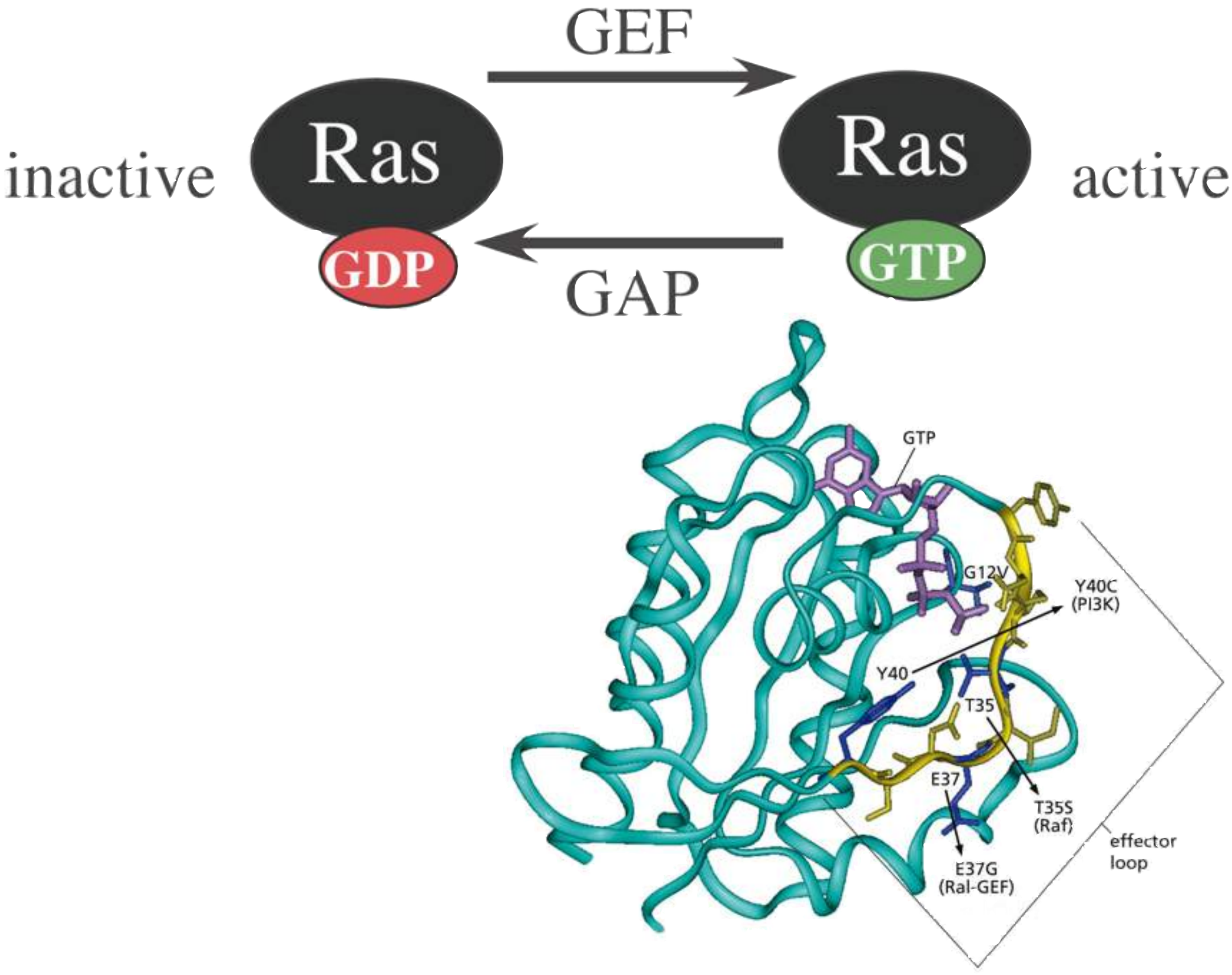



H-Ras

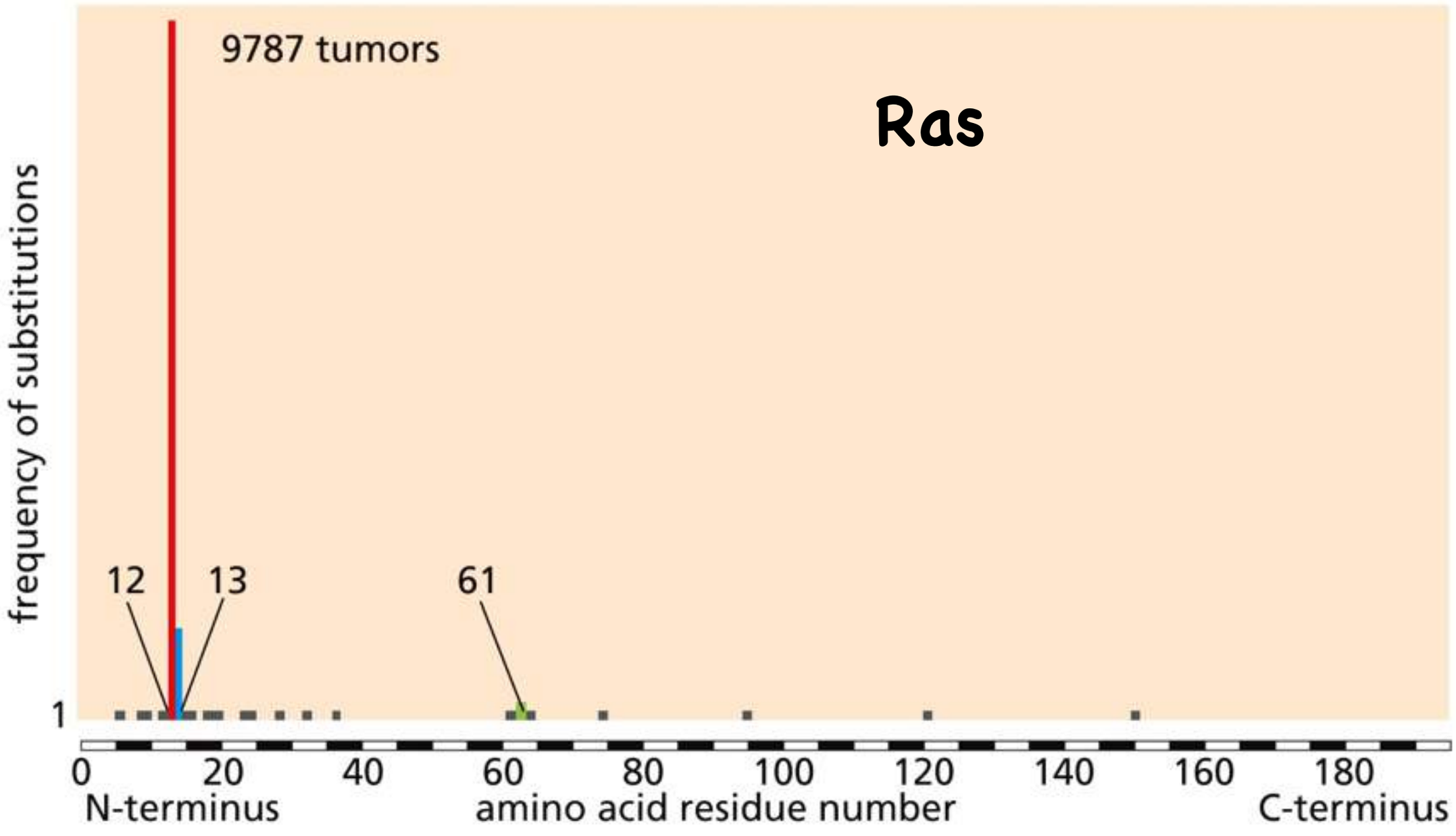
**<u>Mutations</u> can structurally damage gene products**

```
                                                    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
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
```

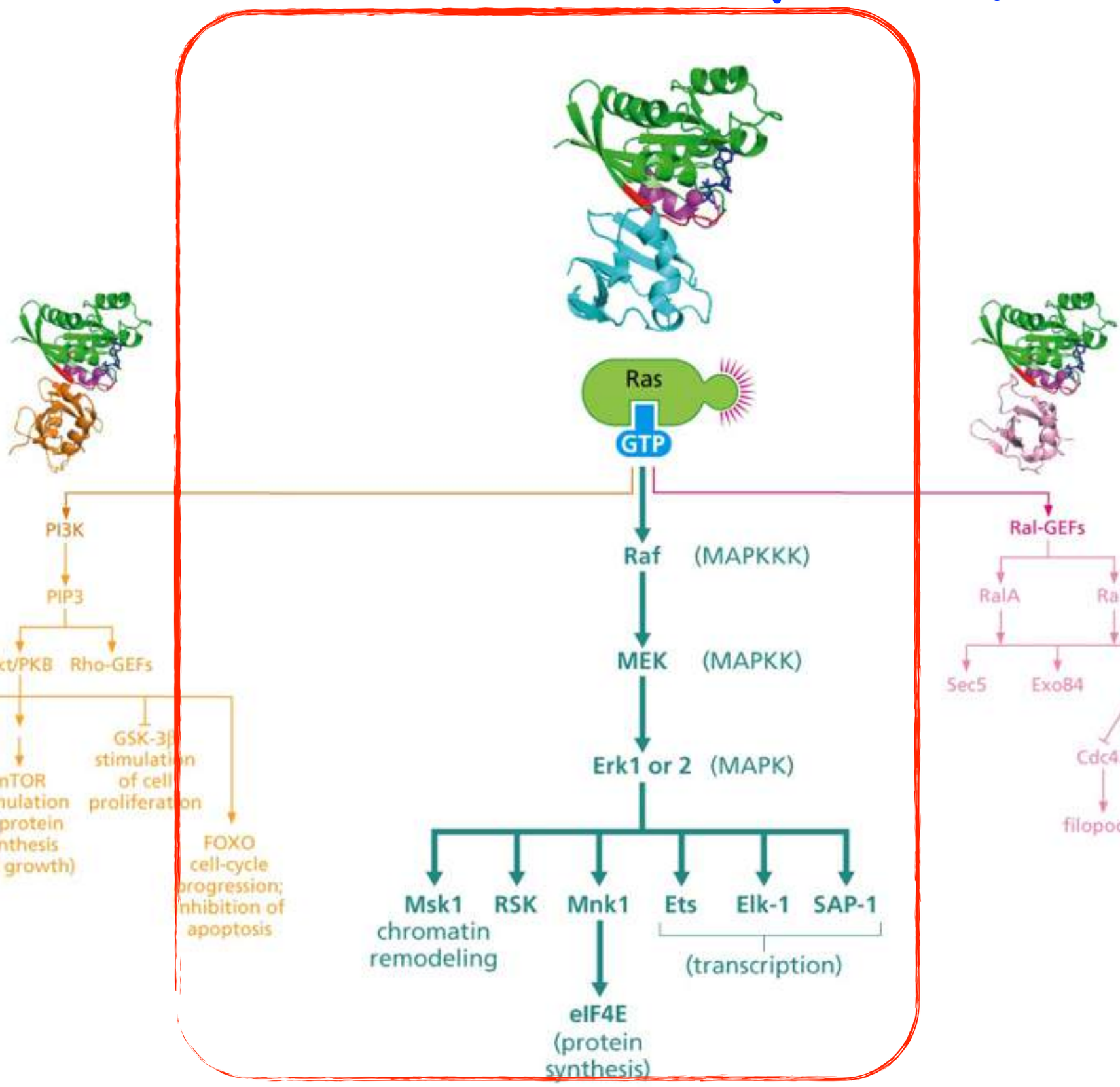
# Ras is a small G-protein



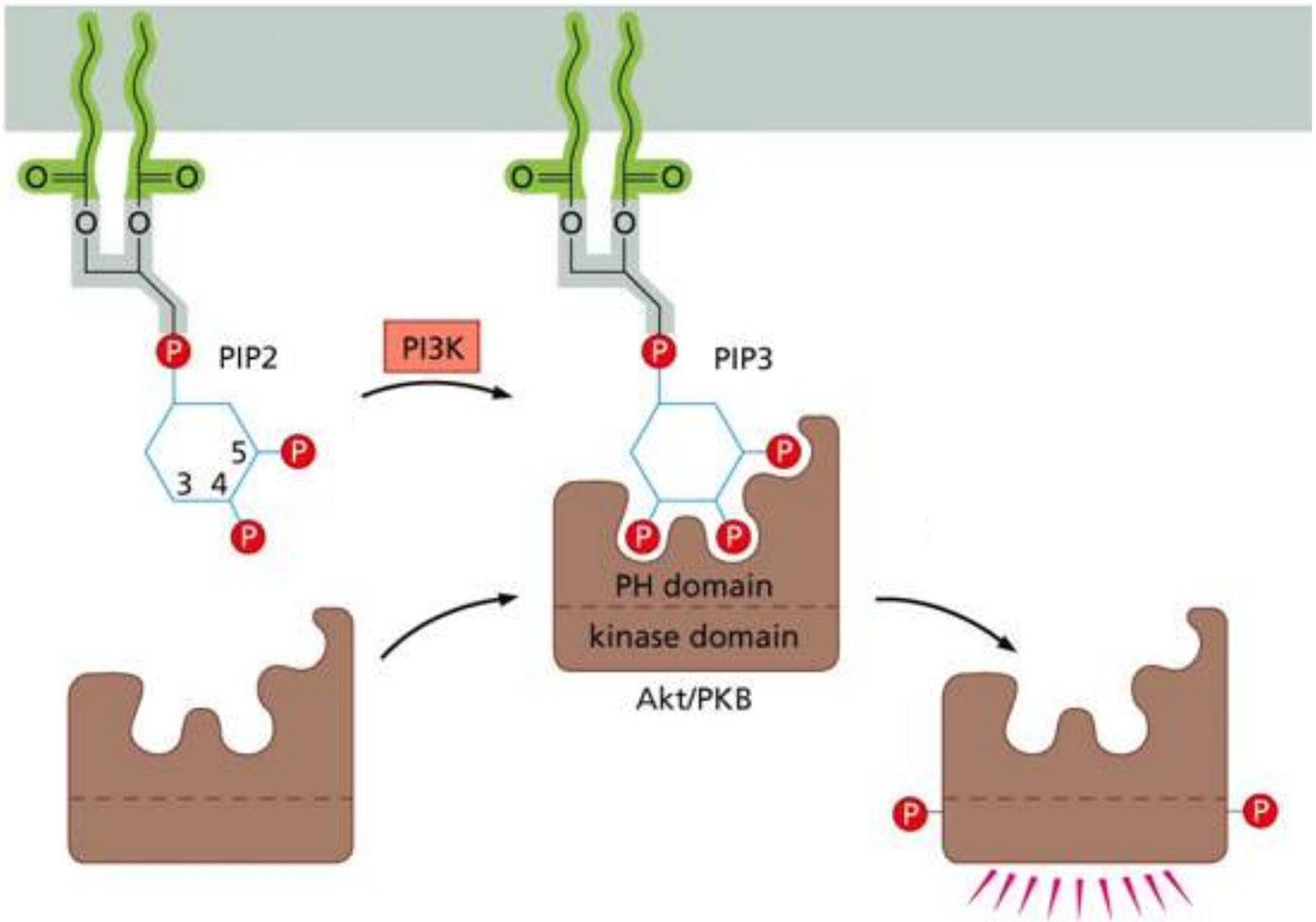
# Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure

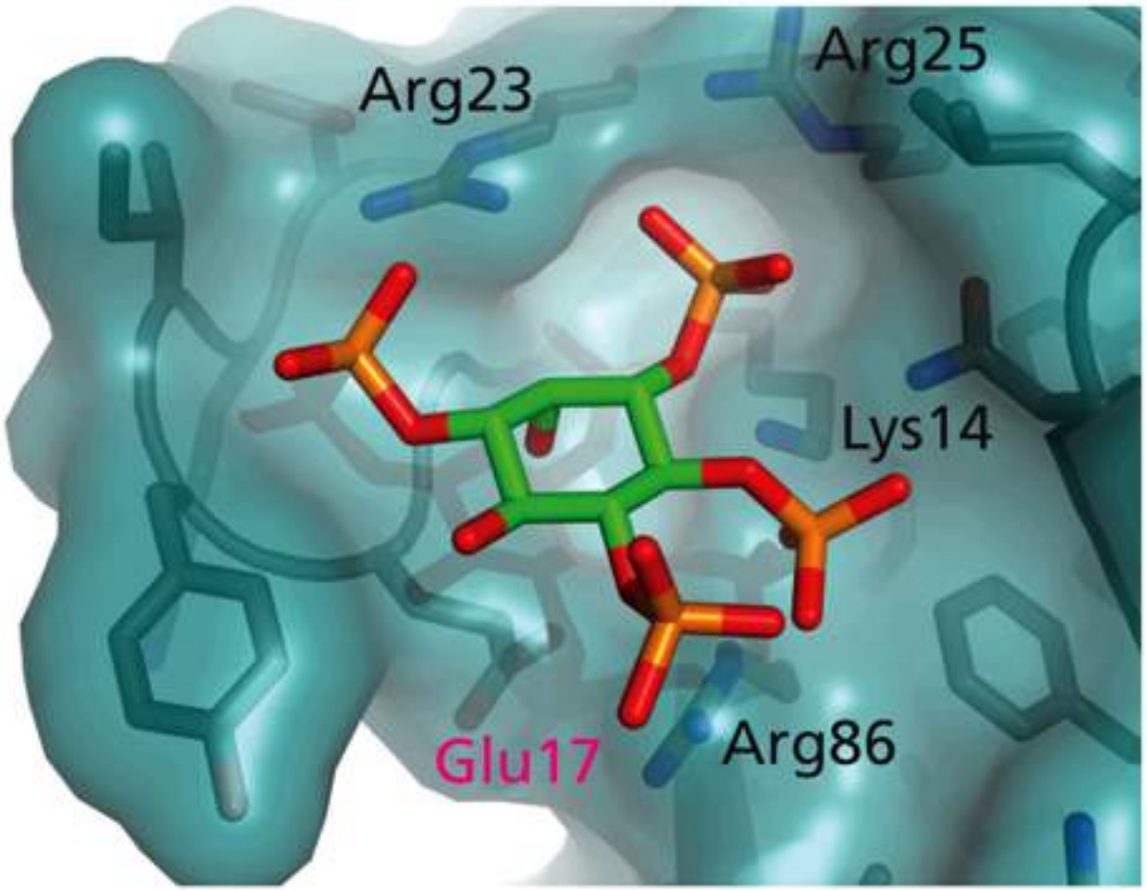


# Ras is an extremely potent oncogene that controls numerous downstream pathways



# Through activating PI3K, Ras initiates AKT signaling

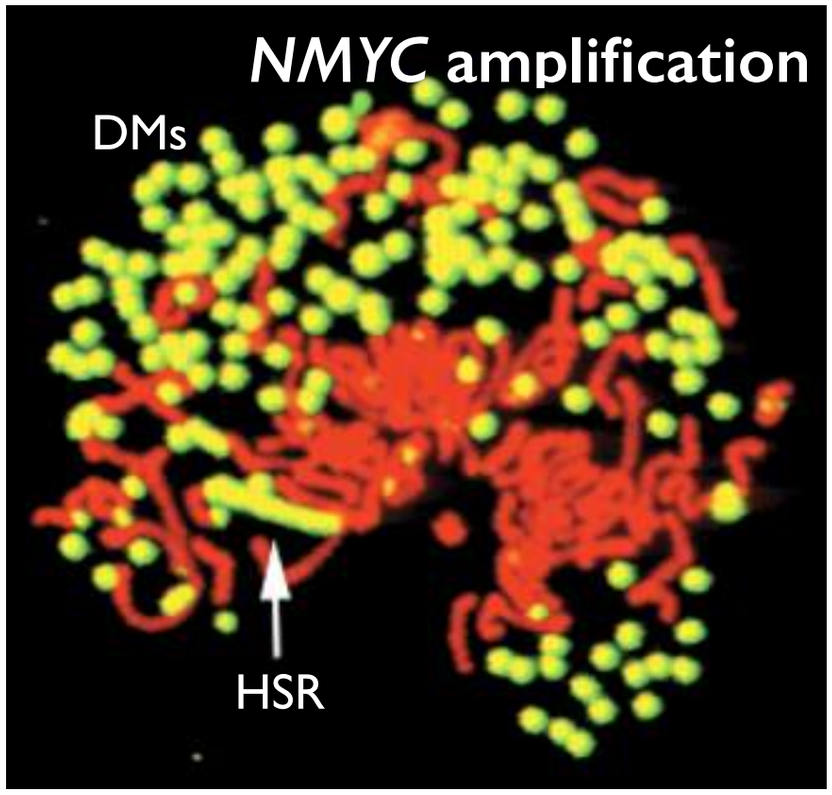


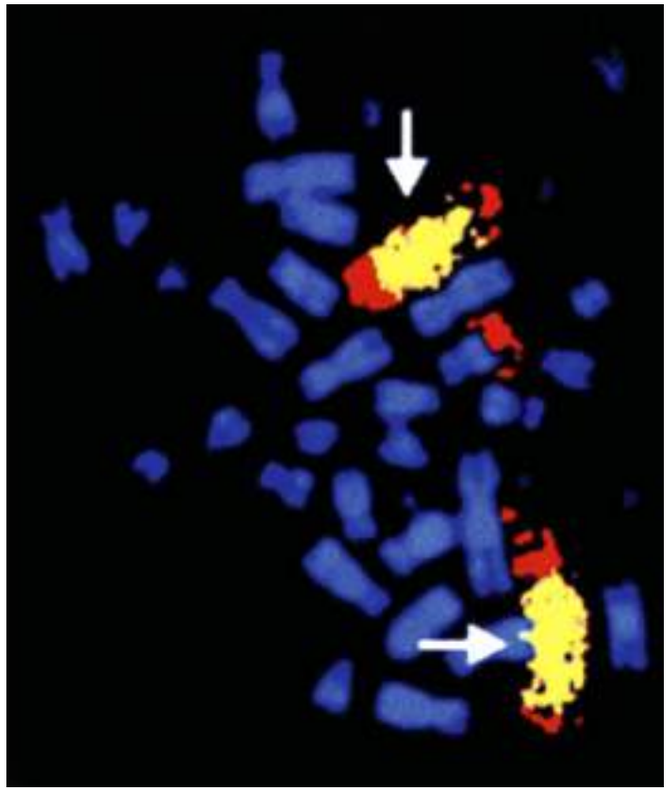



## Take home message #2:

## Proto-oncogenes can be turned into oncogenes through point mutations

# Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure



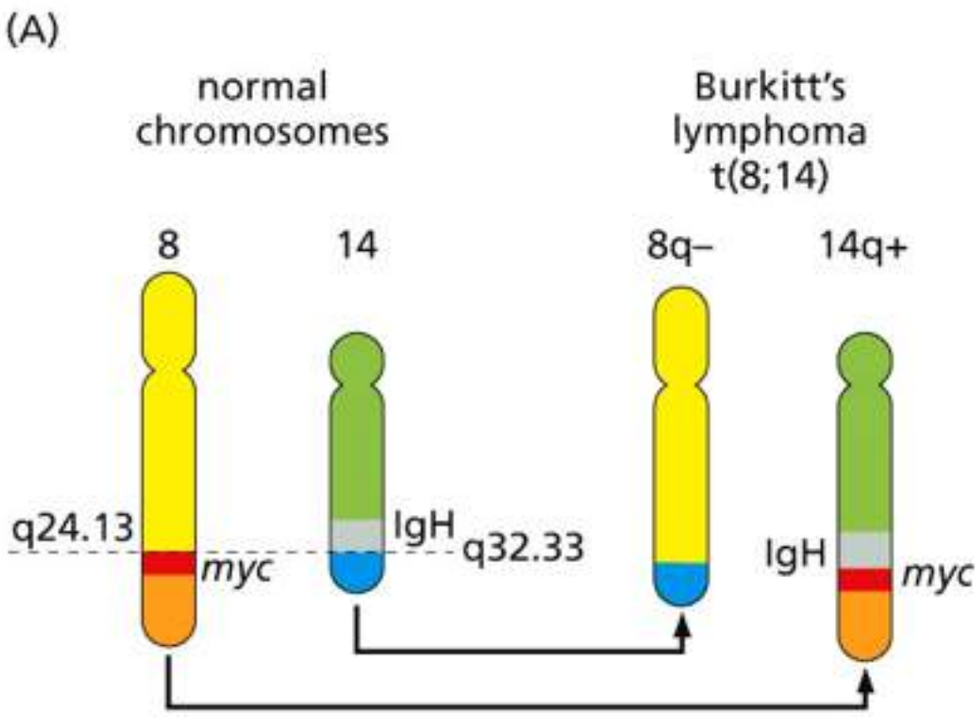



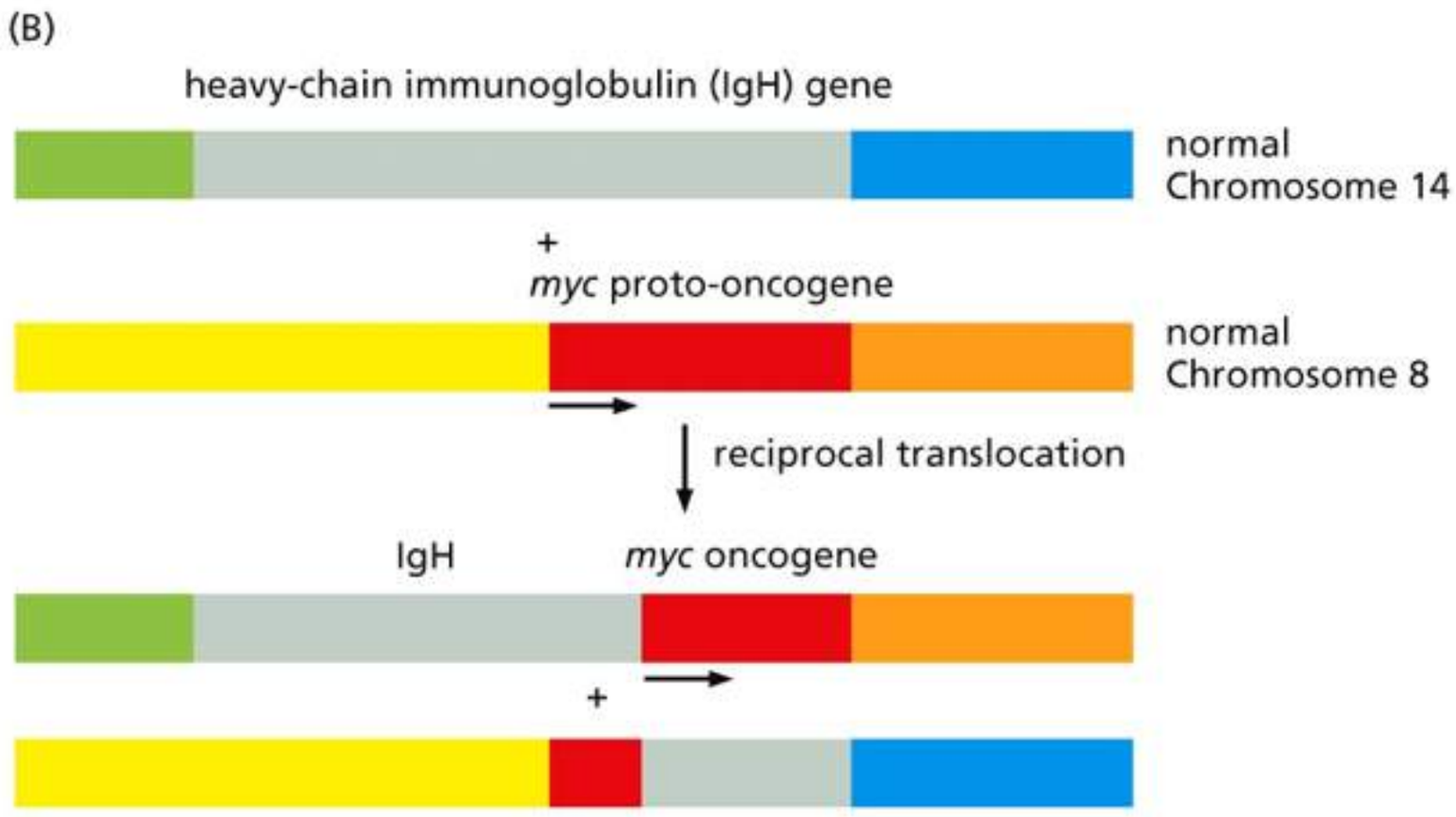
Amplifications can lead to increased gene dosage of proto-oncogenes

## Take home message #3:

## Proto-oncogenes can be turned into oncogenes through amplifications

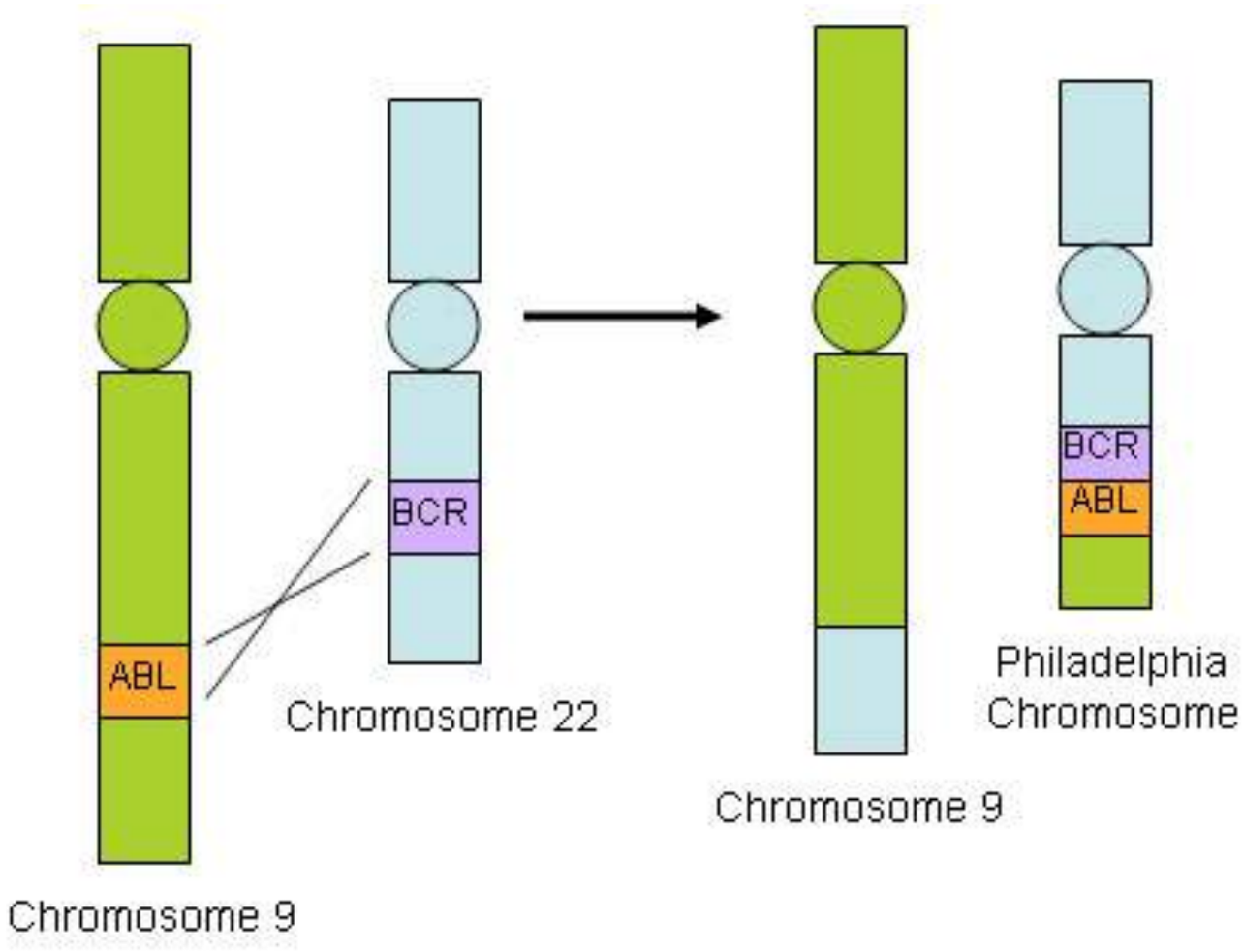
# Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure



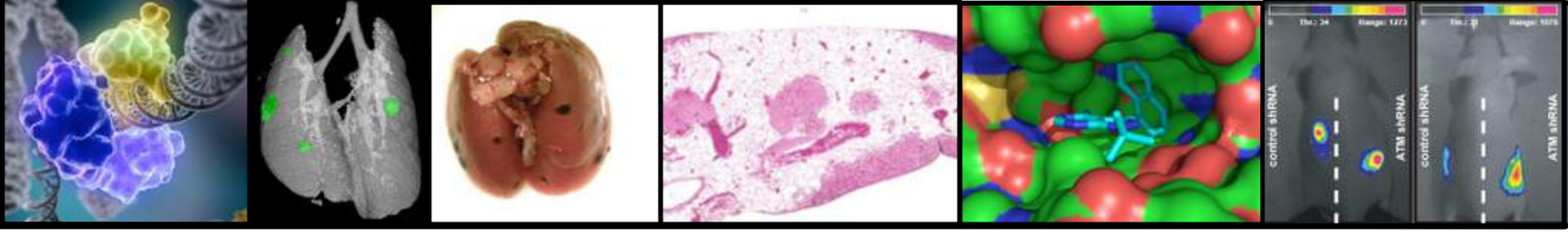




Translocations can structurally damage gene products

# Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure




Translocations can structurally damage gene products

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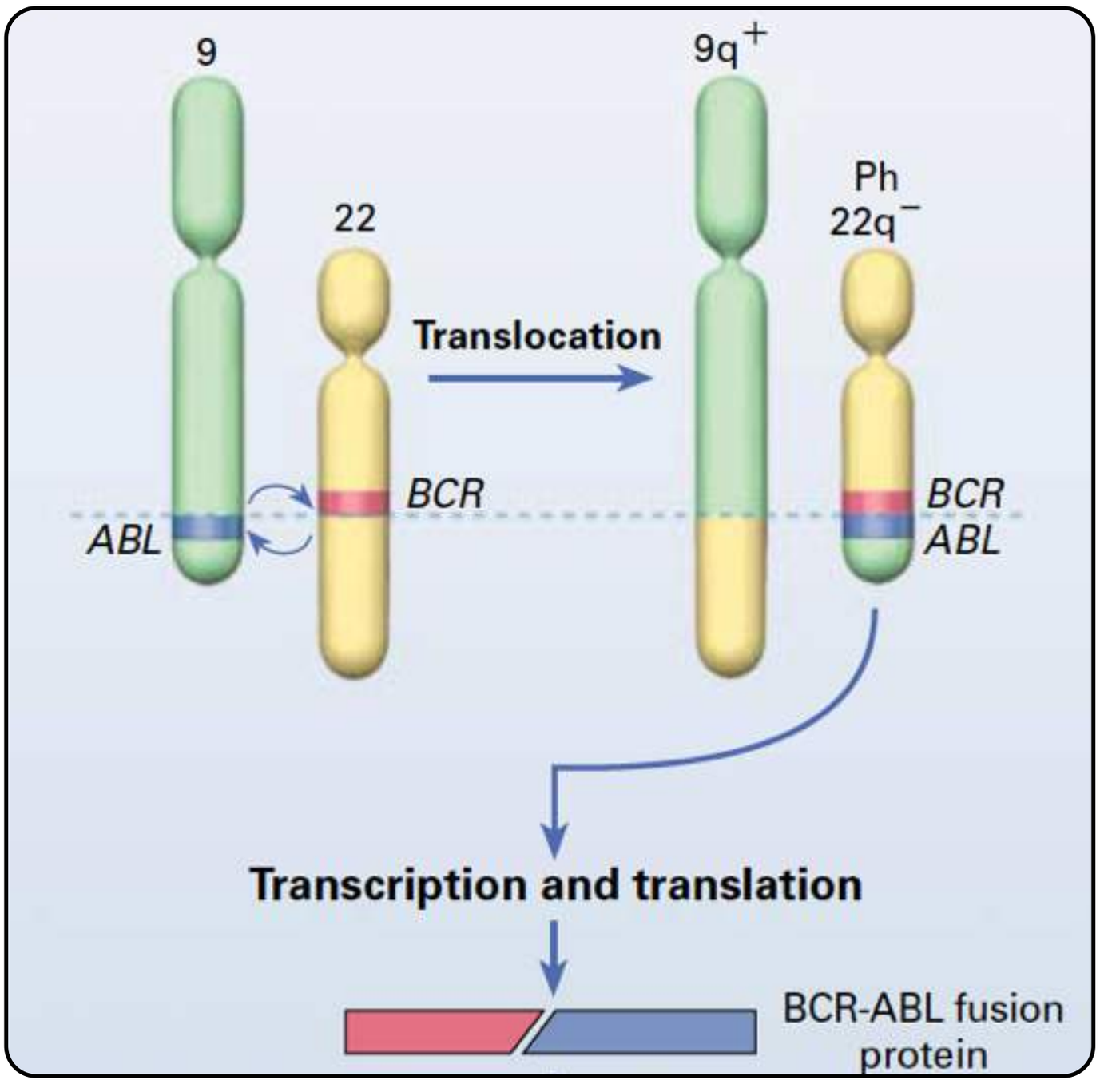
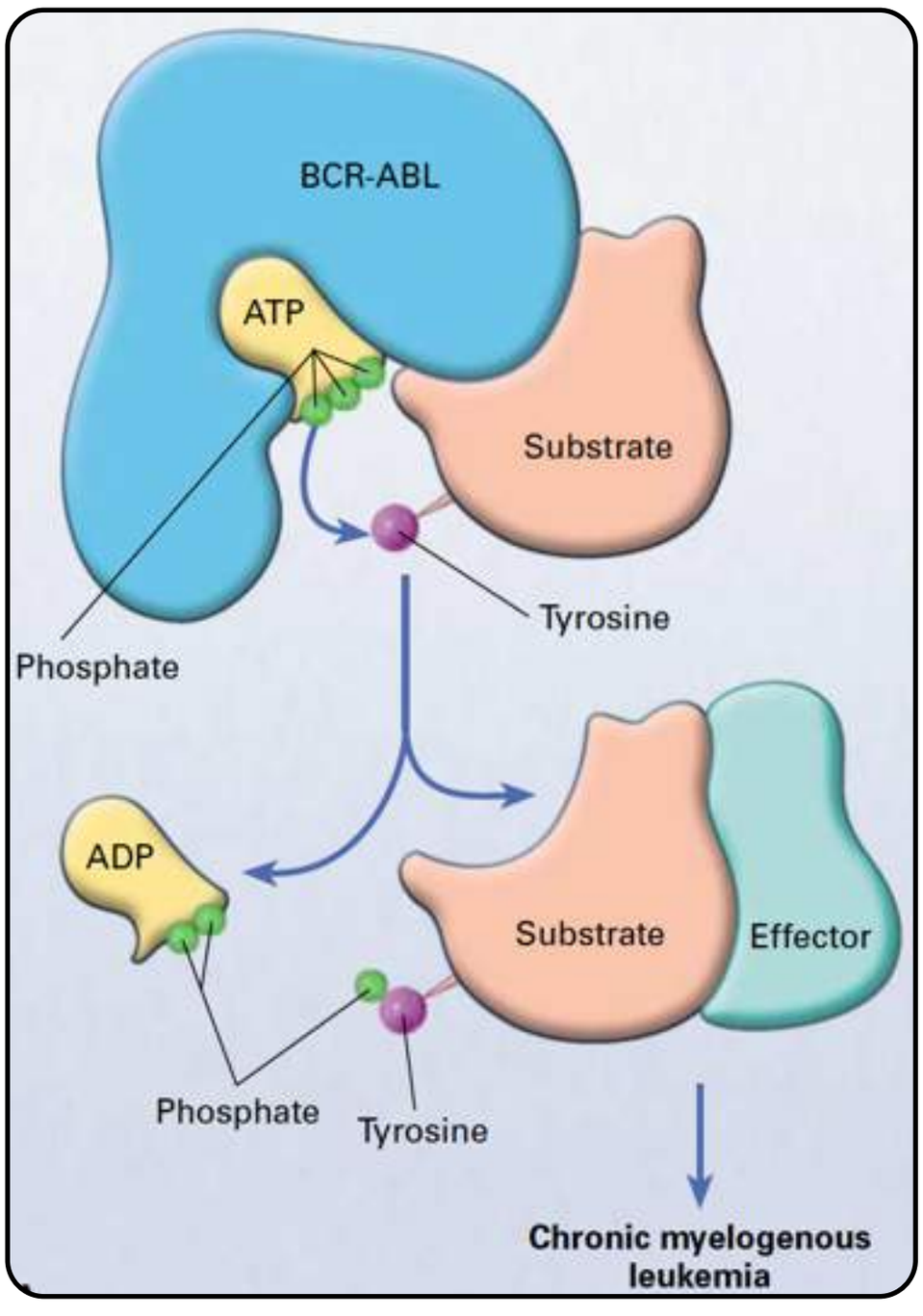
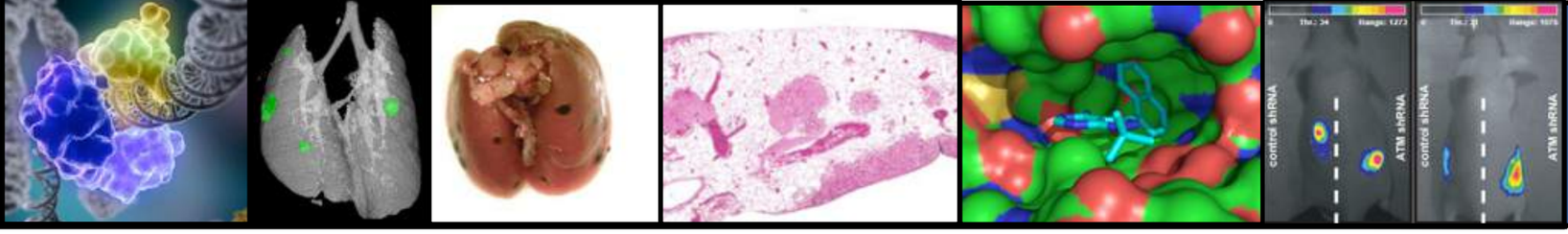
# The BCR-ABL fusion is the key driver of CML



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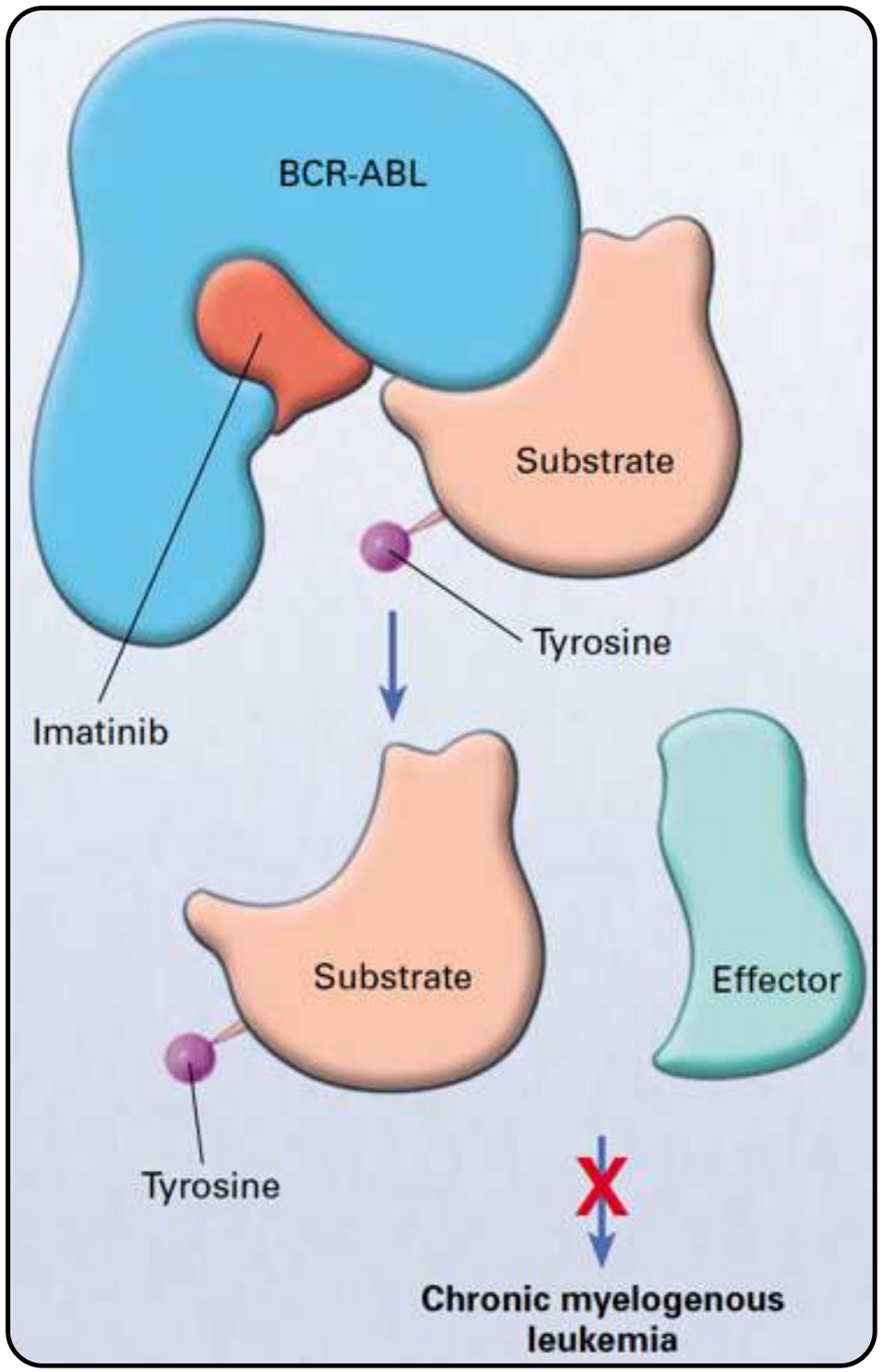
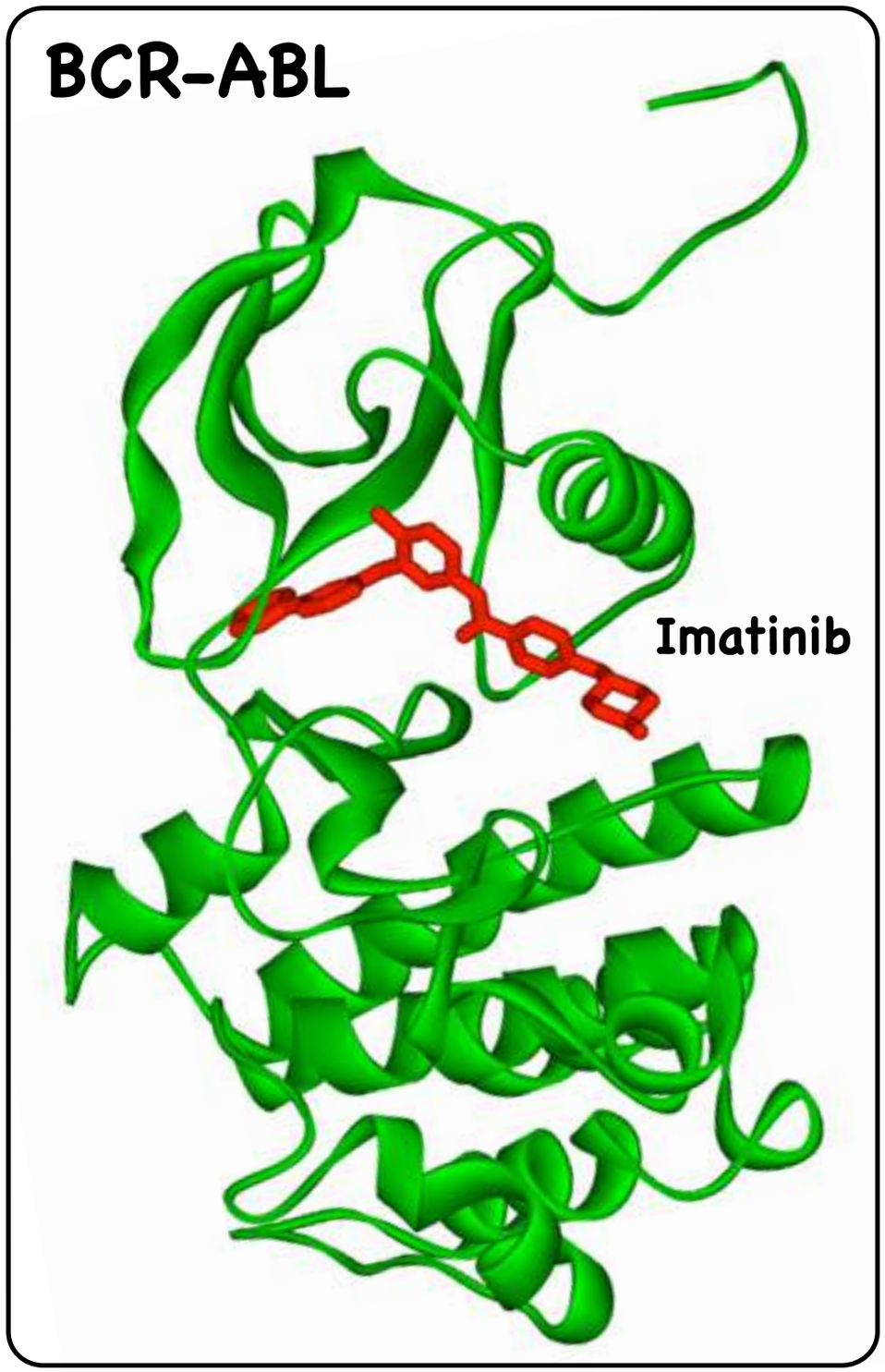
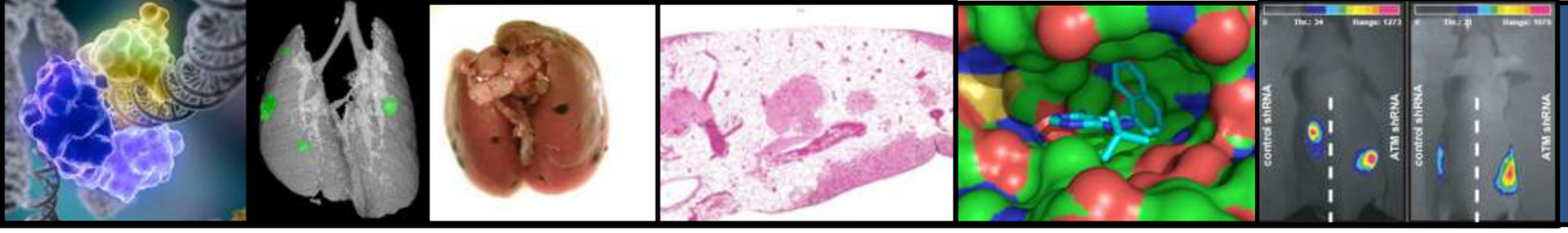
# Imatinib is a potent inhibitor of (BCR-)ABL



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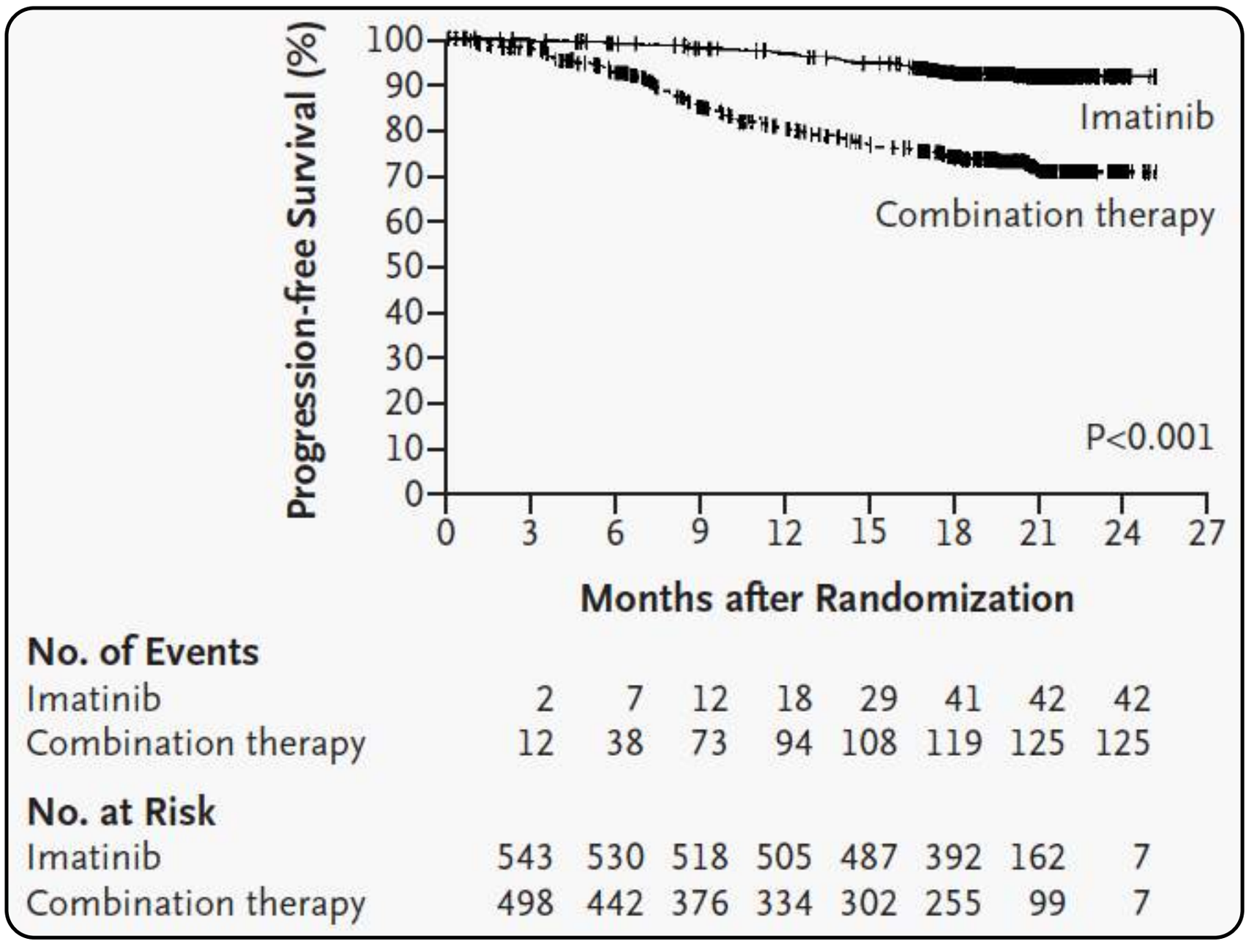
# Imatinib is superior compared to IFNa/Ara-C in the first line

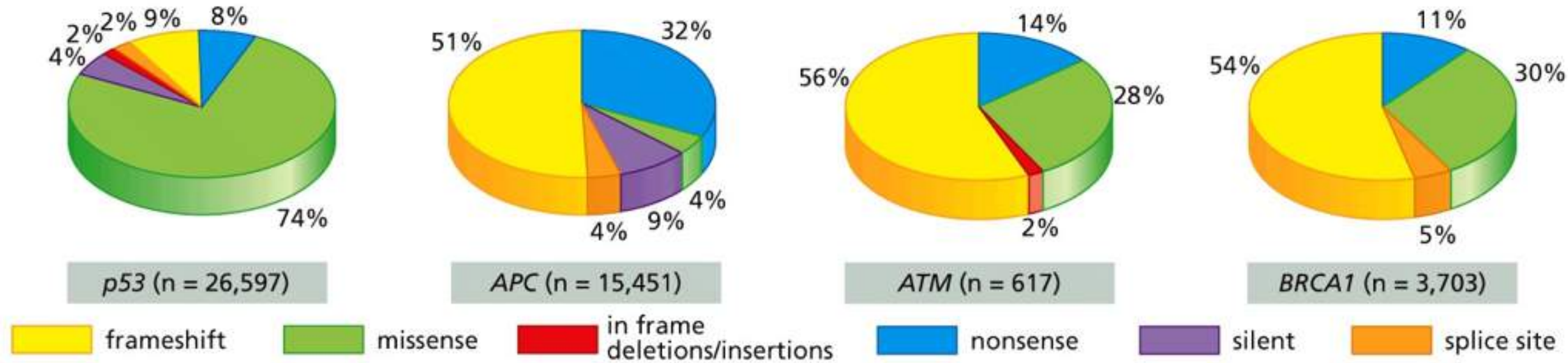



| No. of Events | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Imatinib | 2 | 7 | 12 | 18 | 29 | 41 | 42 | 42 |
| Combination therapy | 12 | 38 | 73 | 94 | 108 | 119 | 125 | 125 |
| **No. at Risk** | | | | | | | | |
| Imatinib | 543 | 530 | 518 | 505 | 487 | 392 | 162 | 7 |
| Combination therapy | 498 | 442 | 376 | 334 | 302 | 255 | 99 | 7 |

## Take home message #4:

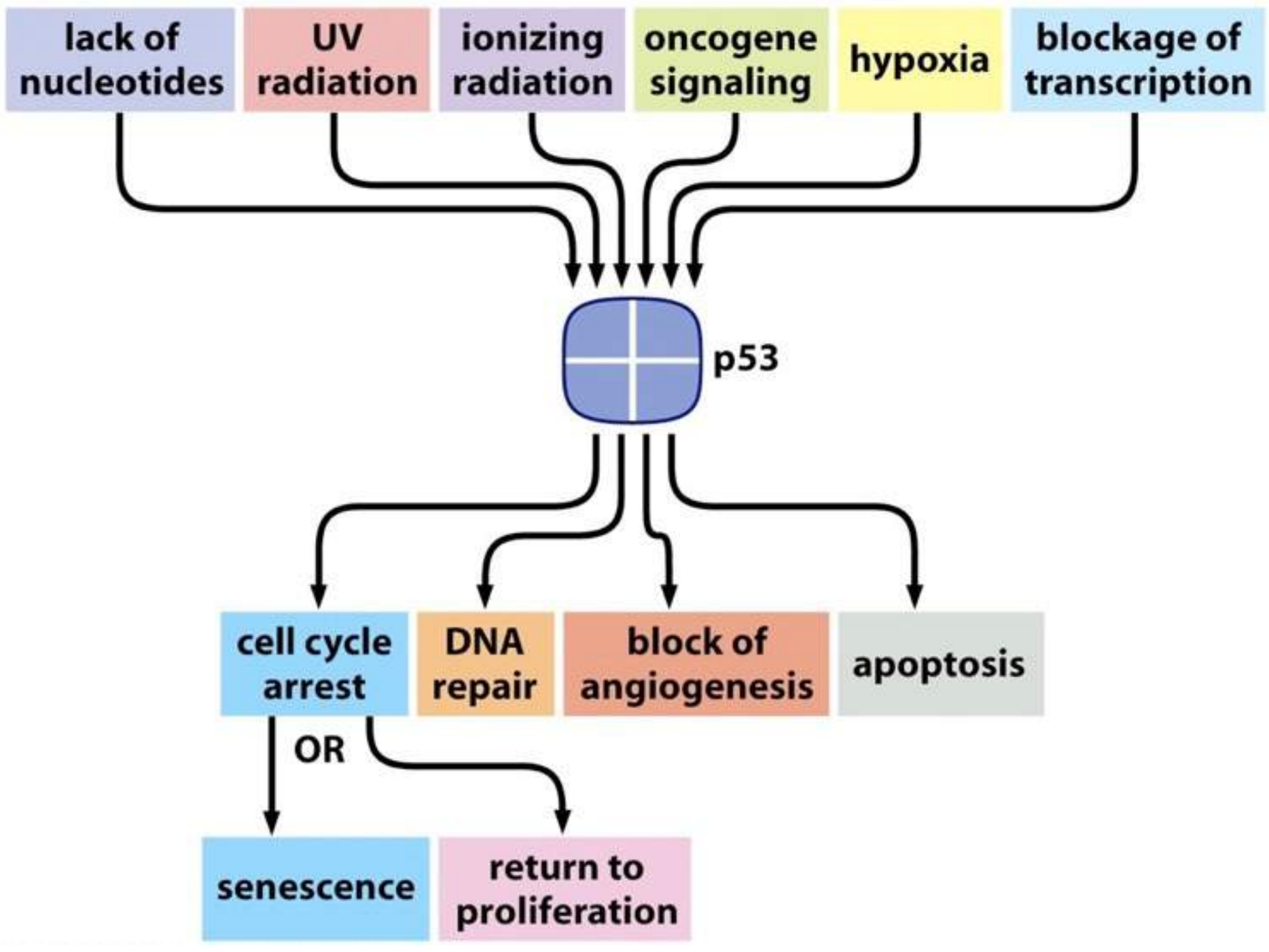
## Proto-oncogenes can be turned into oncogenes through translocations

# Tumor suppressor genes can be inactivated by genetic changes affecting either protein expression or structure

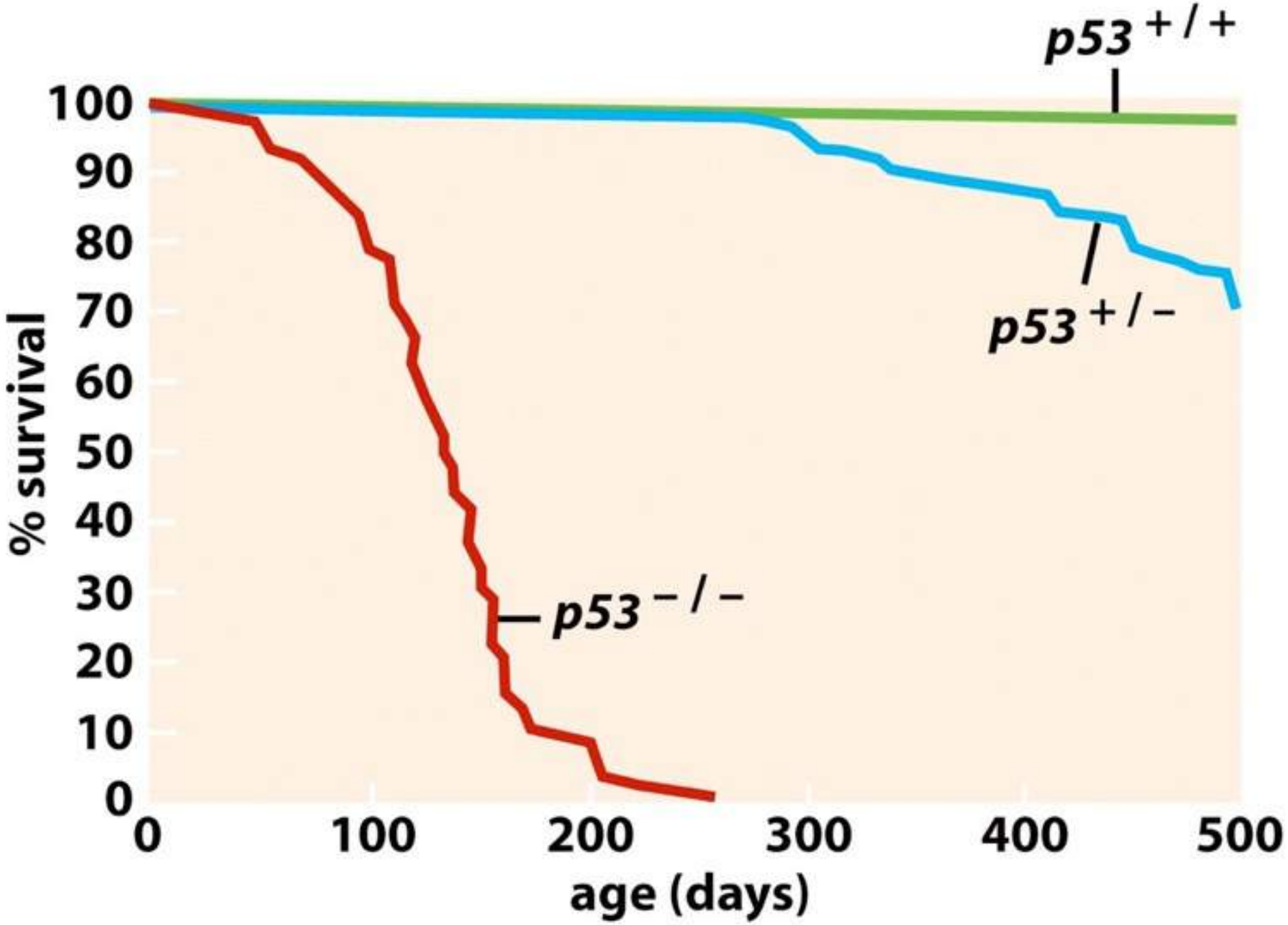



## Point mutations can structurally damage gene products

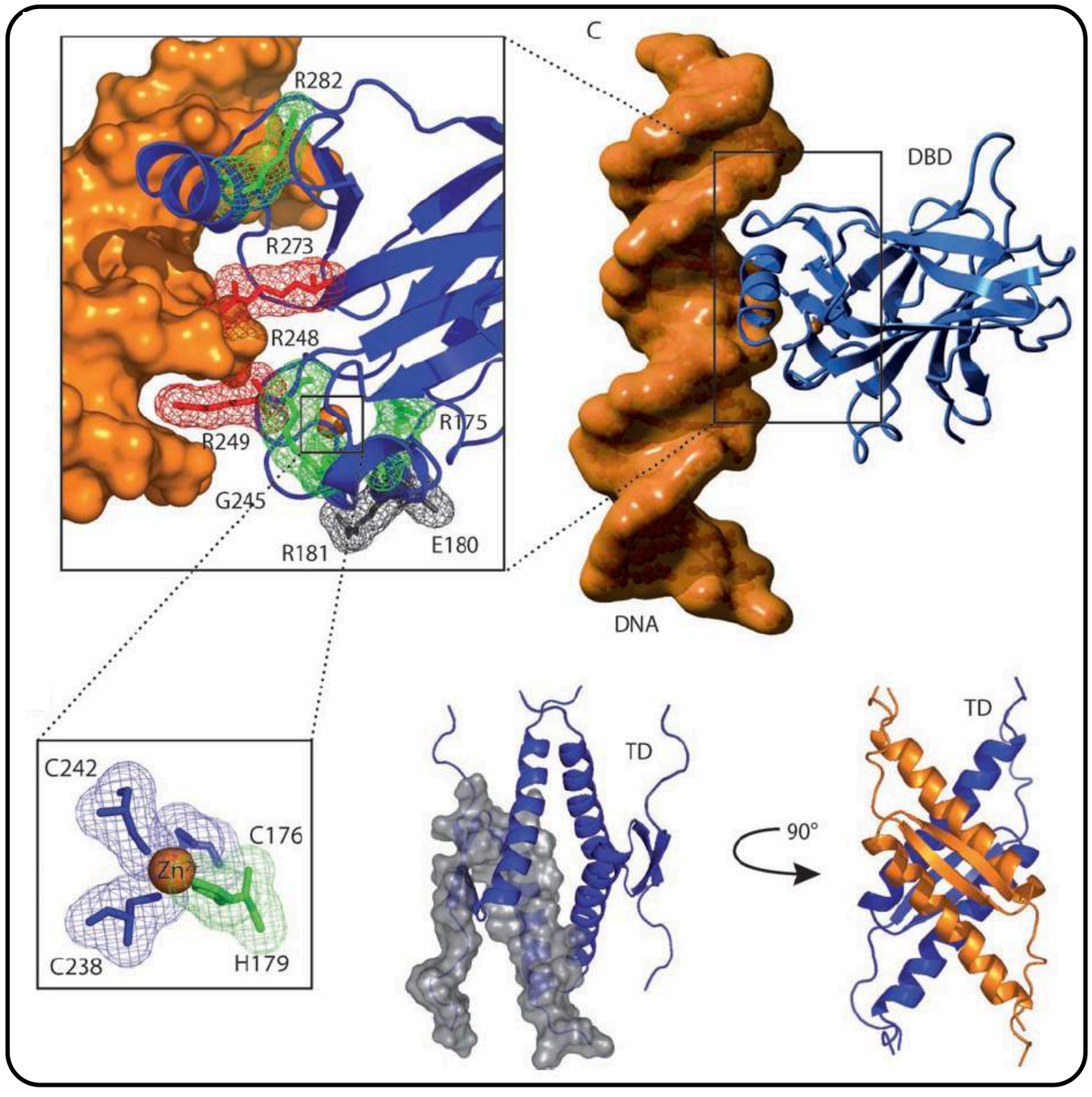
# p53 is a potent tumor suppressor gene



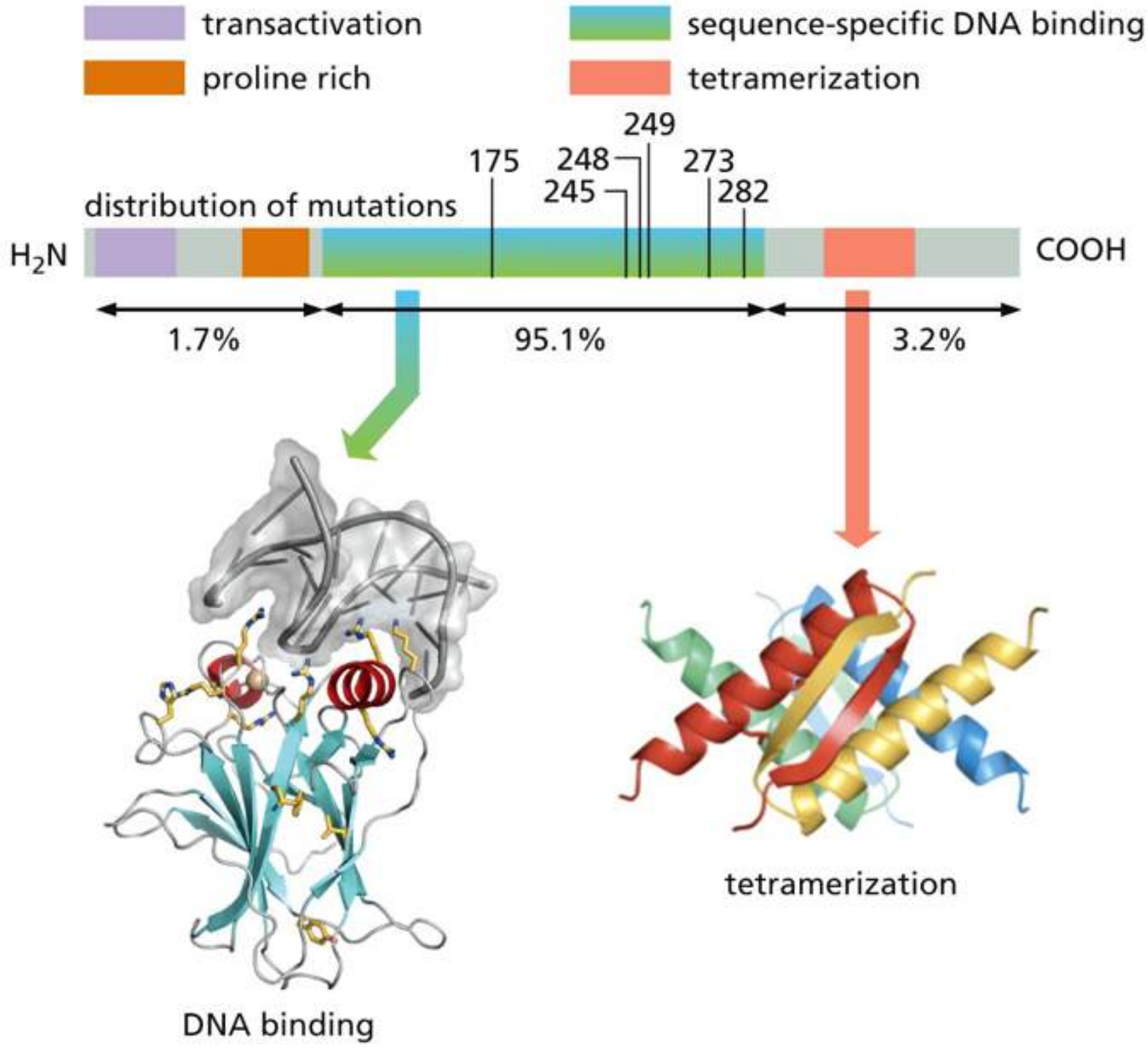
# p53 is a potent tumor suppressor gene



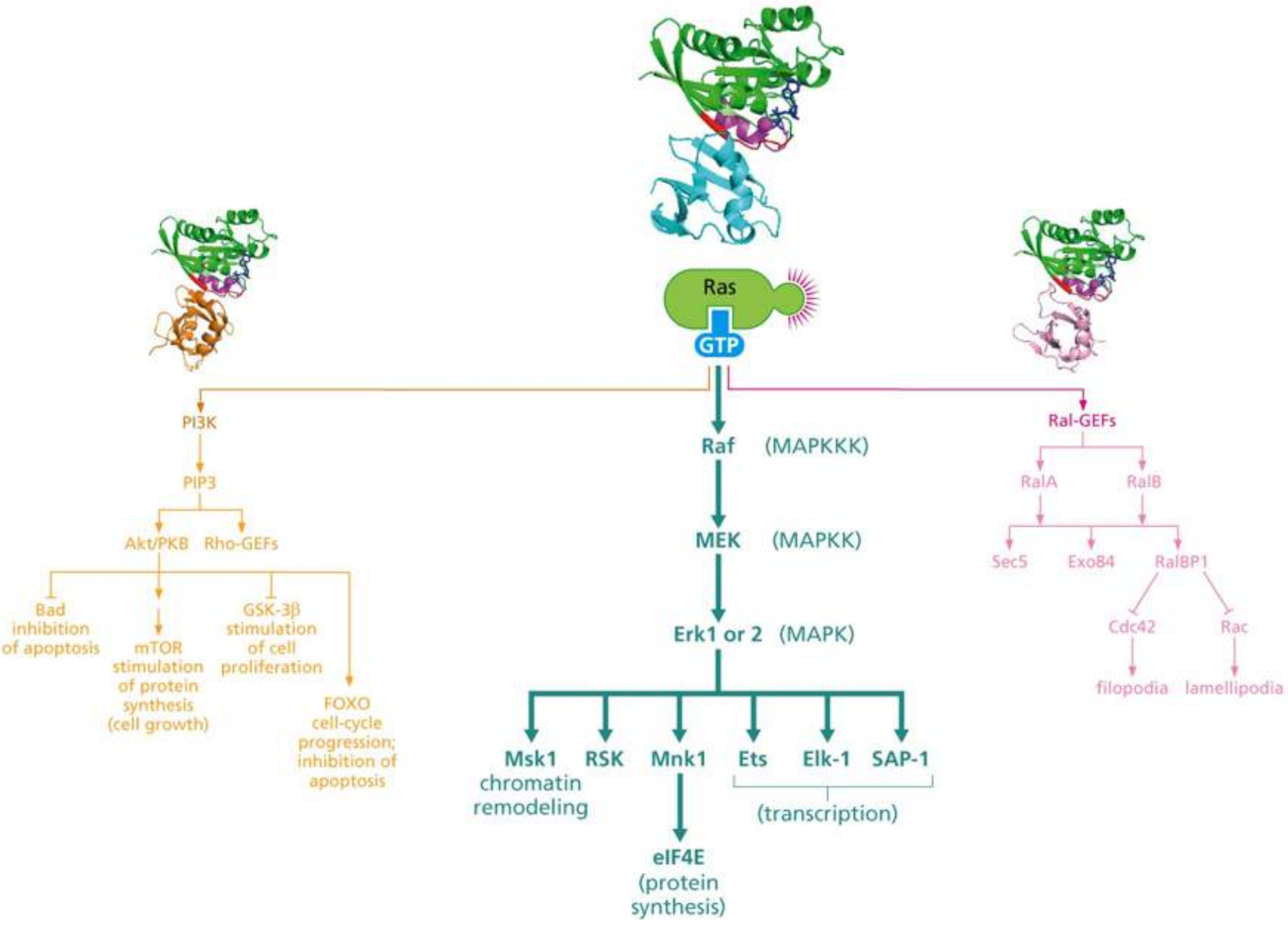
# p53 acts as a transcription factor



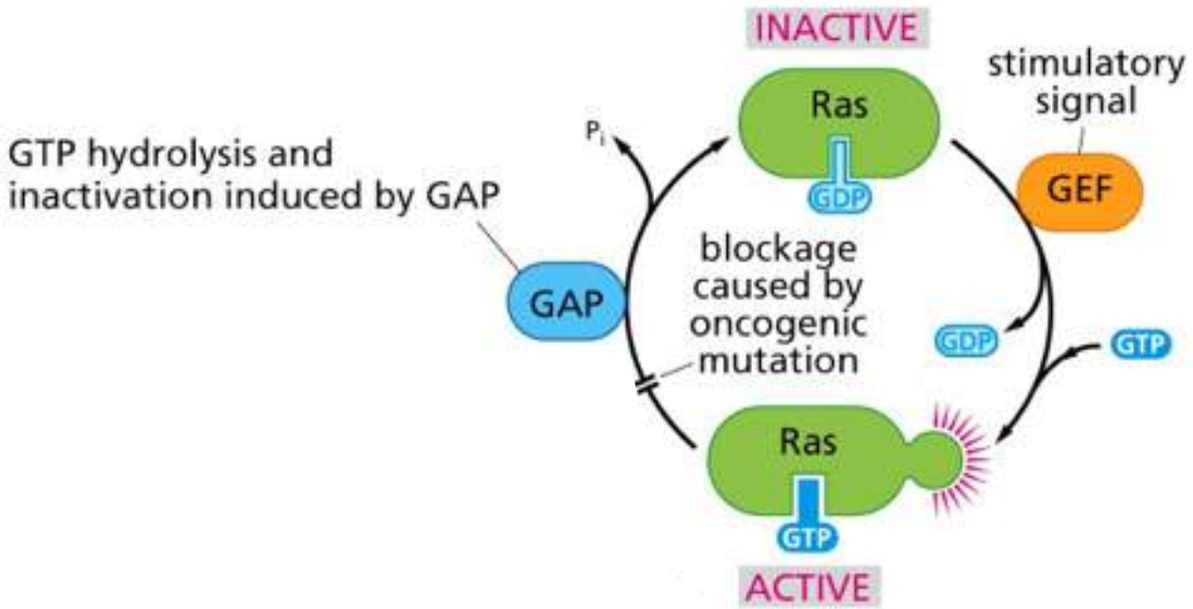
# Oncogenic p53 mutations frequently inactivate the DNA binding domain



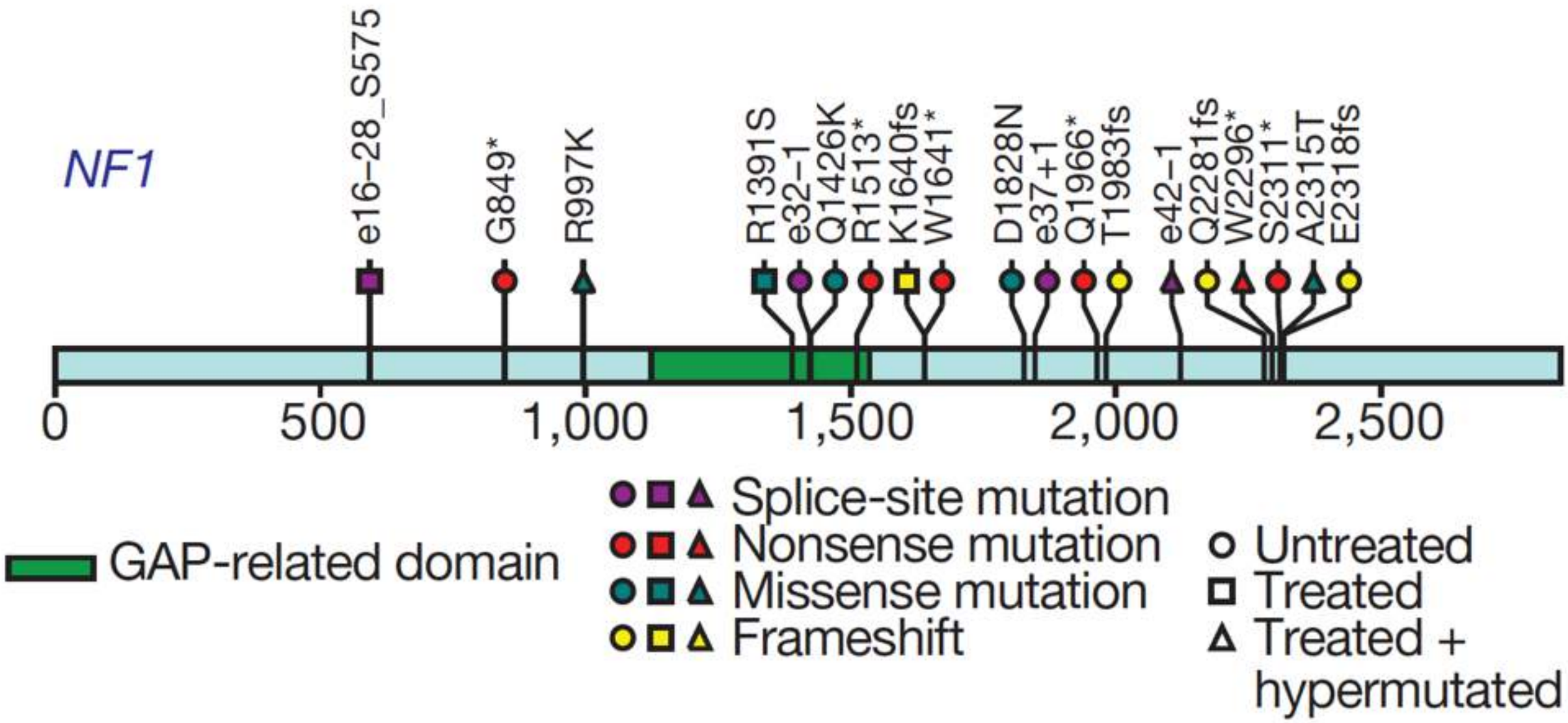
# Ras can be inactivated by GTPase-activating proteins (GAPs)



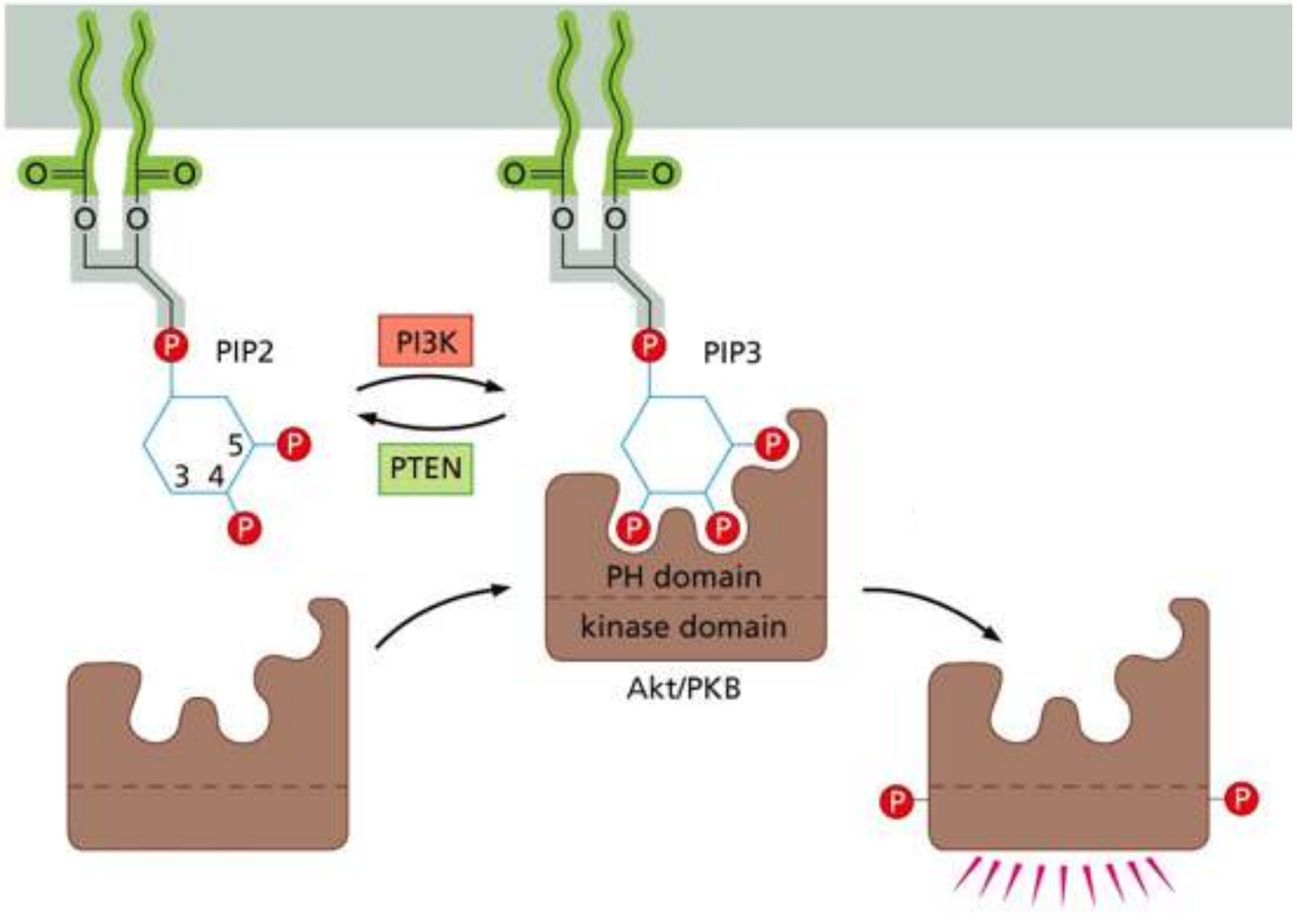
# NF1 is a RAS GAP that is frequently mutated in cancer

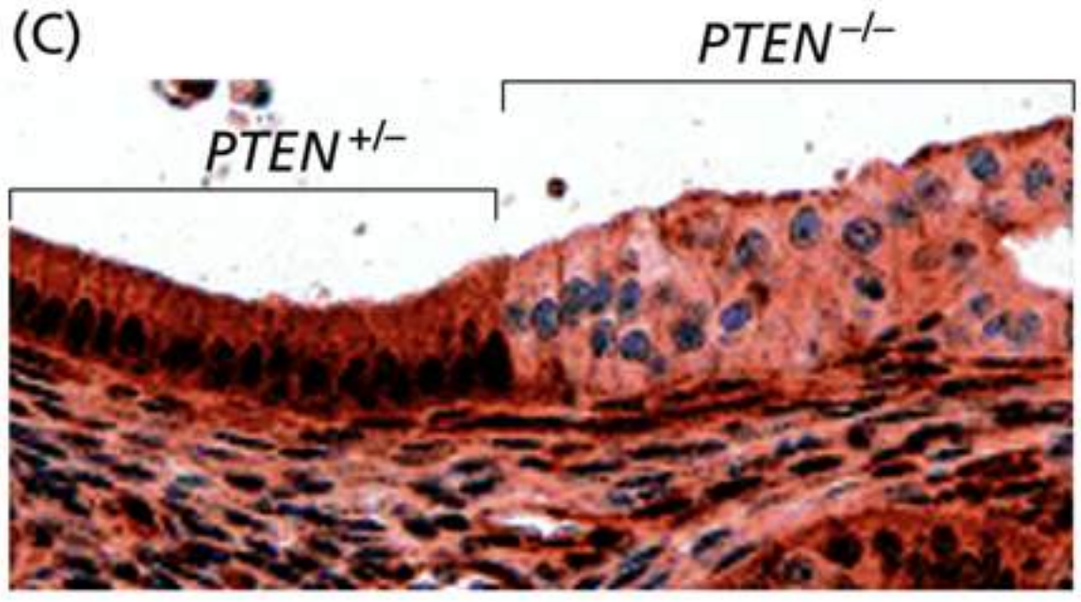


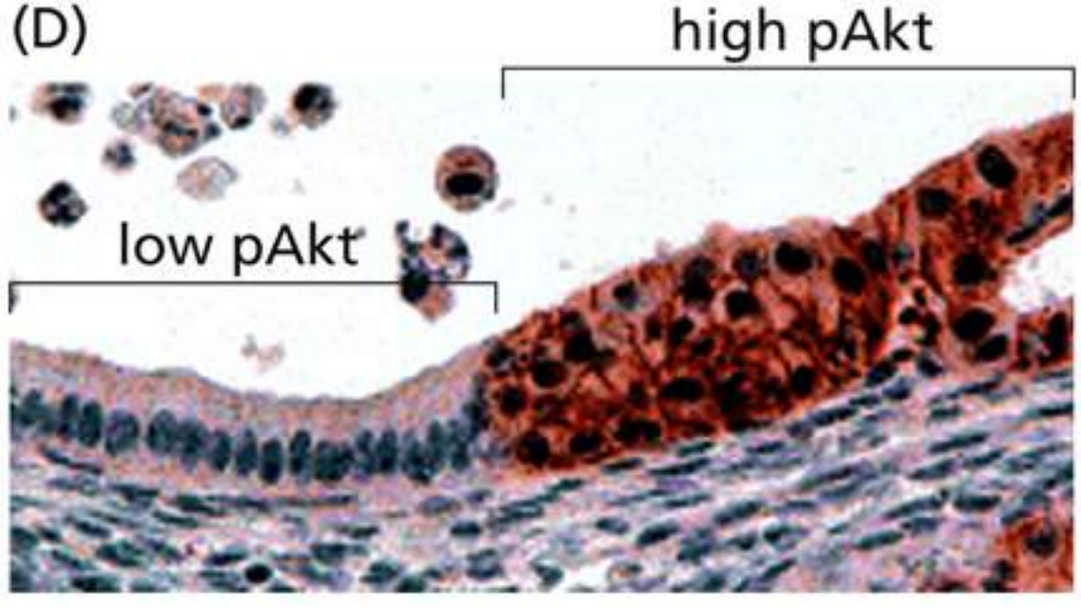
# NF1 is a RAS GAP that is frequently mutated in cancer



# PTEN is a phosphatase the counteracts PI3K-mediated AKT activation



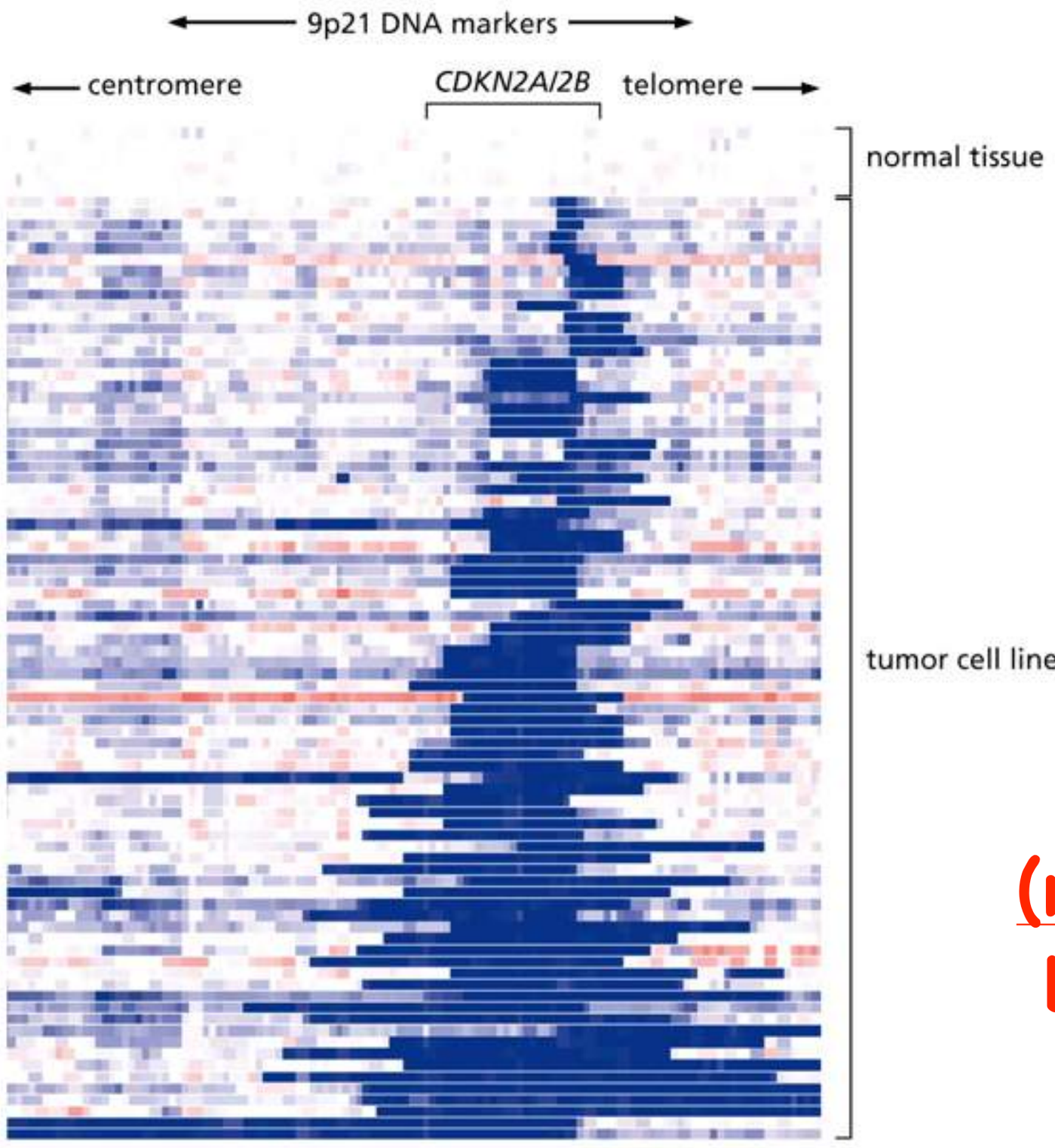



## Take home message #5:

## Tumor suppressor genes can be inactivated by point mutations

# Tumor suppressor genes can be inactivated by genetic changes affecting either protein expression or structure

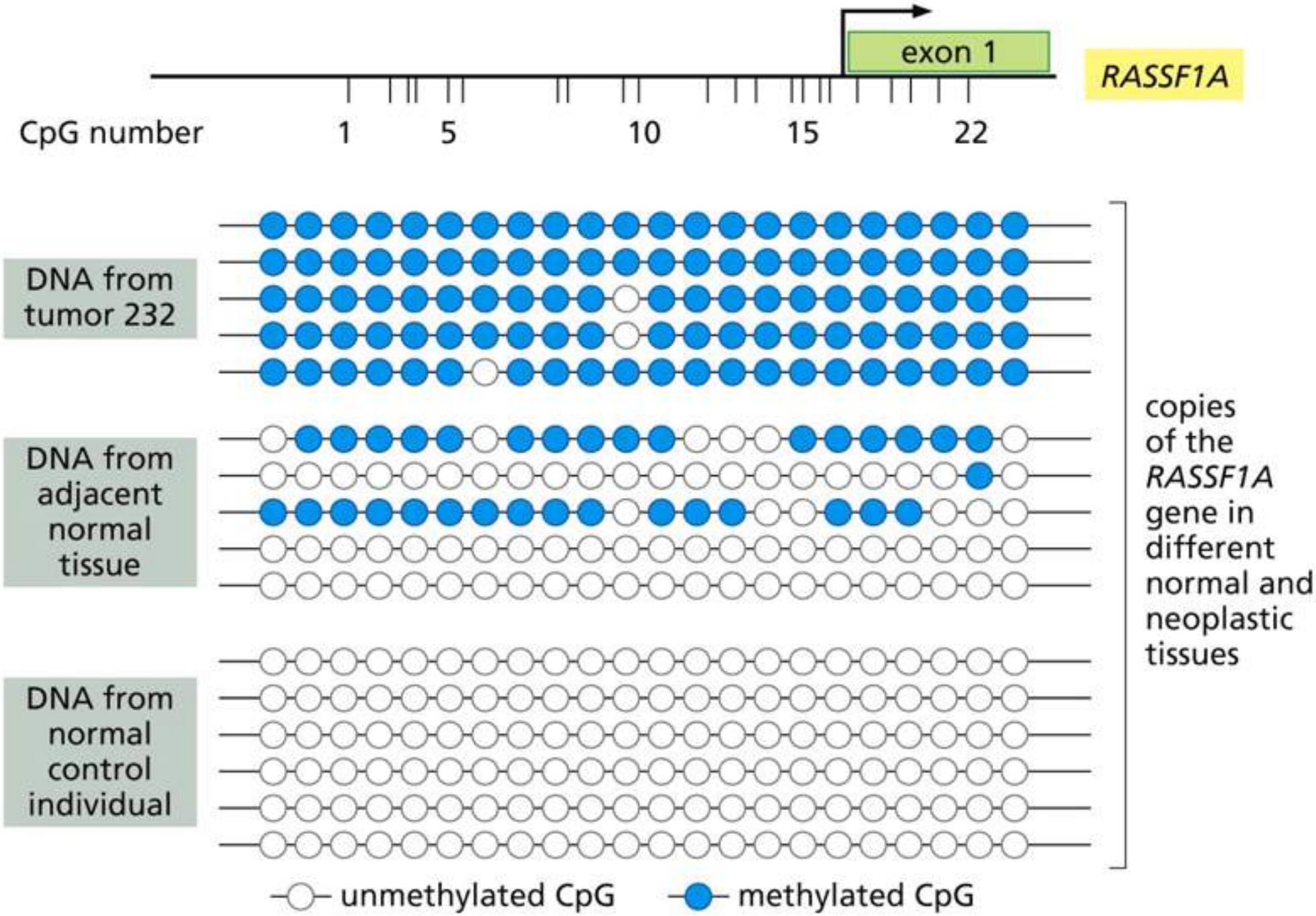



(micro) deletions can lead to inactivation of TSGs

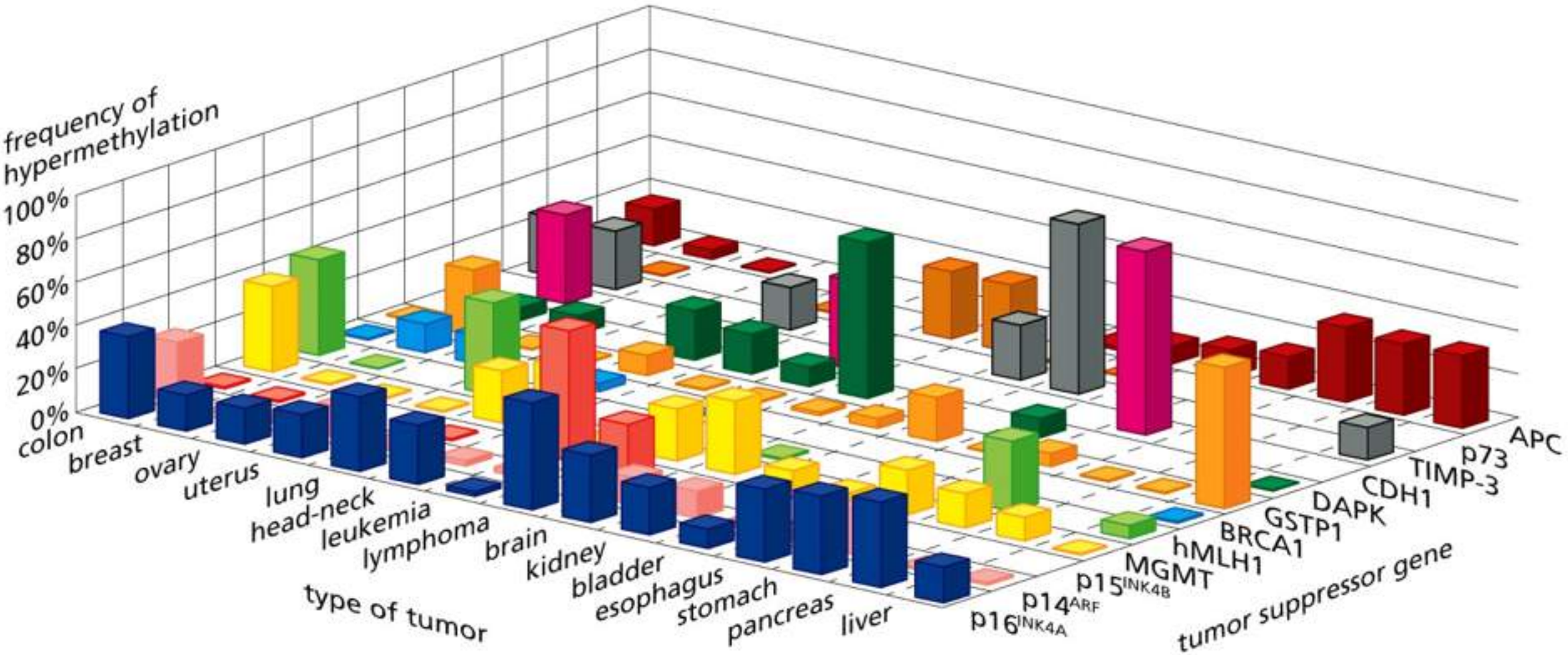
## Take home message #6:

## Tumor suppressor genes can be inactivated (micro) deletions

# Tumor suppressor genes can be inactivated by genetic changes affecting either protein expression or structure



# Tumor suppressor genes can be inactivated by genetic changes affecting either protein expression or structure

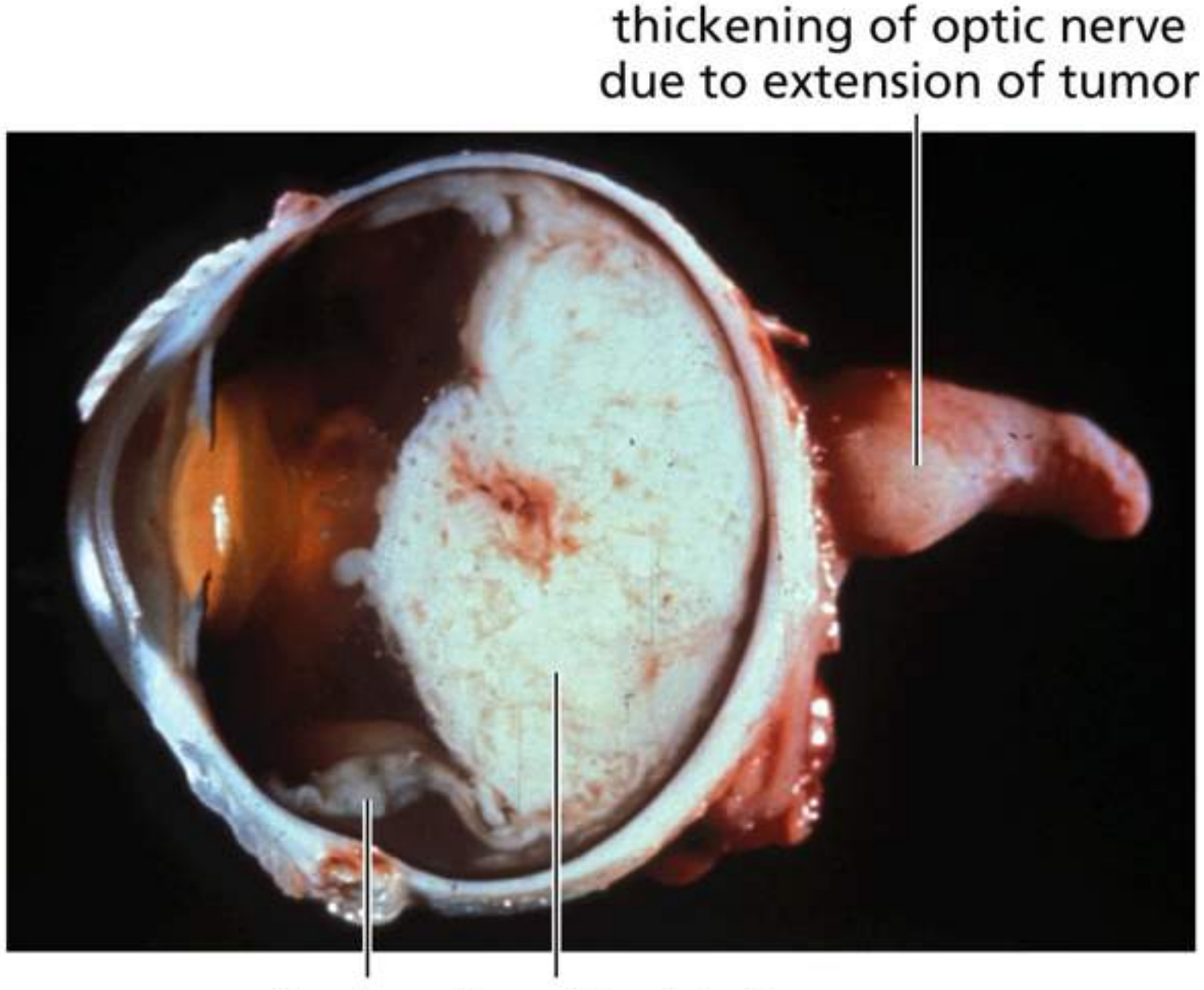



Promoter hypermethylation can lead to inactivation of TSGs

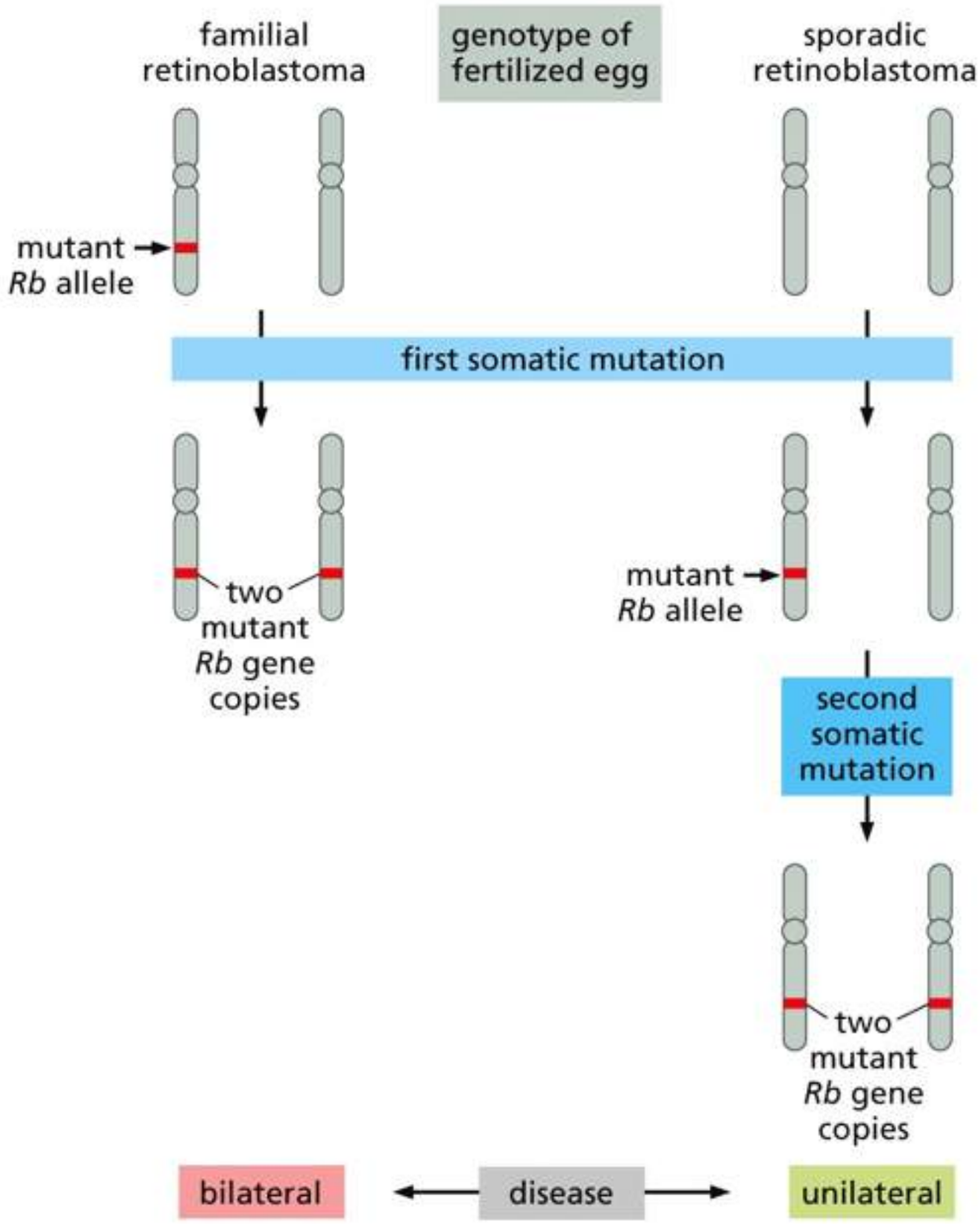
## Take home message #7:

## Tumor suppressor genes can be inactivated promoter hypermethylation

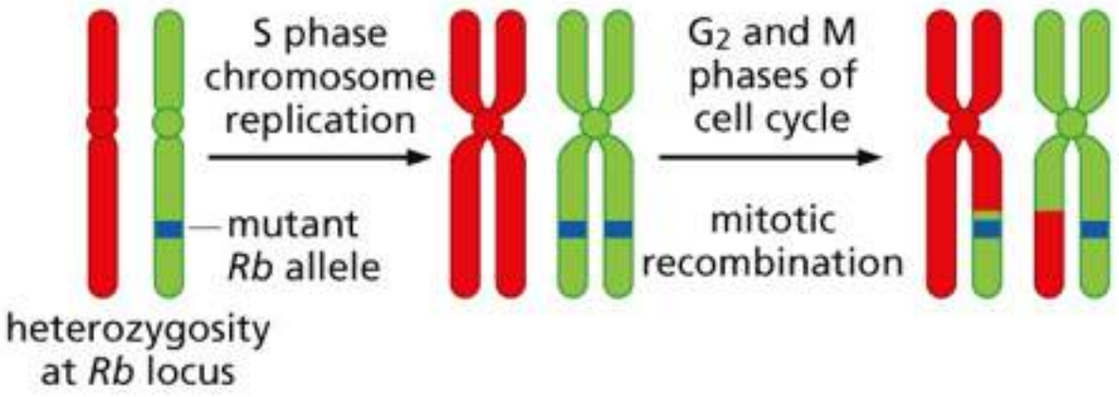
# Unlike in proto-oncogenes, the second allele of a tumor suppressor gene typically has to be inactivated to drive tumorigenesis



# Rb1 and the Knudson hypothesis

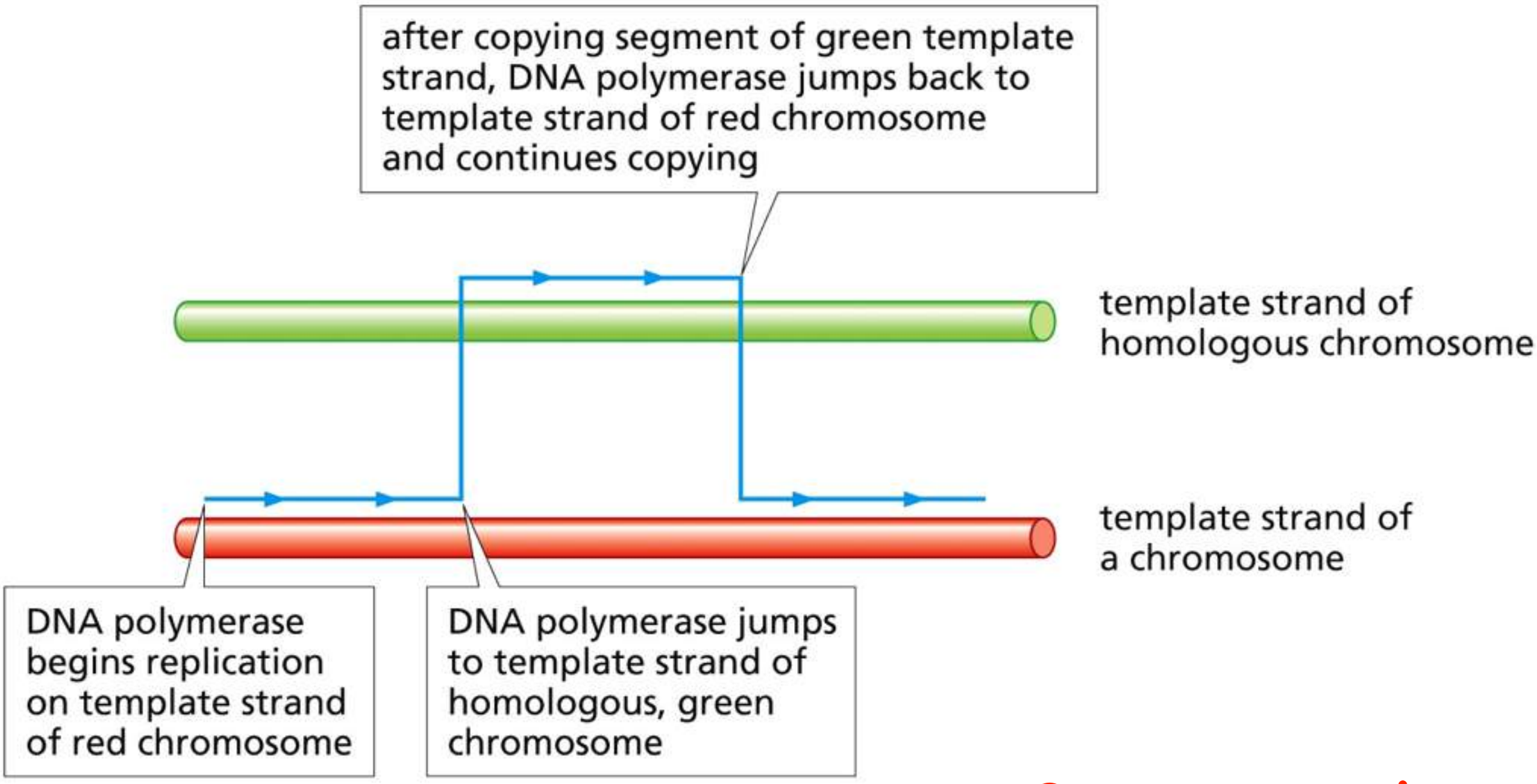


# Loss of heterozygosity can be achieved through mitotic recombination



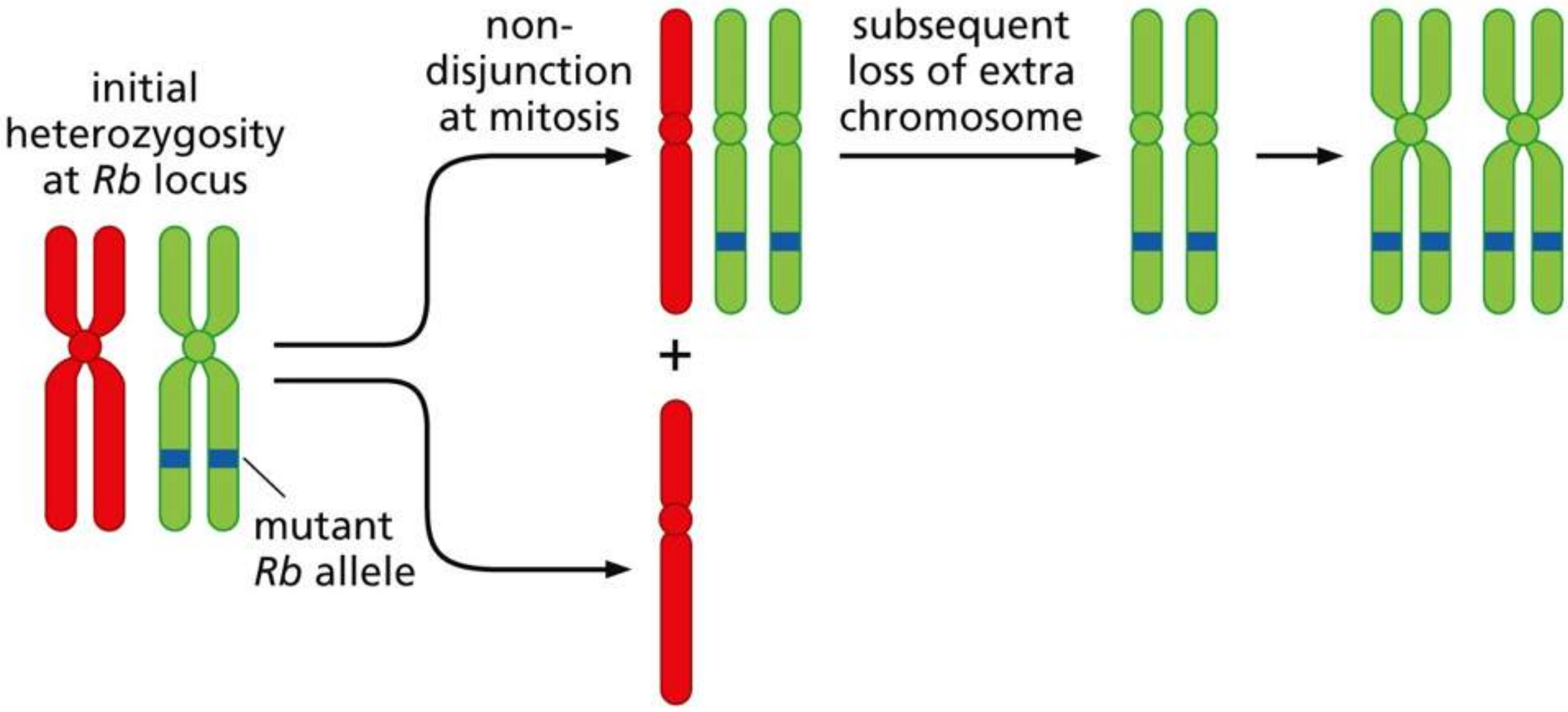

Mitotic recombination can lead to loss of heterozygosity (LOH)

# Loss of heterozygosity can be achieved through gene conversion




**Gene conversion can lead to LOH**

# Loss of heterozygosity can be achieved through mitotic non-disjunction

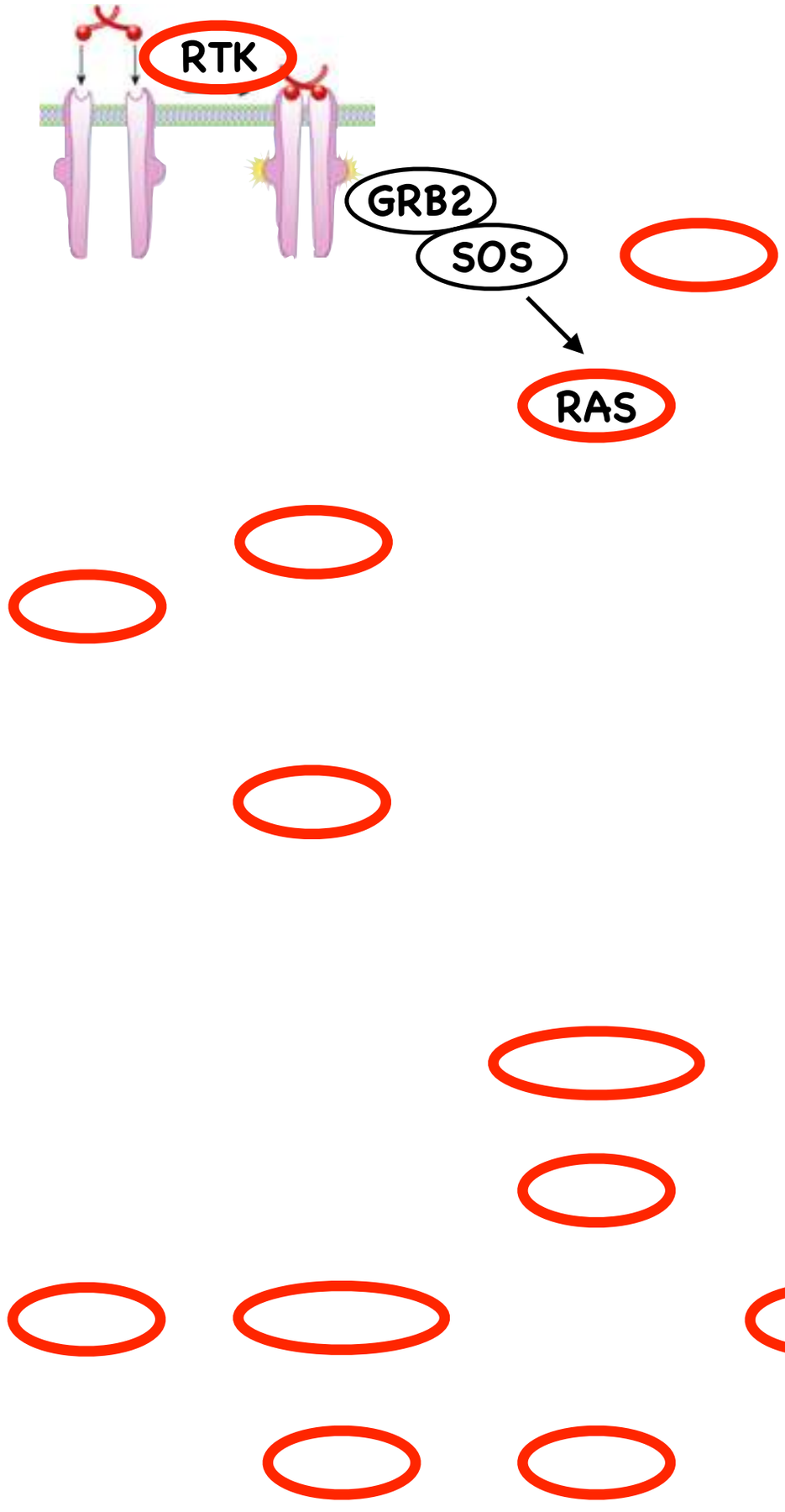



Mitotic non-disjunction can lead to LOH

## Take home message #8:

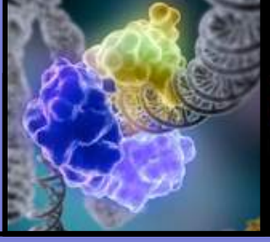
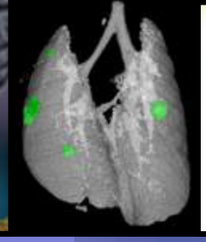
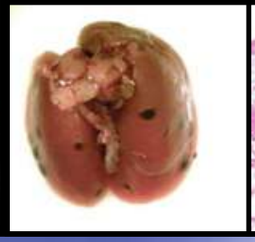
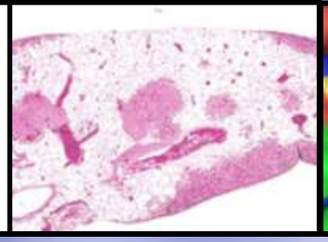
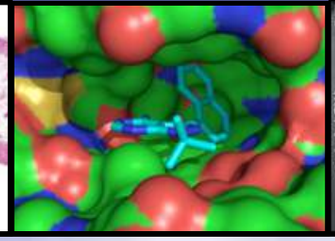
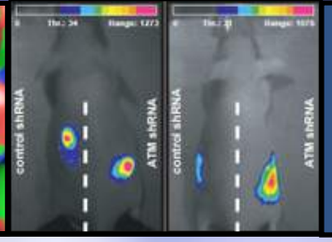
## Loss of heterozygosity can be achieved through mitotic cross-overs, mitotic non-disjunction or gene conversion

# Pathway review



# Summary

- Progression through the cell cycle is driven by CDKs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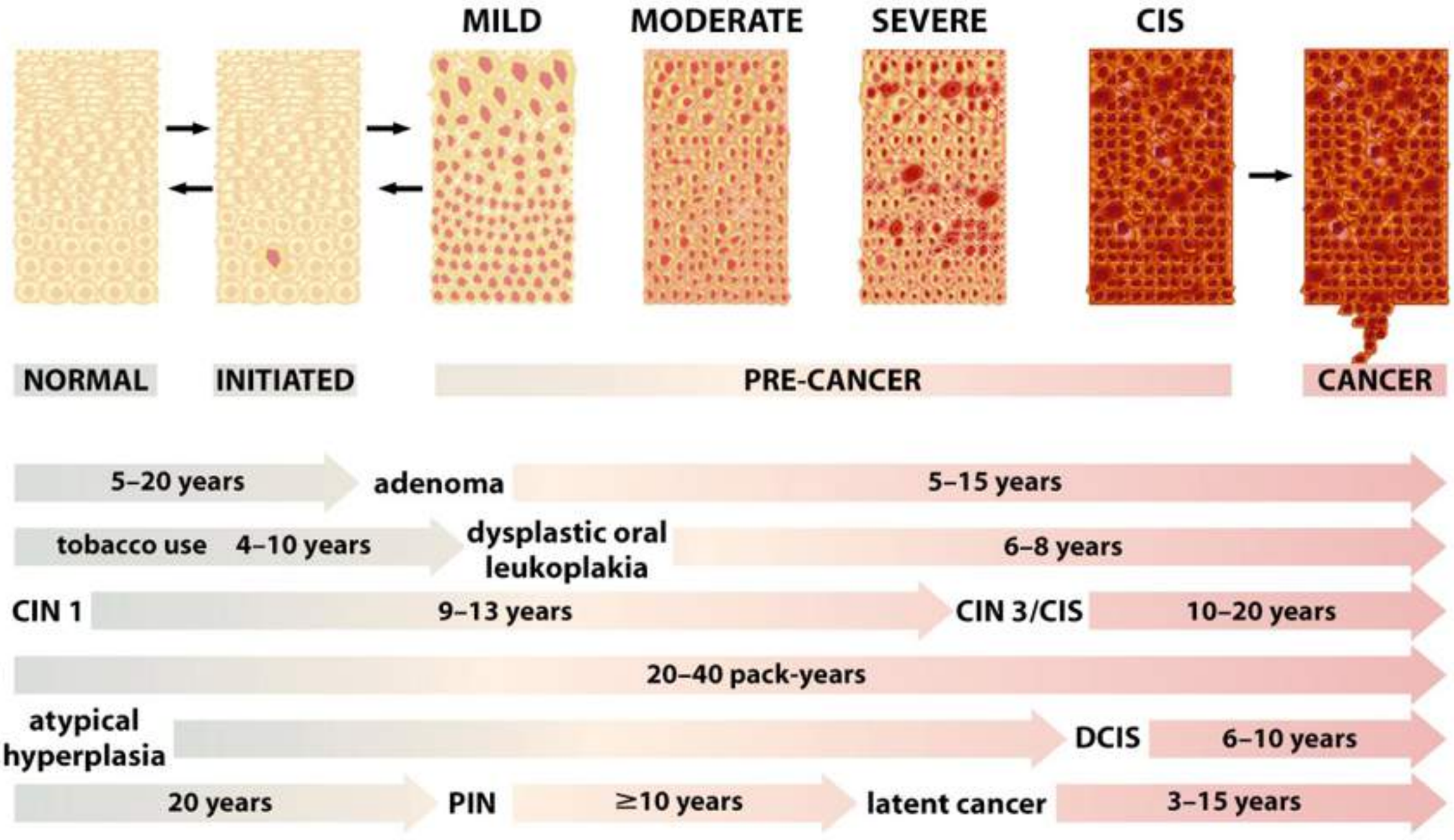
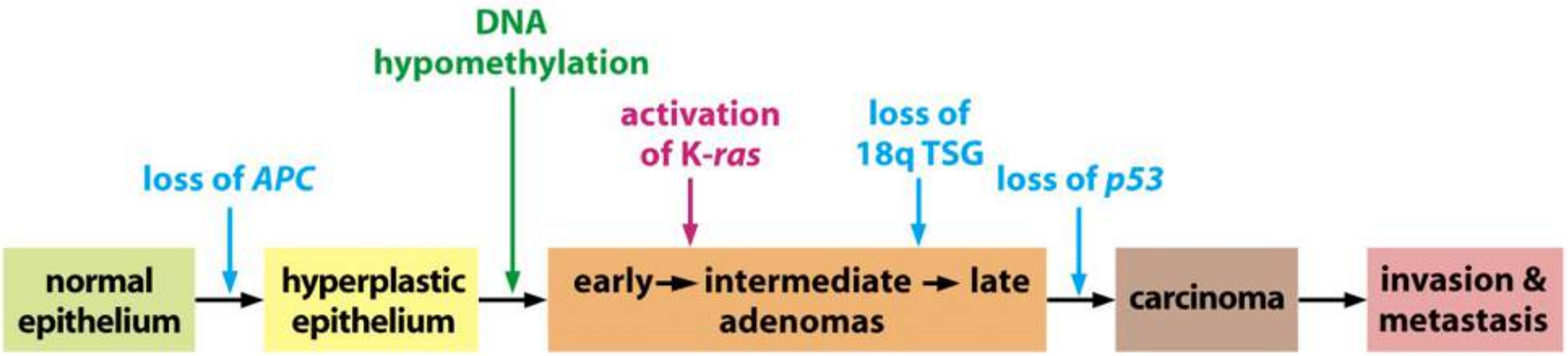
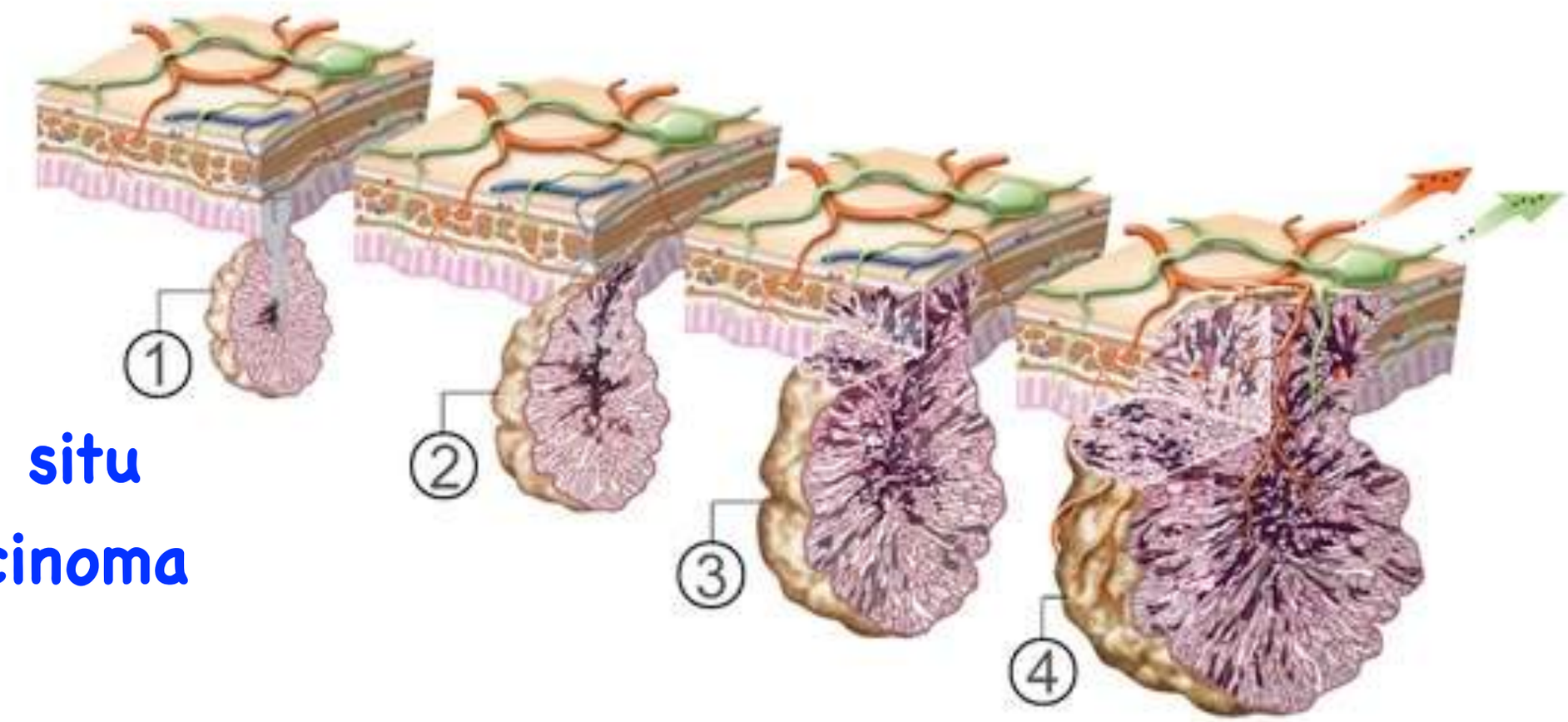
# Tumorevolution can be visualised by histology



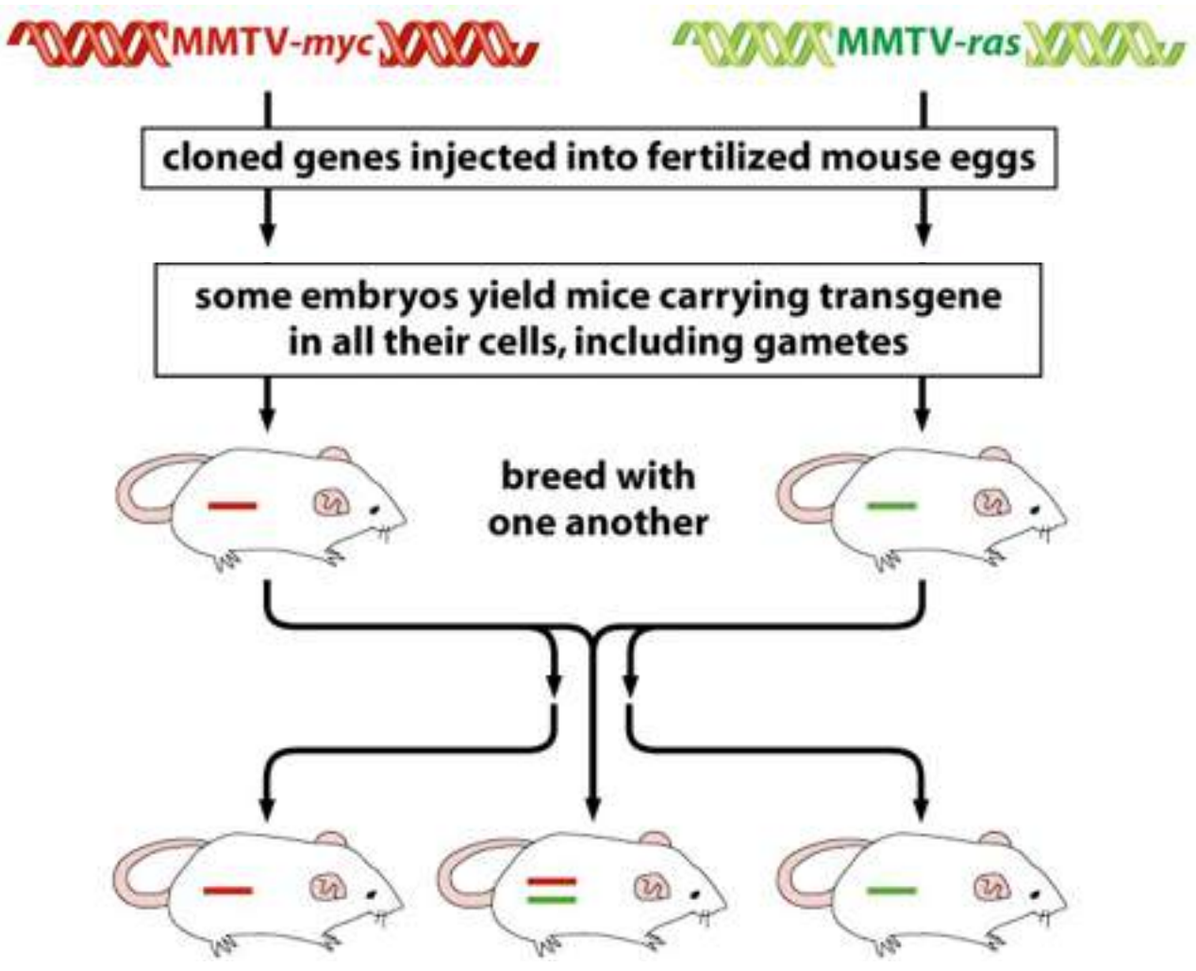
# The genetic evolution of colorectal carcinomas

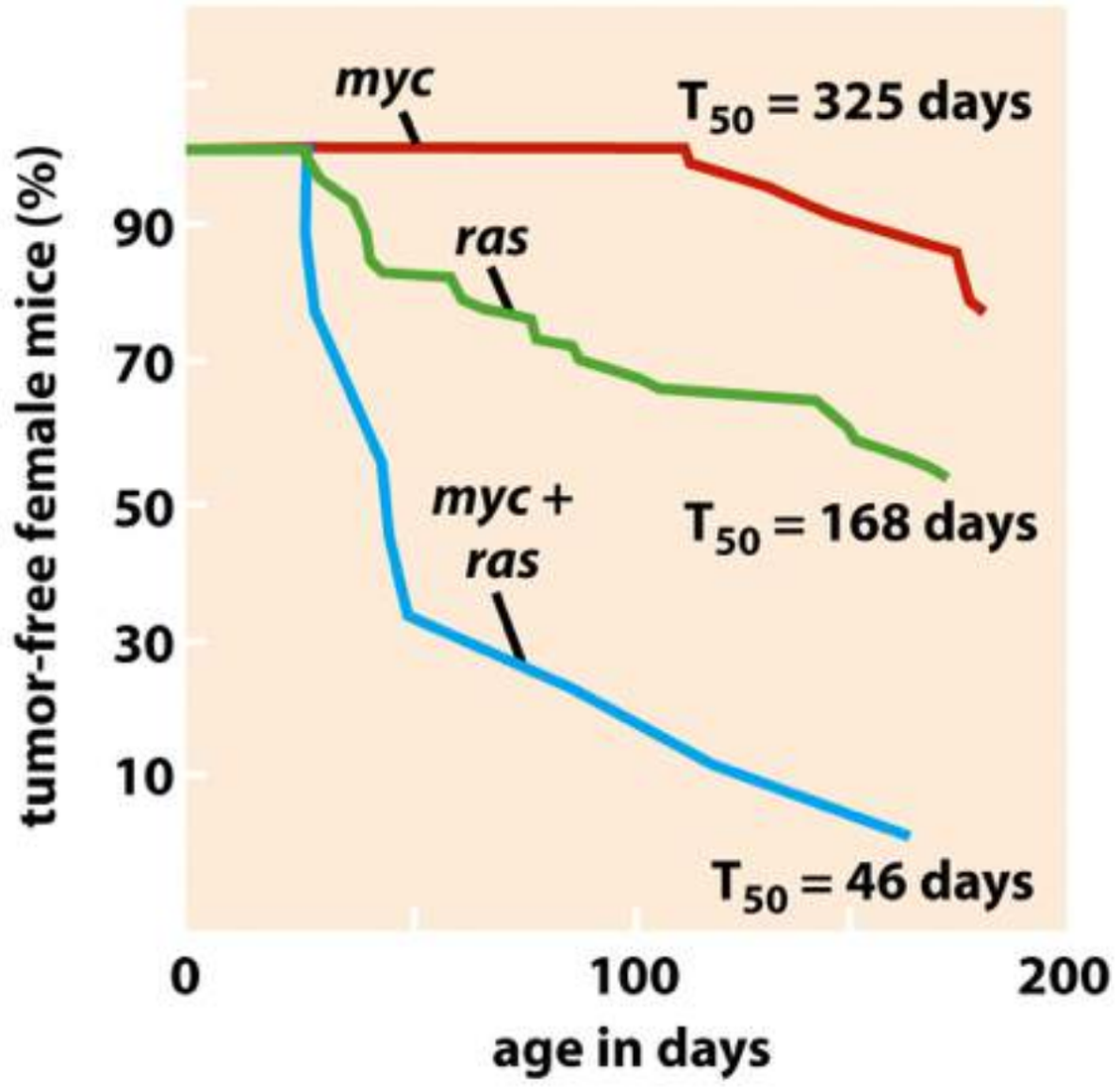



1) Adenoma
2) Carcinoma in situ
3) Invasive carcinoma
4) Metastasis



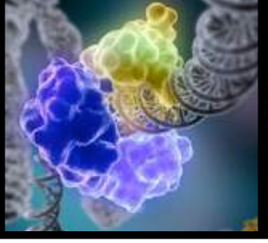
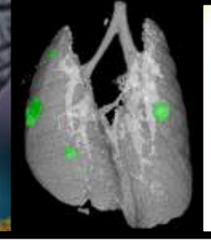
# Oncogenes cooperate

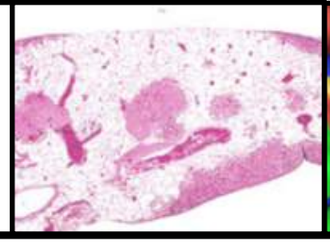
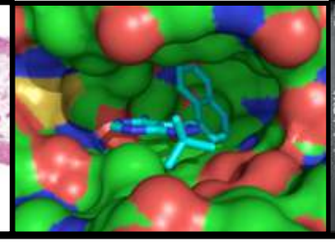
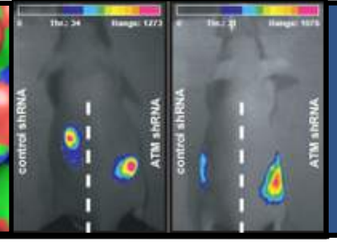


# Take home message #9:

# Human neoplastic diseases are the result of a process called"multi-step-tumorigenesis"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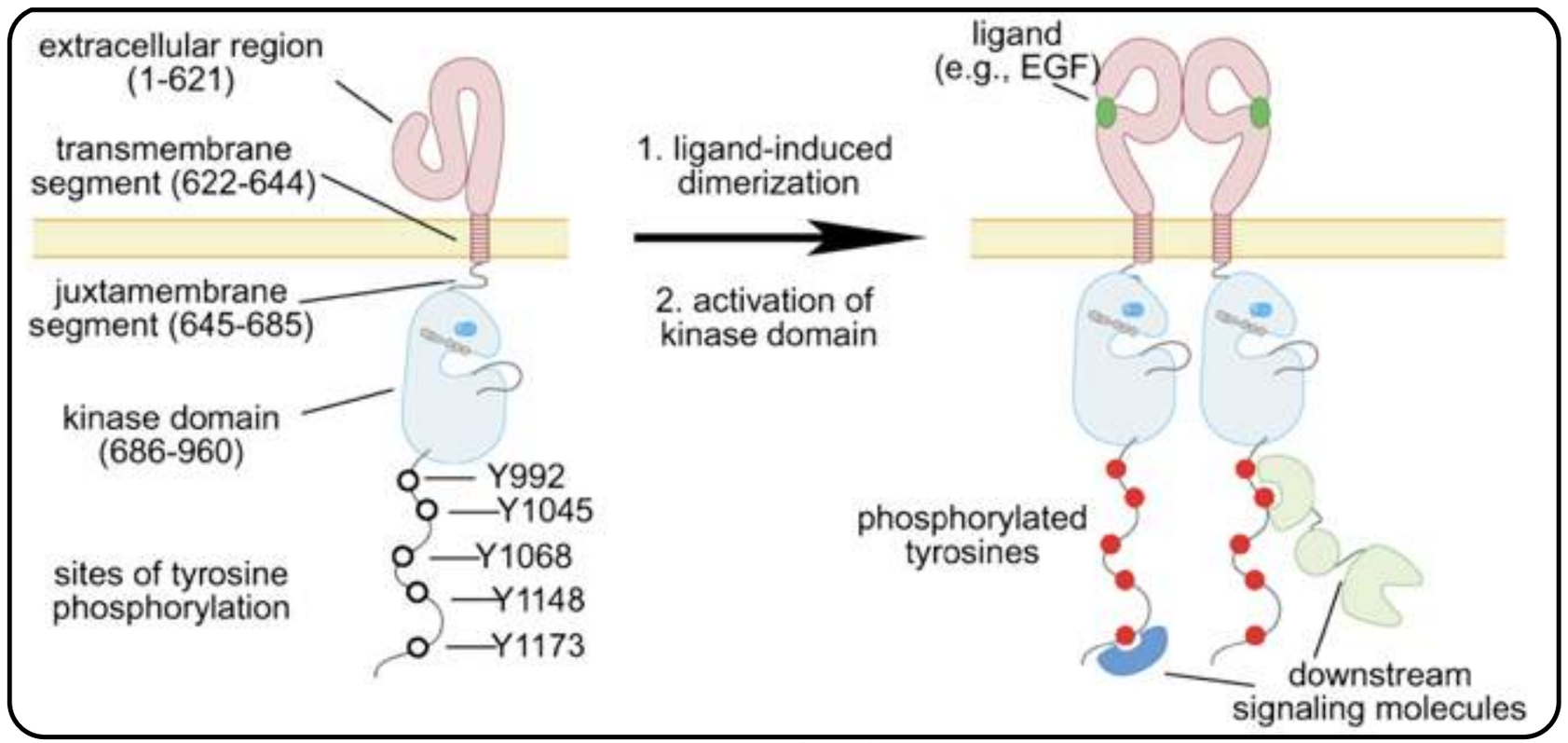
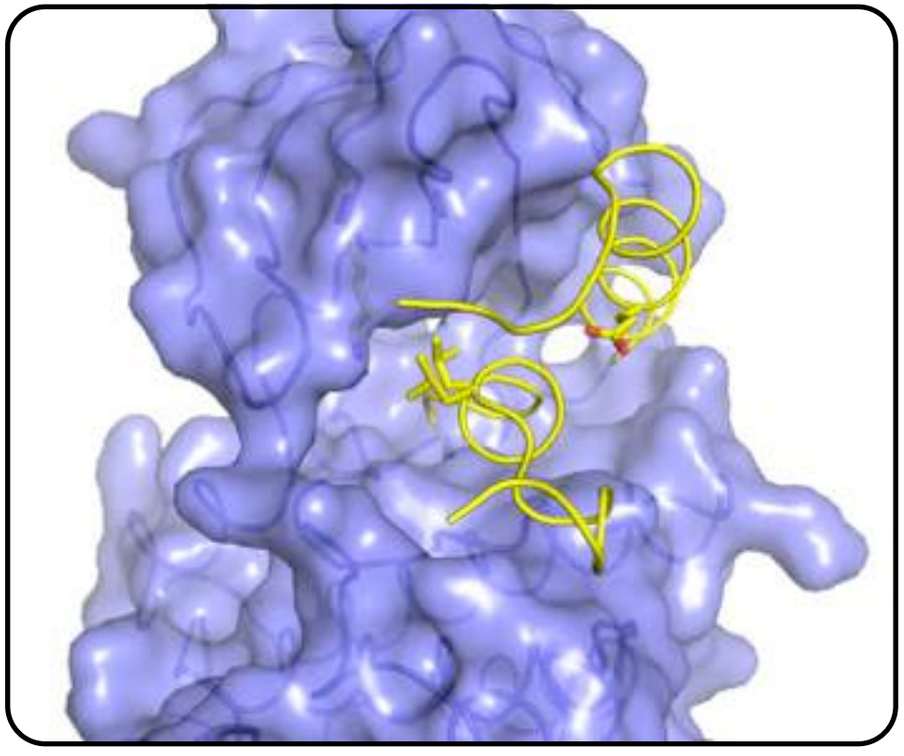
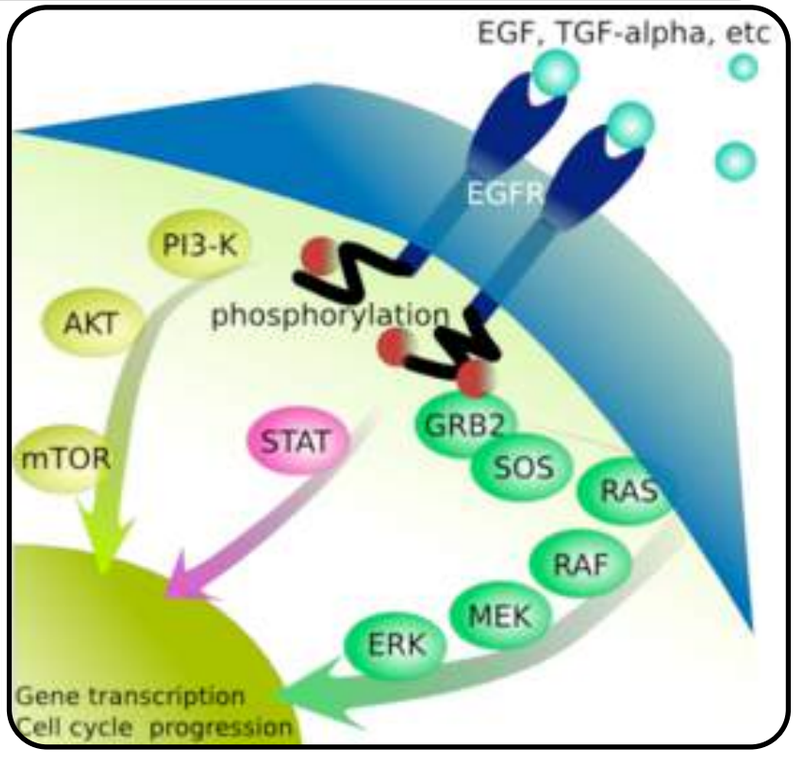
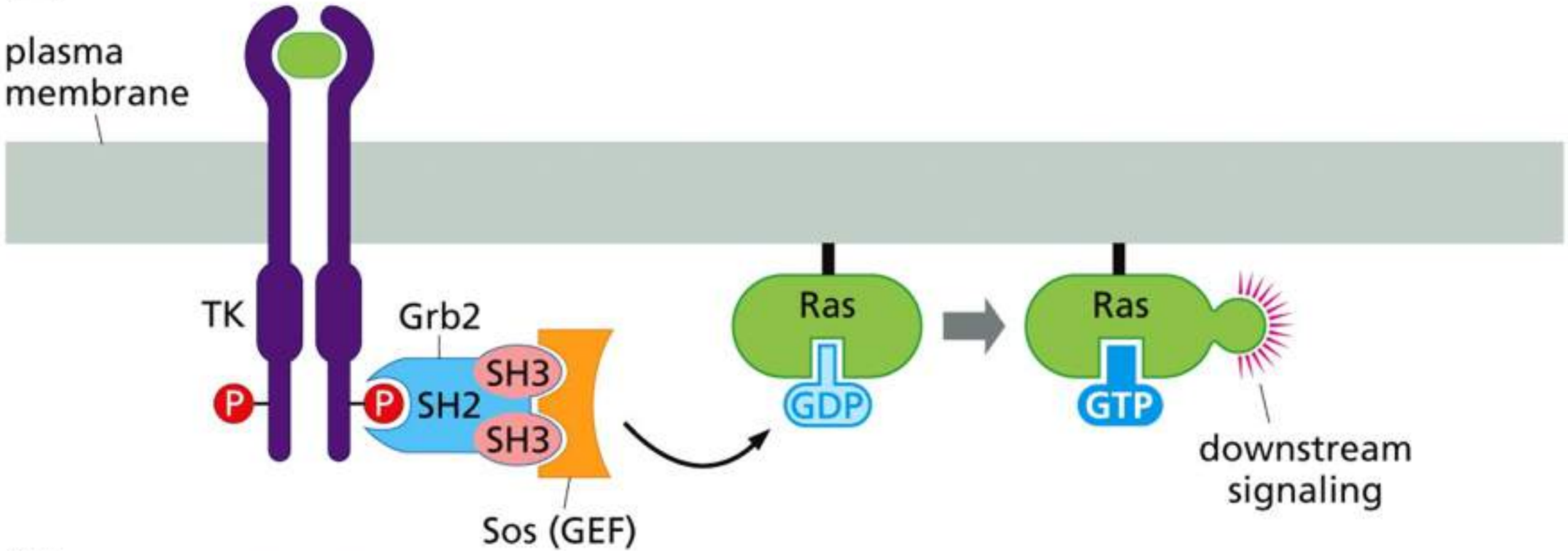
# The biology of EGFR signaling

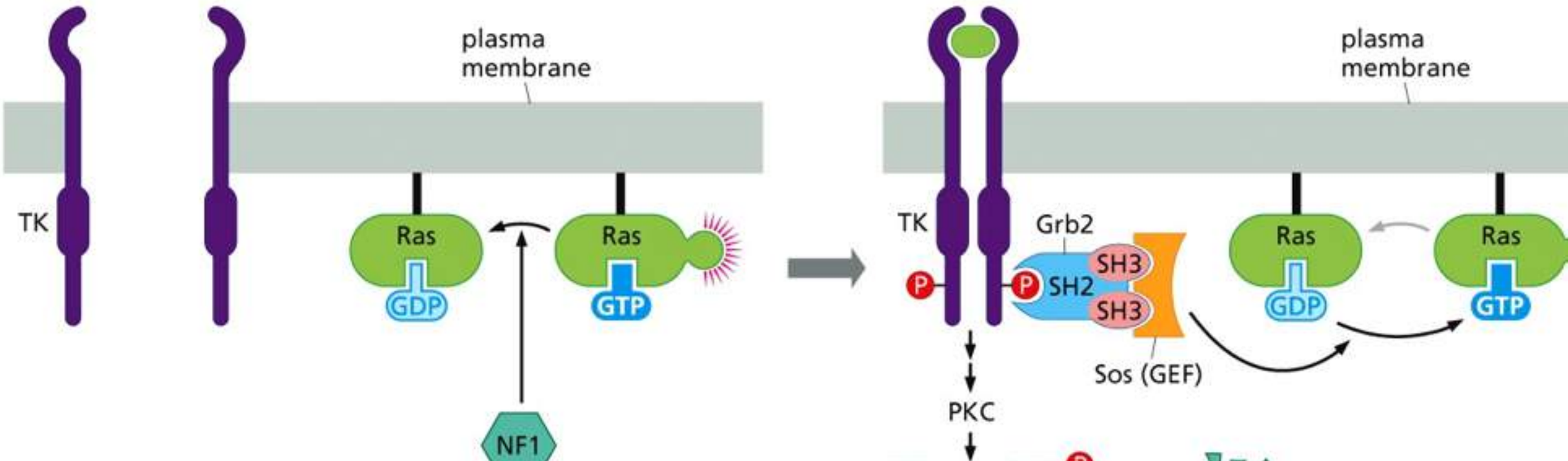


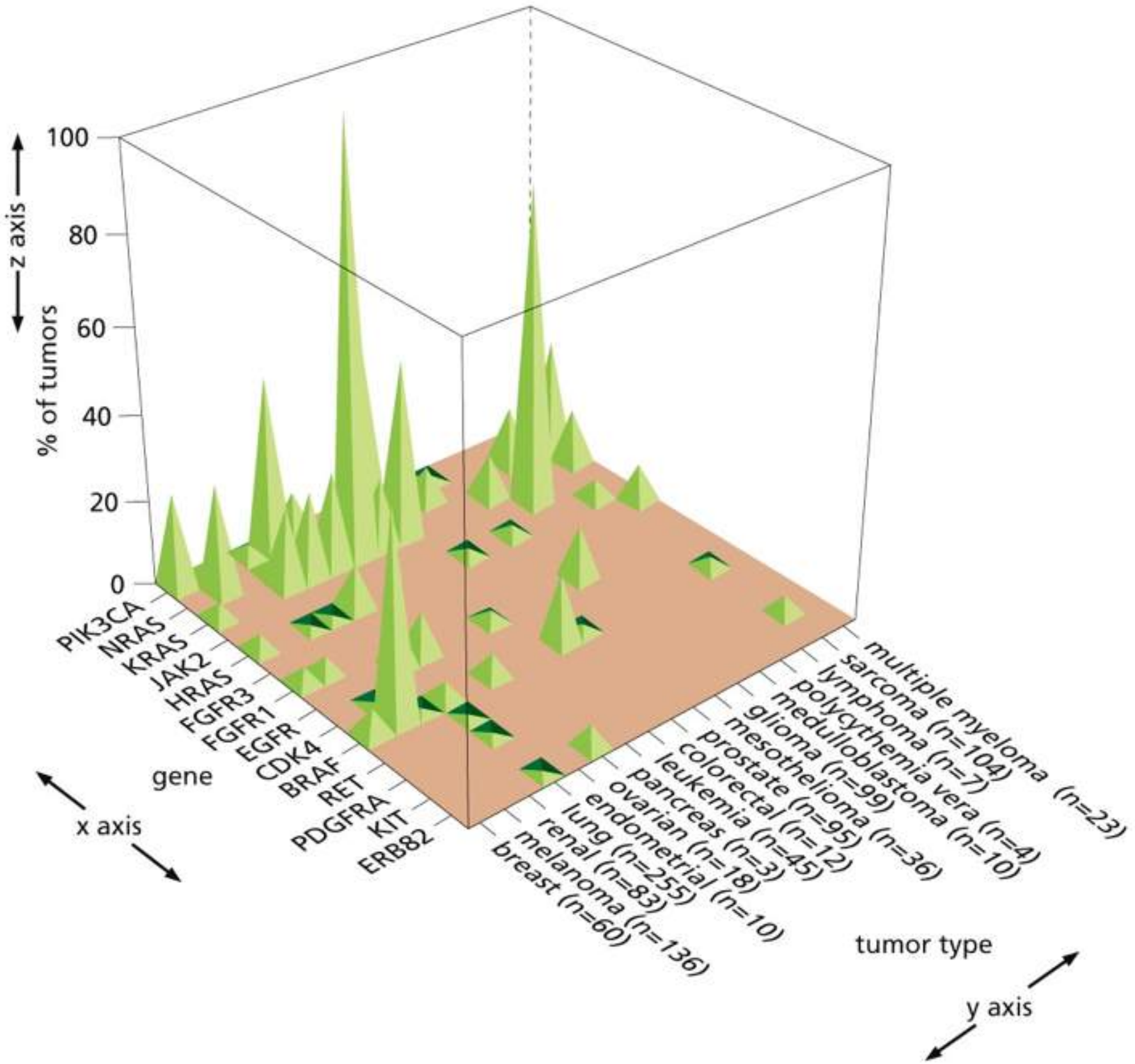



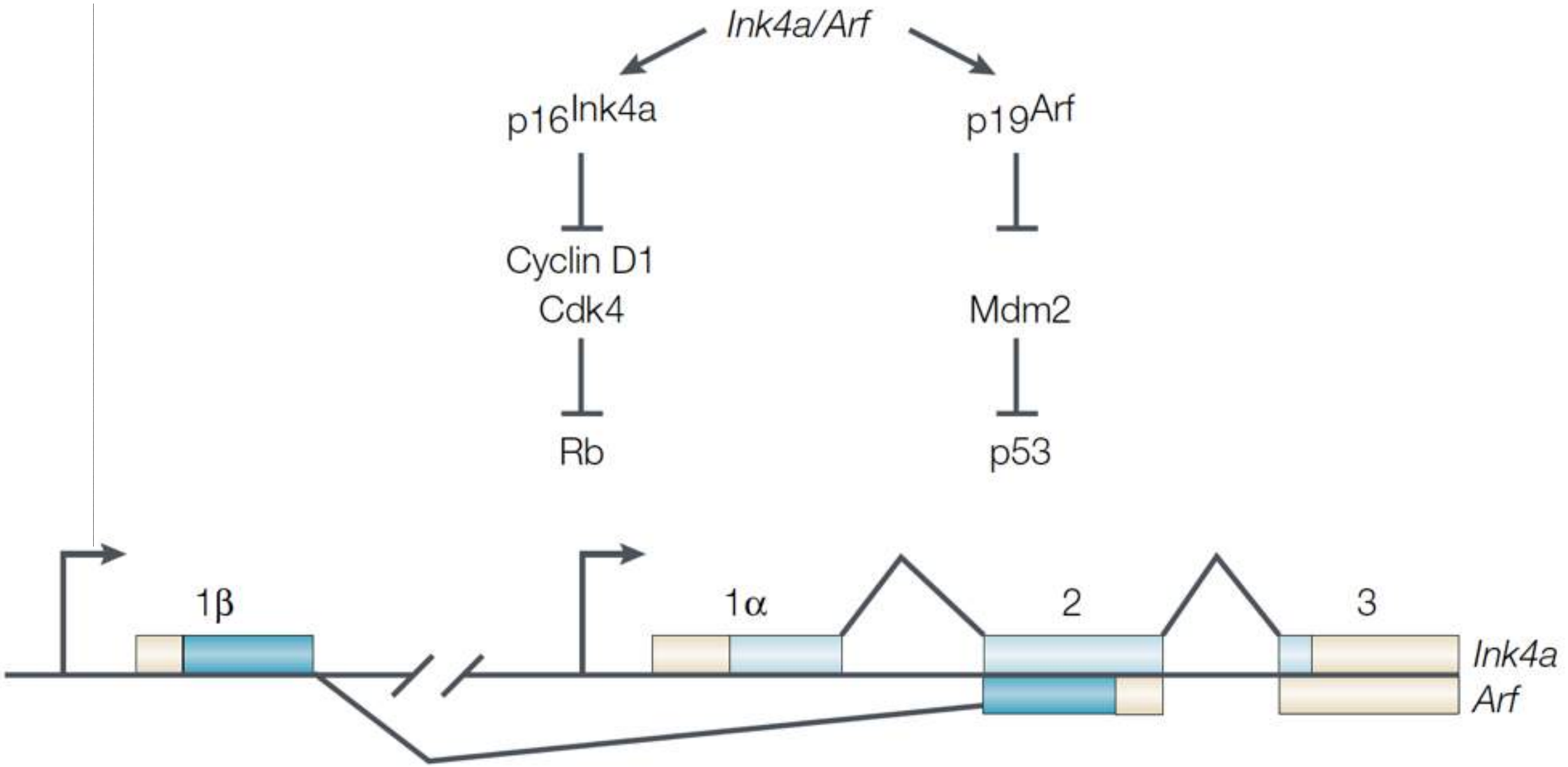


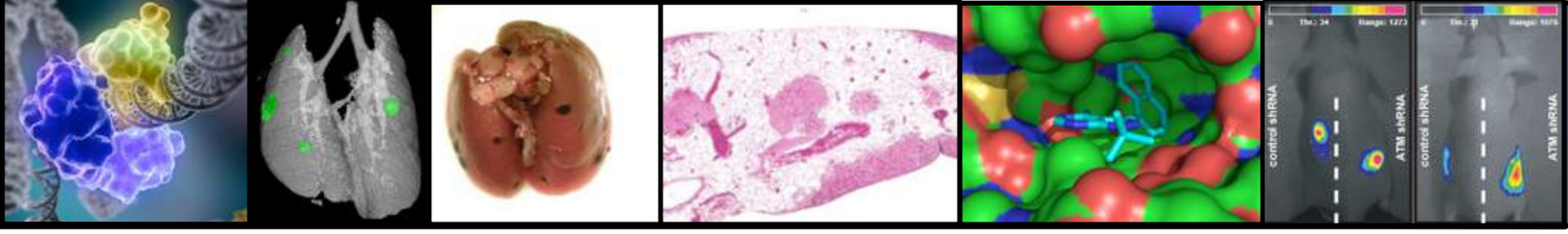
(A)


plasma
membrane
TK
Grb2
SH3
SH2
SH3
P
P
Sos (GEF)
Ras
GDP
Ras
GTP
downstream
signaling


plasma
membrane
TK
Ras
GDP
Ras
GTP
NF1
TK
Grb2
SH3
SH2
SH3
P
P
Sos (GEF)
PKC
plasma
membrane
Ras
GDP
Ras
GTP


z axis
100
80
60
40
20
0
% of tumors
PIK3CA
NRAS
KRAS
JAK2
HRAS
FGFR3
FGFR1
EGFR
CDK4
BRAF
RET
PDGFRA
KIT
ERB82
gene
x axis
multiple myeloma (n=23)
sarcoma (n=104)
lymphoma (n=7)
polycythemia vera (n=4)
medulloblastoma (n=10)
glioma (n=99)
mesothelioma (n=36)
prostate (n=95)
colorectal (n=12)
leukemia (n=45)
pancreas (n=3)
ovarian (n=18)
endometrial (n=10)
lung (n=255)
renal (n=83)
melanoma (n=136)
breast (n=60)
tumor type
y axis


Ink4a/Arf
p16Ink4a
p19Arf
Cyclin D1
Cdk4
Mdm2
Rb
p53
1β
1α
2
3
Ink4a
Arf

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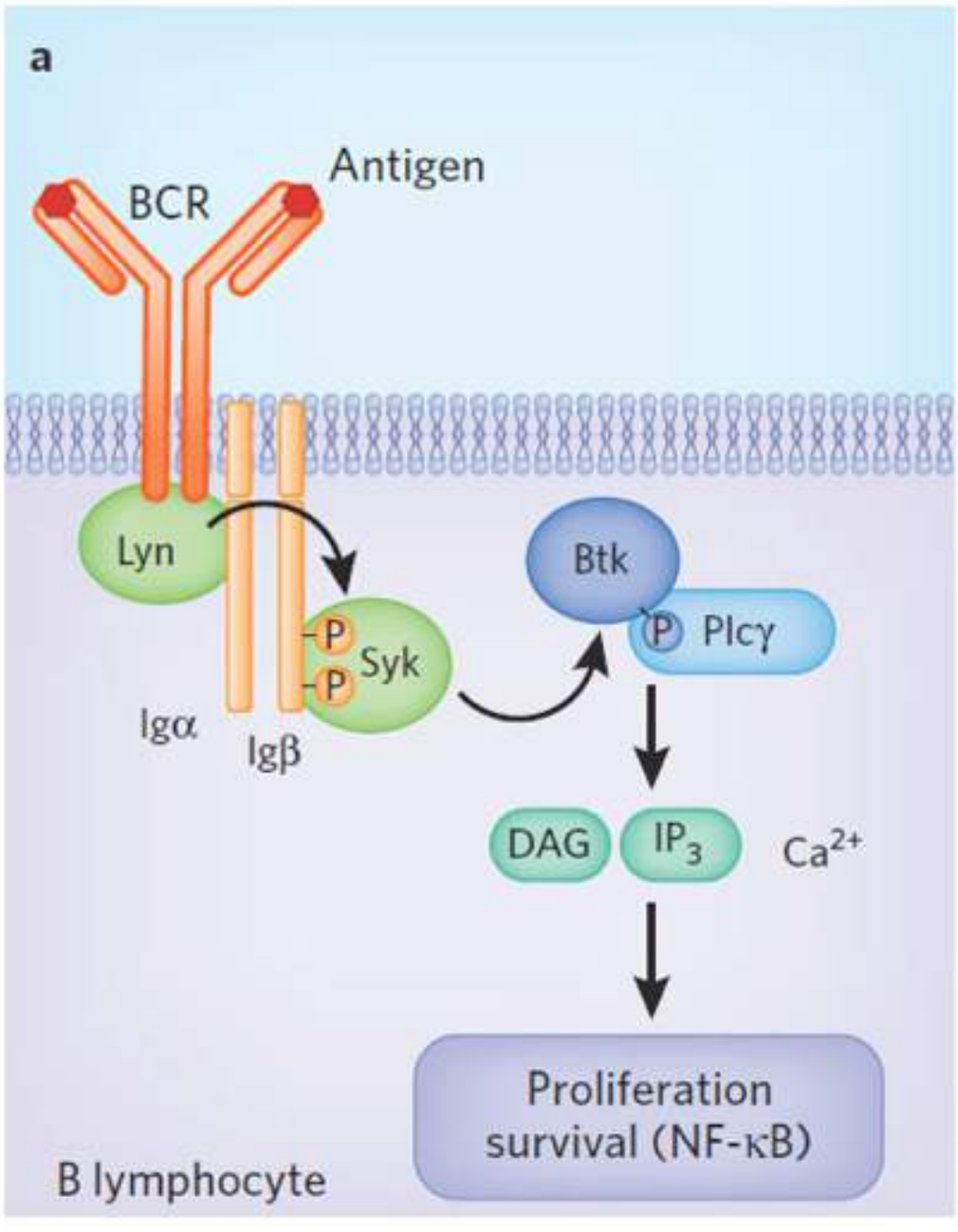
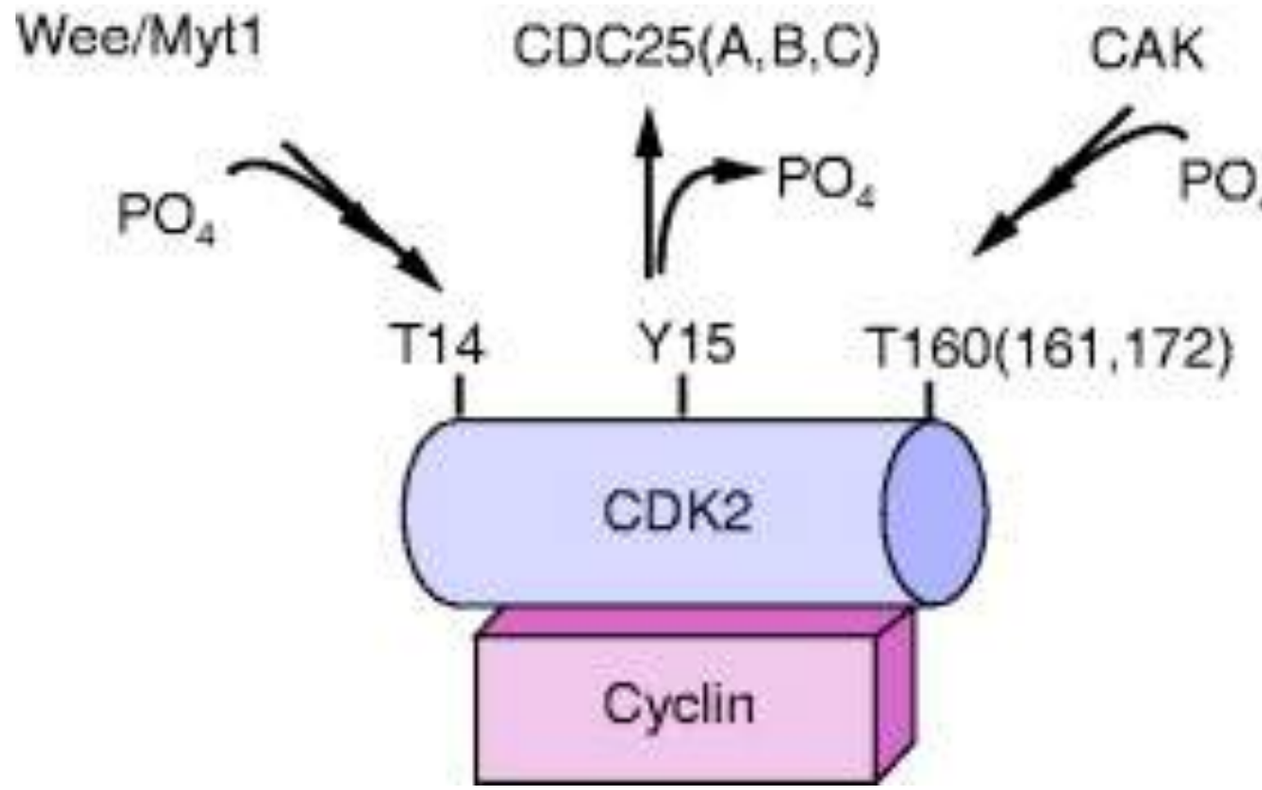
# The SRC gene encodes for an oncogenic tyrosine kinase




Wee/Myt1
CDC25(A,B,C)
CAK
PO4
PO4
PO4
T14
Y15
T160(161,172)
CDK2
Cyclin