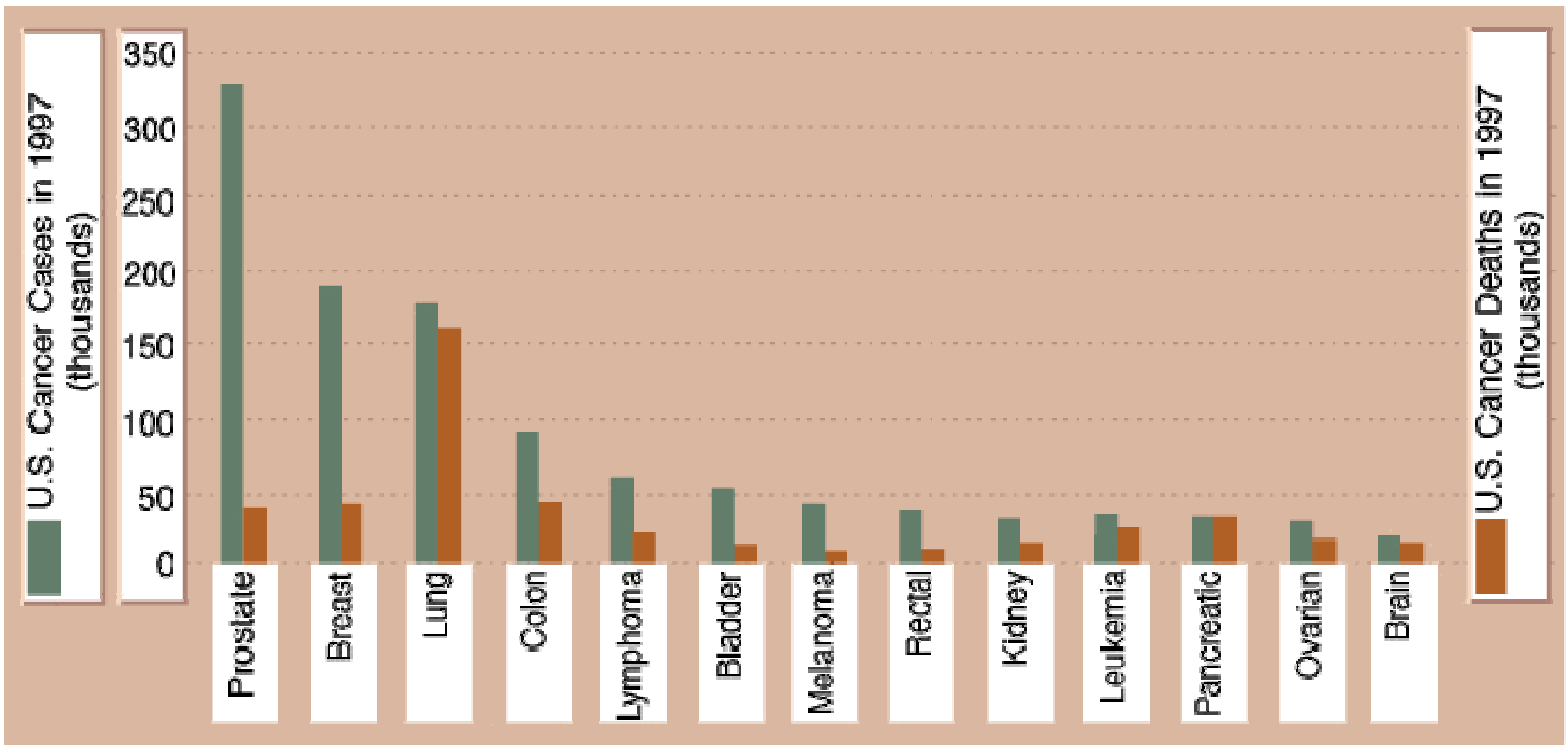
Genetics of Cancer

Lecture 32

“Cancer II”

Prof. Bevin Engelward, MIT Biological Engineering Department

Why Cancer Matters



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New Cancer Cases in 1997 Cancer Deaths in 1997

Genetics of Cancer:

Today: What types of genetic changes turn a normal cell into a cancer cell?

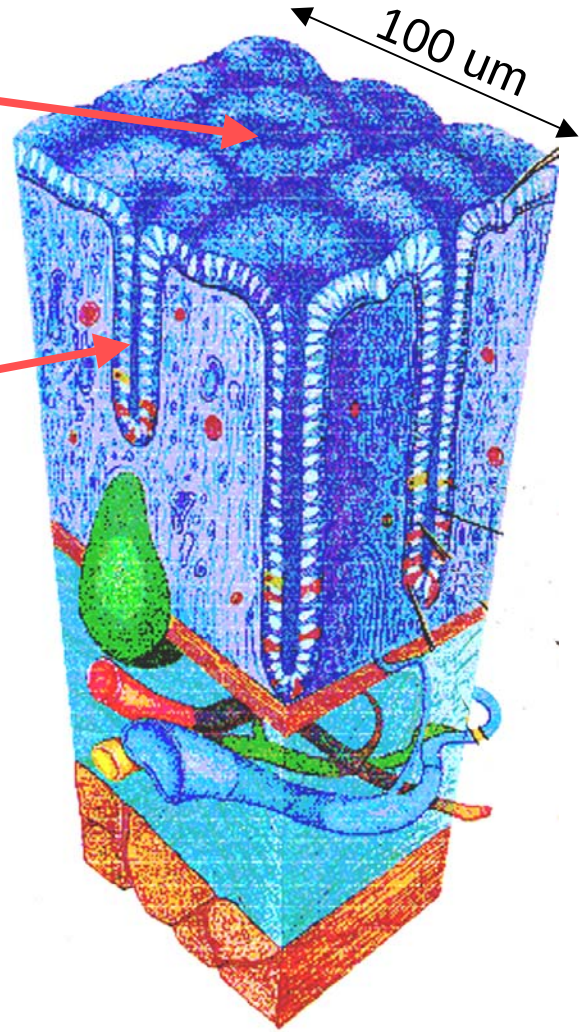
Next Class: Where do these genetic changes come from?

Normal Colon Tissue

TOP: Inner surface of the colon

Divits = "Crypts"

Cell Lining = Epithelial Cells



Most colon cancers appear to be of epithelial origin

Normal Colon Tissue

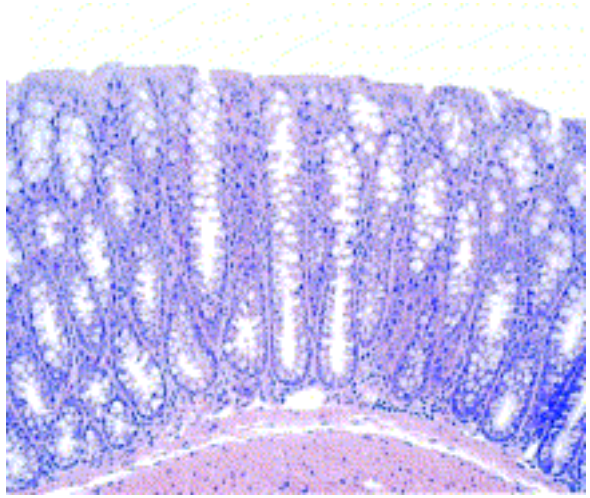
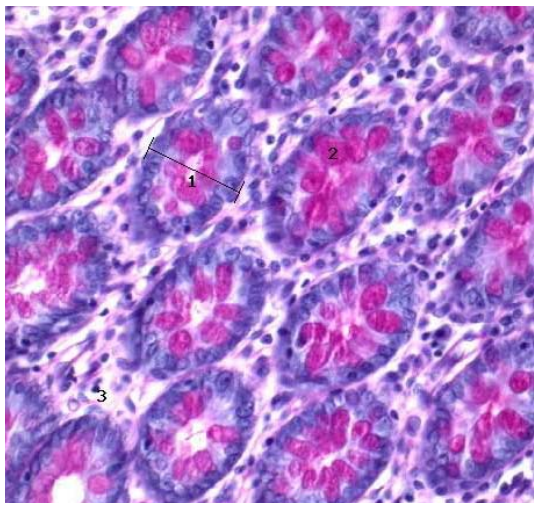


Image from D. Schauer

Definitions:

Crypt
Somatic Stem Cell
Conveyor Belt
1 Crypt = 1 Clone



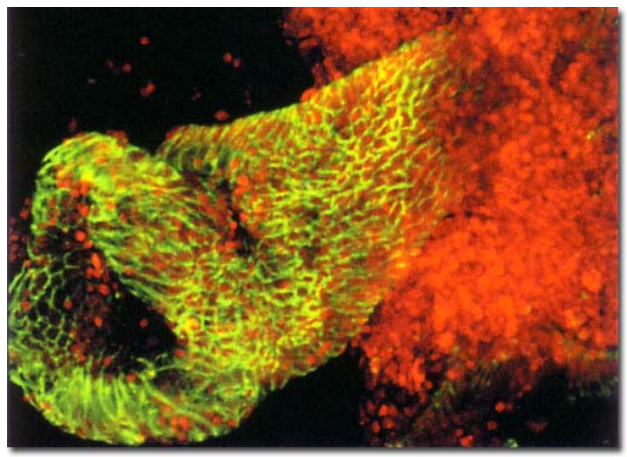
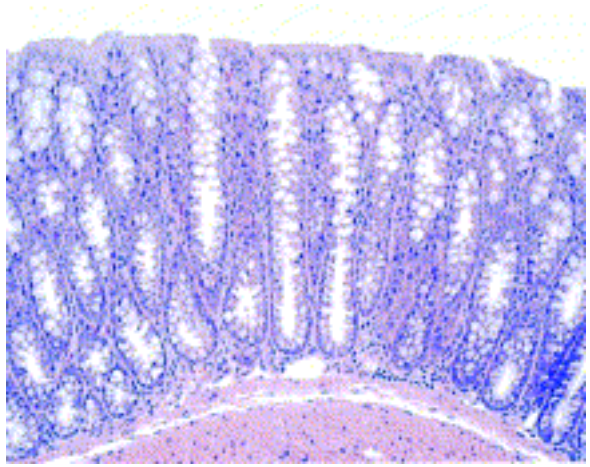
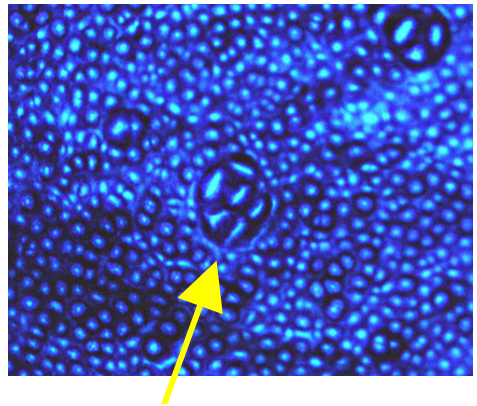


Image by Christine Andersen

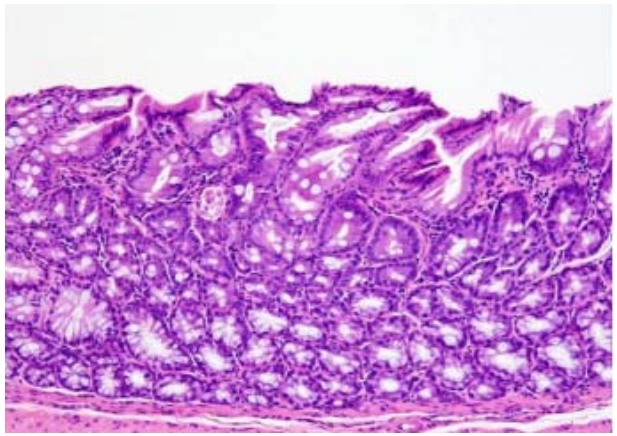
Progression from Normal to Cancer



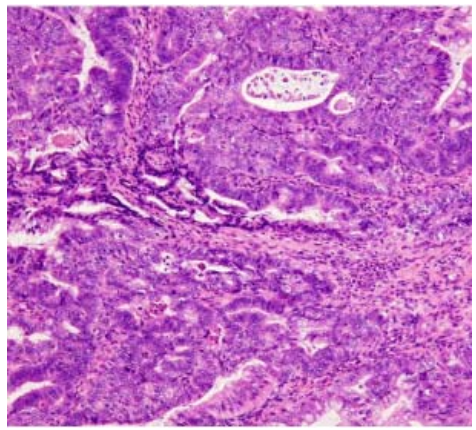
Normal Colonic Epithelium



Dysplasic Crypt



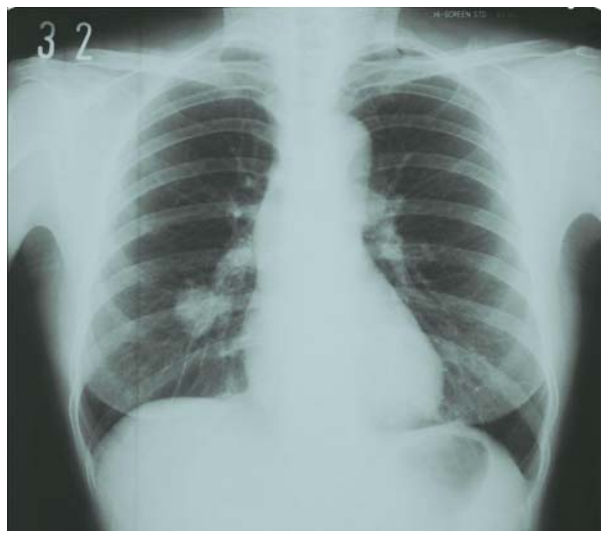
Mild Dysplasia



Cancer

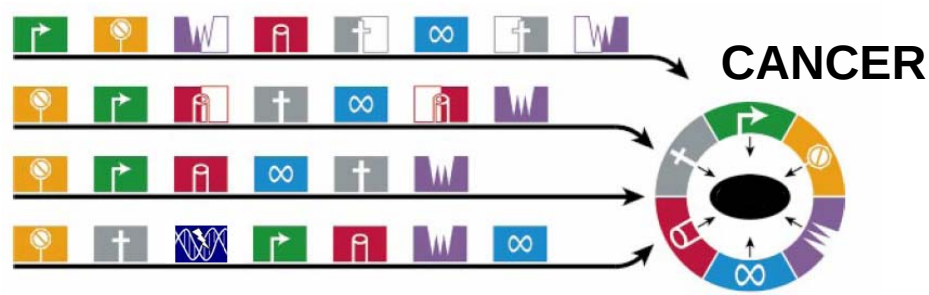
What are the genetic steps?
What does a cancer cell need to be able to do?

Normal Cell → Metastatic Tumor: Many Changes are Necessary



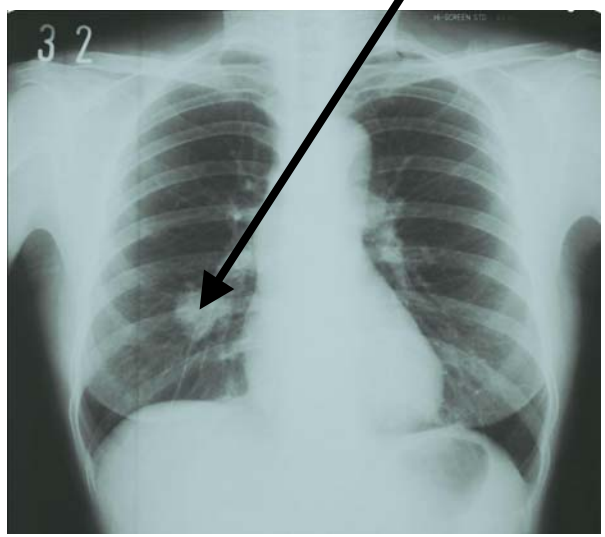
Concept & parts of figure from Hanahan and Weinberg

Normal Cell → Metastatic Tumor: Many Changes are Necessary



Definitions:

Apoptosis
Immortal
Angiogenesis
Metastasis



Concept & parts of figure from Hanahan and Weinberg

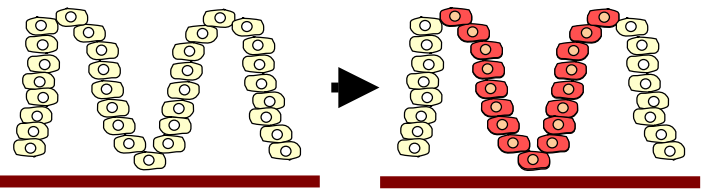
Where do cancer cells come from?

"Survival of the Fittest"

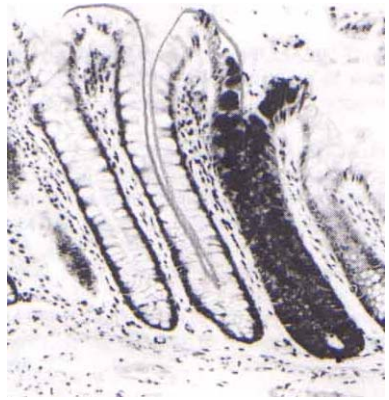
Most fully blown cancers require many mutations

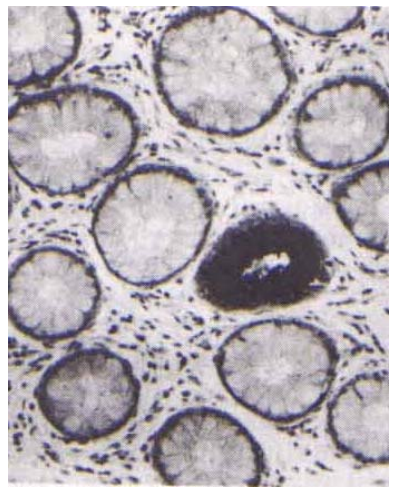
Colon Cancer…

Normal Colonic Epithelium



Mutation 1

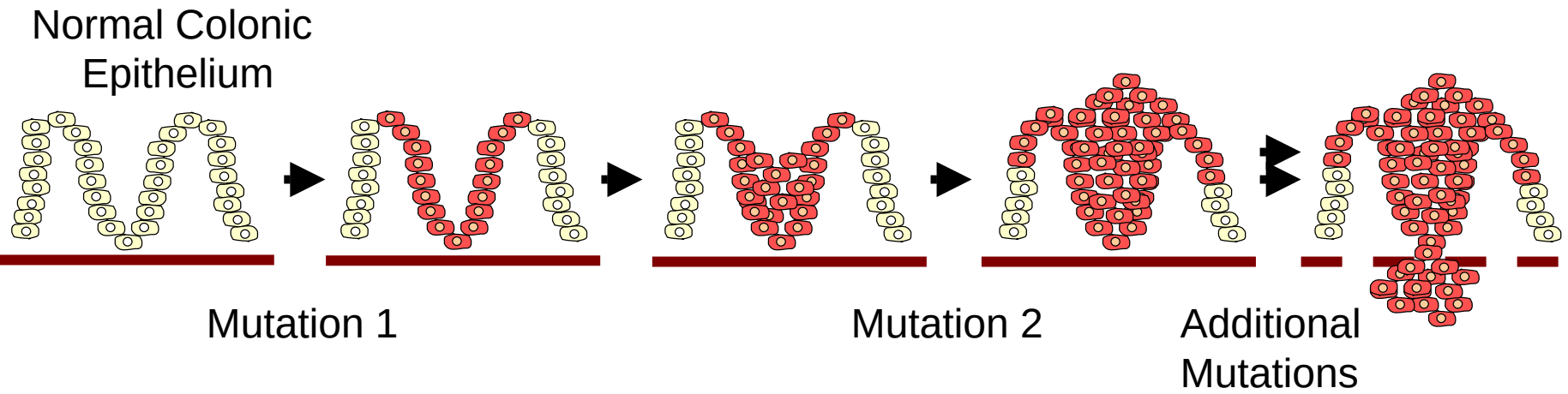




Photographs: C.E.Fuller & E.D.Williams; Br.J.Cancer (1990)

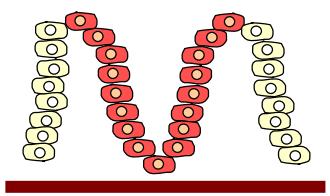
Most fully blown cancers require many mutations

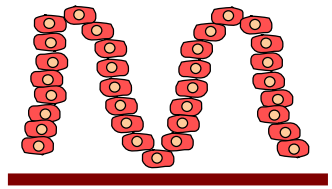
Colon Cancer…

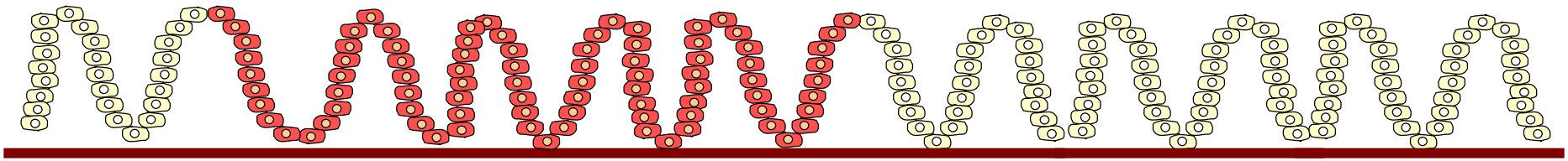


20 – 40 Years

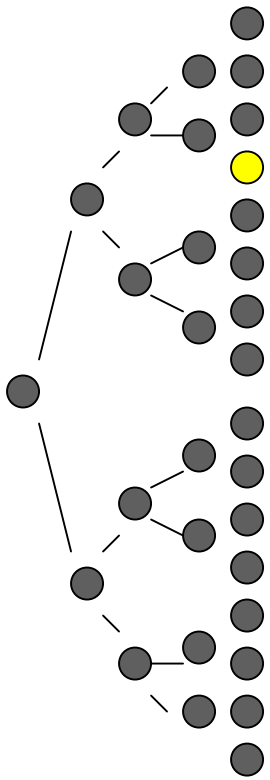
Most of the mutations occur in somatic cells – but germ line mutations can also contribute to cancer



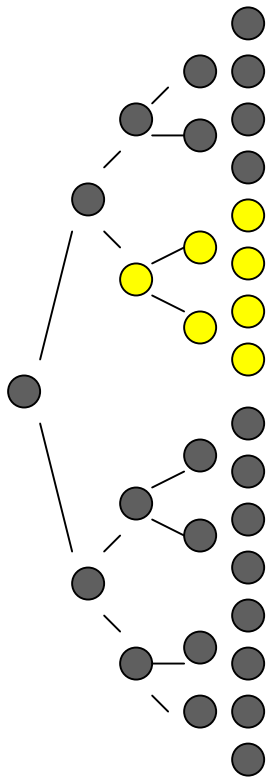




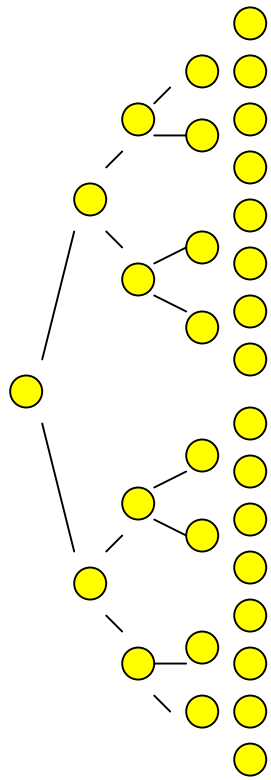
Clonal Expansion of Mutant Cells



Single Mutant Cell

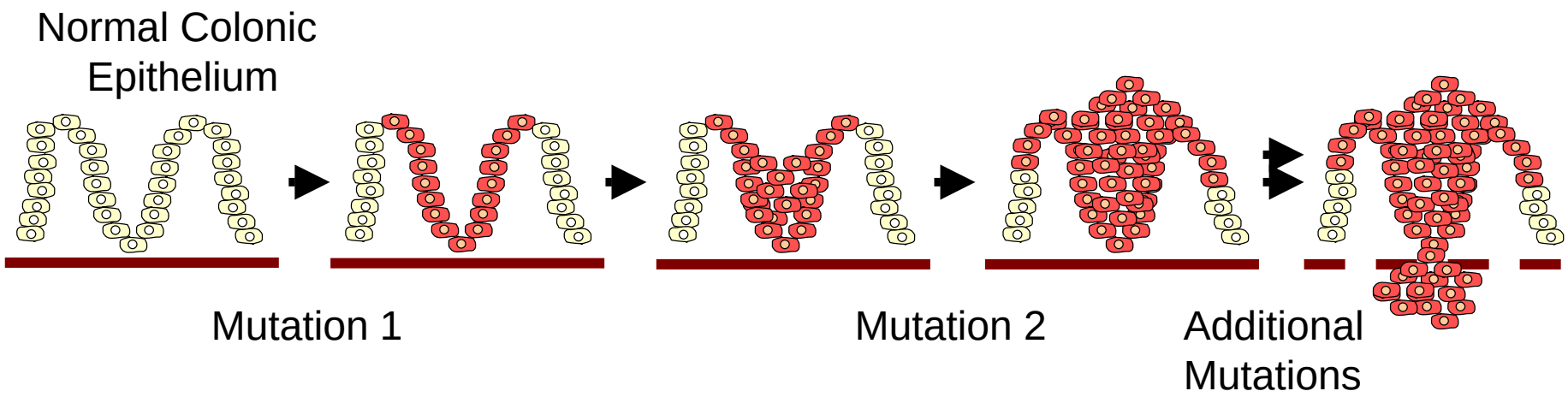


Segment



Inherited Mutation

How do you figure out Which mutations promote cancer?



What types of genetic changes turn a normal cell into a cancer cell?

Oncogenes

gene that makes a cell cancerous

dominant gain-of-function mutations

Proto-Oncogenes = Normal genes (often involved in growth regulation)

Oncogene = mutant form of an otherwise-normal gene that when mutated gives a cancer cell a selective advantage

What types of genetic changes turn a normal cell into a cancer cell?

Cancer is Uncontrolled Cell Proliferation

Normal signaling machinery
can be exploited by cancer cells:

Independent "Go!" signal

Mutations in Cancer Genes Transform Normal Cells into Cancer Cells

Oncogenes

gene that makes a cell cancerous
dominant gain-of-function mutations

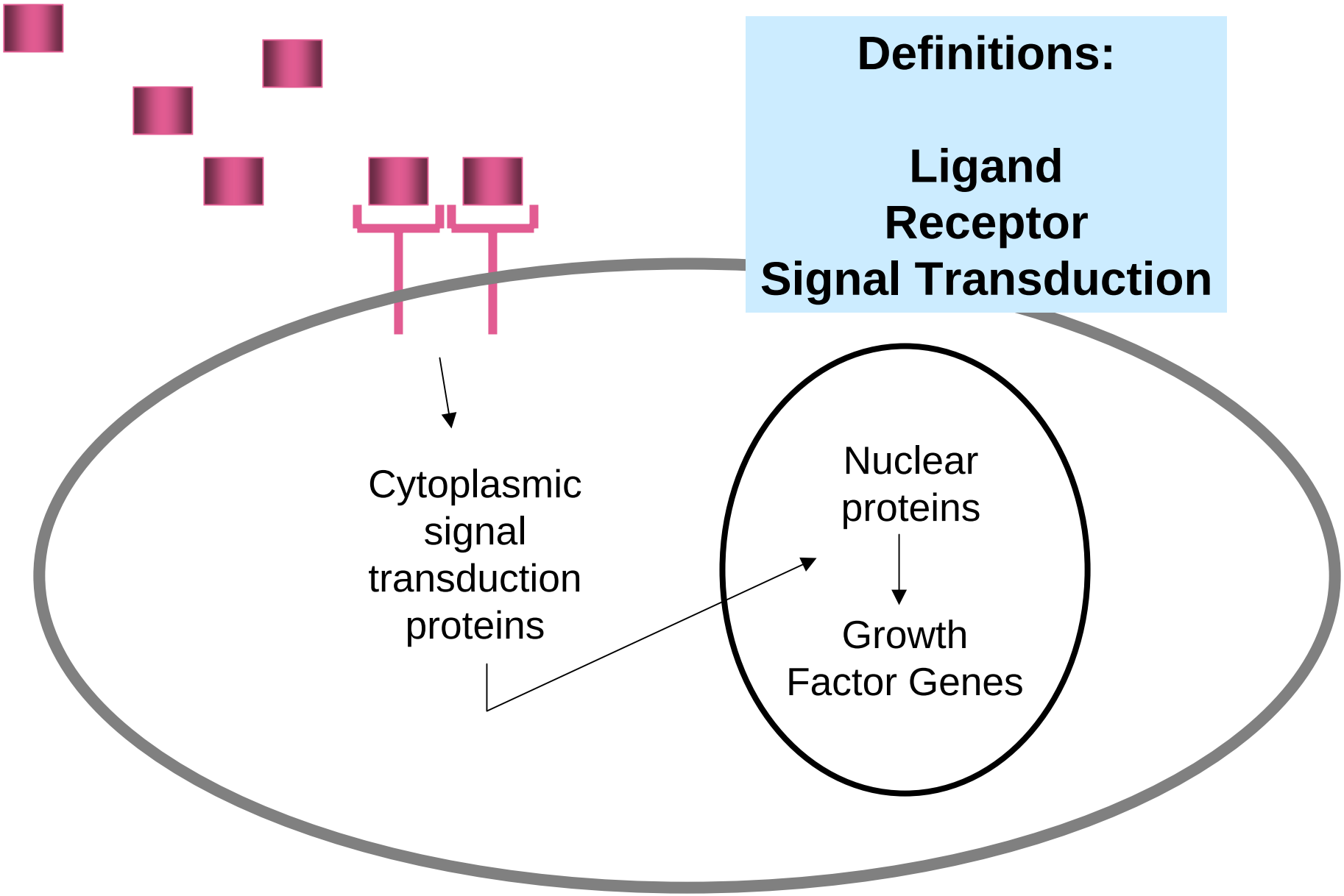
Ras ⟶ Ras(G12D)

"Go!"
Growth Signal Independent

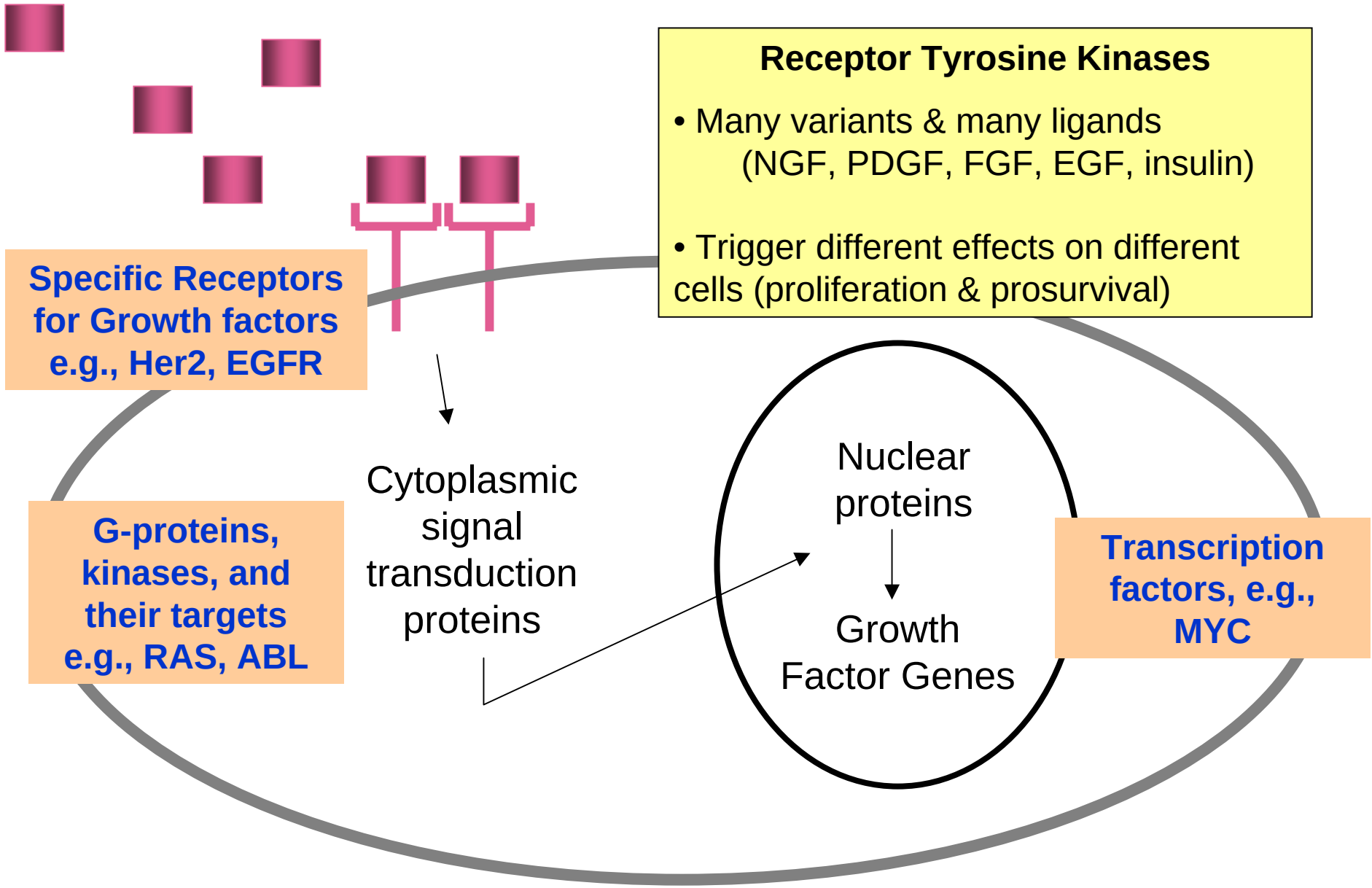
Normal Ras is involved in sensing growth signals
Mutant Ras gives the "go signal" without growth factors

(H-Ras, N-Ras, and K-Ras)

Signal Transduction and Growth Regulation



Signal Transduction and Growth Regulation

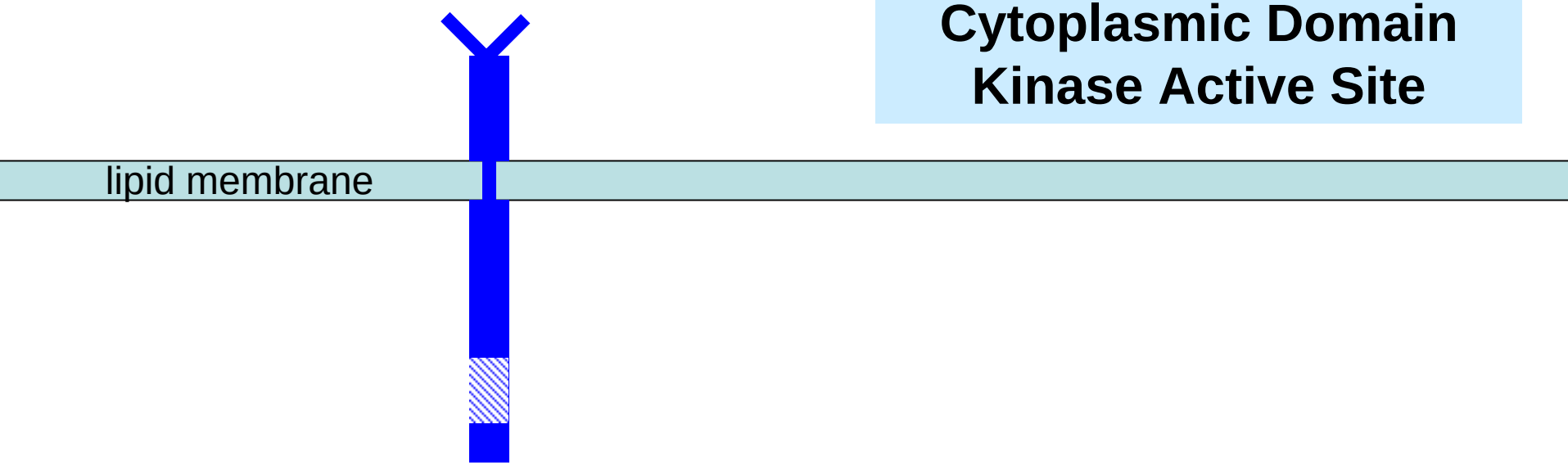


EGFR: Receptor Tyrosine Kinase

Definitions:

Extracellular Domain
Transmembrane Domain
Cytoplasmic Domain
Kinase Active Site

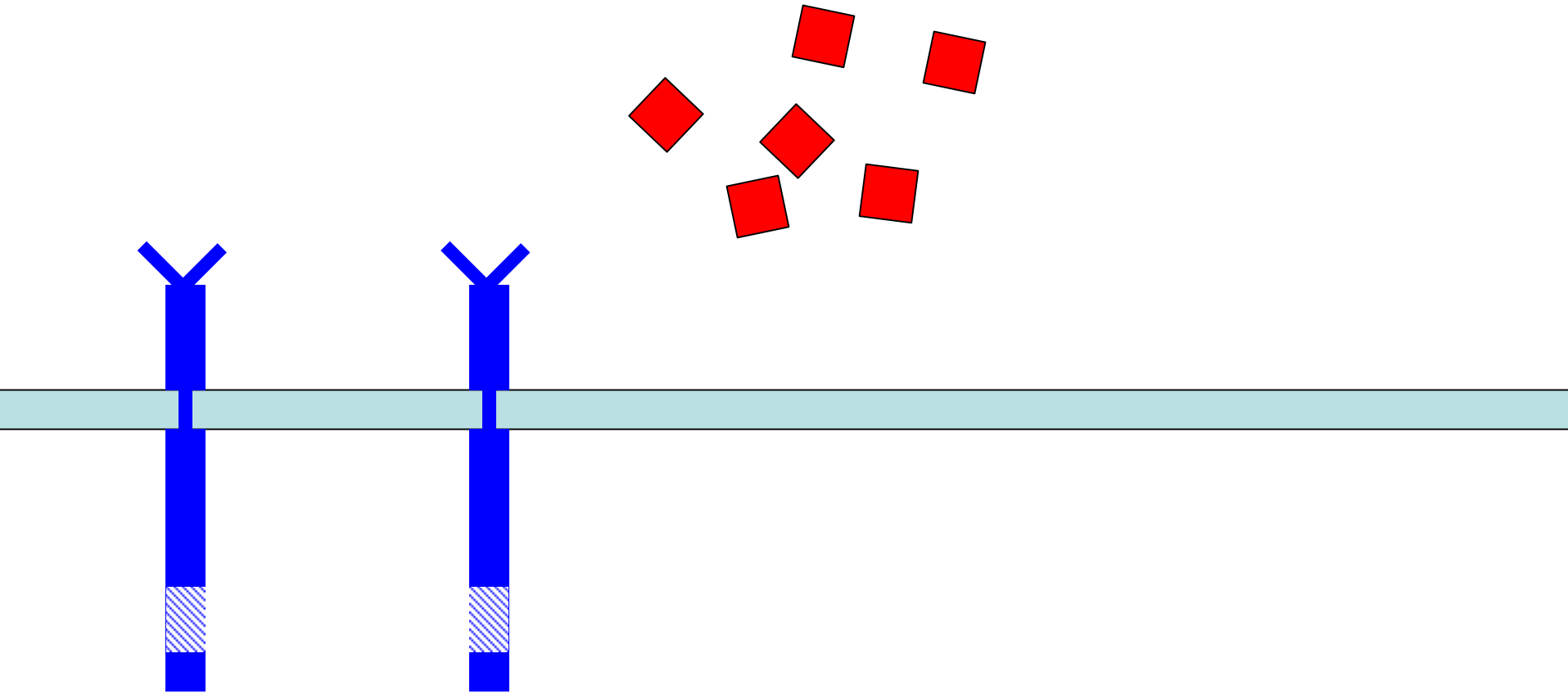
Outside the cell



Inside the cell

EGFR = Epidermal growth factor receptor

EGFR: Receptor Tyrosine Kinase



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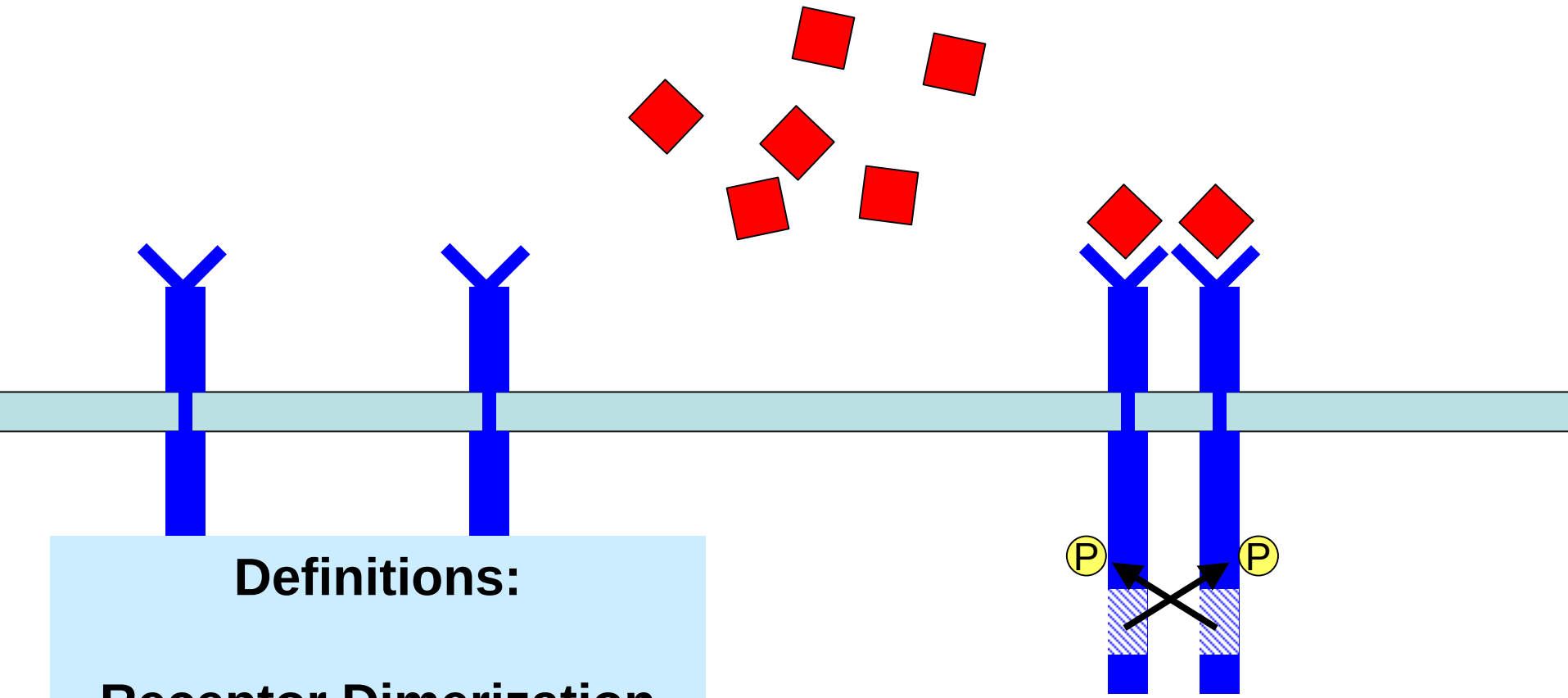
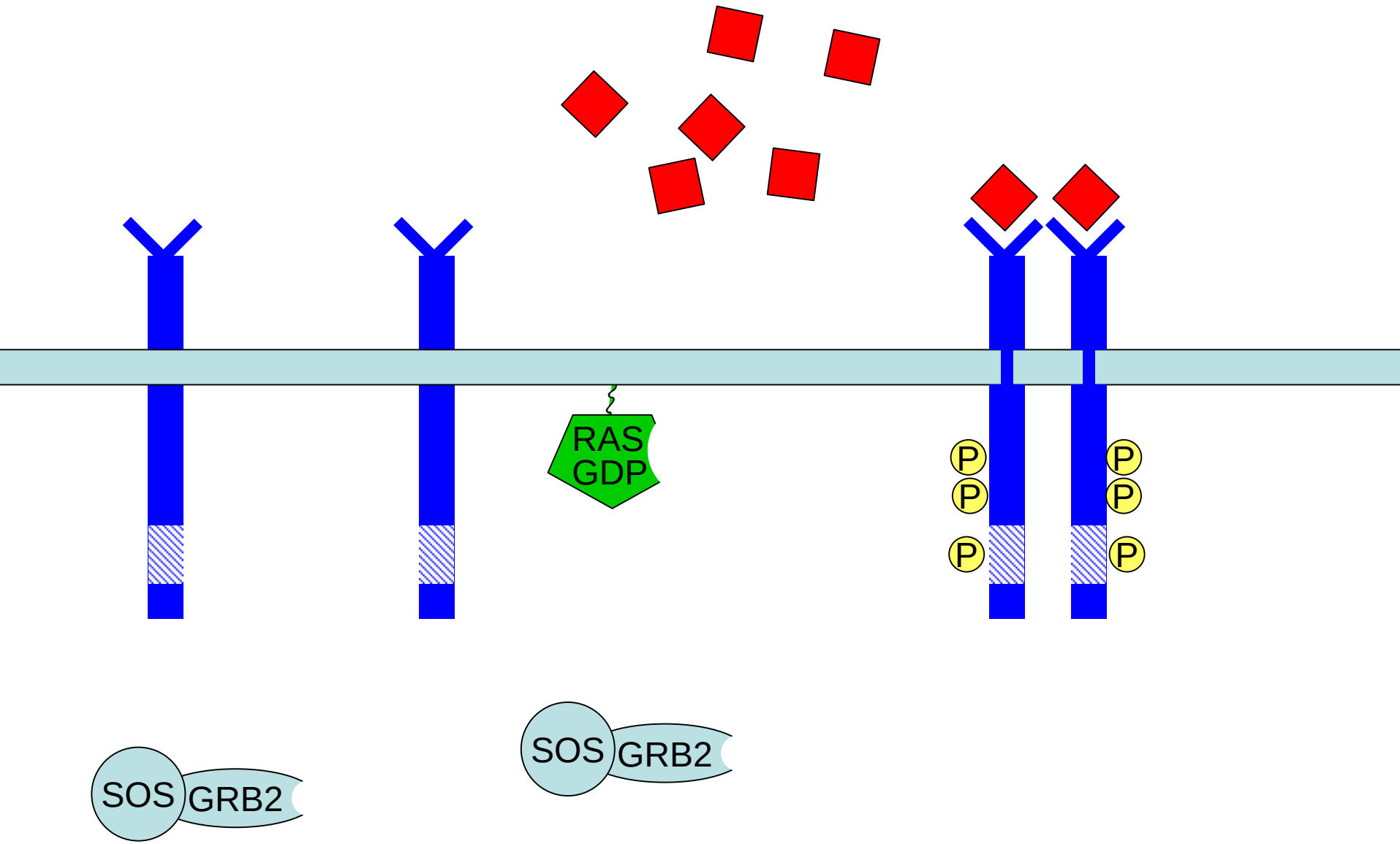


Definitions:

Receptor Dimerization
Kinase Activation
Autophosphorylation

EGFR: Receptor Tyrosine Kinase



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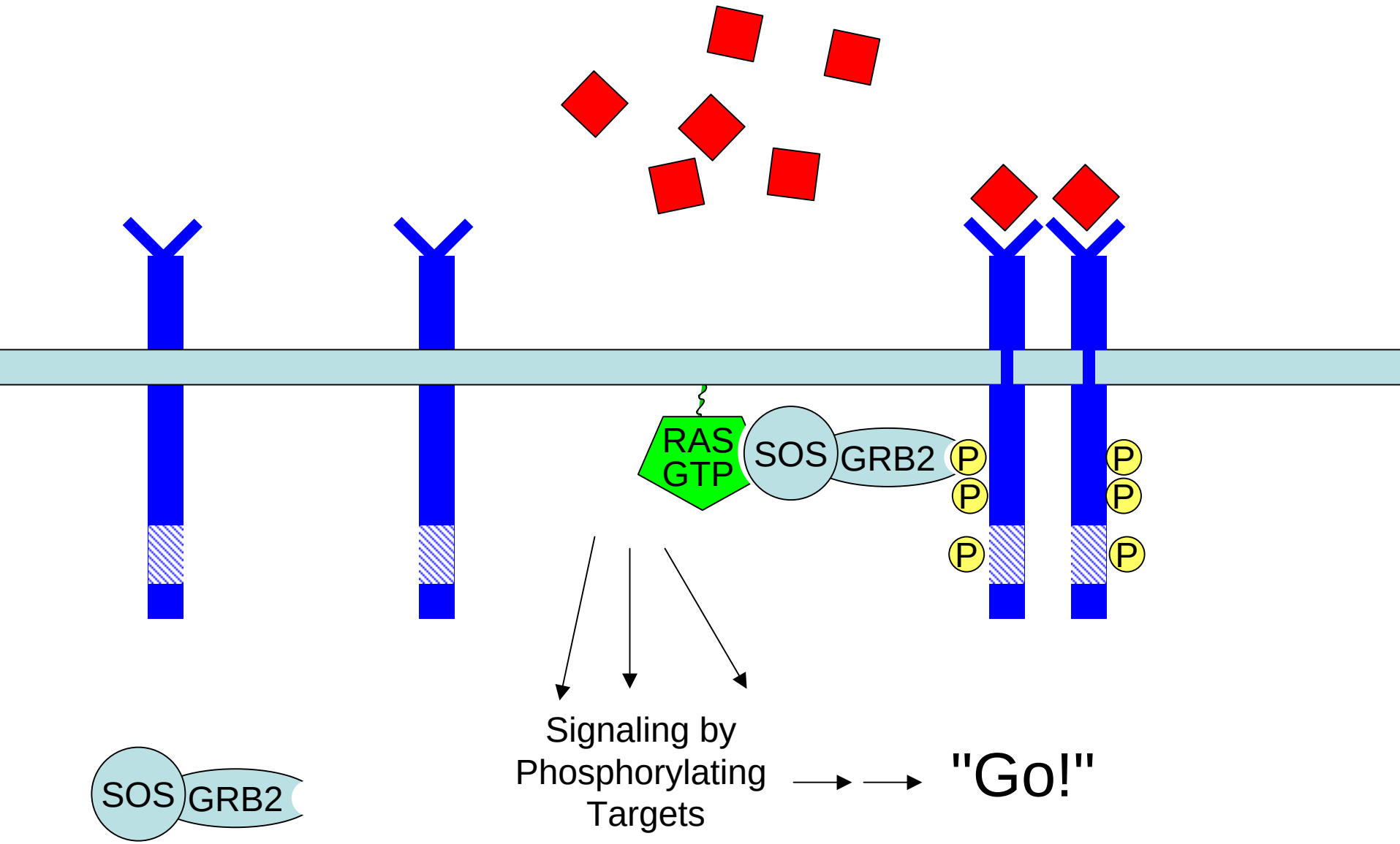
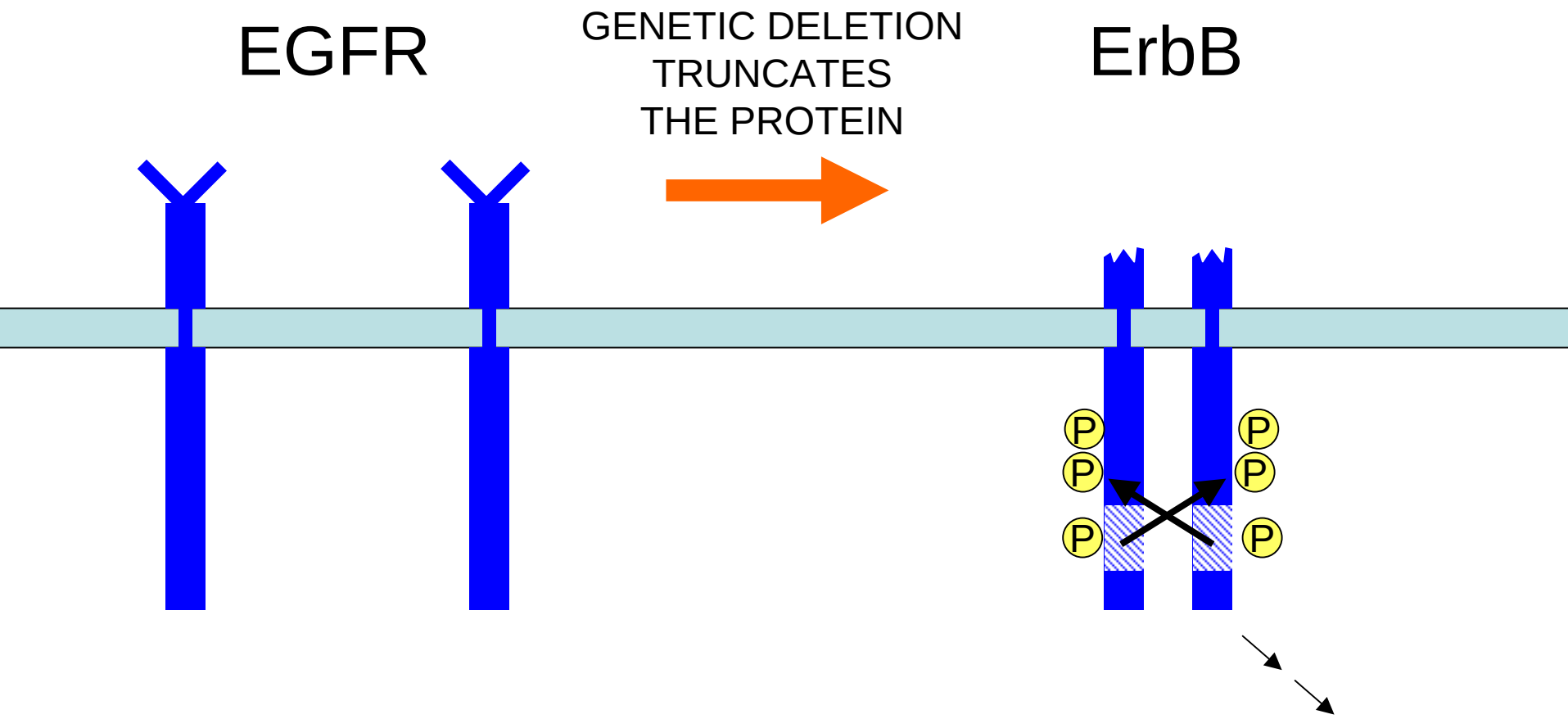
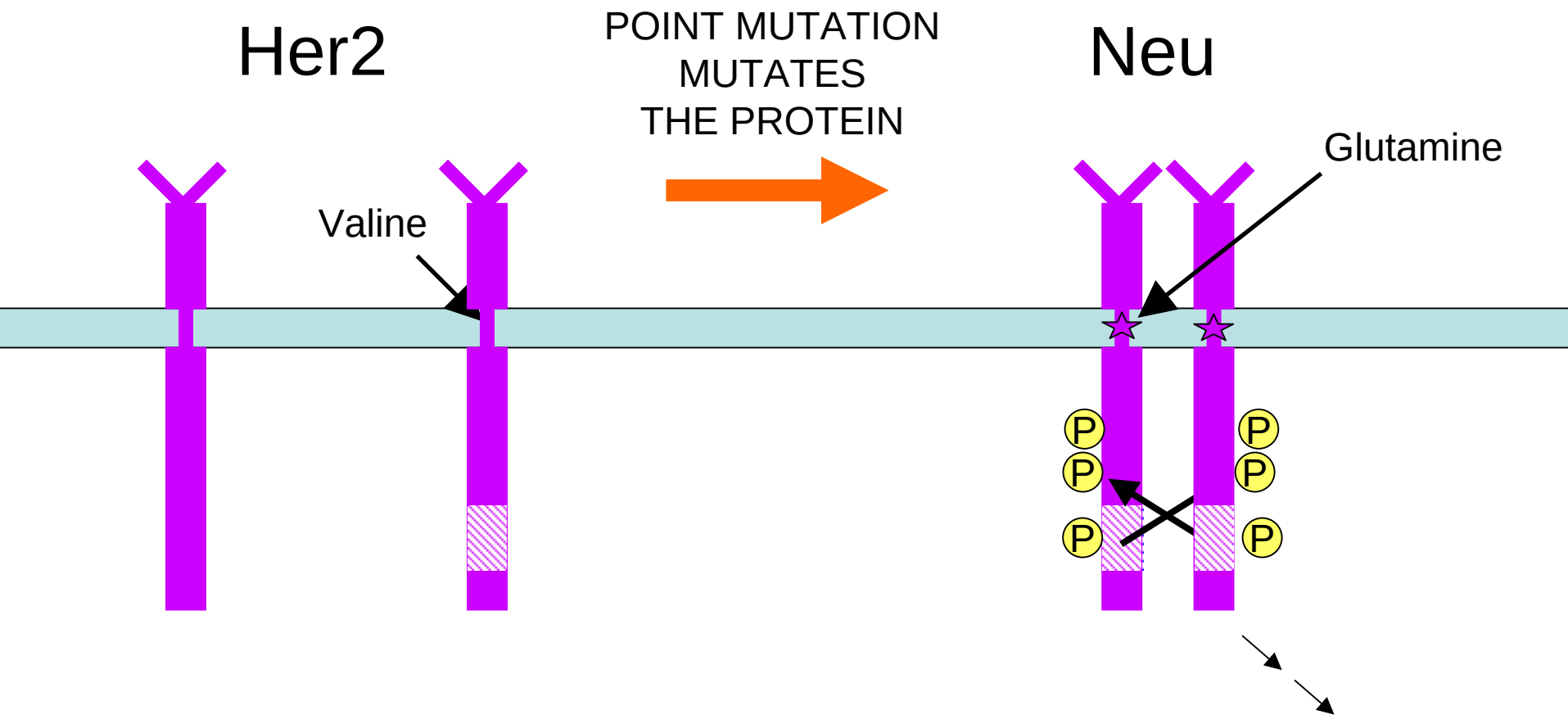


Cancer Cells Often Exploit Receptor Tyrosine Kinases



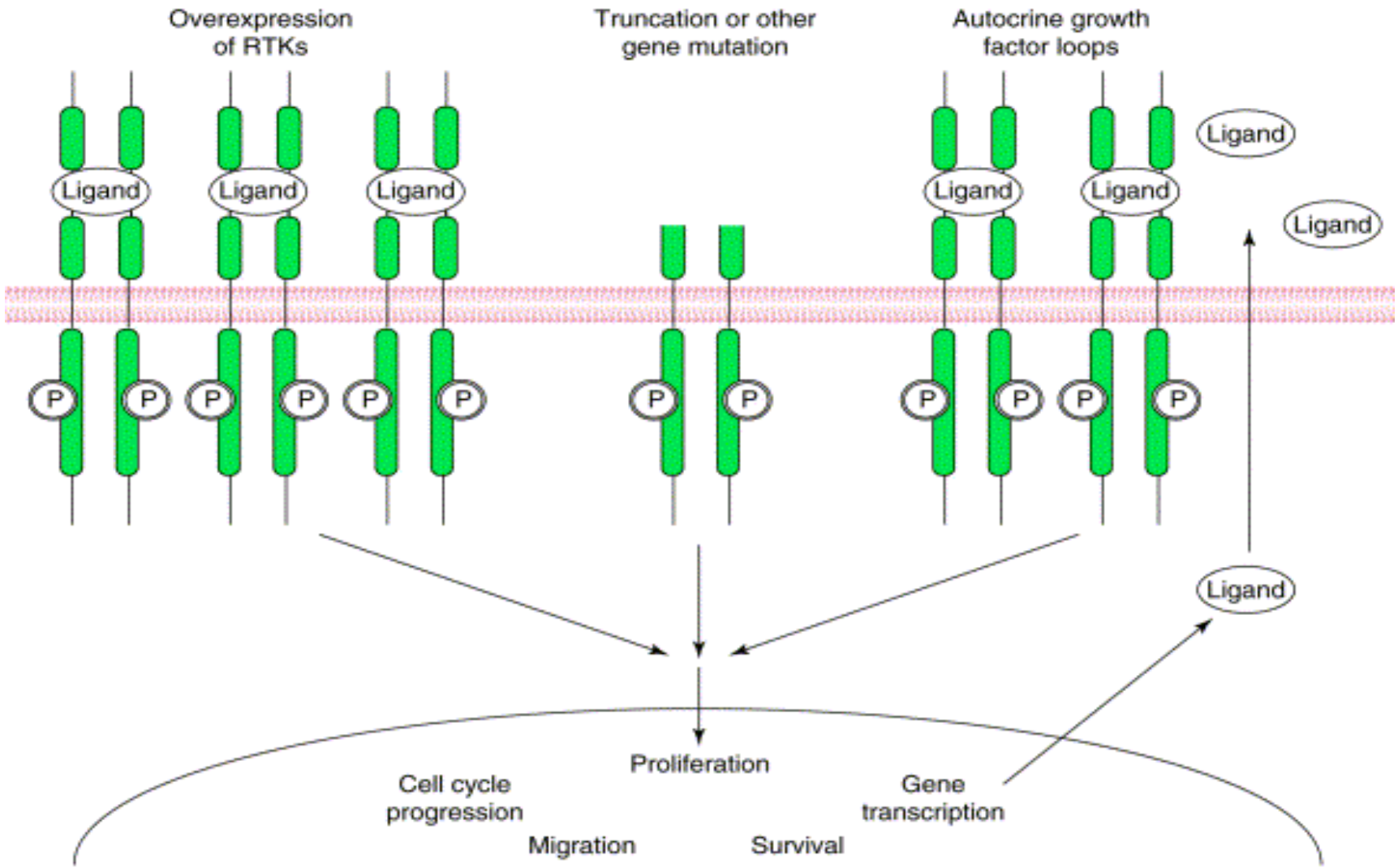
Constitutively Active
Without Need for Growth Factors

Cancer Cells Often Exploit Receptor Tyrosine Kinases



Constitutively Active
Without Need for Growth Factors

Constitutive Activation converts RTKs to Dominant Acting Oncogenes



Zwick et al, (2002) TIMM **8:**17-23

TRENDS in Molecular Medicine

Genetic alterations leading to Constitutive Activation of RTKs

- Deletion of extracellular domain
- Mutations that stimulate dimerization without ligand binding
- Mutations of the kinase domain
- Overexpression of Ligand
- Overexpression of Receptor

Mutations in Cancer Genes Transform Normal Cells into Cancer Cells

Oncogenes

gene that makes a cell cancerous
dominant gain-of-function mutations

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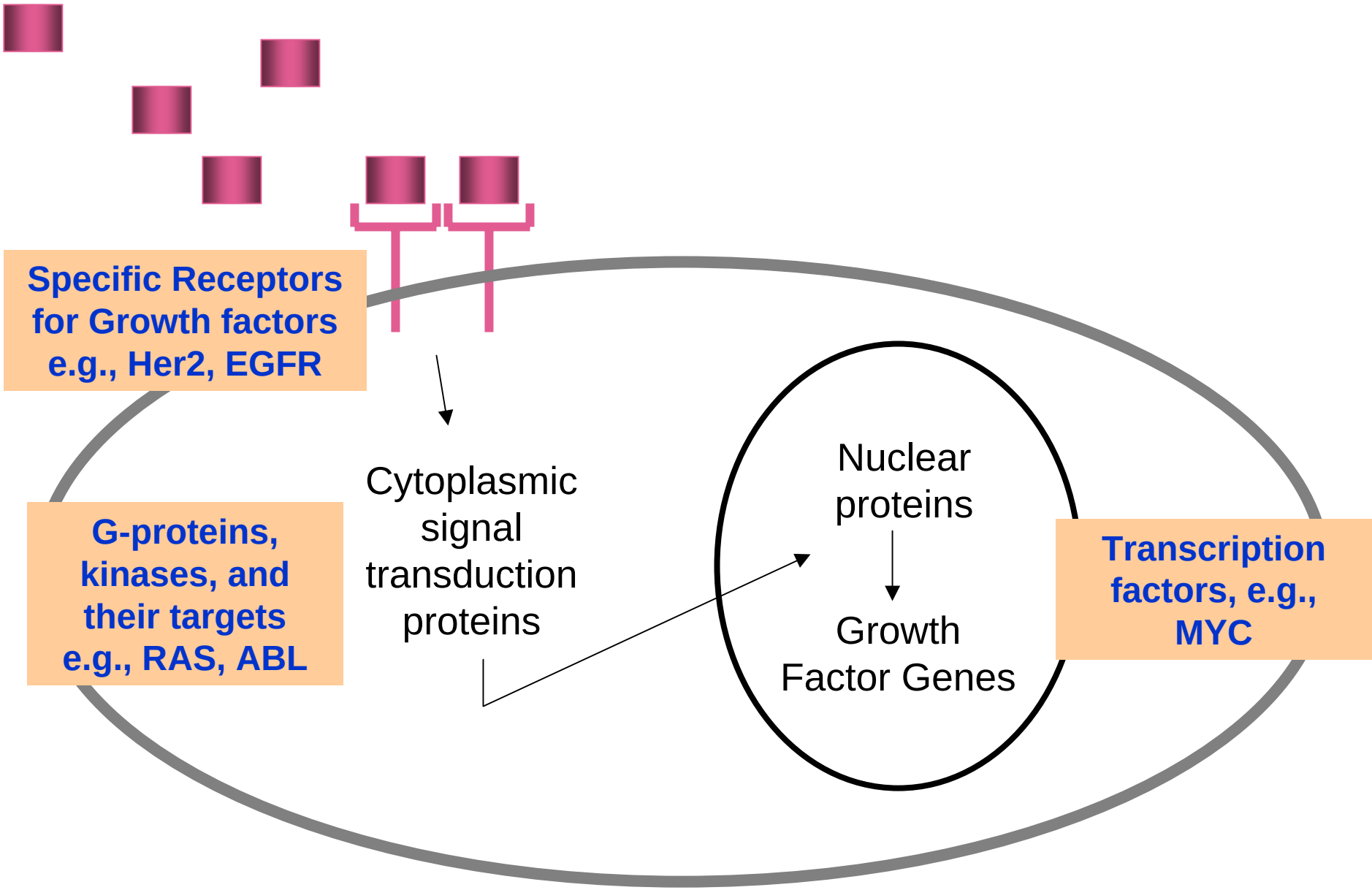
Signal Transduction and Growth Regulation



EGFR: Receptor Tyrosine Kinase

ON 

<u>Point Mutations</u> in Ras turn it from a normal protein into an oncoprotein

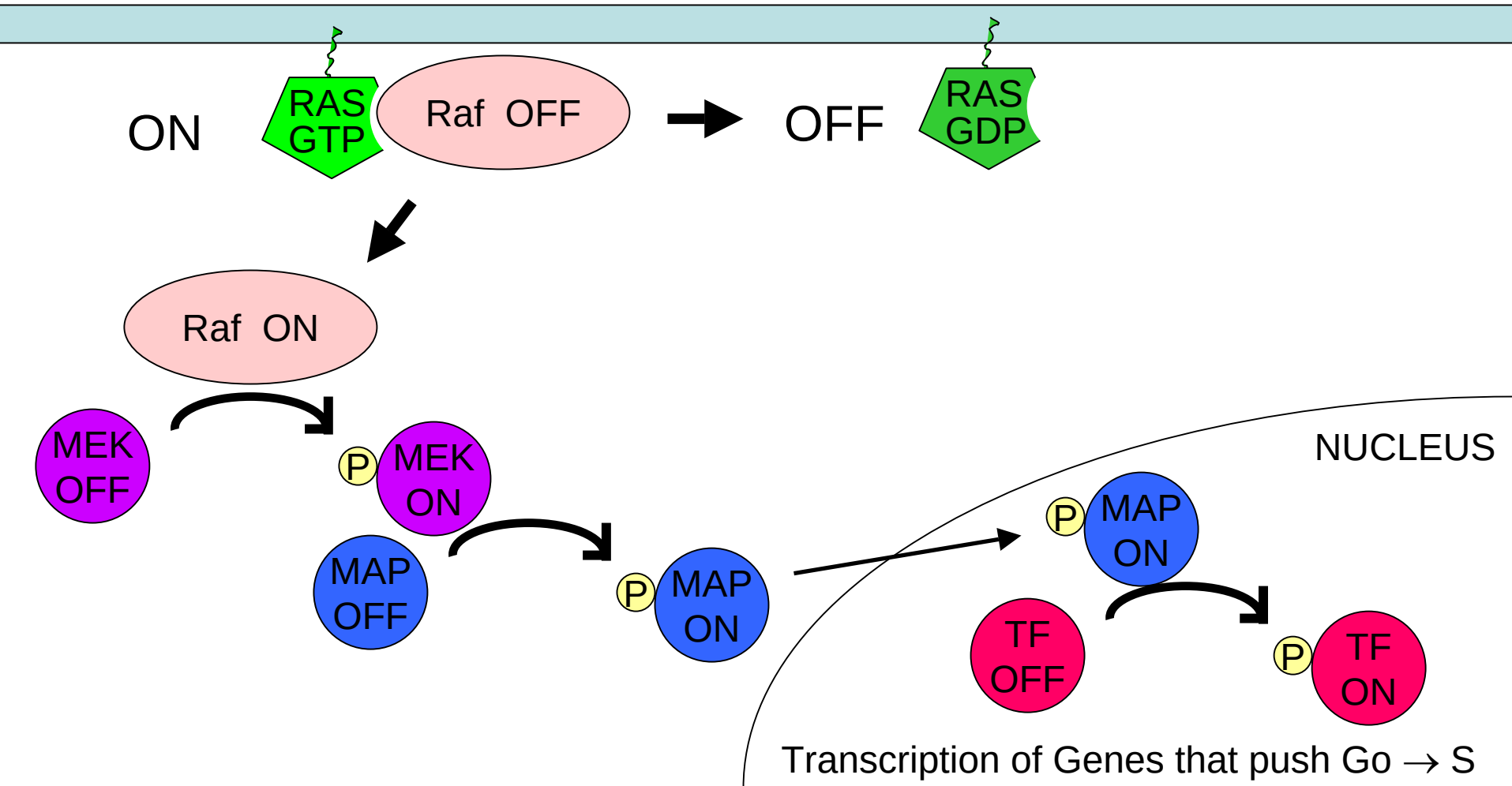
Oncogenic mutations “Lock” Ras into active GTP bound state

Codon 12 - Normally glycine; almost anything else and it is stuck “ON”

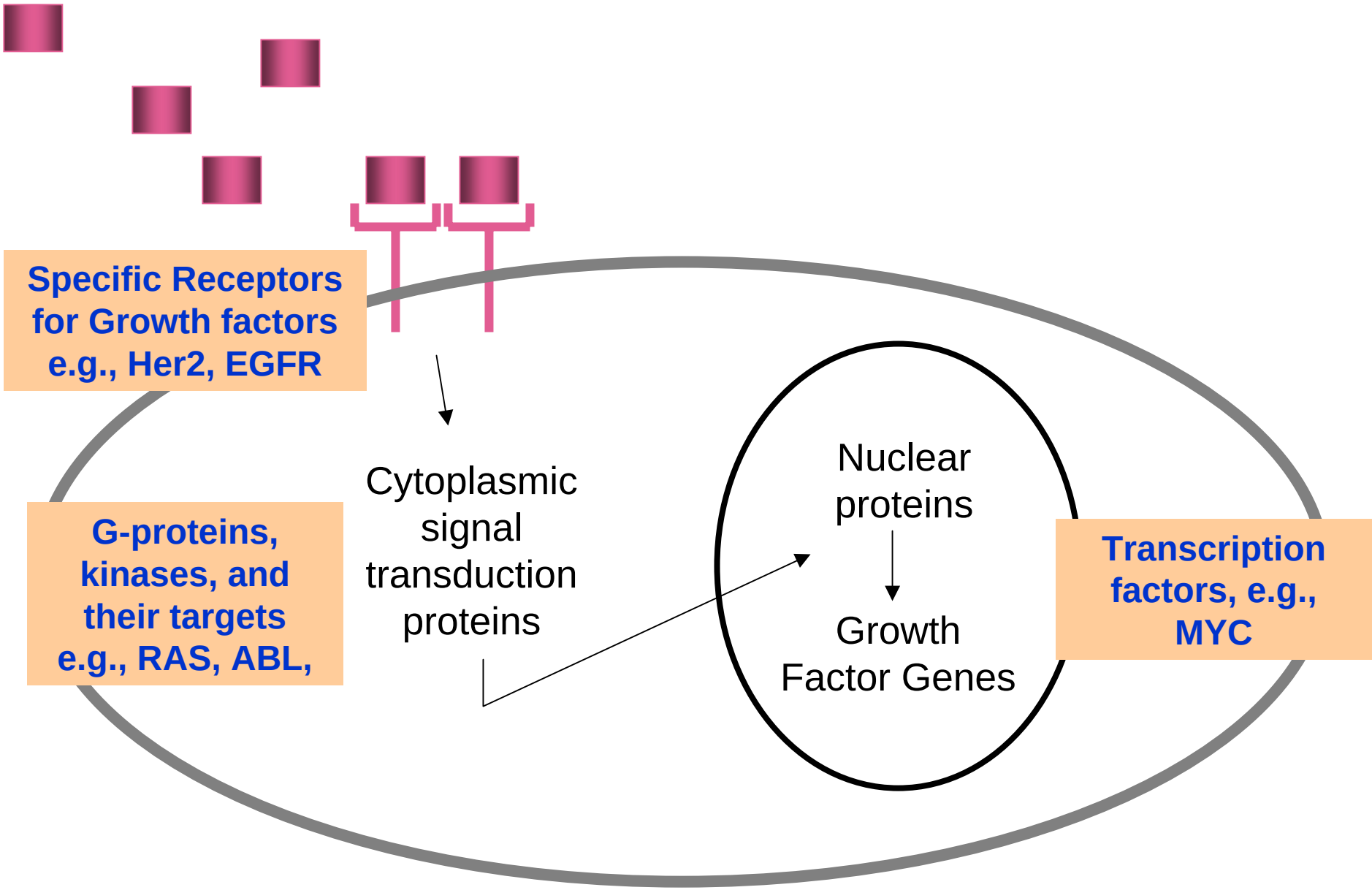
Reminder:

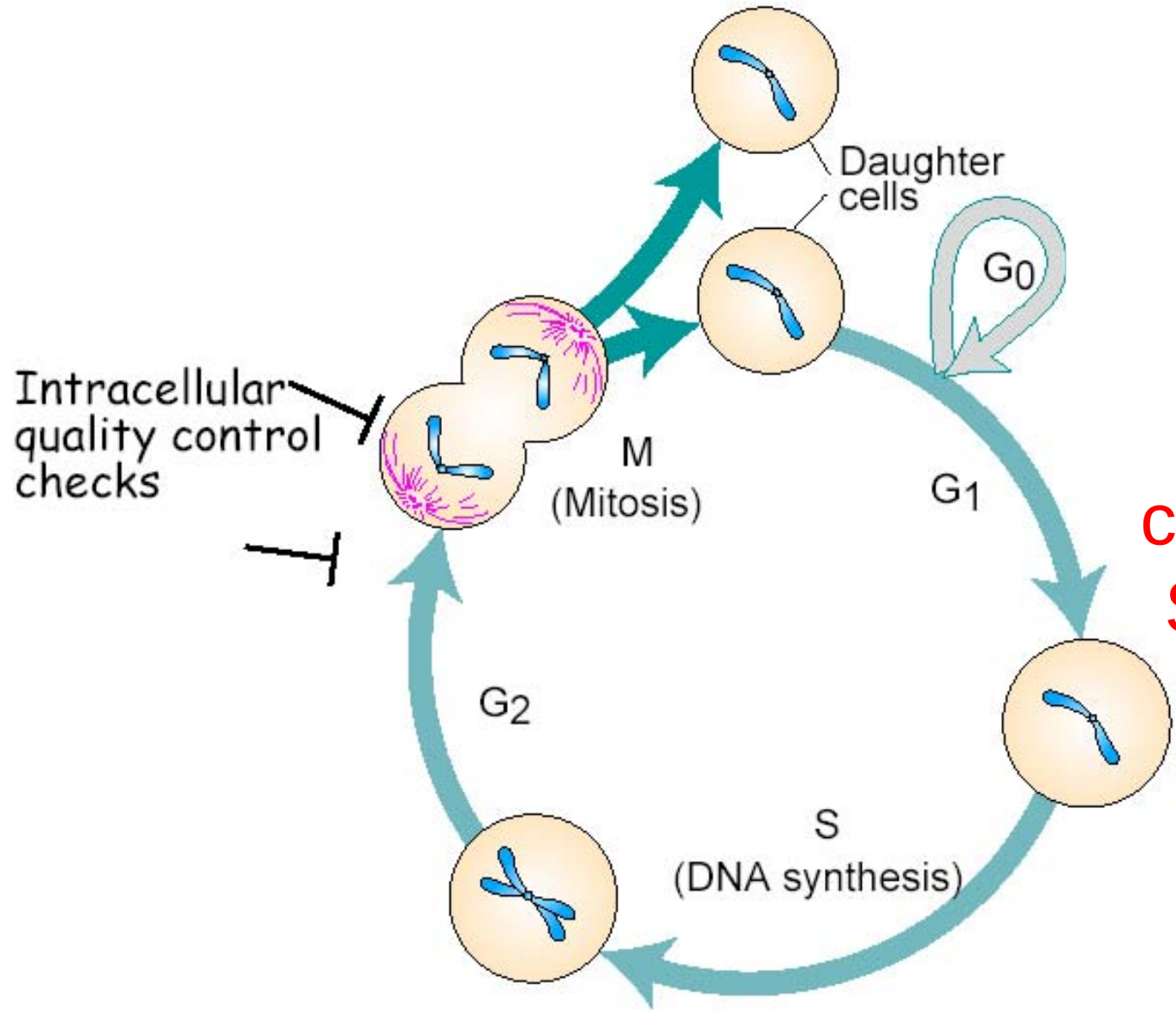
Ras was the gene that transformed the 3T3 Cells

EGFR: Receptor Tyrosine Kinase



Signal Transduction and Growth Regulation



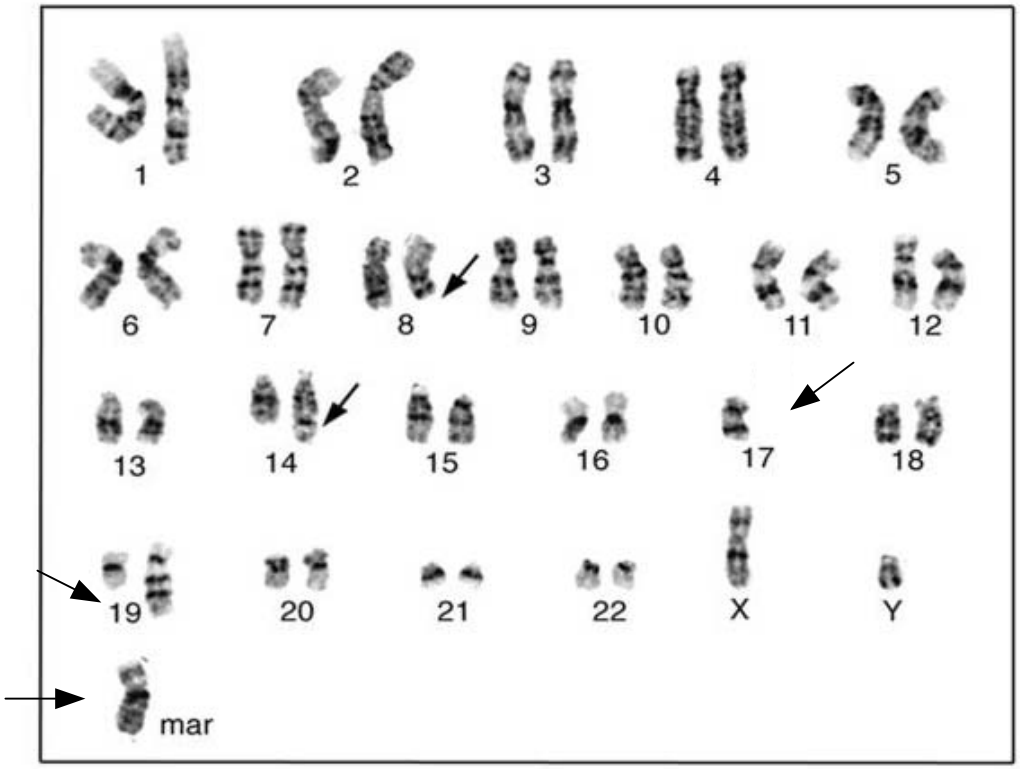


cMYC drives cells from G1 to S – so pushes cells through the cell cycle

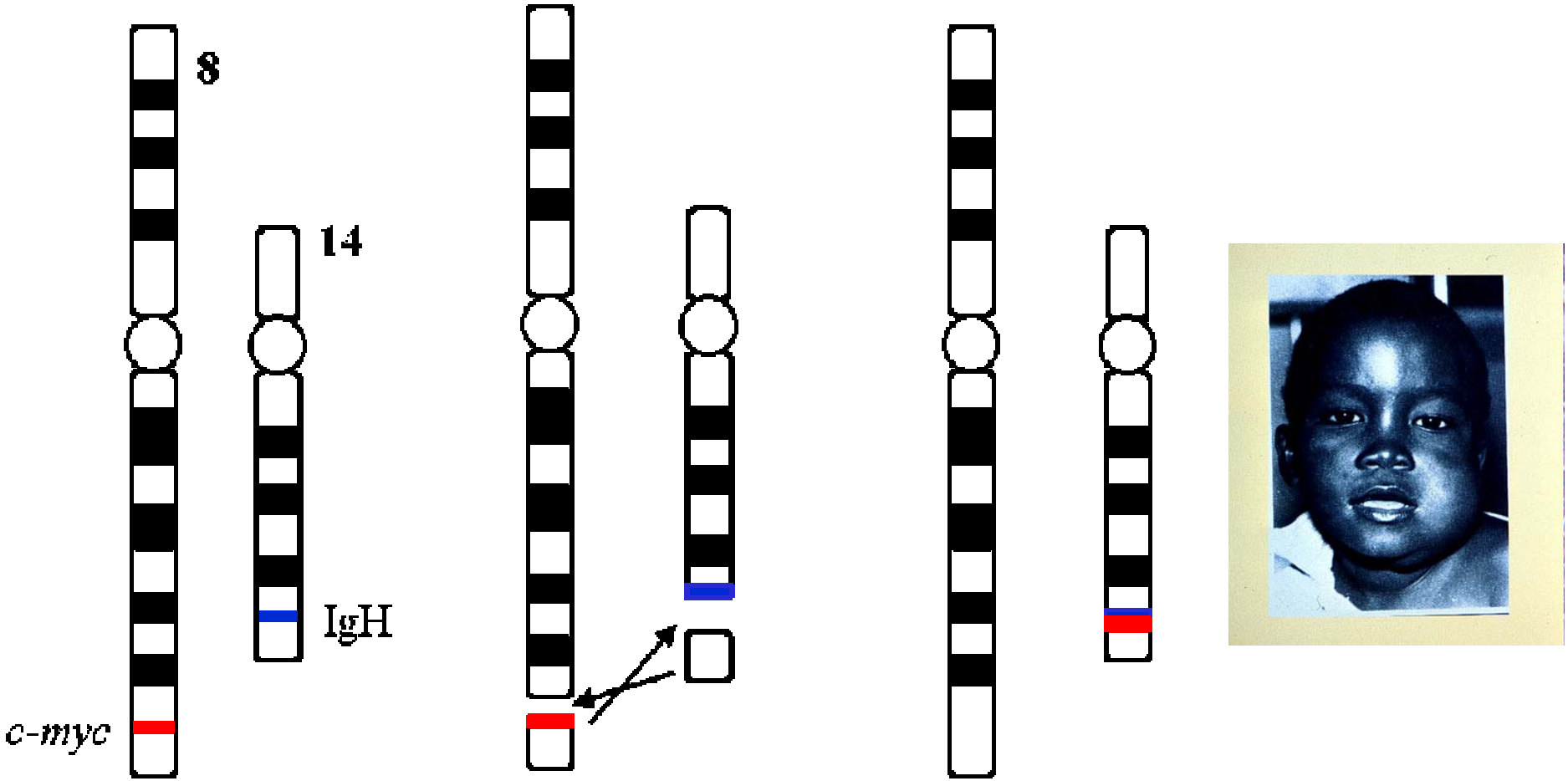
Burkitts Lymphoma

There are many chromosomal abnormalities in the cancer cells

How do you figure out which changes promote the disease?



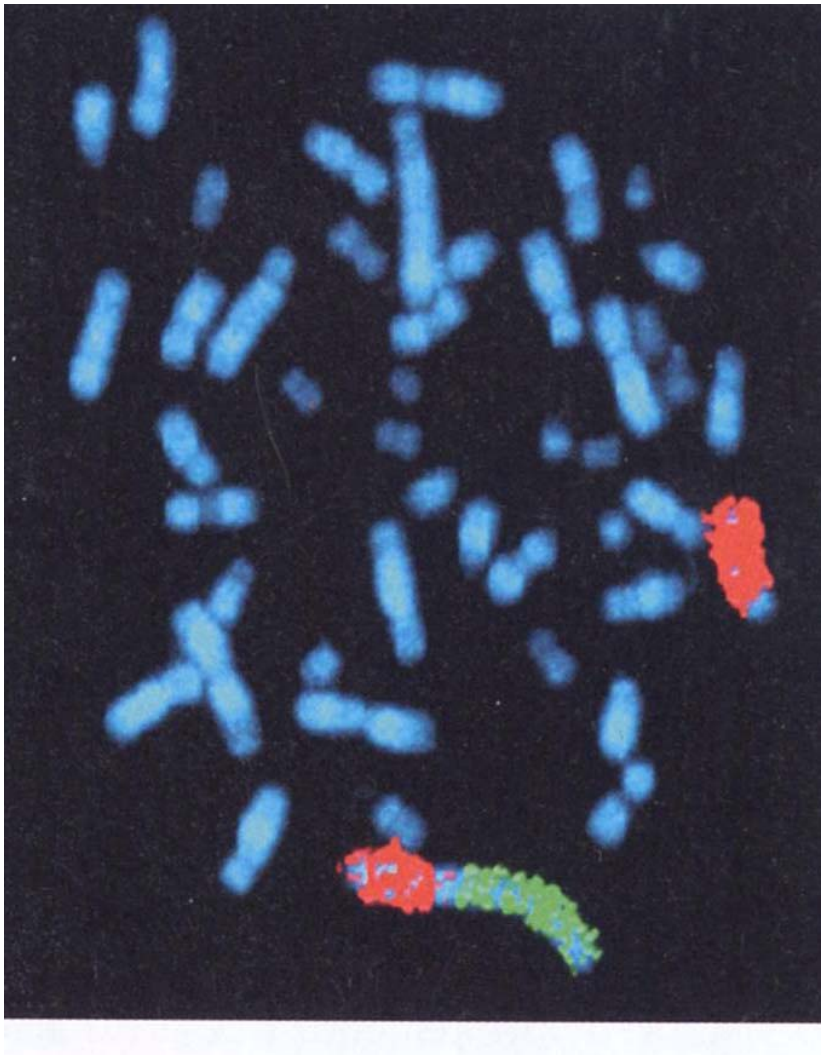
Burkitt's Lymphoma: A chromosome translocation cMYC is expressed inappropriately in B-cells



MYC drives cells from G1 to S

Another way that oncogenic transcription factors can be up-regulated: Gene Amplification

Chromosome from a Cancer Cell



Blue – staining of all chromosomes

Red – staining of chromosome 4

Green – staining of the MYC gene

Two Classes of Mutations that Increase Myc

Translocation:

A fusion-gene is created

Myc coding sequence is put behind a strong constitutive promoter

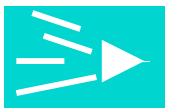
Amplification:

Cell harbors *many* copies of Myc

Normal Cell → Metastatic Tumor: Many Changes are Necessary

"Go!"
Growth Signal Independent

"Don't Stop"
Resist anti-growth signals



"Hurry Up!"
Resist signals to wait for repairs

"Don't Die"
Resist Apoptosis

"Keep Going"
Be Immortal

"Feed Me"
Recruit & Sustain Blood Flow

"Take Over"
Escape/Invade = Metastasize

"Mutate!"

Concept & parts of figure from Hanahan and Weinberg

Where do cancer cells come from?

"Survival of the Fittest" is Happening in You Right Now

You can reduce your odds of cancer by "closing the competition":

REDUCE THE NUMBER OF CELL DIVISIONS YOU EXPERIENCE

The Genetic Basis of Cancer and Theodor Boveri 1862 - 1915

- Established that chromosomes carry the hereditary information
- Suggested that mis-segregation of human chromosomes could be responsible for a normal cell becoming a tumor cell

Gains/Losses of Chromosomes are an important class of mutations

- Suggested that some chromosomes promote cell growth and others inhibit cell growth

Marcella O'Grady Boveri (1863-1950) also contributed