Genetics of Cancer

Lecture 32

“Cancer II”

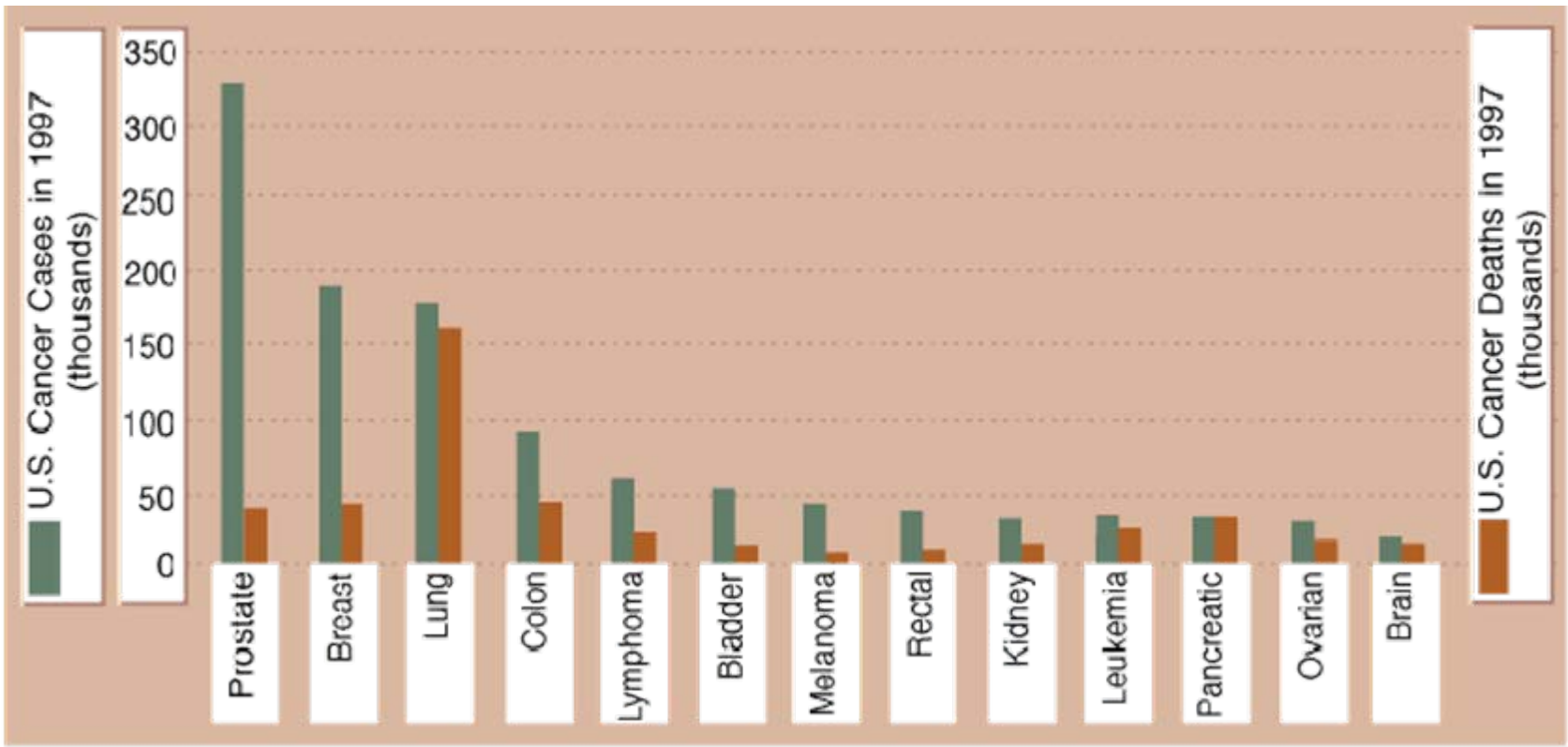
Prof. Bevin Engelward, MIT Biological Engineering Department

Based on a lecture by Prof. Leona Samson

Why Cancer Matters

Unless things improve….

- 1/3 of the people in this room will get cancer
- Many cancers are quite treatable; others are not



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?

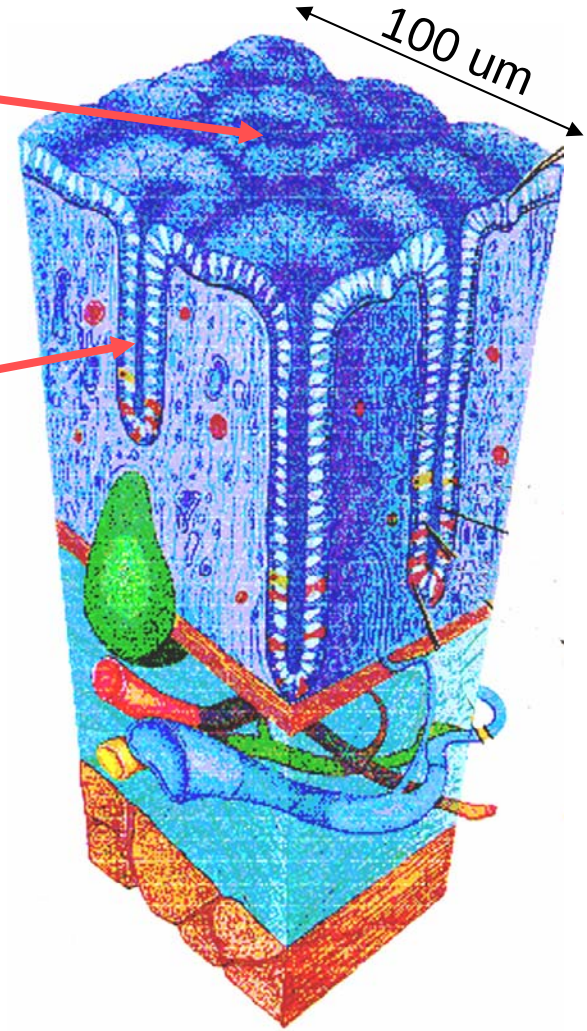
Next Class: Where do these genetic changes come from?

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

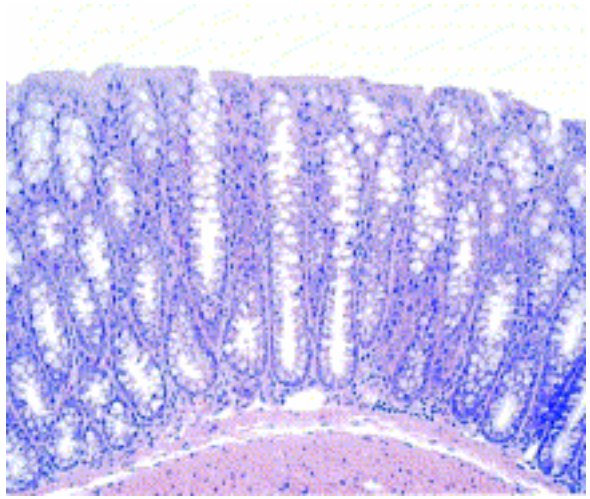
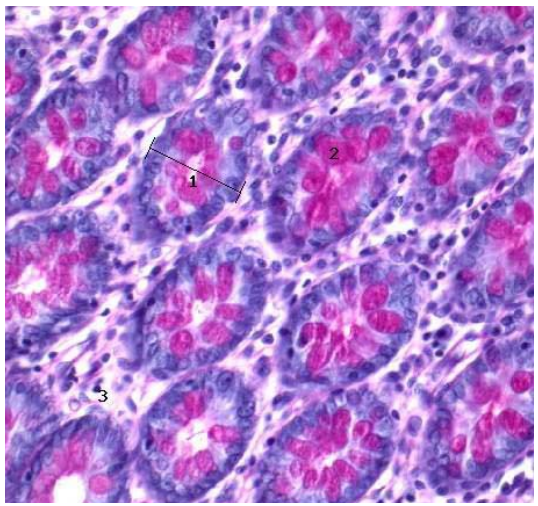


Image from D. Schauer

Definitions:

Crypt
Somatic Stem Cell
Conveyor Belt
1 Crypt = 1 Clone



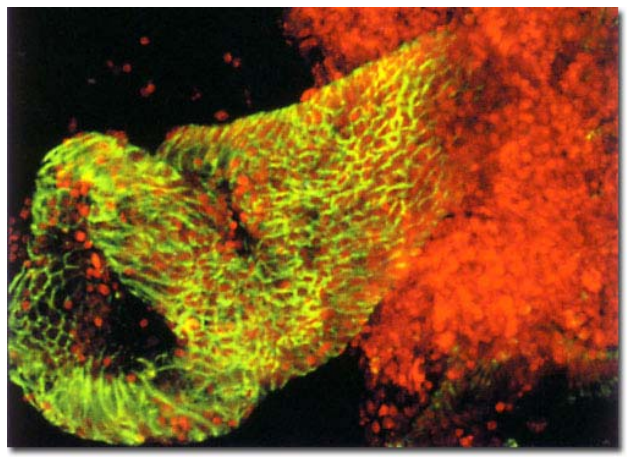
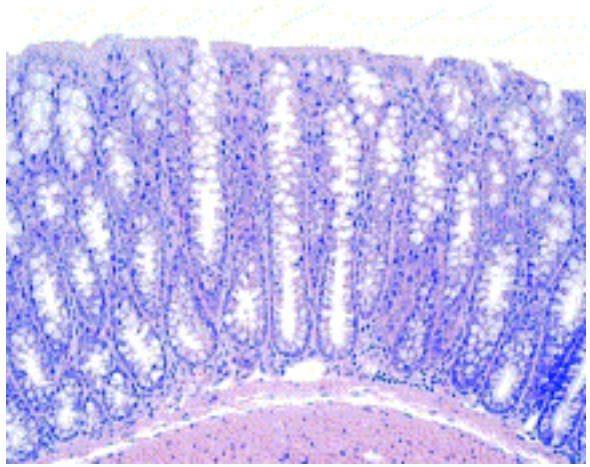
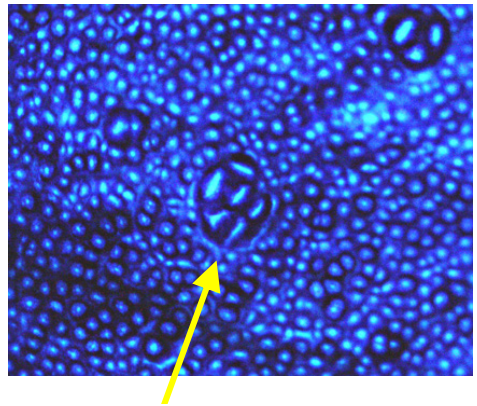


Image by Christine Andersen

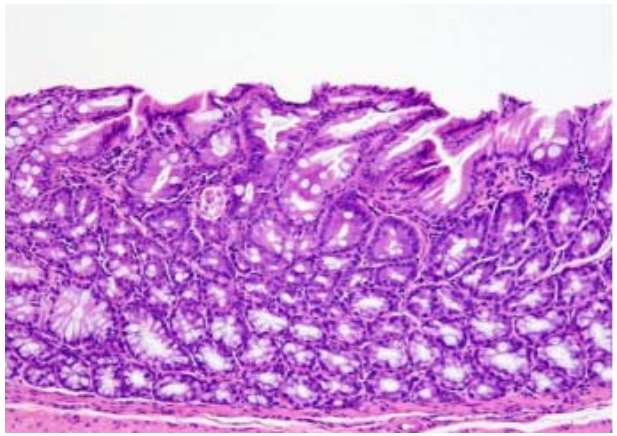
Progression from Normal to Cancer



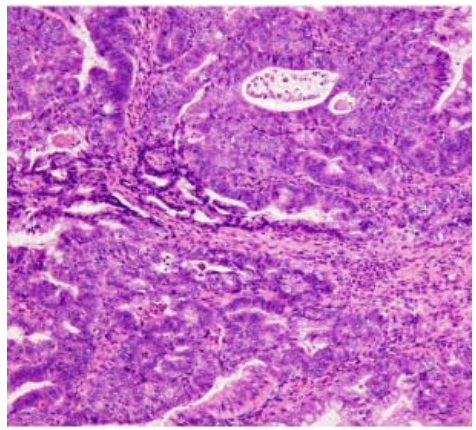
Normal Colonic Epithelium



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

"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

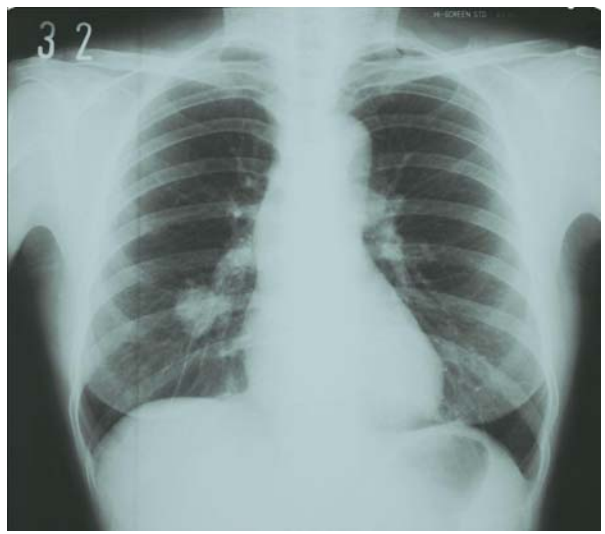
"Feed Me"
Recruit & Sustain Blood Flow

"Take Over"
Escape/Invade = Metastasize

"Mutate!"

Definitions:

Apoptosis
Immortal
Angiogenesis
Metastasis



Concept & parts of figure from Hanahan and Weinberg

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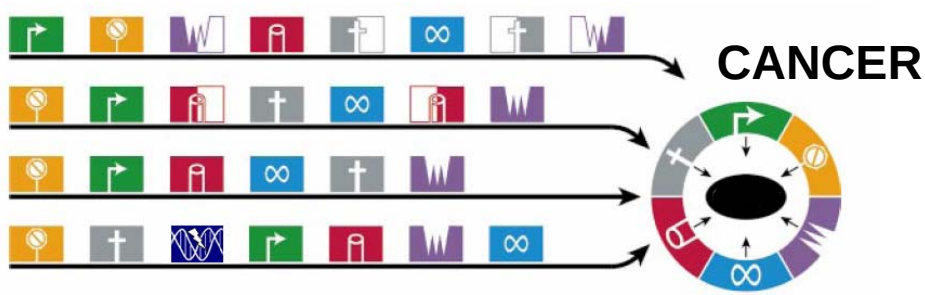
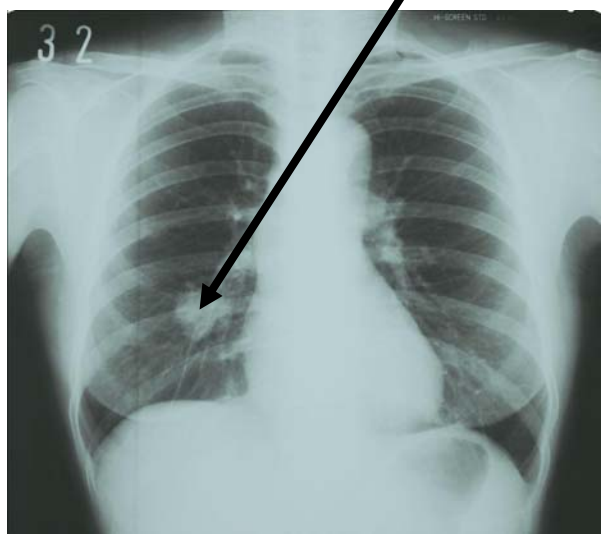




Concept & parts of figure from Hanahan and Weinberg

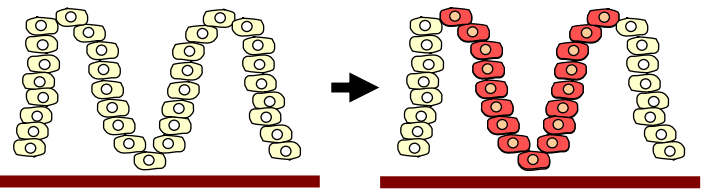
Where do cancer cells come from?

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

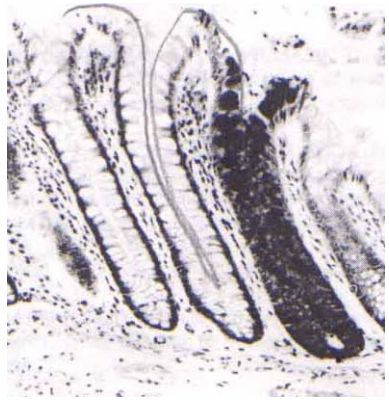
Most fully blown cancers require many mutations

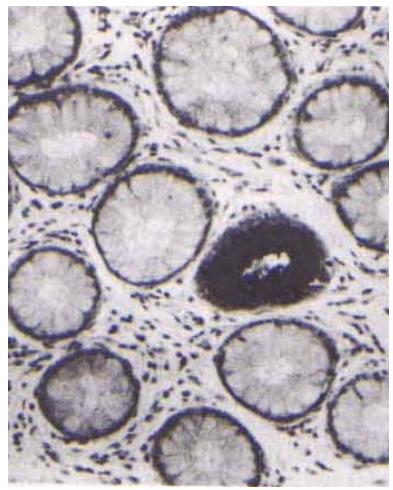
Colon Cancer…

Normal Colonic Epithelium



Mutation 1

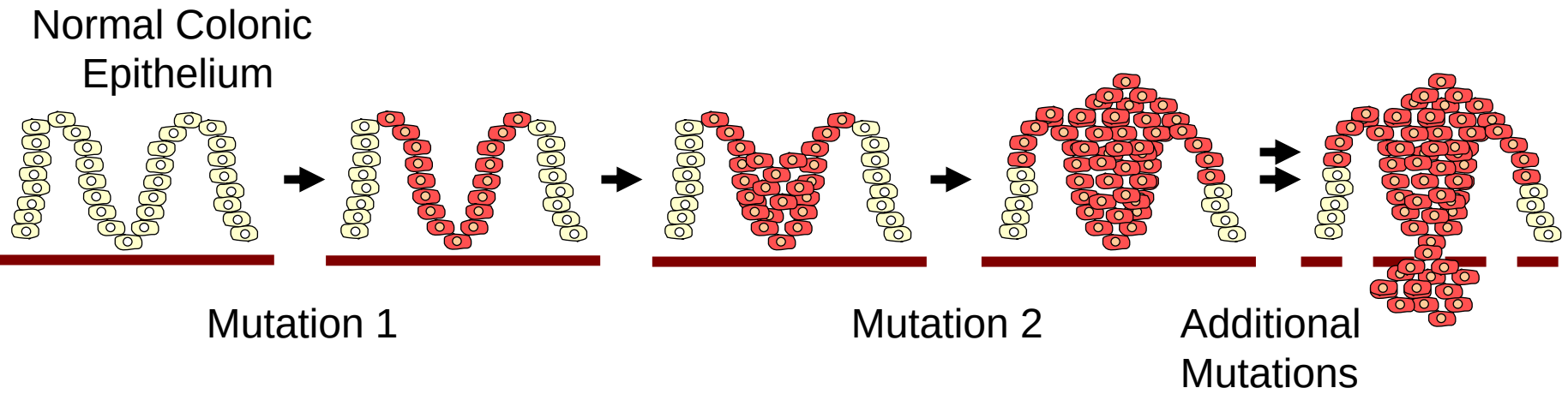




Photographs: C.E.Fuller & E.D.Williams; Br.J.Cancer (1990)

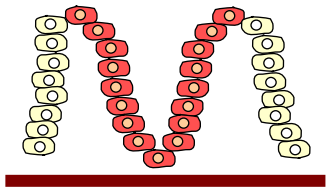
Most fully blown cancers require many mutations

Colon Cancer…

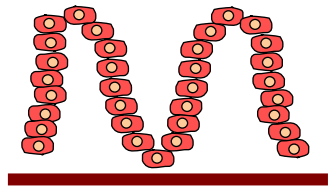


20 – 40 Years

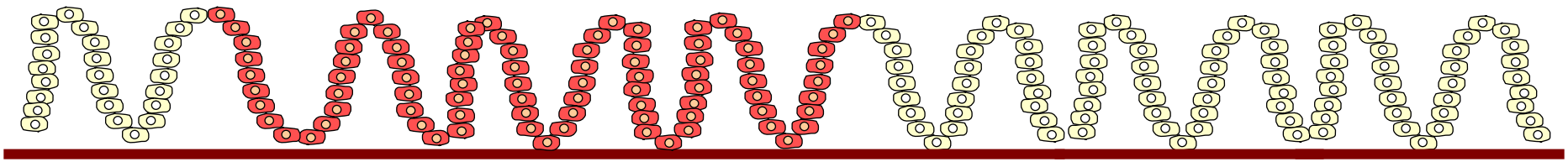
Most of the mutations occur in somatic cells – but germ line mutations can also contribute to cancer



Somatic Mutation:
Mutation arises within a tissue

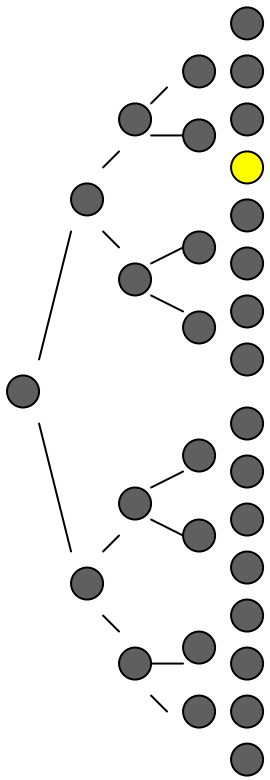


Germline Mutation:
All Cells Harbor
Cancer-Promoting Mutation

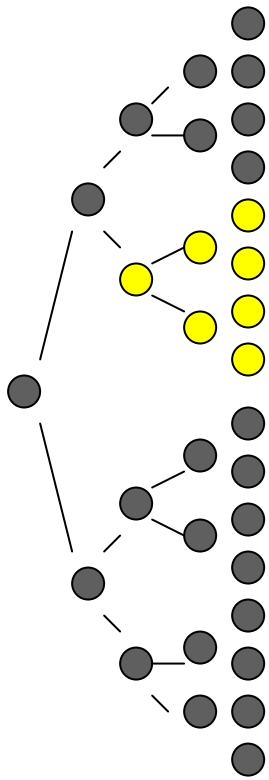


Mutation During Development followed by Clonal Expansion:
Cells within a tissue region share the same mutation

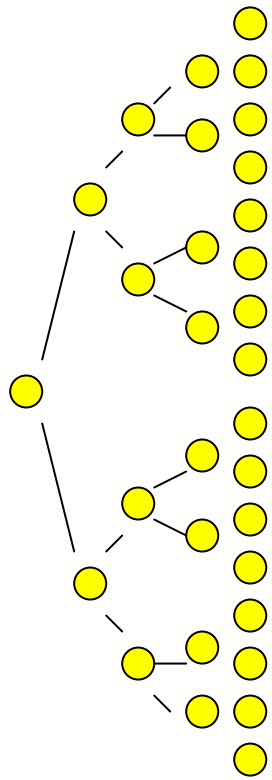
Clonal Expansion of Mutant Cells



Single Mutant Cell



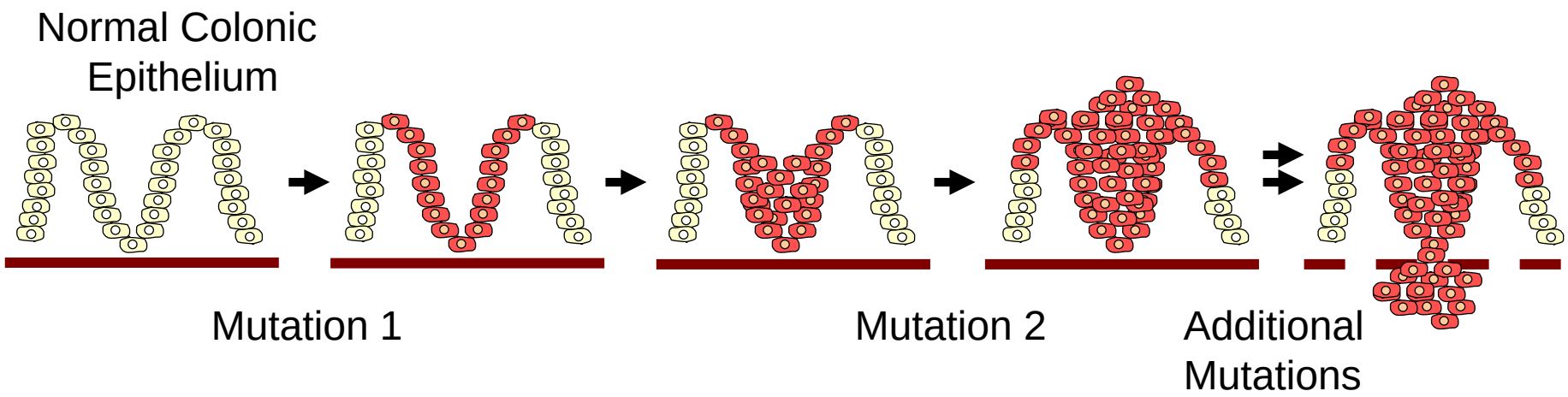
Segment



Inherited Mutation

How do you figure out Which mutations promote cancer?

Colon Cancer - can see every stage – compare stages and look for shared changes



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

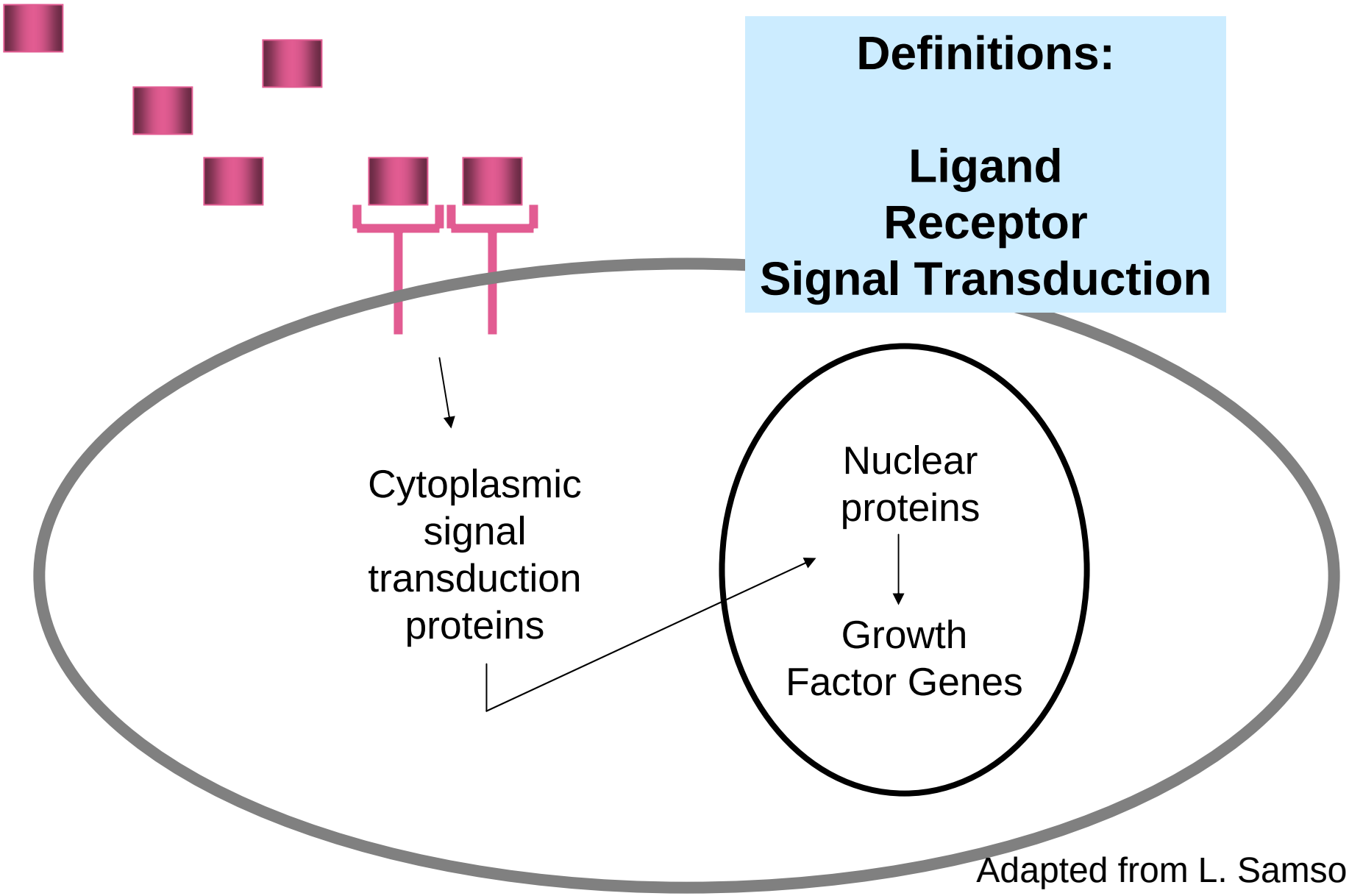
Ras ⟶ Ras(G12D)

"Go!"
Growth Signal Independent

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

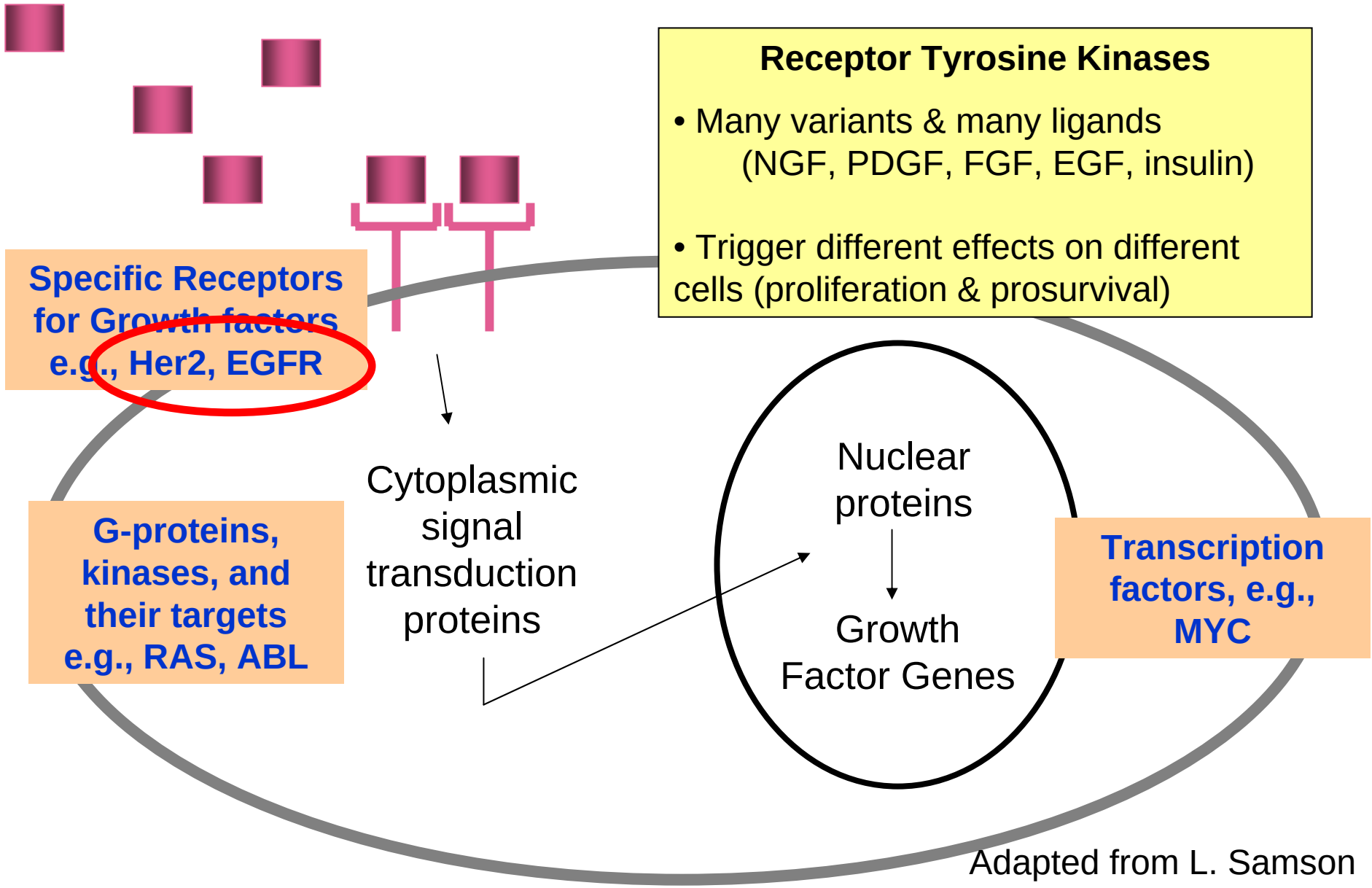
(H-Ras, N-Ras, and K-Ras)

Signal Transduction and Growth Regulation



Adapted from L. Samson

Signal Transduction and Growth Regulation



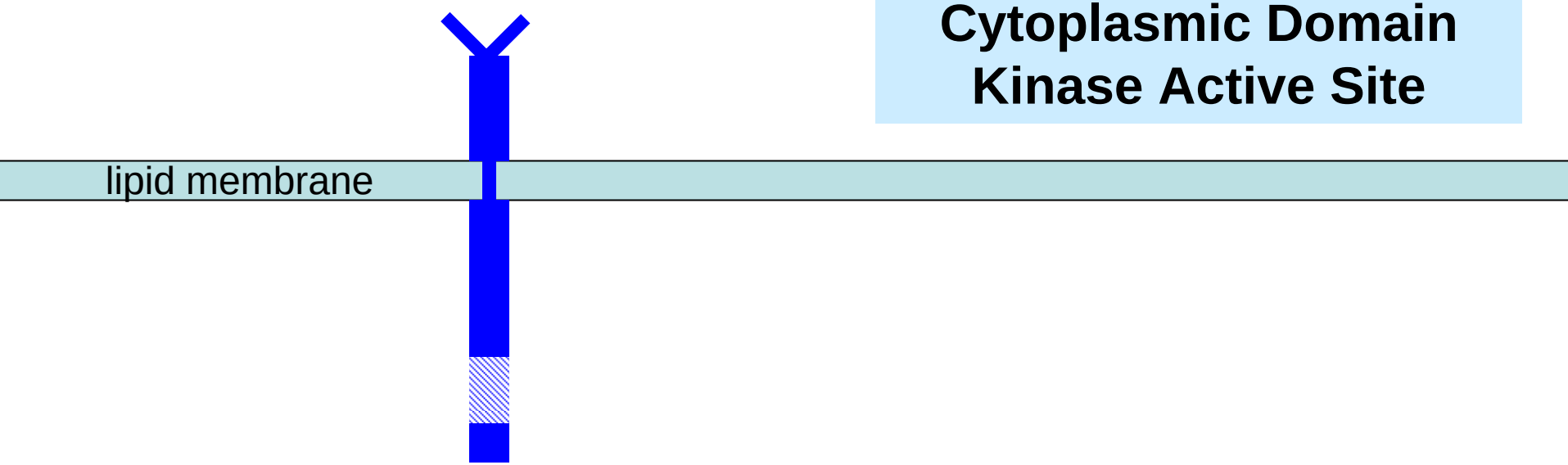
Adapted from L. Samson

EGFR: Receptor Tyrosine Kinase

Definitions:

Extracellular Domain
Transmembrane Domain
Cytoplasmic Domain
Kinase Active Site

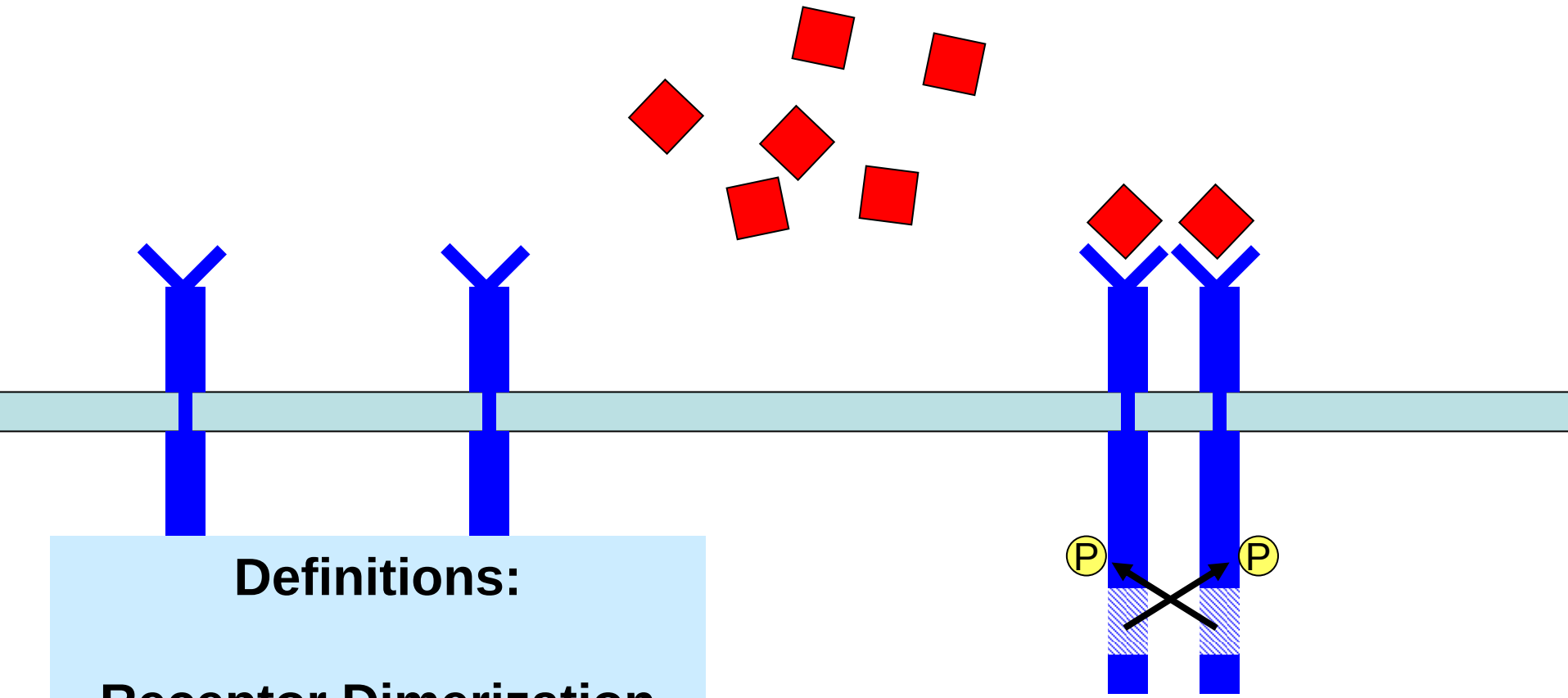
Outside the cell



Inside the cell

EGFR = Epidermal growth factor receptor

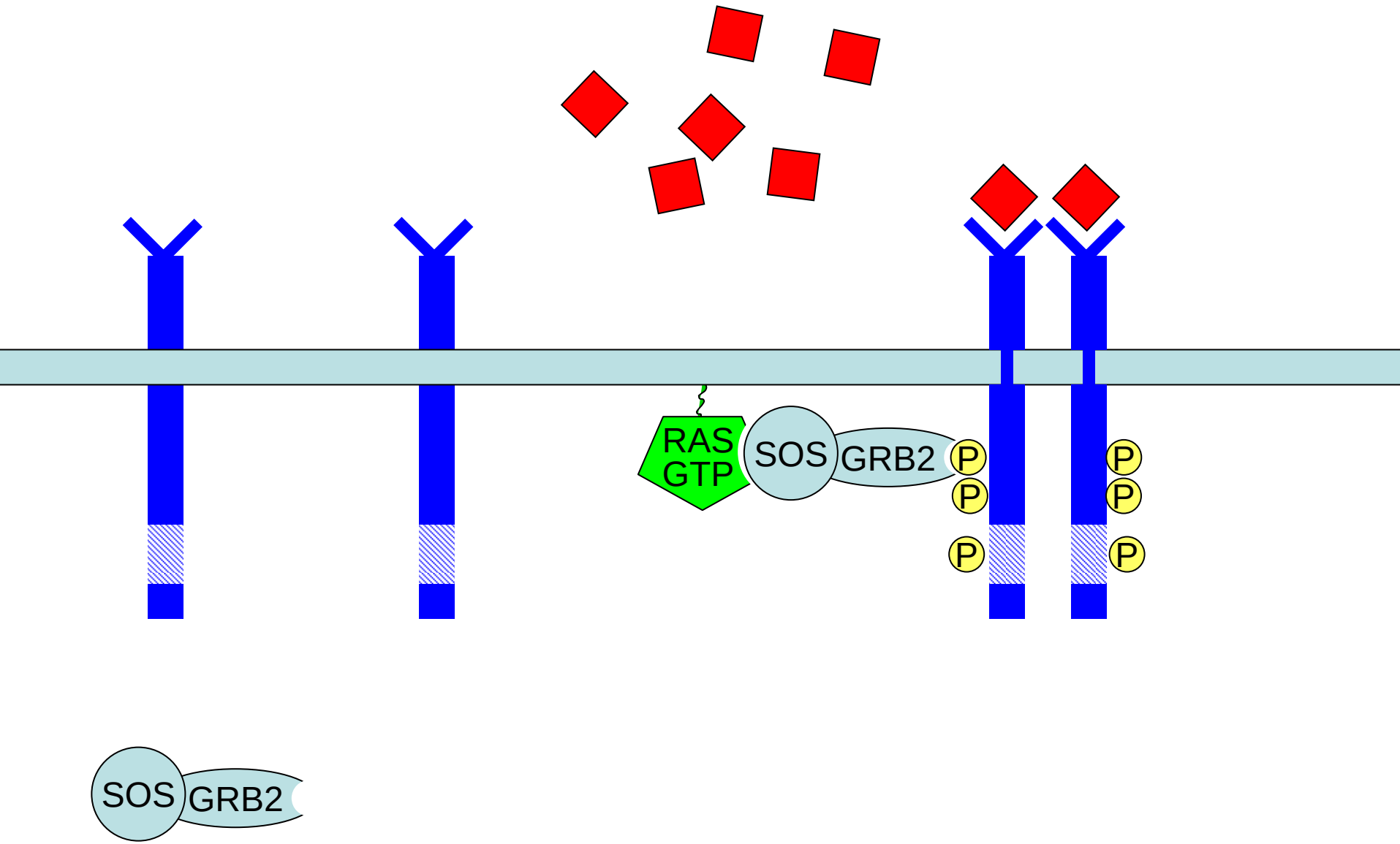
EGFR: Receptor Tyrosine Kinase



Definitions:

Receptor Dimerization
Kinase Activation
Autophosphorylation

EGFR: Receptor Tyrosine Kinase



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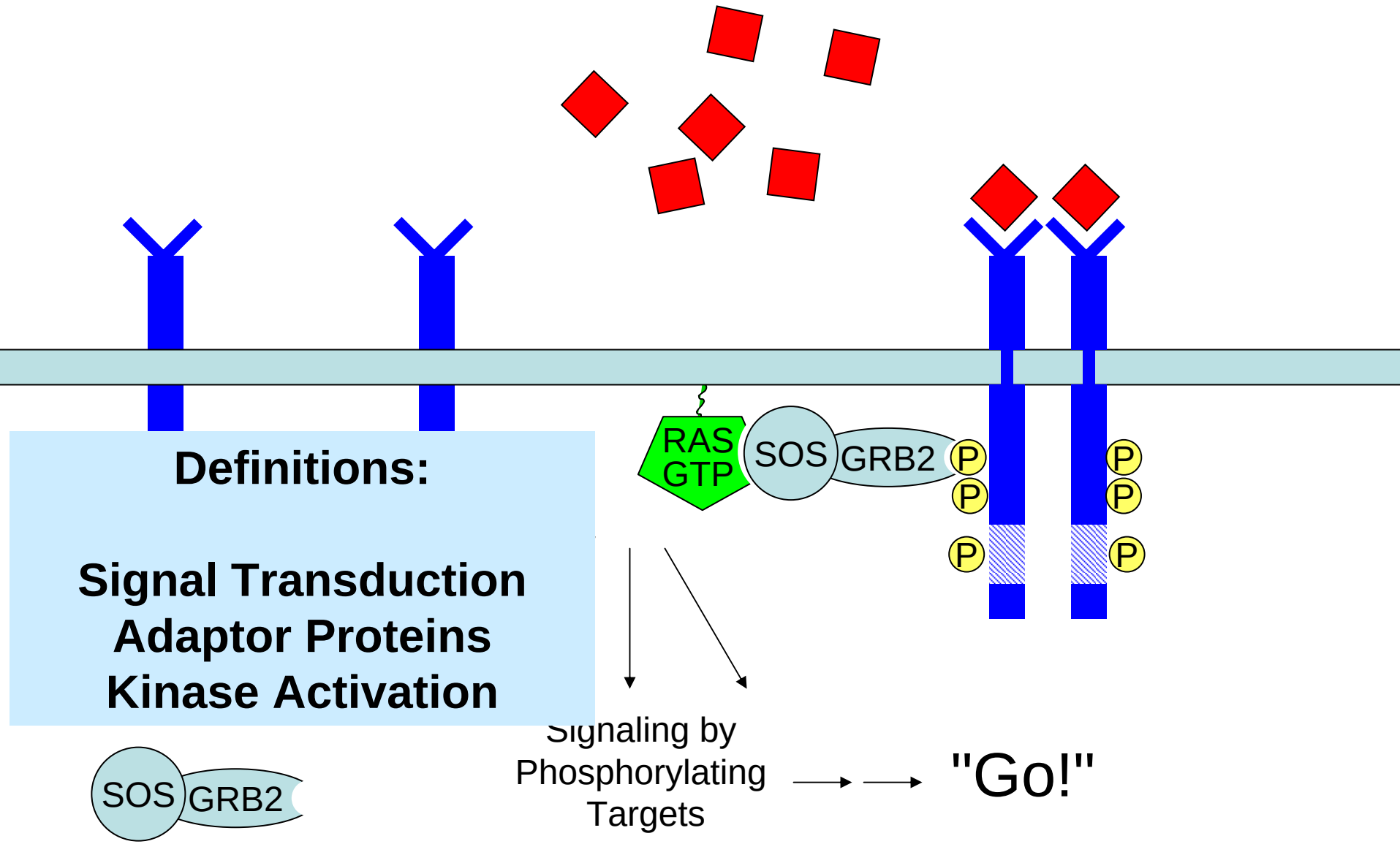


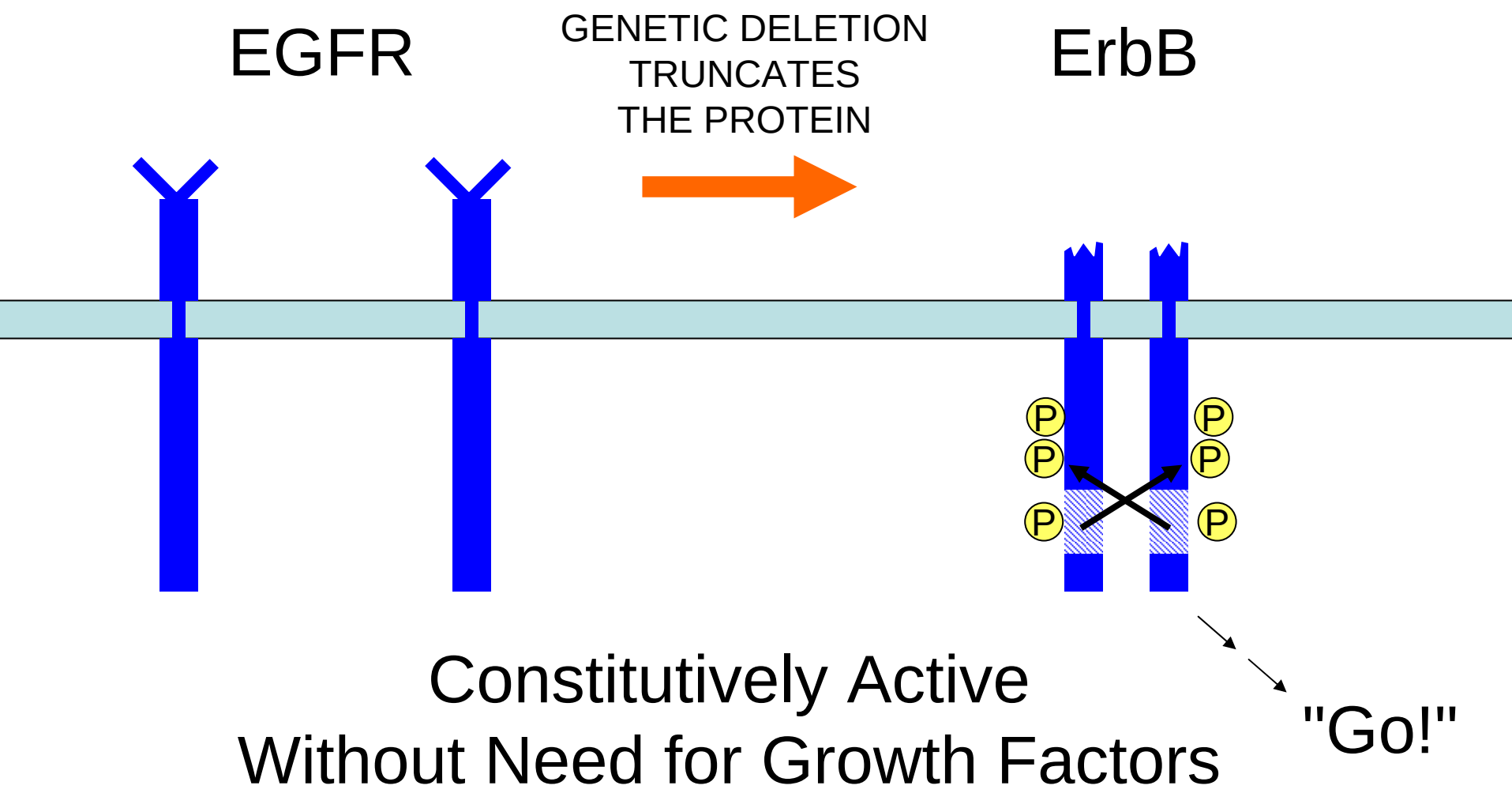
Definitions:

Signal Transduction
Adaptor Proteins
Kinase Activation

SOS GRB2

Signaling by Phosphorylating Targets → → "Go!"

Cancer Cells Often Exploit Receptor Tyrosine Kinases



Slide adapted from L. Samson

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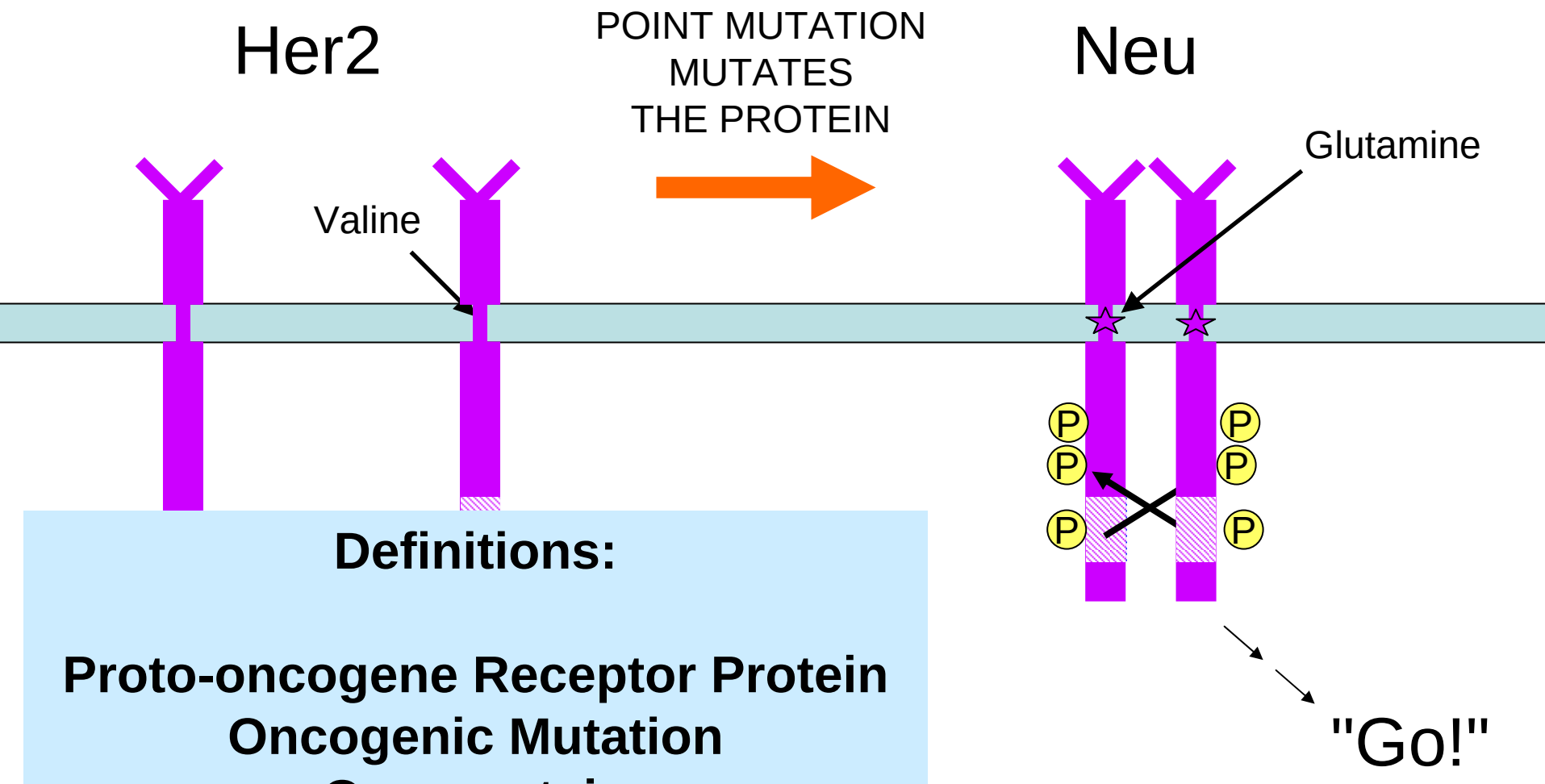
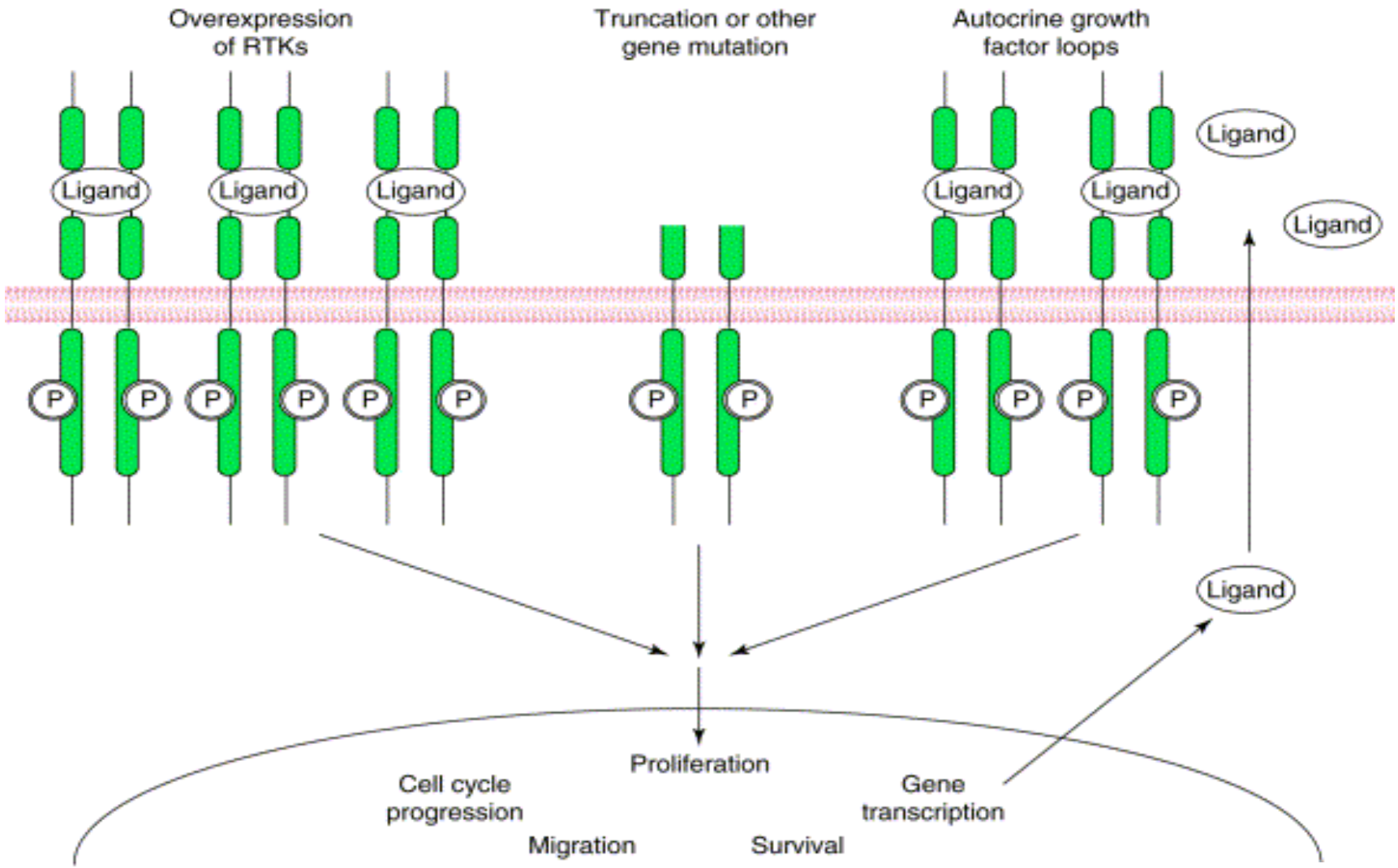


Definitions:

Proto-oncogene Receptor Protein
Oncogenic Mutation
Oncoprotein

Constitutive Activation converts RTKs to Dominant Acting Oncogenes



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

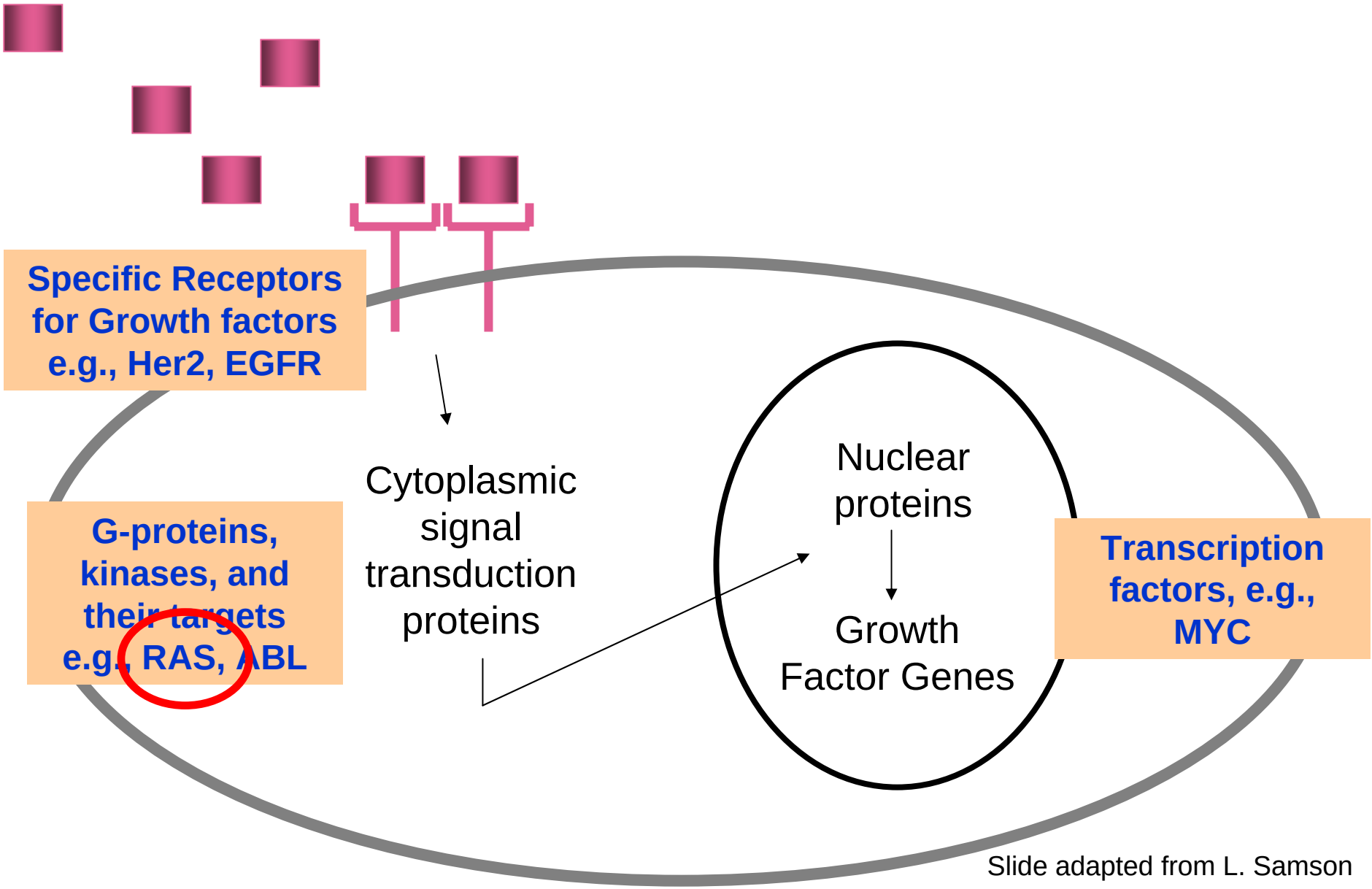
Slide adapted from L. Samson

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

Slide from L. Samson

Signal Transduction and Growth Regulation



Slide adapted from L. Samson

EGFR: Receptor Tyrosine Kinase

ON 

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

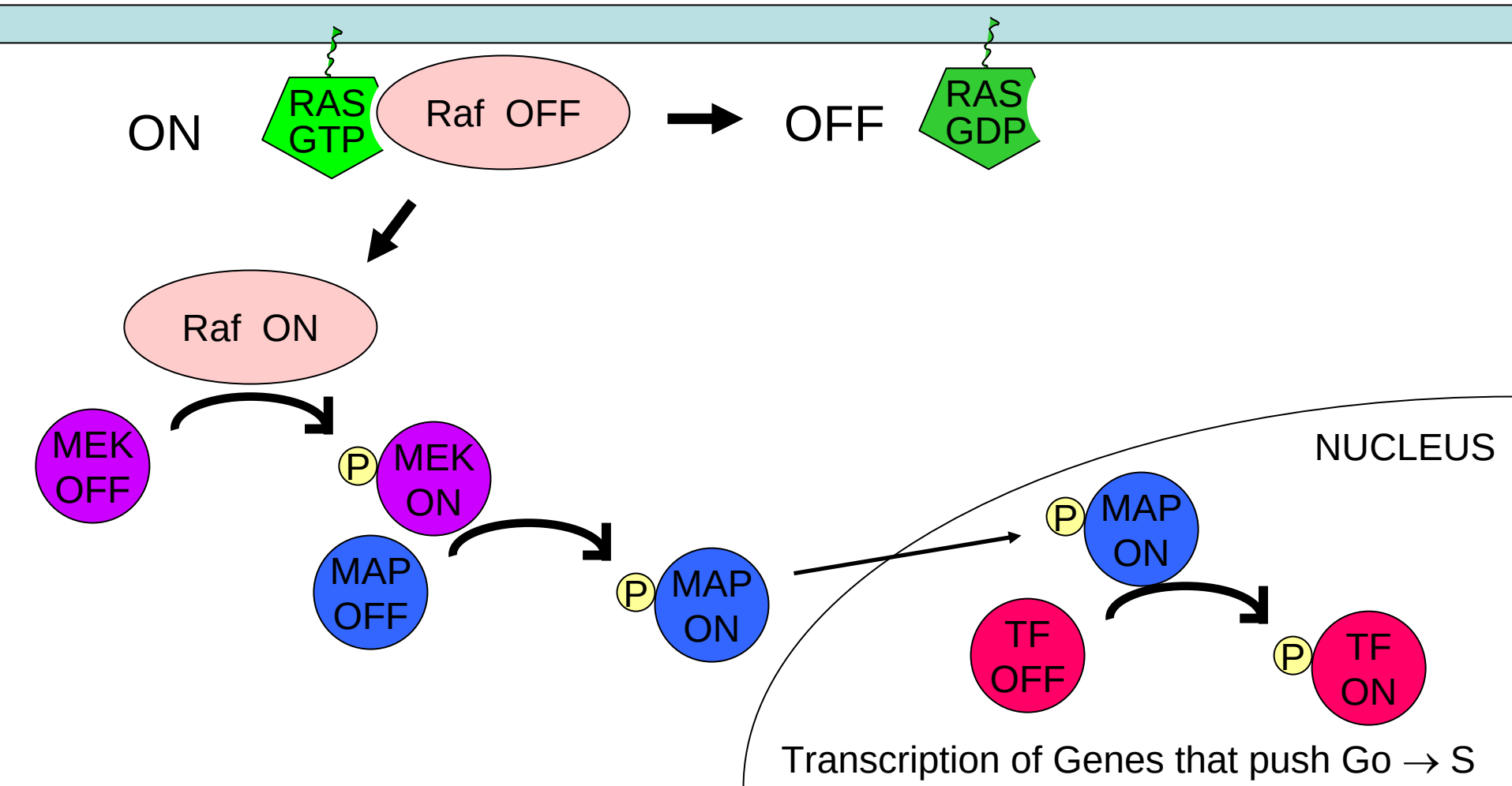
Oncogenic mutations “Lock” Ras into active GTP bound state

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

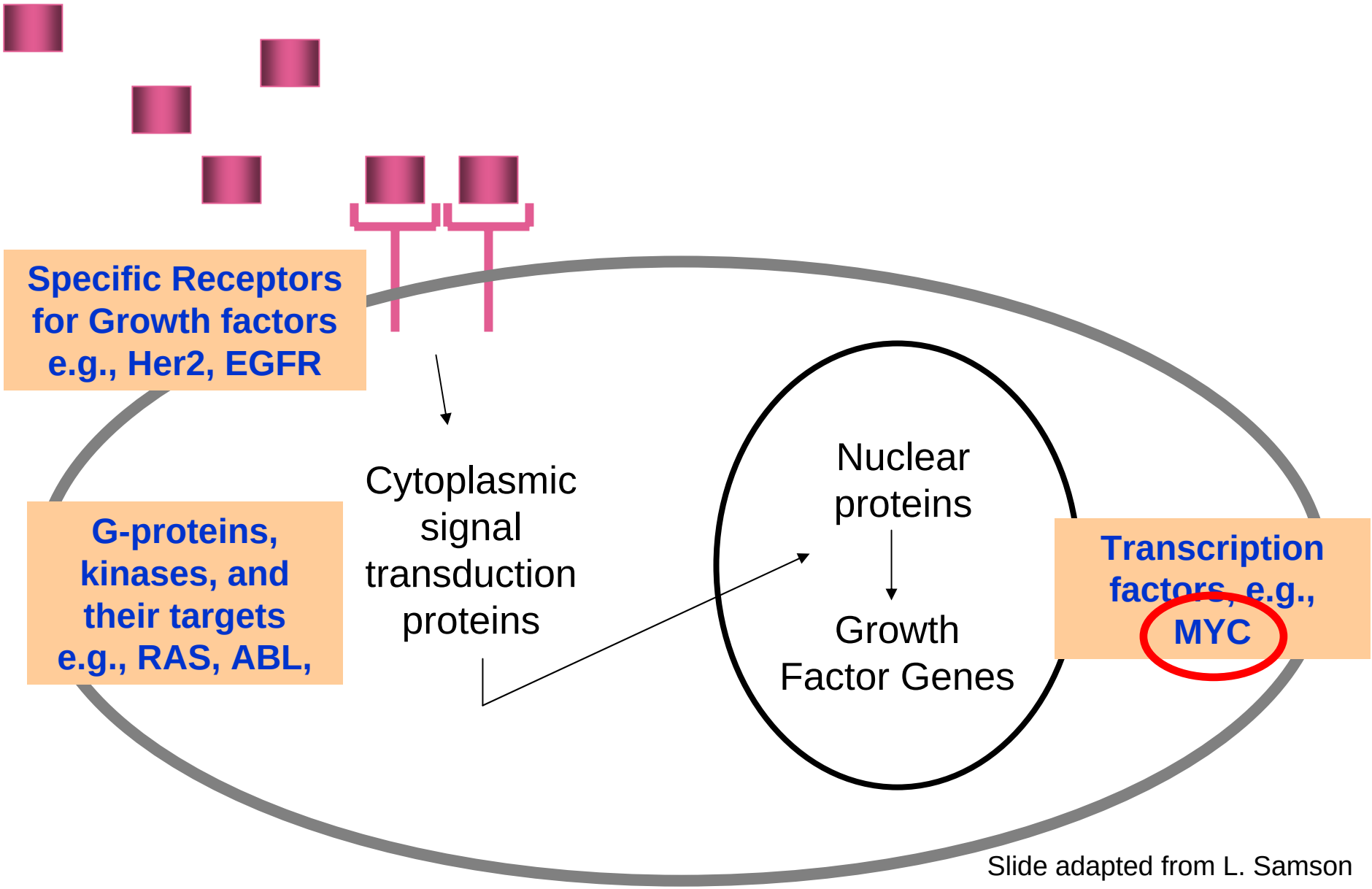
Reminder:

Ras was the gene that transformed the 3T3 Cells

EGFR: Receptor Tyrosine Kinase



Signal Transduction and Growth Regulation



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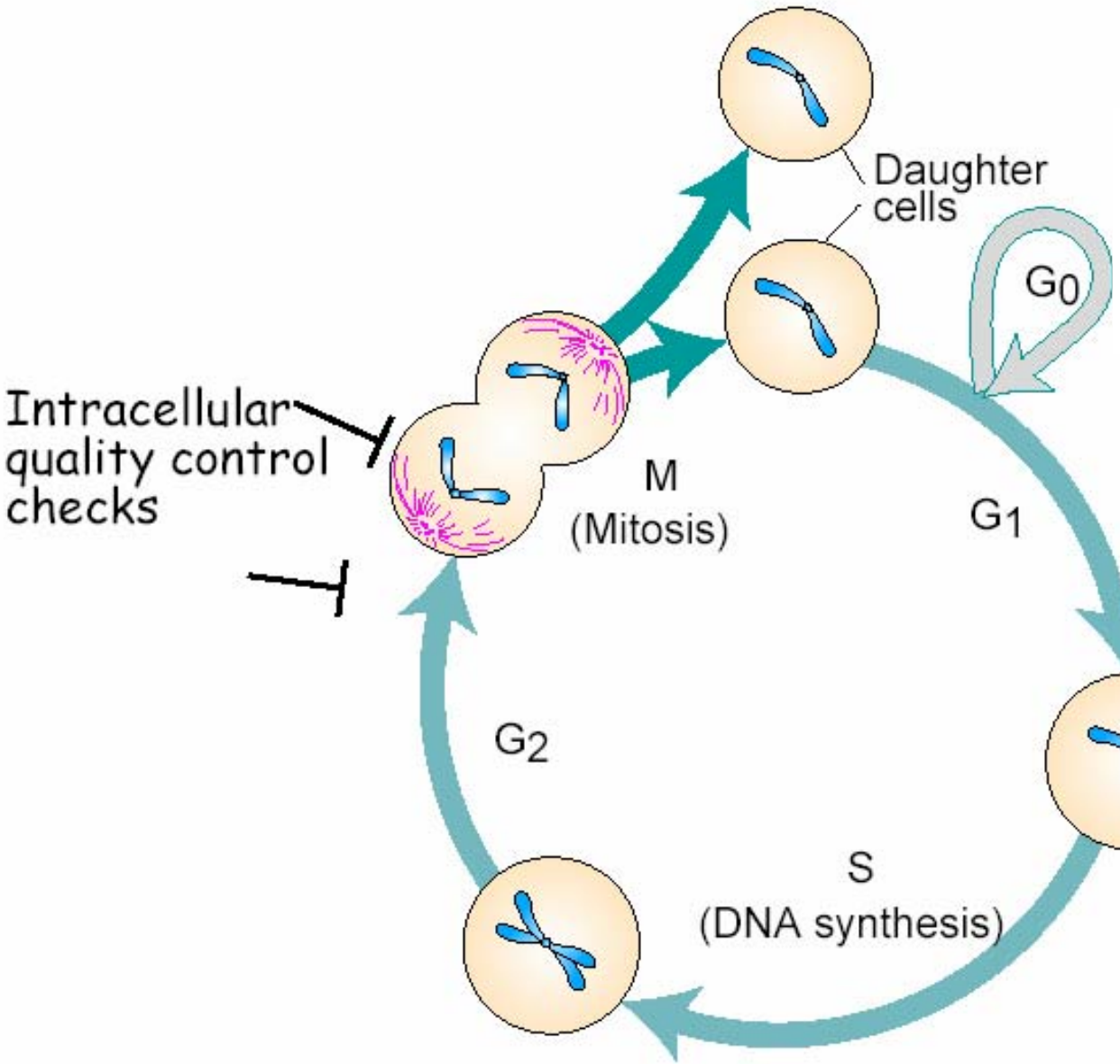


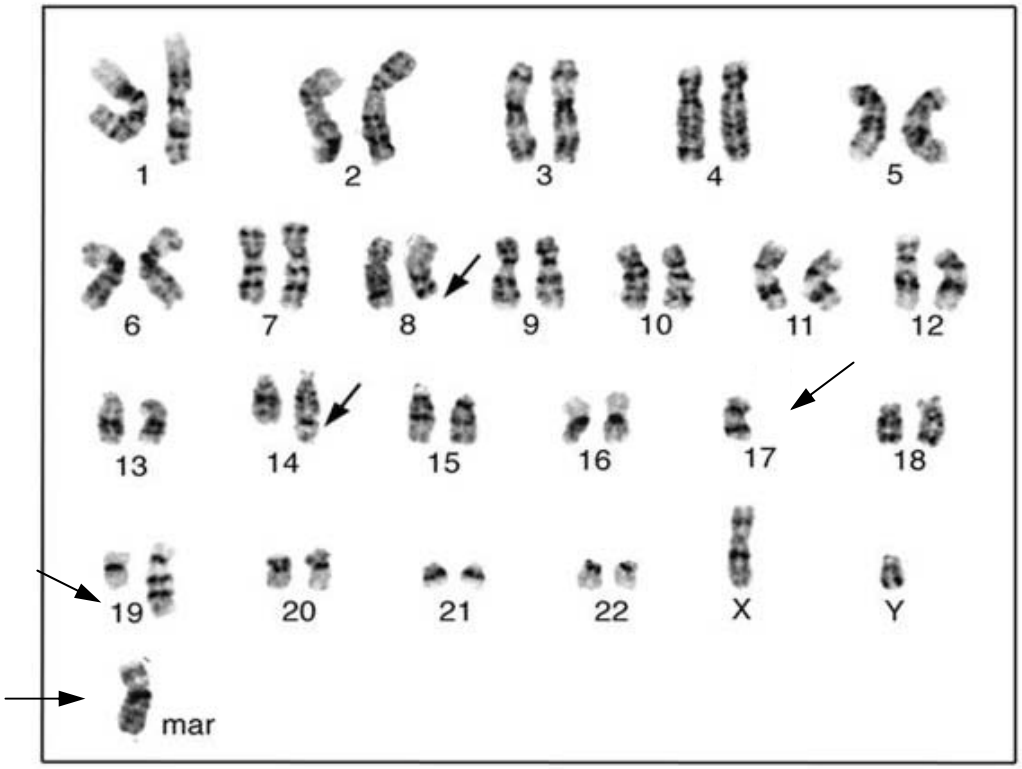
cMYC drives cells from G1 to S – so pushes cells through the cell cycle

Slide adapted from L. Samson

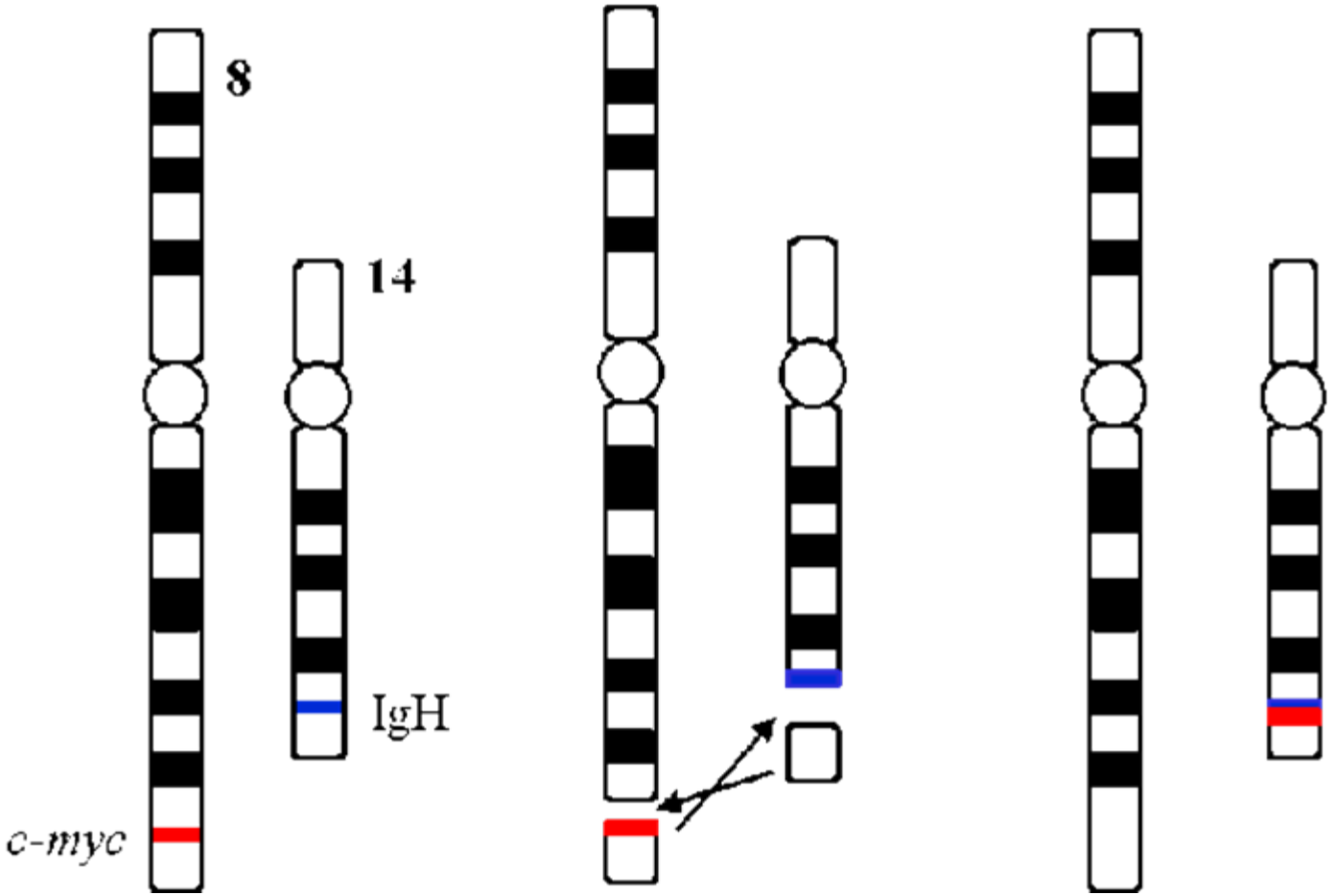
Burkitts Lymphoma

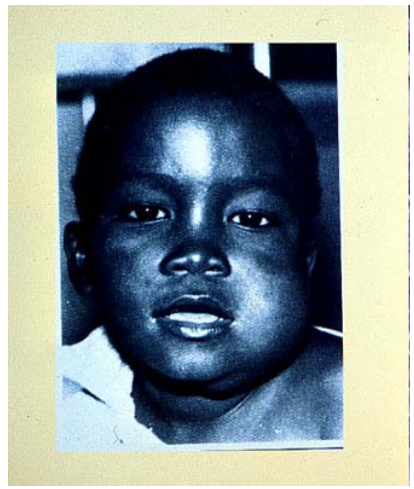
There are many chromosomal abnormalities in the cancer cells

How do you figure out which changes promote the disease?



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



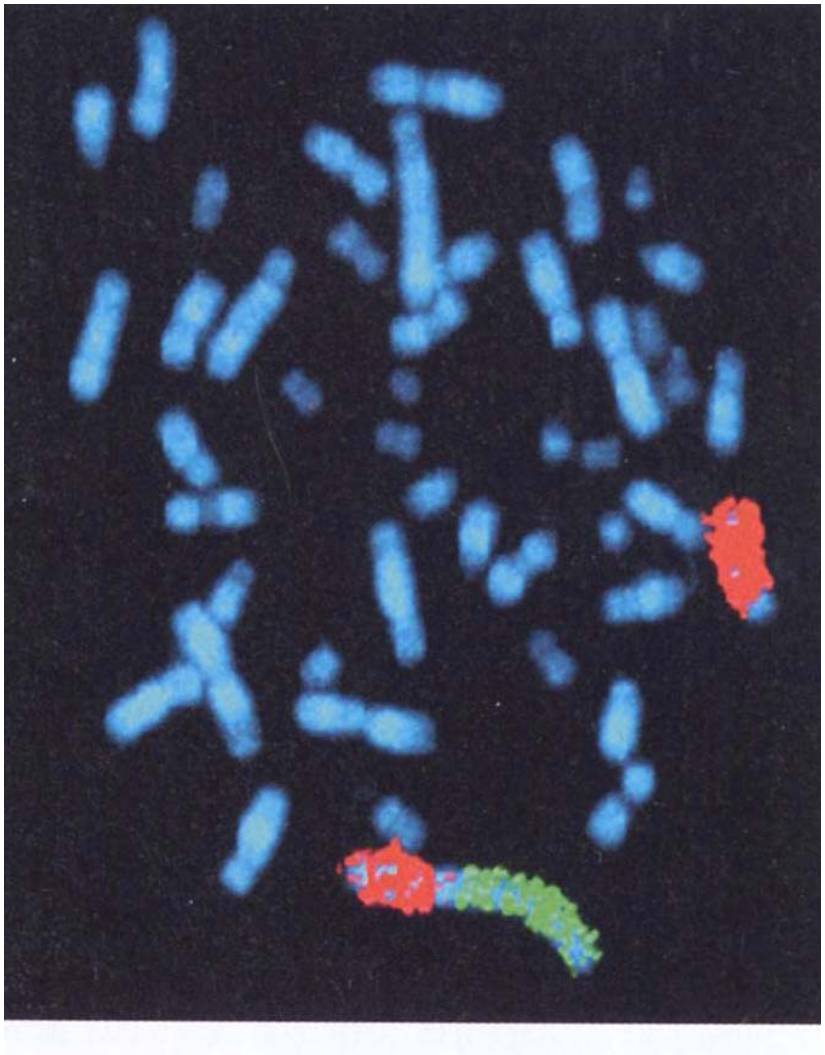


MYC drives cells from G1 to S

Slide adapted from L. Samson

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

Slide adapted from L. Samson

Classes of Mutations that Convert Proto-Oncogenes into Oncogenes (Gain of Function Mutations)

Deletion: constitutively active protein - EGFR

Point Mutation: constitutively active protein

- Her2; Ras

Translocation: increased expression

-Myc ORF put under strong constitutive promoter

Translocation: fusion of two genes to make a new product – Bcr-Abl

Amplification: many copies

- Myc

Slide adapted from L. Samson

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"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

Why don't all tumors have the same mutations?

- Different Niches in different parts of the body
- More than one way to get a feature (like "Go!")
- Some mutations accelerate cancer, but aren't essential

Major complications in understanding the genetic basis of cancer

- **Multiple mutations are necessary to produce a cancer cell**

- **Different types of cancers have different genes mutated**

- **Early initiating events occur rarely in complex tissues and are therefore extremely difficult to detect**

- **Key initiating events often lead to an increase in mutation rate thus tumor cells often bear many <u>fortuitous mutations</u>**

Slide adapted from L. Samson

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

Slide adapted from L. Samson

Take-Home Messages

- RTK→RAS→RAF→MEK→MAPK→TF→“Go!”
- Cancer is a disease of over-prolif; it’s advantageous to cancer cells to trick cells into “Go!”
- Cancer cells need many new traits, therefore multiple mutations (proliferation is one example)
- Many cancers experience a high mutation rate, so its hard to know which mutations matter to cancer
- Most carcinogenic mutations occur in somatic cells, but they can also arise in germline or during development

Mutations in Cancer Genes Transform Normal Cells into Cancer Cells

Oncogenes

Tumor suppressor genes

Mutator genes