Cancer Biology

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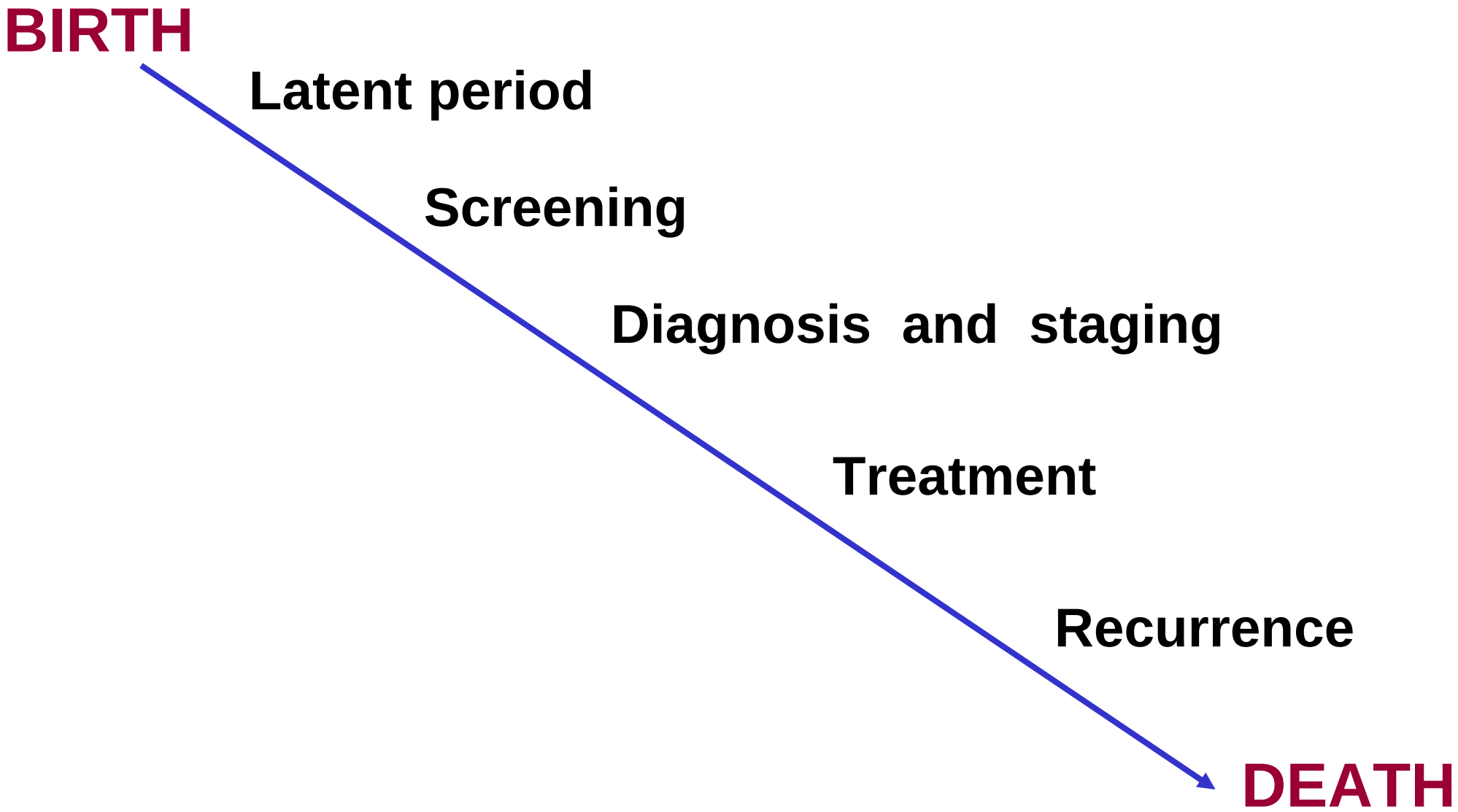
University Medical Center, Tucson, Arizona

Learning Objectives

After participating in this module, attendees should be able to

- Discuss tumor biology at the cellular level
- Describe the cell cycle and tumorigenesis
- Discuss molecularly targeted therapy

Multidisciplinary Cancer Management Course



Case Study

A 48-year-old woman has a three-month history of a painless mass in the right breast mass

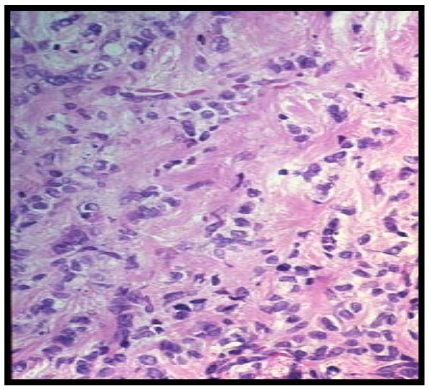
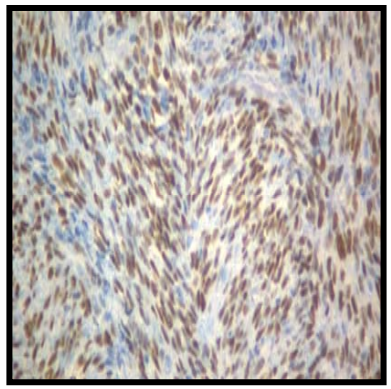
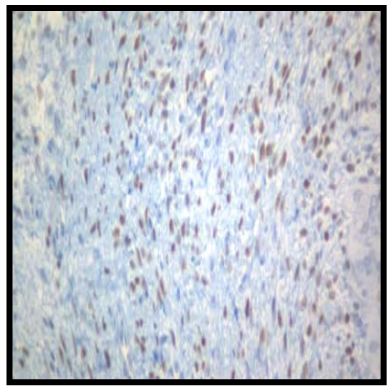
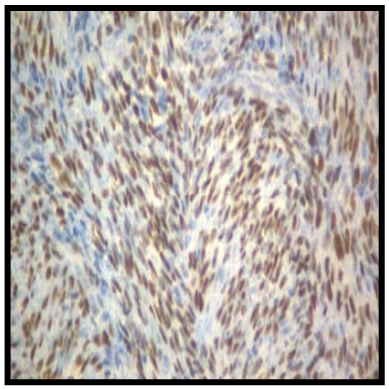
Her mother, aunt, and older sister had breast cancer

Her grandmother had ovarian cancer

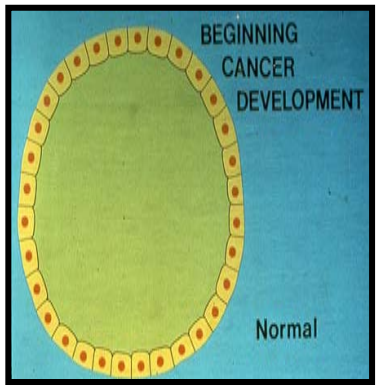
Case Study (cont.)

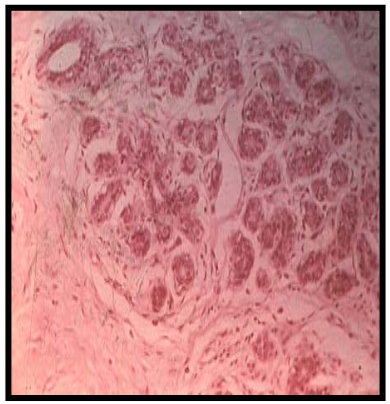
Biopsy results

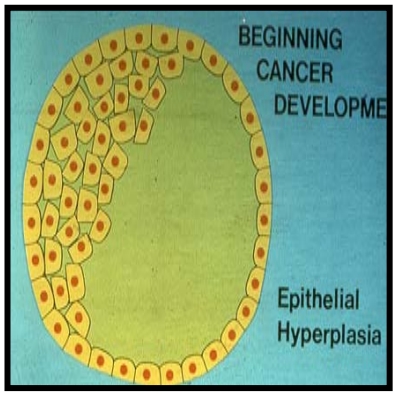
- Infiltrating ductal carcinoma
- Estrogen receptor/progesterone receptor negative
- MIB-1index: 37% HER-2/*neu* expression: 3.5

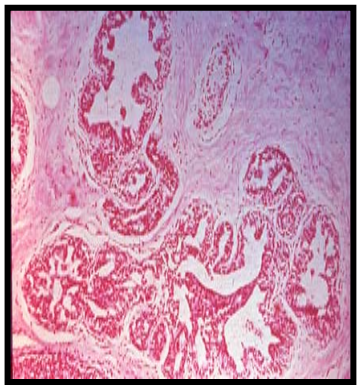





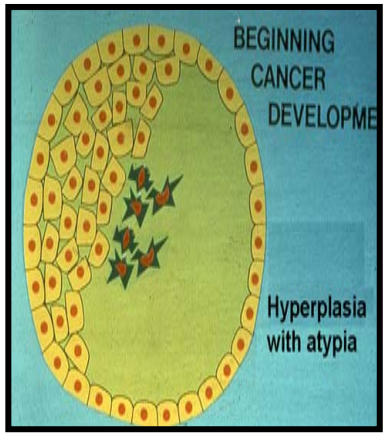
Beginning Cancer Development

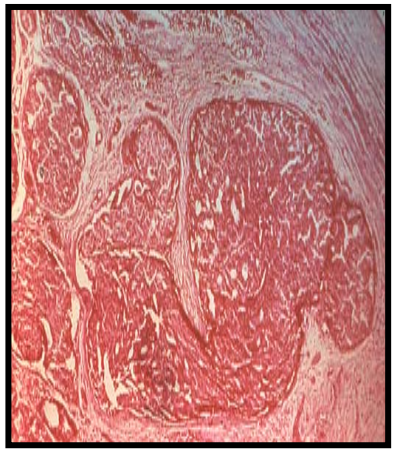


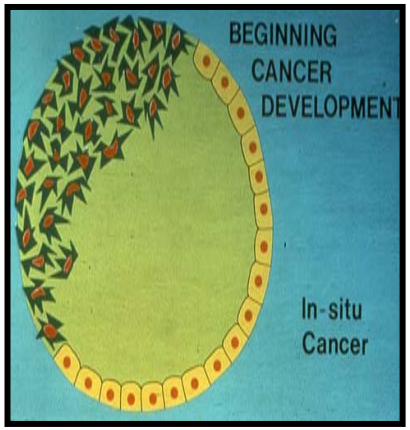


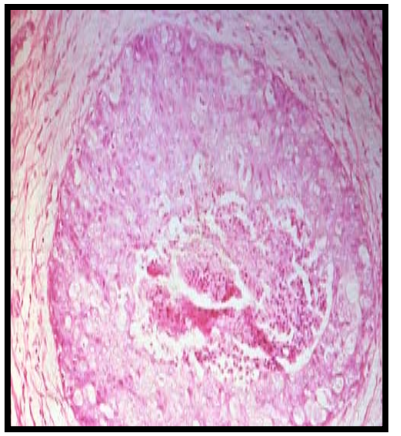












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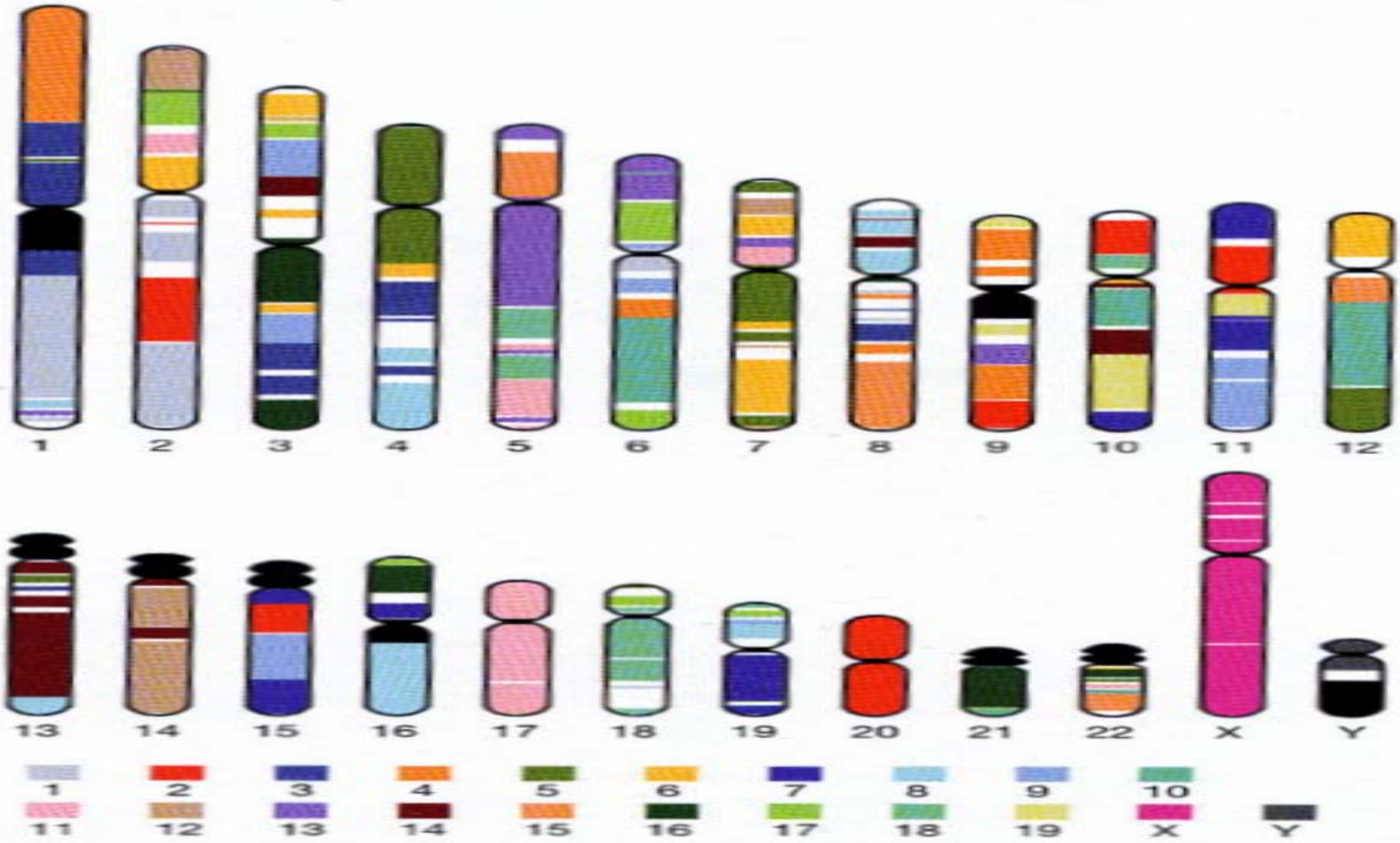
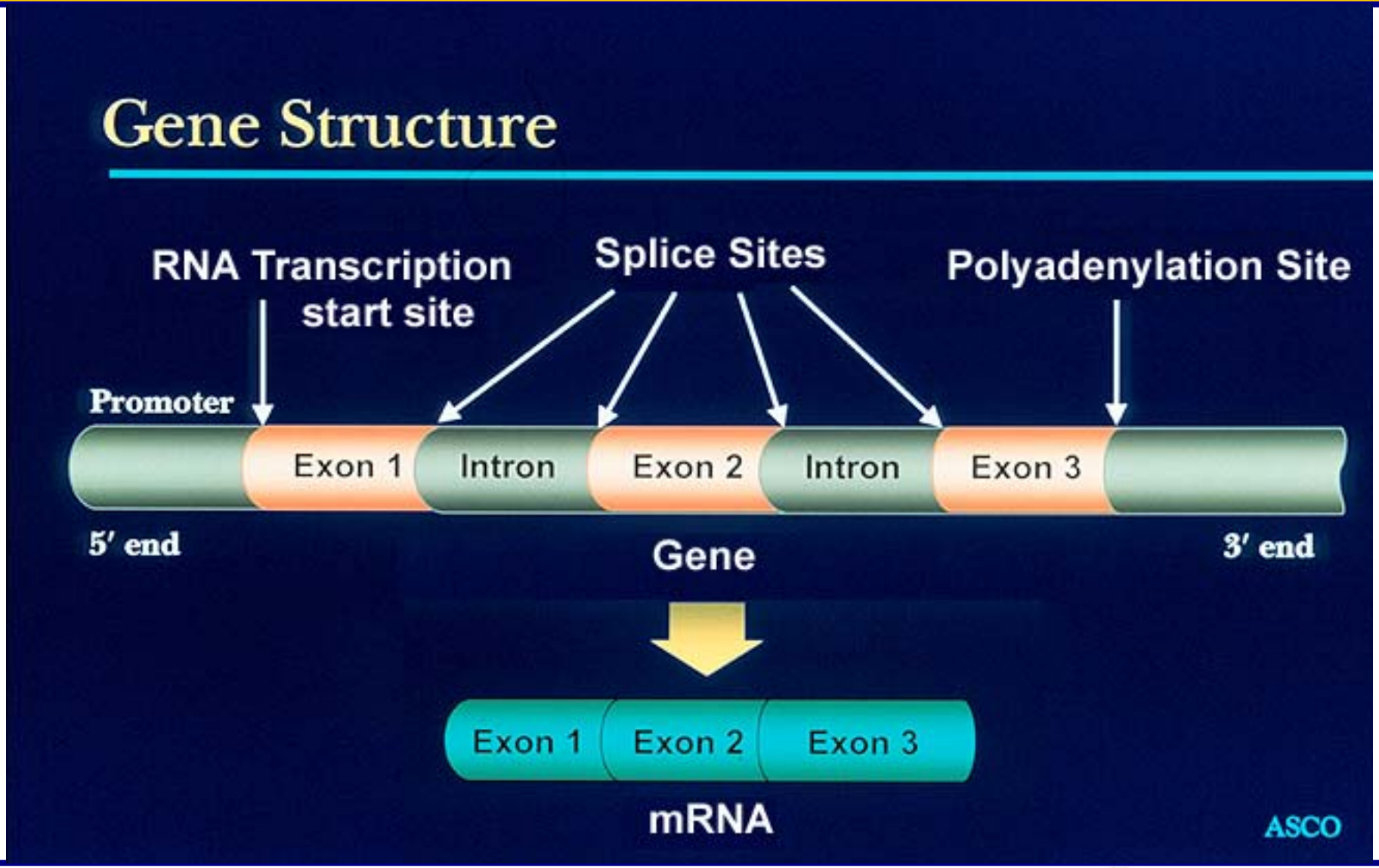
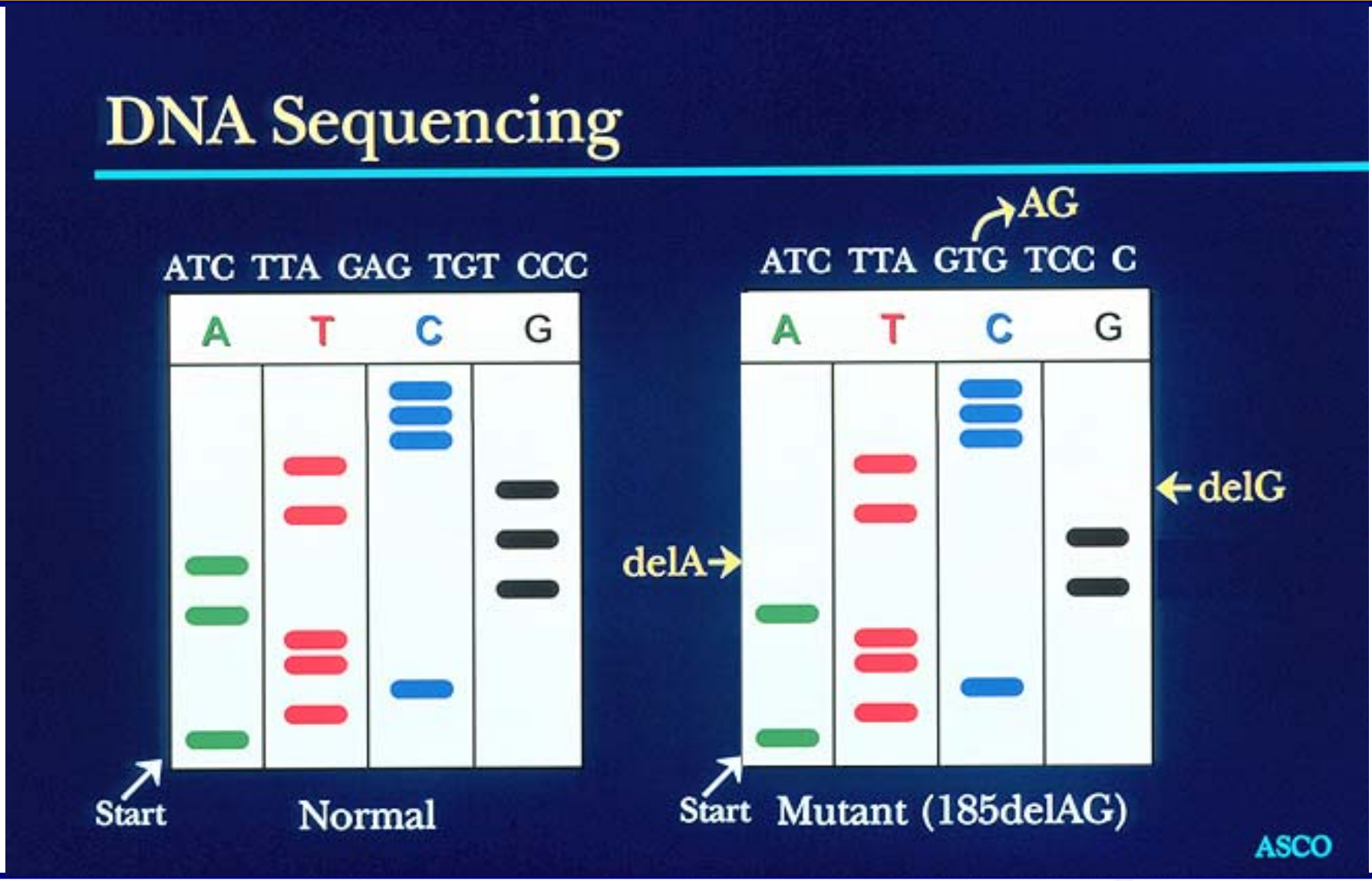
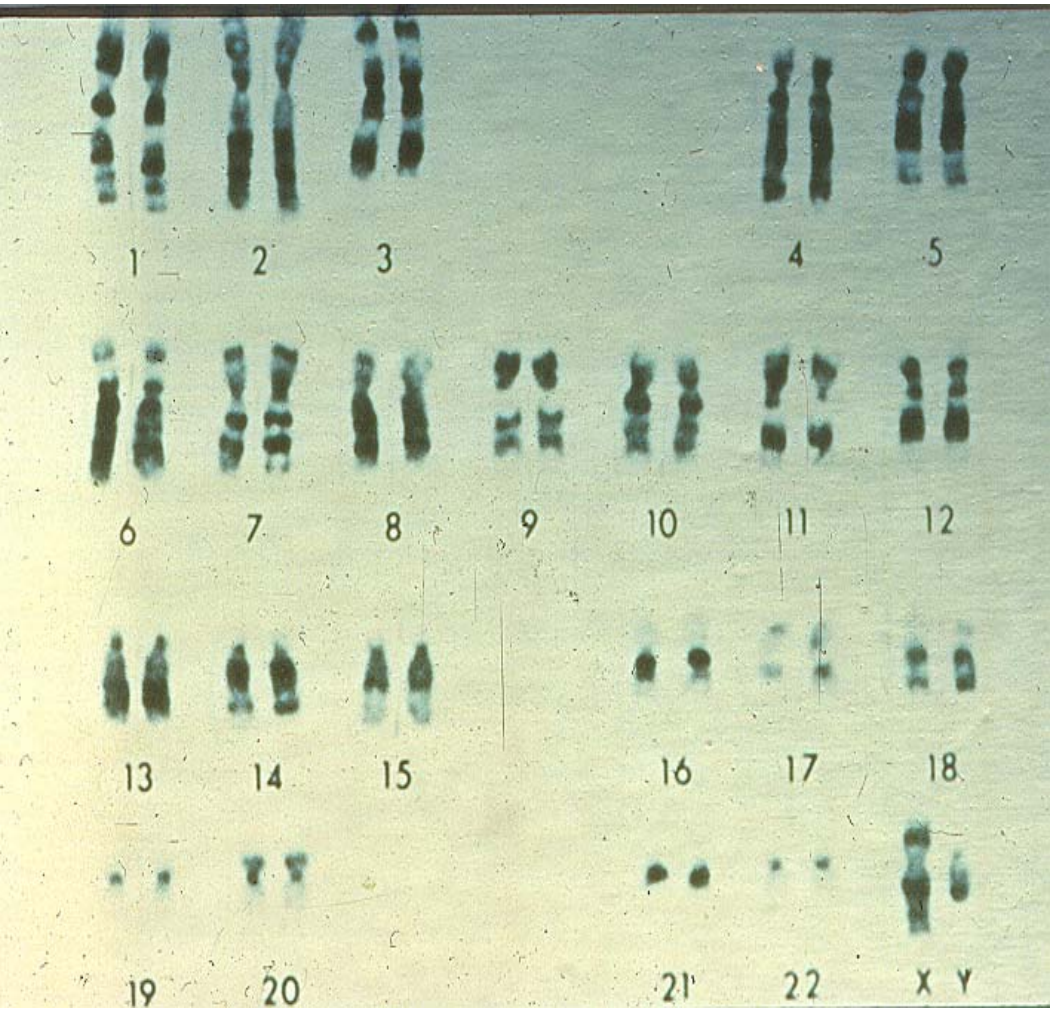


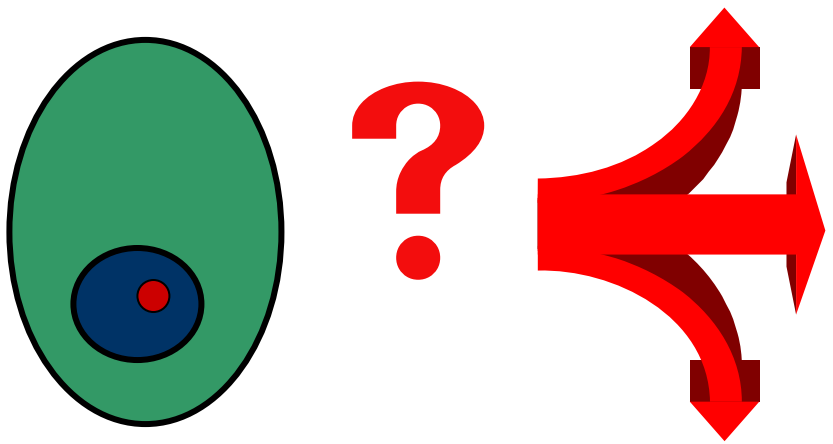

Gene Structure
RNA Transcription start site
Splice Sites
Polyadenylation Site
Promoter
Exon 1
Intron
Exon 2
Intron
Exon 3
5′ end
Gene
3′ end
Exon 1
Exon 2
Exon 3
mRNA
ASCO


DNA Sequencing
ATC TTA GAG TGT CCC
A T C G
Start
Normal
AG
ATC TTA GTG TCC C
A T C G
delA
delG
Start
Mutant (185delAG)
ASCO

Multidisciplinary Cancer Management Course



Cell Options



Division (cell cycle)

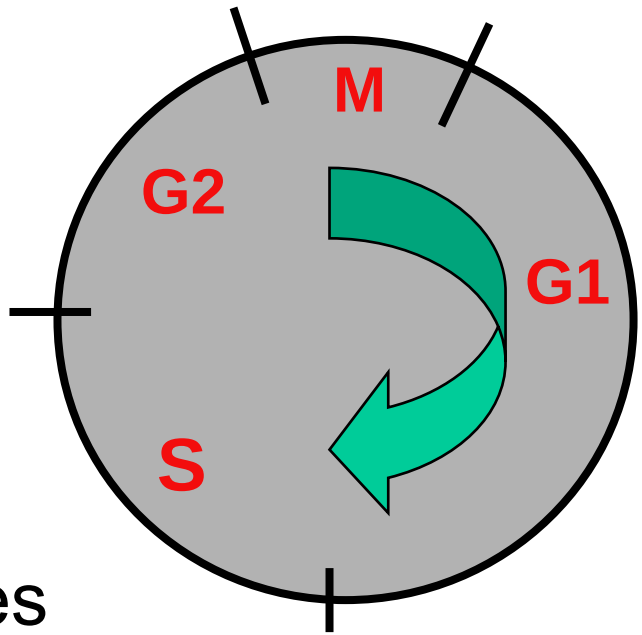
Normal metabolic activity (G0)

Cell death (apoptosis)

G1 to S Phase Transition

↑ Growth factors

G1 to S phase transition



↑ Cyclins

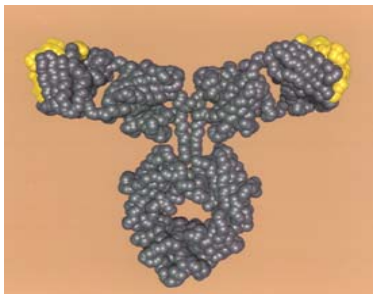
↑ Transcription factors

↑ Cyclins/kinases

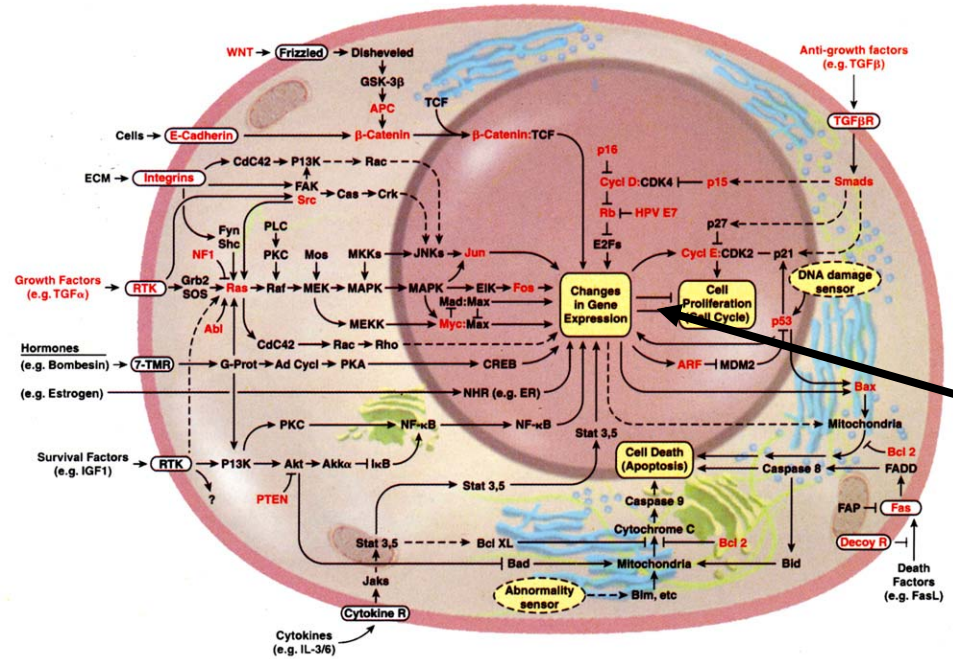
pRb phosphorylation

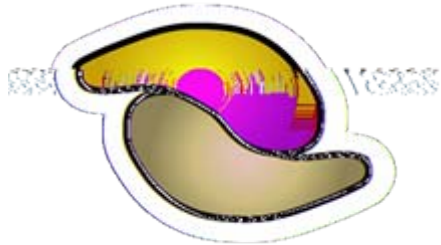
Multidisciplinary Cancer Management Course

Epidermal growth factor receptor

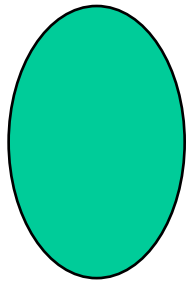


Antiangiogenesis VEGF





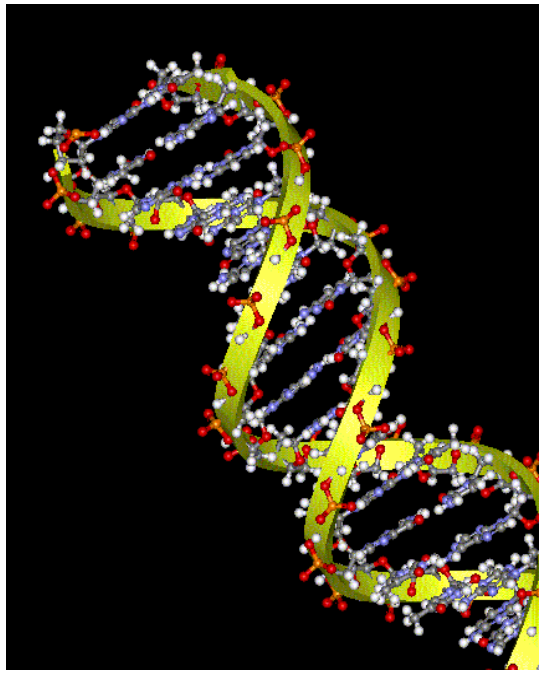
HER-2/*neu*



Estrogen receptor/
Progesterone receptor

Cancer Tumorigenesis

- Genetic instability and mutations
- Activation of proto-oncogenes
- Inactivation of tumor suppressor genes



DNA Alterations Leading to Cancer

- Deletion
- Translocation
- Loss of heterozygosity (LOH)
- DNA methylation
- DNA amplification
- Point mutation
- DNA loss
- DNA exchange
- Allele loss
- Gene silencing
- DNA gain
- Small DNA change

Normal Cell

APC **mutation (5q)**

↑ **proliferation**

DNA hypomethylation

Adenoma I

K-ras **mutation**

Adenoma II

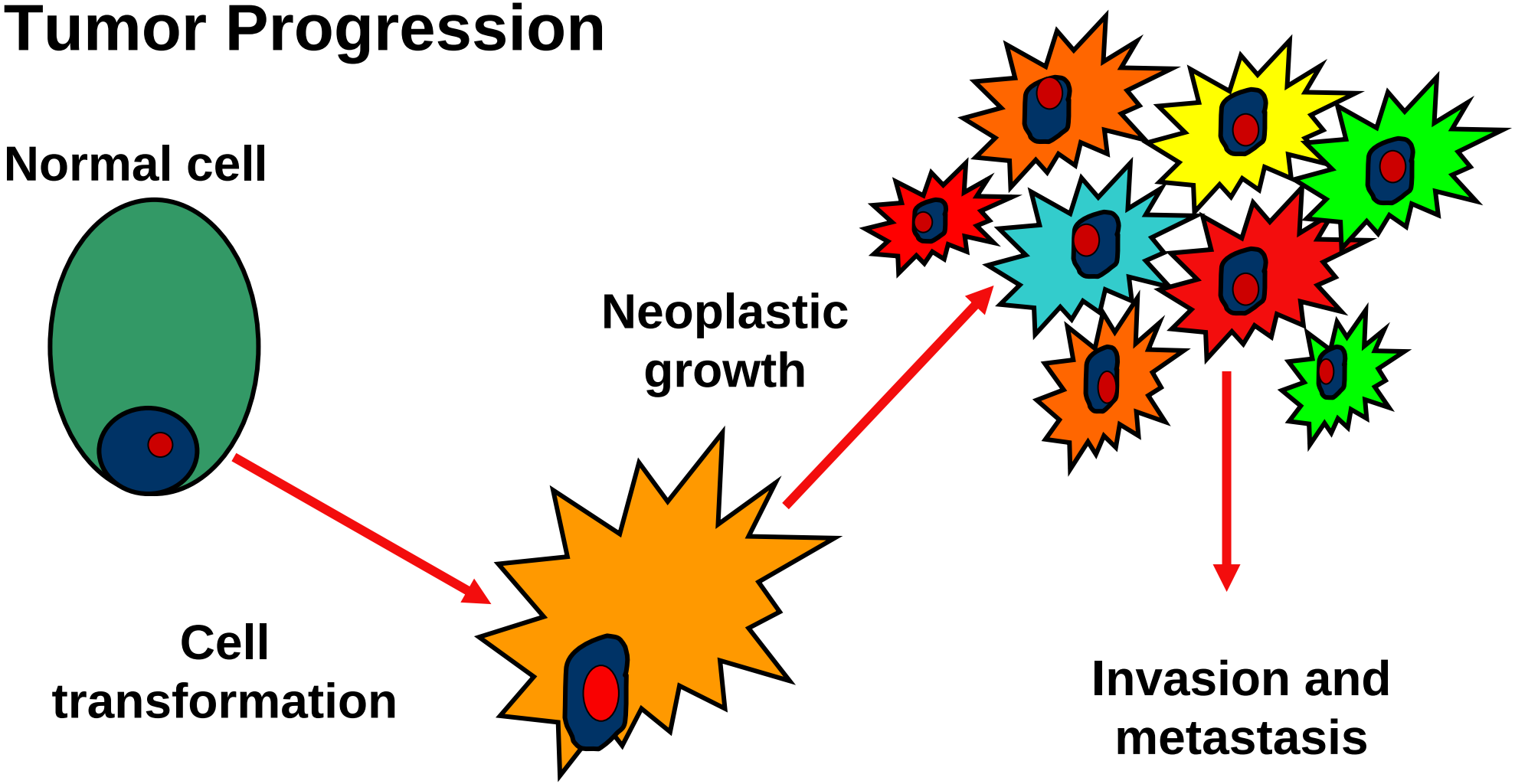
DCC **deletion (18q21)**

Adenoma III

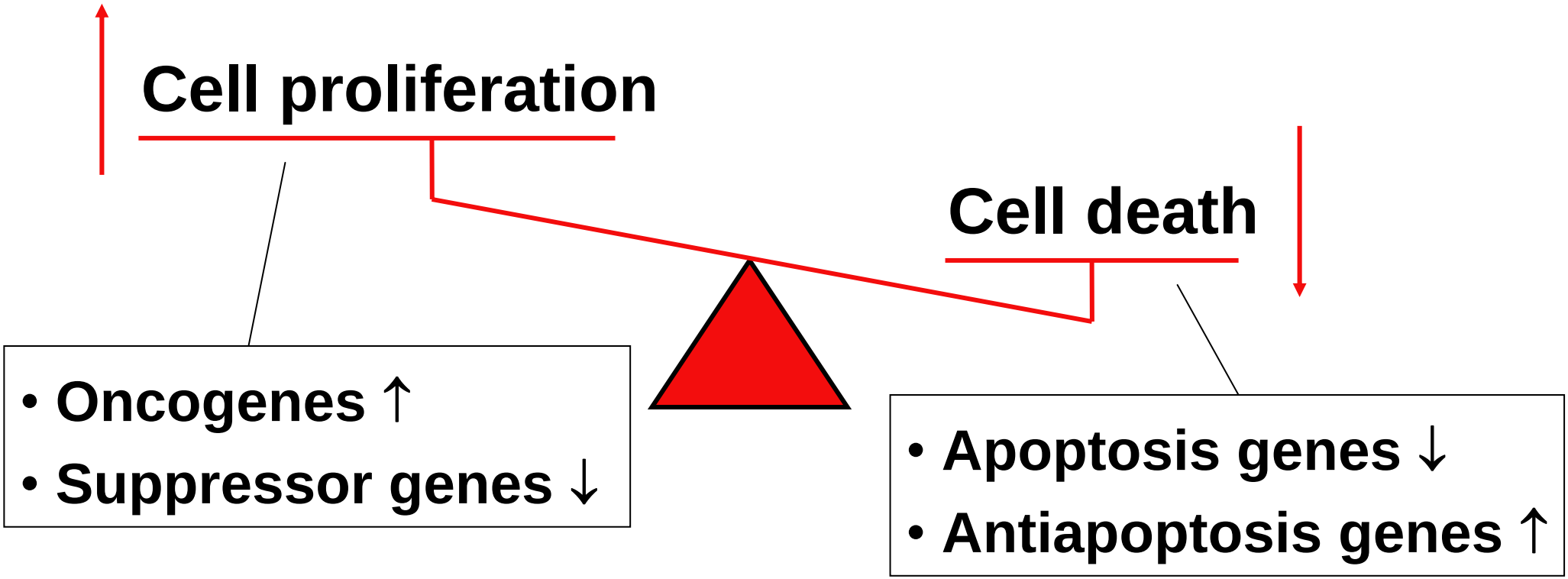
p53 **mutation (17p)**

Cancer

Tumor Progression



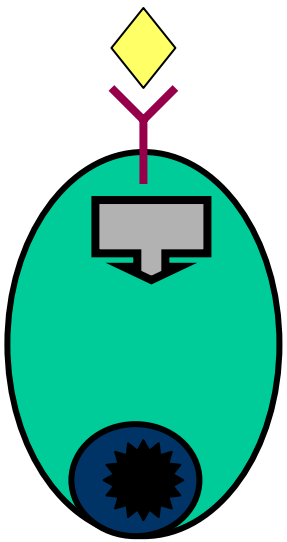
Tumor Mass


Cell proliferation
Cell death
• Oncogenes ↑
• Suppressor genes ↓
• Apoptosis genes ↓
• Antiapoptosis genes ↑

- **Accelerator:** ↑ **Oncogenes (*Ras*)**
  - ↑ **Antiapoptosis genes (*Bcl-2*)**

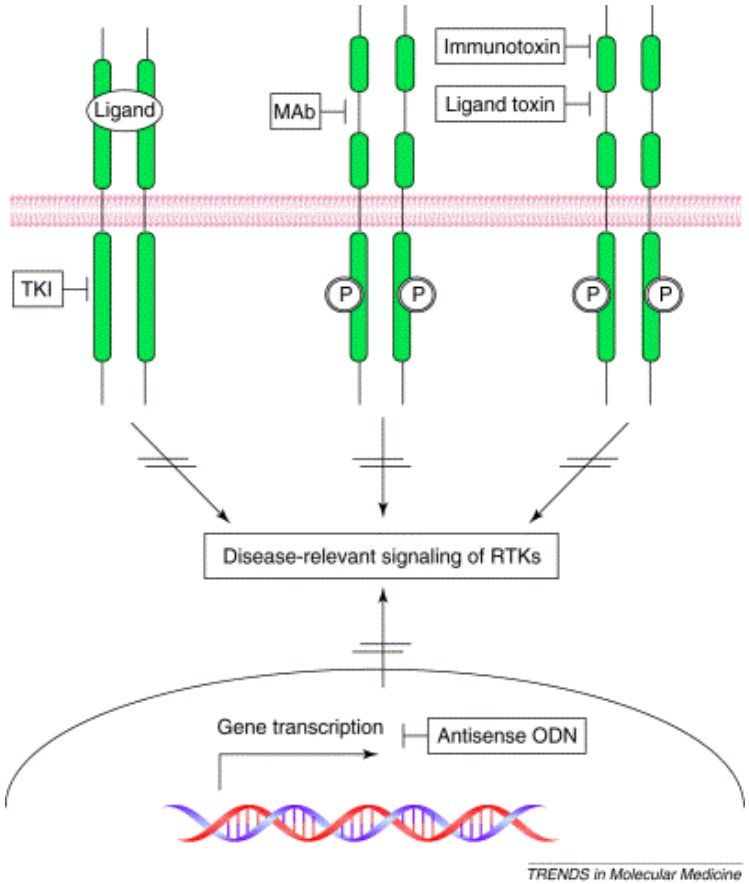
- **Brake:** ↓ **Suppressor genes (*p53*, *Rb*)**
  ↓ **Proapoptosis genes (*Bax*)**

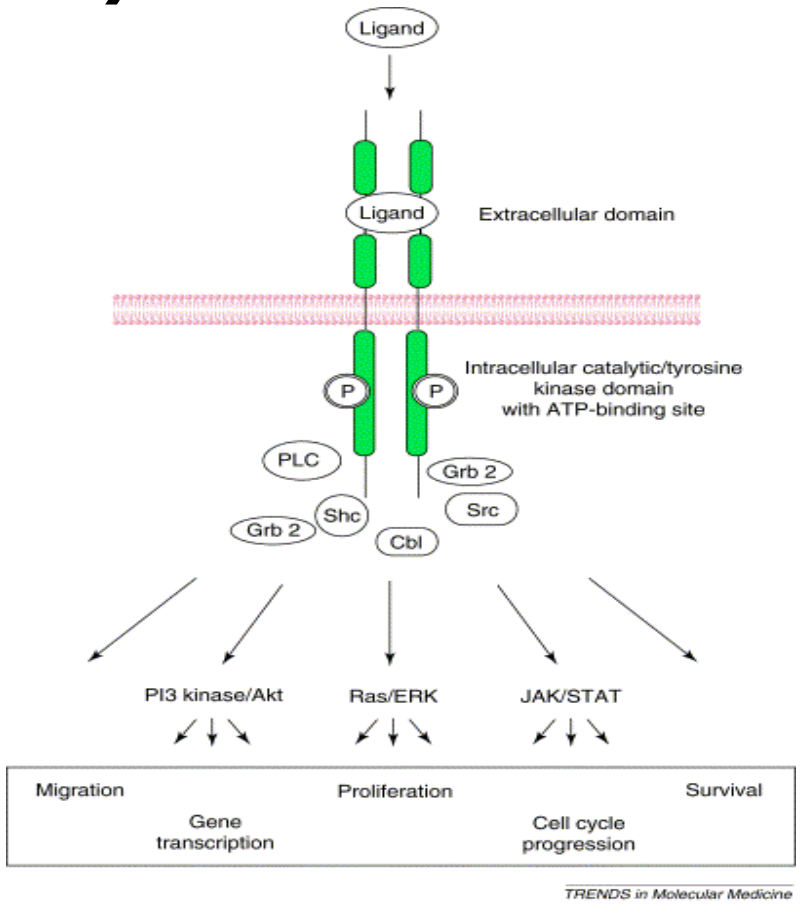
Cellular Functions of Oncogenes



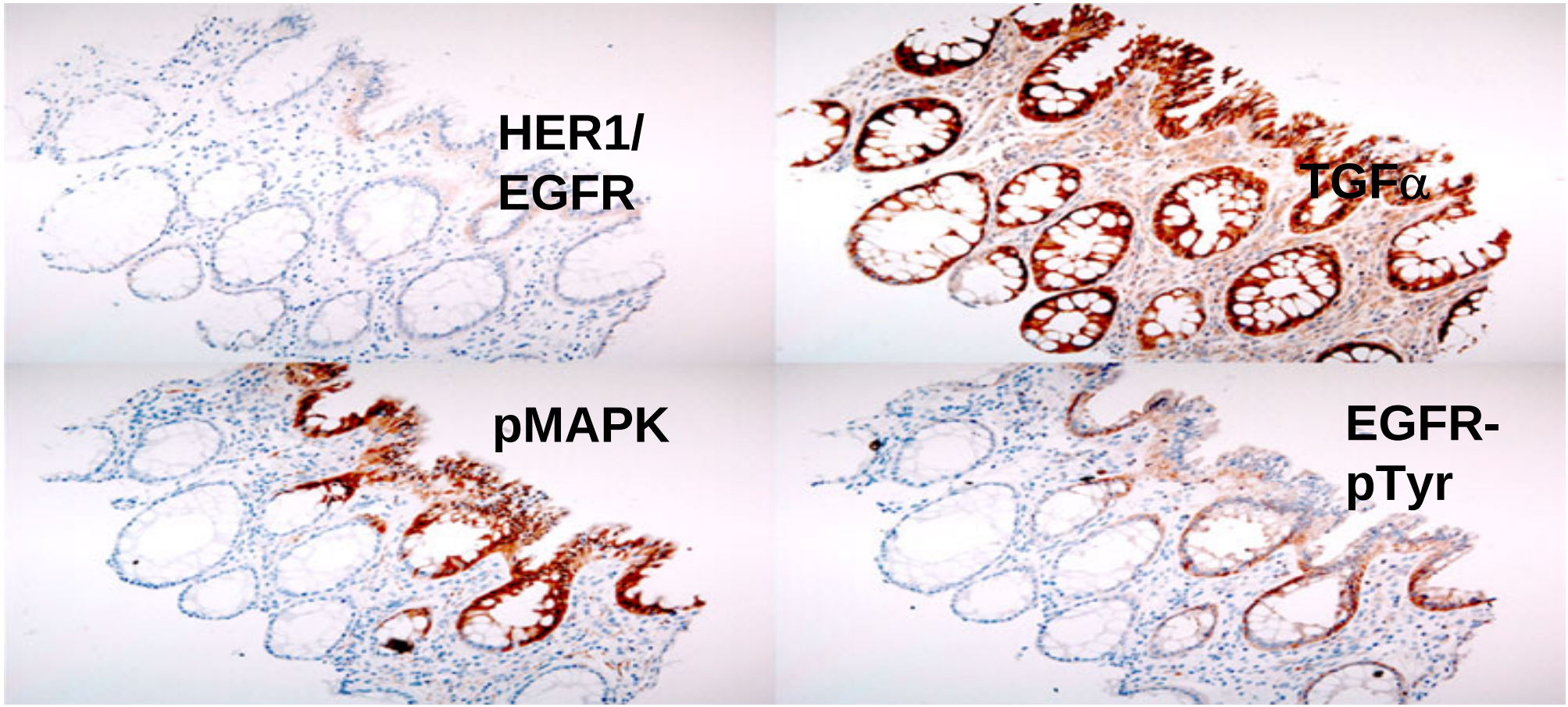
- Growth factors
  c-sis, EGF, PDGF
- Growth factor receptors
  HER-2/*neu*, EGFR, PDGFR
- Signal amplification
  Ras, Raf, MEK
- Nuclear transcription factors
  c-Myc

Targeted Therapy: Tyrosine Kinase Inhibitiors (Imatinib)





HER1/EGFR and TGFα Expression in Colorectal Adenocarcinoma

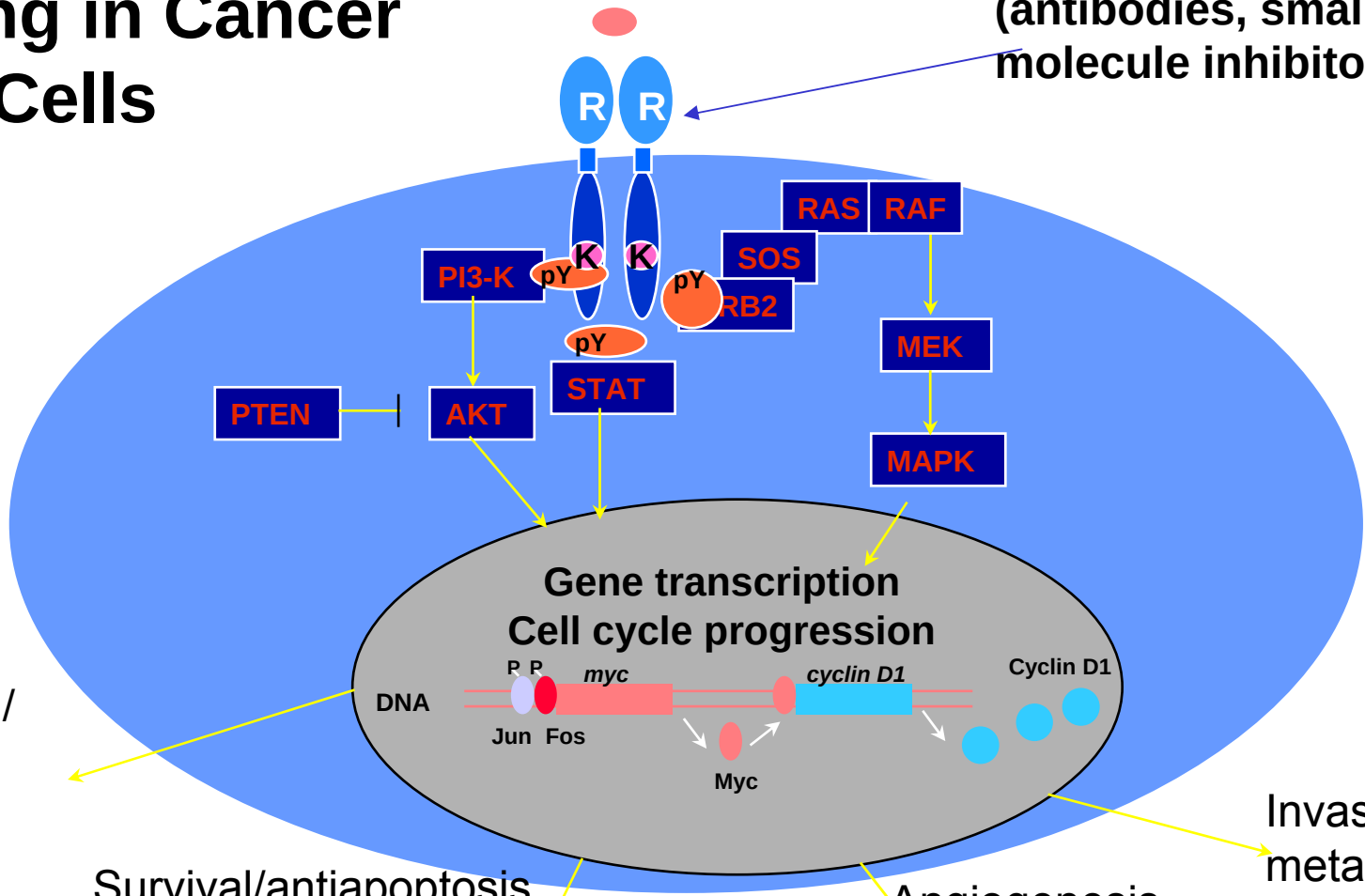


Bevacizumab

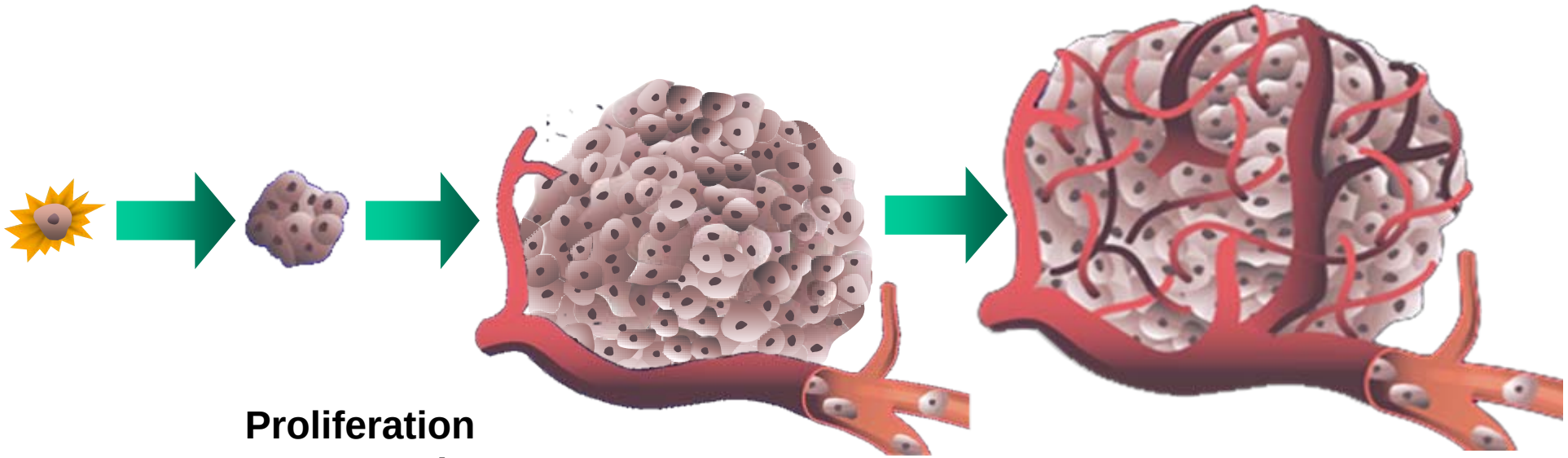
- Recombinant humanized monoclonal IgG_1 antibody
- Recognizes all isoforms of vascular endothelial growth factor (VEGF) A
- Estimated half-life is approximately 20 days (range, 11-50 days)

Avastin™ (bevacizumab) PI. February 2004.
Presta et al. *Cancer Res*.1997;57:4593.

Target: EGFR Signaling in Cancer Cells



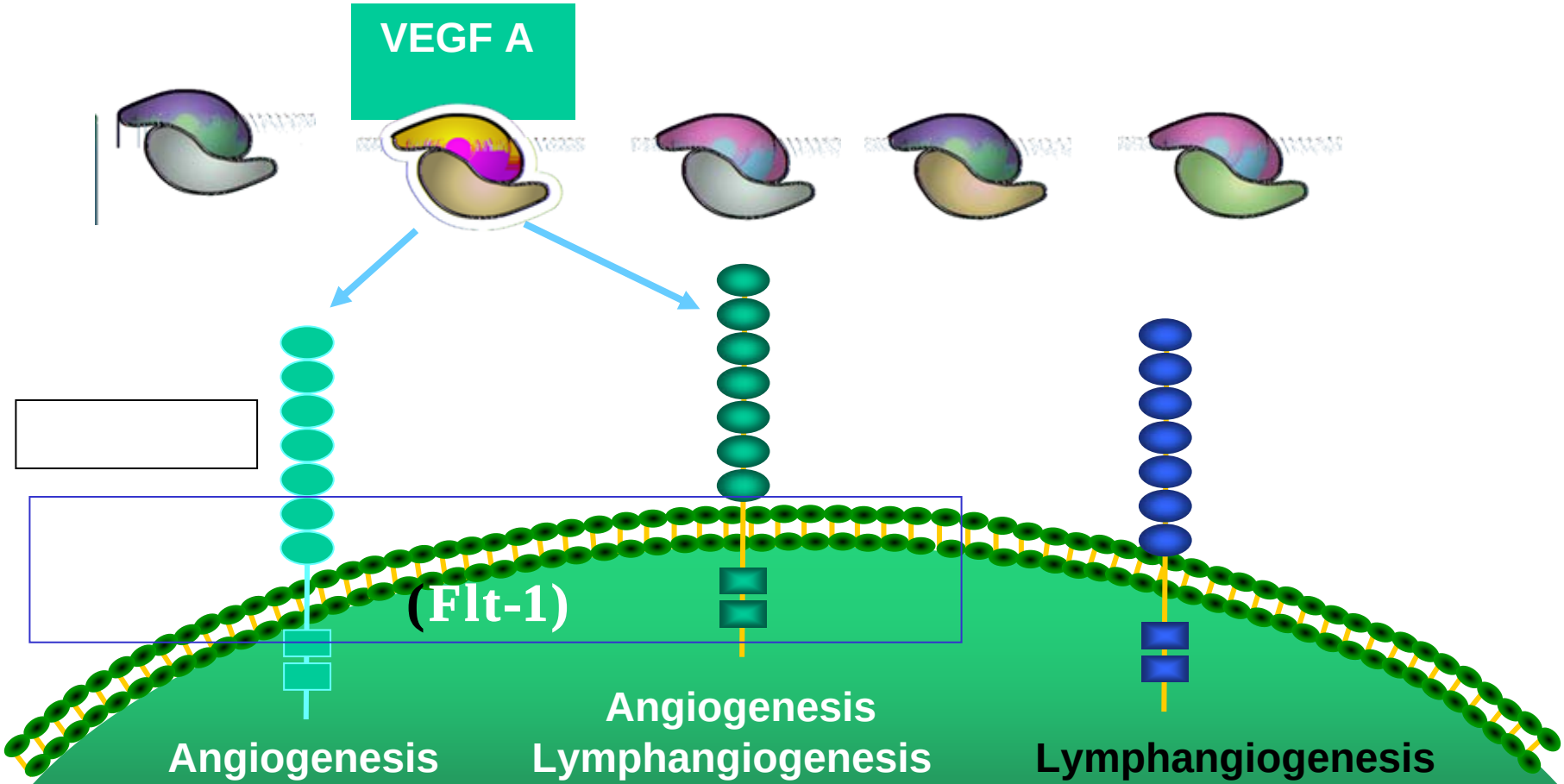
New Target: Angiogenesis



Proliferation
= apoptosis

Hanahan and Weinberg. *Cell.* 2000;100:57.

VEGF Family and Its Receptors



Suppressor Gene: *p53*

- Chromosome 17p
- Inactivated by mutations
- Arrest of cell cycle in G1
- Increased DNA repair
- Apoptosis
- Mechanism: ↑ transcription of p21 (cyclin inhibitor)
  ↑ transcription of DDB2 (DNA repair gene)

Tumor Growth

- 30 doublings are required for one cell to grow to a 1 cm^3 tumor
- Only 3 additional doublings are required for a 1 cm^3 tumor to grow to 2 cm^3

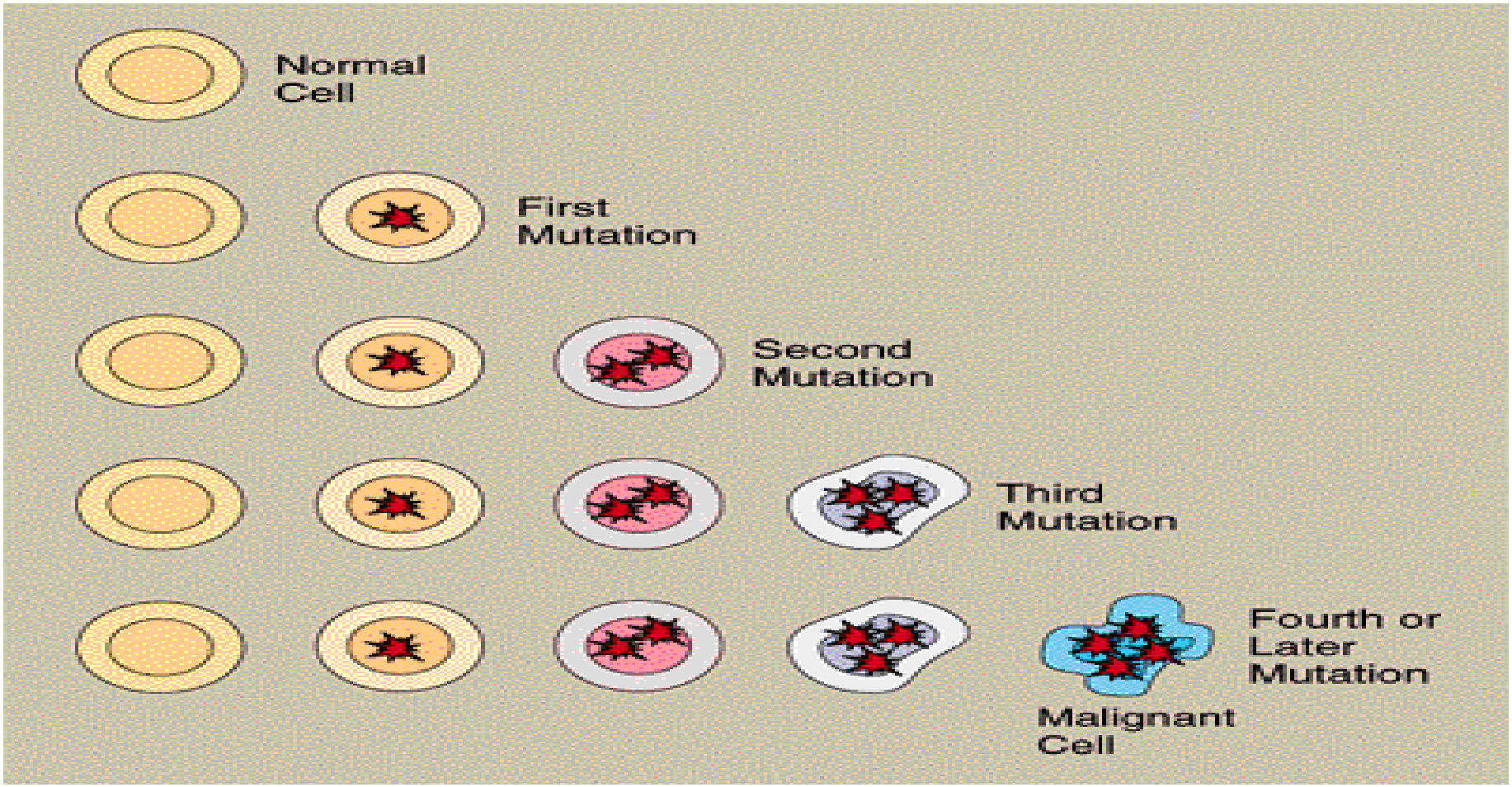
$$\text{Sphere volume} = {}^{4}/_{3}\,\pi r^3$$

Tumor Growth (cont.)

- 30 doublings = 1 cm^3
- 33 doublings = 2 cm^3
- 36 doublings = 4 cm^3

Doubling time = one month

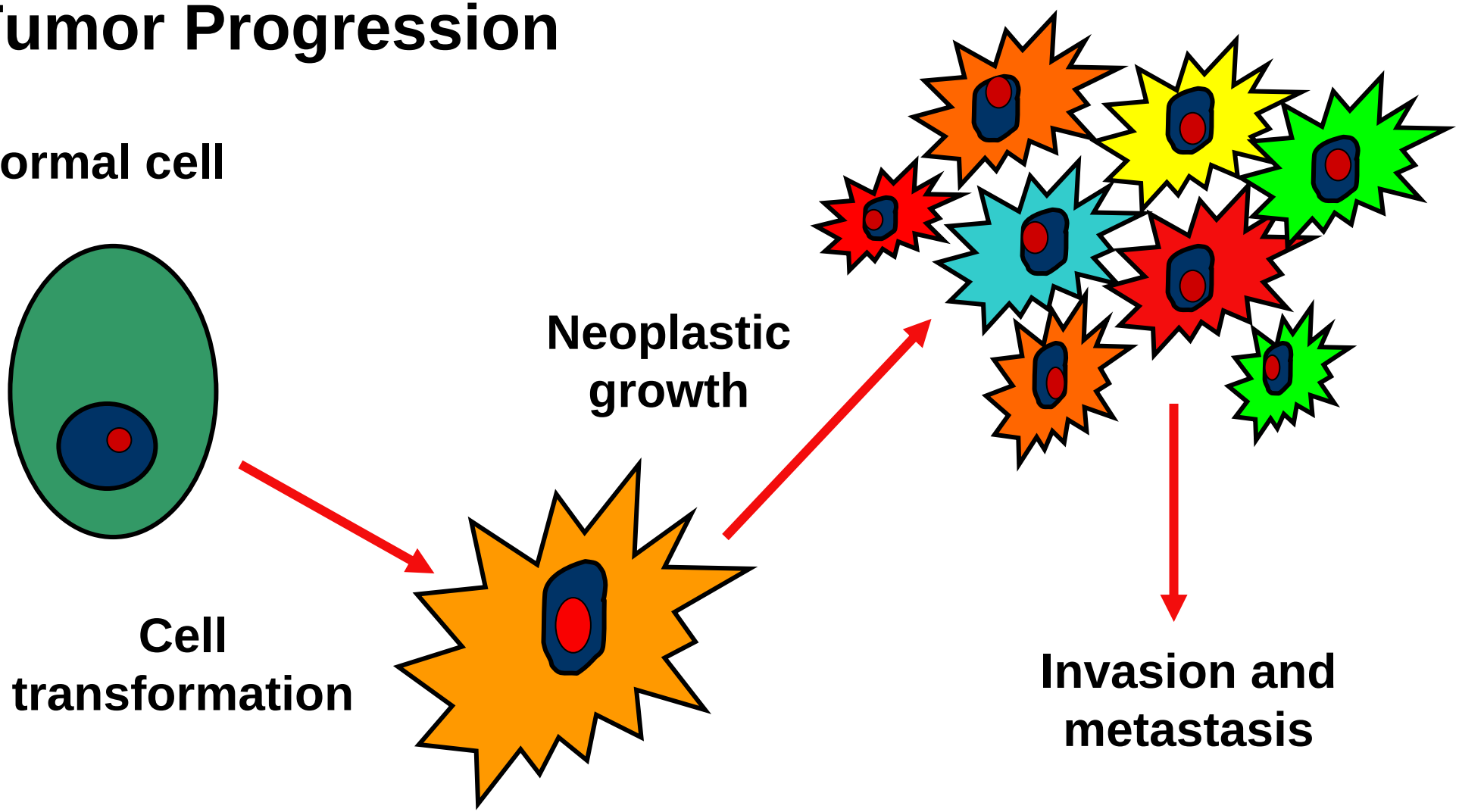
Cellular Heterogeneity



BRCA1 and BRCA2 Genes

- Tumor suppressor genes
- Two copies of each gene in each individual
- Defects in both copies of either gene lead to breast or ovarian cancer
- Transmission is autosomal dominant and both parents may transmit mutations

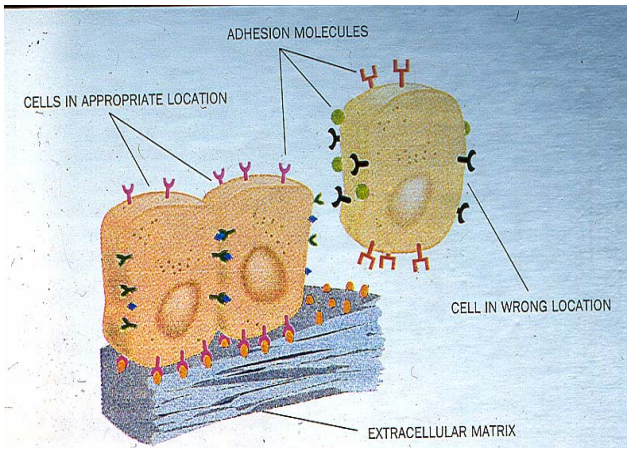
Tumor Progression

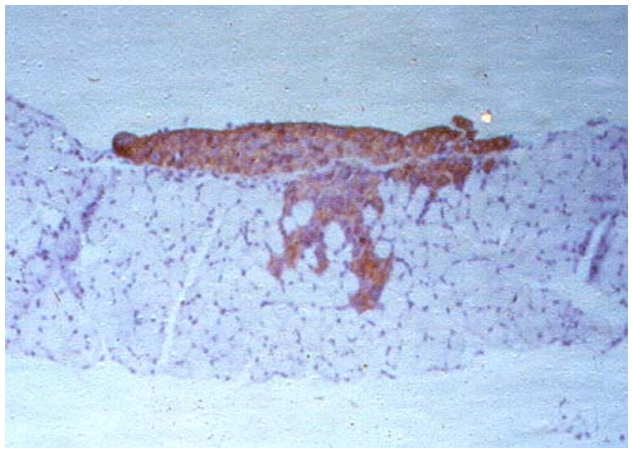


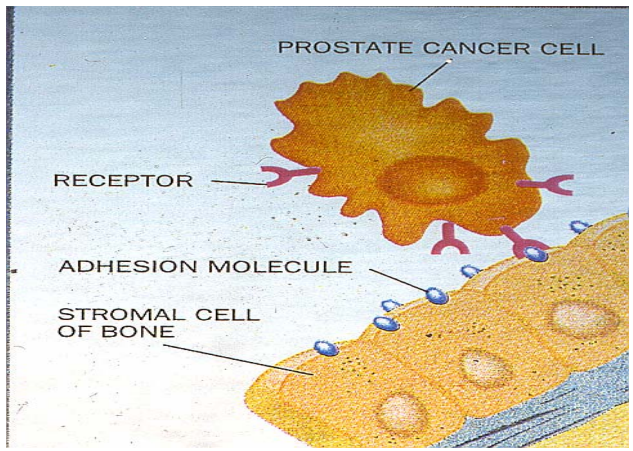
Metastatic Sequence

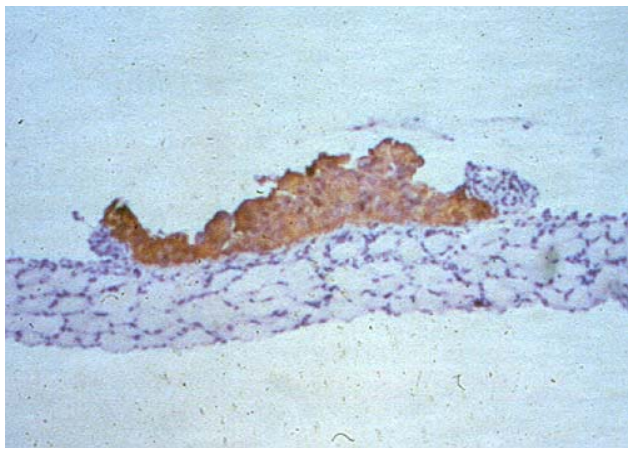
- Proliferation and angiogenesis
- Detachment from site of origin
- Invasion of blood vessels and lymphatic system
- Survival in blood stream and lymphatic system
- Adhesion and extravasation

Cellular Adhesion and Invasion









Case Study

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Case Study (cont.)

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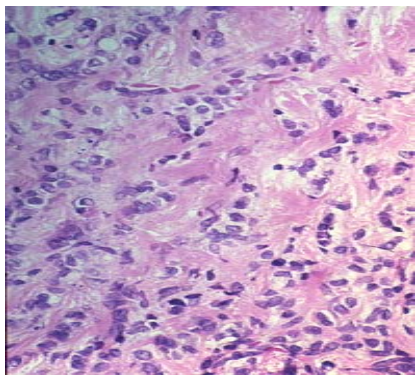
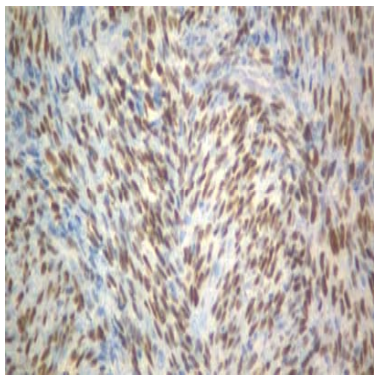
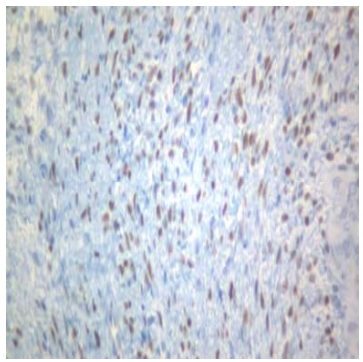
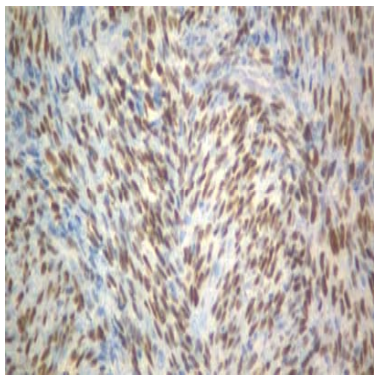
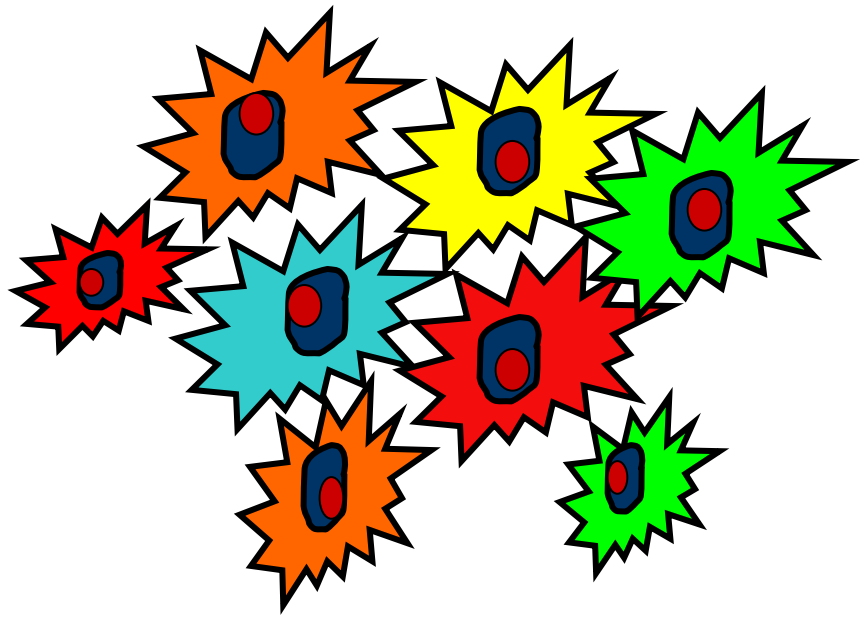





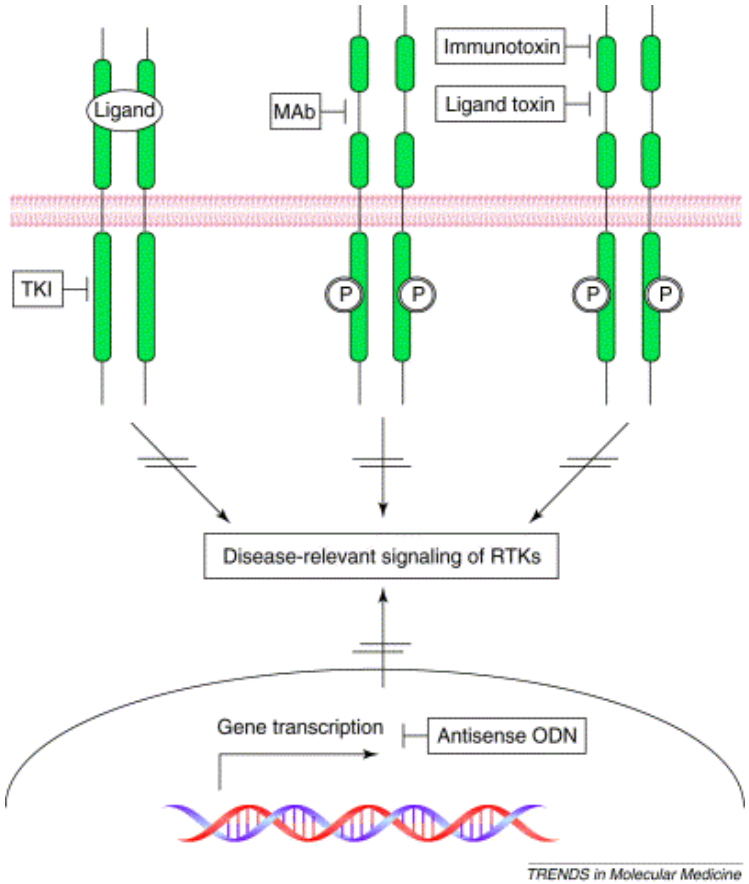
Multidisciplinary Cancer Management Course

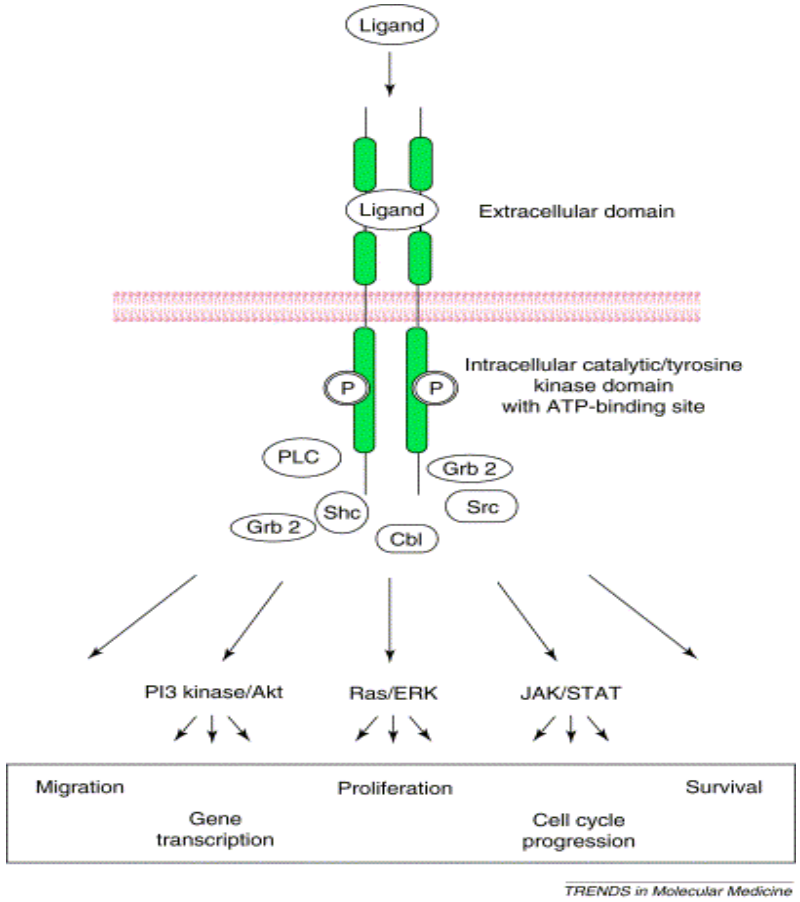
Conventional Therapeutic Strategies

- Surgery
- Radiation therapy
- Chemotherapy
- Hormone therapy



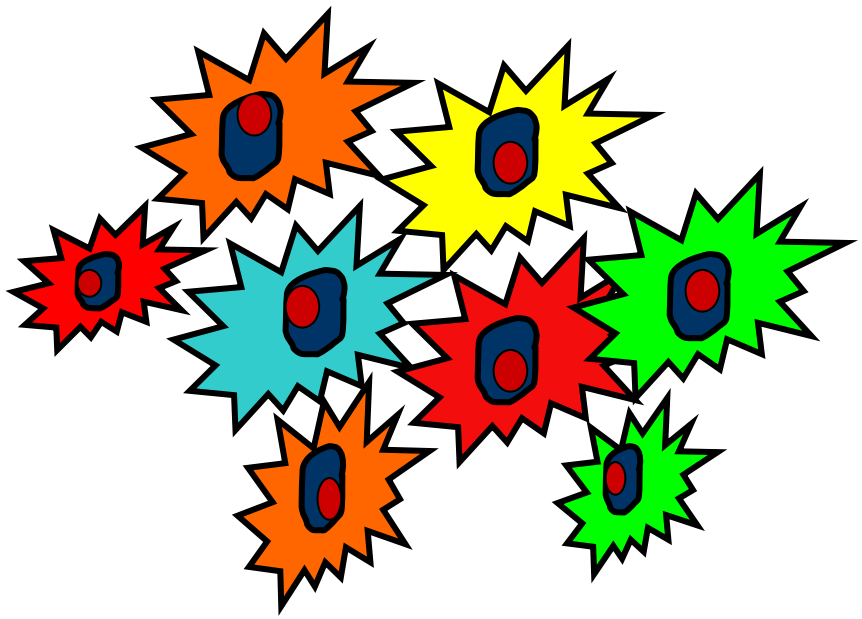
Targeted Therapies in Cancer: Tyrosine Kinase Inhibitors and Monoclonal Antibodies



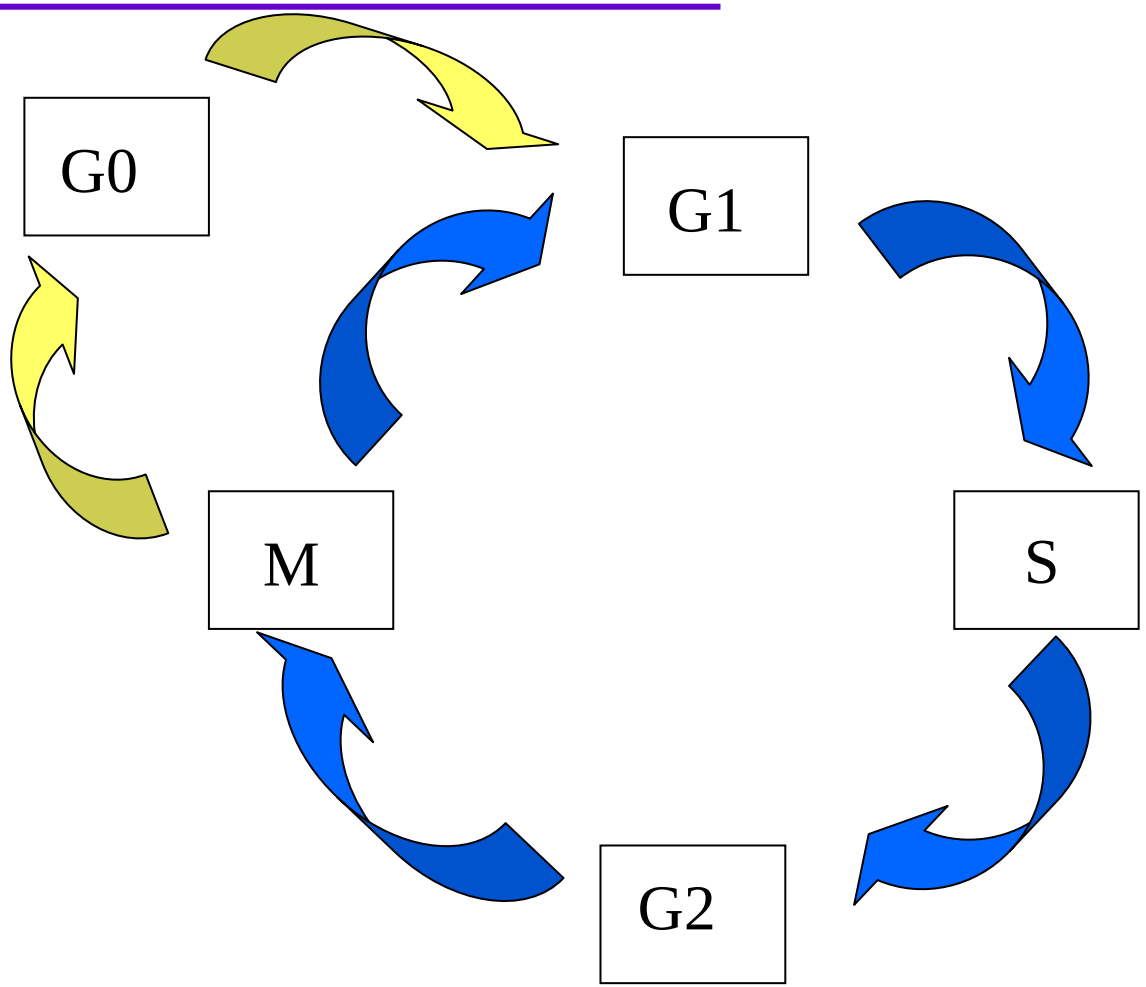


New Targeted Therapies

- Tyrosine kinase inhibitors (imatinib, erlotinib)
- Monoclonal antibodies (trastuzumab, bevacizumab)
- Antiangiogenesis
- Gene therapy (Bcl-2)



Cell Cycle



G0 Dormant cell

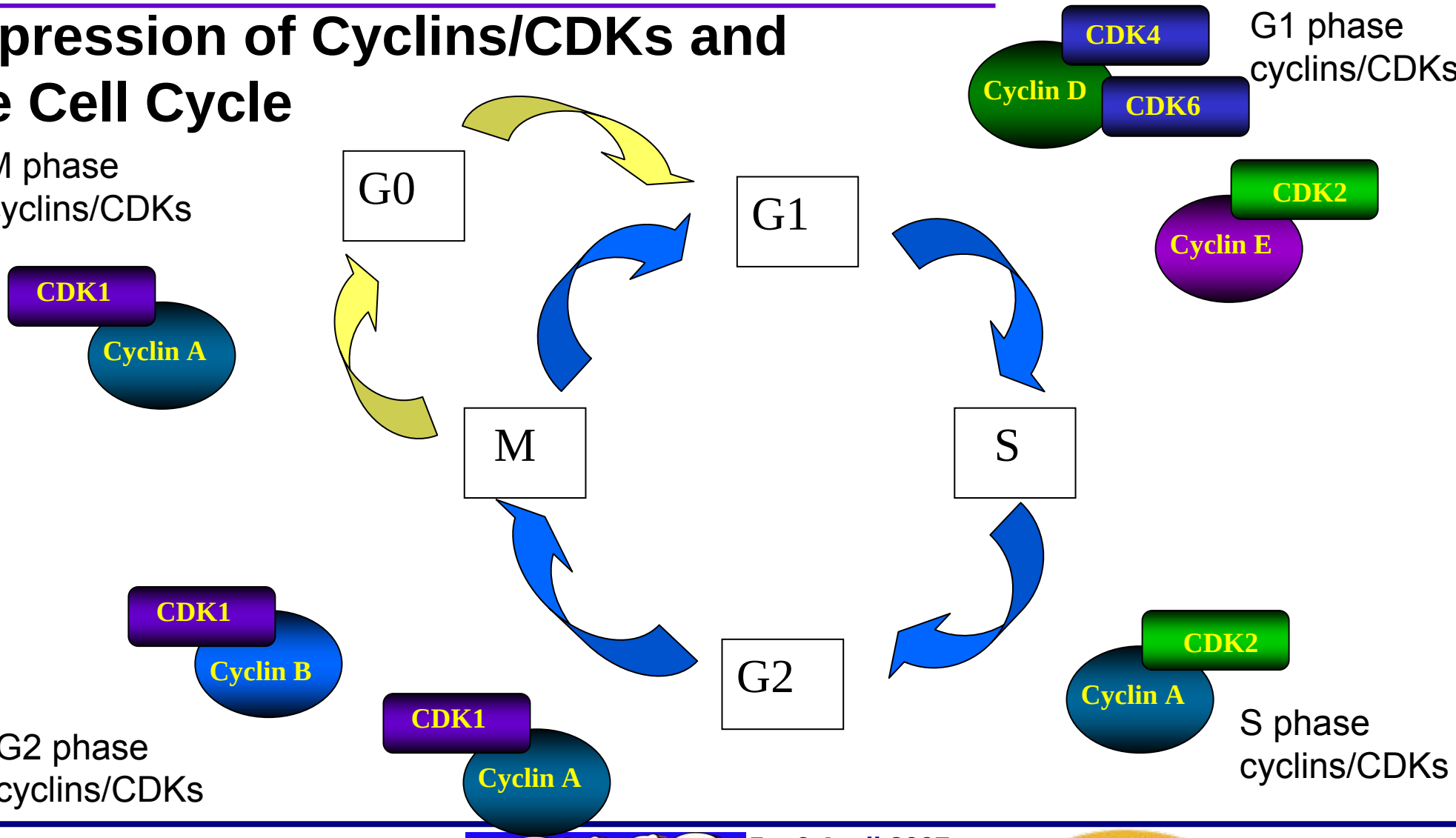
G1 Resting phase

S DNA synthesis

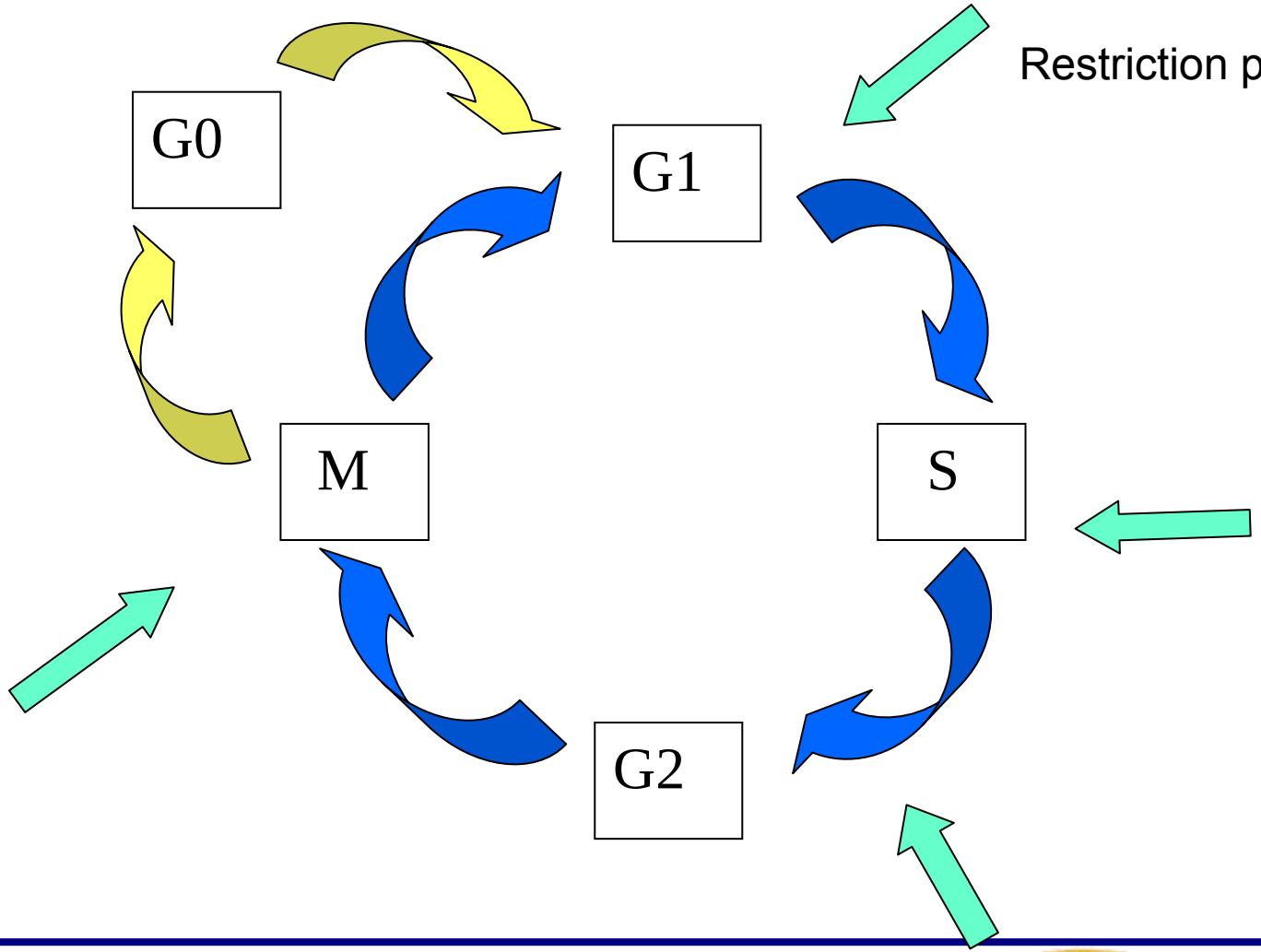
G2 Pre-mitotic phase

M Mitotic phase

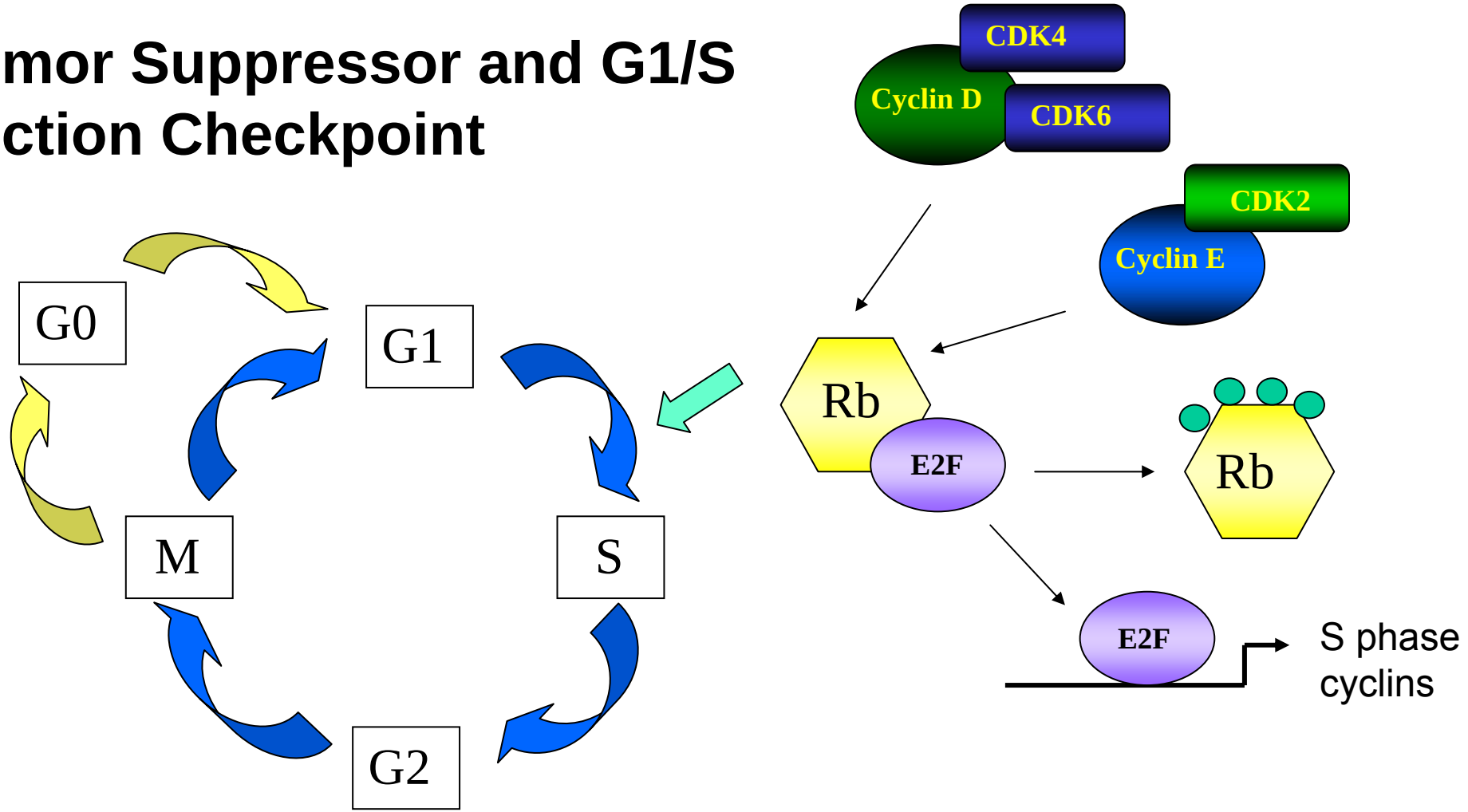
Expression of Cyclins/CDKs and the Cell Cycle

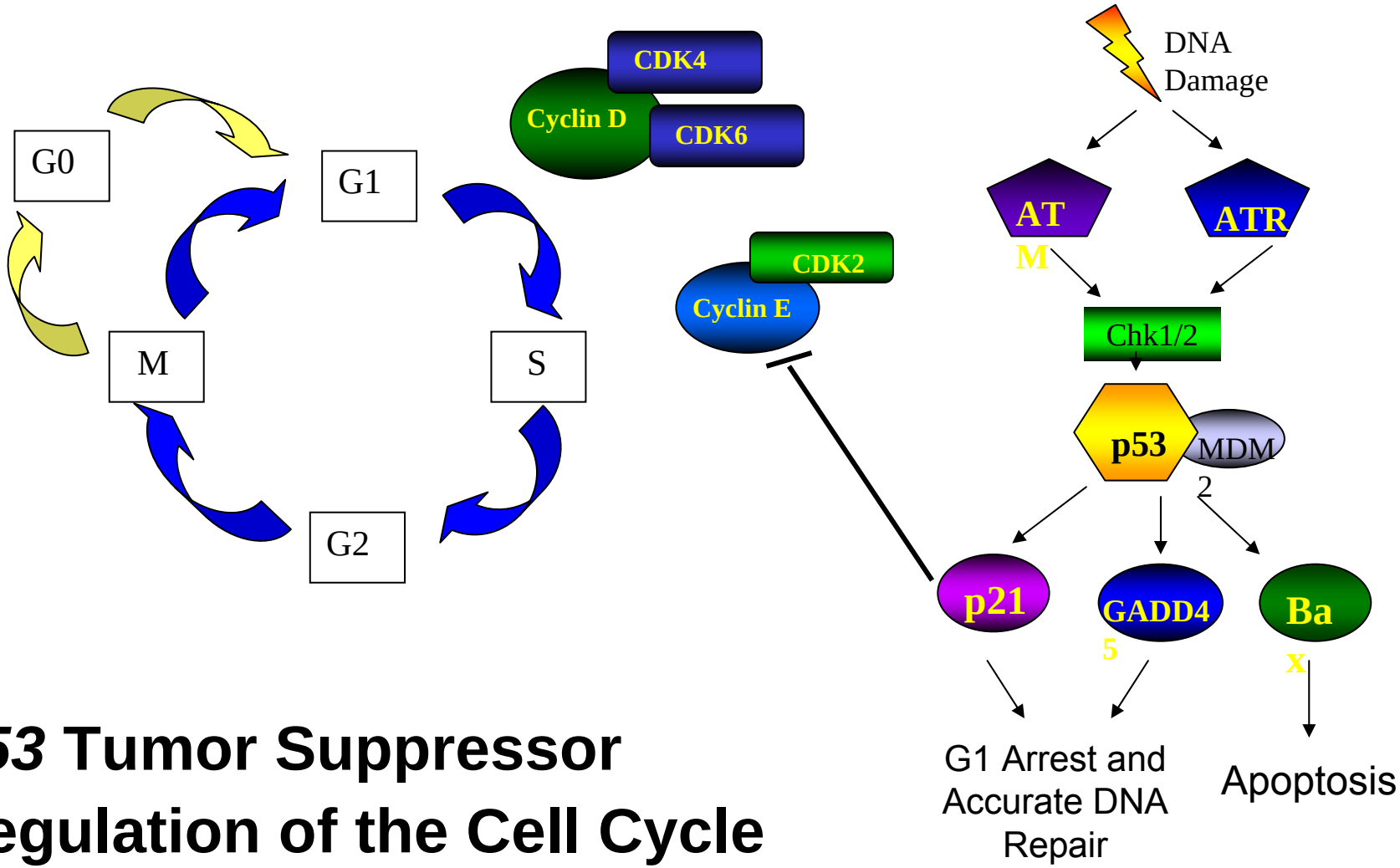


Cell Cycle Checkpoints



Rb Tumor Suppressor and G1/S Restriction Checkpoint





p53 Tumor Suppressor Regulation of the Cell Cycle