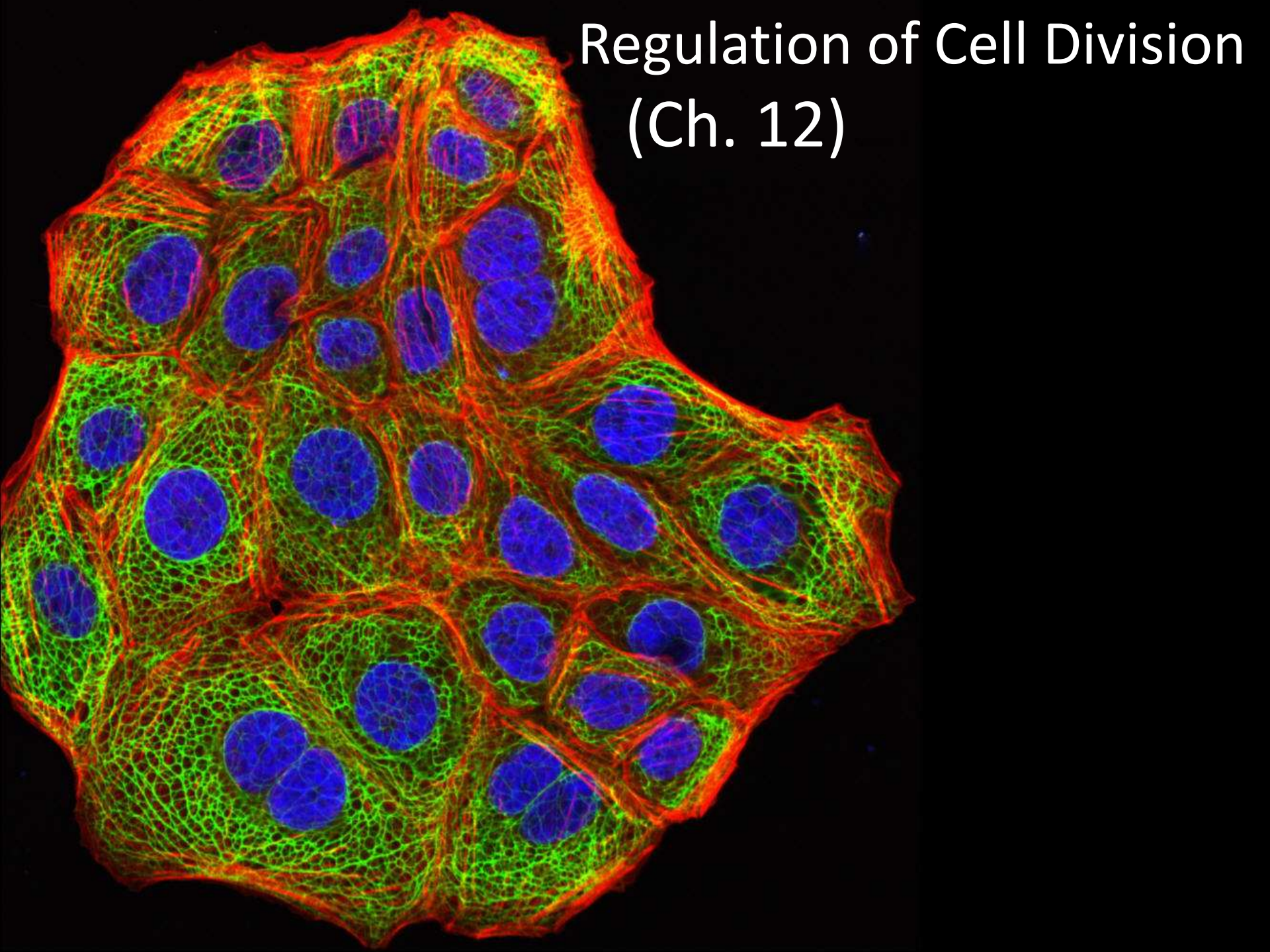
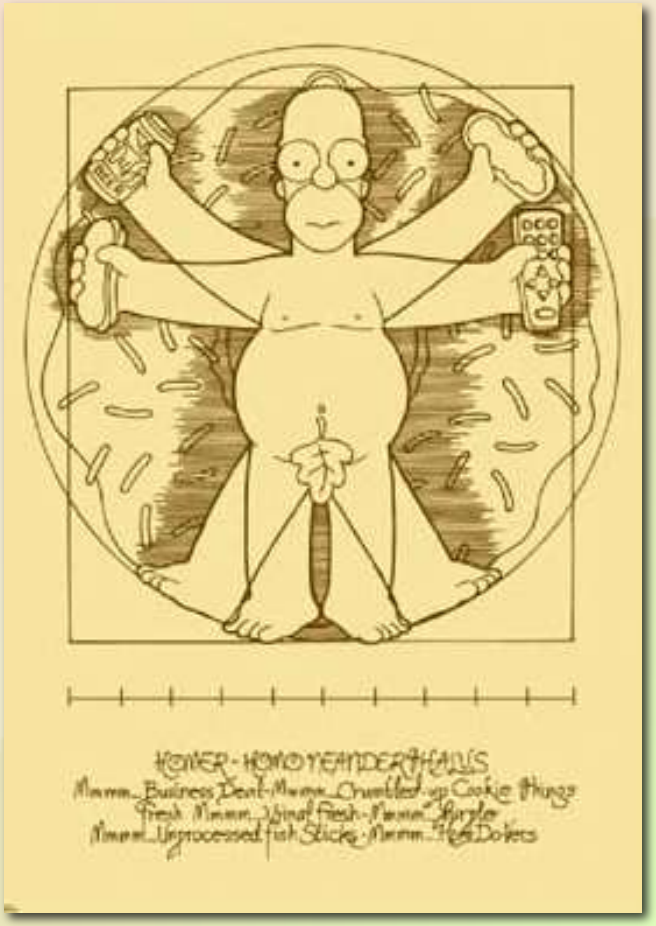


Regulation of Cell Division (Ch. 12)

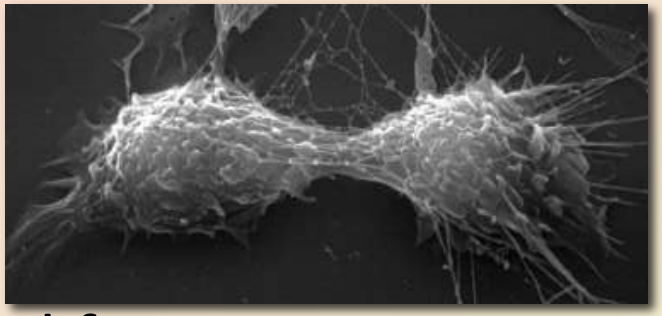
Coordination of cell division

- A multicellular organism needs to coordinate cell division across different tissues & organs
  - critical for normal growth, development & maintenance
  - Timing, Rates and Orchestration all need to be controlled



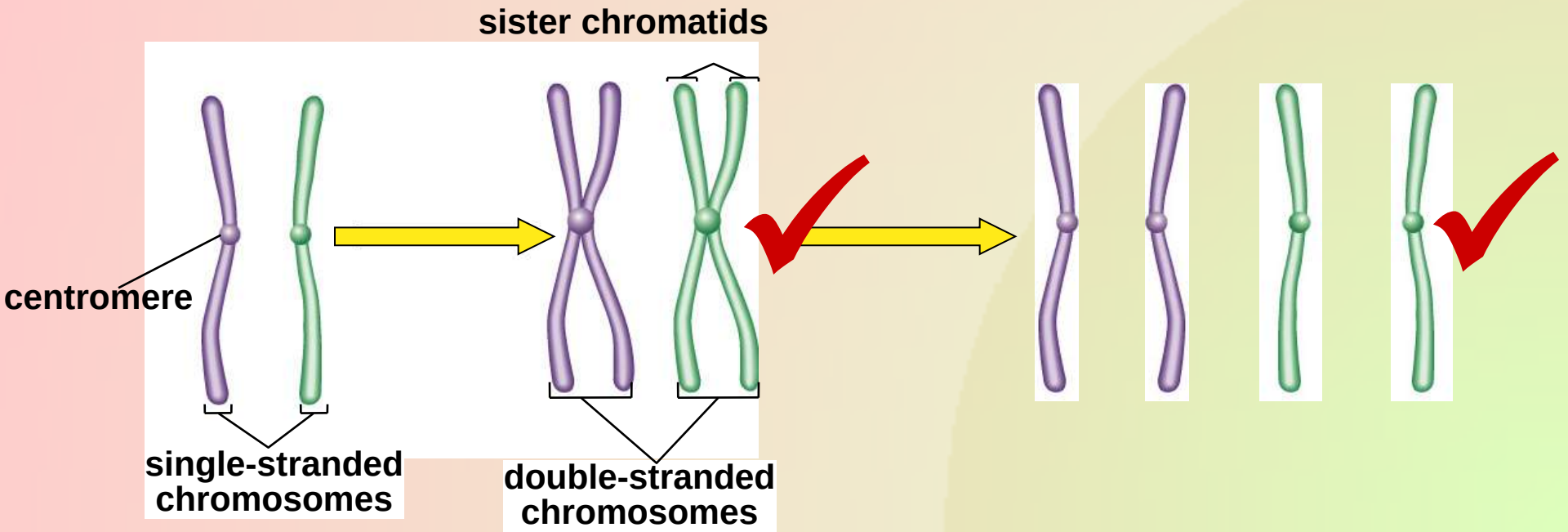
Frequency of cell division

- Frequency of cell division varies by cell type
  - embryo
    - cell cycle < 20 minute
  - skin cells
    - divide frequently throughout life
    - 12-24 hour cycle
  - liver cells
    - retain ability to divide, keep it in reserve
    - divide once every year or two
  - mature nerve cells & muscle cells
    - do not divide at all after maturity (?)
    - permanently in G_0



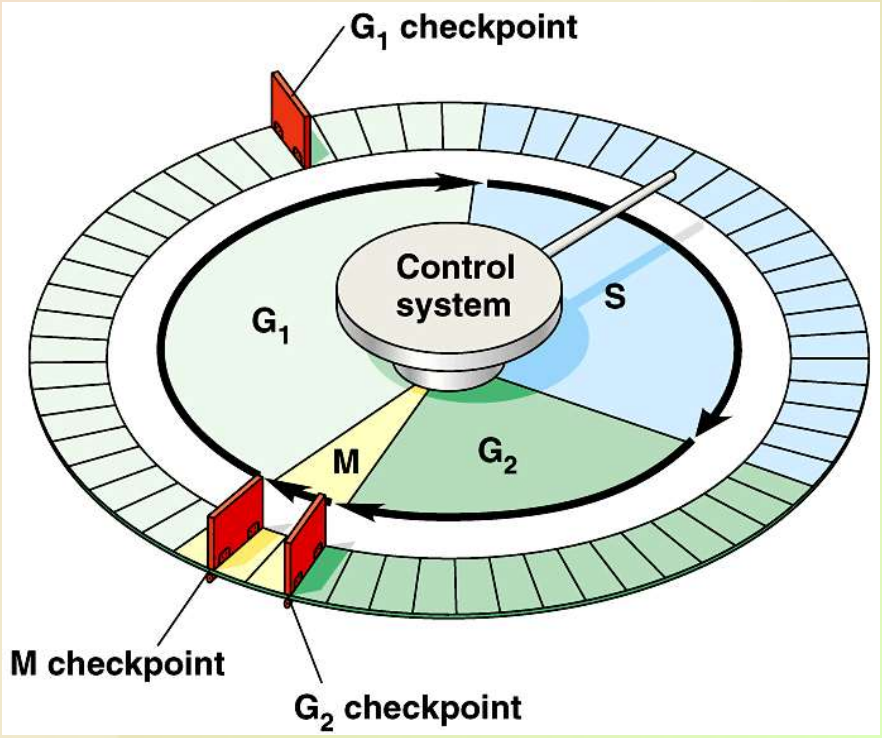
Overview of Cell Cycle Control

- Two <u>irreversible points</u> in cell cycle
  - replication of genetic material
  - separation of sister chromatids
- <u>Checkpoints</u>
  - process is assessed & possibly halted



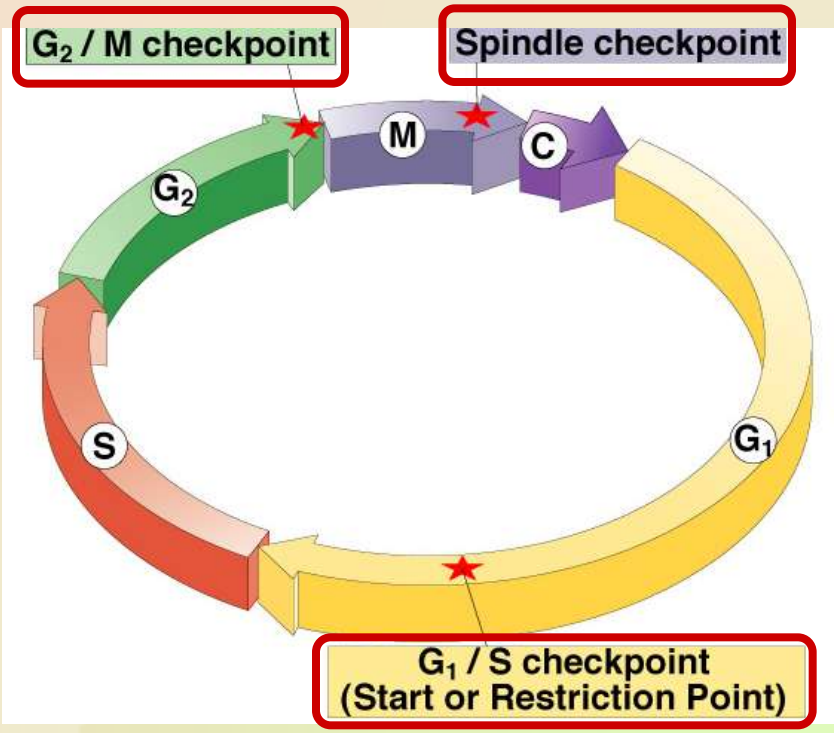
Checkpoint control system

- Checkpoints
  - cell cycle controlled by STOP & GO chemical signals at critical points
  - signals indicate if key cellular processes have been completed correctly



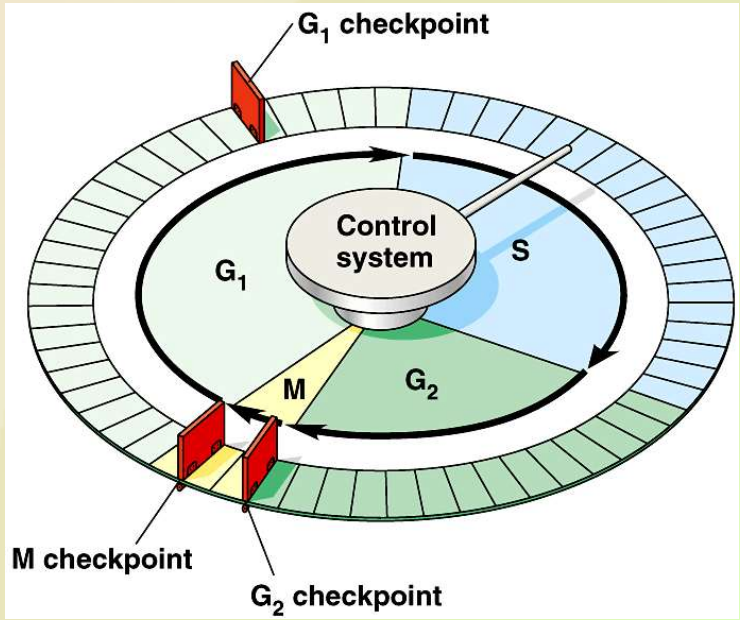
Checkpoint control system

- 3 major checkpoints:
  - G_1/S
    - can DNA synthesis begin?
  - G_2/M
    - has DNA synthesis been completed correctly?
    - commitment to mitosis
  - spindle checkpoint
    - are all chromosomes attached to spindle?
    - can sister chromatids separate correctly?



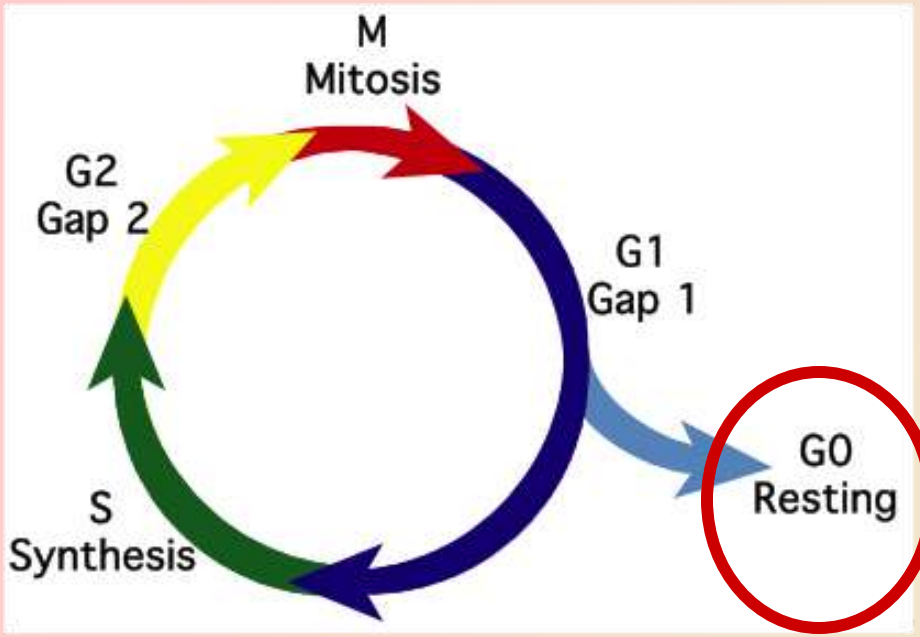
G_1/S checkpoint

- G_1/S checkpoint is most critical
  - primary decision point: "restriction point"
  - if cell receives "GO" signal, it divides
    - internal signals: cell growth (size), cell nutrition
    - external signals: "growth factors"
  - if cell does not receive signal, it exits cycle & switches to G_0 phase
    - non-dividing, working state



G_0 phase

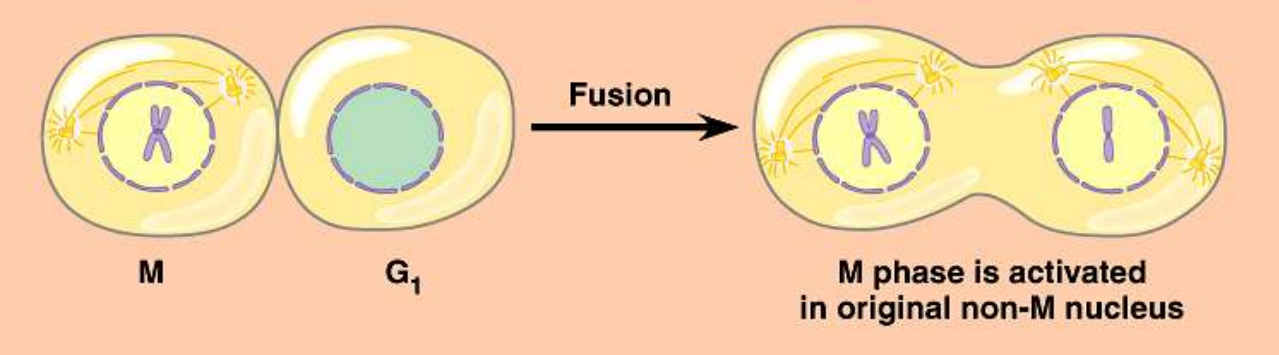
- G_0 phase
  - non-dividing, differentiated state
  - most human cells in G_0 phase



- **liver cells**
  - **in G_0, but can be "called back" to cell cycle by external cues**
- **nerve & muscle cells**
  - **highly specialized**
  - **arrested in G_0 & can never divide**

Activation of cell division

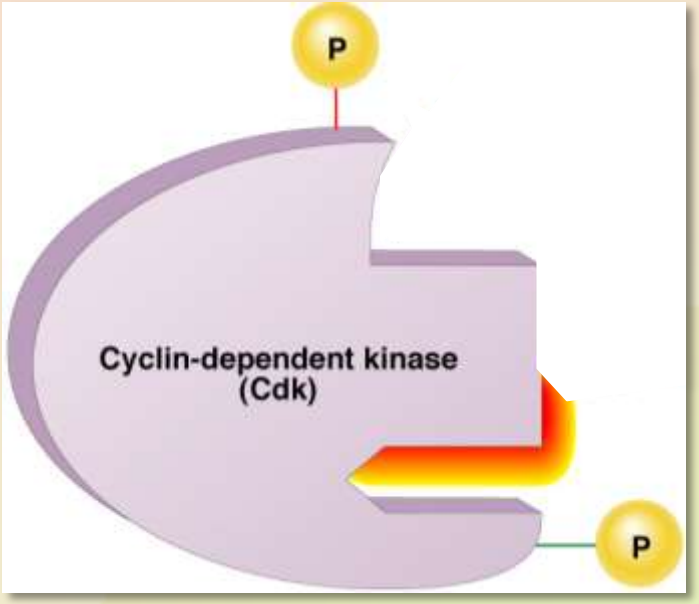
- How do cells know when to divide?
  - cell communication signals
    - chemical signals in cytoplasm give cue
    - signals usually mean proteins
      - activators
      - inhibitors



experimental evidence: Can you explain this?

"Go-ahead" signals

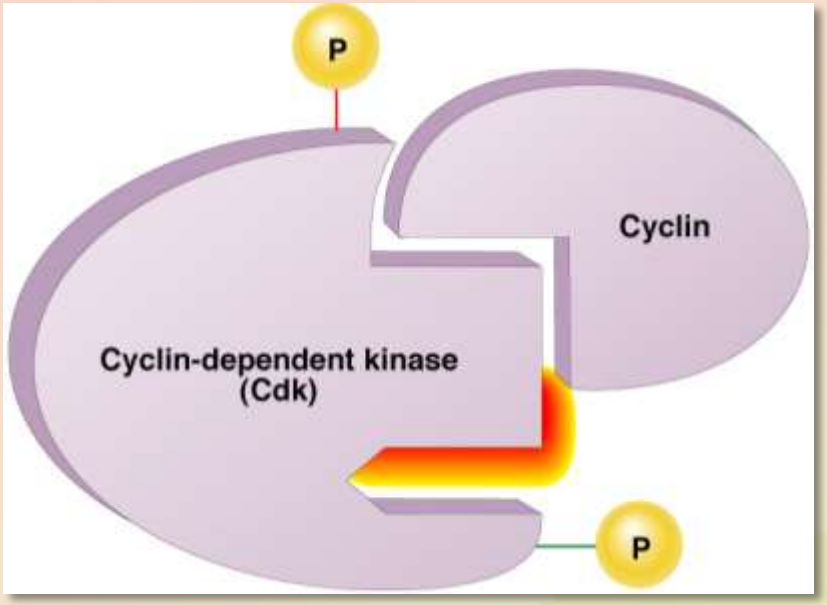
- Protein signals that promote cell growth & division
  - internal signals
    - "promoting factors"
  - external signals
    - "growth factors"
- Primary mechanism of control
  - phosphorylation
    - kinase enzymes
    - either activates or inactivates cell signals



Cell cycle signals

- Cell cycle controls
  - cyclins
    - regulatory proteins
    - levels cycle in the cell
  - Cdks
    - cyclin-dependent kinases
    - phosphorylates cellular proteins
      - activates or inactivates proteins
  - Cdk-cyclin complex
    - triggers passage through different stages of cell cycle

inactivated Cdk

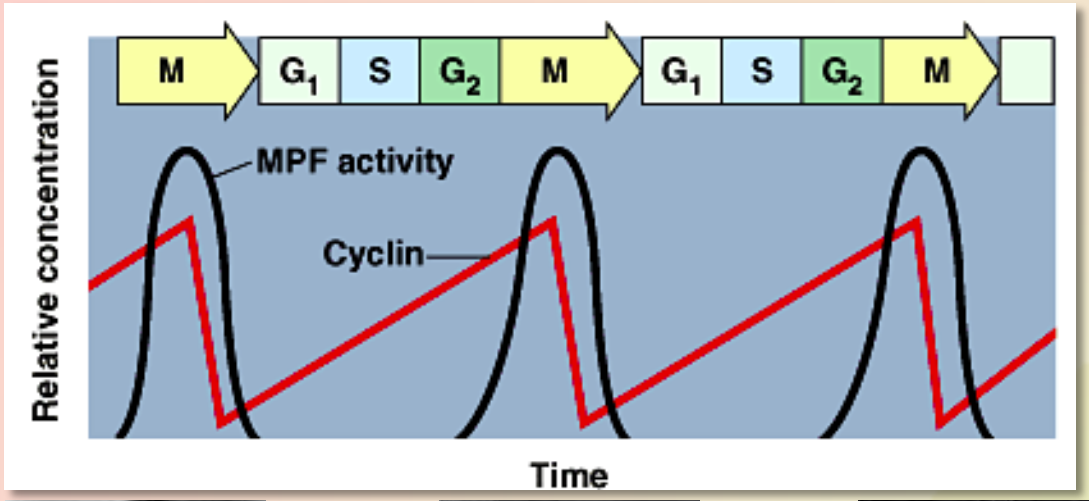


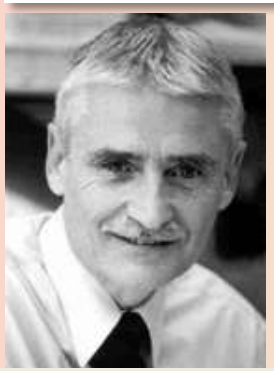
activated Cdk

Cyclins & Cdks

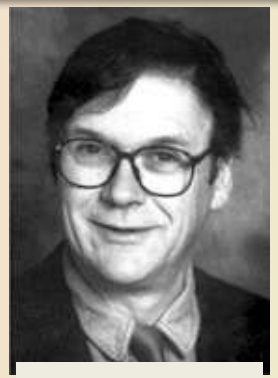
1970s-80s | 2001

- Interaction of Cdk's & different cyclins triggers the stages of the cell cycle





Leland H. Hartwell
checkpoints



Tim Hunt
Cdks

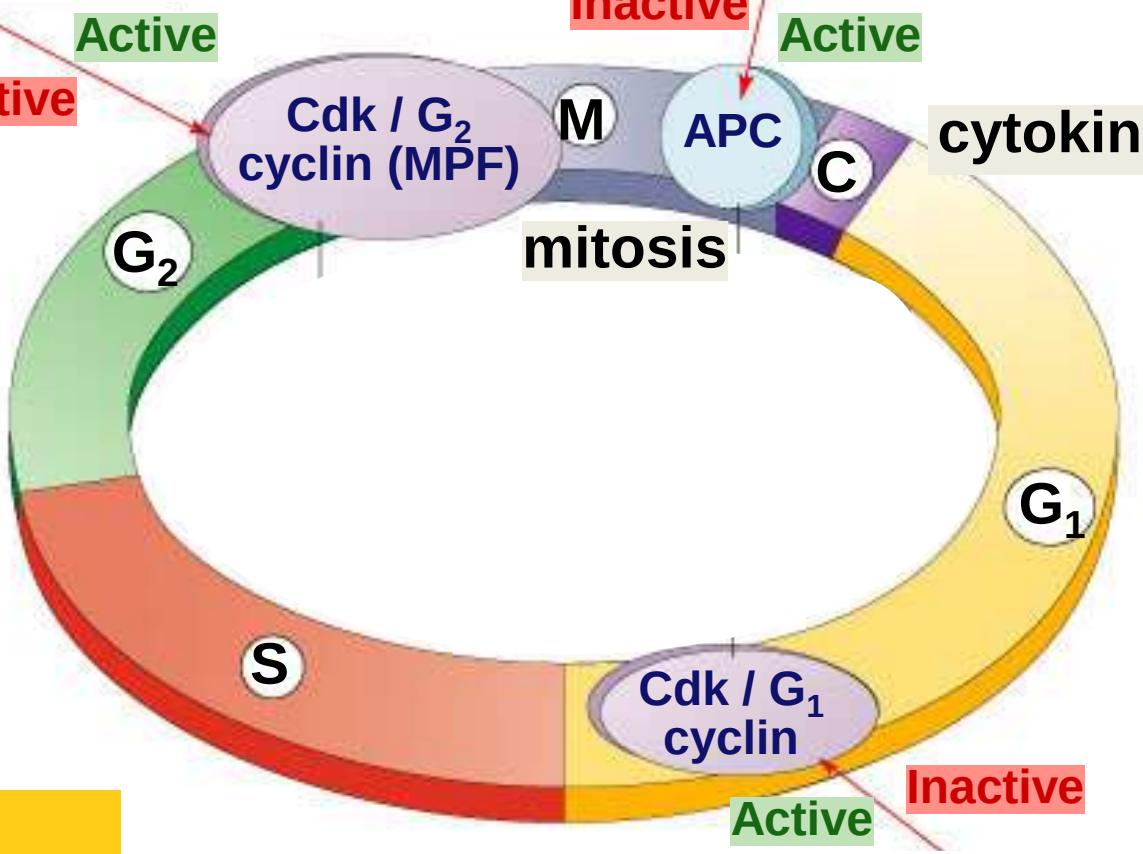
Sir Paul Nurse
cyclins

G_2 / M checkpoint

- Replication completed
- DNA integrity

Spindle checkpoint

Chromosomes attached at metaphase plate



G_1 / S checkpoint

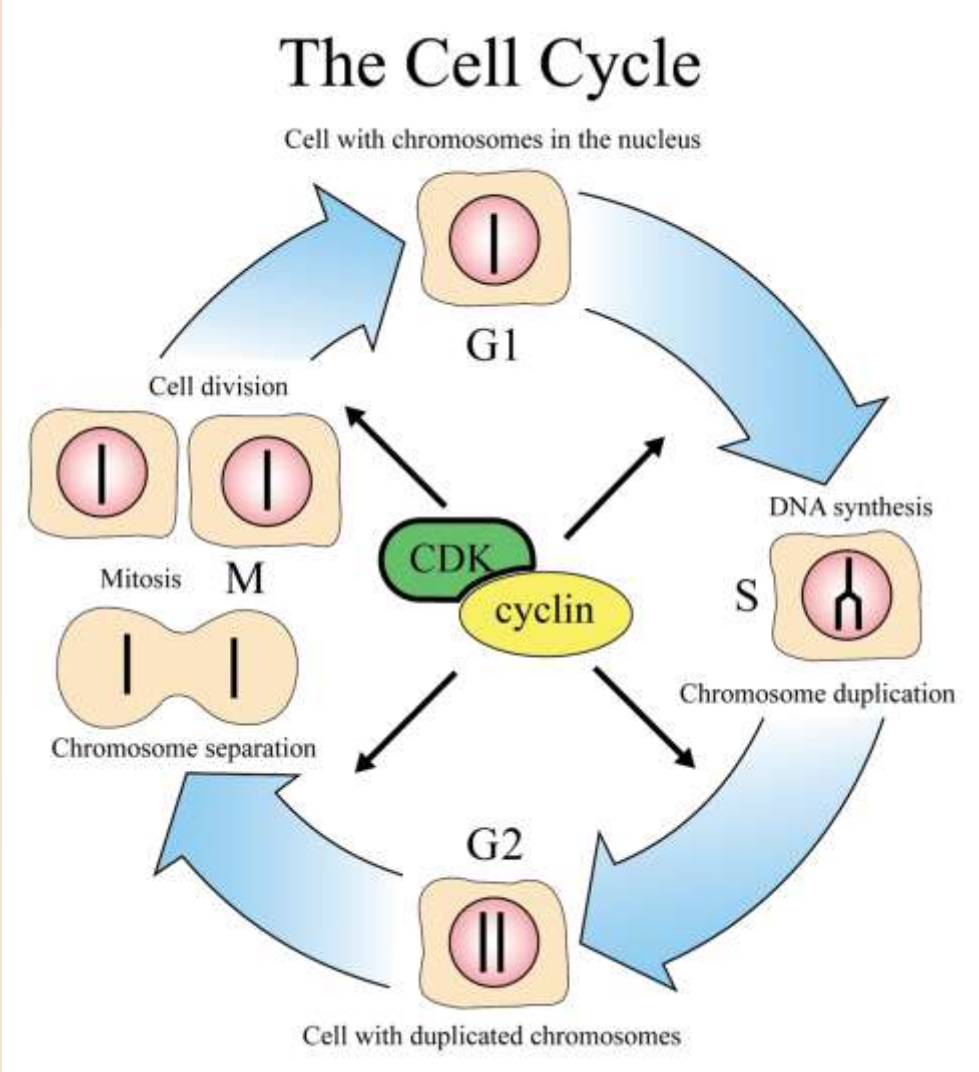
- Growth factors
- Nutritional state of cell
- Size of cell

MPF = Mitosis Promoting Factor
APC = Anaphase Promoting Complex

Cyclin & Cyclin-dependent kinases

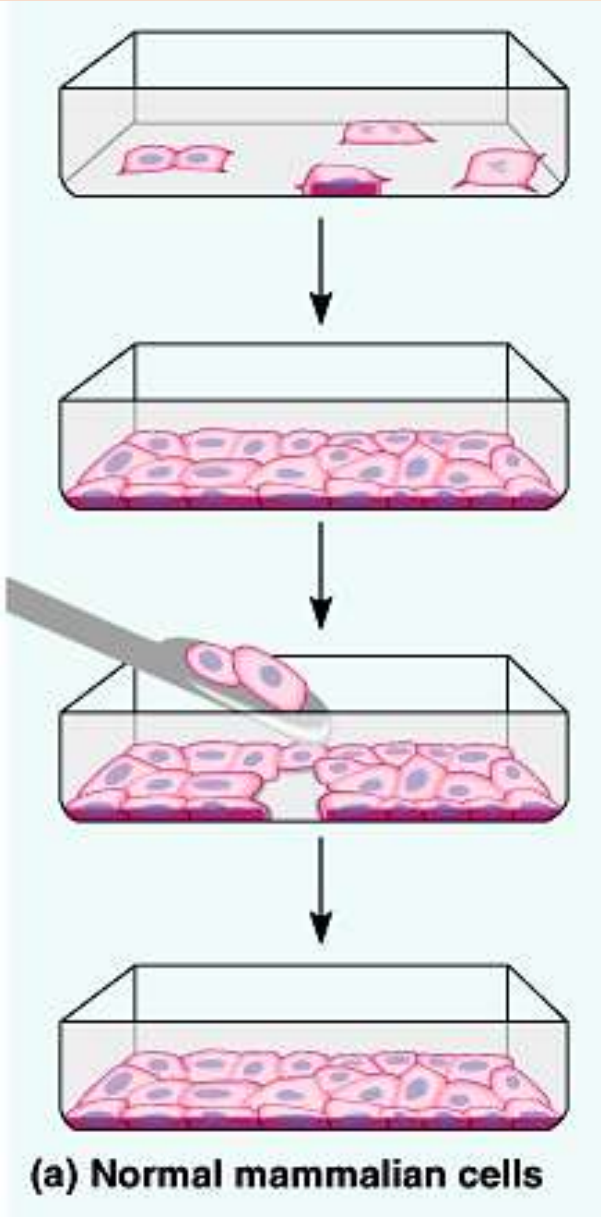
- CDKs & cyclin drive cell from one phase to next in cell cycle

- **proper regulation of cell cycle is so key to life that the <u>genes for these regulatory proteins have been highly conserved</u> through evolution**
- **the genes are basically the same in yeast, insects, plants & animals (including humans)**

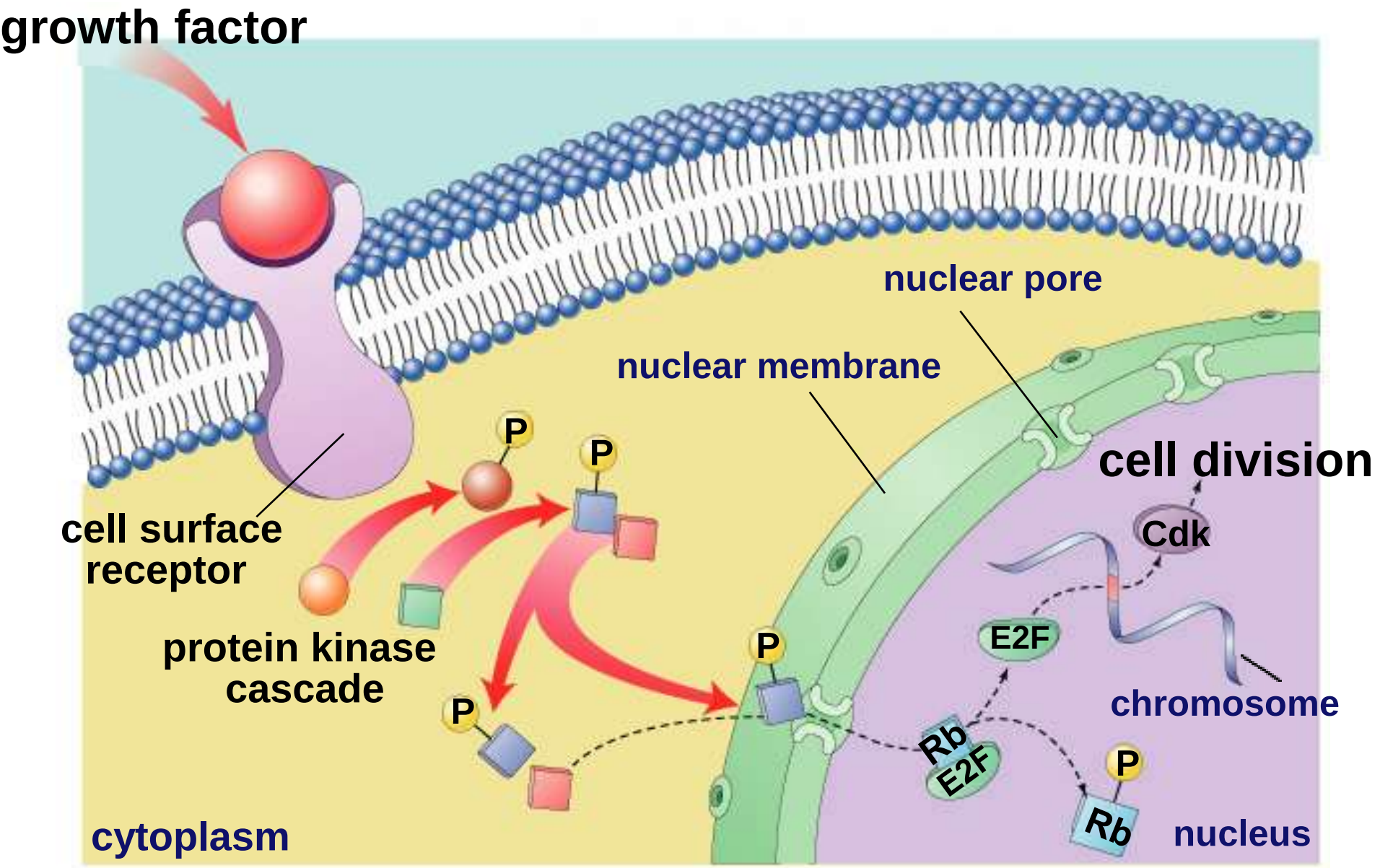


External signals

- Growth factors
  - coordination between cells
  - Proteins released by body cells that stimulate other cells to divide
    - density-dependent inhibition
      - crowded cells stop dividing
    - anchorage dependence
      - to divide cells must be attached to a substrate

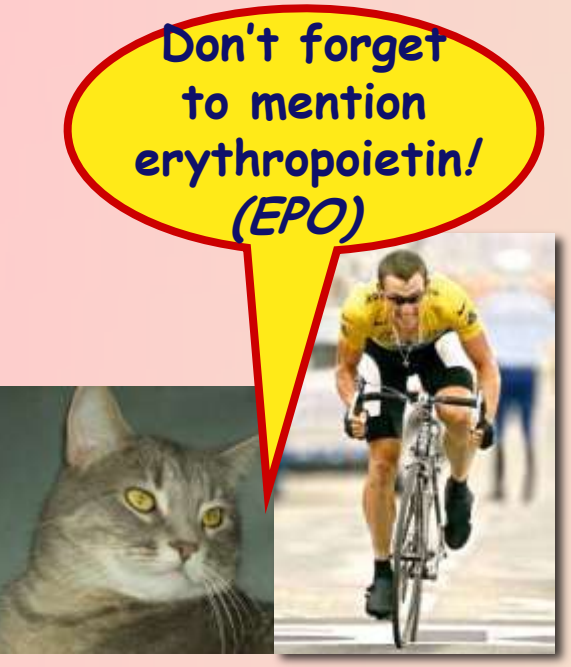


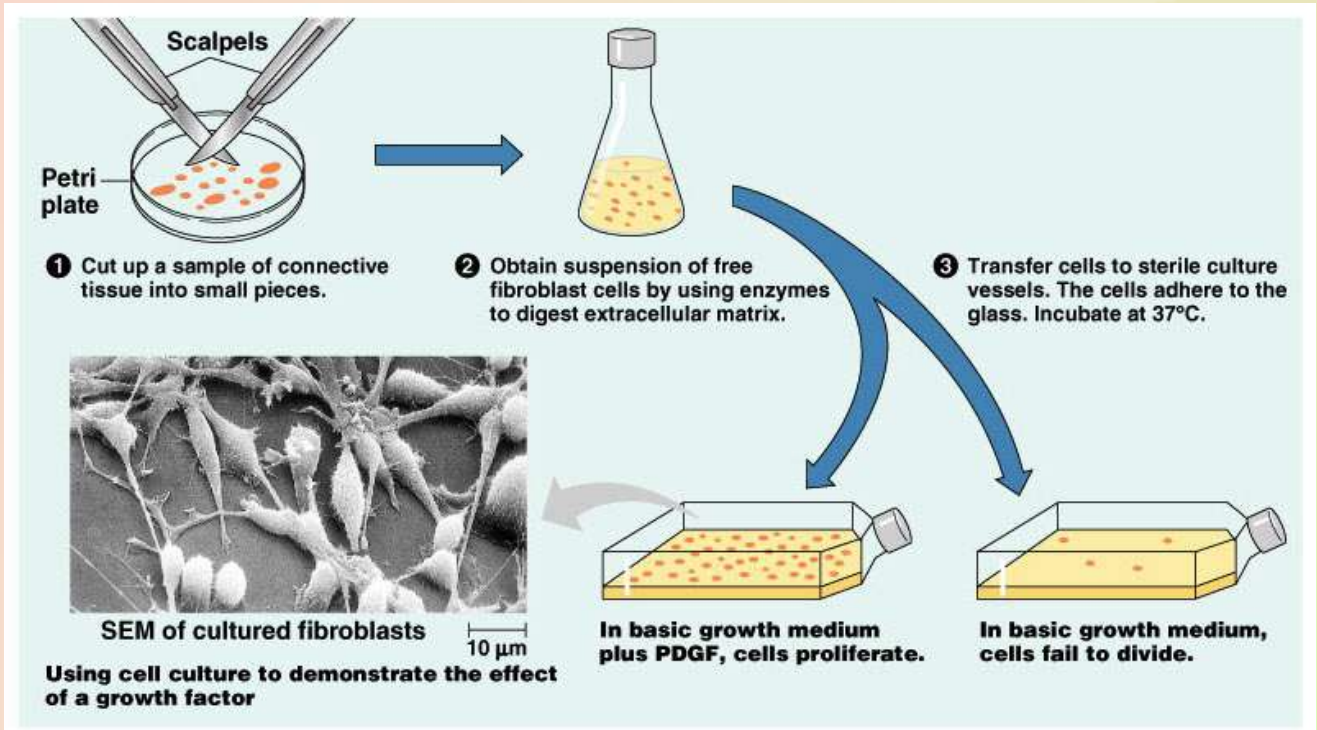
Growth factor signals



Example of a Growth Factor

- Platelet Derived Growth Factor (PDGF)
  - made by platelets in blood clots
  - binding of PDGF to cell receptors stimulates cell division in connective tissue
    - heal wounds

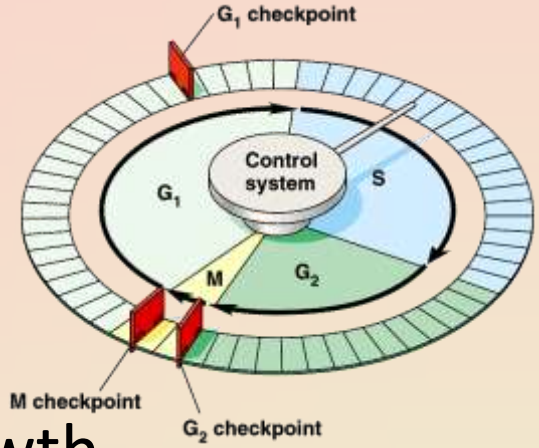




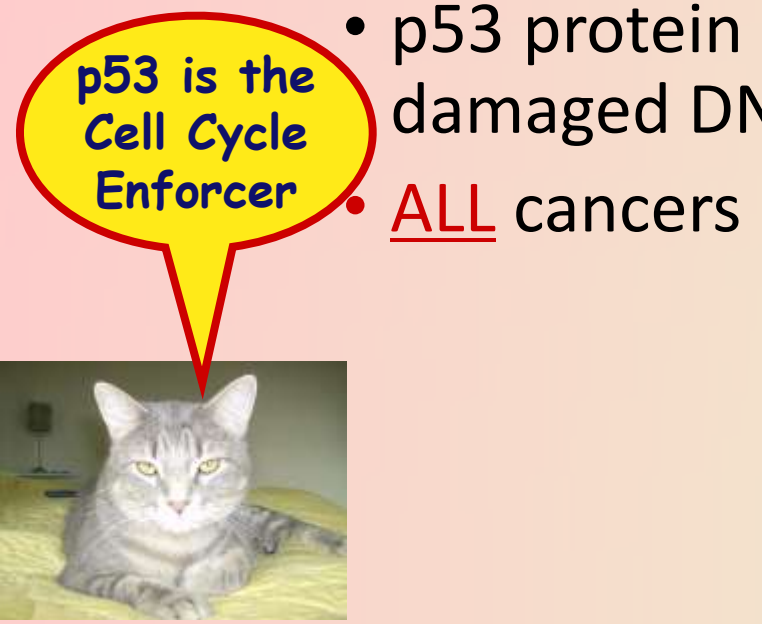
Growth Factors and Cancer

- Growth factors can create cancers
  - proto-oncogenes
    - normally activates cell division
      - growth factor genes. Become "oncogenes" (cancer-causing) when mutated
    - if switched "ON" can cause cancer
    - example: RAS (activates cyclins)
  - tumor-suppressor genes
    - normally inhibits cell division
    - if switched "OFF" can cause cancer
    - example: p53

Cancer & Cell Growth

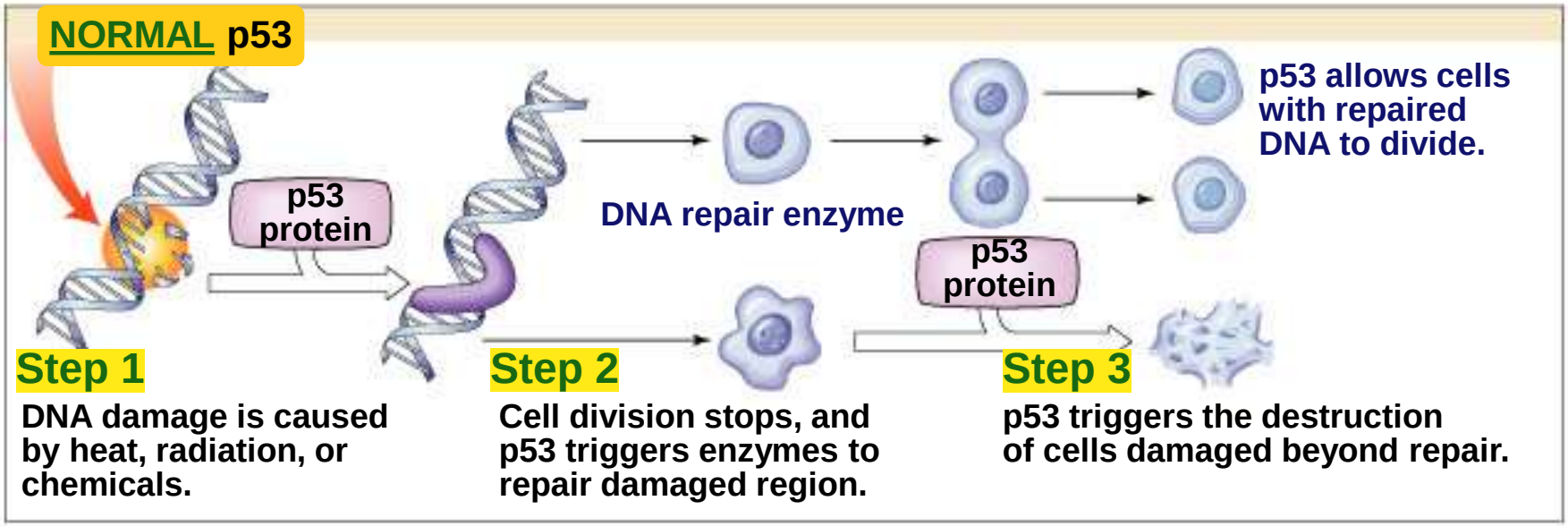


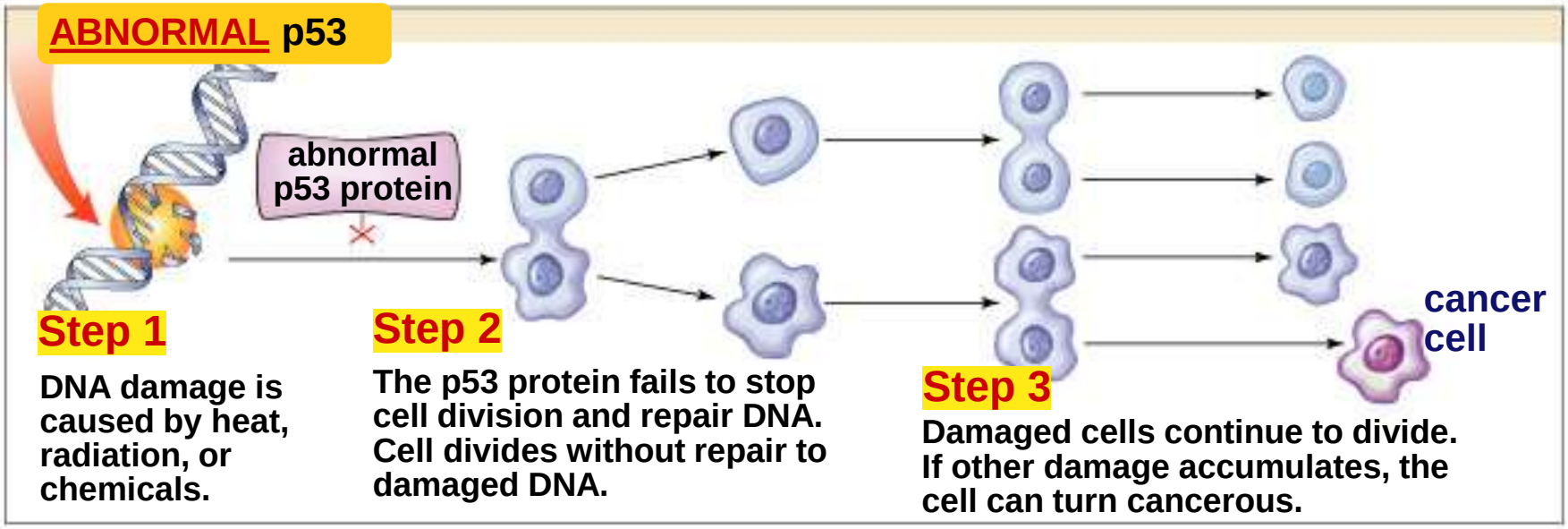
- Cancer is essentially a failure of cell division control
  - unrestrained, uncontrolled cell growth
- What control is lost?
  - lose checkpoint stops
  - gene p53 plays a key role in G_1/S restriction point
    - p53 protein halts cell division if it detects damaged DNA
    - ALL cancers have to shut down p53 activity



p53 discovered at Stony Brook by Dr. Arnold Levine

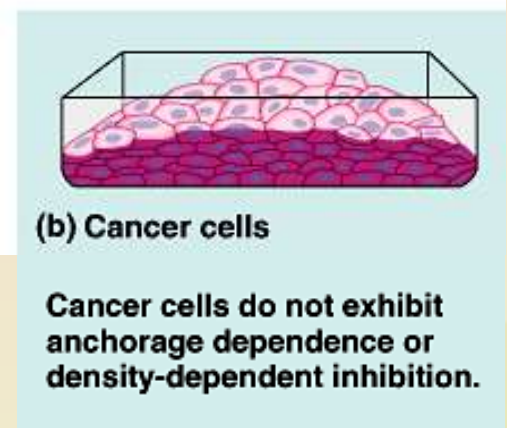
p53 — master regulator gene





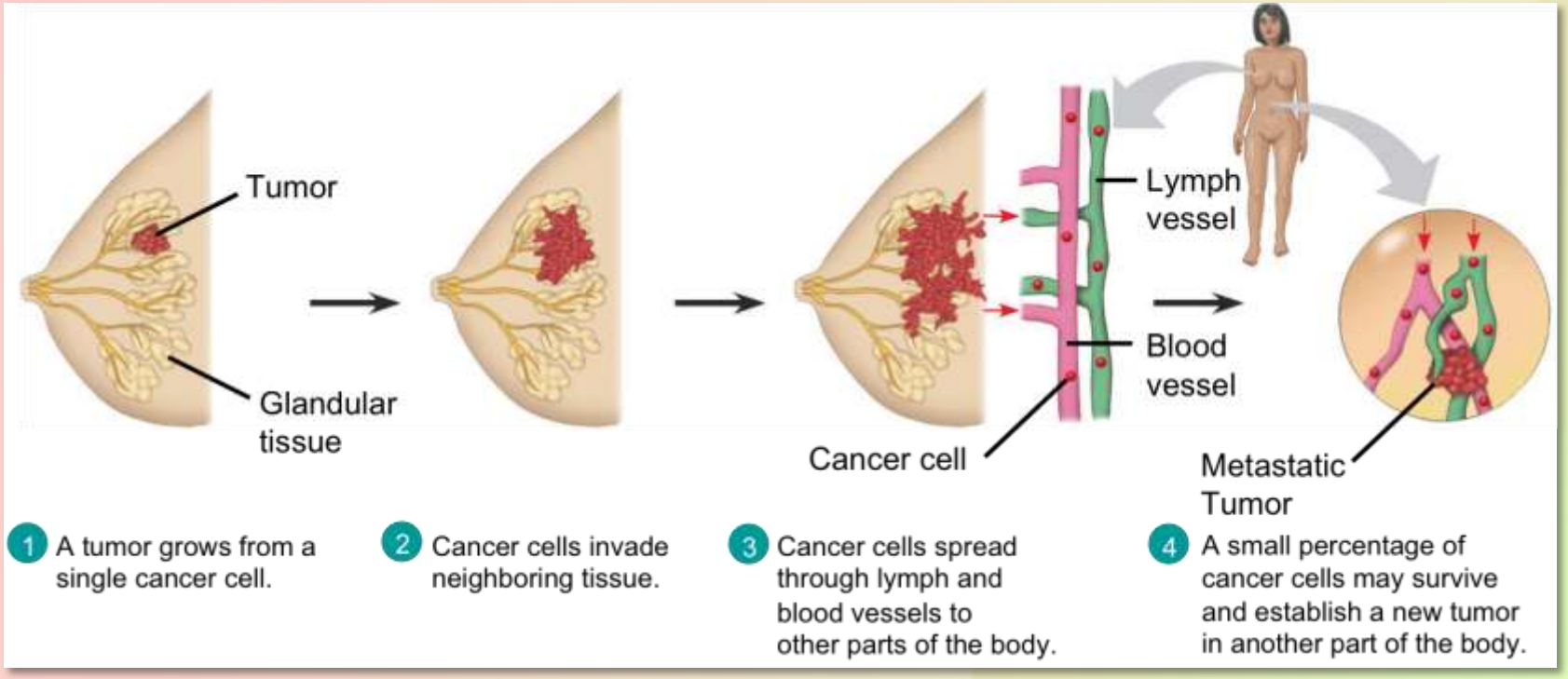
Development of Cancer

- Cancer develops only after a cell experiences ~6 key mutations (“hits”)
  - unlimited growth
    - turn on growth promoter genes
  - ignore checkpoints
    - turn off tumor suppressor genes (p53)
  - escape apoptosis
    - turn off suicide genes
  - immortality = unlimited divisions
    - turn on chromosome maintenance genes
  - promotes blood vessel growth
    - turn on blood vessel growth genes
  - overcome anchor & density dependence
    - turn off touch-sensor gene



What causes these “hits”?

- Mutations in cells can be triggered by
  - **UV radiation**
  - **chemical exposure**
  - **radiation exposure**
  - **heat**
  - **cigarette smoke**
  - **pollution**
  - **age**
  - **genetics**



Tumors

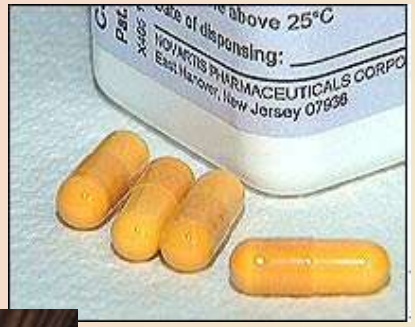
- Mass of abnormal cells
  - Benign tumor
    - abnormal cells remain at original site as a lump
      - p53 has halted cell divisions
    - most do not cause serious problems & can be removed by surgery
  - Malignant tumor
    - cells leave original site
      - lose attachment to nearby cells
      - carried by blood & lymph system to other tissues. start more tumors = metastasis
    - impair functions of organs throughout body

Traditional treatments for cancers

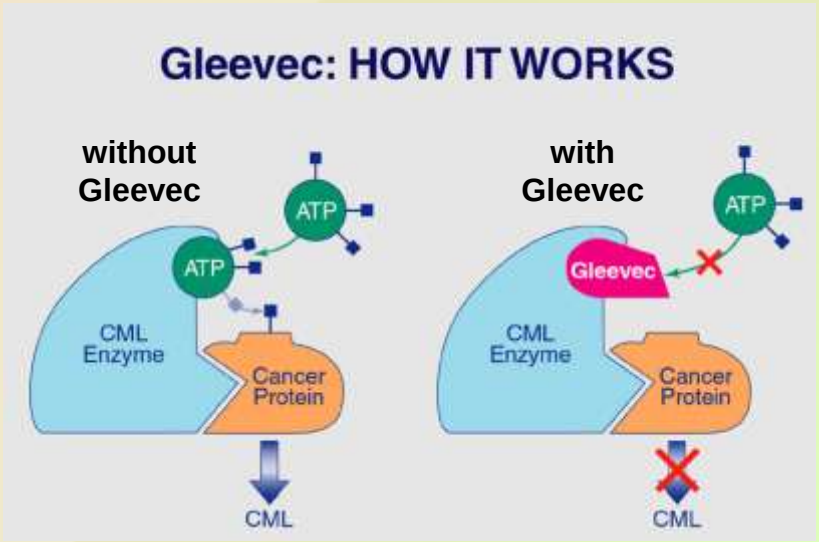
- Treatments target rapidly dividing cells
  - high-energy radiation: kills rapidly dividing cells
  - chemotherapy
    - stop DNA replication
    - stop mitosis & cytokinesis
    - stop blood vessel growth

New “miracle drugs”

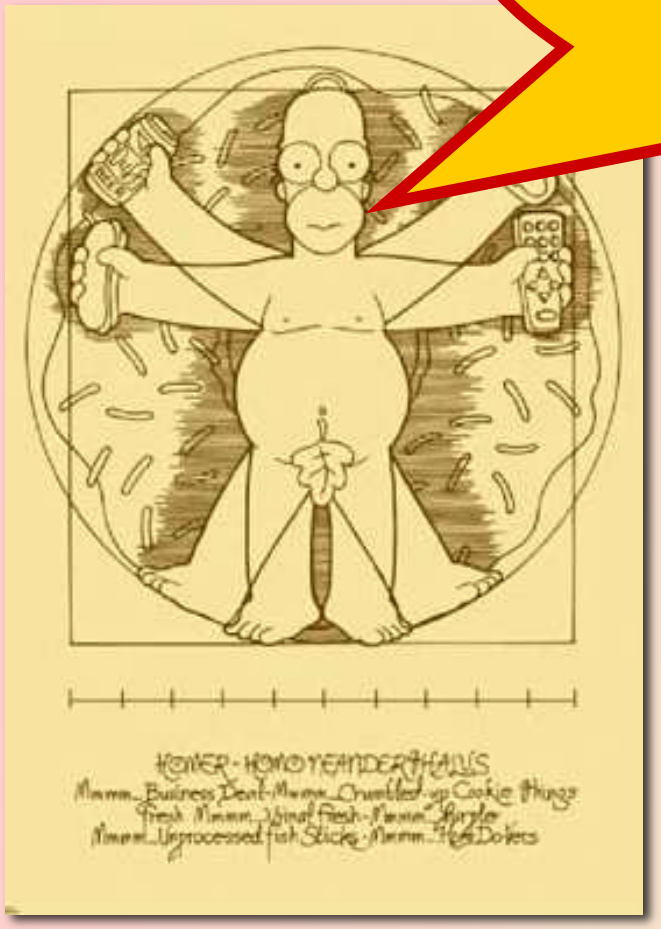
- Drugs targeting proteins (enzymes) found only in cancer cells
  - Gleevec
    - treatment for adult leukemia (CML) & stomach cancer (GIST)
    - 1st successful drug targeting only cancer cells



Novartes



Any Questions??



1. The rhythmic changes in cyclin concentration in a cell cycle are due to
   A. its increased production once the restriction point is passed.
   B. the cascade of increased production once its enzyme is phosphorylated by MPF.
   C. its degradation, which is initiated by active MPF.
   D. the correlation of its production with the production of Cdk.
   E. the binding of the growth factor PDGF.