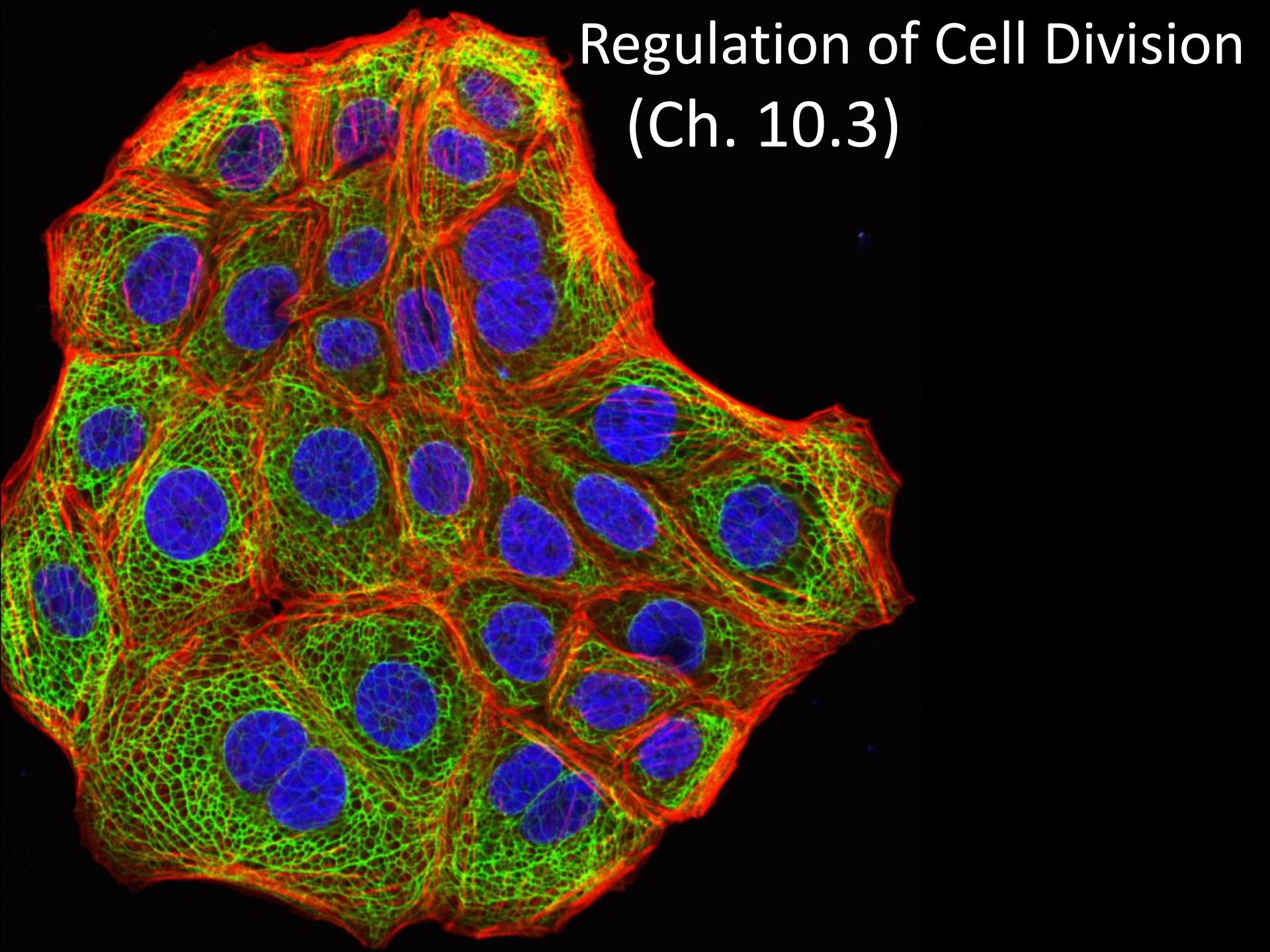


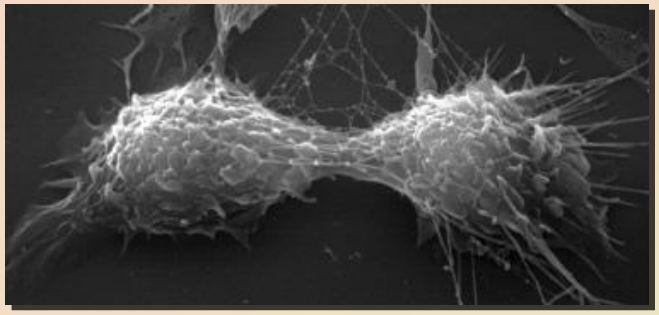
Regulation of Cell Division (Ch. 10.3)

Coordination of cell division

- A multicellular organism needs to coordinate cell division across different tissues & organs

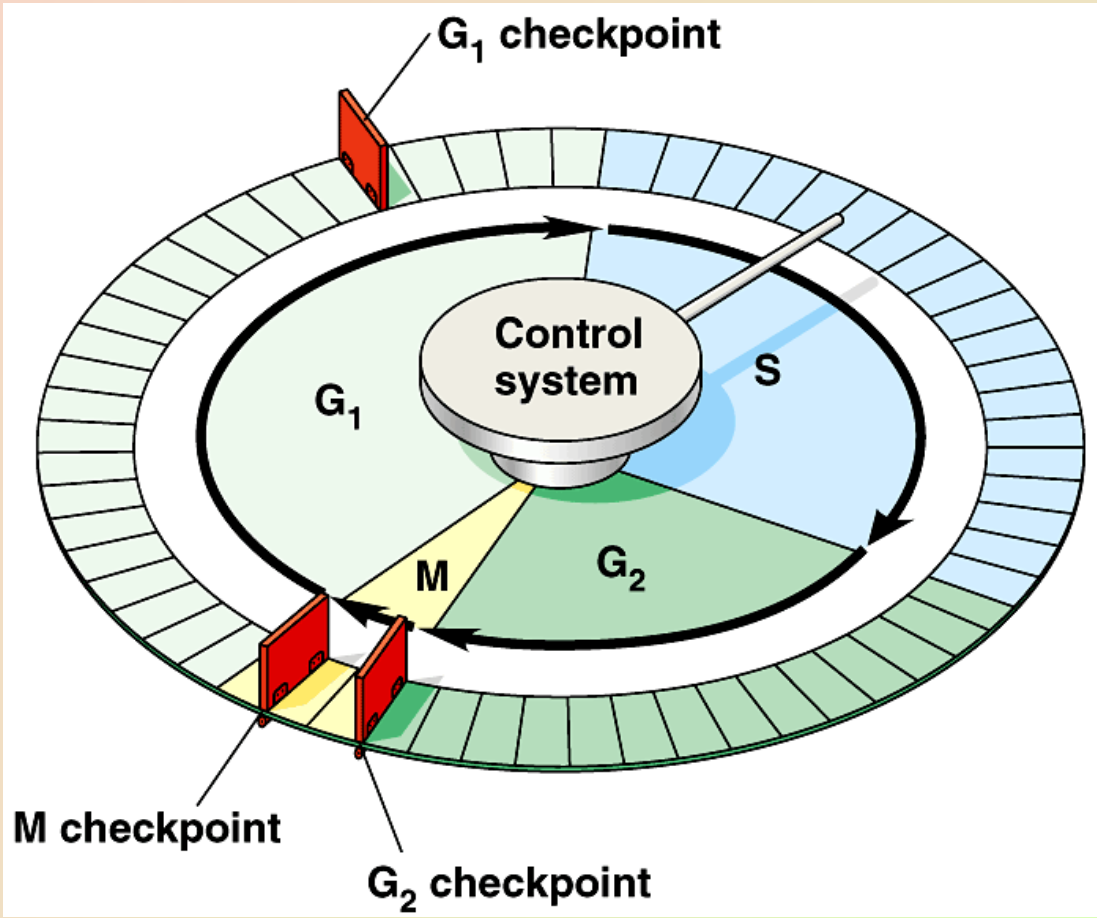
Frequency of cell division

- Varies by cell type
  - embryo
    - cell cycle < 20 minute
  - skin cells
    - 12-24 hour cycle
  - liver cells
    - divide once every year or two
  - mature nerve cells & muscle cells
    - do not divide at all after maturity (?)
    - permanently in G_0



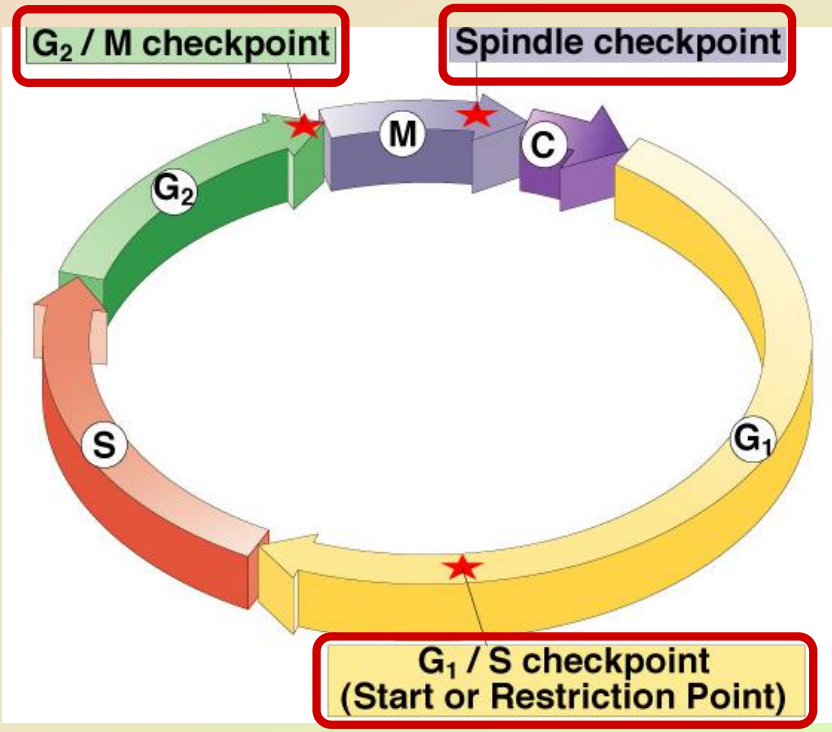
Checkpoint control system

- STOP & GO chemical signals at critical points
- signal if key process has been completed correctly

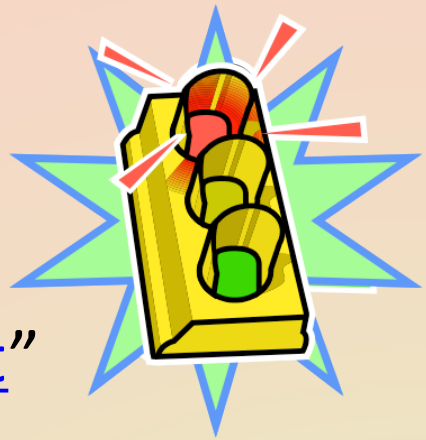


3 major checkpoints:

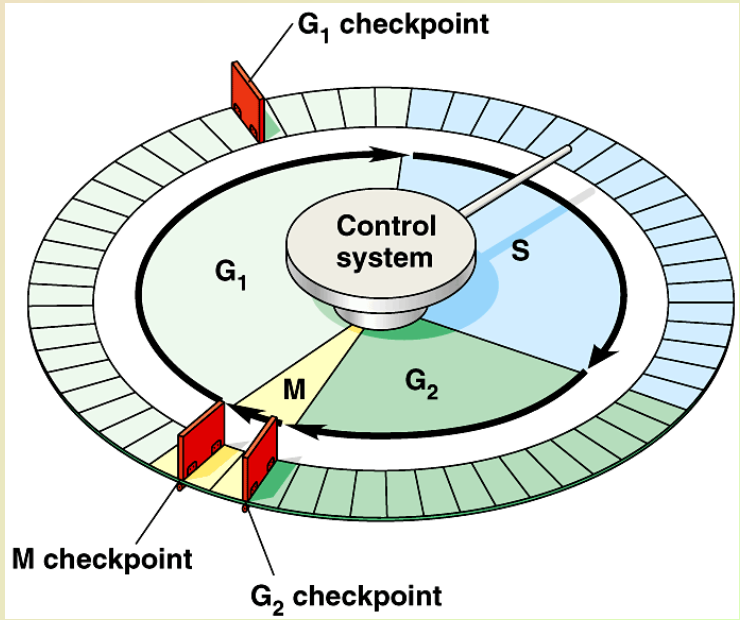
- G_1
  - can DNA synthesis begin?
- G_2
  - has DNA synthesis been completed correctly?
- Spindle checkpoint (M)
  - are all chromosomes attached to spindle?
  - can sister chromatids separate correctly?



G_1 checkpoint



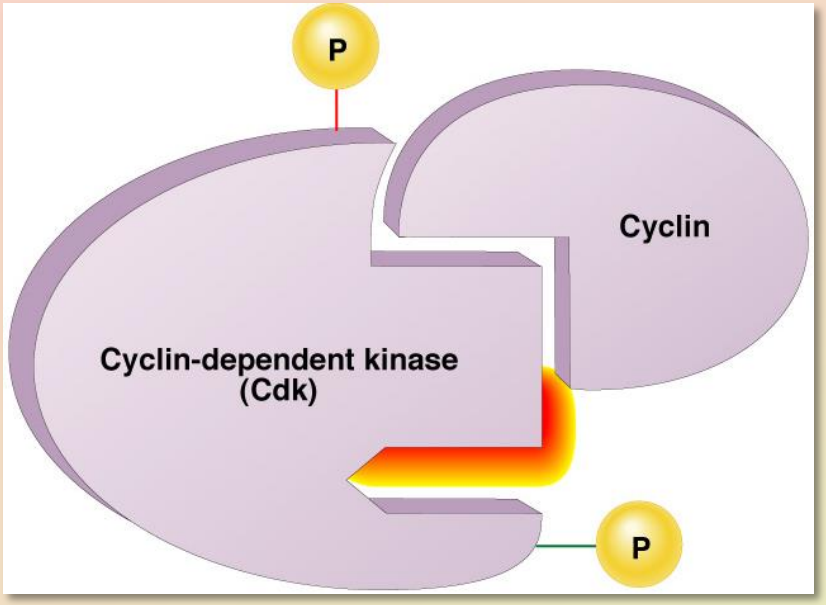
- Most critical
  - primary decision point: "restriction point"
  - if cell receives "GO" signal, it divides
  - if cell does not receive signal, it exits cycle & switches to G_0 phase
    - non-dividing, working state



Cell cycle signals

- cyclins
  - regulatory proteins
  - levels cycle in the cell

inactivated Cdk



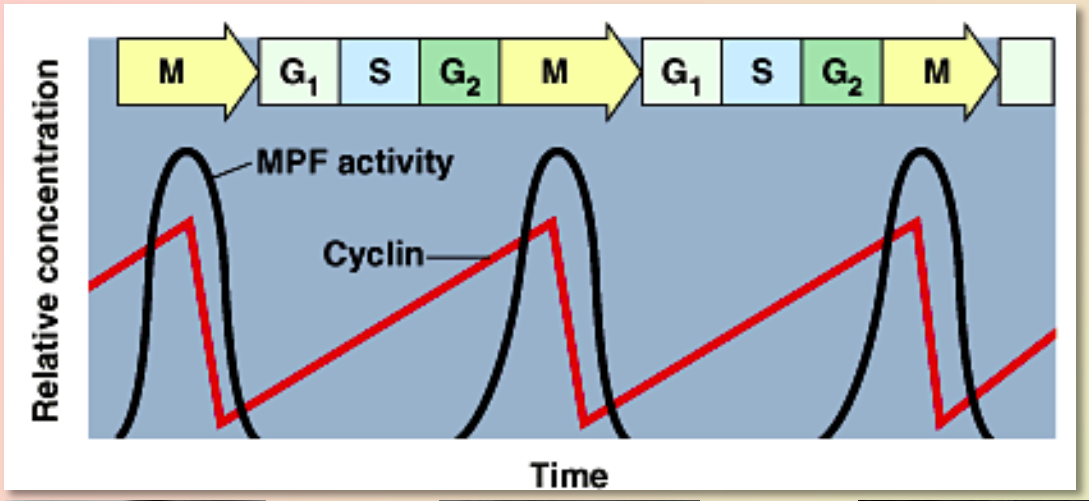
activated Cdk

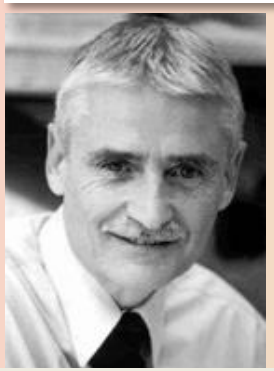
- Cdks cyclin-dependent kinases
  - activates or inactivates proteins
- Cdk-cyclin complex (MPF)
  - triggers different stages of cell cycle

Cyclins & Cdks

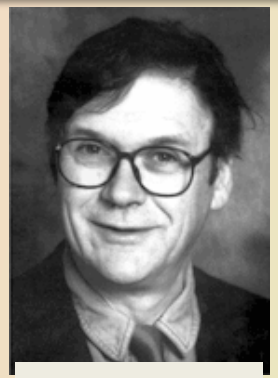
1970s-80s | 2001

- Interaction of Cdk's & 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

Active

Inactive

Cdk / G_2 cyclin (MPF)

Spindle checkpoint

Chromosomes attached at metaphase plate

Inactive

Active

APC

M

mitosis

C

cytokinesis

G_2

G_1

S

Cdk / G_1 cyclin

Inactive

Active

G_1 / S checkpoint

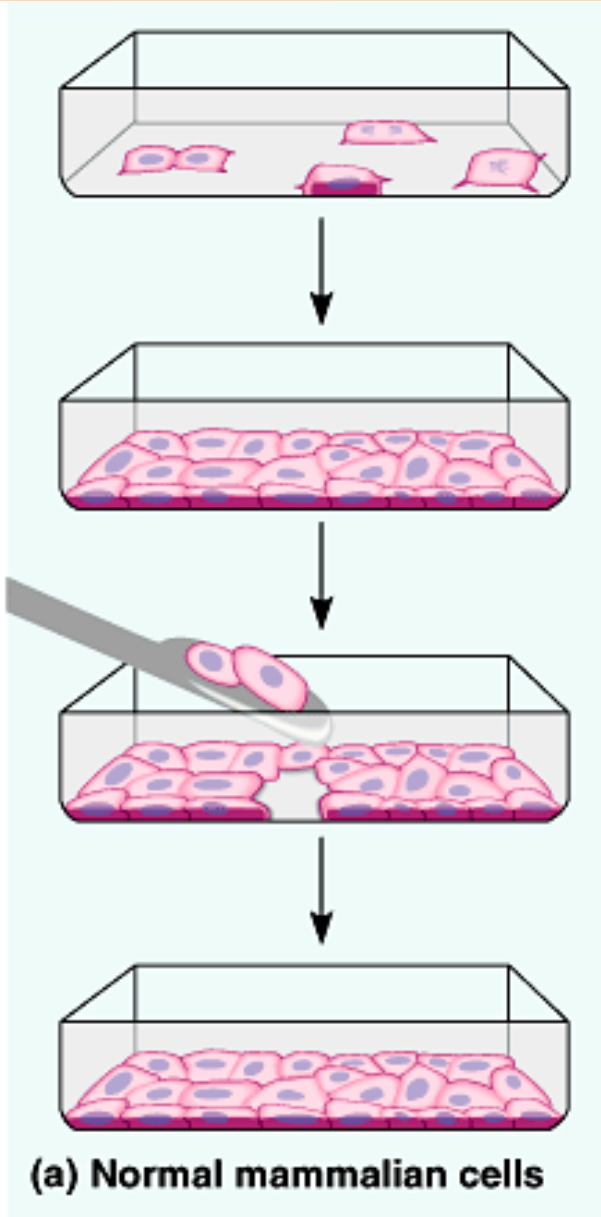
- Growth factors
- Nutritional state of cell
- Size of cell

MPF = Mitosis Promoting Factor

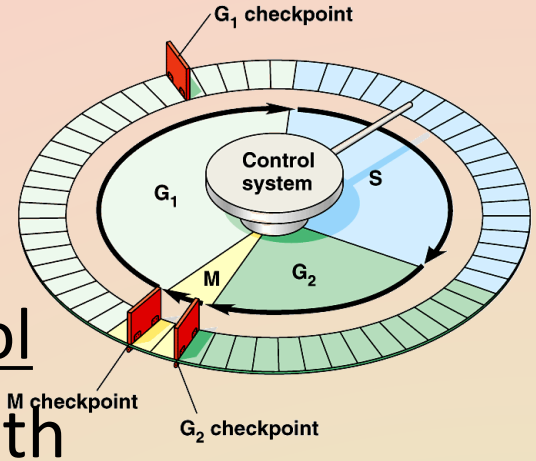
APC = Anaphase Promoting Complex

External signals

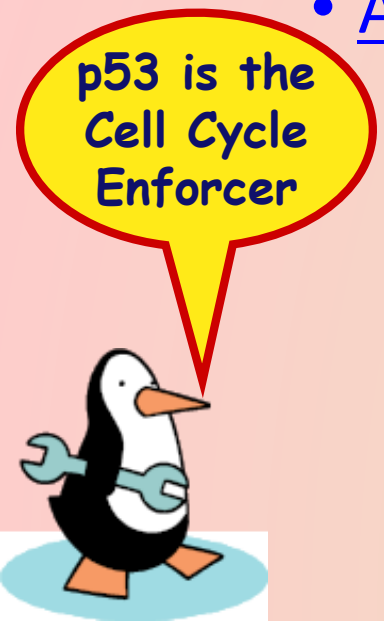
- Growth factors
  - Proteins released by body cells stimulate other cells to divide – lead to:
    - density-dependent inhibition
      - crowded cells stop dividing
    - anchorage dependence
      - to divide cells must be attached to a substrate



Cancer & Cell Growth

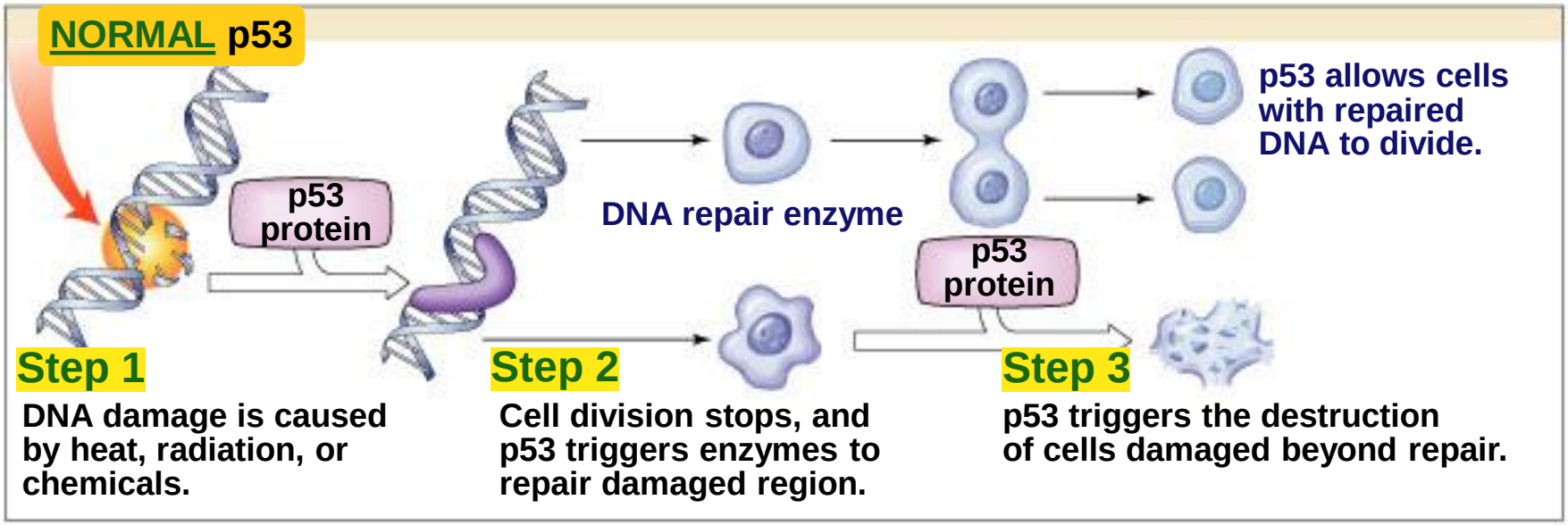


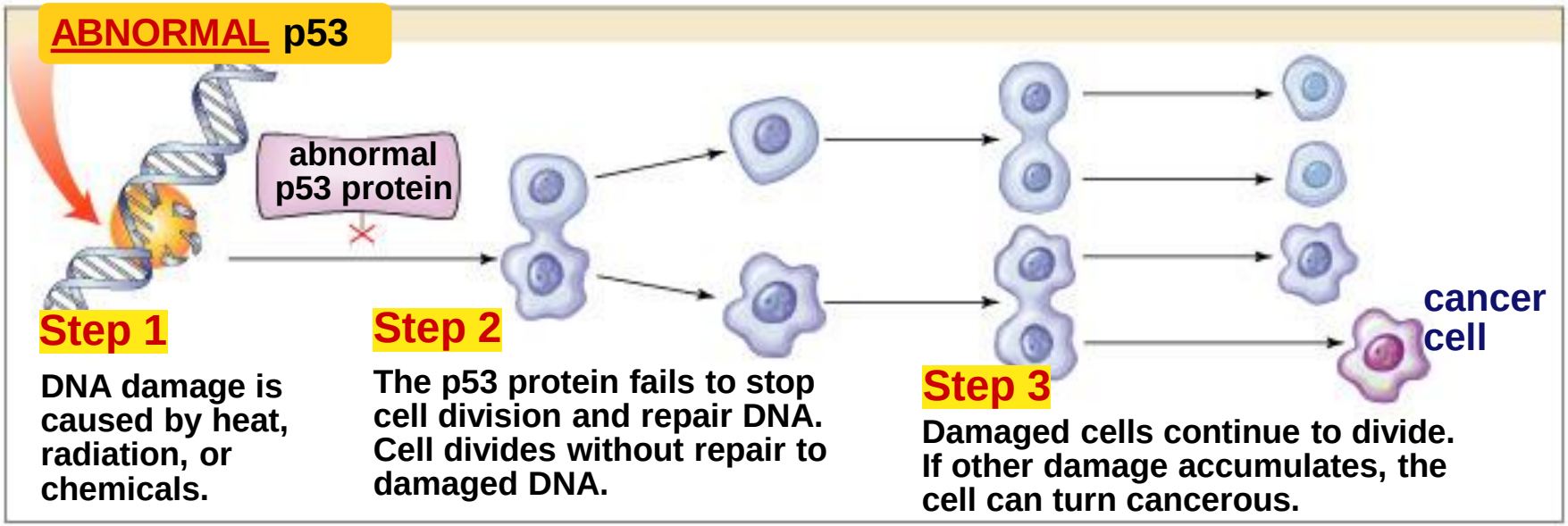
- Cancer is a failure of <u>cell division control</u>
  - unrestrained, uncontrolled cell growth
- What control is lost?
  - lose checkpoint stops
  - Gene p53 stops division if DNA damaged
    - <u>ALL</u> cancers have to shut down p53 activity



p53 discovered at Stony Brook by Dr. Arnold Levine

p53 — master regulator gene



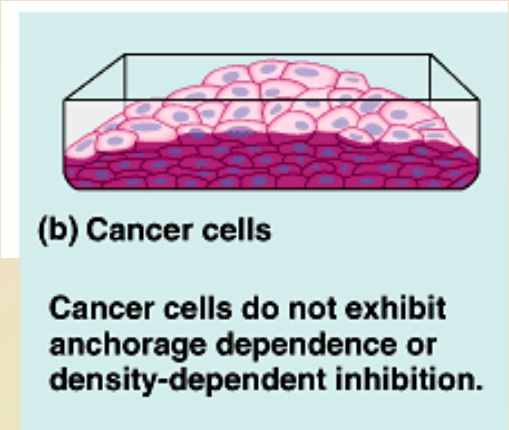


Growth Factors and Cancer

- Proto-oncogenes
  - Protein coded by this gene activates cell division
    - Become "oncogenes" (cancer-causing) when mutated
  - if switched "ON" can cause cancer
- Tumor-suppressor genes
  - Protein coded by this gene inhibits cell division
  - if switched "OFF" can cause cancer
  - example: p53

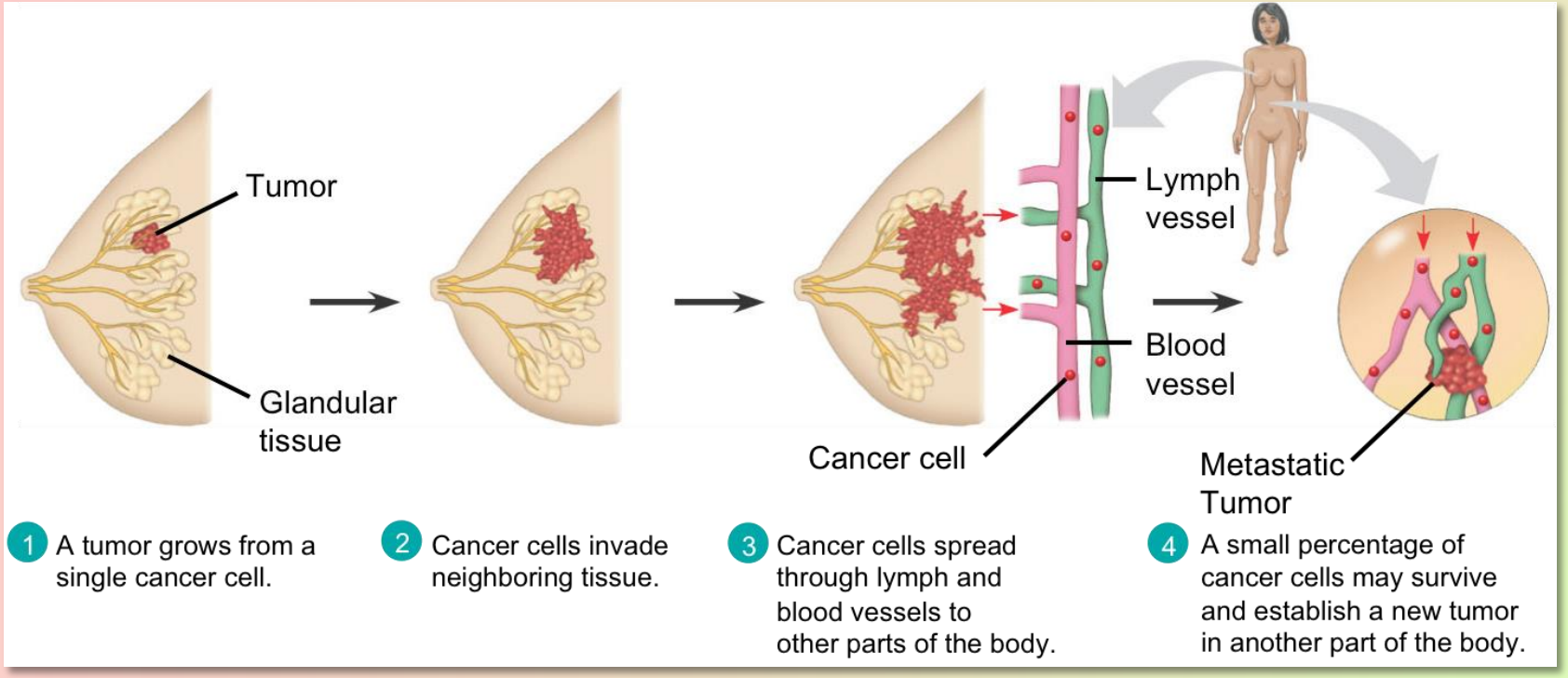
Development of Cancer

- 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 lump
    - p53 has halted cell divisions
  - most do not cause problems & can be removed
- Malignant tumor
  - cells leave original site
    - lose attachment to nearby cells
    - carried by blood & lymph to other tissues. start more tumors = metastasis

Traditional treatments for cancers

- Target rapidly dividing cells
  - high-energy radiation: kills rapidly dividing cells
  - chemotherapy
    - stop DNA replication, mitosis, or 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