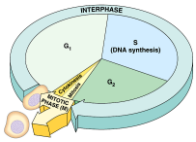
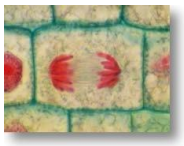
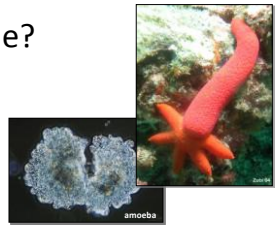


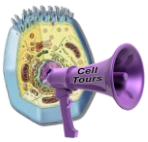
The Cell Cycle: Cell Growth, Cell Division



Why do cells divide?

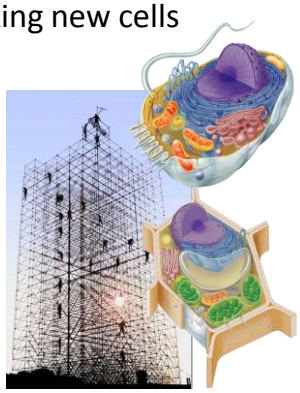
- For reproduction
  - asexual reproduction
    - one-celled organisms
- For growth
  - from fertilized egg to multi-celled organism
- For repair & renewal
  - replace cells that die from normal wear & tear or from injury





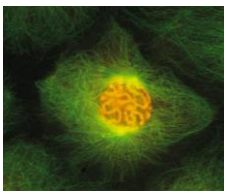
Making new cells

- Nucleus
  - chromosomes
  - DNA
- Cytoskeleton
  - centrioles
    - in animals
  - microtubule spindle fibers



Getting the right stuff

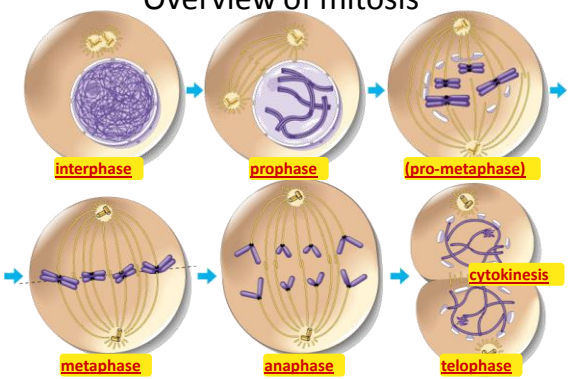
- What is passed on to daughter cells?
  - exact copy of genetic material = DNA
    - mitosis
  - organelles, cytoplasm, cell membrane, enzymes
    - cytokinesis



chromosomes (stained orange) in kangaroo rat epithelial cell →notice cytoskeleton fibers

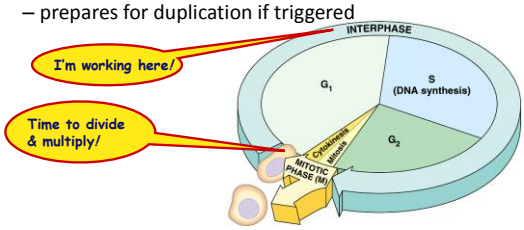
Overview of mitosis

I.P.M.A.T.



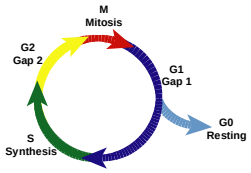
Interphase

- 90% of cell life cycle
  - cell doing its "everyday job"
    - produce RNA, synthesize proteins/enzymes
  - prepares for duplication if triggered



Cell cycle

- Cell has a "life cycle"



cell is formed from a mitotic division

cell grows & matures to divide again

cell grows & matures to never divide again

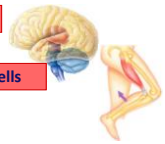
G_1, S, G_2, M

liver cells

$G_1 \rightarrow G_0$

Skin cells, blood cells, stem cells

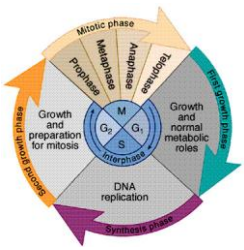
brain / nerve cells



Interphase

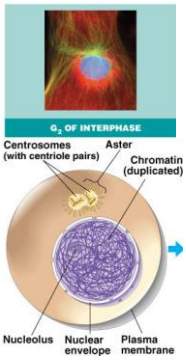
- Divided into 3 phases:
  - G1 = 1st Gap (Growth)
    - cell doing its "everyday job"
    - cell grows
  - S = DNA Synthesis
    - copies chromosomes
  - G2 = 2nd Gap (Growth)
    - prepares for division
    - cell grows (more)
    - produces organelles, proteins, membranes

Signal to divide



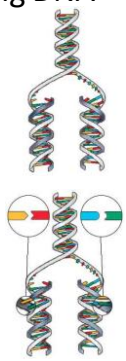
Interphase

- Nucleus well-defined
  - DNA loosely packed in long chromatin fibers
- Prepares for mitosis
  - replicates chromosome
    - DNA & proteins
  - produces proteins & organelles



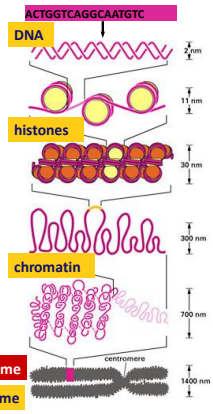
S phase: Copying / Replicating DNA

- Synthesis phase of Interphase
  - dividing cell replicates DNA
  - must separate DNA copies correctly to 2 daughter cells
    - human cell duplicates ~3 meters DNA
    - each daughter cell gets complete identical copy
    - error rate = ~1 per 100 million bases
      - 3 billion base pairs in mammalian genome
      - ~30 errors per cell cycle
        - » mutations (to somatic (body) cells)



Organizing DNA

- DNA is organized in chromosomes
  - double helix DNA molecule
  - wrapped around histone proteins
    - like thread on spools
  - DNA-protein complex = chromatin
    - organized into long thin fiber
  - condensed further during mitosis

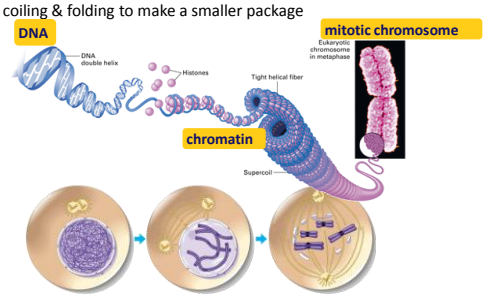


double stranded chromosome

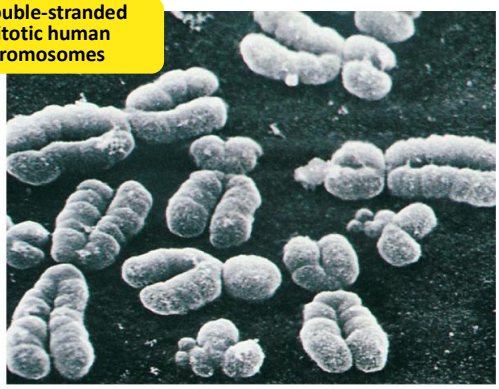
duplicated mitotic chromosome

Copying DNA & packaging it…

- After DNA duplication, chromatin condenses
  - coiling & folding to make a smaller package

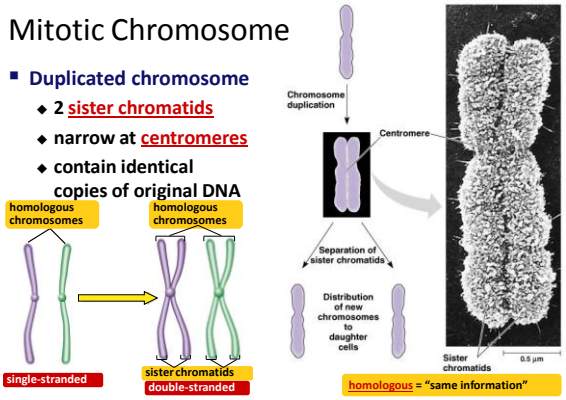


double-stranded mitotic human chromosomes



Mitotic Chromosome

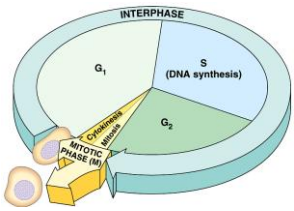
- **Duplicated chromosome**
  - **2 sister chromatids**
  - **narrow at centromeres**
  - **contain identical copies of original DNA**



homologous = "same information"

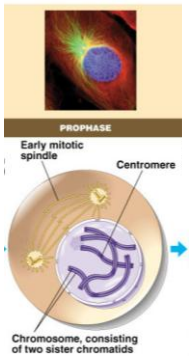
Mitosis

- Dividing cell's DNA between 2 daughter nuclei
- 4 phases
  - prophase
  - metaphase
  - anaphase
  - telophase



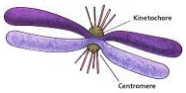
Prophase

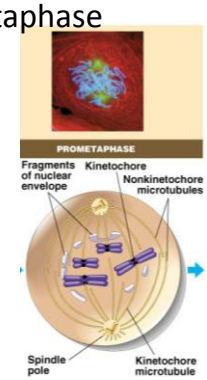
- Chromatin condenses
  - visible chromosomes
    - chromatids
- Centrioles move to opposite poles of cell
  - animal cell
- Protein fibers cross cell to form mitotic spindle
  - microtubules
    - actin, myosin
  - coordinates movement of chromosomes
- Nucleolus disappears
- Nuclear membrane breaks down



Transition to Metaphase

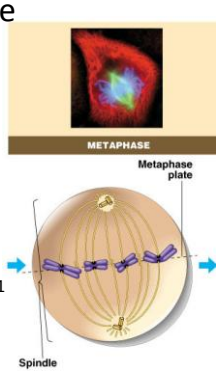
- Prometaphase
  - spindle fibers attach to centromeres
    - creating kinetochores
  - microtubules attach at kinetochores
    - connect centromeres to centrioles
  - chromosomes begin moving





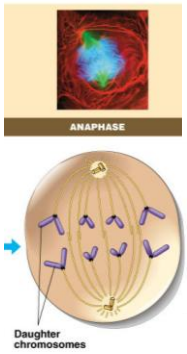
Metaphase

- Chromosomes align along middle of cell
  - metaphase plate
    - meta = middle
  - spindle fibers coordinate movement
  - helps to ensure chromosomes separate properly
    - so each new nucleus receives only 1 copy of each chromosome



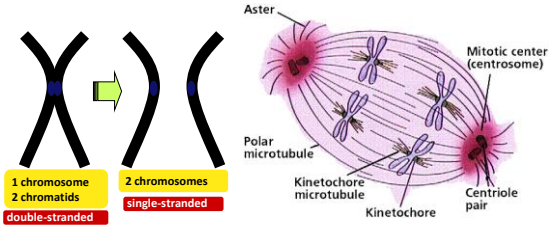
Anaphase

- Sister chromatids separate at kinetochores
  - move to opposite poles
  - pulled at centromeres
  - pulled by motor proteins "walking"along microtubules
    - actin, myosin
    - increased production of ATP by mitochondria
- Poles move farther apart
  - polar microtubules lengthen



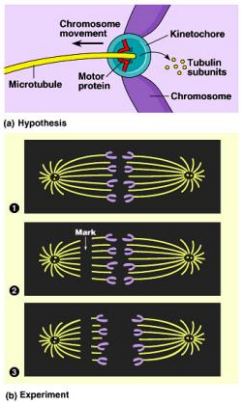
Separation of chromatids

- In anaphase, proteins holding together sister chromatids are inactivated
  - separate to become individual chromosomes



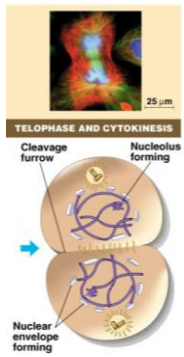
Chromosome n

- Kinetochores use motor proteins that "walk" chromosome along attached microtubule
  - microtubule shortens by dismantling at kinetochore (chromosome) end



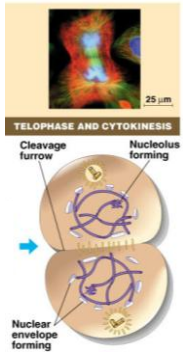
Telophase

- Chromosomes arrive at opposite poles
  - daughter nuclei form
  - nucleoli form
  - chromosomes disperse
    - no longer visible under light microscope
- Spindle fibers disperse
- Cytokinesis begins
  - cell division

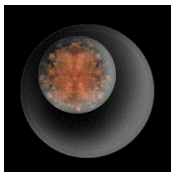


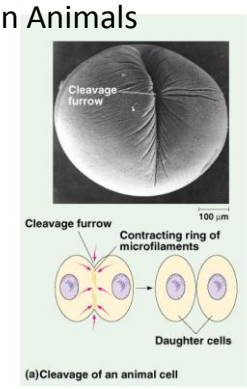
Cytokinesis

- Animals
  - constriction belt of actin microfilaments around equator of cell
    - cleavage furrow forms
    - splits cell in two
    - like tightening a draw string

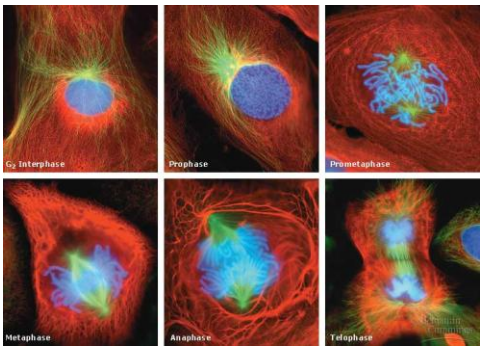


Cytokinesis in Animals



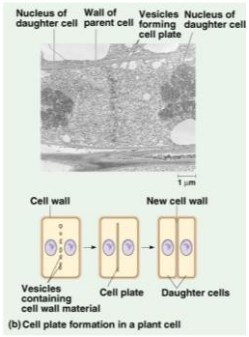


Mitosis in animal cells

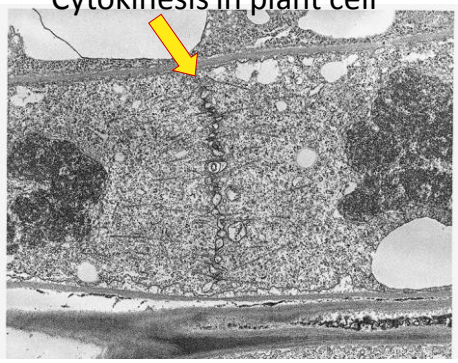


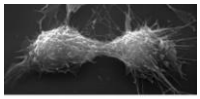
Cytokinesis in Plants

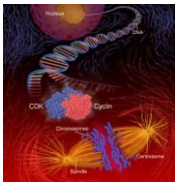
- Plants
  - cell plate forms
    - vesicles line up at equator
      - derived from Golgi
    - vesicles fuse to form 2 cell membranes
  - new cell wall laid down between membranes
    - new cell wall fuses with existing cell wall



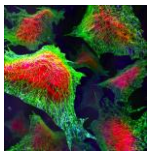
Cytokinesis in plant cell







Regulation of Cell Division

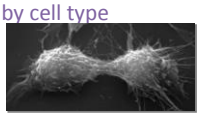


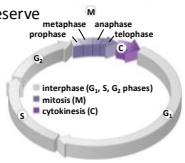
Coordination of cell division

- A multicellular organism needs to coordinate cell division across different tissues & organs
  - critical for normal growth, development & maintenance
    - coordinate timing of cell division
    - coordinate rates of cell division
    - not all cells can have the same cell cycle

Frequency of cell division

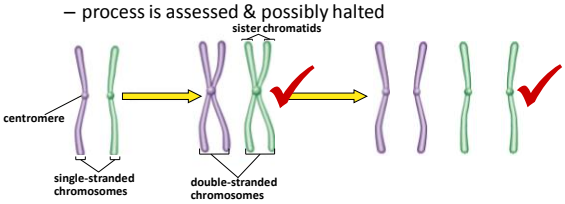
- Frequency of cell division varies by cell type
  - embryo
    - cell cycle < 20 minute
  - skin cells
    - divide frequently throughout life
    - 12-24 hours cycle
  - liver cells
    - retain ability to divide, but keep it in reserve
    - divide once every year or two
  - mature nerve cells
    - do not divide at all after maturity
    - permanently in G0





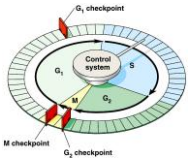
Overview of Cell Cycle Control

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



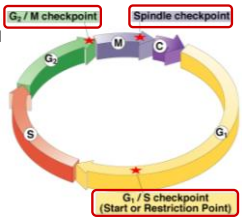
Checkpoint control system

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



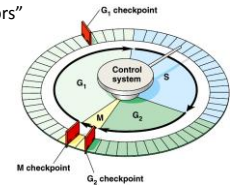
Checkpoint control system

- 3 major checkpoints:
  - G1/S
    - can DNA synthesis begin?
  - G2/M
    - has DNA synthesis been completed correctly?
    - commitment to mitosis
  - spindle checkpoint
    - are all chromosomes attached to spindle?
    - can sister chromatids separate correctly?



G1/S checkpoint

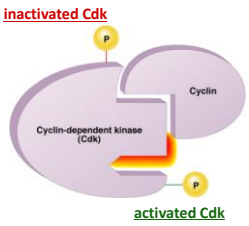
- G1/S checkpoint is most critical
  - primary decision point
    - "restriction point"
  - if cell receives "GO" signal, it divides
    - internal signals: cell growth (size), cell nutrition
    - external signals: "growth factors"
  - if cell does not receive signal, it exits cycle & switches to G0 phase
    - non-dividing, working state



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

Cell cycle signals

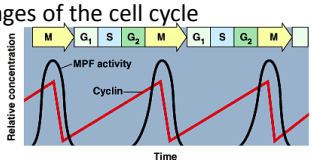


- Cell cycle controls
  - cyclins
    - regulatory proteins
    - levels cycle in the cell
  - Cdks
    - cyclin-dependent kinases
    - phosphorylates cellular proteins
      - activates or inactivates proteins
  - Cdk-cyclin complex
    - triggers passage through different stages of cell cycle

1970s-80s | 2001

Cyclins & Cdks

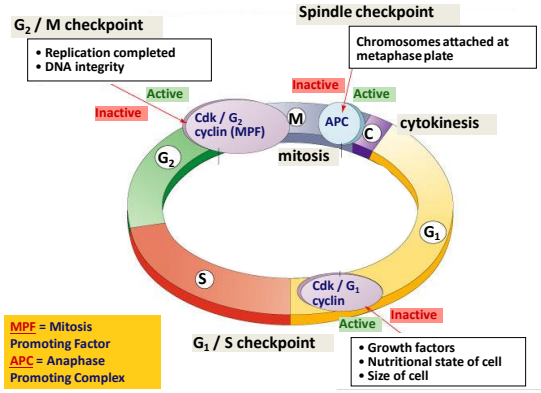
- Interaction of Cdk's & different cyclins triggers the stages of the cell cycle




Leland H. Hartwell
checkpoints

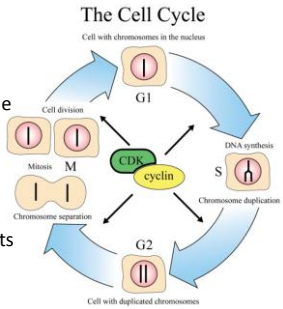

Tim Hunt
Cdks


Sir Paul Nurse
cyclins



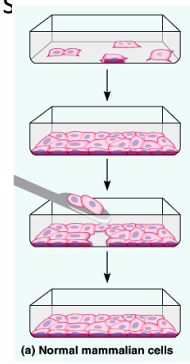
Cyclin & Cyclin-dependent kinases

- CDKs & cyclin drive cell from one phase to next in cell cycle
  - proper regulation of cell cycle is so key to life that the genes for these regulatory proteins have been highly conserved through evolution
  - the genes are basically the same in yeast, insects, plants & animals (including humans)

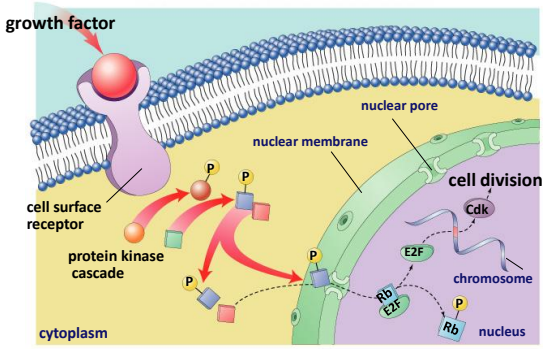


External signals

- Growth factors
  - coordination between cells
  - protein signals released by body cells that stimulate other cells to divide
    - density-dependent inhibition
      - crowded cells stop dividing
      - each cell binds a bit of growth factor
        - » not enough activator left to trigger division in any one cell
    - anchorage dependence
      - to divide cells must be attached to a substrate
        - » "touch sensor" receptors

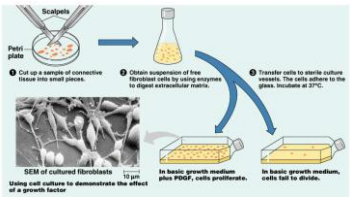

(a) Normal mammalian cells

Growth factor signals



Example of a Growth Factor

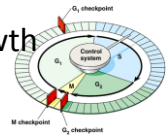
- Platelet Derived Growth Factor (PDGF)
  - made by platelets in blood clots
  - binding of PDGF to cell receptors stimulates cell division in connective tissue
    - heal wounds



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

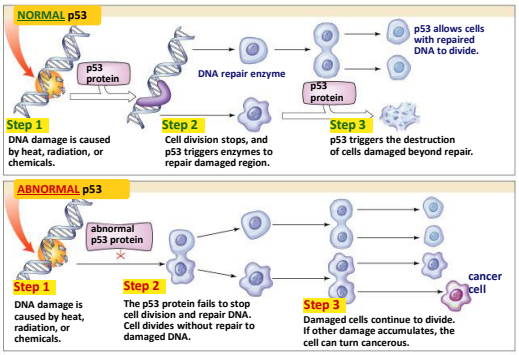
Cancer & Cell Growth



- 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 G1/S restriction point
    - p53 protein halts cell division if it detects damaged DNA
      - options:
        - » stimulates repair enzymes to fix DNA
        - » forces cell into G0 resting stage
        - » keeps cell in G1 arrest
        - » causes apoptosis of damaged cell
    - cancers have to shut down p53 activity

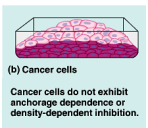
p53 is the Cell Cycle Enforcer

p53 — master regulator gene



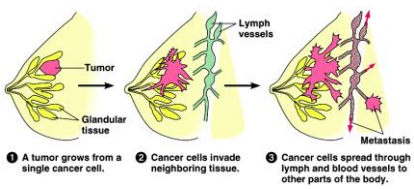
Development of Cancer

- 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

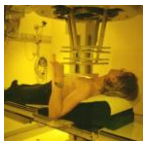


Tumors

- Mass of abnormal cells
  - Benign tumor
    - abnormal cells remain at original site as a lump
    - 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

Novartis