Chem 227 / Organic Chemistry II

Expanding and Connecting Concepts

Past & Present / New & Old

Small Organic Molecules

Lipids / Sugars

Proteins / DNA

Cells

Human Health

or

Human Health

Cells

Proteins / DNA

Chem 227 Lipids / Sugars

Small Organic Molecules

Beginning with the topics at course's end, considering small organic molecules within the context of the chemistry of living organisms

•Chapters: 24, 25, 26, 27

Human Health

Cells

Proteins / DNA

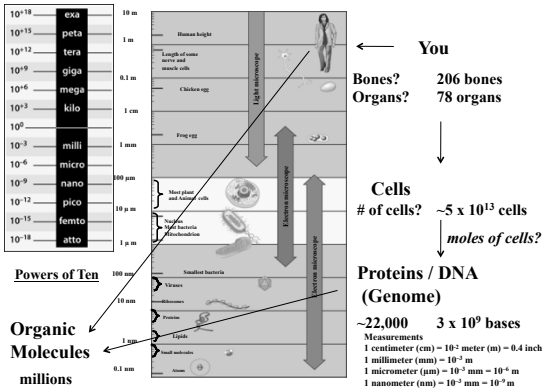
Chem 227 Lipids / Sugars

Small Organic Molecules

• How are they connected?

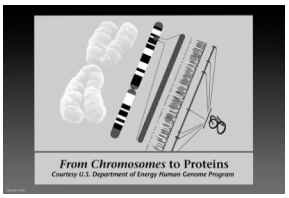
• What is cancer?

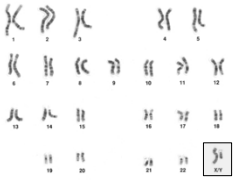
•Why do certain types of organic molecules such as benzene cause cancer in some of us but not all?



Genetic Controls

Chromosomes (DNA/RNA)





Male or female?

Small Organic Molecules

Common Functional Groups

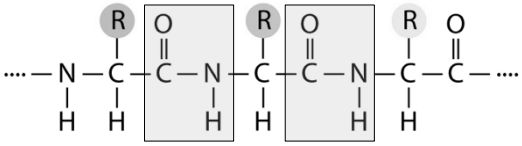
Name	General Formula
Alcohols	R−OH
Ethers	R−O−R′
Amines	$R-NH_2$

Small Organic Molecules

Common Functional Groups

Name	General Formula
Aldehydes	
Ketones	
Carboxylic Acids	
Esters	
Amides	

Amides & Proteins



Proteins

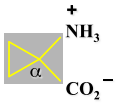
Polypeptides, Amides and Proteins

- **Proteins are polyamides, each amide group is called a peptide bond.**
- **Peptides are formed by condensation of the -COOH group of one amino acid and the NH group of another amino acid.**

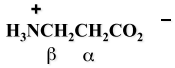
Fundamentals

- **While their name implies that amino acids are compounds that contain an —NH_2 group and a —CO_2H group, these groups are actually present as —NH_3^+ and —CO_2^- respectively.**
- **They are classified as α, β, γ, *etc*. amino acids according the carbon that bears the nitrogen.**

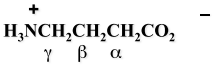
Amino Acids



an α-amino acid that is an intermediate in the biosynthesis of ethylene



a β-amino acid that is one of the structural units present in coenzyme A

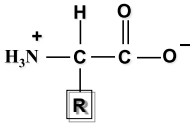


a γ-amino acid involved in the transmission of nerve impulses

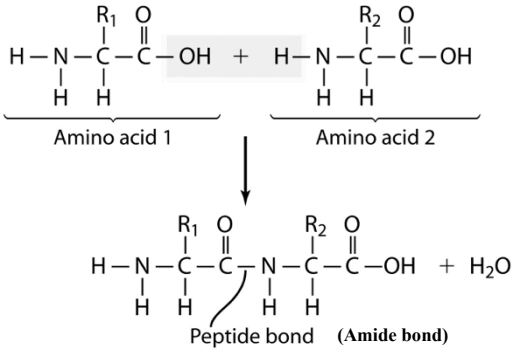
The 20 (22) Key Amino Acids

- More than 700 amino acids occur naturally, but 20 (22?)of them are especially important.
- These 22 amino acids are the building blocks of proteins. All are α-amino acids.
- They differ in respect to the group attached to the α carbon.

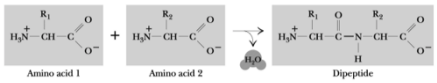
Amino Acids



- The amino acids obtained by hydrolysis of proteins differ in respect to R (the side chain).
- The properties of the amino acid vary as the structure of R varies.



Proteins are Polymers of Amino Acids



- Peptides have various numbers of amino acids.
- Peptides are always written with the -NH_2 terminus on the left, -CO_2H on the right.
- Each amino acid unit is called a residue.
- 2 residues = dipeptide,
- 3 residues = tripeptide,
- 12-20 residues = oligopeptide,
- Many residues = polypeptide.

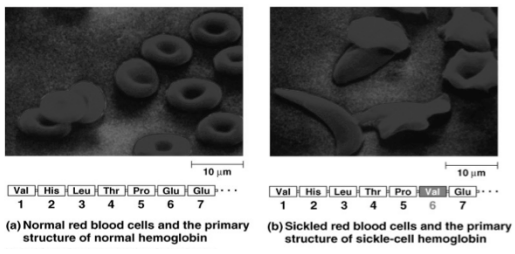
Proteins (Polypeptides)

Polypeptides

- Polypeptides are formed with a large number of amino acids (usually result in proteins with molecular weights between 6000 and 50 million amu).

Protein Structure

- Primary structure is the sequence of the amino acids in the protein.
- A change in one amino acid can alter the biochemical behavior of the protein. *Eg. Sickle Cell Anemia*



Four Levels of Protein Structure

- **1º : The linear sequence of amino acids and disulfide bonds eg. ARDV:Ala-Arg-Asp-Val.**
- **2º : Local structures which include, folds, turns, ∝-helices and β -sheets held in place by hydrogen bonds.**
- **3º : *3-D* arrangement of all atoms in a single polypeptide chain.**
- **4º : Arrangement of polypeptide chains into a functional protein, eg. hemoglobin.**

Different Protein Types -

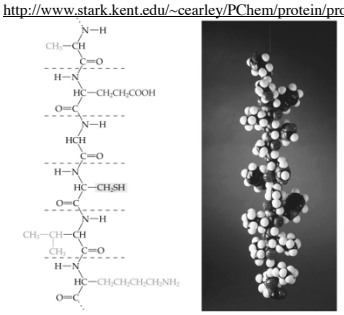
- **Enzymes: *Glutamine synthetase* - 12 subunits of 468 residues each; total mol. wt. = 600,000 daltons**
- **Regulatory proteins: *Insulin* - α -alpha chain of 21 residues, β - beta chain of 30 residues; total mol. wt. of 5,733 amu**
- **Structural proteins: *Collagen***

  ***Connectin proteins*, β - MW of 2.1 million g/mol; length = 1000 nm; can stretch to 3000 nm.**
- **Transport proteins: *Hemoglobin***
- **Contractile proteins: *Actin, Myosin***
- **Specialized proteins: *Antifreeze in fish***

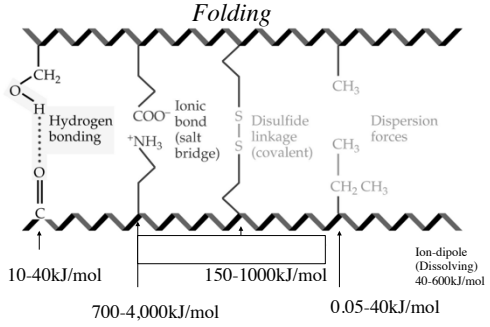
(A gene was first defined as: one piece of DNA that codes for one protein. The definition is being expanded beyond proteins to include certain types of RNA.)

Proteins: Size, Shape & Self Assembly

http://www.stark.kent.edu/~cearley/PChem/protein/protein.htm



Protein Shape: Forces, Bonds, Self Assembly, Folding



Protein Structure

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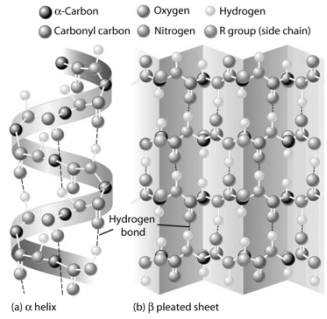
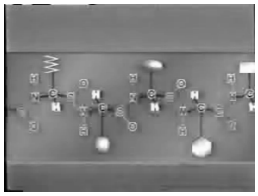


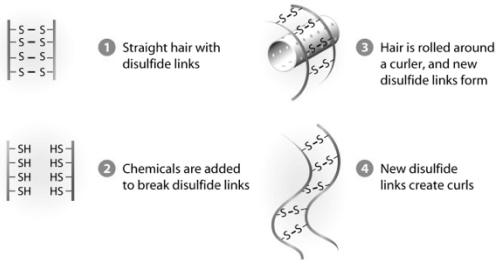
Hair: α-Helix

Annenberg World of Chemistry

#23 Proteins : http://www.learner.org/resources/series61.html



Hair: α-Helix

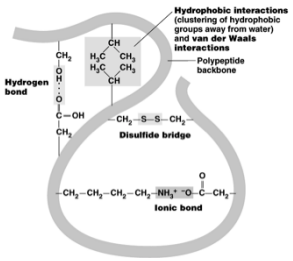


Silk: β-Sheets

Protein Structure

- **1º : The linear sequence of amino acids and disulfide bonds eg. ARDV:Ala-Arg-Asp-Val.**
- **2º : Local structures which include, folds, turns, ∝-helices and β -sheets held in place by hydrogen bonds.**
- **3º : *3-D* arrangement of all atoms in a single polypeptide chain.**
- **4º : Arrangement of polypeptide chains into a functional protein, eg. hemoglobin.**

- ***Tertiary structure* is determined by the interactions among and between R groups and the polypeptide backbone.**



- **While these three interactions are relatively weak, disulfide bridges, strong covalent bonds between the sulfhydryl groups (SH) of cysteine monomers, stabilize the structure.**

Protein Structure

- **1º : The linear sequence of amino acids and disulfide bonds eg. ARDV:Ala-Arg-Asp-Val.**
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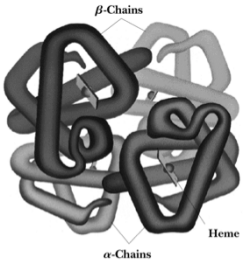
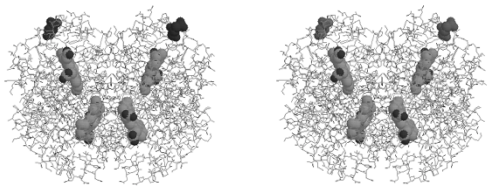
The quaternary structure of hemoglobin, Hb

(A tetramer)



Hb: two alpha units of 141 residues, 2 beta units of 146

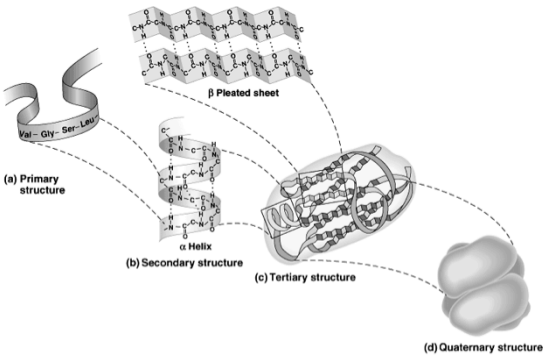
Normal hemoglobin vs sickle cell hemoglobin



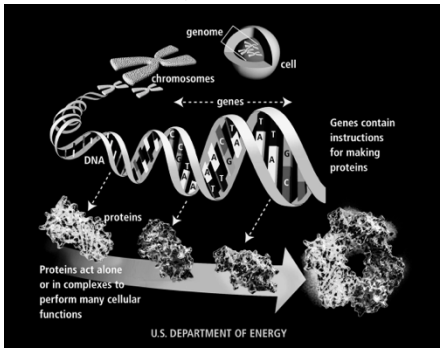
Valine replaces Glutamate

http://chemconnections.org/Presentations/Columbia/slide8-3.html

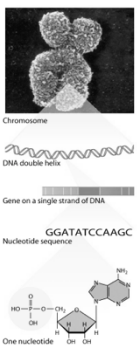
Summary

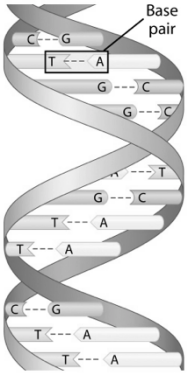


Globular Proteins: Enzymes / Genomic Control: DNA



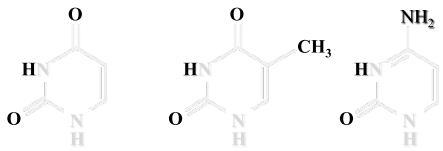
Genomic Control: DNA





Important Pyrimidine Amines

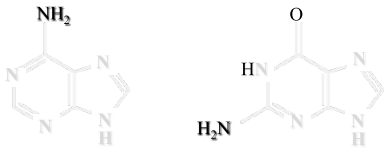
- Pyrimidines that occur in DNA are cytosine and thymine. Cytosine and uracil are the pyrimidines in RNA.



Uracil Thymine Cytosine

Important Purine Amines

- Adenine and guanine are the principal purines of both DNA and RNA.



Adenine **Guanine**

Globular Proteins: Enzymes

Antibodies

Epigenetic,
Prolific Immunoproteins

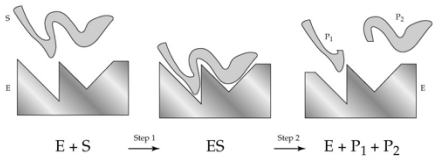
Human's total ~ 100 x 10 ^{6} immunoproteins

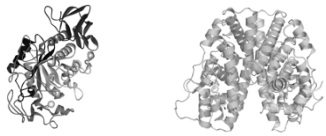
Combinatorial syntheses from libraries of 250, 10, and 6 possible contributors

Human Genome ~22,000 - 23,000 DNA encoded proteins

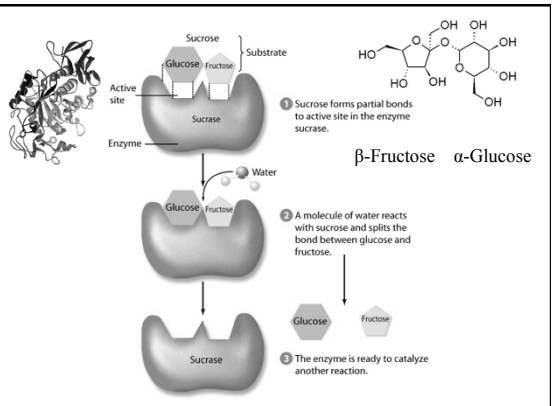
Globular Proteins: Enzymes

Enzymes / Substrates / Docking





Enzyme: α-amylase **Enzyme: ER-α**



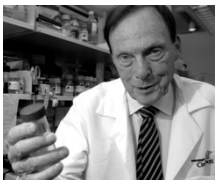
Enzymes: Inhibitors & Effectors

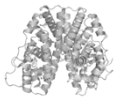
Michaelis-Minton Kinetics

$$E + S \rightleftharpoons [ES] \longrightarrow E + Product$$

- **E = Enzyme; S = Substrate**
- **Enzyme Activity is reduced by inhibitors.**
- **Four types of inhibitors:**
  - ***Reversible, Irreversible, Competitive, Non-competitive***
- **Equilibrium Constant & Free Energy**
  - ***$K_{[ES]eq} = 10^{-2}$ to 10^{-6} ; Free Energies -3 to -12 kcal/mol***
  - ***vs. covalent bonds -50 to -110 kcal/mol***
- **Enzyme Activity is increased by effectors.**
- ***Small molecules and proteins which bind to allosteric sites and increase the binding at the active site by lowering the Free Energy***

Elwood V. Jensen (1920-2012)
Estrogen & Breast Cancer





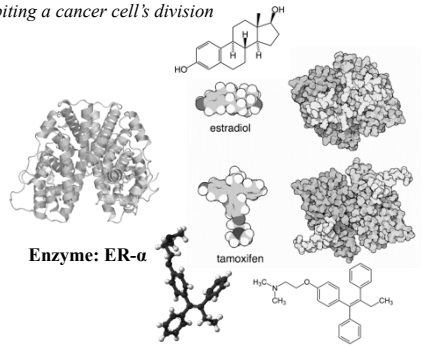
Enzyme: ER-α

Using radiolabeled markers, Dr. Jensen discovered that estrogen (steroid based hormones) bind to a specific receptor protein, ER, in about 30% of breast cancer cells. In those cancers that are ER positive, inhibition of estrogen stops cell growth.

What type of enzyme inhibition could best stop the multiplication of breast cancer cells?

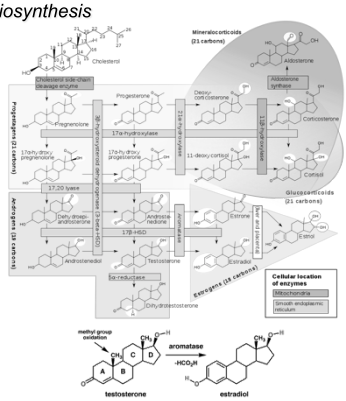
Enzyme Inhibition: Estrogen & Breast Cancer

Inhibiting a cancer cell's division

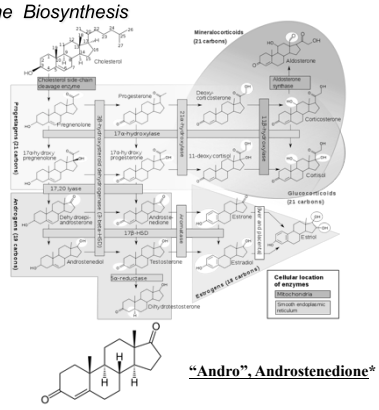


Enzyme: ER-α

Estrogen Biosynthesis



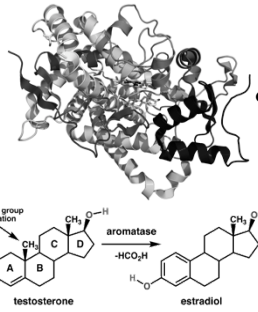
Testosterone Biosynthesis



"Andro", Androstenedione*

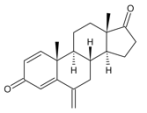
Enzyme Inhibition: Estrogen & Breast Cancer

Inhibiting a cancer cell's division

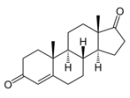


Cytochrome p450

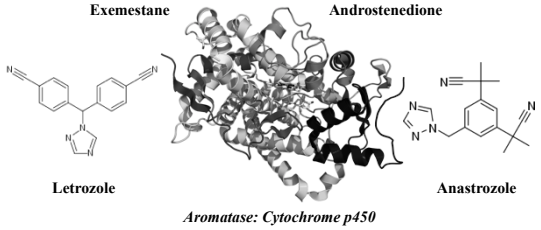
Enzyme Inhibition *Inhibiting a cancer cell's division*



Exemestane



Androstenedione



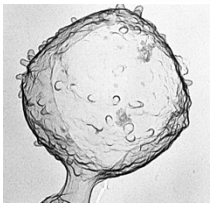
Letrozole **Anastrozole**

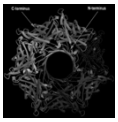
Aromatase: Cytochrome p450

Mechanical Proteins

Pathogens & Cell Invasion

http://chemconnections.org/organic/chem226/Announcements-info/Staph-infection/infection.html





Streptococcus pyogenes
96,000 x
Vincent A. Fischetti Ph.D., Rockefeller University

Cells:

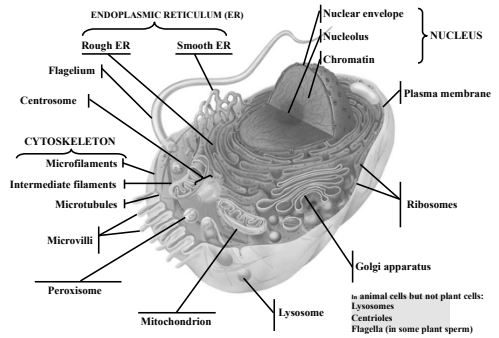
Division / Replication / Sexual Reproduction

Equilibrium: *Balance / Homeostasis*

Imbalance: *Cancer*

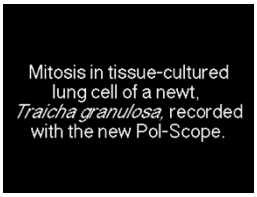
Chemical Therapy (Chemotherapy)

Animal Cell

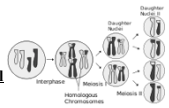


Cell Propagation

- **Mitosis (Newt lung cell)**
- **http://www.bio.davidson.edu/misc/movies/mitosisnewt.mov**



PBS/Nova: mitosis vs. meiosis (*sexual reproduction*)
http://www.pbs.org/wgbh/nova/miracle/divi_flash.html



Definitions:

Homeostasis – ***maintenance of stable equilibria: in part through the critical replacement of dead cells with new cells***

Apoptosis – ***programmed cell death with cell disposal that does not harm the organism***

Neoplasm – ***abnormal new cell growth: excessive and uncontrolled compared to normal cells***

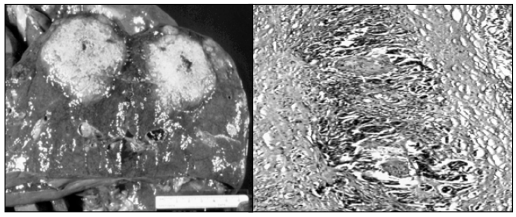
Tumor - ***a non-specific term meaning lump or mass of tissue. Often synonymous for neoplasm***

Cancer - ***any malignant neoplasm or tumor***

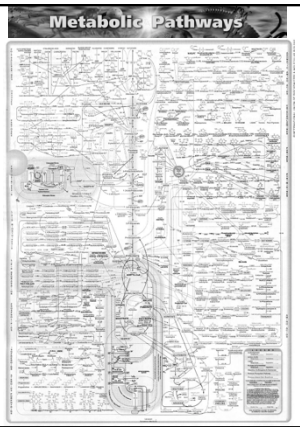
Metastasis - ***discontinuous spread of a malignant neoplasm to distant sites***

Neoplasia: Defying Cell Death

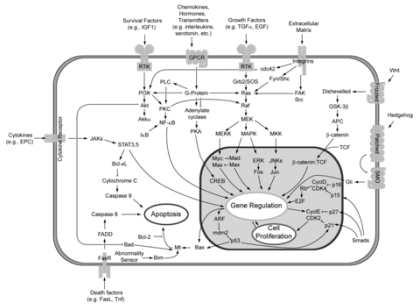
Cells characterized by abnormal growth & dysfunctional regulatory mechanisms.
(Disrupted homeostasis)



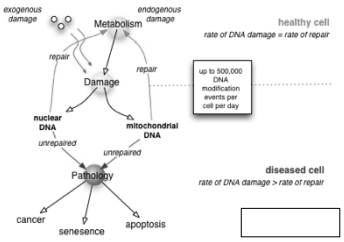
Human Metabolism



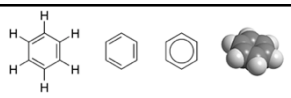
Apoptosis Metabolic Pathway



DNA Repair / Cell Health

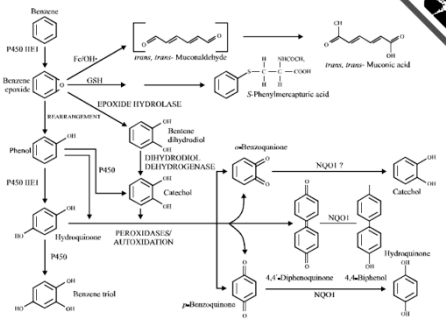


Benzene:

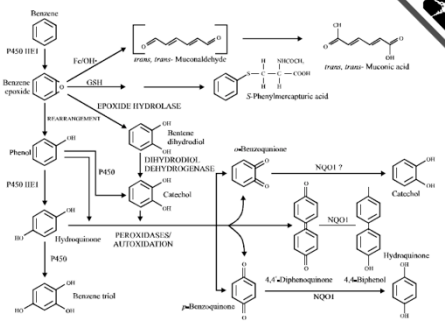


- **Benzene is classified as a Group A, human carcinogen by the EPA.**
- **Increased incidence of leukemia has been observed in humans occupationally exposed to benzene.**
- **Chronic inhalation has caused various blood disorders, including reduced red blood cell count and aplastic anemia.**
- **Reproductive effects have been reported for women exposed to high levels by inhalation.**
- **Adverse effects on the developing fetus have been observed in animal tests.**

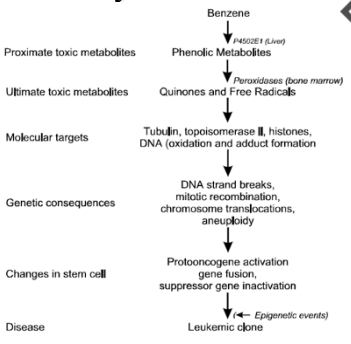
Benzene: Toxic Metabolites



Benzene: Toxic Metabolites



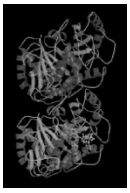
Benzene: Toxicity

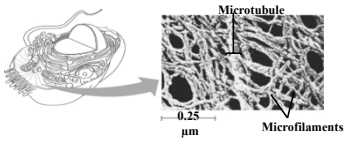


Inhibiting a cancer cell's division

Microtubules / Tubulin

- **The cytoskeleton of a cell consists of a network of fibers extending throughout the cytoplasm**

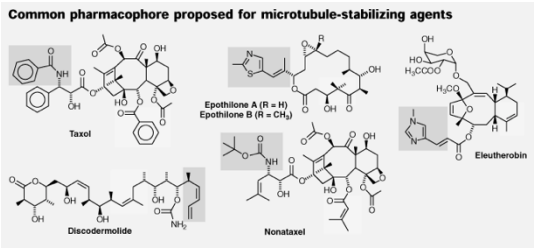




Inhibiting a cancer cell's division

Microtubules / Tubulin

- **Mitotic Inhibitors:**



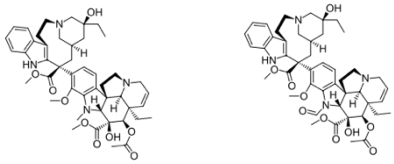
What are the chemical functions and their respective names in the structures? How could the functions be determined experimentally? How could the entire 3-d structure be identified?

Inhibiting a cancer cell's division

Microtubules / Tubulin

- **Mitotic Inhibitors:**

Vinca alkaloids: vinblastine, vincristine, et. al.

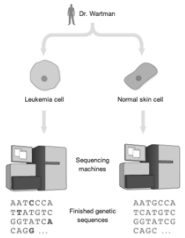


What are the chemical functions in the two structures?

Finding targets in a cancer cell's division

Genomic Screening

- *Comparing the DNA sequence of a patient's (Dr. Waterman's) normal cell to the cancerous cell:*

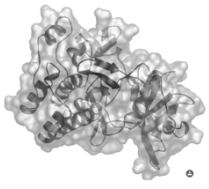


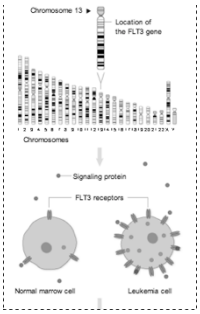
What is the genetic difference in the DNA sequences?

Inhibiting a cancer cell's division

Inhibit the identified FLT3 gene's protein

- FLT3 protein:



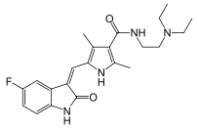


Inhibiting a cancer cell's division

Enzyme inhibition of the FLT3 gene's protein

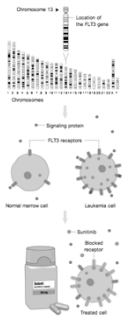
- *Blocking the receptors*

Sunitinib (*Sutent*)



N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide

What are the chemical functions in Sunitinib?

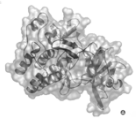


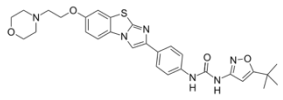
~$200/ pill (~$50,000/ yr)

Inhibiting a cancer cell's division

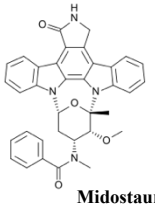
Enzyme inhibition of FLT3

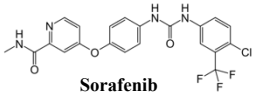
- *Blockers of FLT3 receptors*





Quizartinib





Sorafenib

Midostaurin

What are the chemical functions and stereochemical centers in the FLT3 blockers above?
How can these structures be verified?

Do you want to know if you carry a cancer gene?

- *Accessing/purchasing your DNA sequence:*
https://www.23andme.com

http://well.blogs.nytimes.com/2012/12/31/carrying-a-cancer-gene-unsure-i-want-to-know/?ref=health?src=dayp