Magic Bullets:

Drugs and their Delivery

Drugs and their Delivery

> Matter and the Making of Things

> Cancer: Drugs and Toxins

> Drug Delivery: Targeting, Imaging, Release

Drugs and their Delivery

- Matter and the Making of Things
- Cancer: Drugs and Toxins
- Drug Delivery: Targeting, Imaging, Release

> Matter and the Making of Things

- Understanding nature: theories of matter, elements
- Copying nature
- Making brand new things (chance vs design)

- Aristotle/Ancient Greeks: earth, air, fire, water; atomistic

•Theories of matter: old

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- Alchemy: spiritual/magical and technological/practical

    idea: all metals same; degrees of purity/maturation

    goal: hasten maturation; catalyst/Philosopher's stone

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- Bacon, natural philosophers, 17th c

  old: vitalist notion: matter spirits; living matter special

  new: study natural laws separate from spiritual/magic
  experimental scientific communities
  knowledge shared not secret

  goals: "Nature to be commanded must be obeyed"
  dominate, improve upon nature
  wish list: Magnalia Naturae (natural wonders)

•Theories of matter: new

- Isolation, identification of fundamental particles

elements (vs compounds): 18th: e.g. Lavoisier, O

atoms: 19th: theory, wts, Dalton; 20th: experiment

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- Structure of matter

  molecular shape: 19th, valency, stereochemistry;
  (M's: 20th variable valency)

  subatomic particles: protons, neutrons, electrons

  quantum theory: energies, orbitals, probabilities,
  spectroscopy (session 1)

•Copying nature

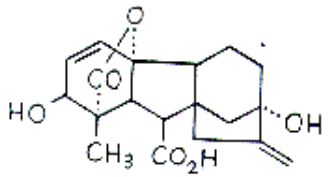
- Isolation, characterization of natural products

  determine active agents

- Duplicating in laboratory:

  by synthetic pathways:

  E.J. Corey, Nobel Prize in Chemistry 1990



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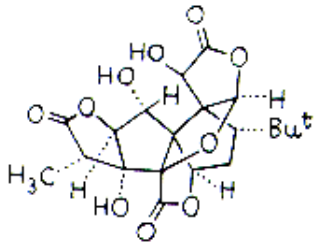

2

gibberillic acid — plant hormone

ginkgolide — chinese medicine: circulation

by natural pathway: molecular biology, protein engineering

*structures from www.nobel.se.

•Making brand new things

- Elaboration, improvement, optimization of nature

sweeteners: sucrose vs saccharin, nutrasweet

fats/oils: natural vs olestra

soaps: fatty acids vs detergents

drugs: natural products vs synthetic drugs; SARs

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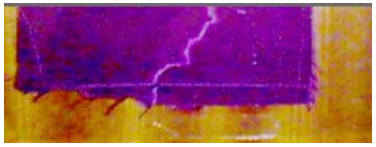
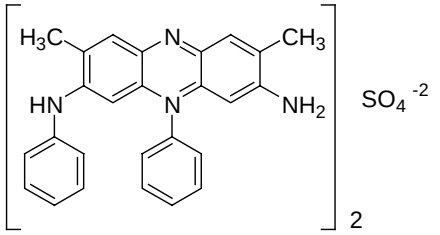


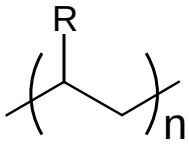


  dyes: 1856, Perkins mauve, aniline dye
  trying to make quinine, first synthetic dye
  start of chemical industry, retired age 36

  polymers: plastics, molecular biology (DNA, RNA, proteins)
  aggregates/colloid (glue) vs giant molecules
  early egs: vulcanized rubber, celluloid, Bakelite

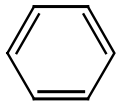
-Some important synthetic polymers

Polyolefins



poly(vinyl chloride) (PVC)
R = Cl (1927)

polystyrene (PS)
R = phenyl (1930)



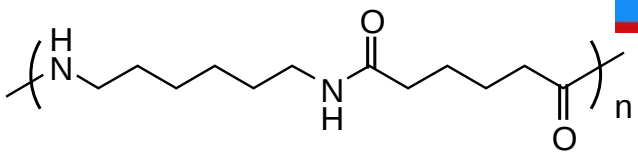
poly(methyl methacrylate) (PMMA)
R = -C(O)OCH_3 (1938)

polyethylene (PE)
R = H (1941)

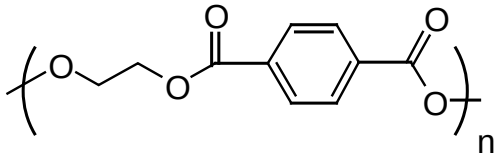
polypropylene (PP)
R = CH_3 (1951)

Condensation polymers

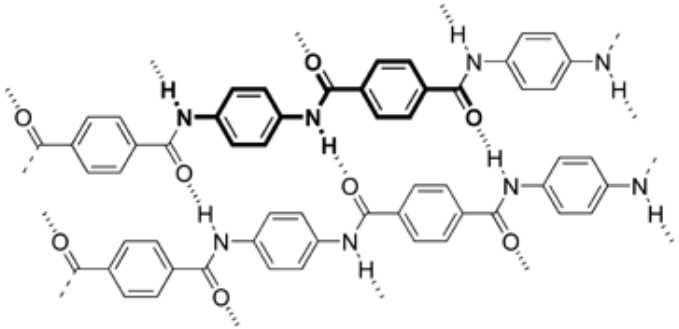
Nylon 6,6 (1938)



Dacron polyester
poly(ethylene teraphthalate) (PET) (1941)



Kevlar (1971)

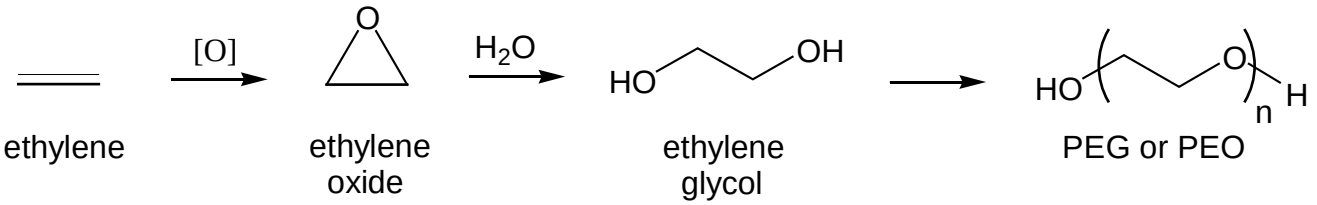


Stephanie Kwolek, Dupont

-Biocompatible/biodegradable

Biocompatible polymers from non-renewable resources

Poly(ethylene glycol) (PEG) or polyethylene oxide (PEO)

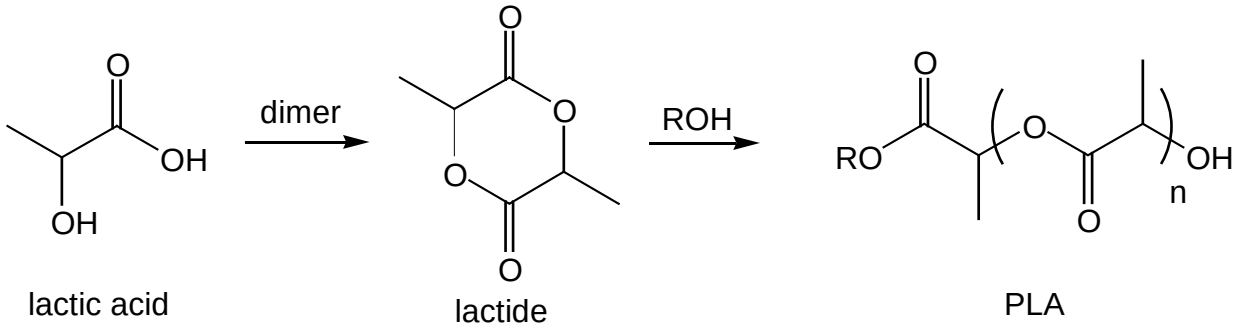


Polymers/plastics from renewable resources (biopolymers)

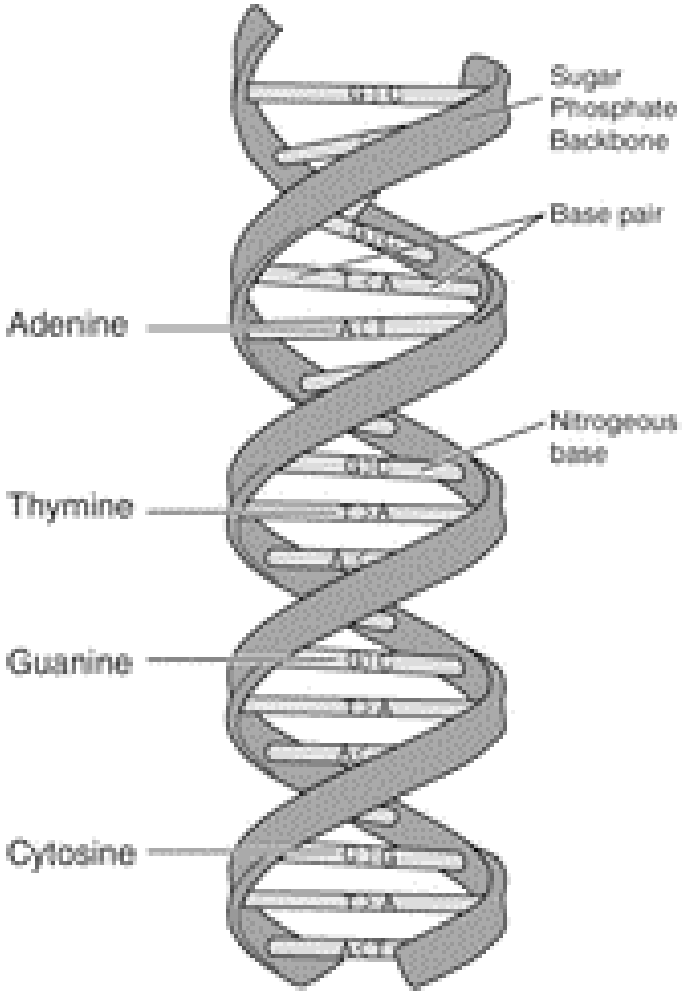
Poly(lactic acid) (PLA) or Polylactide

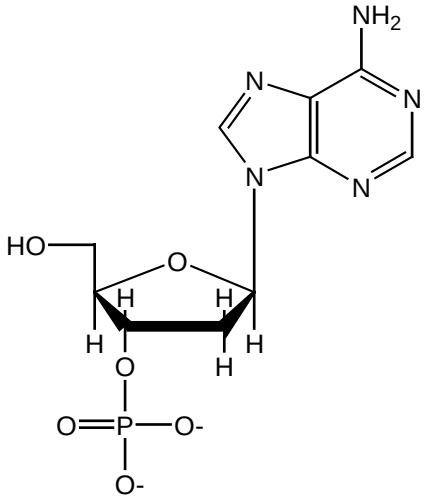
PLA is made from lactic acid, via dextrose, and cornstarch

Lactic acid is made from dextrose by fermentation.

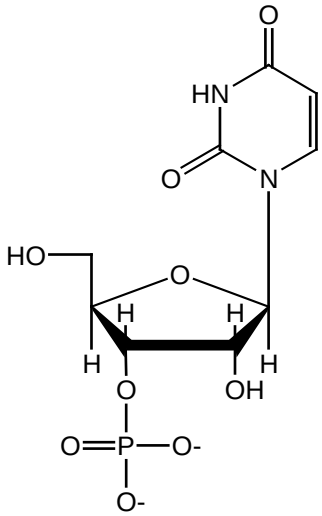


-Natural polymers: Nucleic Acids





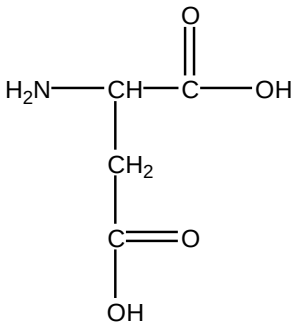
DNA nucleotide:
adenine (purine base)



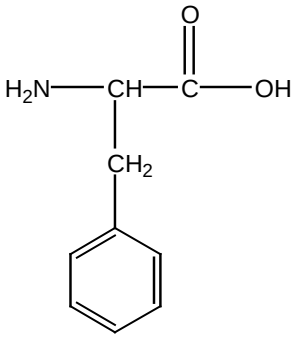
RNA nucleotide:
uracil (pyrimidine base)

-Natural polymers: proteins

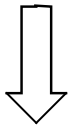
Amino Acids and Peptides



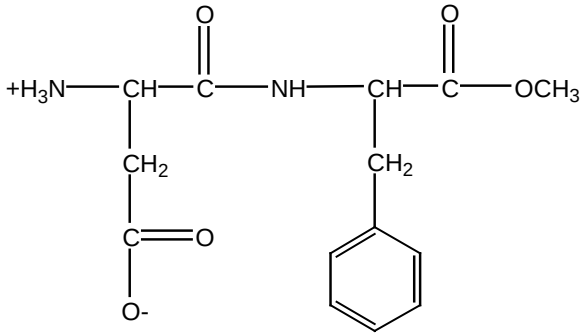
Aspartic acid



Phenylalanine

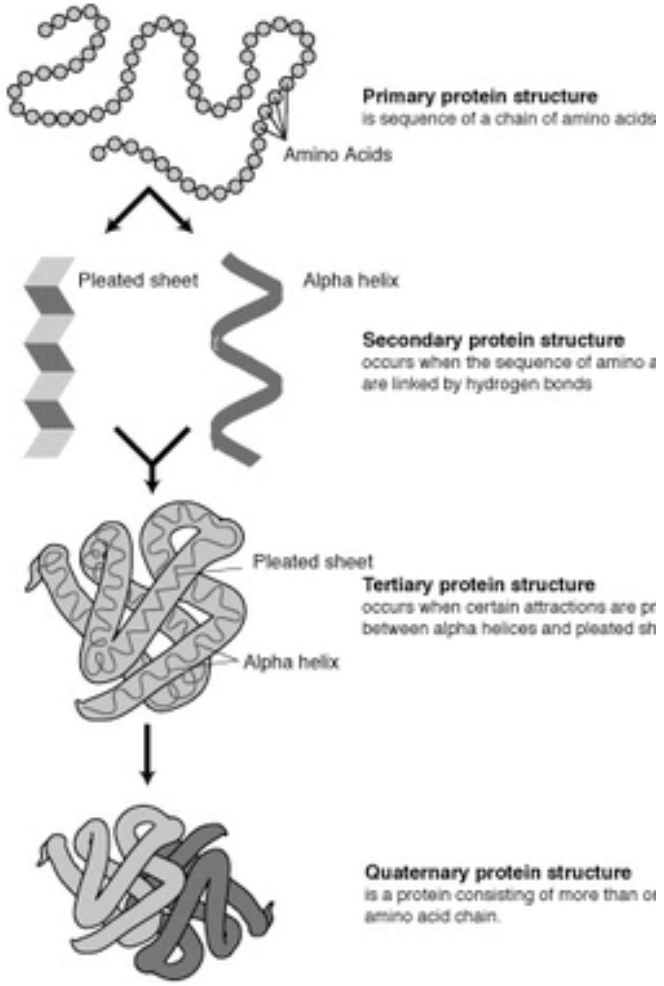


+ methanol

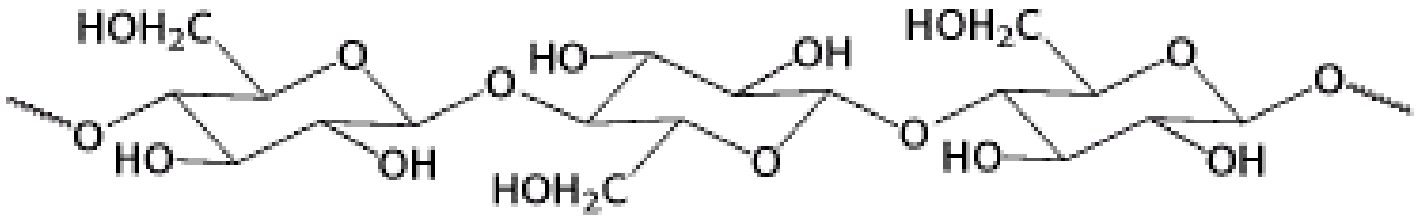


Dipeptide: Aspartame or Nutrasweet

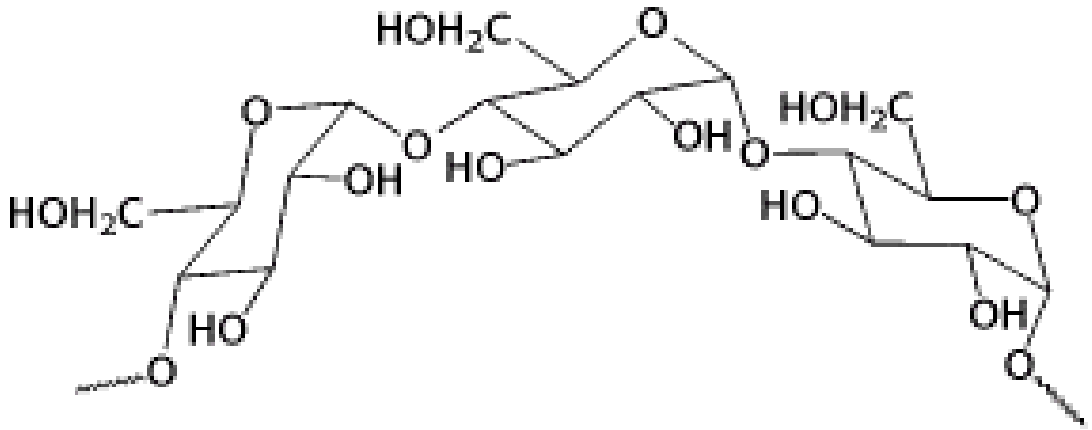
Protein Structure



-Natural polymers: carbohydrates

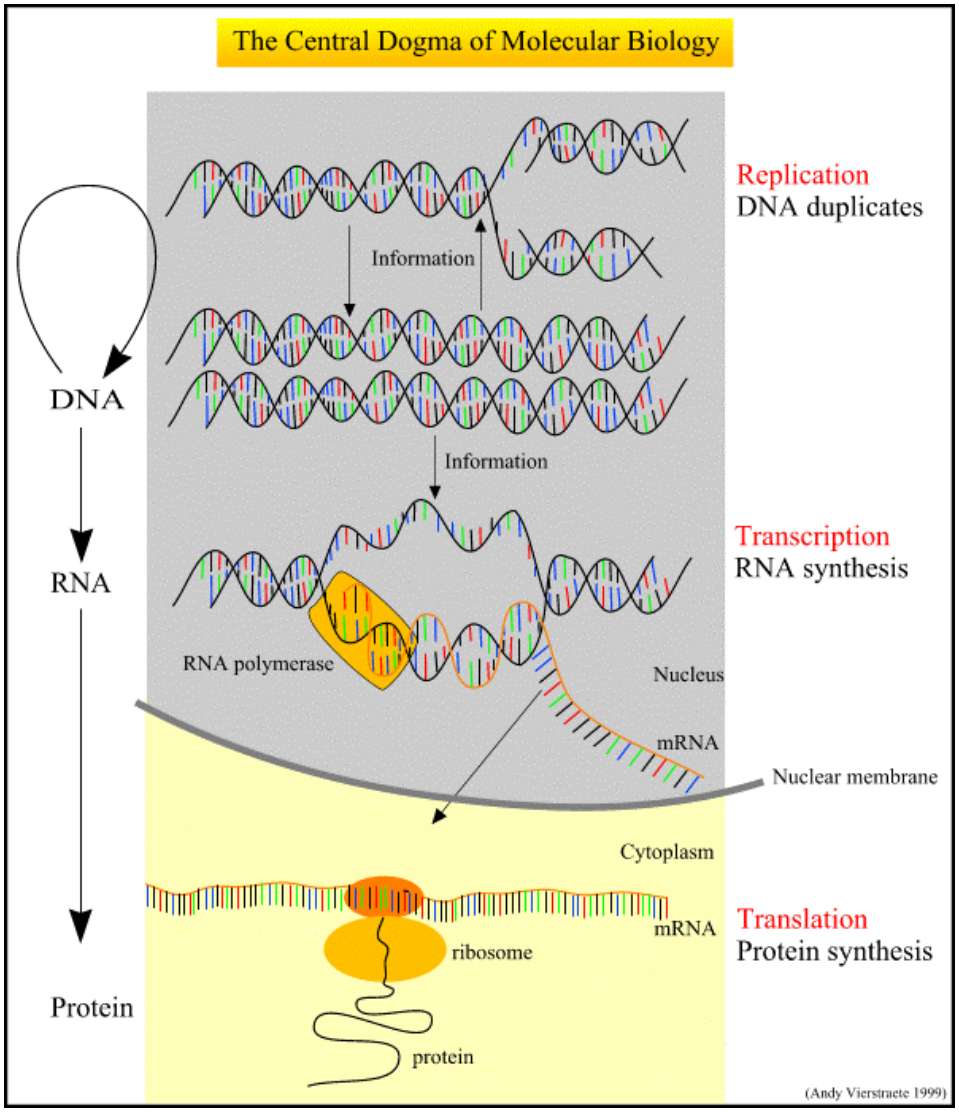


Cellulose
(β-1,4 linkages)



Starch and Glycogen
(α-1,4 linkages)

-Central dogma of molecular biology



Many natural polymers involved in pathway advanced by Crick, 1950s.

Plus post translational modification, carbohydrates on cell surfaces, and many complex signaling and regulatory pathways too

•Other important concepts

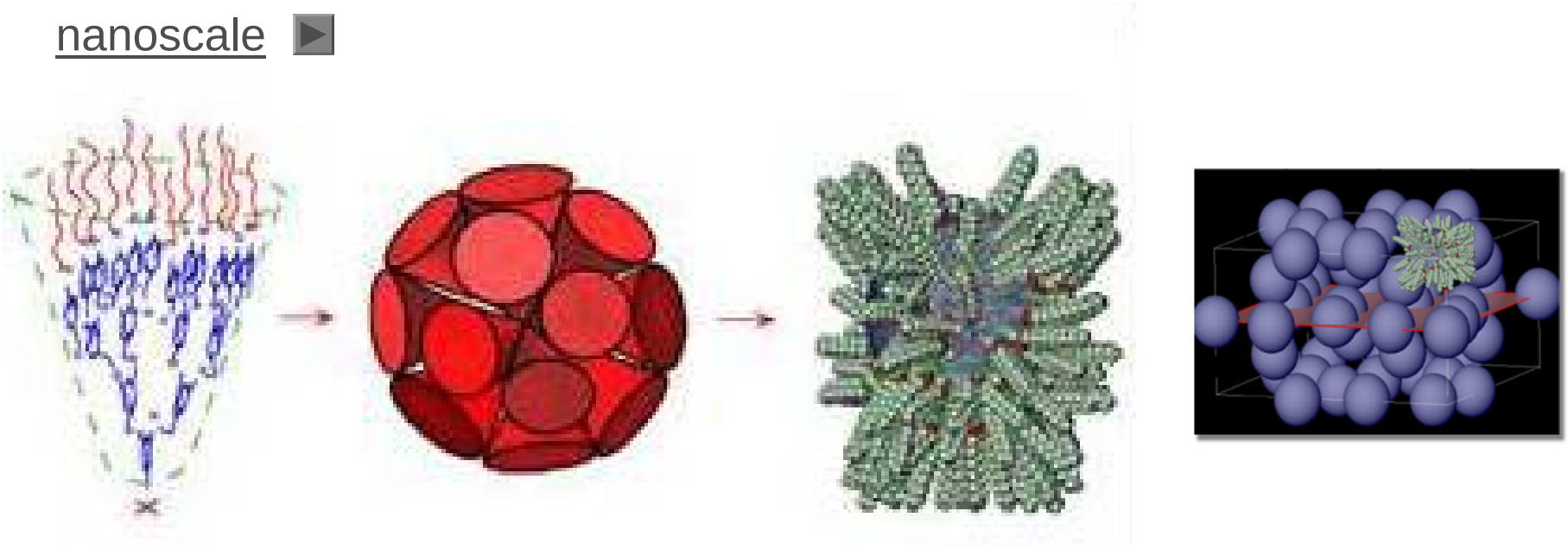
- Molecular recognition
  - self assembly
  - receptors and ligands
- Hierarchical structure
- Smart materials/stimuli responsive materials

-Molecular recognition

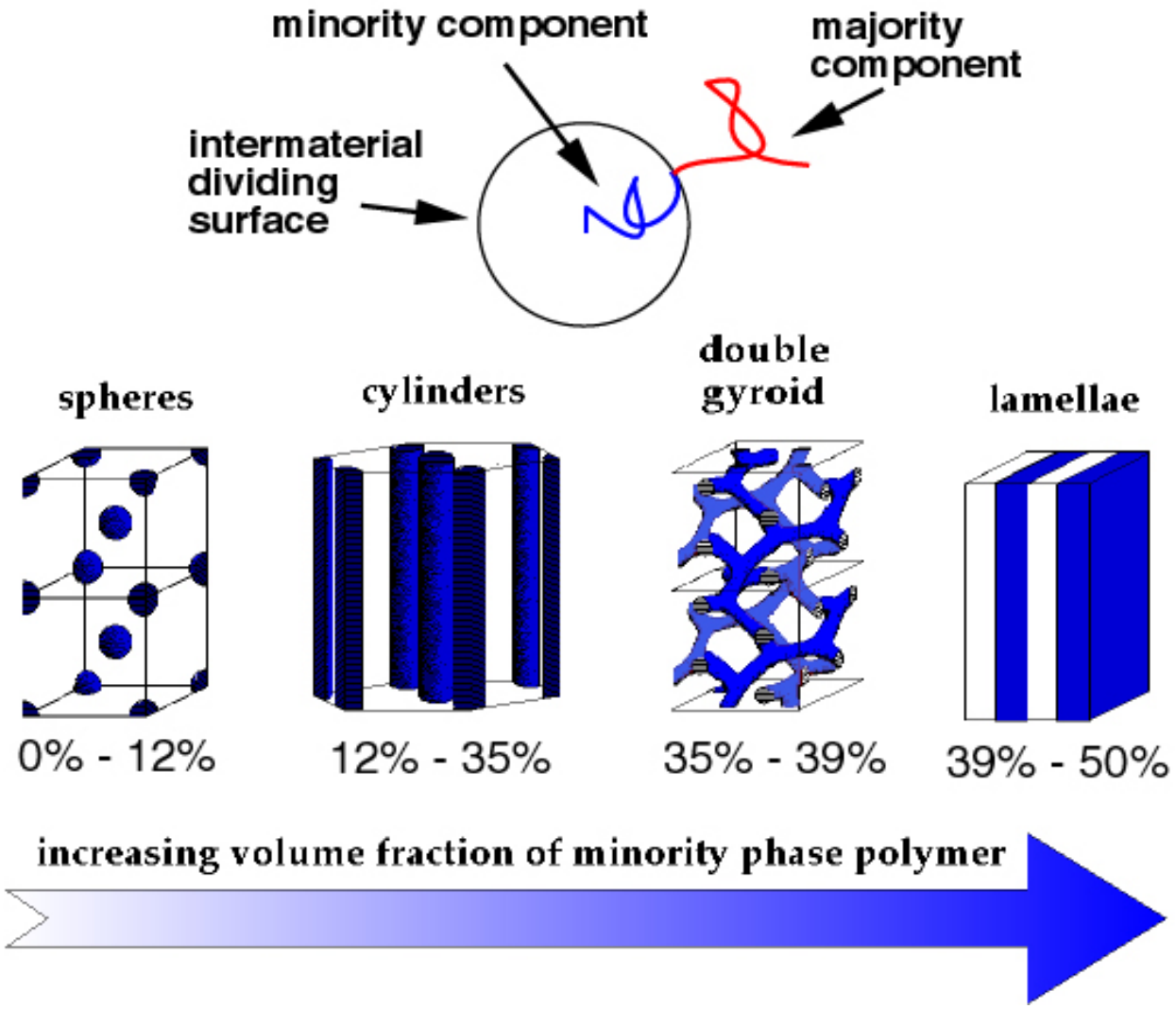
- Like with like: self assembly
- Like with unlike: receptor/ligand; host/guest (charge/shape/energy match)

microscale

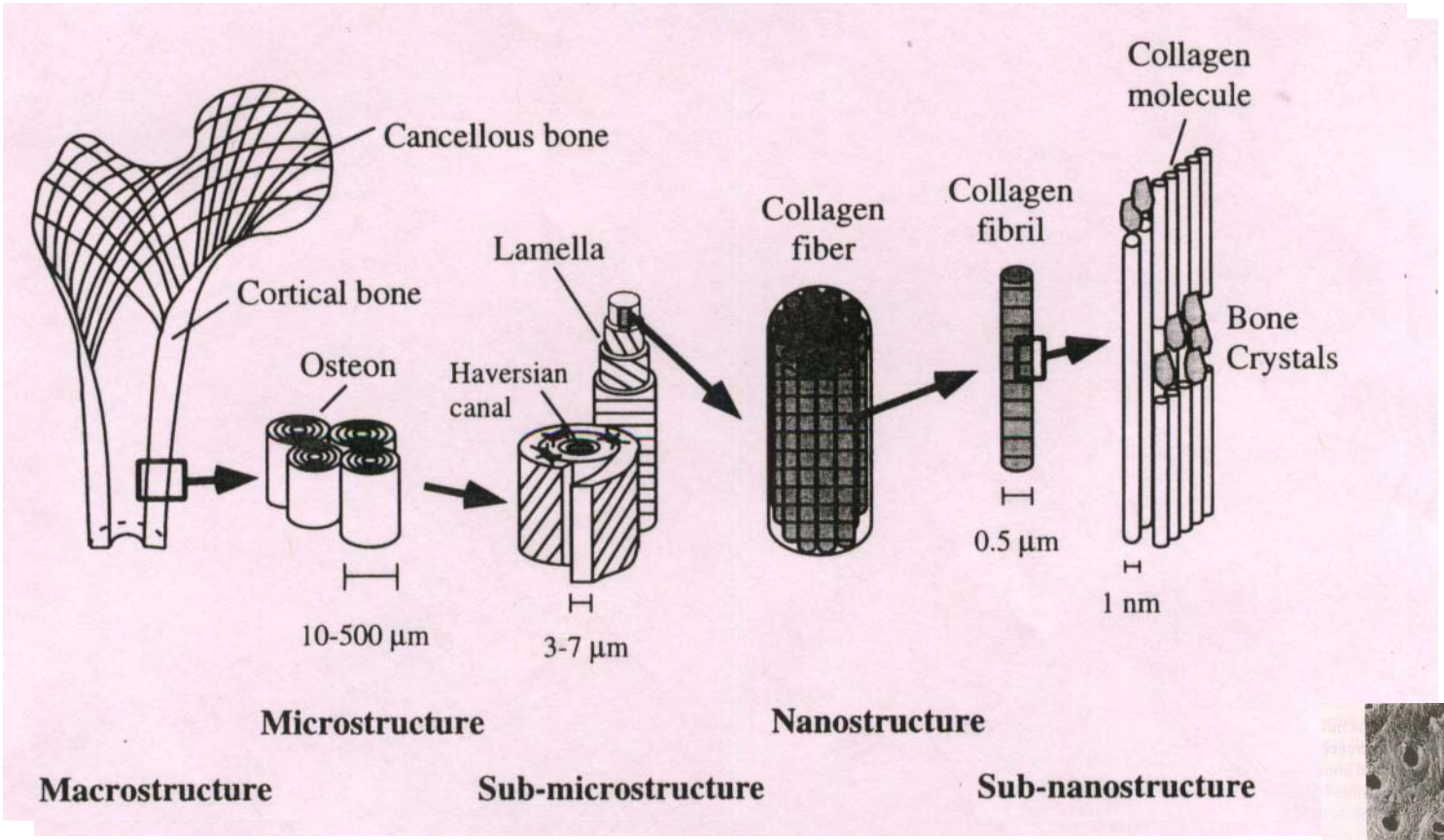
nanoscale

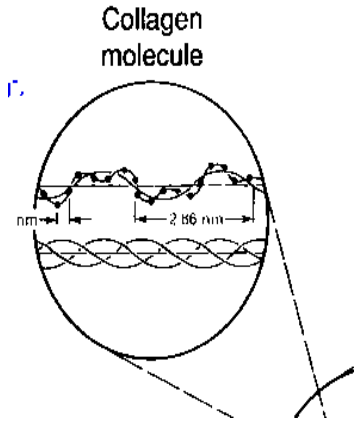


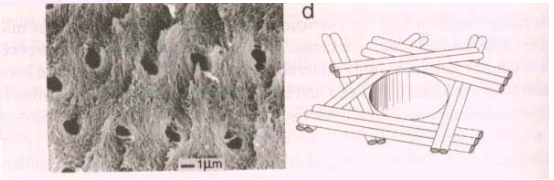
-Block copolymer nano self-assembly

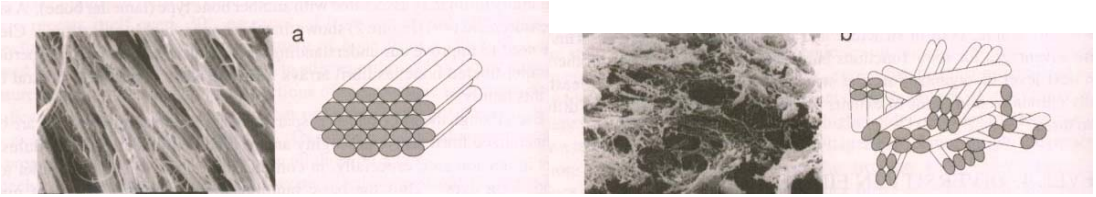


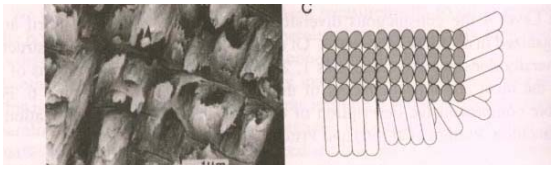
-Hierarchical structure: bone











-Smart/responsive materials

- Stimuli responsive materials: fluid to solid with heating, magnetic field

- Lotus effect: bio-inspired water and dirt repellant surfaces

•Chemical ethics: good or bad?

Things to think about:

- Natural/synthetic: what's the difference?
- Organic/inorganic: a clear distinction?
- Biocompatible/biodegradable
- Biopolymers/biomaterials
- The matter lifecycle
- Can matter be "chemical-free?"
- Why do chemicals get a bad rap?

Drugs and their Delivery

> Matter and the Making of Things

> Cancer: Drugs and Toxins

> Drug Delivery: Targeting, Imaging, Release

> Cancer: Drugs and Toxins

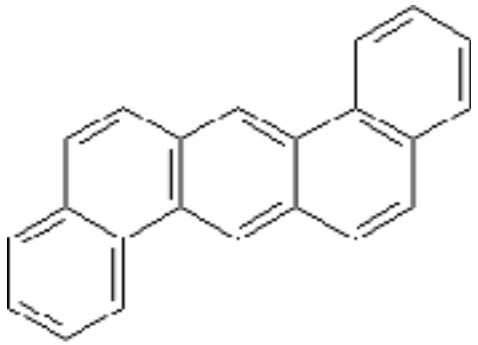
- Carcinogens: chemicals cause cancer
- Cancer biology
- The patient: a human perspective
- Chemotherapy: chemicals treat cancer

•Carcinogens: chemicals cause cancer

First example: polycyclic aromatic hydrocarbons (PAHs)

- Pott, 1775: high incidence of cancer in chimney sweeps
  early epidemiological study; public health issue
- Yamigiwa, 1910: coal tar induces cancer in mice
- 1930s: dibenzanthracene 1st pure cpd linked to cancer
- Not PAHs but arene oxide metabolite is toxic.
- Intercalate, alkylate DNA. Interfere with normal function.

Magic Bullets: Chemistry vs Cancer



1,2:5,6-dibenzanthracene

•Other examples: causes of cancer

- Other environmental: 1700s Hill, linked snuff and nasal tumors; 1964 smoking and lung cancer
- Viruses: Rous sarcoma virus tumor extracts, HPV
- Radiation: mutations from sunlight, radioactive substances Xrays
- ACS list of known carcinogens 

Note: Many causes are also cancer treatments!

•Cancer biology

"Six diabolical super powers of cancer"

1. Growth even in the absence of normal "go" signals.
2. Growth despite "stop" commands issued by neighboring cells.
3. Evasion of built-in autodestruct mechanisms.
4. Ability to stimulate blood vessel construction.
5. Effective immortality.
6. Power to invade other tissues and spread to other organs.

Note: Many drugs are aimed at disrupting unique features of these processes.

From: Gibbs, W.W. Untangling the Roots of Cancer, *Scientific American*, 2003.

•Who gets cancer?

- •1 million people get cancer each year
- • Approximately 1 in every 2 men and 1 in every 3 American women will have some type of during their lifetime
- • 77% of cancers are diagnosed in people 55 and older
- • Rate of cancer occurrence and likelihood of mortality varies among racial and ethnic groups
- • Risk factors: Diet, exercise, environment
- • Early detection is important!

From: “Who gets cancer?” www.cancer.org

•The patient: a human perspective 1

Dear All -

I promised an update today, but I am not sure what it is yet. I have recovered from the second surgery. The margins on that excision were cancer-free. I am feeling absolutely fine.

Now, the dilemma is in deciding how to proceed. The surgeon and the medical oncologist both recommend chemotherapy while recognizing that it carries risks. There is modest benefit (shift from 90% chance of no recurrence to 93% chance of no recurrence). Yet, there is a 1% chance of developing leukemia. There is risk of heart damage, but mostly for people with a pre-existing heart problem (not me). Plus, it will be uncomfortable (nausea, hair loss, fatigue, instant menopause, sleeplessness, weight gain), not to mention decreased cognitive function. I am apparently right on the borderline diagnosis (tumor size, type, and grade; age) of patients advised to get it and those not. I am scheduled to begin on Thursday and I can call and cancel or postpone if I wish. It is my decision. Once I begin, it would be four treatments each three weeks apart. They would be on Thursdays, and I should be able to limp through Friday, recover on the weekend, and be OK enough to work on Monday. Then, radiation for 2 months. Then, hormone drugs for 5-10 years....

Feeling a little overwhelmed tonight. I guess I'll be letting you know what I decide later. All your kind thoughts and gestures have been a great help to me and my family.

Thank you,

Mary

•The patient: a human perspective 2

Dear All -

After long conversations with nurse practitioners in the surgeon's office and in the oncologist's office, I feel better about the decision to go ahead with chemotherapy. Liquid poison starts flowing through my body this afternoon. "Death to cancer cells!"

I'll let you know how it feels soon.

Cheers,
Mary

•Kinds of therapy

- Local therapy: surgery to remove tumor, tissue, organ; radiation
- Systemic therapy: oral, IV
- Chemotherapy: can be local or systemic (usual course: 6 months, multiple treatments)

neoadjuvant therapy: before surgery, to shrink tumor
adjuvant therapy: chemotherapy after surgery, to kill hidden cancer cells that may have spread throughout the body
hormone therapy: e.g. anti-estrogen or anti-androgen agents
immunotherapy: cancer vaccines (cell, antigen, DNA, etc.)

www.cancer.org

•Chemotherapy: drug combinations

- Chemotherapy: usually drug combinations
- Some common drugs for breast cancer

  -cyclophosphamide

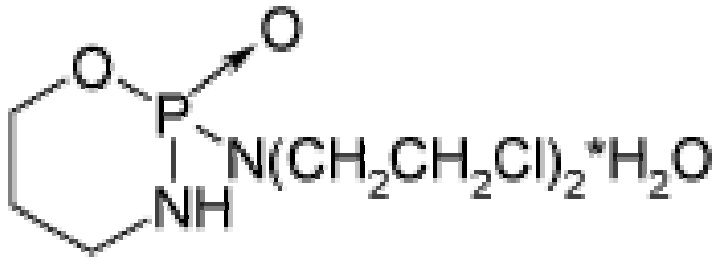
  -doxorubicin (adriamycin)

  -paclitaxel (taxol)

- Drugs often given in cycles, for example:
  4 cycles of doxorubicin and cyclophosphamide followed by
  4 cycles of paclitaxel

•Chemotherapy: cyclophosphamide

- Nitrogen mustard, related to mustard gas used in WWI
- First drug treatment for cancer
- Used to treat: breast and ovarian cancer, lymphoma, leukemias, neuroblastoma, retinoblastoma
- Mode of action: alkylating agent, stops cancer cell growth



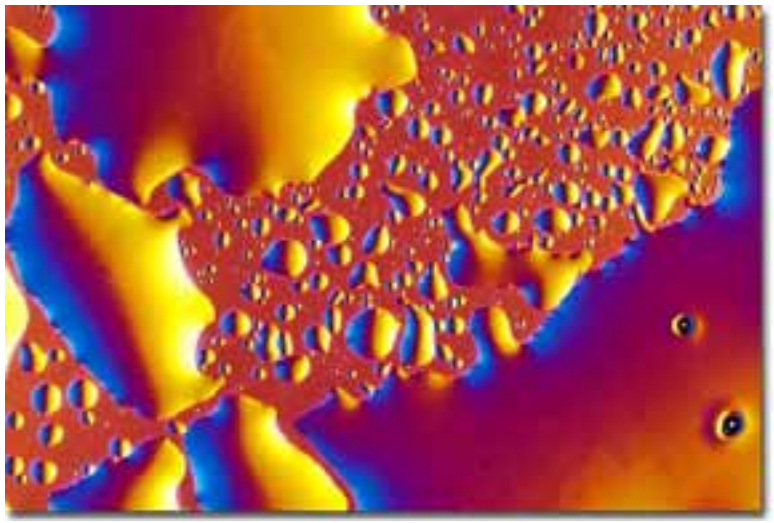
Especially targets:

-Rapidly dividing cancer cells
-Bone marrow cells such as developing blood cells
-Stimulated lymphocytes (in proliferation, antibody production)
-Fetal cells
-Hair follicle cells
-Intestinal cells

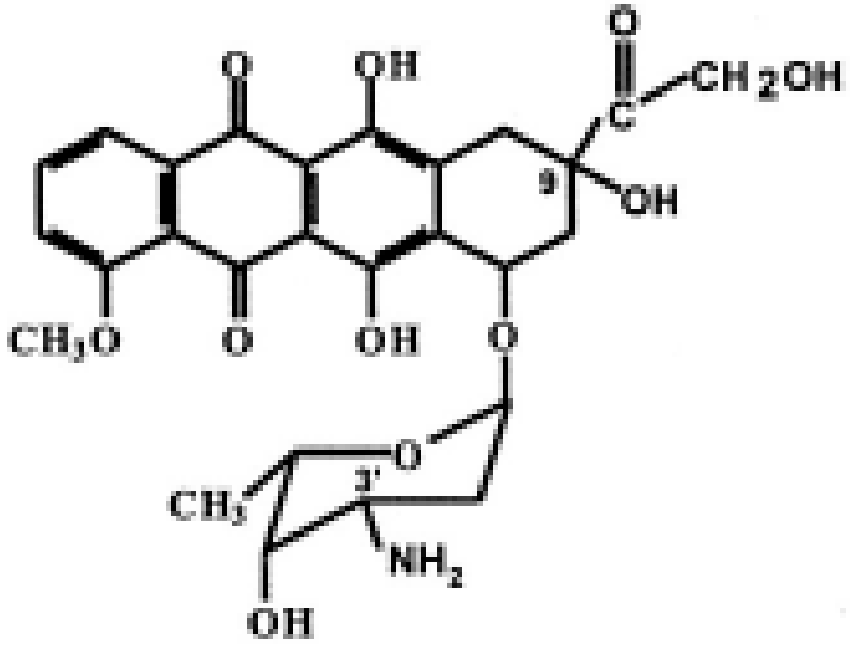
Note: Helps to explain side effects.

•Chemotherapy: doxorubicin

- Also called adriamycin, an anthracycline antitumor antibiotic.
- Used to treat: breast, ovarian, bladder, lung cancer, non-Hodgkin's lymphoma, multiple myeloma, acute leukemias
- Mode of action: binds to DNA, blocks topoisomerase II

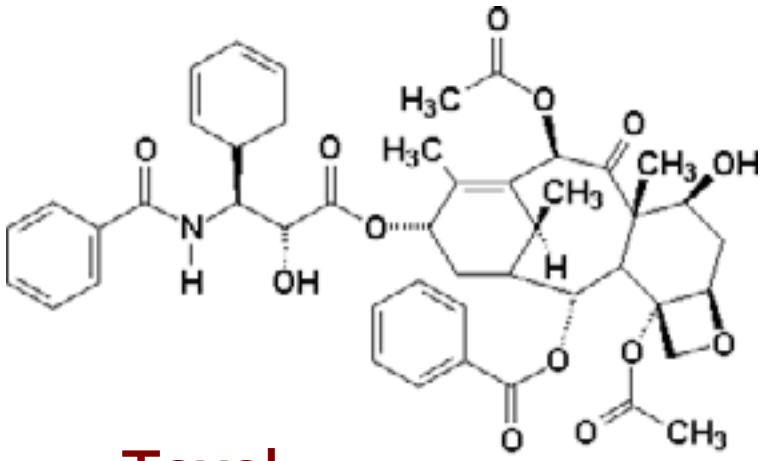


Adriamycin

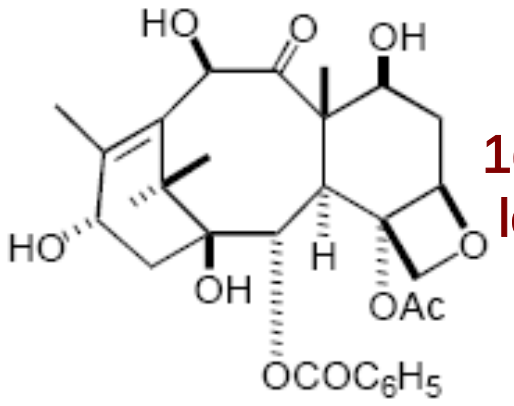


•Chemotherapy: paclitaxel (taxol)

- 1962: Extract from Pacific Yew tree exhibits antitumor activity
- 1967: Active agent isolated
- 1971: Structure elucidated
- 1980: New mode of action: induces microtubules; antimitotic
- Problem: six 100 yr old trees needed to treat one patient!
- Early 90s: shown to be effective against breast, ovarian cancer
- 1994: 1st total synthesis (Holton), many steps, not economical
- Discovery: precursors in renewable, European Yew needles, leaves



Taxol



10-deacetylbaccatin

1g/kg in leaves

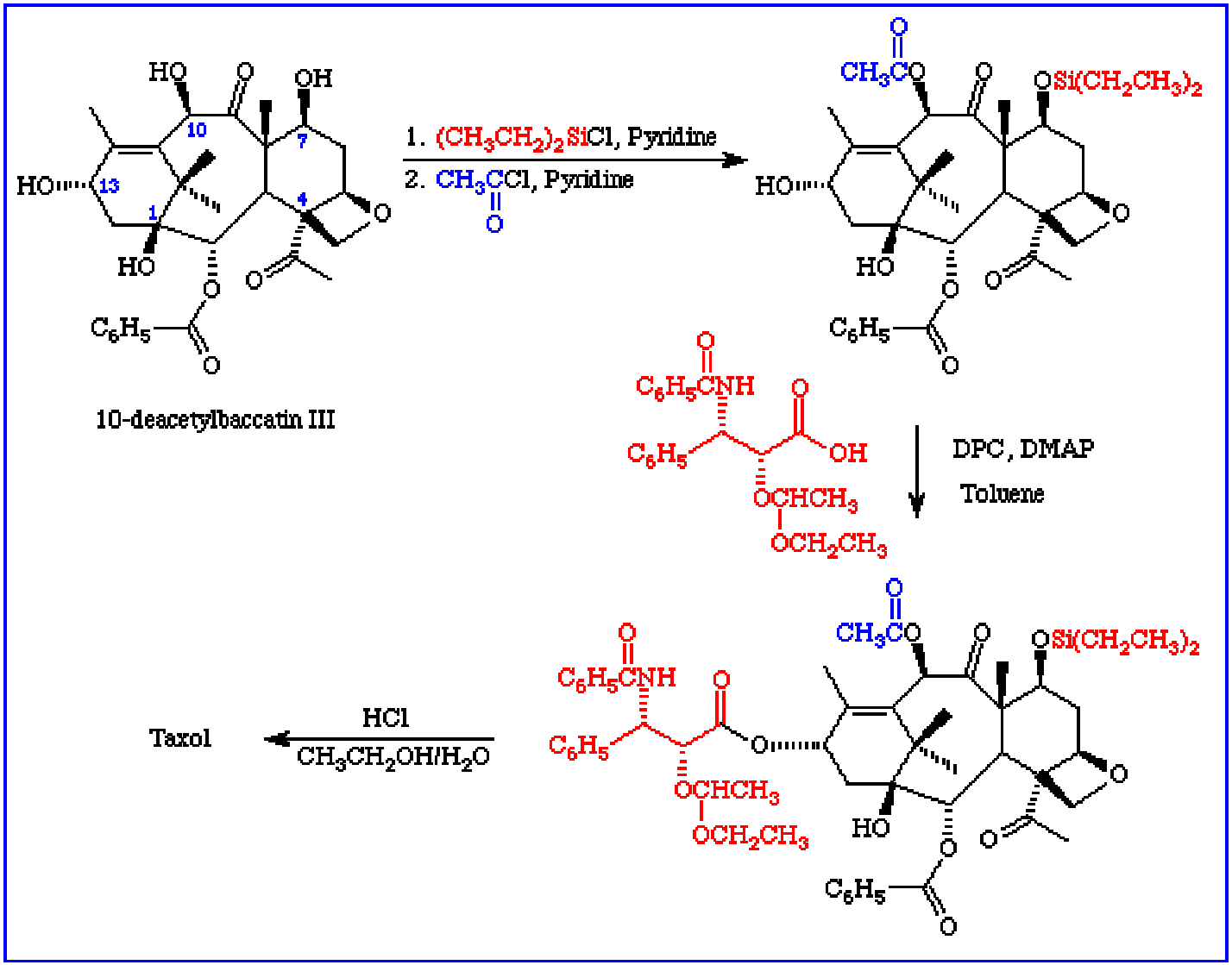
•Total synthesis of taxol

"First Total Synthesis of Taxol," Holton, R. A. et al
J. Am. Chem. Soc., 1994, *116*, 1597.

“Total Synthesis of Baccitin III and Taxol” Danishefsky et al
J. Am. Chem. Soc., 1996, 118, 2843.

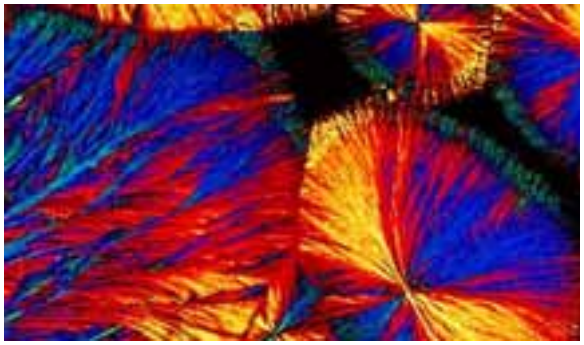
Many steps! Low yields. Not economically feasible.

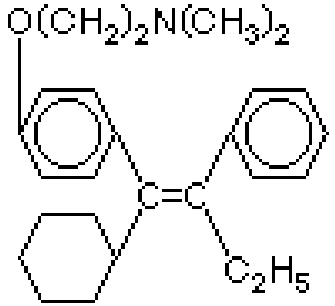
•Semi-synthesis of taxol



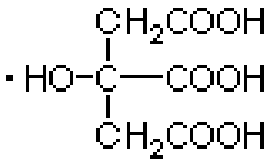
•Hormone therapy: tamoxifen

- 1950s: Emerged in search for anti-estrogen oral contraceptives
- 1970s: Commercially available
- Many breast cancers: estrogen mediated growth
- Mode of action: estrogen antagonist (inhibits function of)
- Fewer devastating side effects than other cancer chemotherapies
- Also used as a preventative treatment for those at high risk



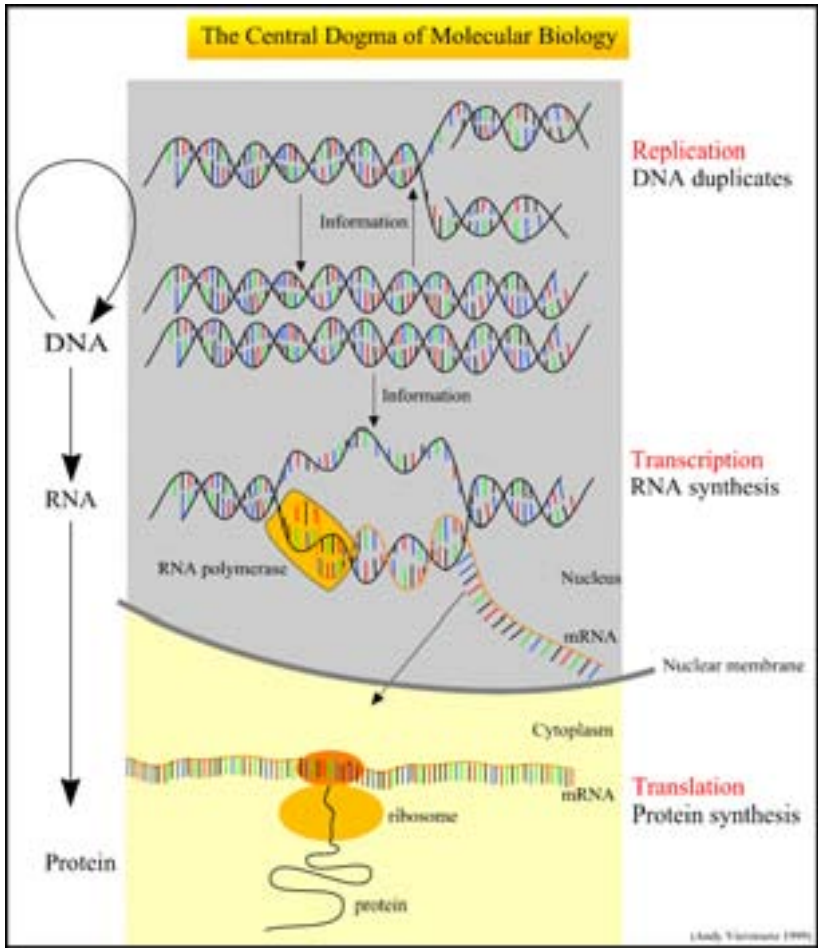


$C_{26}H_{29}NO \cdot C_6H_8O_7$

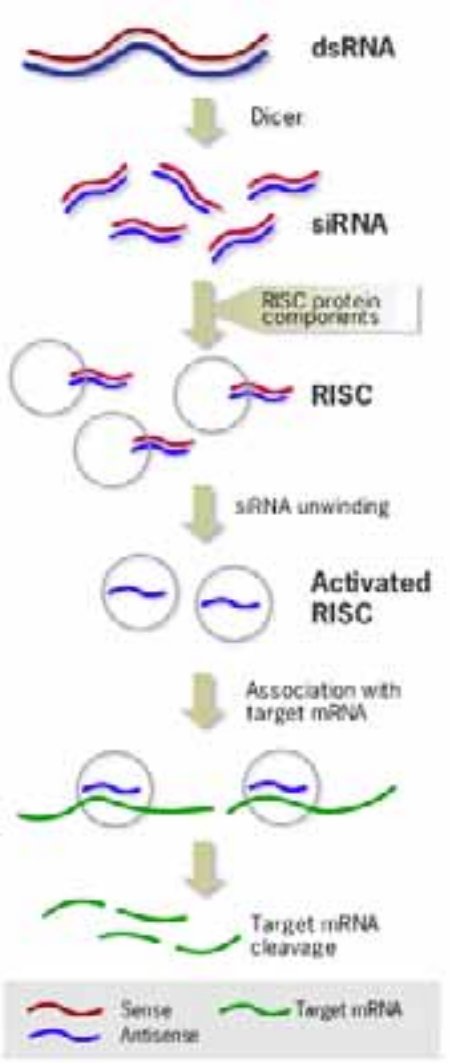


Monocitrate salt

•Hormone-related therapy: siRNAs



siRNA mode of action



-post translational modification
-cell surface carbohydrates, receptors
-signaling and regulatory pathways

•Hormone therapy: siRNA/prostate cancer

- Most frequently diagnosed cancer among men
  Second leading cause of male cancer deaths (1st: lung)

- Early stages: Androgen hormone dependent
  Late stages: Androgen independent
  Both stages: Dependent on the androgen receptor (AR)

- Knockdown of AR gene expression slows cancer cell growth

- Small inhibitory RNAs (siRNAs) show promise for inhibiting AR expression in vitro

- Delivery systems are needed for in vitro studies and in vivo therapies (viral, polymers)

Drugs and their Delivery

> Matter and the Making of Things

> Cancer: Drugs and Toxins

> Drug Delivery: Targeting, Imaging, Release

•The need for magic bullets

- Magic bullets: term coined by Ehrlich; late 19th c search for antibiotics

If we picture an organism as infected by a certain species of bacterium, it will . . . be easy to effect a cure if substances have been discovered which have a specific affinity for these bacteria and act…on these alone. . . while they possess no affinity for the normal constituents of the body. . . such substances would then be . . . magic bullets.

- Important prior work by Ehrlich in specific affinity:
  chemical dyes that stain specific cells and tissues for imaging
- Molecular structure leads to biological effects
- Ehrlich found drugs against bacteria causing syphilis (arsenic cpds), malaria, and sleeping sickness

Selectivity, specificity: very important in chemistry, drug delivery!

> Drug Delivery

- Drug solubility and stability
- Delivery systems: biocompatibility
- Controlled release: biodegradability
- Targeting
- Imaging
- Activation

•Drug therapy: glossary

dose: how much drug is given; how often

administration route: oral, iv, transdermal, inhalation, subcutaneous, etc

pharmacokinetics: what the body does to the drug. Absorption and disposition (i.e. biodistribution, metabolism, elimination, excretion.)

pharmacodynamics: what the drug does to the body. The biochemical and physiological effects of drugs. Mechanisms of drug action. The relationship between drug concentration and effect.

bioavailability: rate and extent a therapeutically active drug reaches the systemic circulation and is available at the site of action.

drug delivery system/vector/vehicle: how the drug is packaged

•Solubility, stability, biocompatibility

- Many drugs are not water soluble
- Many drugs (e.g. proteins, DNA, RNA) are not stable in circulation and are cleared or degraded by enzymes
- Many drugs are toxic
  - are immunogenic (i.e. elicit an immune response)
  - not entirely specific (i.e. have side effects)

Need for well designed, non-toxic packaging to:

-solubilize

-increase circulation time

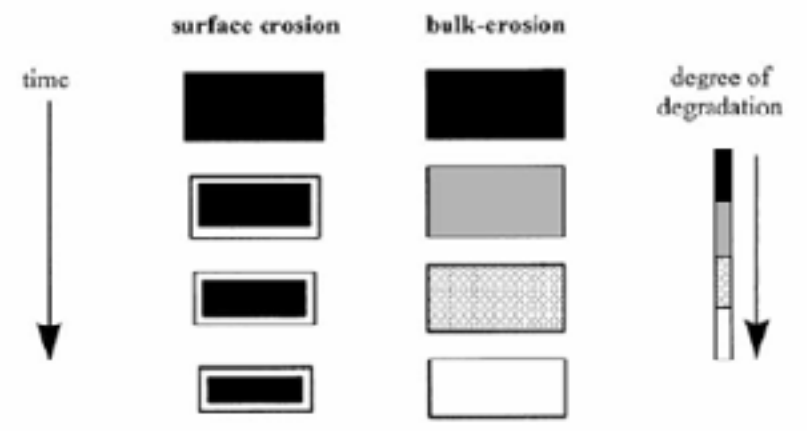
-target organ, tissues, cells, receptors of interest

•Polymeric delivery systems

- Lipids: form assemblies in solution that can entrap drugs (vesicles, micelles; like biomembranes)
- Natural polymers: dextran, dextrin, chitosan
- Biopolymers
  - poly(amino acids): poly(lysine), poly(glutamic acid)
  - biodegradable polyesters PLA, PCL, PGA
- Synthetic polymers
  - PEG: water soluble, protein non-adhesive, non-toxic
  - HPMA: N(2-hydroxypropyl methacrylamide)

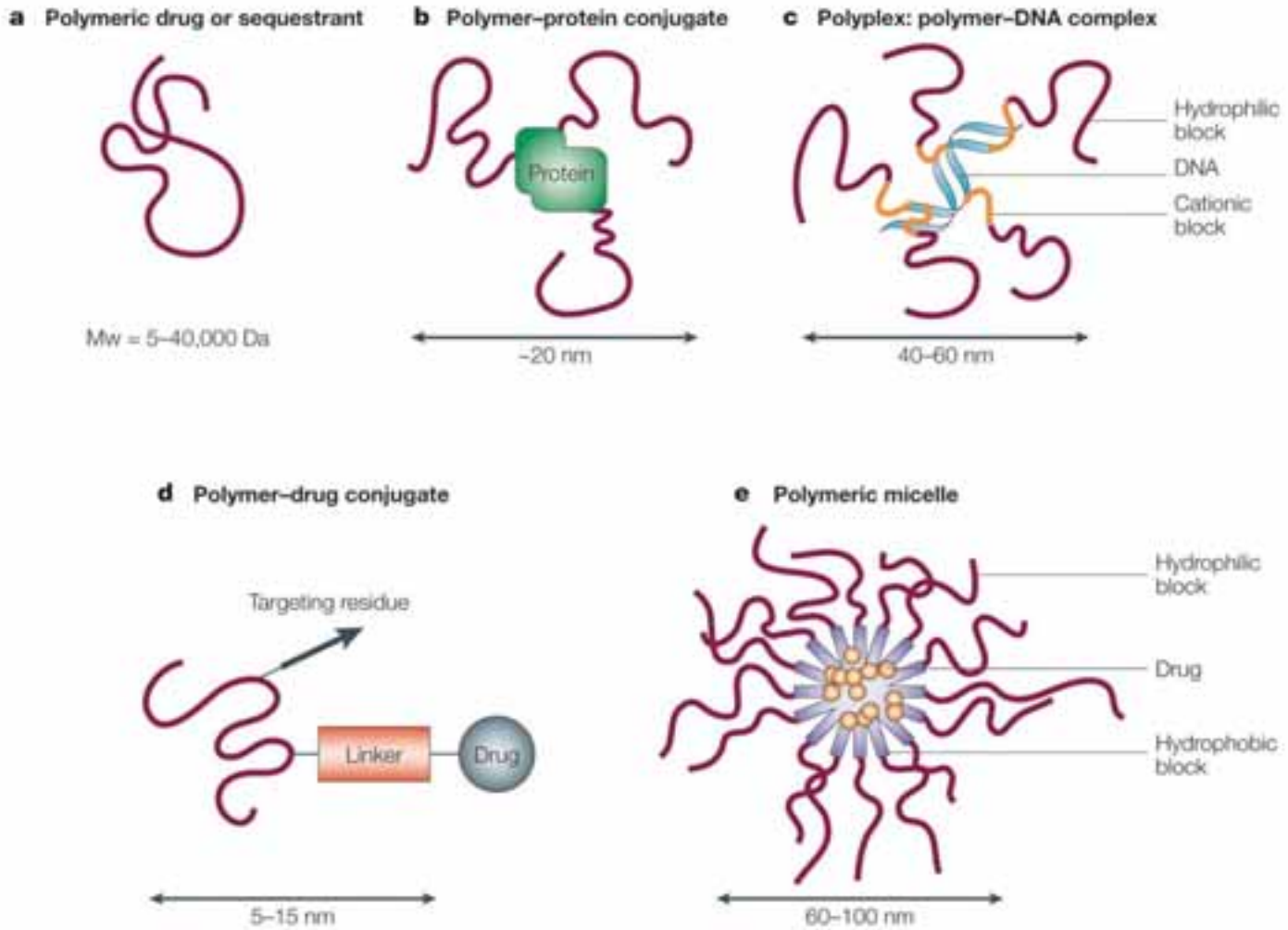
•Controlled release: biodegradability

- Drug release rate is important to control
  (too soon or too late, in the wrong place, is no good!)
- Liposomes: easy to formulate; not so stable in circulation
- Mode of degradation in water
  - PLA: bulk erosion, water penetrates whole structure
  - Poly(anhydrides): surface erosion, like bar of soap



Bulk: can have burst release
Surface: steady, controlled release

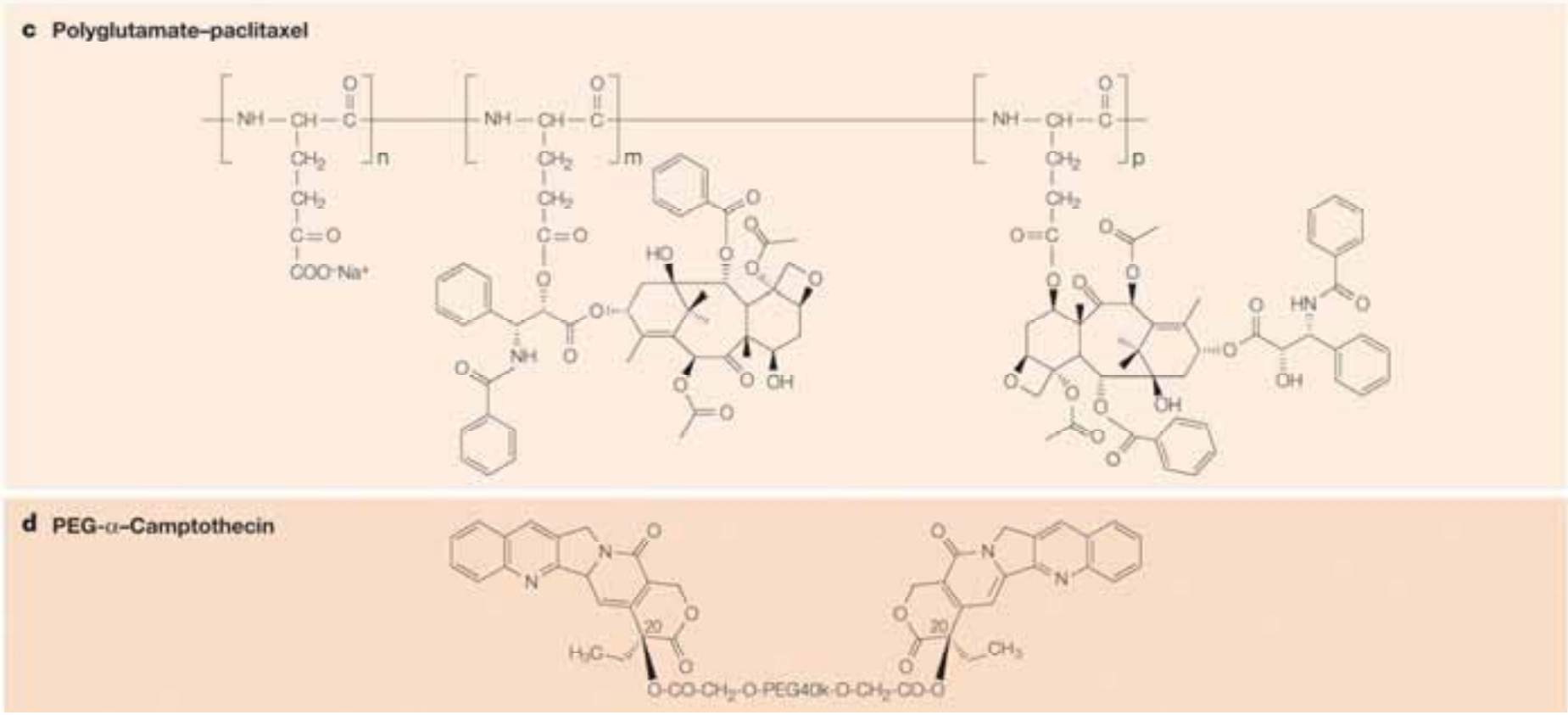
•Polymeric delivery systems



Important issues: loading capacity, stability, release rate, toxicity

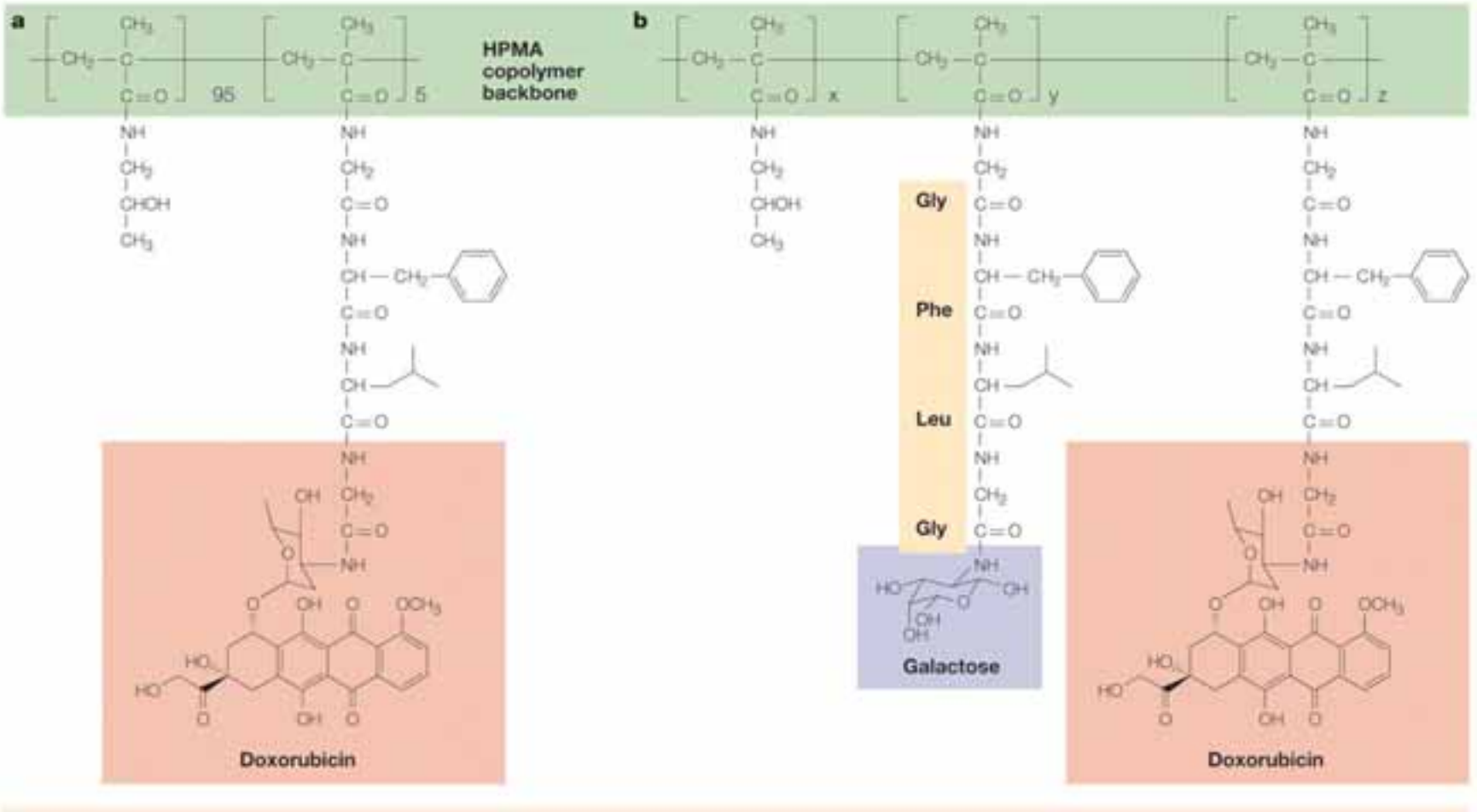
From: Duncan, *Nature Rev. Drug Disc.* **2003**, *2*, 347.

•Polymer/cancer drug conjugates



From: Duncan, *Nature Rev. Drug Disc.* **2003**, *2*, 347.

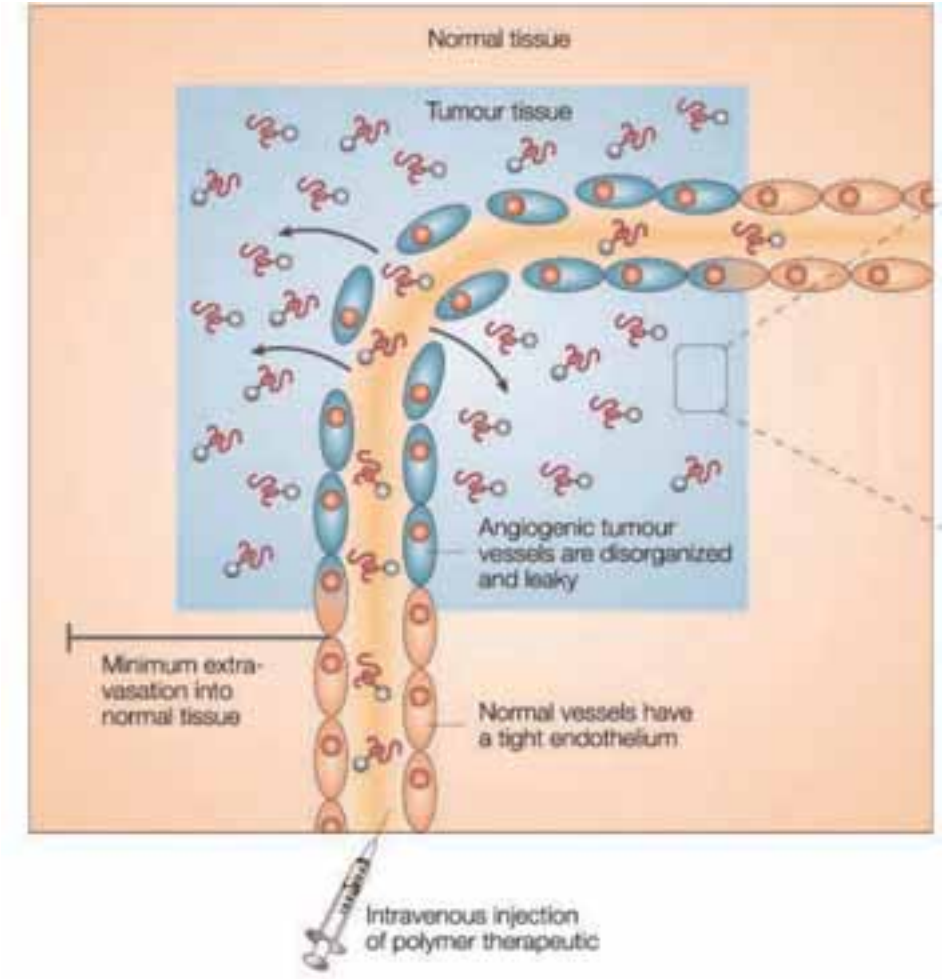
•Cleavable links and targeting



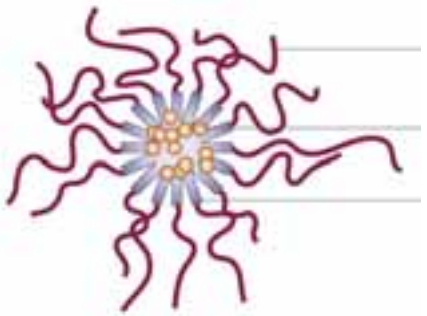
Multifunctional vector: polymer, drug, cleavable link, targeting agent

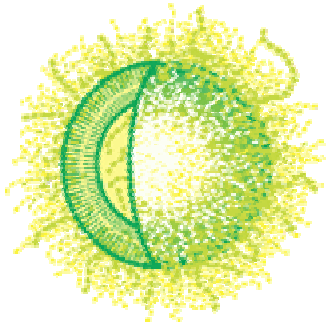
From: Duncan, *Nature Rev. Drug Disc.* **2003**, *2*, 347.

•Targeting: passive



Doxil: doxorubicin + "stealth liposomes"





Enhanced permeability and retention (EPR) effect

From: Duncan, *Nature Rev. Drug Disc.* **2003**, *2*, 347.

•Targeting: active

•Chemical: targeting molecules

- galactose-liver

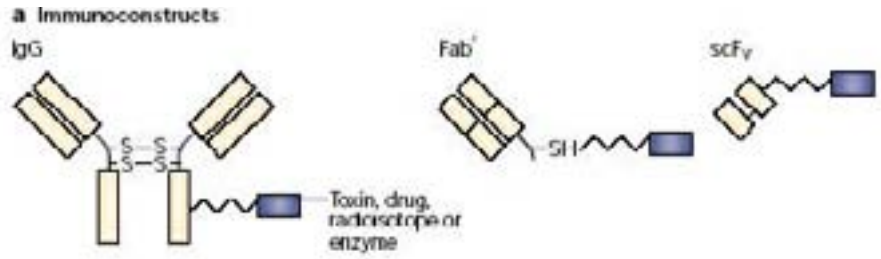
- folate: receptors on cancer cell surfaces

- antibodies, fragments: specific tissues, tumor antigens

• Physical

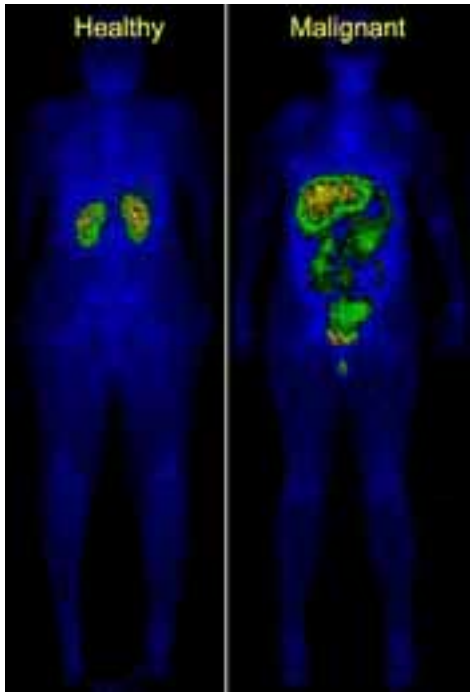
- magnetic guidance

- nanodevices?!

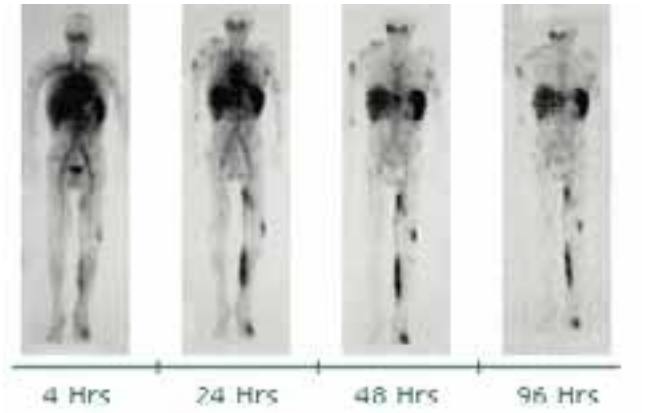


• Imaging

Radioactive probes

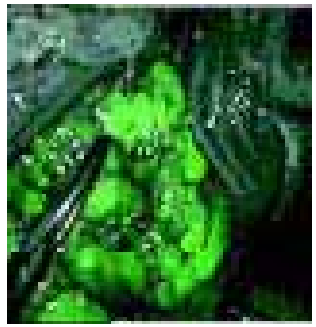


111In-DTPA-folate targeting ovarian cancer

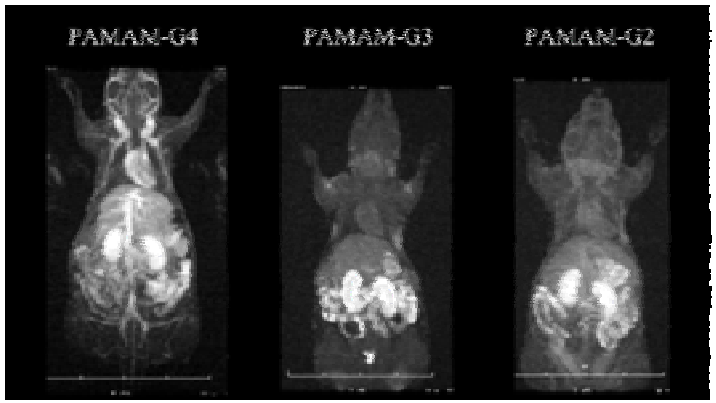


Serial scintigrams of a Kaposi's Sarcoma patient after injection of radioactive STEALTH® liposomes containing ^{111}IN-DTPA

Fluorescence Imaging: GFP (liver tumor model)



Magnetic (MRI): Gd Dendrimers

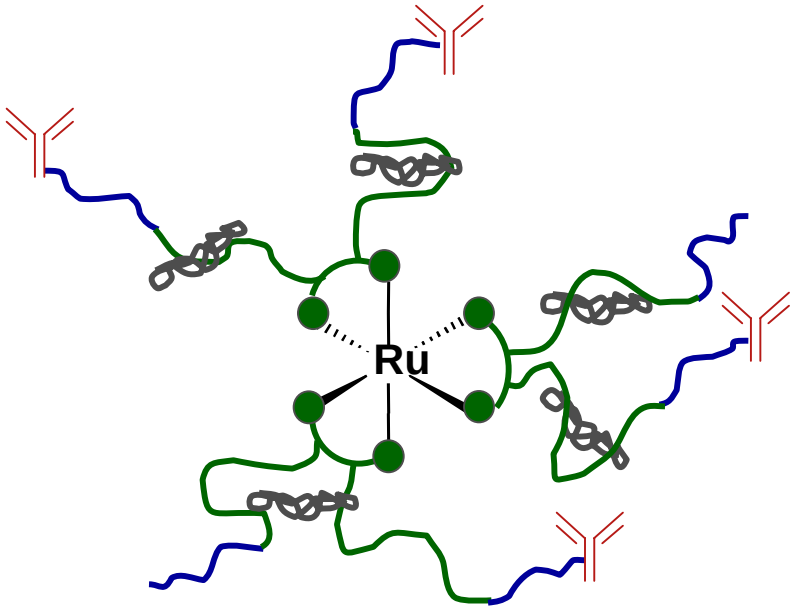


Quantum Dots

New: Functional Imaging

•Multifunctional agent

Targeting, imaging, and biomolecule protection



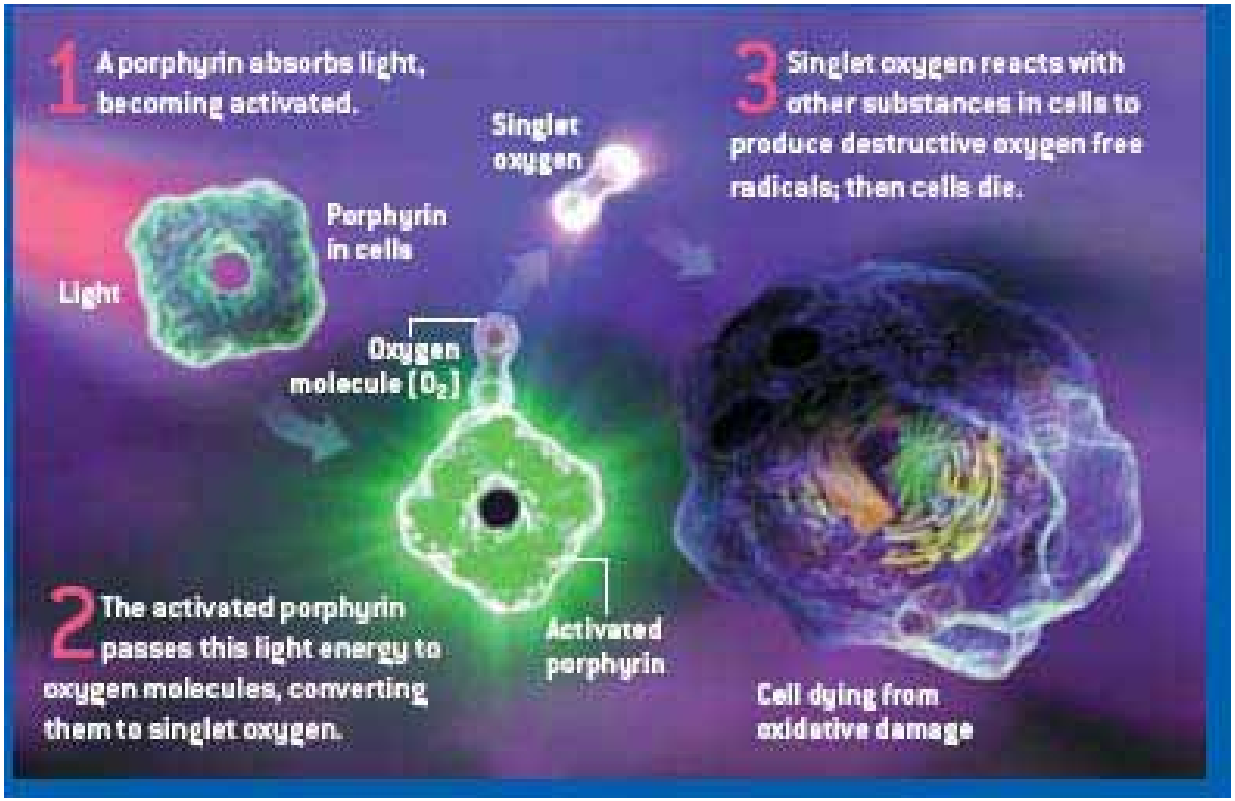
star block

PEG
PEI
Targeting group
siRNA, DNA

Prostate cancer siRNA/gene therapy targeting the AR

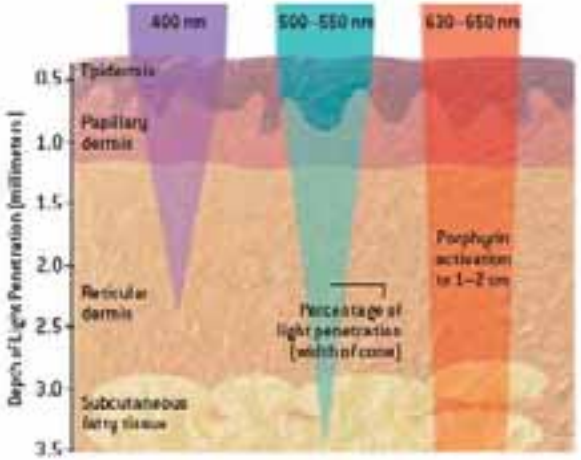
(Fraser group collaboration with D. Gioeli, UVA Cancer Center)

•Activation: photodynamic therapy



PDT approved for:
breast, lung cancer
macular degeneration
skin conditions

Key Issue:
Tissue penetration by light

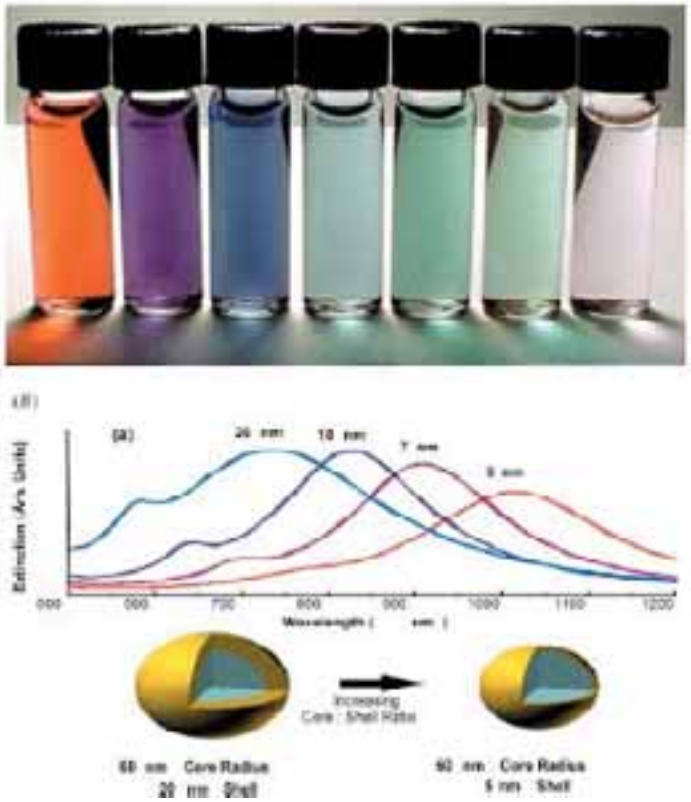


Mode of action:
- direct tumor cell kill–lethal ROS flux
- tumor-associated vasculature damage
- post-treatment immune response against tumor cells.

From: Lane, New Light on Medicine, *Scientific American* Jan 2003, 38-45.

•Activation: hyperthermal therapy

Gold nanoparticles:
absorb or scatter light over visible, IR spectrum



Gold nanoshells and Near IR light

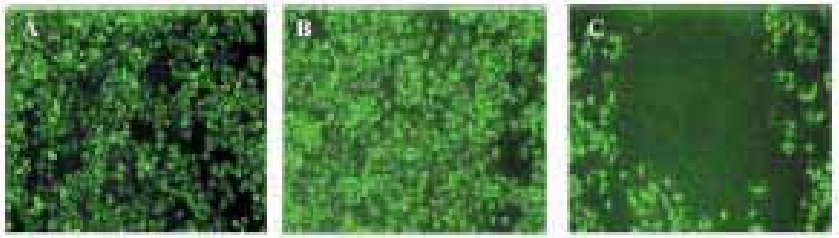


Figure 5 Breast carcinoma cells were exposed to either nanoshells (*A*), near-infrared light (*B*), or the combination of nanoshells and near-infrared light (*C*). As demonstrated

Temperature rise/depth profile: in vivo

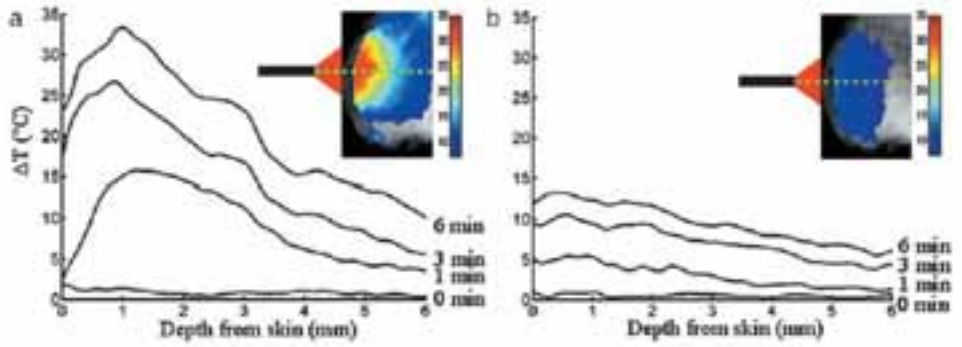


Fig. 4. Measured temperature rise plotted as a function of depth along the trajectory. Measured temperature rise in a region of interest at 0, 1, 3, and 6 min for nanoshell treatment (a) and control treatment (b).

From: West, Halas, et al., *Annu. Rev. Biomed. Eng.* **2003**, *5*, 285; *PNAS*, **2003**, *100*, 13549.

> Other things to think about

- Delivery systems: the way to capitalize on genomics, proteomics, metabolomics, etc
- Who should regulate and pay for programs on drug research, testing, treatments?
- Why do we use military language in describing disease treatments? (e.g. bullets, stealth, battle)
- What can we do to lower cancer risk?
- What does all of this have to do with designing matter? (the design process? matter lifecycle?)