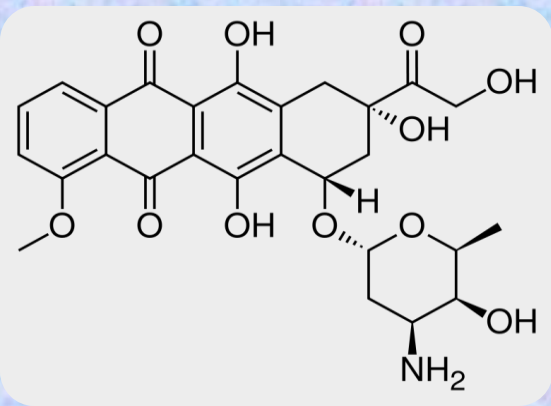
In the name of God

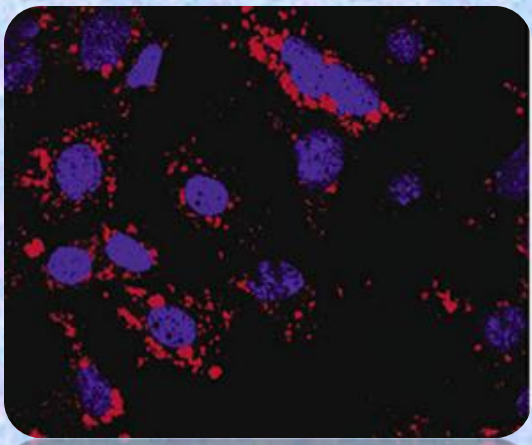
Biocompatible and Biodegradable polymer and their medical applications

Presenter: Hirbod Karimi

Superior in Charge: Dr. A.R. Hajipour

Contents

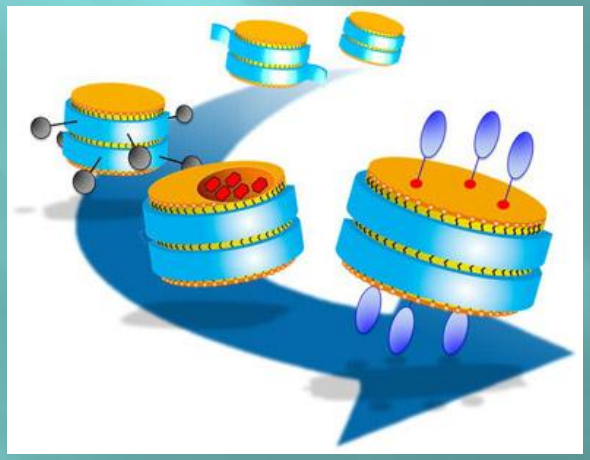




Defenitions

Biocompatible material

A biocompatible material (sometimes shortened to biomaterial) is a synthetic or natural material used to replace part of a living system or to function in intimate contact with living tissue. Biocompatible materials are intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body. Biomaterials are usually non-viable, but may also be viable.



A biocompatible material is different from a biological material such as bone that is produced by a biological system. Artificial hips, vascular stents, artificial pacemakers, and catheters are all made from different biomaterials and comprise different medical devices.

Jan W. Gooch, Biocompatible Polymeric Materials, Springer New York, 2010.

Properties of Biocompatible materials

1. The ability of a material to perform with an appropriate host response in a specific application. (Williams' definition).

2. The quality of not having toxic or injurious effects on biological systems.

3. Comparison of the tissue response produced through the close association of the implanted candidate material to its implant site within the host animal to that tissue response recognized and established as suitable with control materials.

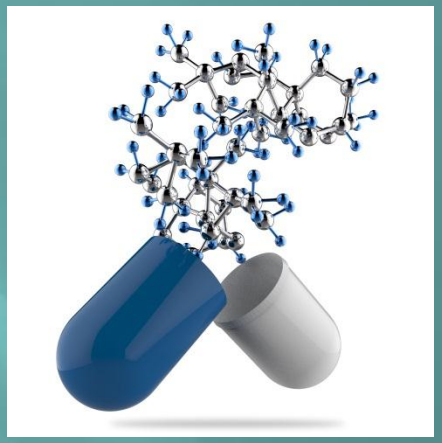
4. Refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy.

5. Biocompatibility is the capability of a prosthesis implanted in the body to exist in harmony with tissue without causing deleterious changes.

Jan W. Gooch, Biocompatible Polymeric Materials, Springer New York, 2010.
https://en.wikipedia.org/wiki/Biocompatibility

Biodegradable polymer

Biodegradable polymers are a specific type of polymer that breaks down after its intended purpose to result in natural byproducts such as gases (CO_2, N_2), water, biomass, and inorganic salts. These polymers are found both naturally and synthetically made, and largely consist of ester, amide, and ether functional groups. Their properties and breakdown mechanism are determined by their exact structure. These polymers are often synthesized by condensation reactions, ring opening polymerization, and metal catalysts.



The concept of synthetic biodegradable plastics and polymers was first introduced in the 1980s.

In 1992, an international meeting was called where leaders in biodegradable polymers met to discuss a definition, standard, and testing protocol for biodegradable polymers.

As of 2013, 5-10% of the plastic market focused on biodegradable polymer derived plastics.

Properties of Biodegradable polymers

1. All biodegradable polymers should be stable and durable enough for use in their particular application, but upon disposal they should easily breakdown.

2. Biodegradable polymers, have extremely strong carbon backbones that are difficult to break, such that degradation often starts from the end-groups.

3. Biodegradable polymers also tend to have minimal chain branching as this cross linking often decreases the number of end groups per unit weight.

4. Biodegradable polymers should be hydrophill.

5. Non-toxic, capable of maintaining good mechanical integrity until degraded and capable of controlled rates of degradation.

P.C. Hiemenz, Polymer Chemistry: The Basic Concepts, Wiley, New York, 1984.

Examples of Biocompatible Polymers

Poly(methymethacr

Poly(N-isopropylac

Bo

Poly(ether-urethan

Poly(ethyleneoxide

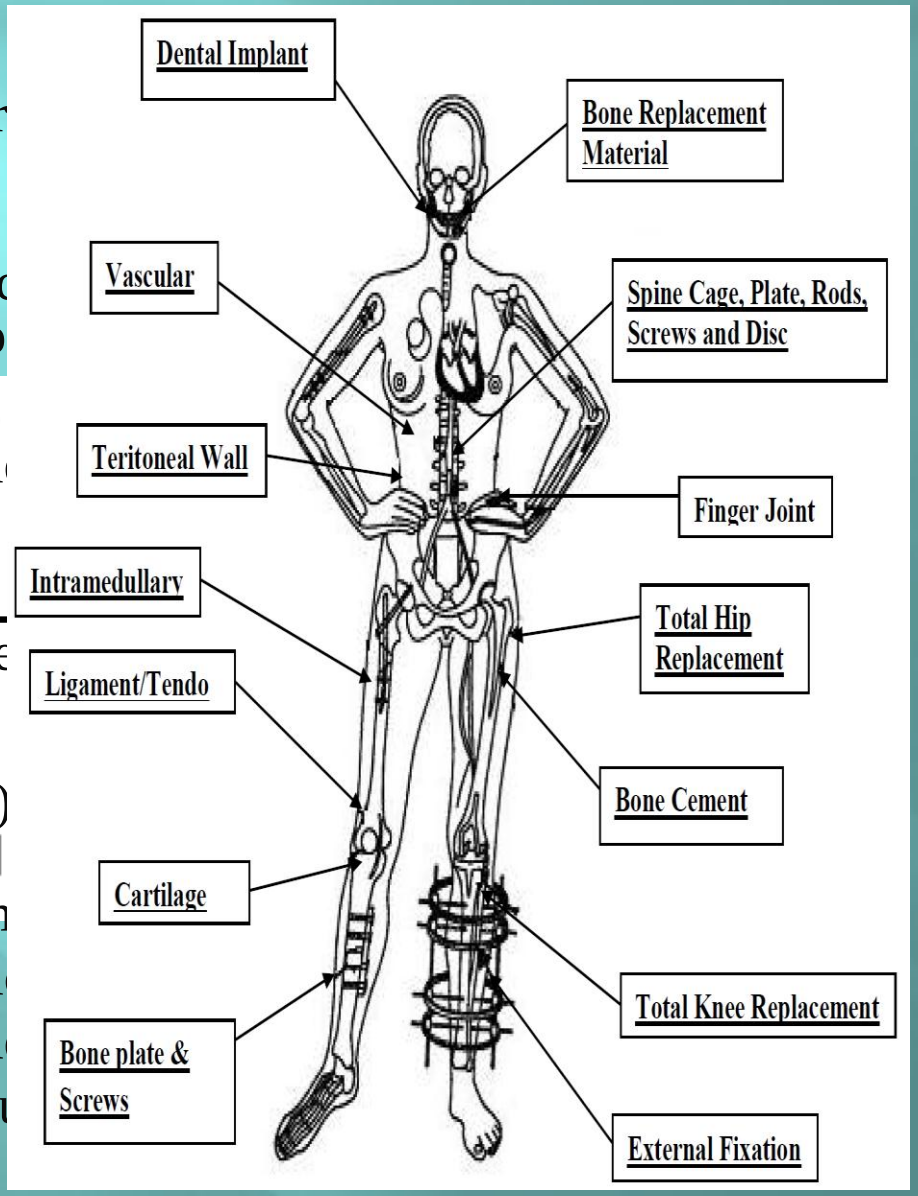
Poly(vinylalcohol)

En

en

an

dr



Applications of Biocompatible Polymers

PIPAAm polymer

surface

1) coat surface with polymer

surface

2) apply live cells

surface

3) allow cells to grow

37 °C

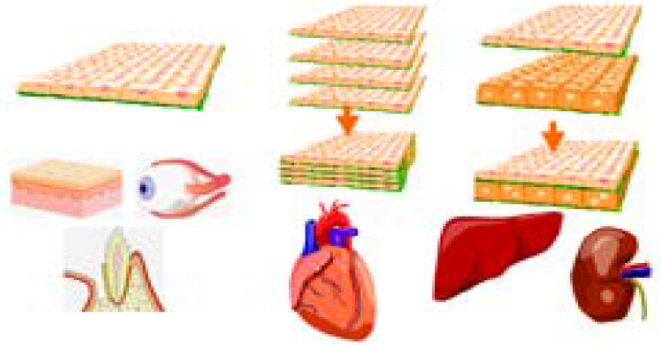
4) reduce temperature

32 °C

surface

5) harvest cells

Tissue Reconstruction from Cell Sheets



Cells can be grown outside of the body

Biomaterials, 25, 5735-5742, 2004.

Regenerative Medicine for the Heart

Using the right growth factors, stem cells can become any kind of tissue in the body! In the patch method, stem cells are placed on flexible scaffold patch designed to be absorbed into the body. The fabric patch is placed on the heart and the stem cells on the patch grow into heart muscle cells. These cells replace the damaged heart cells, allowing the cell to continue to beat.

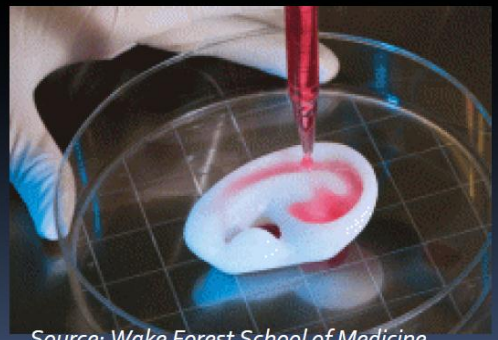
Circulation research, 90, 40-48, 2002.

Damaged ear

Source: Institute of Science & Technology in Medicine Keele University

Source: Prof. Yongniam Yan

Rehabilitated ear



Source: Wake Forest School of Medicine

Seed cells onto scaffold

Source: Stelios Arcadiou

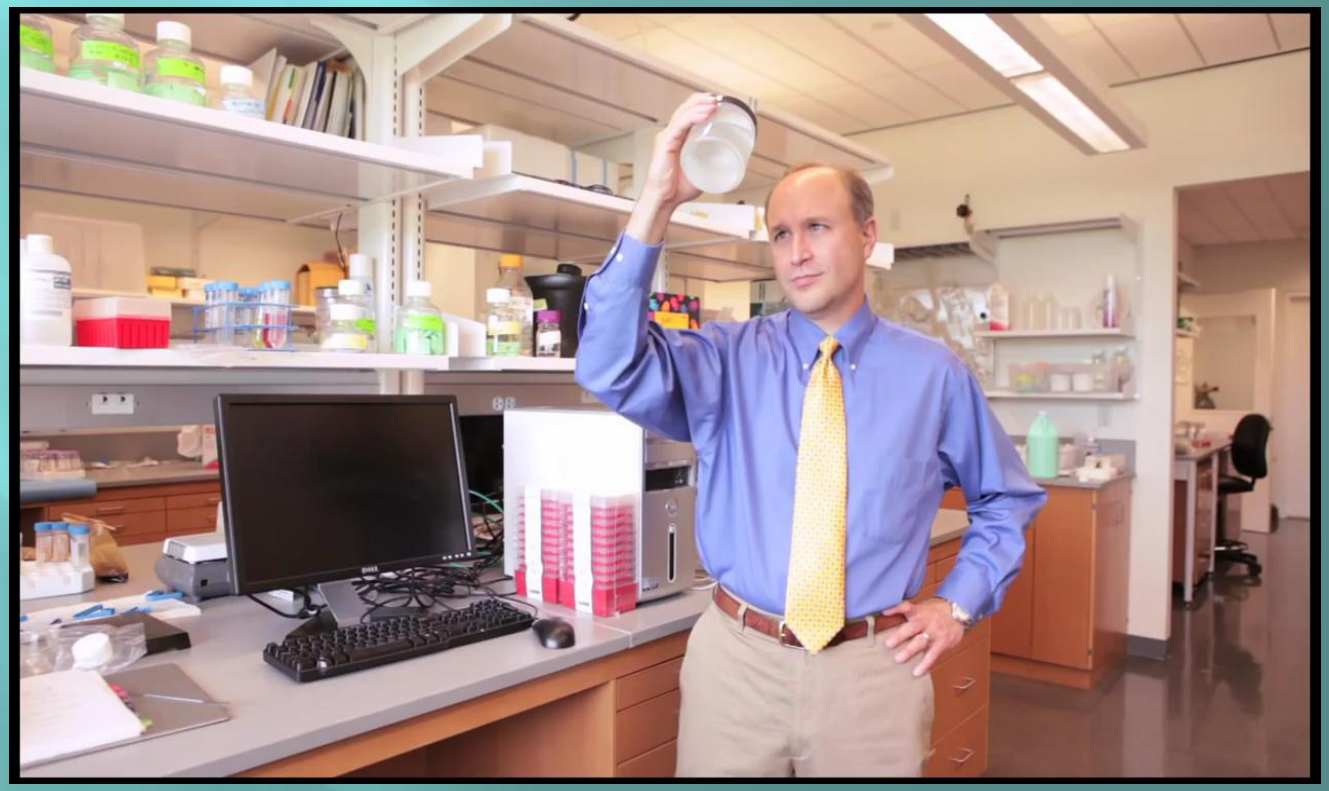
Grow cells

Harvest ear

Tissue Engineering, 8, 278-286, 2013.

3-D Printing Body Parts Will Revolutionize Medicine

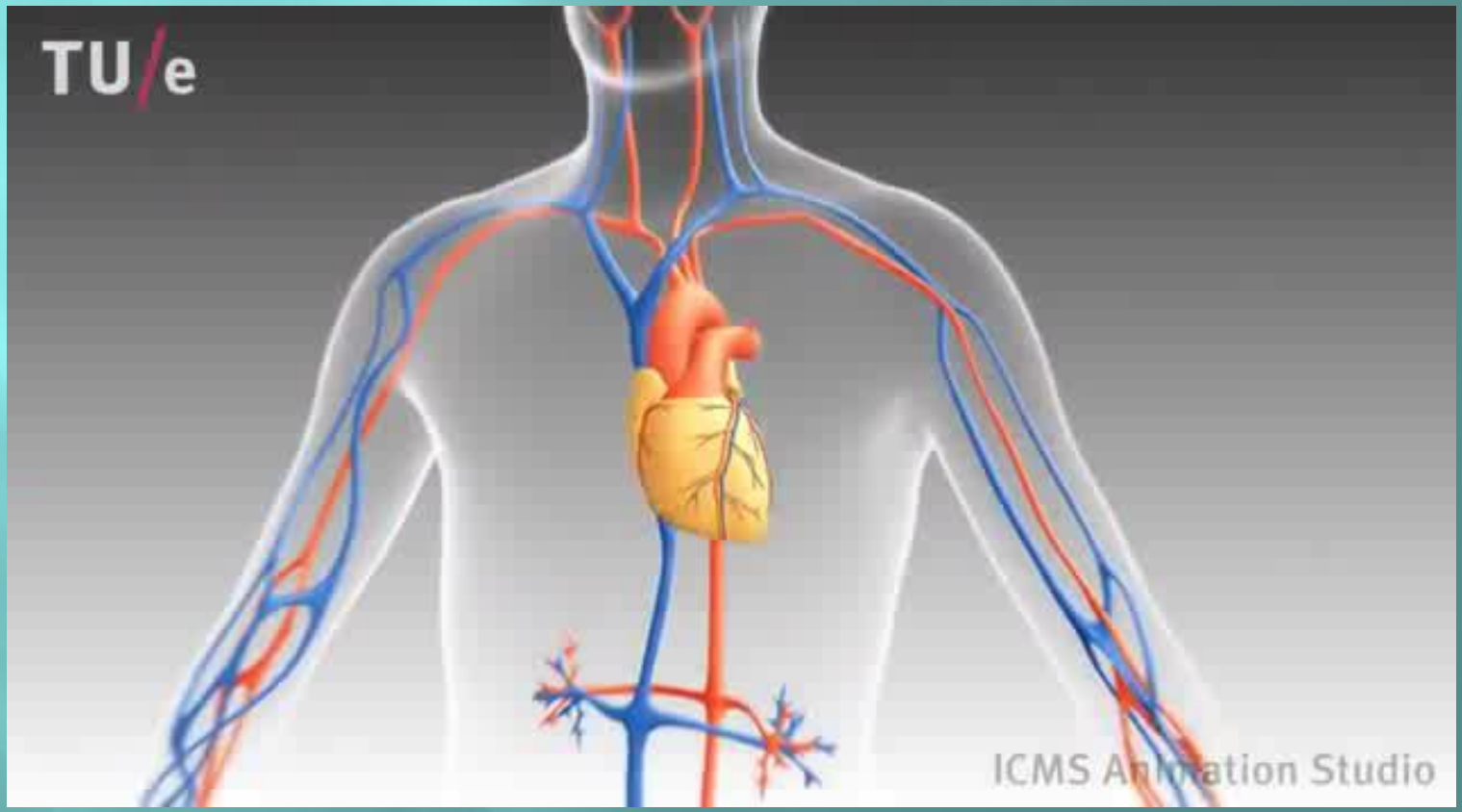
In 2000, bioengineer Thomas Boland, the self-described "grandfather of bioprinting," eyed an old Lexmark printer in his lab at Clemson University. Boland emptied the Lexmark's ink cartridge and filled it with collagen. He then glued a thin, black silicon sheet onto blank paper and fed it into the printer. He opened a Word document on his PC, typed his initials, and hit print. The paper spooled out with "TB" clearly delineated in off-white proteins.



http://www.popsci.com/science/article/2013-07/how-3-d-printing-body-parts-will-revolutionize-medicine

Bioactive polymeric scaffolds

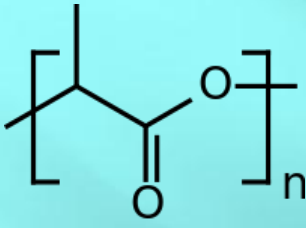
Bioactive polymeric scaffolds are a prerequisite for the ultimate formation of functional tissues. Here, a supramolecular polymers based on quadruple hydrogen bonding ureido-pyrimidinone (UPy) moieties which are eminently suitable for producing such bioactive materials. Particularly, the reversible nature of the hydrogen bonds allows for a modular approach to gaining control over cellular behaviour and activity both *in vitro* and *in vivo*.



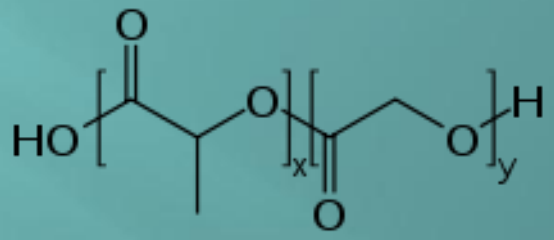
Nature Materials, 4, 568-574, 2005.

Examples of Biodegradable polymers

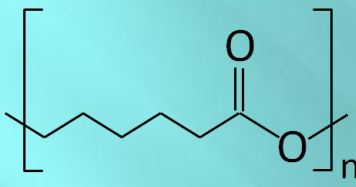
Polylactic acid (PLA)



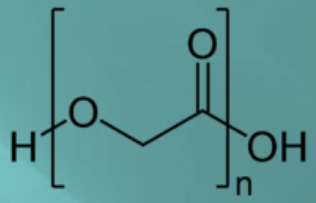
Poly(lactic-co-glycolic acid) (PLGA)



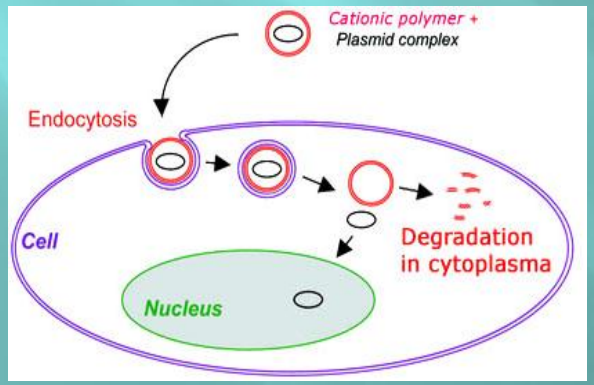
Polycaprolactone (PCL)

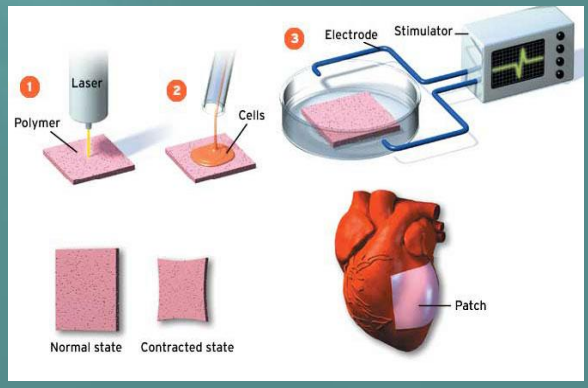


Poly(glycolic acid) (PGA)



Drug delivery **Tissue engineering** **Implants** **Sutures** **Bone fixtures**

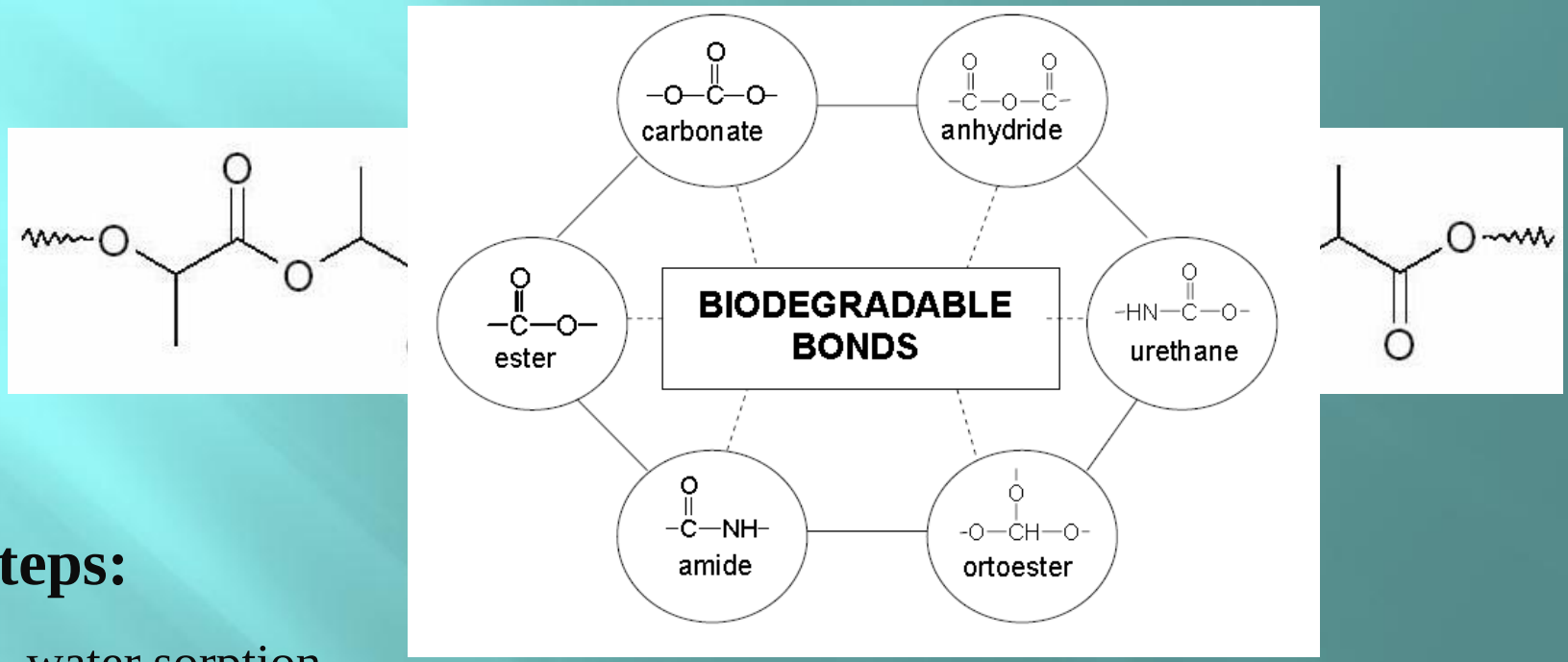




P.C. Hiemenz, Polymer Chemistry: The Basic Concepts, Wiley, New York, 1984.

Degradation Mechanisms

- Enzymatic degradation
- Hydrolysis
  (depend on main chain structure)



Steps:

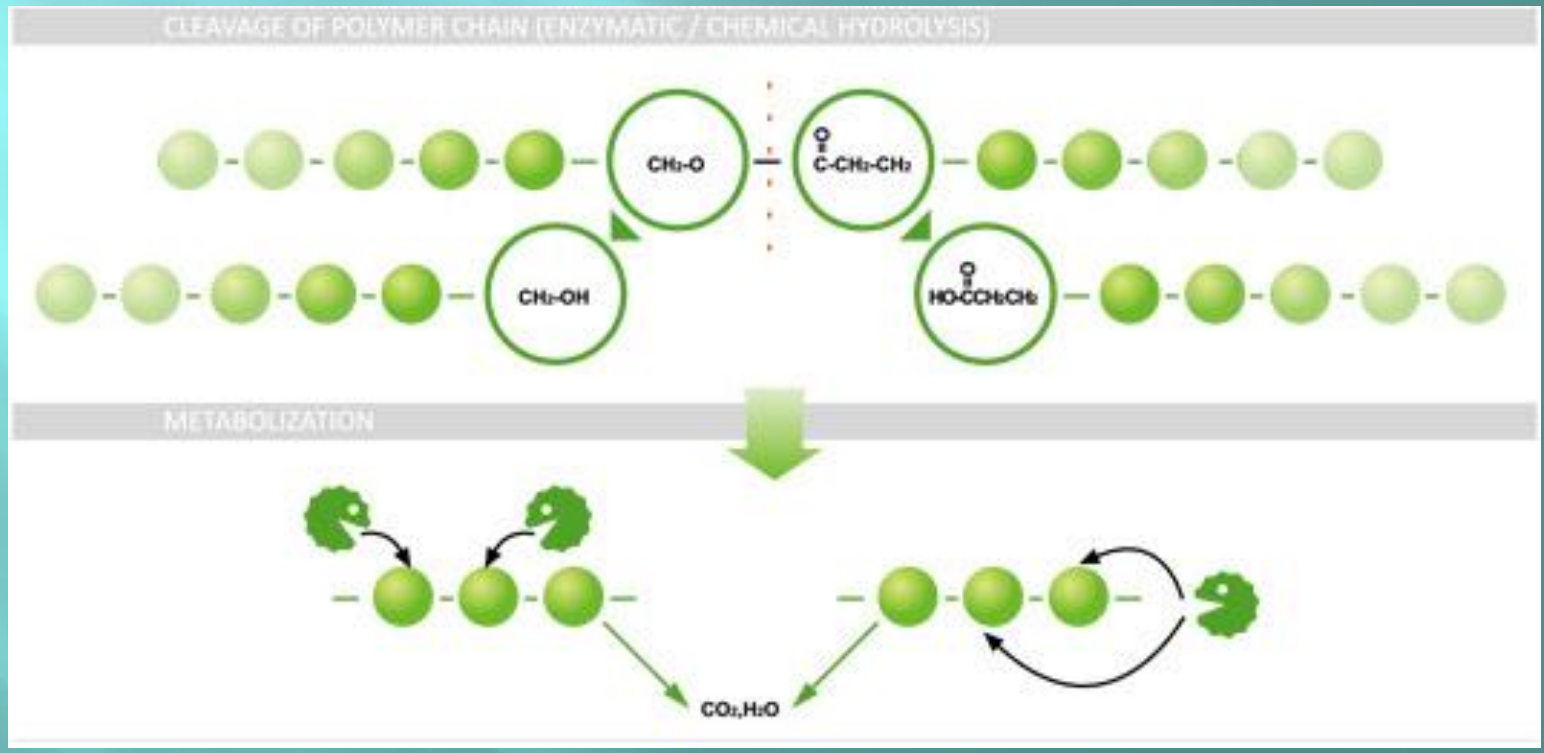
- water sorption
- reduction of mechanical properties (modulus & strength)
- reduction of molar mass
- weight loss

Suture

Historically, polyhydroxyester was the first biodegradable polymer utilized in a biomedical application as a biodegradable suture material.

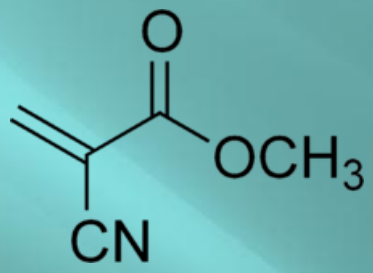
As early as 1970, PGA was targeted as a highly biocompatible biogradable polymer marketed as Dexon for use as surgical sutures.

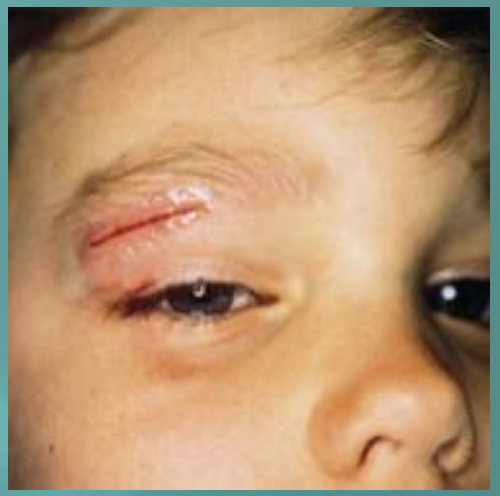
PLA, PGA, PLGA



Tissue Adhesive

Tissue adhesives are compounds that can be used for hemostasis, wound closure, or fistula repair. The main classes of tissue adhesives are cyanoacrylate glues, fibrin glue, and thrombin. Cyanoacrylate glues are used primarily for endoscopic control of bleeding from gastric varices and less commonly for hemostasis of other bleeding lesions.



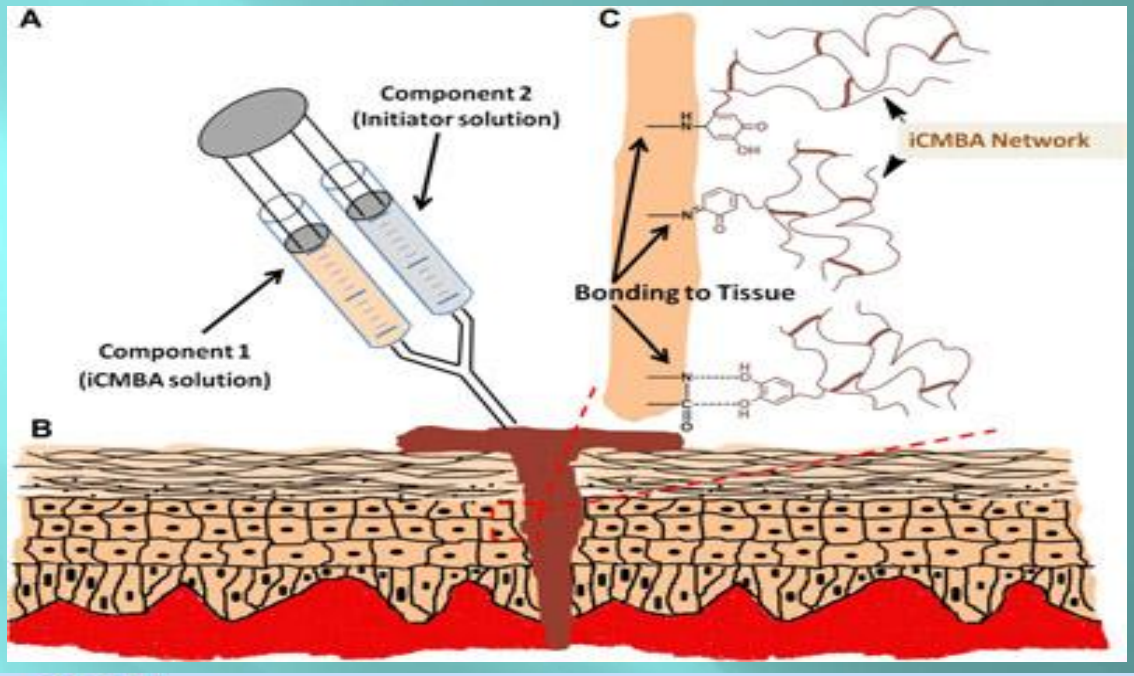


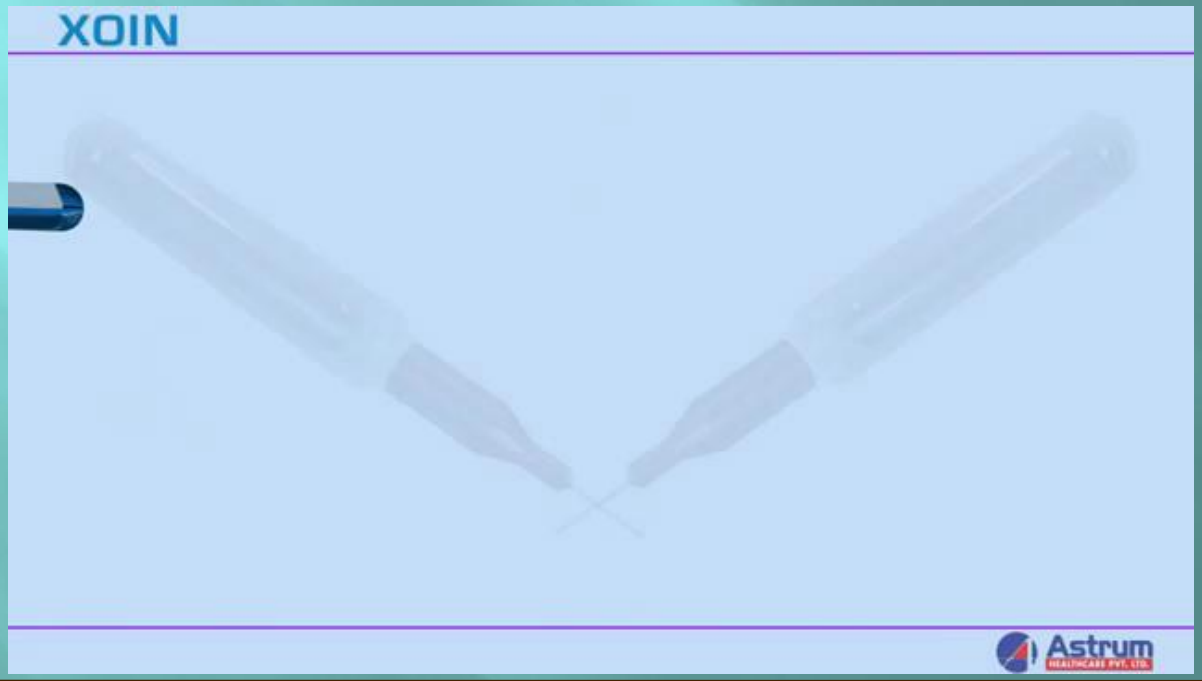
Cyanoacrylate tissue adhesives combine cyanoacetate and formaldehyde in a heat vacuum along with a base to form a liquid monomer.

When the monomer comes into contact with moisture on the skin's surface, it chemically changes into a polymer that binds to the top epithelial layer.

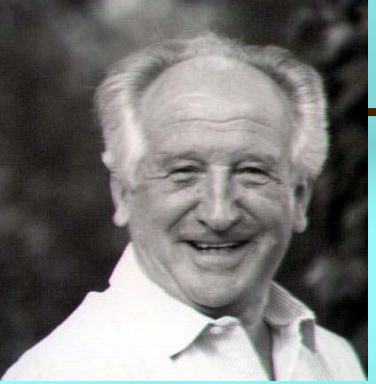
This polymer forms a cyanoacrylate bridge, binding the two wound edges together and allowing normal healing to occur below.

Gastrointestinal endoscopy, 78, 209-306, 2013.



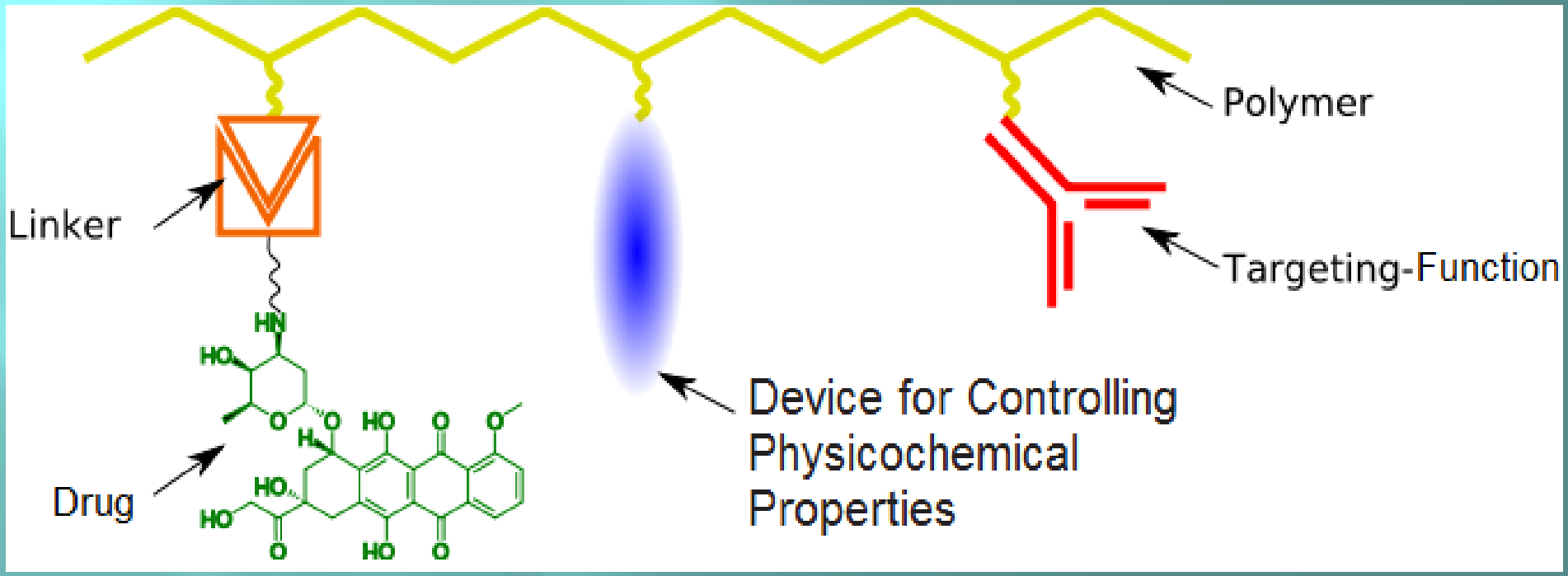


https://www.youtube.com/watch?v=5RD2cAERD0c

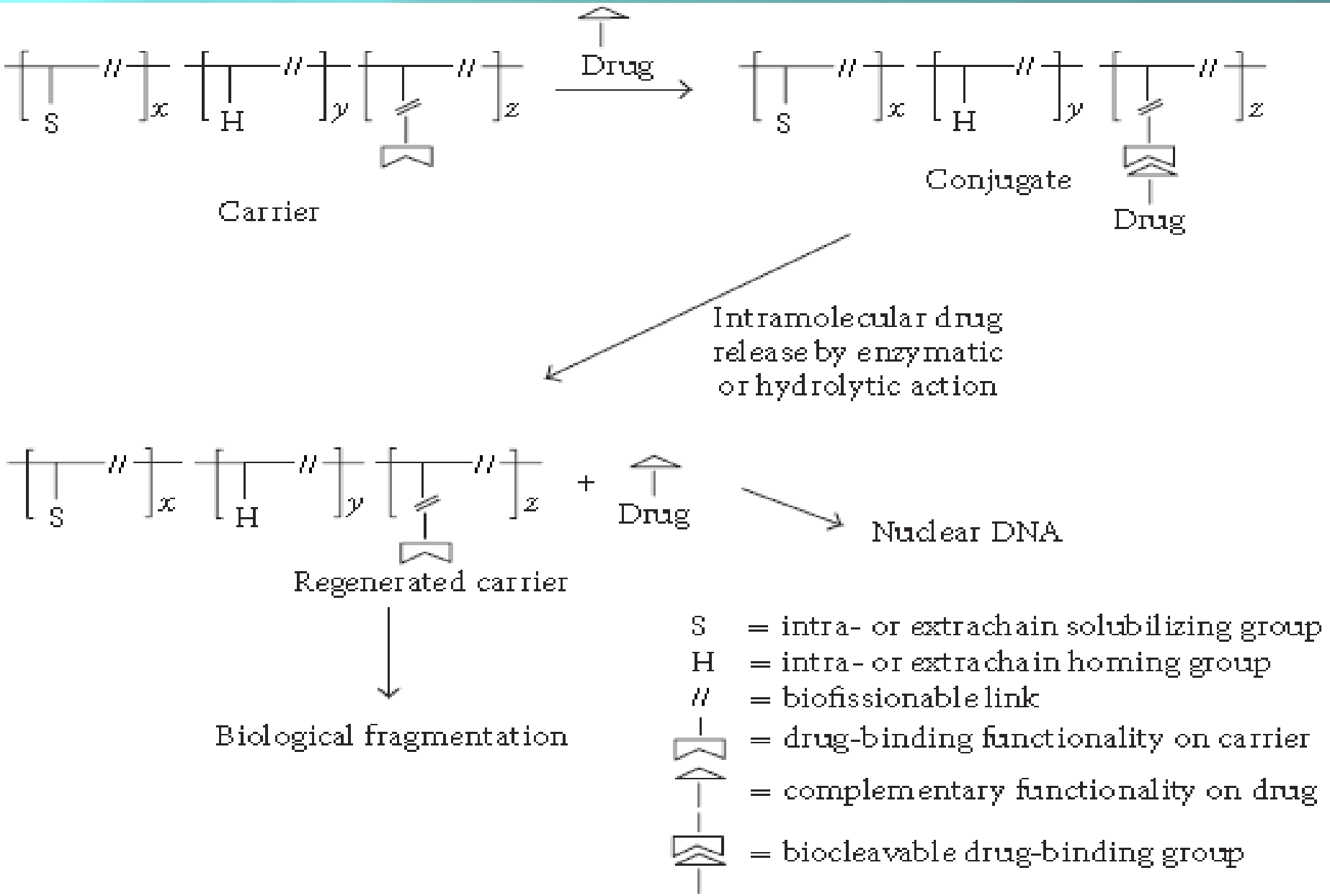


Drug Delivery

Ringsdorf Drug Delivery Model



Ringsdorf, H., in Polymeric Delivery Systems, Kostelnik, Gordon & Breach Publishers, New York,1978.

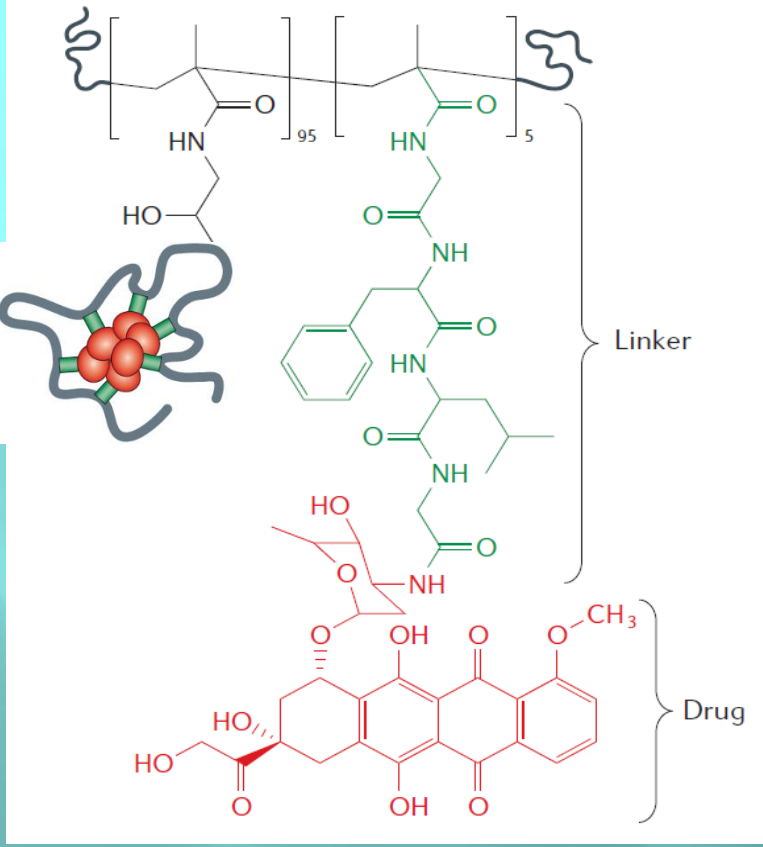

S
x
H
y
z
Drug
Carrier
Conjugate
Drug
Intramolecular drug release by enzymatic or hydrolytic action
Regenerated carrier
Biological fragmentation
Nuclear DNA
S = intra- or extrachain solubilizing group
H = intra- or extrachain homing group
// = biofissionable link
= drug-binding functionality on carrier
= complementary functionality on drug
= biocleavable drug-binding group

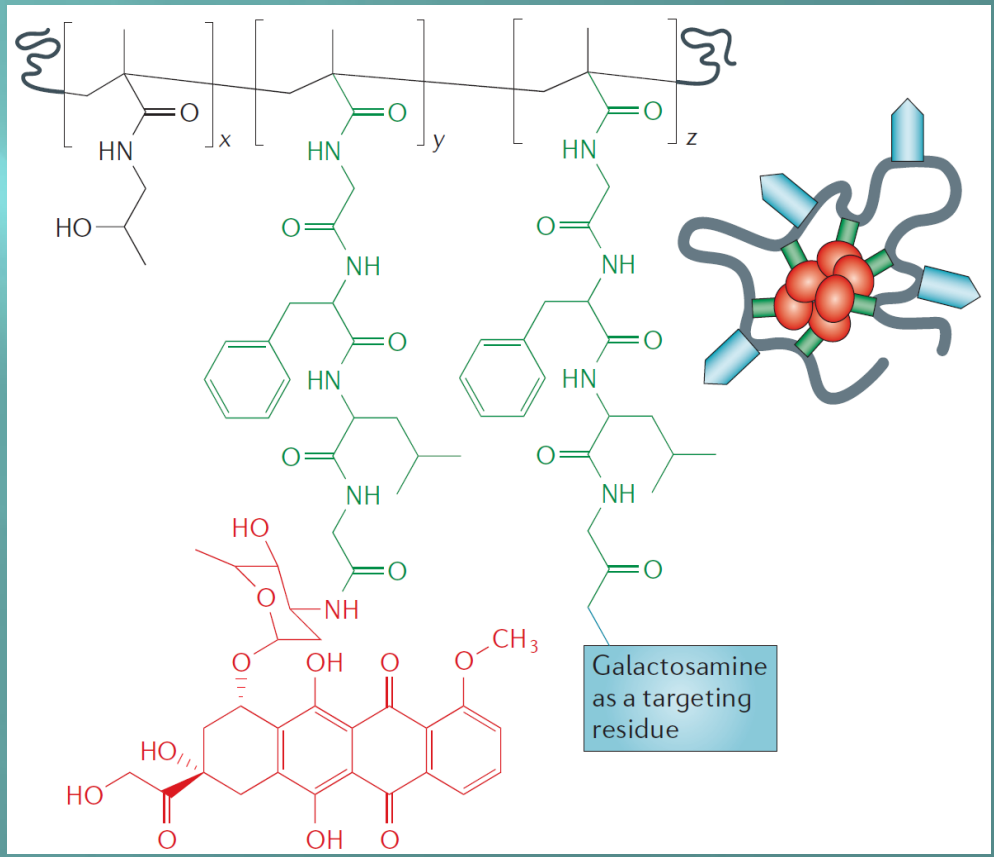
Polymer–drug conjugates

Compound	Name	Status	Indication
Polyglutamate–paclitaxel	CT-2103; Xyotax	Phase III	Various cancers, particularly non-small-cell lung cancer; ovarian cancer as a single agent or in combination therapy
Polyglutamate–camptothecin	CT-2106	Phase I	Various cancers
HPMA copolymer–doxorubicin	PK1; FCE28068	Phase II	Various cancers, particularly lung and breast cancer
HPMA copolymer–doxorubicin–galactosamine	PK2; FCE28069	Phase I/II	Particularly hepatocellular carcinoma
HPMA copolymer–paclitaxel	PNU166945	Phase I	Various cancers
HPMA copolymer–camptothecin	MAG-CPT	Phase I	Various cancers
HPMA copolymer–carboplatin platinate	AP5280	Phase I/II	Various cancers
HPMA copolymer–DACH-platinate	AP5346; ProLindac	Phase I/II	Various cancers
Dextran–doxorubicin	AD-70, DOX-OXD	Phase I	Various cancers
Modified dextran–camptothecin	DE-310	Phase I	Various cancers
PEG–camptothecin	Prothecan	Phase II	Various cancers

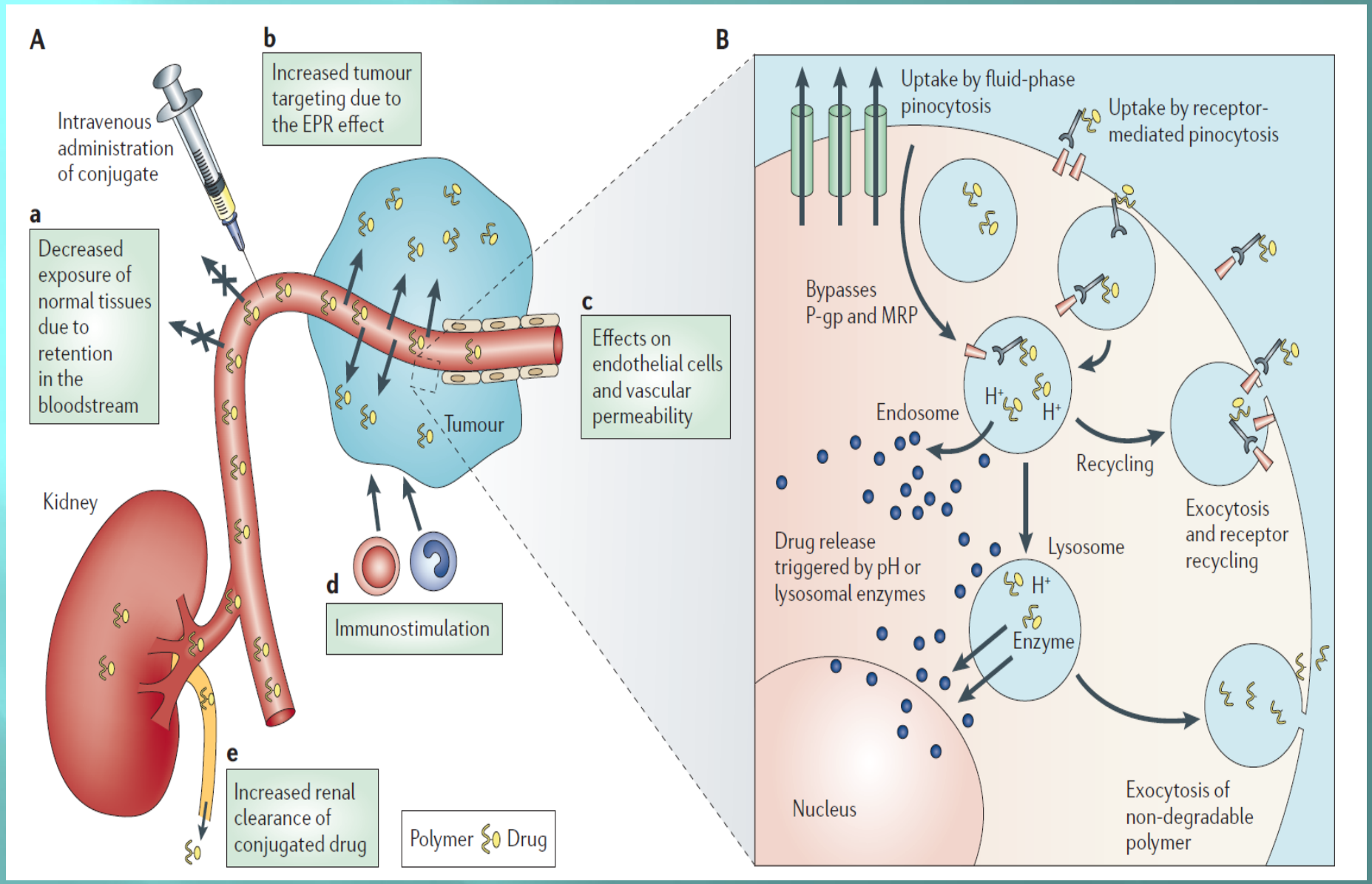
DACH, diaminocyclohexane; HPMA, *N*-(2-hydroxypropyl)methacrylamide; PEG, poly(ethyleneglycol).

PEG and HPMA copolymers are non-biodegradable in the main chain, so larg size was chosen to ensure the elimination of the carrier from the body. A lysosomally degradable peptidyl linker (Gly-Phe-Leu-Gly) was favoured for drug conjugation, as it is stablein the circulation but is cleaved by lysosomal proteases (for example, cathepsin B) once it has been internalized by endocytosis.

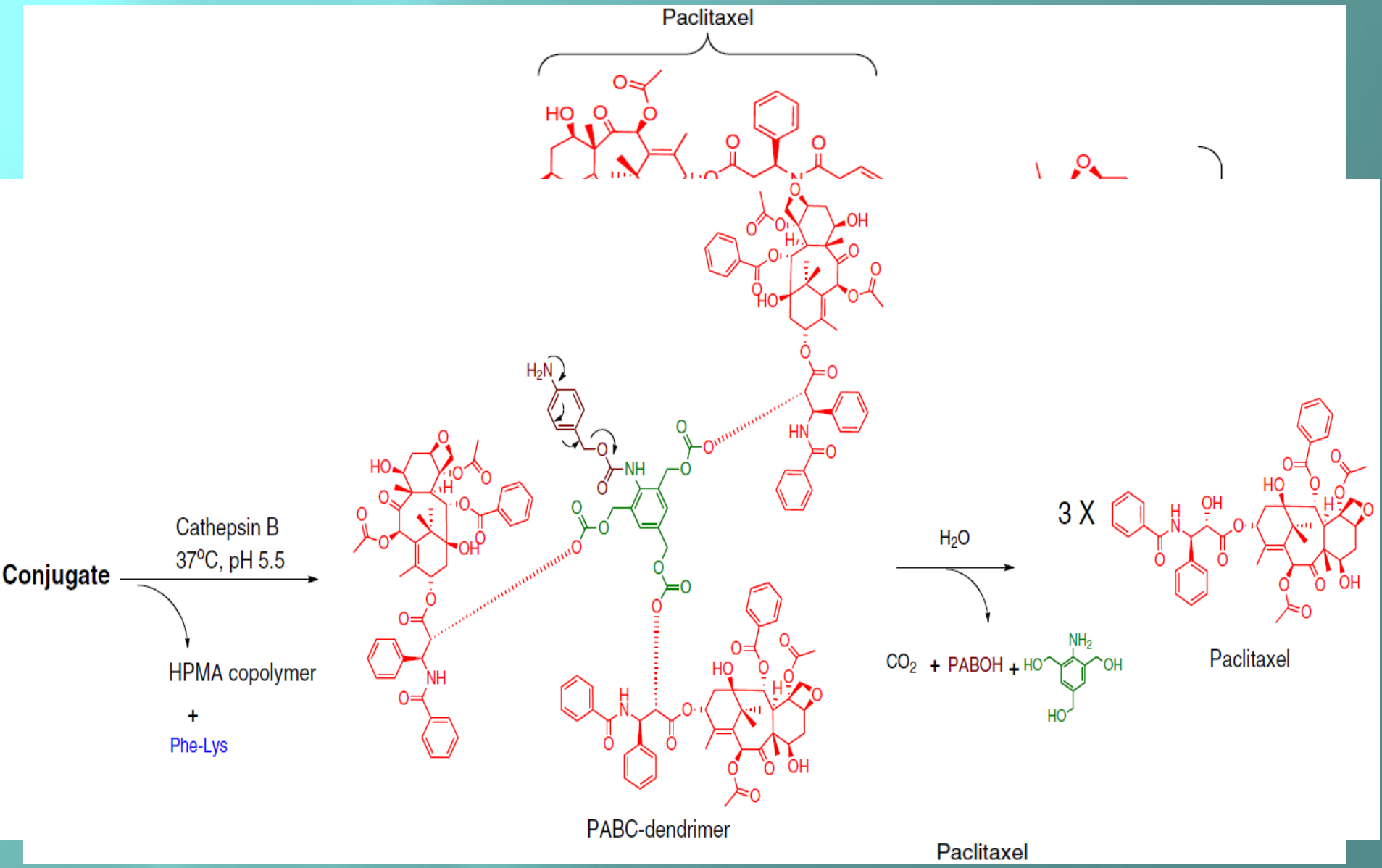


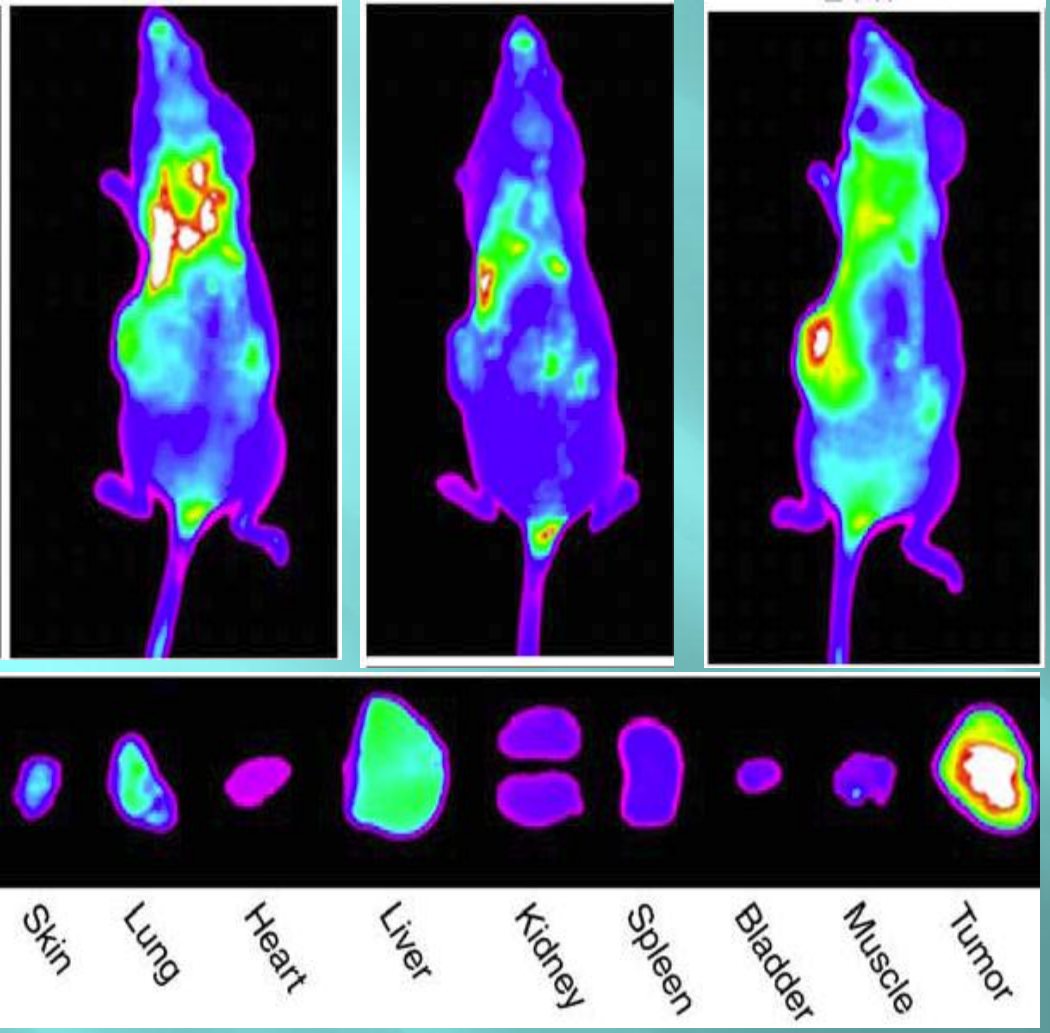


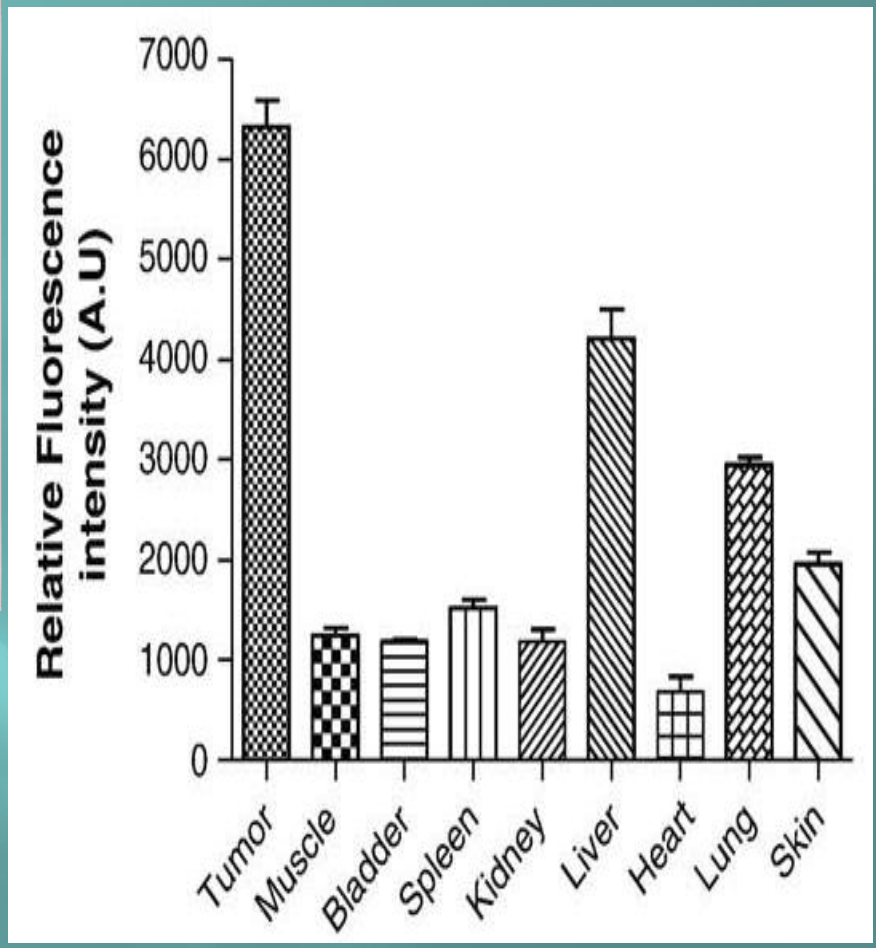
Targeting ligands: sugars, peptides and antibodies.

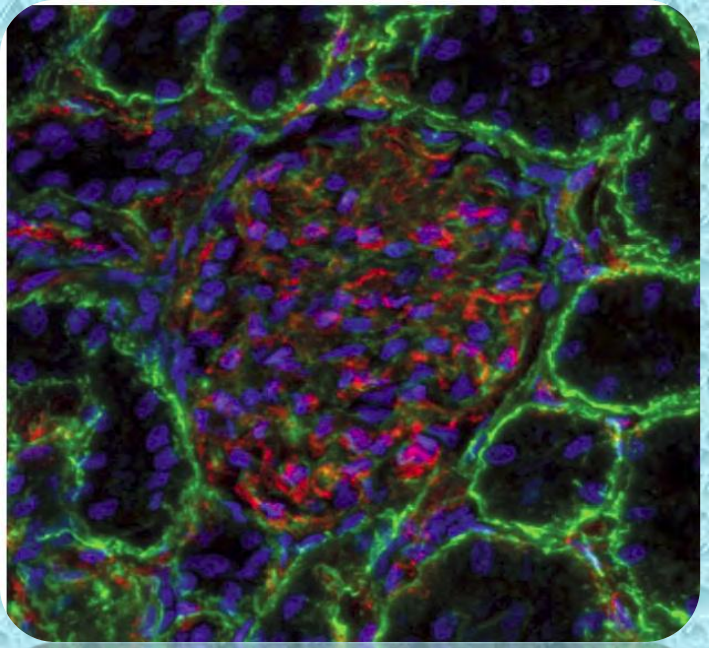


Nature Reviews Cancer, 6, 688-701, 2006.

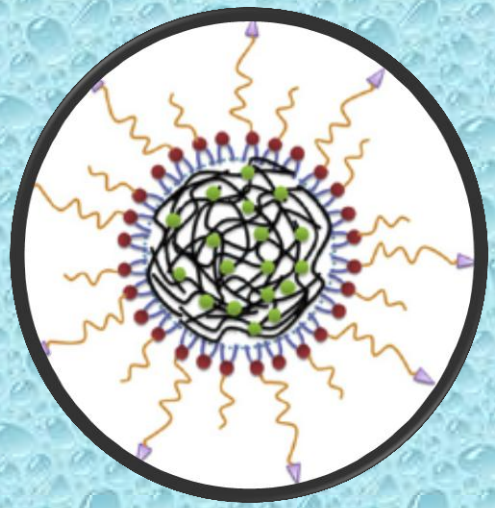

Paclitaxel
Conjugate
Cathepsin B
37°C, pH 5.5
HPMA copolymer
+
Phe-Lys
PABC-dendrimer
H2O
CO2 + PABOH +
3 X
Paclitaxel
Paclitaxel


Skin
Lung
Heart
Liver
Kidney
Spleen
Bladder
Muscle
Tumor


Relative Fluorescence intensity (A.U)
7000
6000
5000
4000
3000
2000
1000
0
Tumor
Muscle
Bladder
Spleen
Kidney
Liver
Heart
Lung
Skin



هر شب، همه چيز و همه كس را مي بخشم. ((ويليام كاينور))

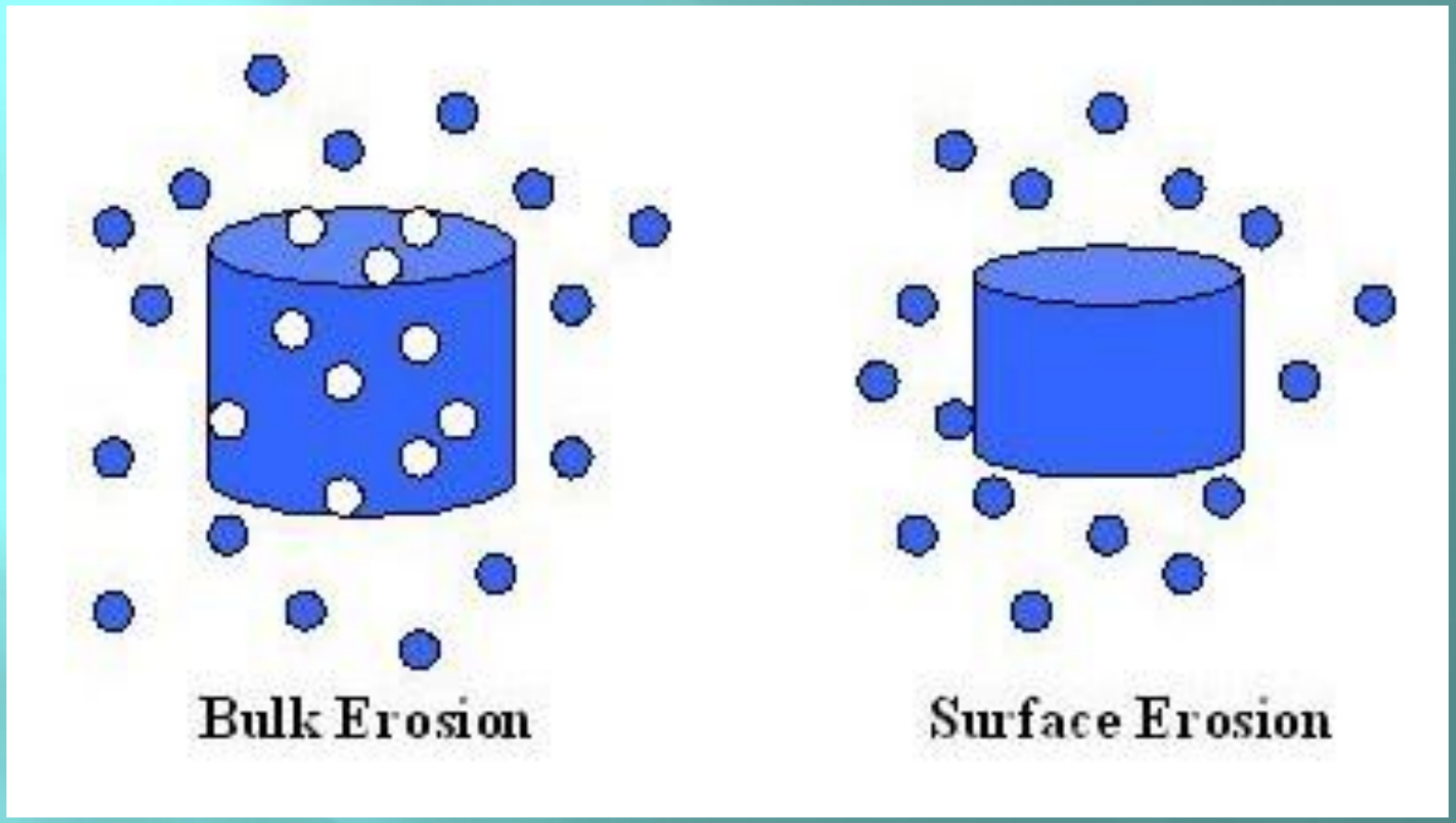


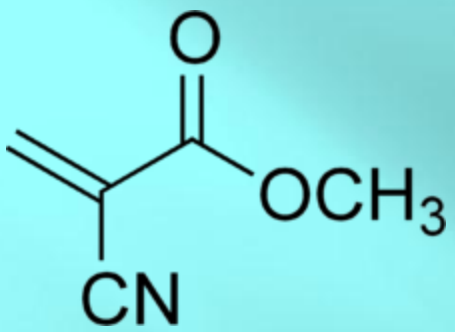
Back up

N-(2-Hydroxypropyl)methacrylamide HPMA

The initiative to the three SSF programmes ”Biocompatible Materials” (BM), ”Molecular Engineering in Polymer Science” (MEPS) and ”Graduate School in Materials Science” (GMS) was taken at Chalmers in Göteborg, and in mid 1997 the programmes could start after comprehensive preparation and planning.

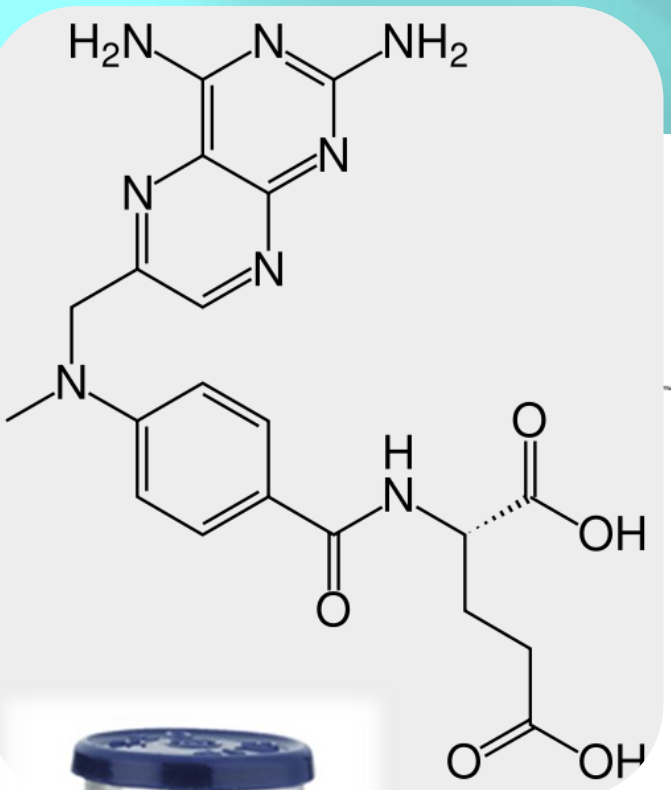
Bioactive polymeric scaffolds are a prerequisite for the ultimate formation of functional tissues. Here, a supramolecular polymers based on quadruple hydrogen bonding ureido-pyrimidinone (UPy) moieties which are eminently suitable for producing such bioactive materials. Particularly, the reversible nature of the hydrogen bonds allows for a modular approach to gaining control over cellular behaviour and activity both *in vitro* and *in vivo*. Bioactive materials are obtained by simply mixing UPy-functionalized polymers with UPy-modified biomolecules. Low-molecular-weight bis-UPy-oligocaprolactones with cell adhesion promoting UPy-Gly-Arg-Gly-Asp-Ser (UPy-GRGDS) and the synergistic UPy-Pro-His-Ser-Arg-Asn (UPy-PHSRN) peptide sequences are synthesized and studied. The *in vitro* results indicate strong and specific cell binding of fibroblasts to the UPy-functionalized bioactive materials containing both UPy-peptides. An even more striking effect is seen *in vivo* where the formation of single giant cells at the interface between bioactive material and tissue is triggered.

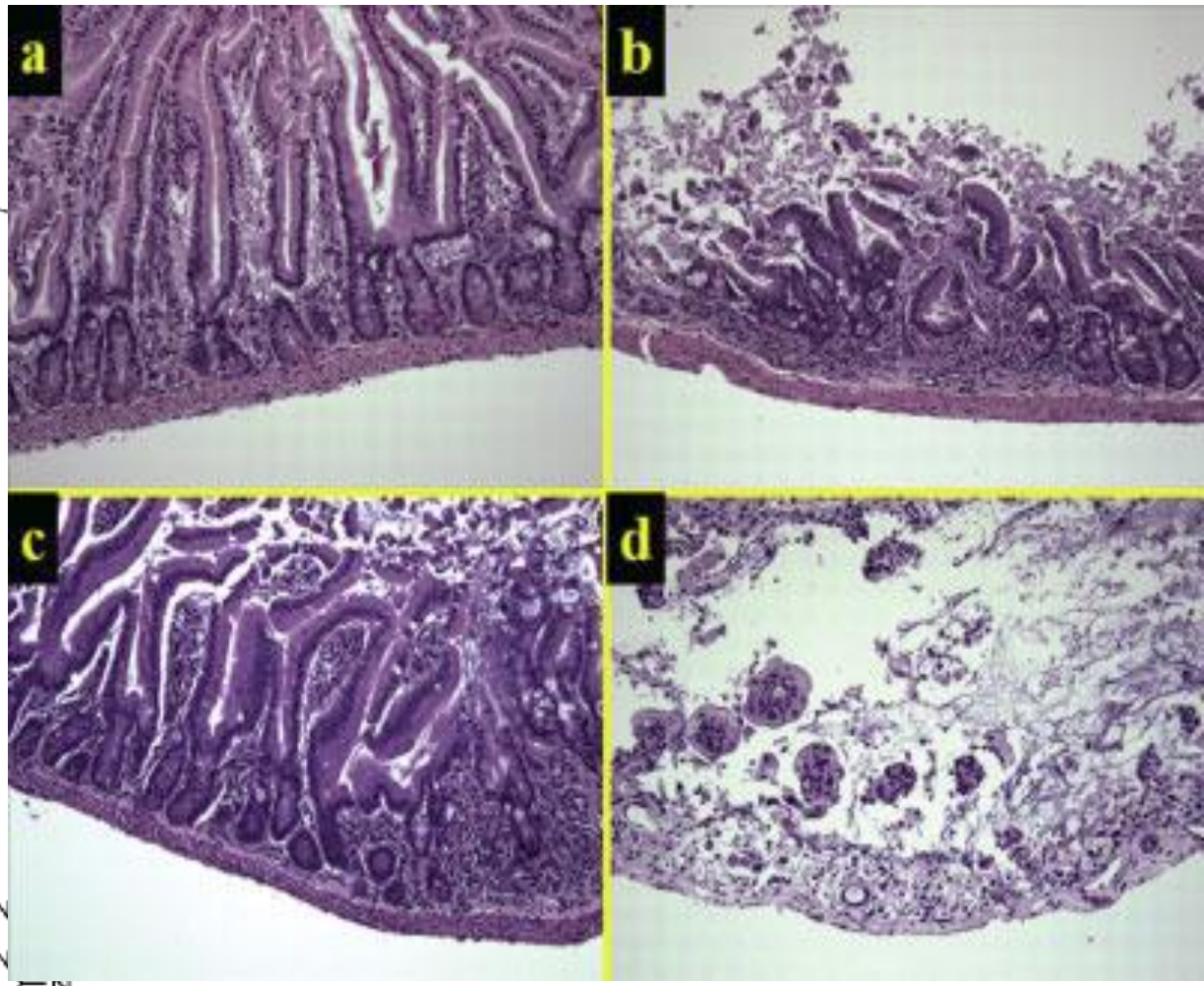

Bulk Erosion
Surface Erosion



Cathepsins (Ancient Greek *kata-* "down" and *hepsein* "boil"; abbreviated **CTS**) are proteases (enzymes that degrades proteins) found in all animals as well as other organisms. There are approximately a dozen members of this family, which are distinguished by their structure, catalytic mechanism, and which proteins they cleave. Most of the members become activated at the low pH found in lysosomes. Thus, the activity of this family lies almost entirely within those organelles. There are, however, exceptions such as cathepsin K, which works extracellularly after secretion by osteoclasts in bone resorption.

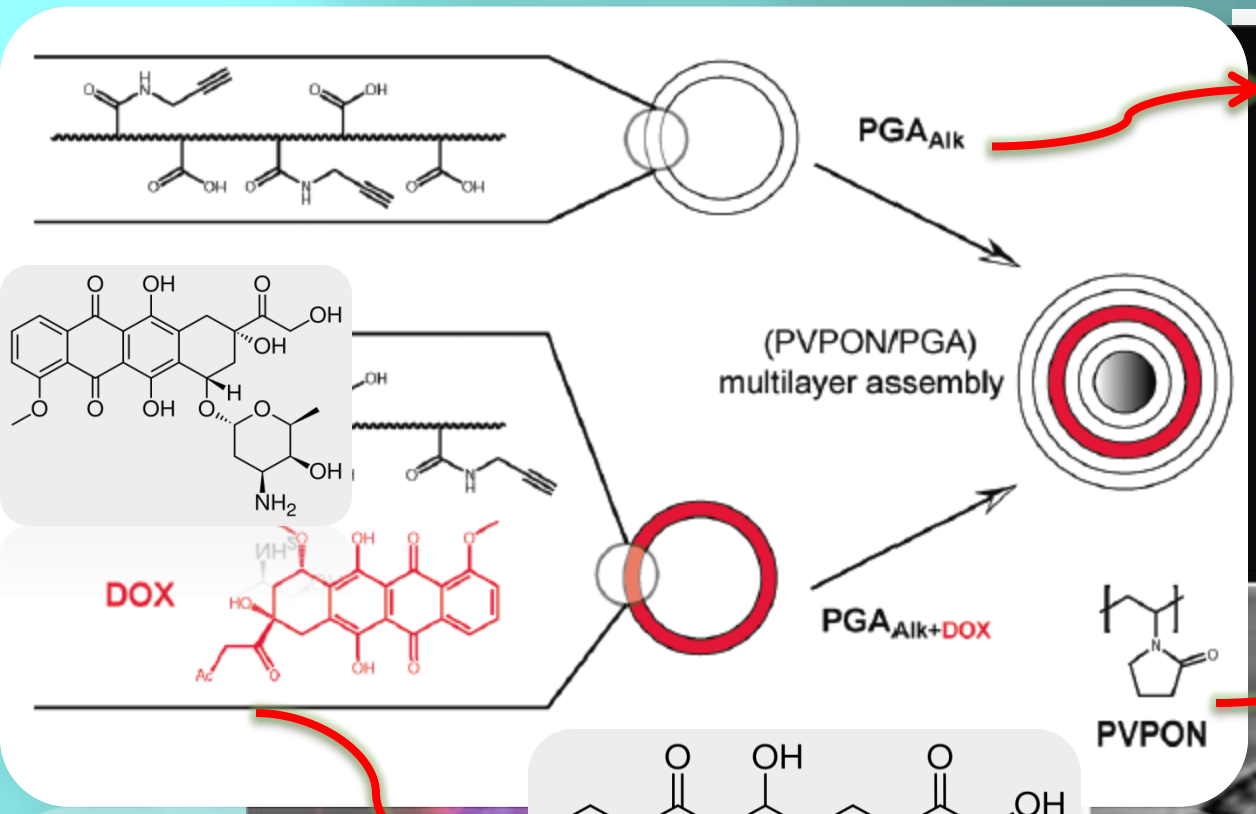
Methotrexate

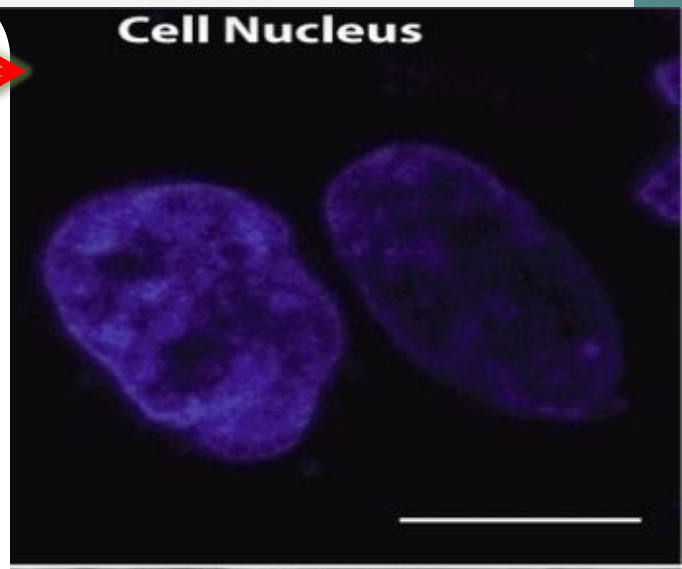


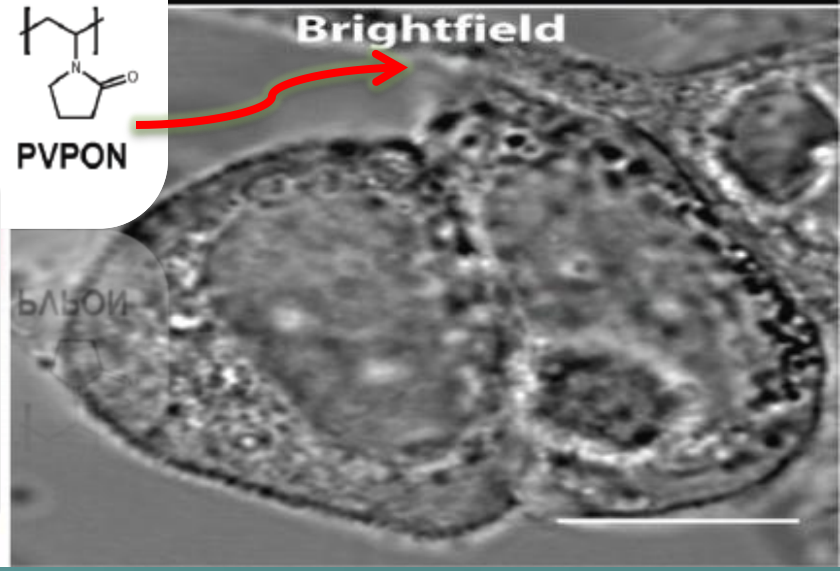


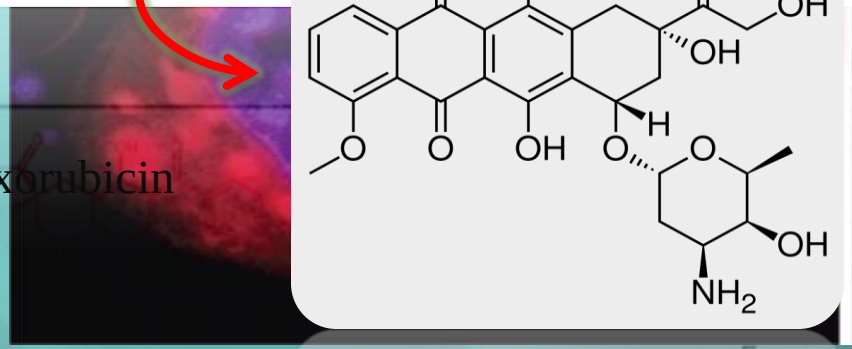
Robert F. Padera, Natalie M. DangInt , Int. J. Cancer, 118, 1519,2006

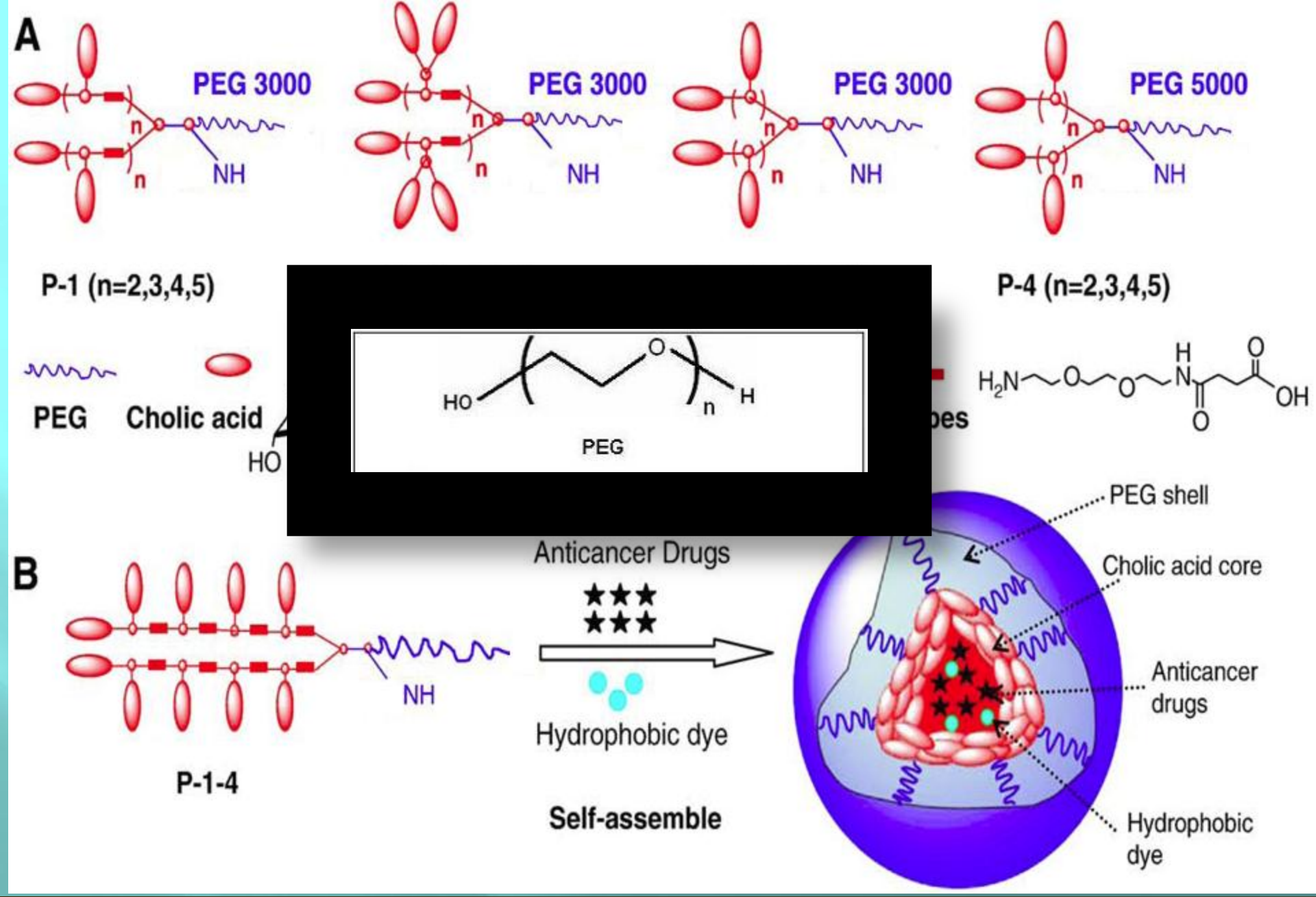
Doxorubicin (DOX)



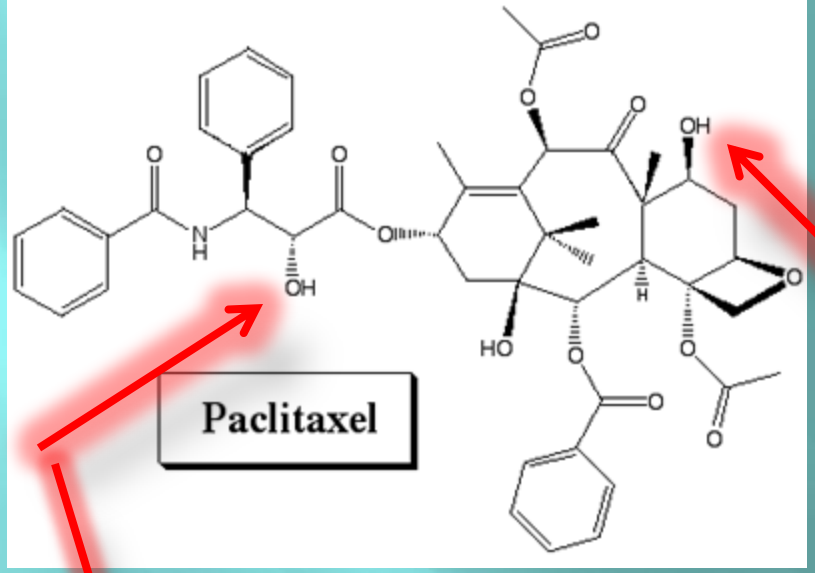


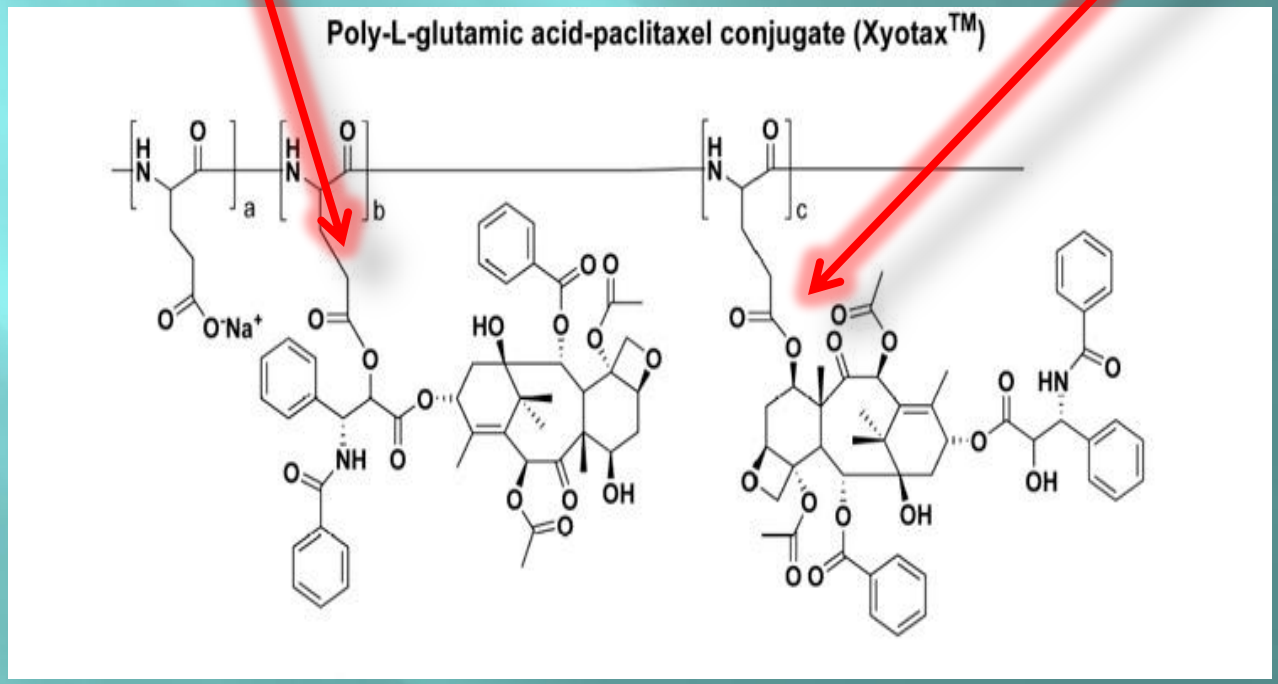





A
PEG 3000
PEG 3000
PEG 3000
PEG 5000
NH
P-1 (n=2,3,4,5)
P-4 (n=2,3,4,5)
PEG
Cholic acid
HO
HO
O
H
n
PEG
B
NH
P-1-4
Anticancer Drugs
Hydrophobic dye
Self-assemble
PEG shell
Cholic acid core
Anticancer drugs
Hydrophobic dye

Xyotax





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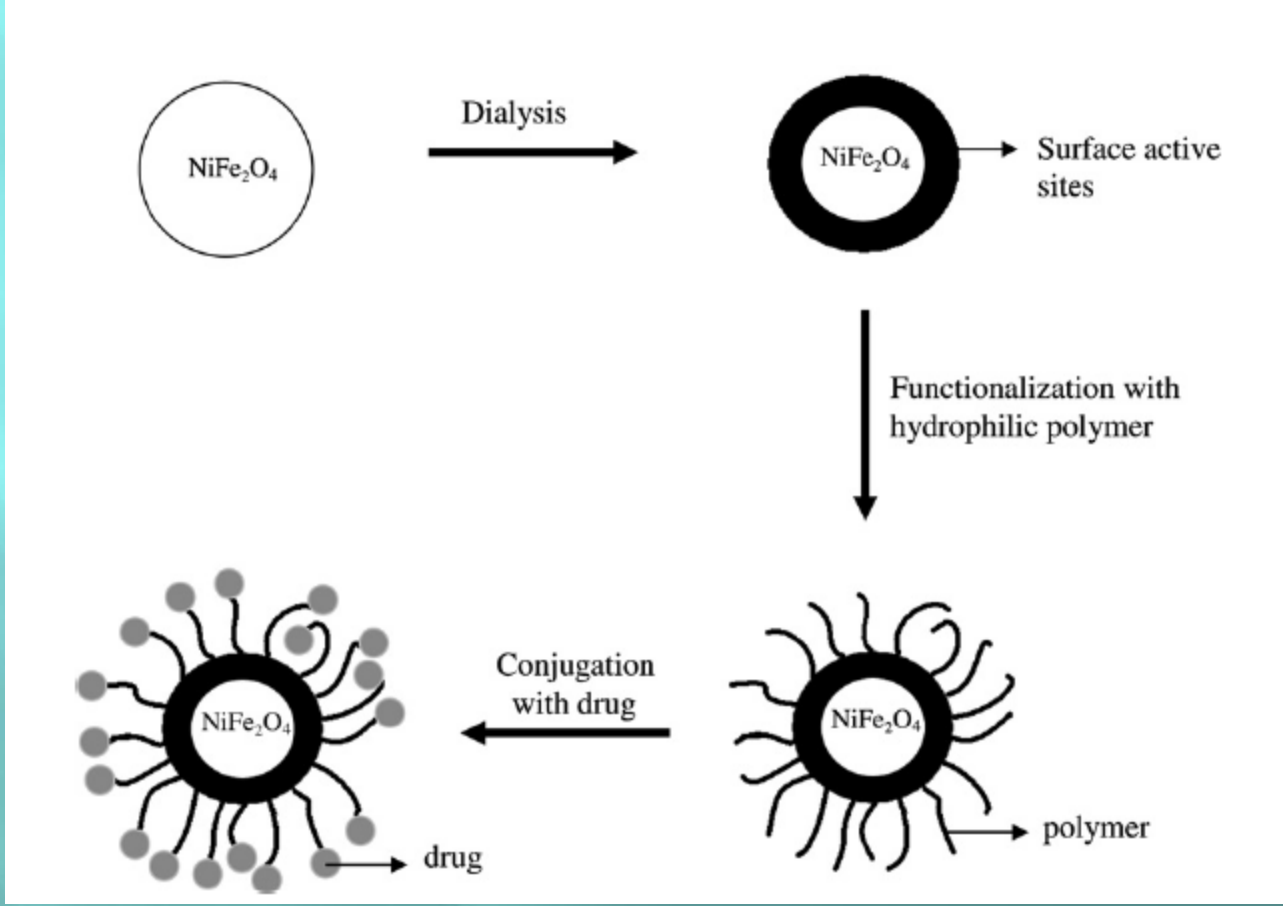
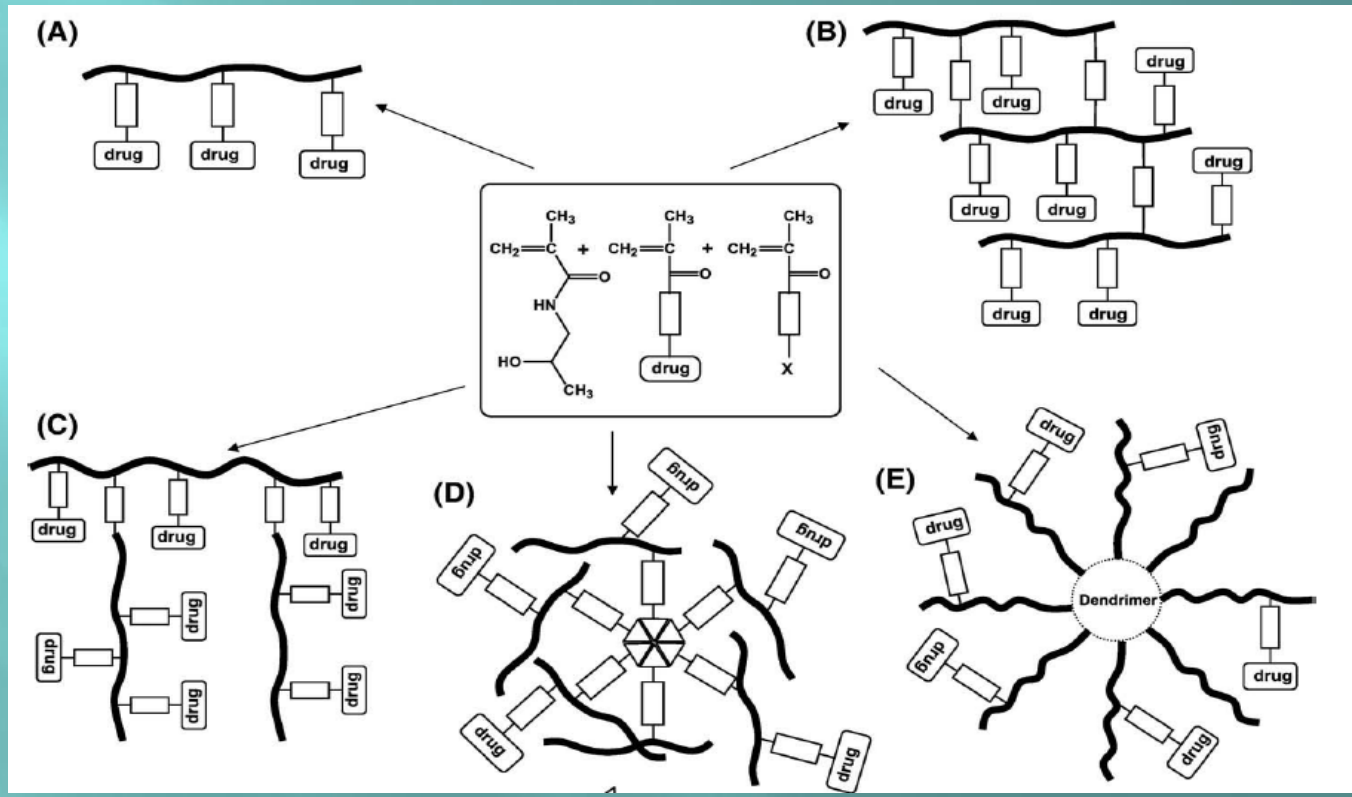
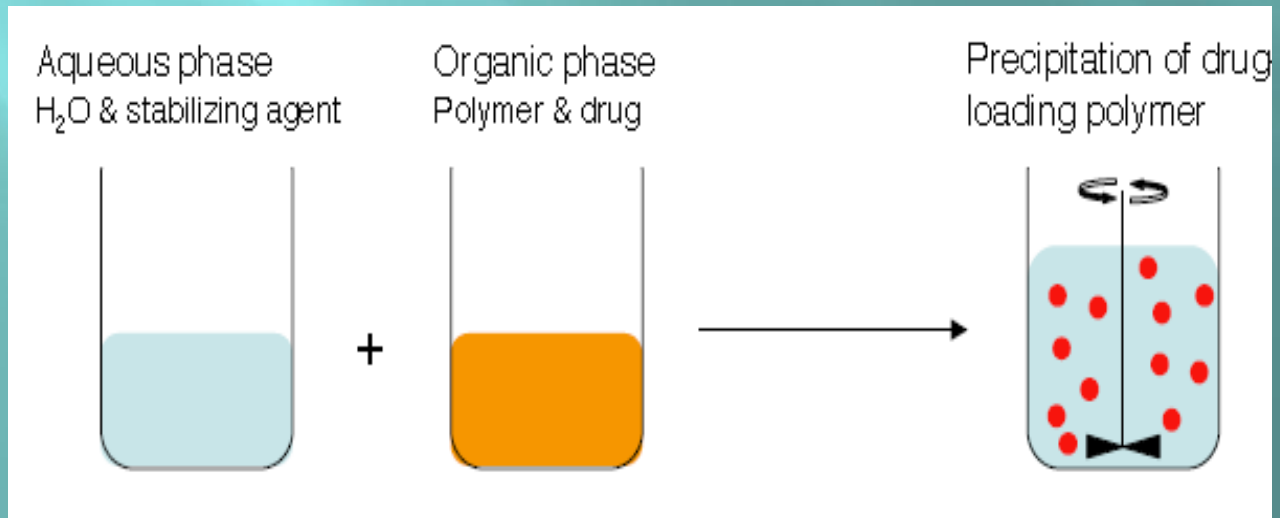
مغناطيسي

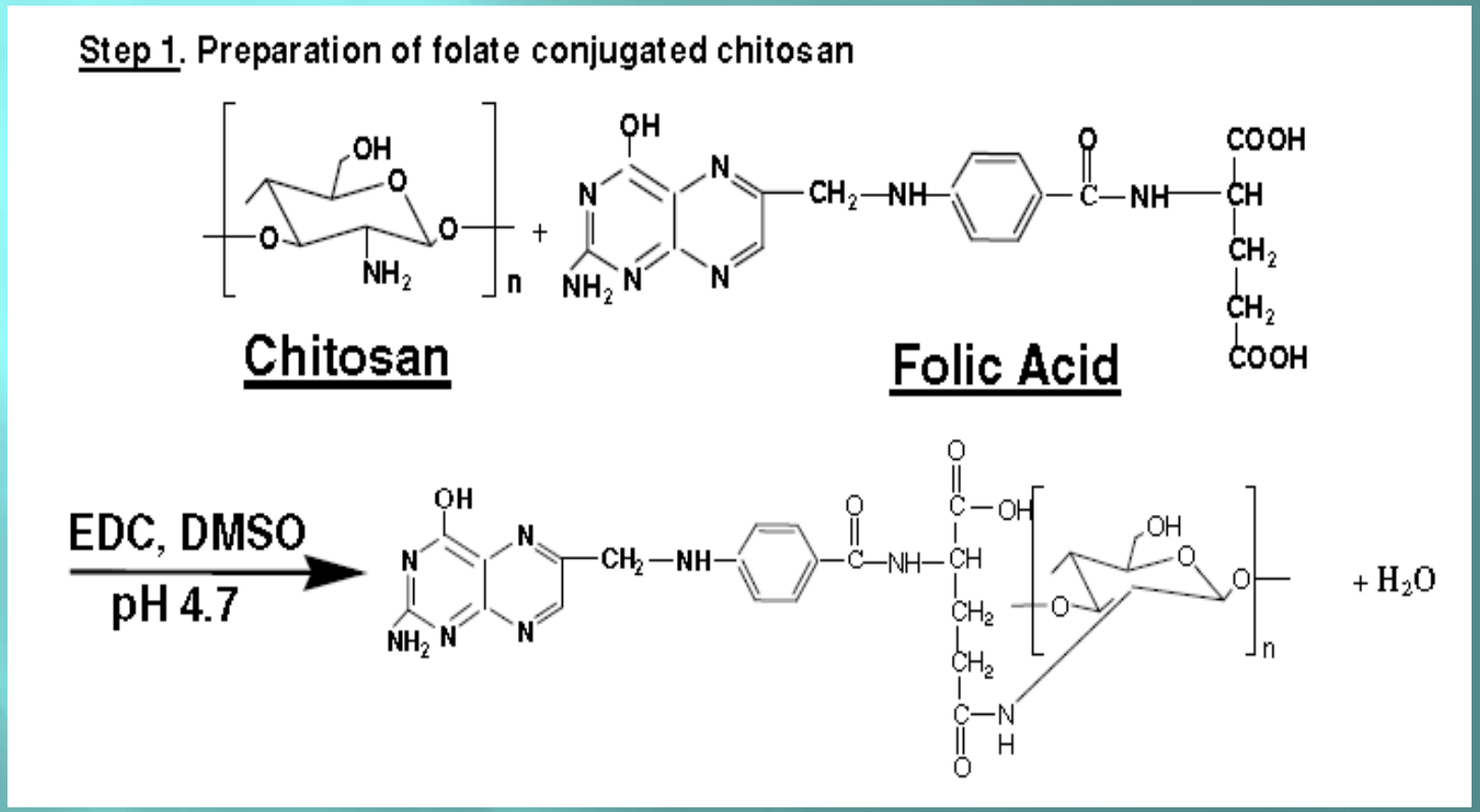

$NiFe_2O_4$
Dialysis
$NiFe_2O_4$
Surface active sites
Functionalization with hydrophilic polymer
$NiFe_2O_4$
polymer
Conjugation with drug
$NiFe_2O_4$
drug

نحوه مخلوط کردن

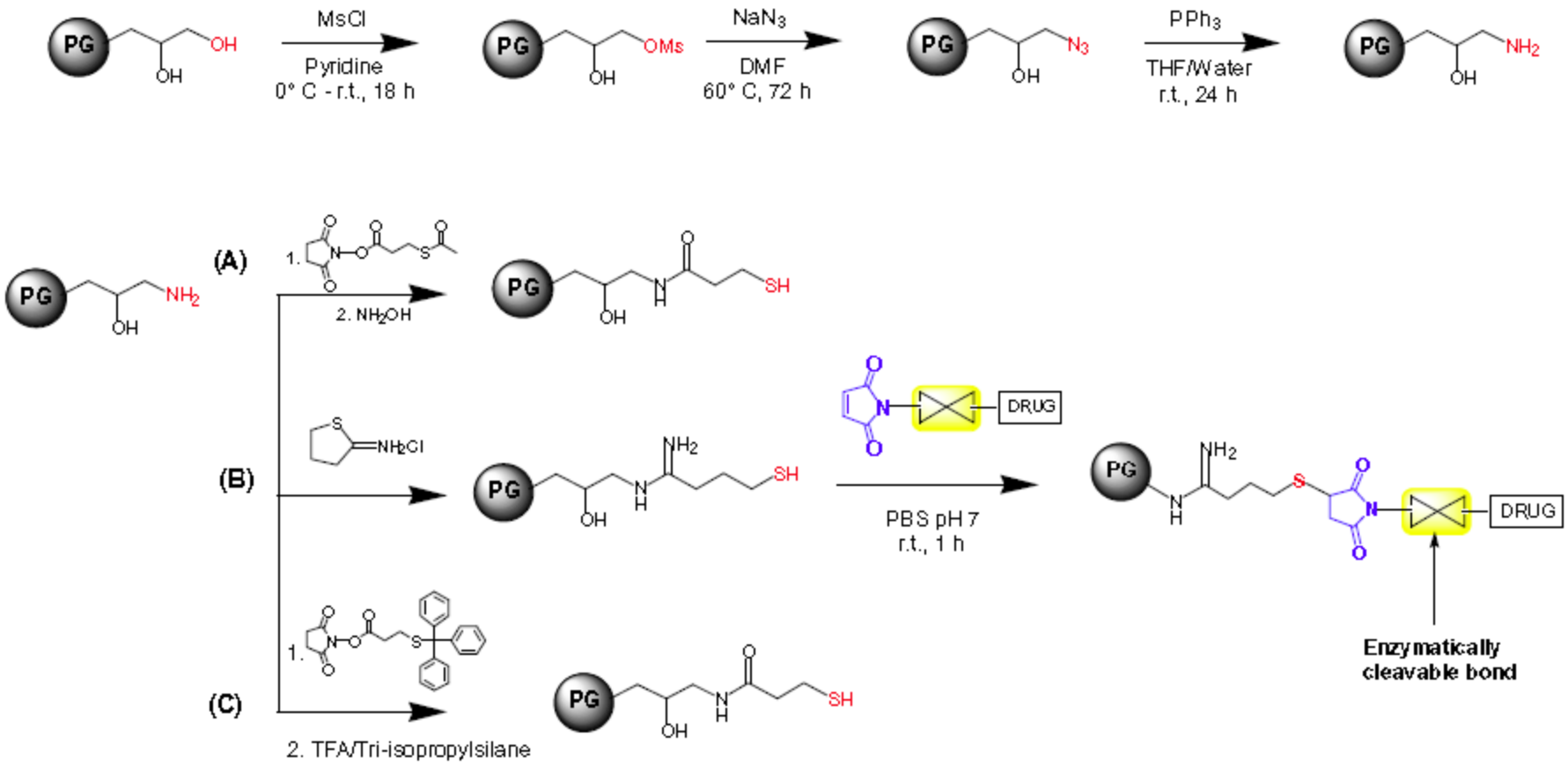




chitosan



Acta Biomaterialia, Q. Yuan a, S. Hein b, R.D.K. Misra, xxx (2010) xxx–xxx



Scheme 1. Studied pathways for synthesis of thiolated polyglycerol and prodrug coupling.

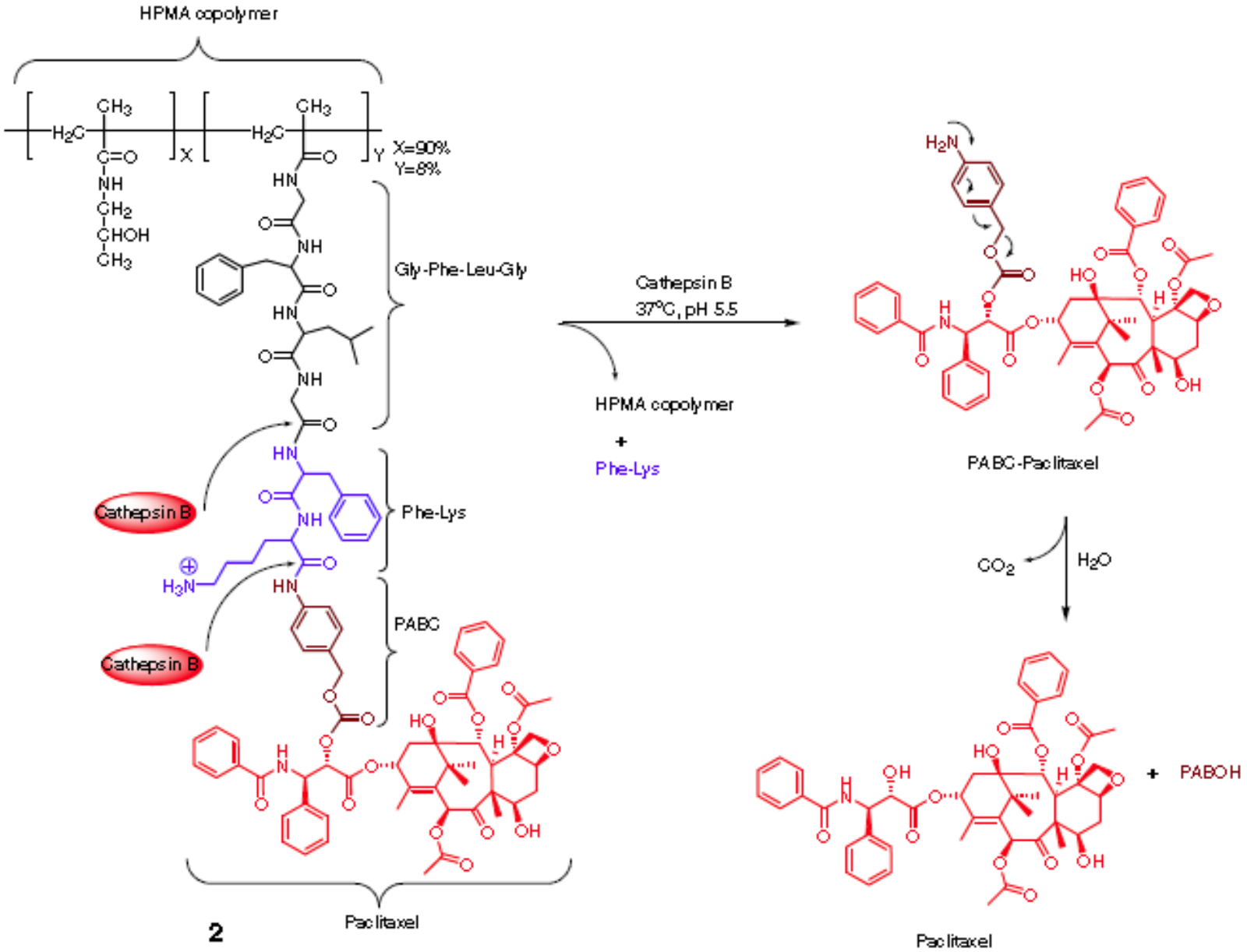
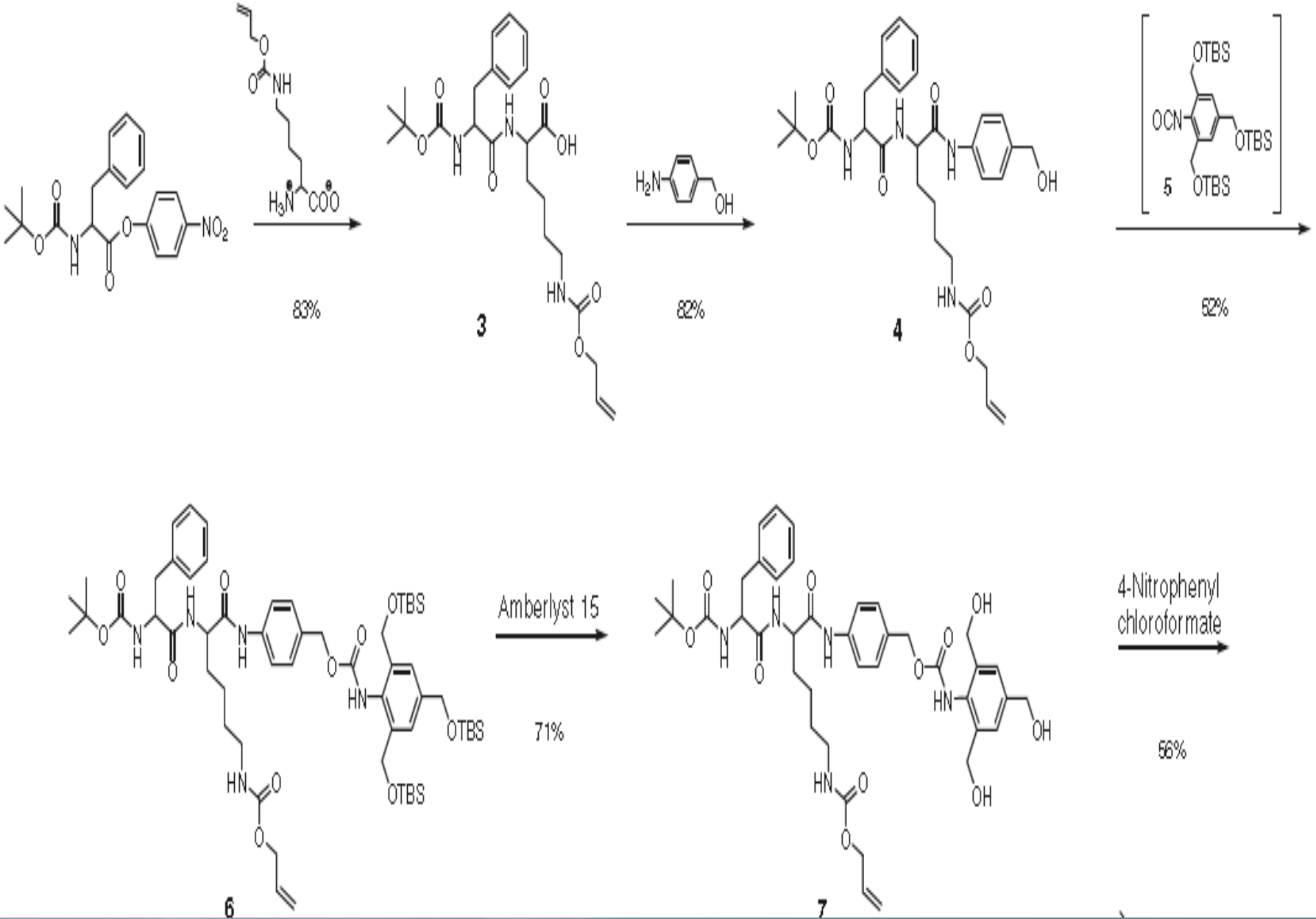
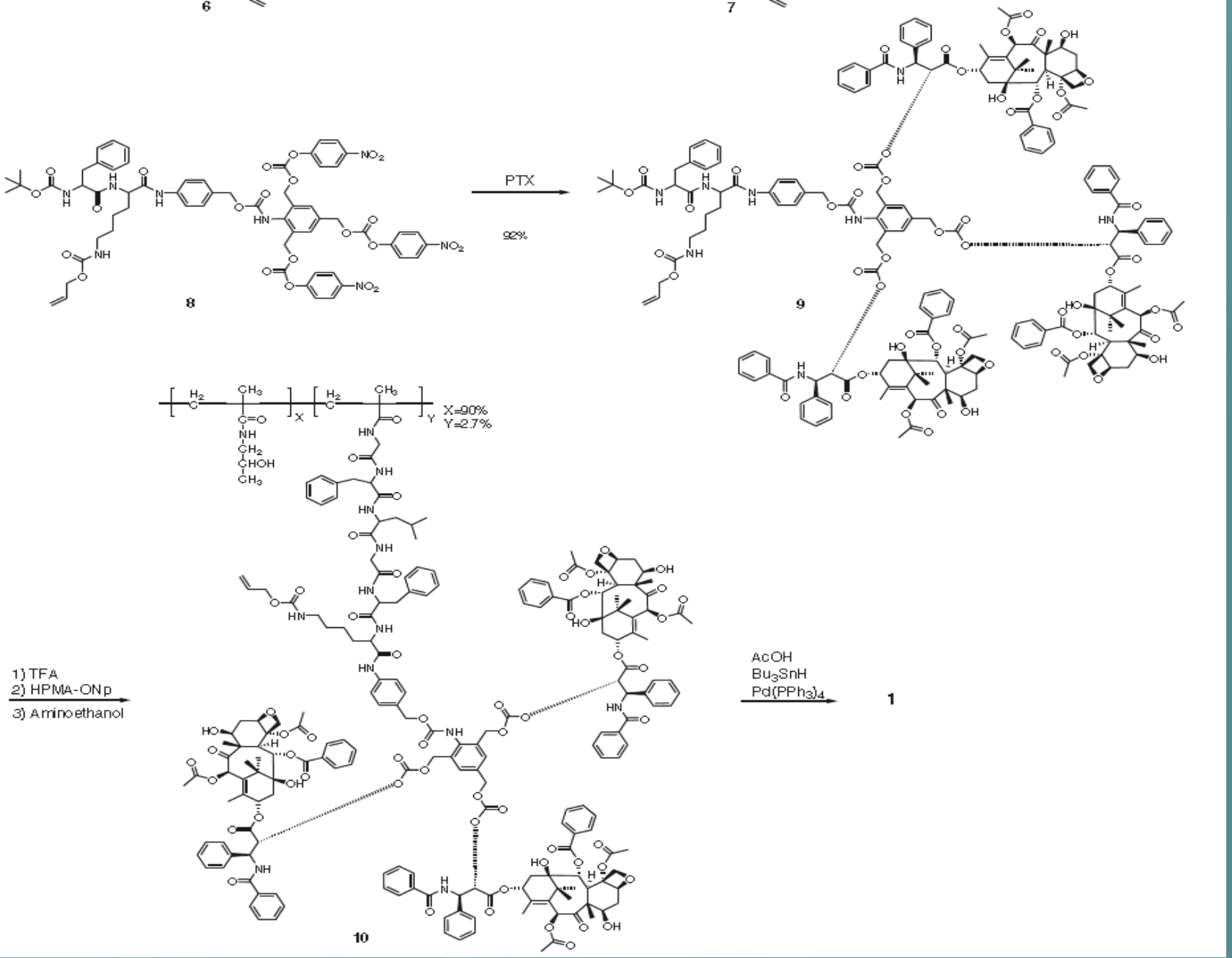
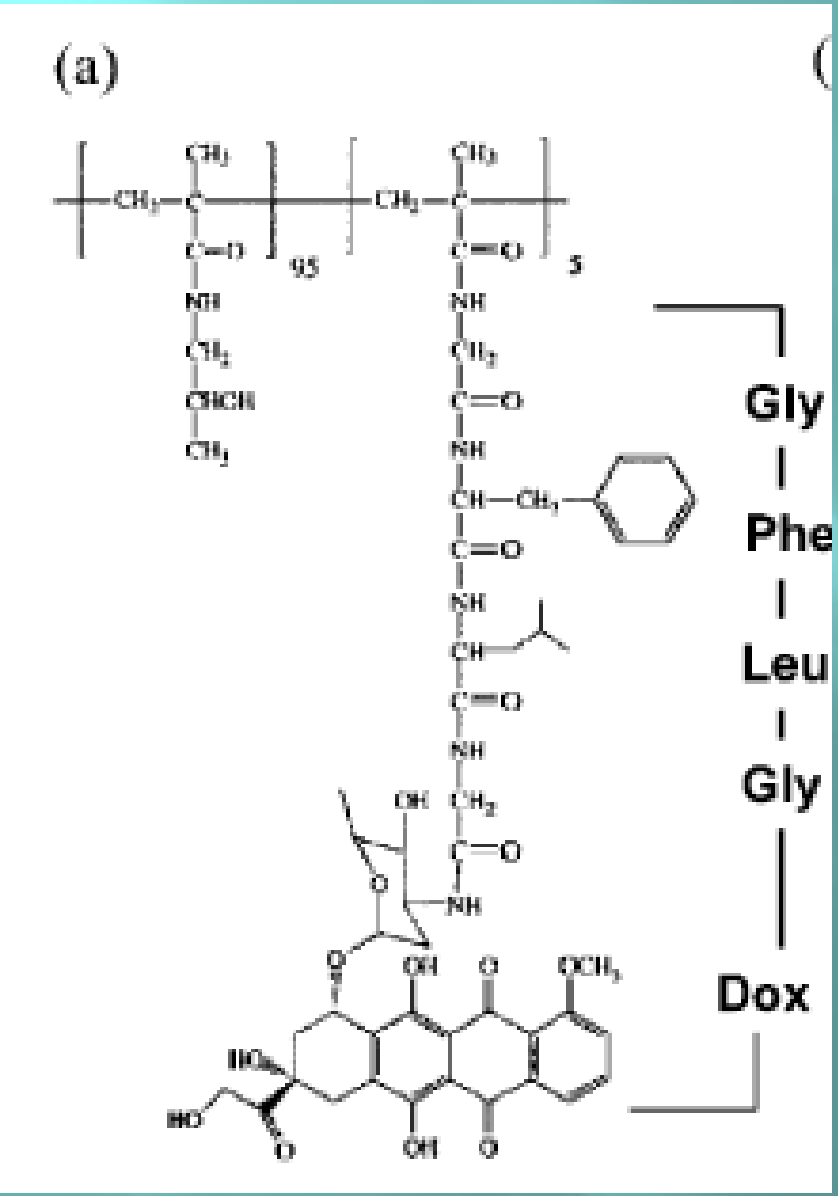


Figure 5. Disassembly mechanism of conjugate **2**.


83%
3
82%
4
5
OTBS
OCN
OTBS
OTBS
82%
Amberlyst 15
71%
6
7
4-Nitrophenyl
chloroformate
56%


6
7
8
PTX
92%
9
X=90%
Y=2.7%
1) TFA
2) HPMA-ONp
3) Aminoethanol
10
AcOH
Bu_3SnH
$Pd(PPh_3)_4$
1


(a)
95
5
Gly
Phe
Leu
Gly
Dox