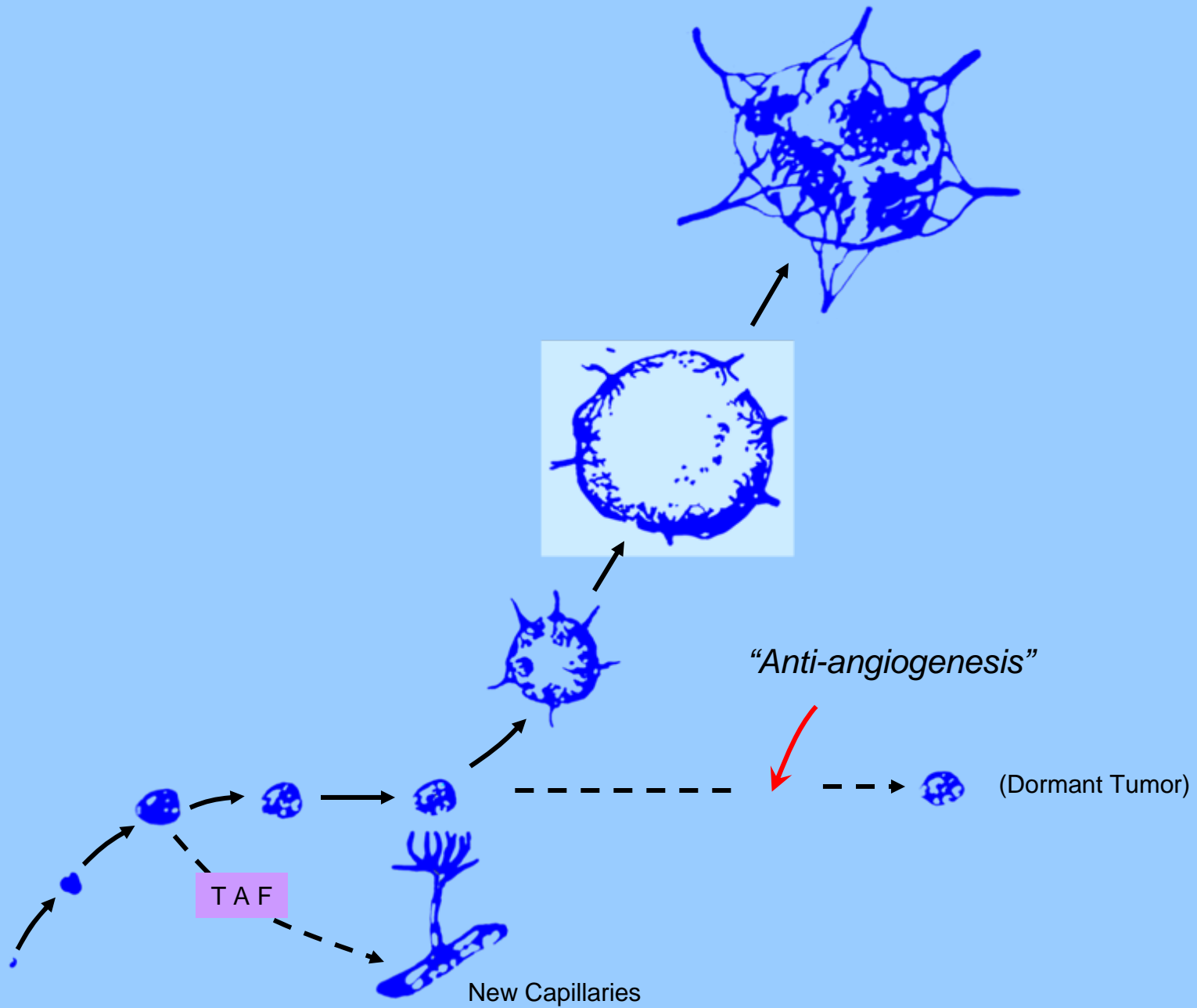


New directions in drug delivery

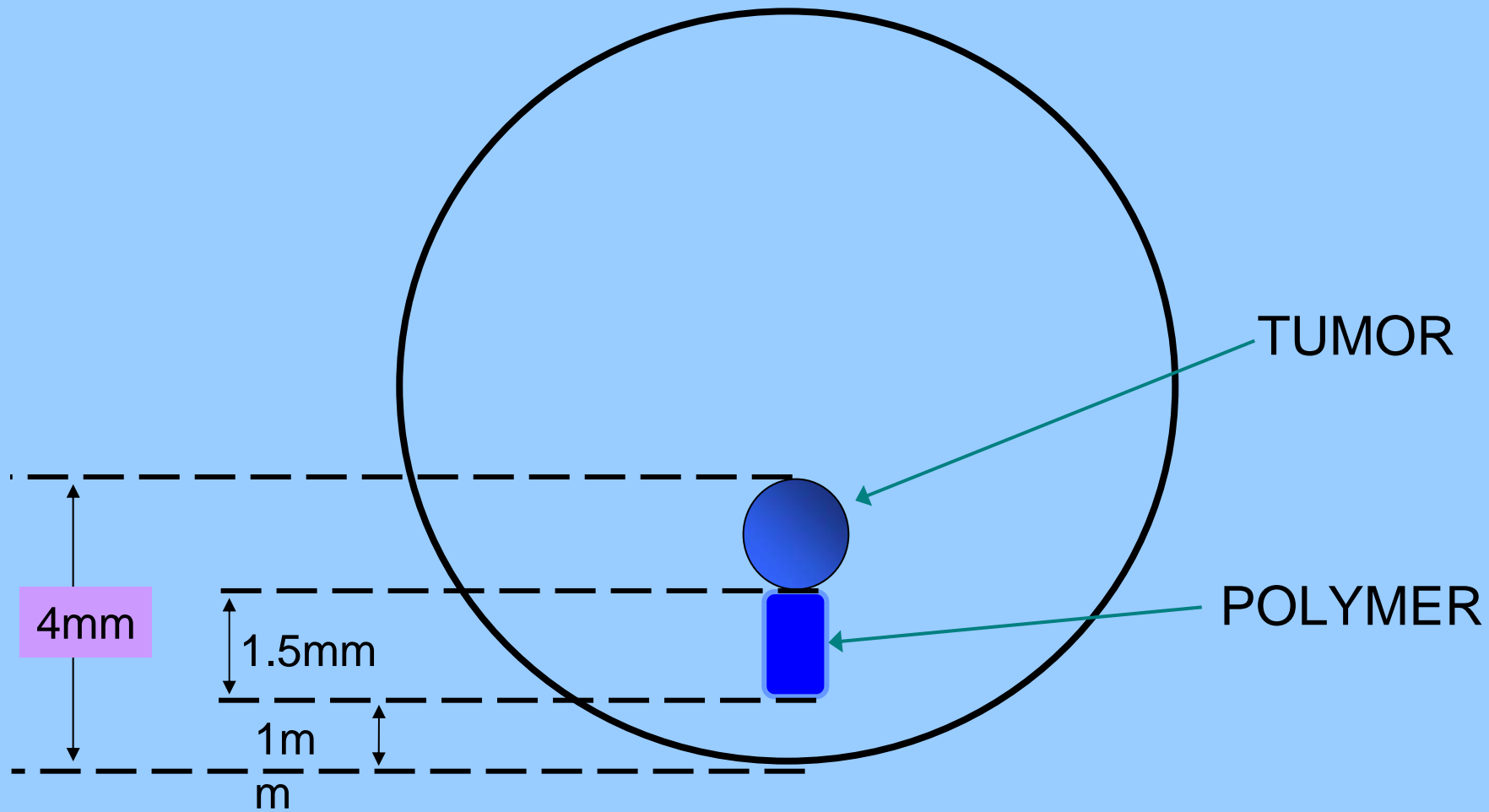
Dr. Robert S. Langer

David H. Koch Institute Professor

Massachusetts Institute of Technology



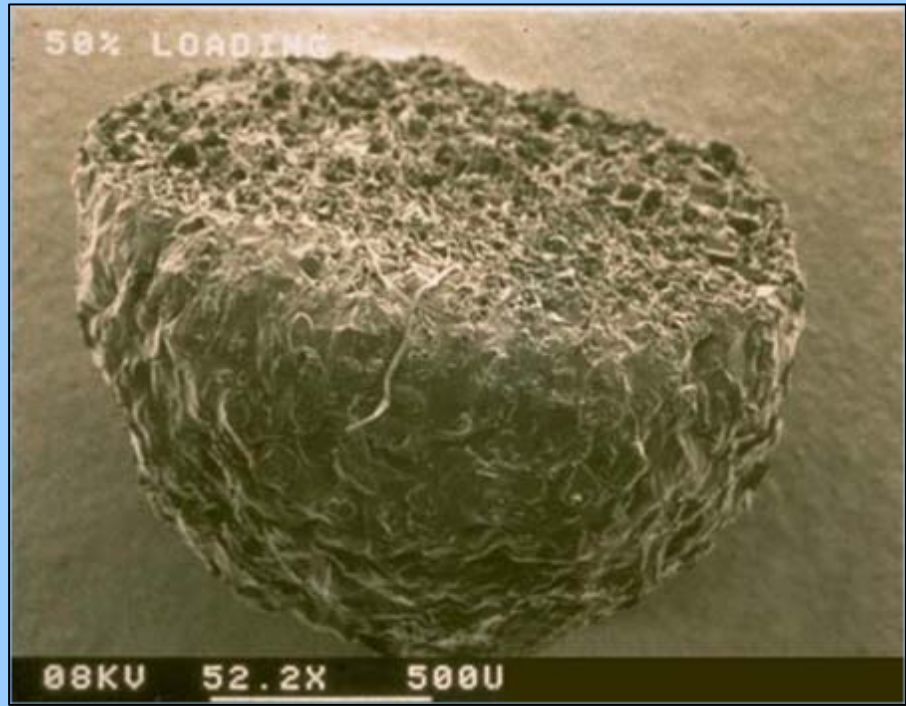
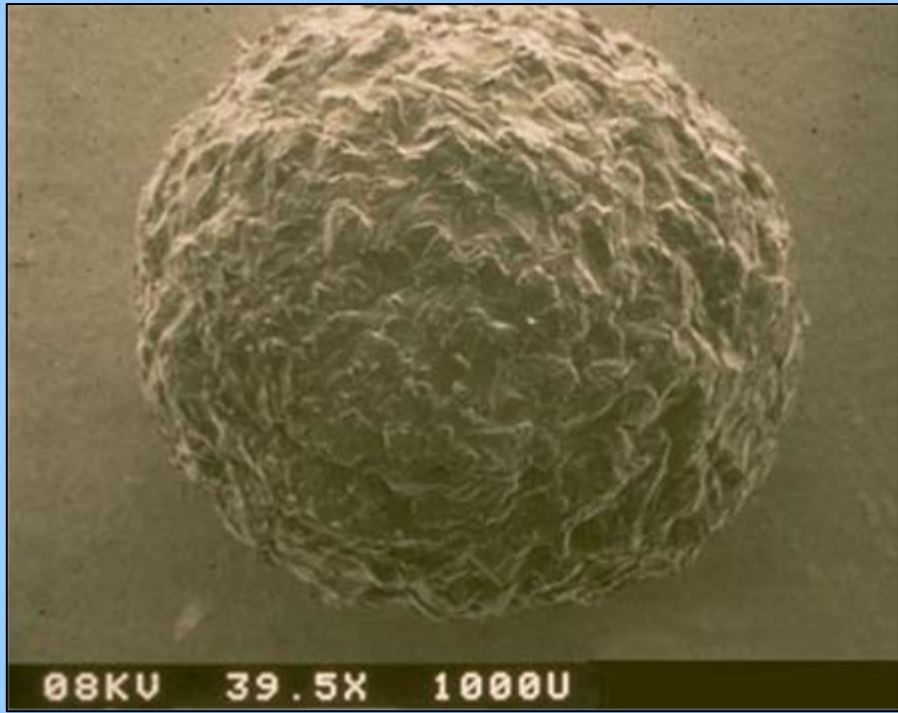


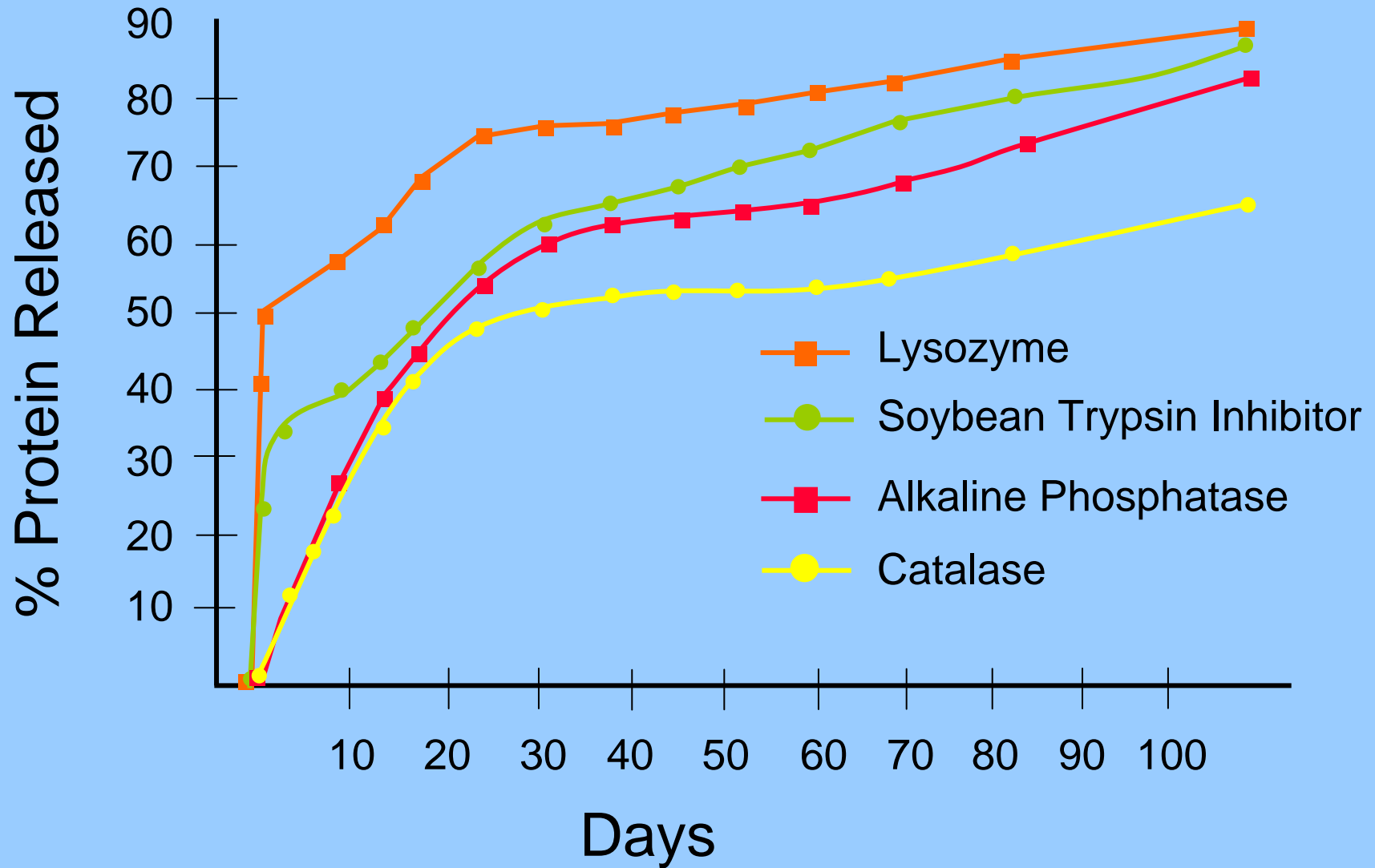


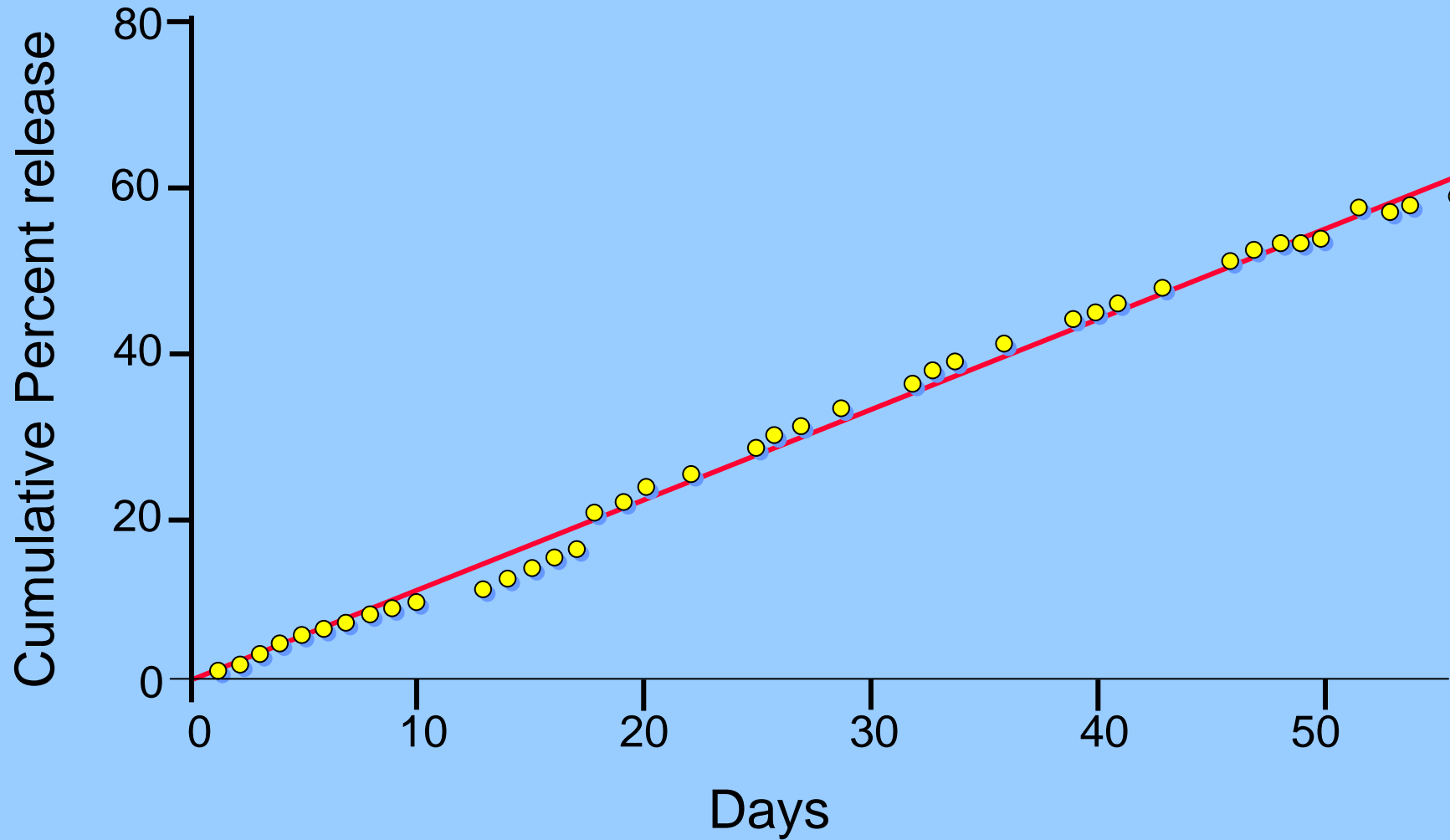
POLYPEPTIDE	Mol. Wt.	Half-Life
Growth Hormone	22,600	< 25 minutes
Insulin	6,000	< 25 minutes
Oxytocin	1,007	2 minutes
Parathyroid Hormone	9,500	< 15 minutes
Vasopressin	1,200	4 minutes

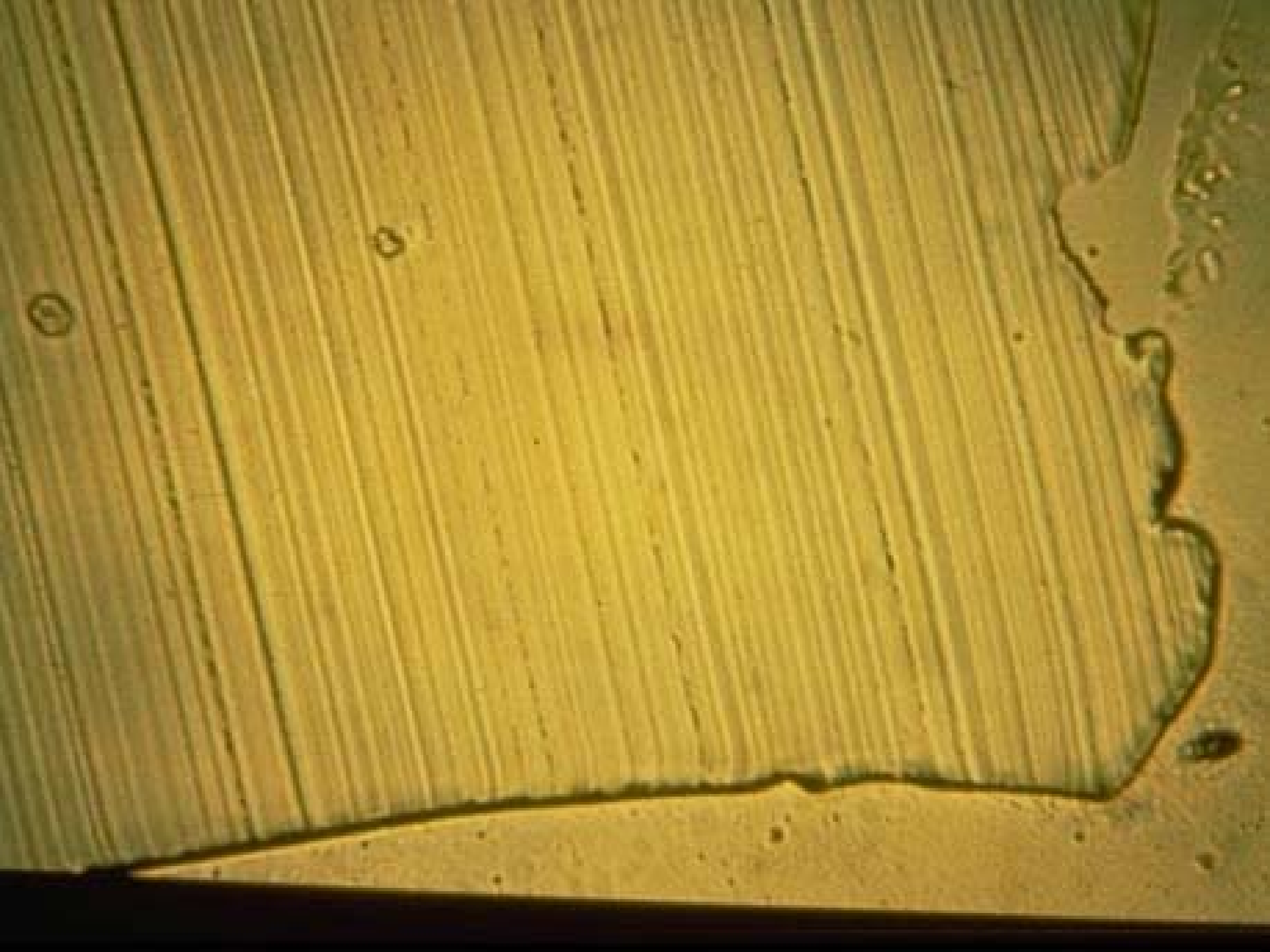
“The agent to be released is a small molecule with a molecular weight no larger than a few hundred. One would not expect that macromolecules e.g. proteins, could be released because of their extremely small permeation rates through polymers.”

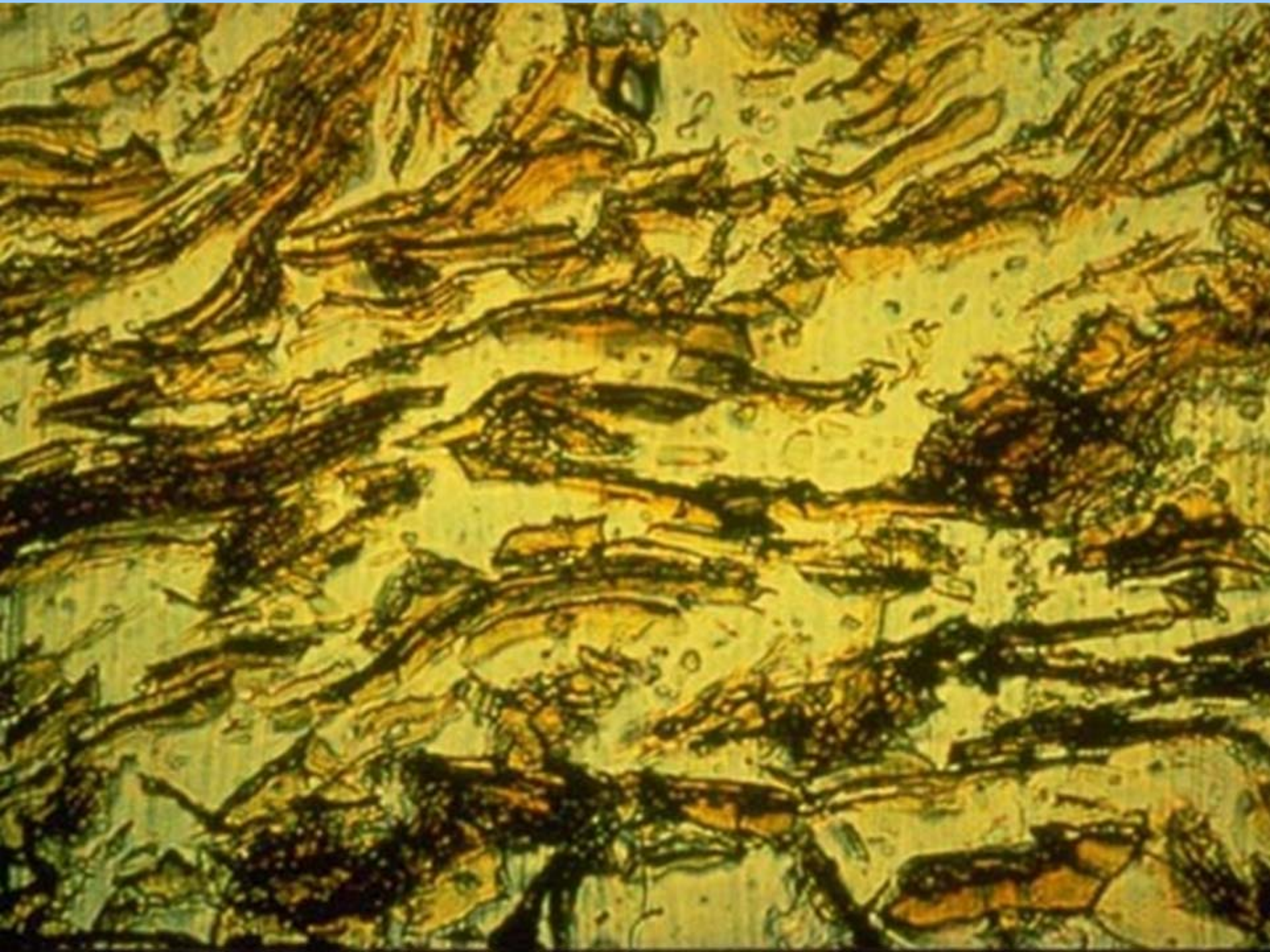
Adv. Poly. Sci., 1977

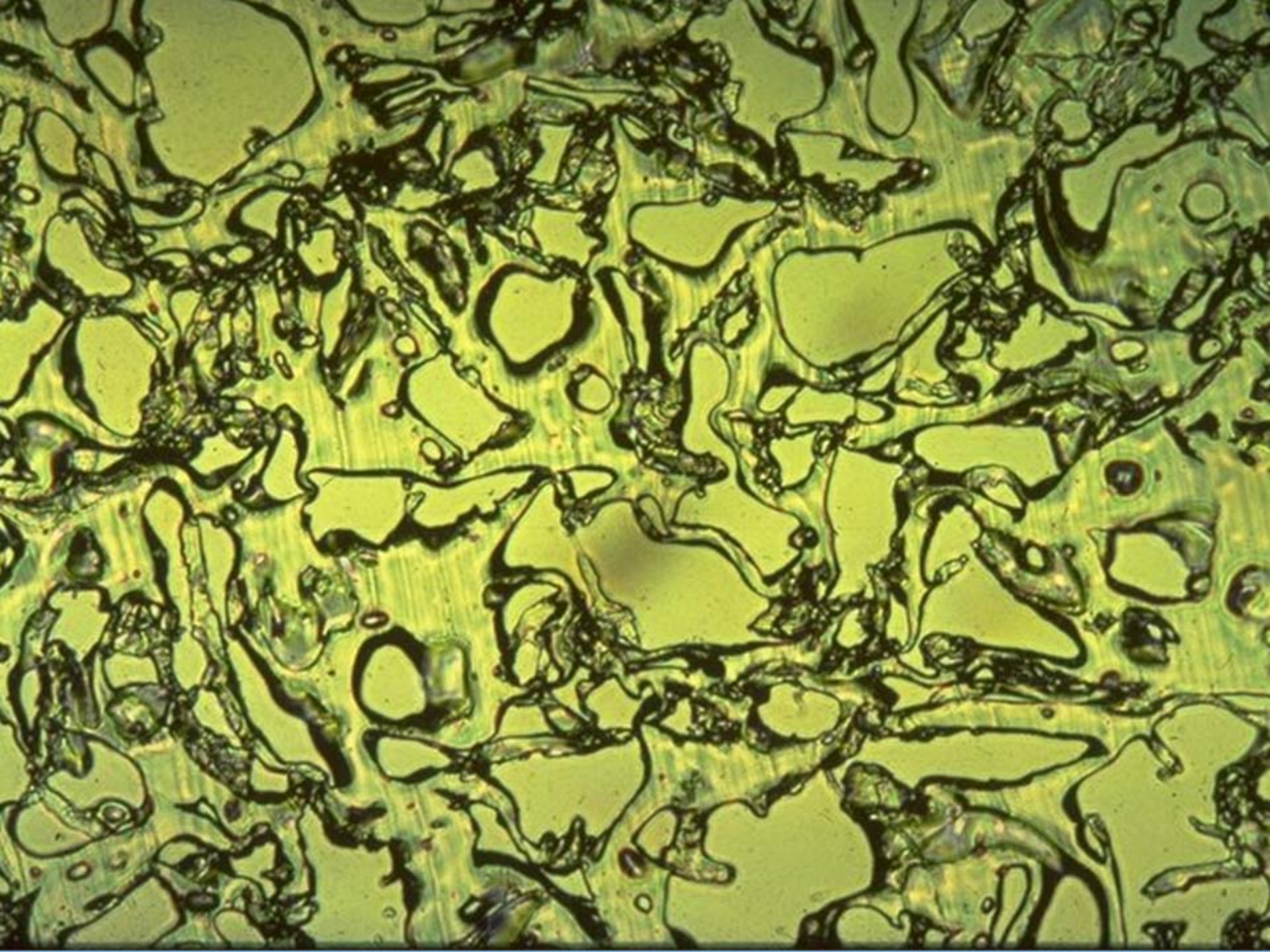


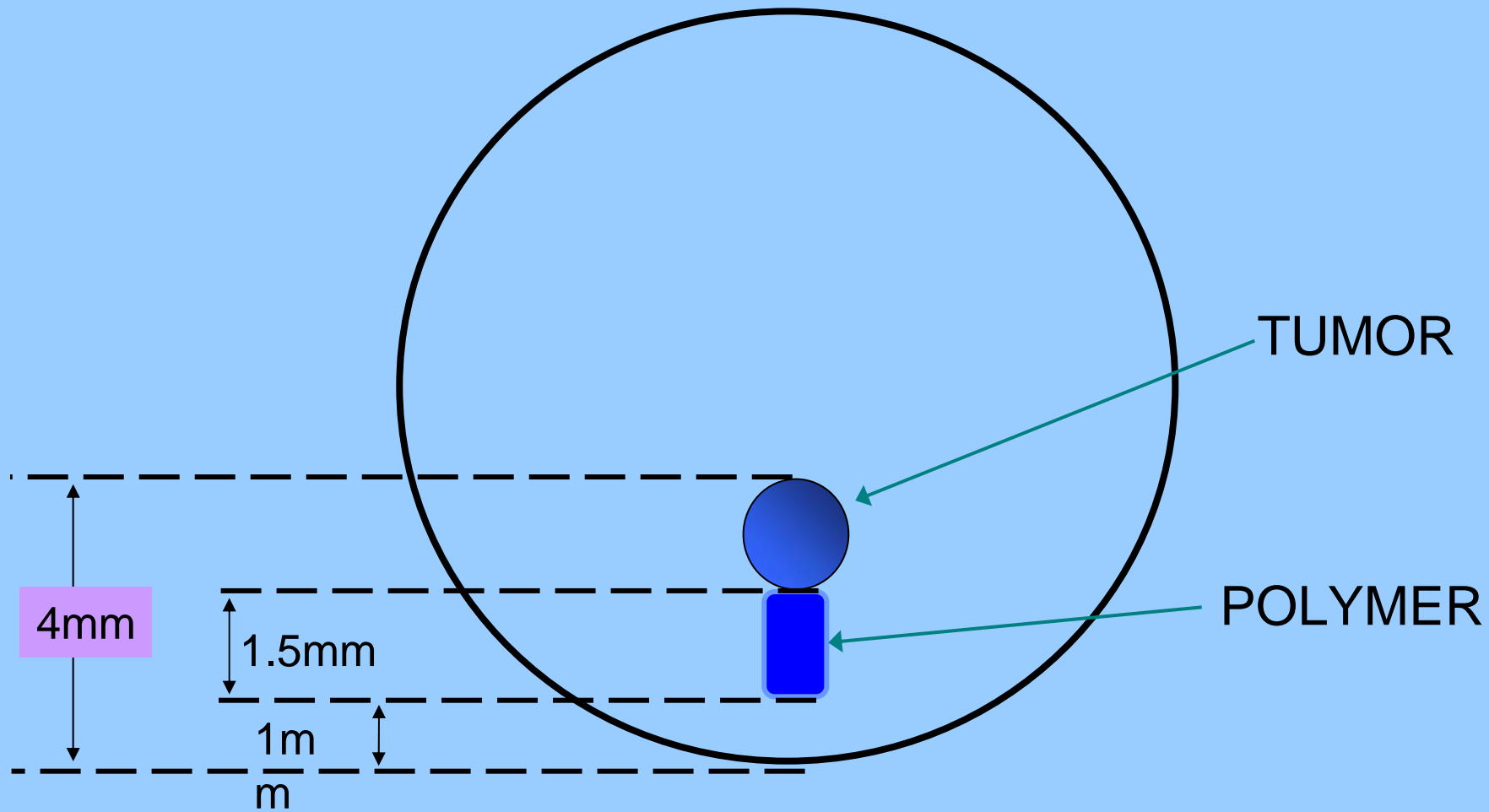






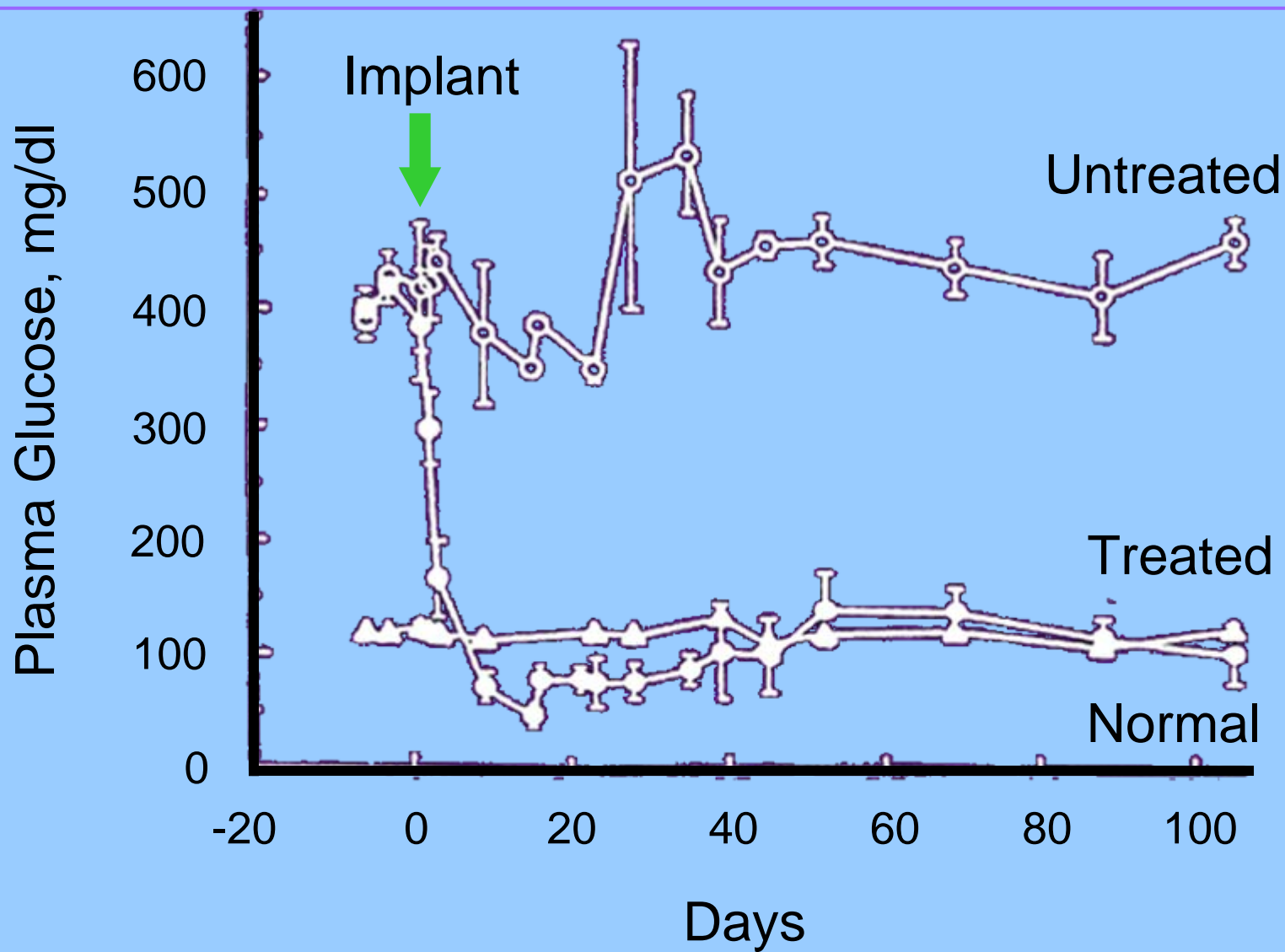






Angiogenesis inhibitors approved for clinical use

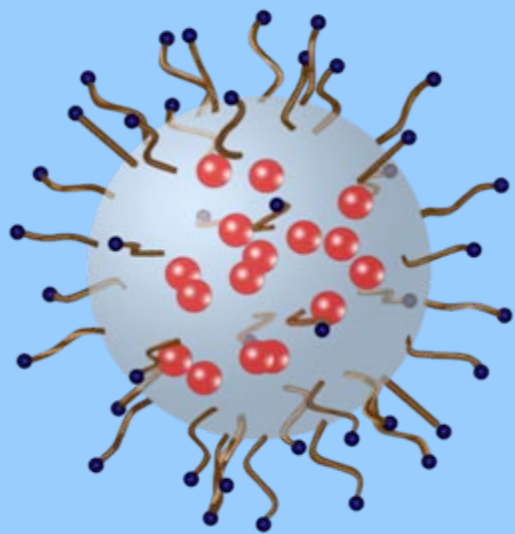
Date Approved	Drug	Disease
February 2004	Avastin (Bevacizumab)	Colorectal Cancer
November 2004	Tarceva (Erlotinib)	Lung Cancer
December 2004	Macugen	Macular Degeneration
December 2005	Nexavar (Sorafenib)	Kidney Cancer
December 2005	Revlimid	Myelodysplastic syndrome
January 2006	Sutent (Sunitinib)	Gastric (GIST), Kidney Cancer
June 2006	Lucentis	Macular Degeneration



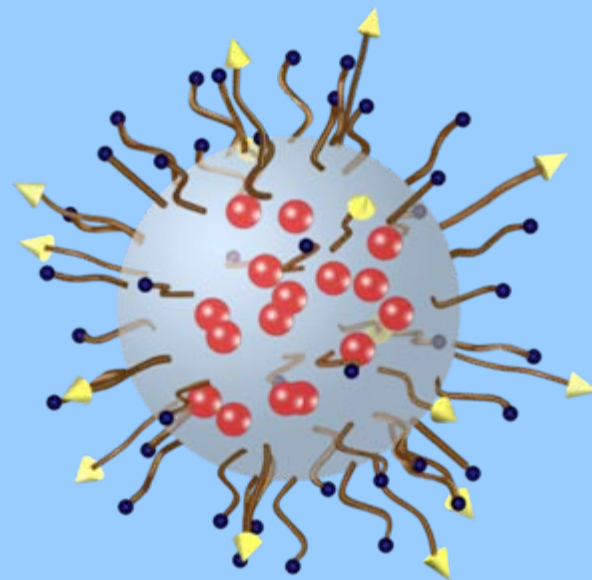


Overview of targeted therapies

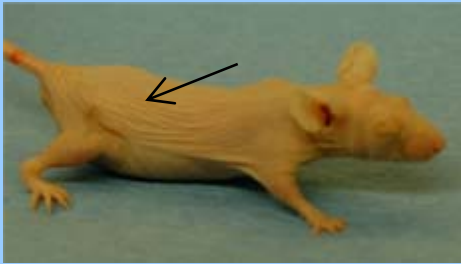
Technology	Example	Approved drugs	Payload
Single molecules	Humira	20	1 molecule
Nanoparticle conjugates		0	$10^3 - 10^5$ molecules



Targeting
molecule



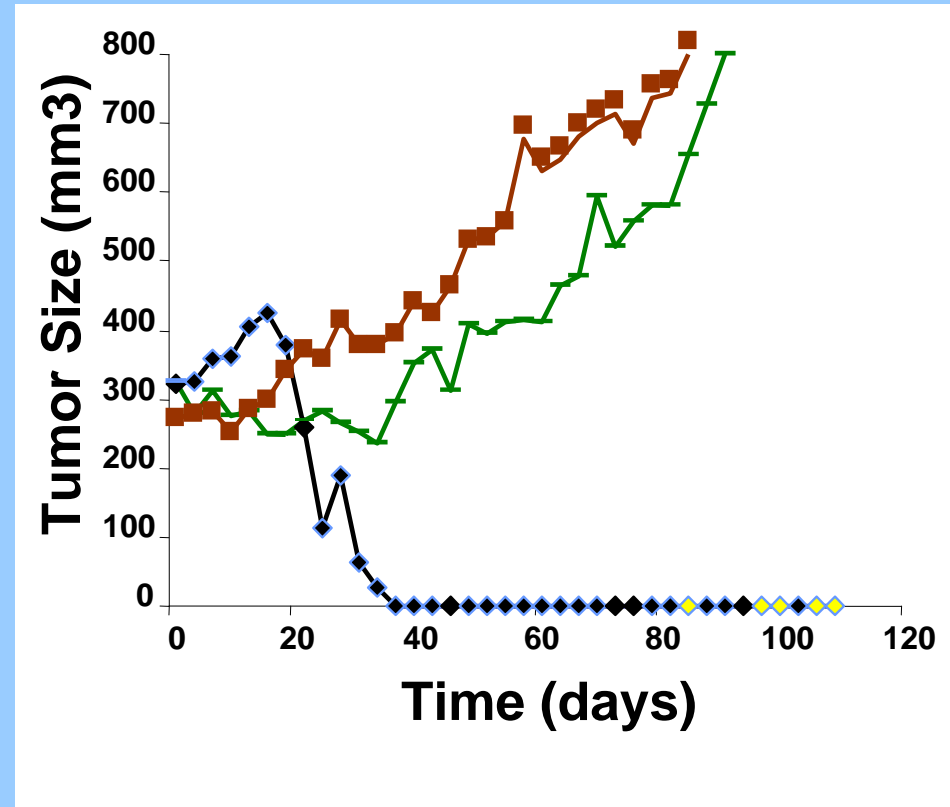
Targeted NP



Docetaxel

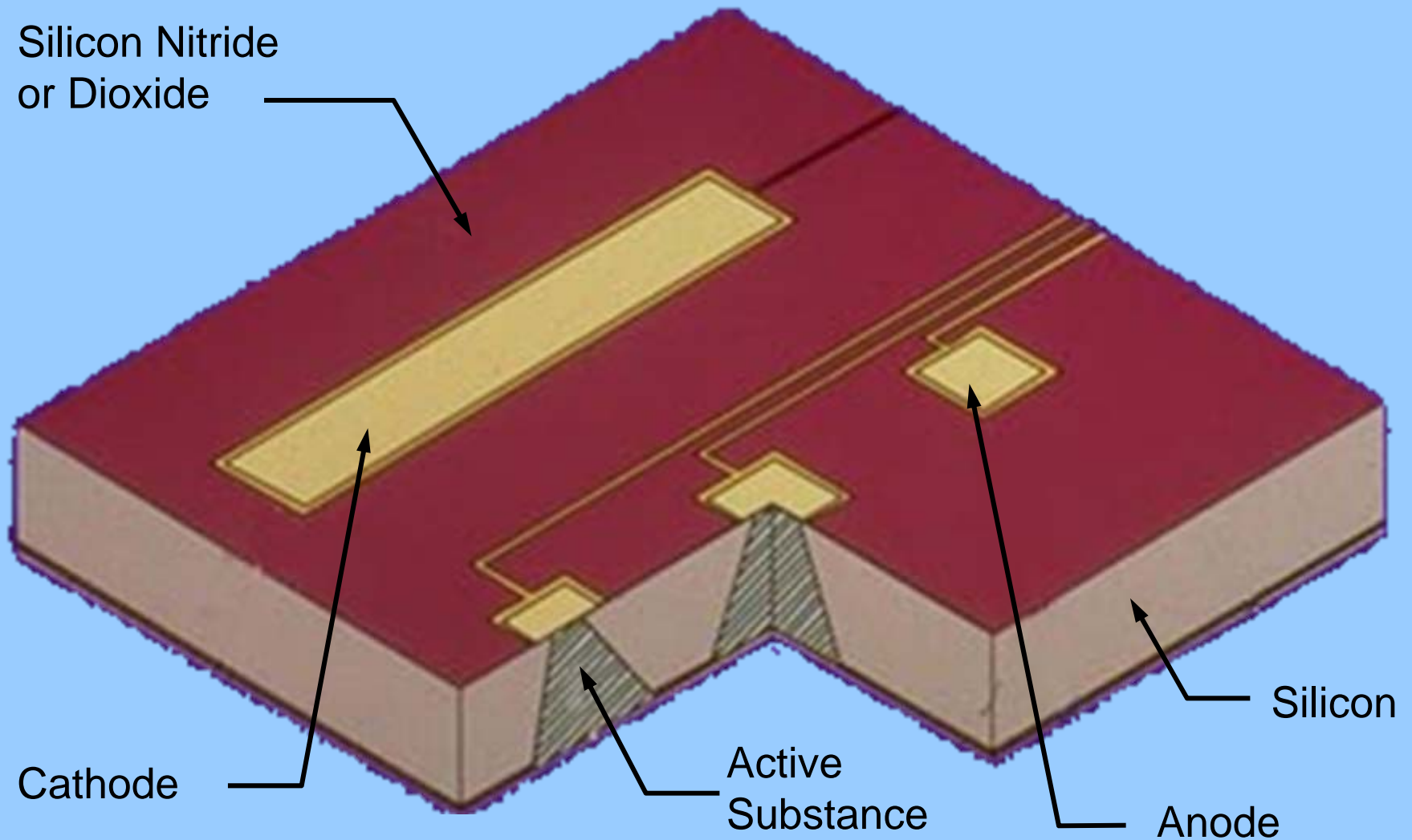


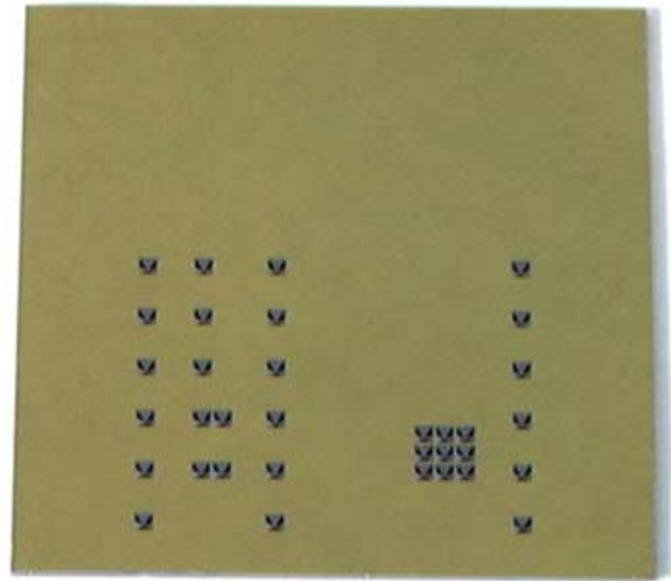
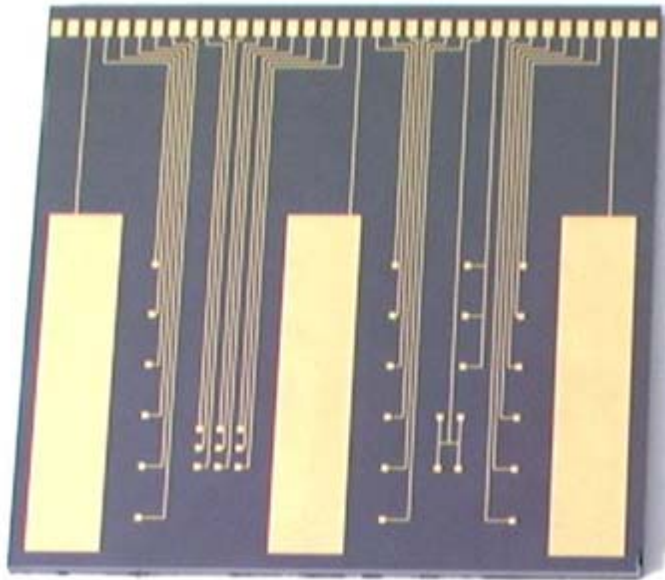
Control NP



- Control NP
- Docetaxel
- Targeted NP

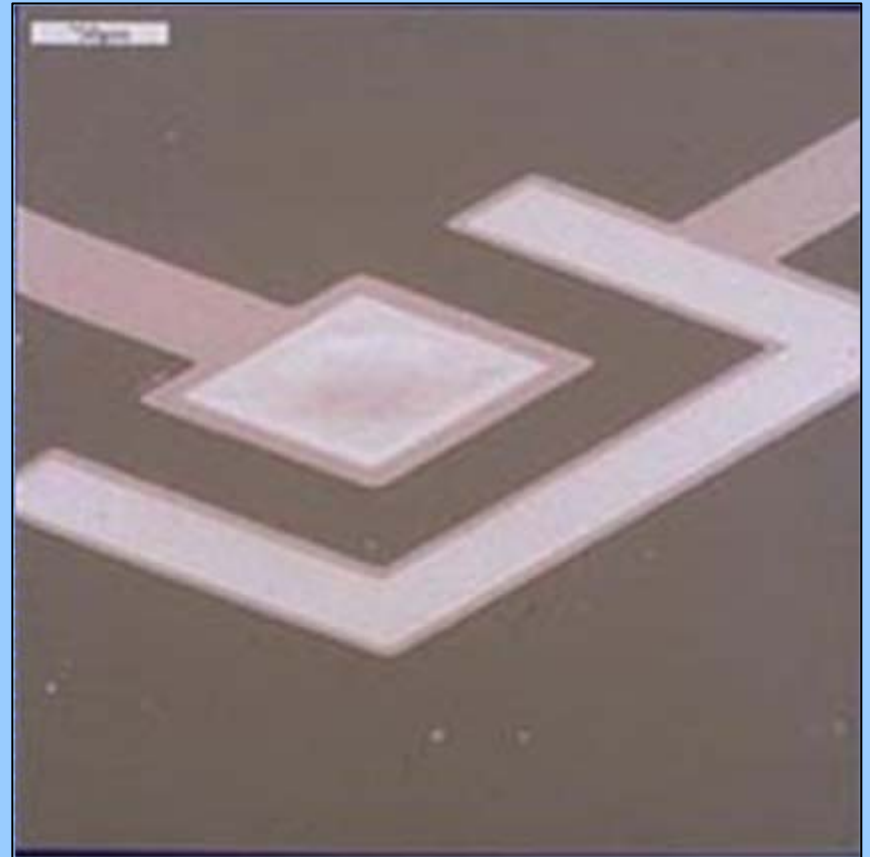
Prototype device



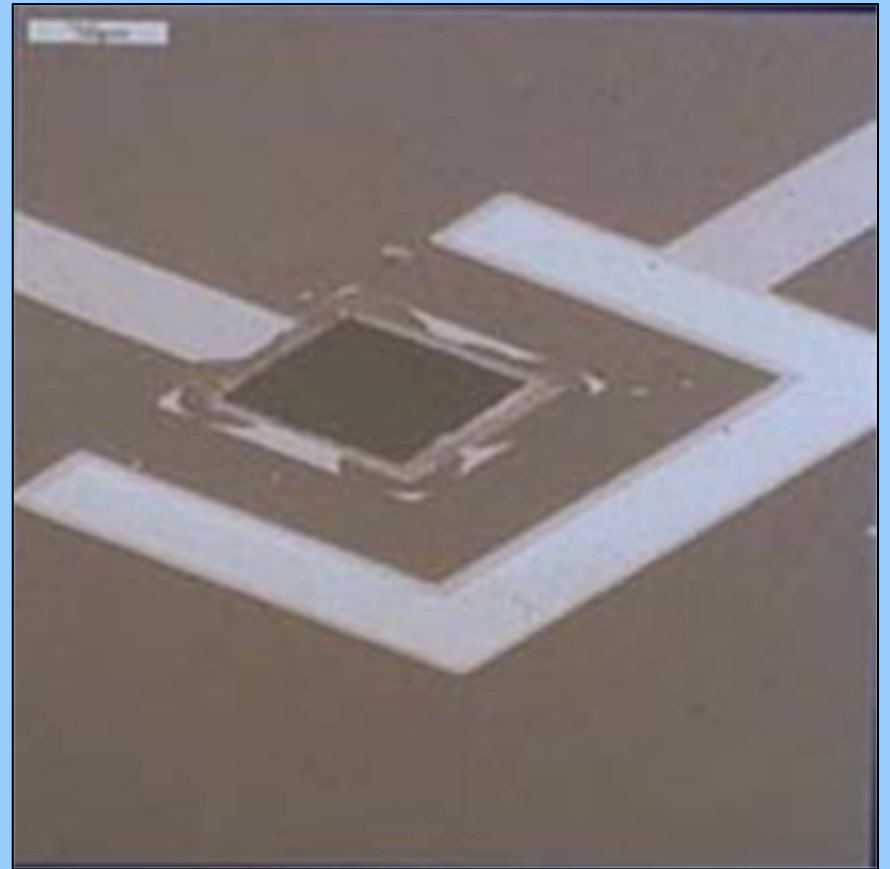
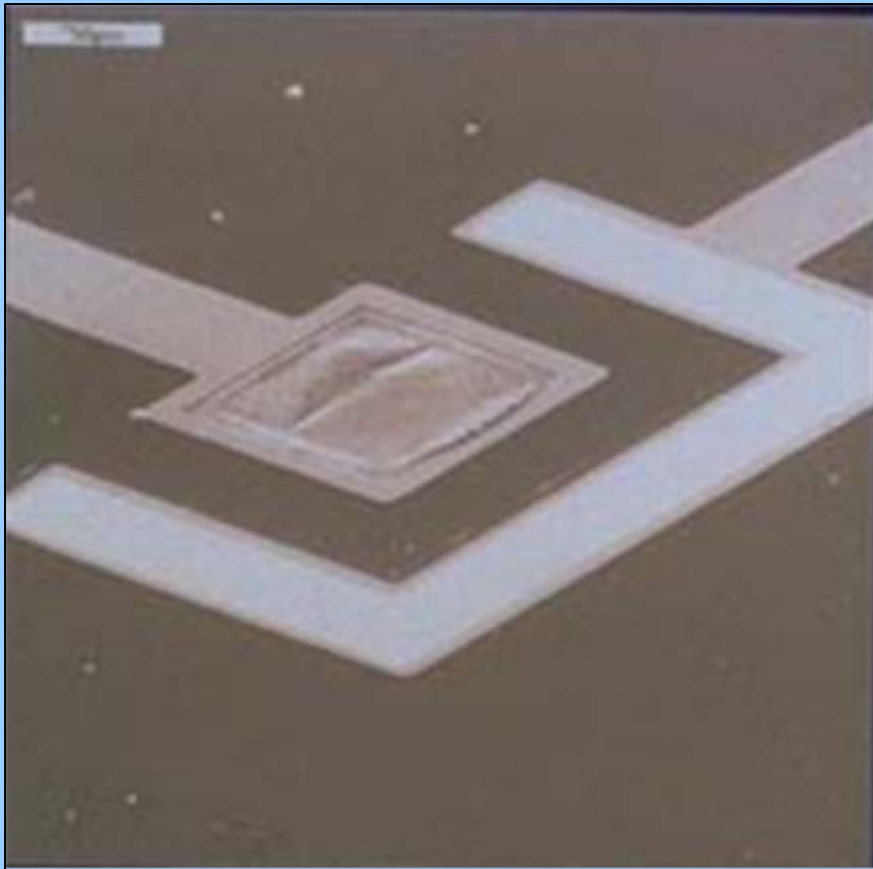


Reservoir activation

- SEM of a reservoir – electrode system before application of an electric potential

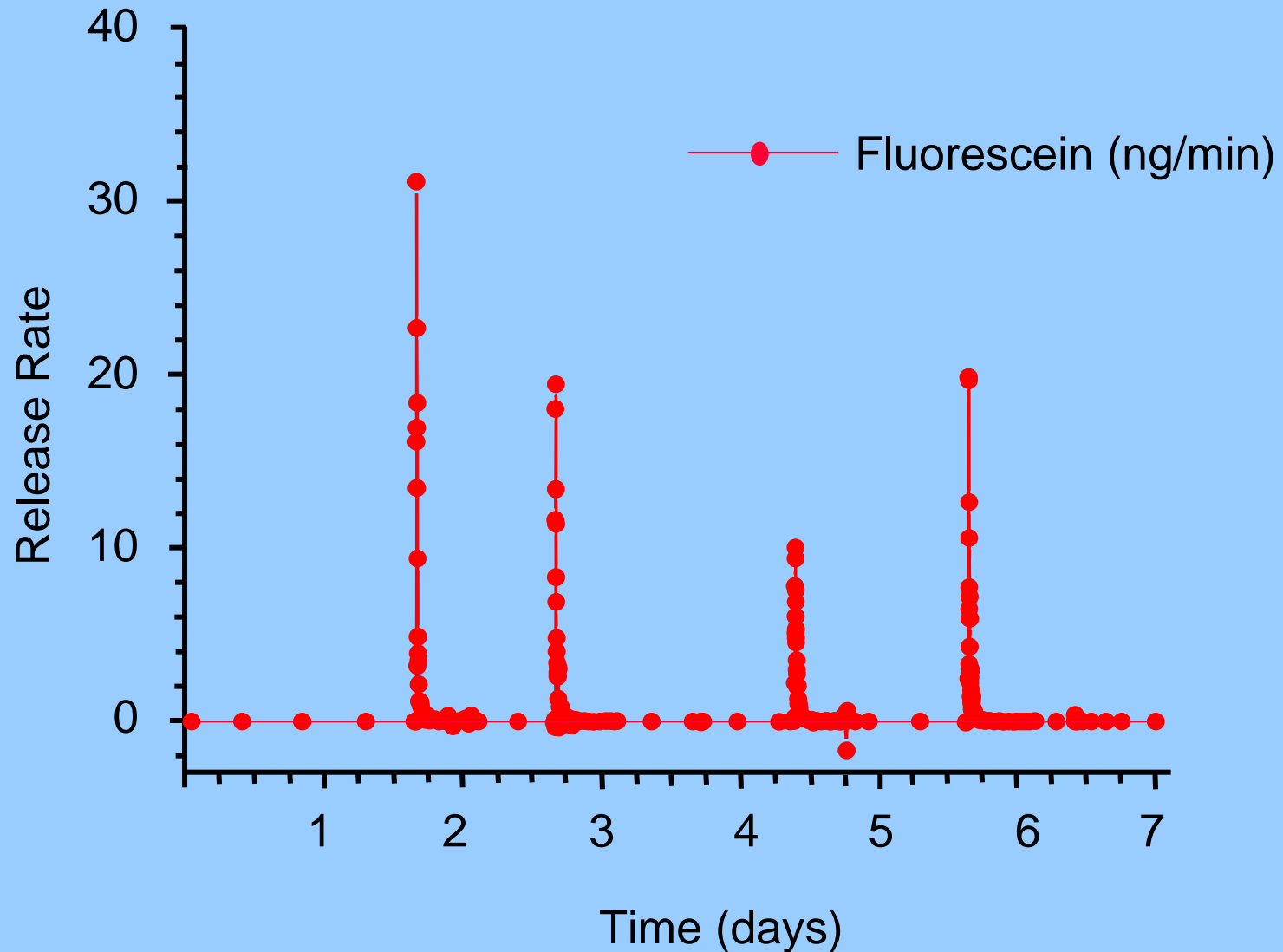


Reservoir activation

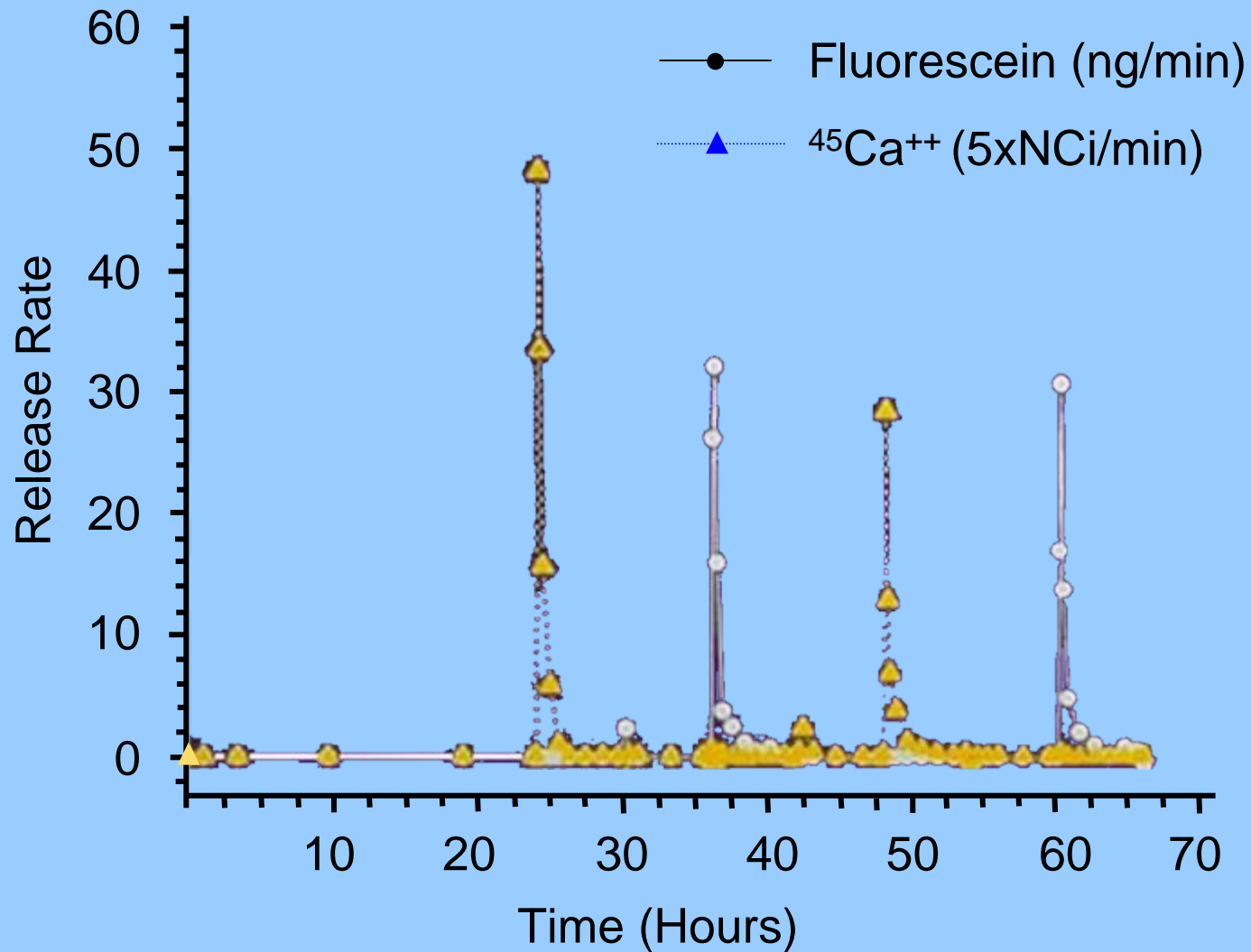


- SEMs taken after application of 1.04 volts vs. SCE in PBS

Single compound release



Multiple compound release



Medical Use

Initial Use

Polymer

Artificial Heart

Ladies Girdles

Polyether Urethane

Dialysis Tubing

Sausage Casing

Cellulose Acetate

Vascular Graft

Clothing

Dacron

Breast Implants

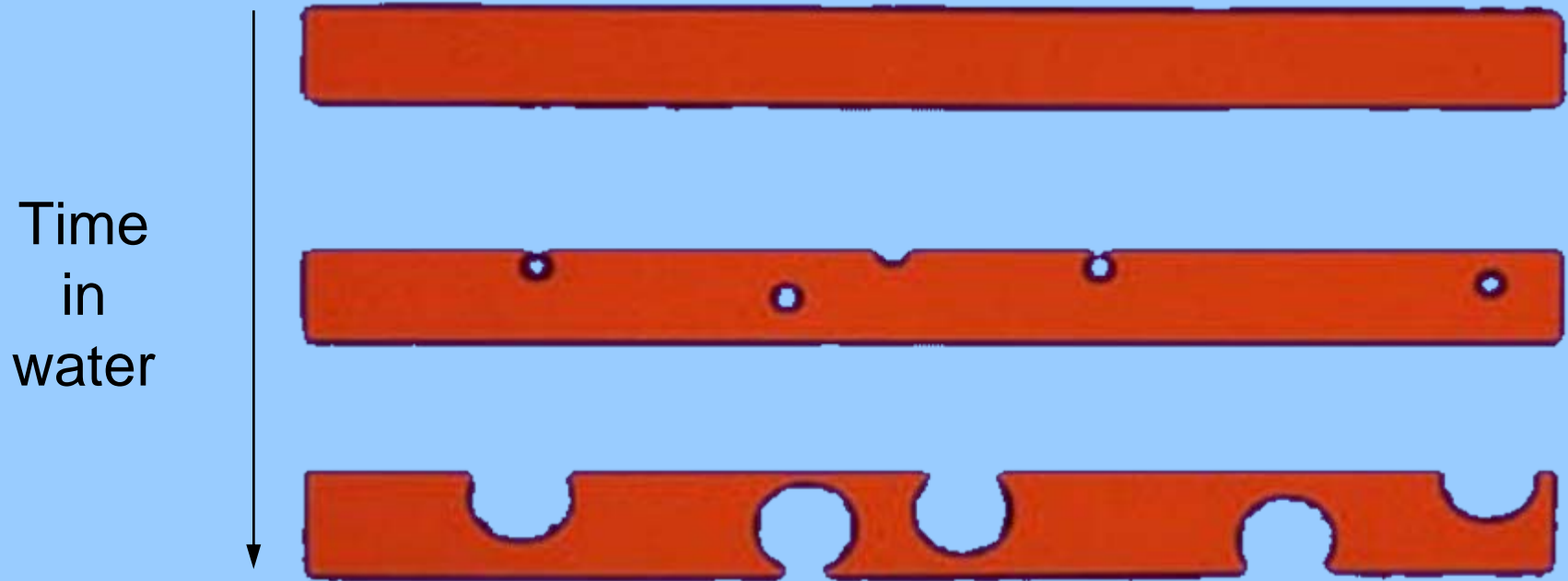
Lubricant

Silicone

Mattress Stuffing

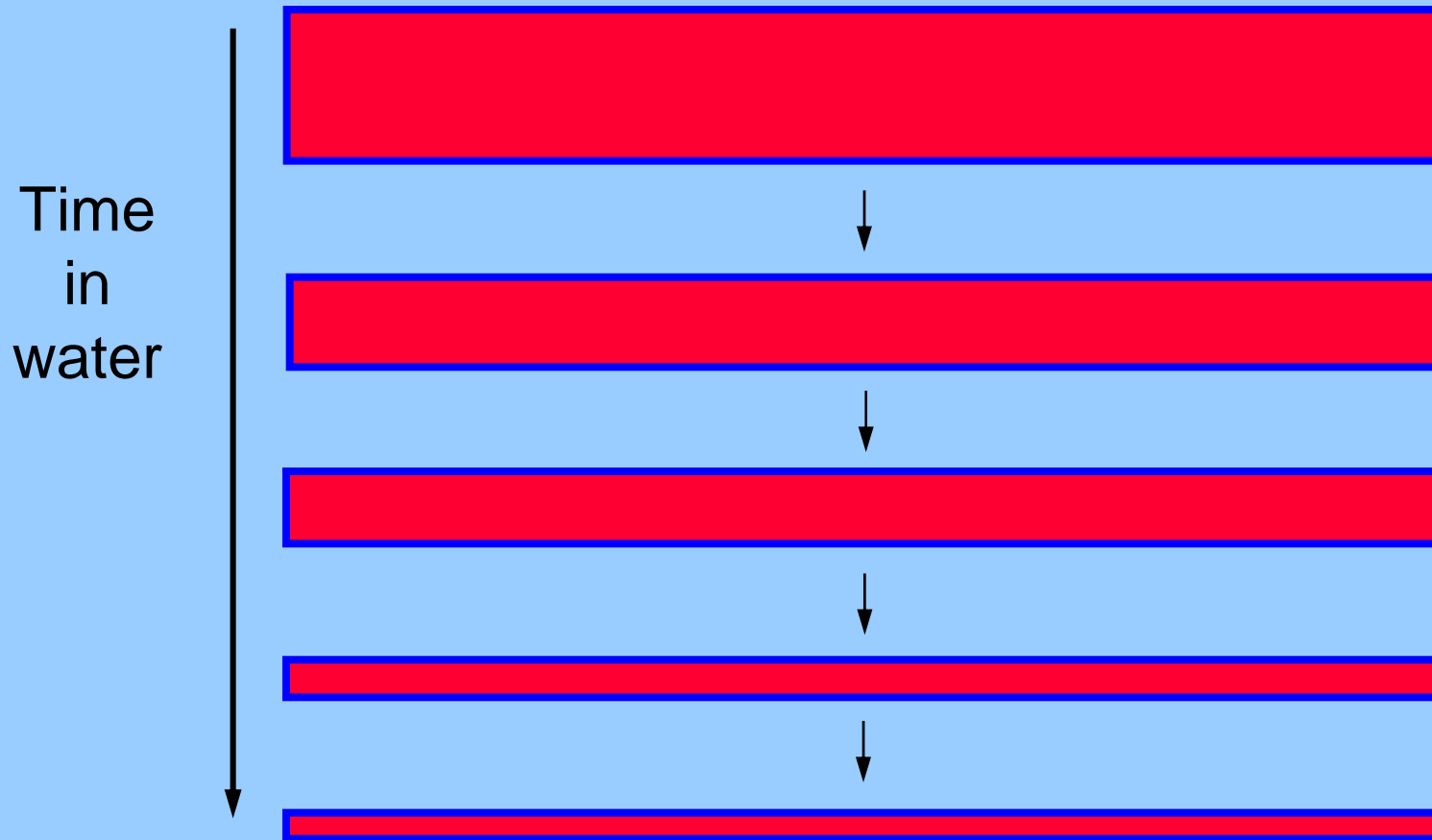
Polyurethane

Bulk erosion

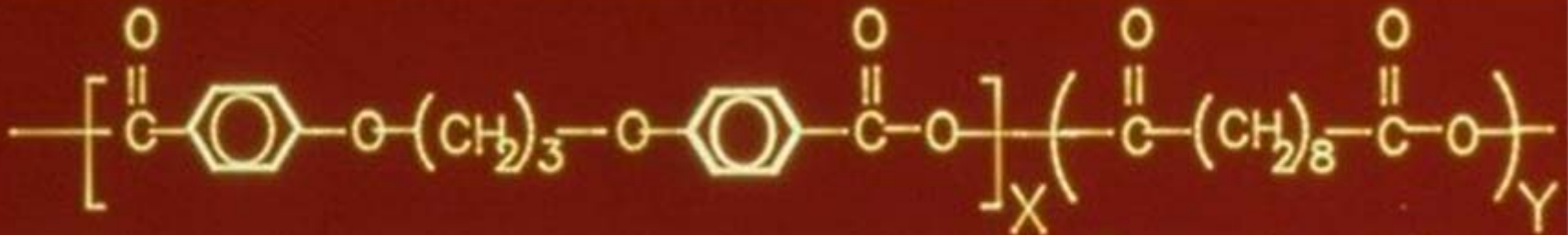


Leads to burst drug release
which can be fatal for
potent drugs

Surface erosion

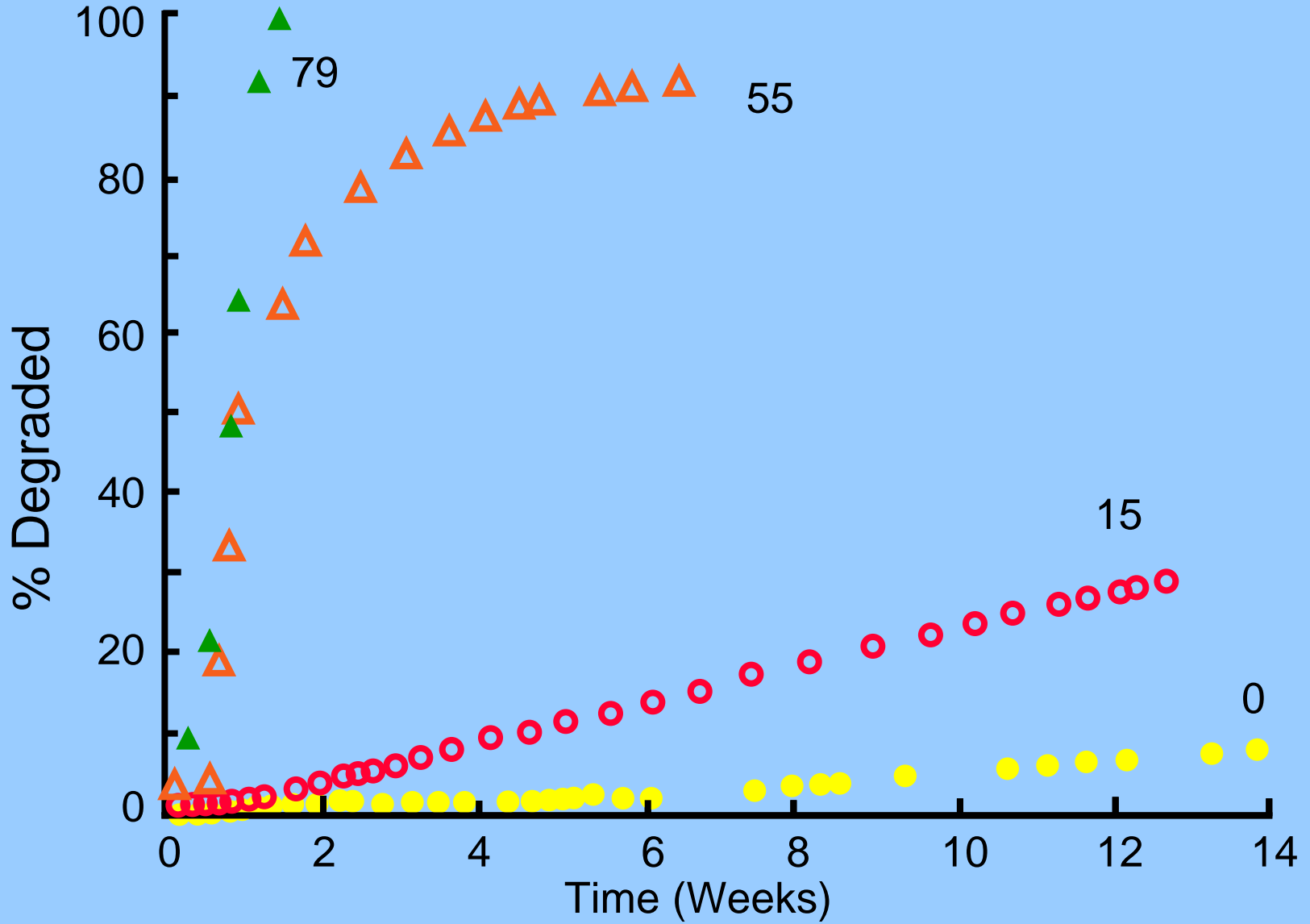


Structure of the polymer



poly[bis(p-carboxyphenoxy) propane anhydride]
(PCPP)

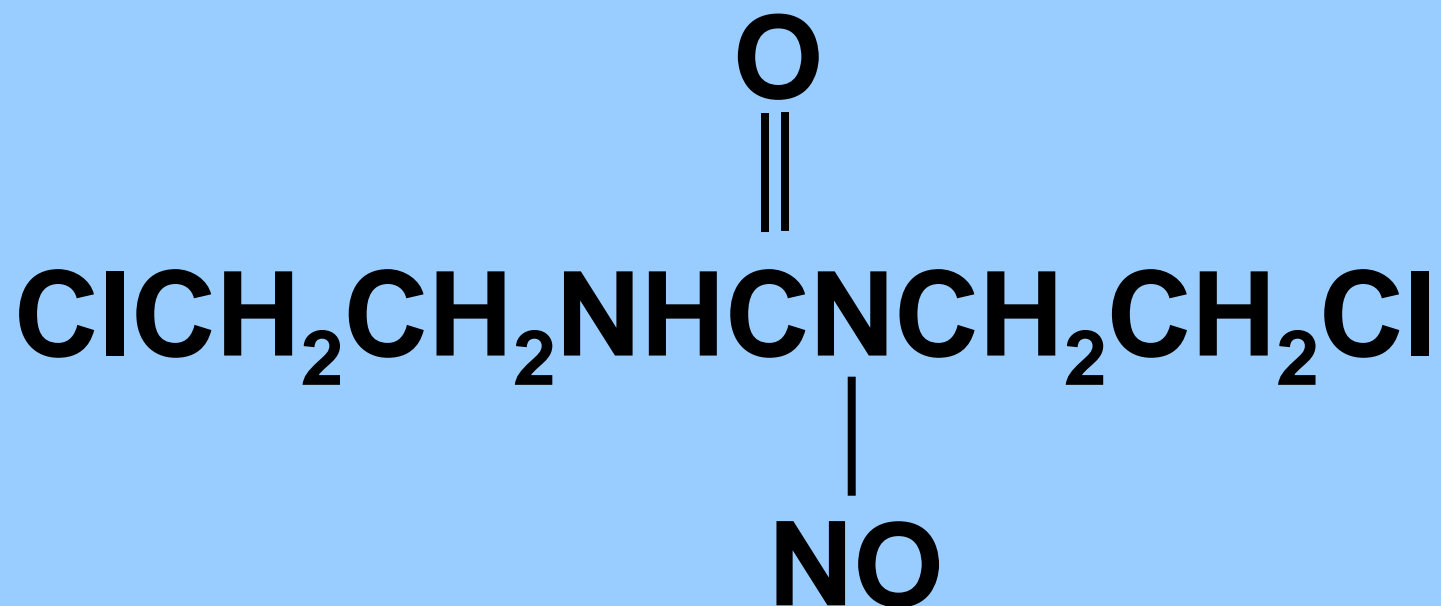
Sebacic Acid



Glioblastoma multiforme

- Statistics: Uniformly fatal disease
- Untreated, median life expectancy = 4 weeks
- Surgery yields median life expectancy = 16 weeks
- Surgery + radiation = 40 weeks
- Surgery + radiation + chemotherapy = 50 weeks

Structure of BCNU



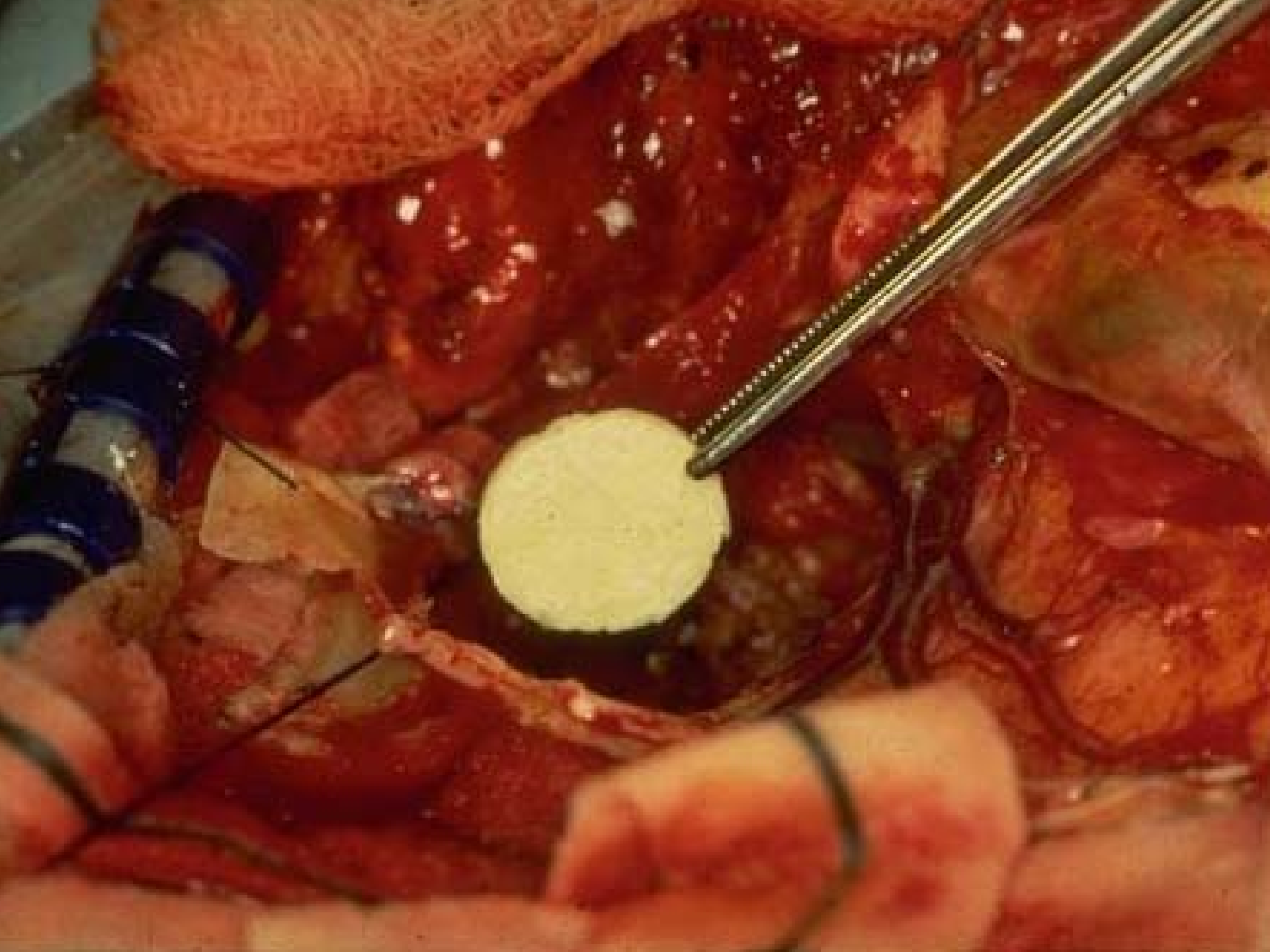
1,3-bis(2-chloroethyl)-1-nitrosourea

Principle of the therapy

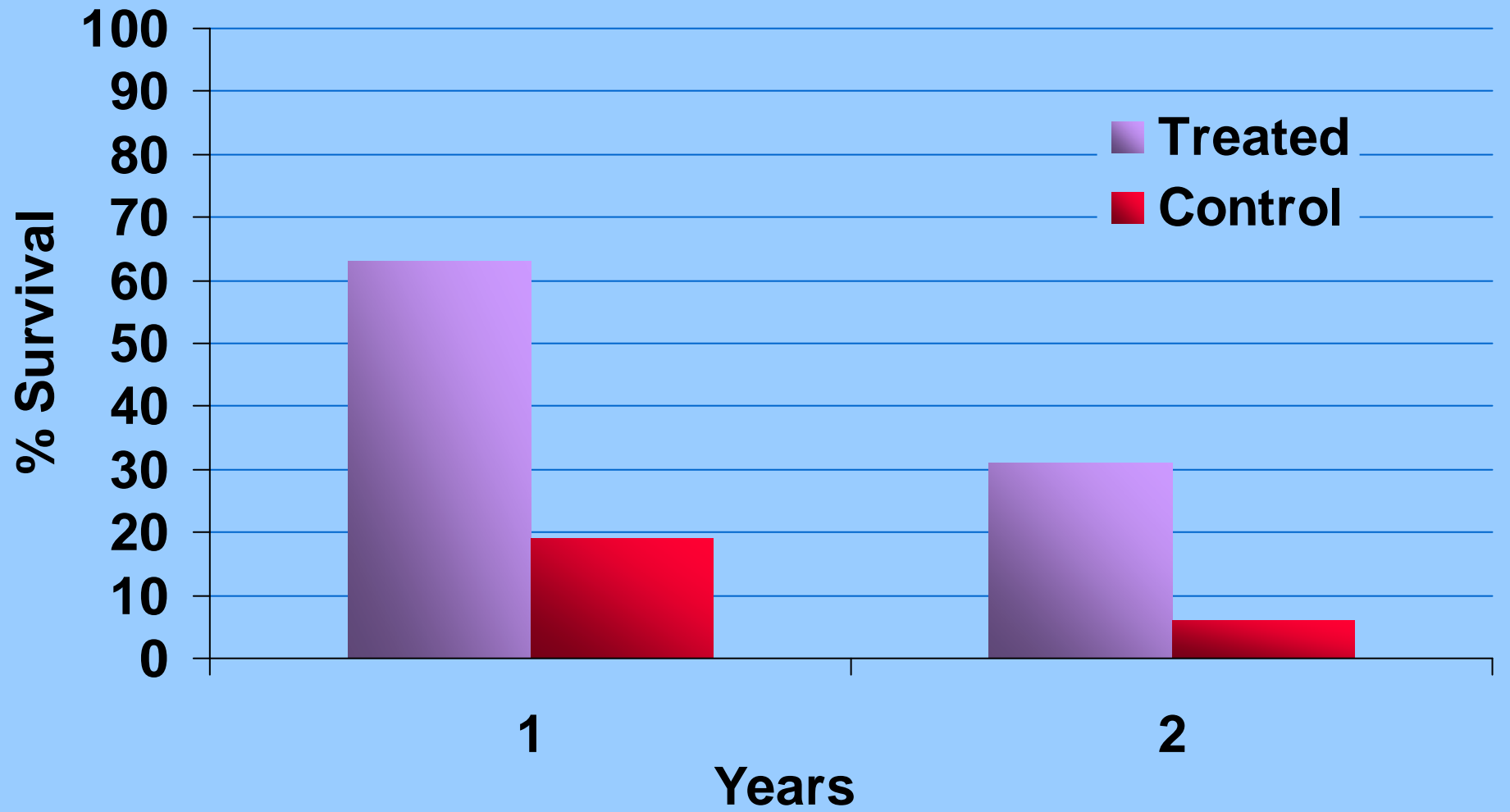
- Line the surgical cavity with BCNU-polymer
- BCNU half life *in vivo* = 12 minutes
- Polymer protects the BCNU from degradation
- Expose only the cells you want to BCNU

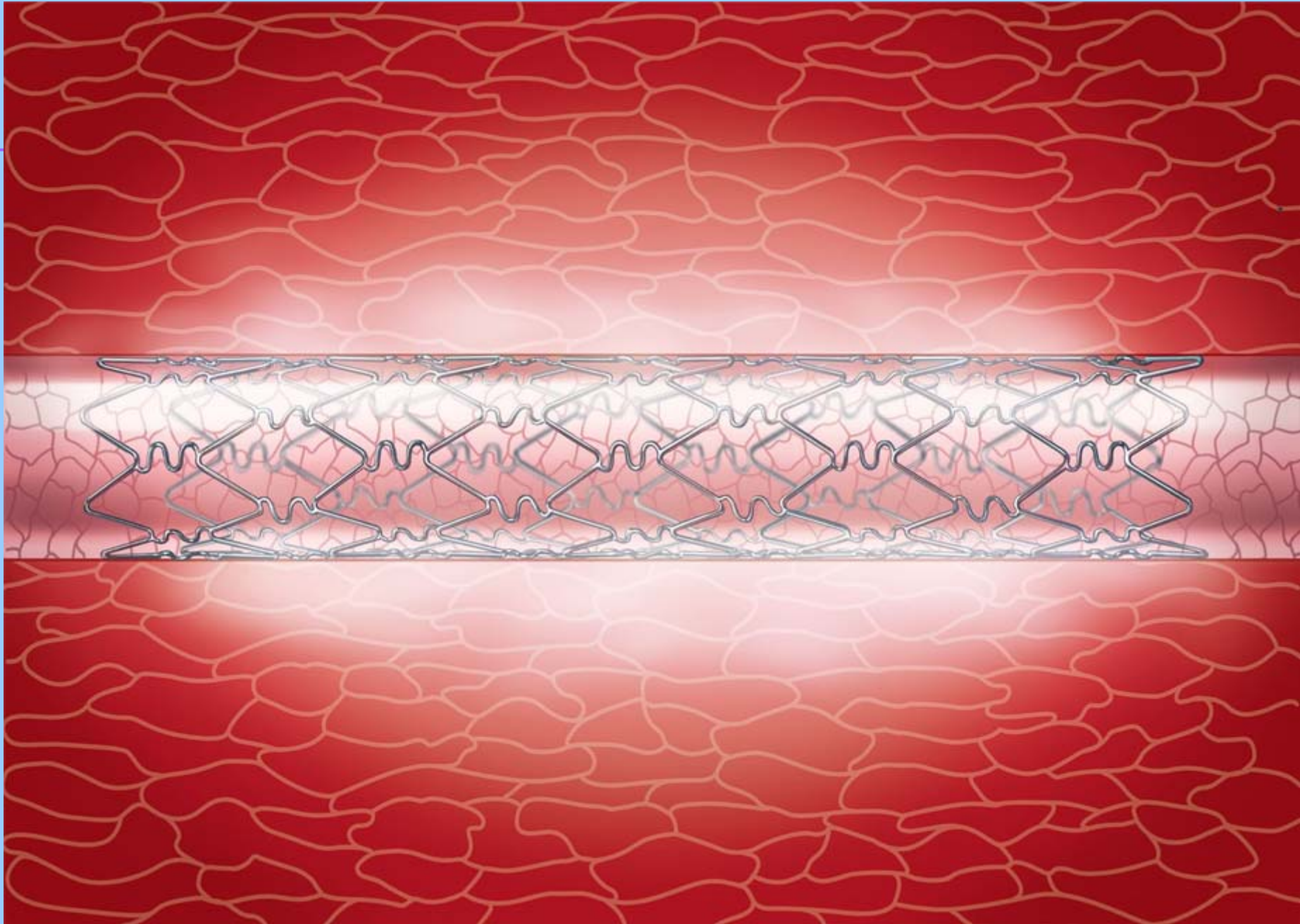
This approach will not work because:

- The polymers cannot be synthesized (1981)
- The polymers will react with encapsulated drug (1983)
- The polymers are fragile (1985)
- The polymer-drug system would be toxic (1986)
- The drug will not diffuse far enough to kill remaining tumor (1988)
- Even if it does, it is a very poor drug (1990)
- The drug delivery systems cannot be manufactured (1993)

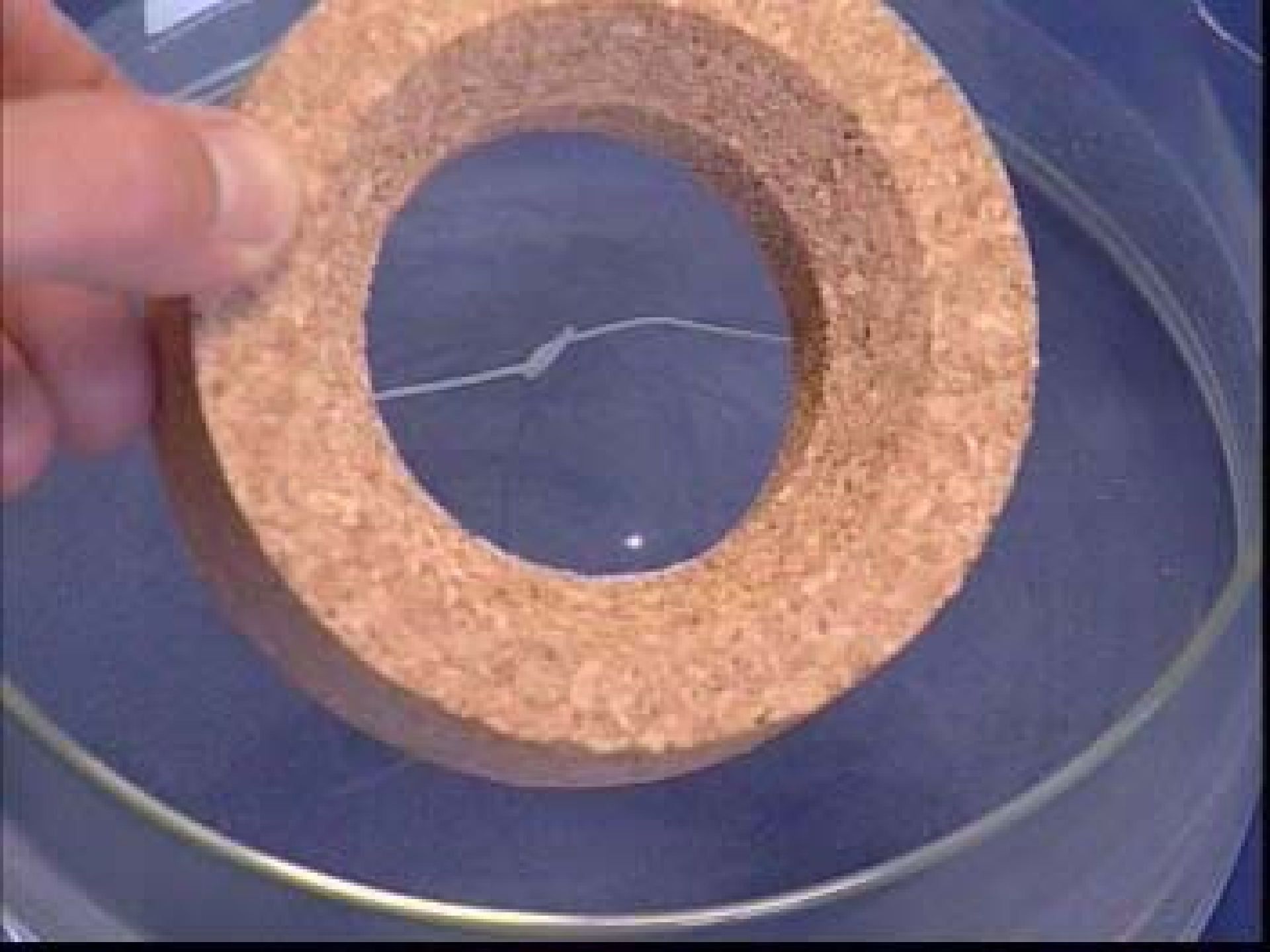














Biodegradable
polymer scaffold



In vitro tissue culture

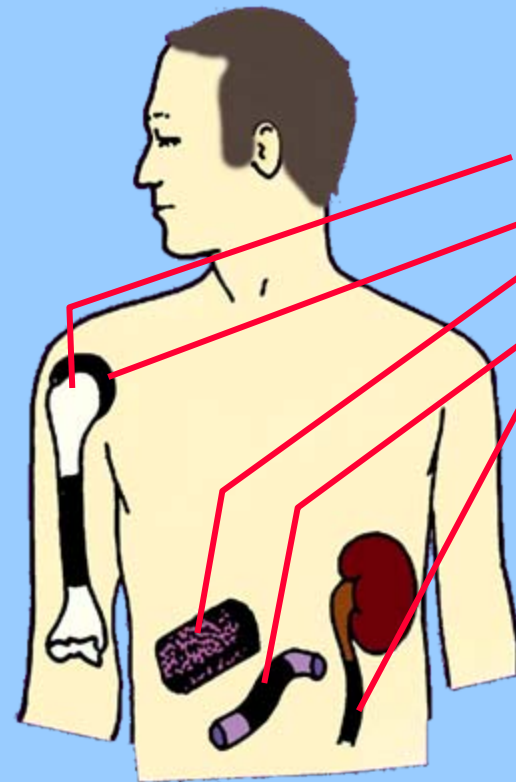


Cells

- Osteoblasts
- Chondrocytes
- Hepatocytes
- Enterocytes
- Urothelial cells



In vivo implantation



New

- Bone
- Cartilage
- Liver
- Intestine
- Ureter



20KV

121X

100U

1873

V-HEPTA

Cartilage tissue engineering

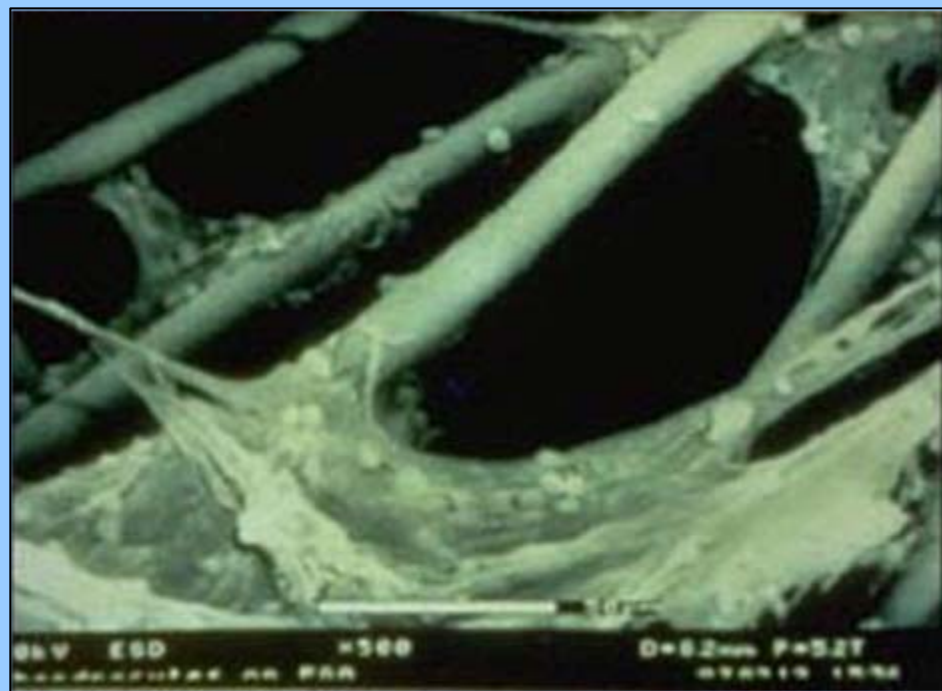


BEFORE
cell seeding



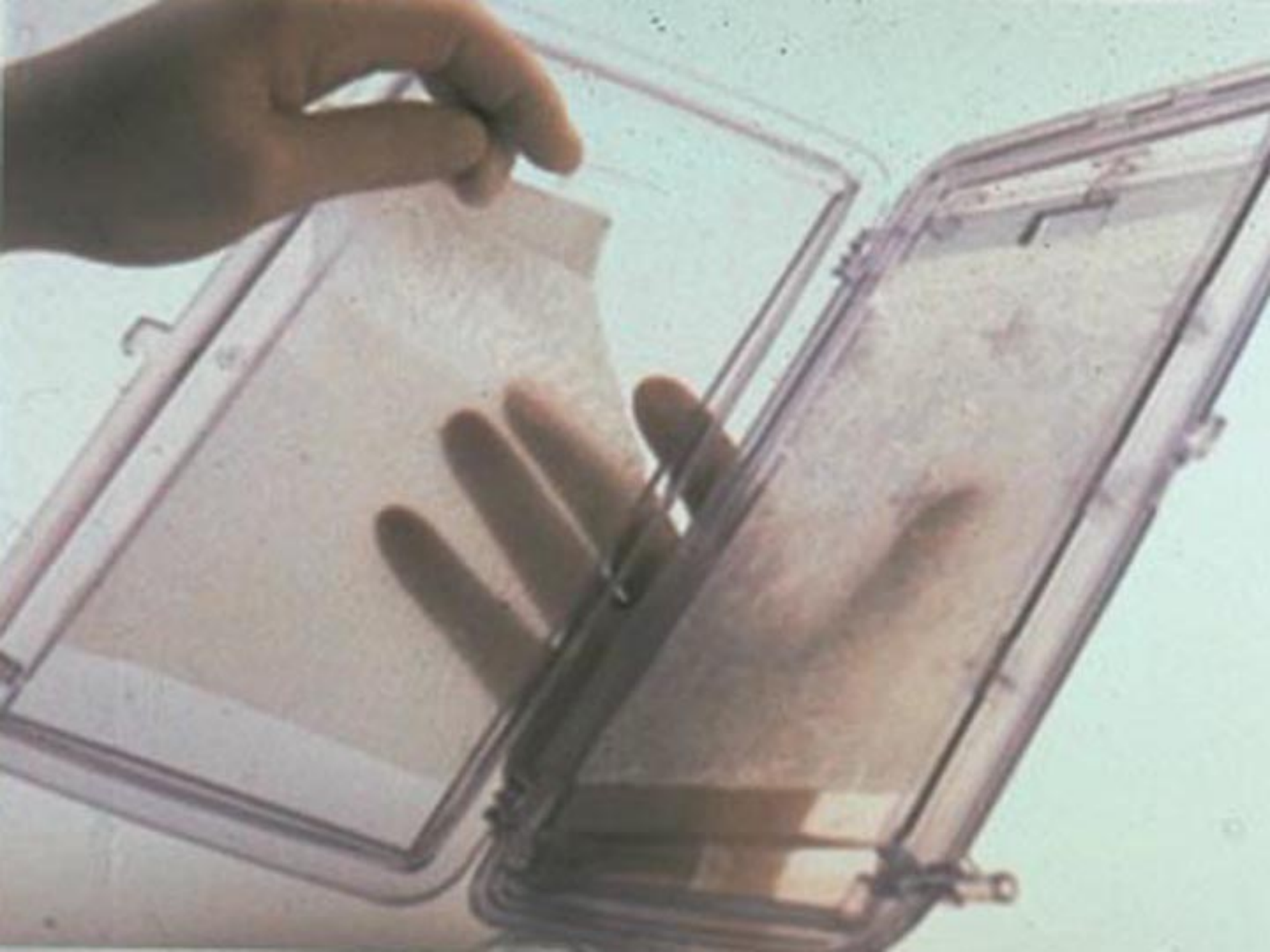
AFTER
2 weeks in culture













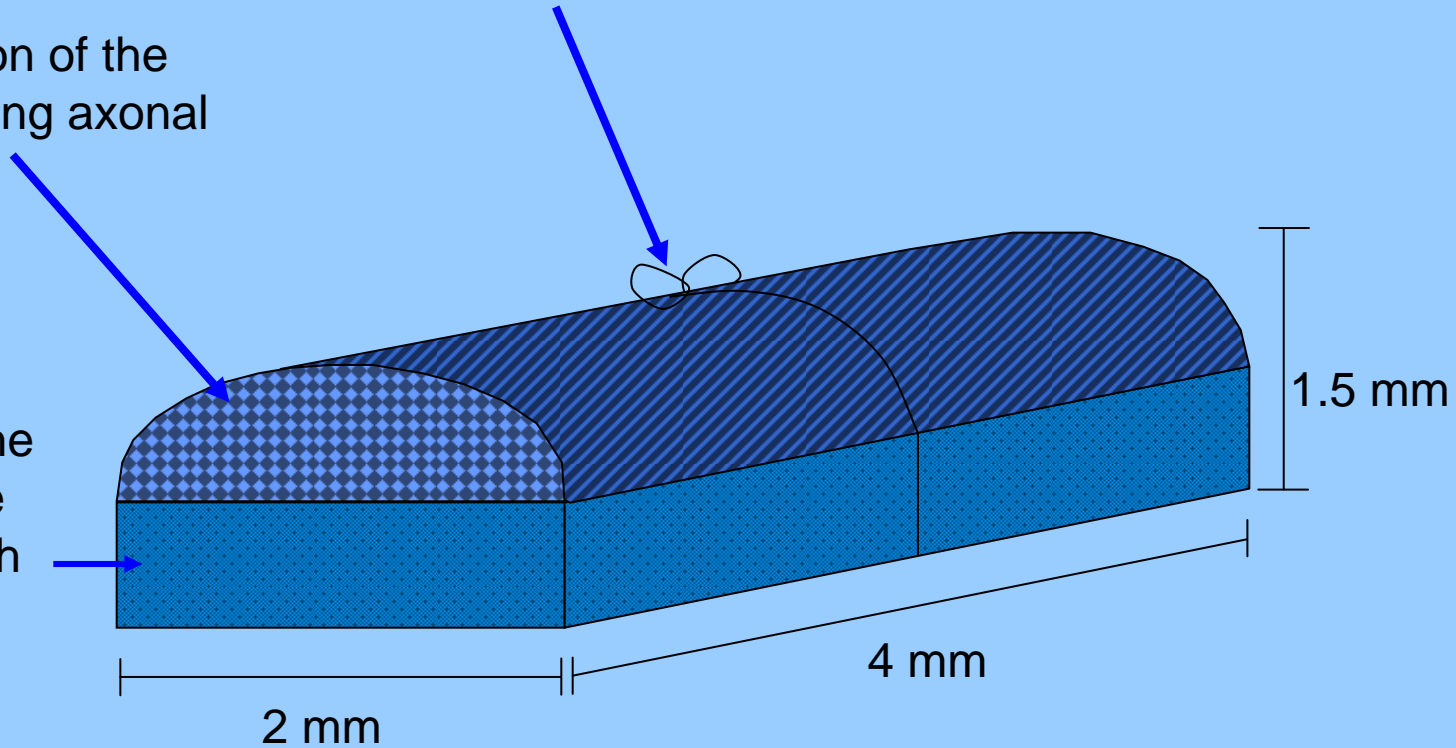




Degradable suture material tied to hold both parts of the implant together

Oriented portion of the implant providing axonal guidance

Inner portion of the implant with large pores seeded with neural stem cells



Lesion control



