Special Topic III: Polymeric Biomaterials

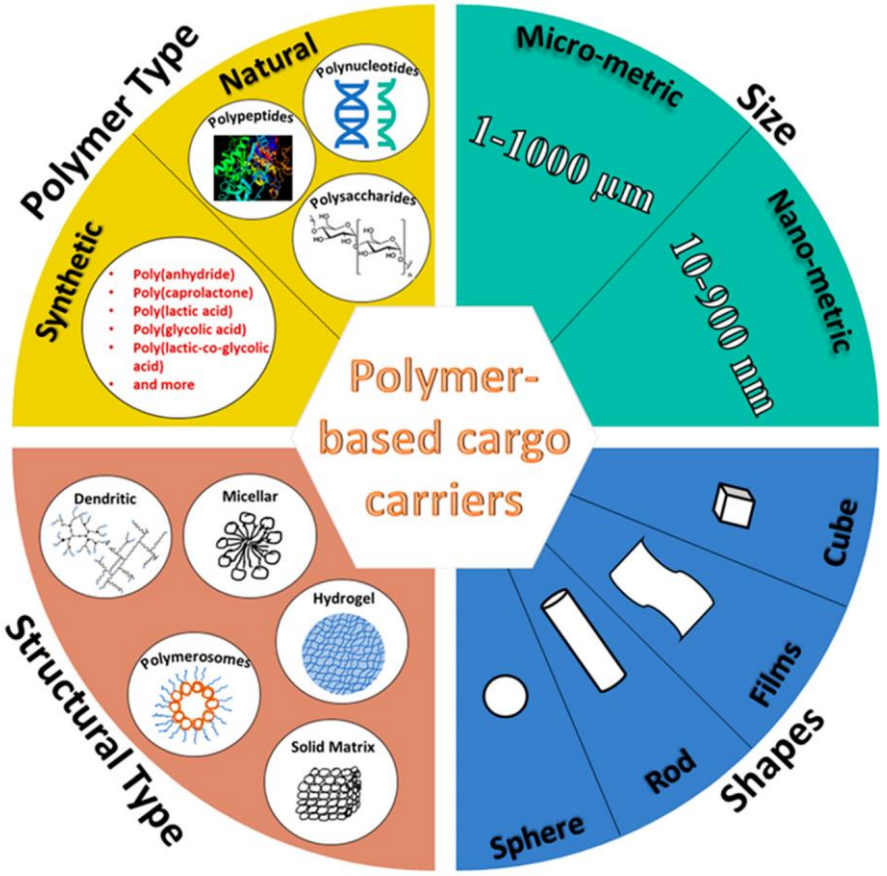
16:160:509 – Polymer Chemistry

Lecture 22

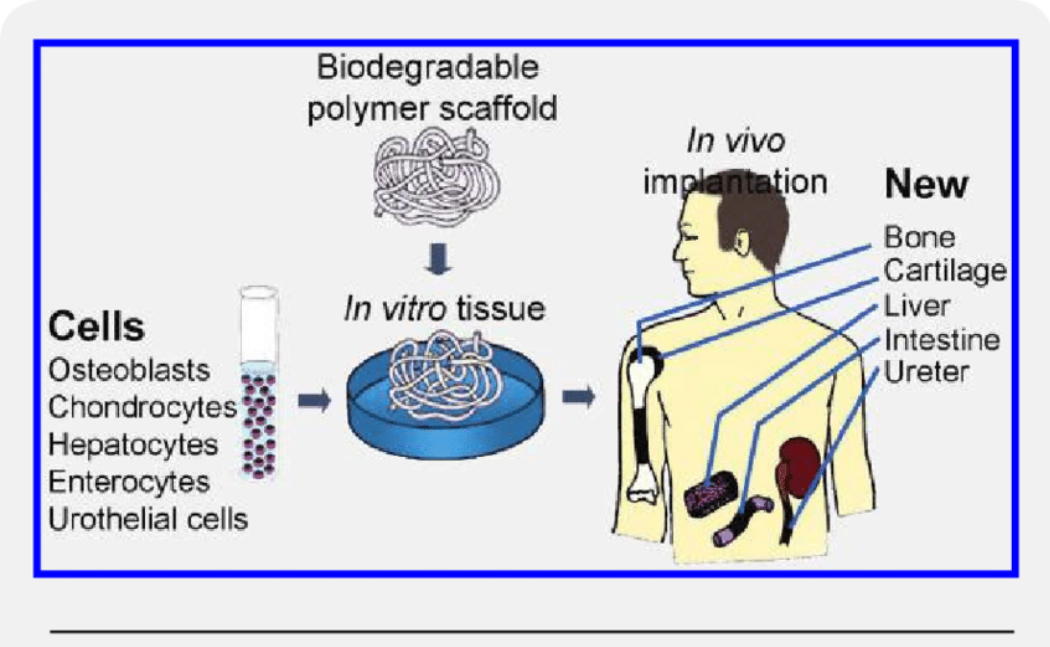
RUTGERS
School of Arts and Sciences
DEPARTMENT OF CHEMISTRY
AND CHEMICAL BIOLOGY

Polymeric Biomaterials

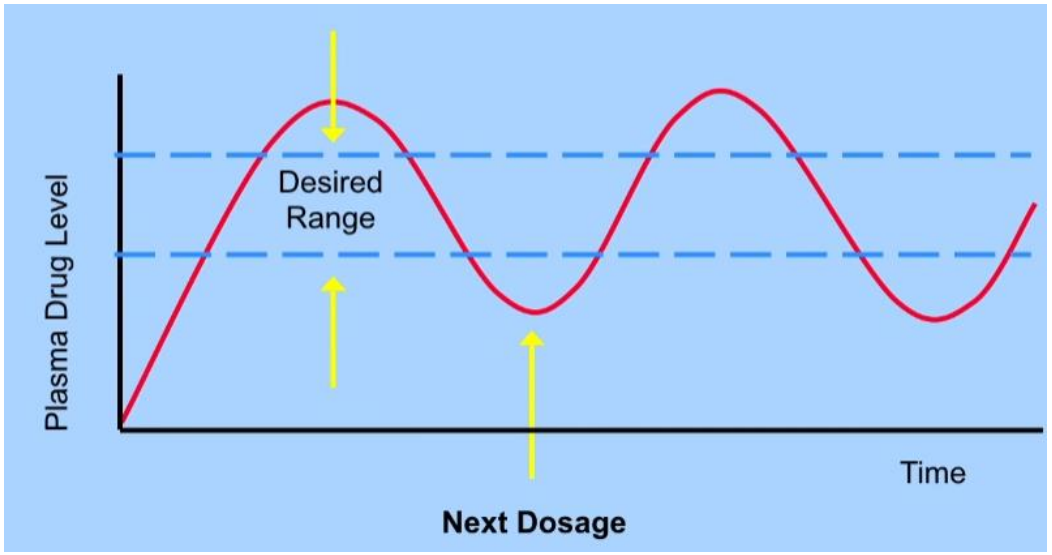
Drug Delivery System

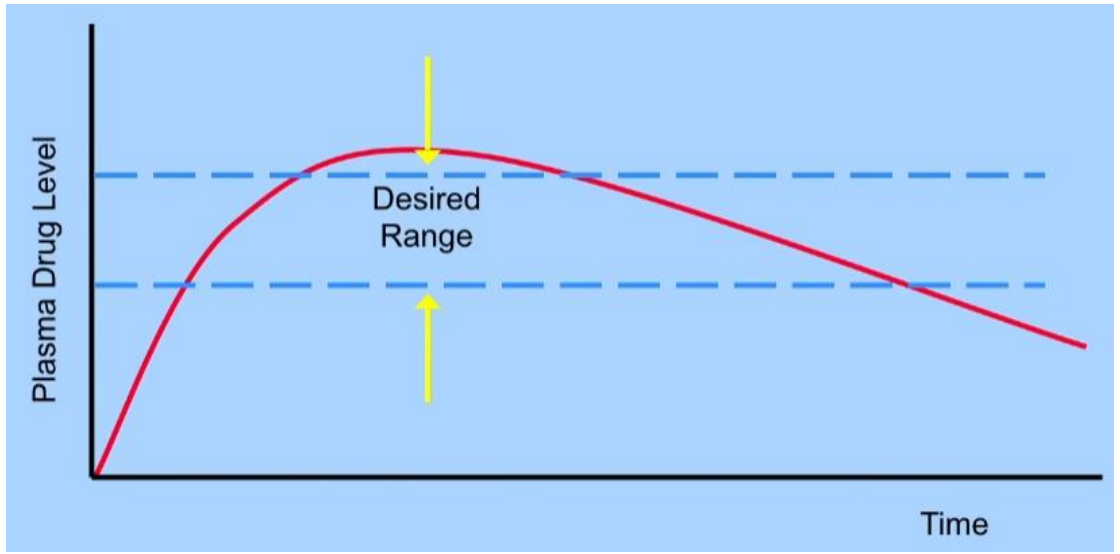


Tissue Engineering



Release Profiles of Medication



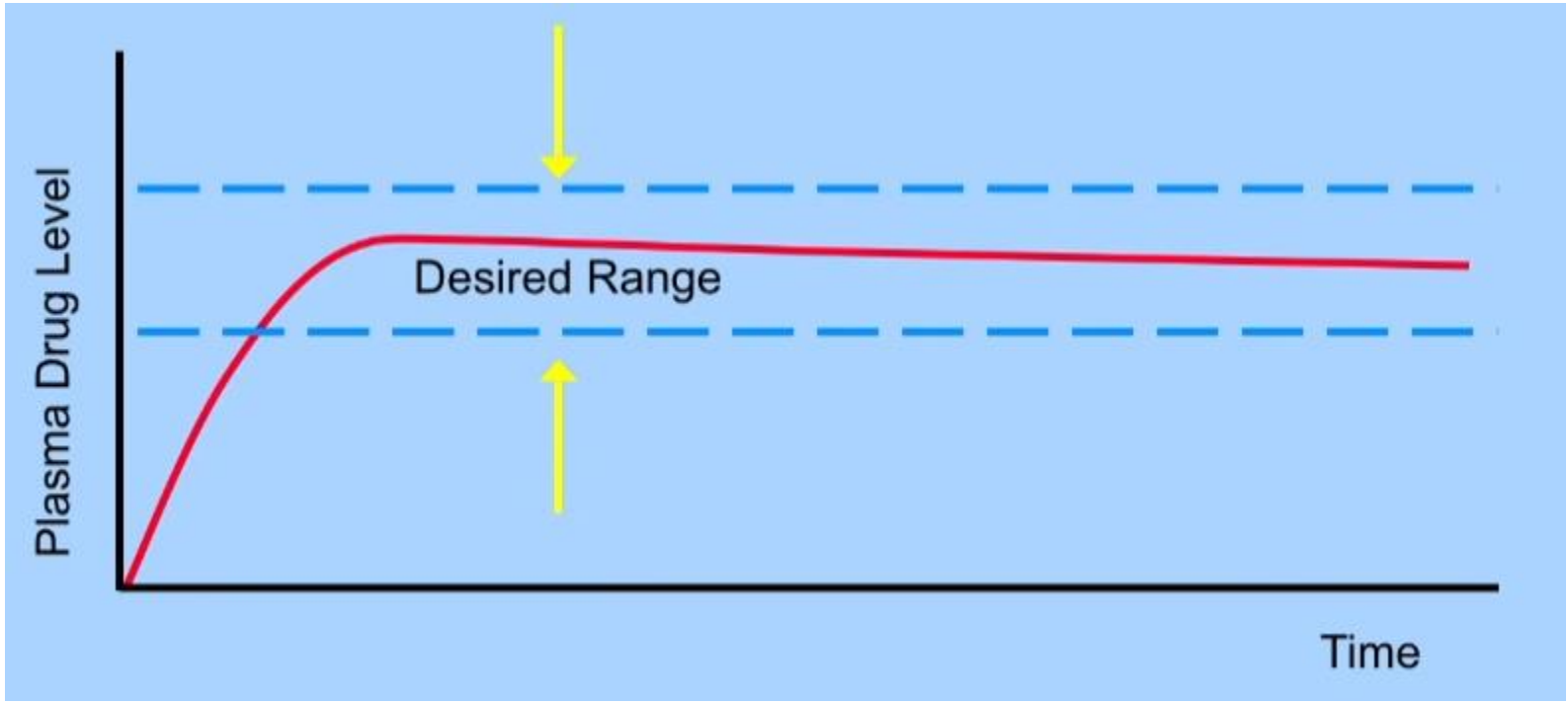


Immediate Release

Sustained Release

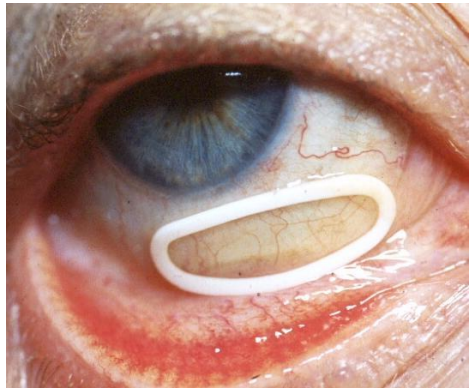
Generally for short periods of time (hours) and still requires repeated administration.

Controlled Release

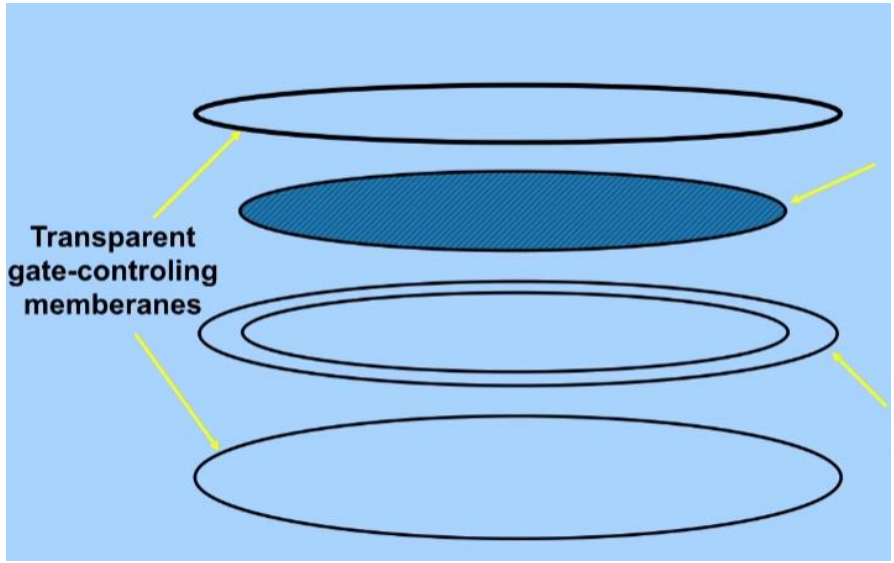


How do we design a controlled release system that can continuously release dosage over long periods of time (e.g., days or months)?

Ocusert



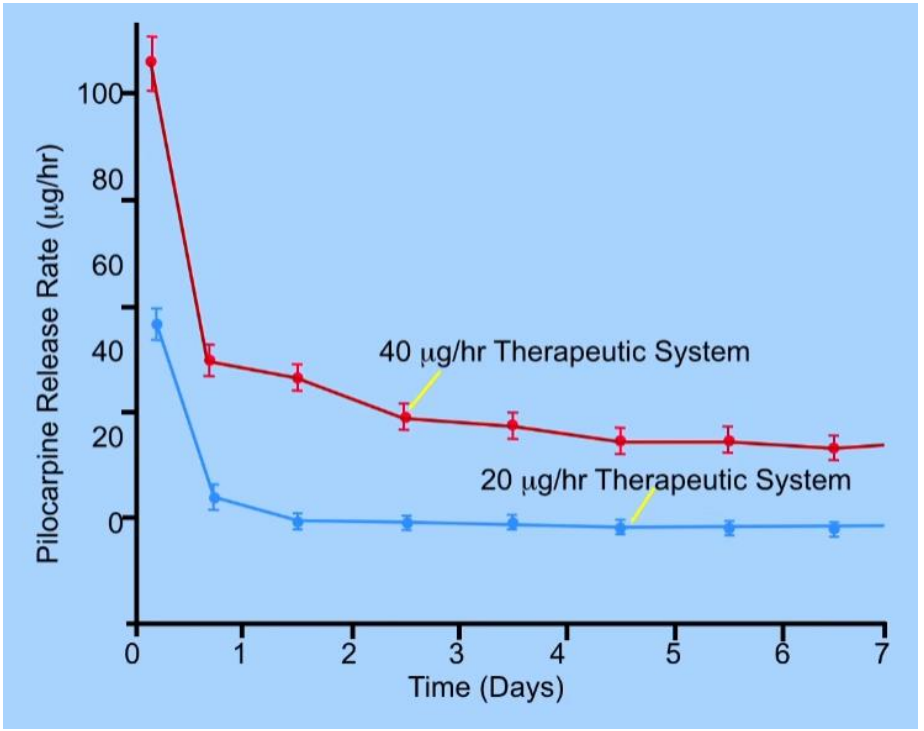
- For glaucoma treatment.
- Without this device, 28 eye drops would be required per week.
- It operates as a reservoir system, with the thickness of the polymer membrane controlling the release rate.
- Developed by Alza Corporation in the 1970s, one of the earliest commercial advancements in controlled release systems.



Pilocarpine reservoir

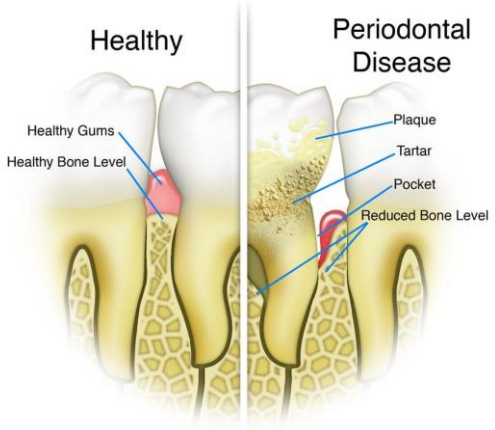
Annular ring
(surrounds reservoir, opaque white for visibility in handling and inserting)

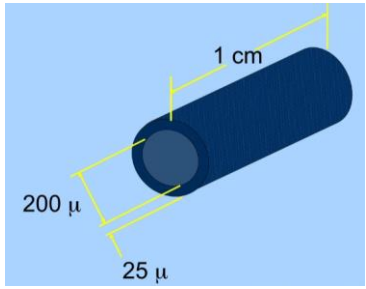
Semi-permeable polymer



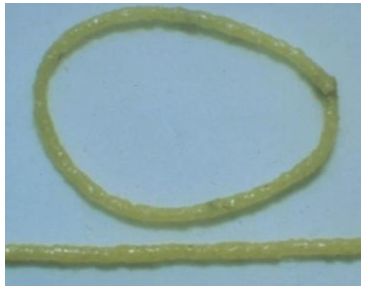
Reservoir vs Matrix Delivery System

Periodontal disease can be treated with the antibiotic tetracycline, but we need to deliver tetracycline locally to teeth.

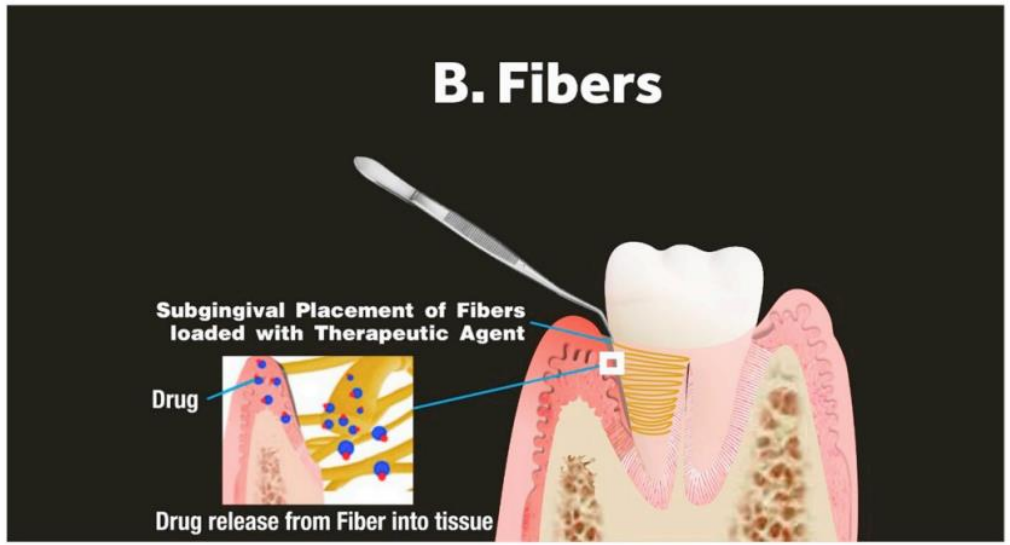


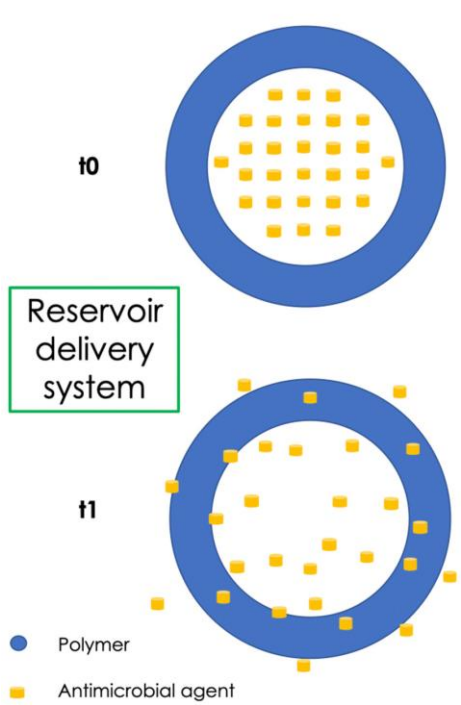


Hollow polymer fiber

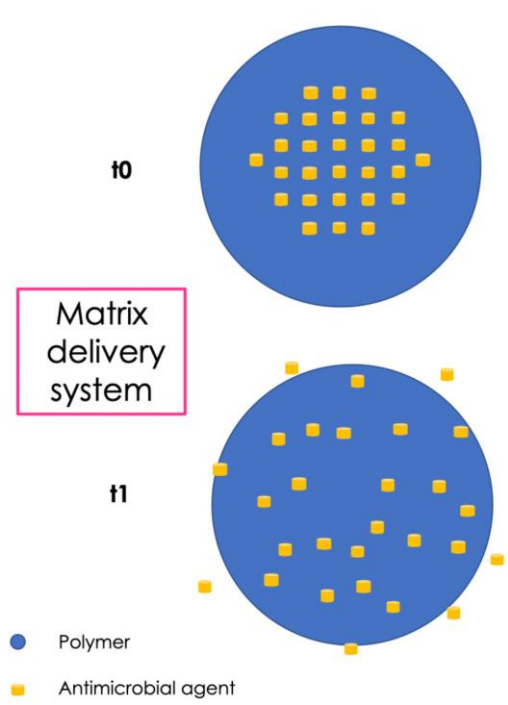


Polymer matrix



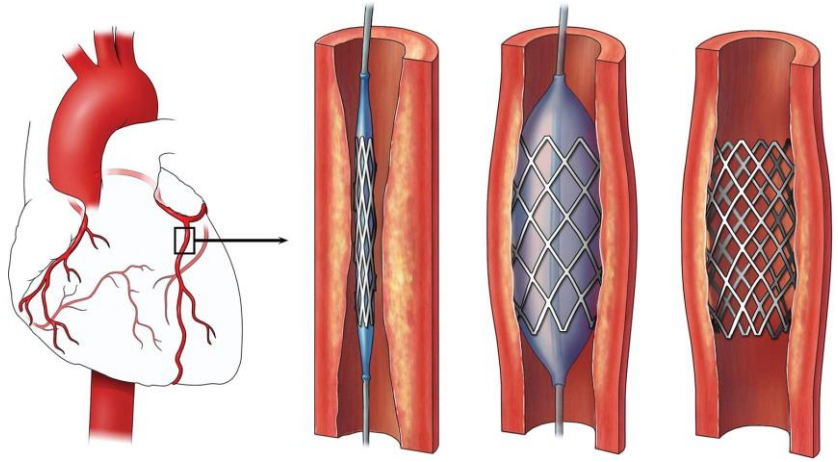


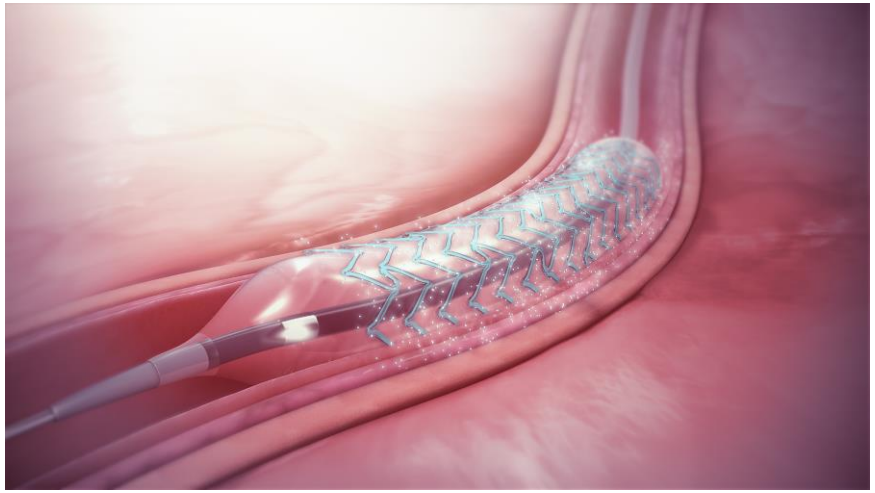
Potential for bursting if a leak occurs

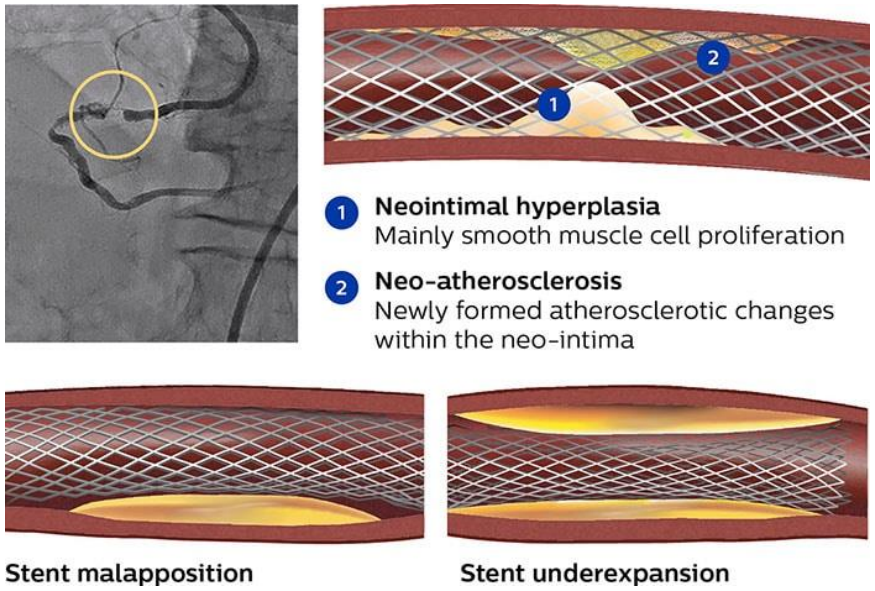


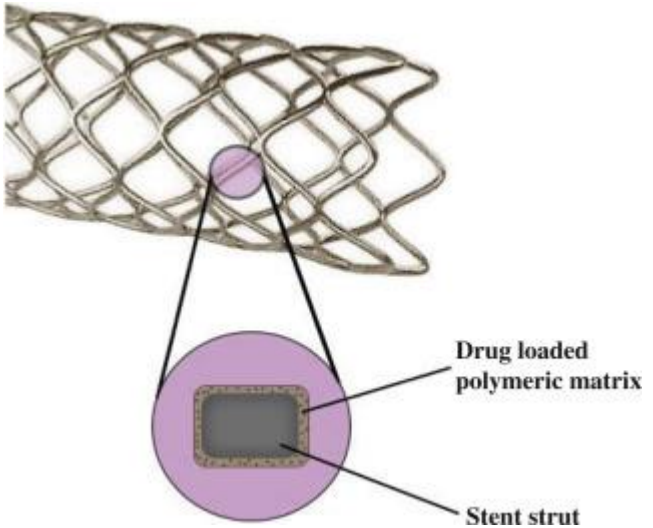
More controlled release

Drug-Eluting Stent



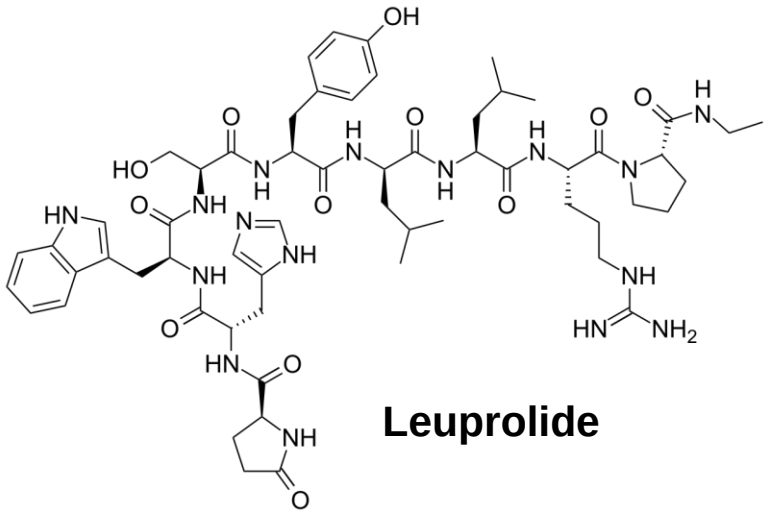






- Sirolimus
- Paclitaxel

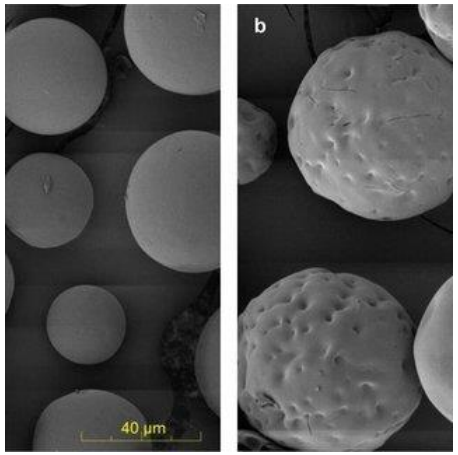
LUPRON DEPOT



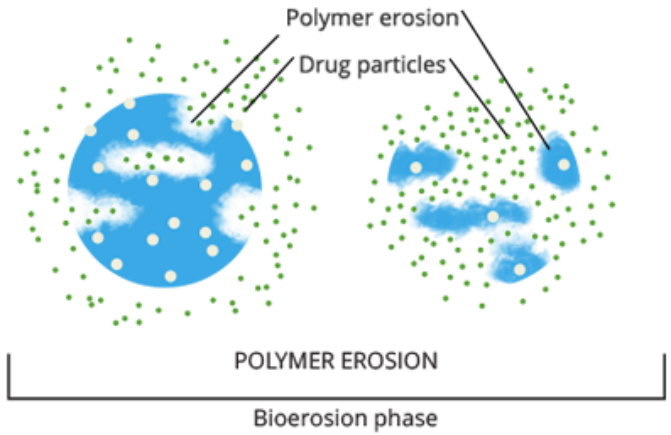
Leuprolide

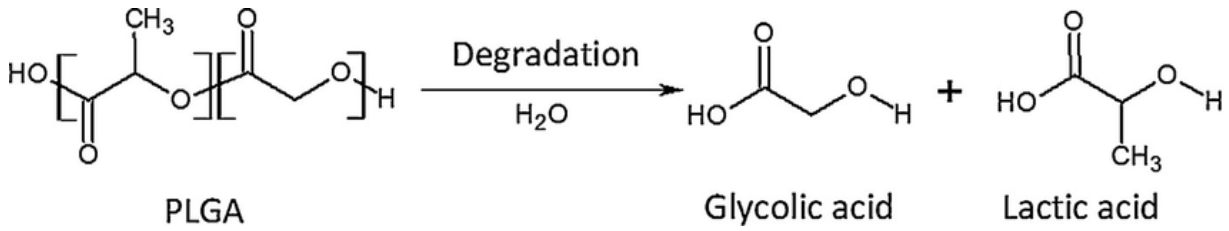
Treatment of prostate cancer, breast cancer
A highly unstable peptide that degrades easily in the body

Lupron Depot: long-acting depot intramuscular injection
First FDA-approved synthetic particle therapy (in 1989)



PLGA microparticles

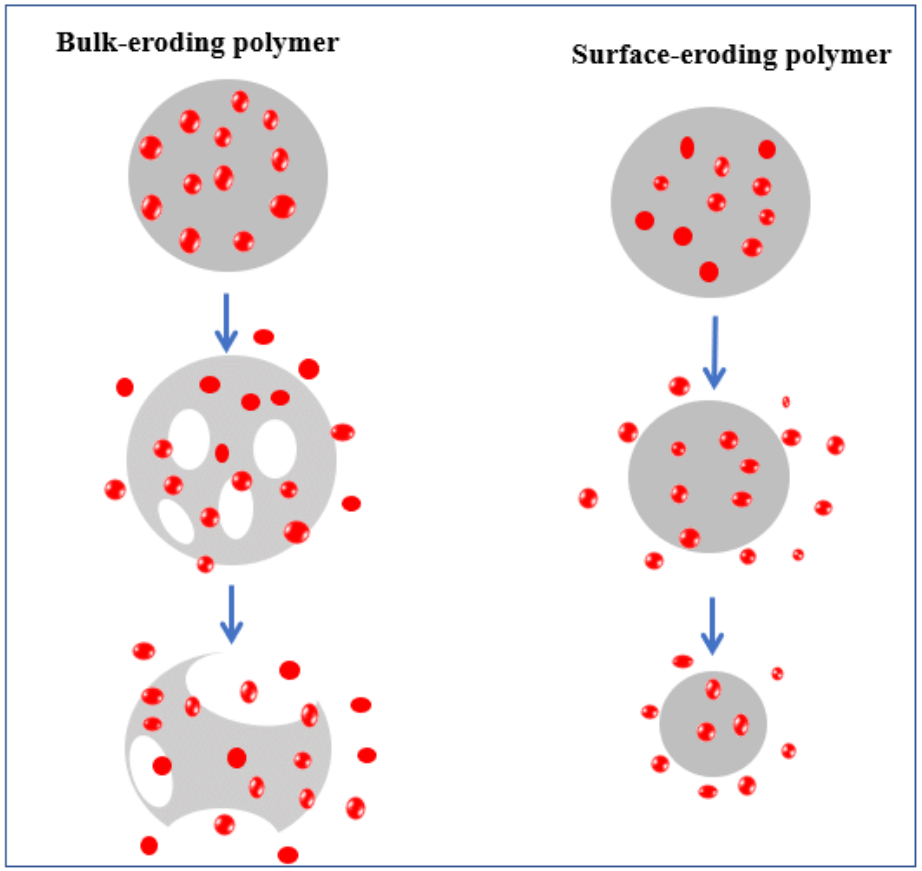


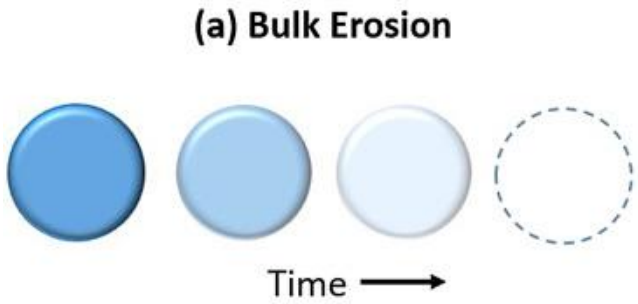


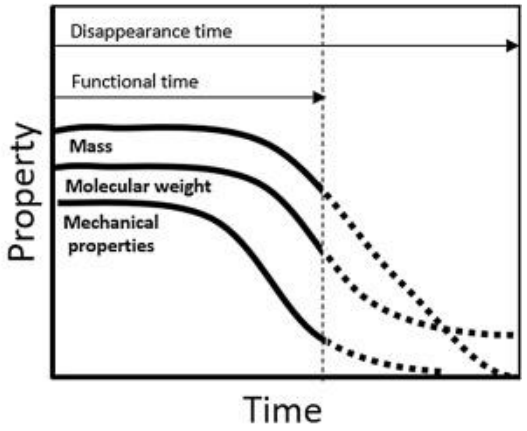
Microparticles localized at the injection site

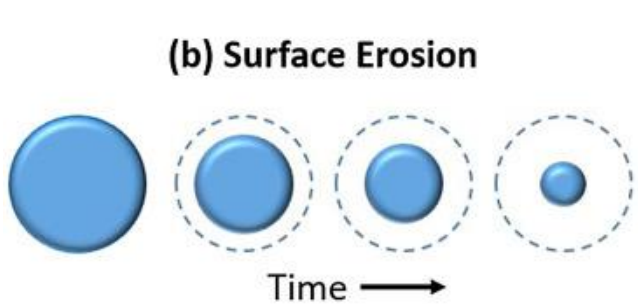
Biodegradable (or bioerodible)

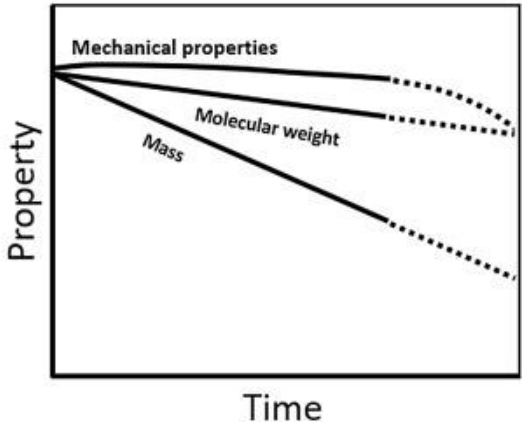
Bulk vs Surface Erosion







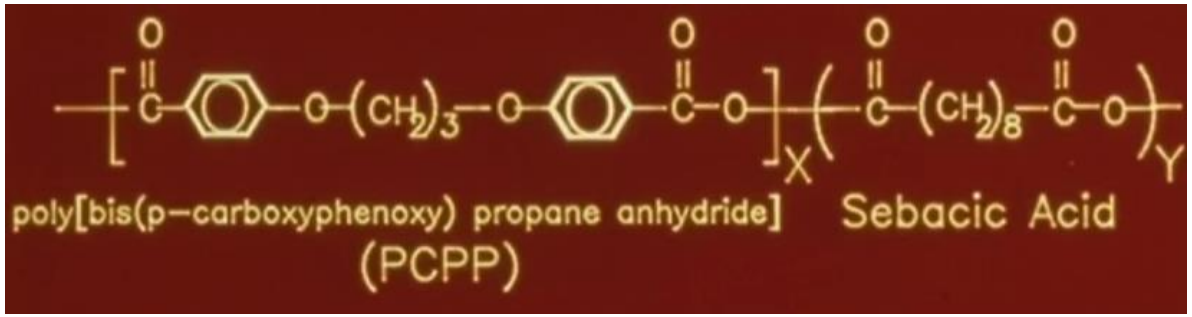


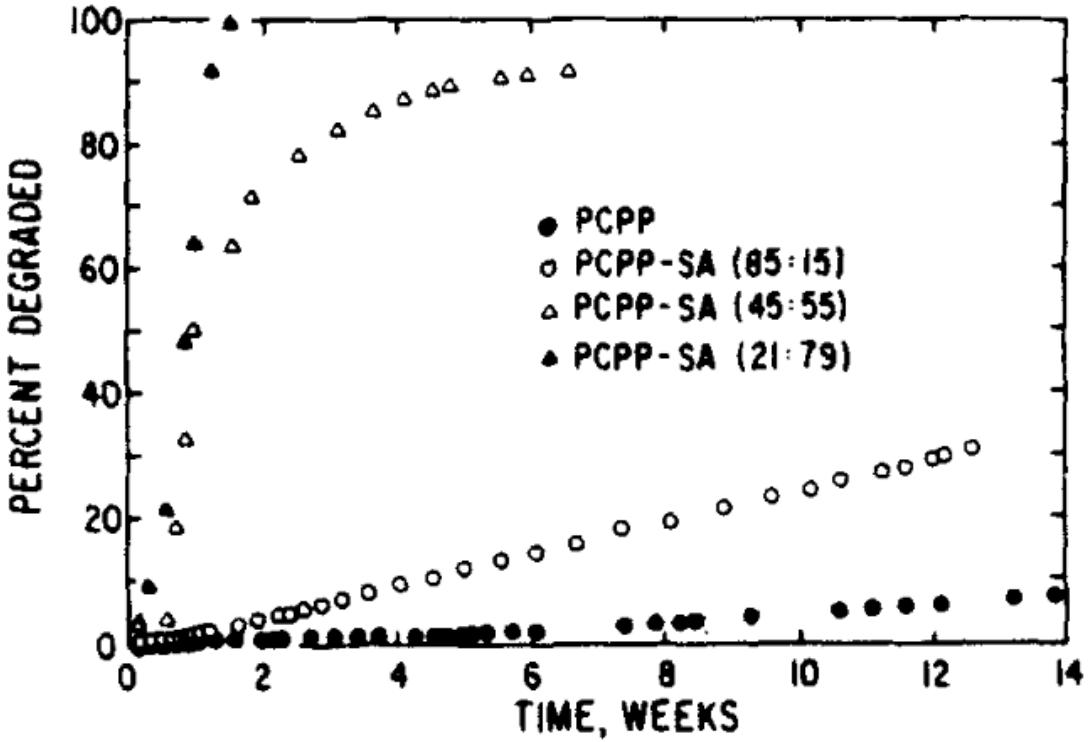


- PLGA undergoes bulk erosion because it is a hydrophilic polymer.
- Bulk erosion can potentially lead to “bursting” once a critical point is reached.

How Do We Design a Polymer That Can Undergo Surface Erosion?

To facilitate surface erosion, the polymer used should be hydrophobic yet contain water labile linkages.

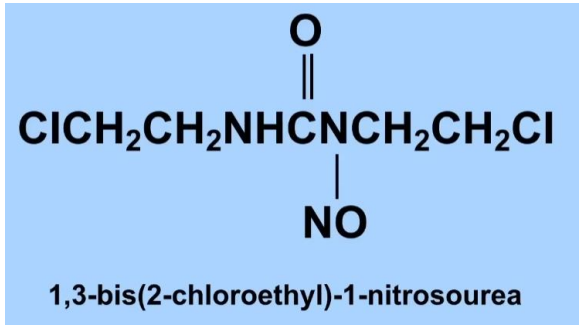




Tunable degradation rate

Leong, K. W.; Brott, B. C.; Langer, R., *J. Biomed. Mater. Res.* **1985,** *19*, 941-955.

GLIADEL® Wafer



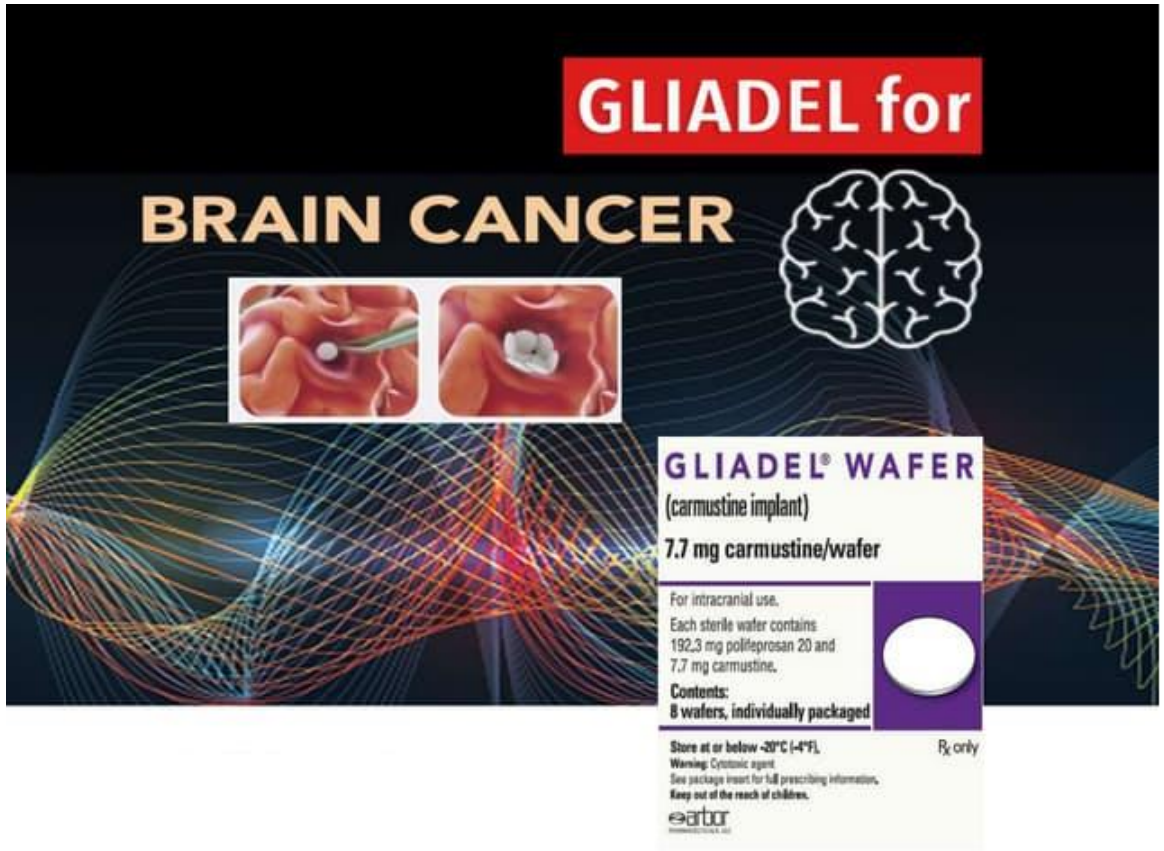
BCNU is an effective drug for brain cancer but:

- A very short half-life in vivo (12 minutes)
- Difficulty in reaching the cancer site in the brain

Robert Langer

Henry Brem

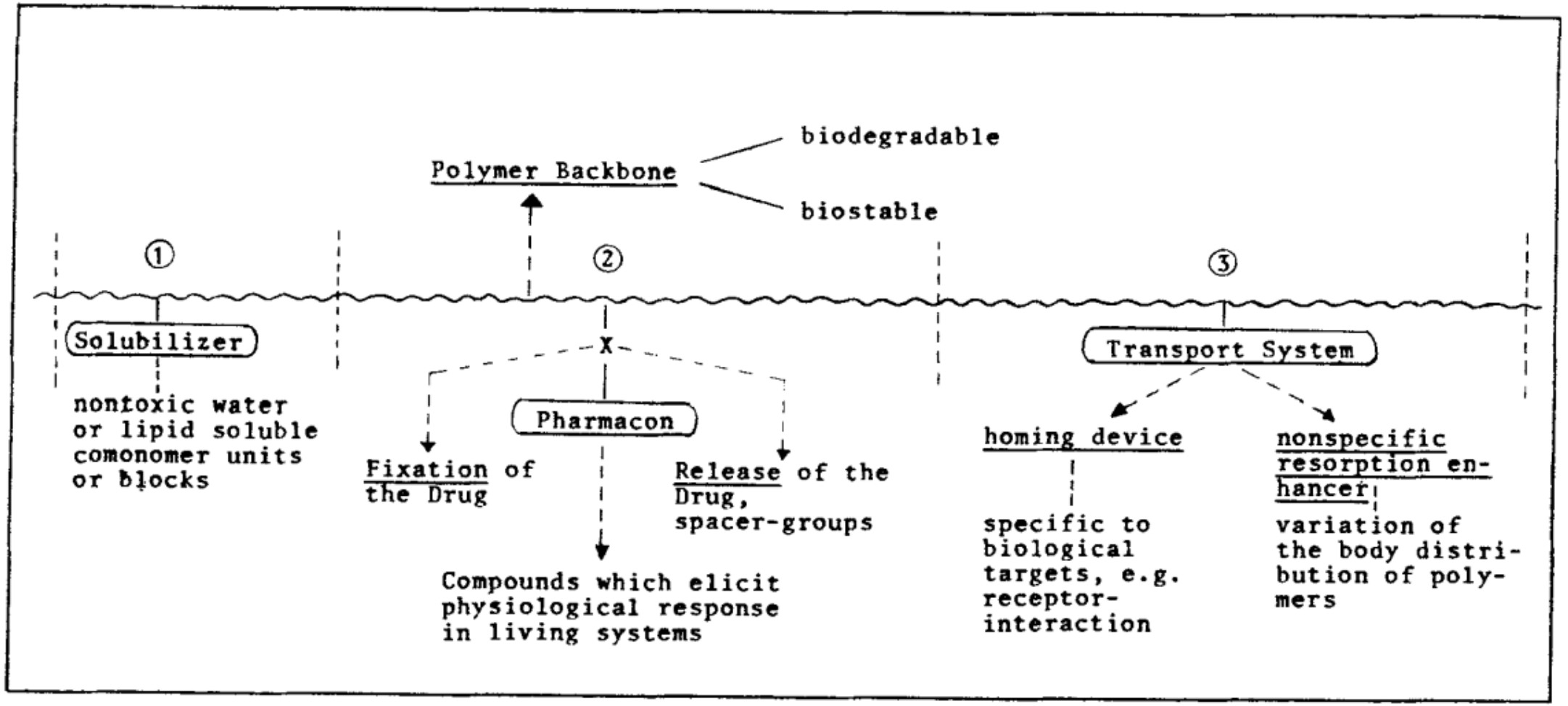
BCNU is embedded within a polyanhydride wafer



FDA approved in 1996 (first new major brain cancer treatment in more than two decades)

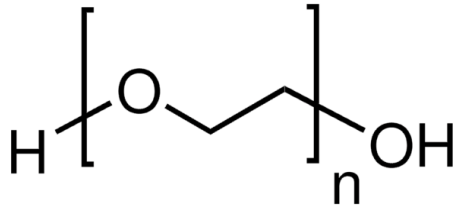
Brem, H.; Piantadosi, S.; Burger, P. C.; Walker, M.; Selker, R.; Vick, N. A.; Black, K.; Sisti, M.; Brem, S.; Mohr, G.; Muller, P.; Morawetz, R.; Schold, S. C., *Lancet* **1995,** *345*, 1008-1012.

Ringsdorf's Model for Pharmacologically Active Polymers

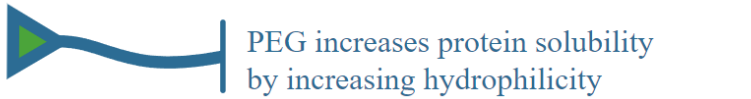


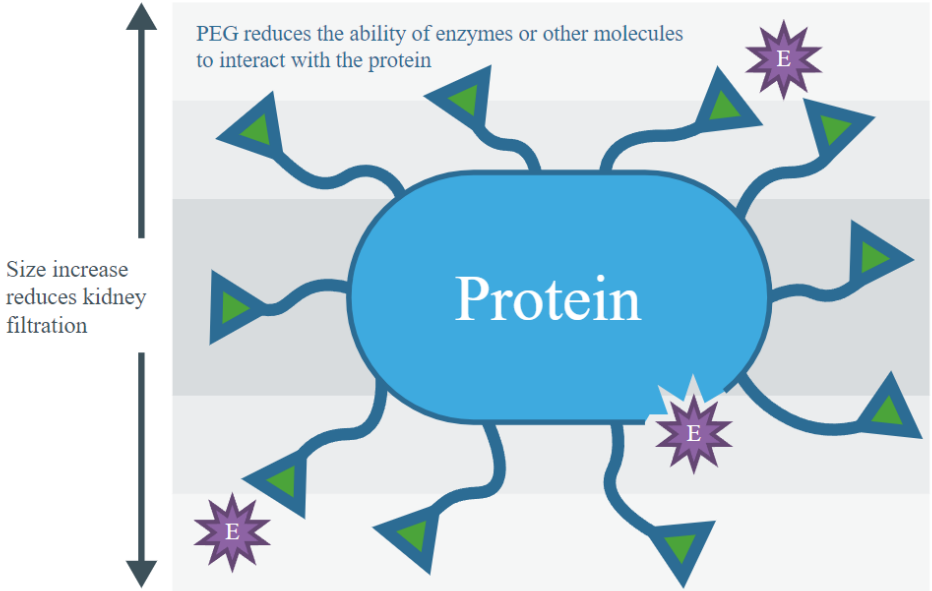
Ringsdorf, H., *Journal of Polymer Science: Polymer Symposia* **1975,** *51*, 135-153.

PEGylation: A Breakthrough Pioneered by Rutgers Chemists



Polyethylene glycol (PEG)





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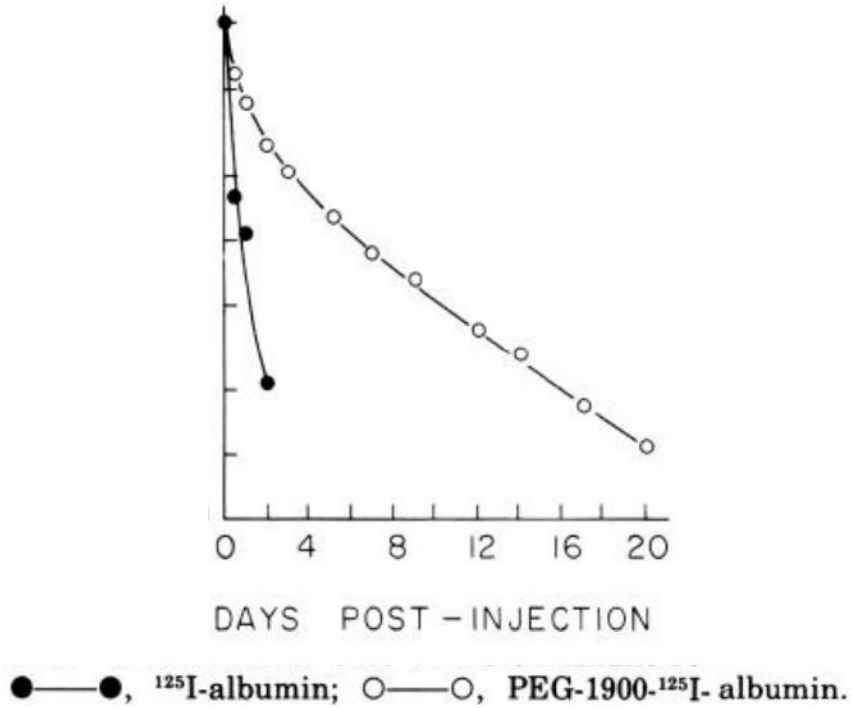
Vol. 252, No. 11, Issue of June 10, pp. 3578-3581, 1977
Printed in U.S.A.

Alteration of Immunological Properties of Bovine Serum Albumin by Covalent Attachment of Polyethylene Glycol*

(Received for publication, December 6, 1976)

ABRAHAM ABUCHOWSKI,‡ THEO VAN ES, NICHOLAS C. PALCZUK, AND FRANK F. DAVIS§

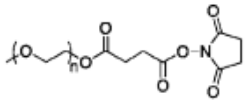
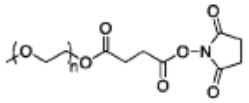
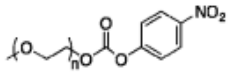
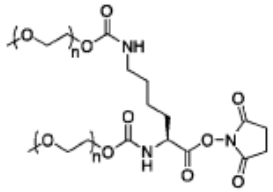
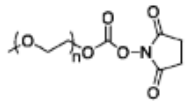
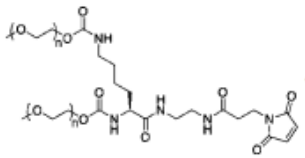
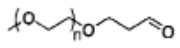
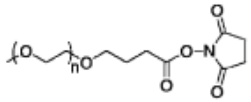
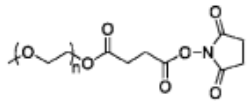
From the Departments of Biochemistry and Zoology, and the Bureau of Biological Research, Rutgers University, New Brunswick, New Jersey 08903



Abuchowski, A.; van Es, T.; Palczuk, N. C.; Davis, F. F., *J. Biol. Chem.* **1977,** *252*, 3578-3581.

FDA-Approved Protein-PEG Conjugates

Table 1 List of FDA-approved protein–polymer drug conjugates and their properties

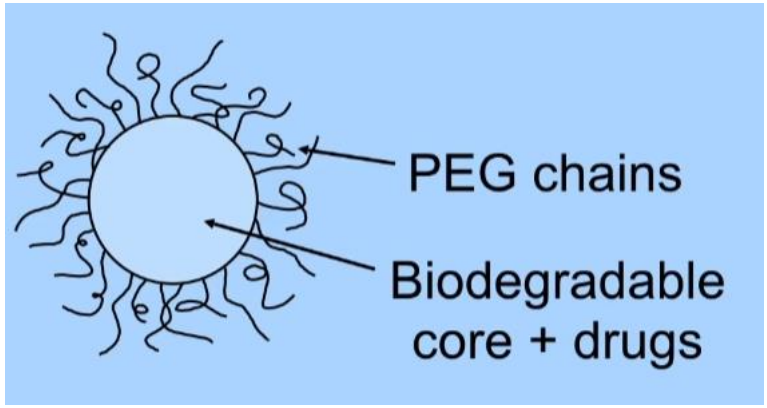
Drug	PEG attachment	PEG size	Protein name	Site(s) of attachment	Native half-life	Conjugate half-life
Adagen		5 kDa	Adenosine deaminase	Nonspecific, lysine, serine, tyrosine, histidine	—	—
Oncaspar		5 kDa	L-Asparaginase	Nonspecific, lysine, serine, tyrosine, histidine	20 h	357 h
Krystexxa		10 kDa (10–11 units)	Mammalian urate oxidase (monomer)	Nonspecific, lysines	4 h	154–331 h
PEGASYS		40 kDa	Interferon alfa-2a	Lysines 31, 121, 131, or 134	3–8 h	65 h
PEG-INTRON		12 kDa	Interferon alfa-2b	Histidine 34 (major)	7–9 h	48–72 h
Cimzia		40 kDa	Anti-TNFα Fab'	*C*-Terminal cysteine	—	—
Neulasta		20 kDa	G-CSF	*N*-Terminal methionine	3.5–3.8 h	42 h
Mircera		30 kDa	Continuous erythropoietin receptor activator	Lysine 52 or 46	7–20 h	134–139 h
Somavert		5 kDa (4–6 units)	hGH antagonist B2036	Nonspecific, lysines, *N*-terminal phenylalanine	—	—

PEGylation of Polymer Nanoparticles

Biodegradable Long-Circulating Polymeric Nanospheres

RUXANDRA GREF, YOSHIHARU MINAMITAKE, MARIA TERESA PERACCHIA, VLADIMIR TRUBETSKOY, VLADIMIR TORCHILIN, AND ROBERT LANGER Authors Info & Affiliations

SCIENCE · 18 Mar 1994 · Vol 263, Issue 5153 · pp. 1600-1603 · DOI: 10.1126/science.8128245

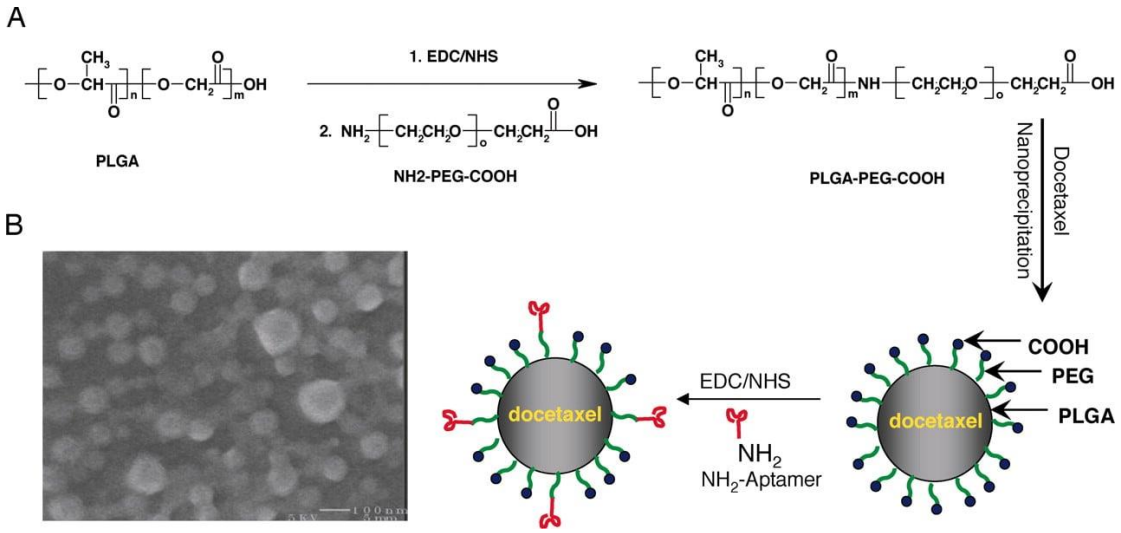


PLGA-*b*-PEG

Exhibited dramatically increased blood circulation times and reduced liver accumulation.

Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy *in vivo*

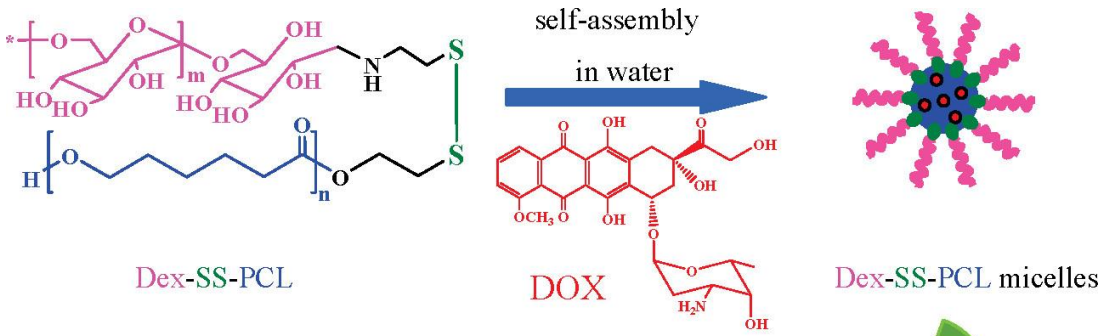
Omid C. Farokhzad*†‡§, Jianjun Cheng‡¶‖, Benjamin A. Teply*‡¶, Ines Sherifi*¶, Sangyong Jon**, Philip W. Kantoff††, Jerome P. Richie‡‡, and Robert Langer†§¶

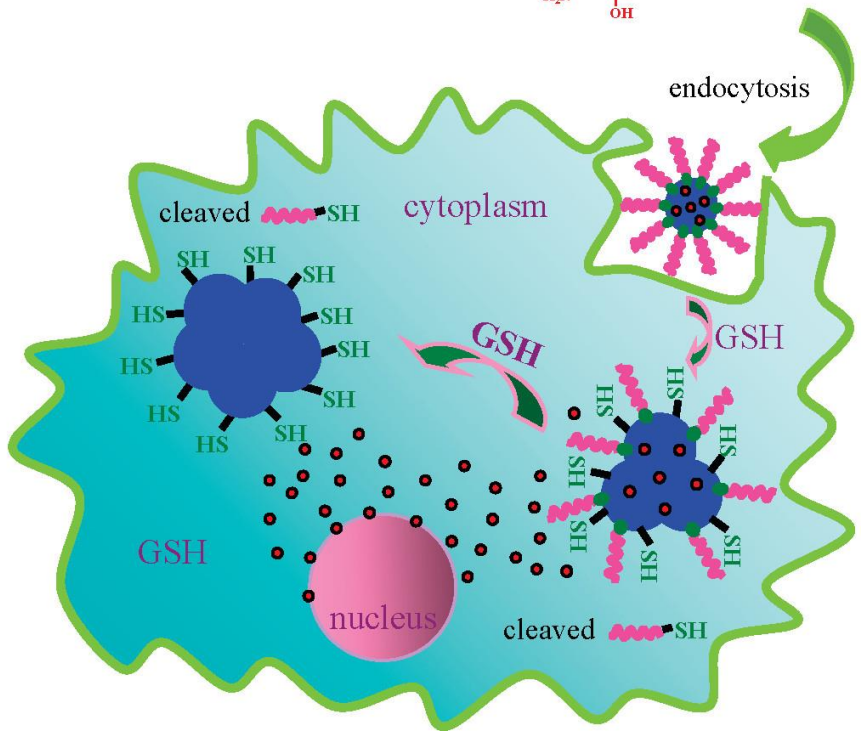


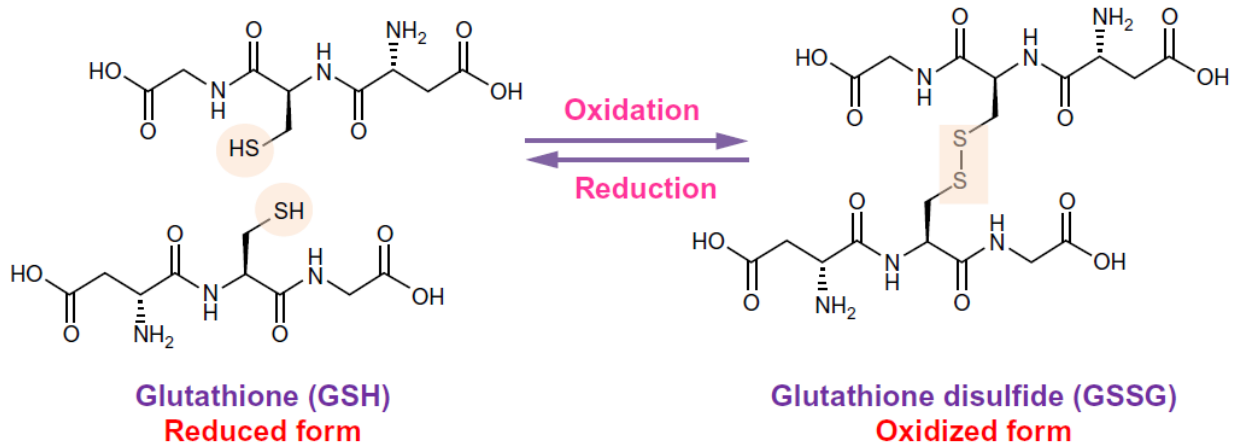
Polymer NPs are functionalized with RNA aptamers that recognize the extracellular domain PSMA, a well characterized antigen expressed on the surface of prostate cancer cells.

Gref, R.; Minamitake, Y.; Peracchia, M. T.; Trubetskoy, V.; Torchilin, V.; Langer, R., *Science* **1994,** *263*, 1600-1603.
Farokhzad, O. C.; Cheng, J.; Teply, B. A.; Sherifi, I.; Jon, S.; Kantoff, P. W.; Richie, J. P.; Langer, R., *Proc. Natl. Acad. Sci. USA* **2006,** *103*, 6315-6320.

Stimuli-Responsive Drug Delivery Systems



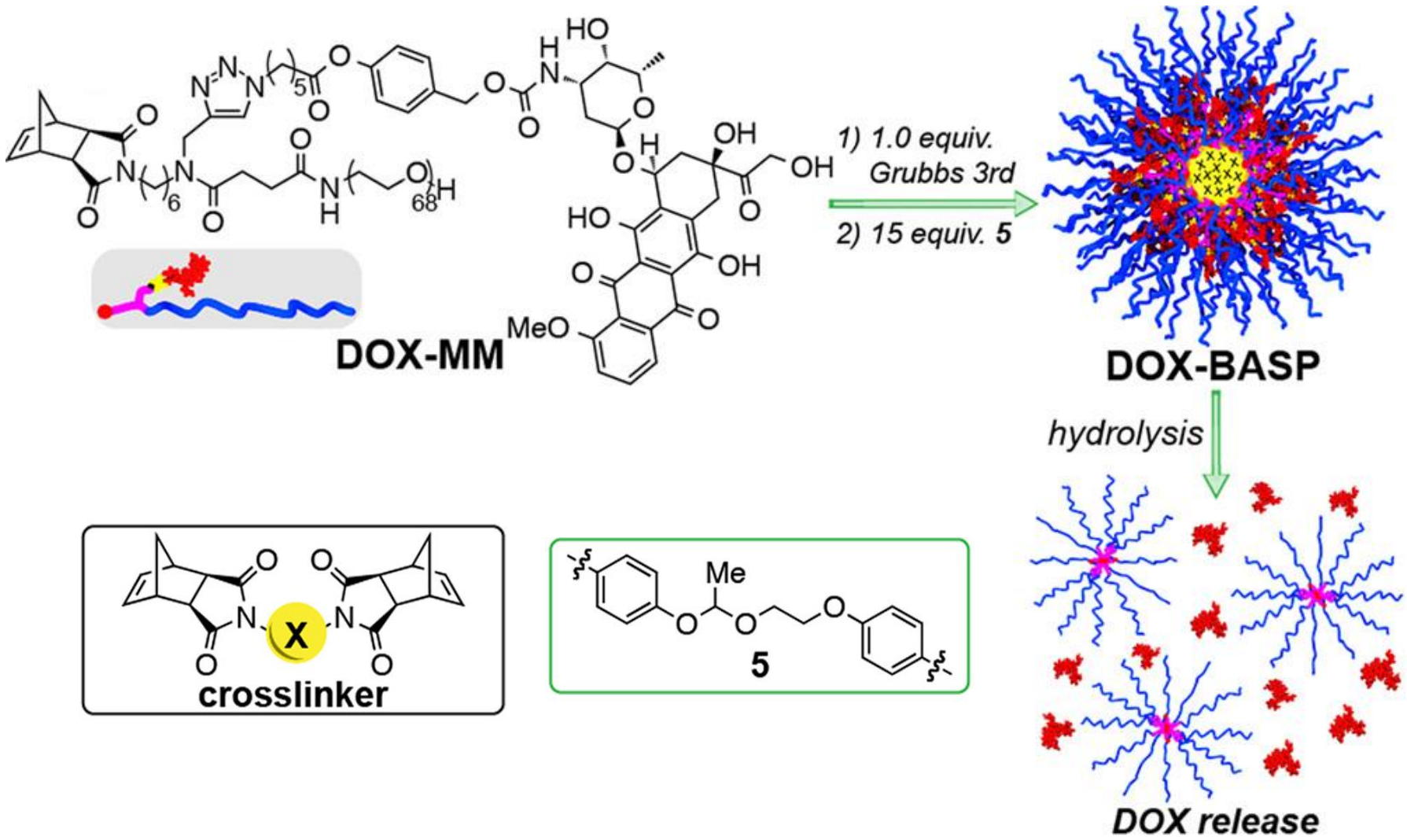




Glutathione is a reducing tripeptide that is over expressed in cancer cells by 100 to 1000 folds than in the blood.

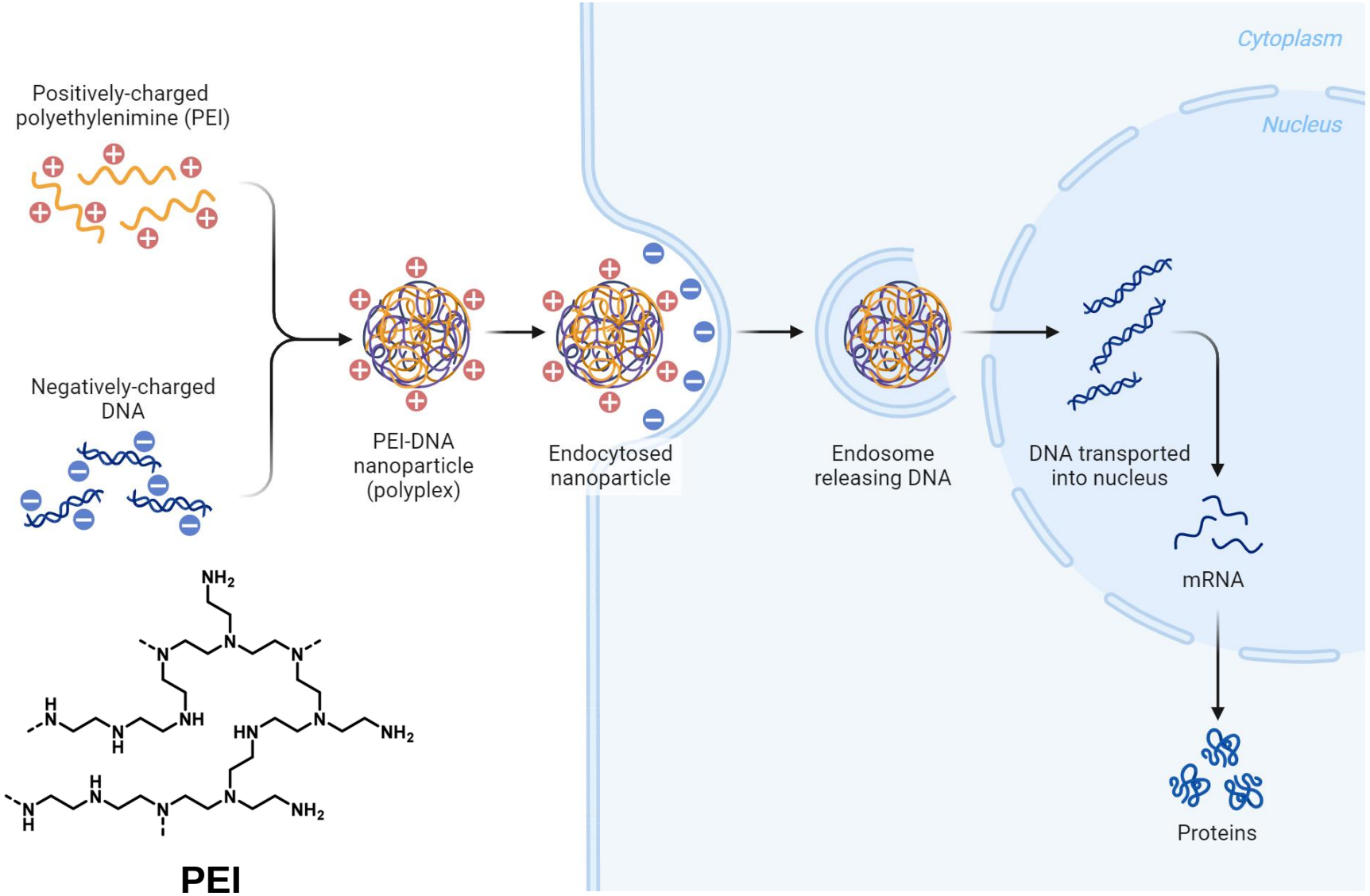
Sun, H.; Guo, B.; Li, X.; Cheng, R.; Meng, F.; Liu, H.; Zhong, Z., *Biomacromolecules* **2010,** *11*, 848-854.

Stimuli-Responsive Drug Delivery Systems



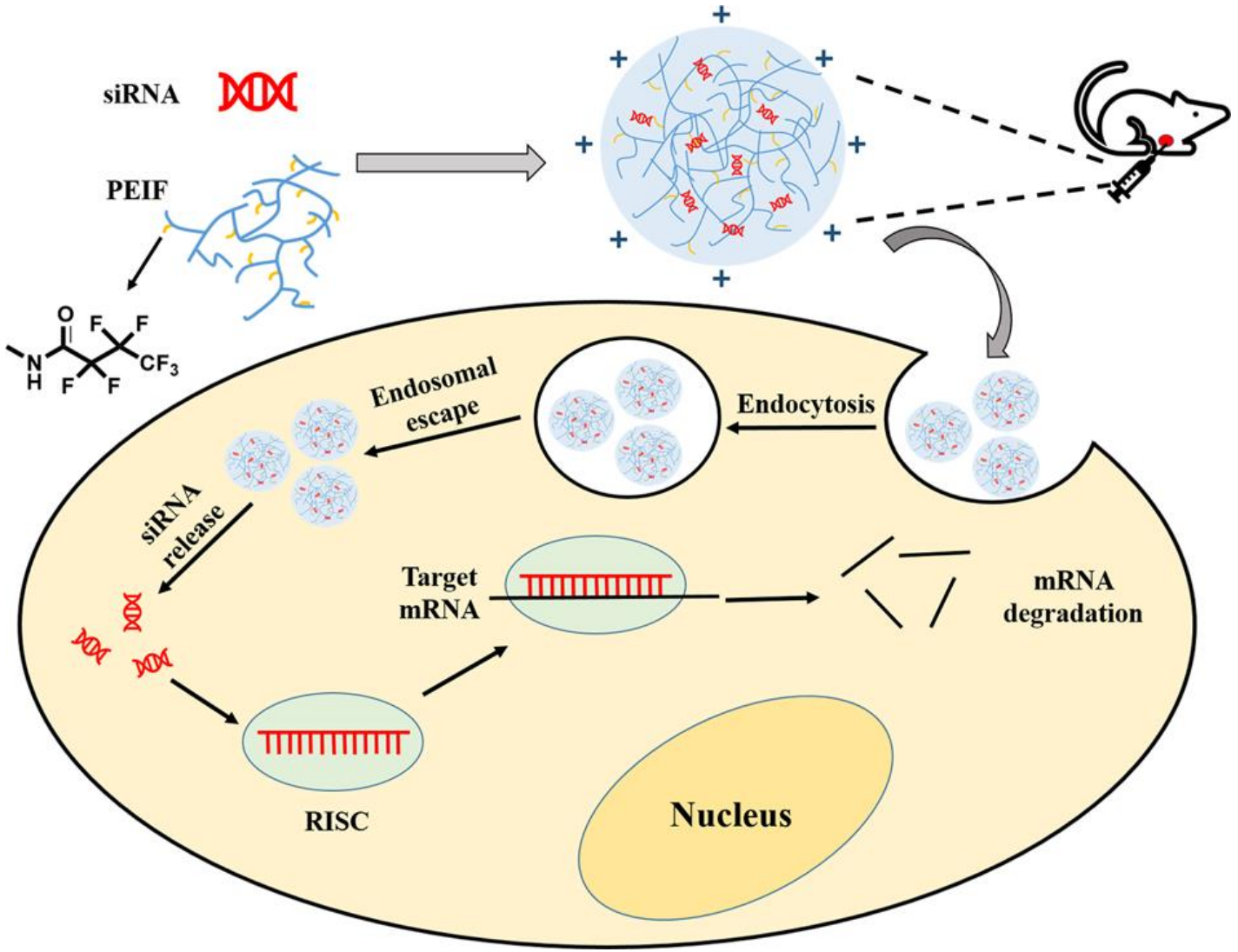
Gao, A. X.; Liao, L.; Johnson, J. A., *ACS Macro Lett.* **2014,** *3*, 854-857.

Gene Transfection Using Cationic Polymer Vehicles



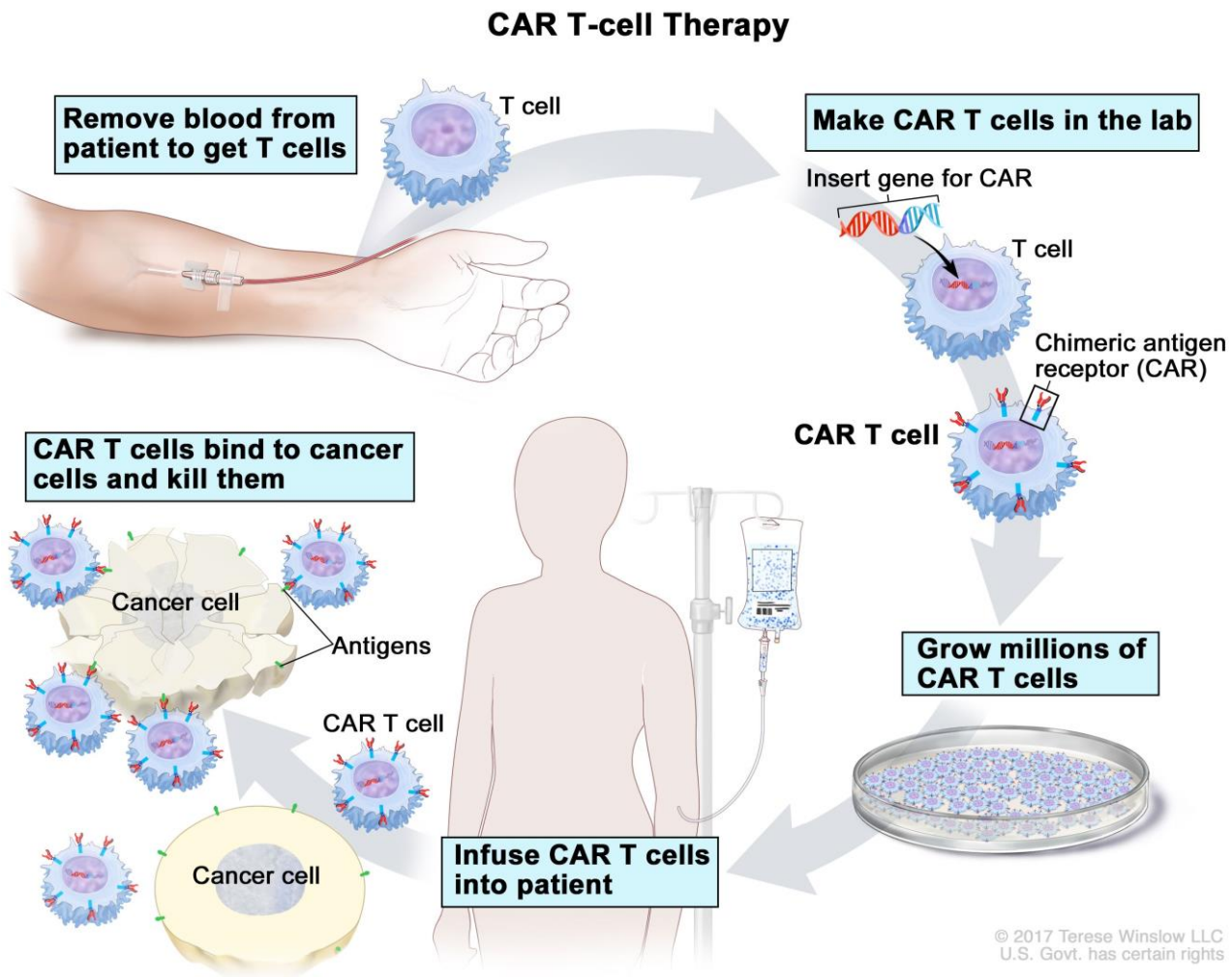
PEI

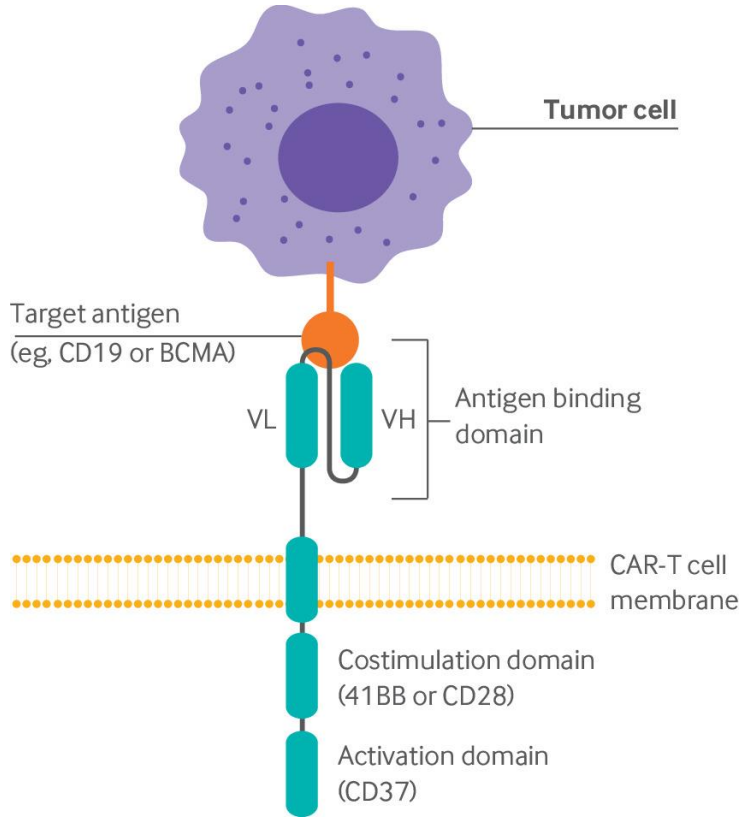
Polycationic Delivery of siRNA for Gene Silencing



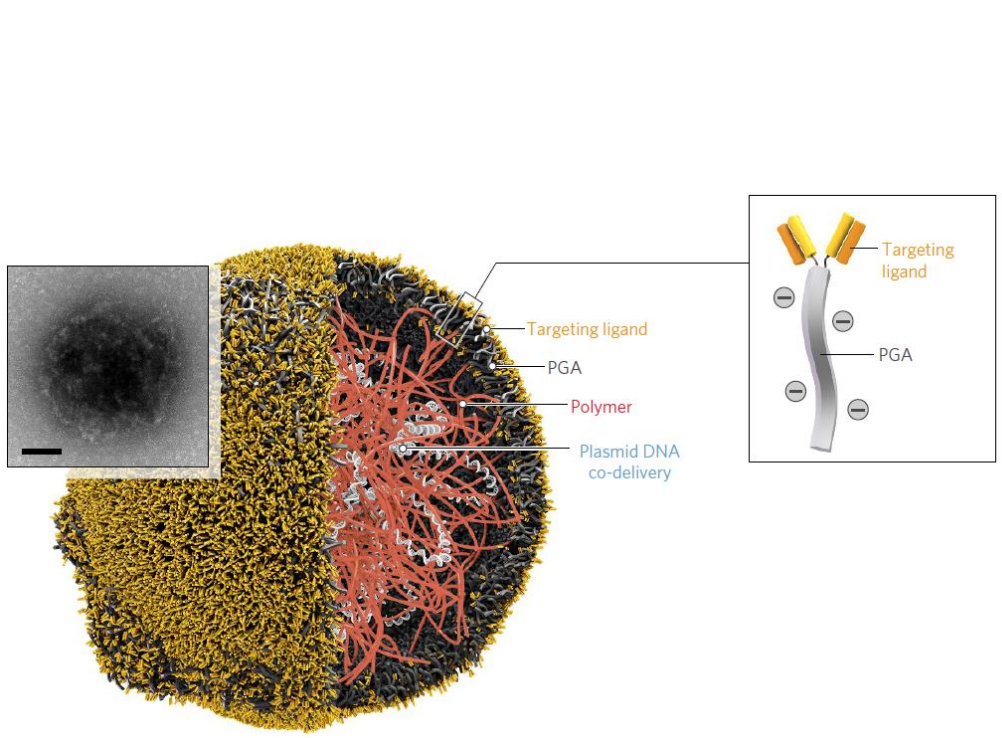
Yuan, Z.; Guo, X.; Wei, M.; Xu, Y.; Fang, Z.; Feng, Y.; Yuan, W.-E., *NPG Asia Materials* **2020,** *12*, 34.

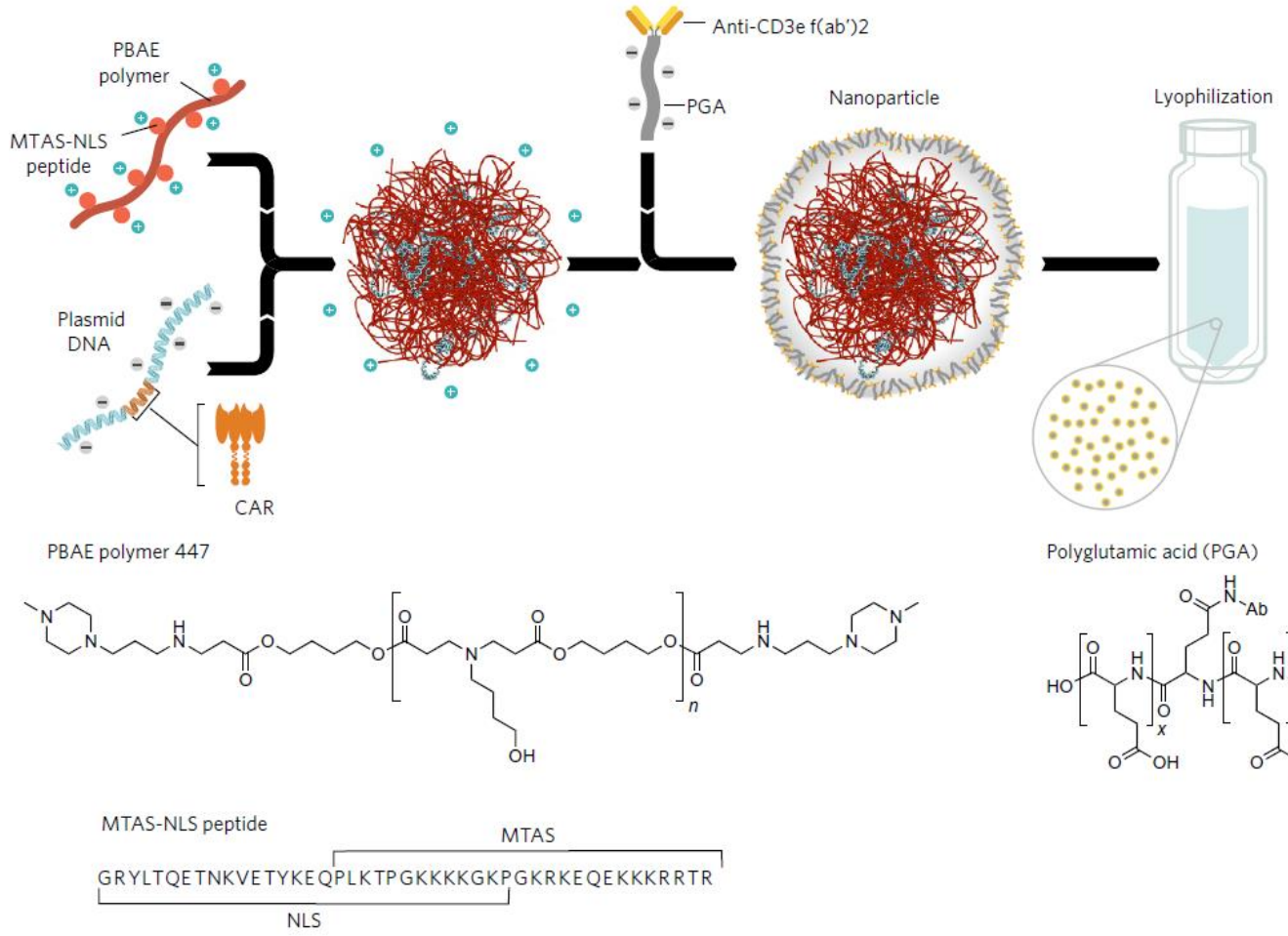
Cancer Immunotherapy





Polymer-Based DNA Nanocarriers for Cancer Immunotherapy

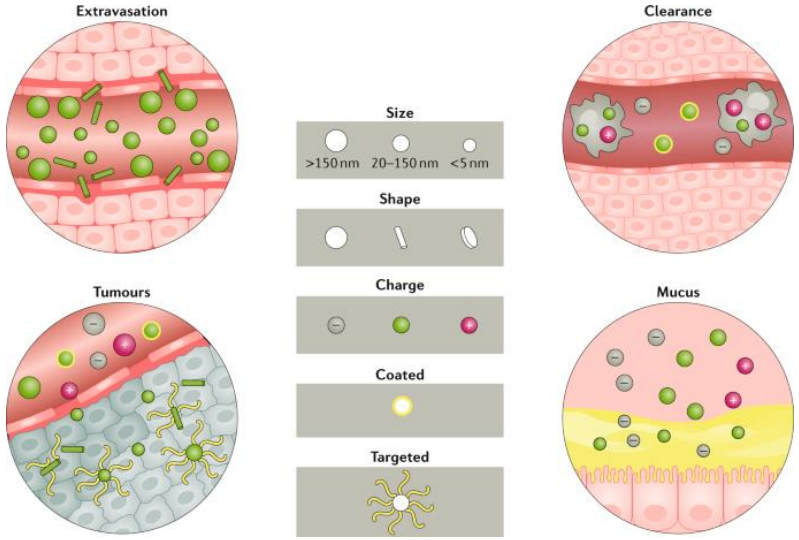




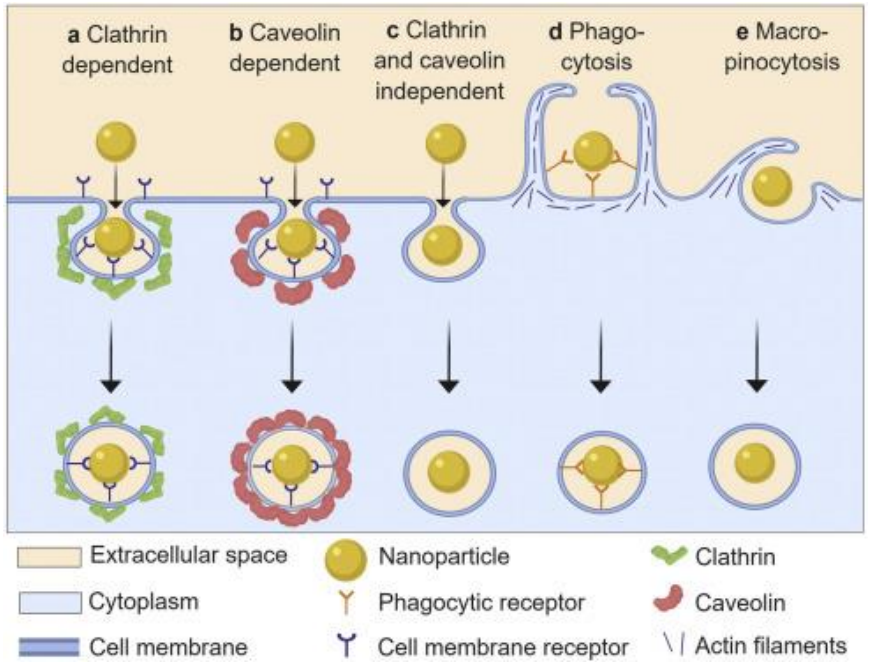
Smith, T. T.; Stephan, S. B.; Moffett, H. F.; McKnight, L. E.; Ji, W.; Reiman, D.; Bonagofski, E.; Wohlfahrt, M. E.; Pillai, S. P. S.; Stephan, M. T., *Nat. Nanotechnol.* **2017,** *12*, 813-820.

Practical Considerations for Polymer Drug Delivery Systems

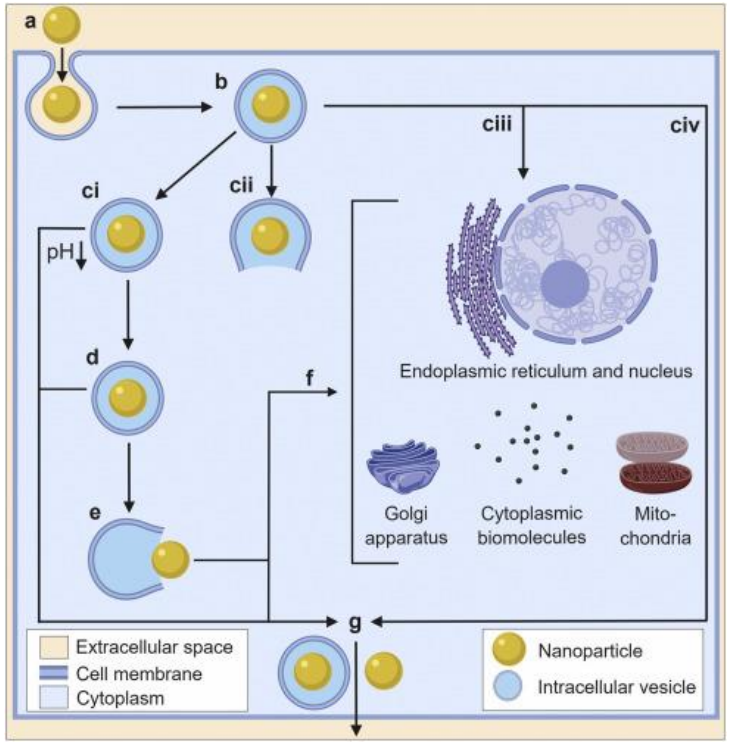
Organ Distribution



Cellular uptake



Intracellular trafficking



Mitchell, M. J.; Billingsley, M. M.; Haley, R. M.; Wechsler, M. E.; Peppas, N. A.; Langer, R., *Nat. Rev. Drug Discov.* **2021,** *20*, 101-124..
Donahue, N. D.; Acar, H.; Wilhelm, S., *Adv. Drug Deliv. Rev.* **2019,** *143*, 68-96.

Tissue Engineering

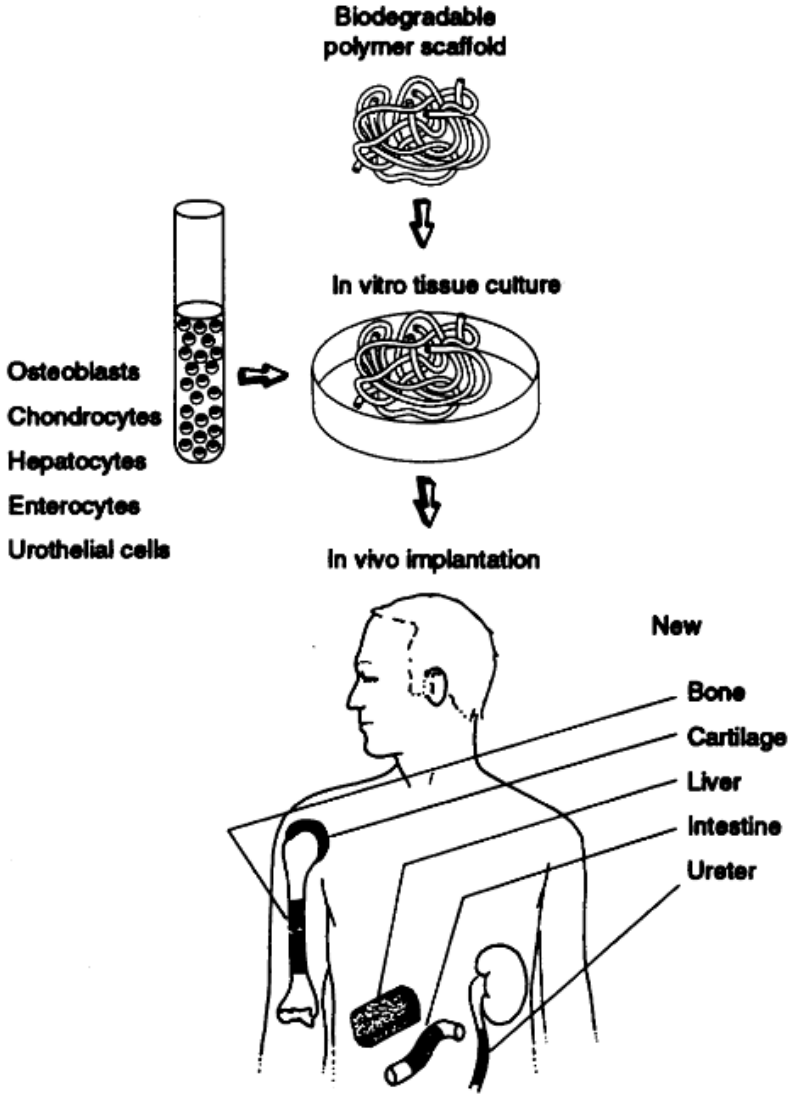
Tissue Engineering

Robert Langer* and Joseph P. Vacanti

The loss or failure of an organ or tissue is one of the most frequent, devastating, and costly problems in human health care. A new field, tissue engineering, applies the principles of biology and engineering to the development of functional substitutes for damaged tissue. This article discusses the foundations and challenges of this interdisciplinary field and its attempts to provide solutions to tissue creation and repair.

their continuous production of enkephalins and cathecholamines they appeared to relieve chronic intractable pain (*10*).

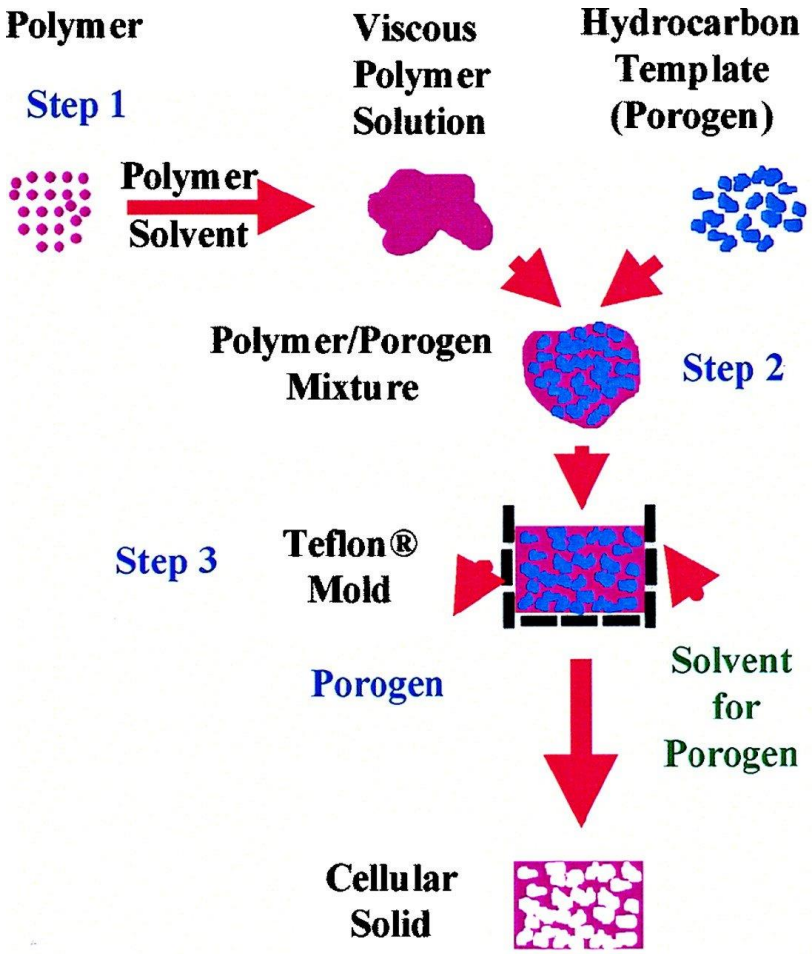
Nerve regeneration has also been studied. Peripheral nerves are capable of regeneration

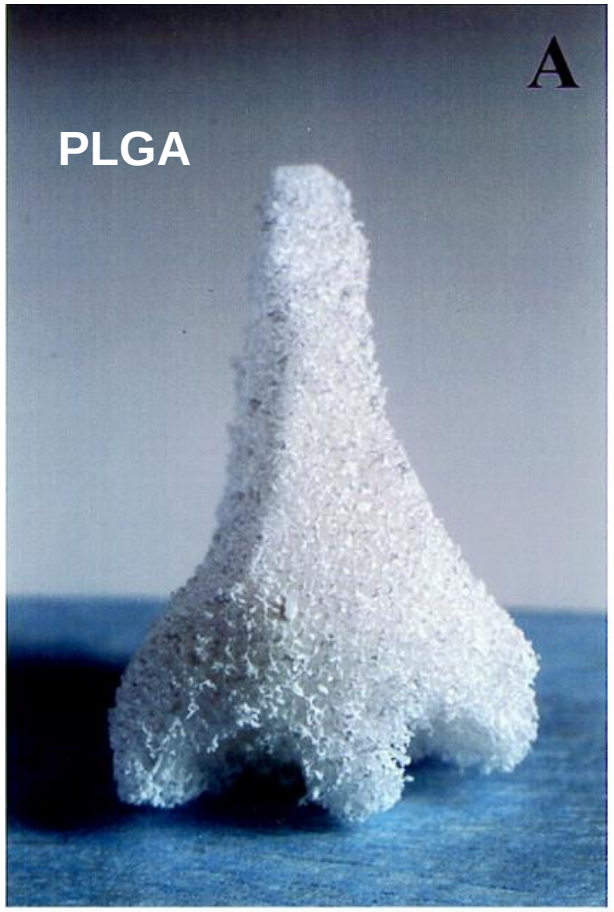


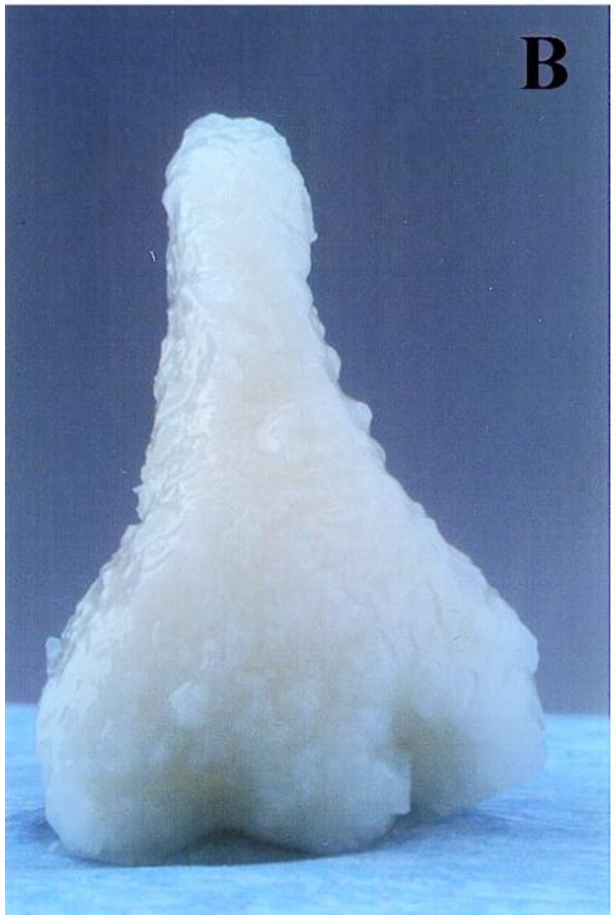
- Biocompatible
- Biodegradable
- Microenvironment
- Mechanical properties
- Cell growth and differentiation

Langer, R.; Vacanti, J. P., *Science* **1993,** *260*, 920-926.

Polymeric Foams for Guided Tissue Regeneration



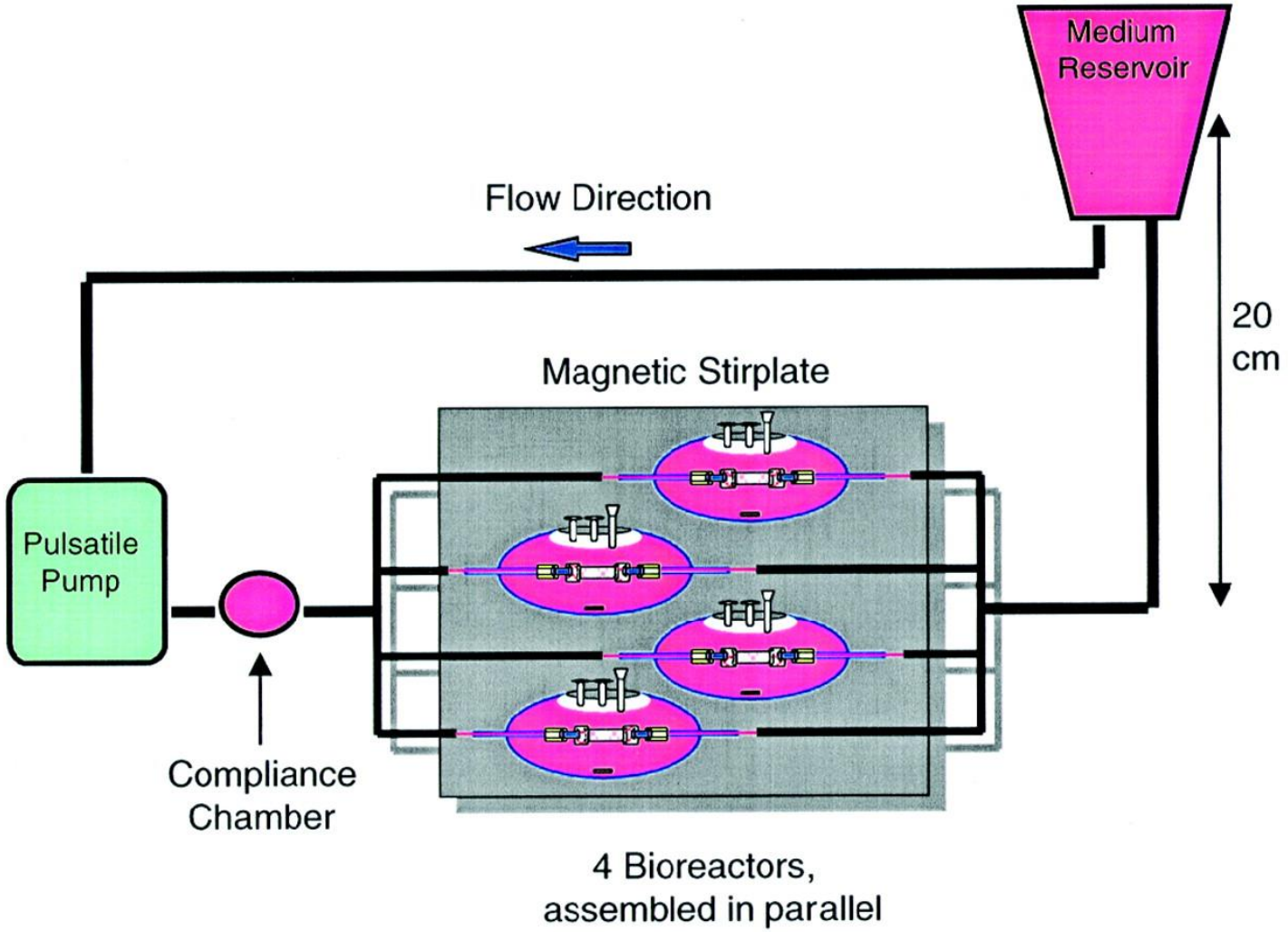


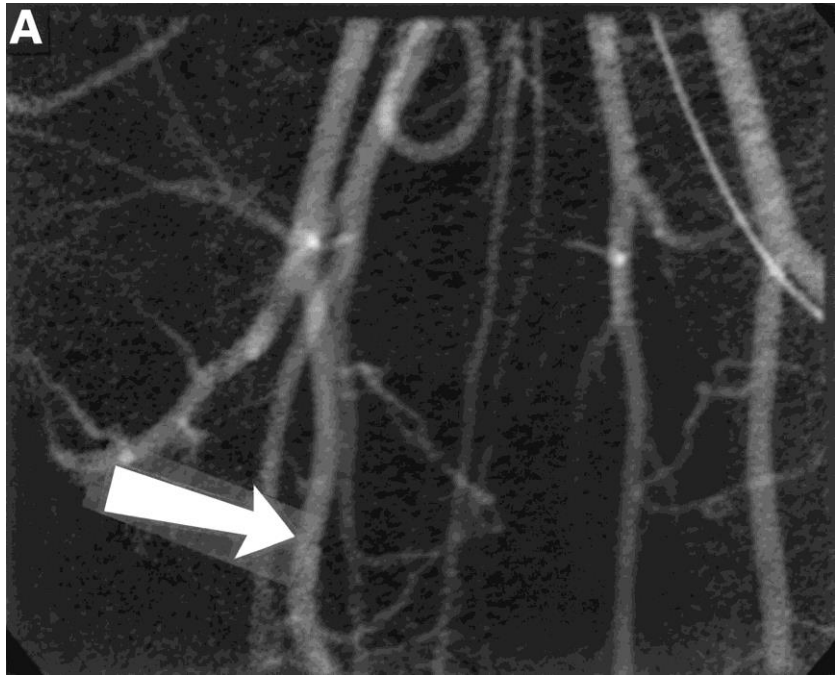


a cartilaginous tissue-polymer composite produced by seeding the scaffold with bovine chondrocytes

Shastri, V. P.; Martin, I.; Langer, R., *Proc. Natl. Acad. Sci. USA* **2000,** *97*, 1970-1975.

Artificial Blood Vessels

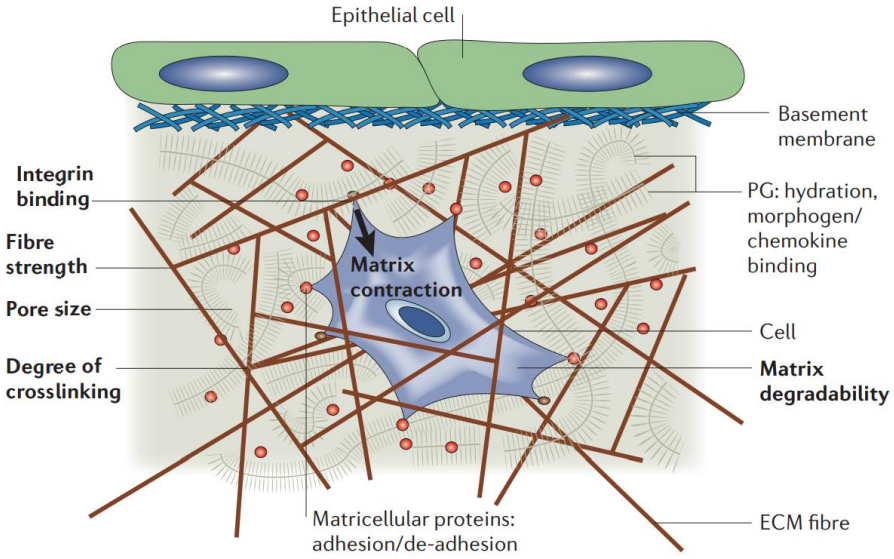




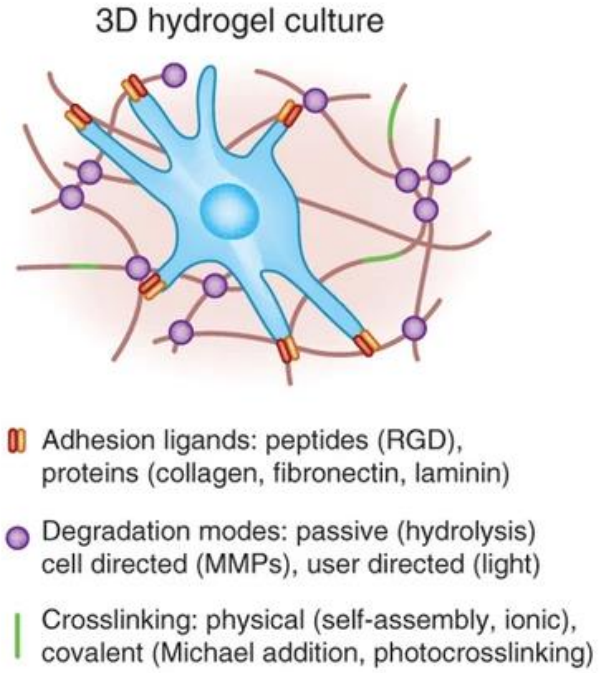
Smooth muscle cells on biodegradable polyglycolic acid (PGA) scaffolds

Niklason, L. E.; Gao, J.; Abbott, W. M.; Hirschi, K. K.; Houser, S.; Marini, R.; Langer, R., *Science* **1999,** *284*, 489-493.

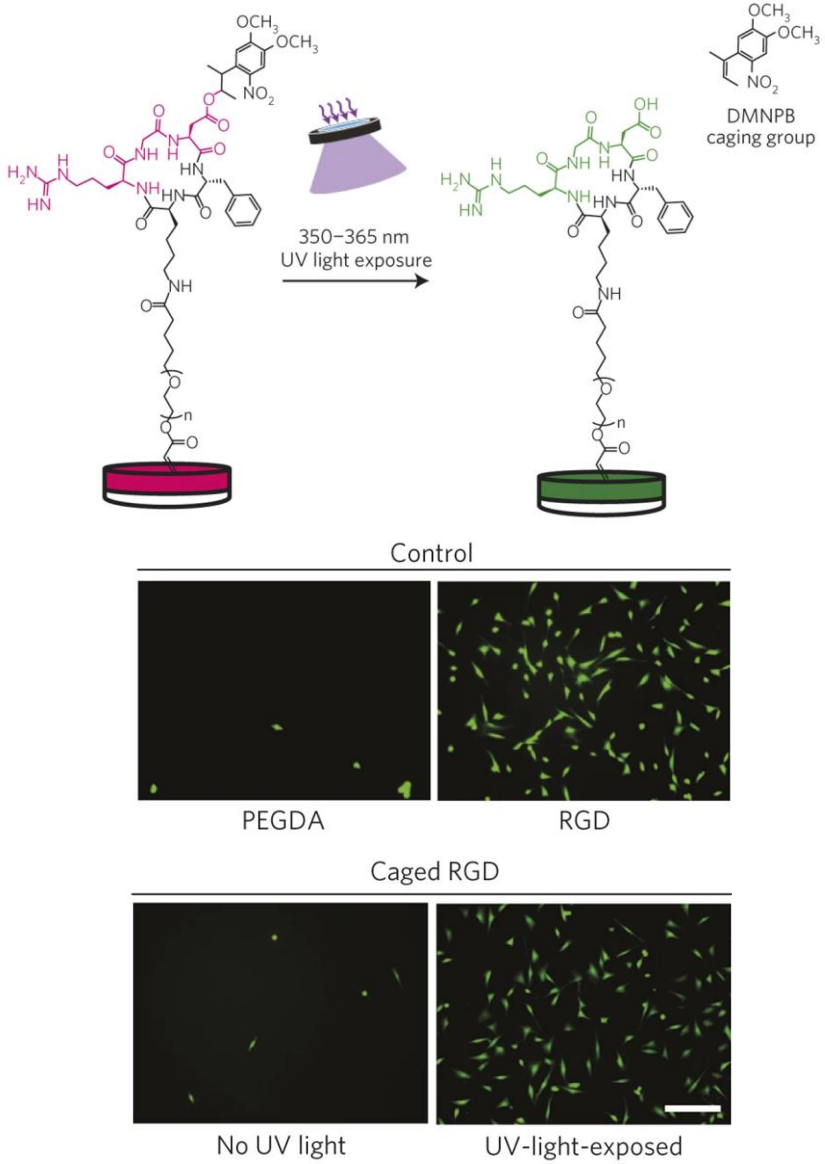
Controlling Microenvironment



Microenvironment of ECM



Hydrogel culture

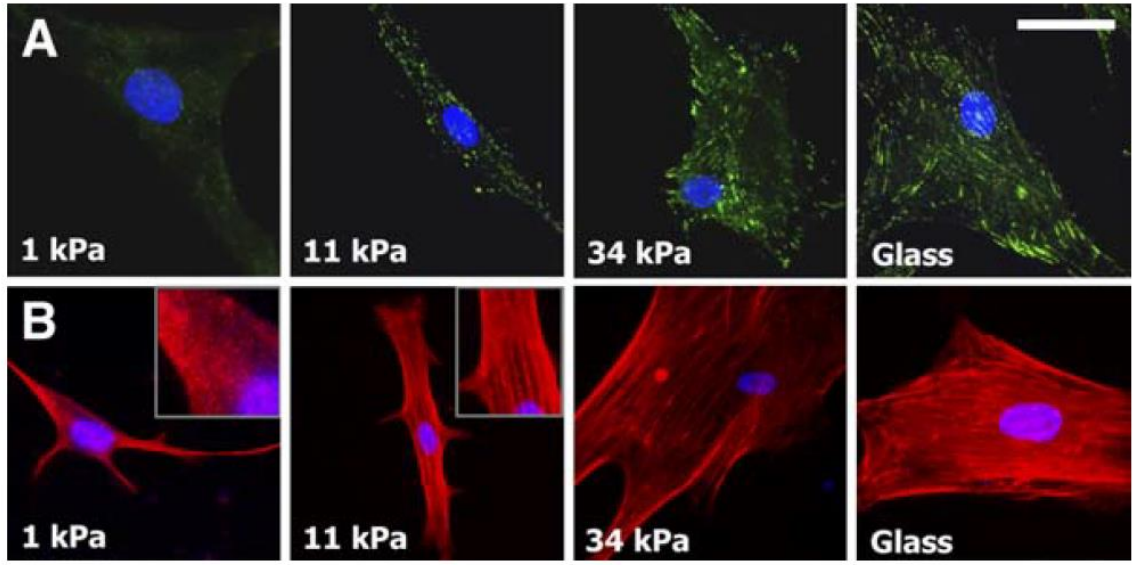


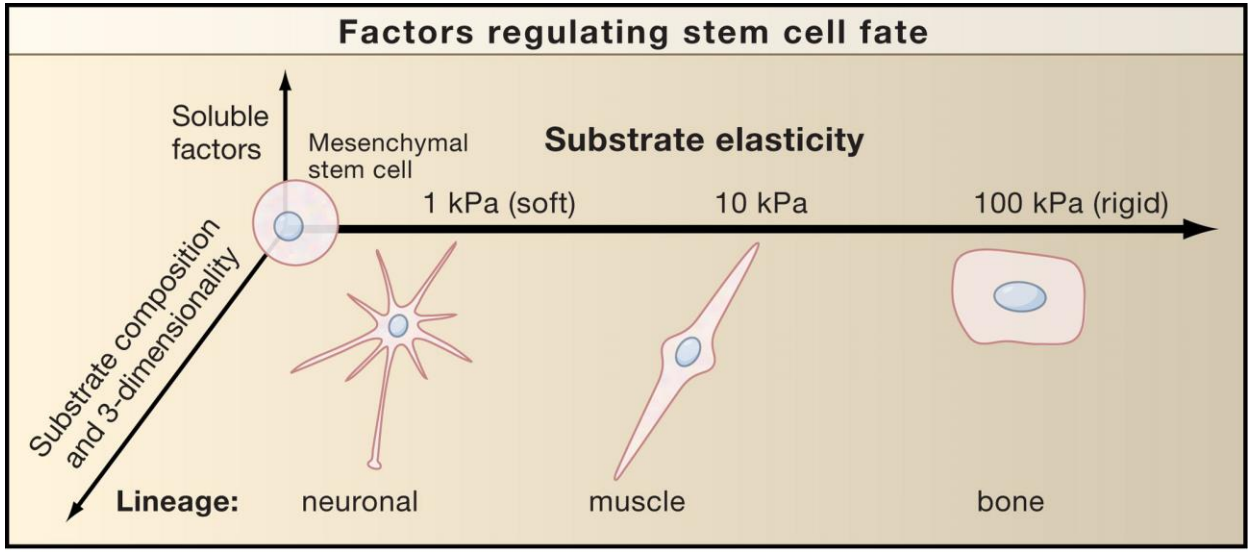
Caliari, S. R.; Burdick, J. A., *Nat. Methods* **2016,** *13*, 405-414.

Lee, T. T.; García, J. R.; Paez, J. I.; Singh, A.; Phelps, E. A.; Weis, S.; Shafiq, Z.; Shekaran, A.; del Campo, A.; García, A. J., *Nat. Mater.* **2015,** *14*, 352-360.

Stiffness of Substrates

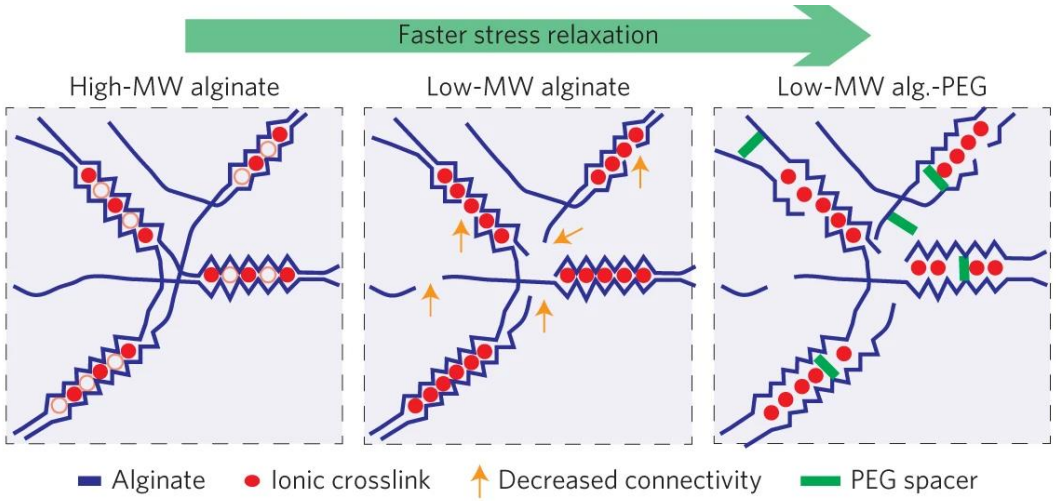
Mesenchymal stem cells





Engler, A. J.; Sen, S.; Sweeney, H. L.; Discher, D. E., *Cell* **2006,** *126*, 677-689.

Stress Relaxation of Substrates



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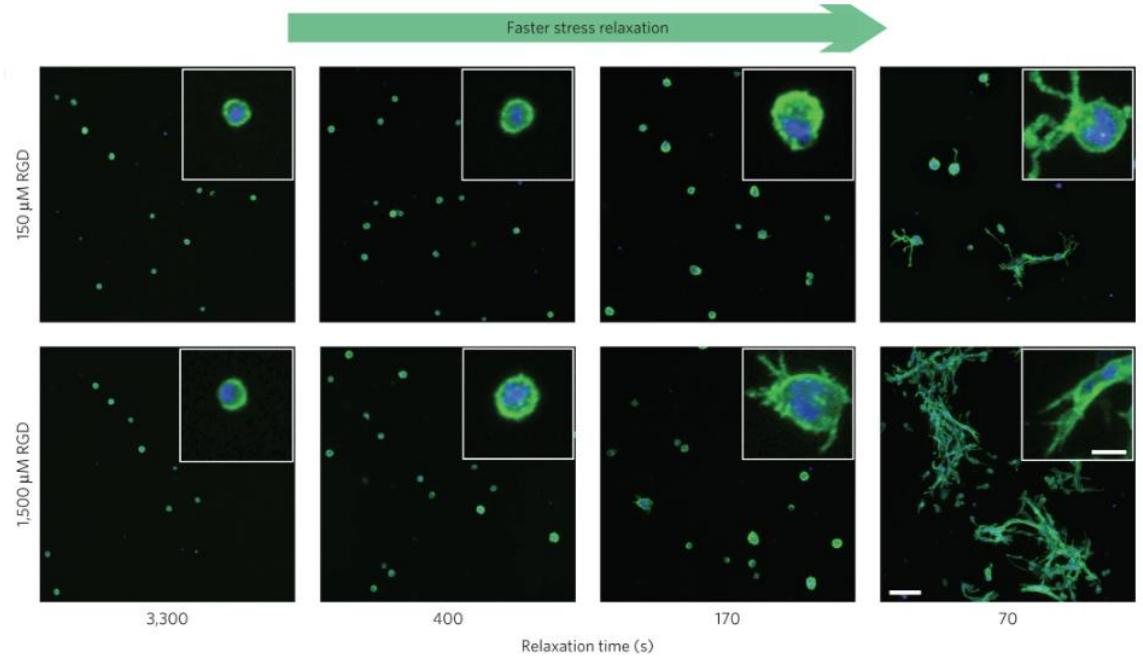
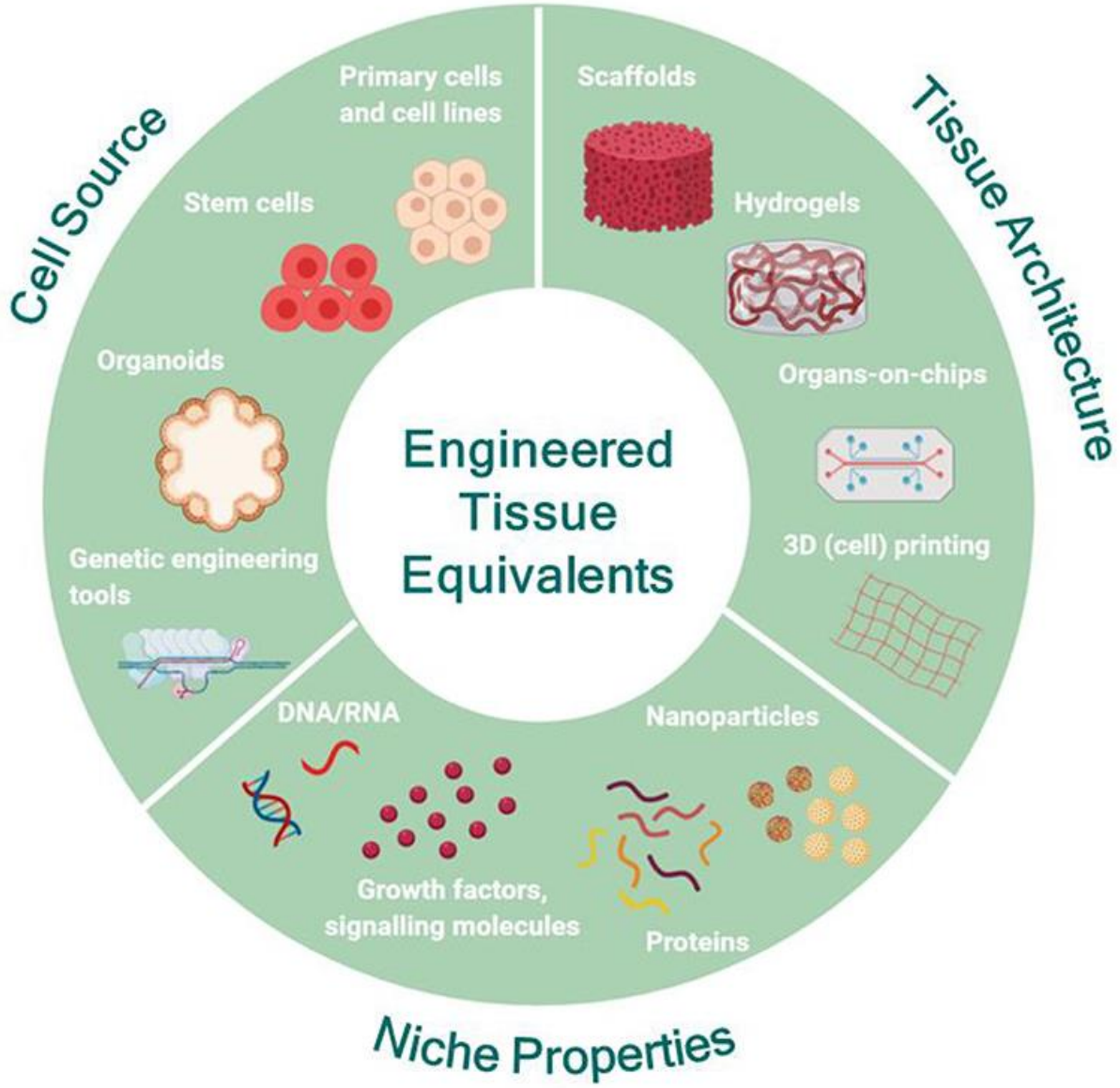


Chaudhuri, O.; Gu, L.; Klumpers, D.; Darnell, M.; Bencherif, S. A.; Weaver, J. C.; Huebsch, N.; Lee, H.-p.; Lippens, E.; Duda, G. N.; Mooney, D. J., *Nat. Mater.* **2016,** *15*, 326-334.

Factors to Consider in Tissue Engineering