Self-assembly and Nanotechnology 10.524

Lecture 5.
Nanobiotechnology and Nanomedicine

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Lecture 5: Nanobiotechnology and Nanomedicine

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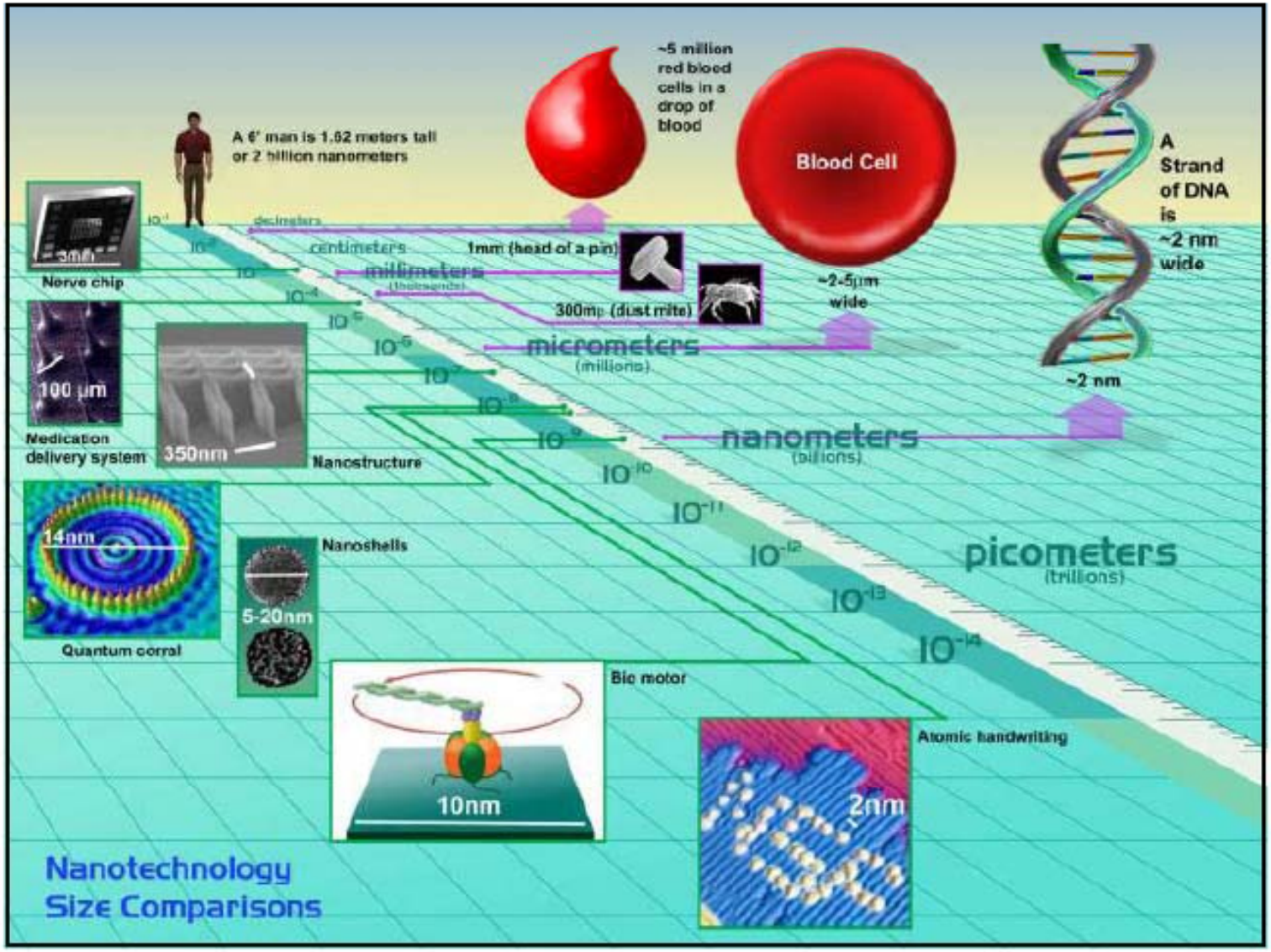
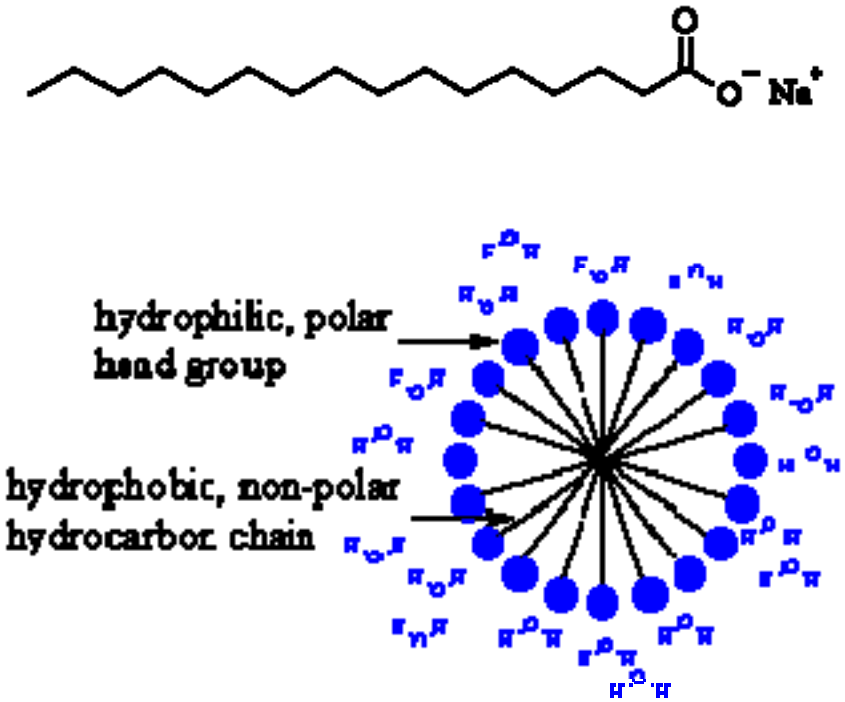
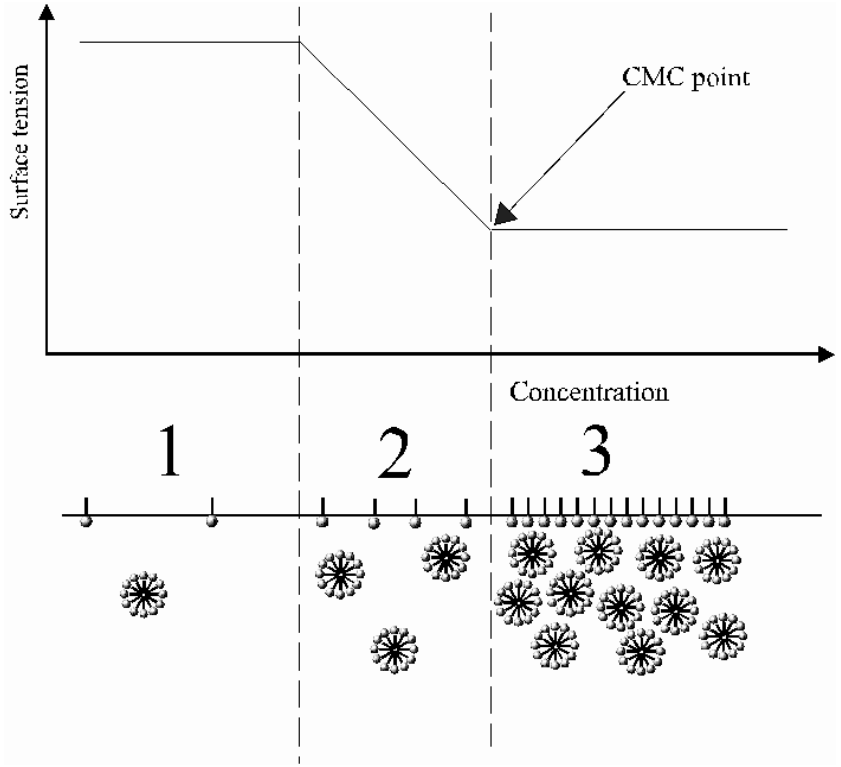


Kenneth Dormer, Professor of Physiology
University of Oklahoma Health Sciences Center

Drug Delivery Vehicle: Micelles

Micelle formation

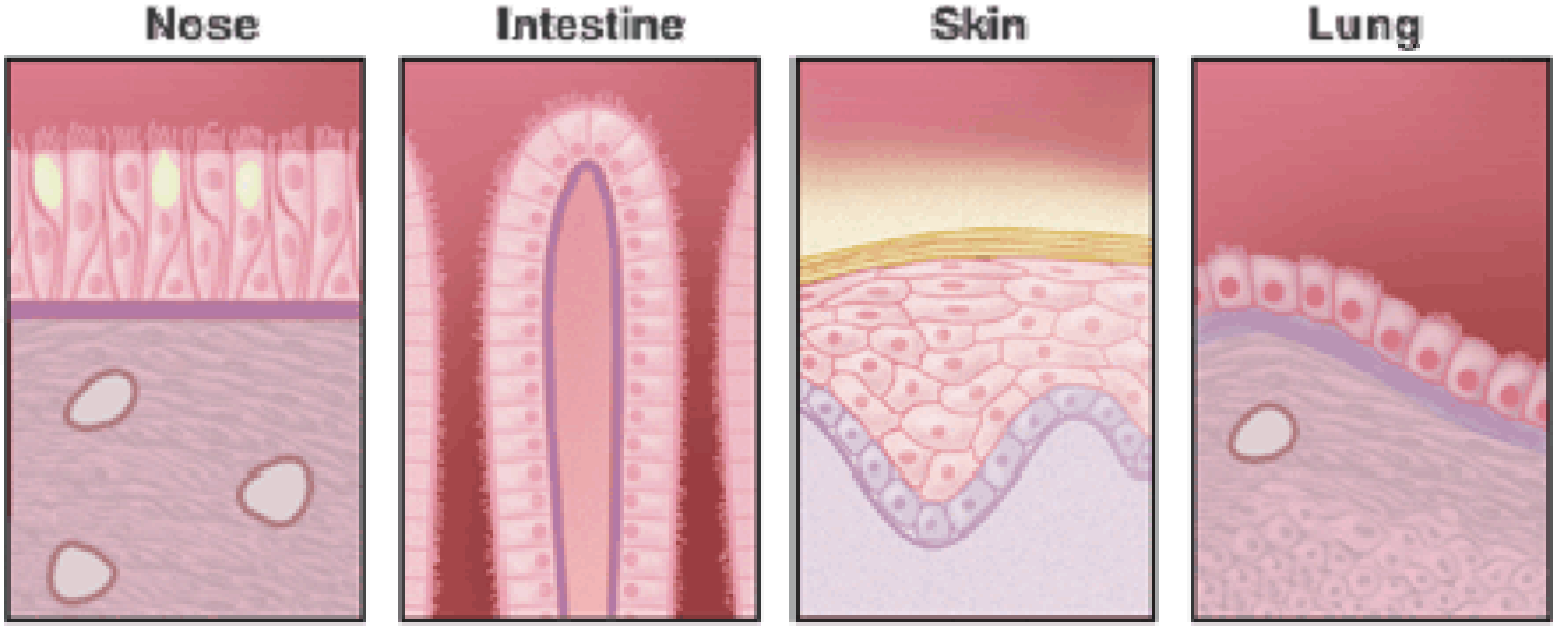




Three phases for micelle formation

1) At very low concentrations of surfactant only slight change in surface tension is detected.
2) Additional surfactant decreases surface tension
3) Surface becomes fully loaded, no further change in surface tension.

Drug Delivery: Drug Barriers



Crossing the barrier. In the case of the nose, intestine, and skin, the cellular barrier is difficult to cross for some drug molecules. In the case of the lung, the main difficulty lies in getting a drug to the deep lung. Epithelial cells, dark pink; basement membrane, purple; blood vessels, red; stratum corneum of skin, yellow.

Robert Langer, *Science* 2001: 293, pp. 58 - 59

Robert Langer Lab at MIT, http://web.mit.edu/langerlab/

Drug Delivery: Brain Barriers

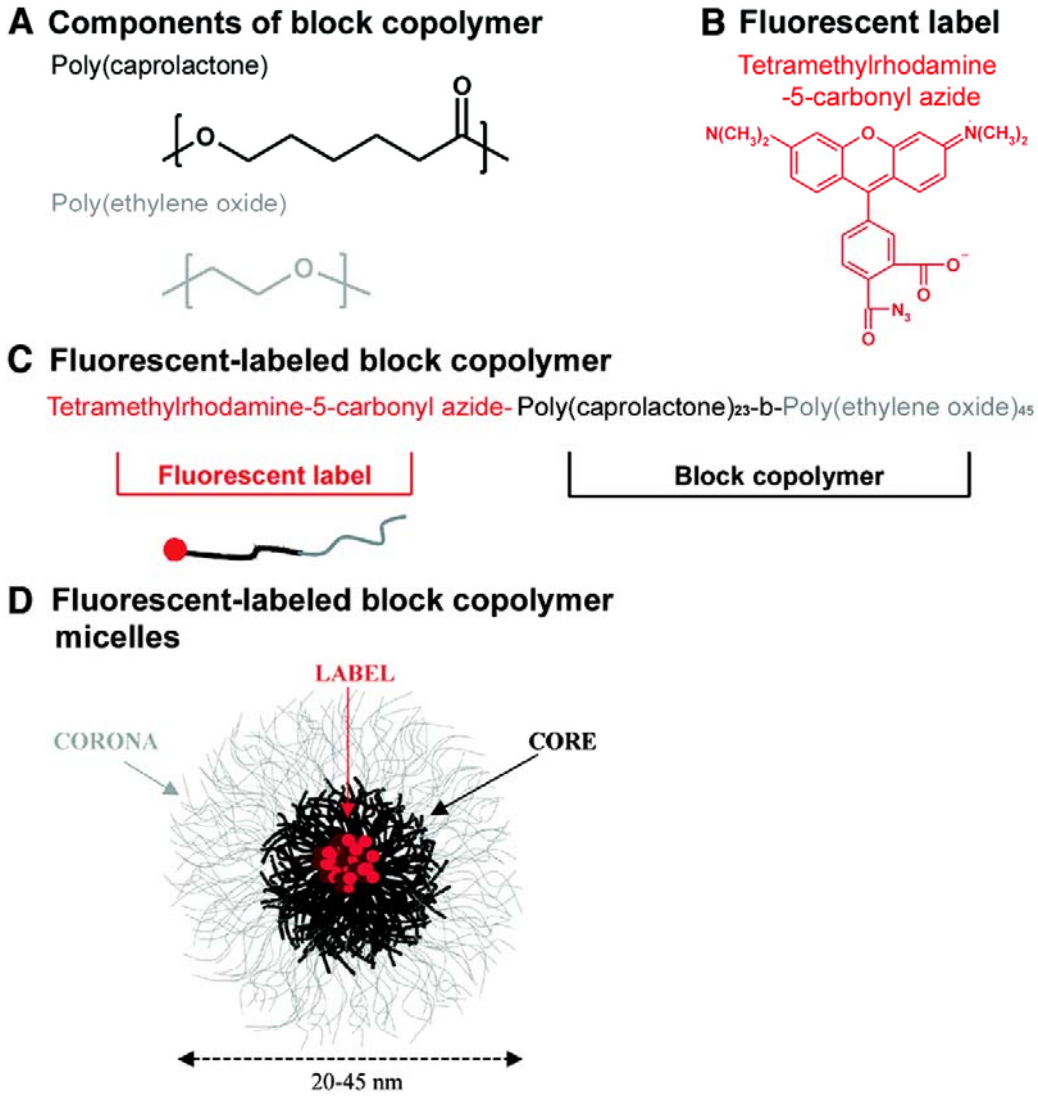
Freeze-fracture morphology of the blood-brain barrier of a rat

The **blood-brain barrier** (abbreviated **BBB**) is composed of endothelial cells packed tightly in brain capillaries that more greatly restrict passage of substances from the bloodstream than do endothelial cells in capillaries elsewhere in the body. Processes from astrocytes surround the endothelial cells of the BBB providing biochemical support to those cells.

The blood-brain barrier blocks all molecules except those that cross cell membranes by means of lipid solubility and those that are allowed in by specific transport systems. Substances with a molecular weight higher than 500 daltons (500 u) generally cannot cross the blood-brain barrier, while smaller molecules often can.

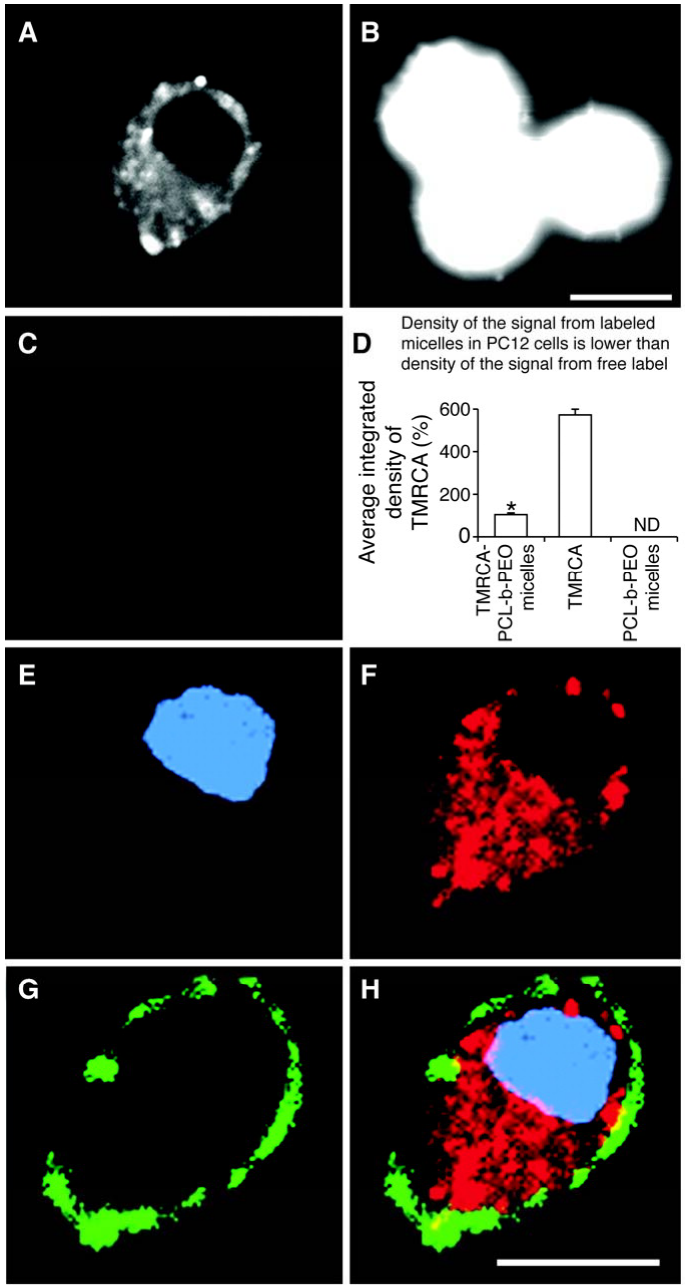
From Wiki

Block Copolymer Micelles for Drug Delivery



Schematic drawing of the fluorescent-labeled micelles used. (**A**) The block copolymer was made from PCL and PEO segments. (**B**) The fluorescent label was covalently bound to the PCL part of the block copolymer. (**C**) Each polymer chain consisted of 45 units of PEO (gray) covalently linked to 23 units of PCL (black) and 1 molecule of TMRCA (red) covalently linked to the PCL part of the copolymer. The fluorescent-labeled block copolymer was used to make fluorescent micelles. (**D**) A schematic cross-section view of a micelle. The hydrophobic(PCL) parts of single polymer chains aggregate in the aqueous environment to form the core of the micelles, and the hydrophilic (PEO) parts form a water-soluble corona that separates the core from the environment. The label (TMRCA) resides in the core of the water-soluble micelles.

Science 2003: 300, pp. 615 - 618

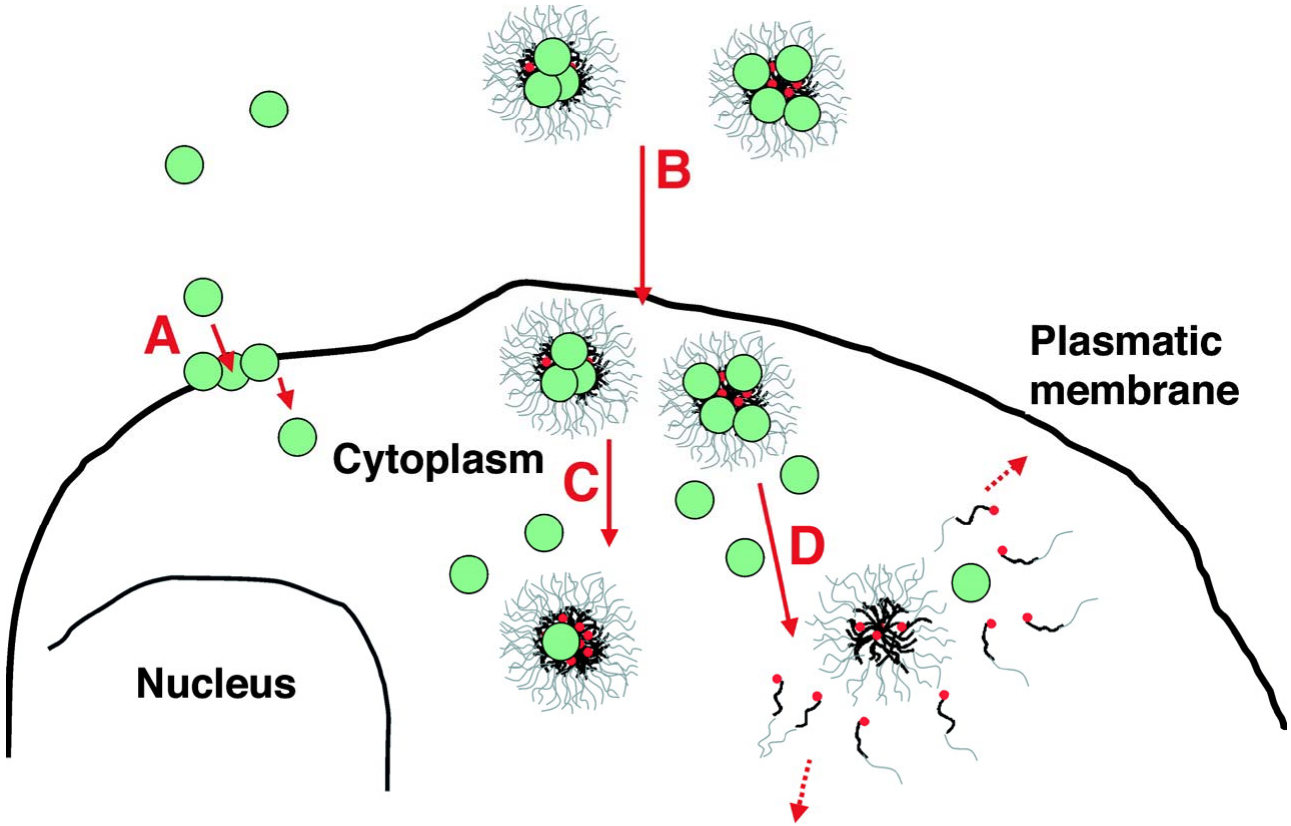


Internalization and localization of fluorescent micelles in the cytoplasmic compartment of PC12 cells. PC12 cells were incubated in the presence of TMRCA-PCL-b-PEO micelles, free TMRCA, or PCL-b-PEO micelles for 24 hours. Images were acquired with a Zeiss LSM 510 confocal unit. (**A**) **A representative cell from the cells incubated in the presence of micelles** (**B**) Cells treated with free TMRCA equimolar to that in (A). (**C**) Cells treated with nonfluorescent PCL-b-PEO micelles equivalent to the concentration of TMRCA-PCL-b-PEO micelles in (A). (**D**) Integrated densities of the signals from TMRCA-PCL-b-PEO micelles, free TMRCA, or nonfluorescent PCL-b-PEO micelles inside the PC12 cells. Error bars represent the mean plus SEM (*n* = 30 cells). ND, not detectable. (**E**) Nuclear staining with Hoechst 33342 (2μM). (**F**) A representative cell from the cells incubated in the presence of TMRCA-PCL-b-PEO micelles as in (A) and subsequently stained with nucleus-(E) or plasma membrane–selective dyes (G). (**G**) Plasma membrane staining with DAF (0.7 μM). (**H**) An overlay of (E) to (G). Yellow and pink areas indicate colocalization of micelles (red) with the plasma membrane (green) and the nucleus (blue), respectively. Scale bar, 10 μm.

Science 2003: 300, pp. 615 - 618

Self-assembly and Nanotechnology

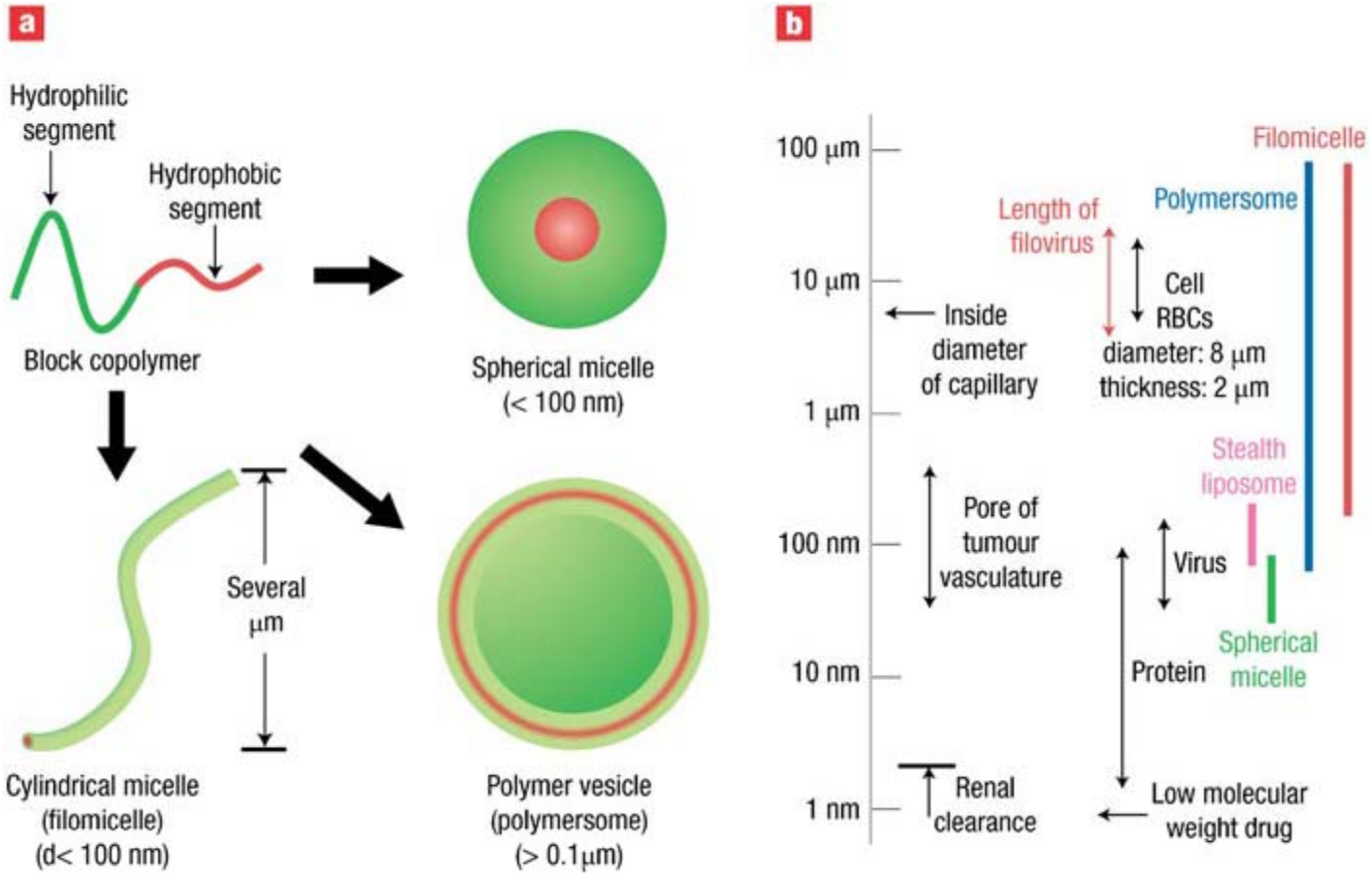
nano manufacturing center at UML



A proposed model for the cellular internalization of free DAF and DAF incorporated in TMRCA-PCL-b-PEO micelles. (**A**) Free DAF diffuses first through the cell membrane and then slowly in the cytoplasmic space. (**B**) Micelle-incorporated DAF enters the cytoplasmic compartment by endocytosis. (**C**) Inside the cell, DAF molecules from micelle-incorporated DAF eventually diffuse out from the micelle and distribute through the cytoplasm. (**D**) Some of the micelles inside the cell may disassemble into single chains and act locally to permeabilize the membranes of the cellular organelles (dotted arrows). In serum-deprived cells, the accumulations of micelle-incorporated DAF and micelles act in synergism to decrease the cell viability

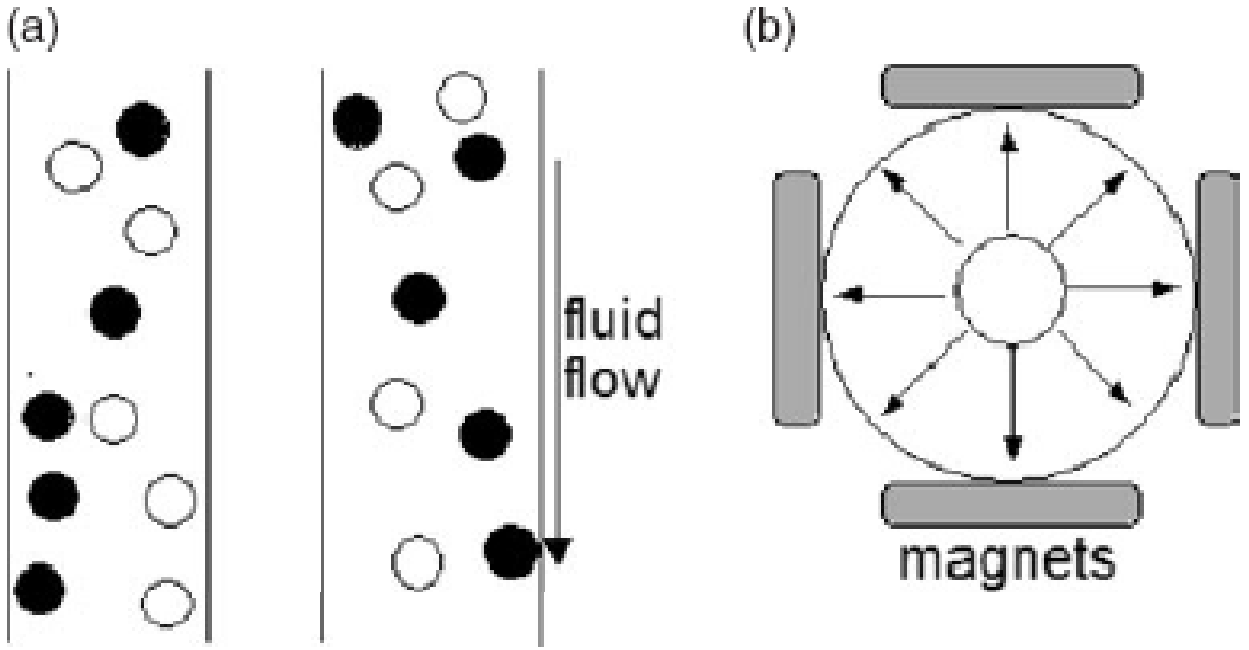
Science 2003: 300, pp. 615 - 618

Other Polymer Structures for Drug Delivery



a, Depending on rigidity, length and ratio of the polymer segments, these synthetic copolymers can self-assemble into spherical micelles, polymer vesicles (polymersomes) or cylindrical micelles (filomicelles). Discher *et al*. showed filomicelles circulate longer than their spherical counterparts. **b**, Length scales showing how the various copolymer assemblies compare with structures in the body.

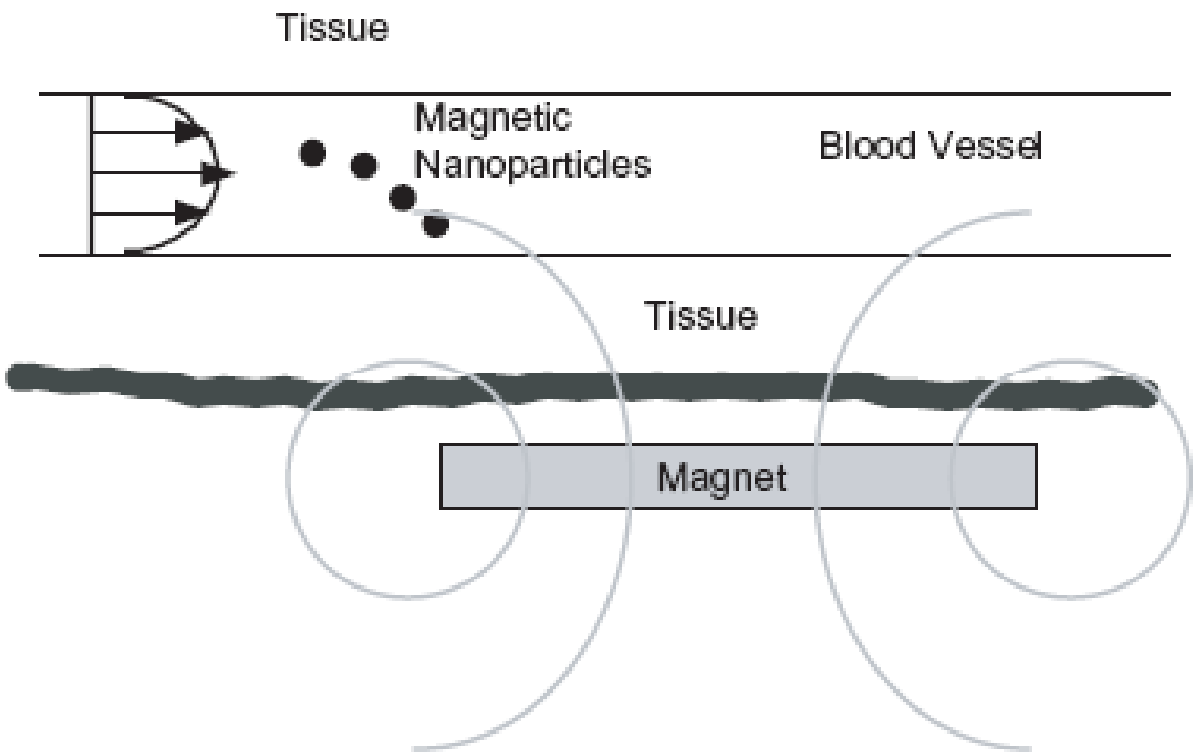
Magnetic Separations



A rapid throughput method of magnetic separation, in which an annular column containing a flowing solution of magnetically tagged (•) and unwanted (◦) biomaterials is placed within a set of magnets arranged in quadrature: (*a*) longitudinal cross-section of the annular column; (*b*) transverse cross-section of the four magnets with the resulting magnetic field lines. Under the action of the magnetic field gradient the tagged particles move to the column walls, where they are held until the field is removed and they are recovered by flushing through with water. The central core of the column is made of non-magnetic material to avoid complications due to the near-zero field gradients there.

J. Phys. D: Appl. Phys. **36** (2003) R167–R181

Magnetic Drug Delivery System



A hypothetical magnetic drug delivery system shown in cross-section: a magnet is placed outside the body in order that its magnetic field gradient might capture magnetic carriers flowing in the circulatory system.

J. Phys. D: Appl. Phys. **36** (2003) R167–R181

Computer Controlled Stereotaxic External Magnetic Field

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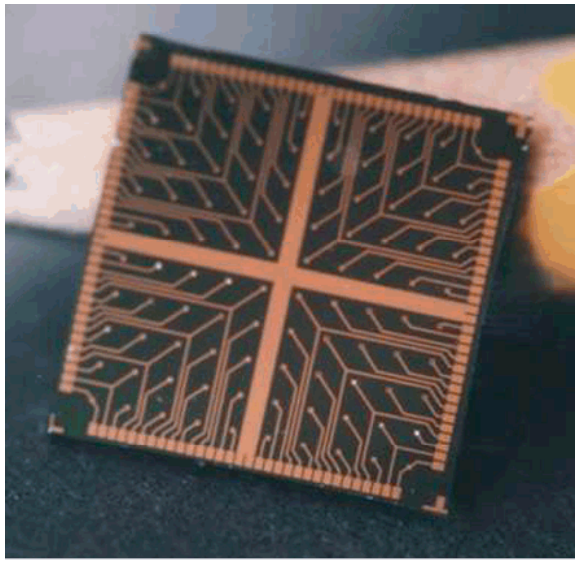
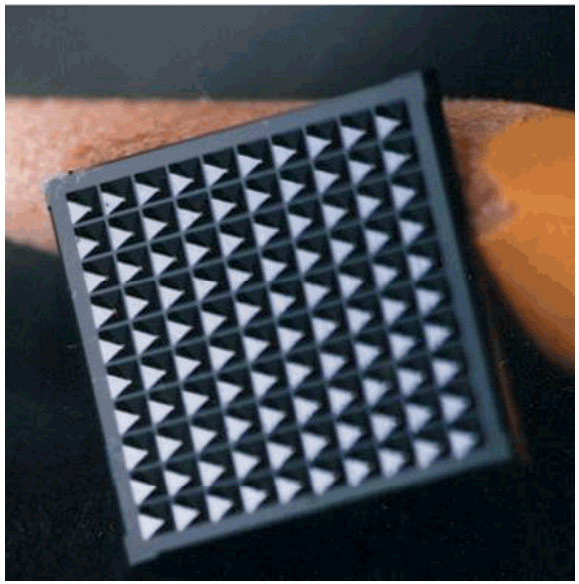
University of Oklahoma Health Sciences Center

Drugs on Chips





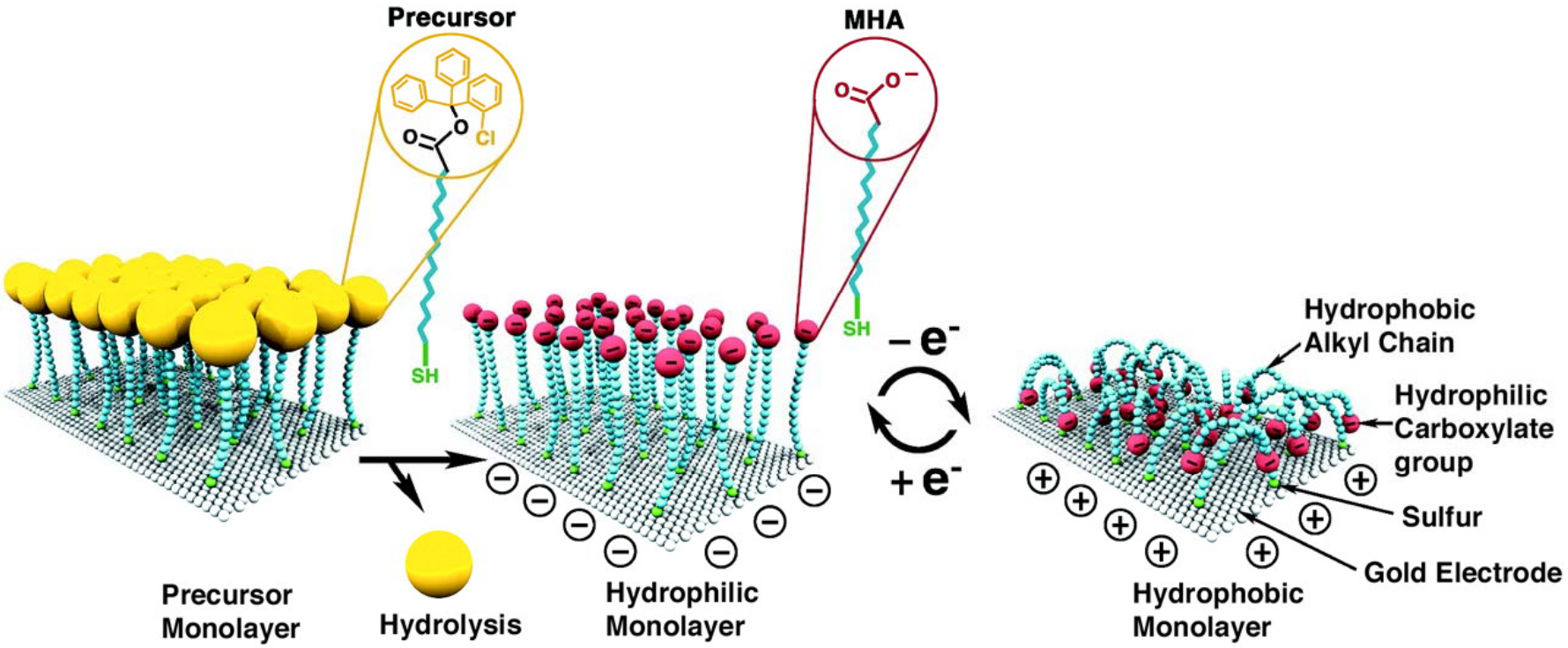
Drugs on chips. (**Top**) Front side of controlled release microchip showing an array of 100 gold reservoir caps and their associated electrodes (the tip of a pencil in the background is shown for scale). (**Bottom**) Back side of same microchip showing 100 reservoirs each containing a different drug or a different dose of the same drug or any combination thereof. These microchips measure 1 cm by 1 cm by 0.53 cm. Each reservoir has a volume of 150 nl.

CREDIT: CARITA STUBBE

Robert Langer, *Science* 2001: 293, pp. 58 - 59

Self-assembled Monolayers (SAMs)

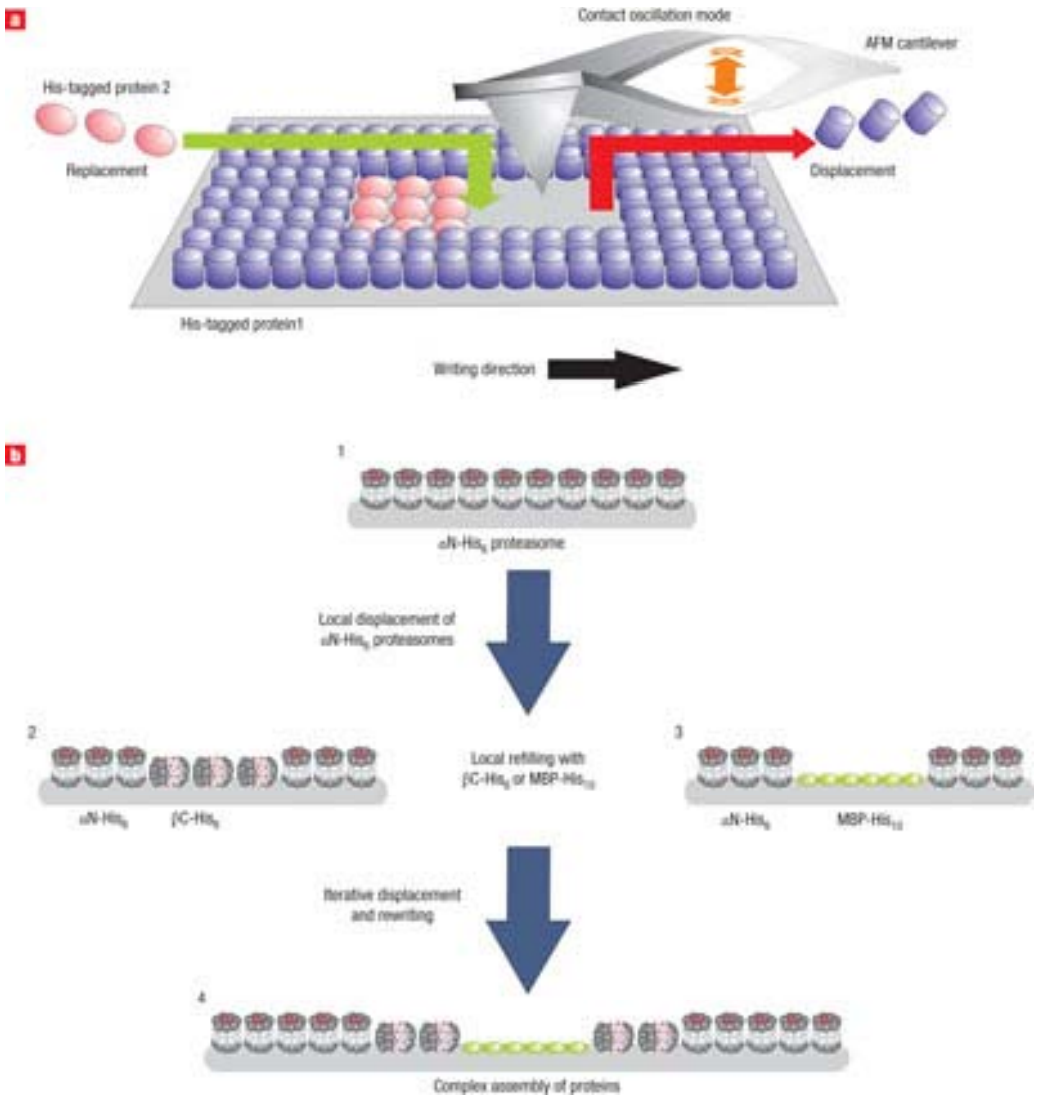
A Reversibly Switching Surface



Idealized representation of the transition between straight (hydrophilic) and bent (hydrophobic) molecular conformations (ions and solvent molecules are not shown). The precursor molecule MHAE, characterized by a bulky end group and a thiol head group, was synthesized from MHA by introducing the (2-chlorophenyl)diphenylmethyl ester group.

Science 2003: 299, pp. 371 - 374

Protein Nanolithography

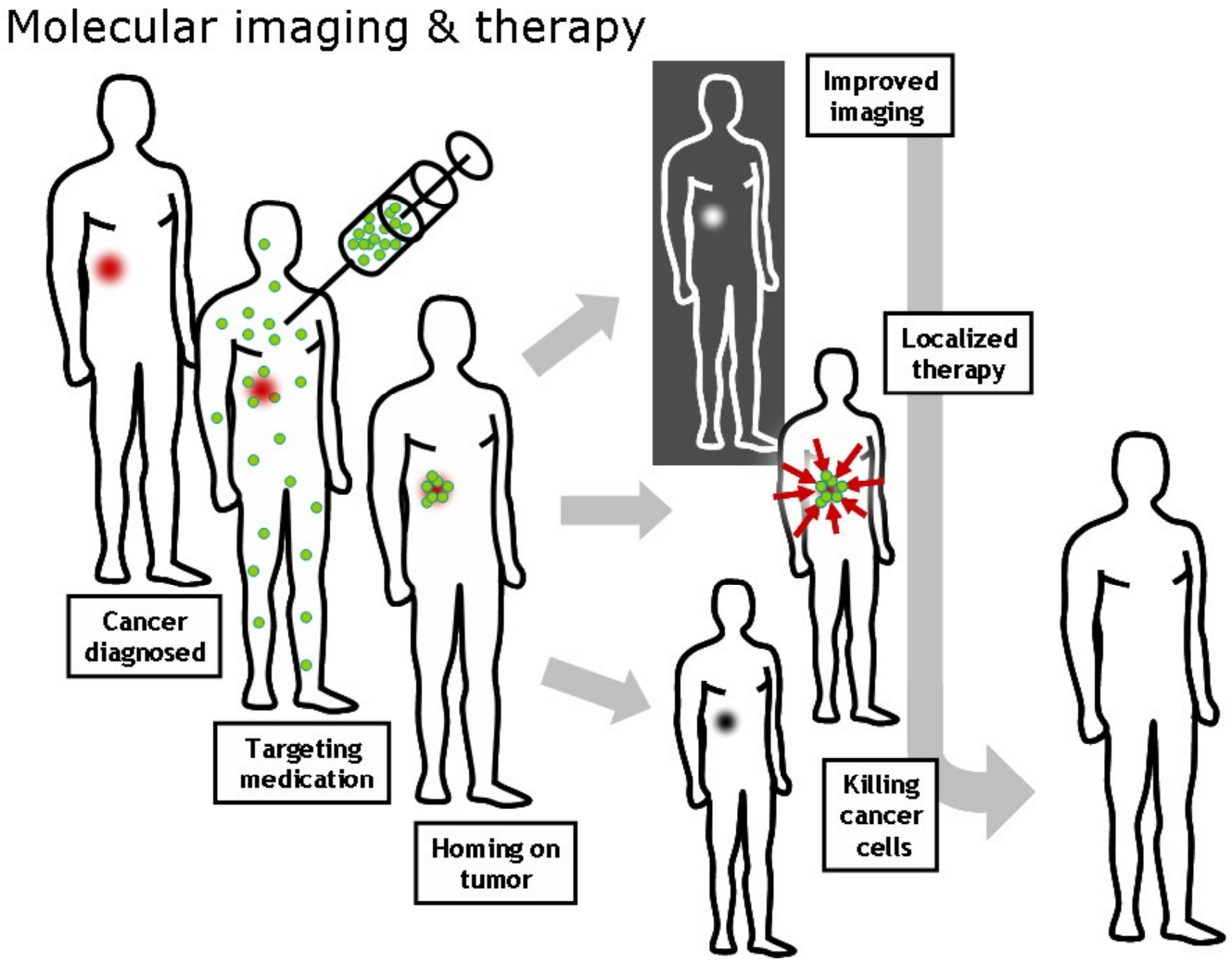


Fabrication of rewritable protein nanoarrays on SAMs by native protein nanolithography

a, Uniformly oriented His-tagged proteins are removed ('displacement') with an AFM tip in contact oscillation mode and substituted either simultaneously or sequentially with other His-tagged proteins ('replacement'). **b**, A monolayer of proteasomes is locally replaced by different proteins in subsequent displacement and refilling processes. Proteins and protein complexes in different orientations (here N- or C-His_6 proteasome or maltose-binding protein, MBP-His_{10}) are organized in nanostructured arrays and assemblies (1–4).

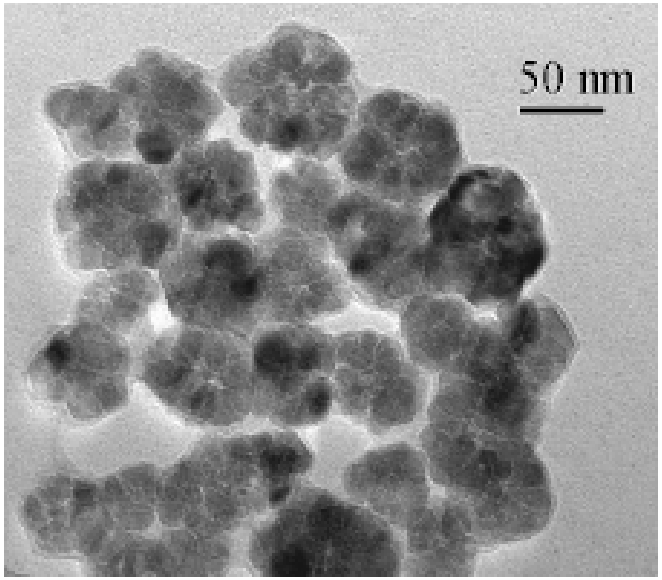
Nature Nanotechnology 2, 220 - 225 (2007)

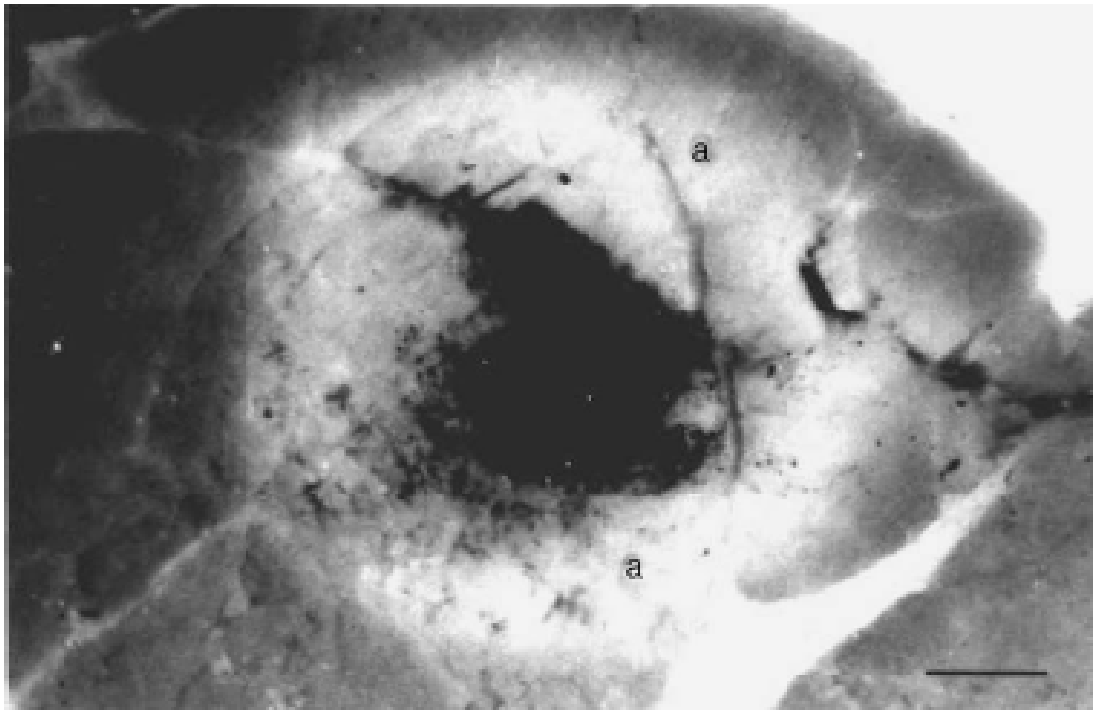
Imaging and Therapy



A schematic illustration showing how nanoparticles or other cancer drugs might be used to treat cancer.

Magnetic Nanoparticle Hyperthermia

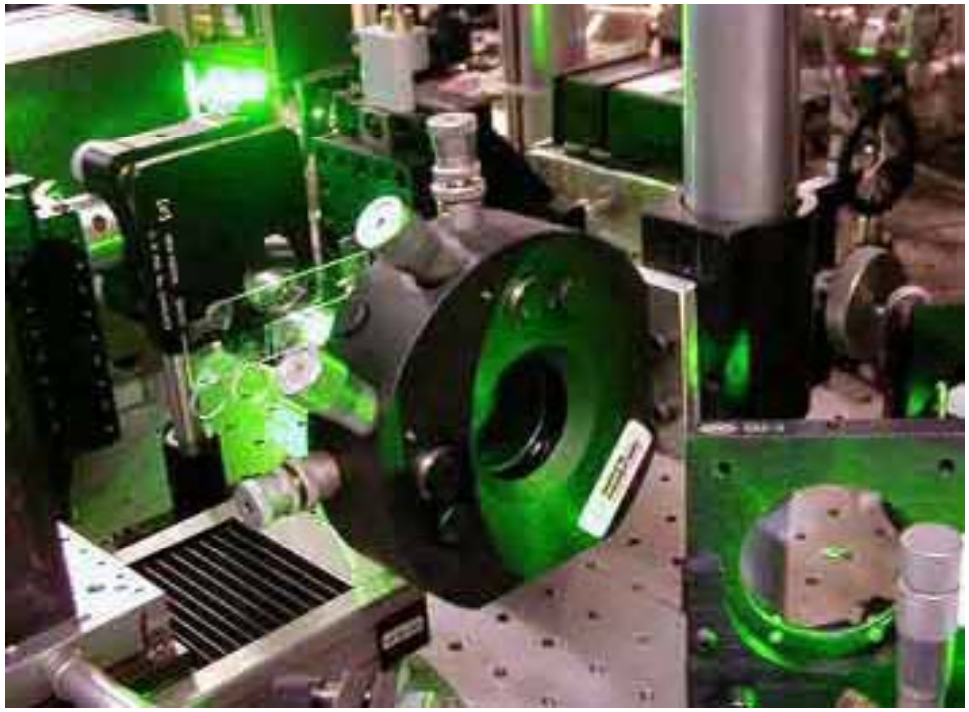




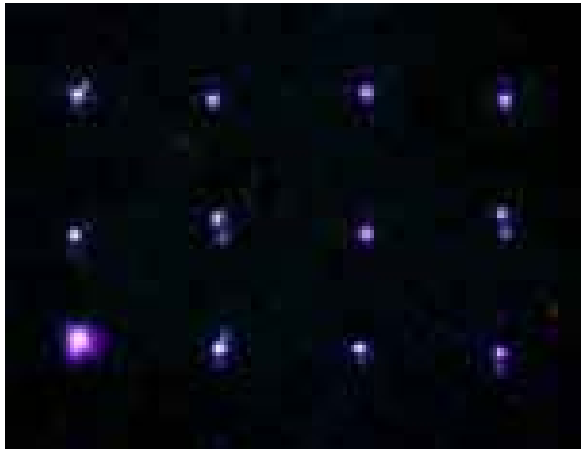
Macroscopically visible tissue alterations (a: tissue necrosis) around magnetic nanoparticles injected into muscle tissue after exposure to an alternating magnetic field for 2min (frequency: 410 kHz, amplitude: 8.8 kA/m). Bar: 1.4mm

IEE Proc.-Nanobiotechnol., Vol. 152, No. 1, February 2005

Nanosurgery with Femto-lasers



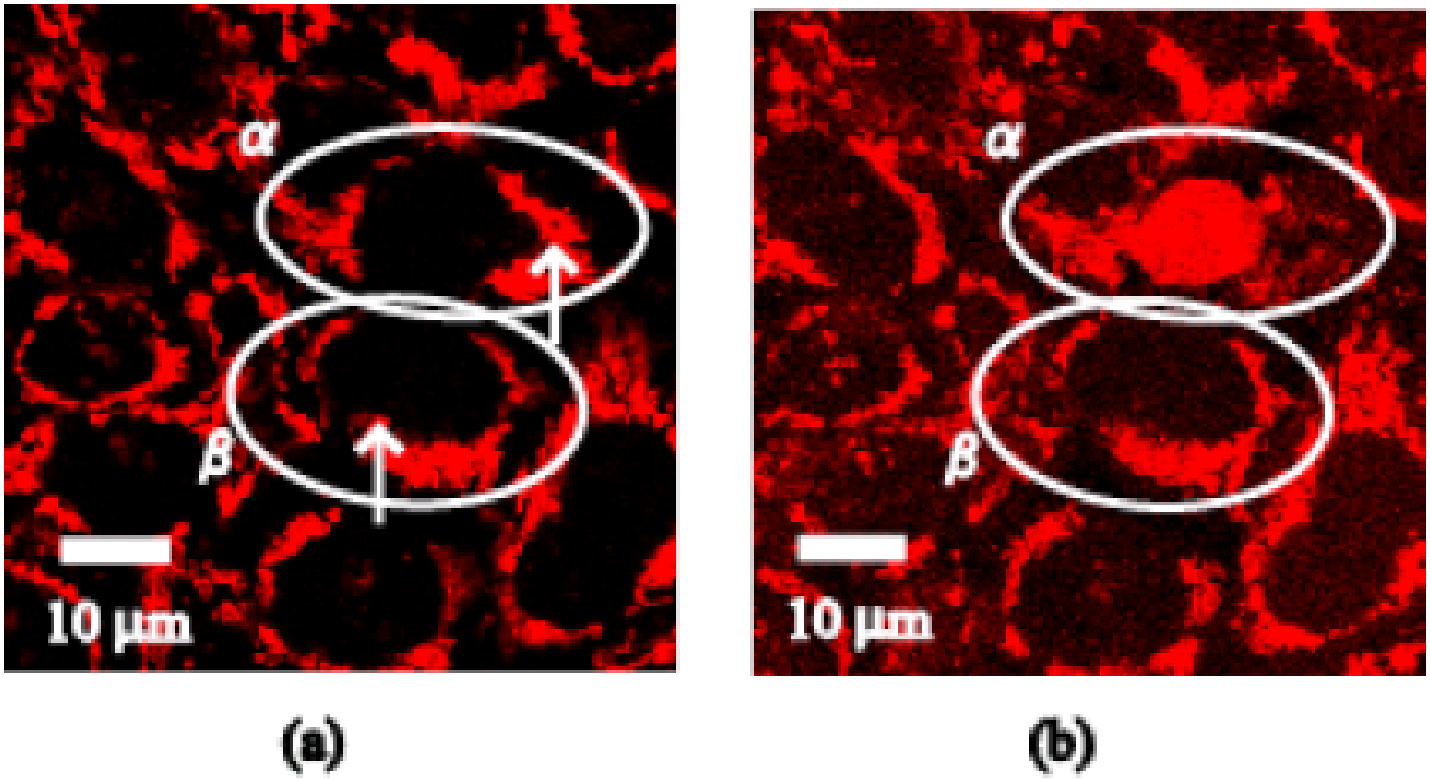
Pulses of intense laser light a millionth of a billionth of a second long (Femtoseconds:10^{-15} of a second).



Array of microscopic holes in glass produced using a femtosecond laser

Eric Mazur group, Harvard University

Nanosurgery with femto-lasers



(a) (b)

Confocal images of the cells (a) before and (b) after laser irradiation. Red fluorescence shows mitochondria of HeLa cells stained with MitoTracker Red. The white circles and arrows indicate individual HeLa cells and target mitochondria, respectively. Additional red fluorescence in b is derived from propidium iodide (PI). The laser pulses were focused inside cells α and β at energies of 7 nJ/pulse and 3 nJ /pulse, respectively.

Watanabe and Arakawa, 2004