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Nano-applications in opthamology

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Nano-Ophthalmology

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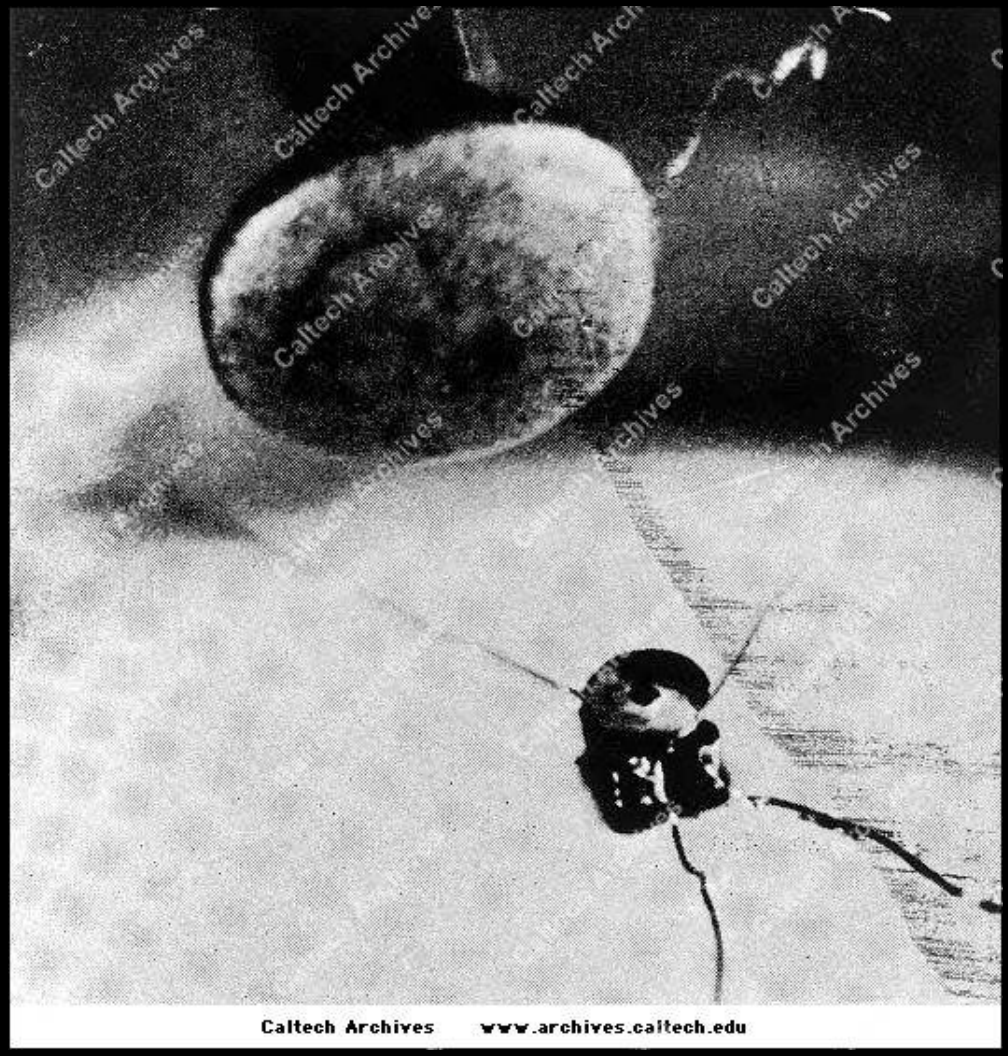
Some definitions from Wikipedia:

- **Bionanotechnology is the intersection of biology and nanotechnology. Bionanotechnology is a broad and somewhat vague term which is sometimes used interchangeably with nanobiotechnology, which usually refers more specifically to the use of nanotechnological devices for applications in biotechnology.**
- **Bionanotechnology may also refer to the use of biomolecules for applications in nanotechnology. A major example of this is DNA nanotechnology, which uses self-assembling nucleic acid structures to control matter at the nanoscale.**
- **In a wider sense, bionanotechnolgy refers to synthetic technology based on the principles and chemical pathways of living organisms. It encompasses the study, creation, and illumination of the connections between structural molecular biology and nanotechnology, since the development of nanomachinery might be guided by studying the structure and function of the natural nano-machines found in living cells.**

- **Richard Feynman “tiny nano-robots and related machines that could be designed, manufactured in the human body to perform cellular repairs at the molecular level” – predicted the development of nanotechnology**

McClennan micromotor



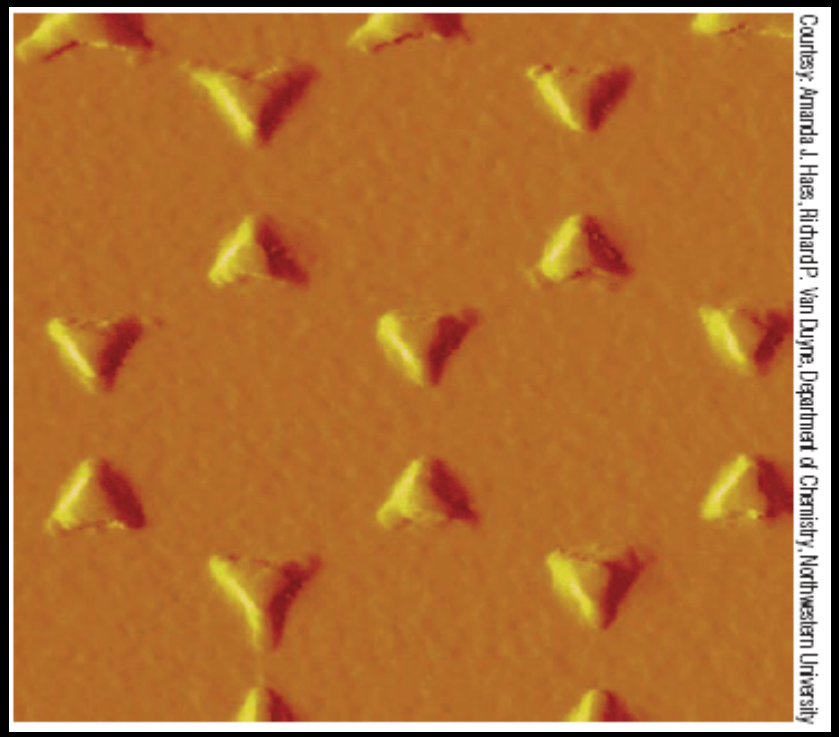
Building blocks

- Nanometer scale (10-9 meters)
- 1 nm is smaller than a living cell and human hair: 80,000nm3.
- DNA 2.5nm long

Spatial and temporal scales

- Materials and devices engineered at the nanometer scale implies controlled manipulation of individual constituent molecules and atoms in how they are arranged to form the bulk macroscopic substrate.
- Nanoengineered substrates can be designed to exhibit very specific and controlled bulk chemical and physical properties as a result of their control over their molecular synthesis and assembly

Biosensor: made from an array of silver nanoparticles depsited on glass. The electrical and magnetic fields change when molecules from the enviroment bind to the sensor.



Courtesy: Amanda J. Haes, Richard P. Van Duyne, Department of Chemistry, Northwestern University

Medical applications:

- **Materials and devices can be designed to interact with cells and tissues at a subcellular level with a high degree of integration between technology and biological not previously attainable.**

Synthetic and assembly approaches

- **Top-down approaches: begin with a macroscopic material or group of materials and incorporate small scale details on them (analogous to photolithography used to make ICs).**

Applicaton to cell biology

- Microscale connected wells in agar using poly(polymethylsiloxane) molds to study neuron-astrocyte communication. Cell cultures are set up where neurons are in one well and astrocytes in another adjacent well and are connected by a channel.

Other nanolithographic techniques applied to biology/medicine

- Dip pen nanolithography (Science, 295:1702-1705, 2002)
- Electrostatic atomic force microscope nanolithography (Nature Materials, 2:468-472,2003)

Individual molecules are deposited or moved respectively into desired configurations

Bottom Up approaches

- **Begin by designing and synthesizing custom made molecules that have the ability to self assemble or self organize into higher order mesosclae and macroscale structures.**

- **Challenge: synthesize molecules that spontaneously self-assemble upon controlled change of a specific chemical or physical trigger (eg., change in pH, electric field, concentration of a specific solute, etc).**
- **Physical mechanisms: thermodynamics and competing molecular interactions (hydrophobic/hydrophilic forces, hydrogen bonding, van der waals interactions, etc.)**

Scaffolding or templating methods

- Still bottom up; however use pre-existing structures to guide nucleation and growth of a nanostructured material.
- E.g., biominearlization type applications such as the growth of artificial bone biomemtics -
- Science, 294:1684-1688, 2001

- As technologies develop, it is thought that advanced materials will not only provide suitable mechanical properties, but also incorporate functional cell signalling properties such as neurotrophic support or anti-inflammatory effects.

Spatial and temporal considerations

- Spatial: few to about a hundred nanometers
- Temporal: nanosecond to femtosecond time scales if atomic bond oscillations are to be taken into account.

- **Visualization, characterization and manipulation of materials and devices require sophisticated imaging and quantitative techniques with spatial and temporal resolutions of the order of 10-6 and below to the molecular level.**

Current important tools available

- Highly focused (1-2 micron) synchrotron X ray sources
- Scanning electron and scanning tunneling microscopy
- In situ monitoring techniques that allow monitoring and evaluation of building block assembly and growth (reflection high energy diffraction)

Some applications

- MEMS and biocompatible electronic devices that have potential for improving treatment of many disorders
- However, at present applied nanotechnology to medicine and physiology is in its infancy

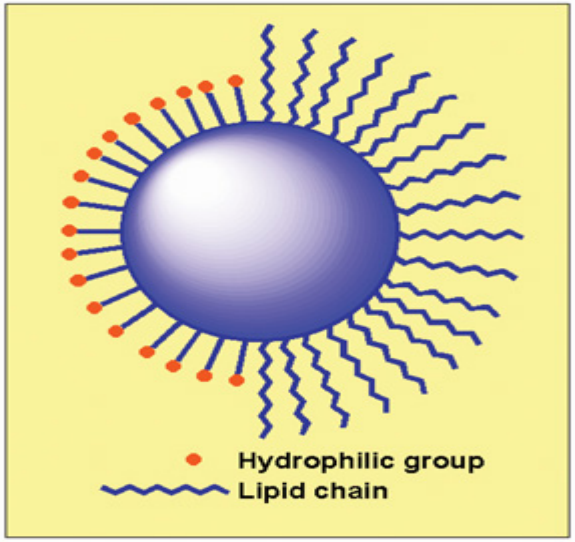
Some applications

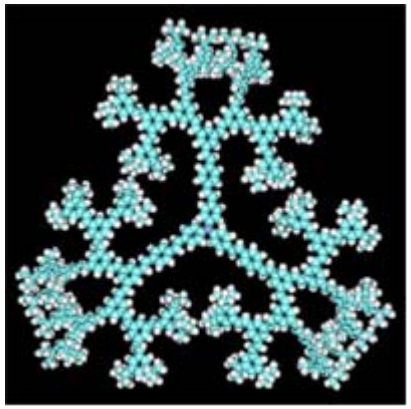
- **Novel drug delivery systems (specifically for the blood brain barrier), using nanoparticles or highly porous self assembling bilayer tubule systems (Nat Rev Drug Discovery, 1:77-84, 2004; Science, 262;1669-1676, 1993)**

- **Chemically functionalized dendrimers (highly branched molecules with a tree like branching structure) that can be used as molecular building blocks for gene therapy agents or as MRI contrast agents.**

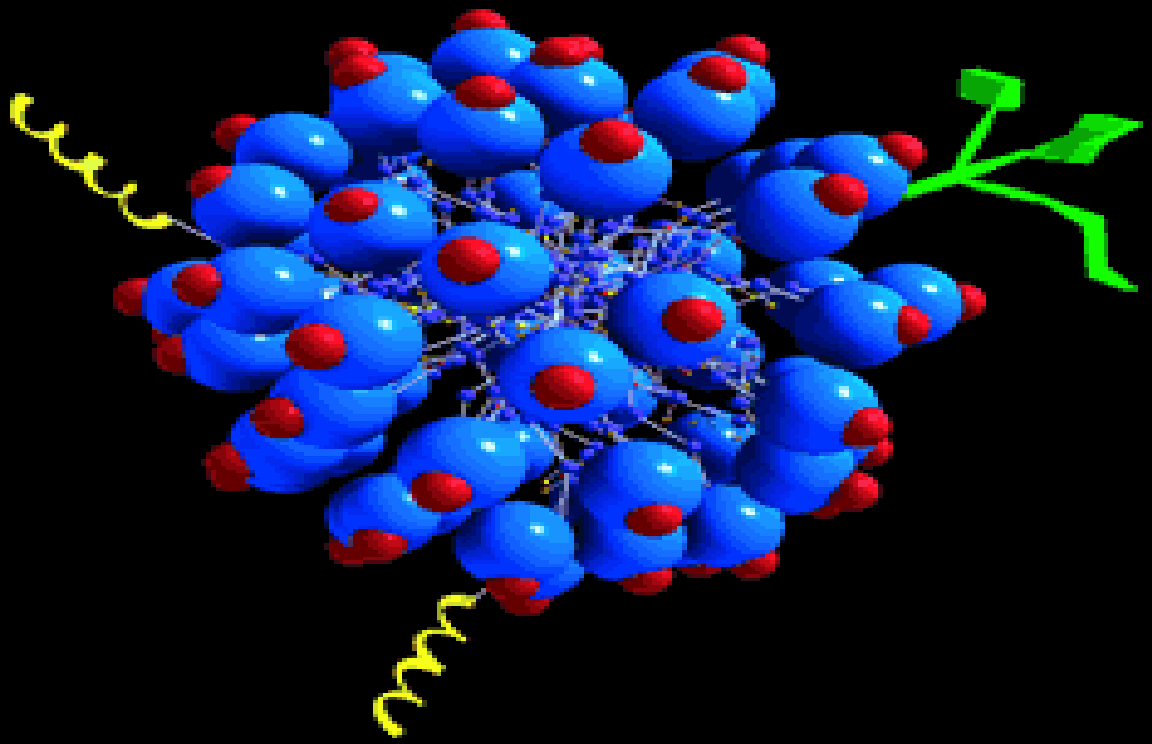
FIGURE 1b

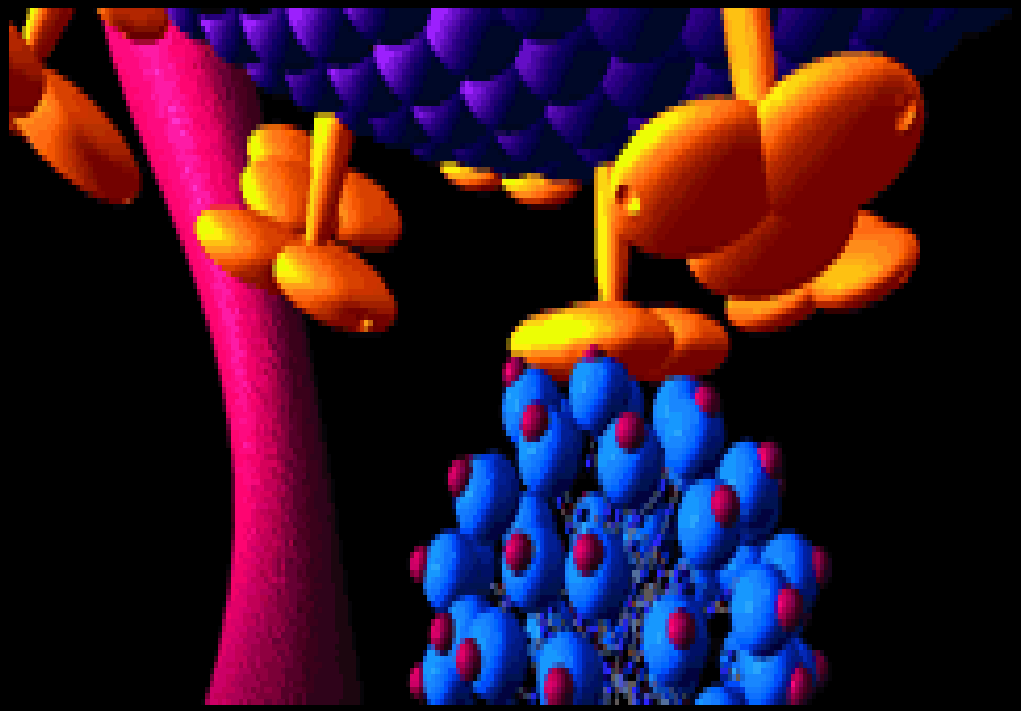
A schematic representation of an amphipathic dendrimer with hydrophilic head groups on one hemisphere and alkyl subtituents on the other, after Fréchet.





Graphic representation of a dendrimer modified for pharmacological activity. The red and blue areas are active groups; the yellow groups modify bioavailability and other pharmacokinetic properties and the green groups target specific organs and tissues





- **The active dendrimer in VivaGel binds to surface proteins on HIV preventing the virus from infecting human T-cells**

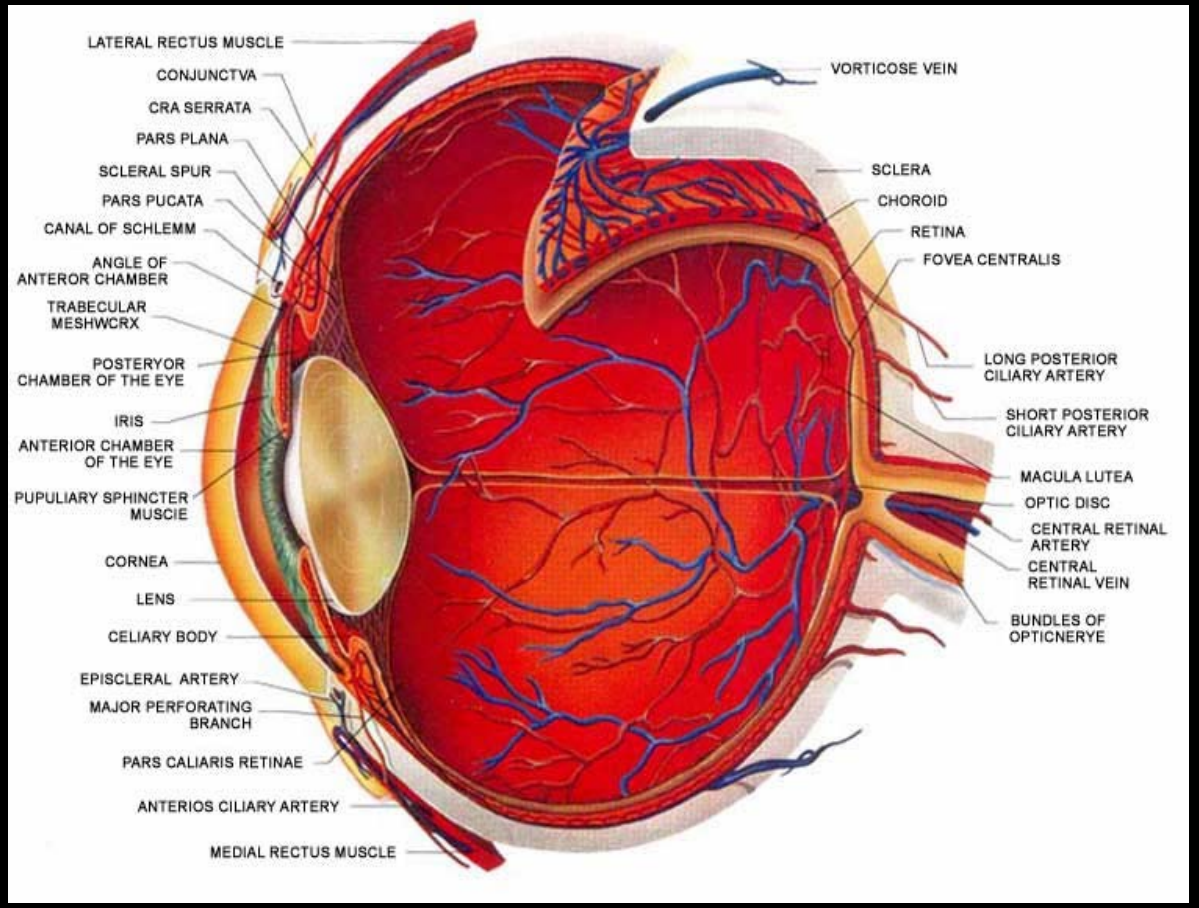
- Specialized membranes for separation of low weight organic compounds from aqueous solutions
- Can be used for ultrafiltration of physiologic toxic compounds

- **Biologically inspired functional nanodevices such as DNA polymerase chain reaction or protein based molecular computers**

- **Biomimetic self assembling molecular motors such as flagella of bacteria or the mechanical forces produced by RNA polymerase during protein transcription**

Applications in Ophthalmology

- **Structure of the eye**

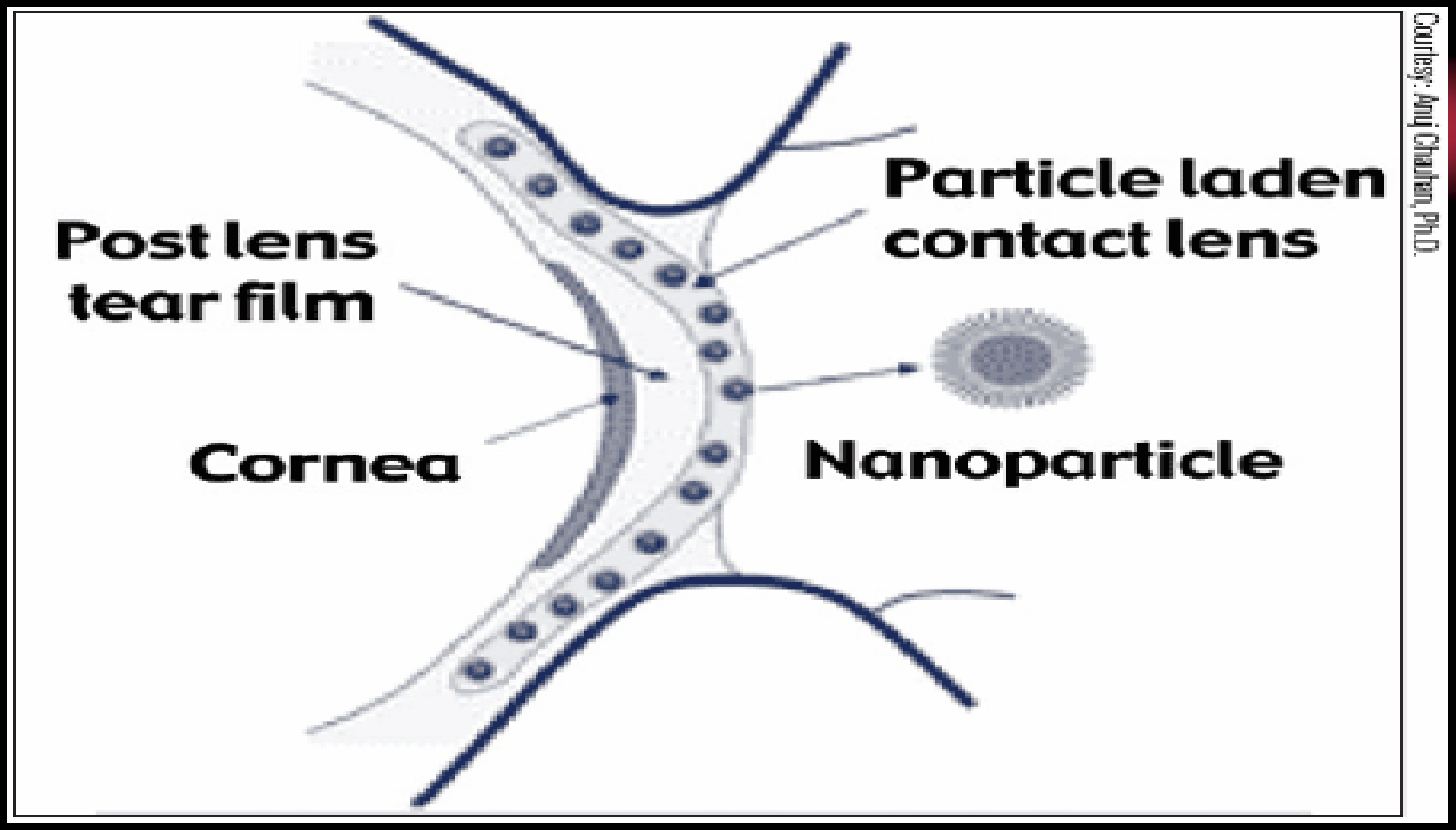


Drug delivery

- Traditionally: drops, ointments, and injectable agents.
- Problem: incidental contact with tissues that do not require treatment.
- As little as 5% of medicine applied to cornea reached the target inside the eye, leaving the other 95% to be absorbed by cells adjacent to the site.
- Depends upon the agents solubility and penetration.
- Might produce unwanted toxic effects to the affected and surrounding medium.
- Undesirable side effects, cost, difficulty of administration

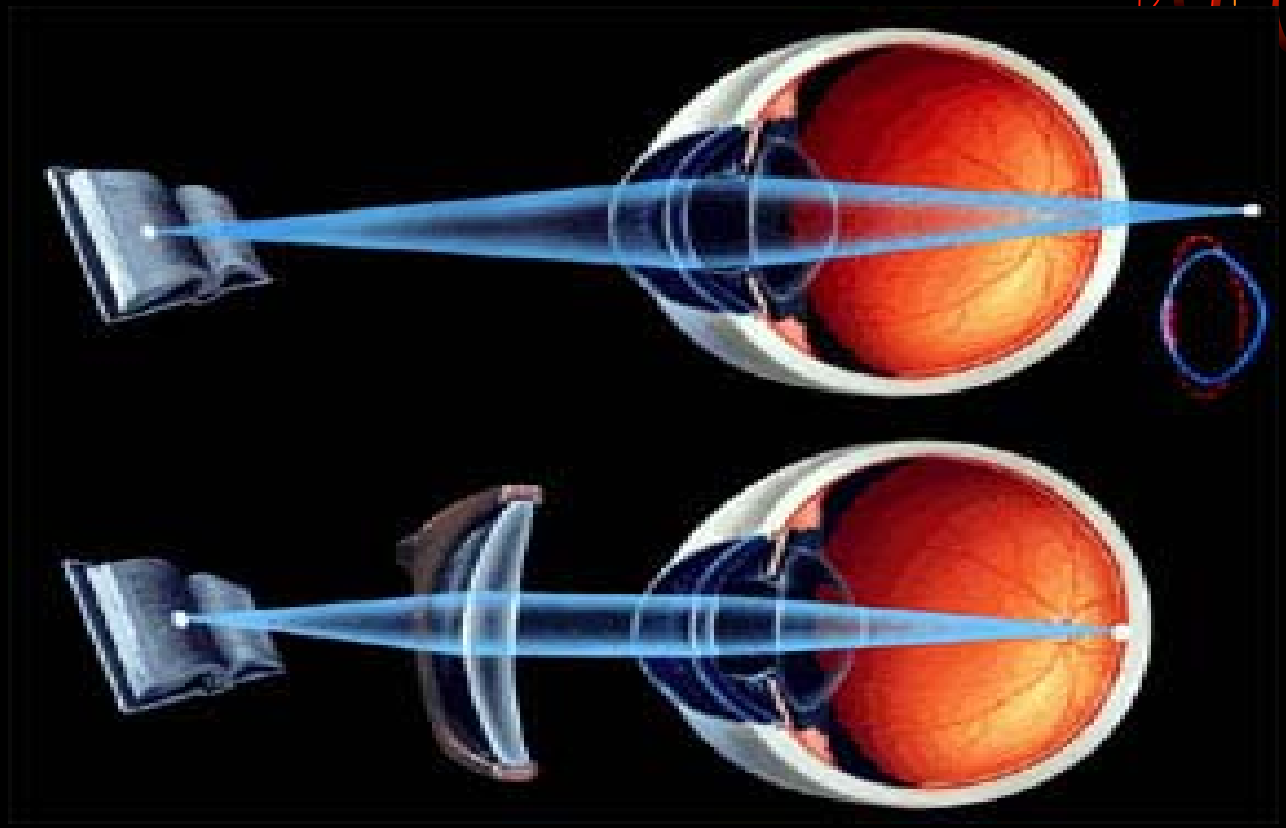
- Soft hydrophilic contact lenses in medication
- 2004: Singapore Institute of Bioengineering and Nanotechnology: contact lenses that release compound drugs.
- New lens polymer that could have medicine directly added to the material that would become the lens
- Because the drug is part of the lens material, it can be released from the matrix into channels to slowly filter onto the eye surface.

Schematic of a nanoparticle laden contace lens. Researchers at UFL are attempting to integrate nanoparticles into a currently available contact lens material so that all drug classes can be delivered through the contact lens.



- Specifically, the researchers at Florida are attempting to integrate nanoparticles into currently available contact lens material so that all categories of drug classes could be delivered through the contact lens. The nanoparticles would allow for a programmed time-release of drugs.
- a pilot study that employed the use of a poly-2-hydroxyethyl methacrylate (p-HEMA) hydrogel lens laden with nanoparticles that encapsulated lidocaine, a hydrophobic drug. The contact lenses made up of the nanoparticle-laden hydrogels released therapeutic doses of lidocaine for several days creating levels that approached nearly 100%. Further studies, including animal trials, are ongoing.
- goal: delivery of at least 50% to 60% of medication to the intended target tissue. The ultimate goal is to deliver close to 100% of the medication.These lenses available for commercial use within five to 10 years.

Presbyopia



presbyopia

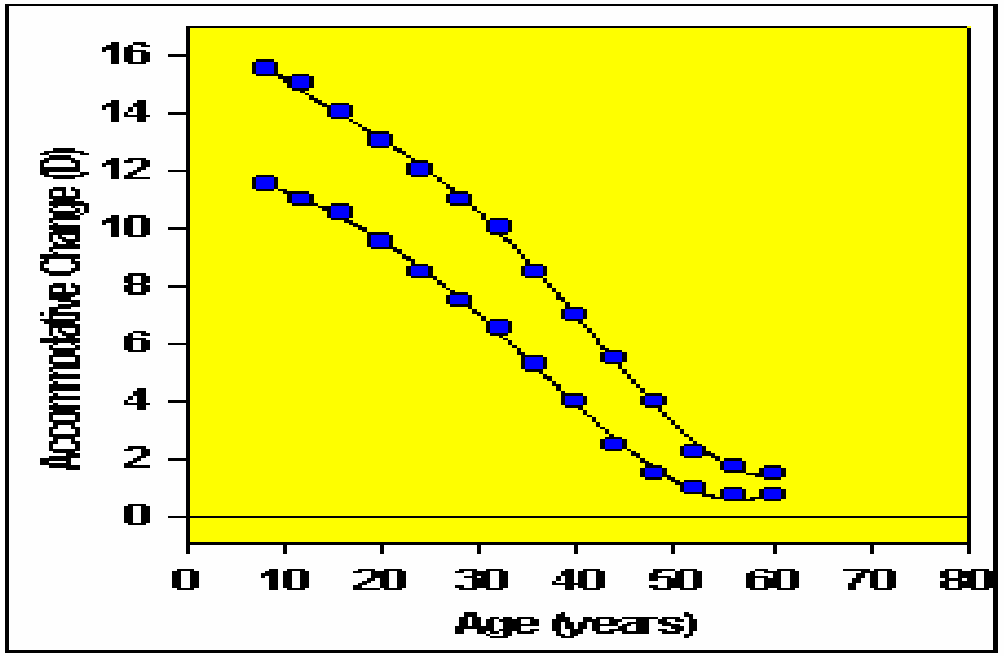


Figure 1: Maximal and minimal accommodative amplitudes as a function of age measured in 1500 subjects using a "push up" technique (Duane, 1912).

Reversal of presbyopia

- Matthew O'Donnell, Ph.D., and his colleagues at the University of Michigan are in the early stages of developing a material to reshape the crystalline lens and restore its flexibility and focusing ability, thus reversing presbyopia.
- A new application of technology, known as microscale bubbles, has shown some promise in accomplishing this. Microscale bubbles were previously applied experimentally in the area of alternative drug delivery for tumor destruction.
- Dr. O'Donnell's team has applied ultrafast laser pulses to create tiny gas bubbles within the crystalline lens. Before the bubbles diffuse, they are hit with high-frequency sound waves that push the bubbles against lens fibers.
- As with ultrasound imaging, vibrating a lens fiber can identify its vulnerablility. Finding these areas will permit directed treatment by laser with the goal of correction to that fiber.
- Measuring the movement of the microscale bubbles also helps indicate the current pliability of the lens. In the future, surgeons may use this technique to determine the necessary flexibility a patient may desire or require.
- University of Michigan. Cure for reading glasses may be in view. www.yubanet.com/artman/publish/article_36379.shtml

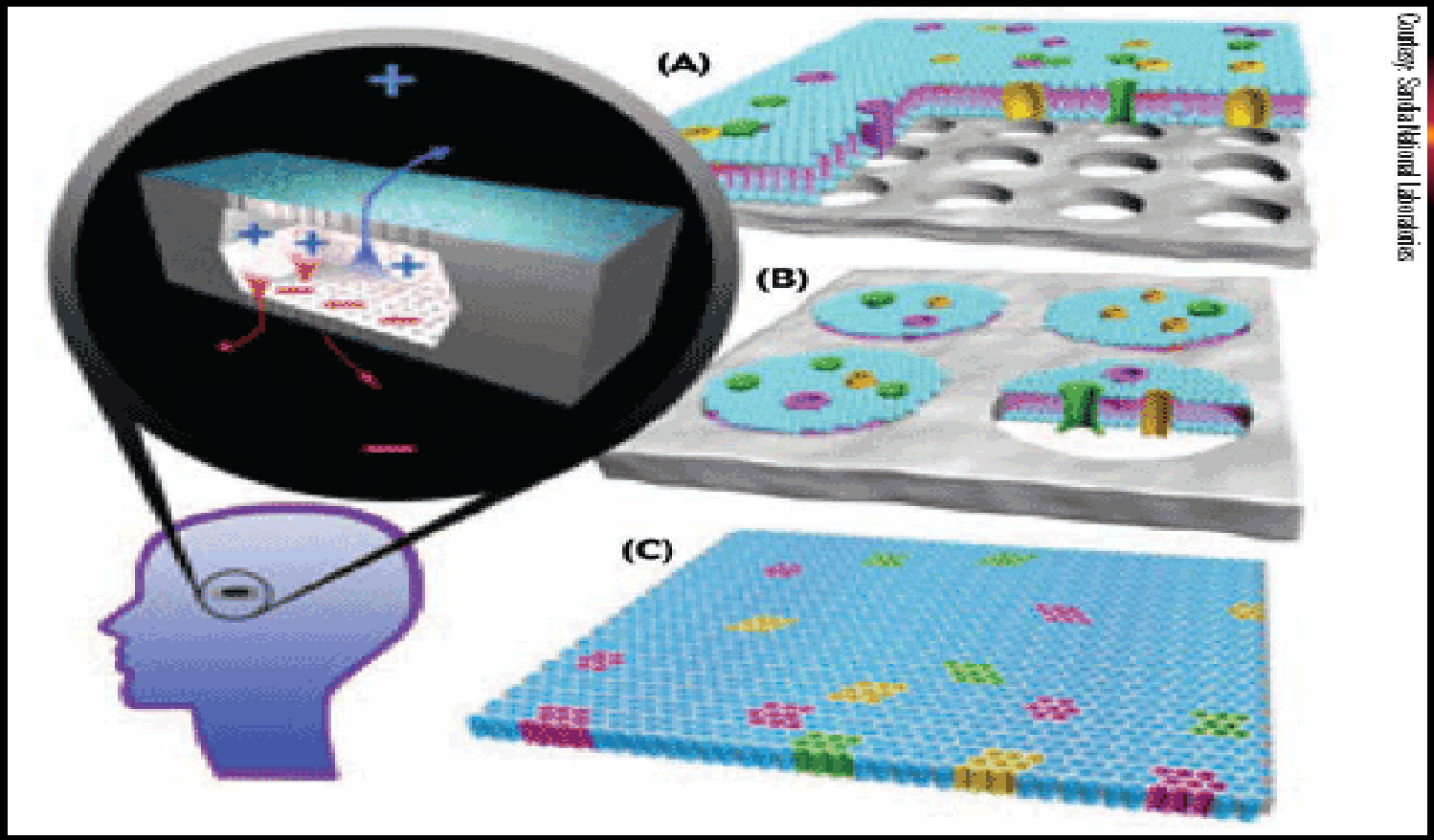
Bacteria elimination

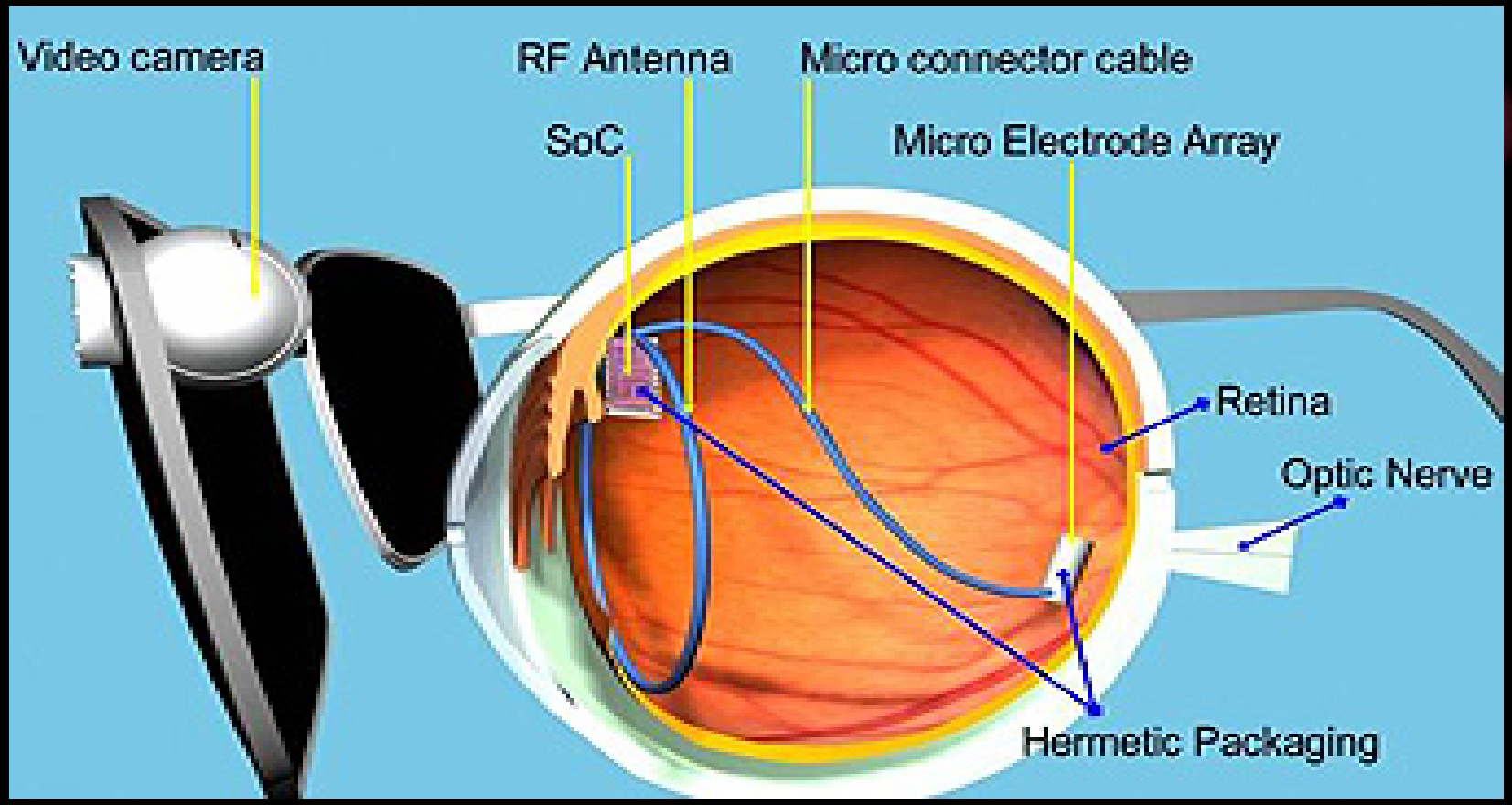
- Nanotechnology also has resulted in a contact lens material that has natural antibacterial and antifungal properties. Nanoscientists have produced nanosilver particles that measure approximately 25nm.
- Silver has been used to treat medical ailments for more than 100 years. The large relative surface area of nanosilver particles increases their contact with bacteria and/or fungi, vastly improving bactericidal and fungicidal effectiveness.
- One example of how nanosilver is used: Marietta Vision Specialty Contact Lenses, Marietta, Ga., distributes a contact lens case that has incorporated nanosilver. The case is designed so that these particles, which carry positive charges, collide with the cells of microorganisms, which carry negative charges.
- Once contact is made, the nanosilver adversely affects the microorganism's cellular metabolism by inhibiting cell growth, suppressing respiration, reducing basal metabolism of the electron transfer system and shutting down transport of substrate in the microbial cell membrane. The nanosilver helps inhibit multiplication and growth of those bacteria and fungi that may cause infections or may otherwise threaten the integrity and health of the cornea.

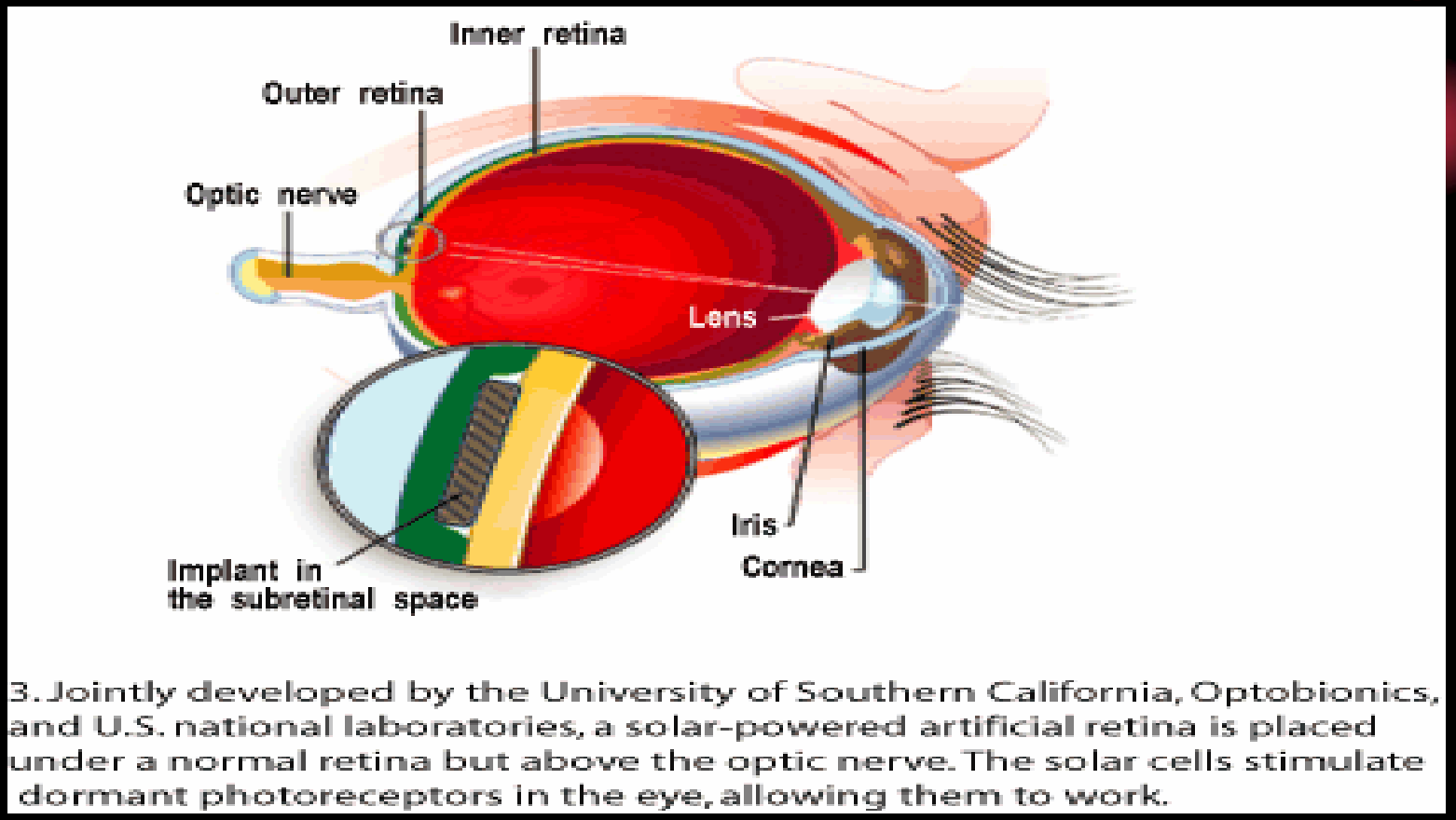
Corneal wound healing

- Nanotechnologists are researching the use of dendrimers for alternative methods of drug delivery, diagnostic imaging, and as carriers of genetic material.
- A dendrimer is a synthetic, 3-D molecule that consists of branching parts that are formed using a nano-scale, multistep fabrication process.20 Each step of the process results in a new “generation” of dendrimer that has twice the complexity of the previous generation.
- At Boston University, Mark Grinstaff, and his team have developed a dendritic polymer that has applications as an adhesive for corneal wound repair. This dendrimer is composed entirely of two biocompatible products: glycerol and succinic acid.
- Potential situations in which the adhesive would be advantageous over sutures include repair of corneal lacerations, securing of unstable LASIK flaps and closure of leaky cataract surgical incisions Other potential uses for the adhesive include ocular emergencies that involve perforation of tissue due to trauma or infections and using it to strengthen or build up weak areas that have been compromised by destructive processes associated with inflammation.
- Pure Appl Chem 2004;76(7-8):1375-85.
  J Am Chem Soc 2004 Oct 13;126(40):12744-5.
  J Cataract Refract Surg 2005 Jun;31(6):1208-12.

Artificial retina




Video camera
RF Antenna
Micro connector cable
SoC
Micro Electrode Array
Retina
Optic Nerve
Hermetic Packaging



3. Jointly developed by the University of Southern California, Optobionics, and U.S. national laboratories, a solar-powered artificial retina is placed under a normal retina but above the optic nerve. The solar cells stimulate dormant photoreceptors in the eye, allowing them to work.


IN GOD WE TRUST
LIBERTY
2000
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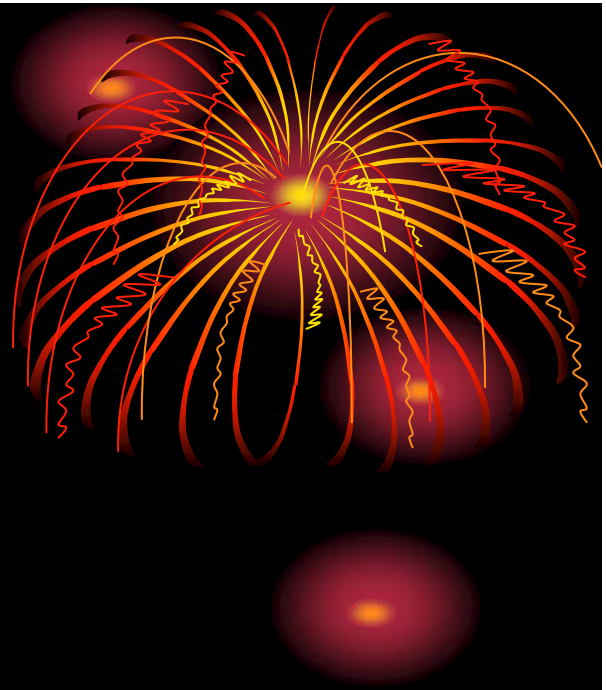
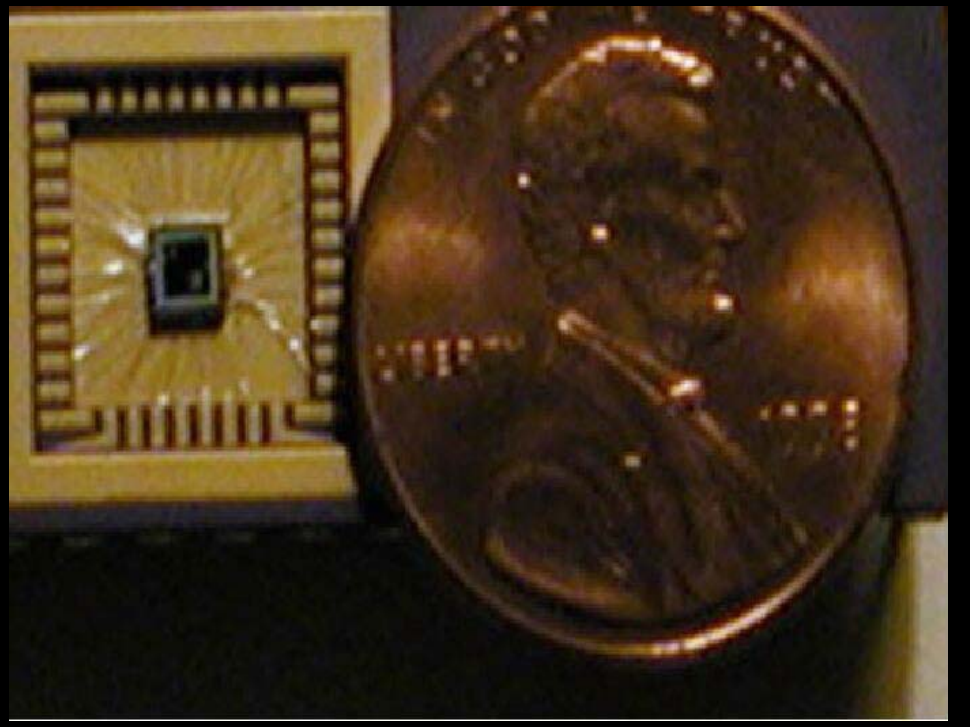


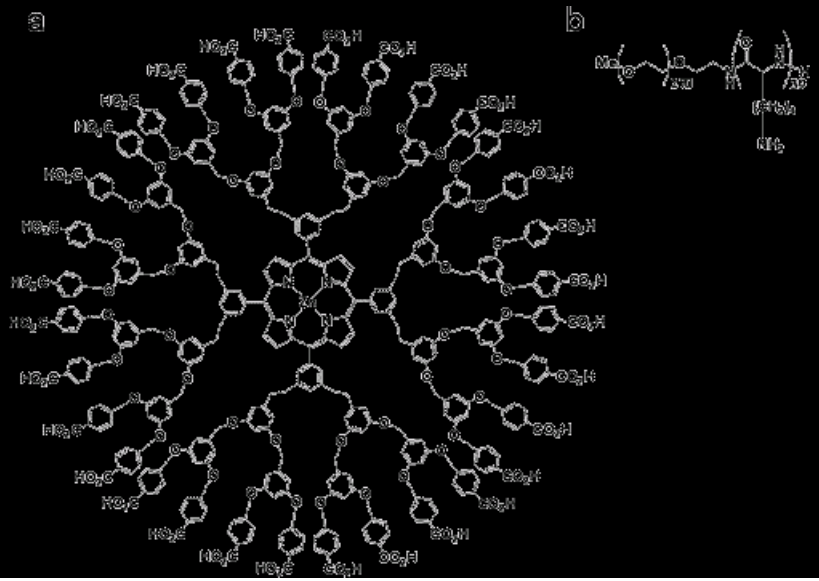


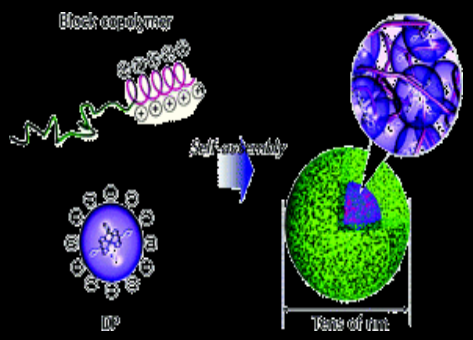
Phtodynamic therapy

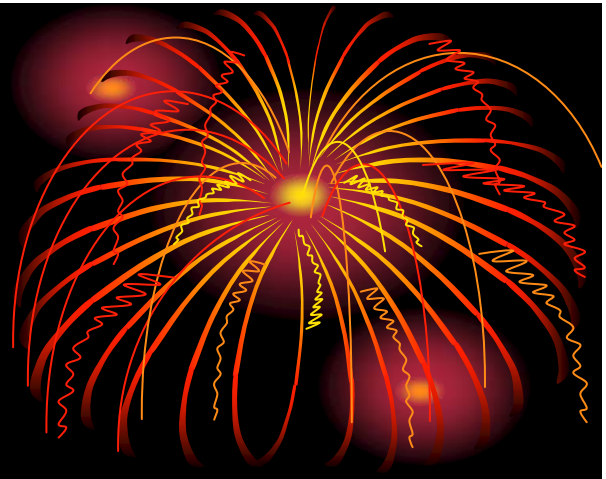
- **Nanotechnology-Based Photodynamic Therapy for Neovascular Disease Using a Supramolecular Nanocarrier Loaded with a Dendritic Photosensitizer**

Photodynamic therapy (PDT) is one of the noninvasive ways of treating malignant tumors or macular degeneration.PDT is based on the delivery of a photosensitizer (PS) to the target tissue after the administration of PS. Photoirradiation by appropriate laser light generates highly reactive oxygen species, such as singlet oxygen, which results in the oxidative destruction of target tissue

There are several kinds of already developed PSs for the clinical evaluation of their photodynamic efficacy. Most of the conventional PSs have large π -conjugation domains to extend their absorption cross sections and basically have hydrophobic characteristics. Therefore, PSs form aggregates easily, which produce the self-quenching of the excited state, in aqueous medium because of their ππ- interaction and hydrophobic characteristics. To improve the photodynamic efficacy, the efficient delivery of PSs and high quantum yield of the singlet oxygen generation are significantly important. A dendrimer-based PS dendrimer porphyrin (DP), in which the focal porphyrin is surrounded by the third generation of poly(benzyl ether) dendrons . Unlike conventional PSs, the DP ensures the efficacy of singlet oxygen production even at an extremely high concentration because the dendritic envelope of DP can prevent aggregation of the central porphyrin. Also, the 32 negative charges on DP allow its stable incorporation into a supramolecular nanocarrier, the polyion complex (PIC) micelle, through electrostatic interaction with oppositely charged block copolymers

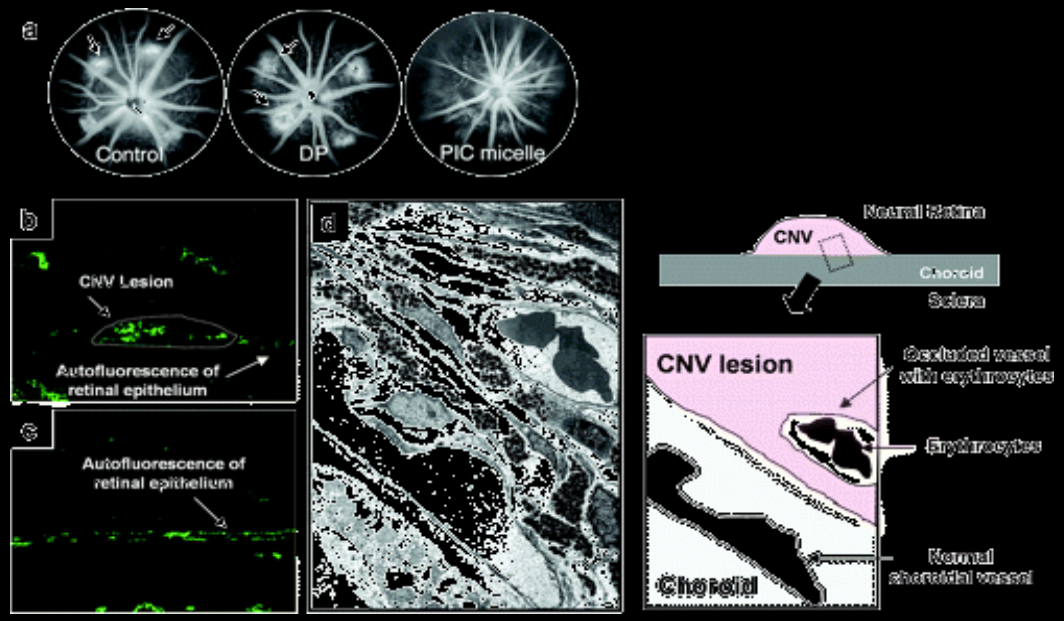






Photodynamic therapy (PDT) for exudative age-related macular degeneration (AMD) was evaluated using a supramolecular nanomedical device, that is, a novel dendritic photosensitizer (DP) encapsulated by a polymeric micelle formulation. The characteristic dendritic structure of the DP prevents aggregation of its core sensitizer, thereby inducing a highly effective photochemical reaction. With its highly selective accumulation on choroidal neovascularization (CNV) lesions, this treatment resulted in a remarkably efficacious CNV occlusion with minimal unfavorable phototoxicity.

- Alternatively, age-related macular degeneration (AMD), a condition caused by choroidal neovascularization (CNV), is a major cause of legal blindness in developed countries. Recently, large randomized control studies demonstrated that PDT with Visudyne, a liposomal formulation of verteporfin, prevents severe visual loss due to CNV and was approved for clinical use.However, because of the intractableness of AMD, most patients require repeated treatments every three months, still suffering from a reduced quality of life.It should also be noted that even with the repeated PDT treatment, most patients end in visual loss because of recurring CNV, thus prompting investigators to search for alternative PSs with even higher PDT efficacies. For effective PDT against AMD, the selective delivery of PS to the CNV lesions and an effective photochemical reaction at the CNV sites is necessary. In regard to the delivery of PS, low-density lipoproteins and antibodies against endothelial cell markers have been used as carrier molecules;however, PS also distributes to normal vessels to some extent because normal vessels also express such markers. In addition, as described previously, the increased loading of PSs to drug vehicles could change the photochemical reaction mechanism from type II to type I because of the formation of aggregates, leading to a diminished photodynamic efficacy.Thus, there is a strong impetus to develop novel PS formulations from the standpoint of both the efficiency of the delivery and photochemical reactions of the PS itself.



Efficacy of PDT laser after administration of the DP-loaded micelle. (a) Representative images of fluorescein angiograms in control, PDT-laser-irradiated eye after free DP was administered (DP), and PDT-laser-irradiated eye after the DP-loaded micelle was administered (PIC micelle). Note that the enhanced accumulation of DP-loaded micelles in CNV lesions resulted in a significantly pronounced photodynamic effect, whereas almost all of the CNV lesions showed a strong hyperfluorescence (marked with arrows), and the CNV endothelial cells appeared normal when free DP was administered. (b) Immunostaining of the endothelial cells with factor VIII antibody. Strong fluorescence from the CNV lesion is observable. (c) Immunostaining of the endothelial cells with factor VIII antibody after PDT treatment with DP-loaded micelle. Note that CNV lesion is occluded, and only autofluorescence from retinal pigment epithelium is observable. (d) Transmission electron microscopy of the CNV lesion of the PDT laser-irradiated eye after the DP-loaded micelle was administered. The neovascular blood vessel in CNV lesion is occluded by erythrocytes, whereas the normal choroidal vessel is not destroyed.

Table 1 Applications of nanotechnologies in neuroscience

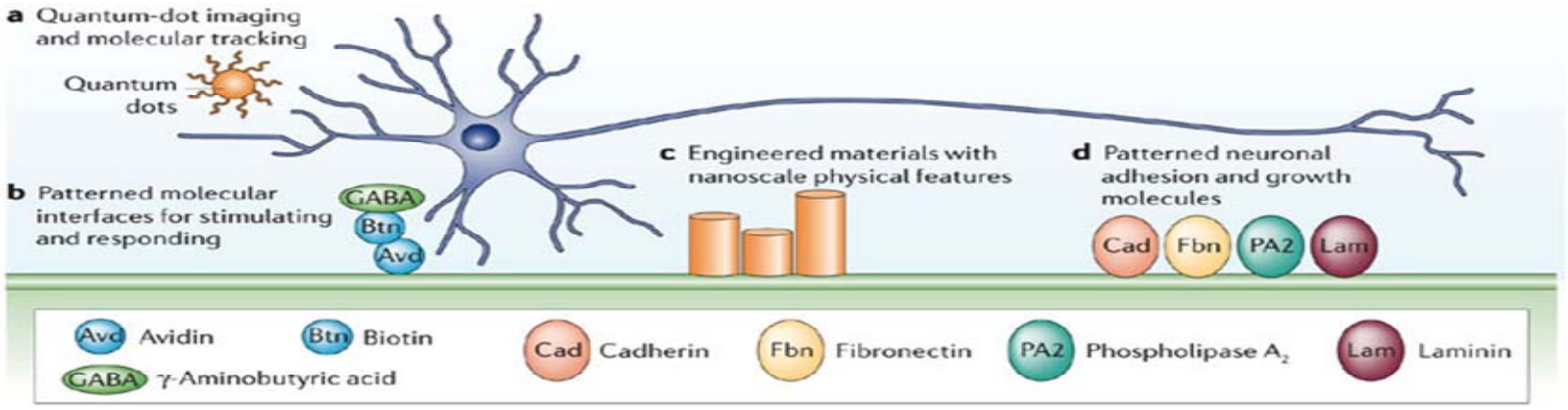
Table 1 | **Applications of nanotechnologies in neuroscience**

Nanotechnology	Applications	Refs
Basic neuroscience		
Molecular deposition and lithographic patterning of neuronal-specific molecules with nanometre resolution	Study of cellular communication and signalling; test systems for drugs and other molecules	5–10
Atomic force microscopy (measures molecularly functionalized surfaces)	Interact, record and/or stimulate neurons at the molecular level	11–13
Functionalized quantum dots	High-resolution spatial and temporal imaging; molecular dynamics and tracking	14–19
Clinical neuroscience		
Self-assembling peptide amphiphile nanofibre networks	Neuronal differentiation from progenitor cells; neural regeneration	20
Derivatives of hydroxyl-functionalized fullerenes (fullerenols)	Neuroprotection mediated by limiting the effects of free radicals following injury	23–26
Poly(ethylene glycol) and polyethylenimine nanogels; poly(butylcyanoacrylate) nanoparticles	Transport of drugs and small molecules across the blood–brain barrier	27–36

Silva GA (2006) Neuroscience nanotechnology: progress, opportunities and challenges
Nat. Rev. Neuro. **7:** 1–10 doi:10.1038/nrn1827

nature REVIEWS NEUROSCIENCE

Figure 1 Applications of nanotechnologies in basic neuroscience.



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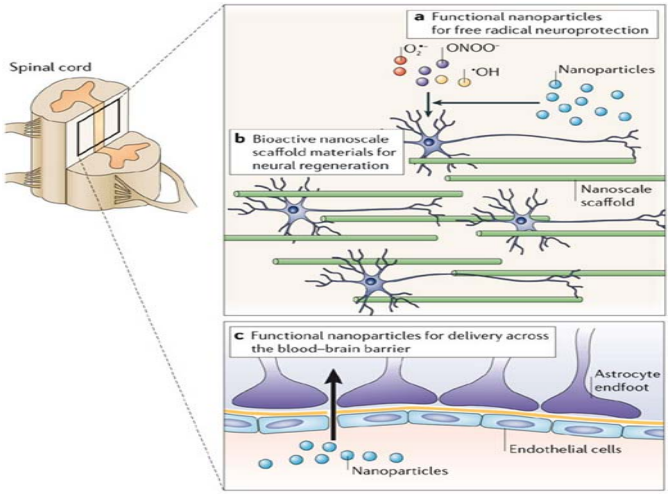
Nanomaterials and nanodevices that interact with neurons and glia at the molecular level can be used to influence and respond to cellular events. In all cases, these engineered technologies allow controlled interactions at cellular and subcellular scales. a | Chemically functionalized fluorescent quantum dot nanocrystals used to visualize ligand–target interactions. b | Surfaces modified withneurotransmitter ligands to induce controlled signalling. For example, GABA (γ-aminobutyric acid) was immobilized, via an avidin–biotin linkage, to different surfaces to stimulate neurons in predictable (that is, patterned) ways. c | Engineered materials with nanoscale physical features that produce ultrastructural morphological changes. d | Surfaces and materials functionalized with different neuronal-specific effector molecules, such as cadherin and laminin, to induce controlled cellular adhesion and growth.

Figure 2 Applications of nanotechnology in clinical neuroscience.



Silva GA (2006) Neuroscience nanotechnology: progress, opportunities and challenges
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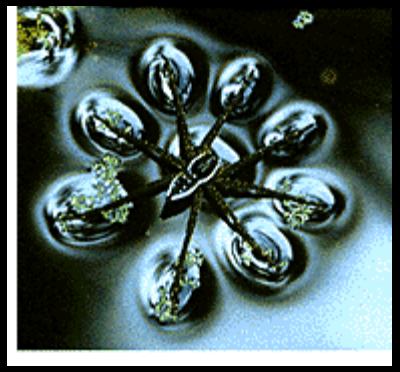
nature REVIEWS NEUROSCIENCE

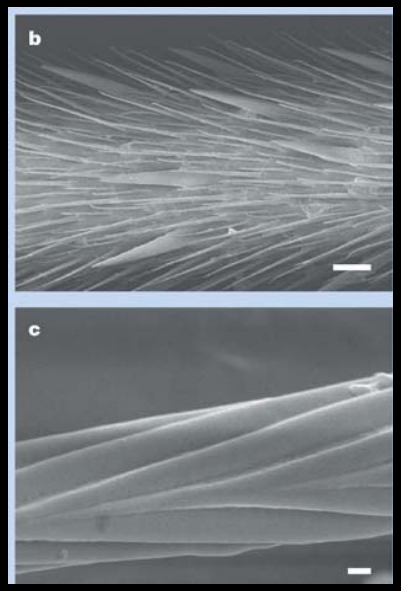
Nanotechnology can be used to limit and/or reverse neuropathological disease processes at a molecular level or facilitate and support other approaches with this goal. a | Nanoparticles that promote neuroprotection by limiting the effects of free radicals produced following trauma (for example, those produced by CNS secondary injury mechanisms). b | The development and use of nanoengineered scaffold materials that mimic the extracellular matrix and provide a physical and/or bioactive environment for neural regeneration. c | Nanoparticles designed to allow the transport of drugs and small molecules across the blood–brain barrier.

So, Why Don't Water Striders Get Wet?



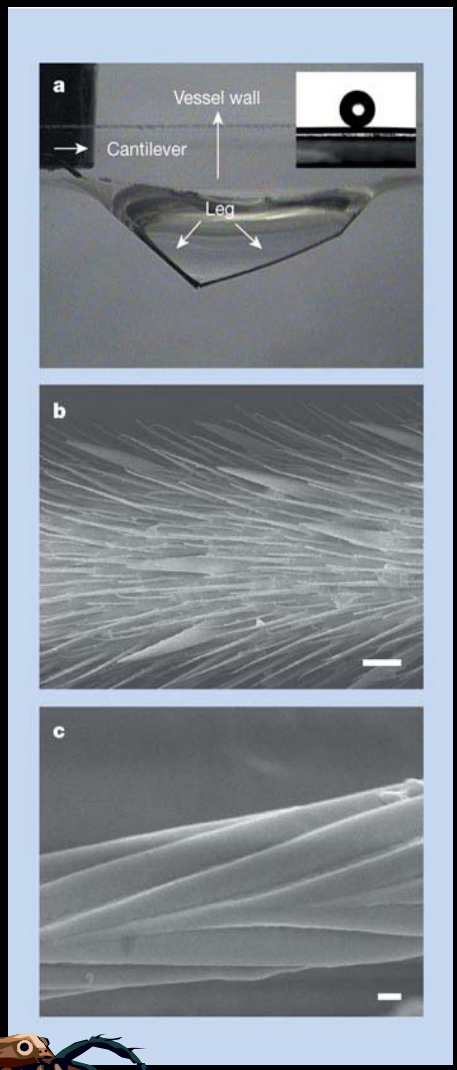
surface area
gravitational forces
surface forces (van der Waals force)
a waxy (hydrophobic) surface on their legs

The microhairs on their feet are 'nano-groovy' !



Water striders have remarkable non-wetting legs that enable them to stand and move quickly on water! Each leg is covered with large numbers of angled tiny hairs (microsetae) with tiny nanogrooves. Air is trapped in spaces in the microsetae and nanogrooves to form a cushion where the leg touches the water. This prevents the leg from getting wet.

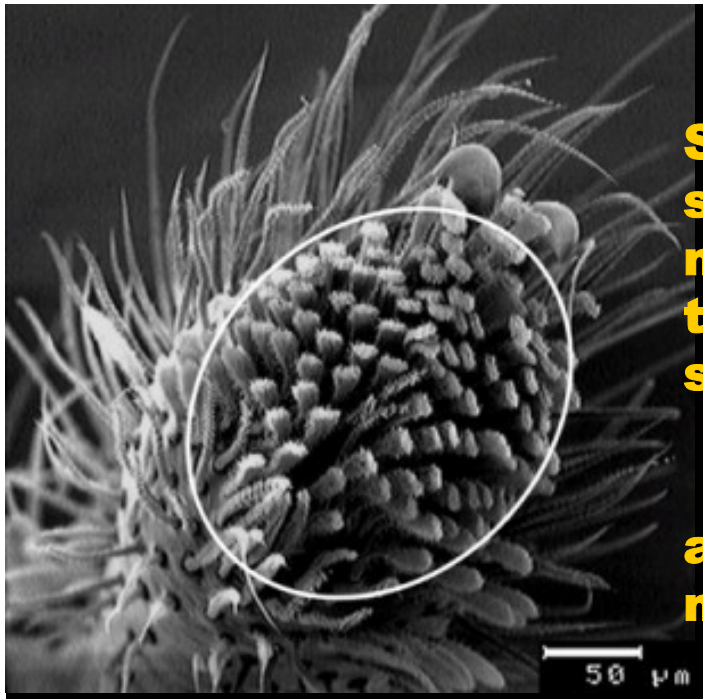
This arrangement allows water striders to survive on water even if they are being bombarded by raindrops. When it rains the strider <u>bounces</u> to avoid being drowned.



a. The illustration: **a. A dimple of water in which a spider foot stands.**

b. Scanning electron microscope image (at 20μm) of a leg showing numerous spindly microsetae.

c. Nanoscale grooved structures on a seta (at 200nm scale on an SEM).

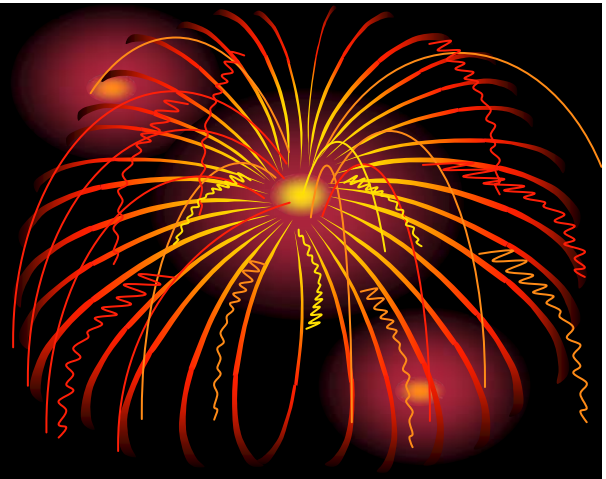


Spiders: These are the single hairs (setae) that make up the tuft of hair on the bottom of a jumping spider's foot.

The oval represents the approximate size of the foot magnified to 270x.

This picture, magnified 8750x, shows the very dense nanosized setules on the underside of just one of those many seta (hairs) shown in the picture above.

http://www.primidi.com/2004/04/26.html

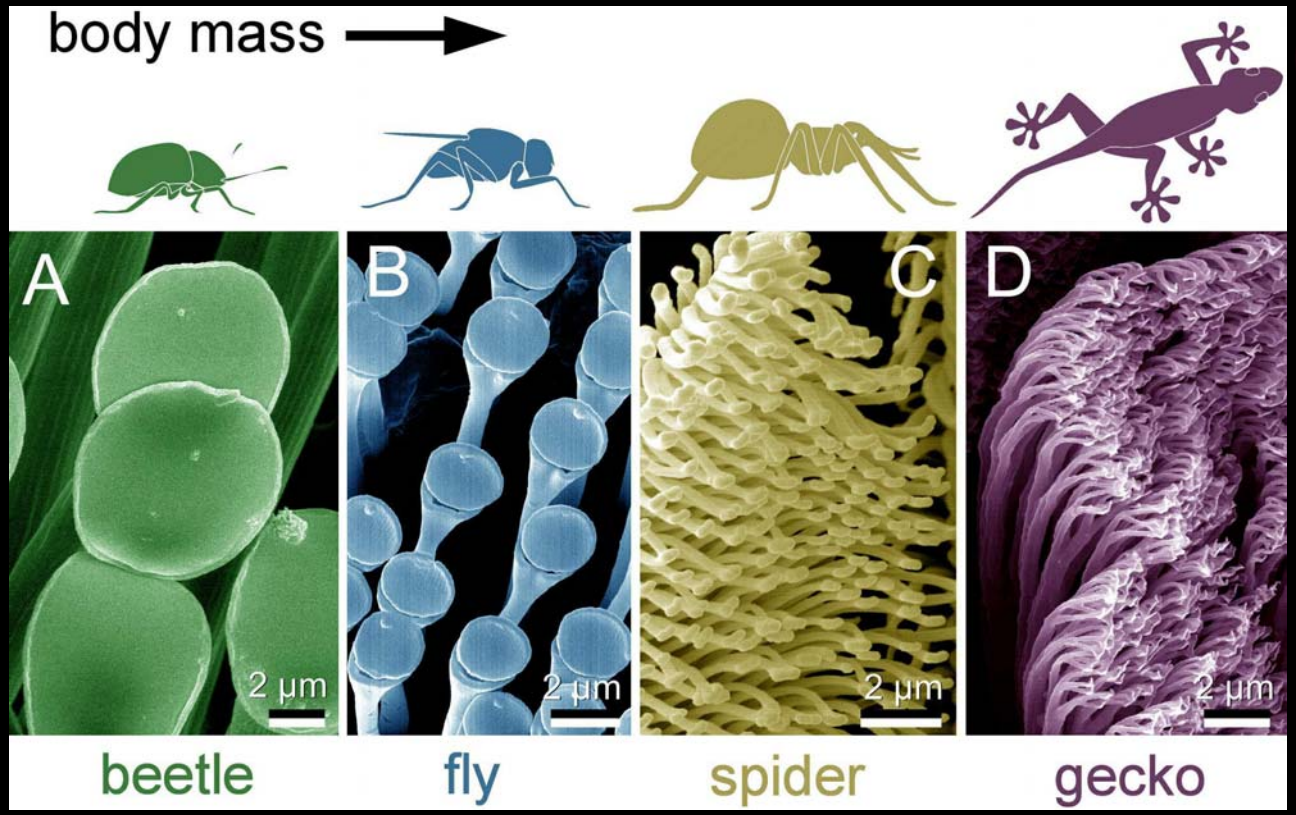


- Check out this jumping spider’s foot. Jumping spiders use nanoscale structures, too! Below thicker hairs on this spider’s leg are the nanoscale fibers that look like toes. These fibers are on the bottom of the spider's leg, and each individual hair is covered in more hairs. These smaller hairs are called setules. Because these setules are so small they can use van derWaals force to make the spider stick to surfaces. The van der Waals force acts between individual molecules that are within a nanometer of each other (about ten thousand times smaller than the width of a human hair.) What makes the van der Waals force an interesting form of adhesion is that, unlike many glues, the surrounding environment does not affect it. The only thing that affects it is the distance between the objects (in this case, setules and the surface).

- These nanofibers are small enough that the van de Waals force create a very high degree of waterproof, grease-proof, dirt-proof stickiness. When all 600,000 tips are in contact with a surface the spider can produce an adhesive force of 170 times its own weight. That's like Spiderman clinging to the flat surface of a window on a building by his fingertips and toes only, while rescuing 170 adults who are hanging onto his back!

- The total van der Waals force on the spider's feet is very strong, but since it is due to many very small forces on each molecule the spider can lift its leg so that the nanosized setules are lifted successively, not all at once. It doesn’t need to be strong to do that.

Beetles and flies also have nanostructures that help them stick to surfaces



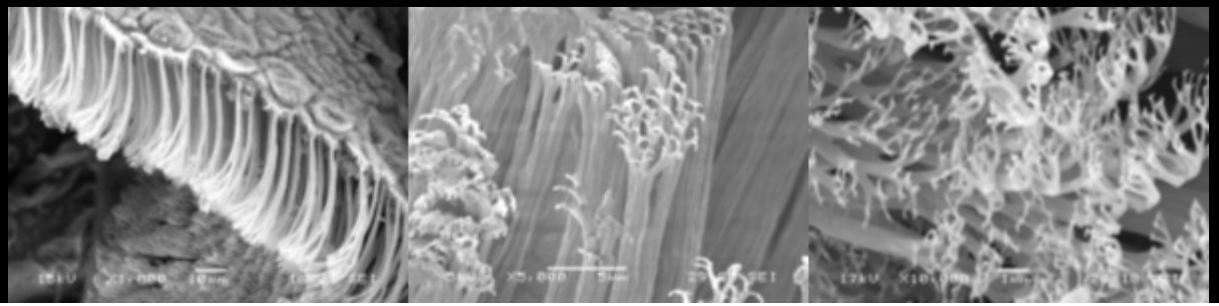
Bio-tribology:study of friction lubrication and wear applied to biological systems Consider the Gecko

500,000 hairs per toe

Hundreds of nanoprojections (spatulae) per hair

Adhesive force in one foot = 100 newtons

One dime-sized spot could lift a child weighing 45 pounds.

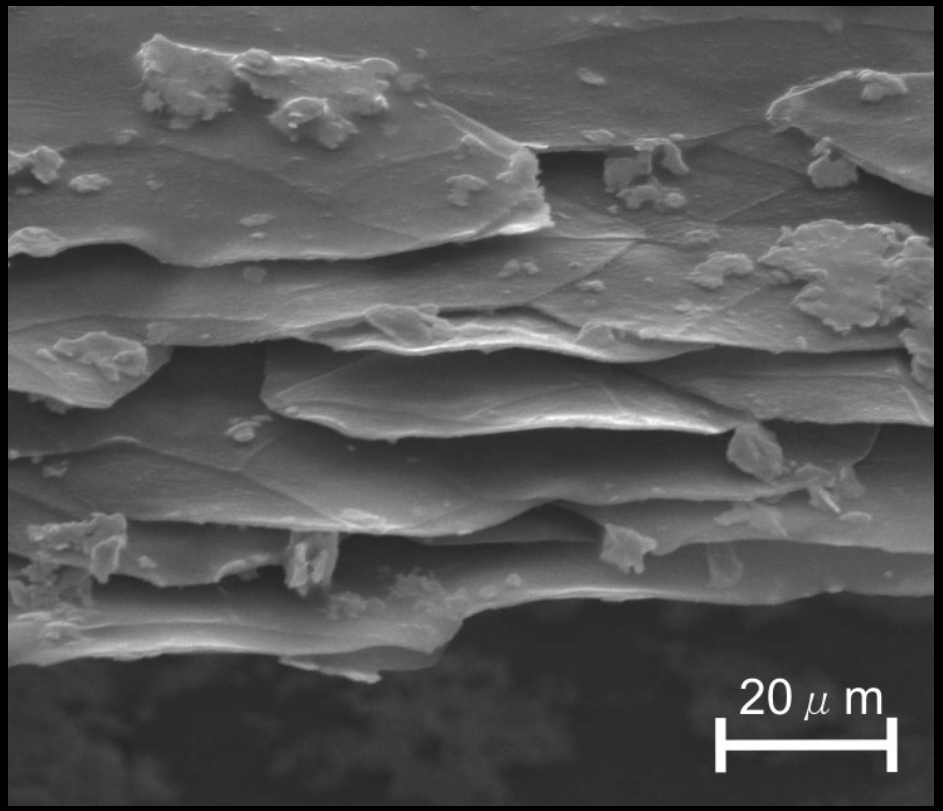


- These lizards uncurl their toes like a paper party favor whistle when putting their feet down and peel the toes back up as if removing a piece of tape when they step away.
- http://pubs.acs.org/cen/critter/gecko1.html

Silk: how strong is it??

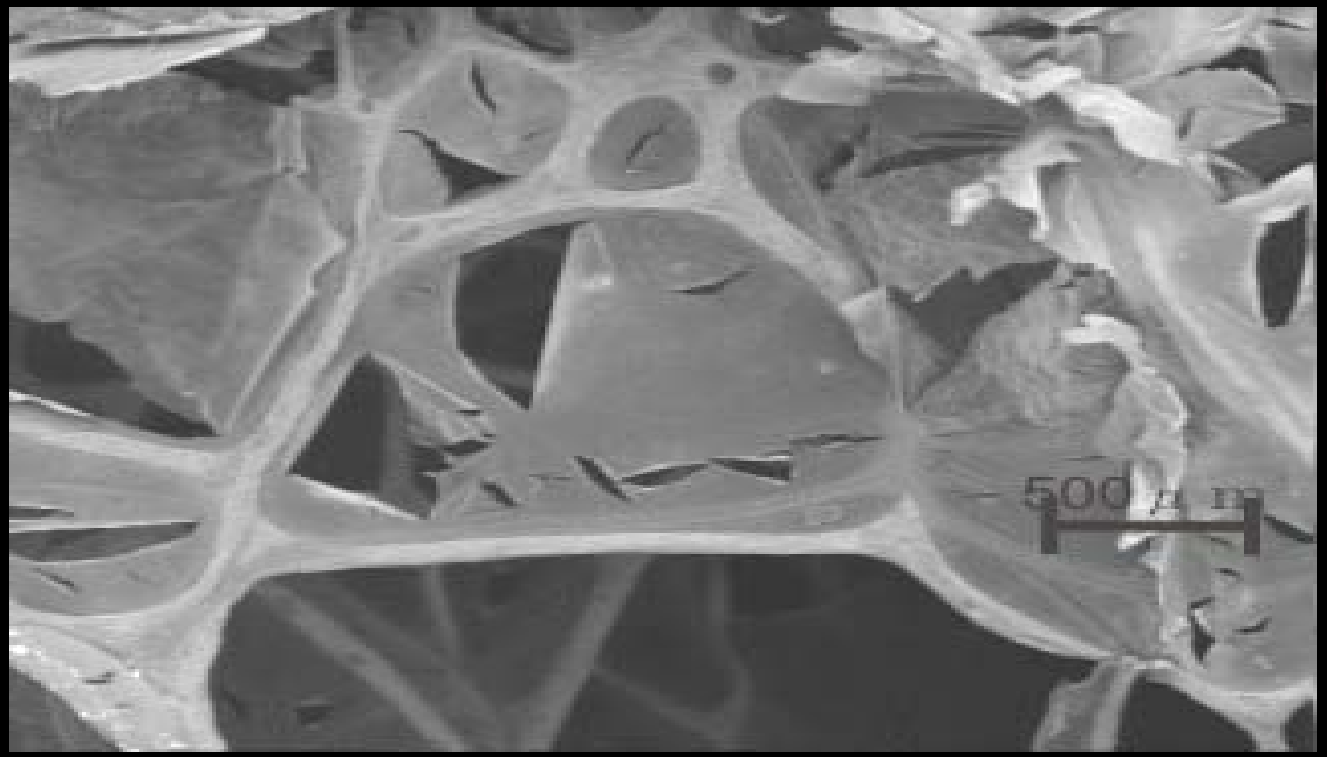
- The nanometer-sized biodegradable threads of spider silk are stronger, by weight, than high-tensile steel.
- It is also elastic enough to stretch up to 10 times its initial length

Toucan beaks –strong and light



- The exterior of the toucan beak is made up of overlapping nanosized tiles of keratin, the same protein that makes up hair, fingernails, and horn.

The interior of the beak is a rigid foam made of a network of nanosized bony fibers connected by membranes. This allows the beak to absorb high-energy impacts.



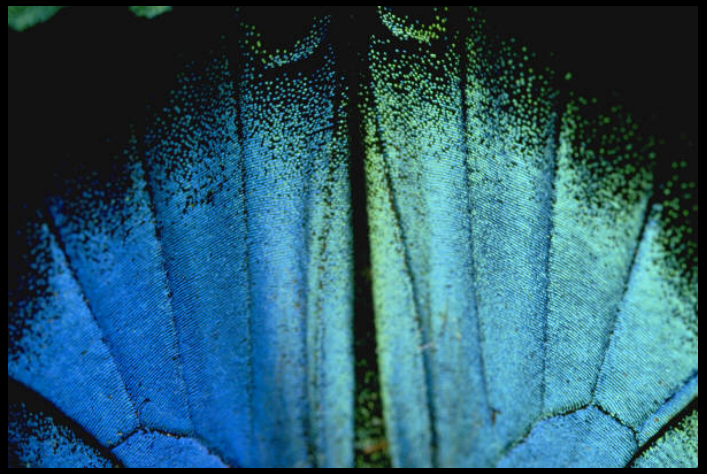
Nanoscale, light and nature

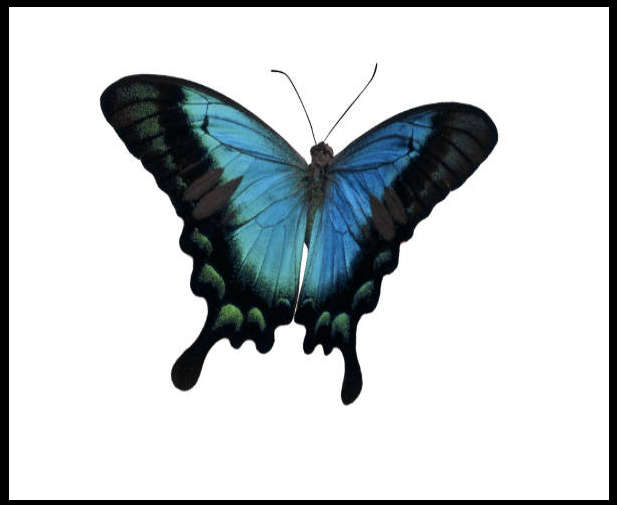
Color – why?

- One reason is pigment. If color is due to pigment, the color never changes.

Nanoscopic color

- The colors of beetle and butterfly wings come from the scattering of light.
- Light hits the nanostructures on their scales. These nanostructures are typically smaller than the wavelengths of visible light (smaller than 400 nanometers, for example).

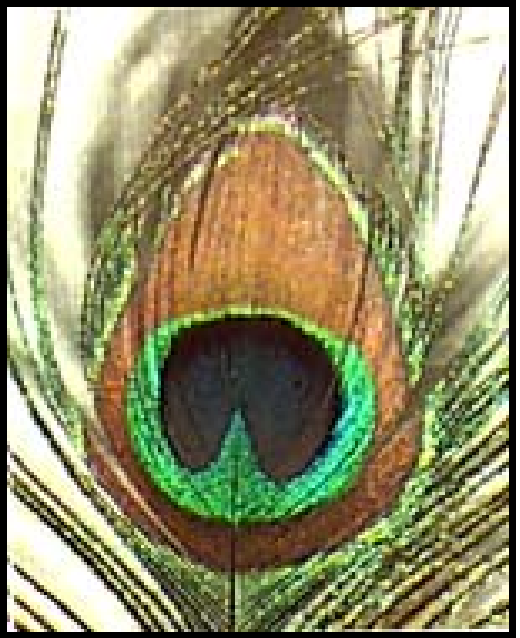




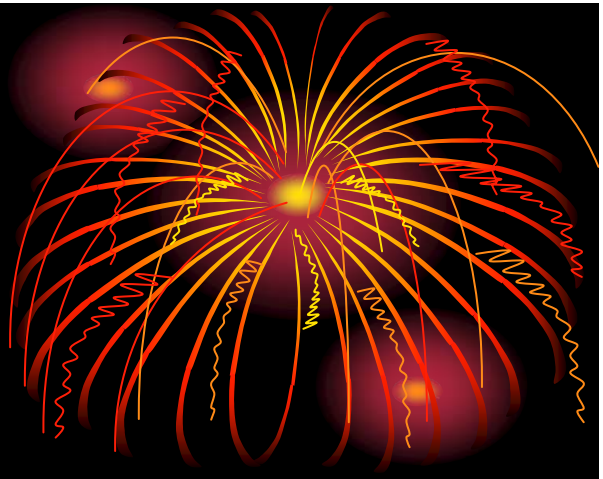
3.The third reason for color is the interference of different wavelengths of light (like oil on water).

Thin films are made of nanoparticles, smaller than 400 nanometers, that produce iridescent (rainbow-like) colors when light strikes them.

Iridescent colors change when you look at the object from different angles



Squid lights on a nanoscale



The Hawaiian bobtail squid uses a two part process to hide from predators at night.

First, it has a light-producing organ on its underside. How does it produce light? Why, it contains bacteria that produce luminescent light on the nanoscale.

- Secondly, the squid has stacks of silvery nanoplatelets made of proteins behind the tissue to reflect the light downward from the squid.
- The light prevents it from casting a shadow when seen from above or forming a silhouette when seen from below.

Hippo sweat and nanoscience

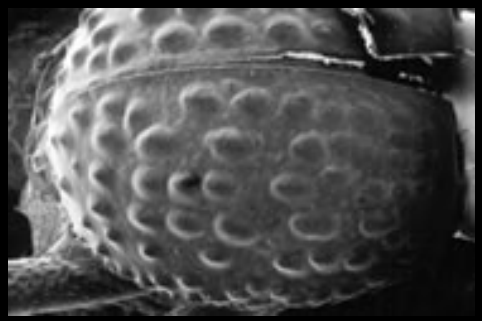
Hippo sweat contains compounds that absorb light in the range of 200 – 600 nanometers. This compound protects the hippo's skin like sunscreen.

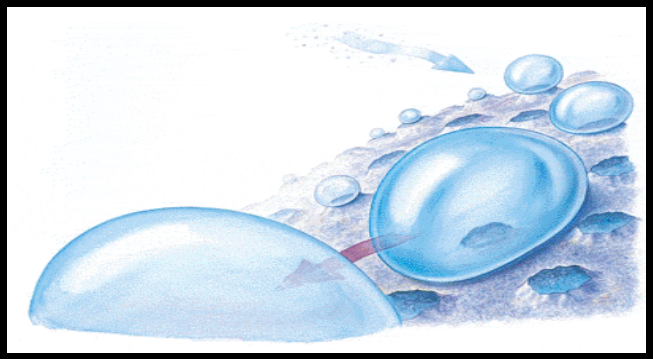
One of the compounds in hippo sweat, hipposudoric acid, inhibits bacterial growth and is hydrophilic

- **Imagine you're a very thirsty tiny beetle in a desert. How can you get a drink?**

- **The Namib desert beetle in the deserts of southwest Africa has a novel idea.**

- **First it must collect drinking water using its wings, which are waxed and covered with raised unwaxed nanobumps. The bumps attract water (hydrophilic). When enough water collects it rolls down the waxy areas, which repel water (hydrophobic), into the beetle's mouth.**

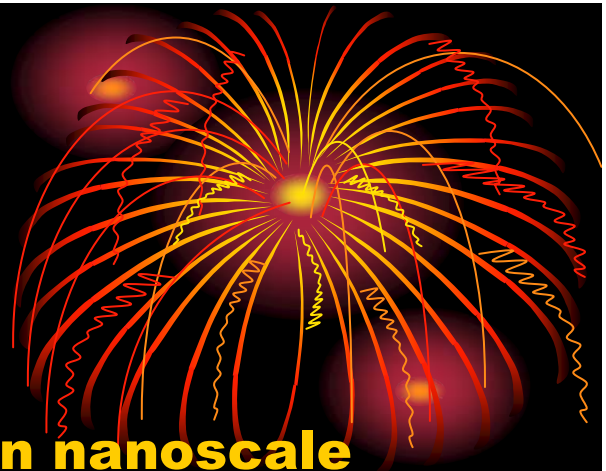




- **Six times a year when the fog blows in from the Atlantic the Namib beetle turns a 45 degree angle to the wind so that the droplets of water from the fog stick to the unwaxed bumps on its back. This water builds up before rolling down the water-repelling waxed troughs on the beetle's back and into its mouth.**

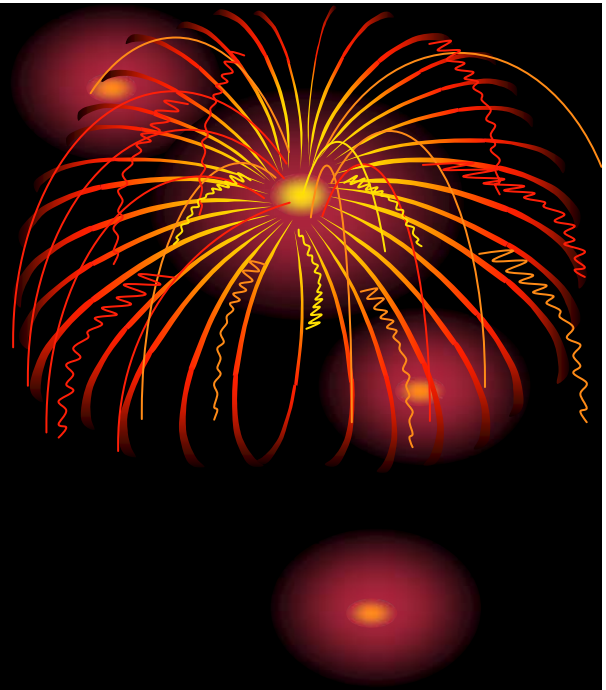
Nanoflake snowflakes

They build up on the nanoscale, one molecules at a time. Their size and shape is determined by the altitude and air pressure where they are formed.



- **Living cells have been using their own nanoscale devices to create structures one atom or molecule at a time for millions of years.**
- **To be specific, DNA is copied, proteins are formed, and complex hormones are manufactured by cellular devices far more complex than the most advanced manufacturing processes we have today**
- **Mankind has always found inspiration in Mother Nature. Today developing technologies allow us to probe and better understand the nanoscience of Mother Nature.**

Now, a biological novelty: the only man in the world to have his heart in his abdomen



- **The end (has finally come!)**