Nano-Medicine

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History of Human Industry

(1) Late 1800s' Mechanical Technology:
Steam Engine…
(2) 1910~ Electrical Technology:
Franklin/Edison, generator, vacuum tube, semiconductor…
(3) 1970 Informatics Technology:
computer & informatics
(4) Nano Technology

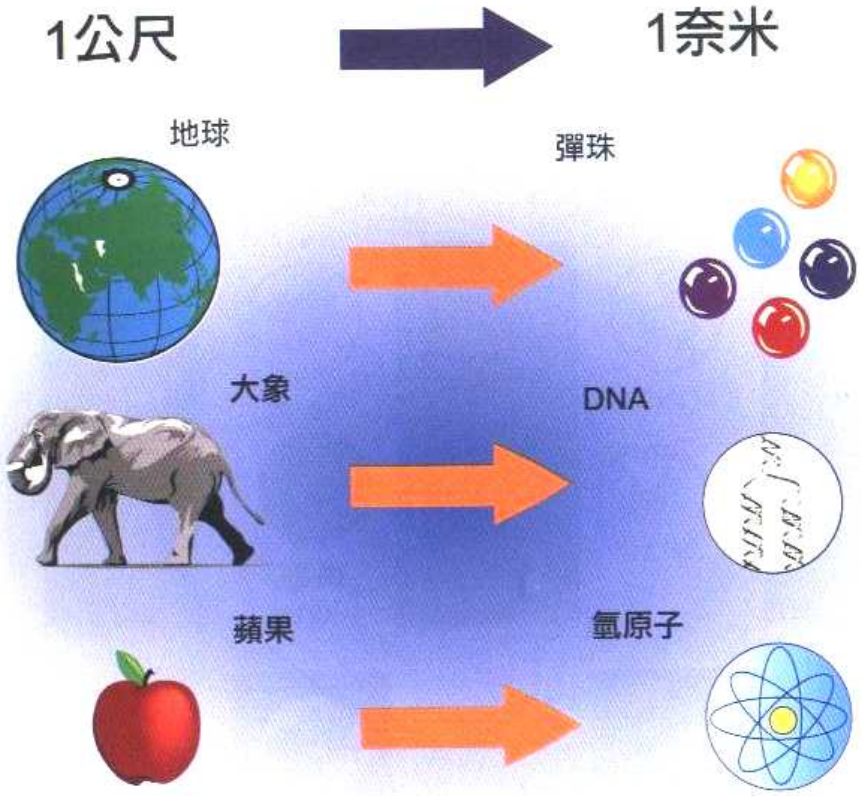
What is Nano?

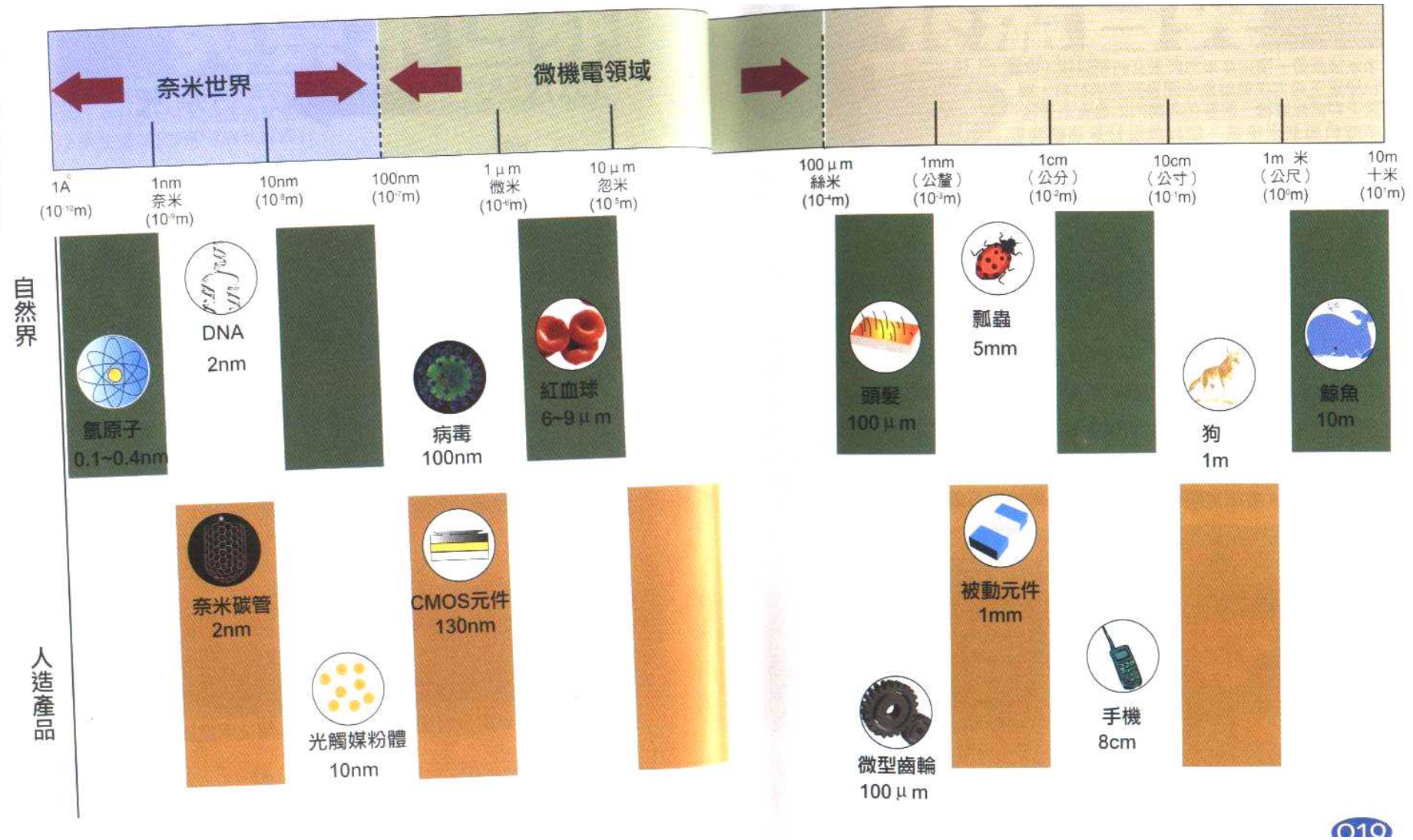
Dwarf in Greek

Dimension, Size, or Scale?

1 nm = 10^{-9} m?

1 nm ~ 3-4 atoms




奈米世界
微機電領域
1A°
(10⁻¹⁰m)
1nm
奈米
(10⁻⁹m)
10nm
(10⁻⁸m)
100nm
(10⁻⁷m)
1μm
微米
(10⁻⁶m)
10μm
忽米
(10⁻⁵m)
100μm
絲米
(10⁻⁴m)
1mm
（公釐）
(10⁻³m)
1cm
（公分）
(10⁻²m)
10cm
（公寸）
(10⁻¹m)
1m 米
（公尺）
(10⁰m)
10m
十米
(10¹m)
自然界
氫原子
0.1~0.4nm
DNA
2nm
病毒
100nm
紅血球
6~9μm
頭髮
100μm
瓢蟲
5mm
狗
1m
鯨魚
10m
人造產品
奈米碳管
2nm
光觸媒粉體
10nm
CMOS元件
130nm
被動元件
1mm
微型齒輪
100μm
手機
8cm

Clear lotus comes out from mud?

Leaf surface covered with a thin film hydrophobic cilia about 100 nm in length.

Auto-clean effect!!

Outer wall of a building, auto-body, interior tile… can be covered with such a film for auto-cleaning.

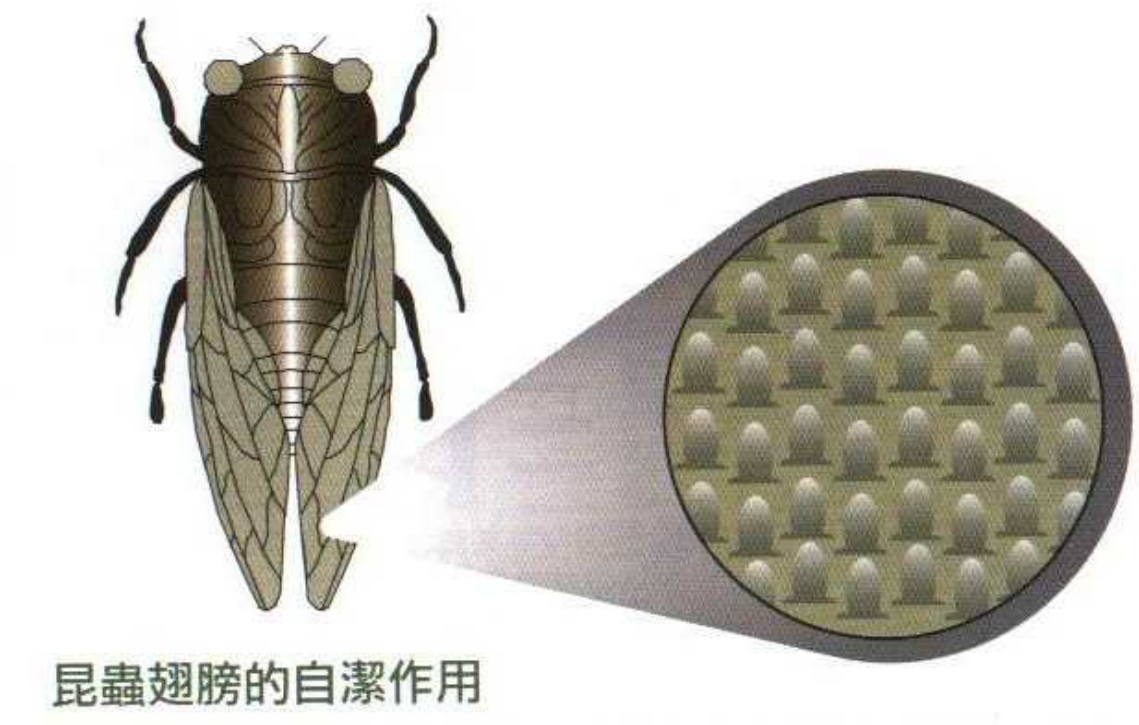
Dolphin and Whale stay in the sea for all the life with a polish and smooth skin, no marine life attach on.

Corrosion-resistant ship body will be attached by lots of marine life or corroded by sea water, after sailing for a short of time.

Ship body or diver should be covered with a artificial whale or dolphin “coat” before go into water.

Insects flying in the air should balance the wings on both side.

Nano-structure on the wing surface keeps it from grime and water.

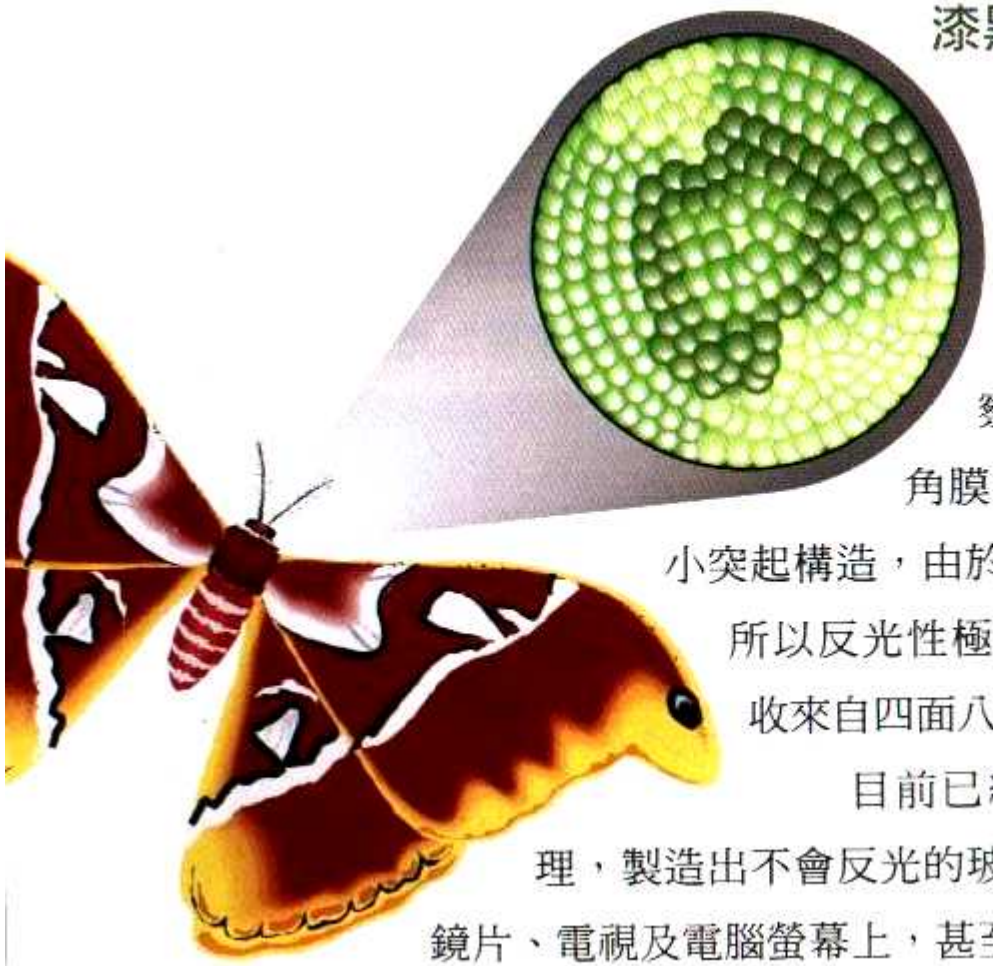


昆蟲翅膀的自潔作用

No reflection and black in color of moth eyes prevent it from attack during flying at night.

Cornea surface with nano-structure ridges can absorb the light from all the directions and no reflection due to ridge size much smaller than wavelength of light.

Prepare no reflection glass for glasses, TV & computer monitor, and automobile glass…..

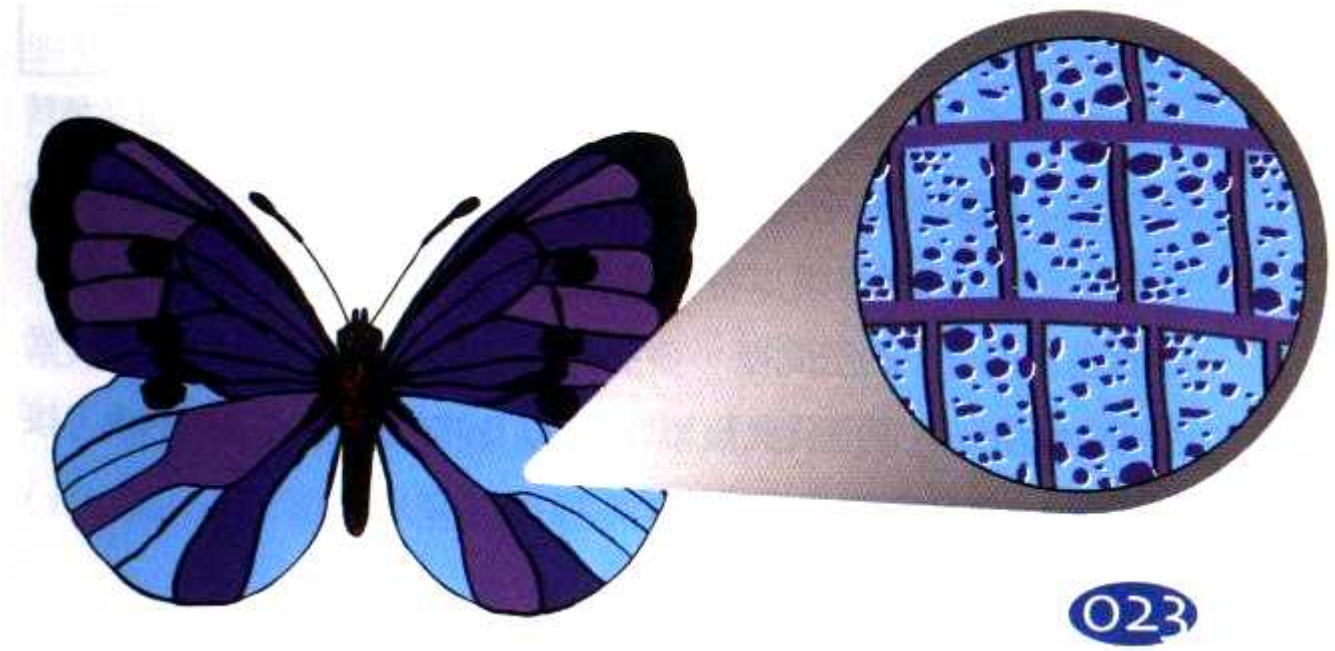


漆黑的飛蛾眼睛

飛蛾的眼睛看起來異常漆黑且不會反光，所以在夜間飛行時，不容易為敵人所察覺。這是因為在其角膜表面具有奈米級的微小突起構造，由於比光線的波長還小，所以反光性極低，而且似乎可以吸收來自四面八方的光線。

目前已經有企業依據此種原理，製造出不會反光的玻璃，將來可望運用在鏡片、電視及電腦螢幕上，甚至是汽車玻璃。如此就

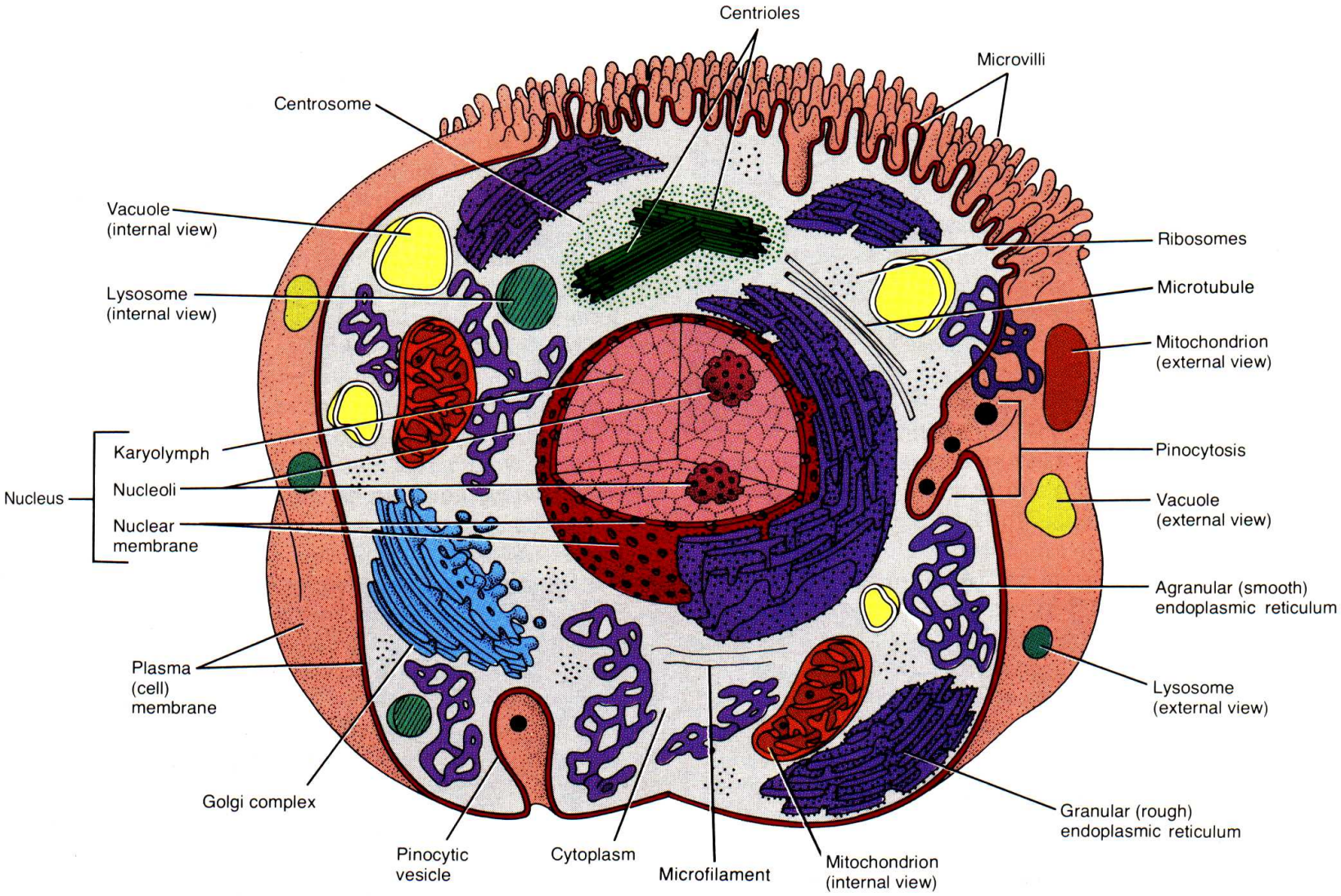
Some of creatures with photonic crystals on the wings or fish scale can reflect specific wavelength and show a colorful appearance.
The color will change with different view side.



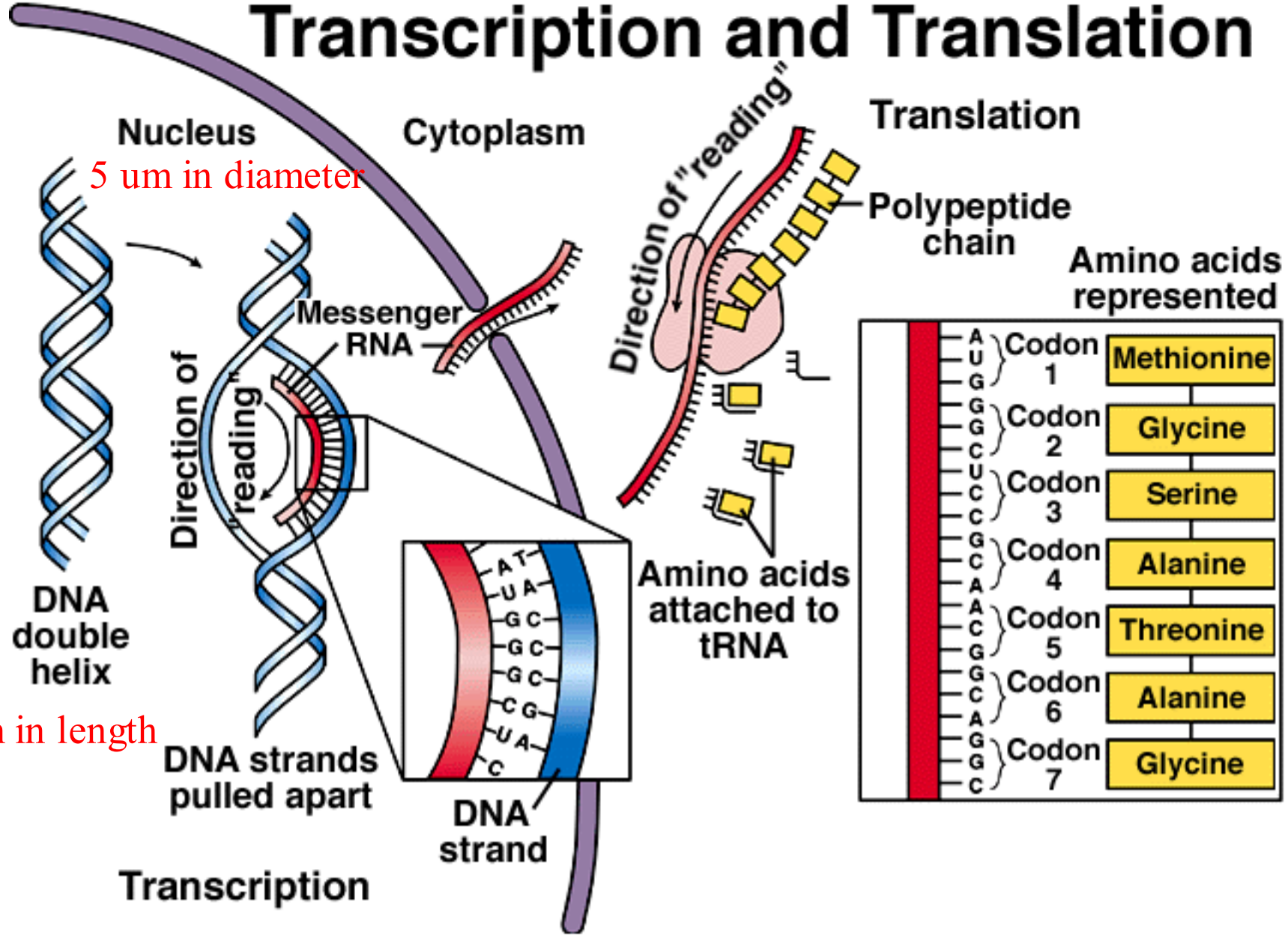
Nano- and Human

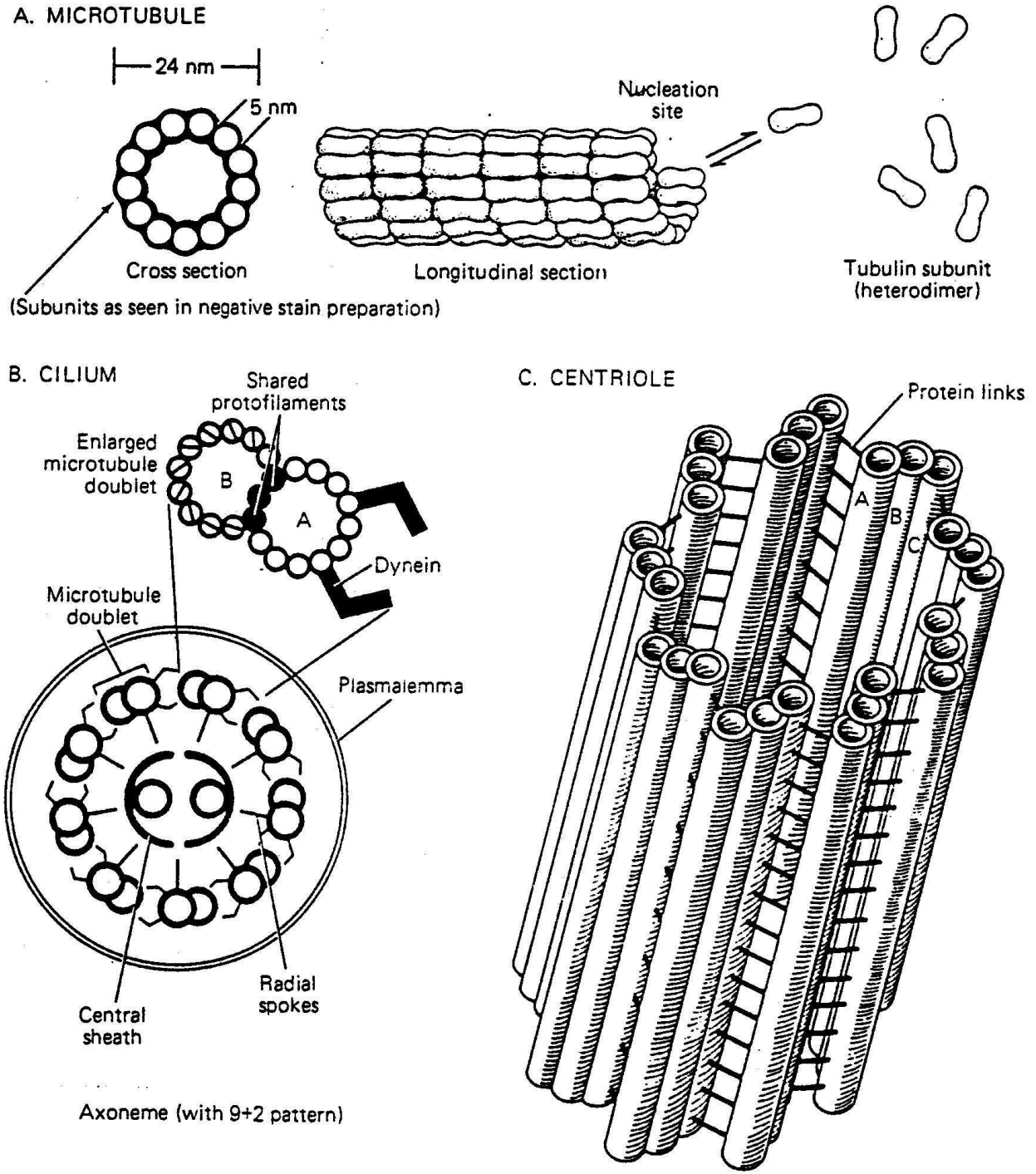
$6x10^{13}$ cells in human

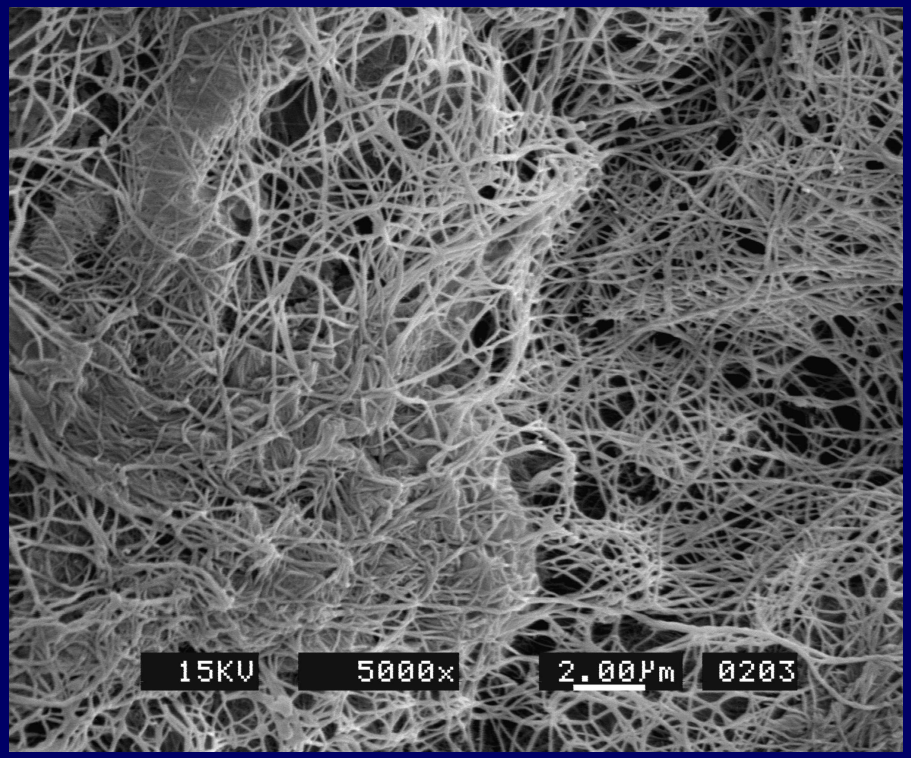
20 um in diameter for each cell

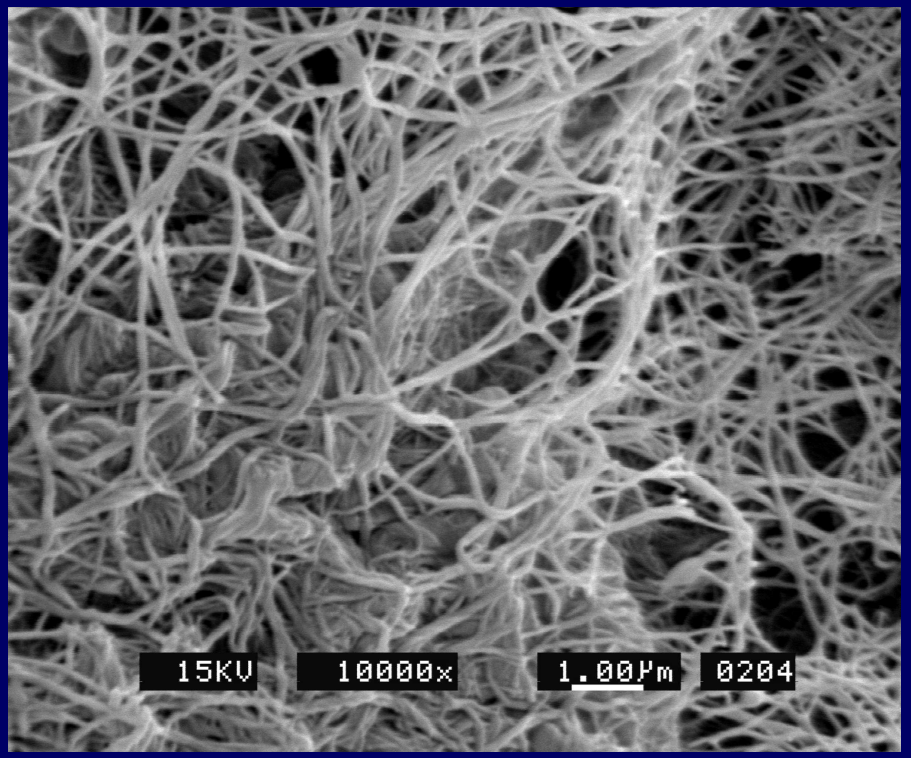


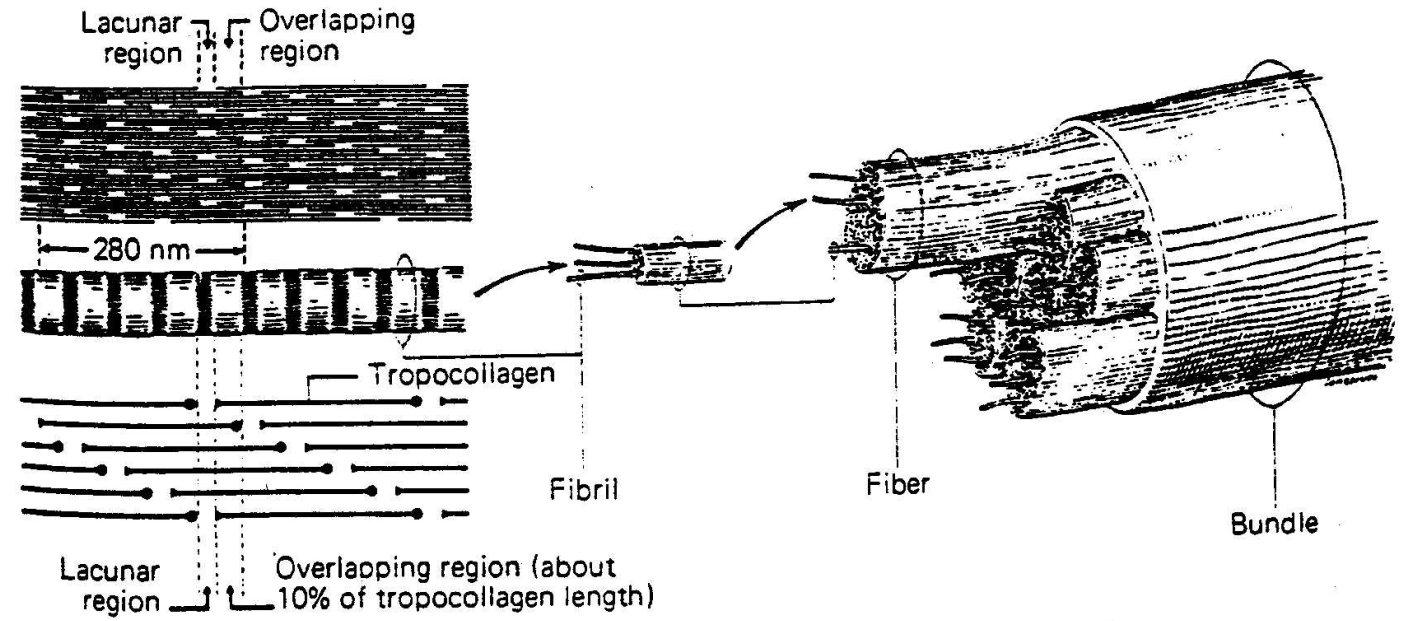
Transcription and Translation

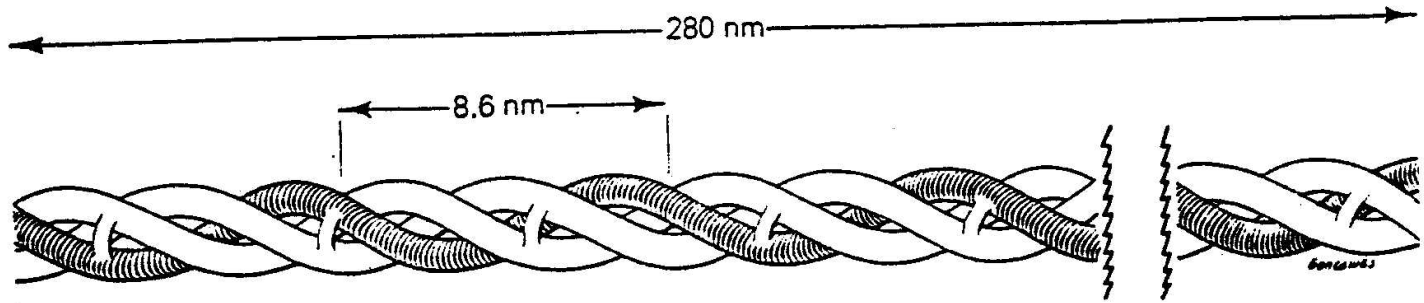



A. MICROTUBULE
24 nm
5 nm
Cross section
(Subunits as seen in negative stain preparation)
Nucleation site
Longitudinal section
Tubulin subunit (heterodimer)
B. CILIUM
Shared protofilaments
Enlarged microtubule doublet
B
A
Dynein
Microtubule doublet
Plasmalemma
Central sheath
Radial spokes
Axoneme (with 9+2 pattern)
C. CENTRIOLE
Protein links
A
B
C

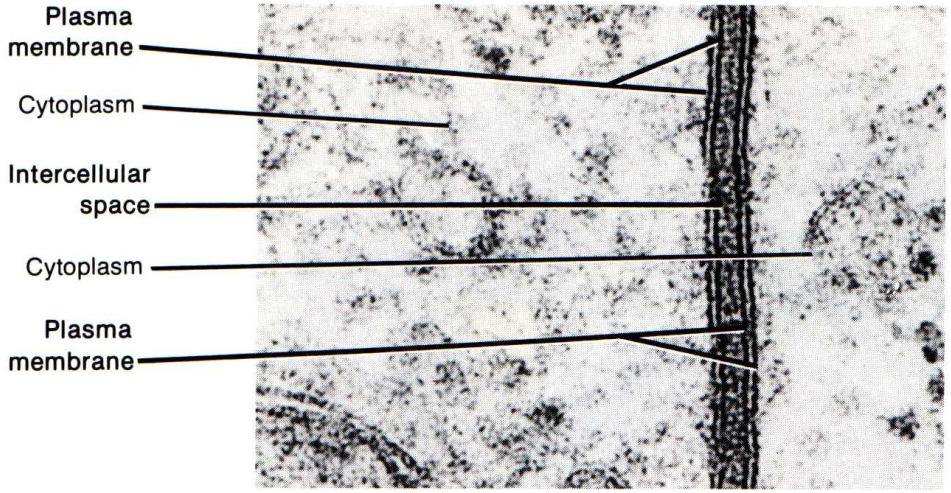

15KV
5000x
2.00µm
0203


15KV
10000x
1.00µm
0204

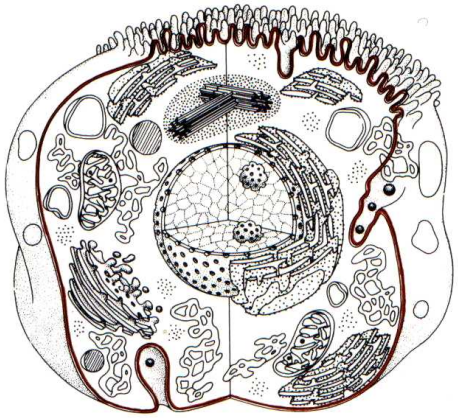




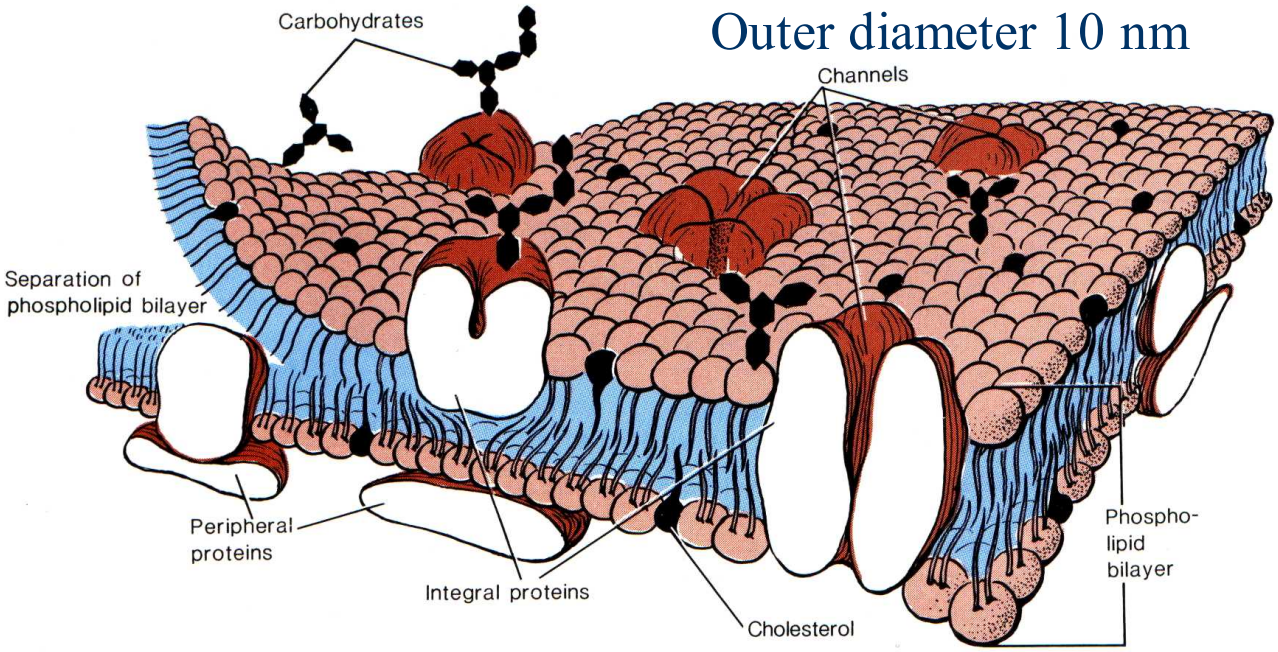
. In the most abundant form of collagen, known as type I, each molecule (tropocollagen) is composed of 2 alpha-1 and one alpha-2 (shaded area) peptide chains, each with a molecular weight of approximately 100,000, intertwined in a helix and held together by hydrogen bonds. Each complete turn of the helix spans a distance of 8.6 nm.



(a)



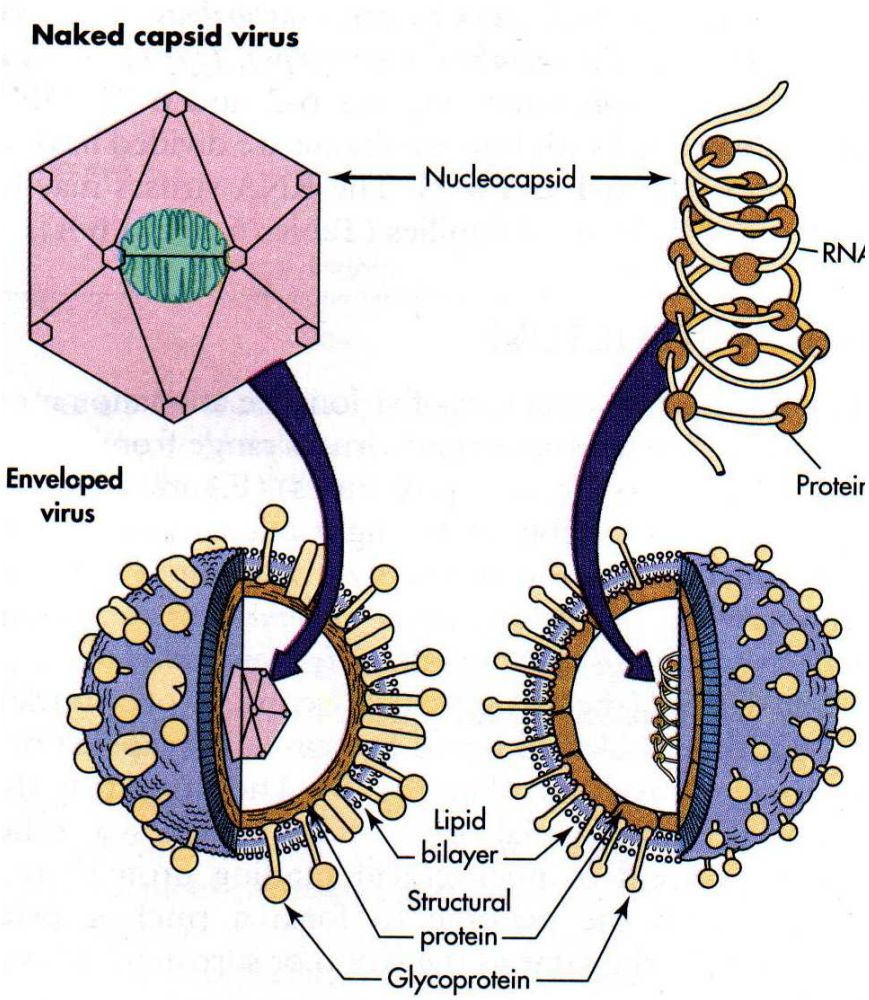
Inner diameter 1-2 nm
Outer diameter 10 nm



7-10nm

(b)

FIGURE 3-2 Plasma membrane. (a) Electron micrograph of portions of two plasma membranes separated by an intercellular space at a magnification of 200,000×. (Copyright © Dr. Donald Fawcett, Science Source/Photo Researchers.) (b) Enlargement of the plasma membrane showing the relationship of the phospholipid bilayer and protein molecules. The separation of the bilayer is for illustrative purposes only.


Naked capsid virus
Nucleocapsid
RNA
Protein
Enveloped virus
Lipid bilayer
Structural protein
Glycoprotein

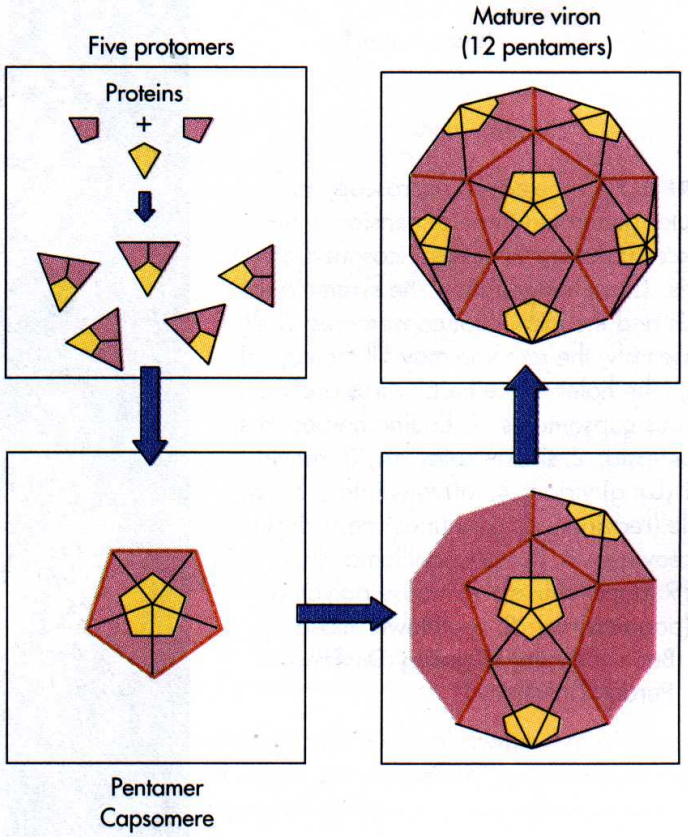
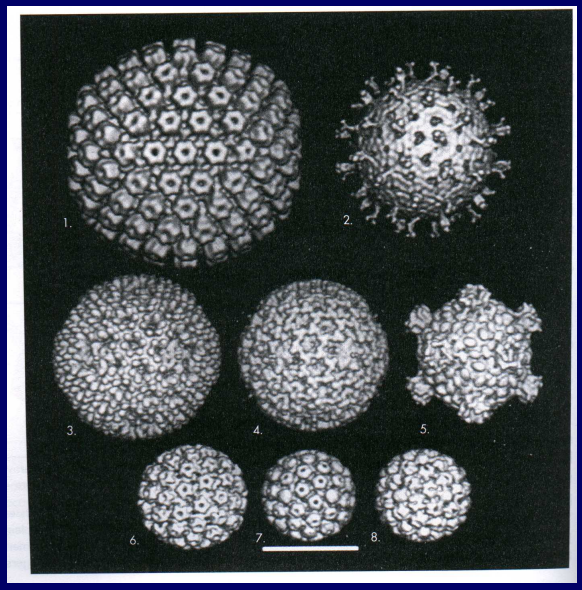


FIGURE 6-6 Capsid assembly of the icosahedral capsid of a picornavirus. Individual proteins associate into subunits, which associate into protomers, capsomeres, and an empty procapsid. Inclusion of the (+) RNA genome triggers its conversion to the final capsid form.



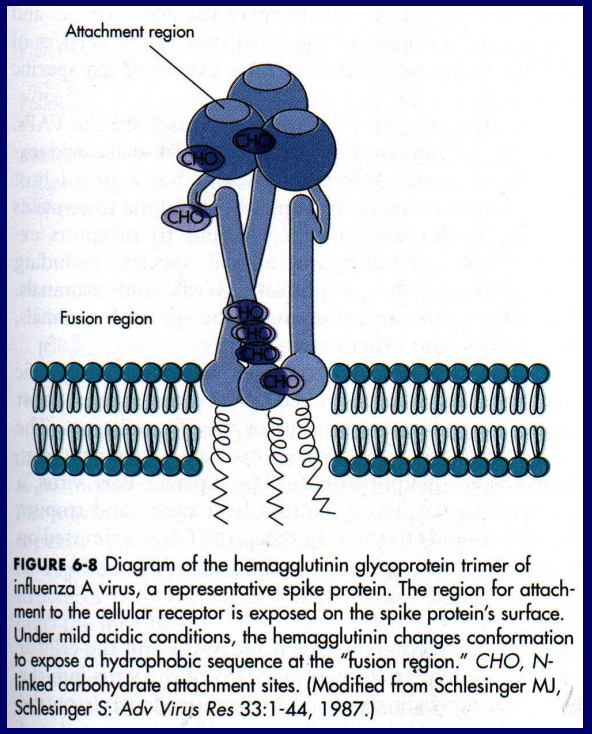
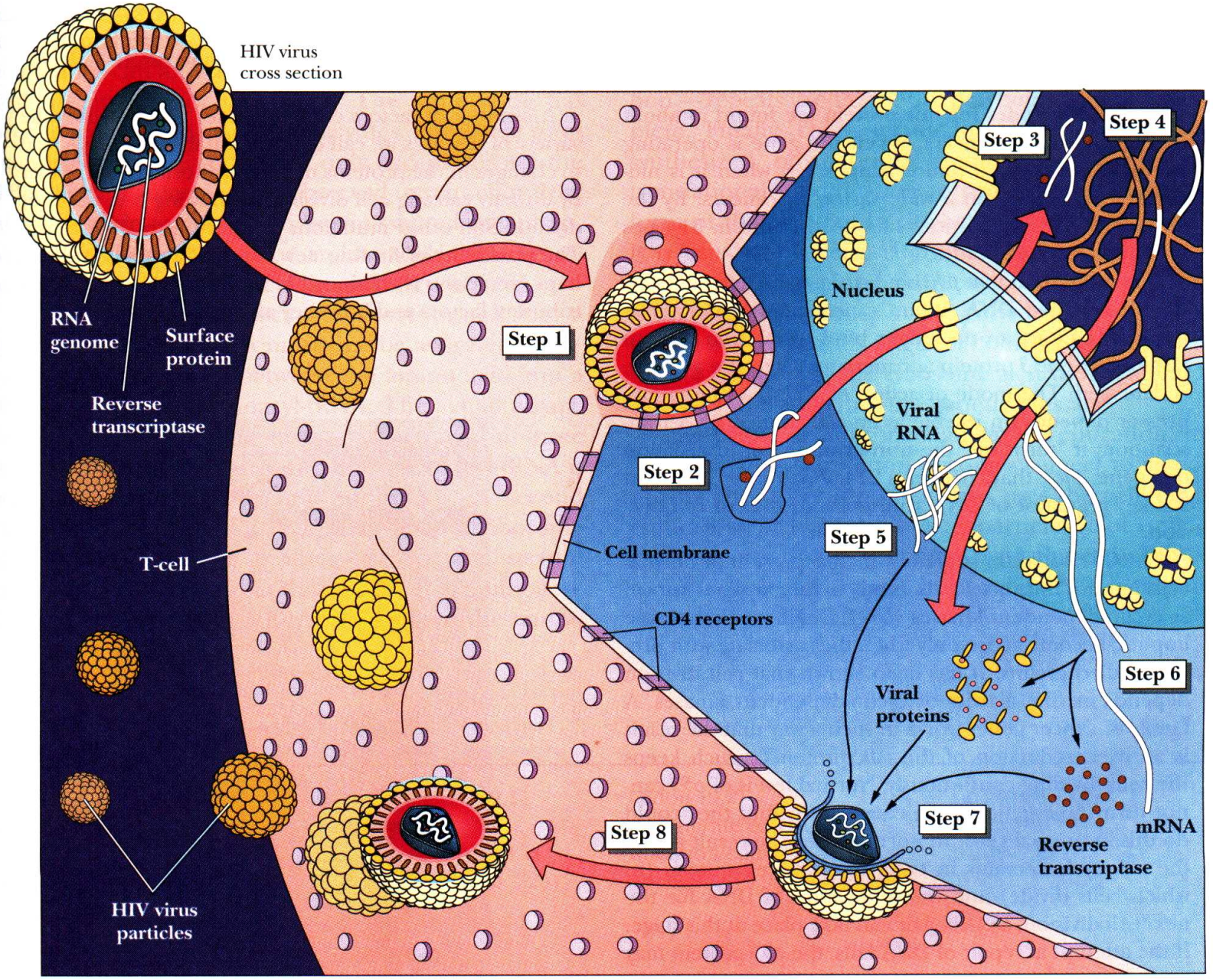
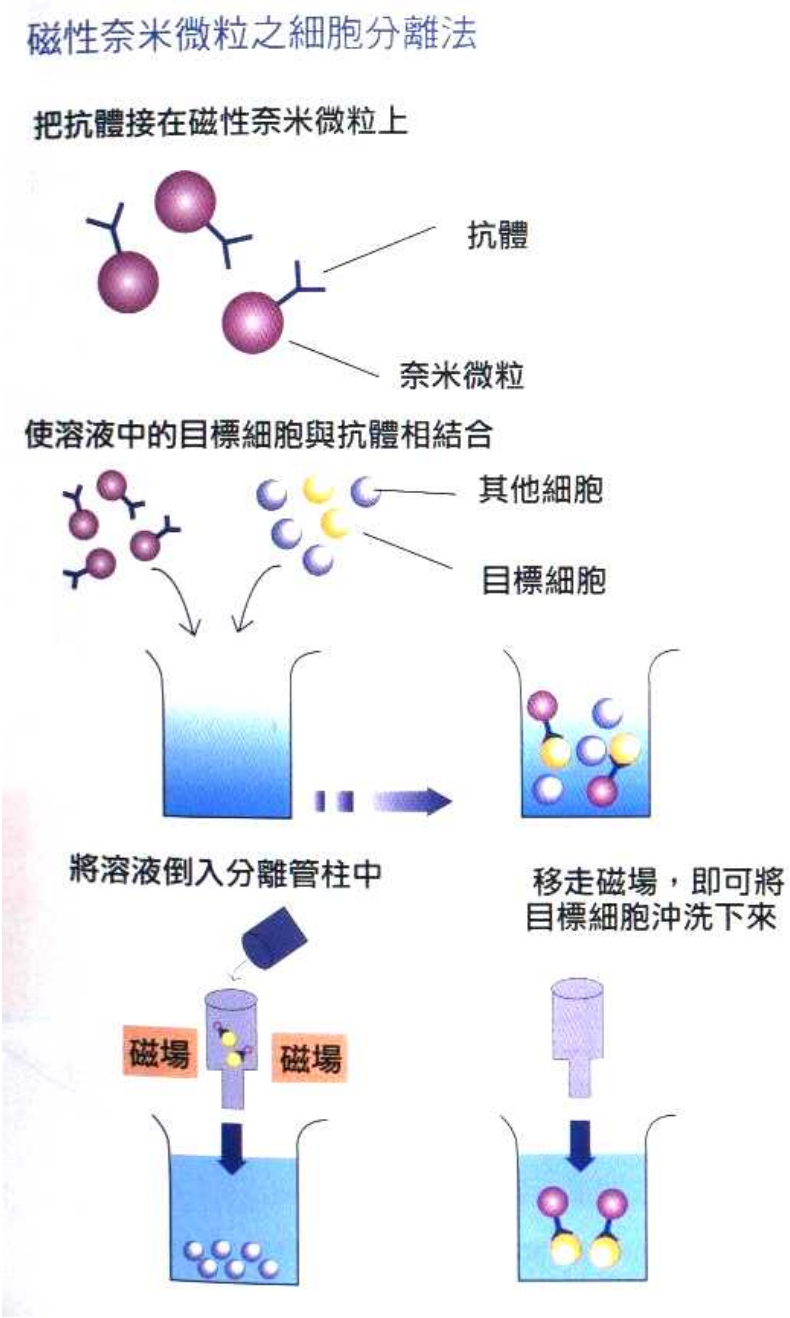
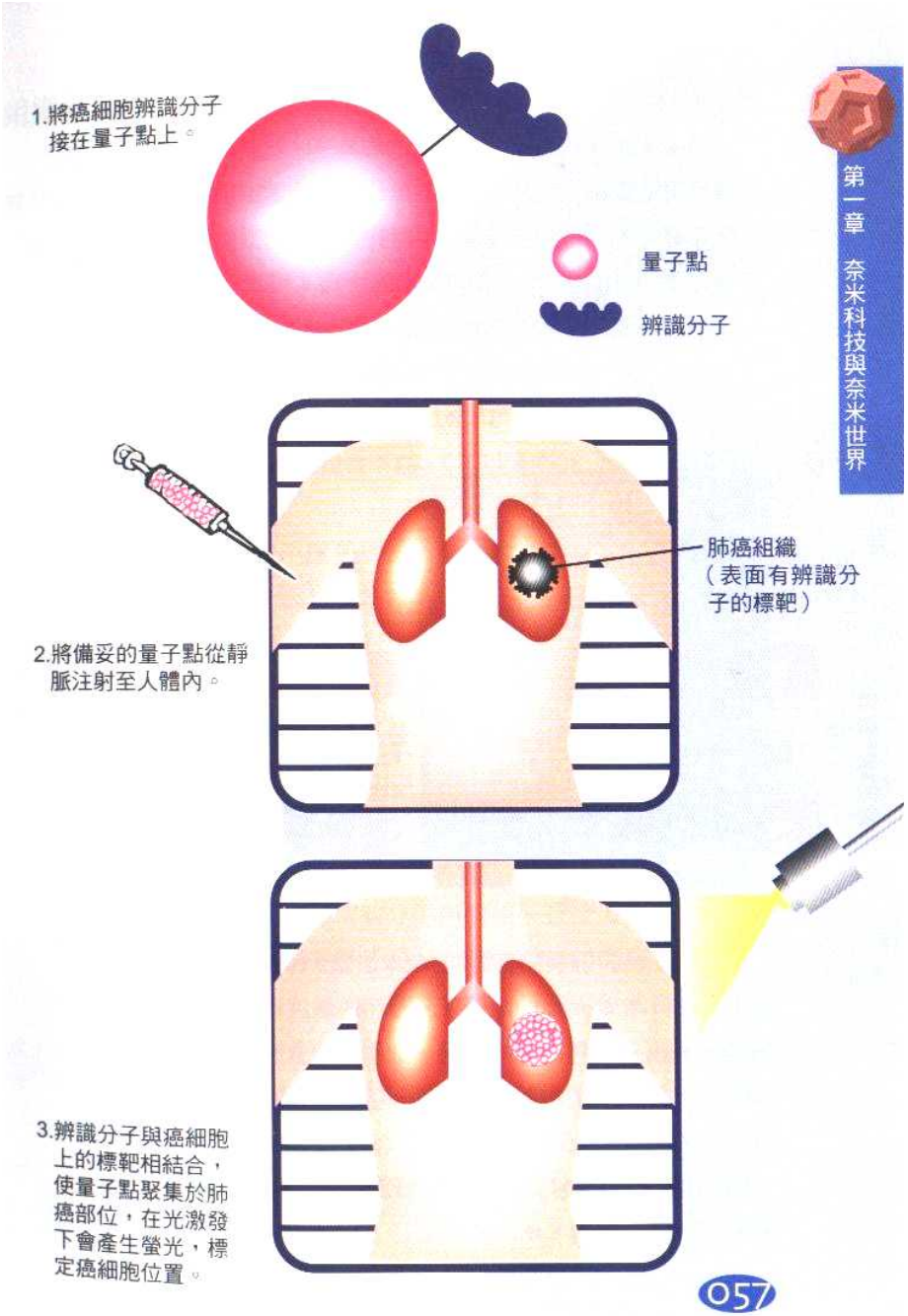


FIGURE 6-8 Diagram of the hemagglutinin glycoprotein trimer of influenza A virus, a representative spike protein. The region for attachment to the cellular receptor is exposed on the spike protein's surface. Under mild acidic conditions, the hemagglutinin changes conformation to expose a hydrophobic sequence at the "fusion region." *CHO*, N-linked carbohydrate attachment sites. (Modified from Schlesinger MJ, Schlesinger S: *Adv Virus Res* 33:1-44, 1987.)


HIV virus
cross section
RNA
genome
Surface
protein
Reverse
transcriptase
T-cell
HIV virus
particles
Step 1
Step 2
Step 3
Step 4
Step 5
Step 6
Step 7
Step 8
Nucleus
Viral
RNA
Cell membrane
CD4 receptors
Viral
proteins
mRNA
Reverse
transcriptase

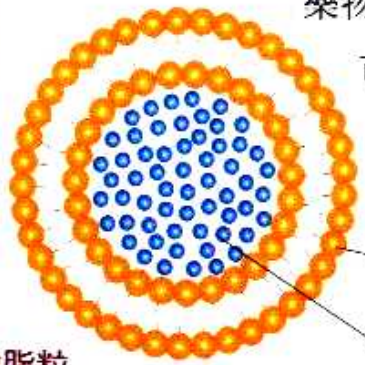
1 billion cells can be isolated within 15 mins. You can isolate one target cell from hundreds & thousands cells within relative short time.



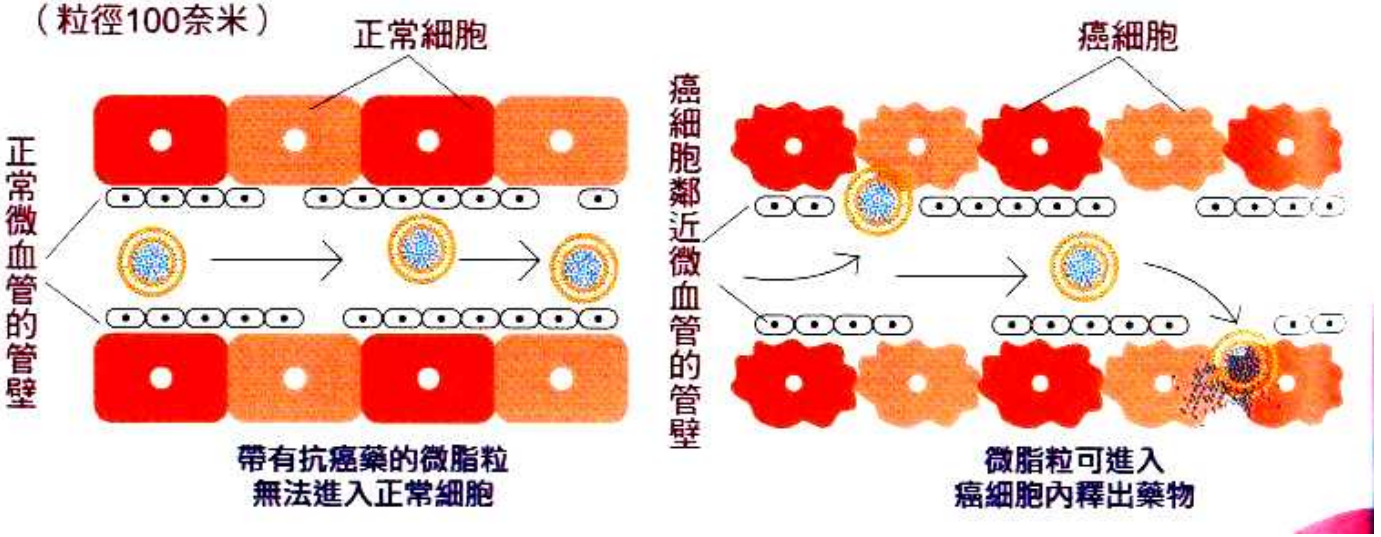

1.將癌細胞辨識分子接在量子點上。
量子點
辨識分子
肺癌組織（表面有辨識分子的標靶）
2.將備妥的量子點從靜脈注射至人體內。
3.辨識分子與癌細胞上的標靶相結合，使量子點聚集於肺癌部位，在光激發下會產生螢光，標定癌細胞位置。

藥物傳輸

日前奈米藥物的研究以癌症治療為主。一般的化學治療藥劑雖能殺死癌細胞，但正常細胞亦無法倖免，遂出現噁心、嘔吐、掉髮等副作用。癌細胞周圍會伴隨許多新生的微血管，但因結構不夠完整而有許多300～600奈米的小孔。科學家們於是將抗癌藥物包裹在100奈米左右的微粒中，此種大小的微粒可穿透癌細胞旁的微血管，並進入癌細胞內釋出藥物，但無法越過正常細胞的微血管（孔隙在80奈米以下），故不會對正常細胞產生毒性。



微脂粒
（粒徑100奈米）

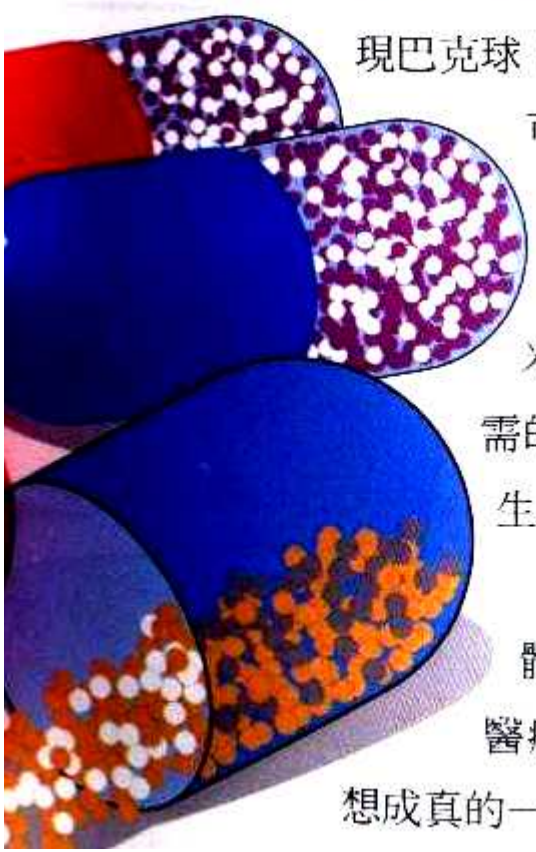


組織修復及人工植入物

奈米技術可以修飾生醫材料的表面，幫助新生細胞的貼附及生長。骨骼重建手術常用「骨水泥」進行修補及填充，加入奈米碳管可發揮補強效果。像是人工心臟瓣膜、血管支架、人工關節等植入物，可運用奈米技術「包上」一層具有生物相容性的外套，降低發炎或引起免疫反應的風險。

非藥物療法

某些奈米級微粒即使不與藥物結合，也能發揮治病功效。例如，超順磁性氧化鐵奈米顆粒在外加磁場的作用下，溫度可升高至45℃左右，足以殺死腫瘤細胞。研究也發現巴克球（buckyball）可對抗愛滋病毒，它是由60個碳分子所構成、直徑僅數個奈米的球狀小分子，能使愛滋病毒複製所需的一種酵素喪失功能，達到抑制病毒增生之目的。



奈米科技的發展日新月異，像是進入人體內幫助治療疾病的奈米機器人和微型醫療潛艇等電影情節，在將來或許會有夢想成真的一天。

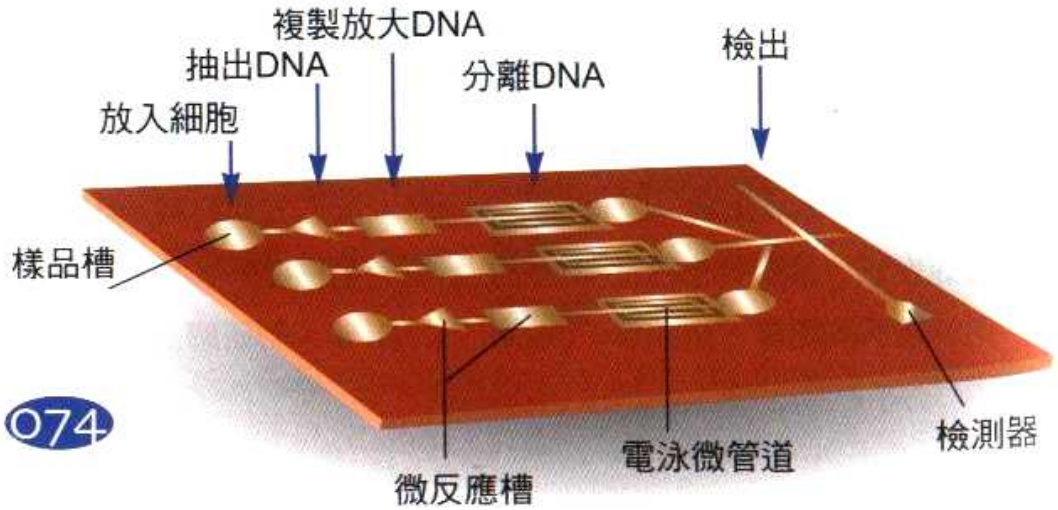
生物晶片

生物晶片（biochip）結合了微電子、微機械、分析化學、分子生物學、基因資訊等知識，利用矽晶片或玻璃等材質，製成可運用於生醫分析的高科技產品。生物晶片的優點在於操作簡單、攜帶方便、快速、精準，且靈敏度高。其應用層面涵蓋醫療診斷、癌症篩檢、新藥研發、食品檢測及環境評估等。

生物晶片的類型

處理型晶片：

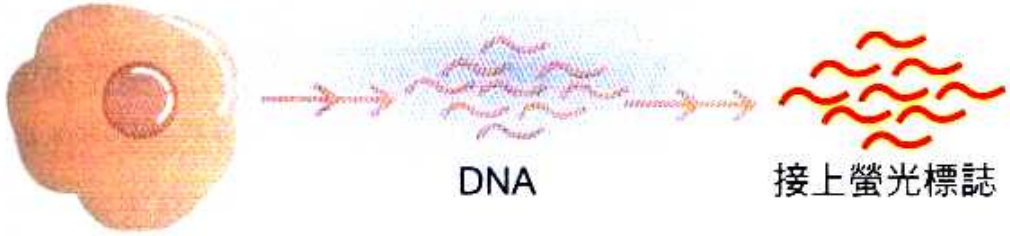
處理型晶片（processing chip）是藉由微機電加工技術和微流體學（microfluidics），將實驗室中的樣品前處理、試劑混合、反應、分析等一系列步驟微型化，並整合於單一晶片上，所以亦稱為實驗室晶片（lab-on-a-chip）。[9]



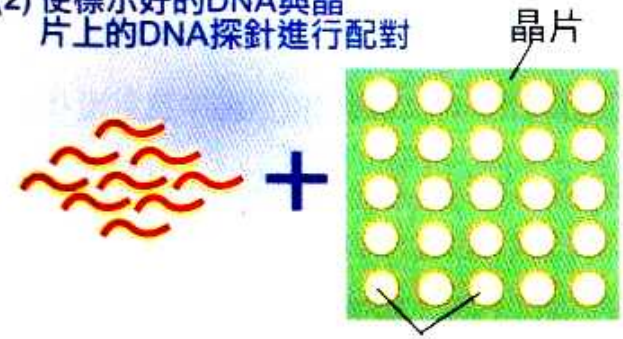
感測晶片：

感測晶片（sensing chip）以DNA晶片最為常見，也有可檢測蛋白質、醣類、病毒、細菌、細胞的晶片。一般是以微陣列（microarray）的設計，在晶片上以特定的順序放置成千上萬個DNA探針，使其與檢體中的DNA發生配對反應，再以光學儀或雷射儀掃瞄有反應的點的位置，即可得知檢體中是否有欲檢測的DNA片段。

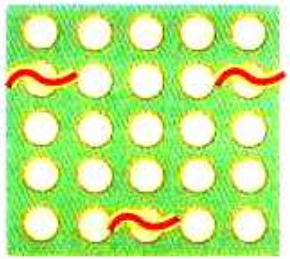
(1) 以前置處理從檢體分離出DNA，並接上螢光標誌



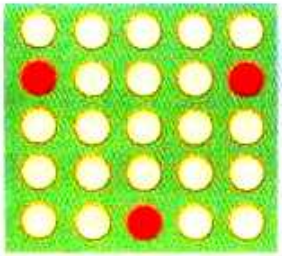
(2) 使標示好的DNA與晶片上的DNA探針進行配對



(3) 帶有螢光標誌的樣品DNA與互補對應的DNA探針相結合

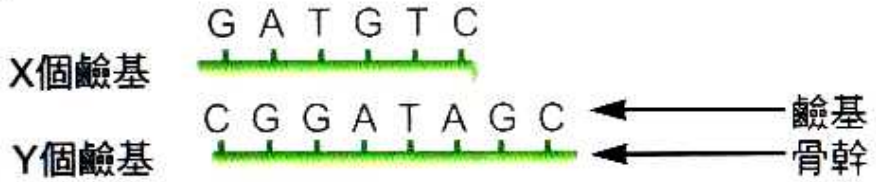


(4) 以螢光燈進行掃瞄，由亮點位置可檢出樣品中含有何種DNA片段

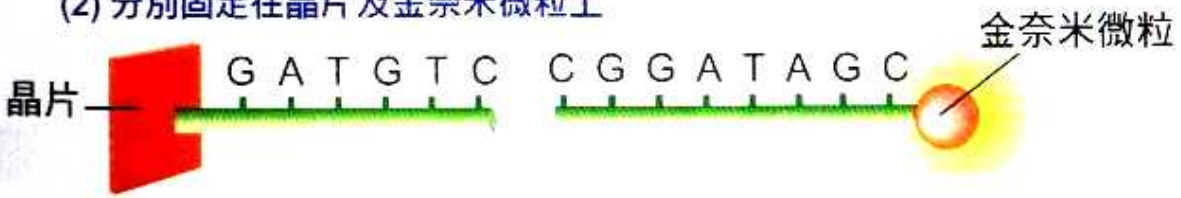


掃瞄式DNA感測法原理

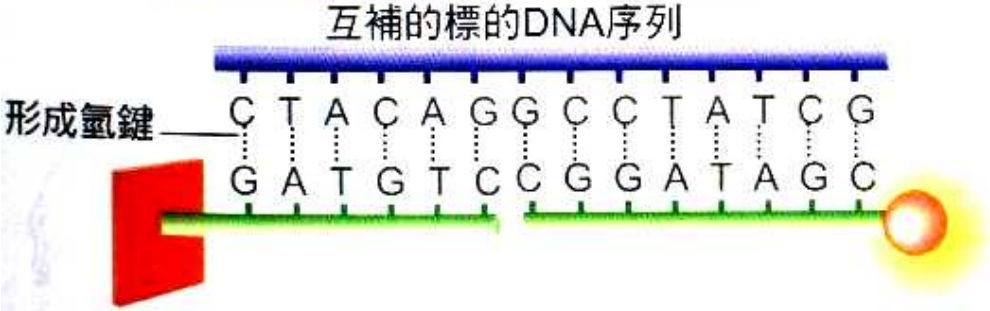
(1) 人工合成兩股長度不同的DNA片段



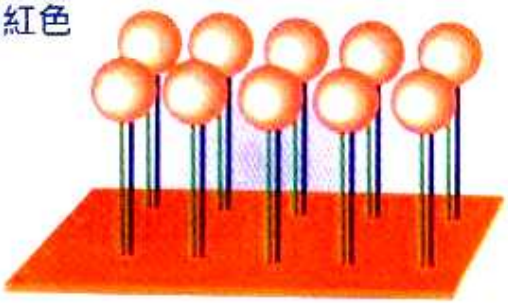
(2) 分別固定在晶片及金奈米微粒上



(3) 與樣品中的互補性標的DNA序列形成配對



(4) 晶片在掃瞄儀下呈現粉紅色



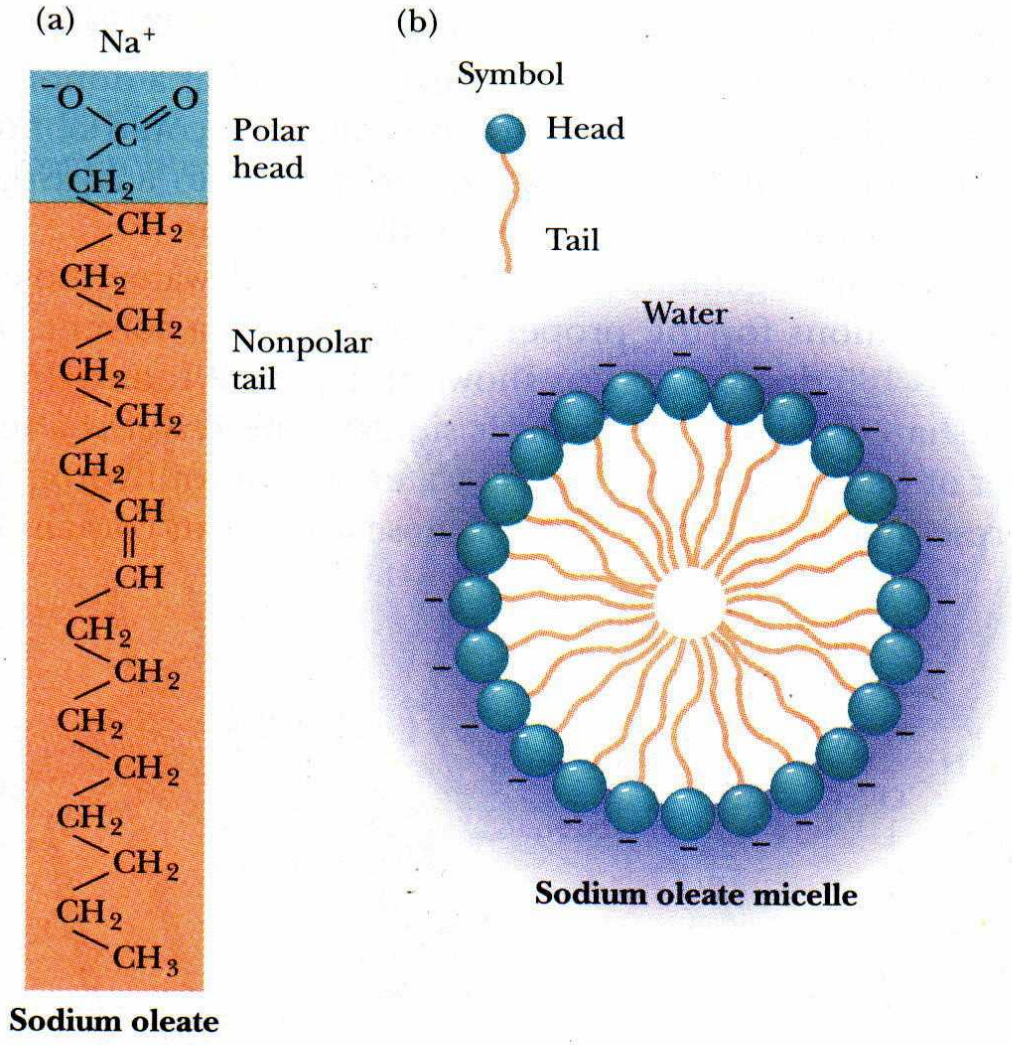
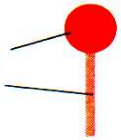


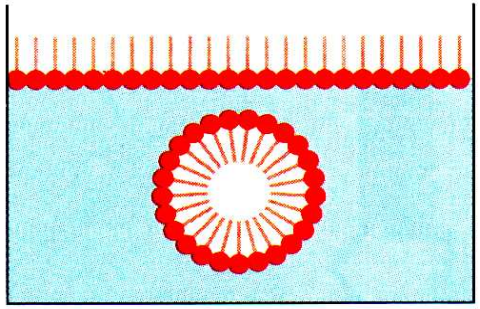
FIGURE 2.3

(a) A sodium salt of fatty acid with an ionized polar head and a nonpolar tail. (b) Formation of a micelle, with the ionized polar groups in contact with the water and the nonpolar parts of the molecule protected from contact with water.

LIPID AGGREGATES

Fatty acids have a hydrophilic head and a hydrophobic tail.

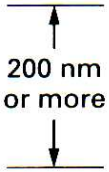




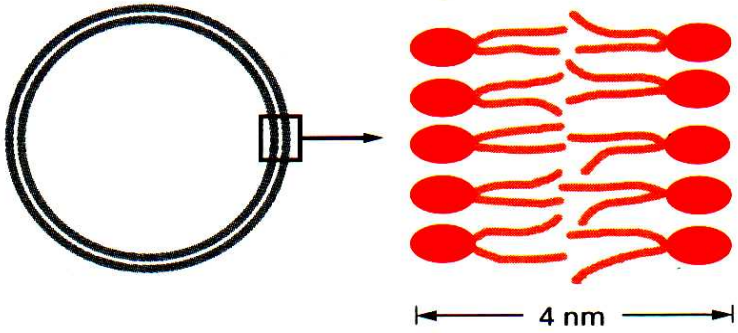
In water they can form a surface film or form small micelles.

Their derivatives can form larger aggregates held together by hydrophobic forces:

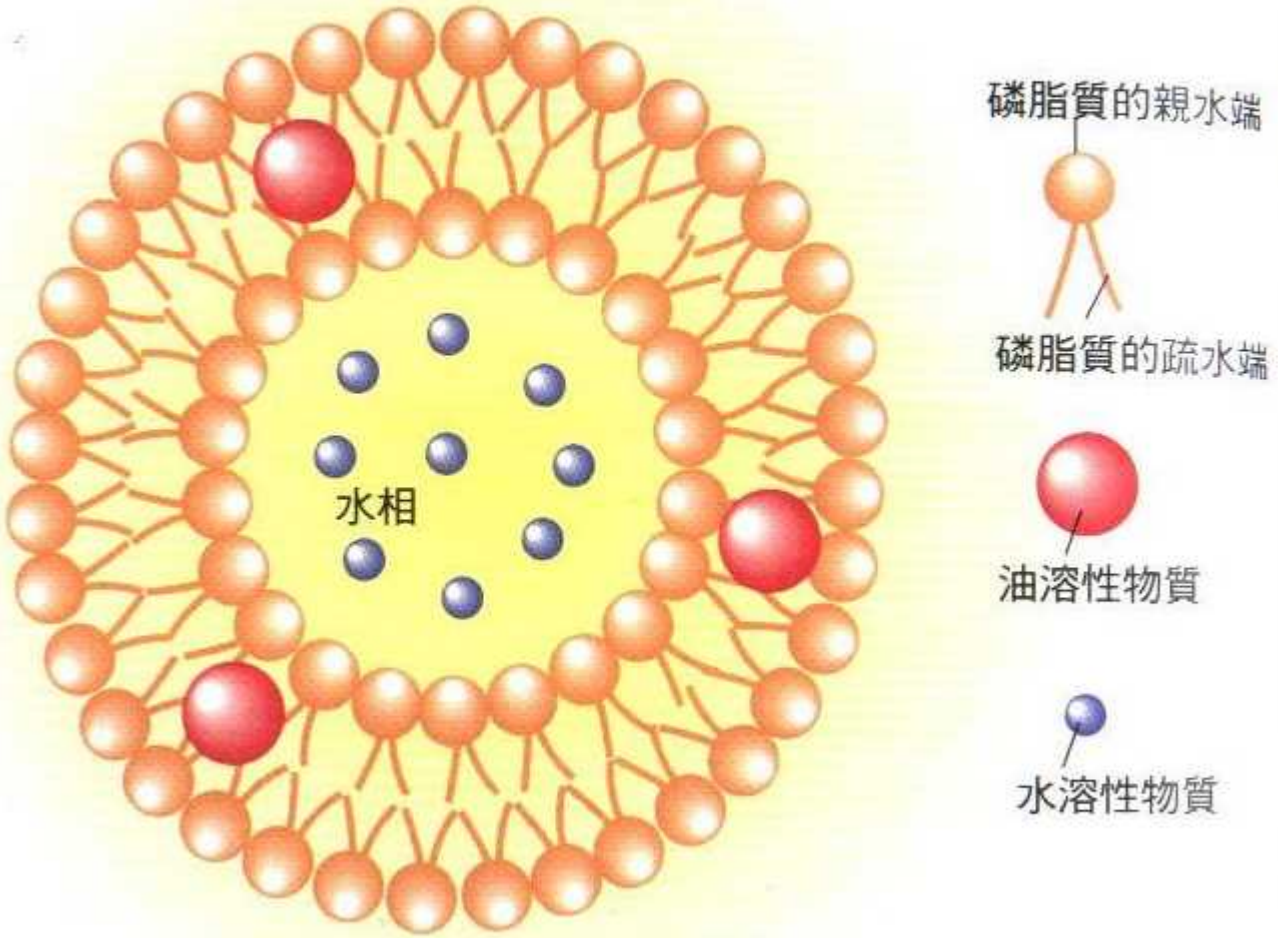
Triglycerides form large spherical fat droplets in the cell cytoplasm.



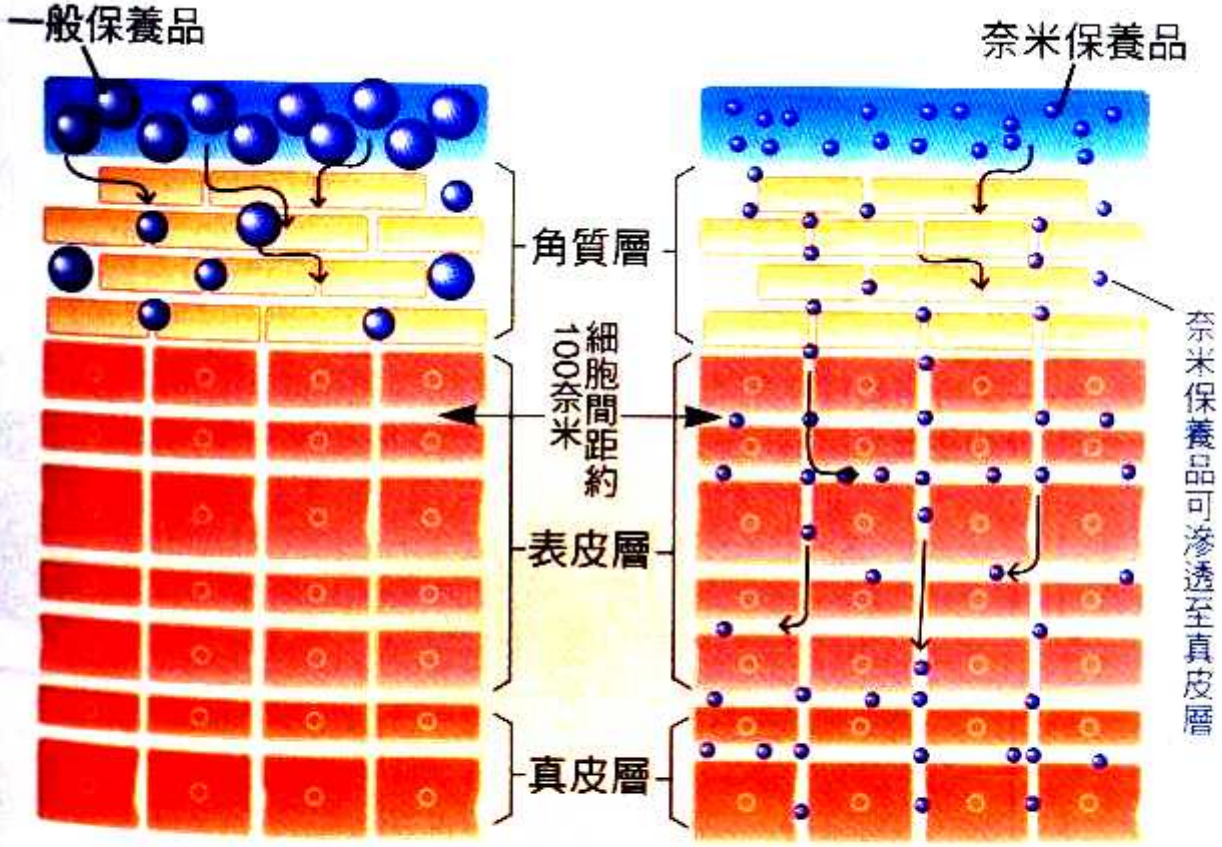
Phospholipids and glycolipids form self-sealing lipid bilayers that are the basis for all cellular membranes.



微脂粒的結構

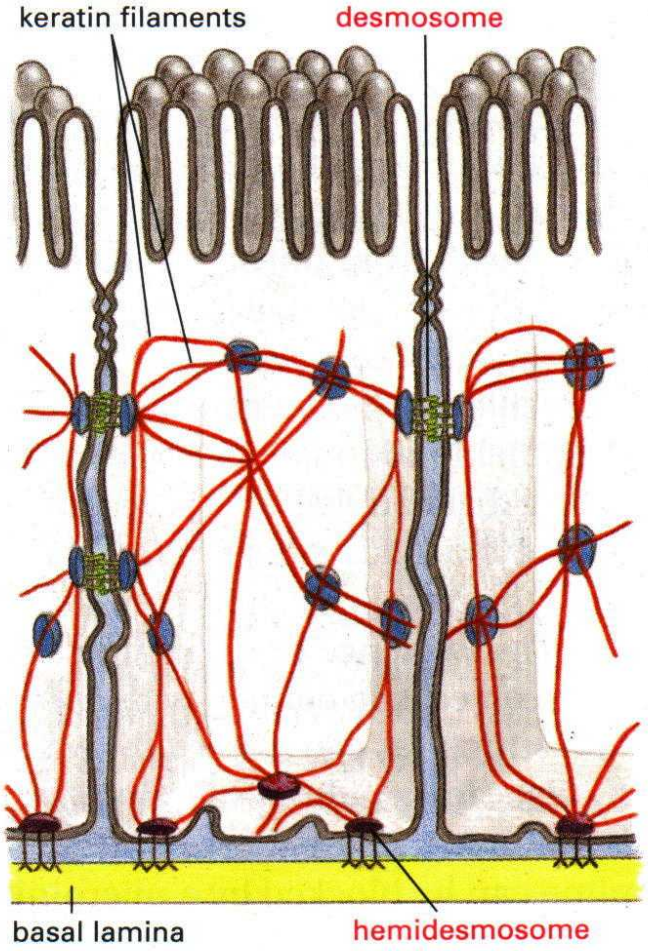


一般保養品 vs. 奈米保養品



一般保養品粒子（約數百至數千奈米）

奈米微脂粒（約20～100奈米）



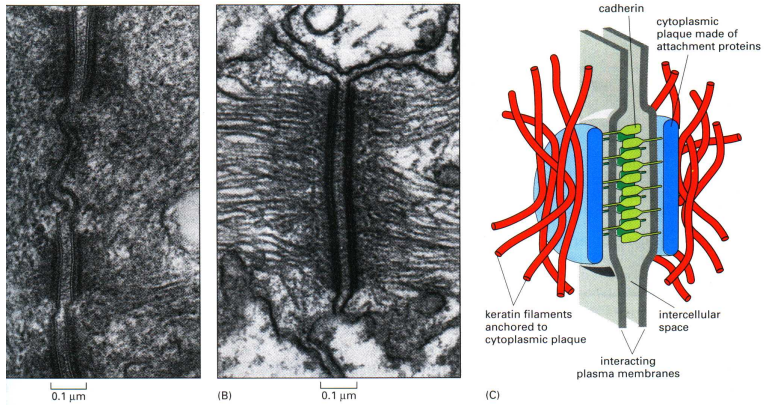


Figure 19–12 **Desmosomes.** (A) An electron micrograph of three desmosomes between two epithelial cells in the intestine of a rat. (B) An electron micrograph of a single desmosome between two epidermal cells in a developing newt, showing clearly the attachment of intermediate filaments. (C) A schematic drawing of a desmosome. On the cytoplasmic surface of each interacting plasma membrane is a dense plaque composed of a mixture of intracellular attachment proteins (including *plakoglobin* and *desmoplakins*). Each plaque is associated with a thick network of keratin filaments, which are attached to the surface of the plaque. Transmembrane linker proteins, which belong to the cadherin family of cell-cell adhesion molecules, bind to the plaques and interact through their extracellular domains to hold the adjacent membranes together by a Ca^{2+}-dependent mechanism. (A, from N.B. Gilula, in Cell Communication [R.P. Cox, ed.], pp. 1–29, New York: Wiley, 1974. Reprinted by permission of John Wiley & Sons, Inc.; B, from D.E. Kelly, *J. Cell Biol.* 28:51–59, 1966, by copyright permission of the Rockefeller University Press.)

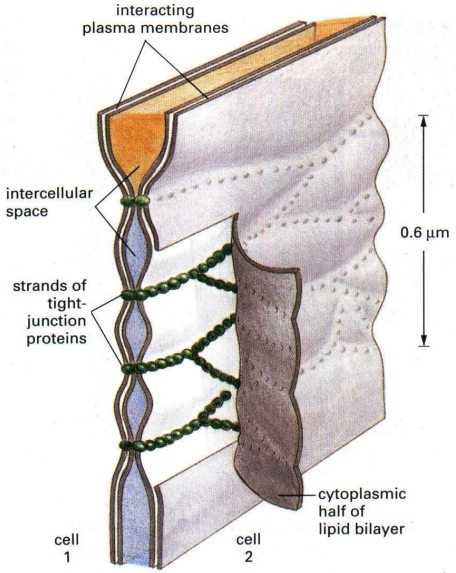
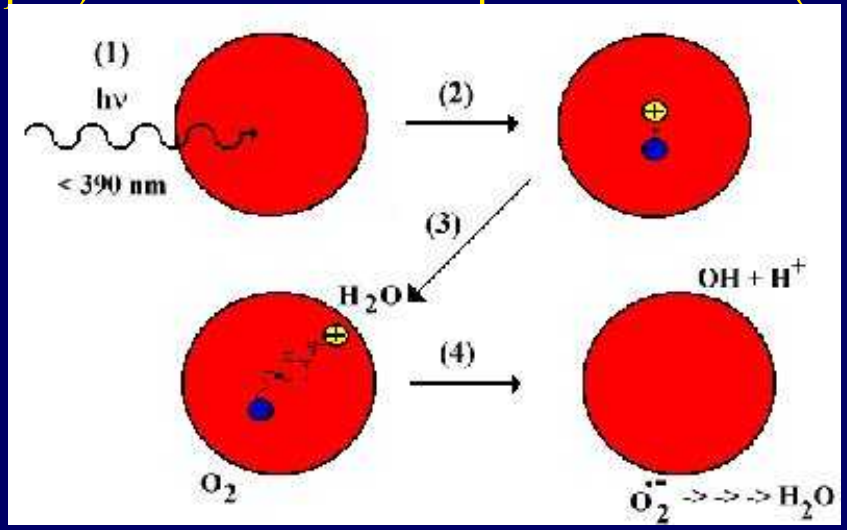


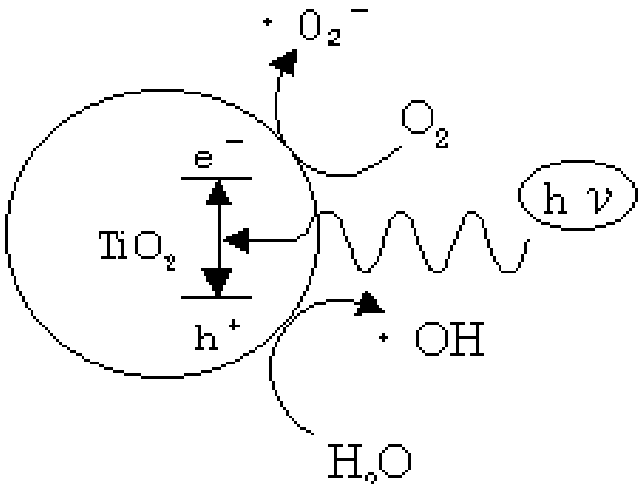
Figure 19–5 **A current model of a tight junction.** It is postulated that the sealing strands that hold adjacent plasma membranes together are formed by continuous strands of transmembrane junctional proteins, which make contact across the intercellular space and create a seal. In this schematic the cytoplasmic half of one membrane has been peeled back by the artist to expose the protein strands. Two peripheral proteins associated with the cytoplasmic side of tight junctions have been characterized, but the putative transmembrane protein has not yet been identified.

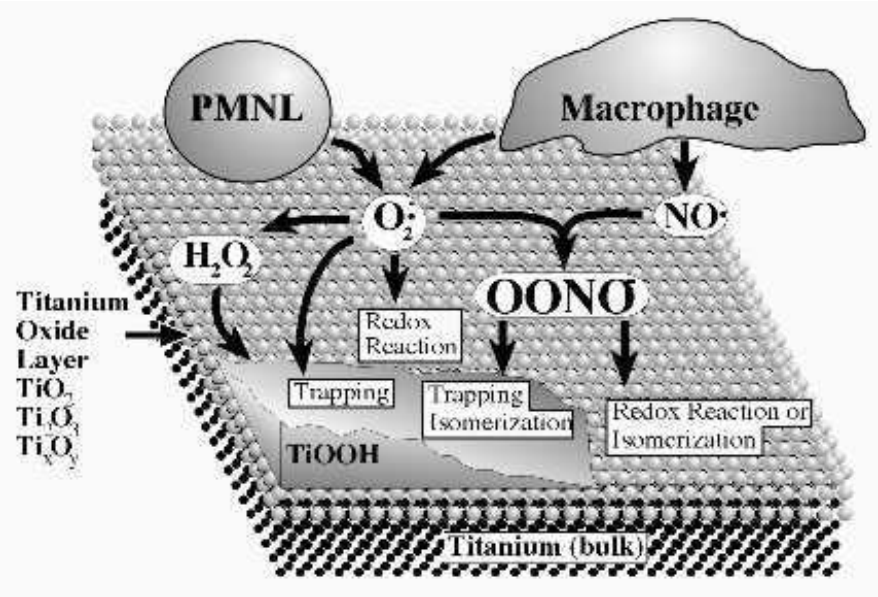
The importance of nano-particles lies in
→inherently large surface-to-volume ratio relative to that of larger particles

When UV light of wavelength < 390 nm is absorbed by TiO_2, (step 1) an electron/hole pair is formed (step 2):



Scheme showing the photochemical generation of superoxide and hydroxyl radicals at the surface of TiO_2

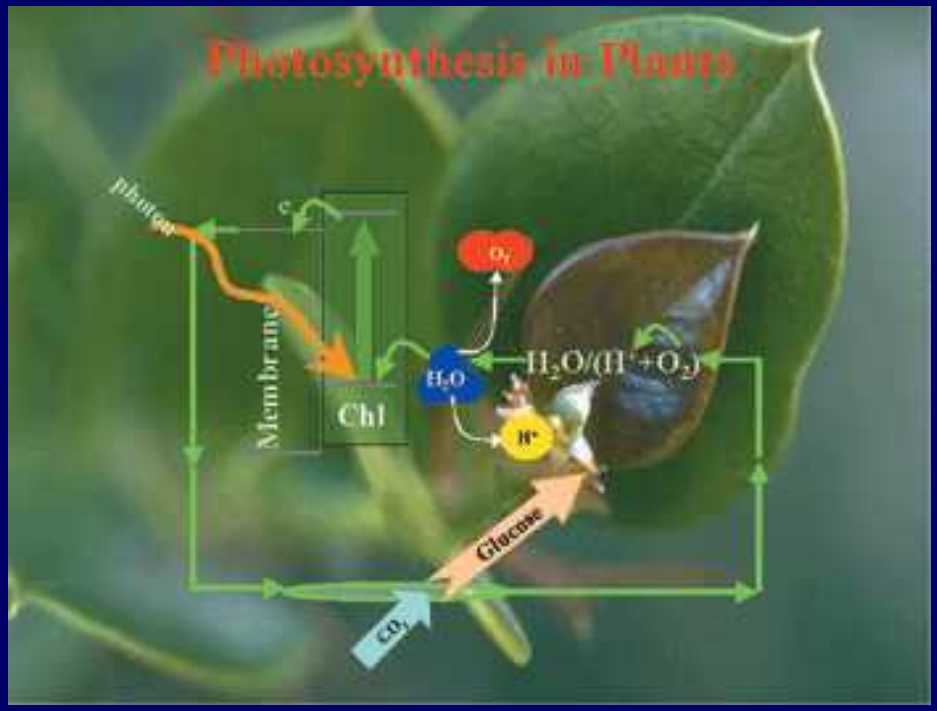

$\cdot O_2^-$
O_2
e^-
TiO_2
h^+
$h\nu$
$\cdot OH$
H_2O

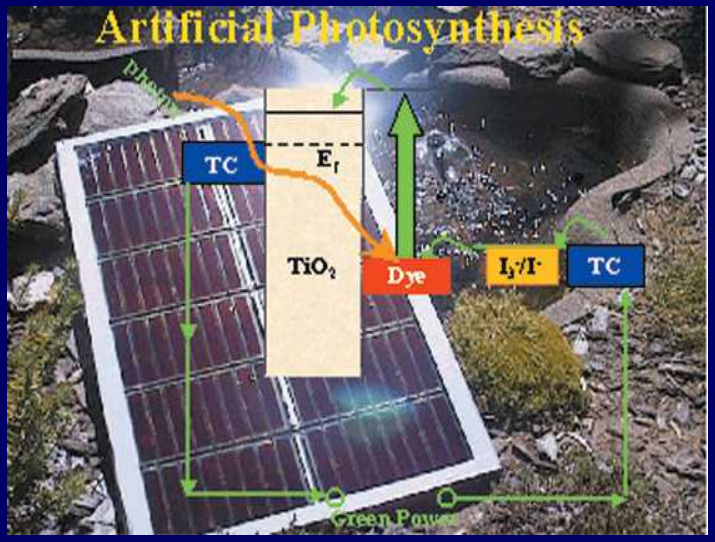

PMNL
Macrophage
$O_2^{\cdot}$
NO·
H_2O_2
OONO
Titanium
Oxide
Layer
TiO_2
Ti_xO_y
Ti_xO_y
Redox
Reaction
Trapping
Trapping
Isomerization
Redox Reaction or
Isomerization
TiOOH
Titanium (bulk)

Power from Nature

Photosynthesis

Plant leaves are tiny factories in which sunlight absorbed by chlorophyll converts carbon dioxide gas and water into carbohydrates and oxygen, thus providing for the energy requirements of the plant.



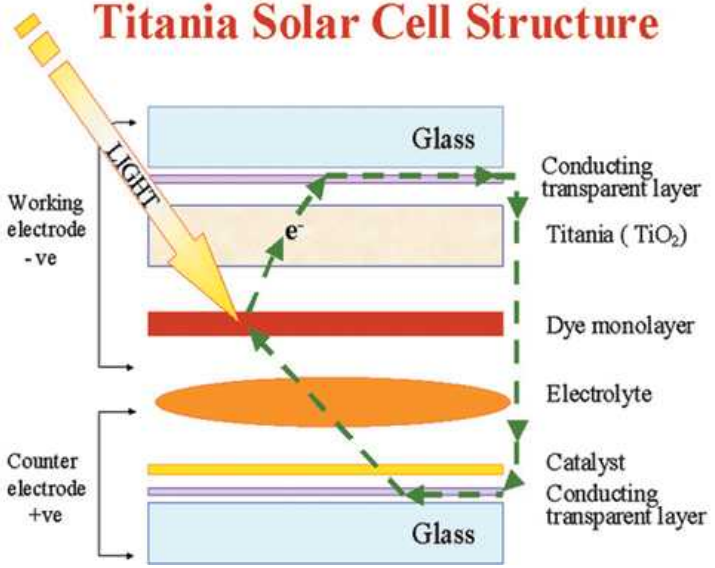


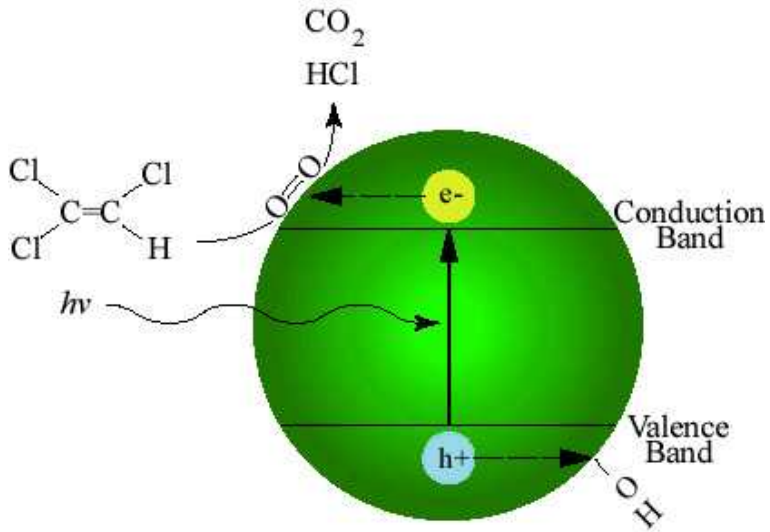
Artificial Photosynthesis

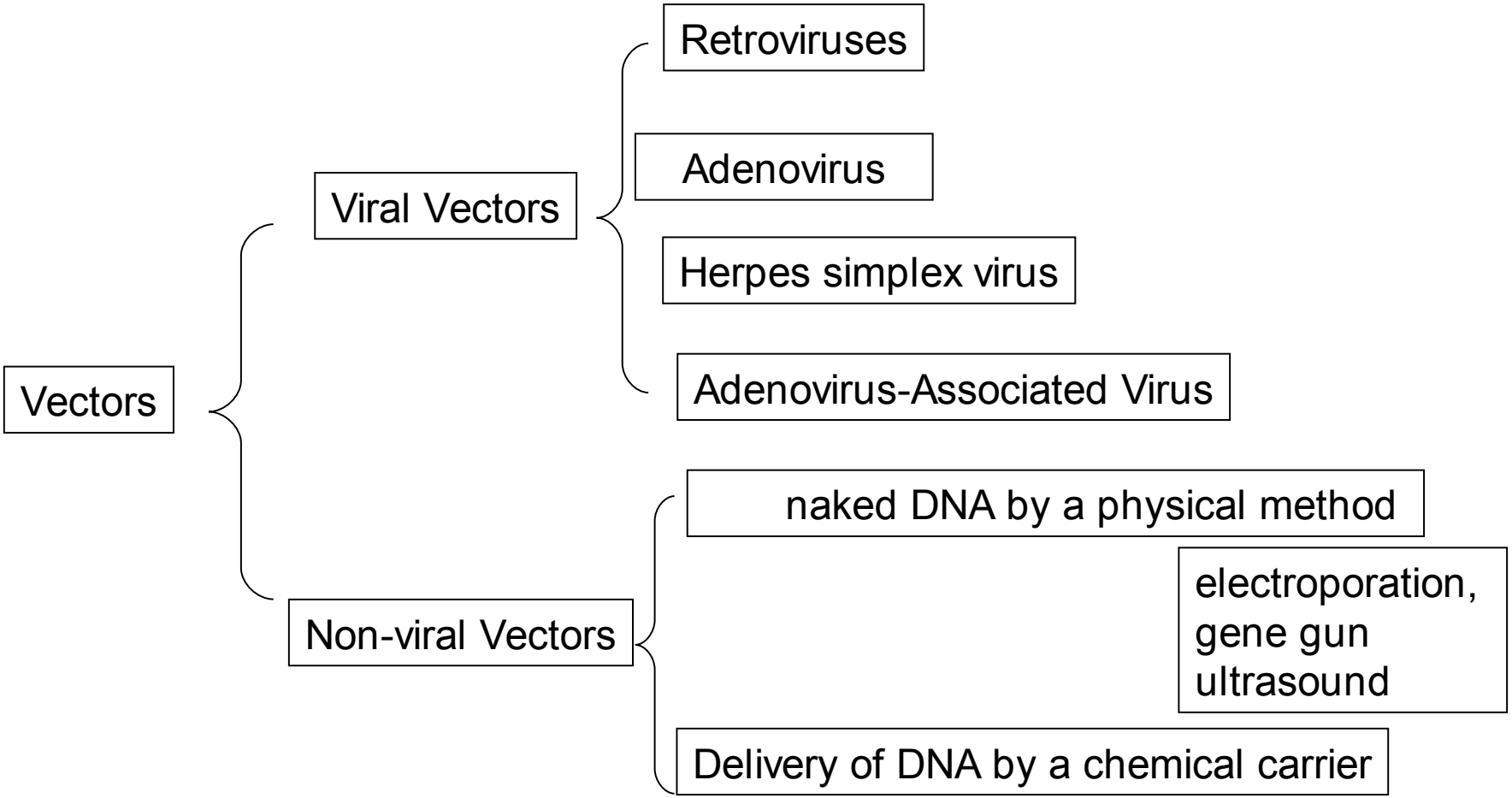
Artificial photosynthesis is based on the concept of a dye analogous to chlorophyll absorbing light and thus generating electrons which enter the conduction band of a high surface area semiconductor film.

This is a two step photovoltaic process, unlike the one step process of conventional PV.

Titania Solar Cell Structure



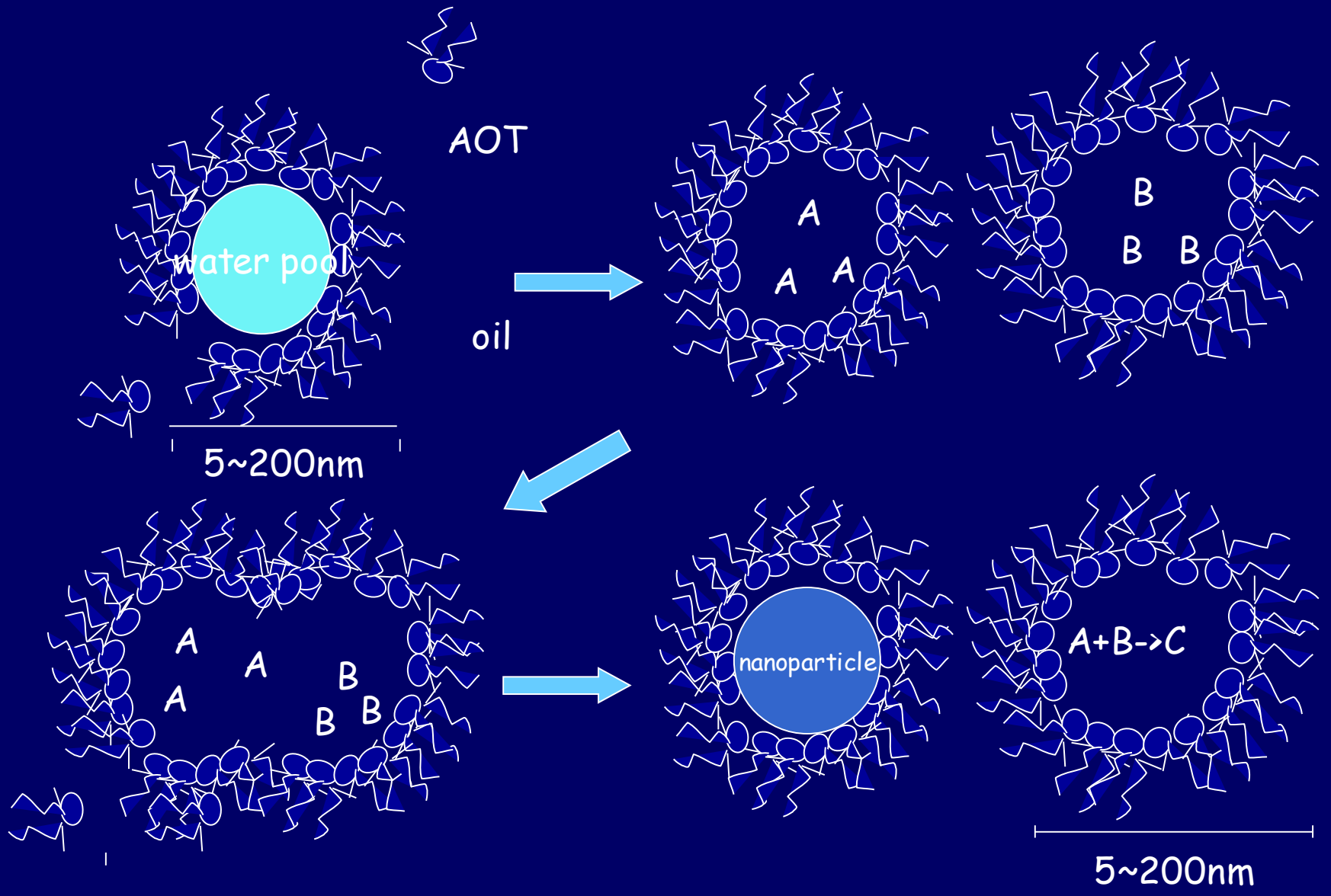




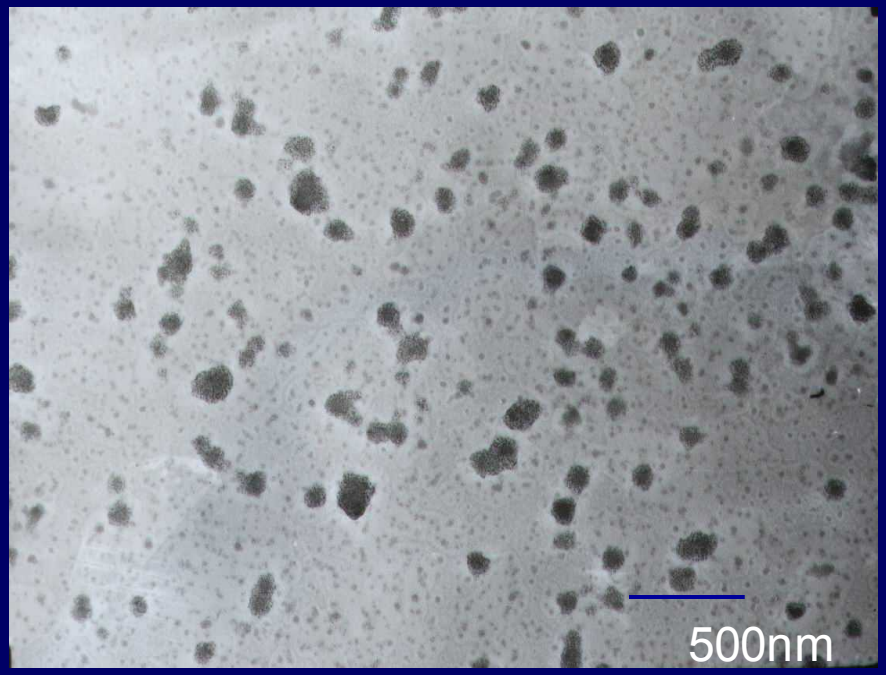
（1） polycations ,cationic polymers and cationic lipids
Ex:polylysine polyethylenimine ,dendrimers and chitosan or liposomal preparations containing cationic lipids
（2） calcium phosphate, DEAE-dextran

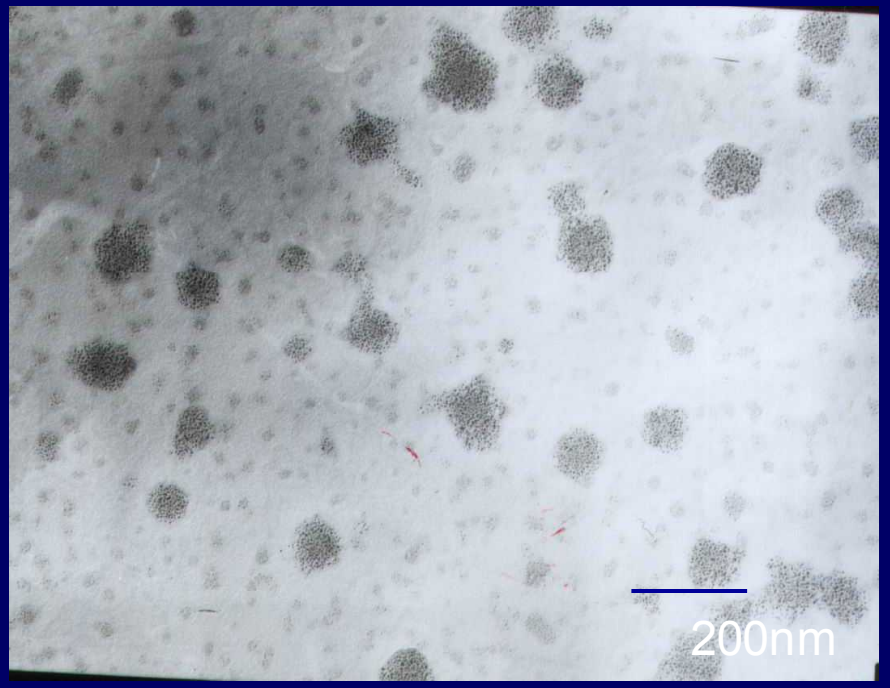
載體	反轉錄病毒	腺病毒	腺相關病毒	皰疹病毒	脂質體	裸 DNA	物理方法
插入大小	<8(kb)	~8(kb)	<7.5(kb)	<4(kb)	>20(kb)	>20(kb)	-
轉殖效率	低	高	高	低	變數	變數	-
基因遞送效率	中等	高	中等	高	高	中等	-
穩定 VS 短暫	穩定	短暫	穩定	短暫	短暫	短暫	短暫或穩定
基因表現程度	變數	變數	變數	高	高	變數	變數
標定細胞	個別細胞	個別及非個別細胞	個別及非個別細胞，所有組織型式	個別及非個別細胞，多數組織型式	個別及非個別細胞	個別及非個別細胞	個別及非個別細胞
免疫性	低	高	低	低	低	低	低
載體製備	複雜	簡單	複雜	簡單	簡單	簡單	簡單
主要優點	嵌入穩定，穩定的長期表現，缺少病毒蛋白	體內直接感染，高力價，轉殖的宿主及細胞範圍廣	幾乎感染所有組織，非常安全，尺寸小有利於擴散及分布在腦內	多種基因的大基因尺寸，宿主範圍廣， DNA 插入的容量高	容易製備，成本效益 安全	容易製備，成本效益 安全	所有細胞中基因均勻表現
主要缺點	需在有絲分裂時嵌入	觸發宿主免疫反應	有效治療基因小	原始病毒可能導致疾病	短暫表現，劑量限制，毒性	短暫表現	短暫表現

Microemulsion processes

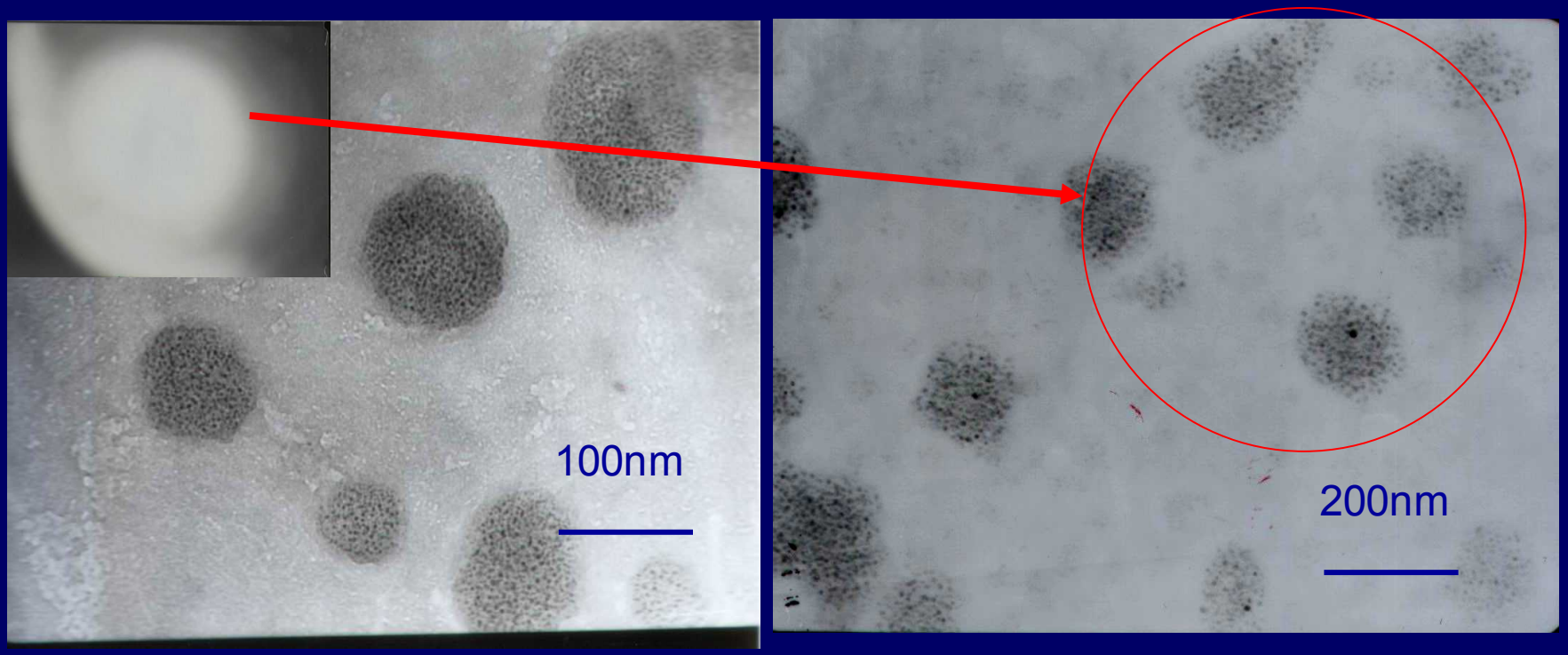


TEM 20000X ,50000X

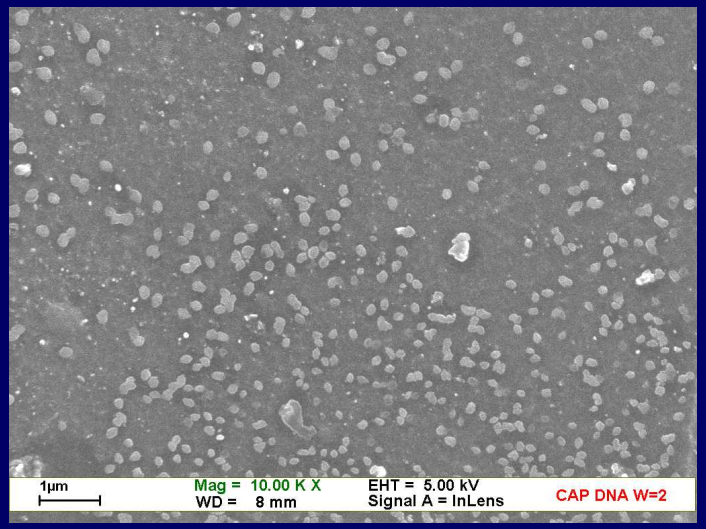


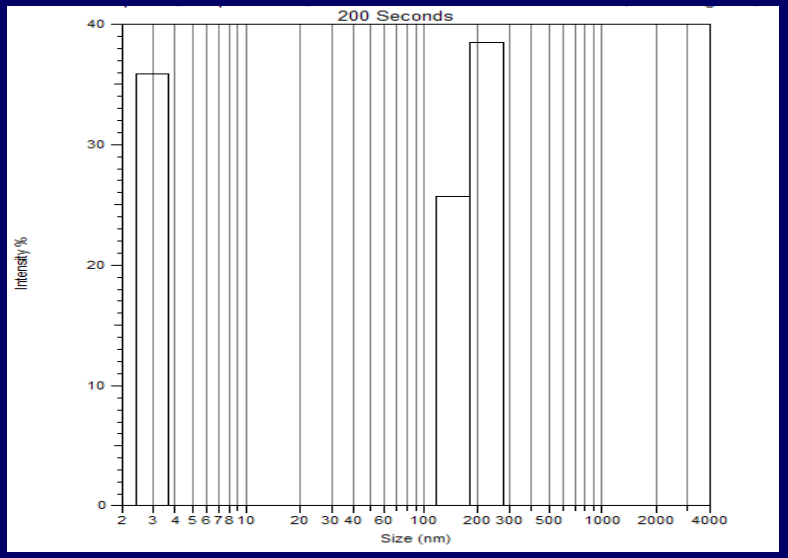


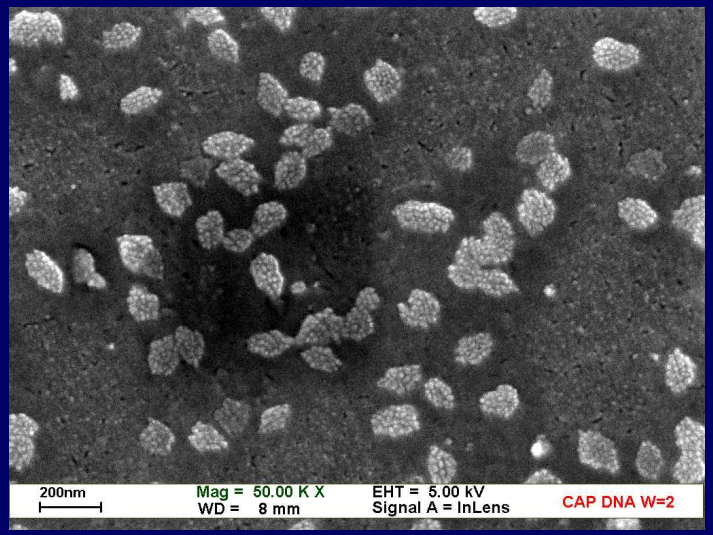
TEM 100000X and 50000X



Determination of size of the nanoparticles by dynamic light scattering and FE-SEM







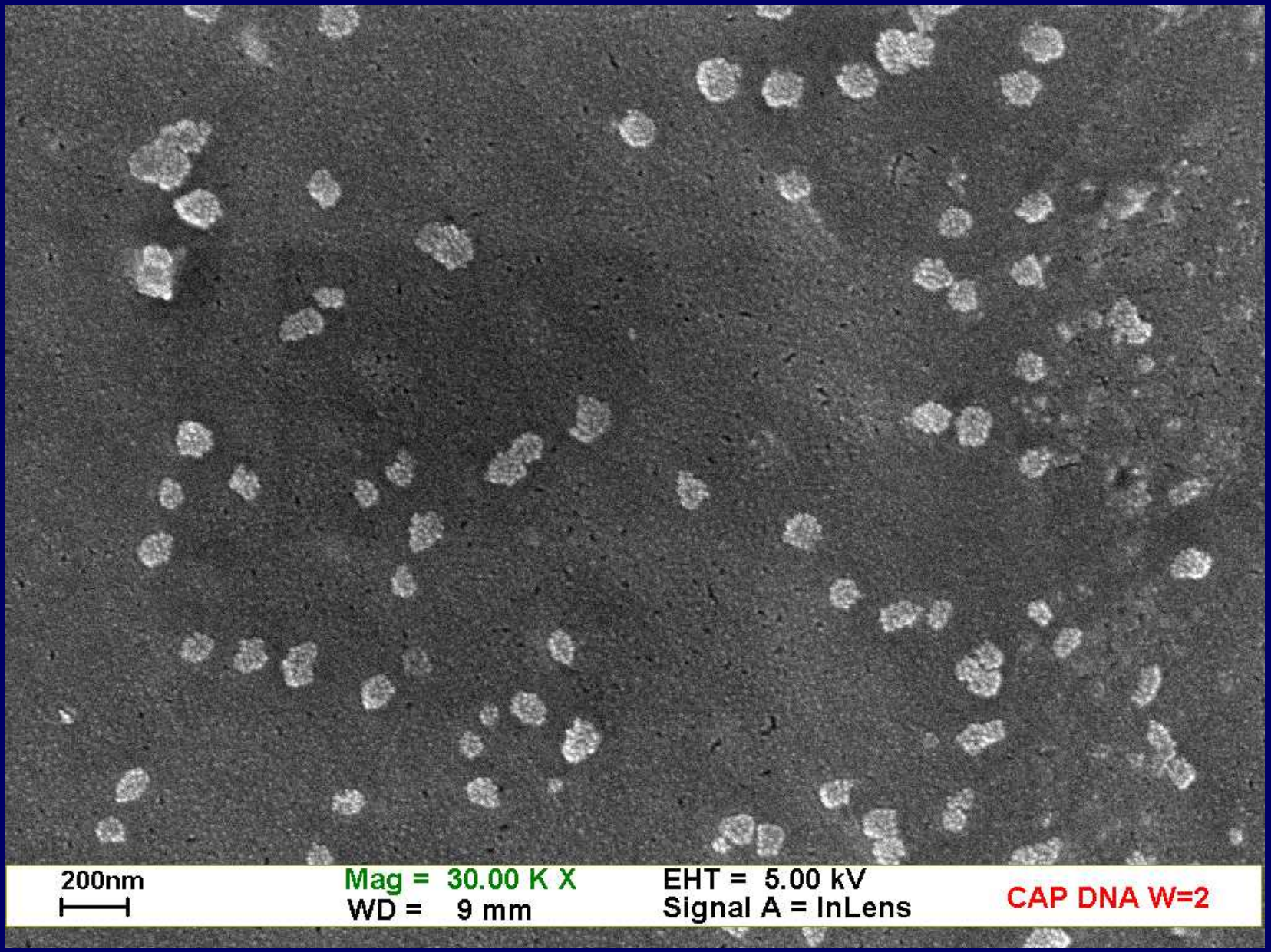
Run Parameters:

Temperature: 25.0°C Refractive Index: 1.333

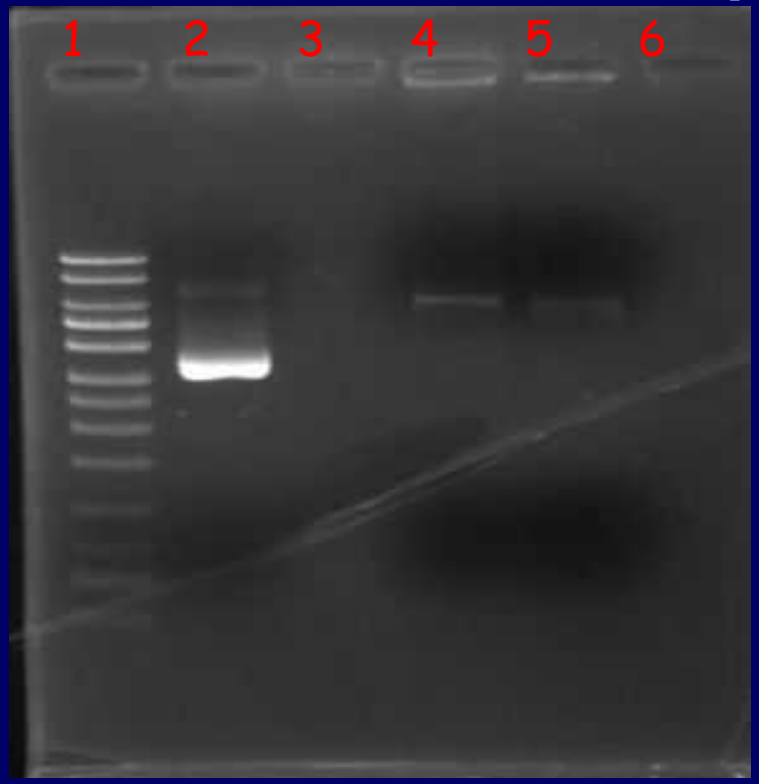
Date: 17-Feb-04 Viscosity: 0.890 centipoise

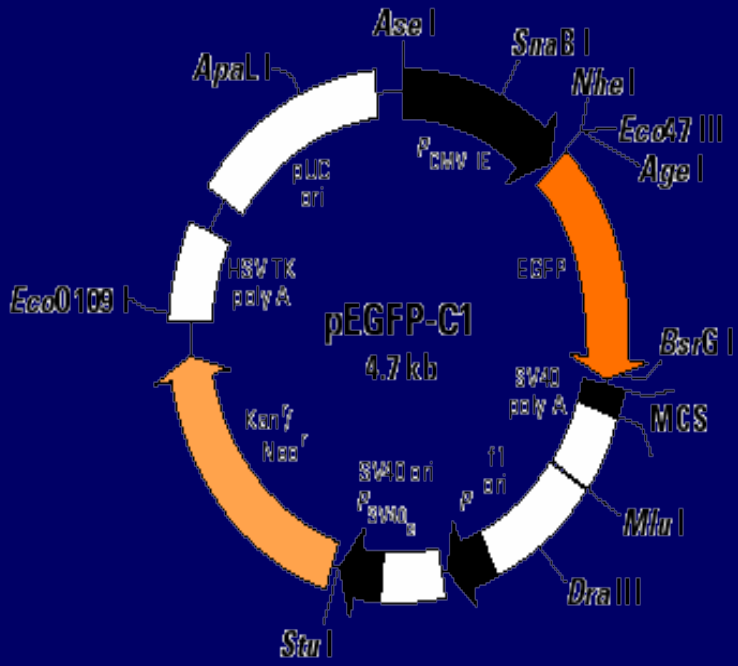
Time: 07:07:50 PM

Angle	Mean Dia. (nm)	Std. Dev. (nm)	Polydispersity Index	Run Time (sec)
90.0°	50.6	Broad	3.711	200
Run Avg:	50.6	24.5	3.711	


200nm
Mag = 30.00 K X
WD = 9 mm
EHT = 5.00 kV
Signal A = InLens
CAP DNA W=2

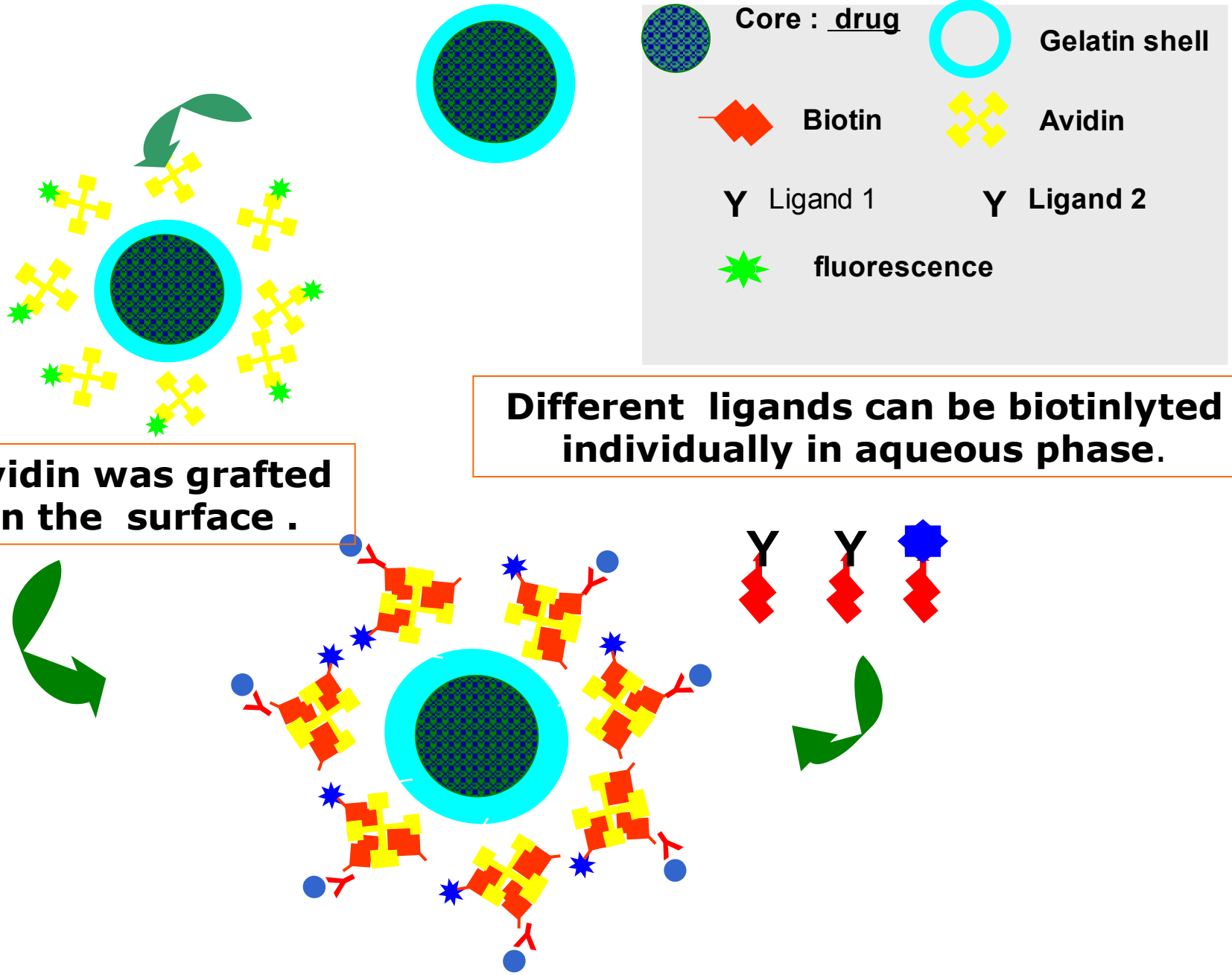
Agarose (1%) gel electrophoresis of free and entrapped pEGFP DNA

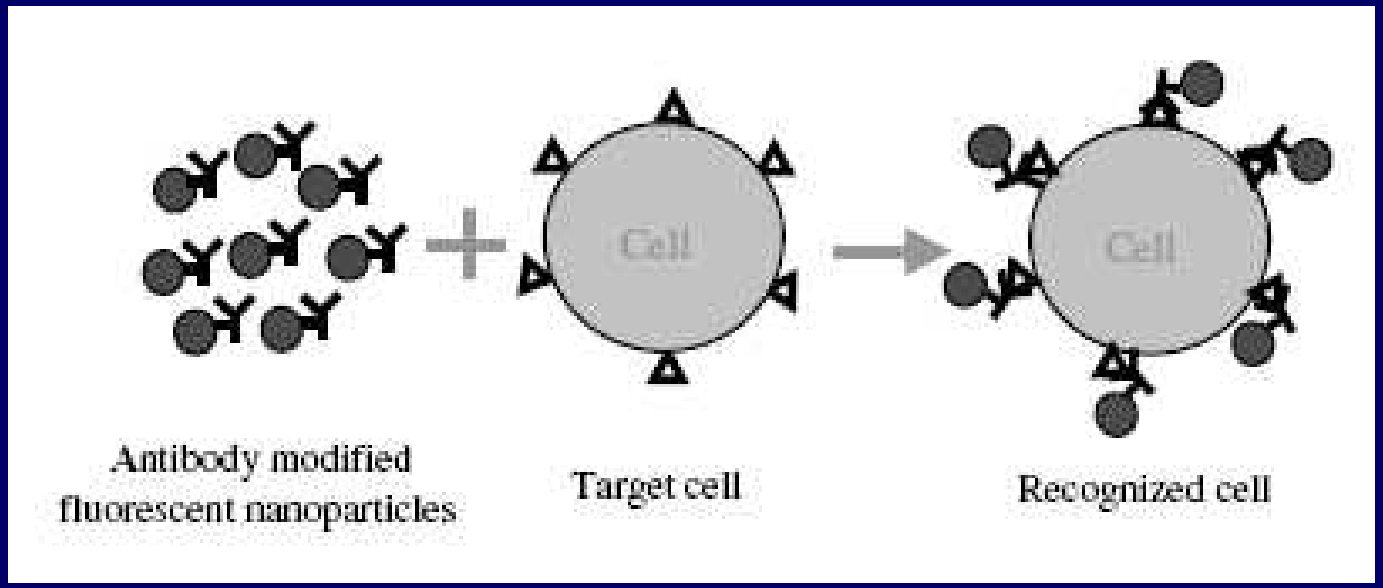




naker,
ake pEGFP,
EGFP with DNaseI,
CaP/DNA complex
CaP/DNA complex with DNaseI

Gelatin nanoparticle preparation (with or without drugs)





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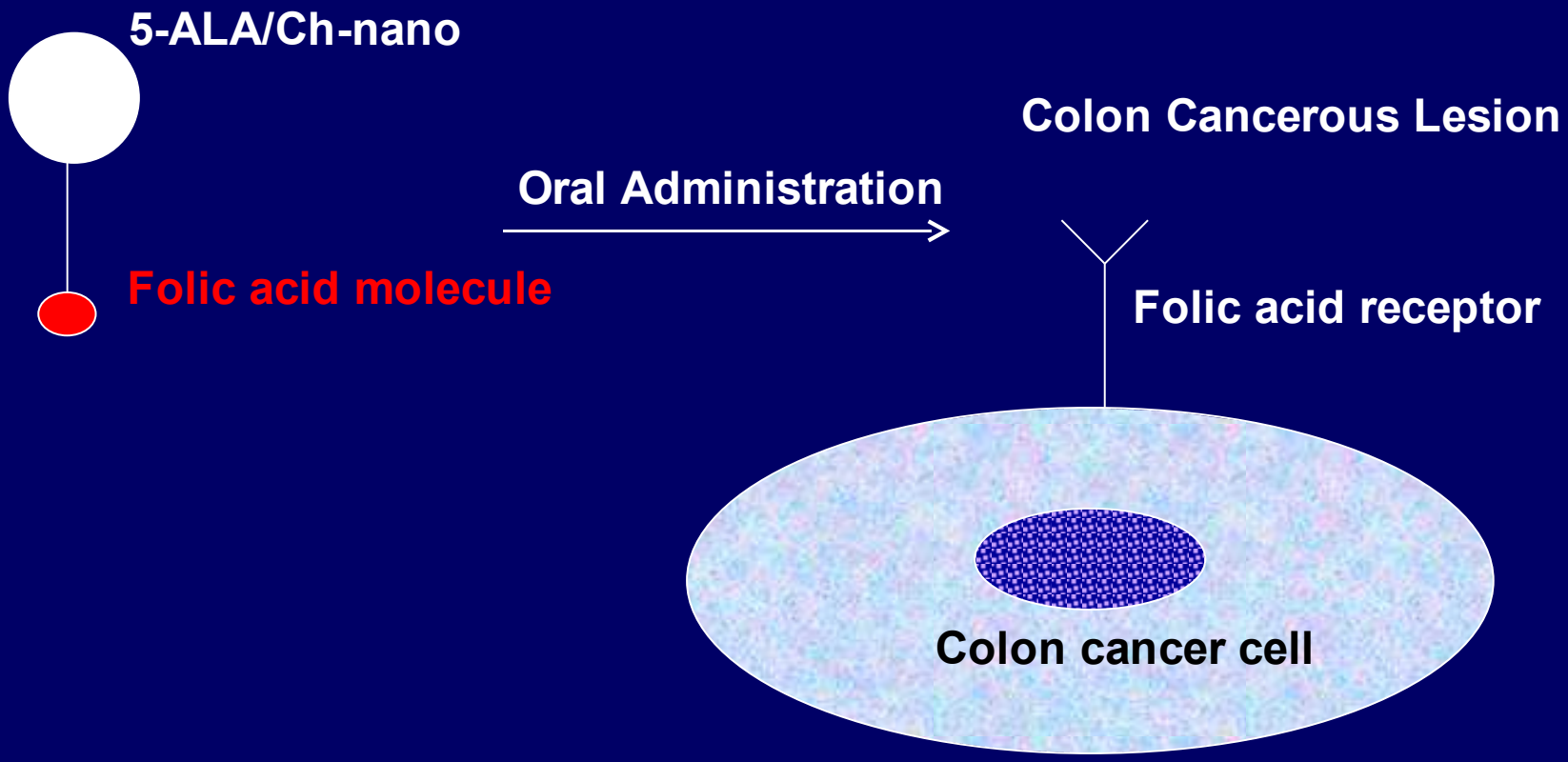
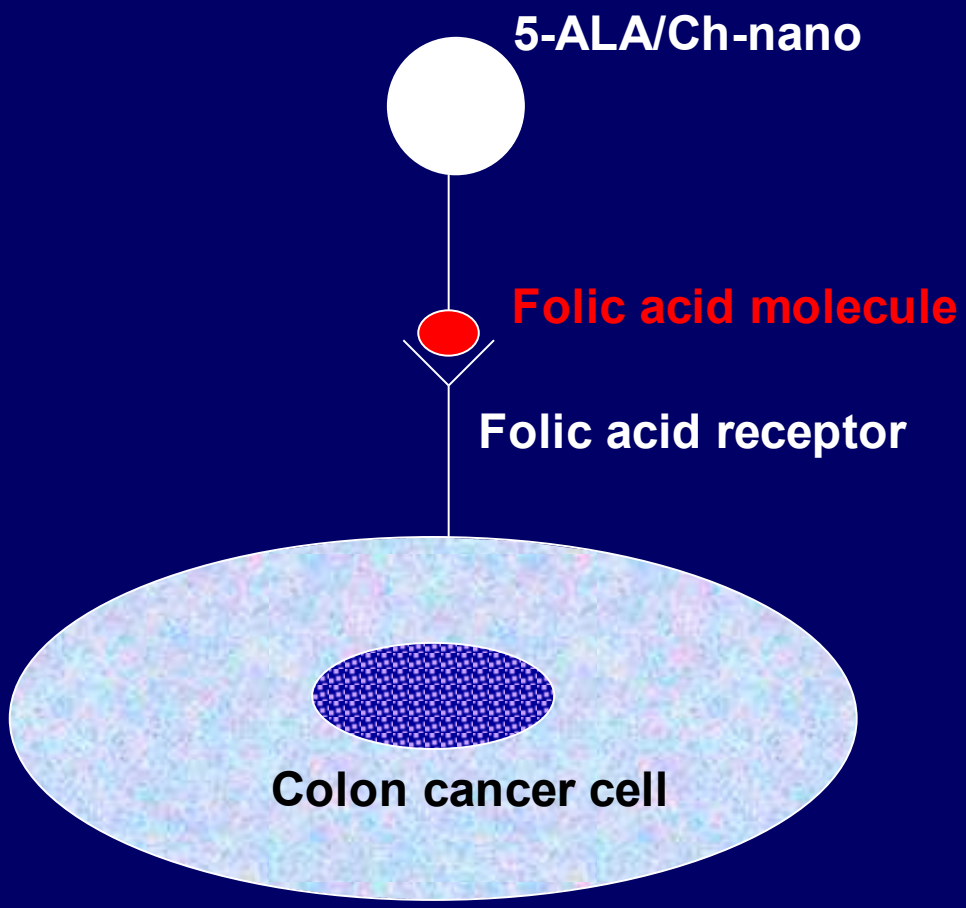
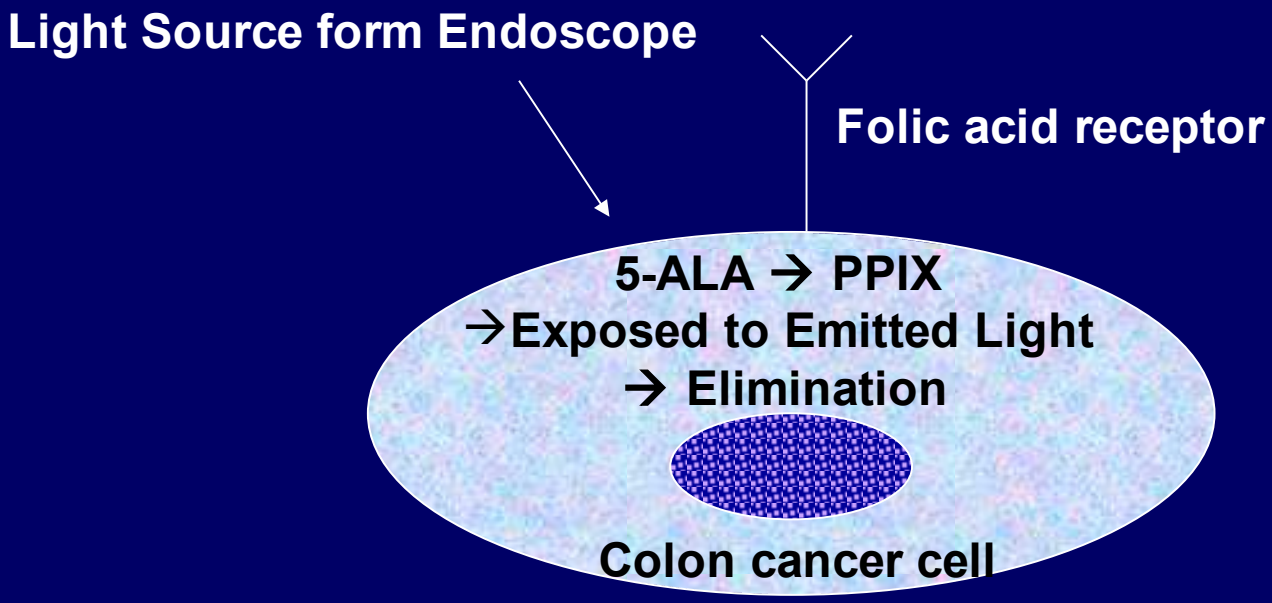
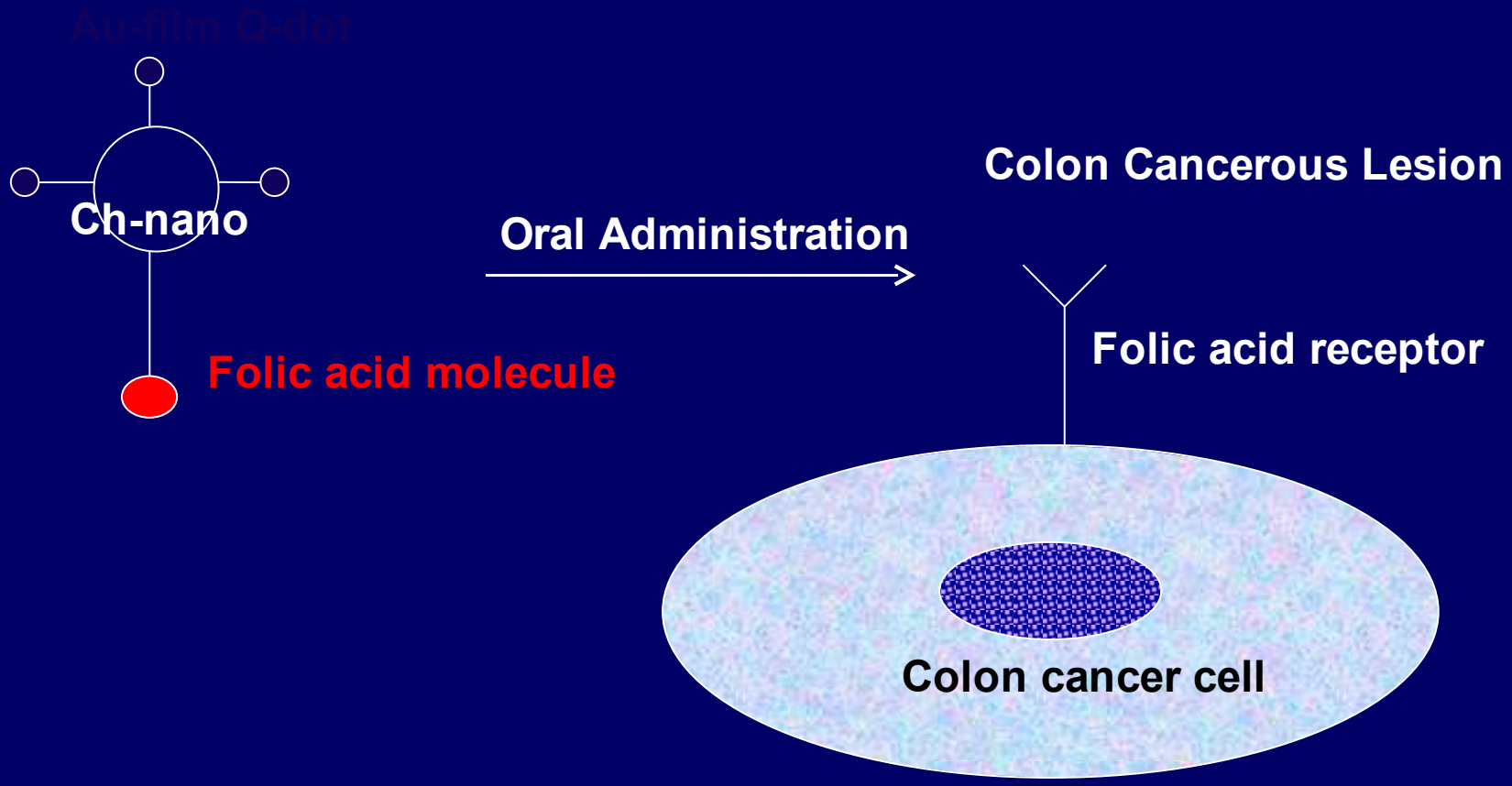
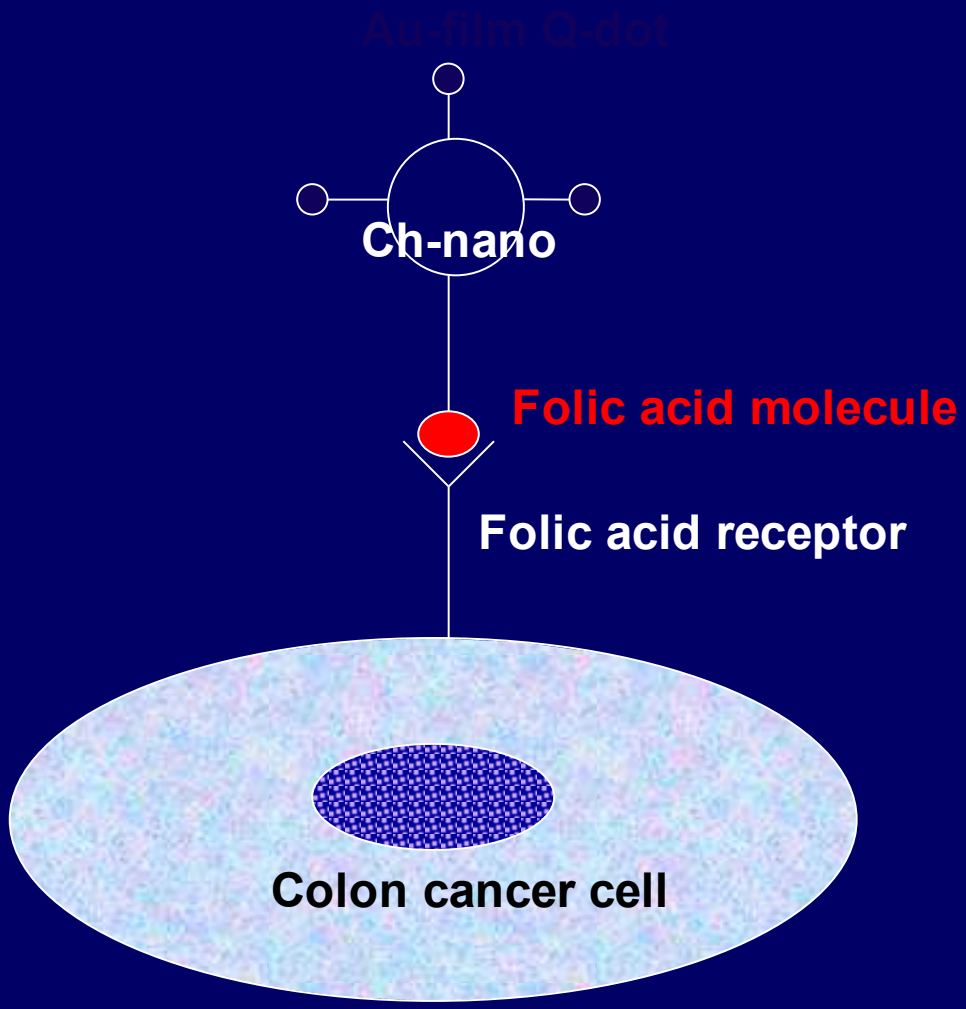
www.aspbs.com/enn

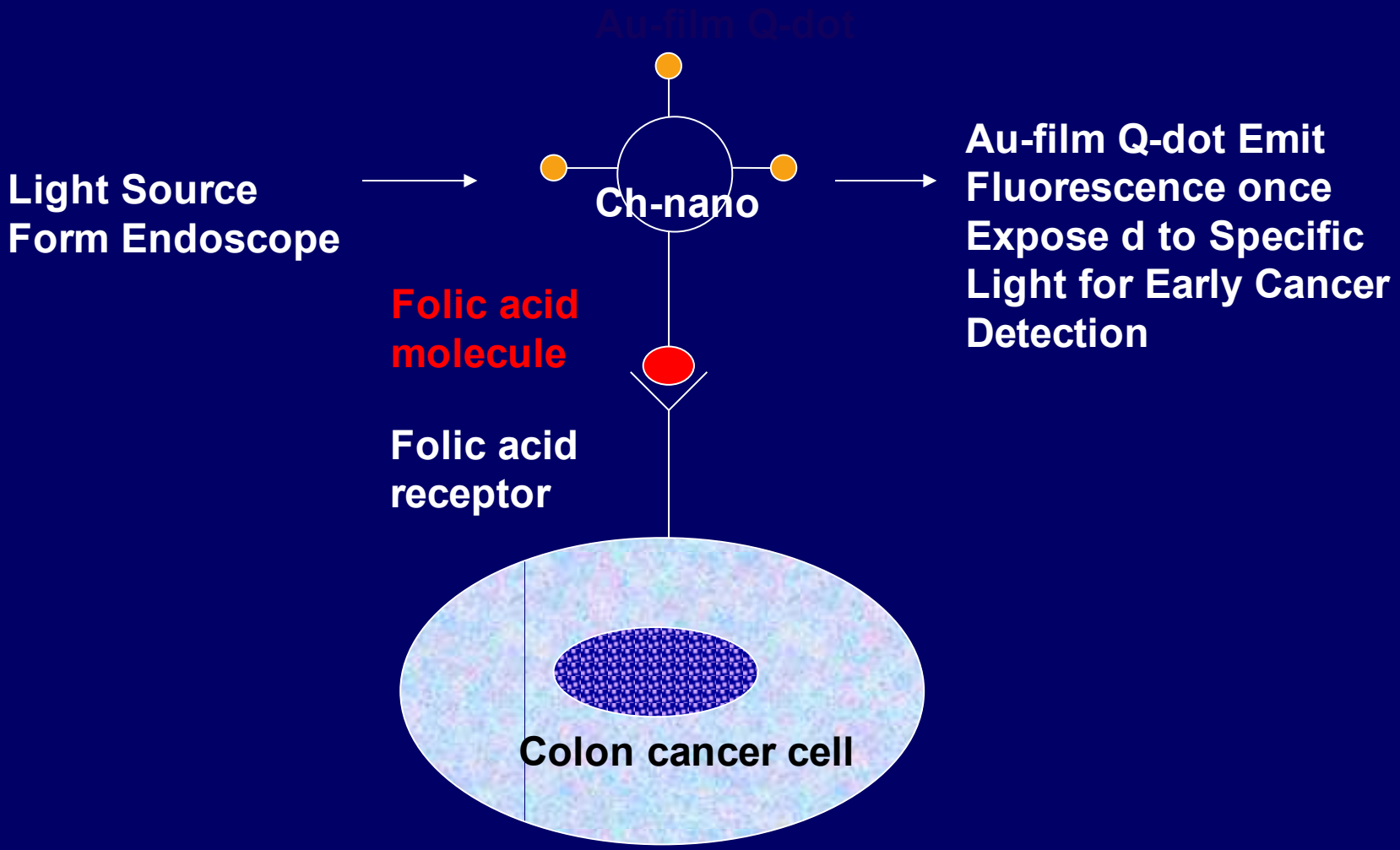

5-ALA/Ch-nano
Folic acid molecule
Oral Administration
Colon Cancerous Lesion
Folic acid receptor
Colon cancer cell


5-ALA/Ch-nano
Folic acid molecule
Folic acid receptor
Colon cancer cell


Light Source form Endoscope
Folic acid receptor
5-ALA → PPIX
→Exposed to Emitted Light
→ Elimination
Colon cancer cell


Au-film Q-dot
Ch-nano
Folic acid molecule
Oral Administration
Colon Cancerous Lesion
Folic acid receptor
Colon cancer cell


Au-film Q-dot
Ch-nano
Folic acid molecule
Folic acid receptor
Colon cancer cell

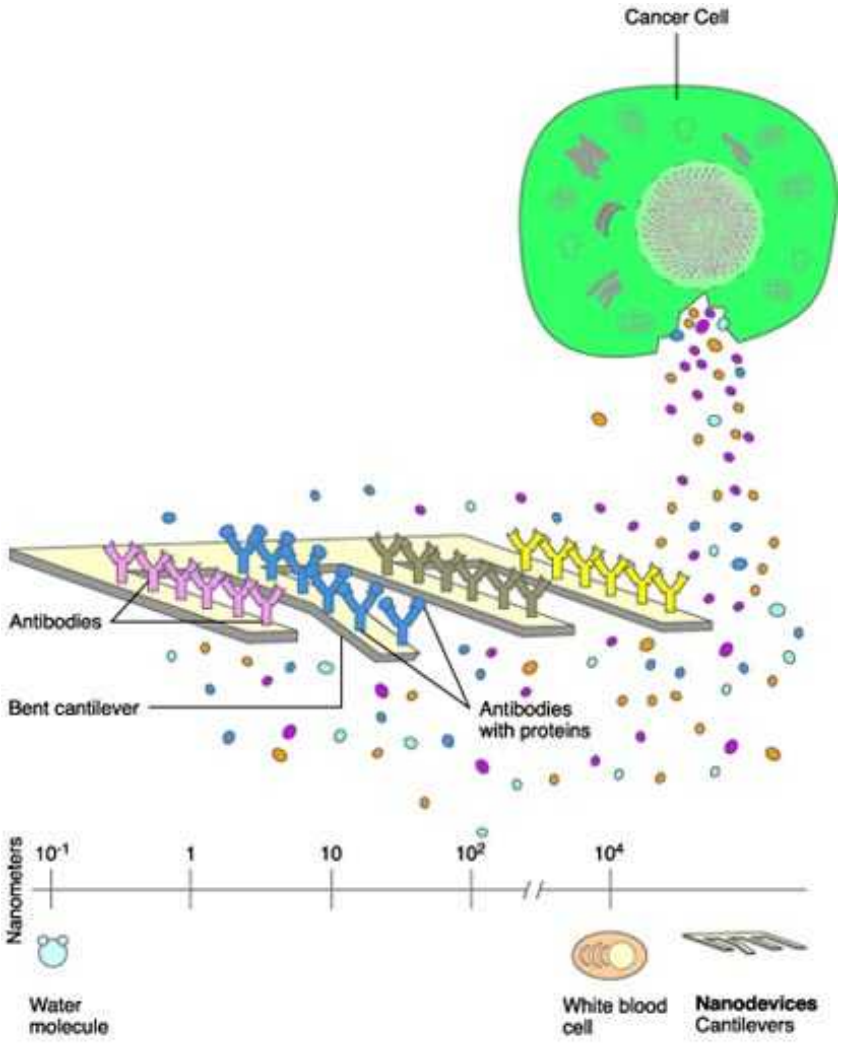

Au-film Q-dot
Light Source
Form Endoscope
Ch-nano
Au-film Q-dot Emit
Fluorescence once
Expose d to Specific
Light for Early Cancer
Detection
Folic acid
molecule
Folic acid
receptor
Colon cancer cell

Internal examination using tiny swallowed camera

By Michael Seaforth

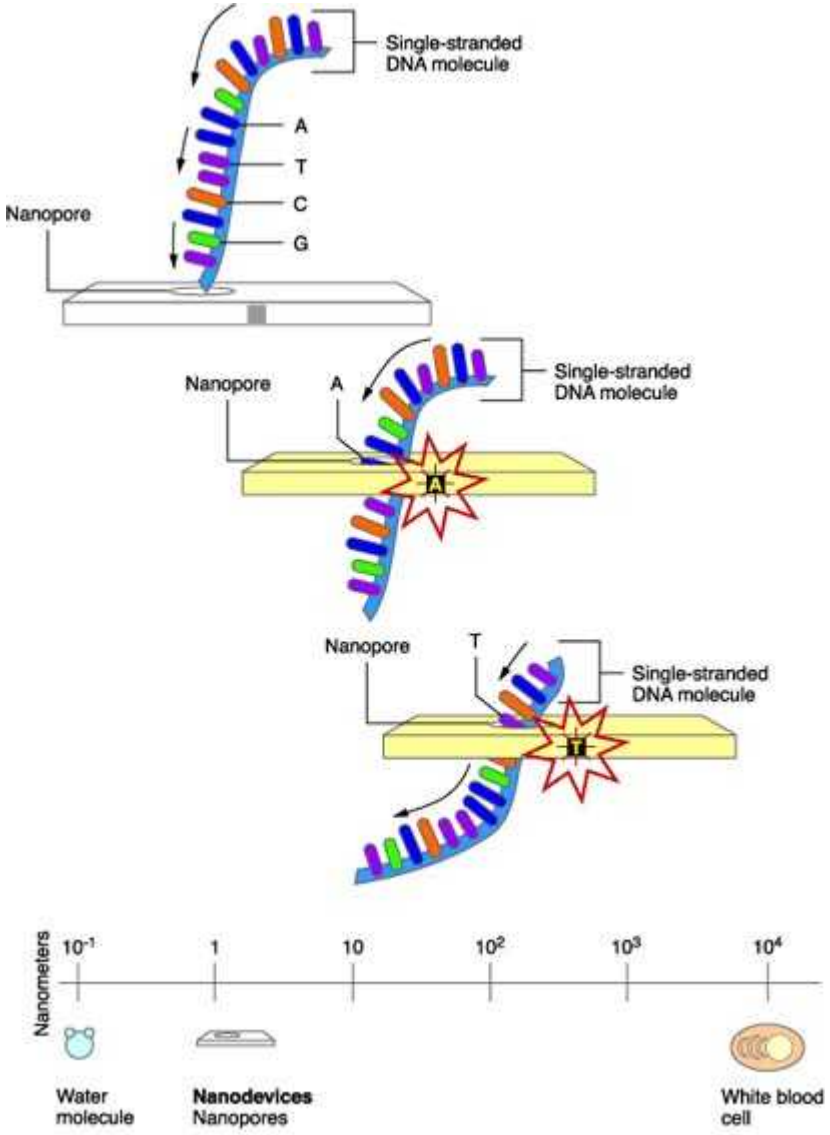
Currently, the easiest way to obtain a picture of someone's stomach or small intestines is to insert an endoscope attached to fiber optic cables through the person's mouth and extend it down to the area of interest. However, a much simpler procedure is undergoing clinical trials. **Given® Imaging** has developed a unique method of peering inside even the hard to reach areas of the small intestine that promises to be simple to implement and virtually painless.

The procedure requires the patient to swallow a tiny capsule that incorporates a light source, miniature color video camera, battery, antenna and radio transmitter. As the capsule moves through the body, it transmits a signal to tiny antennas attached to the patient' skin. The images are stored in a device attached to the patient's belt for examination later by a doctor on a medical workstation. The capsule is expelled naturally from the body in 24 to 48 hours. A picture of the capsule, courtesy of Given® Imaging, is shown above and more information is available at: http://www.givenimaging.com



Cantilevers can make cancer tests faster and more efficient

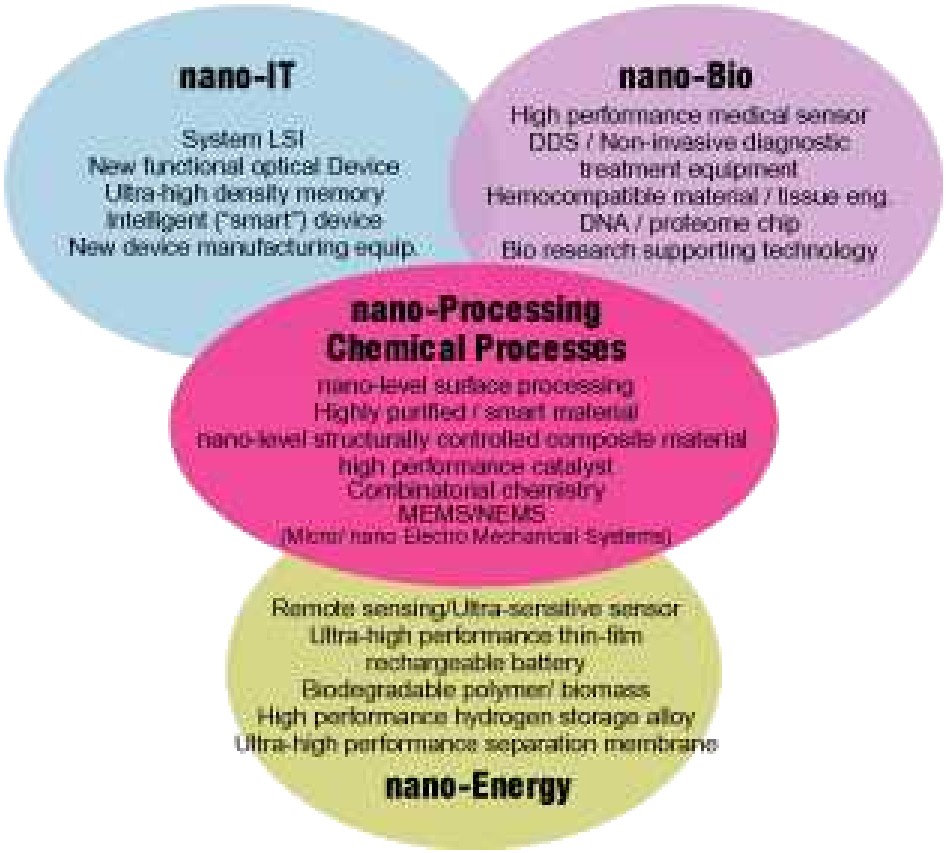
One nanodevice that can improve cancer detection and diagnosis is the cantilever. These tiny levers, which are anchored at one end, can be engineered to bind to molecules that represent some of the changes associated with cancer. They may bind to altered DNA sequences or proteins that are present in certain types of cancer. When these molecules bind to the cantilevers, surface tension changes, causing the cantilevers to bend. By monitoring the bending of the cantilevers, scientists can tell whether molecules are present. Scientists hope this property will prove effective when cancer-associated molecules are present--even in very low concentrations--making cantilevers a potential tool for detecting cancer in its early stages.



Nanopores

Another interesting nanodevice is the nanopore. Improved methods of reading the genetic code will help researchers detect errors in genes that may contribute to cancer. Scientists believe nanopores, tiny holes that allow DNA to pass through one strand at a time, will make DNA sequencing more efficient. As DNA passes through a nanopore, scientists can monitor the shape and electrical properties of each base, or letter, on the strand. Because these properties are unique for each of the four bases that make up the genetic code, scientists can use the passage of DNA through a nanopore to decipher the encoded information, including errors in the code known to be associated with cancer.

Prioritized Technological Fields for investment



Market Potential for nanotech Related Businesses:
27 trillion yen market in 2010 (Keidanren estimate)
Japanese Governmental Budget for R&D in nanotech:
65,200 MJPY(FY2002)