A nanotechnológia egészségügyi alkalmazásának jelenlegi helyzete a világban

Szebeni János

Bay Zoltán Nanotechnológiai Intézet,

Miskolc

Témák

- **A nanomedicina**
  - **Alapfogalmak, tudományos és gazdasági térnyerés**
  - **Jövőkép**
  - **Példák az alkalmazásra**
    - **Irányitott gyógyszertherápia**
      - **Liposzómák**
    - **Diagnosztikus képalkotó eljárások**
      - **Quantum dots**
      - **Fullerének**
- **A nanomedicina osztály konkrét munkái**
  - **Liposzómális gyógyszek (generikus Doxil)**
  - **Biokompatibilis mesterséges vér**

Nanomedicina

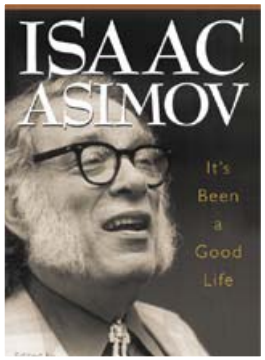
- **A nanotechnológia alkalmazása az orvosbiológiai és anyagtudományok integrációjával**
  - **Normális életműködések megismerésére**
  - **Betegségek jobb diagnosztizálására, megelőzésére**

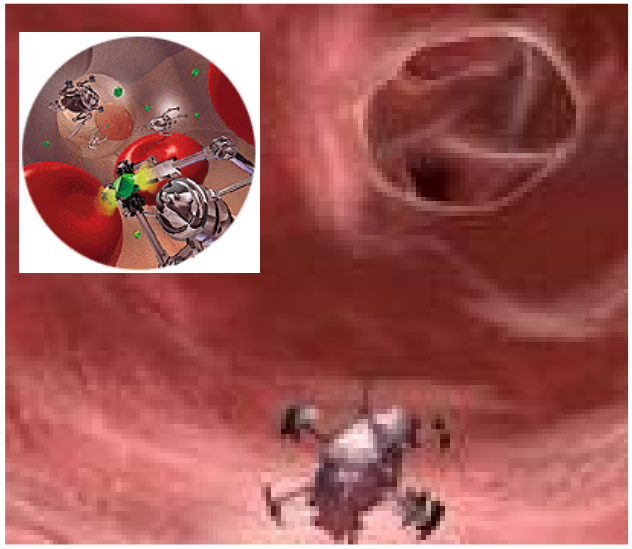
- **interdiszciplináritás -> intenziv fejlődés**

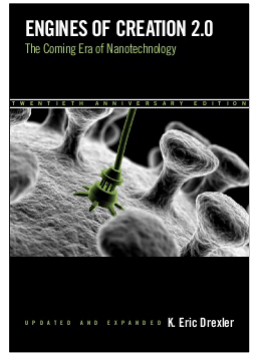
Nanomedicina két irányvonala

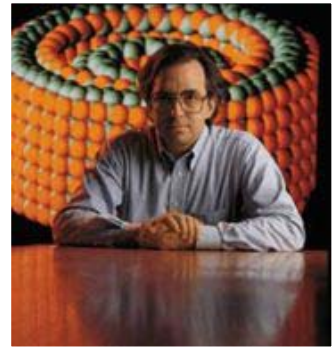
- **Diagnosis - Megelőzés**
  - **Életmüködések, betegségek megelőzése, diagnózisa újfajta nagy felbontású képalkotó eljárások alkalmazásával**
- **Therápia**
  - **gyógyszerek irányitása hatás helyére**
  - **mellékhatások csökkentése**
  - **adagolás szabályozása, egyszerűsítése**

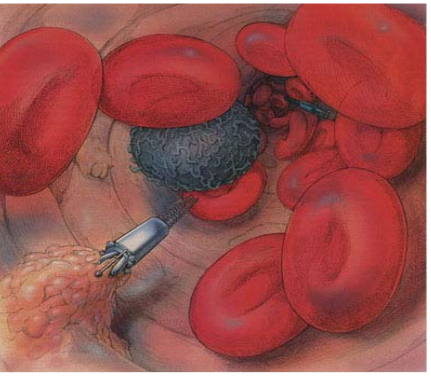
Kezdetek a Sci Fi-ben

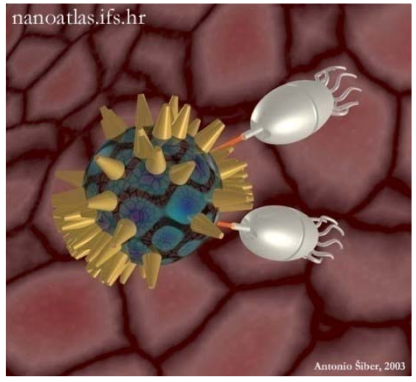


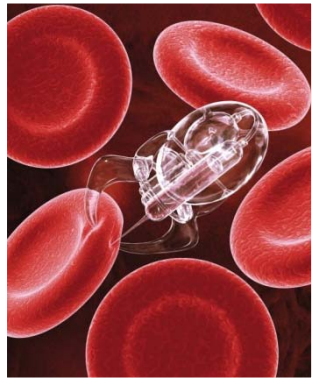


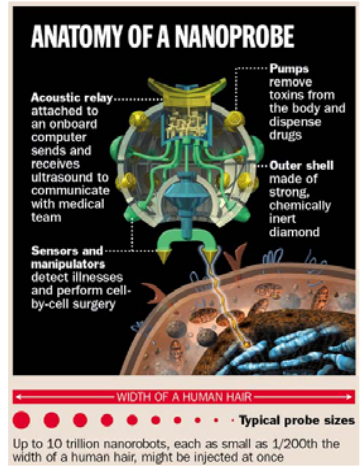




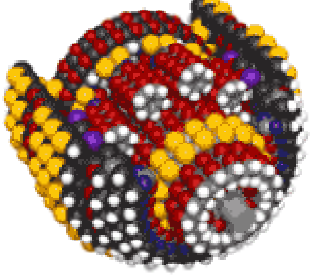








Jövőkép

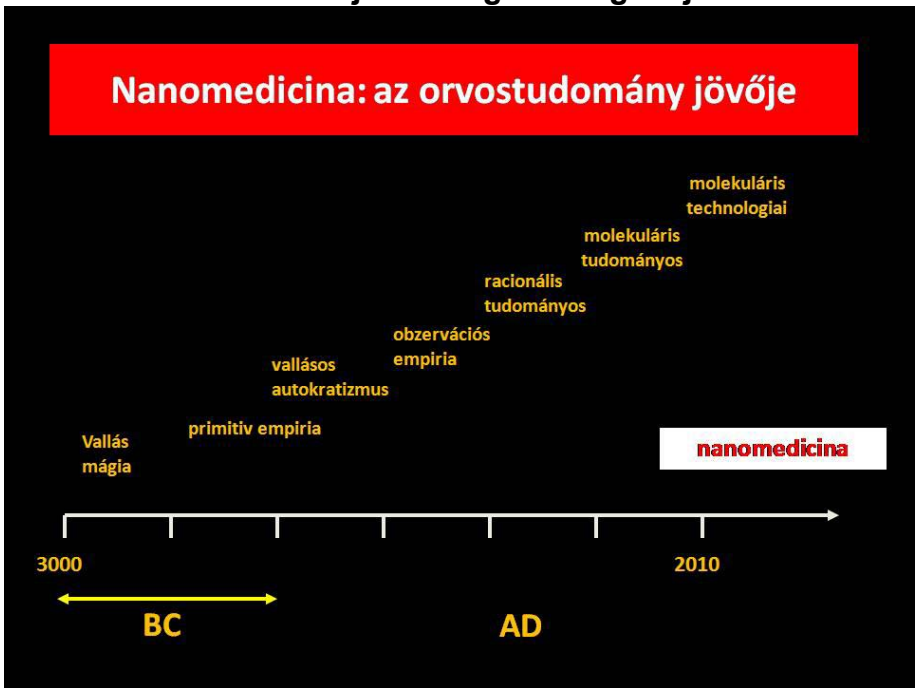


Pesszimista: kritikus bizonytalanság

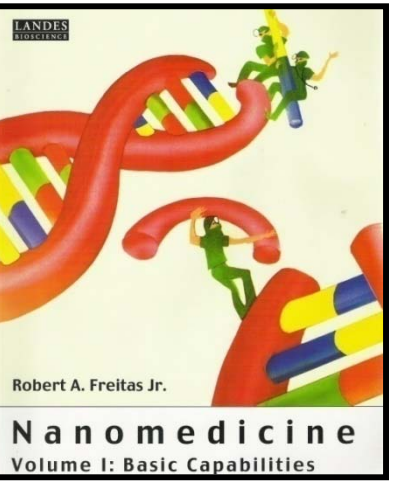
- **Kritikus**
  - **mint minden, szerteágazó területeket (közlekedést, energiaellátást, információs hálózatokat, üzleti életet, hadviselést, stb.) alapjaikban befolyásoló technológiai és társadalmi fejlődés.**
- **Bizonytalan**
  - **egyrészt tudjuk, hogy rövid időn belül meghatározó tényezővé válik, másrészt viszont nem tudjuk pontosan, miként válik azzá.**

Optimista: Korunk ipari forradalma

- **A rák és más krónikus betegségek megoldásának útja**
  - **Alzheimer kór, diabetes, sziv és érrendszeri betegségek**
  - **5-10 éven belül jelentős gazdasági hajtóerő**



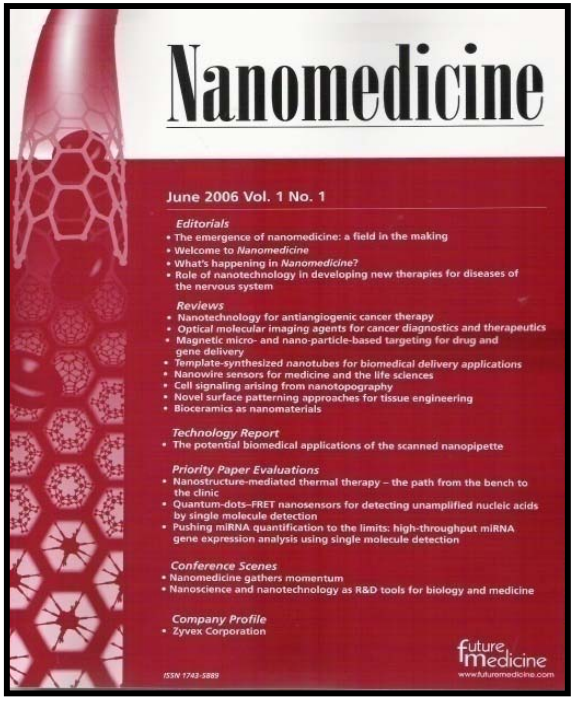
Tudományos térnyerés

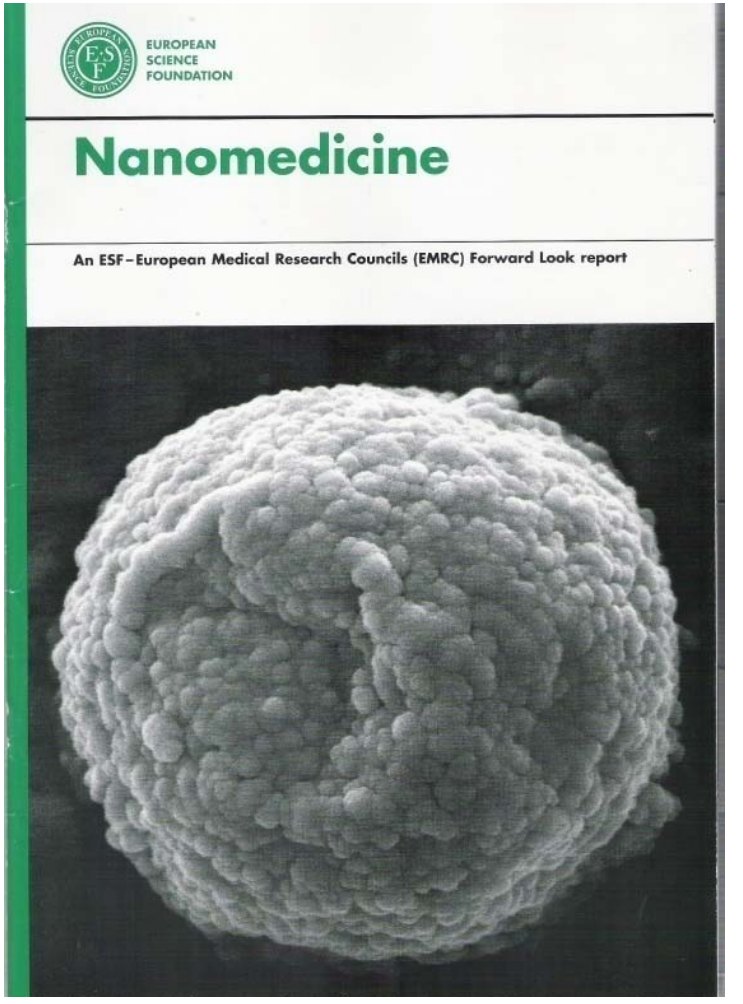


MEDLINE

Nanomedicine: 1999
óta >50 review paper

Liposomes: 29,356
Micelles: 10,230
Nanoparticle: 7366





Gazdasági előretörés

- **A gyógyszerkereskedelem jelenleg kb. 11%-át lefedő új-generációs (kontrollálható) nanomedicinális termékek világpiaca 2004-ban kb. 6 milliárd EUR volt**
- **2012-re várhatóan a kétszeresére nő**
- **Ma több mint 200 speciális nanotechnológiai gyógyszerhordozóra szakosodott vállalat működik világszerte**

Európai 7-es keretprogram támogatott témái

Téma	Célok	€ billion (MD HUF/mo	%
1. Health	DNA sequencing, tissue, cell and gene therapies, as well as biotech medicines	6.1 (19)	18
2. Food, agriculture, fisheries and biotechnology	EuropeanKnowledge Based Bio- Economy (KBBE)(food, feed, forest, fisheries, agriculture, aquaculture, chemistry	1.9 (6)	6
3. Information and communication technologies	Bioinformatics, personal healthcare, computer power to speed up DNA sequencing plus research into 'Future and emerging technologies	9,1 (28)	27
4. Nanoscience	get to the bottom of a disease, and develop and integrate new technologies and materials.	3.4 (11)	10
5. Energy	A major opportunity for biotech. From the development of bio refineries to marine biomas	2.3 (7)	7
6. Environment	emphasize the sustainable management of resources, climate change, pollution, and conservation.	1.8 (6)	5
7. Transport	safer, "greener" and "smarter" pan European transport systems that will benefit all citizens, respect the environment, and increase the competitiveness of European industries in the global market.	4.1 (13)	12
8: Socio-economic Sciences and Humanities	Every technological development has a societal consequence. Opportunities especially for National Association led projects like BioImpact, EuroBioJobs portal, BioLife TV, BioPicture Festival.	1.8 (6)	5
9: Space	Biotech can support the EU's long term needs, including space transportation (biofuels), bio-medicine, life and physical sciences in space	1.4 (4)	4
10: Security	The biotech industry contributes to the safety of citizens not only by developing detection technologies and the knowledge needed to ensure security, but also by producing bionedical vaccines.	1.4 (4)	4

Példák a nano-therápia és diagnózis jelen alkalmazásaira

Liposomes
Quantum dots
Fullerenes
Carbon nanotubes

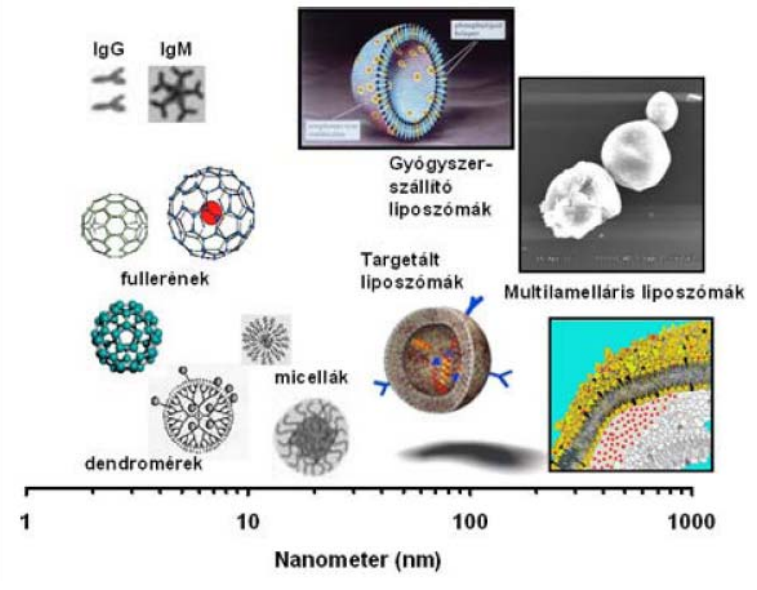
Irányitott gyógyszertherápia

Multimodularitás és multifunkcionalitás

1. **A gyógyszer legkisebb eleme, ami a tápcsatornába vagy a keringésbe kerül, több modulból áll, melyek egymástól független funkciókat látnak el.**

2. **A gyógyító funkcióért a hagyományos gyógyszermolekula felelős.**

3. **A további modulok a felszívódás, metabolizmus, szöveteloszlás javítását ill. a kezelendő sejtekhez történő célbavitelt biztosítják.**

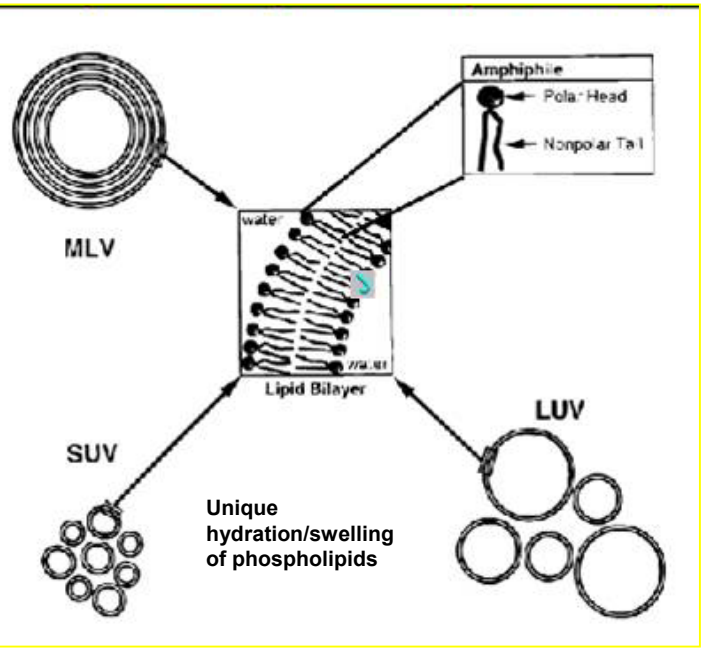


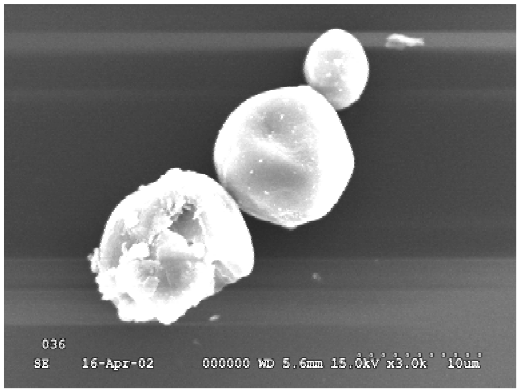
Portrait of A. D. Bangham and the Liposome by Humphrey Bangham (1988). From the Collection of the Royal Society, reproduced with permission of A. D. Bangham.

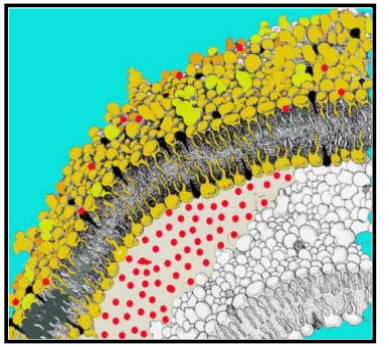
Liposzómák

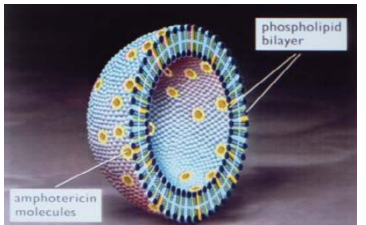
Bangham A D, Standish M M & Watkins J C. Diffusion of univalent ions across the lamellae of swollen phospholipids. *J. Mol. Biol.* 13:238-52, 1965.
[Agricultural Research Council Institute of Animal Physiology, Babraham, Cambridge, England]

- **Foszfolipid molekulák spontán szerveződése kétrétegü membránokba**
- **A membránok zárt gömböket, zsákokat képeznek amikbe gyógyszert lehet zárni**
- **A foszfolipid kettősréteg a sejtmembránok modellje**
- **A liposzómák nem toxikusak, tápanyagként megemesztődnek a szervezetben**





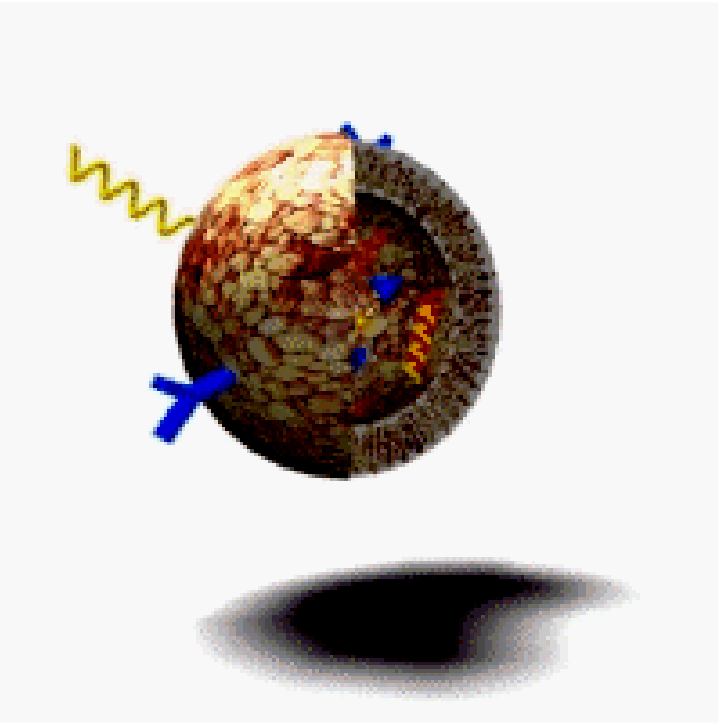




A liposzómák felhasználásának előnyei

- **Lokalizált, kontrolált bevitel**

- **Irányithatóság célzó ligandok beültetésével**



- **Jobb gyógyitási hatásfok**
  - –Vér és szöveti gyógyszerszintek kedvezőbbek

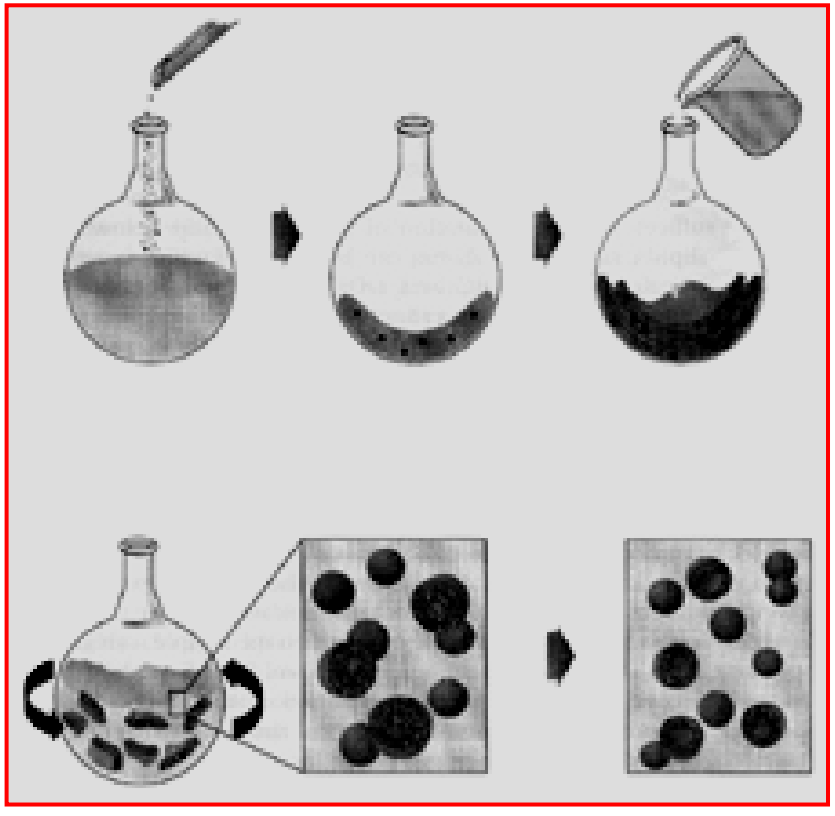
- **Mellékhatatások csökkennek**
  - –Kevesebb gyógyszert lehet adni
  - –Irányitani lehet a hatást

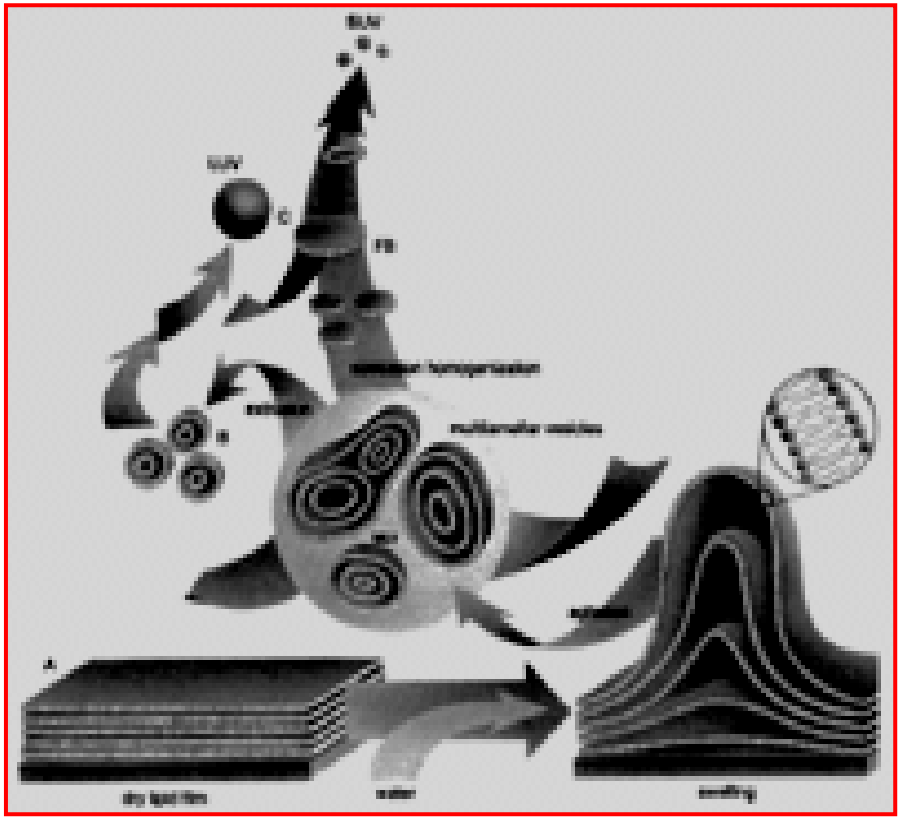
- **Az adás gyakorisága csökkenthető**
  - –Betegek jobban collaborálnak
  - –Adagolás egyszerűsödik
  - –Költségek csökkennek

- **Kiszerelésre alkalmatlan gyógyszerek**

Liposzómák készitése

spontán gömbformálódás





Forgalomban lévő liposzómális gyógyszerek

Név	Bezárt gyógyszer	Alkalmazás	Engedély
Doxil, Caelyx	Doxorubicin	Ovarian cancer, breast cancer, Kaposi's	1995
Abelcet	Amphotericin B	Systemic fungal infections	1995
DaunoXome	Daunorubicin	Solid tumors	1996
Ambisome	Amphotericin B	Fungal infections	1997
Epaxal-Berna	Hepatitis A	Hepatitis vaccine	1997
DepoCyt	Cytarabin	Tumors	1999
Amphotec	Amphotericin B	Systemic fungal infections	2000
Myocet	Doxorubicin	Fungal infections	2000
Visudyne	Verteporfin	Macular degeneration, ocular histoplasmosis	2000

Fejlesztés alatt álló liposzómális gyógyszerek

	Encapsulated drug	indication
1	All-trans retionoic acid	T cell lymphoma
2	amikacin	bacterial infections
3	ampicillin	listeria infection
4	Annamycin	breast cancer, leukemia
5	Antisense oligo	pancreatic cancer
6	Camptosar	colon cancer
7	chloroquine	malaria
8	ciprofloxacin	pseudomonas aeroginosa
9	cis-platin	cancer
10	clodronate	macrophage suppression
11	cyclosporin	immunosuppression
12	doxorubicin	breast cancer
13	gangciclovir	cytomegalovirus infection
14	interleukin-2	immunostimulation
15	Lipid A	immunostimulation
16	methotrexate	various cancers
17	mitoxantrone	prostate cancer
18	Mitoxantrone	breast and other cancers
19	muramyl di- and tripeptide	immunostimulation
20	organo platinum compounds	ovary/colorectal tumors
21	paclitaxel	various solid tumors
22	pentosam	leishmaniosis
23	Prostaglandin PGE-1	anti-restenosis, anti-inflammatory
24	ribavirin	herpes simplex
25	streptozotocin	lymphocyte activation
26	suramine	trypanosomy
27	topotecan	Various tumors
28	vincristine	hematiological cancer
29	vinorelbine	lung cancer

A liposzomális gyógyszertherápia fejlődése

1. generáció

1970-90, instabil,
Alacsony bezárási kapacitás
toxicitás

3. generáció

2000 >
Multi-modular, multi-functional
Steric hindrance + targeting ligand
Multiple drug payload
Remote control for visualization & release

2. generáció

(1990th)

sterically stabilized

surface-grafted, “pegylated” stealth liposomes

Ligand-targeted

antibodies, immunoglobulins, lectins, oligosaccharides

Fusogenized

cationic and fusogenic lipids utilized in gene therapy to deliver DNA into target cells

In situ-activated

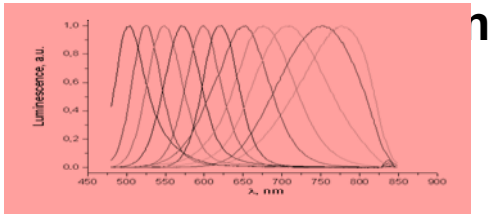
pH, ions, heat and light-sensitive phase transition

Quantum dots

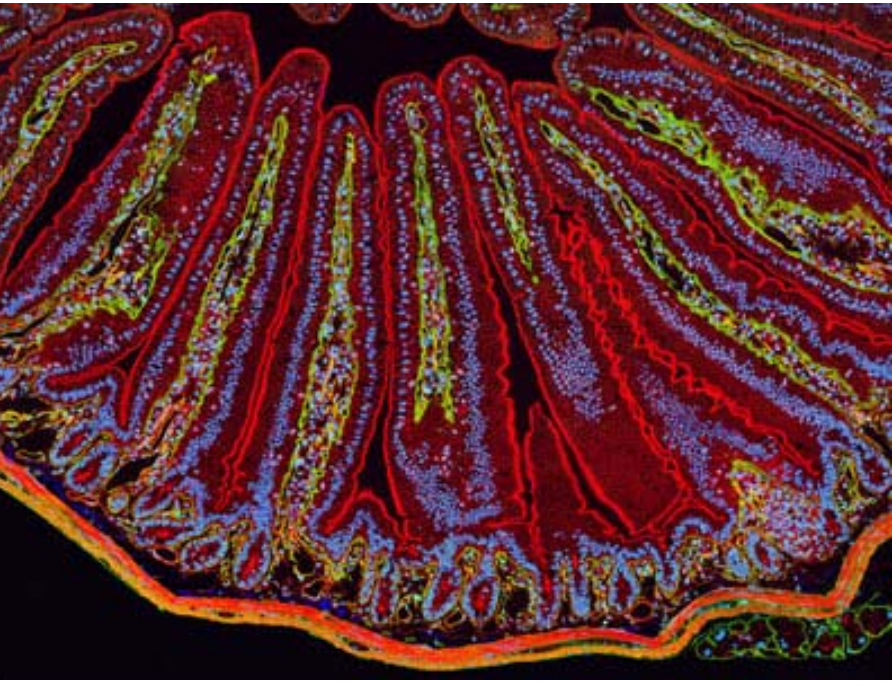
- **2 to 10 nm semiconductor core-shell nanocrystals, with CdSe in the core and ZnS in the shell or from special forms of Silica called Ormosil**

- **A total of 100 to 100,000 atoms within the quantum dot volume, 10 and 50 nm in size. Lateral dimensions can exceed 100 nm**

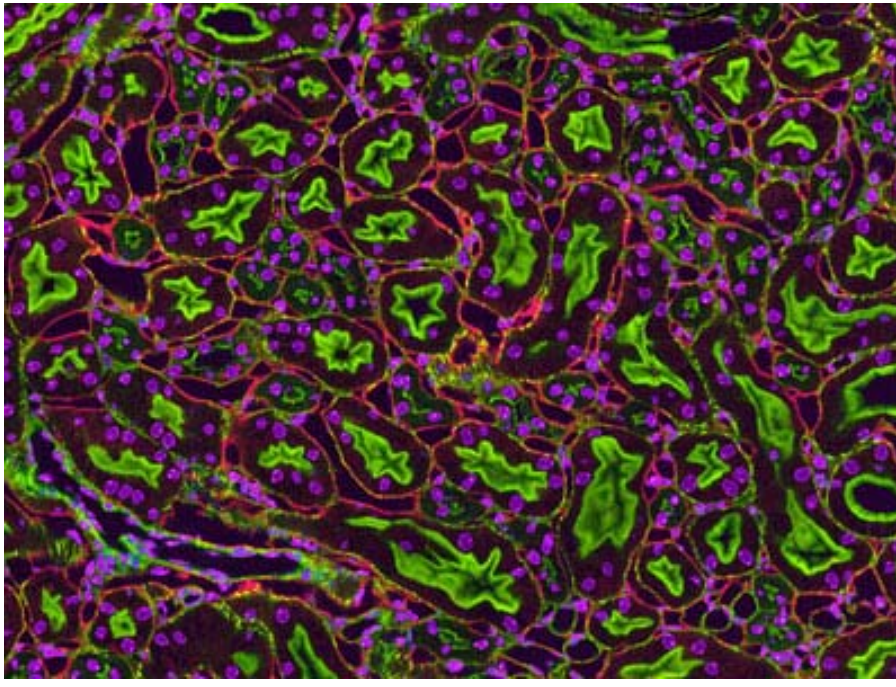
- **the motion of electrons is confined in two spatial dimensions and allow free propagation in the third- high energy, non-quenching fluorescence**

- **Emission**  **ned by size**

A quantum dots használata az orvosi diagnozisban

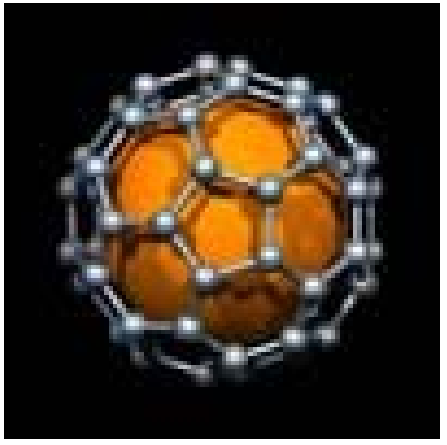


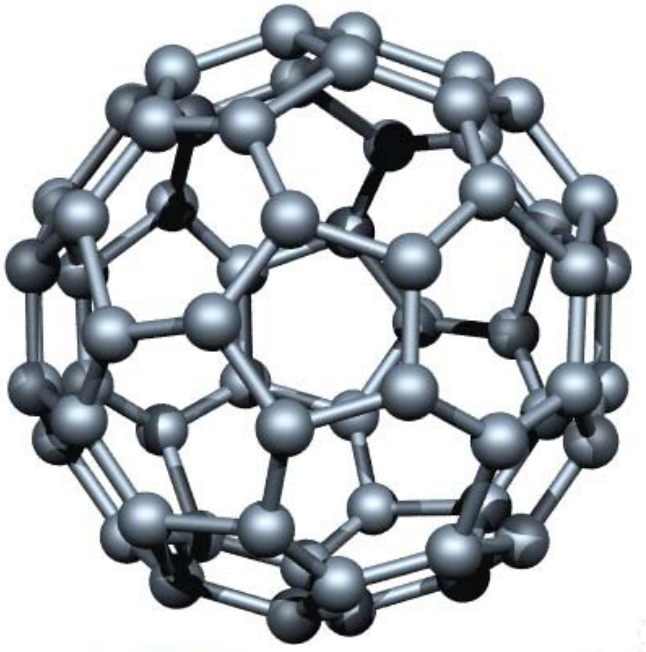
Quantum dot fluorescence image of mouse small intestine (20x)

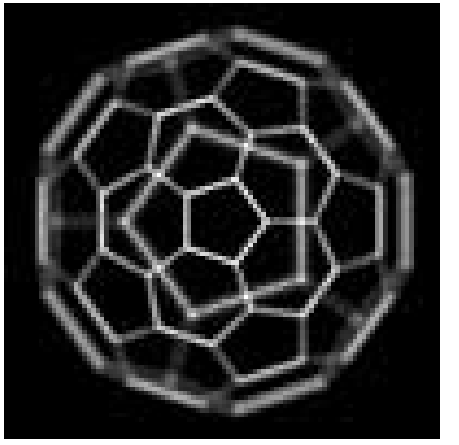


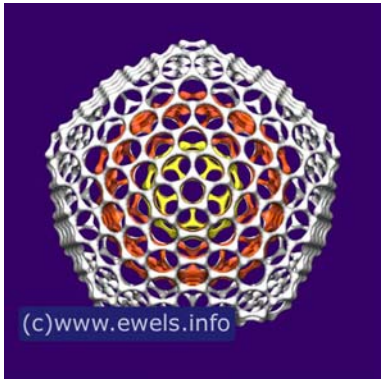
Quantum dot fluorescence image of mouse kidney section (240x)

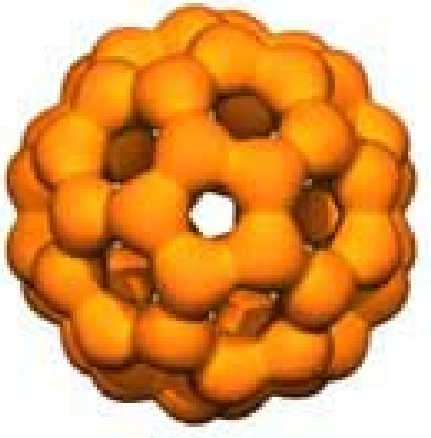
Fullerenes

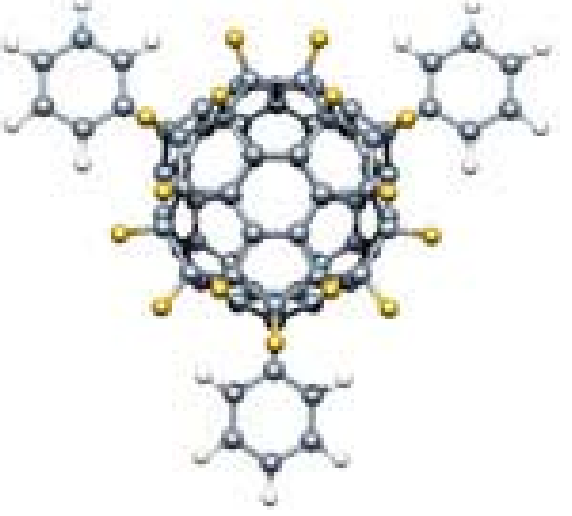




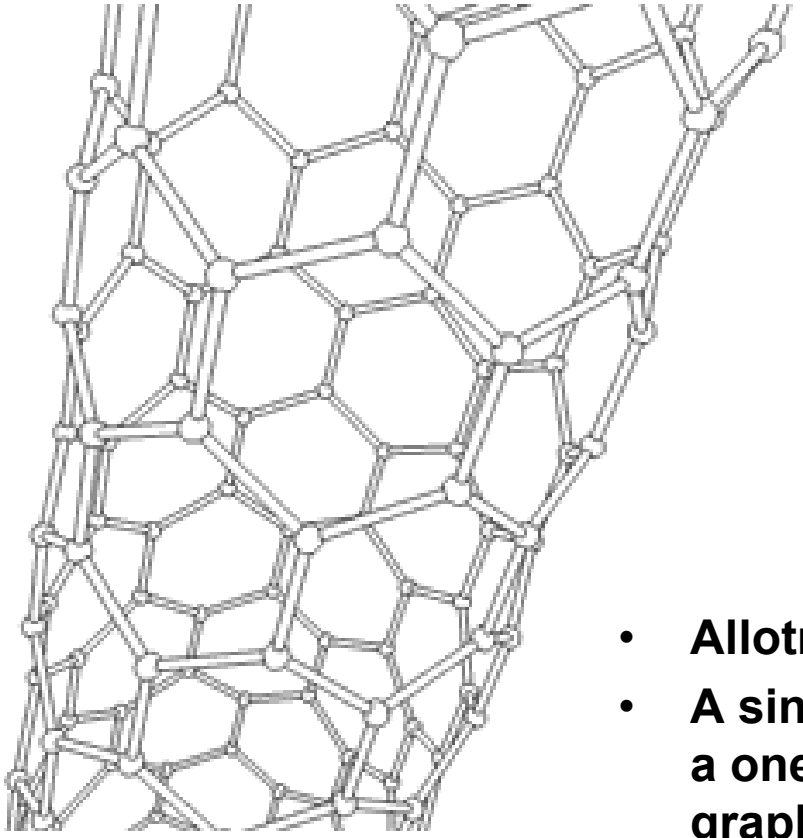


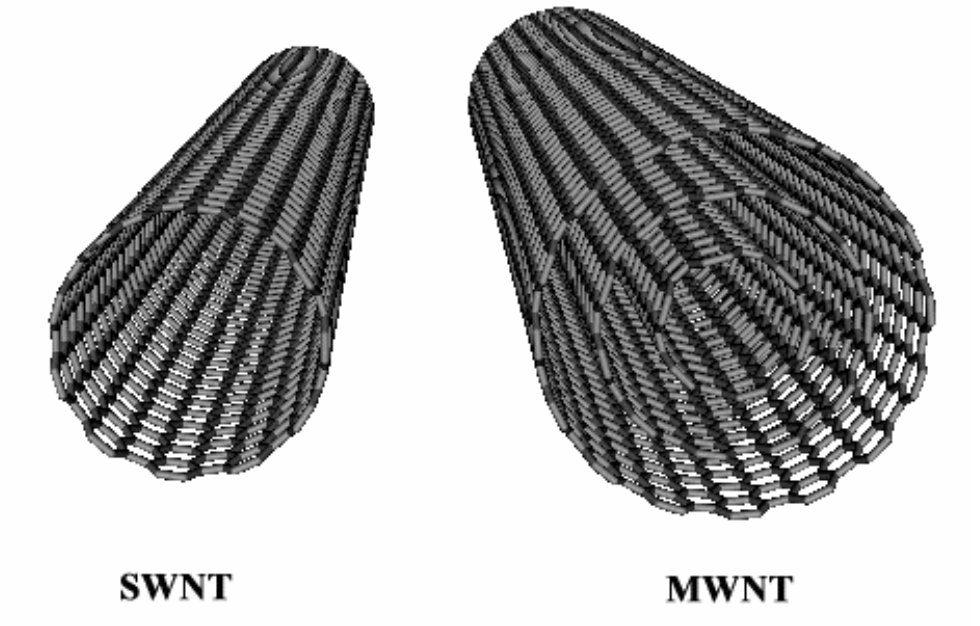






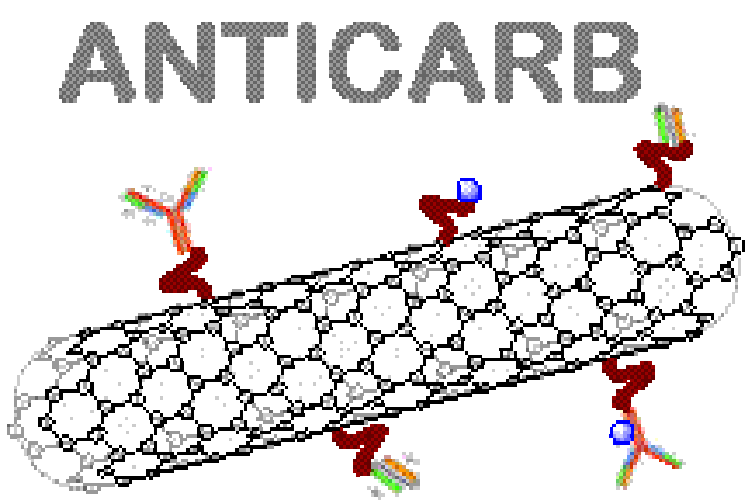
Carbon nanotubes





- **Allotropes of carbon**
- **A single-walled carbon nanotube (SWNT) is a one-atom thick sheet of graphite (called graphene) rolled up into a seamless cylinder with diameter on the order of a nanometer.**
- **length-to-diameter ratio exceeds 1,000,000.**
- **Extraordinary strength**

Medical use of CNTs



Monoclonal ANTIbody-targeted CARBon nanotubes against cancer

SEVENTH FRAMEWORK PROGRAMME

B.2.6. ANTICARB Resource Deployment

The following tables summarise the main information on ANTICARB financial resources to be deployed and requested (human and material) and the indicative deployment of existing resources and infrastructure.

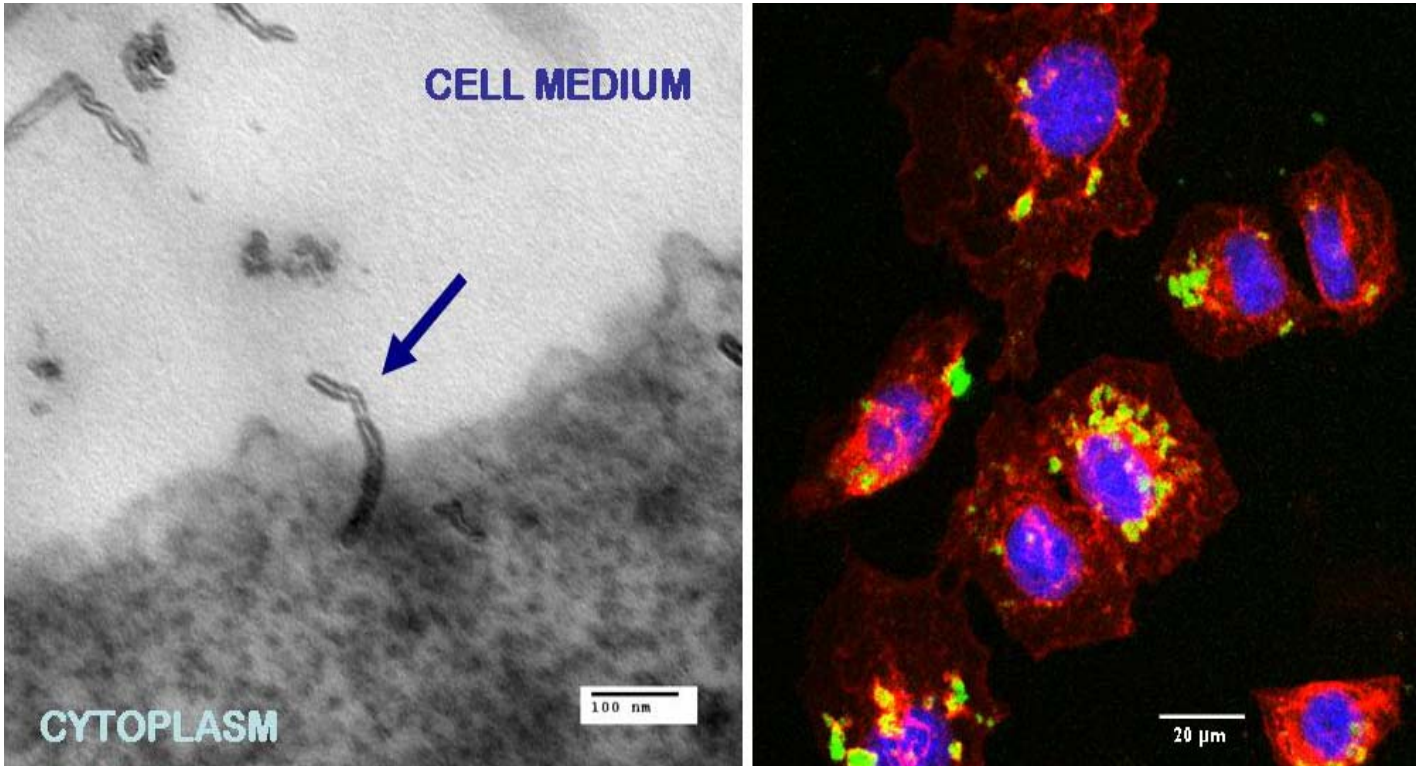
Partner	Personnel resources (person-months)	All Costs (k€)	EC Requested Budget (k€)
ULSOP	122	1,034,066	894,880
UCB	28.8	360,000	204,000
NANOCYL	49	326,480	249,860
CNRS	87	674,045	506,734
UTr	91	499,500	387,000
GSF	40	396,000	300,125
UoI	52	276,224	207,168
SeroS	48	288,480	222,560
Total	**517.8**	**3,854,795**	**2,972,327**

HEALTH

Call identifier: FP7-HEALTH-2007-2.4.1-7

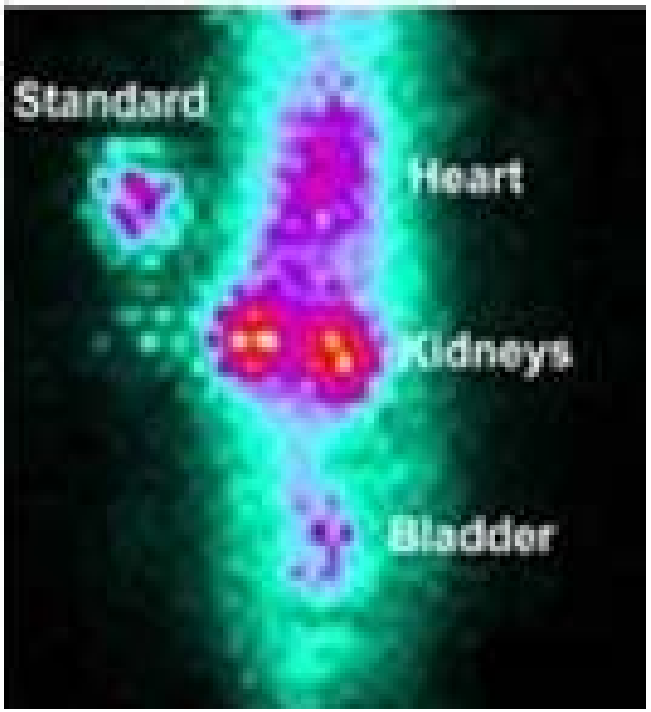
COLLABORATIVE PROJECT
(Small or medium-scale focused research project)

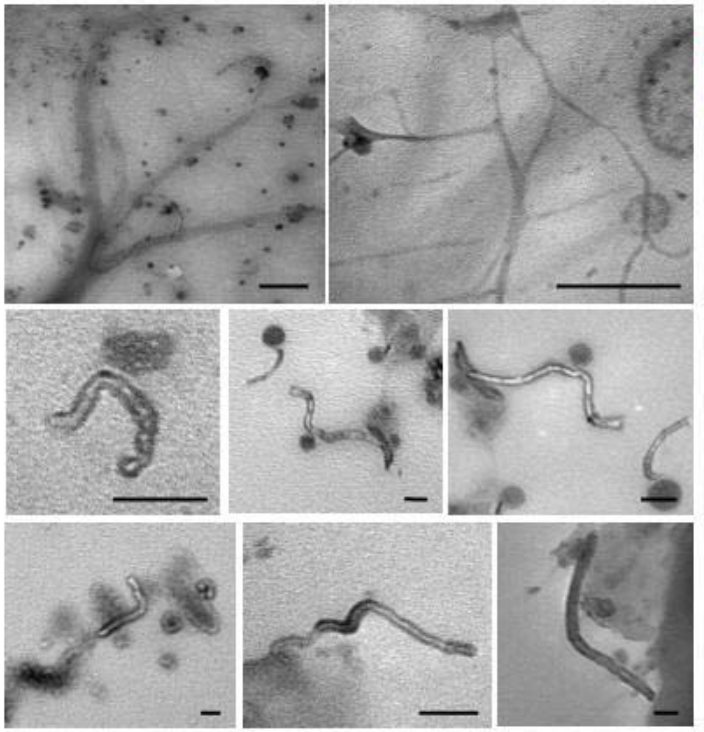
Intracellular targeting of nucleus



Cell biology of nanomaterials can reveal previously unknown cellular mechanisms and responses. On the right, multiwalled carbon nanotubes (MWNT-NH_3 – blue arrow) penetrating a human cell line (HeLa) imaged by TEM. On the right, confocal laser scanning microscopy of single-walled carbon nanotubes (SWNT-NH_3) trafficking to the perinuclear region of epithelial lung carcinoma cells (adapted from Refs. Pantarotto, et al. Angew.Chem.Int.Ed. 2004, 43, 5242-5246; and Kostarelos, K. et al. Nature Nanotech. 2007, 2, 108-113 respectively).

Kidney function assay





Chemically functionalised carbon nanotube body elimination through the renal route. The left image is a microSPECT image of an animal injected with radiolabelled *f*-CNT (red signal), indicating translocation to the kidneys within minutes. On the right handside, the two top images show single-walled carbon nanotubes (SWNT) and the rest of the images multi-walled carbon nanotubes as imaged by TEM from urine samples (Singh et al, PNAS, 2006).

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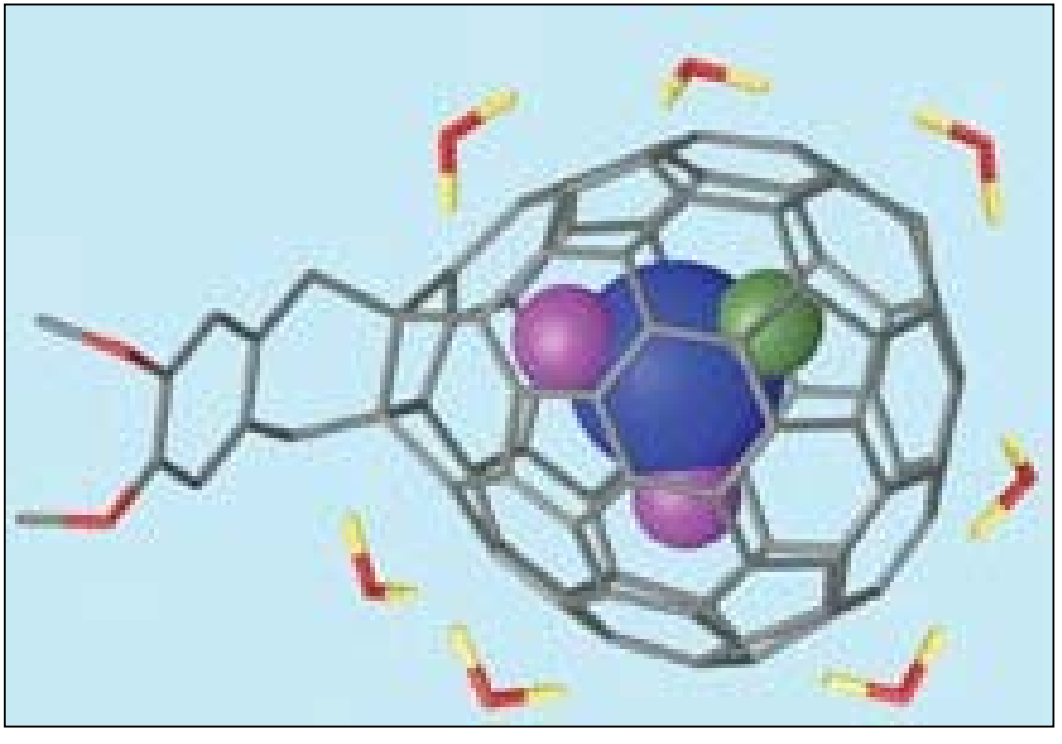
Fullerenes Yield Stable, Powerful MR Imaging Agent

Fullerenes, the soccer ball-shaped spheres of carbon that helped usher in the nanotechnology era, have been touted as versatile containers for delivering drugs and other clinically useful molecules to tumors. Turning promise into reality, investigators from the National Cancer Institute's Cancer Nanotechnology Platform Partnership at Virginia Commonwealth University have developed a new imaging agent that is 40 times more potent at boosting magnetic resonance imaging (MRI) signals than agents currently approved for human clinical use.



CAGED ATOMS.

A water-soluble contrast agent being developed for magnetic resonance imaging encapsulates two gadolinium metal atoms (purple) and one scandium metal atom (green) that are attached to a central nitrogen atom (blue). The molecule's tail (gray and red) makes the cage water-soluble. Water molecules (red and yellow Vs) surround the molecule.

In 1991, graduate student Simon Friedman was studying drug design at the University of California in San Francisco. One day, he was chatting with Diana Roe, a fellow student, about one of the field's latest rages?HIV protease inhibitors designed to combat the AIDS virus?and the discussion turned to unexpected new therapies that might come from medicinal chemists. Suddenly, Roe exclaimed, "What are they going to try next? Buckyballs?" Buckyballs?microscopic, soccer ball–shaped cages made of exactly 60 carbon atoms?had been recognized just 5 years earlier. The Nobel prize was awarded in 1996 to their discoverers, who had formally named the molecule buckminsterfullerene for its resemblance to the geodesic domes of architect R. Buckminster Fuller.

BUCKY DRUG. Model of a fullerene-based HIV protease inhibitor recently designed by Simon Friedman.
Friedman

Although these molecules resembled nothing found in any pharmacy, Friedman's mind started calculating after his friend mentioned them. A buckyball, he mused, might just be exactly the right size to block the active site on the HIV protease enzyme?like a cork in a crazy-shaped wine bottle. HIV requires the protease's active site to build new copies of itself. On his computer, Friedman soon modeled the interaction of a buckyball with the HIV protease and suddenly Roe's casual suggestion seemed profound.

More than a decade after Friedman and others first pondered the idea, research toward medical uses for buckyballs continues trekking forward. Buckyballs are members of a class of all-carbon, cage-shaped molecules now known as fullerenes. In recent months, for example, daylong sessions at national meetings of both the American Chemical Society and the Electrochemical Society were devoted to the topic, and at least three companies are working toward medical uses of fullerenes.

Friedman notes that fullerenes' unique qualities have promise for certain types of drug design. Their small size, spherical shape, and hollow interior all provide therapeutic opportunities. Moreover, a cage of 60 carbon atoms has 60 places at which to attach chemical groups in almost any configuration. Such opportunity has led to the development of not only drug candidates for treating diseases including HIV, cancer, and neurological conditions, but also new diagnostic tools. Among these are contrast agents for X-ray and magnetic resonance imaging (see box, below).

Molecular pincushion

One of the best ways to use fullerenes' unique structures is as scaffolding for building drug molecules, says Friedman, now at the University of Missouri in Kansas City. "You can think of the fullerene as a molecular pincushion," agrees Uri Sagman of C Sixty, a small, Toronto company specializing in developing fullerenes for biomedical uses.

A buckyball is akin to a benzene molecule, a hexagonal ring of carbon atoms used widely to make pharmaceuticals, says Sagman. Benzene can be tailored with various chemical appendages, but it's planar and floppy, so the added chemical groups sometimes interfere with one another, he says.

Most drug molecules are, like benzene-based pharmaceuticals, flexible in solution. So, it's difficult to build a molecule with the precision needed to dictate intimate interactions with a target molecule, such as a protein on a cell surface, says Sagman. Because a buckyball is rigid, researchers can decorate it with clusters of atoms at specified angles and distances from one another, features that hold steady as they match up with a target.

For example, chemical groups have been added to one side of a buckyball that make the molecule soluble in water while the other side of the fullerene interacts with a biological target.

New York University chemist Stephen Wilson, who does research for C Sixty, has used the fullerene pincushion as a support for a variety of chemical groups with many different configurations. This effort has led to libraries of new buckyball-based molecules that the company plans to test for potential therapeutic value.

Working independently, Friedman takes a different approach. He carefully synthesizes only those carbon-60 variants that his modeling and theoretical calculations suggest will be valuable. By adding this or that chemical group to specific locations on a carbon-60 scaffolding, Friedman has designed HIV protease inhibitors that bind to the protease's active site 50 times as readily as the molecules he considered in the early 1990s did. Taking a break from HIV work while waiting for further funding, Friedman is now aiming newly developed fullerenes at other biological targets.

One misconception some people have is that a fullerene's many carbons, make it is very large for a drug, says Wilson. It's not?a carbon-60 fullerene is only one nanometer in diameter, roughly the size of many small pharmaceutical molecules, including Prozac and Tagamet. In comparison, a human hair is as wide as 50,000 buckyballs, he says.

Drugs in the pipeline

Research groups worldwide are developing fullerene drug candidates for a variety of diseases and testing them in animals. C Sixty reports that some of these candidates have moved well beyond the chemistry phase of drug development and that it plans to conduct human trials of fullerene-based molecules in about a year for two diseases.

Rather than just absorbing the free radicals, the fullerene neuroprotectant, dubbed C_3, seems to transform them into a harmless form, Dugan says. In rat studies, the potential drug has shown good results against disorders resembling Parkinson's disease or ALS and seems to be well-tolerated, she says. Dugan and her colleagues are now about to begin a study of how well the molecule works against a monkey version of Parkinson's disease.

In some diseases, notably Parkinson's, part of the molecule's effectiveness might be due to its infiltration of neurons' mitochondria, cells' energy factories, Dugan says. Because mitochondria seem to play an important role in some neurodegenerative diseases, discovering that fullerene drugs get inside mitochondria "may not be a trivial finding," says Bernard Erlanger of Columbia University, who made the molecular tools that Dugan used to demonstrate the mitochondria-fullerene connection.

An immunologist, Erlanger had been curious whether fullerenes injected into an animal would produce an immune response. He found that, indeed, they did. Erlanger harvested some of the antibodies that resulted in mice so that researchers could then inject them into other animals or cultured cells. Once inside such specimens, the antibodies zoom in on previously added fullerene neuroprotectant molecules. Then, the scientists added fluorescently labeled mouse antibodies that sought out the antifullerene antibodies. Dugan then located fullerenes by viewing tissue with a fluorescence microscope.

A different type of antibody-fullerene duo could work therapeutically, says Lon Wilson of Rice University, who has tested a variety of potential buckyball treatments (SN: 5/8/99, p. 292). In this case, researchers would bind fullerenes to antibodies made to attach to specific cellular locations. Once there, the fullerene component would perform its medicinal duty. Alternatively, researchers have suggested, a radioactive atom might be encapsulated inside an antibody-rigged fullerene that could then carry the radiation to a target location, such as a tumor.

Fullerene's future

Even though they're excited by the fullerene drug candidates and diagnostic products now at various points along the development pipeline, the researchers caution that more toxicity tests in animals and various human trials are needed to prove the safety and efficacy of these newcomers to the biomedical arena. For some of the potential molecules, these tests might take a couple years; for others, much longer. Many of the proposed drugs, of course, will suffer the same fate as most conventional drug candidates do: They'll fall short of some important criterion and never make it into the pharmacopoeia.

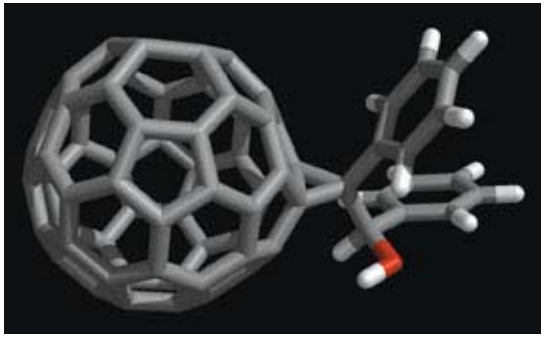
"I don't think we know all there is to know about long-term toxicity of fullerenes," comments Lon Wilson.

Even so, he says, the potential benefits of using fullerenes encourage researchers to continue developing candidates suitable for clinical trials. "We're not there yet," Wilson told the attendees at the Electrochemical Society meeting. "But I expect in the next few years, we'll be hearing more talks with human clinical trials."

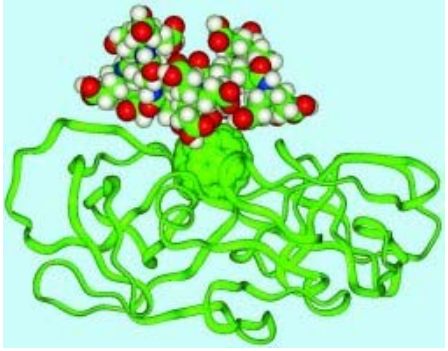
Better Contrast?

Fullerene-based agents could give physicians a new view

"It's important to exploit fullerenes' special properties," Robert Bolskar of the Wheat Ridge, Colo., company TDA Research told a meeting of the Electrochemical Society in May in Philadelphia. In diagnostic medicine, physicians often need to put molecules containing potentially hazardous metal atoms into a patient's body temporarily to highlight certain tissues so that physicians can see them better. If the contrast material remains in the patient long enough, the metal atoms may break free. However, these atoms can't escape from a fullerene cage and do mischief in the patient.



BUCKY DRUG. Model of a fullerene-based HIV protease inhibitor recently designed by Simon Friedman



IN THE GROOVE. This fullerene-based protease inhibitor fights HIV by binding to the active site of the protease enzyme (green ribbon). The carbon-60 molecule (green ball) is decorated with various chemical appendages (green, red, white, and blue). C Sixty plans to test it in patients.

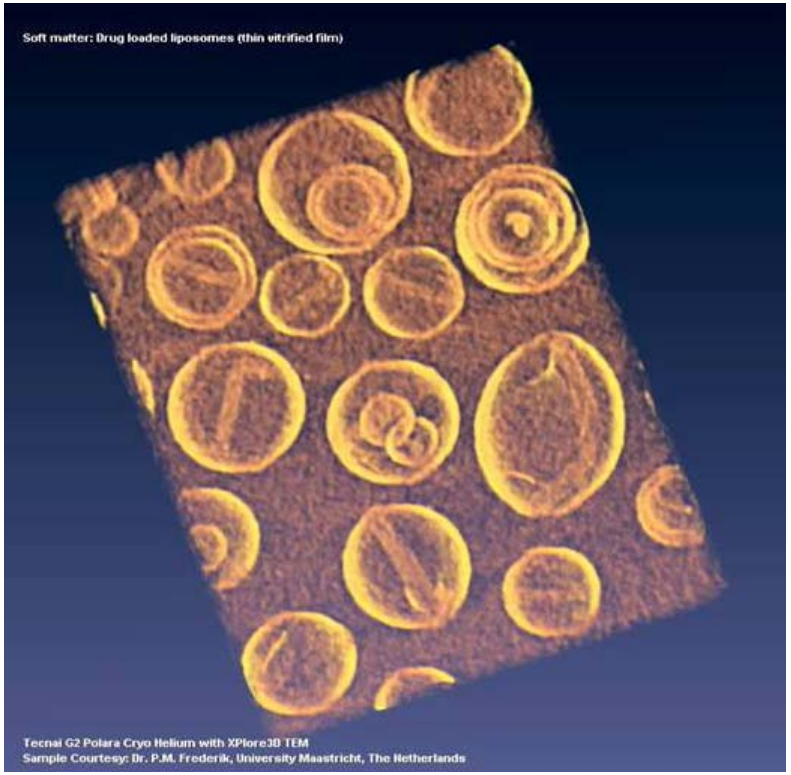
A BZAKA nanomedicina osztály liposzóma programja

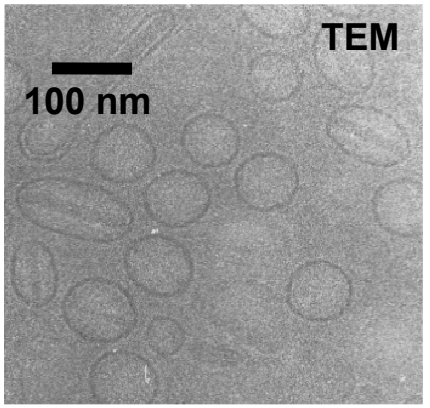
Generikus Doxil

Szuper-generikus Doxil

Biokompatibilis liposzómába zárt hemoglobin, mint mesterséges vér

Liposomális Doxorubicin (Doxil)

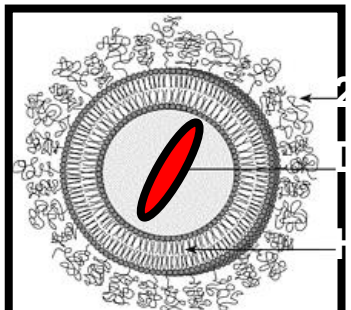




Petefészek és sok egyéb rák hatásos gyógyszere

Preferenciáltan halmozódik a tumorszövetben, mig a szivet nem bántja

Az első forgalomba hozott nanogyógyszer melynek generikus változatai már piacon vannak



Doxil hiperszenzitivitás

DOXIL® (doxorubicin HCl liposome injection) for intravenous infusion
Initial U.S. Approval: 1995

WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, SUBSTITUTION

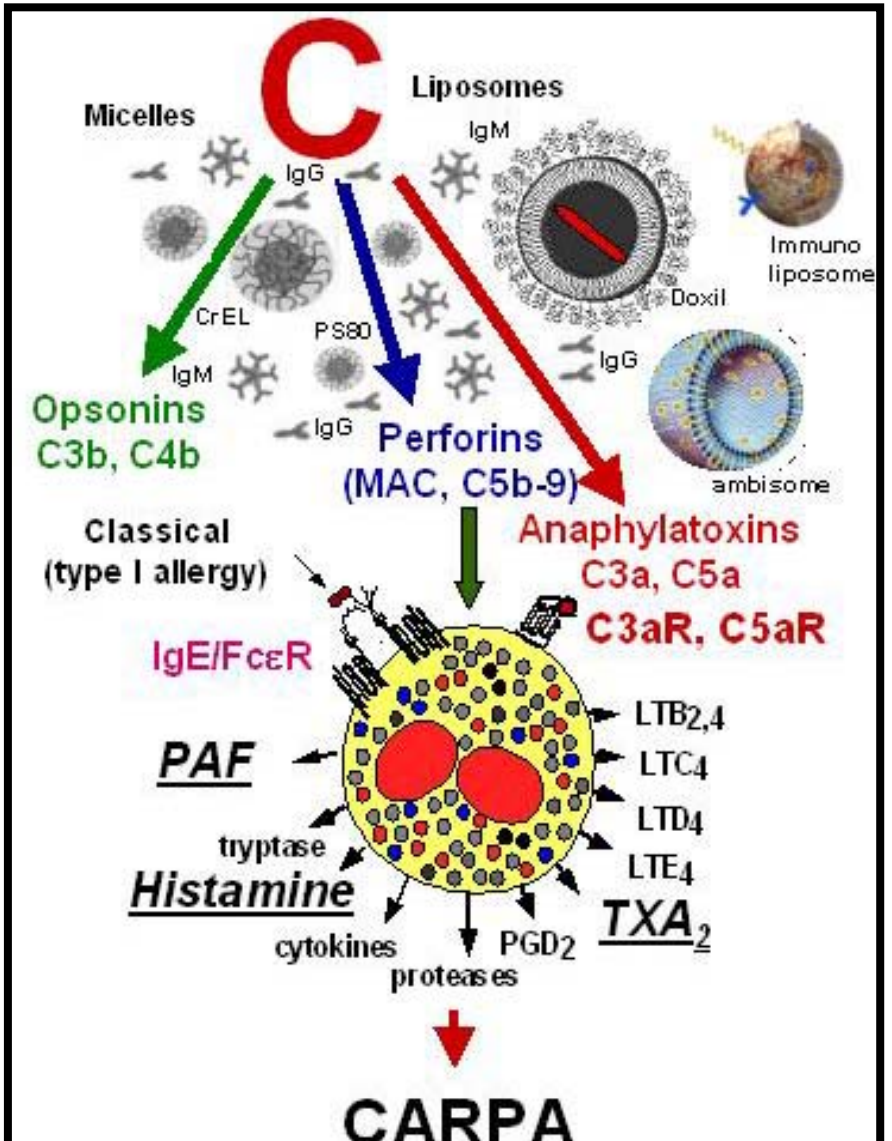
See full prescribing information for complete boxed warning.

- **Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m^2. Cardiac toxicity may also occur at lower cumulative doses with mediastinal irradiation or concurrent cardiotoxic agents (5.1).**
- **Acute infusion-related reactions, sometimes reversible upon terminating or slowing infusion, occurred in up to 10% of patients. Serious and sometimes fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications/emergency equipment to treat such reactions should be available for immediate use (5.2).**
- **Severe myelosuppression may occur (5.3)**
- **Reduce dosage in patients with impaired hepatic function (2.6).**
- **Accidental substitution of DOXIL resulted in severe side effects. Do not substitute on mg per mg basis with doxorubicin HCl (2.1).**

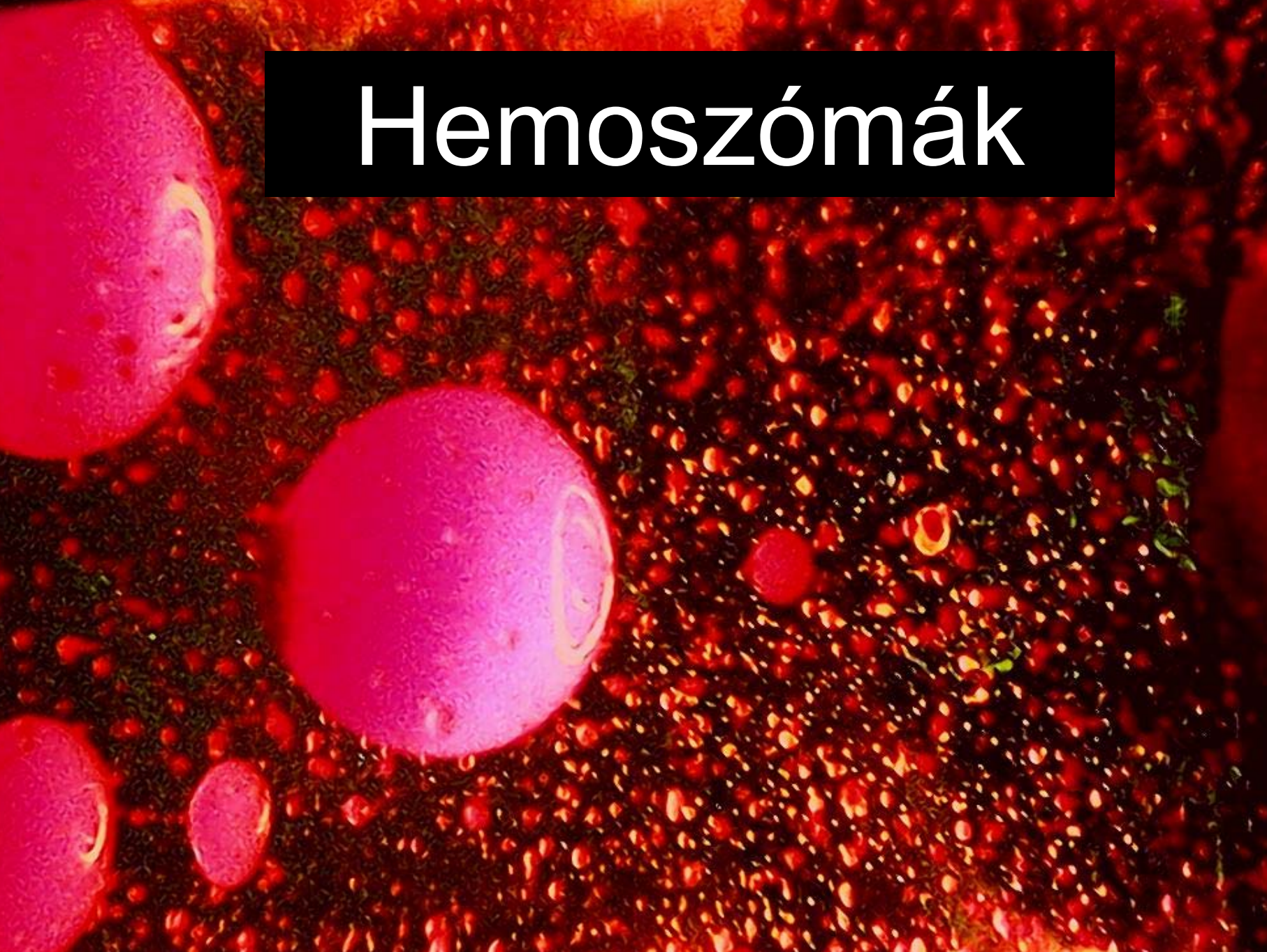
Pseudo-allergiát okozó gyógyszerek (nagy része nanoformulált)

Liposomal drugs and diagnostics	Micellar drug formulations	Radio and ultrasound contrast agents	Antibody-based Therapeutics & diagnostics	Enzymes Proteins Peptides	Miscellaneous other
Doxyl (Caelix) Ambisome Amphocyl Myocet DaunoXome Tc^{99}-HINIC-PEG	Taxol Taxotere Cyclosporine Etoposide poloxamers	Diatrizoate Iodixanol Iohexol Iopamidol Iopromide Iothalamate Ioversol Ioxaglate Ioxilan SonoVue Magnevist	Avastin Enbrel Herceptin Humira Raptiva Synagis Xolair Compath Erbitux Mylotarg Remicade Rituxan Vectibix Tysabri	Avonex Actimmune Abbokinase Aldurazyme Activase Zevalin Neupogen Neulasta Fasturtec Plenaxis	Cancidas Copaxone Orencia Eloxatin Salicilates

Doxil allergia mechanizmusa: komplement aktiváció



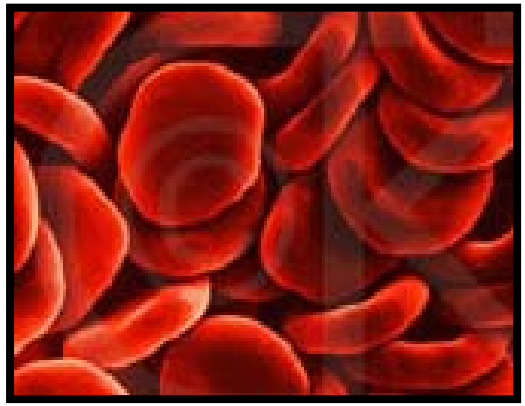
Hemoszómák

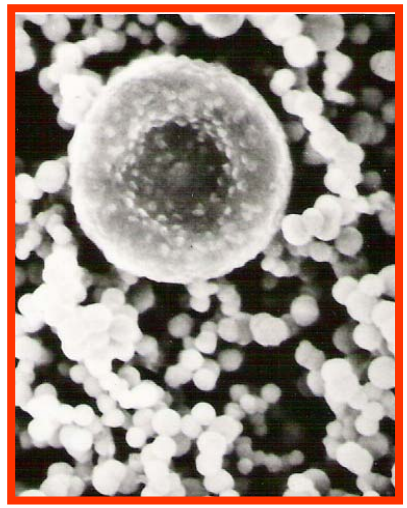


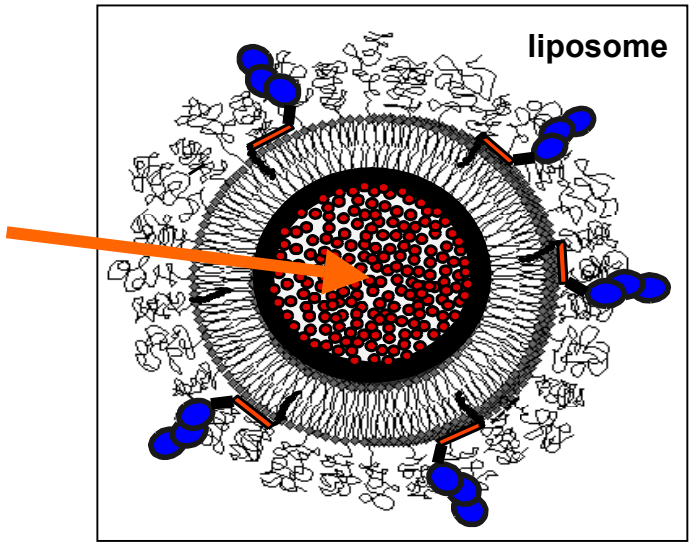
Biokompatibilis liposzómába zárt hemoglobin

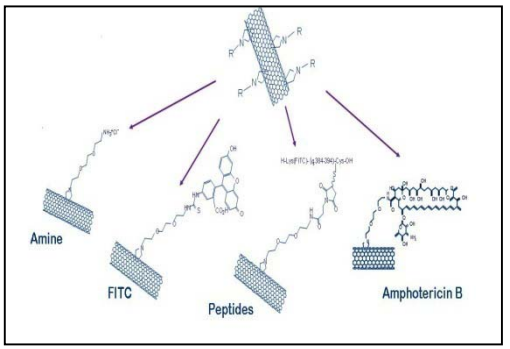
Háttér :

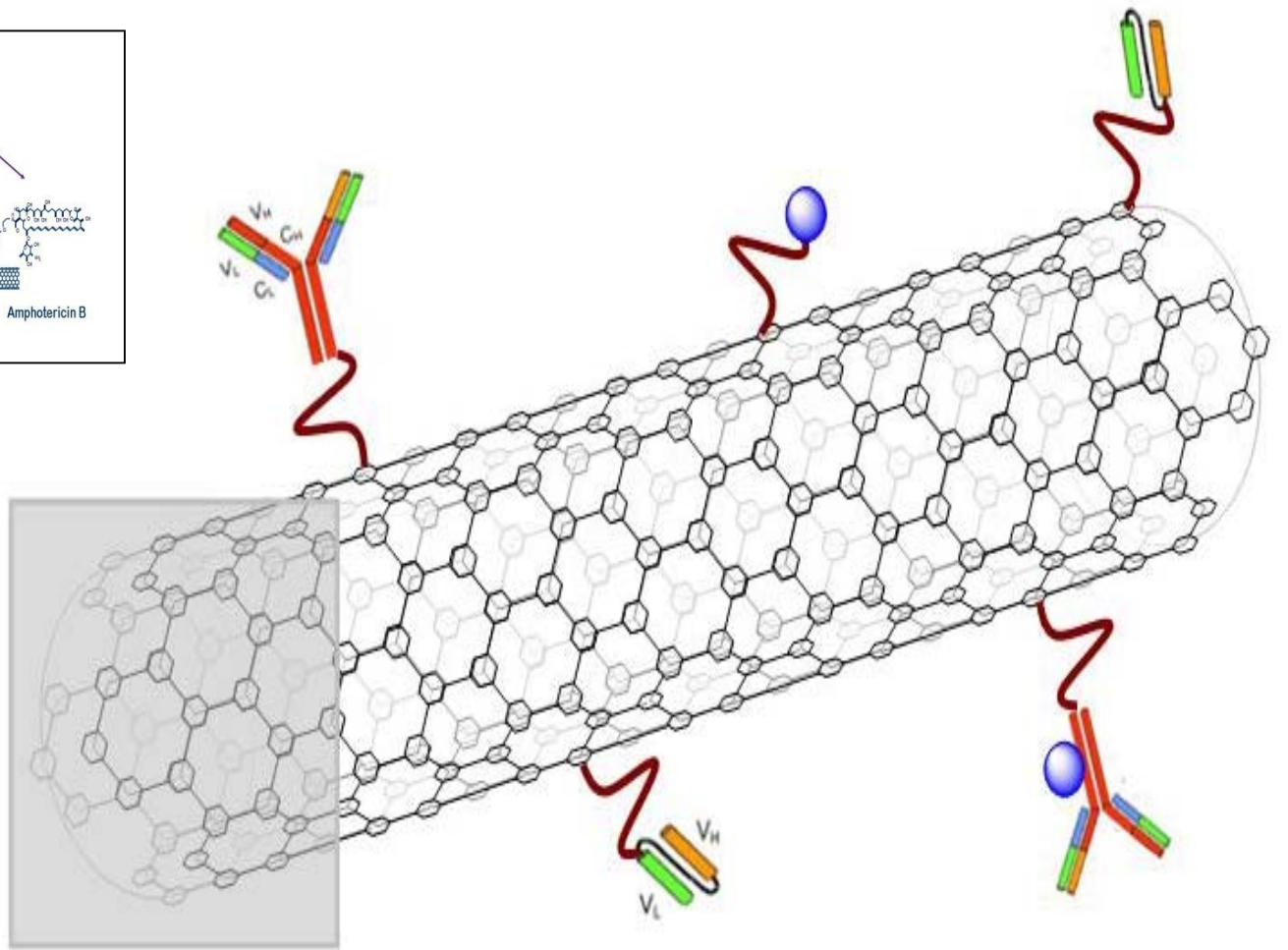
- **Huge market for a safe blood substitute**
  - **Shortage of donor blood in emergency situations, mass catastrophes**
  - **Risk of**
    - **incompatible transfusions**
    - **transmission of infection (Hepatitis, HIV)**
  - **Expensive and labor-intensive testing of donor blood**
  - **Short shelf life of donor blood**








Amine
FITC
Peptides
Amphotericin B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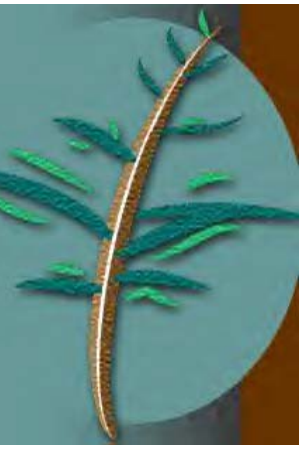
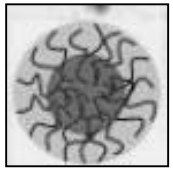
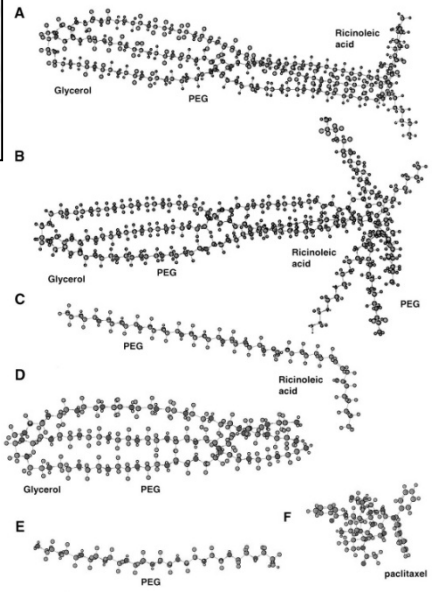
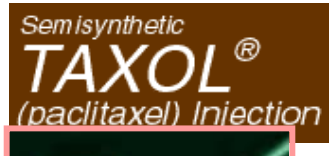
C_H
V_L
C_L
V_H
V_L

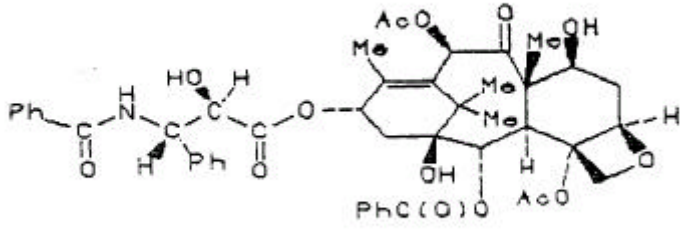


Micellizált gyógyszerek





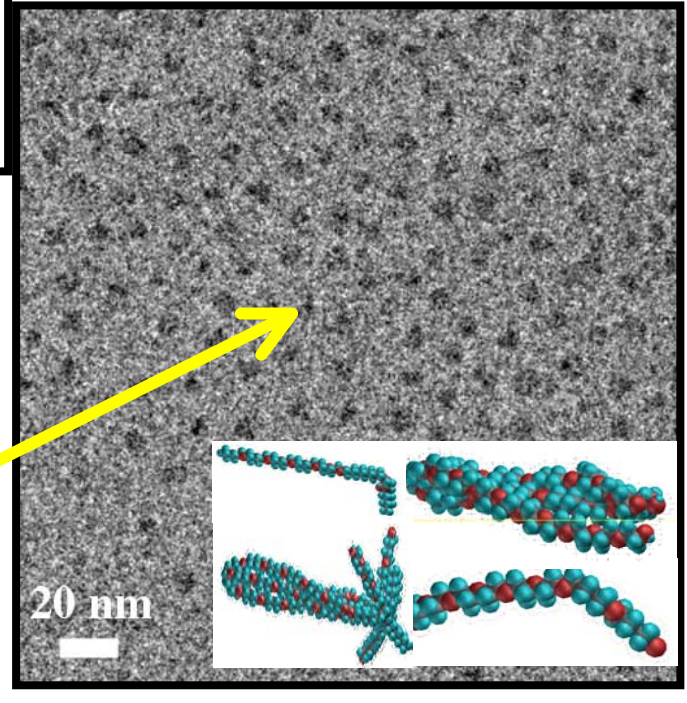




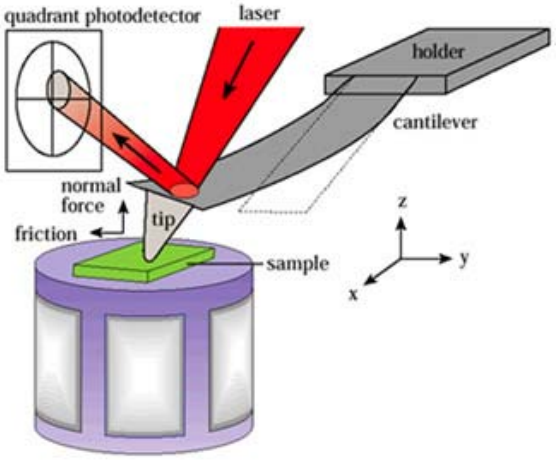
Vizben oldhatatlan paclitaxel

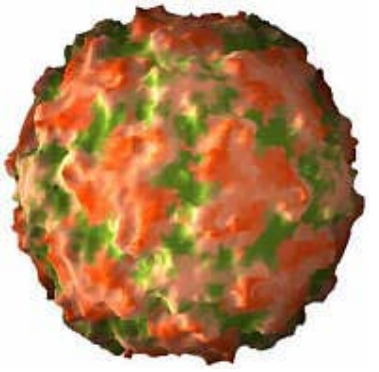
- **Petefészekrák,**
- **méhrák**
- **mellrák**
- **tüdő cc**

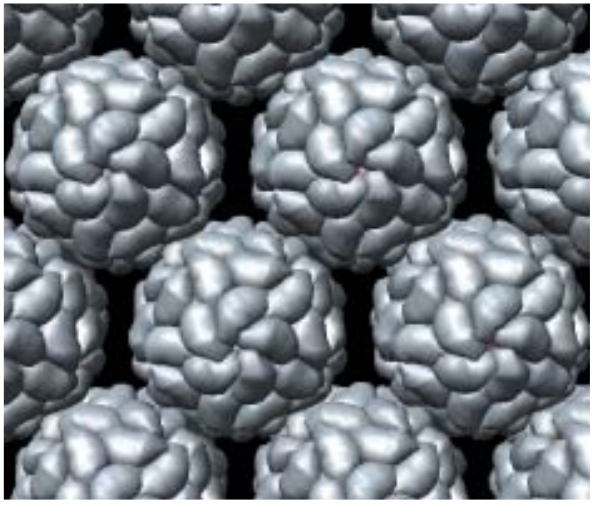
Cremophor EL-ben oldott paclitaxel, kezelésre alkalmas infúziós oldat

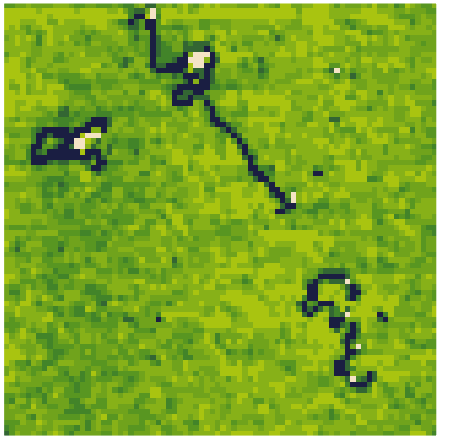


Az atomerő mikroszkóp (AFM) alkalmazása a viruskutatásban









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0022-538X/03/$08.00+0 DOI: 10.1128/JVI.77.22.11896–11909.2003

Atomic Force Microscopy Investigation of Human Immunodeficiency Virus (HIV) and HIV-Infected Lymphocytes

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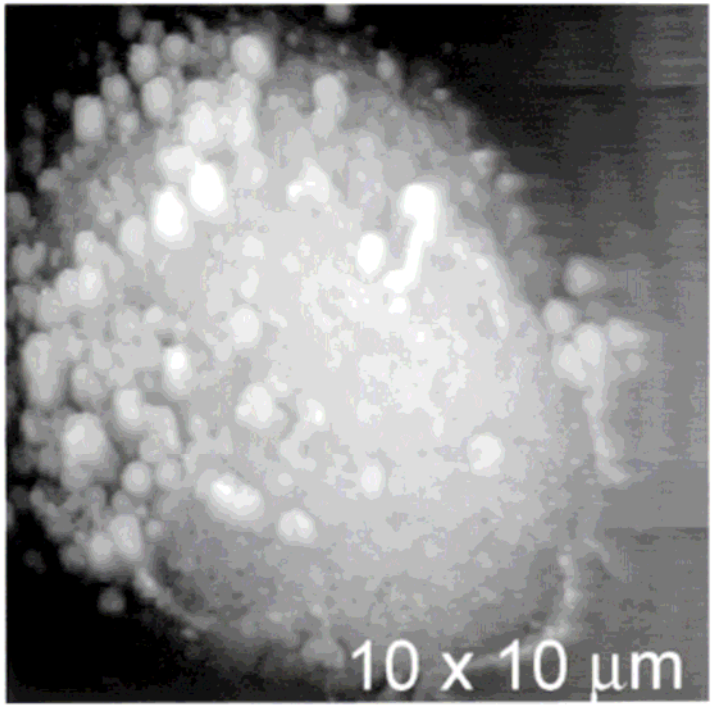

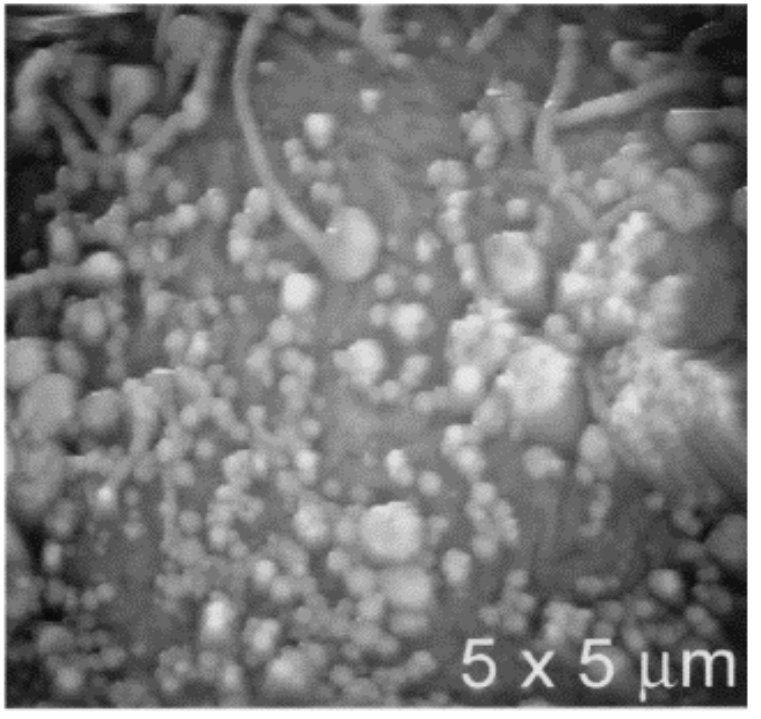

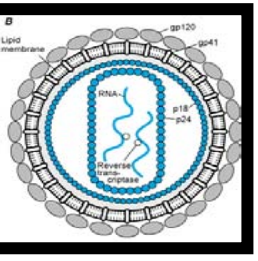

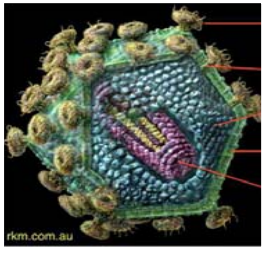

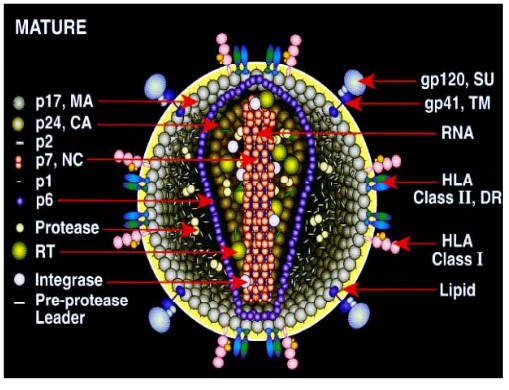

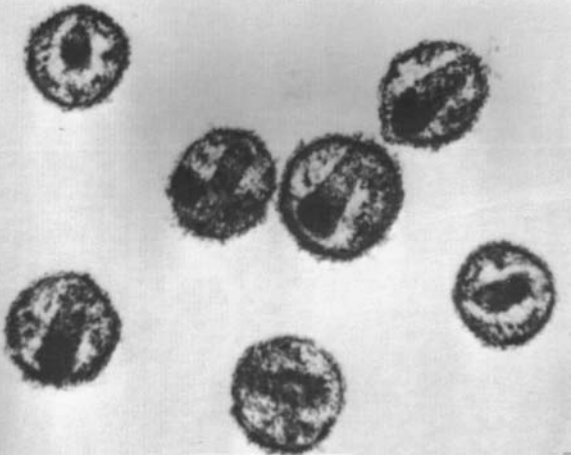

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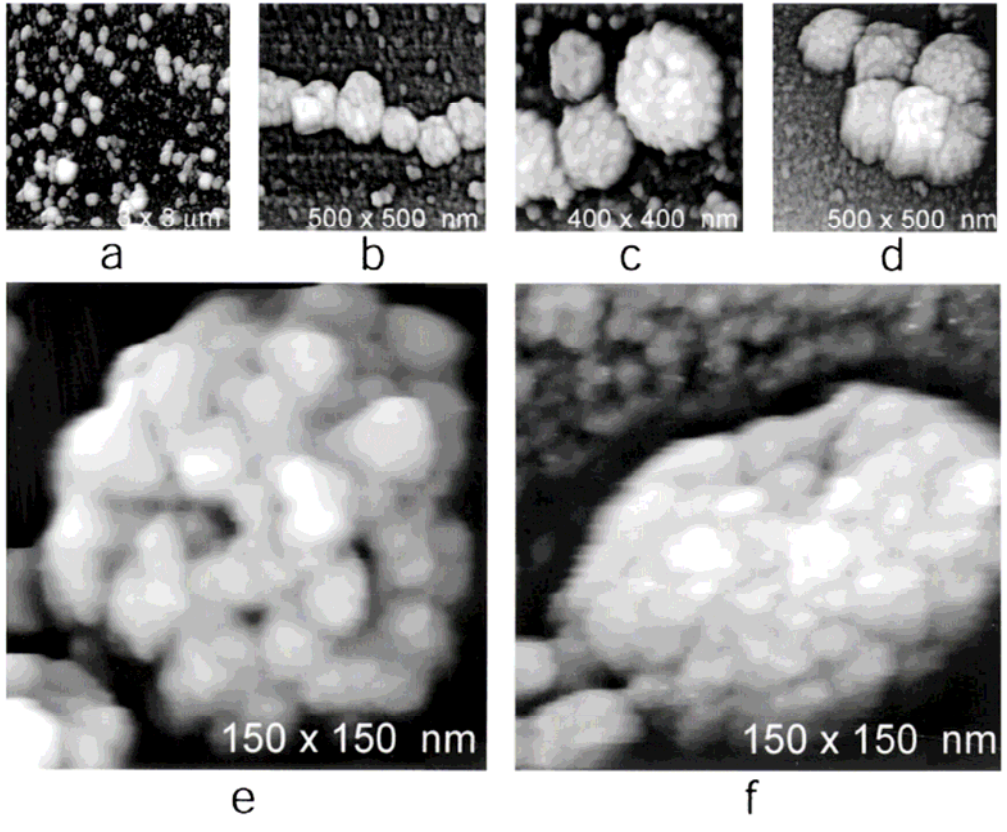

FIG. 1. Isolated HIV particles. AFM images of particles obtained by centrifugation of the culture medium from an HIV-infected cultured human lymphocytic cell line are shown. The resuspended virions were spread on poly-L-lysine-coated glass coverslips, fixed with 0.1% glutaraldehyde and 1.0% osmium tetroxide, and imaged by AFM under ethanol. (a to d) Groups of virus particles adhering to the glass substrate. The tendency to form clusters is likely due to packing of particles as a result of centrifugation. (e and f) Two isolated viruses imaged at high resolution showing the distinctive but arbitrary distribution of protein tufts covering their exterior surfaces. The roughly spherical particles have average heights of 120 nm, although some, as in panel f, are seen to be slightly compressed, probably due to contact with the substrate. The particles appear to be soft and easily deformed from a spherical shape. The images seen here are typical of many such particles found on the substrate.

- **GADOLINIUM CONTAINING FULLERENES AS MRI CONTRAST AGENTS**
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Summary Endohedral fullerenes containing Gd atoms are a promising new class of compounds with the potential to be superior MRI contrast agents. Fullerenes are a newly discovered class of hollow, closed shell, all carbon molecules that can hold single or multiple lanthanide atoms such as gadolinium inside their shell. Such compounds have a number of important advantages as contrast agents in imaging applications. Unlike conventional compounds, the trapped lanthanide is complete protected from the outside environment, and therefore will not be released into the body. In addition, the compounds show very high relaxivities, on the order of five times higher than current imaging agents. As a result, they are ideal in applications where the imaging agent is to be retaining in the body for a long period of time. This project will improve the methods for extracting and purifying the Gd-metallofullerenes, develop improved methods of making the compounds water soluble, and measure the water solubility, relaxivity and stability of the resulting derivitized compounds. The best compounds will be further tested to determine their toxicity, elimination pathways, in vivo distributions and half lives, and their performance in actual MRI imaging experiments. PROPOSED COMMERCIAL APPLICATIONS: This research will lead to the development of an entirely new class of lanthanide fullerene compounds that have potential applications not only in improving contrast in magnetic resonance imaging, but in scintillation imaging, PET imaging and SPECT imaging. This class of compounds could also have applications to the delivery of radio-pharmaceuticals.

- **Fullerenes Yield Stable, Powerful MR Imaging Agent** Fullerenes, the soccer ball-shaped spheres of carbon that helped usher in the nanotechnology era, have been touted as versatile containers for delivering drugs and other clinically useful molecules to tumors. Turning promise into reality, investigators from the National Cancer Institute's Cancer Nanotechnology Platform Partnership at Virginia Commonwealth University have developed a new imaging agent that is 40 times more potent at boosting magnetic resonance imaging (MRI) signals than agents currently approved for human clinical use. Reporting its work in the journal Radiology, a team headed by Panos Fatouros, Ph.D., and Harry Dorn, Ph.D., has shown that C 80 fullerenes – spheres made of 80 carbon atoms – can act as stable cages for gadolinium ions, the key component of MRI contrast agents. Gadolinium can be toxic, so creating a stable platform for its delivery in the body is critical. Equally as important, the manner in which gadolinium sits within the fullerene provides a more optimal physical environment in which gadolinium can interact with a magnetic field, thereby boosting signal enhancement. The researchers also described methods they used to render the gadolinium-containing fullerenes soluble in water.
- In vitro experiments demonstrated that their gadolinium-loaded fullerene not only boosted MRI signals but had the interesting property of providing a bigger signal enhancement at low concentrations. Subsequent in vivo studies imaging brain tumors in experimental animals also found that this agent was better at delineating tumors at low concentrations than it was at high concentrations. These latter experiments also showed that the fullerene-based imaging agent remained in tumors far longer than did a conventional gadolinium contrast agent, and as a result was better able to discern the margins of growing tumors.
- The researchers note that the methods they used to create their gadolinium agent will also produce fullerenes loaded with other clinically useful metals, such as lutetium, terbium or holmium. A combined gadolinium-terbium fullerene, for example, could image a tumor and deliver a lethal dose of radioactivity to a tumor simultaneously. The investigators also comment that since the metal atoms are loaded stably inside the fullerene particle it is likely that the pharmacological properties of different formulations would not change, an advantage that could speed clinical development of a family of agents based on the same fullerene.
- This work, which was supported by the NCI, is detailed in a paper titled, "In vitro and in vivo imaging studies of a new endohedral metallofullerene nanoparticle." Investigators from Virginia Polytechnic Institute and State University and Emory and Henry College also participated in this study. This paper was published online in advance of print publication. An abstract of this paper is available at the journal's website.
- View abstract.

- **Amplitude contrast of a single gadolinium atom reconstructed by a wave field restoration method**
- **Appl. Phys. Lett. 89, 253106 (2006)** ***(3 pages)***
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- Single gadolinium atoms in fullerenes encapsulated in a single-wall carbon nanotube were observed by a wave field restoration method based on three-dimensional Fourier filtering in transmission electron microscopy. Single gadolinium atoms were clearly resolved not only in the imaginary part image but also in the real part image of the exit wave field due to an improved signal-to-noise ratio by Fourier filtering and resolution enhancement by correcting spherical aberration and twofold astigmatism. This result indicates that the present method has potential to clarify compositional details of the sample by using their image contrasts.