


# LE NUOVE FRONTIERE DELLE NANOTECNOLOGIE

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# Perché Terapie Mirate e Nanotecn

- Nonostante i progressi ottenuti nel monitoraggio e nella terapia, alcune forme di malattia (cardiovascolare, tumore) a tutt'oggi determinano una scarsa aspettativa di vita per il paziente.
- Le numerose scoperte ottenute dalla ricerca di base forniscono nuovi potenziali bersagli terapeutici e marcatori predittivi adatti al follow-up.
- La terapia mirata (a target) rende possibili cure personalizzate.

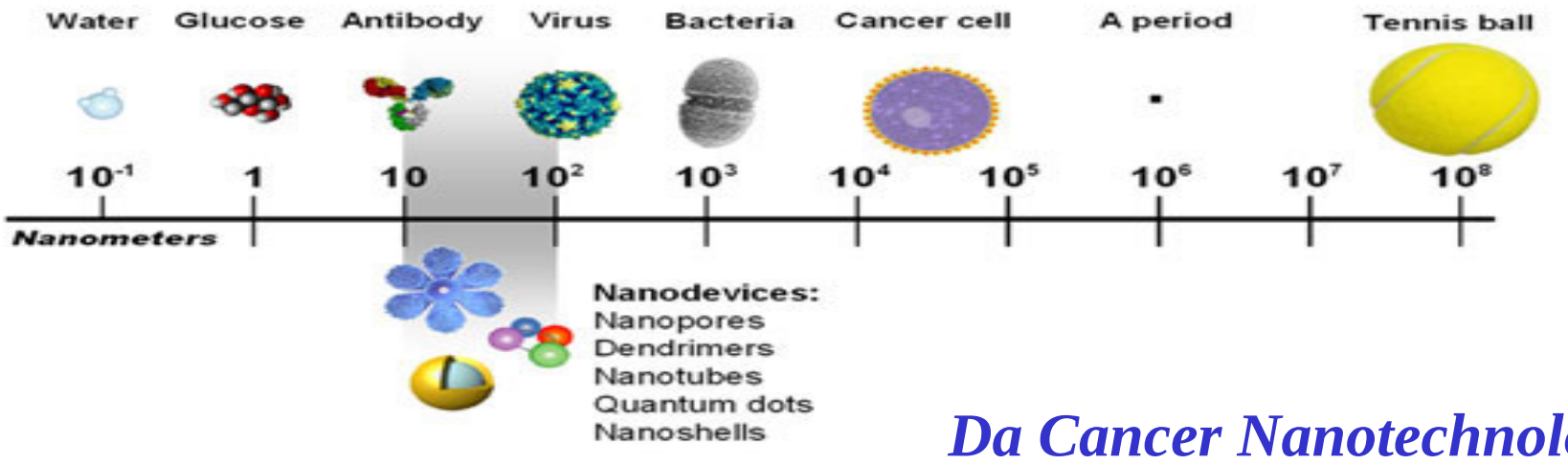
  Le Nanotecnologie sono utili in diagnostica e terapia mirata

# Nanotecnologie: la dimensione di “oggetti” biologici

Le nanotecnologie sono lo sviluppo e la costruzione di materiali così piccoli che sono misurati su scala molecolare.

## La dimensione dei materiali in nanotecnologie:

È simile a quella delle molecole biologiche (“biomolecole”)
come ad esempio il DNA, le proteine tra cui enzimi e recettori (Es. la molecola di emoglobina è circa 5 nanometri di diametro).

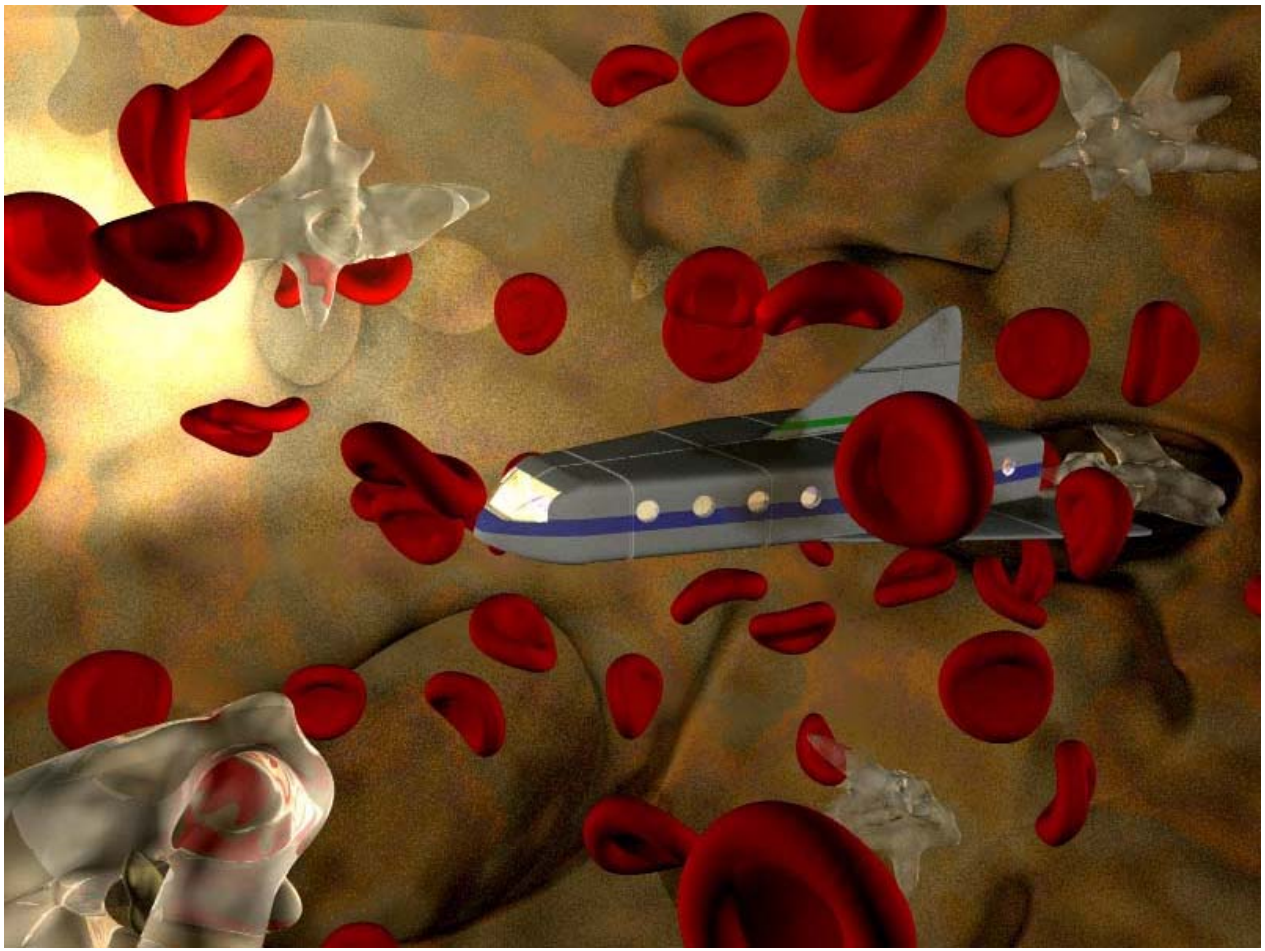



*Da Cancer Nanotechnology*

# Nanotecnologie: una visione d'insieme

Le Nanotecnologie sono la creazione di materiali, invenzioni, e sistemi innovativi e utili attraverso la manipolazione di materiale minuscolo
(che abbia almeno una dimensione più piccola di 100 nanometri).
Il campo emergente delle nanotecnologie coinvolge scienziati provenienti da diverse discipline, compresi Fisici, Chimici, Ingegneri, Biologi, Farmacologi fino alla Medicina.

# Fantastic Voyage



**Dal Fantastic Voyage di Isaac Asimov ad oggi la scienza ha fatto molti passi avanti.**

# Nanoscienze e Nanotecnologie in Medicina: Finalità

- Creare e utilizzare dispositivi allo scopo di raggiungere e localizzare malattie, per terapie, diagnostica o prevenzione.

- Concepire e sviluppare test per analizzare particelle biologiche in nanoscala di rilevanza per la BIOMEDICINA.

# Nanoscienze e Nanotecnologia in Biologia e Medicina

## I Vantaggi:

Grazie alla loro piccola dimensione, i materiali in nanoscala possono facilmente interagire con biomolecole sia sulla superficie sia all'interno delle cellule.

Attraverso l'accesso a molte aree del corpo, i materiali in nanoscala hanno la potenzialità di localizzare una malattia e di consentire di somministrare il trattamento farmacologico attraverso vie innovativa.

## Sconfiggere il Cancro con le Nanotecnologie

Le Nanotecnologie offrono un'opportunità senza precedenti di studiare e interagire fra le cellule normali e quelle cancerogene, a livello di scala molecolare e cellulare, anche durante gli stadi precoci dei processi di cancerogenesi.

Si possono anche creare nuove e perfezionate tecniche di immagine per trovare piccoli tumori inziali:

Diagnostica precoce.




Le Nanotecnologie cambieranno i fondamenti della diagnosi, del trattamento e della prevenzione dei Tumori.

# Sfide associate alle nanotecnologie: IL CANCRO

- 1) Nanovettori per il trasporto di farmaci.

  Uso di nanotrasportatori, nanoparticelle atte alla somministrazione mirata di sostanze terapeutiche.
  La veicolazione ha diversi scopi:
  -diminuire tossicità
  -riconoscere del tumore in modo specifico
  -migliorare la penetrazione del farmaco
  Esempio: utilizzo Liposomi, che vengono caricati di chemioterapici per raggiungere più facilmente la neoplasia.

- 2) Nanoparticelle “telecomandate”.

  Le particelle si legano selettivamente alle singole cellule cancerose e le distruggono in modo mirato (ex irraggiamento).

# Sfide associate alle nanotecnologie: IL CANCRO

- 3) Nanoprocessori da inserire nelle cellule.

  Per analizzare e controllare l'espressione genica.
  In futuro si pensa di poter costruire un nanocomputer che controlli dall'interno molecole di acido nucleico mutate (nano-diagnostica molecolare)

- 4) Chip di silicio come nano-farmaco.

  Nanodispositivo in silicio da introdurre nell'organismo.
  Il Chip è in grado di condurre il farmaco proteggendolo dal sistema immunitario fino al bersaglio, dove il farmaco verrà rilasciato.

# Sfide associate alle nanotecnologie: IL CANCRO

- 5) Nanoterapia genica.
  Riparazione dei difetti e mutazioni del DNA.
- 6) Nanobiomateriali.

  Materiali biocompatibili nella fabbricazione di protesi.
- 7) Microrobot per la diagnostica.

  Emettono continuativamente immagini per analizzare l'organismo dall'interno.
- 8) Nanosonde di DNA per la biologia molecolare.

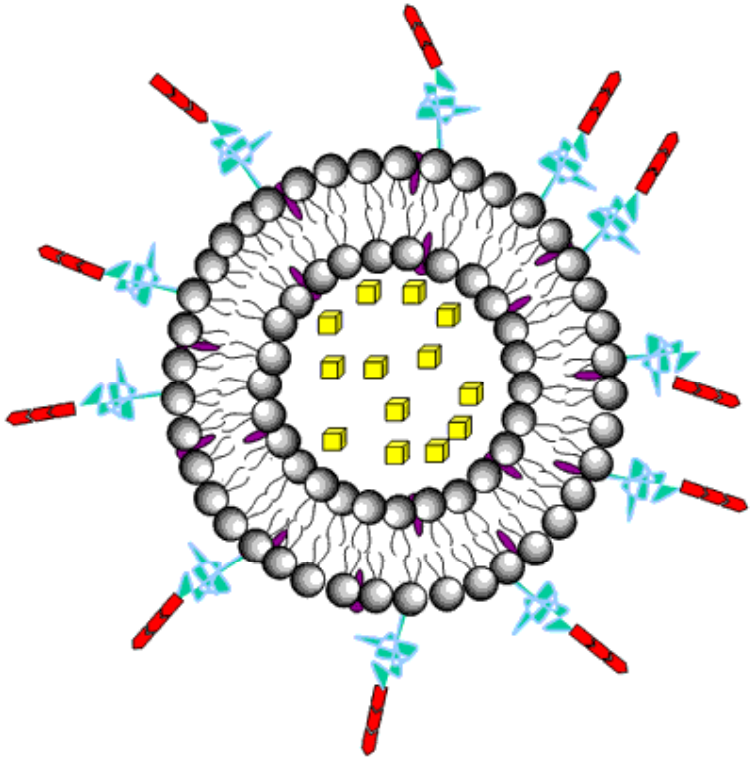
  Per caratterizzare meglio le neoplasie e creare trattamenti finalizzati.
- 9) Nano-diagnosi genetica.

  Per diagnosticare tumori di origine genetica.



# Dal trasporto dei farmaci

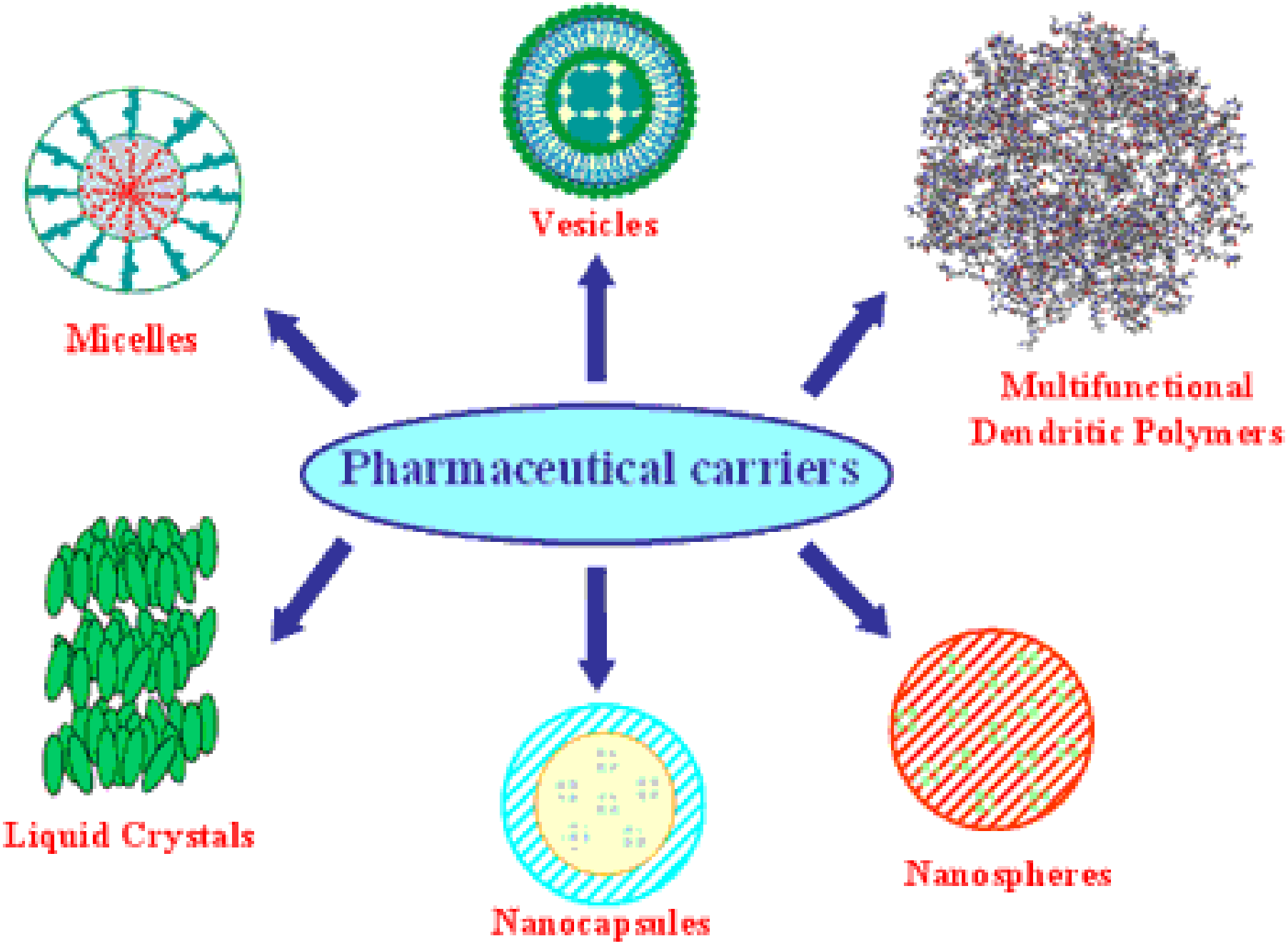
# ai proiettili-particella



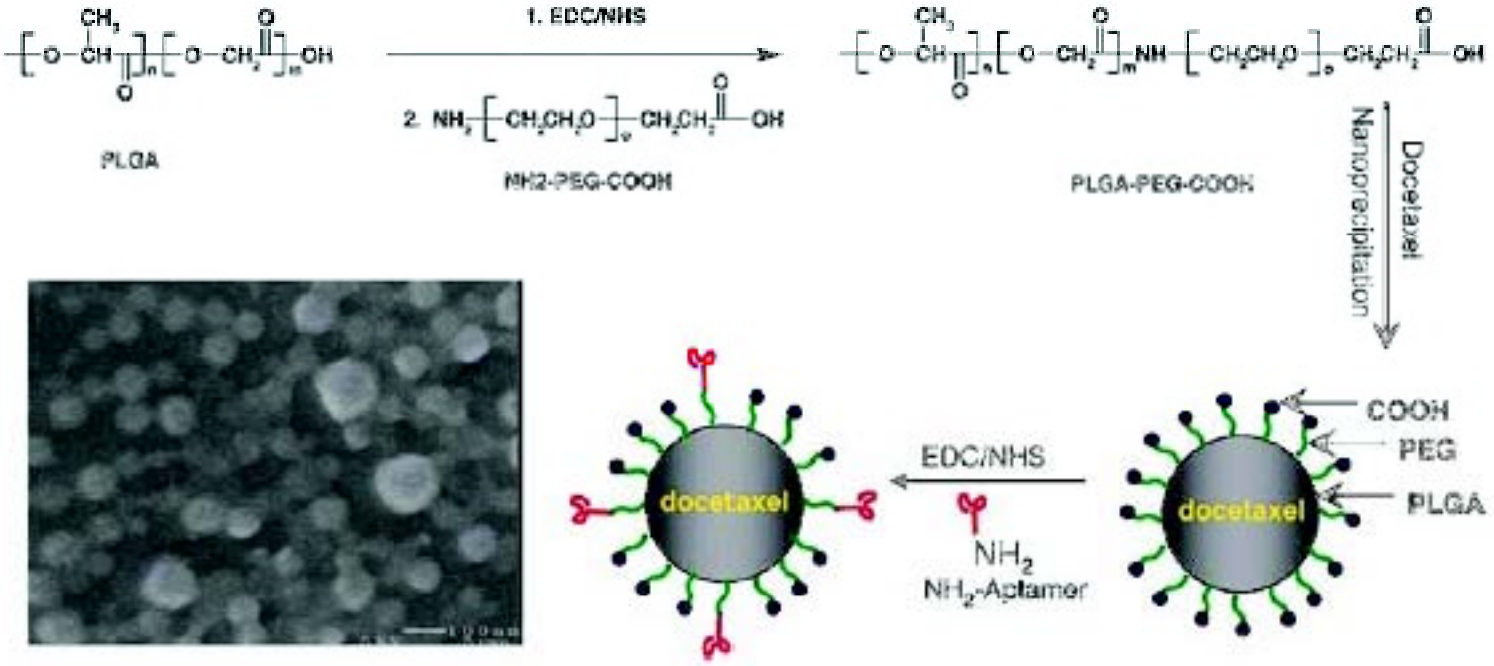
Inclusione di farmaci in Liposomi.

# Transportatori Liposomici



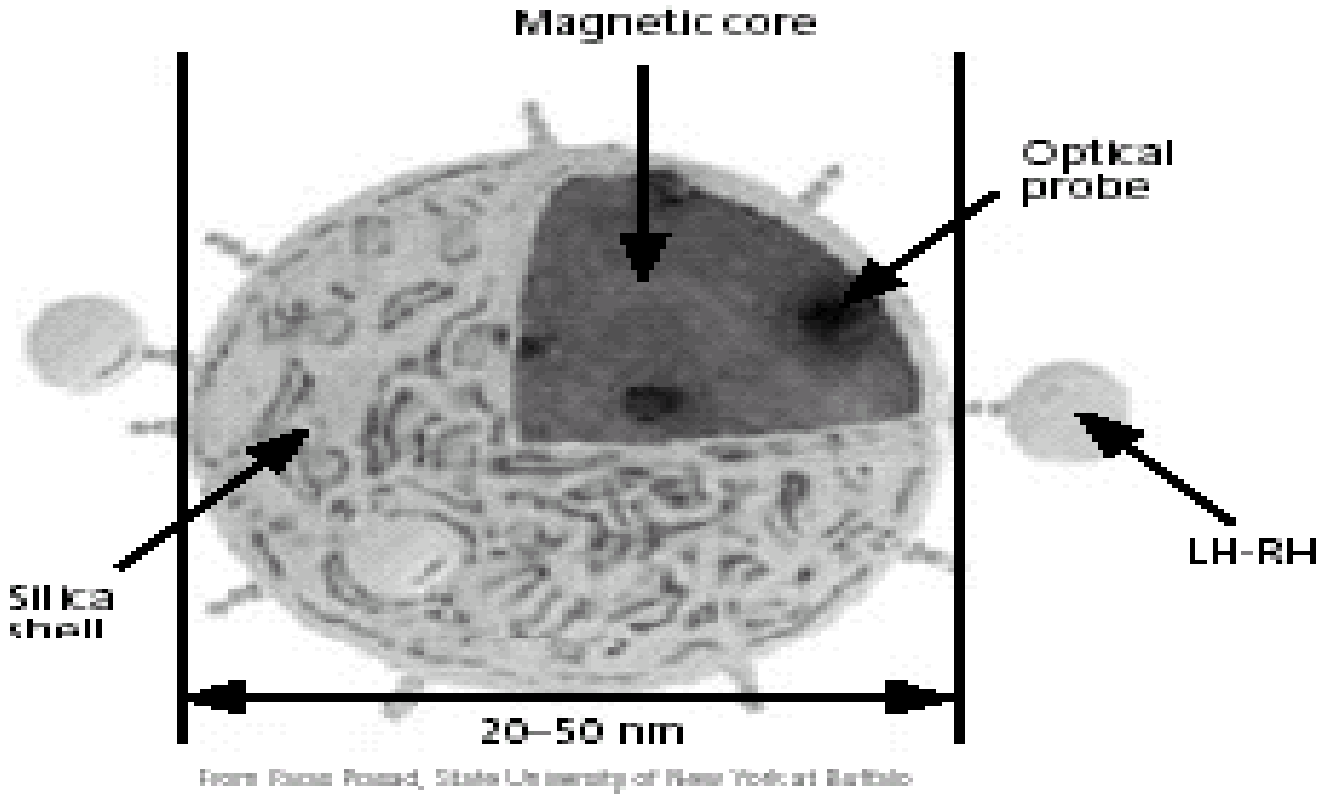

Pharmaceutical carriers
Micelles
Vesicles
Multifunctional Dendritic Polymers
Liquid Crystals
Nanocapsules
Nanospheres

# Nanoparticelle con PEG che incapsulano Antraciclina-Coniugata ad aptameri




Aptamers are DNA or RNA oligonucleotides that bind to antigen with high affinity and specificity

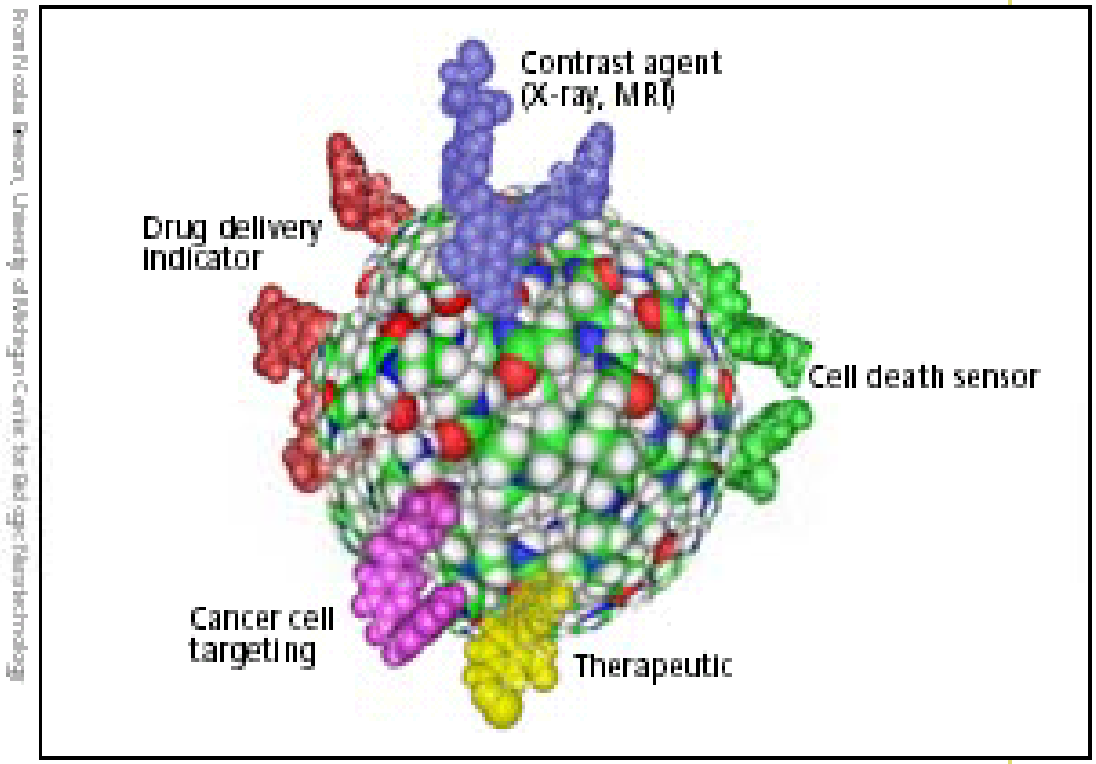
# Guscio di silice: un esempio




Nanoparticelle multifunzionali possono essere dirette contro cellule Cancerogene usando recettori-ligandi.

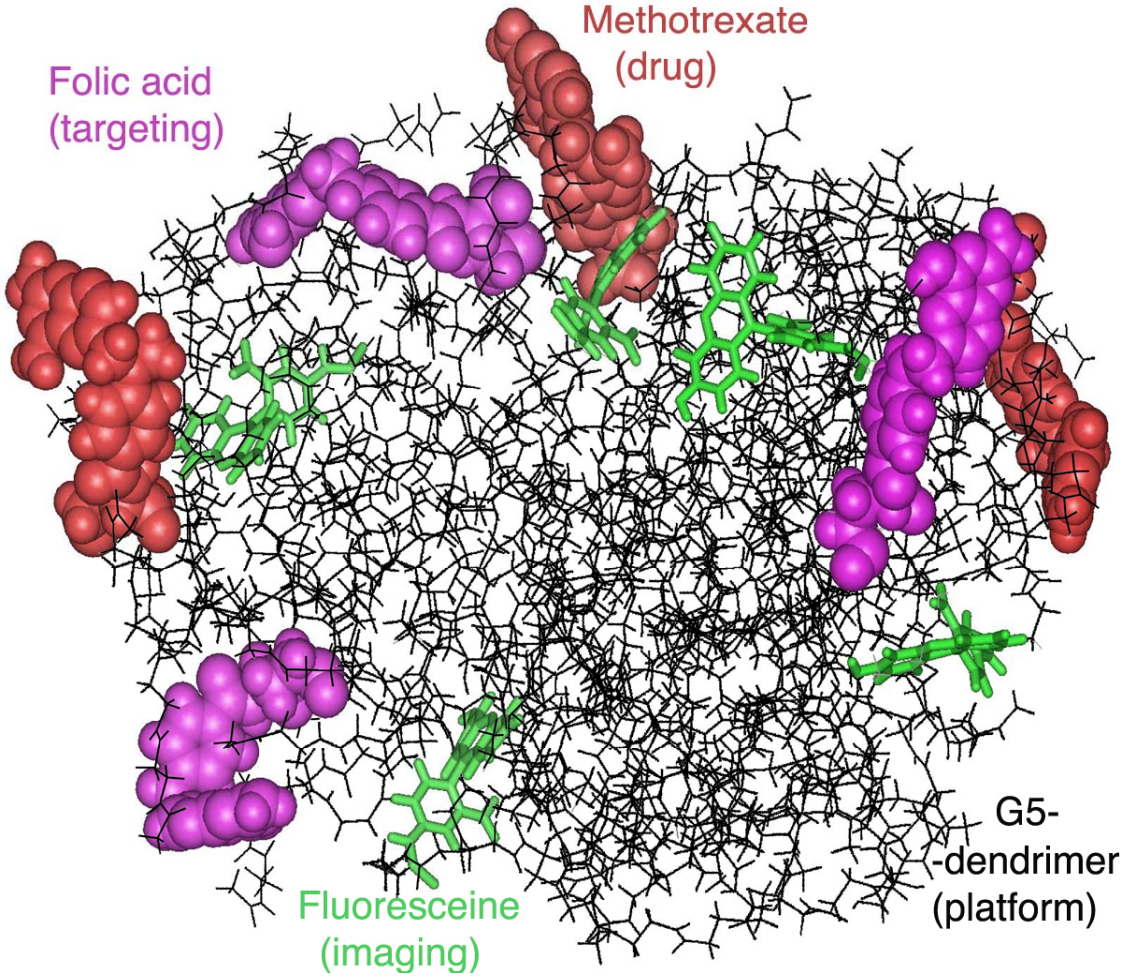
*Da Cancer Nanotechnology, NIH & National Cancer Institute*

# Dendrimeri e applicazioni

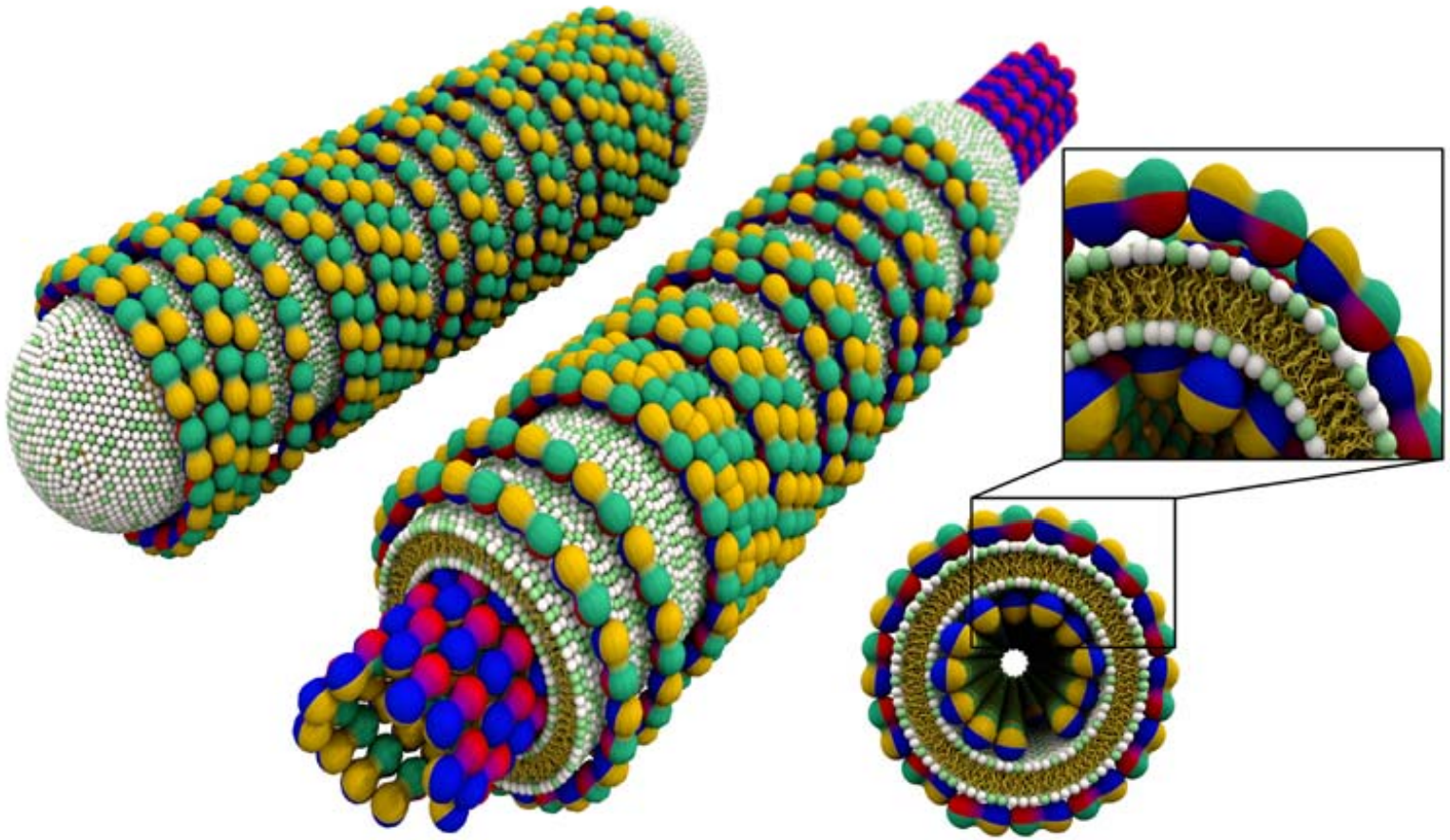



I Dendrimeri possono servire come piattaforme versatili per localizzare La cellula tumorale e somministrare farmaci.

*Da Cancer Nanotechnology, NIH & National Cancer Institute*

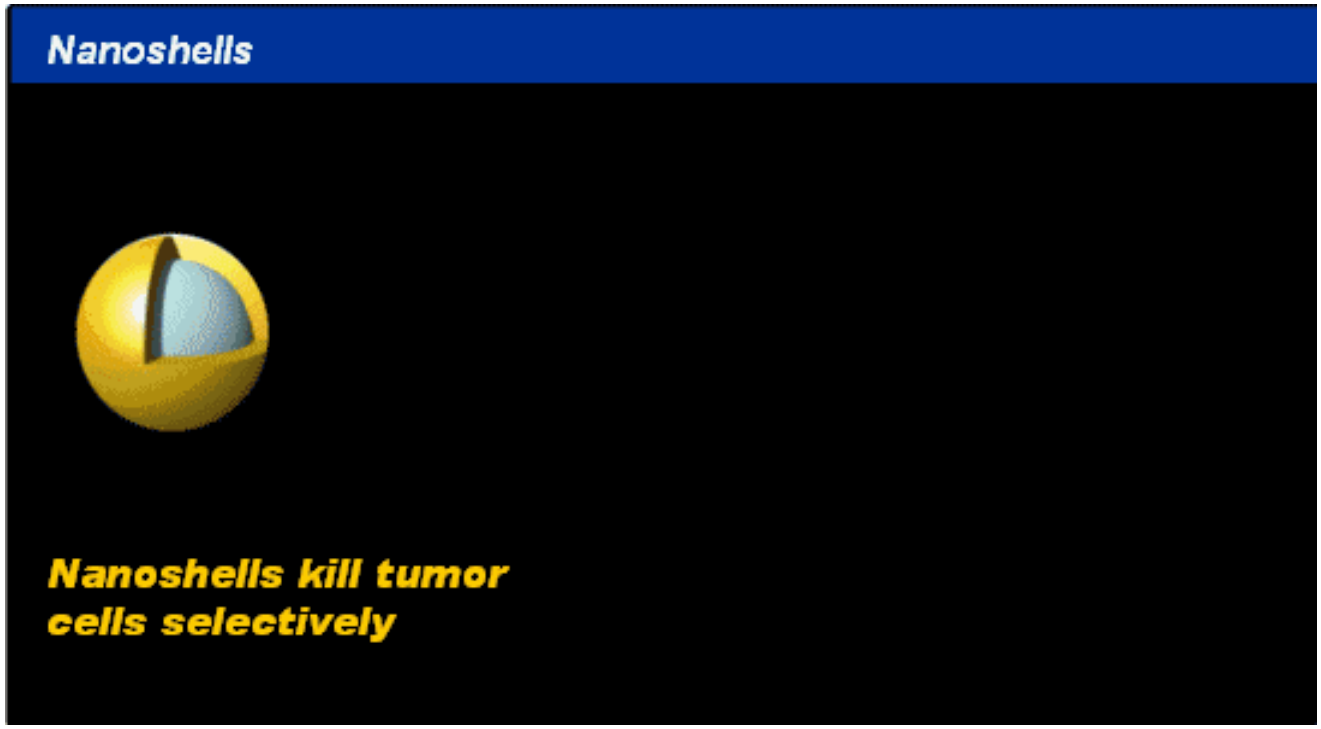



This simplified computer model of the U-M nanoparticle shows the dendrimer's branching structure and how molecules and drugs are attached. Photo credit: Jolanta Kukowska-Latello, Michigan Nanotechnology Institute for Medicine and the Biological Sciences.

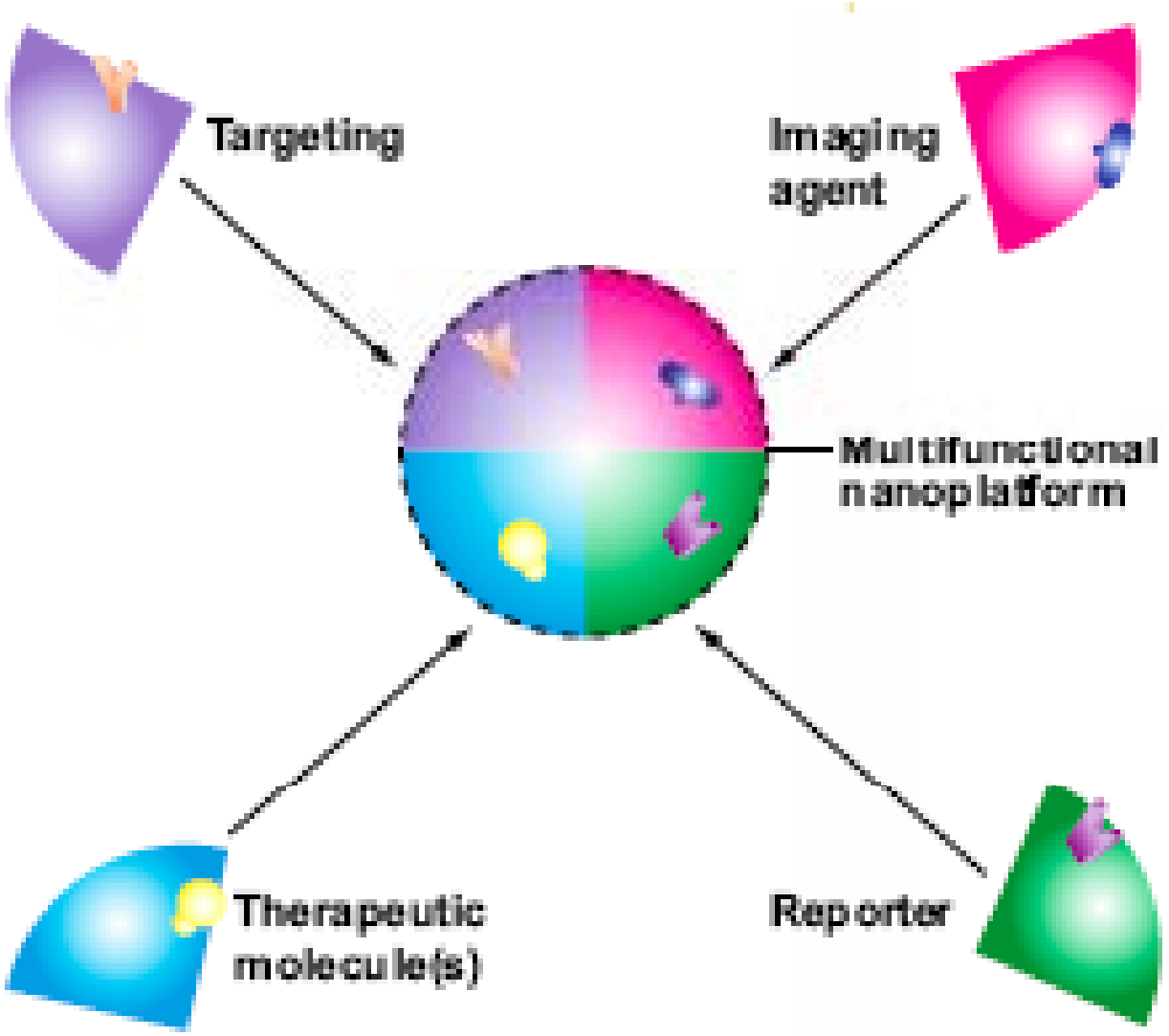


Bionanotubi "Smart" fatti di proteine dei microtubuli rosso blu; ricoperto di uno strato lipidico giallo verde Controllando lipidi
E proteine si possono dosre l’incapsulazione e i rilascio di farmaci.

# Nanogusci: uccidono la cellula tumorale in modo selettivo

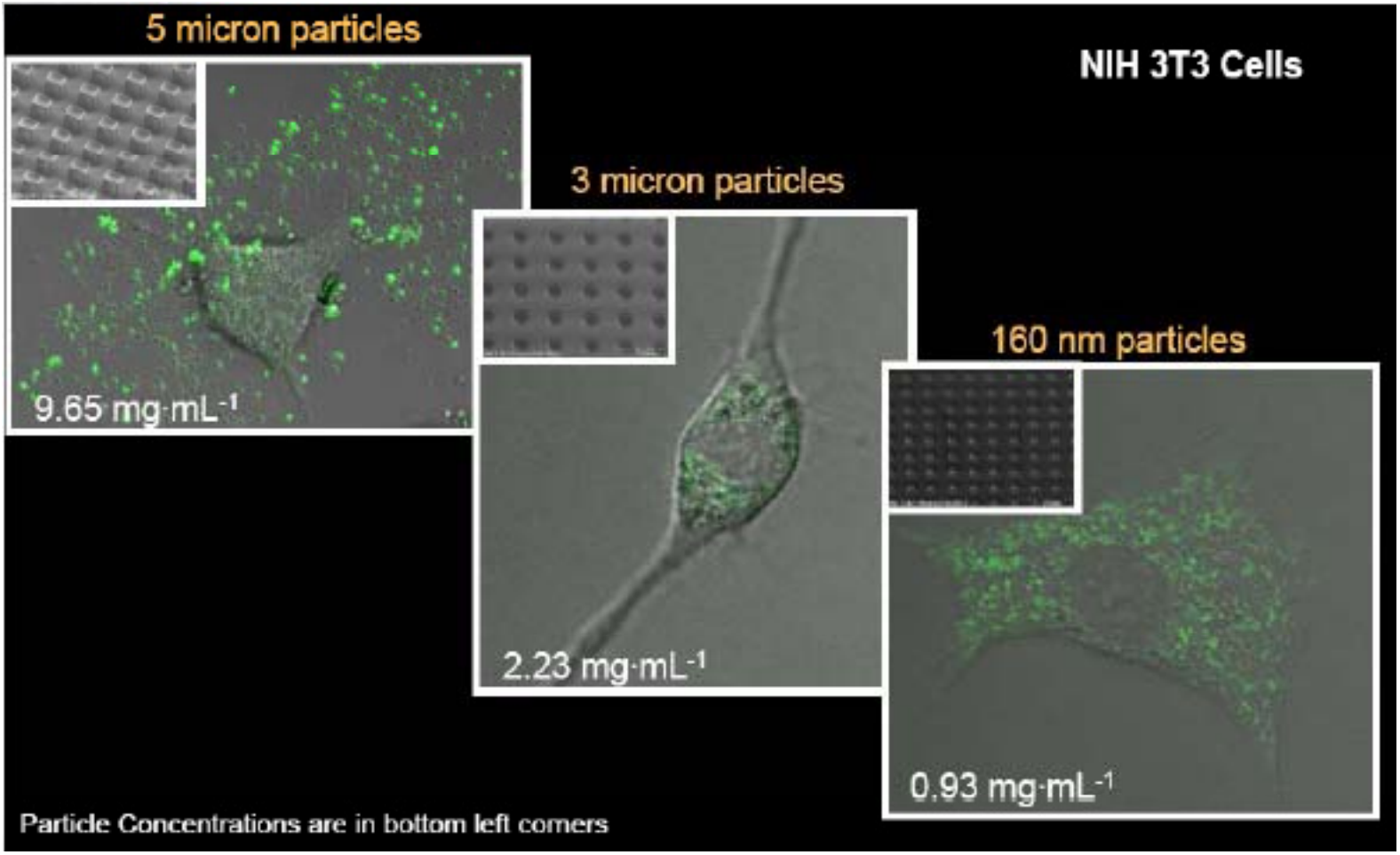


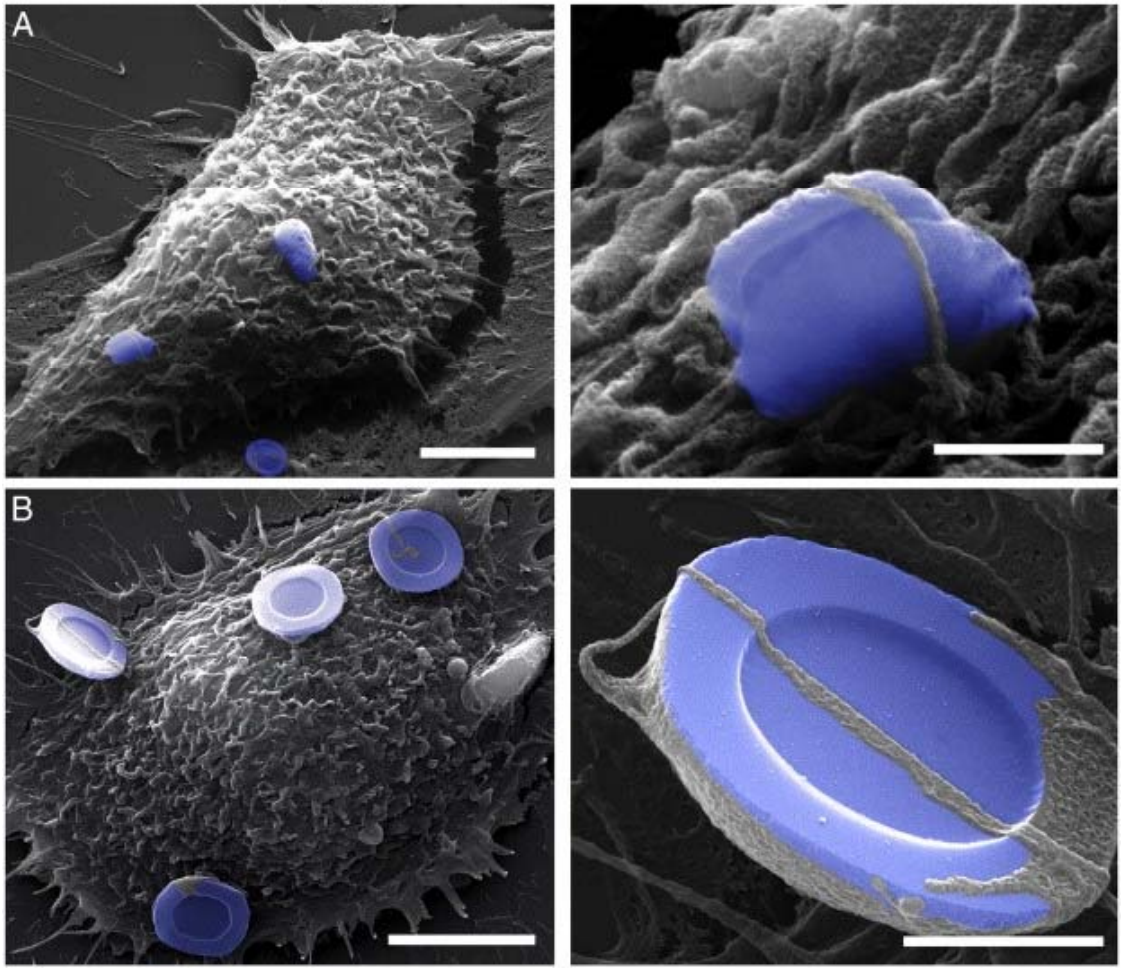

*Da Cancer Nanotechnology, NIH & National Cancer Institute*




An important aspect of biomedical nanotechnology research is that most systems are being designed as general platforms that can be used to create a diverse set of multifunctional diagnostic and therapeutic devices.

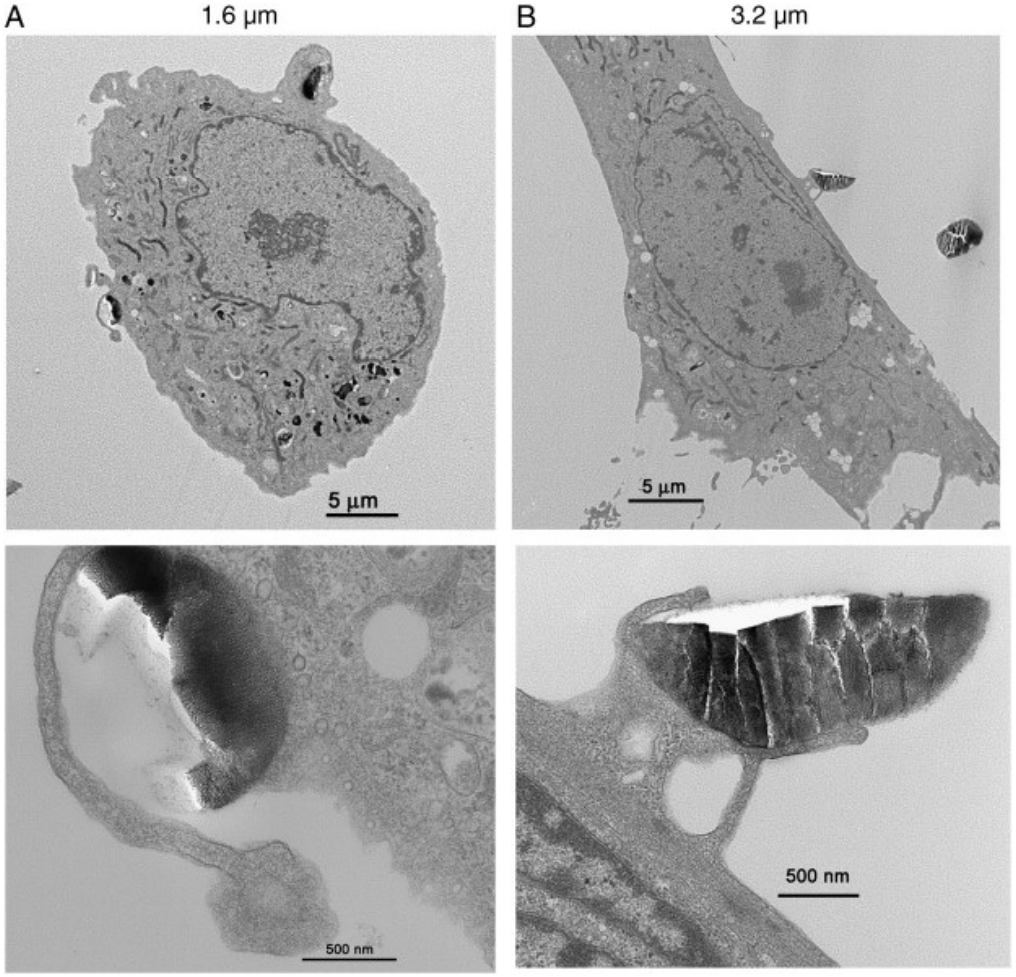
# Size Effects on Particle Uptake






Scanning electron micrographs show endothelial binding and engulfment of 1.6 µm (top row) and 3.2 µm (bottom row) silicon microparticles [bars 5 µm (left) and 1 µm (right)].

R.E. Serda, et al., Multi-stage delivery nano-particle systems for therapeutic applications Biochim. Biophys. Acta (2010) doi:10.1016/j.bbagen.2010.05.004

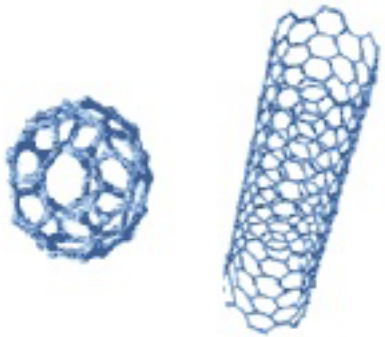



Endothelial cells internalize silicon microparticles by rearrangement of the actin cytoskeleton. Transmission electron micrographs show internalization of larger, 3.2 µm particles by phagocytosis (A) and smaller, 1.6 µm, particles by macropinocytosis (B).

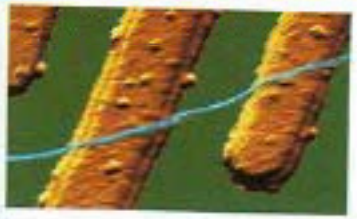
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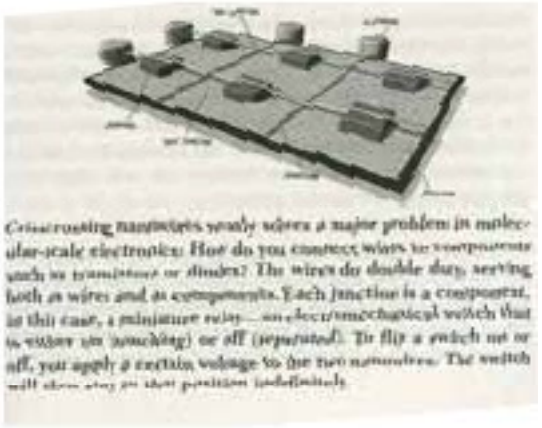
The dream of a space elevator



*Their electric and mechanical properties are exeptional, such that researchers are working towards their use in electronic circuits*



A new form of carbon, bucky-balls and nanotubes are one of the promise tools of nanotechnology. Carbon nanotubes can be conductive or semi-conductive depending on their structure. They can be made of a single sheet of graphite rolled into a tube (SWCNT) or of many concentric sheets (MWCNT)



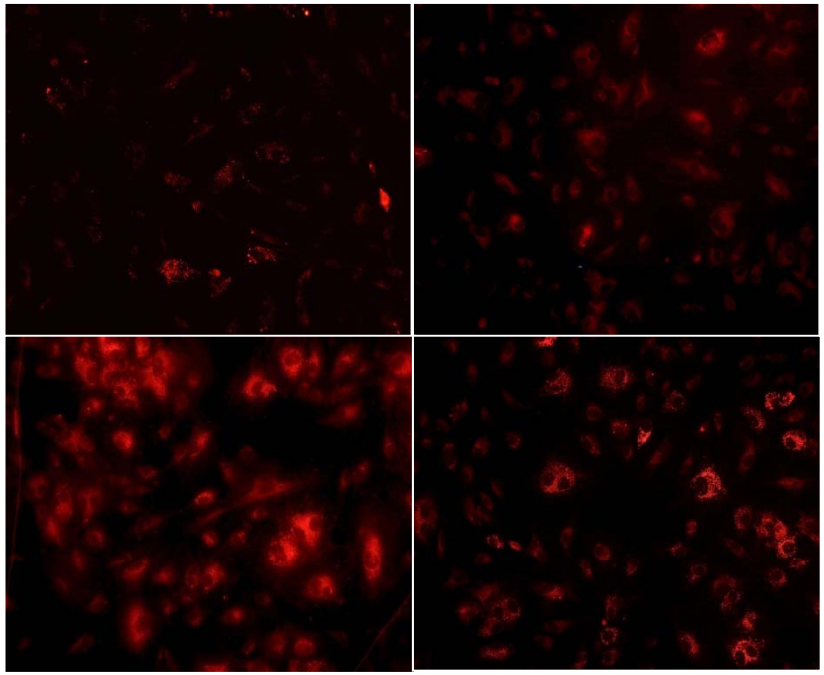
Crisscrossing nanowires neatly solves a major problem in molecular-scale electronics: How do you connect wires to components such as transistors or diodes? The wires do double duty, serving both as wires and as components. Each junction is a component, in this case, a miniature relay—an electromechanical switch that is either on (touching) or off (separated). To flip a switch on or off, you apply a certain voltage to the two nanowires. The switch will then stay in that position indefinitely.

# Carbon Nanotubes and endothelium (HUVEC)

## Intracellular Localization:

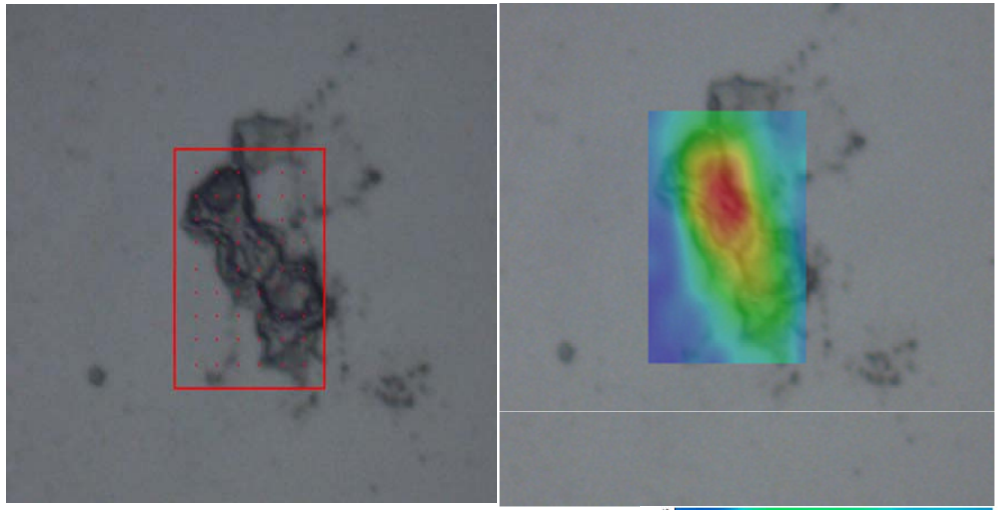
Control

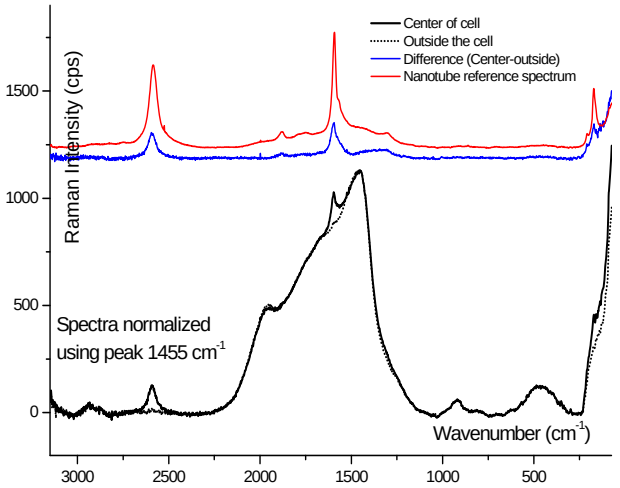
10000 ng/ml

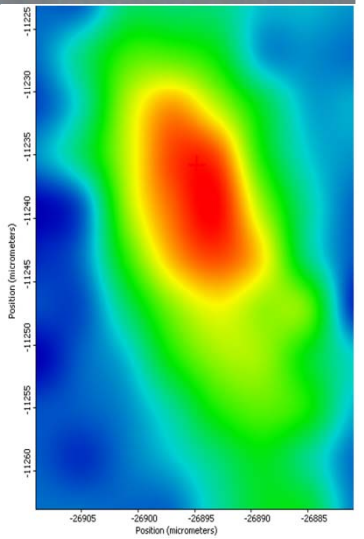


25000 ng/ml

50000 ng/ml



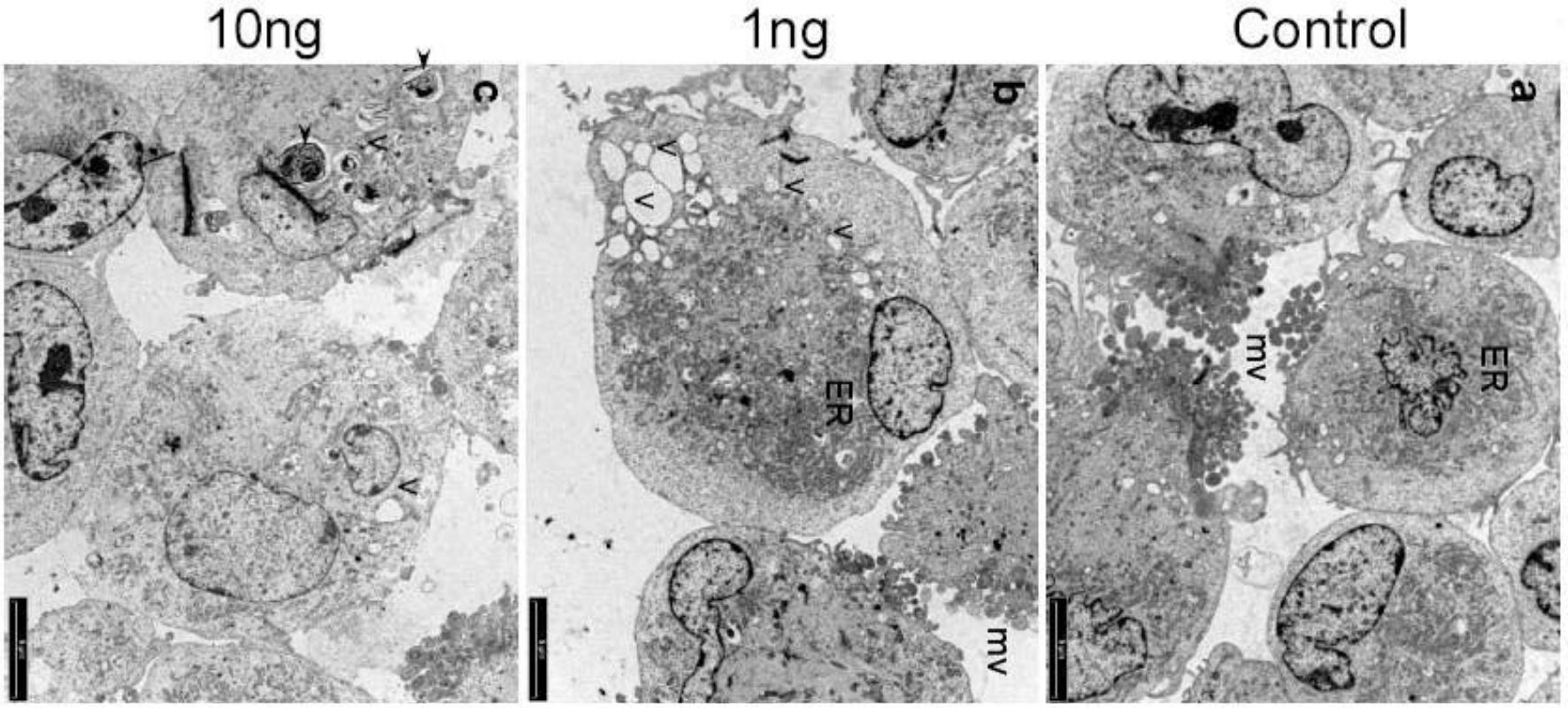



*Nanomedicine*, 2010

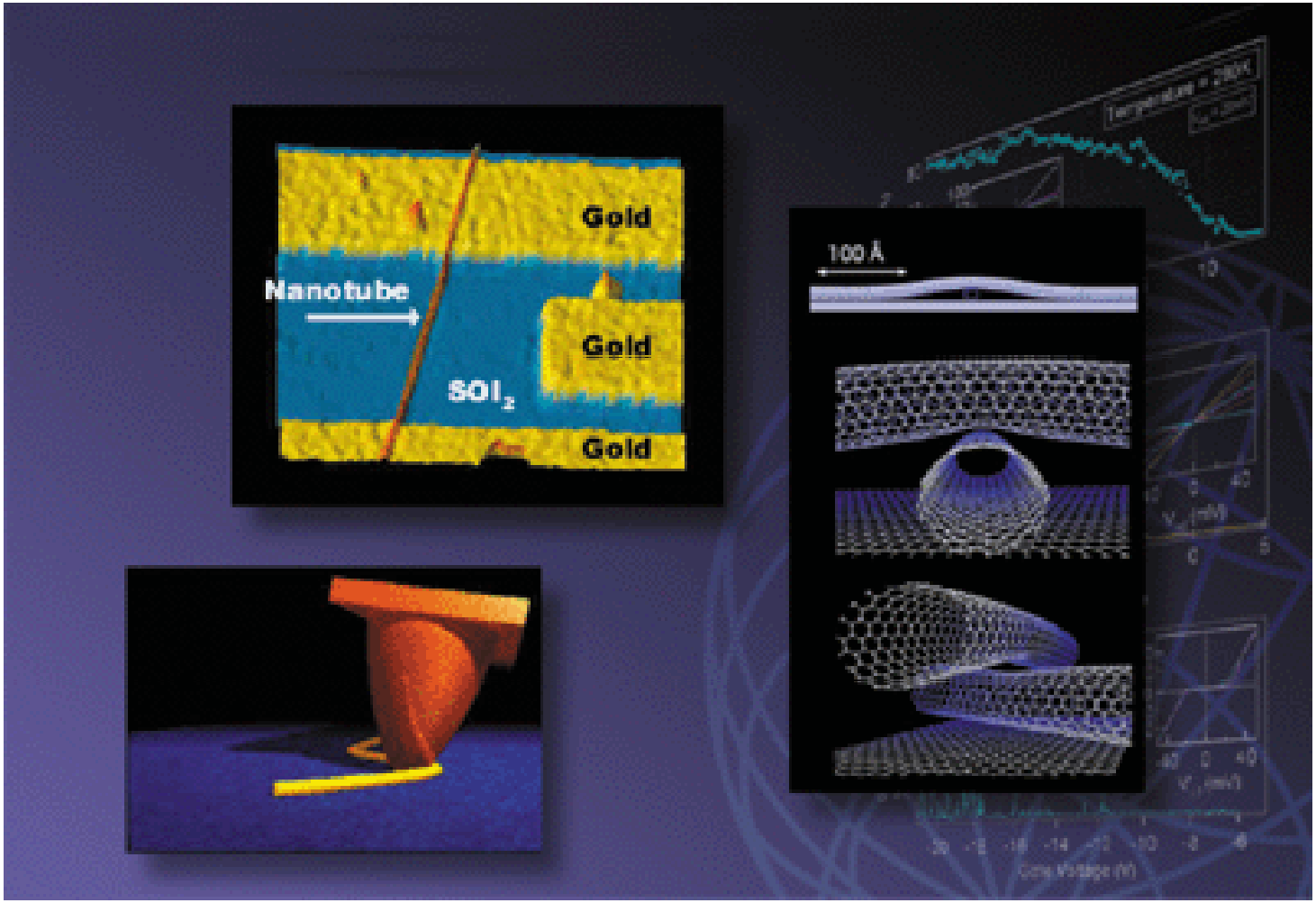
# Carbon Nanotubes and endothelium (HUVEC)

Intracellular Localization:

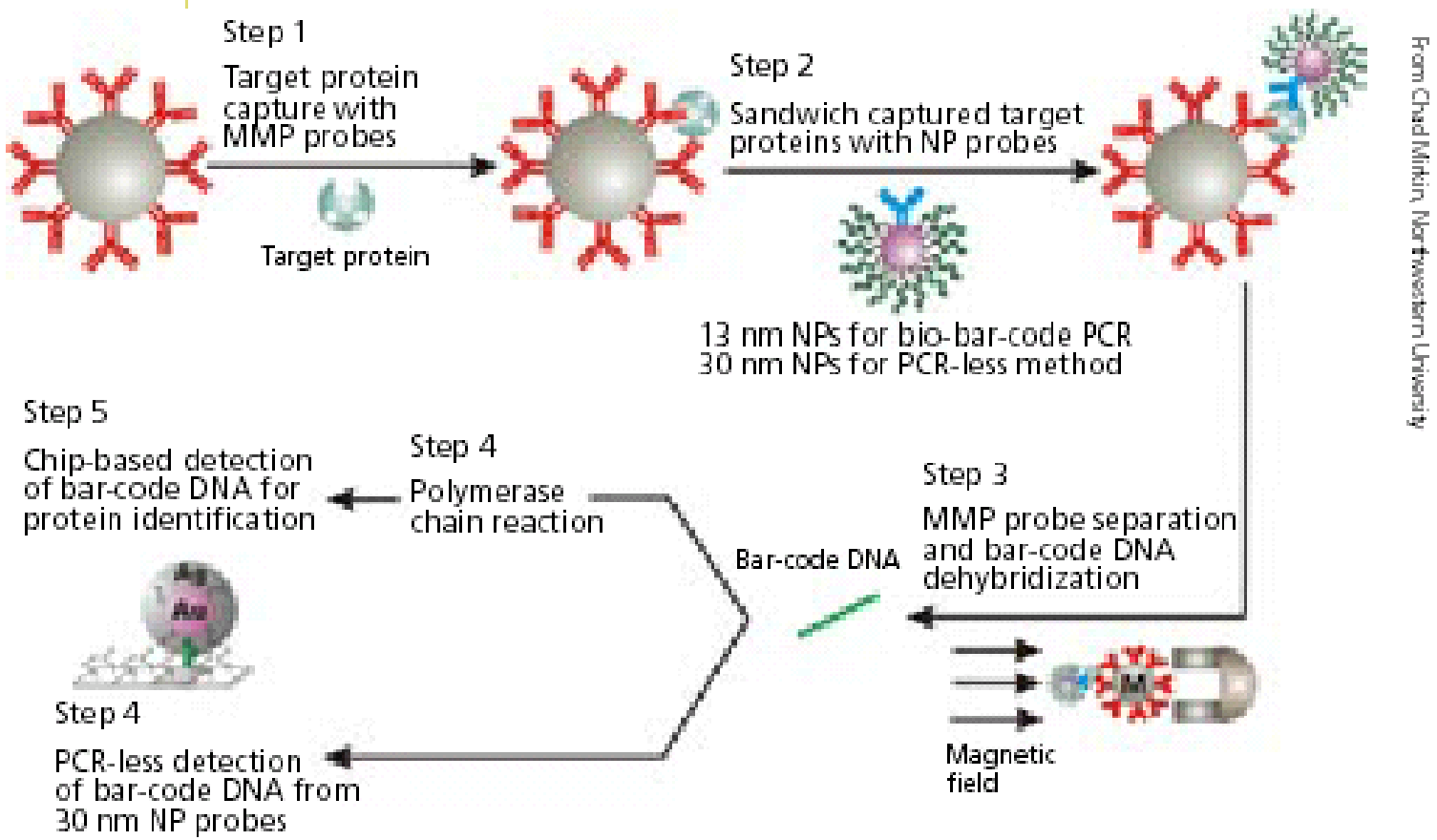



*Albini et al, Nanomedicine,* 2010

# Computer molecolare



# Nanotecnologia e Diagnostica: un Esempio



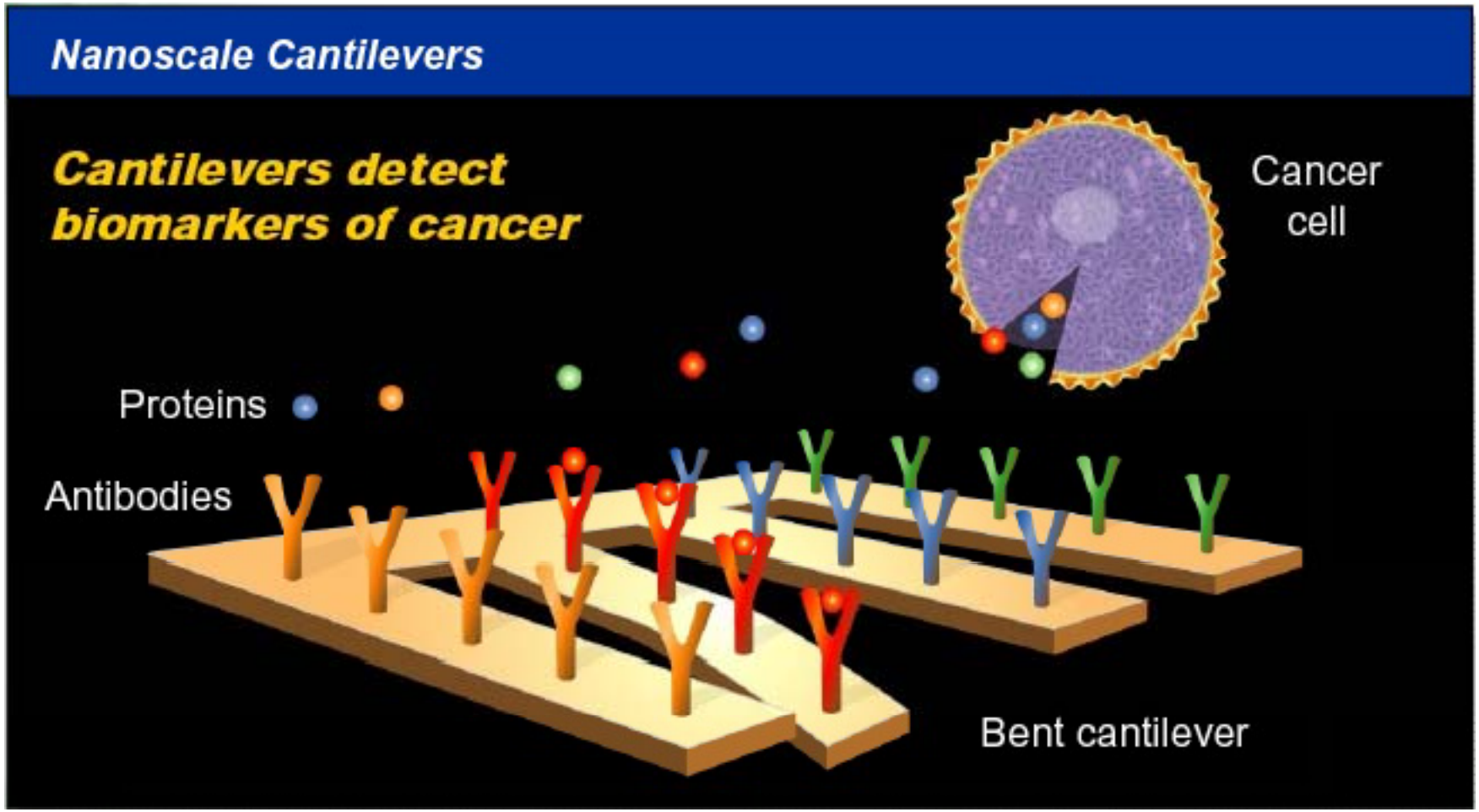

Un anticorpo monoclonale contro un antigene specifico per la prostata è stato legato a microparticelle metalliche (MMP) che a loro volta sono legate a Nanoparticelle di oro. Un secondo anticorpo legato è poi aggiunto per creare un sandwich, legato alle nanoparticelle. Nanobeads magnetici servono a localizzare la proteina e separarle.

# Microanalisi del sangue

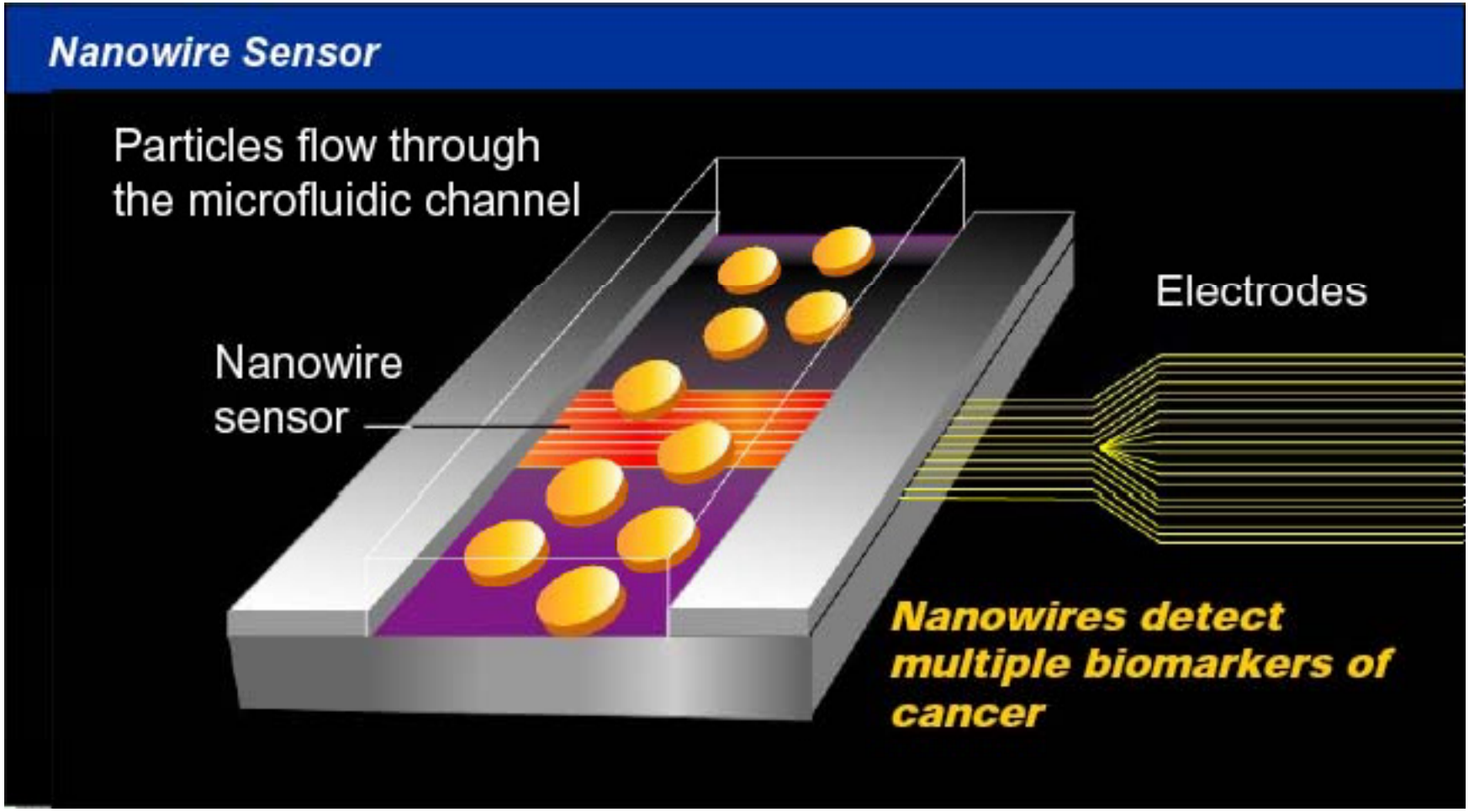
I ricercatori
separano le
proteine del sangue
per isolare
frammenti e peptidi



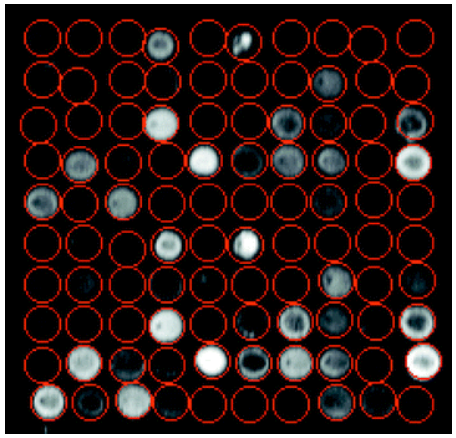
# Piattaforme Nanotecnologiche per diagnosi precoce



# Nanotecnologie e Nano-fluidica ha il Potenziale di cambiare la Diagnostica oncologica

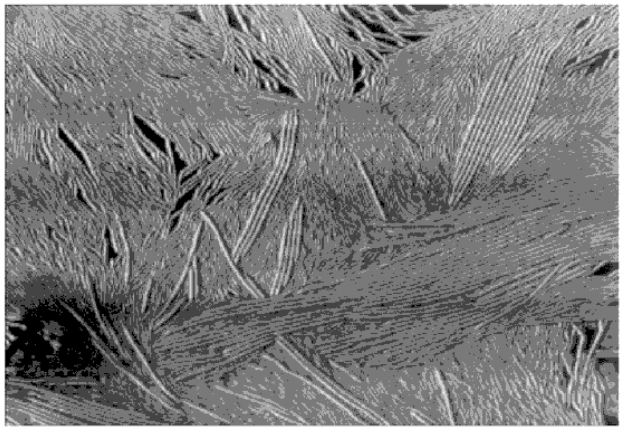


# Analisi di espressione in parallelo: Microarray



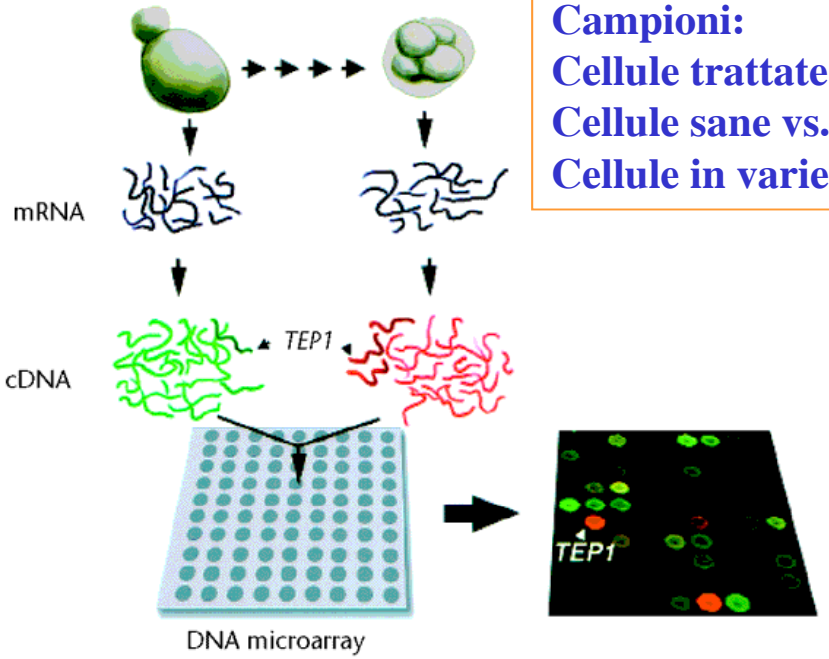
Il segnale originale

**Microarray vengono prodotti mediante l'applicazione di sonde per geni noti ad una superficie di vetro o silicone attraverso sintesi fotolitografica (Affymetrix), "spotting" (Pat Brown).**



Microscopia a forza atomica:
il DNA sul vetrino

**I campioni da analizzare (mRNA estratto da cellule) marcati con due fluorofori diversi vengono ibridati con le sonde. Un filamento marcato (campione) si lega alla sonda complementare generando così il segnale fluorescente.**




**Campioni:**
**Cellule trattate vs. non trattate**
**Cellule sane vs. normali**
**Cellule in varie situazioni fisiologiche**

# Development of BarCode Assays for the Detection of Ovarian Cancer

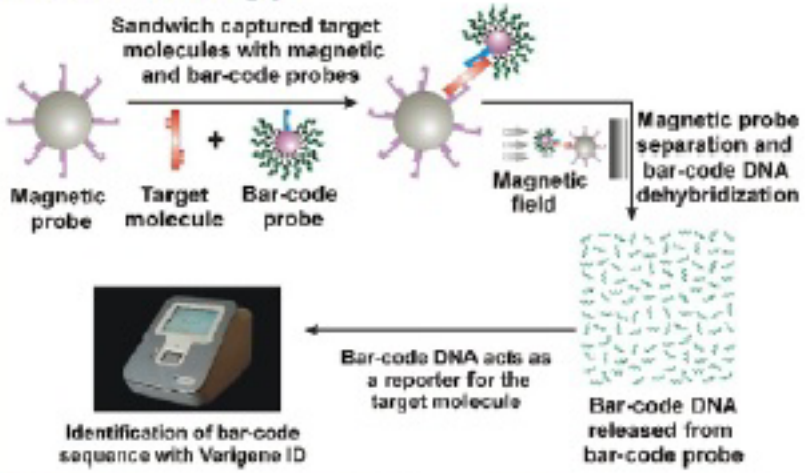
## Problem

- Ovarian cancer is the leading cause of gynecologic cancer death
- With early diagnosis, the cure rate is high. However, ~70% of patients present in later stages of the disease
- Better biomarkers with higher sensitivity are needed

## Approach

- Nanoparticle-based bio barcode assay allows for the identification and study of protein markers at concentrations many orders of magnitude lower than conventional assays

## Technology

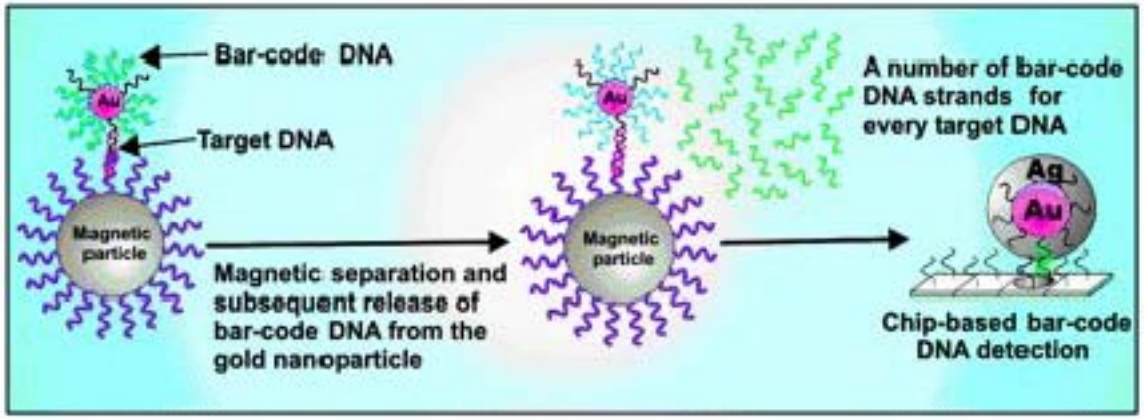


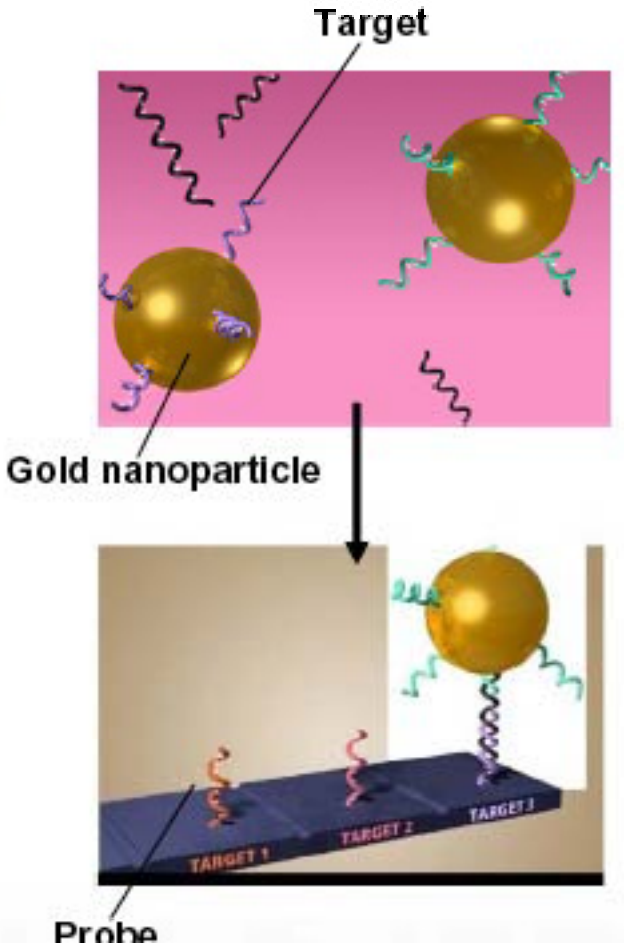

## Goal

- Use bio barcode assay to develop a gynecologic oncology screening tool capable of identifying patients in early stages of ovarian cancer or cancer recurrence (simple, sensitive, highly multiplexed)

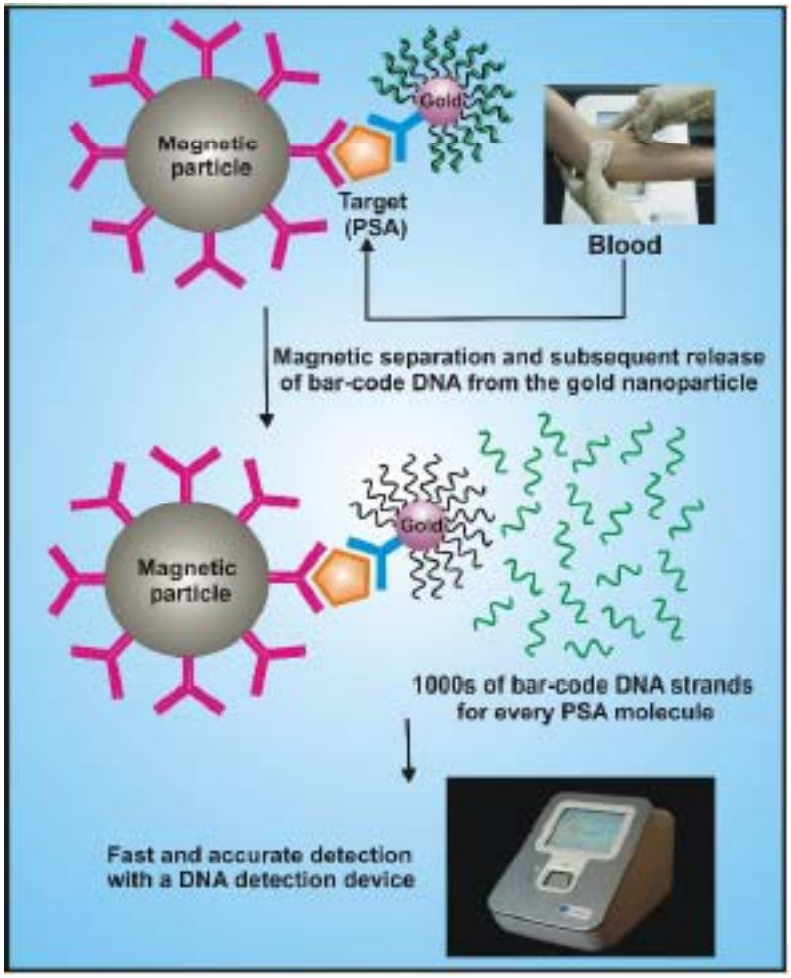
# Early Detection
# Nanoparticle-based Detection

- Developing platforms with high specificity, sensitivity, reproducibility (better than ELISA)
- Nanoparticles enable detection sensitivity for proteins equivalent to PCR for nucleic acids



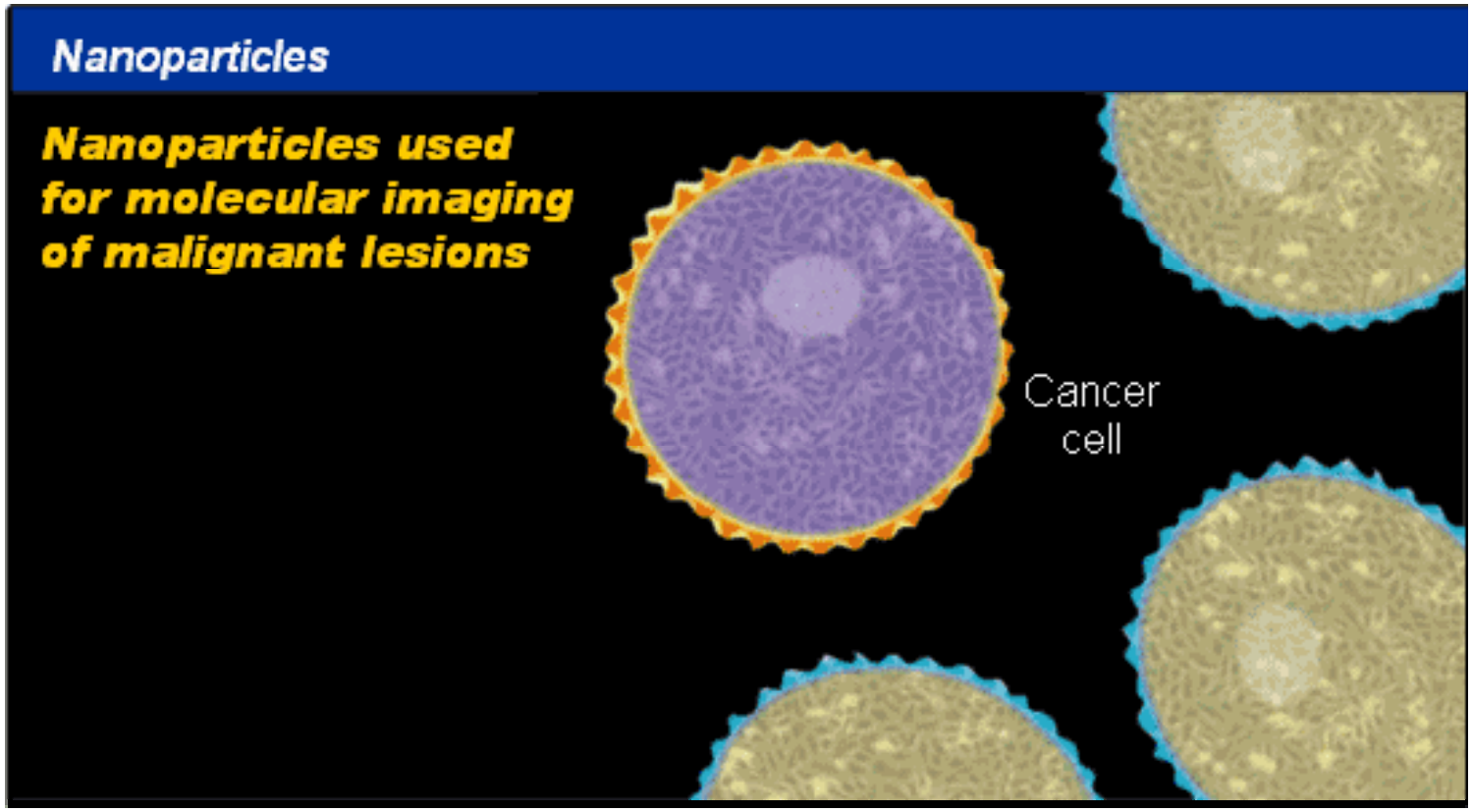



# Multiplexed, High-Sensitivity Detection of Protein Cancer Markers with Bar Code Assay




- $10^4$ - $10^6$ more sensitive than ELISA
- Changing what proteins we look for and where we can look for them in terms of disease detection.
- One platform that can detect protein and nucleic acid markers with the sensitivity of PCR

# Nanoparticelle



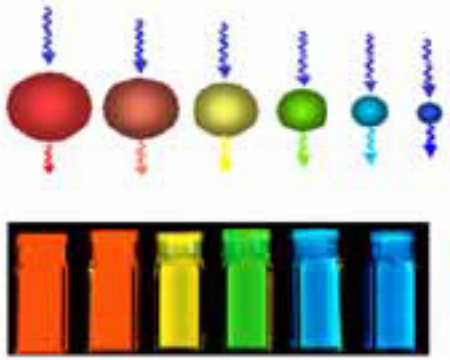

*Da Cancer Nanotechnology, NIH & National Cancer Institute*

## EFFETTI DI SCALA

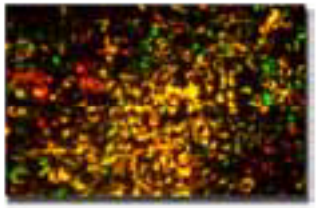
Molte proprietà fisiche hanno una dimensione caratteristica. Quando una particella (o una dimensione di un oggetto) diventa più piccola di questa dimensione, allora mostra proprietà nuove e caratteristiche.

Ad esempio,la struttura elettronica, la conduttività, la reattività, la temperatura di fusione, le proprietà meccaniche cambiano quando la dimensione delle particelle scende sotto una soglia critica. Le nanoparticelle sono più piccole della lunghezza d'onda della luce e interagiscono con essa con effetti quantistici: il loro colore non dipende solo dal materiale, ma anche dalle loro dimensioni. Già nelle vetrate delle chiese medievali, si usavano nanoparticelle di ossidi metallici per colorare: oggi si utilizzano perché sono spesso molto più colorate (o fluorescenti) dei corrispettivi coloranti organici e durano molto più a lungo.

quantum-dots come fluorofori

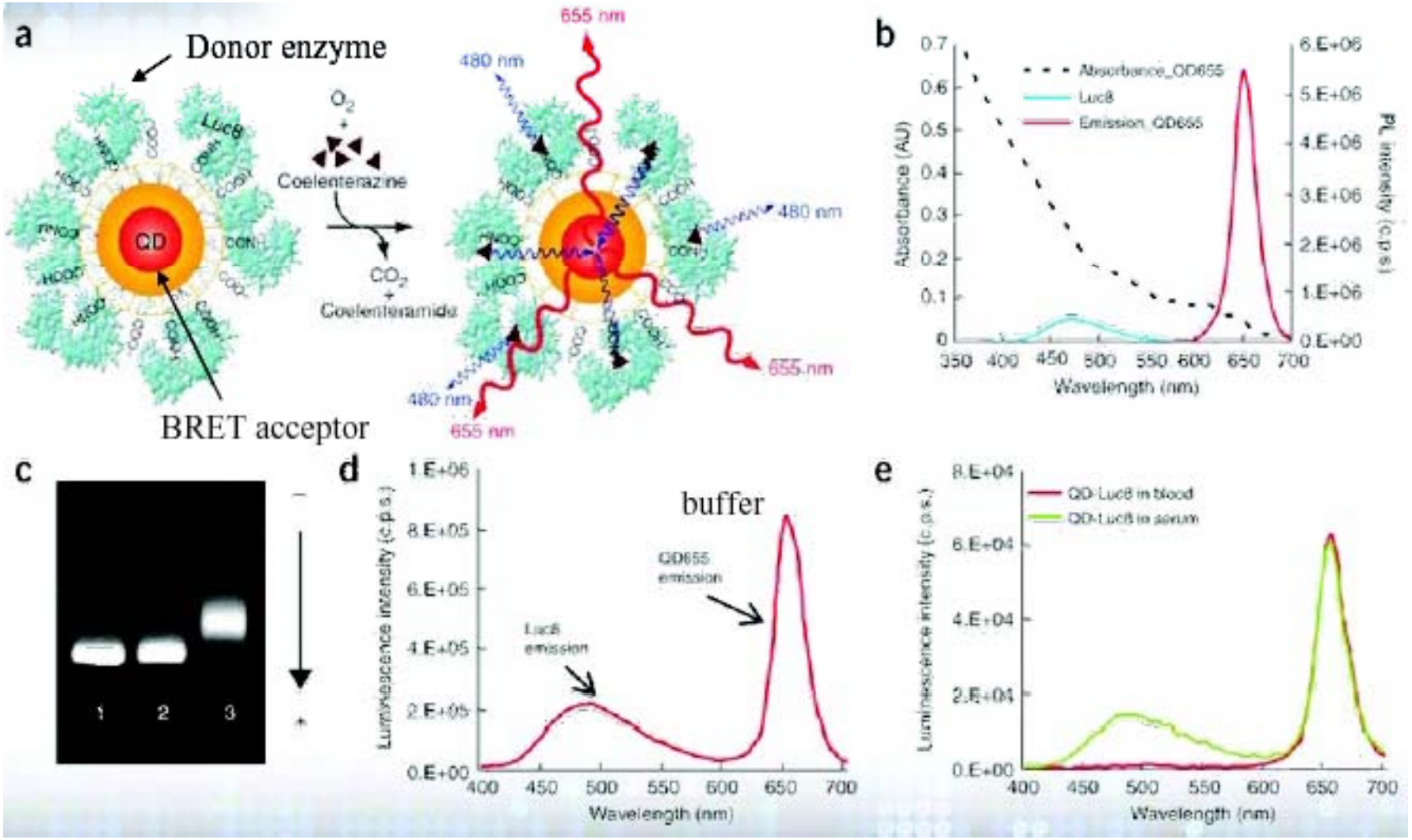


A family of Qdot particles can be made to emit a full spectrum of colors when excited with a single excitation source.



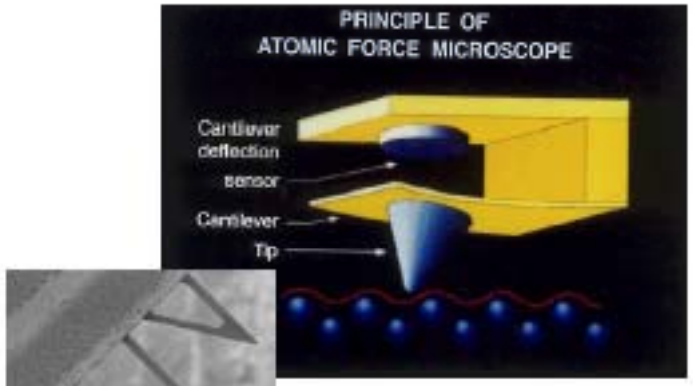
Fluorescence microscopy of quantum dots internalized in CHO-K1 cells. Cells were labeled in four separate reactions with quantum dots having emission maximas of 519 nm, 535 nm, 587 nm, or 616 nm. Cells were mixed, fixed, and mounted for fluorescence microscopy.

# Self-illuminating Quantum Dot Conjugates Using Bioluminscence Resonance Energy Transfer (BRET)

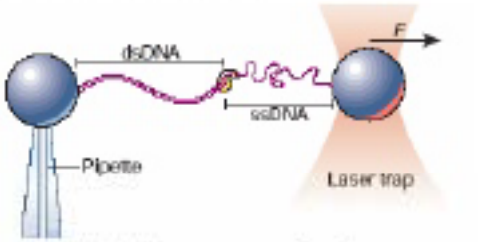


# Nanotecnologie per diagnostica

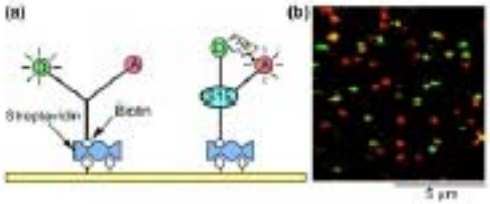
- Le tecniche di fluorescenza (spettroscopia e microscopia) di singola molecola
- Le microscopie a sonda
- Le pinzette laser (optical tweezers)



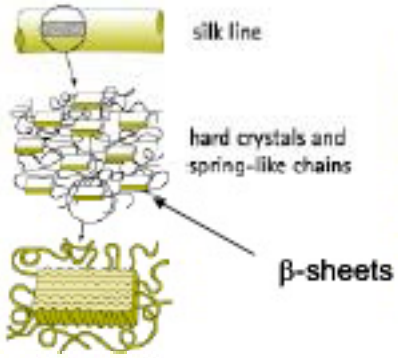

Principio dell'AFM e cantilevers



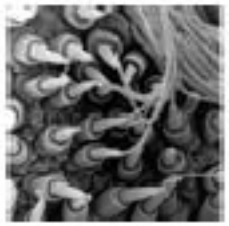

Manipolazione con optical tweezers




Microscopia a fluorescenza
di singole molecole




Le proprietà sono dovute sia alla sequenza di amminoacidi, che alla tecnica di filatura: questi producono una nanostrutturazione sia resistente che elastica.



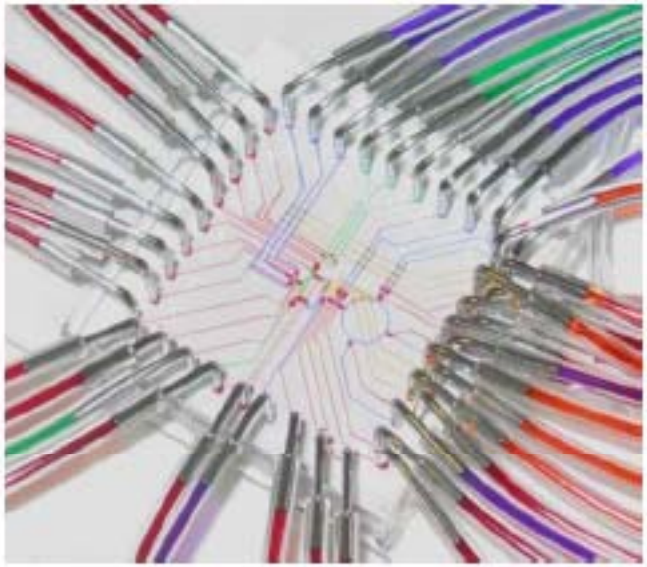
Gli organi del ragno che filano la seta

# Technologies for Expanding and Diversifying Molecular Imaging Capabilities for Cancer Diagnostics and Therapeutics



100 cm
Traditional Laboratory
Automation System

$^{18}$FDG yield: 70%
Time: 40 minutes



2 cm
Microfluidics Chemical
Reaction Circuit

$^{18}$FDG yield: >95%
Time: ~15 minutes

# Diagnostica x immagine

Problems:

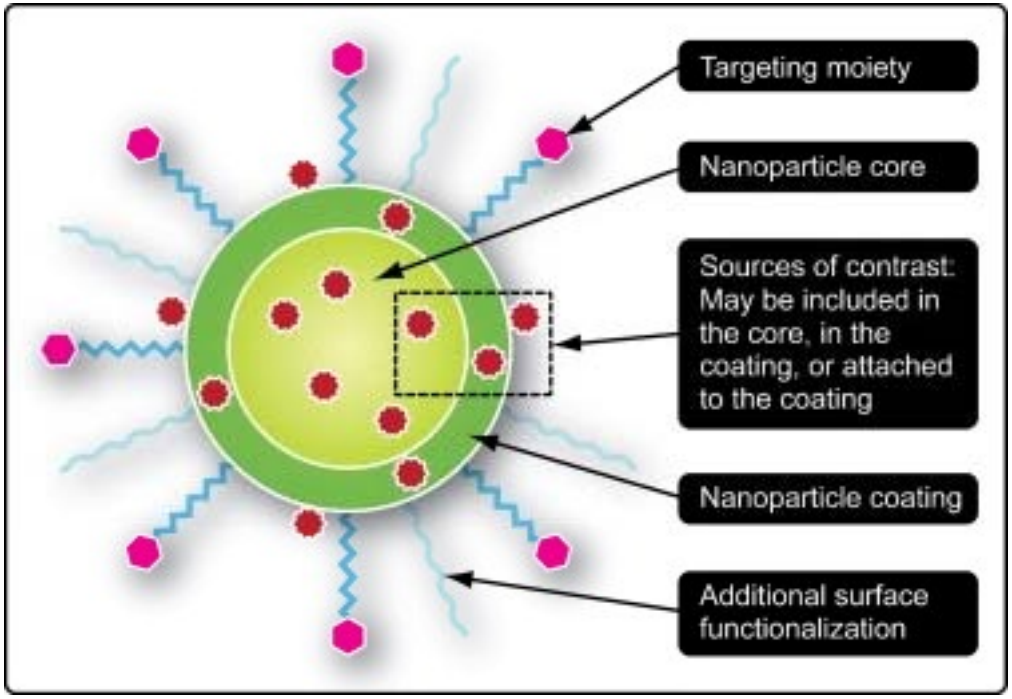
- Cancer metastasizes before it can be detected
- No reliable risk/exposure assays for carcinogenesis

Approaches:

- Multifunctional nanoparticles functionalized with specific antibodies target tumor cells
- Subsequent imaging allows for pinpointing of tumor cell conglomerates

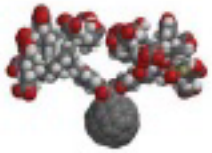
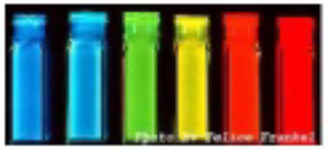



Source: Sh. Nie, JAMA, Vol. 292, No.16, p.1944-1945, 2004.

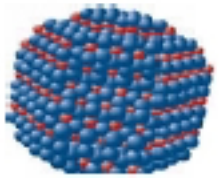



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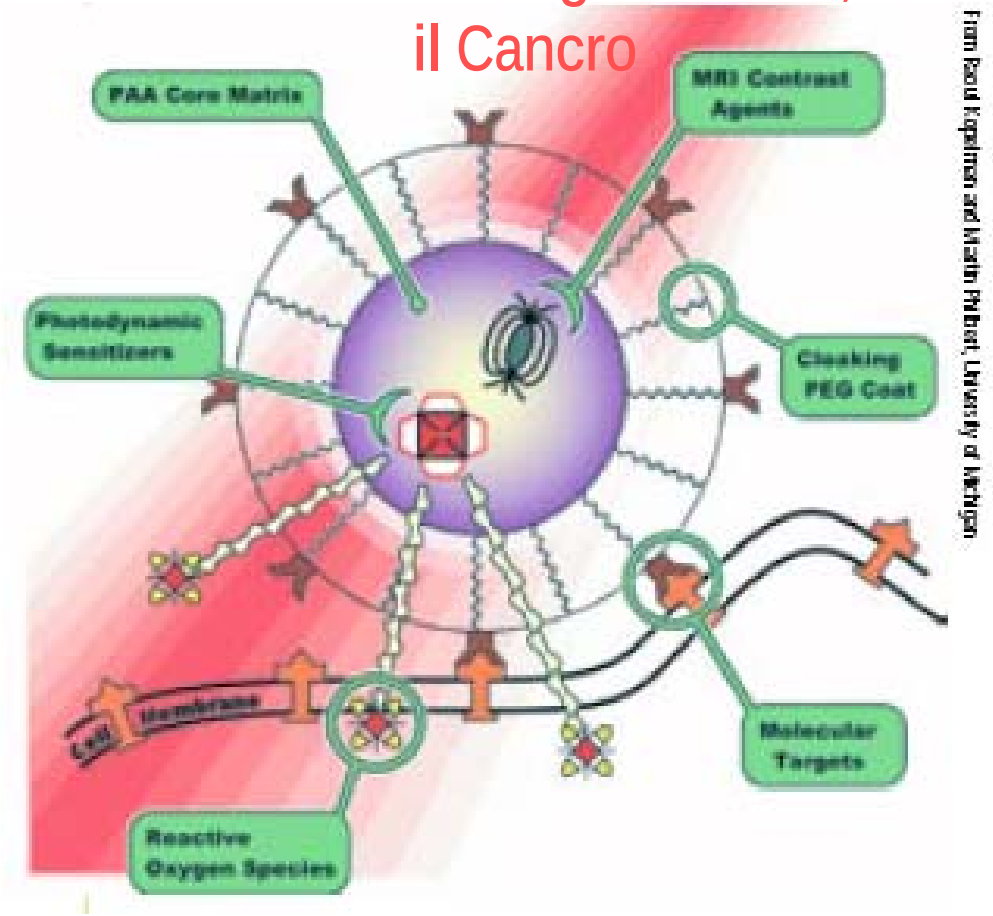
# Riassunto di Nanotecnologie Usate in ricerca e applicazioni (1)

| Modality | | Potential Applications |
|---|---|---|
| **Nanoparticles** |  | • Multifunctional therapeutics<br>• Targeted drug delivery, permeation enhancers<br>• MRI and ultrasound image contrast agents<br>• Reporters of apoptosis, angiogenesis, etc. |
| **Nanoshells** |  | • Deep tissue tumor cell thermal ablation<br>• Tumor-specific imaging |
| **Nanowires** |  | • High-throughput screening<br>• Disease protein biomarker detection<br>• DNA mutation detection (SNPs)<br>• Gene expression detection |
| **Quantum Dots** |  | • Optical detection of genes and proteins in animal models and cell assays<br>• Tumor and lymph node visualization |

# Riassunto di Nanotecnologie Usate in ricerca e applicazioni (2)

| *Modality* | *Potential Applications* |
|---|---|
| **Cantilevers**  | • High-throughput screening<br>• Disease protein biomarker detection<br>• DNA mutation detection (SNPs)<br>• Gene expression detection |
| **Carbon Nanotubes**  | • DNA mutation detection<br>• Disease protein biomarker detection |
| **Dendrimers**  | • Target sequestration<br>• Controlled release drug delivery<br>• Image contrast agents |
| **Nanocrystals**  | • Improved formulation for poorly soluble drugs |

# Nanoclinica: il modo diverso di diagnosticare , trattare e prevenire il Cancro




Le nanopiattaforme Smart''dynamic nella diagnosi dei tumori, trattamento e prevenzione.
La parte esterna della particella può essere decorata con un anticorpo monoclonale e ricoperta di poli-etilen glicole (PEG) per proteggere il device dal sistema immune. La matrice polimerica delle particelle può essere caricata con agenti di contrasto che identificano la localizzazione del tumore nel corpo e anche agenti terapeutici come molecole che genrarno specie rattive dell'ossigeno, attivabili quando la particella ha raggiunto una cellula maligna

***Da Cancer Nanotechnology, NIH & National Cancer Institute***

Clinically approved nanoparticle-based contrast agents.

| Composition | Trade name | Company | Indication | Administration |
|---|---|---|---|---|
| Dextran-coated SPIO (ferumoxides) | Feridex I.V./Endorem | Bayer Healthcare Pharmaceuticals, Inc. | Detection and evaluation of liver lesions associated with an alteration in the RES | i.v. |
| Carboxydextran-coated SPIO (ferucarbotran) | Resovist/Cliavist (EU, AUS, JPN only) | Bayer Schering Pharma AG | Detection and evaluation of liver lesions associated with an alteration in the RES | i.v. |
| Silicon-coated SPIO (ferumoxsil) | GastroMARK | Covidien, Ltd. | Bowel marking | Oral |

Nanoparticle-based contrast agents in clinical trials.

| Composition | Trade name | Developer | Indication | Administration | Status |
|---|---|---|---|---|---|
| Dextran-coated USPIO (ferumoxtran-10) | Combidex/Sinerem | AMAG Pharmaceuticals, Inc. | Differentiation of cancerous from noncancerous lymph nodes | i.v. | Phase III |
| Carboxy dextran-coated USPIO (ferucarbotran) | Supravist | Bayer Schering Pharm AG | Detection of blood pooling using MRA | i.v. | Phase III |
| Polyglucose sorbitol carboxymethyl ether-coated SPIO (ferumoxytol) | – | AMAG Pharmaceuticals, Inc. | Nervous system disease, brain neoplasms, peripheral artery disease | i.v. | Phase II |
| Citrate-coated very small SPIO | VSOP-C184 | Charité - Universitätsmedizin Berlin | Detection of blood pooling using MRA | i.v. | Phase I |
| Radiolabeled Her-2 affibody | ABY-025 | Affibody Holding AB | Breast cancer | i.v. | Phase I |

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Nanoparticle-based contrast agents in preclinical development.

| Composition | Contrast source | Target | Indication | Ref. |
|---|---|---|---|---|
| *Superparamagnetic metal nanoparticles* | | | | |
| Poly-L-lysine coated IO | IO | Mammalian cells | Tracking of transplanted cells | [330–333] |
| Antibody-targeted IO | IO | Her-2 | Breast cancer | [334] |
| Peptide/protein-targeted SPIO | IO | Clotted plasma proteins, MMP-2 | Various tumors | [335,336] |
| Radiolabeled antibody-targeted SPIO | $^{111}$In, IO, IRDye 800CW | Membrane glycoproteins, EGFR-2 | Various cancers | [337,338] |
| Aptamer-doxorubicin SPIO conjugate | IO, doxorubicin | PSMA | Prostate cancer | [339] |
| Peptide-targeted USPIO | IO | $\alpha_v\beta_3$, E-selectin | Various tumors, inflammation | [340,341] |
| Antibody-targeted USPIO | IO | CD20 antigen, E-selectin | Non-Hodkin's lymphoma, inflammation | [342,343] |
| Baculovirus-targeted USPIO | IO, LacZ | Mammalian cells | Gene therapy | [344] |
| Micelle-encapsulated MnSPIO | IO | Macrophages | Liver lesions | [345] |
| Antibody-targeted MnMEIO | IO | Her-2 | Breast cancer | [346] |
| Radiolabeled passive-targeted MnMEIO | $^{124}$I, IO | Lymph nodes | Lymph node mapping | [347] |
| Fluorescent CLIO | IO, Cy5.5 | Macrophages | Macrophage infiltration | [348] |
| Radiolabeled fluorescent CLIO | $^{64}$Cu, IO, Cy5.5 | Macrophages | Macrophage infiltration | [349] |
| Fluorescent peptide-targeted CLIO | IO, Cy5.5/FITC | Proteases, bombesin receptor, plectin, uMUC-1, hepsin, $\alpha_v\beta_3$, H-2K$^d$, VCAM-1, phosphatidylserine | Various tumors, autoreactive T-cells, inflammation, apoptosis | [350–357] |
| Fluorescent siRNA-CLIO conjugate | IO, Cy5.5 | *Birc5 gene* | Various cancers | [358] |
| *Other metal nanoparticles* | | | | |
| Polymer-coated gold nanoshells | Au | Tumor accumulation | Solid tumors | [287] |
| Fluorescent passive-targeted gold | Au, Hilyte 647 | Tumor accumulation | Solid tumors | [359] |
| Fluorescent antibody-targeted gold | Au, ICG | EGFR | Epithelial cancer | [360] |
| Antibody-targeted QD | QD | Her-2, PSMA, VEGFR | Various tumors | [361,362] |
| Growth factor-targeted QD | QD | EGFR | Epithelial cancers | [363] |
| Radiolabeled peptide-targeted QD | $^{64}$Cu, QD | $\alpha_v\beta_3$, VEGF | Various cancers | [364,365] |
| Protein-targeted paramagnetic QD | Gd, QD | Phosphatidylserine | Apoptosis | [366] |
| *Liposome-based nanoparticles* | | | | |
| Radiolabeled peptide-targeted liposomes | $^{18}$F | Macrophages | Inflammation | [367] |
| Antibody-targeted paramagnetic liposomes | Gd, Texas red | ICAM-1 | Inflammation and neuroinflammatory disease | [368] |
| Radiolabeled, dye-filled liposomes | $^{99m}$Tc, blue dye | Lymph nodes | Lymph node identification, inflammation | [369,370] |
| Fluorescent protein-targeted paramagnetic liposomes | Gd, AF680 | Transferrin receptor, E-selectin | Various cancers | [371,372] |
| Electron dense liposomes | Iodine | – | Blood pooling | [373] |
| *Synthetic carbon-based nanoparticles* | | | | |
| Peptide-targeted SWNT | SWNT | Integrin $\alpha_v\beta_3$ | Various cancers | [374] |
| Gd-filled fullerenes, fullerenols, and SWNT | Gd | Macrophages | Macrophage infiltration, blood pooling | [375–377] |
| Radiolabeled antibody-targeted SWNT | $^{111}$In, SWNT | CD20 | Lymphoma | [378] |
| Radiolabeled peptide-targeted SWNT | $^{64}$Cu, $^{111}$In, SWNT | Integrin $\alpha_v\beta_3$, EGFR | Various cancers | [379] |
| Radiolabeled MWNT | $^{99m}$Tc, $^{125}$I | – | TBD | [380] |
| *Other platforms* | | | | |
| Bismuth sulfide polyvinylpyrrolidone nanoparticles | Bi | – | Blood pooling | [381] |
| Radiolabeled hormone-targeted bacteriophage | $^{111}$In | MC-1 receptor | Melanoma | [382] |
| Ioxilan carbonate particles | Iodine | Macrophages | Liver lesions | [383] |
| Antibody-targeted paramagnetic perfluorocarbon emulsions | Gd, $^{19}$F | Fibrin, $\alpha_v\beta_3$, collagen III | Atherosclerosis | [384–386] |
| Radiolabeled amphiphillic block copolymers | $^{64}$C | Folate receptor | Various cancers | [387] |
| Iodinated amphiphillic block copolymers | Iodine | Macrophages | Lymph lesions | [388] |
| Fluorescent paramagnetic dendrimers | Gd, Cy5.5 | – | Sentinal lymph node identification | [389] |

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# Nanoprodotti sotto sviluppo per l'oncologia

| Product | Type of nanomaterial | Indication | Phase | Company |
|---|---|---|---|---|
| AmBisome | liposome | fungal infections | approved | Gilead Sciences |
| Doxil | pegylated liposome | metastatic ovarian cancer | approved | OrthoBiotech |
| VivaGel | dendrimer | topical microbicide for HIV | Phase I | StarPharma |
| MRX-952 | branching block copolymer self-assembled nanoparticulate formulation of irinotecan metabolite | oncology | preclinical | ImaRx Therapeutics |
| Definity | lipid-encapsulated octofluoropropane nanospheres | echocardiogram contrast agent | approved | ImaRx/BMS |
| MRX-815 | nanobubbles | vascular thrombosis | Phase I | ImaRx |
| Abraxane | nanoparticulate albumin | non-small cell lung cancer, breast cancer, others | NDA filed | American Pharmaceutical Partners |
| Cyclosert-camptothecin | cyclodextrin nanoparticle | metastatic solid tumors | IND filed | Insert Therapeutics |
| TNT-Anti-Ep-CAM | polymer-coated iron oxide | solid tumors | preclinical | Triton BioSystems |
| Rapamune | nanocrystalline drug | immunosuppressant for kidney transplantation | approved | Elan/Wyeth |
| Emend | nanocrystalline drug | nausea | approved | Elan/Merck |
| Leunesse | solid lipid nanoparticles | cosmetics | on market | Nanotherapeutics |
| Verigene platform | DNA-functionalized gold nanoparticles | diagnostics | on market | Nanosphere |
| INGN-401 | liposome | metastatic lung cancer | Phase I | Introgen |
| Combidex | iron oxide nanoparticle | tumor imaging | NDA filed | Advanced Magnetics |

Le nuove prospettive delle nanotecnologie sono:

**Diagnostica avanzata:**

**Molecolare, genomica, proteomica, imaging**

Terapie mirate, su bersaglio

- **Terapia molecolare, genica, anticorpi, delivery,**

# Le macchine ‘intelligenti’, la salute l’uomo

- La nuova civiltà delle macchine, è caratterizzata dalla prospettiva di macchine “intelligenti” e dalla convergenza di alcuni settori scientifici quali l’informatica, le nanotecnologie, le biotecnologie e le scienze cognitive.

- Per quanto tecnologiche siano le scienze
- Della salute non dimentichiamo che
- Dietro la macchina c’è sempre l’uomo,
- La sua individualità, la sua sofferenza
- Le sue speranze.

# Many thanks to:

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-Prof Douglas Noonan
-Dr. Antonino Bruno

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